THE ROLE OF OCCUPATIONAL EXPOSURE IN THE DEVELOPMENT OF LATEX HYPERSENSITIVITY

Corena de Beer

The role of occupational exposure in the development of latex hypersensitivity

Corena de Beer

The role of occupational exposure in the development of latex hypersensitivity

Corena de Beer

Dissertation submitted in fulfilment of the requirements for the Master's Degree in Technology (Biomedical Technology) in the Faculty of Applied Sciences at the Cape Technikon

External supervisor: Prof J Cilliers

Internal supervisor: Prof EJ Truter

Date of submission: December 2000

Dedicated to Johan and Elané

I declare that this dissertation, except where otherwise stated, represents my own work. It is submitted for the Master's Degree in Technology (Biomedical Technology) to the Cape Technikon. It has not been submitted for any degree or examination to any other Technikon or tertiary institution. Most of the work was carried out at the University of Stellenbosch Medical School, Tygerberg Campus.

The opinions and conclusions drawn are my own and not necessarily those of the Cape Technikon.

CdeZee

24-10-2000

Corena de Beer

Date

University of Stellenbosch / Tygerberg Hospital

Cape Town

TABLE OF CONTENTS

Appendices

PUBLICATIONS

1. De Beer C, Cilliers J, Truter EJ, Potter PC. Latex gloves – more harm than good? ***Med Tech SA 1999;13:1:282-288.***

2. De Beer C, Cilliers J, Truter EJ, Potter PC, Crombie I, Kosheva O. The role of occupational exposure in the development of latex hypersensitivity. ***Curr Allergy Clin Immunol 1999;12:3:36(Abstract).***

CONGRESS PRESENTATIONS

1. **Latex allergie: Die rol van blootstelling as 'n etiologiese faktor.**
   De Beer C, Cilliers J, Truter EJ.

   Presented at:

   - 43th Academic Yearday, Faculty of Medicine, University of Stellenbosch. 19/08/1999

2. **The role of occupational exposure in the development of latex hypersensitivity.**
   De Beer C, Cilliers J, Truter EJ, Potter PC, Crombie I, Kosheva O.

   Presented at:

   - Congress of the Dermatological Society of South Africa, Cape Town. 22-24/09/1999.
   - ALLSA Rhinitis Update, Spier Estate, Stellenbosch. 07-09/10/1999

3. **The role of occupational exposure in the development of latex hypersensitivity.**
   De Beer C, Cilliers J, Truter EJ, Potter PC.

   Presented at:

   - 24th World Congress of Medical Technology, Vancouver, Canada. 18-23/06/2000.
   - 44th Academic Yearday, Faculty of Medicine, University of Stellenbosch. 24-25/08/2000.

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation and heartfelt thanks to:

- My supervisors, Prof Jacques Cilliers, Department of Dermatology, University of Stellenbosch and Tygerberg Hospital, and Prof Ernie Truter, Faculty of Applied Sciences, Cape Technikon, for their advice, guidance and assistance throughout this study

- Prof Jacques Cilliers, Department of Dermatology, University of Stellenbosch and Tygerberg Hospital, for performing dermatological examinations on all patients

- Prof Paul Potter, Department of Allergology, Groote Schuur Hospital, for his advice and assistance throughout the study

- Prof H Francois Jordaan, Department of Dermatology, University of Stellenbosch and Tygerberg Hospital, for his advice and attendance to the grammar and style of this dissertation

- Tygerberg Hospital Management, in particular Dr AKMM Rahman, Chief Medical Superintendent, for permission to use various personnel sectors to include in the study groups and for implementing safety measures for which the need was identified during the study

- Dr D Eloff, Sr Blanckenberg (Personnel Clinic), Mrs Ria Gouws and Mrs Millie Julies (Department of Dermatology), Tygerberg Hospital, for assistance in identifying and recruiting volunteers for the study

- Dr Olga Kosheva and Sr Ivette Crombie, Department of Allergology, Groote Schuur Hospital, for performing skin prick tests on selected patients

- The Department of Immunology, Groote Schuur Hospital, for performing all cross-reacting IgE tests

- Prof Dirk van Schalkwyk, Cape Technikon, for the statistical analyses and interpretation of the results

- Mr Graham Barrett, Diagnostic Products Corporation, Johannesburg, for the loan of the required equipment for the manual immunoassays and supply of reagents for subsequent automated immunoassays

- University of Stellenbosch Doris Crossley Bursary and Dermatology Research Fund for financial support to conduct this research

ABBREVIATIONS

AA	amino acid(s)
ACD	allergic contact dermatitis
AL	ammoniated latex
CLA	cutaneous lymphocyte antigen
D	dalton
EIA	enzyme-labelled immunometric assay
ELISA	enzyme-linked immunosorbent assay
FDA	Federal Drug Administration
GE	glove extract
HCW	healthcare worker(s)
HIV	human immunodeficiency virus
Ig	immunoglobulin
IPP	isopentenyl pyrophosphate
kD	kilodalton
LH	latex hypersensitivity
MHC	major histocompatibility complex
MW	molecular weight
NAL	non-ammoniated latex
NRL	natural rubber latex
OR	operating room
RAST	radioallergosorbent test
REF	rubber elongation factor
SB	spina bifida
SPT	skin prick test
TBH	Tygerberg Hospital
TEWL	transepidermal water loss
UK	United Kingdom
USA	United States of America

ABSTRACT

Professionals in a healthcare setting use latex gloves on a daily basis, primarily to prevent transmission of microbial and viral organisms to and from patients and specimens. Repeated exposure to latex proteins (through direct skin contact or mucous membrane absorption) leads to the formation of circulating latex-specific antibodies and increases the risk of sensitisation. Among all known risk groups, healthcare workers have the highest risk to develop latex hypersensitivity. Early detection of antibodies or predisposing factors (e.g. atopy or impaired skin barrier function), could assist in the identification and management of risk groups and limit possible sensitisation.

An experimental group with high occupational latex exposure is compared to a control group with low or no occupational latex exposure at Tygerberg Hospital, Cape Town. A questionnaire was completed by all subjects to obtain a thorough history of past and present latex exposure and to identify other risk factors. A complete physical examination was done to evaluate clinical signs and symptoms of risk factors and latex hypersensitivity. Atopy was evaluated by means of the United Kingdom's Diagnostic Criteria for Atopy, personal and / or family history of atopy, haematogram and total serum IgE analyses. Latex-specific IgE antibodies were measured immunometrically. Skin prick tests were performed on subjects with negative in vitro results, but with pre-defined clinical symptoms suggestive of latex hypersensitivity.

An overall 20.8% prevalence of latex hypersensitivity in the study group was found. Only 28.6% of these patients suspected that they had latex hypersensitivity, while 7.3% did not suspect it and a further 35.7% were not sure. In the areas with high latex exposure alone, the prevalence reached 30.7%.

It is imperative to start instituting safety measures to manage the affected personnel and prevent additional staff becoming positive. Prevention will in the long-term be far more cost-effective than management of sensitised individuals.

AIMS

1. To determine the prevalence of latex hypersensitivity in healthcare workers at Tygerberg Hospital, Cape Town
2. To evaluate the efficacy of the questionnaire as a screening method
3. To evaluate high and low exposure environments as possible risk factors
4. To evaluate atopy and skin barrier function as contributing factors in the development of latex hypersensitivity
5. To compare the allergy score, eosinophil and total serum IgE levels in latex hypersensitive individuals to individuals with allergies other than latex hypersensitivity
6. To identify specific serum cross-reactivities in individuals with latex hypersensitivity
7. To educate staff about the risks of latex hypersensitivity and help to implement latex avoidance measures for affected staff members

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

Introduction

Over the past two decades, there has been a dramatic increase in the reported incidence of latex hypersensitivity (LH). Many authors regard a case report of a housewife with an IgE-mediated allergy to latex as the first positive LH case in history (Nutter 1979). However, earlier reports of confirmed LH date back to 1927 (Downing, 1933; Nieto *et al*, 1996).

Allergic reactions to latex can range from mild local urticaria to fatal anaphylaxis once a person is sensitised to latex. LH, therefore, necessitates radical changes to one's lifestyle. Specific high-risk groups are known to develop LH, e.g. healthcare workers (HCW) who bear the highest risk, patients with spina bifida (SB) or a history of multiple surgical operations and workers in the rubber manufacturing industry. Further predisposing factors are also known, e.g. atopy, asthma, eczema, multiple allergies and impaired skin barrier function. Early identification of personal risk factors (e.g. frequent exposure), antibodies or predisposing factors could assist in the identification and management of high-risk groups.

HCW use latex gloves to prevent transmission of microbial and viral infections to and from patients. Latex proteins in most surgical gloves are readily extractable and are absorbed when in direct contact with the skin and / or mucous membranes of the HCW and patient. Repeated exposure and subsequent absorption of the latex proteins result in the formation of circulating latex-specific antibodies. This increases the risk of sensitisation with wide-ranging implications - permanent morbidity, loss of expensively trained staff and possible legal consequences. Primary prevention of sensitisation to latex means absolute avoidance of exposure to latex. This is virtually impossible, given the large number of latex products encountered since childhood. Secondary prevention, the principal therapeutic approach, consists of avoiding exposure to latex by sensitised persons, a method, which likewise may be difficult because of the ubiquity of latex products and their similarity to non-allergenic synthetic rubber products.

The main purposes of this study were to evaluate LH in HCW in an academic hospital setting and to assess the role of occupational exposure to the proteins in the development of LH. Approval was obtained from the Ethical Committees of the University of Stellenbosch and Cape Technikon and permission was granted by Tygerberg Hospital

(TBH) management to commence with the study. Written informed consent was obtained from all patients before inclusion in the study.

A statistically planned cohort from TBH personnel was identified in order to be able to extrapolate results to the total population of TBH personnel. An experimental group consisting of personnel working in areas with high daily latex exposure (e.g. theatre, laboratories) was compared to a control group (from low latex exposure at TBH (e.g. administration). A questionnaire was completed by all subjects to obtain thorough history of previous and current exposure to latex of any kind, the presence and severity of predefined symptoms, history of operations, as well as identification of atopy and other risk factors. All patients underwent a complete physical examination to identify possible clinical signs and symptoms of risk factors and LH. Atopy was quantified by evaluation of the atopy index, total allergy score, complete haematogram and total serum IgE. Latex-specific immunoglobulin E (IgE) antibodies were measured on serum. Radioallergosorbent tests (RAST) for cross-reacting foods were done on serum where latex-specific IgE measured > 0.35 IU/ℓ only. All patients with normal specific IgE levels, but who experienced specific predefined and work-related symptoms were additionally subjected to skin prick tests (SPT) with commercially available latex extract as well.

For statistical purposes, the experimental group was primarily compared with the control group. The study population was then redivided into a LH positive and LH negative group, for further comparisons. Odds and risk ratio's, contingency tables, chi square and analysis of variance were done on all parameters where applicable within the 4 different groups, with a basic significance level of $p=0.05$ for all tests.

At the time of the study, a total of 4 920 people were employed by TBH. Of these, 2 744 (56%) were exposed to latex on a daily basis, while the remaining 2 176 (44%) were in administrative posts where latex exposure was non-existent or very low. A total of 148 786 pairs of latex gloves were utilised by HCW at TBH during the financial year in which the study was conducted (personal communication with the Department of Purchasing, TBH). Only 5 (0.01%) persons working at TBH have previously been diagnosed with LH. Furthermore, no routine testing facilities were available for diagnosing this condition immunologically or by SPT. The low prevalence of 0.01% should not be seen as representative of the LH status of the hospital. This study found a prevalence very much in keeping, or even marginally higher than other published data in the literature (see Table 4). Since only a small cohort of employees was tested, this could possibly be

the tip of the proverbial iceberg. If the results of the current study are being extrapolated to the study population, the worst case scenario would imply that more than a thousand employees might already be affected by LH, of which more than 800 are working in areas with high latex exposure.

Major latex allergens have been identified over the last decade. It is not clear which of these proteins are absorbed percutaneously. Integumental reactions to latex trigger urticaria after direct skin contact or lead to spongiotic or psoriasiform dermatitis within hours or days after exposure. It is postulated that latex proteins penetrate the skin to react with Langerhans cells, T-lymphocytes and mast cells to initiate a type I or IV immunological defence cascade. However, further research is necessary to prove this hypothesis.

CHAPTER II

Literature Review

2.1. ORIGIN OF NATURAL RUBBER LATEX (NRL)

Wild rubber was originally obtained from the *Hevea brasiliensis* tree of the family Euphorbiaceae (Czuppon *et al,* 1993), which is indigenous to Brazil. In 1896, seeds were collected and replanted as seedlings in Ceylon and South East Asia (Cronin, 1980). Gradually, plantations in Malaysia and Indonesia flourished and today some of the major producers of natural rubber world-wide include China, India, Indonesia, Liberia, Malaysia, Sri Lanka, Thailand and Vietnam (Jaeger *et al,* 1992).

H.brasiliensis trees take 6-8 years to reach harvesting maturity, and an average tree yields enough latex to make approximately 10 pairs of gloves per week. To gather latex from the trees, a diagonal cut angled downward is made through the bark; one-third to one-half of the circumference of the trunk. The latex flows upwards into the incision for an hour or two, slows down and finally stops as the latex coagulates within the cut ends of the laticiferous ducts. Latex coagulates on the tapping cut and seals the wound. The laticiferous system then regenerates lost cell material before the next tapping, typically 2-3 days later. The latex that exudes from the cut is collected in a small cup, usually about 30 mℓ on each tapping. In order to retap the tree, a thin strip of bark is shaved from the bottom of the original cut. When the cuttings reach the ground, the bark is permitted to renew itself before a new tapping panel is started. Autocoagulation, deterioration and bacterial contamination occur rapidly in fresh latex unless preservatives and anticoagulants, such as ammonia, are immediately added.

When a rubber tree is wounded by tapping, the cytoplasmic contents of its laticifers are expelled, and the wounded sites are sealed by coagulation. This process is considered to involve two successive events. One is bursting of lutoid bodies in the laticifers and the release of their proteins. The second is interaction of the released cationic proteins with negatively charged rubber particles. Citrate and phosphatases are released from the fragile lutoids and neutralise the negative charge on the rubber particles, allowing them to adhere to each other and coagulate (Pumphrey, 1994).

Most plants are able to protect themselves against various stresses, such as wounding, pathogen attacks, application of chemicals, including phytohormones and heavy metals, air pollutants like ozone, ultraviolet rays, and harsh growing conditions. This reaction is known as the defence response of higher plants (Figure 1) and a series of proteins actively synthesised with this reaction, is called defence-related proteins. Any plant has the potential to induce such proteins under certain conditions and these defence-related proteins can construct a group of plant pan-allergens. These proteins induced by stresses have structural and serologic similarities, irrespective of the plant species and include class I, II and IV endochitinases, endo-ß-1,3-glucanases, lysozymes and other chitin-binding lectins (Bowles, 1990).

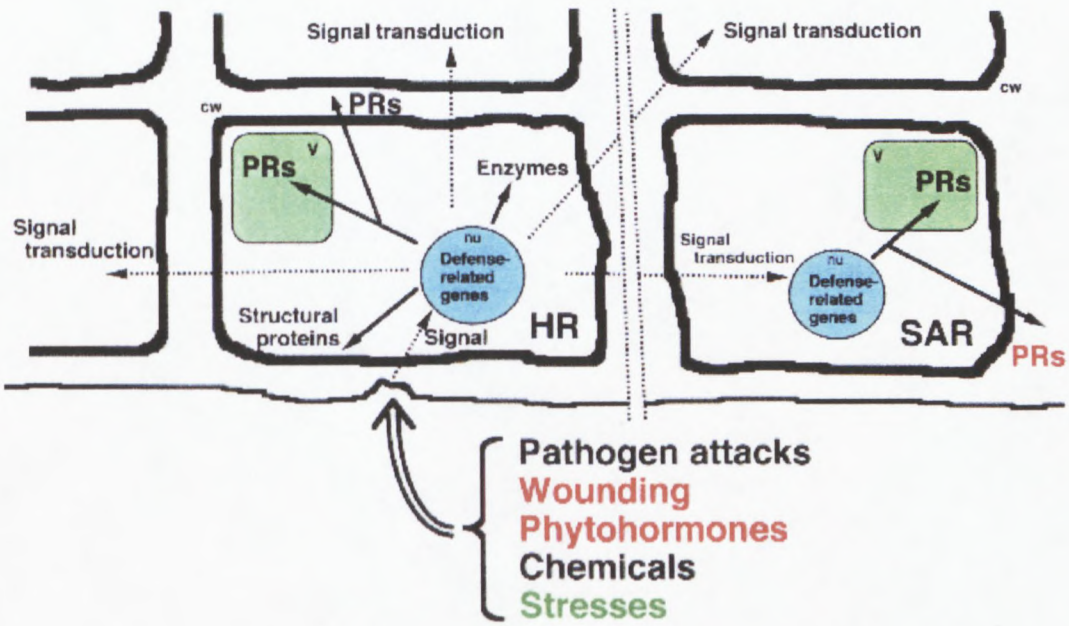


Figure 1: Plant defence responses (PR = pathogenesis-related proteins)

In the case of the *H.brasiliensis* tree, repeated wounding of the tree through tapping, increases the content of defence-related proteins in the laticifers, which may form a major part of latex allergens (Yagami *et al,* 1995). These defence-related proteins, also known as wound-repair proteins, play an important role in cross-reactive allergies (Figure 2).

The raw latex typically contains 30-33% rubber particles with a diameter of 400 nm (Cronin, 1980; Jaeger *et al,* 1992) and approximately 67-70% cytoplasm. The rubber particle is a hydrophobic, hydrocarbon, spherical droplet. It consists mainly of long-chain polymers of *cis*-1,4-polyisoprene, which are surrounded by a thin phospholipoprotein coat (Levy, *et al* 1992; Warshaw, 1998). About 25% of the latex proteins are bound to the rubber particle surface (Arreguin *et al,* 1988). These include prenyltransferase, which is

found both free in the cytosol and in association with the rubber particle (Slater & Trybul, 1994a), and rubber elongation factor (REF), which is involved with rubber biosynthesis.

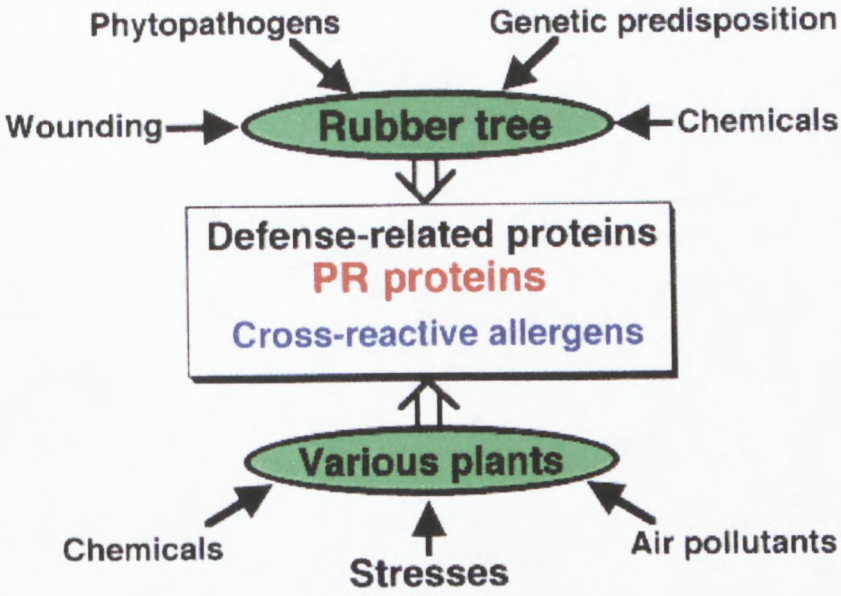


Figure 2: Latex hypersensitivity and defence-related proteins

The cytoplasm contains 2% resin, 1.8-2% proteins and enzymes. Frey Wyssling organelles, which are cytoplasmic structures capable of energy consumption, are also present in small amounts, but their biological role in this context has not been clearly defined. Other substances present in the cytoplasm are lipids, cofactors, nuclei, mitochondria, soluble carbohydrates, organic acids, amino acids (AA), nucleotides and various other organelles, e.g. the specialised lysosome-like lutoids. Lutoids are small vacuoles that are important for coagulation, and the major lutoid proteins are hevein, prohevein and hevamine (Warshaw, 1998). The remaining 60% of the cytoplasm is water (Cronin, 1980; Jaeger *et al,* 1992; Potter, 1998a, 1998b; Wakelin & White1999).

2.2. CHEMICAL AND PHYSICAL PROPERTIES

Natural latex is a highly processed colloidal polymer derived from the sap of the *H.brasiliensis* tree (Zerin *et al,* 1996). This emulsion of rubber particles exists in an aqueous serum with cytoplasm, which is milky white due to numerous granules, which contain terpenoids. The laticiferous cells form rings of interconnecting ducts in the bark to facilitate tapping of the cytoplasm.

Pure crude rubber is a white or colourless hydrocarbon. The simplest unit of natural rubber is isoprene (C_5H_8 or CH_2 C $(CH_3)CH:CH_2$) (Figure 3) and the monomer is a *cis*-1,4-

polyisoprene spherical droplet. The *trans* form, gutta percha, is a different kind of material and is used in golf ball covers. At the temperature of liquid nitrogen (± -195°C), crude rubber is a hard, transparent solid; from 0° to 10°C, it is brittle and opaque, and above 20°C it becomes soft, resilient and translucent. When rubber is mechanically kneaded or heated above 50°C, it becomes plastic and sticky, and above 200°C it decomposes. It is insoluble in water, alkali and weak acid, but soluble in benzene, gasoline, chlorinated hydrocarbons and carbon disulphide. It is rapidly oxidised by chemical oxidising agents, and slowly by atmospheric oxygen.

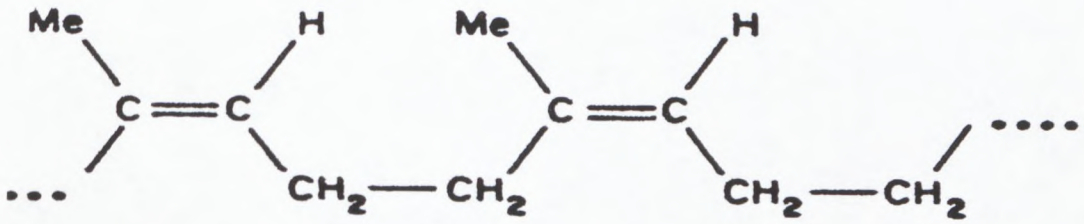


Figure 3: The structure of rubber. Two *cis*-isoprene repeats: in *H.brasiliensis* rubber the molecules have a wider range of sizes, with about 30 000 repeats (Pumphrey, 1994)

Rubber biosynthesis appears to occur in the following sequence. Three acetyl coenzyme A molecules are converted into hydroxymethylglutaryl coenzyme A, which in turn is reduced to mevalonic acid, and phosphorylated and decarboxylated to the five-carbon isopentenyl diphosphate. This isoprene subunit forms the backbone of monoterpenes (2 isoprene units), diterpenes (4 isoprene units) and sterols (6 isoprene units). REF and prenyltransferase on the rubber particle facilitate elongation of polyisoprene chains to lengths of up to 10^6 D in latex-producing species (Slater & Trybul, 1994a).

Fresh NRL can be separated into three layers by centrifugation. The upper layer contains rubber particles; an aqueous middle layer is known as the serum (B fraction); and the bottom layer (C fraction) contains lutoids and other intracellular particles. Each layer contains unique proteins, and 47% of the total protein is located in the middle serum layer. Chemically, most rubbers contain double bonds, which are reactive and allow the molecules to vulcanise and polymerise (Cronin, 1980). Certain manufacturing processes can result in the hydrolysis and further alteration of the proteins. End-use latex medical devices contain varying length polypeptides derived from the original proteins (Beezhold *et al,* 1994b).

2.3. MODERN MANUFACTURING PROCESSES

After collection, the latex is filtered to remove particulate debris, diluted with water, and treated with acid causing the suspended rubber particles within the latex to clump together. It is then preserved by adding either ammonia or sodium sulphite and can be coagulated by adding acetic or formic acid, which reduces the pH to less than 4 (Cronin, 1980). After being pressed between rollers to consolidate the rubber into 0.6 cm slabs or thin crepe sheets, the rubber is air- or smoke-dried for shipment. Approximately 10% of the latex is kept in a colloidal form in which the water content has been reduced and ammonia and sodium pentachlorophenate added as preservatives to prevent spontaneous coagulation. Rubber in this form is used for crepe soles in shoes, tyres and tubes. The latex concentrate, containing rubber particles suspended in ammoniated cytoplasm, is kept in this form for at least 3-4 weeks to mature before manufacture into gloves, condoms, catheters, elastic bands, foam, rubber adhesives or other latex goods (Cronin, 1980; Pumphrey, 1994; Spaner *et al,* 1989).

Early rubber products, however, became brittle under cold conditions, and sticky with age. These problems were solved in 1839 when Goodyear accidentally discovered vulcanisation, a process by which latex is slowly heated in the presence of sulphur. The elasticity and thermostability of rubber is hereby greatly improved. This process creates disulphide bonds that cross-link *cis*-1,4-polyisoprene chains to each other (Warshaw, 1998). The principal vulcanising agent continues to be sulphur, but selenium and tellurium are also used, generally with large proportions of sulphur. In the process of hot vulcanising, the sulphur is ground and mixed with the rubber at the same time as the other dry ingredients. The proportion of sulphur to rubber varies from 1 : 40 in soft rubber goods to as much as 1 : 1 in hard rubber. Cold vulcanising, used mainly for soft, thin rubber goods, such as gloves and sheeting, is accomplished by exposing the uncured articles to the vapour of sulphur chloride (S_2Cl_2). This process was named in memory of Vulcan, the Roman god of fire and smiths (Cronin, 1980) and it enabled Dunlop to invent the inner tube and hollow tyre in 1888 (Warshaw, 1998).

Various other chemical additives may be added during the manufacturing process to provide rubber with enhanced strength, ability to stretch and durability. Ammonia is added as preservative and it disrupts the rubber particles and produces a two-phase product of about 30-40% solids. It is then concentrated to 60% solids, producing ammoniated latex (AL) concentrate, which contains 1.6%, or as little as 0.15-0.25%, ammonia by weight.

However, at such low ammonia concentrations, a secondary preservative (e.g. sodium pentachlorophenate, tetramethylthiuram disulphide, sodium dimethyldithiocarbamate or zinc oxide) is necessary to avoid coagulation and contamination (Slater & Trybul, 1994a). Accelerators primarily control the rate, uniformity and completeness of vulcanisation. The most common sulphur-containing compounds are amines, benzothiazoles, carbamates, diphenylguanide, mercaptobenzothiazoles, thioureas and thiurams (Cohen *et al,* 1998). Initially, vulcanising accelerators included only metallic oxides, such as white lead and lime, but lately also include a wide variety of organic amines. These accelerators do not only reduce the time of heating necessary for vulcanisation by 60-85%, but also increase the quality of the product.

Antioxidants are used to prevent oxidation and ozone attack and include amines, hydroquinone, monobenzyl ether, paraphenylenediamine, phenol derivates, quinolines, thiocarbamates and zinc oxide. Antioxidants and antiozonants stabilise unsaturated isoprene bonds and prevent deterioration (Warshaw, 1998). Anticoagulants convert the emulsion into approximately 60% liquid and 40% solid phases. Peptisers, such as thio-ß-naphthol, are used to melt the latex colloid gels. They are potent sensitisers responsible for many reported hypersensitivity reactions. These allergens are present in the finished product and both consumer and manufacturer are at risk of being sensitised (Cronin, 1980; Jaeger *et al,* 1992; Marcos *et al,* 1991; Pumphrey, 1994; Spaner *et al,* 1989).

For the majority of applications, the raw rubber is mixed with a variety of compounding ingredients to modify the characteristics. Fillers stiffen the rubber in the final product, but do not materially increase its strength, and include calcium carbonate and barium sulphate. Reinforcing fillers add materially to the strength of the finished product and include carbon black, magnesium carbonate and various clays. Pigments include zinc oxide, lithopone, and a number of organic dyes. Softeners, which are necessary when the mix is too stiff for proper incorporation of the various ingredients, usually consist of petroleum products, such as oils, waxes, pine tar or fatty acids.

In some studies using Western blot analyses, specific protein bands were found to be present in glove extracts (GE) and aged AL sap, but not in fresh latex extracts prepared under similar conditions. These proteins are known as neoantigens, and they can be a result of hydrolysis and denaturation of proteins in gloves and AL sap (Alenius *et al,* 1991; Akasawa *et al,* 1995; Slater 1992b). An alternative explanation for these observations, is that ammonification and perhaps other aspects of glove production, can cause hydrolysis

of larger epitope-bearing proteins into smaller epitope-bearing peptides. This may result in a significant enrichment of the number of epitope sites of the proteins in the gloves, but will not influence raw latex (Slater & Trybul, 1994a).

Raw latex consists of 30-40% polyisoprene by weight. After cross-linking and vulcanisation, the final rubber product typically contains 93-95% polyisoprene and up to 3% protein by weight (Levy *et al,* 1992). In finished latex products, such as gloves and condoms, the protein content has been found to range from < 0.05 - 1 mg extractable protein per gram latex, or approximately 0.1% or less by weight (Weiss, 1995). In the literature there is a mention of 40 000 consumer products that contain latex (Beezhold *et al,* 1996).

2.4. SURGICAL GLOVES

The Goodyear Rubber Company made the first pair of rubber gloves in 1890. This followed the request of the renowned surgeon, William Stuart Halstead, primarily to protect the surgeon and his assistants from the irritating effects of antiseptics, e.g. mercurial salts (Ellis, 1990; Walls, 1996; Warshaw, 1998; Zerin *et al,* 1996). However, soon afterwards, gloves became part of a complicated ritual of aseptic surgery (Ellis, 1997). Today, the most important reason why HCW wear gloves is to protect themselves and their patients against the transmission of microbial, viral and bloodborne diseases, such as hepatitis and human immunodeficiency virus (HIV) (Cohen *et al,* 1998; Committee Report, 1993; Heese *et al,* 1991). In 1987 the United States of America (USA) Center for Disease Control adopted the "Universal Precautions for Prevention of Viral Transmission in the Health Care Setting". These recommendations required the use of adequate barrier protection, including the use of gloves, when in close contact with blood or body fluids, or during intimate direct patient contact (Grzybowski *et al,* 1996).

These precautions resulted in a dramatic increase in the use of disposable medical gloves in subsequent years. Before 1987, an estimated 300 million gloves were used annually in the USA, but this figure has grown to 9.6 billion per year in 1996 (D'Epiro, 1996). Until 1987, Malaysia, the centre of the world's latex glove industry, had 25 glove manufacturers, but by 1990 this number had increased to 400 (Turner, 1997). Available records from the Mayo Medical Center purchasing department showed a linear increase in annual glove purchases from 1986 to 1993. It did, however, not match the peak incidence of LH seen during 1990 to 1992, suggesting that other factors, such as manufacturing changes, were also contributing to the LH epidemic (Hunt *et al,* 1995, 1996).

Originally, gloves were sterilised by boiling and then put on wet over wet hands. With the introduction of dry sterilisation, it was necessary to use dusting powder to prevent the gloves from sticking to the moulds and facilitate donning (Potter, 1998a, 1998b). The first agents used were lycopodium (the spores of club moss), talcum powder or a mixture of the two. Talcum powder is a finely pulverised mineral talc, which consists chemically of a combination of hydrous magnesium silicate (chemically pure talc), calcium magnesium carbonate, calcium magnesium silicate and traces of other related substances (Ellis, 1990).

The first foreign body granuloma was reported in 1917. In 1933 six instances were described where spores of lycopodium were identified in lesions after surgery. In 1936, peritoneal nodules resulting from the use of talcum-containing glove powder, were noted. More reports of postoperative talc granulomas were recorded the following year. In 1941, two patients with intra-abdominal adhesions as a result of talc granuloma, were reported after they underwent laparotomies. In 1943, a total of 50 post-laparotomy talc granulomas were reviewed. In 1947, five women, all of whom had undergone an appendectomy previously, had low grade pelvic inflammation and had thickened fallopian tubes surgically removed. All these specimens showed granulomas containing talc granules. The talc, deposited in the peritoneal cavity during the original appendectomy, appeared to have migrated into the tubes. By the early 1940s, researchers noted the difficulty of removing traces of talc from the outside of surgical gloves and the dangers of talc were well recognised. Increasing numbers of patients with talc granulomas were reported during the late 1940s (Ellis, 1990).

In 1947, the superiority of epichlorhydrin-treated cornstarch powder over talc as a lubricant for surgical gloves, was reported (Ellis, 1997). This, mixed with 2% magnesium oxide as a desiccating agent, remains in use today. Initially, this powder proved inert and caused few problems. However, in 1955 the first two patients with cornstarch powder wound granulomas were reported. Three patients with granulomatous intraperitoneal foreign body reactions as a result of the use of starch powder, were also recorded. Over the next 20 years, numerous reports of starch-induced peritonitis and intraperitoneal granulomas were published from Australia, Europe, Israel, Japan, South Africa, USA and United Kingdom (UK) (Ellis, 1990). The amount of starch powder on powdered gloves can be considerable (up to 80 mg per pair on some brands). It is now known that starch glove powder can no longer be regarded as inert and it should be considered a highly reactive material both *in vitro* and *in vivo* (Giercksky, 1997).

Why was it only in the 1960s that an apparent "epidemic" of patient reports of starch granulomas and starch peritonitis began to appear? This may be explained by a change in the method of sterilisation of the starch or possible talc contamination in the preparation process. Initially, starch was sterilised by autoclaving, but this technique was replaced by gamma sterilisation. In a rat model, it was determined that autoclaved starch was almost totally absorbed from the peritoneal cavity within a period of 48 hours, while irradiated starch was still not fully absorbed after a period of 70 days. Scanning electron microscopic studies on autoclaved starch showed that the surface of the granules was pitted and cracked, while similar studies on irradiated material showed a smooth surface. It was concluded that sterilisation by autoclaving damages the starch in such a way that rapid absorption occurs and a low incidence of granuloma and adhesion formation results (Beezhold & Beck, 1992; Ellis, 1990).

To manufacture latex goods, the mixture is shaped or applied mechanically to a base, and the coated object or shaped mixture is placed in moulds. Latex gloves are generally manufactured over a heated, powdered mould that passes through a slurry of latex compound at room temperature. The glove forms over the heated mould, and this mould is then baked at high temperature. When the glove is removed, the self-adhesive surfaces of the latex must be coated or dusted with talc or cornstarch powder to stop surfaces from sticking together (Bubak *et al,* 1992). Dry cornstarch may be blown onto the finished gloves, or, as in the commonly used wet-powdering process, the starch may be applied by dipping the vulcanised gloves into a water-based slurry. During the wet process, water-soluble, potentially allergenic latex proteins may leach from the gloves into the slurry and contaminate the powder. The same powdering slurry may be used for many weeks, and hundreds of thousands of latex gloves may be dipped into the same slurry. This leads to contamination of the glove powder, since the water-based slurries in reality function as a leaching bath for the gloves. The protein content of the glove may be reduced by leaching or may be actively denatured by chlorination (Potter, 1996a). Peptides from the *Hevea* proteins trapped during manufacture then can migrate out of the latex and become bound to starch particles. Sweat or other body secretions can leach out the peptides, which are then absorbed through skin or mucosae, introduced into the body during surgery, or inhaled on the glove powder (Pumphrey, 1994).

Leaching of latex products is a procedure known to reduce the allergen content (Lundberg *et al,* 1995). The amount of latex allergen leaching into the powder suspension depends on the original allergen content and the previous leaching of the product. Water soluble

proteins leach out of rubber very rapidly (1-5 minutes), however, complete extraction may take up to 18 hours or more. Surface localisation of latex proteins in latex gloves takes place when water-soluble proteins in wet natural rubber films migrate with the evaporation stream to the surface when the film dries. These surface proteins are nearly insoluble in water and have limited solubility in carbonate buffer. They are remarkable in their ability to non-specifically bind to IgM from human serum or activate the serum complement system and thereby have the potential to cause anaphylactoid reactions (Beezhold, 1993).

Between 1988 and 1992, an estimated 11.8 billion examination gloves and 1.8 billion surgical latex gloves were used in the USA (Sussman & Beezhold, 1995). However, it is important to note that there are more potential hazards from gloves, both for the patient and for the glove user. Apart from granulomatous reactions and the risk of delayed healing caused by foreign body reactions, there is also the risk of allergic reactions to the glove latex proteins and residual allergens. It has already been shown that latex allergens adsorb to cornstarch particles inside the gloves and that starch particles from latex gloves could evoke positive results to inhalation challenge tests in latex-sensitive persons (Bubak *et al,* 1992; Jaeger *et al,* 1992). Although surgical gloves are made from AL of which polyisoprene is the main constituent, it also contains about 2% proteins (Jaeger *et al,* 1992; Potter, 1998a, 1998b). Surface localisation of latex proteins results in latex allergens being localised on the interior, as well as exterior surfaces of latex gloves (Grote *et al,* 2000). These proteins can be absorbed by the skin or mucous membranes, or airborne contaminated glove powder appear to be responsible for the various respiratory symptoms in LH patients (Mäkinen-Kiljunen *et al,* 1993; Slater & Chhabra, 1992a).

The comfort, barrier and tactile properties of powdered latex gloves have been thought to be ideal, but alternatives had to be evaluated over the past decade or two. Latex offers nine times more barrier protection than polyvinyl chloride (PVC or vinyl), thus showing vinyl to be of limited use in high risk, heavy usage situations (Smith *et al,* 1993). Furthermore, vinyl gloves are less flexible and less durable than latex. However, vinyl is unique when its physical properties and cost advantages are compared to those of other polymers. In general, vinyl exhibits good mechanical toughness, resistance to weathering, as well as excellent resistance to inorganic acids, alkalis, and water, and very good resistance to oxygen and ozone degradation. Vinyl products are extremely rare causes of ACD, but have not been shown to be efficient barriers to viral transmission, including HIV. Therefore, vinyl gloves should not be used for prolonged procedures involving contact with blood or body fluids that require manual dexterity. If it is used in such cases, it should be

changed at least every 30 minutes (Fisher, 1997a). Increasing thickness of gloves also impair dexterity and sensitivity, since sensory tests are significantly affected by the use of thicker gloves, in general it takes about twice as long to perform and results in higher error rates (Phillips *et al,* 1997).

2.5. LATEX PROTEINS / ALLERGENS

Identification of the major allergens in latex is important for several reasons. It will make it possible to determine whether latex allergens are all found in native latex as it comes from the tree or whether some new allergic epitopes are created during processing (Mäkinen-Kiljunen *et al,* 1992). If new allergens are created during processing, it may be possible to alter processing to reduce the allergen content of finished products. If the major allergens are all found in native latex, it may be necessary to determine the function of the allergenic proteins. Identification of major allergens (Table 1) should lead to the preparation of potent, standardised, and well-characterised latex extracts for diagnosis of LH and to the development of more accurate tests of allergen content in finished products (Ownby, 1993).

Storage of latex in ammonia alters the electrophoretic profiles of the proteins such that the sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) profile changes from distinct bands to a smear of polypeptides with an increase in high molecular weight (MW) material. Many of the changes are due to hydrolysis and denaturation of the proteins. However, hydrolysis does not entirely explain the changes. Since non-ammoniated latex (NAL) serum proteins migrate primarily below 46 kD, the appearance of high MW polypeptides suggests that ammonification (and / or other compounding ingredients) induce a type of polymerisation of the latex proteins that produces the larger polypeptides. Haptenisation with various compounding chemicals may alter the bioavailability and antigenicity (Warshaw, 1998). In addition, ammonification also extracts some of the rubber bound proteins, making them soluble proteins and thus potential allergens.

Latex allergens appear to be unique. Patients recognise many different proteins rather than a few allergens. The immune response to latex proteins is dependent on the denaturing of the latex proteins and the routes of exposure (Beezhold *et al,* 1994b). There is no obvious association between the immunoreactive pattern and the symptoms observed in different patients. The concentration of latex-specific IgE does also not predict the severity of the allergic reaction (Akasawa *et al,* 1995; Lundberg *et al,* 1997).

Table 1: Registered natural rubber latex allergens*

Name	Trivial Name	Physiological roles	MW (kD)	Length (AA)
Hev b 1	REF	rubber biosynthesis	14.6	137
Hev b 2	ß-1,3-glucanase	defence-related protein	36	
Hev b 3	small rubber-particle protein	rubber biosynthesis	23	
Hev b 4	microhelix component	?defence-related protein	± 50	
Hev b 5	acidic latex protein	unknown	16	
Hev b 6.01	prohevein (hevein preprotein)	defence-related protein, latex coagulation	20	187
Hev b 6.02	hevein	defence-related protein, latex coagulation	4.7	43
Hev b 6.03	prohevein C-terminal domain	defence-related protein, latex coagulation	14	138
Hev b 7b	patatin-like proteins	defence-related protein	46	
Hev b 7c	patatin-like proteins	inhibits rubber biosynthesis		
Hev b 8	latex profilin	structural protein	15	
Hev b 9	latex enolase	unknown		
Hev b 10	Mn-superoxide dismutase	unknown		

* Allergen designation by the International Union of Immunological Societies (IUIS);
MW = molecular weight in kilodalton; AA = amino acids

Latex proteins may be characterised as a family of water-soluble, thermostable proteins or glycoproteins with MW of 5 kD - 200 kD (Dennis & Light, 1989b; Siler & Cornish, 1995). The major protein bands are usually observed from 10 kD - 14 kD (Slater 1992b), 20 kD - 45 kD, and 50 kD - 67 kD (Jaeger *et al,* 1992; Kurup *et al,* 1993; Slater, 1992b) with a doublet at 27 kD and 28 kD as demonstrated by Slater (Slater & Chhabra, 1992b). This variability may have resulted in part from interlaboratory differences in the methods used in extraction, protein purification, and allergen identification, but most likely from the diversity of latex sources (origin, climate, and soil) and the specificity of immune sera used for immunoblot evaluation (Tomazic *et al,* 1995).

Although more than 240 separate polypeptides can be discerned by two-dimensional electrophoresis in latex sap, only 57 are reportedly allergenic (Czuppon *et al,* 1993; Potter, 1994b; Raulf-Heimsoth *et al,* 1996; Slater, 1992b). Most identified allergens are found as soluble C-serum proteins and as proteins that are normally bound to rubber particles (Kostyal *et al,* 1998).

Table 2 summarises the known AA sequences for selected latex proteins (Beezhold, 1993; Beezhold *et al,* 1994a).

Table 2: Amino acid sequences of selected natural rubber latex proteins

Protein Name	Amino acid Sequence
Rubber elongation factor (*Hev b 1*)	M-A-E-D-E-D-N-Q-Q-G-Q-G-E-G
Hevein (N domain) (*Hev b 6.02*)	E-Q-C-G-R-Q-A-G-G-K-L-C-P-N
Hevein (C domain) (*Hev b 6.03*)	G-G-S-A-S-N-V-A-T-Y-N-S-Q-D
Hevamine	G-G-I-A-I-Y-W-G-Q-N-G-N-E-G
Prenyltransferase	W-V-E-R-V-L-Y-N-X-L-K-L

2.5.1. Rubber elongation factor (*Hev b 1*)

REF is a common allergen in children with SB where the major route of exposure to latex appears to be direct contact with mucous membranes (Alenius *et al,* 1994, 1996; Lu *et al,* 1995; Turjanmaa *et al,* 1996; Yeang *et al,* 1996). This allergen is recognised only by 50% of sensitised HCW (Posch *et al,* 1997a).

REF is a spherical, homotetrameric molecule with a MW of 14.59 kD and no disulphide bridges (Czuppon *et al,* 1993; Posch *et al,* 1997a). It is a water-insoluble protein, which is tightly bound to serum-free rubber particles, specifically in whole latex, and mainly on large particles (> 350 nm in diameter). REF has a hydrated specific volume of 0.93 mℓ/g, creating a molecular diameter of 35.1 Å. REF has a length of 137 AA and lacks four AA: cysteine, methionine, histidine, and tryptophan. The NH_2 terminus is highly charged and contains only acidic residues (5 of the first 12 AA) (Dennis & Light, 1989b). It makes up between 10-60% of the total protein, but is absent in C-serum. The amount of REF in whole latex is stoichiometrically relative to the number of rubber molecules (Dennis *et al,* 1989a; Dennis & Light, 1989b).

REF plays a role in rubber elongation in docking and positioning prenyltransferase on the rubber molecule. Such docking may involve a reorientation of the binding sites for isopentenyl pyrophosphate (IPP) and the allelic primer. Additionally, REF may position and protect the growing pyrophosphate ends on the rubber molecule. REF interacts with *Hevea* prenyltransferase to alter the steochemistry of IPP addition from the normal *trans* addition to *cis* and overrides the normal termination after two *trans* additions to affect the formation of *cis*-polyisoprene (Czuppon *et al,* 1993).

2.5.2. Prohevein (*Hev b 6.01*)

Prohevein is synthesised as a 20 kD preprotein of hevein. It has the capacity to bind IgE (Posch *et al,* 1997a) and is the most frequently recognised NRL allergen among adult patients presenting primarily with cutaneous symptoms (Alenius *et al,* 1994, 1996; Lu *et al,* 1995; Slater & Trybul, 1994a; Turjanmaa *et al,* 1996). It has a length of 187 AA which is post-translationally processed into amino-terminal hevein (138 AA) and the carboxyl-terminal 138-AA C-domain (*Hev b 6.03)* of 14 kD (Beezhold *et al,* 1994a, 1994b; Posch *et al,* 1997a).

2.5.3. Hevein (*Hev b 6.02*)

Hevein is a major allergen for HCW, but not for children with SB (Alenius *et al,* 1994, 1996; Lu *et al,* 1995; Posch *et al,* 1997a; Turjanmaa, 1997). It is a cysteine-rich protein with four disulphide bonds, and was the first isolated protein from latex in rubber trees. It is a mature protein of 4.7 kD MW, containing 5% sulphur and 15 AA, but no carbohydrates (Archer, 1960). The hevein molecule has a length of 43 AA and is present on the amino-terminal of prohevein (Alenius *et al,* 1996; Chen *et al,* 1997b).

Hevein is a chitin-binding protein involved in the coagulation of latex by bridging rubber particles via *N*-acetyl-D-glucosamine residues and 22 kD receptor molecules present on the surface of the rubber particles (Alenius *et al,* 1996). It also is a major wound-repair protein, which inhibits the growth of several chitin-containing fungi at the wound site (Pumphrey, 1994). It results from the proteolytic cleavage of pre-prohevein, a protein of 204 AA including a signal sequence of 17 AA in the amino terminus and a C-terminal propeptide (Chen *et al,* 1997b). Hevein further has structural homology with allergens from ragweed and wheat germ agglutinin. It is synthesised as prohevein (20 kD) which is post-translationally processed into the 4.7 kD amino-terminal hevein and a 14 kD carboxyl-terminal C-domain. The allergenic epitopes in hevein have been mapped to the N-terminal region of the protein (Beezhold *et al,* 1994a; Kostyal *et al,* 1998).

2.5.4. Hevamine

The antigen most frequently recognised by patients with SB, is hevamine. However, it is seldom recognised by HCW.

In 1976 Archer isolated two major basic proteins with very small AA compositions from rubber latex lutoids and called them hevamine A and B, respectively. In 1983 Tata, using

a similar isolation procedure, isolated the same proteins and demonstrated that both are bifunctional lysozymes / chitinases and may also be antifungal (Jekel *et al,* 1991; Posch *et al,* 1997a). The crystallisation of hevamine has been described in 1990 (Jekel *et al,* 1991).

Hevamine A is a 29.5 kD, trypsin-sensitive, basic protein from the lutoids of rubber latex and may have a role in plugging the latex vessels and cessation of latex flow (Beezhold *et al,* 1994a, 1994b; Jekel *et al,* 1991).

2.5.5. Prenyltransferase

Prenyltransferase was first sequenced in 1989 (Light & Dennis, 1989). *Cis*-prenyltransferase is a hydrophobic membrane-bound enzyme, which catalyses the addition of isoprene units, resulting in a polyisoprene chain several thousand isoprene units in length (Light & Dennis, 1989). It is found both free in the cytosol and in association with rubber particles, and together with REF, play a role in the elongation of polyisoprene chains (Dennis & Light, 1989a; Light & Dennis, 1989). It is a dimer with a monomeric MW of 38 kD, requires Mg^{2+}, and is stabilised by thiols. Purified prenyltransferase and deproteinated rubber particles constitute 40-60% of the biosynthetic activity of whole latex in samples matched for rubber content.

Like other prenyltransferases, this enzyme requires a divalent cation (Mg^{2+}) to catalyse thousands of 1-4 *cis* condensations (Z-oligomerisation) of IPP, the prenyl acceptor, to rubber, the prenyl donor, before random termination occurs. Rubber particles between 50 nm and 1 500 nm diameter, microsomes, microfibrils, mitochondria, lutoids and Frey Wyssling particles are suspended in C-serum. Particles from *H.brasiliensis* range between 50 nm to 1 500 nm (Light & Dennis, 1989).

2.5.6. Other

ß-1,3-glucanase (*Hev b 2*), is a 36 kD defence-related protein (Posch *et al,* 1997a), which is highly expressed in latex and appears to have increased allergenic reactivity in children with SB (Beezhold *et al,* 1994b; Czuppon *et al,* 1993; Kostyal *et al,* 1998). This protein shows high homology to several plant endo-1,3-ß-glucosidases and should also be considered as a significant NRL allergen (Alenius *et al,* 1994).

23 kD rubber particle protein (*Hev b 3*), is a rubber-bound protein involved with rubber biosynthesis, and common allergen in children with SB (Yeang *et al,* 1996). Lu *et al* first characterised this protein which reacted with IgE from patients with SB, but not HCW

(1995). The AA sequences of the tryptic peptides derived from a 27 kD and the 23 kD proteins were found to be virtually identical in the studies of Alenius *et al* (1994) and Lu *et al* (1995), and the IgE reactivity against both proteins seemed to be restricted to NRL allergic patients with SB. It could thus be assumed that these proteins are the same or that they represent different isomers or modifications of the same protein. Furthermore, this allergen may also be associated with anaphylactic reactions to latex, because sera from non-SB and non-HCW patient groups where latex caused anaphylaxis previously, also reacted with the purified 23 kD allergen (Lu *et al,* 1995).

Microhelix protein complex (*Hev b 4*) is a defence-related protein with a MW of 50-57 kD in the reduced and 100-110 kD in the unreduced forms (Posch *et al,* 1997a).

An **acidic latex protein** (*Hev b 5*) has a MW of 16 kD, is recognised by > 50% of adult LH patients, and has a high degree of homology to proteins in acidic kiwi fruit and potato (Kostyal *et al,* 1998; Posch *et al,* 1997a).

46 kD patatin-like allergen (*Hev b 7*) is significantly related to patatin, a storage protein found in plant families, such as potato and tomato (Kostyal *et al,* 1998; Posch *et al,* 1997a). Beezhold found a previously unidentified sequence in the bands at 14 kD and 110 kD (Pumphrey, 1994). The sequences obtained for the 46 kD and 110 kD were identical. This suggests that the 110 kD molecule may be a preprotein or possibly an incomplete dimeric dissociation of the 46 kD protein. The n-terminal sequence obtained from these proteins was unique, suggesting this is a previously unrecognised latex protein (Beezhold *et al,* 1994b).

15 kD protein, **profilin**, is an actin-regulating protein, shown to be an important cross-reacting allergen of several plant sources, such as tree, grass and weed pollens and fresh fruit and vegetables. Profilin has been demonstrated in NRL and banana, but not in latex GE (Turjanmaa *et al,* 1996).

There is some evidence that children with SB (sensitised during surgery via mucosal contact) may preferentially produce large amounts of IgE antibodies to latex particle-associated allergens, such as *Hev b 1* and *Hev b 3* (Yeang *et al,* 1996). In contrast, adult HCW appear to produce IgE antibodies to these allergens less frequently; rather, they mount IgE immune responses to soluble latex proteins (e.g. the ß-1,3-glucanases and microhelix proteins) that readily adhere to the cornstarch donning powder (Hamilton & Adkinson, 1996).

2.6. AIRBORNE ALLERGENS

The number of reports of surgical gloves inducing respiratory symptoms and conjunctivitis in operating room (OR) personnel has been on the increase. Baur and Jäger (1990) were the first to suggest that latex antigens might be absorbed by the powders used as lubricant on surgical gloves and become airborne allergens. These allergens can inoculate surgical tissue and contaminate suture material, instruments, drapes or sponges in OR units, affecting both patients and HCW. Because starch granules are only 1-3 μm in diameter, they are respirable, explaining how they could both sensitise and provoke respiratory allergic reactions (Baur *et al,* 1993; Pumphrey, 1994).

The first case report of LH purely via an airborne route was published in 1990 (Lagier *et al,* 1990). In 1992 the air concentration of the starch powder on surgical gloves was directly correlated to asthma attacks in medical personnel in OR units (Czuppon *et al,* 1993). However, no interaction was found with the calcium carbonate powder used as alternative lubricant for gloves. Furthermore, no latex proteins could be detected in powder-free or latex-free gloves (Turjanmaa *et al* 1990).

Antigens composed of a protein-polysaccharide complex are known to be strongly immunogenic. Thus, the addition of starch powders to latex gloves during the glove manufacturing process may create a new set of highly immunogenic antigens. These neoantigens have the ability to favour the development of IgE responses (Beezhold & Beck, 1992). The cornstarch glove powder is not an allergen by itself, but can cause mechanical irritation and may either worsen existing dermatitis (Turner, 1997) or act as a vector for latex proteins (Beezhold *et al,* 1994a). It can cause significant and long-lasting contamination of the atmosphere, sufficient to elicit IgE-mediated symptoms in presensitised individuals (Baur & Jäger, 1990; Baur *et al,* 1993; Jaeger *et al,* 1992; Lagier *et al,* 1990; Wakelin & White, 1999; Warshaw, 1998). Acute rhinitis, asthma or both may be part of a generalised reaction as a result of contact with latex, or they may occur after inhaling the allergens (Mäkinen-Kiljunen *et al,* 1992; Turjanmaa *et al,* 1990). Airborne latex can cause severely allergic patients to discontinue work, usually because of the development of occupational asthma (Lyttle, 1994; Potter *et al,* 1991; Sussman, 1997).

Challenge testing by handling gloves, can induce immediate sneezing, rhinorrhea, and wheezing in LH patients (Baur & Jäger, 1990; Lagier *et al,* 1990). Airborne allergen concentrations in 11 areas of the Mayo Medical Center where gloves were frequently

used, varied from 13 ng/m^3 to 121 ng/m^3. Conversely, in four areas where latex gloves were never or seldom used, allergen levels varied from 0.3 ng/m^3 to 1.8 ng/m^3. The concentration in the personal breathing zone of HCW in high glove-use areas ranged from 8 ng/m^3 to 136 ng/m^3 (Levy *et al,* 1992). Allergens in excess of 1 mg were recovered from a laboratory coat that had been used for a week. Swabs of surfaces in the room also contained large amounts of allergens. In a laboratory using powder-free gloves, the levels of protein were less than 0.02 ng/m^3 air (the analytical detection limit) on each sampling day. In contrast, levels in the laboratory using powdered latex gloves ranged from 39 ng/m^3 to 311 ng/m^3 (Swanson *et al,* 1994; Tarlo *et al,* 1994). Non-ventilated intensive care wards were also statistically worse than any other clinical ward (Newsom & Shaw, 1997). Latex protein concentrations over 50 ng/m^3 is considered high (Sussman, 1997). Latex exposure can also occur via rubber particles released into the atmosphere by vehicle rubber tyres (Potter, 1996a). Extractable proteins from source and environmental samples were the following: latex glove 455 ± 78 µg/g, car radial tyre dust 395 ± 6.6 µg/g, and truck tyre dust 112 ± 1.9 µg/g (Miguel *et al,* 1996).

The allergens are distributed throughout all particle size ranges, and the majority of recovered allergens (usually > 80%) are associated with particles greater than 7 µm in diameter. It seems likely that most of the latex allergens initially become airborne when the gloves are donned or removed, but resuspension from clothing or settled dust also contributes to the allergens in the air of a room where gloves are used. Allergen particles of the size similar to those from latex gloves will settle rapidly (10 kD – 60 kD). This is consistent with the absence of measurable latex allergen in the air at the end of workdays and on weekends when the rooms were not in use. The fact that only a small portion of the allergen is carried on airborne particles with a mean diameter below 7 µm, can explain the observation that most of the subjects had symptoms of rhinitis and conjunctivitis and only some had asthma (Swanson *et al,* 1994).

2.7. ATOPY, ECZEMA AND OTHER PREDISPOSING FACTORS

Atopy was defined by Pepys as the inherited ability to form IgE antibodies against minute quantities of environmental allergens by natural exposure, manifesting as allergic rhinitis, allergic asthma, atopic eczema or urticaria (Potter, 1997a). Atopy and frequent exposure are contributing risk factors for LH. A combination of these two factors, however, considerably increases the risk of sensitisation (Moneret-Vautrin *et al,* 1993). The frequency of atopy in LH patients range from 60-80% (Heese *et al,* 1991; Pecquet *et al,*

1990; Turjanmaa, 1987). Among the group of OR nurses studied in Marseilles (Lagier *et al,* 1992), those with a history of allergic rhinitis and / or asthma showed a 4.4-fold higher risk of being allergic to latex than those without atopy. In another study NRL-allergic HCW were atopic 2.2-4.2 times more often than their co-workers without LH (Lagier *et al,* 1992; Moneret-Vautrin *et al,* 1993; Turjanmaa, 1987; Walls, 1996). Further results indicated that atopic physicians were 19 times more likely to be SPT positive to latex than non-atopic physicians and 9 times more likely to be SPT positive than atopic control subjects who were not occupationally exposed (Warshaw, 1998).

Atopic individuals often suffer from irritant hand eczema secondary to hospital work and must use rubber or vinyl gloves for hand protection. Continuous rubber glove use on eczematous hands may be an important predisposing factor for the development of either delayed or immediate rubber allergy (Axelsson *et al,* 1987; Jaeger *et al,* 1992; Nutter, 1979; Taylor & Praditsuwan, 1996; Turjanmaa, 1987; Wrangsjö *et al,* 1986). In a Finnish survey (Turjanmaa, 1987), 60% of latex-sensitive persons, had a history of hand eczema, whereas only 17.4% of non-sensitised persons had such a history (Levy *et al,* 1992).

Dishydrosis and xerosis are indicators of a damaged barrier function of the skin, whether secondary to atopy or other dermatitis, and may be an important factor in the development of contact urticaria (Belsito, 1990). A progression may occur from localised (hand) to generalised (anaphylactic) allergic responses (Sussman & Beezhold, 1995).

A history of asthma has been shown to increase more than twofold the risk of producing anti-latex antibodies. A history of hay fever approached statistical significance, but none of the other elements of atopy was significantly related to an increased risk of IgE antibodies against latex. Rather than being an independent risk factor, atopy may be a predisposing factor to the development of LH (Lebenbom-Mansour *et al,* 1997).

The age of first exposure to latex seems crucial for the development of sensitisation. The early and repeated exposure to a potent antigen can undoubtedly induce sensitisation even in non-atopic subjects not predisposed to allergy (Mazón *et al,* 1997). In patients with SB the rate of sensitisation increases proportionately with age. However, so does the number of operations, diagnostic and therapeutic procedures, with a subsequent rise in the absolute serum IgE levels (Moneret-Vautrin *et al,* 1993; Slater, 1992b) and specifically, anti-*Hev b 1* antibodies (Chen *et al*, 1997a). In conclusion, the initial exposure to latex at an early age and the massive and repeated exposure to a very potent allergen

through disrupted natural barriers, would cause sensitisation to occur even in children not predisposed to allergy (Nieto *et al,* 1996).

An Australian study of children and adolescents with spinal dysfunction found that the total number of operations was the only factor which significantly and independently contributed to the risk of having latex-specific antibodies. This study, which confirmed the findings of Nieto *et al* (1996), has important implications for medical exposure of children with spinal dysfunction to latex from their first operation onwards (Valentine *et al,* 1999).

An important factor to bear in mind is the fact that the use of skin protection creams may favour the uptake of allergens from gloves and increase the rate of allergic responses, instead of protecting against it (Wakelin & White, 1999). Van der Bijl *et al* (2000) used an *in vitro* continuous flow-through diffusion system to compare the permeability of tritiated water through fresh and frozen human skin in the presence of two barrier creams. In this study, both creams lowered the average flux rates, which indicates a decreased permeability of the skin to water. However, the implication thereof could be that the water-soluble latex proteins are in close contact with the skin for longer periods, providing longer time for the proteins to penetrate. This theory was confirmed by McCaskell *et al* (1995) who found that applying protective hand creams before donning gloves increased the amount of latex proteins transferred to the skin.

2.8. ROUTE OF SENSITISATION

Five routes of exposure to latex allergens exist (Sussman & Beezhold, 1995; Terrados *et al,* 1997; Turjanmaa, 1987; Turner, 1997):

- **cutaneous:** via gloves, masks, adhesives, catheters, drains, ileostomy bags
- **mucosal:** via products used in dentistry and anaesthesia
- **inhalation:** via aerosolisation of glove powder
- **parenteral:** via latex products used in surgery
- **intravascular:** via products stored in syringes

The route of exposure to an antigen is considered to be crucial in determining which type of immunologic response (IgG vs IgE) is induced (Beezhold & Beck, 1992).

Percutaneous absorption of allergens mostly takes place across the stratum corneum. Gloves increase skin temperature and water content on the surface of the skin. Hydration

of the skin, by surgical scrubbing and / or sweating, increases the permeability of the stratum corneum to allergens, which are bound to the glove powder. In cases with impairment of the skin barrier, e.g. eczema, the allergens can reach the blood stream and induce sensitisation (Axelsson *et al,* 1987). The rates of allergen penetration are highest where the stratum corneum is thinnest, e.g. the finger area.

Direct skin contact with latex usually leads to type IV allergies to rubber accelerators and antioxidants. This ACD reaction is largely limited to the sites of direct contact. In the case of NRL glove allergy, skin lesions are most commonly seen on the dorsum of the hand, the dorsum of the metacarpal-phalangeal joints, the thenar and hypothenar surfaces. Type I NRL allergy can be triggered by contact with latex antigen via cutaneous, percutaneous, mucosal and parenteral routes of delivery (Slater & Trybul, 1994a). The majority of systemic anaphylactic reactions occur after mucosal or parenteral exposure (Cohen *et al,* 1998).

Nurses, physicians and patients sensitised to medical or non-medical rubber products may experience allergic reactions during surgery and medical examinations, either from direct surgical glove contact or glove powder contaminated with rubber proteins. There is agreement that rubber proteins eluting from latex gloves are absorbed mainly by cutaneous and mucosal routes and that the symptoms are mediated by IgE (Alenius *et al,* 1991). In such cases, symptoms such as contact urticaria, angioedema, rhinitis, conjunctivitis, asthma and even anaphylaxis may occur (Mäkinen-Kiljunen *et al,* 1992).

Latex protein absorption through the skin is postulated as one of the major routes of occupational exposure for HCW. The initial thought was that body sweat inside latex gloves may make latex proteins soluble; the solubilised proteins are then absorbed through skin, sensitising the wearer to the foreign proteins (Beezhold *et al,* 1994a; Kelly *et al,* 1996). However, a recent study showed that proteins are transferred from latex surfaces to the skin immediately on contact. Previously it was also thought that extended wearing time, especially if the wearer's hands were sweaty, contributed to a higher protein transfer. This research indicates that considerable amounts of protein exist on the surface of the gloves, and that sweat is not needed to liberate them (McCaskell *et al,* 1995).

Latex antigens, carried on the cornstarch used as donning powder in gloves (Beezhold & Beck, 1992; Tarlo *et al,* 1990), can induce symptoms after inhalation (Baur & Jäger, 1990). Thus, airborne starch particles may represent another major route of sensitisation in HCW (Beezhold & Beck, 1992). This was confirmed by inhalation provocation tests with

powdered latex gloves, where symptoms relating to the eyes, nose, bronchial system or systemic reactions were reproducible, in the absence of direct skin contact to latex (Jaeger *et al,* 1992).

Although severe systemic reactions have occurred after cutaneous and respiratory exposure (Beuers *et al,* 1990; Katelaris *et al,* 1996; Spaner *et al,* 1989), it is clear that direct mucosal and parenteral exposure constitute the greatest risk of anaphylaxis. During surgical procedures the surgeon's gloves are constantly in contact with mucous membranes of the patient. This exposure to tissue and blood allows the latex allergens to be transferred from the rubber and be absorbed into the circulation causing severe systemic reactions, such as tachycardia, hypotension, bronchospasm and upper body flushing (Rawlins *et al,* 1992). Anaphylactic reactions have occurred after vaginal examination or caesarean section (Laurent *et al,* 1992) and mucosal contact is especially likely to lead to sensitisation (Katelaris *et al,* 1996; Walls, 1996). Several reports highlight the hazards of latex exposure for patients with previously mild (and easily manageable) cutaneous or respiratory reactions, who experience more severe reactions with mucosal or parenteral exposure (Laurent *et al,* 1992). All of the deaths caused by LH reported to the Federal Drug Administration (FDA) have been associated with barium enemas (Slater & Trybul, 1994a).

2.9. HIGH RISK GROUPS

Definite risk groups have been identified and confirmed by various researchers. A summary of these risk factors are presented in Table 3 (Warshaw, 1998).

The primary cause in the development of LH, remains exposure to the latex proteins, either in medical or non-medical environments (Committee Report 1993).

2.9.1. Healthcare workers

Generally, HCW and dental practitioners are exposed to high doses of latex for prolonged periods on a daily basis. According to the literature, this group bears the highest risk for developing LH (Lagier *et al,* 1992; Tarlo *et al,* 1990, 1994, 1997; Turjanmaa, 1987; Turjanmaa *et al,* 1988a; Weiss, 1995). The usual routes of sensitisation in this group are direct contact via surgical gloves, masks, etc., or inhalation via glove powder.

Table 3: Risk factors for the development of LH

Occupational exposure to latex
HCW
Rubber industry workers
Janitorial workers
Food handlers
Multiple surgical procedures
Patients with SB
Patients with congenital abnormalities
Frequent mucosal exposure to NRL products
Dental
Contraceptive
Daily urinary catheterisation
Manual faecal disimpactation
Pre-existing hand eczema
Atopy
Female gender
Fruit allergy

2.9.2. Individuals with spina bifida / multiple operations

The paediatric experience suggests that the bladder and rectal mucosae are the routes of exposure associated with the greatest risk of sensitisation, e.g. barium enemas with latex balloon catheters (Kurup *et al,* 1993; Slater & Chhabra, 1992a). Children with myelomeningocele or SB typically undergo surgery twice a year because of numerous genitourinary, neurologic and orthopaedic problems associated with this condition. Born with myelomeningocele, most of these children undergo two surgical procedures during the first week of life, one to repair the spinal abnormality and the second to insert a shunt for hydrocephalus. This early and repeated mucosal exposure to a potent allergen, such as latex, results in an extremely high incidence of sensitisation (D'Epiro, 1996). At least one study found a strong correlation between a positive RAST and the number of prior operations, providing evidence that repeated exposure during surgical procedures can induce sensitisation to latex (Slater & Trybul, 1994a).

Other conditions contributing to the development of LH in adults or children include myelodysplasia (Heilman, 1996), congenital cardiac or genitourinary abnormalities (Holme & Lever, 1999), repeated urinary catheterisation (Bubak *et al* 1992), bladder exstrophy, cerebral palsy, Dandy-Walker cysts (Slater & Trybul, 1994a), or any multiple surgical procedures (Moneret-Vautrin *et al,* 1993; Zerin *et al,* 1996).

2.9.3. Workers in the rubber industry

Not much research has been done in this field, but rubber industry workers are also exposed during the course of their occupation (Slater & Trybul, 1994a). They too can be in direct contact with high doses of latex for prolonged periods (Weiss, 1995). This will obviously contribute to the development of LH in this group as well (Tarlo *et al,* 1990).

2.9.4. Individuals with atopy or other allergies

The presence of an atopic diathesis (genetically fixed predisposition to allergic rhinitis, allergic asthma and atopic eczema) appears to add to the risk (Hadjiliadis *et al,* 1996; Heese *et al,* 1991). Atopic individuals are more likely to develop IgE antibodies to latex protein with increased exposure (Katelaris *et al,* 1996) than their non-atopic counterparts.

More than half of latex-sensitive HCW in one study reported a history of hand eczema before the development of contact urticaria and systemic reactions. More than three-quarters of patients in another study, predominantly females, had current or prior hand eczema. The disrupted skin barrier in the case of hand eczema probably facilitates absorption of the latex proteins more rapidly than would be the case with intact skin (Fuchs, 1994; Hunt *et al,* 1995; Warshaw, 1998).

Patients with tropical fruit allergies, e.g. avocado, banana, chestnut and kiwi, may also have life-threatening anaphylactic reactions (Kelly *et al,* 1994). It is unclear whether LH predisposes a person to food allergy or *vice versa*, and it is possible that an allergy to these fruits, can cause a cross-reactive allergic reaction to latex (Lavaud *et al,* 1995; Potter, 1996a).

2.9.5. Other

Female gender seems to increase the incidence of LH and a female predominance of 3:1 was evident in one study (Warshaw, 1998). This may be attributable to the fact that more women are employed in high risk professions. However, it is known that female hormones enhance histamine release and the inflammatory cascade which could also play a role.

The intensity of some skin diseases changes throughout the menstrual cycle. Estradiol suppresses the cellular immune response, possibly by causing an alteration in the responsiveness of the regulatory cells of the cellular immune system. In one study the skin response to an irritant stimulus, measured with patch tests, was significantly stronger

at day 1 in the menstrual cycle than at days 9-11. The male controls showed no difference in skin response between the two tests (Agner *et al,* 1991). Another study used SPT in atopic and non-atopic women to evaluate the skin response at different phases of the menstrual cycle, corresponding to bleeding (day 1-4), midcycle (day 12-16) and the late progesterone phase (day 24-28). They could not demonstrate any difference between the atopic and non-atopic groups. However, they found a significant increase in the wheal-and-flare reaction to histamine and morphine on days 12-16 of the cycle, corresponding to ovulation and peak oestrogen levels (Kalogeromitros *et al,* 1998).

2.10. PREVALENCE OF LATEX HYPERSENSITIVITY

At New York University, the first case of LH contact urticaria to rubber goods, secondary to cornstarch allergy, was seen in 1985 (Belsito, 1990). The first reported LH case in South Africa presented at Groote Schuur Hospital, Cape Town, in 1993 (Marais *et al,* 1997). As time went by, the prevalence of LH in different study populations seems to increase. It is possible that the prevalence of sensitisation is actually increasing over time (real increase), but it could also be that awareness of the problem, and subsequent correct diagnosis thereof (apparent increase), is rising.

Several prevalence studies have been published over the years (Table 4). These reports differ with regard to study populations and prevalence rates. The difference in prevalence rates within a specific risk group can possibly be ascribed to a number of factors. Most studies show a higher prevalence for female patients than for males. This could possibly be ascribed to the presence of rubber in lingerie, which is in contact with the skin for prolonged periods and facilitates sensitisation (Cronin, 1980). On the other hand, it could simply be due to the fact that more females are employed in a healthcare setting, a study population most frequently used for testing (Bubak *et al,* 1992). However, the role of female hormones has been discussed previously.

The wide variation in figures quoted, is possibly a result of lack of a predefined study population (Grzybowski *et al,* 1996), volunteer bias (Turjanmaa, 1987) or the fact that subjects sometimes cannot directly be questioned to clarify other risk factors (Ownby *et al,* 1996). In some instances, the symptoms of the patients can be mild and go unnoticed if specific questions are not systematically asked (Lagier *et al,* 1992). Some studies report a 50% prevalence of clinically asymptomatic LH patients (Sussman & Beezhold, 1995). Additionally, symptomatic HCW may be more likely to leave a working area with high latex

contamination, resulting in fewer latex-sensitive individuals in specific study populations (Grzybowski *et al,* 1996).

Different diagnostic methods with varying sensitivity and specificity used in different studies may also have influenced the reported figure. Generally, SPT produce a higher result than most *in vitro* techniques. Certain prevalence rates are also reported after patch tests are done (Schnuch *et al,* 1998; Wilkinson & Burd, 1998), but ACD is not a true reflection of LH.

All these factors must be taken into account when comparing LH prevalence between different studies.

Table 4: Reported prevalence of latex hypersensitivity in high risk groups

Population	Prevalence	Reference
HCW		
Allergy Clinic (Germany)	4.2%	Fuchs, 1994
Allergy Clinic	4.5%	Hadjiliadis *et al,* 1995
Blood transfusion personnel (RSA)	11-24%	Pretorius, 1999
Clinical units / Labs (Finland)	2.8%	Slater & Trybul, 1994a
Dental Officers US Army (1990)	8.8%	Slater & Trybul, 1994a
Dental students (10^{th} semester)	10.4%	Heese *et al,* 1997
Dental students (2^{nd}-9^{th} semester)	8.7%	Heese *et al,* 1997
Dental students (4^{th} year)	6%	Tarlo *et al,* 1997
Dental students	8.5-10.4%	Konrad *et al,* 1997
Dental workers (Australia)	9%	Katelaris *et al,* 1996
Groote Schuur Hospital (RSA 1997)	10%	Marais *et al,* 1997
HCW – anaesthesiology	15.8%	Konrad *et al,* 1997
HCW – theatre (RSA)	5-17%	Potter, 1996a
HCW – wards	0.8-3%	Yunginger 1994
HCW (Canada / USA)	9.9% physicians; 8.2% OR	Turjanmaa *et al,* 1996
HCW (Canada, Finland, France, USA)	2-15%	Lagier *et al,* 1992
HCW (Croatia)	40-45%	Lipozencic *et al,* 1998
HCW (Europe)	2.8-10.7%	Turjanmaa *et al,* 1996
HCW (Finland)	2.9%	Turjanmaa *et al,* 1988b
HCW (Finland, France, USA)	2.6-16.9%	Kelly *et al,* 1994
HCW (Mayo Medical Centre)	30.4%	Hunt *et al,* 1995
HCW (USA)	10% (1992); 17% (1995)	Kelly, 1995
HCW (USA)	5.5%	Turjanmaa *et al,* 1996
HCW (USA, 1980)	2.9%	Kelly, 1995
HCW with atopy	24%	Sussman & Beezhold, 1995
HCW	6-17%	Cohen *et al,* 1998
HCW	15-17%	D'Epiro, 1996

Table 4 (continued)

Population	Prevalence	Reference
HCW	8-12%	Kelly *et al,* 1996
HCW	9-15%	Lagier *et al,* 1990
HCW	6-10%	Slater, 1994b
HCW	5-10%	Slater & Trybul, 1994a
HCW	11%	Taylor & Praditsuwan, 1996
HCW	7-17%	Terrados *et al,* 1997
HCW	2.8-10.7% (Europe); 5.5% USA	Turjanmaa *et al,* 1996
Laboratory Units	1.6%	Levy *et al,* 1992
Medical Personnel	7%	Czuppon *et al,* 1993
Nurses (Poland)	18.6%	Palczynski *et al,* 1998
Nurses	8.9%	Grzybowski *et al,* 1996
Nurses	10.7%	Lagier *et al,* 1992
Nurses, technologists, cleaners	4.7%	Forster, 1996
OR (Finland)	7.4% surgeons; 5.6% nurses	Turjanmaa, 1987
OR (Finland)	6.5% physicians; 12.5% nurses	Turjanmaa & Reunala, 1988c
OR (Finland, overall)	6.2%	Turjanmaa, 1987
OR nurses (Germany)	22.2%	Brehler *et al,* 1997a
OR nurses (Powder-free)	3.1-7.7%	Brehler *et al,* 1997a
OR nurses	10-14%	Smith *et al,* 1993
OR physicians (Finland)	7.4%	Slater & Trybul, 1994a
OR	10-17%	Konrad *et al,* 1997
OR, Hospital housekeepers	10%	Lyttle, 1994
St John's Hospital	♀ 7.2%; ♂ 5.2%	Cronin, 1980
Surgical Unit (Finland doctors & nurses)	6%	Turjanmaa *et al,* 1990
SB / Atopy		
SB children (Southeast Wisconsin)	68%	D'Epiro, 1996
SB children	36.3%	Heese *et al,* 1997
SB children	28-67%	Kelly *et al,* 1994
SB children	30-65%	Lagier *et al,* 1990
SB children	28-34%	Levy *et al,* 1992
SB children	18-37%	Lu *et al,* 1995
SB children	18-72%	Mazón *et al,* 1997
SB children (France)	32%	Moneret-Vautrin *et al,* 1993
SB children	92%	Nieto *et al,* 1996
SB children	37%	Slater & Trybul, 1994a
SB children	37%	Taylor & Praditsuwan, 1996
SB children	64.0%	Terrados *et al,* 1997
SB children (USA)	50.6%	Turjanmaa *et al,* 1996
SB children (USA)	22%; 34%; 38%	Valentine *et al,* 1999
SB children	65%	Walls, 1996
SB children	34-100%	Weiss, 1995
Allergy clinic (Germany)	4.2%	Fuchs, 1994
Allergy clinic (Canada)	4.5%	Hadjiliadis *et al,* 1995

Table 4 (continued)

Population	Prevalence	Reference
Atopy patients	7%	Hadjiliadis *et al,* 1995
Atopic children	20.8%	Niggeman, 1997
Atopic children	3.0%	Novembre *et al,* 1997
Atopic patients (routine SPT)	1%	Turjanmaa & Reunala, 1988c
Atopic children	3.8%	Weiss, 1995
General Population		
General population	3.5%	Brehler *et al,* 1997b
Ambulatory surgical patients	6.7%	Lebenbom-Mansour *et al,* 1997
Non-atopic patients	< 1%	Lu *et al,* 1995
No identified risk factor	0.8%	Lyttle, 1994
General population (Detroit, Michigan)	6.5%	Miguel *et al,* 1996
Blood donors	6.4-8.8%	Ownby *et al,* 1996
Red Cross volunteer blood donors	6.5%	Pumphrey, 1994
Blood donors (Italy)	3.5%	Senna *et al,* 1998
General population	2.5%	Slater, 1994b
Non-HCW	0.8%	Turjanmaa, 1987
General population	2.5%	Walls, 1996
Rubber Industry Workers		
Glove manufacturing workers	3.2%	Büyüköztürk *et al,* 2000
Rubber industry worker	11%	Taylor & Praditsuwan, 1996
Surgical glove manufacturing plant	11%	Tarlo *et al,* 1990

2.11. LATEX HYPERSENSITIVITY

Hypersensitivity to latex is more commonly referred to as latex allergy. The term "allergy" was first used by Von Pirquet in 1906 to describe "an altered capacity to react". He found that certain individuals treated with horse antiserum to diphtheria toxin reacted with immediate severe acute reactions, after an initial priming with the antiserum. In 1921 Prausnitz and Küstner discovered a humoral factor associated with allergy by transferring cutaneous sensitivity to certain substances from one individual to another. Ishizaka confirmed that this factor was an antibody in 1966 in Denver. He found that ragweed sensitive individuals possessed an antibody which bound to one of the ragweed antigens, called antigen E or IgE. The discovery that mast cells are triggered to release an array of mediators of the allergic response via allergen cross-linking of specific IgE receptors on the mast cell, gave a plausible scientific mechanism for the allergic response (Potter, 1997b). This is a marker of degranulation and does not address other mast cell mediators.

LH is not a new phenomenon, and although Cronin stated that "Sensitivity to rubber itself probably does not occur" (Cronin, 1980), the first report of an adverse reaction to latex was published by Stern in 1927 (Warshaw, 1998). This case presented with recurring urticaria and laryngeal oedema from a rubber dental prosthesis. Another report described asthma caused by a rubber-coated electric cable, which warmed up when the wire was electrified. Even although these cases at that time were not confirmed by skin tests, with knowledge of the materials used in those days, one can still assume that a type I allergy to NRL was operative. After all, results of the provocation tests, which were conducted under partial control, were positive and the symptoms described recurred after re-exposure in both cases (Fuchs, 1994).

During 1931 to 1932, seven cases of dermatitis due to a particular type of rubber glove were reported. The diagnoses were confirmed by the USA standardised patch test method, using a piece of the rubber glove. Cellophane and two other types of gloves served as controls, but no reaction was evident after 24 hours. However, the same type of dermatitis was produced in 2 control patients by application of the same rubber glove to the skin. The manufacturer of this specific type of rubber glove, acknowledged the claim and these gloves were removed from use with no further reports of dermatitis after that (Downing, 1933).

Following these reports, the problem was only mentioned by Hansen in 1957 (Fuchs, 1994). The first case reported in the European literature presented with a contact urticaria (Nutter, 1979). Most researchers incorrectly quote this case as the first known case of LH (Kurup *et al,* 1993; Lagier *et al,* 1992; Moneret-Vautrin *et al,* 1993; Slater & Chhabra, 1992a; Turjanmaa, 1987; Turjanmaa *et al,* 1988a). The first anaphylactoid reaction to latex was reported in 1987 (Axelsson *et al,* 1987; Konrad *et al,* 1997; M'Raihi *et al,* 1991). The first mention of LH in the North American literature was made in 1989 (Spaner *et al,* 1989; Taylor *et al,* 1989). However, the problems were not really discussed in the medical literature until the late 1980s. Between 1989 and 1992, 1 100 reported incidents of allergy to rubber and 15 deaths related to medical exposure to latex were reported world-wide (Nieto *et al,* 1996; Valentine *et al,* 1999).

Today NRL allergy is acknowledged as a major occupational problem among glove-wearing HCW (Turjanmaa *et al,* 1996). However, it was not recognised as a potential etiological agent of occupational asthma until the beginning of the 1990s (Marcos *et al,* 1991; Tarlo *et al,* 1990).

2.12. CLINICAL PATHOGENESIS - OVERVIEW

On first exposure to NRL, plasma cells produce NRL-specific IgE or IgG_4 antibodies that bind through a series of steps, to high-affinity surface receptors on mast cells and basophils. On re-exposure, the allergen induces cross-linking and degranulation of the mast cells and basophils, releasing preformed and newly formed mediators, such as histamine, arachidonic acid metabolites, prostaglandin D_2, leukotriene C_4, platelet activating factor, tryptase, chymase, heparin and chondroitin sulphate. These factors increase vascular permeability, vasodilatation and bronchoconstriction, presenting clinically as urticaria, hypotension and asthma.

Repeated exposure to NRL proteins is essential for the development of LH (Alenius *et al,* 1991; Kelly *et al,* 1996; Levy *et al,* 1992). An allergy to latex is unlike a drug allergy. Often, a drug does not act as an antigen, although the end result may resemble an allergic reaction, and the mechanisms involved in the host are chemical, rather than truly allergic in nature. Furthermore, it is sometimes possible to desensitise a patient to a drug by giving repeated doses under close supervision in a hospital (Jackson & Cerio, 1988). However, this is not possible with LH, because each exposure to latex could be life-threatening. Latex is such a common element within the everyday environment that avoidance becomes very difficult. The concern surrounding HIV and hepatitis has led to increased glove use by HCW. Subsequently, in many health care facilities gloves are being worn without conscious thought of possible consequences of such action. Only 50% of gloves used by nurses are worn for actual patient care activities involving exposure to blood or body fluids (Smith *et al,* 1993).

There are probably two reasons for the exponential increase in the number of reports of LH and anaphylaxis. Universal precautions came to be practised around 1988 because of the AIDS epidemic, and resulted in HCW spending nearly all of their working time in gloves and changing them up to 30 times a day. Added to this was a severe world-wide shortage of rubber because of political conflict in Liberia, a major world supplier. This resulted in marginal producers releasing products that had been inadequately washed and cured. This resulted in a much higher latex antigen content and exposure (Slater & Trybul, 1994a; Walls, 1996).

Contact urticaria can also be a result of contact to glove powder (Carillo *et al,* 1986) or other airborne antigens carried by glove powder (Baur & Jäger, 1990). Contact with the gloves of a physician, dentist or nurse can elicit symptoms (Pecquet *et al,* 1990; Taylor *et*

al, 1989), and hypotension or shock can occur during surgery or delivery (Jaeger *et al,* 1992). Skin lesions such as purpura, pustulosis or dermatitis may result from rubber antigens and bacteria killed during sterilisation. Depigmentation due to rubber chemicals may also occur (Nutter, 1979). Cornstarch or talc granulomas frequently form as a result of glove powder (Ellis, 1990). Once allergy to latex is established, wearing gloves in the presence of other potential allergens can cause broadening of the allergic base or an extended allergen syndrome (Guin, 1992). In some cases, gloves worn by colleagues in the same room can be sufficient to cause reactions (Levy *et al,* 1992). By far the most serious reaction in terms of immediate consequences, are anaphylactic reactions that can occur in medical and paramedical personnel who routinely wear latex gloves, e.g. OR nurses (Lagier *et al,* 1992). The most common clinical manifestations of LH include angioedema, asthma, bronchospasm, conjunctivitis, hand eczema, rhinitis, urticaria and fatal anaphylactic shock (Kelly *et al,* 1994; Turjanmaa, 1987).

2.12.1. Immediate-type / type I allergies

The contact urticaria syndrome was defined by Maibach and Johnson in 1975. It was considered rare in dermatological practice until the increase in knowledge of the eliciting agents and pathomechanisms made it possible to classify contact urticaria into immunological and non-immunological subgroups. In particular, allergens of animal and plant origin penetrating intact or diseased skin can evoke IgE-mediated local and even systemic urticarial reactions in previously sensitised individuals (Turjanmaa & Reunala, 1988c). On re-exposure to the offending allergen, IgE linked to the latex protein, directly induces degranulation of basophils and the release of histamine and other chemical mediators (Chambeyron *et al,* 1992; Cohen *et al,* 1998). Typical symptoms occur within a few minutes up to an hour of exposure to latex allergens (Fisher, 1997b; Taylor & Praditsuwan, 1996). Immediate itching and urticarial wheals are the most common manifestations of allergy to NRL gloves (Holme & Lever, 1999; Pretorius, 1999; Warshaw, 1998). Symptoms usually disappear within hours, but may take up to 24 hours to clear. Type I late-phase reactions are mediated by low-affinity Fc receptors on the mast cell or basophil membranes (Figure 4) and occur 6-12 hours after exposure (Jackson & Cerio, 1988; Warshaw, 1998), depending on the sensitivity of the patient and the dose or route of antigen administration. Type I sensitivity appears to be directed against soluble proteins remaining on the surface of latex-made products (Beezhold *et al,* 1994a, 1994b; Carillo *et al,* 1986; Chen *et al,* 1997b; D'Epiro, 1996; Hadjiliadis *et al,* 1996; Heese *et al,* 1991; Hunt *et al,* 1996; Pretorius, 1999; Miguel *et al,* 1996; Nieto *et al,* 1996; Ownby *et*

al, 1996; Pecquet *et al,* 1990; Slater & Trybul, 1994a; Spaner *et al,* 1989; Sussman, 1997; Tarlo *et al,* 1990; Taylor *et al,* 1989; Taylor & Praditsuwan, 1996; Turjanmaa *et al,* 1988a; Wrangsjö *et al,* 1986).

Type I allergy has been divided into four clinical stages (Turner 1997):

- **stage 1:** localised urticaria where there is a contact wheal-and-flare response
- **stage 2:** generalised urticaria, with dilation of capillaries and relaxation of smooth muscles due to histamine release
- **stage 3:** urticaria and bronchial asthma, sneezing, coughs, nasal congestion and itchy eyes
- **stage 4:** urticaria with anaphylaxis when there is hypotension, shock, difficulty in breathing, possibly leading to death

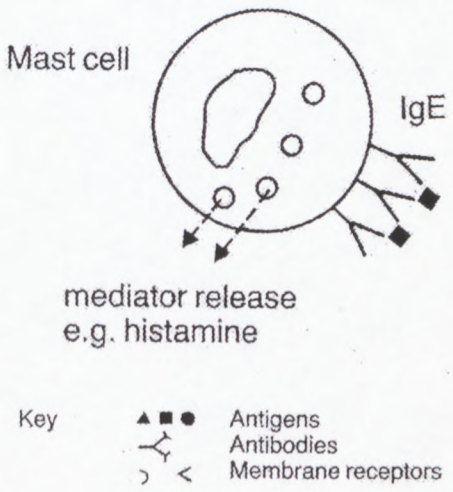


Figure 4: Type I hypersensitivity reaction. The Fc receptors on mast cells bind IgE and induces degranulation and release of mediators from the mast cell.

A broad consensus exists on the pathobiologic features of this type of hypersensitivity, which is similar to other type I IgE-mediated reactions (Carillo *et al,* 1986; Nutter, 1979; Slater & Trybul, 1994a; Spaner *et al,* 1989). Patients may exhibit a full range of reactions from contact urticaria to generalised urticaria, rhinitis, asthma and anaphylaxis (Potter, 1994a), during which mast cell mediators may be detected in increased levels in the serum. Cutaneous exposure usually leads to localised reactions, but mucosal or parenteral exposure can lead to life-threatening reactions. Generally, urticaria is a much better predictor of a positive skin test than redness and itching (Lagier *et al,* 1992; Slater & Chhabra, 1992a). It is highly correlated with occupationally induced glove allergy, especially in atopic persons, where its predictive value approaches 70% (Heese *et al,*

1991; Lagier *et al,* 1992). In contrast, pruritus alone is usually not predictive of LH (Levy *et al,* 1992).

The contact urticaria syndrome includes a broad spectrum of cutaneous and extracutaneous reactions. The most common symptoms found in two European studies are summarised in Table 5. Initially the symptoms may be erythema, urticaria, angioedema, pruritus, colic-like abdominal pain and a faint feeling. Once the specific IgE reaches the circulation via haematogenous spread, involvement of the mucous membranes may arise, eventually leading to an allergic rhinitis, allergic asthma and / or conjunctivitis. Laryngeal oedema may cause severe upper respiratory obstruction, which may then progress to life-threatening asphyxia. The most serious symptoms involve the cardiovascular system, i.e. hypotension and cardiovascular collapse. Loss of consciousness as the initial manifestation of anaphylaxis may also occur (Heese *et al,* 1997).

Table 5: Frequency of the most common clinical signs of latex hypersensitivity in two European studies

	Finland (n=124) (Turjanmaa *et al,* 1996)	**Germany (n=70) (Jaeger *et al,* 1992)**
Contact urticaria	75%	100%
Conjunctivitis	22%	44%
Rhinitis	15%	51%
Severe systemic reactions	8%	6%
Asthma or dyspnea	3%	31%

Mucosal swelling is a typical sign after oral, vaginal, rectal or other mucosal exposure to products such as balloons, catheters, gloves and condoms (Levy *et al,* 1992; Turjanmaa *et al,* 1996). Latex-containing urethral catheters can induce urethritis and subsequent urethral strictures in some patients. These strictures are assumed to be associated with catheter toxicity, since poor blood flow allows toxic substances released from the catheters, to accumulate in the surrounding tissue, thus producing major antigenic complexes, leading to tissue damage and scarring. Furthermore, it has been shown that these catheters activate complement substantially more than catheters that do not induce strictures (Garred *et al,* 1990; Moneret-Vautrin *et al,* 1993). These symptoms appear within 5 to 20 minutes after contact, and disappear without any treatment in 1 to 2 hours. The patients may also have generalised urticaria, facial oedema, rhinitis and respiratory

symptoms, including dyspnea and asthmatic attacks due to airborne allergens (Pecquet *et al,* 1990; Turjanmaa *et al,* 1988b; Turjanmaa & Reunala, 1988c).

Glove powder binds to the extractable latex proteins in the gloves and become airborne (Fisher, 1987). On inhalation, it can cause a wheal-and-flare skin reaction beyond the glove region, asthma, rhinitis, conjunctivitis and even anaphylaxis. Chemical additives are usually not responsible for type I hypersensitivity reactions to latex (Spaner *et al,* 1989). However, immediate hypersensitivity reactions have been elicited by exposure to rubber gloves, condoms, barium enema catheters, bladder catheters, balloons, rubber dental dams, toys, dental prophylaxis cups, and sporting equipment (Slater & Trybul, 1994a).

Localised allergic manifestations may occur intraoperatively. Angioedema of the face may begin after application of an anaesthetic mask, bronchospasm after tracheal intubation, and oedema of the larynx after removal of an intubation cannula, if these devices are made of latex (Moneret-Vautrin *et al,* 1993). Many of the reported cases have occurred during gynaecological or obstetric procedures, e.g. caesarean section or vaginal delivery (Laurent *et al,* 1992; Axelsson *et al,* 1987). Severe anaphylactic shock during medical or dental procedures were also noted in some patients (Alenius *et al,* 1991; Belsito, 1990; Beuers *et al,* 1990; Kurup *et al,* 1993; Raulf-Heimsoth *et al,* 1996; Spaner *et al,* 1989; Tarlo *et al,* 1990). The respiratory symptoms and shock are thought to be due to a massive local release of histamine and other mediators or adsorption and systemic distribution of the antigens (Baur & Jäger, 1990). Death, usually due to organ damage sustained during anaphylaxis, can occur within minutes, but can also occur many days after anaphylaxis (Kelly *et al,* 1994; Manjra, 1994). In 1995, anaphylactoid reactions were reported to occur in about 1 / 5 000 general anaesthesia cases and latex were responsible for 12.5% of these (Porri *et al,* 1995). Wrangsjö & Lundberg (1996) found 18% of preoperative anaphylactic reactions in their study to be related to IgE-mediated allergy to NRL.

2.12.2. Delayed-type / type IV allergies

A type IV allergic reaction is a delayed, cell-mediated and acquired immune reaction (Figure 5), mediated by Langerhans or other dendritic cells, sensitised T-lymphocytes and various lymphokines (Fisher, 1997b; Zerin *et al,* 1996). LH is on the rise among HCW and present most commonly in the form of delayed-type hypersensitivity (Beezhold *et al,* 1994a, 1994b; Heese *et al,* 1991).

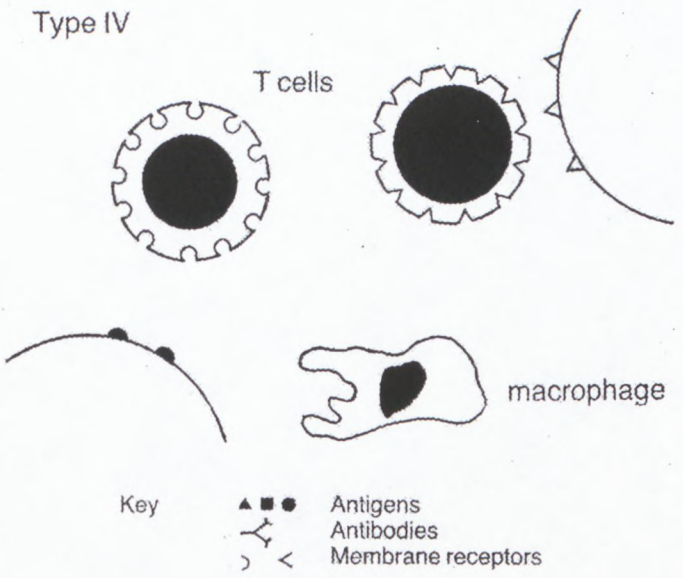


Figure 5: Type IV hypersensitivity reaction. Antigen-sensitised T-cells release lymphokines following secondary contact with the same antigen. Lymphokines induce inflammatory reactions and activate macrophages, which release mediators.

Irritant contact dermatitis results from the direct action of chemicals found in latex or other glove components on the skin and is not directly mediated by the immune system. This form of dermatitis manifests as dry, crusted lesions in latex-exposed areas. The extent of the reaction depends on other physical parameters, such as duration of exposure, skin occlusion and skin temperature. Prolonged and repeated latex exposure is aggravated by sweating and rubbing under the glove, leading to papular and ulcerative lesions (Heese *et al,* 1991).

Unlike irritant contact dermatitis, allergic contact dermatitis (ACD) directly involves the interaction of the immune system and depends on a person's genetic susceptibility (Bubak *et al,* 1992). ACD is caused by T-cell mediated sensitisation to rubber additives, usually the accelerators, e.g. thiurams, mercaptobenzothiazoles and carbamates. Once sensitised, subsequent challenges from the same allergen will cause a type IV hypersensitivity reaction 6-48, or even 96 hours after exposure (Potter, 1996b). It usually affects the dorsum of the hands and is characterised by vesicular, eczematous skin lesions. With continued latex exposure, these skin lesions develop a crusted, thickened appearance (Sussman & Beezhold, 1995). Patients with ACD seldom have systemic symptoms (Potter, 1996b).

Latex-induced protein contact dermatitis was first reported by Kleinhans in 1984. Accelerators and other rubber additives have been found to evoke positive patch test in

82% of patients with occupationally induced ACD to gloves (Heese *et al,* 1991). In one study thiurams were responsible for 72% of all occupationally related glove allergies, followed by carba mix (25%) and mercapto mix (3%). Coincidental sensitisation and cross-reactions have been proposed to be responsible for the frequent simultaneous positive patch tests to thiurams and chemically related carbamates. Other additives, such as antioxidants, antiozonants and vulcanisers, are less important in glove allergies, because they are mainly used in the production of heavy duty or synthetic rubber articles.

2.13. DIAGNOSIS

2.13.1. Questionnaire / History (*in vivo*)

As with any diagnosis, a detailed history and thorough clinical examination are essential. Evidence of risk factors, such as eczema, rhinitis, asthma, etc., and history or immediate symptoms should prompt an evaluation of LH (Warshaw, 1998).

Only a few patients with rubber glove contact urticaria present a typical history of immediate localised urticarial response. Many merely complain of non-characteristic sensations, such as itching and burning, or give a history of recurrent hand eczema. Therefore, the clinical history alone may not be very helpful in indicating whether the patient has contact urticaria (Turjanmaa & Reunala, 1988c).

Advantages: reasonably high sensitivity (Lebenbom-Mansour *et al,* 1997)

Disadvantages: questionnaire alone is unreliable (Levy *et al,* 1992); will not identify all persons at risk for LH (Turjanmaa *et al,* 1996; Sussman & Beezhold, 1995); low specificity and positive predictive value (Lebenbom-Mansour *et al,* 1997)

2.13.2. Skin prick tests (*in vivo*)

A SPT is done by placing a drop of diluted antigen (commercially available or in-house extracts) on the skin and gently pricking the epidermis to a depth of 1 mm with a lancet (Chapel & Haene, 1993; Jackson & Cerio, 1988). The remaining solution is gently wiped away with blotting paper. Fifteen minutes after application, the wheal is measured by adding the two largest perpendicular axes and dividing the sum by 2. A wheal-and-flare reaction of > 2 mm is regarded as positive (Warshaw, 1998).

Advantages: sensitivity and specificity > 90% (Warshaw, 1998); the test solution can be diluted, permitting the reactions to be observed in a dose-dependent way (Turjanmaa &

Reunala, 1988c); best method for confirming contact urticaria (Guin, 1992); results may predict the severity of clinical responses to latex (Hadjiliadis *et al,* 1996); commercial allergens available (Turjanmaa *et al,* 1996)

Disadvantages: risk of anaphylaxis (Warshaw, 1998), but generally safe when performed by skilled personnel in patients with low IgE values (Hunt *et al,* 1995); false positive results can be obtained in highly dermographic patients, with poor technique, by using concentrated extracts, or as a result of non-specific irritant reactions (Williams *et al,* 1992); atopic patients often have positive SPT to multiple antigens, although only one may be responsible for the clinical symptoms (Chapel & Haene, 1993)

2.13.3. Patch tests (*in vivo*)

The diagnostic technique for type IV delayed hypersensitivity to NRL products is established by a positive patch test to one or more of the chemical additives or to a piece of the NRL product. Several panels of common antigens are commercially available. Individual allergens are formulated in appropriate concentrations and placed in a shallow aluminium well of about 1 cm^2, called a Finn chamber. The Finn chambers are applied in strips to the patient's back and kept in place by hypo-allergenic tape. The skin is marked appropriately and the patient is asked to keep the area dry. The patches are removed after 48 hours and the skin examined for a positive response, characterised by itching and erythematous oedema, often accompanied by vesiculation. A second reading of the area at 96 hours is routine and even later responses should be reported by the patient (Jackson & Cerio, 1988).

Advantages: simple and clinically useful (Jackson & Cerio, 1988)

Disadvantages: results not always easy to interpret, difference between irritant and allergic responses not always clear (Jackson & Cerio, 1988)

2.13.4. Scratch chamber test (*in vivo*)

A scratch chamber test is performed by using a lancet to create a 6 mm scratch on the volar aspect of the forearm. A small piece of latex glove moistened with saline, is placed in a Finn chamber and applied over the scratch for 15-20 minutes (Warshaw, 1998). A positive result will be a wheal-and-flare reaction of > 2 mm within 5-30 minutes, as in the case of SPT (Chapel & Haene, 1993).

Disadvantages: risk of anaphylaxis and high rate of false-positive reactions (Warshaw, 1998); imprecise results (Chapel & Haene, 1993)

2.13.5. Intradermal test (*in vivo*)

Intradermal testing involves injecting diluted antigenic solutions directly into the dermis (Chapel & Haene, 1993; Warshaw, 1998)

Advantages: reproducible results (Jackson & Cerio, 1988)

Disadvantages: painful procedure, less specific and more hazardous than SPT, false positive results common (Jackson & Cerio, 1988); risk of anaphylaxis (Warshaw, 1998)

2.13.6. Use test and Rub test (*in vivo*)

A use test involves applying a latex glove directly to a wet hand for 15 minutes. A vinyl glove serves as control. A rub test is a modification of the use test in which latex fluid, a glove piece, and / or glove powder are repeated rubbed onto the volar aspect of the forearm (Warshaw, 1998). Any skin reaction appearing within 5-30 minutes at the site of contact, is regarded as positive.

Advantages: relatively safe and conclusive for patients with allergic diseases of the skin (Palczynaki *et al,* 2000)

Disadvantages: risk of anaphylaxis (Warshaw, 1998); may yield negative results in patients suffering from respiratory symptoms (Palczynaki *et al,* 2000)

2.13.7. Inhalation / Provocation tests (*in vivo*)

Inhalation tests involve spirometry at 15-30 minutes intervals, while subjects handle latex gloves. Vinyl gloves are used as controls. Nasal provocation tests consist of applying a substance on a cotton swab to the nasal mucosa for 5 minutes. These tests simultaneously challenge the eyes, nose and bronchi (Warshaw, 1998)

Advantages: highly sensitive and specific and can identify HCW with occupational asthma (Palczynaki *et al,* 2000)

Disadvantages: risk of anaphylaxis (Warshaw, 1998); requires highly allergenic glove brands; potentially dangerous (Turjanmaa *et al,* 1996); can potentially induce anaphylaxis (Fisher, 1997b); dangerous in subjects with systemic manifestations of allergy (Jaeger *et al,* 1992); may not only indicate patients with allergic rhinitis (Palczynaki *et al,* 2000)

2.13.8. Latex-specific IgE / RAST (*in vitro*)

A capRAST is an *in vitro* test in which solid phase allergen is incubated with serum to induce specific antigen-antibody reactions. Radiolabelled anti-IgE antibodies are mixed with solid-phase antigen-antibody complexes, and bound radioactivity is measured (Warshaw, 1998).

The AlaSTAT allergen-specific IgE system is an enzyme-labelled immunometric assay (EIA) based on patented liquid allergens, monoclonal antibodies and ligand-coated tube separation. It uses raw latex as source material and has been found to be markedly superior when compared to old solid-phase allergens (Weiss, 1995)

Advantages: sensitivity 50-90%, specificity 80-87% (Warshaw, 1998); testing is safe (Weiss, 1995); offers objectivity and increased safety, while decreasing the time required for testing, as compared to *in vivo* tests (Grzybowski *et al,* 1996); provides reproducible results (Lebenbom-Mansour *et al,* 1997)

Disadvantages: not as sensitive as SPT (Turjanmaa & Reunala, 1988c); not as good an indicator for persons with milder symptoms (Turjanmaa *et al,* 1988b); expensive and may be time-consuming (Moneret-Vautrin *et al,* 1993)

2.13.9. Basophil histamine release test (*in vitro*)

In this test donor-washed leukocytes are incubated with diluted antigen. Histamine release by basophils are measured by fluorometric, enzymatic or immunogenic methods, or counting degranulating basophils (Warshaw, 1998)

Advantages: sensitivity 90%, specificity 60% (Warshaw, 1998)

Disadvantages: very expensive and time-consuming (Warshaw, 1998); lengthy procedure (Marais *et al,* 1997); requires fresh blood cells to prevent changes induced by anticoagulants over time

Patients can be screened with an *in vitro* test to detect latex-specific IgE. A false-negative rate of > 30% exists. If this test is positive, no further testing should be done. If the test is negative, a use test utilising a latex glove may be performed as previously described, first with one finger, then an entire hand. If still negative, a SPT should be done with eluted latex protein in solution (Cohen *et al* 1998).

Table 6: Diagnostic tests for latex hypersensitivity (Warshaw, 1998)

Research	Clinical
Cytometric assay	SPT
Radioimmunoassay	RAST
Basophil histamine release test	Latex allergosorbent assay
Flow cytometry	Rub test
Immunoblots	Scratch chamber test
ELISA	Intradermal / inhalation tests
Cross and rocket immunoelectrophoresis	Open and closed patch tests
Reverse enzyme immunoassay	Latex-specific antibody assays

None of the *in vivo* or *in vitro* tests are 100% diagnostically accurate, mainly because of the variety of NRL allergens (Turjanmaa *et al,* 1996). Most investigators agree that the best screening method for LH remains the SPT (Hadjiliadis *et al,* 1995; Turjanmaa *et al,* 1996), provided that it is performed in a safe environment under controlled conditions. Commercially available antigens are provided in 3 dilutions, i.e. 1 : 1 000, 1 : 100 and 1 : 10 and testing should begin with the highest dilution. If the result is negative, the next dilution can be used. When in-house extracts in saline are made, using glove powder or a piece of latex glove, testing should start with very diluted (1:1 million) extracts of the stock testing solution. All these tests should only be done in a well-equipped allergy center by trained personnel. Full emergency equipment must always be available to treat possible systemic reactions (Sussman & Beezhold, 1995).

2.14. CROSS-REACTIVITIES

One of the first reported cases of cross-reactivity between latex and food was published in 1991. This case described a nurse with allergic reactions to latex gloves, which also had an allergy to banana. At that time, it was thought that the association might have been related to the presence of a common, but unknown allergic component in latex and banana (M'Raihi *et al*, 1991). Patients with LH subsequently presented with allergies to avocado, kiwi and chestnut. Clinically, these patients often have perioral itching and local urticaria, and occasionally have life-threatening, food-induced anaphylactic shock. It was thought that the observed cross-reactivity probably occurred because latex proteins are structurally homologous with other plant proteins (Sussman & Beezhold, 1995).

By 1992, it was realised that the basis for this cross-reactivity was not strictly botanical, as the rubber tree and for instance the banana tree (*Musa sapientum*) belong to

phytogenetically dissimilar classes, Mangoliopsida and Liliopsida, respectively (Levy *et al,* 1992).

Many authors have since made an association between LH and other fruit allergies directed to celery, chestnuts, citrus fruits, figs, grape, kiwi fruit, nuts, passion fruit, pineapple, peanuts and tomato (Table 7). In sera from patients allergic to latex and fruits (avocado pear and banana), a constant common electrophoretic protein band was found, linked to common epitopes from 30 kD proteins. In a group of patients who only reacted to latex, this band was usually not found, even if other bands were present. It is possible that a 30 kD protein band is a sign of a latex- and fruit-associated allergy (Lavaud *et al,* 1995; Pastorello *et al,* 1996). In 1993, immunoblotting showed a heavy protein band between 27 kD and 30 kD and smaller bands over the whole range in chestnut extract. Sera from a group of LH patients bound to proteins from latex and chestnut extracts, and there was even evident binding to protein bands of identical molecular mass (14 kD and 25 kD - 30 kD) in both extracts (Añibarro *et al,*1993).

Hevamine is homologous to a pathogenesis-related chitinase from cucumber. Six other chitinases / lysozymes have been isolated from *H.brasiliensis* in 1991. The properties of the separated lysozyme were very similar to those of fig, papaya and other plant lysozymes. Provided that they have common antigenic determinants, lysozymes can be a cause of the cross-reaction between rubber and fruits (Yagami *et al,* 1995).

Because chitinase, enolase, profilin, proteasome subunit, superoxidase dismutase and triosephosphate isomerase are common plant enzymes, they may represent potential cross-reacting proteins present in various foods (Fuchs *et al,* 1997; Posch *et al,* 1997b). Allergens from avocado and banana have already been characterised and reported to belong to the PR-3 proteins, representing class I endochitinases that cross-react with hevein (*Hev b 6.02*) (Alenius *et al,* 1996).

Sequence homology and cross-reactivity between patatin-like NRL allergens and patatins in potato and tomato have been documented (Beezhold 1996). Patatin (*Hev b 7*) is a defence-related protein in potato, which has lipid acyl-hydrolase or esterase activity. The patatin of potato tuber (*Sol t 1*) was recently shown to be a novel food allergen for atopic children. *Sol t 1* and *Hev b 7* have remarkable sequence homology. *Sol t 1* and *Hev b 7* both represent defence-related proteins, which have been connected to cross-reactions between NRL and fruits and vegetables (Seppälä *et al,* 2000). Two other latex allergens *Hev b 6* and *Hev b 5* have also been shown to share homology with potato proteins.

Table 7: Cross-reactivity between fruit and latex reported in the literature

almond, apple, apricot, avocado, banana, chestnut, grape, kiwi, orange, pear, pineapple (Novembre *et al,* 1997)
apple, avocado, banana, cantaloupe, celery, cherry, chestnut, fig, kiwi, mango, melon, papaya, passion fruit, peach, pear, pineapple, potato, spinach, tomato, turnip, wheat (Warshaw, 1998)
apple, avocado, banana, peanut, spinach, sweet pepper (Maillard *et al,* 2000)
apricot, avocado, banana, buckwheat, celery, chestnut, fig, grape, kiwi, mango, melon, orange, papaya, passion fruit, peach, peanut, pineapple, potato, tomato (Brehler *et al,* 1997b)
apricot, avocado, banana, chestnut, grape, kiwi, passion fruit, pineapple (Levy *et al,* 1992)
apricot, avocado, banana, chestnut, kiwi, lemon oil, melon, orange, peach, pineapple, walnut (Taylor & Praditsuwan, 1996)
avocado, banana (Grzybowski *et al,* 1996)
avocado, banana, celery, chestnut, citrus fruit, fig, grape, kiwi, nuts, passion fruit, peanut, pineapple, tomato (Lavaud *et al,* 1995)
avocado, banana, celery, chestnut, fig, papaya, passion fruit, peach (Fisher, 1997b)
avocado, banana, cherry, nectarine, peach, plum, strawberry, tomato (Konrad *et al,* 1997)
avocado, banana, chestnut (Slater & Chhabra, 1992a, 1992b; Tomazic *et al,* 1995; Weiss, 1995)
avocado, banana, chestnut, kiwi (Potter, 1996a, 1996b; Sussman & Beezhold, 1995; Turjanmaa *et al,* 1997; Wakelin & White, 1999)
avocado, banana, chestnut, kiwi, melon, papaya, peach, pineapple, tomato (Turjanmaa *et al,* 1996)
avocado, banana, chestnut, kiwi, melon, raw potato, tomato (Potter, 1998a, 1998b)
avocado, banana, chestnut, kiwi, milk, pineapple, potato, tomato (Beezhold *et al,* 1996)
avocado, banana, chestnut, kiwi, papaya, passion fruit (Lyttle, 1994)
avocado, banana, chestnut, kiwi, papaya, tomato (Cohen *et al,* 1998)
avocado, banana, chestnut, kiwi, potato, tomato (Sussman, 1997)
avocado, banana, chestnut, other fruit (Slater & Trybul, 1994a)
avocado, banana, chestnut, potato, tomato (Posch *et al,* 1997a, 1997b)
avocado, banana, cucumber, fig, papaya, passion fruit (Yagami *et al,* 1995)
avocado, banana, grass, kiwi, weed pollen (Grote *et al,* 2000)
avocado, banana, kiwi, passion fruit, peach (Lebenbom-Mansour *et al,* 1997)
banana (Baur *et al,* 1993; Hadjiliadis *et al,* 1996; Ross *et al,* 1992; M'Raihi *et al,* 1991)
banana, cherry, chestnut, kiwi, passion fruit, peach (D'Epiro, 1995)
banana, chestnut (Pumphrey, 1994)
banana, chestnut, legume, other fruit (Añibarro *et al,* 1993)
weeping fig (Heese *et al,* 1997)

Additionally, hevein shares a great deal of AA homology with the wound-induced proteins from potato. Expressed in tomatoes, it increases the resistance of the plants to fungal pathogens. The primary function of these defence proteins in latex is to wall off the site of a wound (e.g. after each tapping) to prevent pathogen invasion. In general, defence-

related genes show a 10-50 fold greater expression in laticifers than leaves (Kostyal *et al,* 1998).

Fruit-latex cross-reactivity may also be due to ethylene, a gas used to hasten commercial ripening. When forced to ripen quickly under high ethylene concentrations, plants produce allergenic wound-repair proteins that are similar to wound-repair proteins produced by *H.brasiliensis* (Warshaw, 1998).

2.15. JUDICIAL IMPLICATIONS / MANAGEMENT OF PATIENTS

Latex is recognised as a substance hazardous to health, as defined by the Control of Substances Hazardous to Health Regulations (COSHH 1994), and employers have a legal obligation to take measures which ensure the safety of their employees. Employees allergic to latex, may be able to tolerate gloves with very low protein residues, but otherwise should use gloves made from an alternative material, e.g. neoprene (polychloroprene) or elastyrene (styrene butadiene) (Wakelin & White, 1999).

In South Africa, substances causing allergic skin reactions are notifiable to the SA Commissioner for Occupational Diseases (Potter, 1998a, 1998b). Employees' rights are protected by the Occupational Health and Safety Act No 85 of 1993, under which the employer must provide, as far as is reasonably practical, a working environment which is safe and without risk to the health of the employees. However, voluntarily subjecting oneself to further exposure to latex allergens could seriously prejudice any action brought to a court of law (Potter, 1998c).

Accommodating an employee with LH can involve many aspects. The employee will require non-latex gloves for his / her own use. Airborne particles from co-workers in both the immediate area and areas sharing the same ventilation circuits, need to be considered. If a latex-free environment cannot be achieved by e.g. latex- and powder-free gloves, modified work in another area, or retraining for a different occupation may become necessary. In some cases, medical boarding and worker's compensation will be mandatory (Potter, 1996a). The use of gloves in other, non-work areas, e.g. the cafeteria, must be assessed. The risk of employees from other areas introducing latex into latex-free zones must be considered. The psychological impact of LH on employees can be profound, depending on the number of lifestyle changes, both professionally and personally (Lyttle, 1994).

LH may incur considerable cost. The Ontario Worker's Compensation Board estimates that the direct cost of one latex claim is $ 215 000.00. Based on the size of the facility, the employer could be accountable for 90% of this cost. In 1993, LH cases have been responsible for an additional $ 304 900.00 in Worker's Compensation charges and the cost is growing (Gurman *et al,* 1995). Since LH is not as clearly defined as a "loss of limb" or other overt function, the Workmen's Compensation System in the USA has been reluctant to classify HCW with LH as disabled. Consequently, there are very few examples of HCW receiving disability payments for LH in the USA (Taylor, 1997).

The total cost of occupational illness include direct and indirect cost. The direct costs entail the purchase of powder-free or latex-free gloves, the substitution of other hospital equipment and the cost of installing an air filtration / laminar flow changing station. The indirect costs that are worker-related, include job relocation to other sites of the hospital, job change without retraining, or retraining and re-education for a new non-clinical placement. The potential costs of ignoring LH (litigation, retraining, re-structuring hospital environments, compensation) are much higher than those incurred by changing a hospital to low allergy powder-free gloves. Individuals who have already acquired LH must be protected from further exposure. In confirmed cases of LH, the only feasible solution is the use of non-latex devices. Even gloves with extremely low levels of extractable protein can provoke reactions in a proportion of people who have already acquired LH (White, 1997).

The use of prophylactic medications in high risk patients include corticosteroids, H_1 and H_2 antihistamines, and adrenergic agents. However, there has been reports of allergic reactions despite pre-treatment (Lebenbom-Mansour *et al,* 1997).

When the SA Blood Transfusion Service decided to convert to powder-free gloves, they had to find a local supplier who could supply a powder-free, low-protein glove, within a suitable price range. The imported gloves were 80% to 400% more expensive than the gloves currently in use. While not equating the price of a staff member's health with the price of the gloves, cost was a critical factor considering that the SA Blood Transfusion Service uses approximately 20 000 pairs of gloves per month (Pretorius, 1999).

2.16. DIVERSE

LH is a life-threatening condition and the only management is complete avoidance of exposure to all latex proteins. The FDA has recommended that companies producing latex medical devices should attempt to lower the total elutable protein content of their

products, although no standards have yet been set. Both the latex industry and federal regulators have focused on total protein measurements as they begin to develop these standards. Because it is widely agreed that latex allergens are proteins, it is reasonable to assume that measures that lower measurable protein content will lower the antigen content as well (Slater & Trybul, 1994a).

The search for an acceptable alternative led Californian researchers to the guayule plant (*Parthenium argentatum*), a perennial shrub native to the deserts of Mexico and south-western Texas. They have already shown that latex from guayule is free from the allergenic proteins found in rubber latex and does not produce a reaction. They tested a pair of guayule latex gloves by filling them with a solution containing a test virus called phi X174 – smaller than bacteria, HIV, hepatitis B and herpes simplex viruses. They then put the gloves in a centrifuge tube containing a virus-free solution. After an hour in the centrifuge, the virus had failed to pass through the glove into a buffer solution. Condoms made of guayule latex were similarly checked and passed standard tests with flying colours. Guayule latex also seems to have a longer shelf life than conventional rubber, and is harder to pierce. RAST and Western Blot analyses were used to demonstrate that serum IgE antibodies from individuals allergic to *Hevea* latex and IgG antibodies from *Hevea* latex-hyperimmunised mice do not recognise proteins from guayule latex, and that *Hevea* and guayule latex proteins appear to be non-cross-reactive (Siler *et al,* 1996). A Philadelphia company called Yulex is now planning to commercialise the guayule latex. Initially it will focus on reproducing the 300 medical products, such as catheters and surgical gloves currently made from *Hevea* sourced rubber (Walker, 1999).

2.17. OBJECTIVES

Throughout the literature, it is evident that exposure to latex is a main contributor towards the development of LH. The main objectives of this study would be to determine the prevalence of LH among HCW in an academic hospital setting and to compare the influence of high and low exposure in the development of LH. Different parameters will be used to seek significant methods to identify persons at risk. Other indicators of allergy, e.g. allergy score, total serum IgE values, eosinophil counts, will be investigated to quantify their role in the development and course of LH. Further investigations will be done on patients with immunologically confirmed LH to identify cross-reacting food.

All patients will be informed about the clinical presentation of LH and possible warning signs. Those with latex-specific antibodies will be specifically educated about the risks

involved with LH and how to adapt their lifestyles. Precautionary measures would be emphasised and these patients will be notified to the Commissioner of Occupational Health.

Specific recommendations will be forwarded to TBH management about patients with LH, as well as the departments in which they are employed. Patients with LH should be issued with latex-free gloves, while staff members working in close contact with them, will be issued with powder-free gloves. Ideally, a latex-free theatre should be implemented to accommodate LH patients.

CHAPTER III

Materials and Methods

3.1. ETHICAL APPROVAL

Approval from the Ethical Committees of the Cape Technikon and University of Stellenbosch was obtained before commencement. Protocol number 98/046 was assigned to the study by the University of Stellenbosch (Addendum 1). Consent was also obtained from the Chief Medical Superintendent of TBH, to include different personnel sections of the hospital in the study groups (Addendum 2).

The study population was statistically planned, considering the size of the total study population, as well as high and low exposure areas. Recruitment was done with the help of the Personnel Clinic, where all TBH personnel are subjected to an annual medical examination. Once recruited, the patients were redirected to the Dermatology Outpatient Department, TBH, for investigations according to the study protocol.

All patients were fully informed and signed a consent form before inclusion in the study group and commencement of the procedures (Addendum 3). Subjects were included irrespective of age, race or gender.

3.2. PATIENT GROUPS

During 1997, the period when the study was conducted, a total of 4 920 people were employed by TBH. Of these, 2 744 (56%) were exposed to latex previously or on a daily basis, while the remaining 2 176 (44%) were in administrative posts where latex exposure was non-existent or omissibly low. According to these figures the study group was divided into those with high occupational exposure (60%) and those with no or low occupational exposure (40%). Due to financial constraints, a study group of 125 employees was selected and the group was divided accordingly.

3.2.1. Experimental Group

A group of 75 persons working in areas with high latex exposure in TBH, e.g. theatre and laboratories, were randomly selected from staff rotation lists and generated the primary experimental group for the purposes of this study. This group represented 2.7% of all people working in high latex exposure areas at the time.

Code numbers were assigned consecutively from LH 001 to LH 0075.

3.2.2. Control Group

A further 50 persons working in the administration divisions of the hospital, were recruited to form the control group. This group represented 2.3% of all people working in areas with no or low latex exposure at the time.

Code numbers were assigned from LH 076 to LH 125.

3.3. INVESTIGATIONS

3.3.1. Data capture form

A questionnaire was compiled in order to capture demographic and clinical details of each patient (Addendum 4). This questionnaire included details about past and present occupational latex exposure, i.e. exposure present / absent; if present, number of years, number of hours per week, number of pairs of gloves per week. Individuals were also asked if they suspected LH. Personal and family history of atopy was recorded, as well as allergies to medicine, food or other allergies. Detail of all surgical procedures and any side effects, if applicable, were recorded. Patients were asked to score 11 predefined LH-related symptoms, adapted from the Latex Allergy Questionnaire from Groote Schuur Hospital (Addendum 5), as absent, mild, moderate or severe and whether these symptoms were work-related.

3.3.2. Physical Examination

A general physical examination was conducted and vital signs recorded (Addendum 6).

3.3.3. Dermatological Examination

This was followed by a thorough dermatological examination using a dry and propylene glycol dermatoscope technique. The dermatologist, who conducted the examination, was blinded to the LH status and frequency of exposure of the patients. Special reference was made to the UK diagnostic criteria for atopic eczema (Mar & Marks, 1999) (Table 8), as well as the Hanifin and Rajka guidelines for atopic eczema (Hanifin & Rajka, 1980). Additional information or conditions not specified on the clinical examination form were also recorded.

Table 8: United Kingdom Diagnostic Criteria for Atopic Eczema

Must Have:

1. An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus ≥ 3:

1. History of involvement of the skin creases such as folds of elbows, behind the knees, front or ankles or neck
2. A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in those under the age of 4 years)
3. A history of generally dry skin in the past year
4. Visible flexural dermatitis (or dermatitis involving the cheeks or forehead and outer limbs in children under the age of 4 years)
5. Onset under the age of 2 years (not used if the child is younger than 4)

3.3.4. Special Investigations

All patients underwent venepuncture under sterile conditions and 5 mℓ EDTA and 10 mℓ SST blood were collected. The EDTA samples were immediately mixed by gently inverting the tubes and dispatched to the Department of Haematology for full blood and differential counts and plasma viscosity analyses. One of the SST tubes were sent to the Department of Chemical Pathology for determination of total serum IgE and the other was left to clot at room temperature for 30-60 minutes. It was then centrifuged for 10 minutes at 4 500 g, divided into two 5 mℓ cryotubes and frozen at –20°C.

All **full blood and differential counts** and **plasma viscosity** analyses, were done by the Department of Haematology on the day of collection on a Technikon H2® automated analyser. The **total serum IgE** assays were done by the Department of Chemical Pathology according to a RIA Pharmacia-Upjohn® method.

Following collection and storage of all serum, one of the two frozen samples from each patient were thawed at room temperature for 30 minutes and then mixed by gentle swirling or inversion.

Initially, **Latex-specific IgE** was measured according to the AlaSTAT EIA Allergen-Specific IgE Standard Scoring method. This method is based on liquid allergen complexes, monoclonal antibodies and ligand-coated tube separation. During the procedure the allergens are covalently bound to a soluble polymer / co-polymer matrix which in turn is labelled with a ligand – the same ligand used for coating the reaction tubes. The use of an AA co-polymer amplifies the amount of allergens that the matrix can

support. The reagent kit is commercially available from Diagnostic Products Corporation®. The Universal Module consists of 100 ligand-coated tubes, a 22 mℓ vial enzyme-labelled anti-IgE antibody, a 6 mℓ vial anti-ligand, a 60 mℓ vial buffered peroxide solution, one bottle with 15 *o*-phenylenediamine (OPD) tablets and two 75 mℓ buffered wash solution. The Standard Reference Solution contains a Reference Allergen and 5 calibrators, i.e. Calibrator 0 (0 IU/mℓ), Calibrator A (1.5 IU/mℓ), Calibrator B (3 IU/mℓ), Calibrator C (15 IU/mℓ) and Calibrator D (30 IU/mℓ). Four vials Specific Allergen Modules for latex (k82) were also purchased. All reagents were kept at 8°C until the day when the assay was performed.

When all reagents and tubes reached room temperature (± 20°C), two plain 12 x 75 mm polystyrene tubes served as blanks. Two tubes each were then labelled for positive and negative controls, Calibrators 0, A, B, C and D and for each patient sample.

1. **Reaction of the allergen with IgE:** 50 µℓ each of the controls, calibrators and patient samples were pipetted into the corresponding tubes. Immediately afterwards, 100 µℓ of the reference allergen was added to the calibrator tubes and specific allergen (k82) was added to the control and patient tubes. The racks containing the tubes were then shaken for 1 hour at room temperature on a rack shaker set at ± 200 strokes per minute.

2. **Separation of bound from free enzyme:** 50 µℓ of anti-ligand was added to all tubes, except the blanks. It was shaken again for another hour. The contents of all the tubes were then decanted and 2 mℓ buffered wash solution was added and left in the tubes for 2 minutes. All tubes were decanted again and as much moisture as possible was removed. This washing step was repeated for a total of 2 washes.

3. **Reaction with enzyme label:** 200 µℓ enzyme-labelled anti-IgE antibody was added to each tube, except the blanks, and the racks shaken again for 1 hour at ± 200 strokes per minute. Three complete wash cycles, as previously described, followed.

4. **Colour development:** 500 µℓ of substrate working solution was added to all tubes, including the blanks. The substrate working solution must be freshly prepared just before addition by adding the OPD tablets to the buffered peroxide solution and gentle mixing. The racks were then left at room temperature for exactly 15 minutes.

5. **Termination of colour development:** 500 µℓ of 1 N sulphuric acid was added to all tubes, including the blanks. The final colour is stable for up to one hour. A Sophia 1000™ spectrophotometer was set to zero with the blank tubes and the absorption of each tube was measured at 490 nm.

The 0 and A calibrators read within their specified ranges, but readings for calibrators B, C and D were too low. This resulted in a flat calibration curve, which caused all sample readings to be questionable. The entire method was repeated 3 times, every time with fresh reagents and following the procedure with meticulous accuracy. However, still only calibrators 0 and A read within their specified range. All readings were repeated once immediately afterwards on a Perkin-Elmer Lambda 5 UV/VIS spectrophotometer™ at 490 nm, but there was no difference in the readings. The only consistent catalogue number used in the repeat procedures, was that of the calibrators. It was then decided to do the latex-specific IgE analyses on an Immulite™ auto analyser and to include the calibrators as samples. The readings for calibrators B (3 IU/mℓ), C (15 IU/mℓ) and D (30 IU/mℓ) were < 0.35 IU/mℓ, 0.51 IU/mℓ and 0.85 IU/mℓ respectively, which confirmed the suspicion that the calibrators were indeed the culprit, and not the method or other apparatus.

The principle of the automated Immulite™ method is similar to the above, except that the anti-ligand is located on the bead, instead of in the tube. Immulite™ latex-specific IgE is also a chemiluminescent EIA based on liquid ligand-labelled allergen complexes, monoclonal antibodies and separation by an anti-ligand coated solid phase. The Immulite™ latex-specific IgE assay exploits liquid-phase kinetics in a bead format. It represents a significant advantage over conventional methods relying on allergens attached to a solid-phase support, such as a paper disc. The allergens are covalently bound to a soluble polymer / copolymer matrix, which in turn is labelled with a ligand; anti-ligand is coated on the polystyrene bead to capture the ligand labelled allergen complexes. The patient sample and a ligand-labelled latex allergen are simultaneously introduced into the Test Unit (Figure 6), which contains an immobilised anti-ligand and incubated for approximately 30 minutes at 37°C with intermittent agitation. The incubation carousel is maintained at 37°C and agitated intermittently to maximise reaction kinetics.

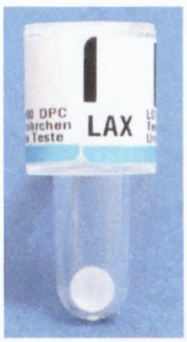
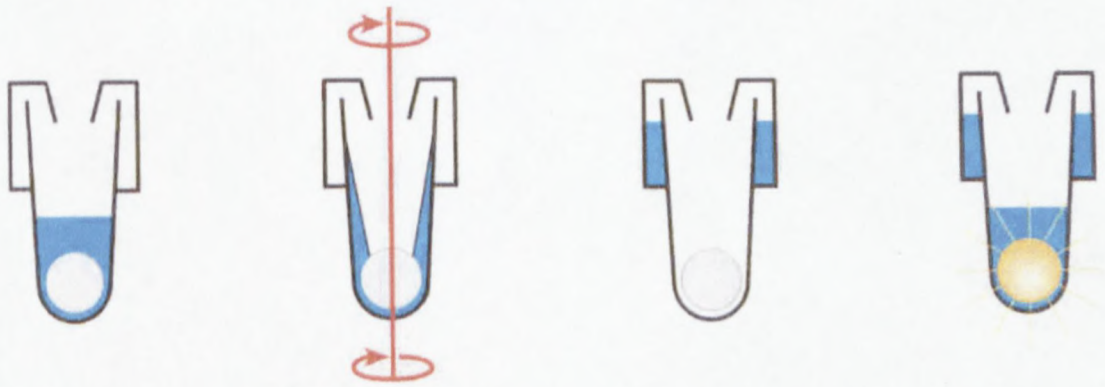


Figure 6: Test Unit of the Immulite™ for Latex-specific IgE assay

During incubation, allergen-specific IgE in the sample binds to the ligand-labelled allergens, which in turn, binds to the anti-ligand on the solid phase. Unbound serum is then removed by a high speed centrifugal wash. Alkaline phosphatase-labelled monoclonal murine anti-IgE antibodies are introduced, and the Test Unit is incubated for another 30 minute cycle. The unbound enzyme conjugate is removed by a centrifugal wash. Chemiluminescent substrate is then added, and the Test Unit is incubated for another 10 minutes. The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustaining emission of light, thus improving precision by providing a window for multiple readings. The bound complex (thus also the photon output), measured by the luminometer, is directly related to the amount of latex-specific IgE.



Sample and reagent are automatically pipetted into the Test Unit, and then incubated at 37°C with intermittent agitation

Following incubation, the Test Unit is spun at high speed. Reaction fluid is forced up and completely captured in the sump chamber

A series of washes efficiently removes unbound material from the bead and inner tube

Chemiluminescent substrate is added to the Test Unit. Photon emission is read with a high sensitivity photon counter

Figure 7: Schematic diagram of the Immulite™ Latex-specific IgE automated assay

The reserve sera from all patients with positive *in vitro* results (> 0.35 IU/mℓ) were sent to the Immunology Department at Groote Schuur Hospital, Cape Town, for further

investigations. **RAST for cross-reacting food** (avocado, banana, carrot, chestnut, kiwi fruit, mango and potato) were done on all sera by means of the capRAST method.

All patients with negative *in vitro* results who indicated that they experienced work-related symptoms or reported more than 1 severe symptom on the questionnaire, were subjected to **SPT** under controlled conditions. Commercially available Soluprick SQ ALK (960)® solution (Figure 8), a positive control (10 mg/mℓ histamine dihydrochloride) and negative control (saline 50% in glycerine) were applied to the medial forearm. The epidermal layer was then punctured with a lancet and the results read 15 minutes after application. The 1 : 1 000 dilution was applied first; if no reaction appeared within 15 minutes, the 1 : 100 was applied and in case of no reaction after another 15 minutes, the 1 : 10 dilution was applied. A wheal of more than 2 mm was regarded as positive. If any of the three dilutions caused a positive reaction, no further testing was done and the person was regarded as LH positive. All patients with positive SPT results (Figure 9), were included in the LH-positive group. However, no further immunologic investigations were done on their serum.

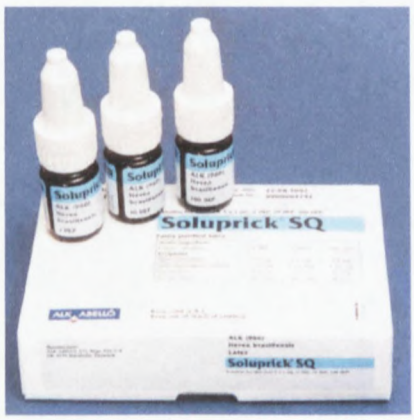


Figure 8: Commercially available skin prick test extracts for latex hypersensitivity testing

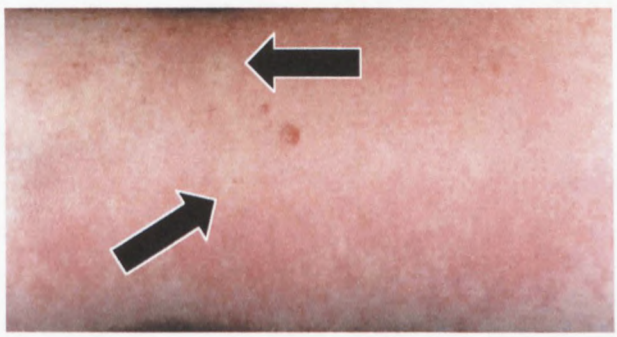


Figure 9: A positive skin prick test reaction. Arrows denote wheal-and-flare reaction

3.3.5. Allergy Score

Patients were asked to rate predefined LH-related symptoms on the questionnaire as being absent, mild, moderate or severe. These symptoms were conjunctivitis, nasal congestion, rhinitis, shortness of breath, bronchospasm, urticaria, angioedema, anaphylactic shock, pruritus, skin rash and hand eczema.

An allergy score was designed and calculated according to the following formula:

Allergy score = [number of symptoms (absent) x 0] + [number of symptoms (mild) x 1] + [number of symptoms (moderate) x 2] + [number of symptoms (severe) x 3]

A patient could thus score a minimum of 0 if all 11 symptoms were absent, or a maximum of 33 if all 11symptoms were severe.

3.4. STATISTICAL ANALYSES

Statistically, the experimental group was primarily compared to the control group. The study population was then redivided into a LH positive (all patients with positive *in vitro* or SPT results) and LH negative group, for further comparisons. Odds and risk ratio's, chi square, contingency table analyses and analysis of variance were done on all parameters, where applicable, within the 4 different groups, with a basic significance level of $p=0.05$ for all tests. Confidence intervals of 95% were used and p values of < 0.05 were regarded as statistically significant.

CHAPTER IV

Results

Arithmetic mean, standard deviation and range (minimum and maximum) were calculated on all numerical data for the study population, experimental, and, control groups.

4.1. STUDY GROUP

The study group comprised 75 persons with high occupational latex exposure and 50 persons with low or no occupational latex exposure. All 125 subjects are staff members at TBH. Their mean age was 36.31 ± 8.60 years and the range 21 – 60 years. The male : female ratio was 18 : 107 and their occupations were nurses (61), administration (31), doctors (10), secretaries / typists (10), medical technologists (4), porters (4), housekeepers (3), radiographer (1) and social worker (1). Fourteen (11.2%) of them thought they were allergic to latex, 82 (65.6%) thought they were not allergic and 29 (23.2%) did not know. All the mean values for the individual parameters for the whole group was within clinically acceptable reference ranges.

4.2. EXPERIMENTAL GROUP

The experimental group comprised 75 persons with high occupational latex exposure at TBH. Their mean age was 35.24 ± 8.05 years and the range 23 – 60 years.

Table 9: Demographic Data of Experimental Group (n = 75)

		n	%
Ethnic group:	Caucasian	20	26.7
	Mixed Race	53	70.7
	Black	2	2.6
Gender:	Male	10	13.3
	Female	65	86.7
Occupation:	Doctor	10	13.3
	Medical Technologist	4	5.3
	Nurse	61	81.3
Personal history of Atopy:	Eczema	13	17.3
	Asthma	7	9.3
	Hay Fever	27	36.0
	Rhinitis	6	8.0
Family history of Atopy:	Yes	30	40.0
	No	45	60.0
Other allergies:	Medicine	3	4.0
	Food	10	13.3
	Other	11	14.7

Table 10: Past / Present Latex Exposure of Experimental Group (n = 75)

		n	%	Mean	Min	Max
Wear latex gloves:	Yes	75	100.0			
	No	0	0.0			
Number of years				9.73 ± 6.98	0.5	27
Hours per week				23.63 ± 12.10	0.5	40
Pairs per week				25.79 ± 25.85	1	200
Suspect LH:	Yes	14	18.7			
	No	37	49.3			
	Don't know	24	32.0			
Previous operations:	Yes	63	84.0			
	No	12	16.0			
	Side-effects	10	13.3			

Table 11: Clinical Signs of Experimental Group (n = 75)

		n	%
Conjunctivitis:	Absent	42	56.0
	Mild	10	13.3
	Moderate	16	21.3
	Severe	7	9.3
Nasal congestion:	Absent	43	57.3
	Mild	11	14.7
	Moderate	11	14.7
	Severe	10	13.3
Rhinitis:	Absent	43	57.3
	Mild	9	12.0
	Moderate	13	17.3
	Severe	10	13.3
Shortness of breath:	Absent	67	89.3
	Mild	5	6.7
	Moderate	3	4.0
	Severe	0	0.0
Bronchospasm:	Absent	61	81.3
	Mild	10	13.3
	Moderate	4	5.3
	Severe	0	0.0
Urticaria:	Absent	59	78.7
	Mild	5	6.7
	Moderate	9	12.0
	Severe	2	2.7
Angioedema:	Absent	71	94.7
	Mild	1	1.3
	Moderate	2	2.7
	Severe	1	1.3
Anaphylaxis:	Absent	74	98.7
	Mild	0	0.0
	Moderate	0	0.0
	Severe	1	1.3

Table 11 (continued)		n	%
Pruritus:	Absent	39	52.0
	Mild	7	9.3
	Moderate	21	28.0
	Severe	8	10.7
Skin Rash:	Absent	42	56.0
	Mild	10	13.3
	Moderate	17	22.7
	Severe	6	8.0
Hand eczema:	Absent	43	57.3
	Mild	8	10.7
	Moderate	15	20.0
	Severe	9	12.0
Other*:	Absent	71	94.7
	Mild	1	1.3
	Moderate	1	1.3
	Severe	2	2.7

The experimental group generated a mean allergy score of 6.13 ± 5.89 with a range of 0 – 29

* Includes additional symptoms not related to LH: allergy to soap (1), dermographism (1), candida paronychia (1) and blepharitis (1)

Table 12: Clinical / Dermatological Examination of Experimental Group (n = 75)

		n	%	Mean	Min	Max
Blood Pressure (mmHg):	Systolic			118.39 ± 7.57	100	135
	Diastolic			74.14 ± 8.03	60	95
Pulse (beats per minute)				74.53 ± 4.64	64	90
Lowered hairline		5	6.7			
Hertoche's sign		15	20.0			
Infraorbital hyperpigmentation		16	21.3			
Photosensitivity		9	12.0			
Cataracts		0	0.0			
Geographical tongue		0	0.0			
Facial erythema		3	4.0			
Facial pallor		13	17.3			
Cutaneous pallor		8	10.7			
White dermographism		2	2.7			
Pityriasis alba		0	0.0			
Dennie Morgan lines		25	33.3			
Keratoconus		0	0.0			
Cheilitis		2	2.7			
Anterior neckfolds		1	1.3			
Eczema		12	16.0			
Pruritus		9	12.0			
Polished nails		0	0.0			
Periostitis		0	0.0			
Areolar dermatitis		0	0.0			
Xeroderma		34	45.3			
Ichthyosis vulgaris		1	1.3			
Dirty neck		2	2.7			
Hyperlinear palms		17	22.7			

Table 12 (continued)	n	%	Mean	Min	Max
Hand / foot dermatitis	4	5.3			
Prominent perifollicular areas	0	0.0			
Cutaneous infections	0	0.0			
Keratosis pilaris	1	1.3			
Keratosis punctata	0	0.0			
Pruritus with sweat	7	9.3			
Subungual haemorrhage	0	0.0			
Shortened body length	1	1.3			
External triggers	1	1.3			
Other	2	2.7			

Table 13: Special Investigations of Experimental Group (n = 75)

	Reference range	n	%	Mean	Min	Max
White blood cells	(4.1 - 10.9 x $10^9/\ell$)			7.50 ± 1.99	3.80	13.10
Red blood cells	(3.82 – 5.78 x $10^{12}/\ell$)			4.44 ± 0.37	3.77	5.69
Haemoglobin (Hb)	(M: 13.05 – 17.95 g/dℓ) (F: 11.55 – 16.45 g/dℓ)			12.73 ± 1.30	8.30	15.90
Haematocrit (Hct)	(M: 40.14 – 53.86%) (F: 37.10 – 46.90%)			38.35 ± 3.20	28.10	47.10
Mean corpuscular volume (MCV)	(M: 80.14 – 93.86 fℓ) (F: 76.20 – 95.80 fℓ)			86.54 ± 5.75	58.40	97.30
Mean corpuscular haemoglobin (MCH)	(27.05 - 31.95 pg)			28.74 ± 2.58	17.20	32.90
Mean corpuscular Haemoglobin concentration (MCHC)	(29.56 – 35.44%)			33.17 ± 1.41	29.40	36.00
Red cell distribution width	(11.60 – 14.00)			12.97 ± 1.18	11.50	18.40
Platelets	(152.5 – 397.5 x $10^9/\ell$)			254.09 ± 57.33	149.00	428.00
Mean platelet volume (MPV)	(6.1 – 8.9 μm^3)			8.68 ± 0.81	6.80	10.20
Neutrophils	(2.06 – 7.45 x $10^9/\ell$)			4.37 ± 1.54	1.35	9.38
Lymphocytes	(1.52 – 3.97 x $10^9/\ell$)			2.33 ± 0.79	0.43	4.84
Monocytes	(0.21 – 0.79 x $10^0/\ell$)			0.51 ± 0.17	0.18	1.08
Eosinophils	(0.05 – 0.45 x $10^9/\ell$)			0.16 ± 0.12	0.02	0.50
Basophils	(0.04 – 0.16 x $10^9/\ell$)			0.04 ± 0.02	0.01	0.10
Large unstained cells				0.10 ± 0.06	0.00	0.26
Plasma viscosity	(1.49 – 1.73 cP)			1.62 ± 0.09	1.47	1.91
Total IgE	(Caucasian: <100 KU/ℓ, Mixed race: <200 KU/ℓ, Black:< 500 KU/ℓ)			121.91 ± 211.07	0.00>1000	
↑ Latex-specific IgE	(< 0.35 IU/ℓ)	11	14.7	7.98 ± 8.39	<0.35	23.90
Only done on patients with ↑ Latex-specific IgE (n = 11)						
↑ RAST – Carrot	(< 0.35 KU/ℓ)	6	54.6	1.20 ± 2.02	0.00	6.86
↑ RAST – Potato	(< 0.35 KU/ℓ)	6	54.6	0.90 ± 1.38	0.00	4.35
↑ RAST – Kiwi fruit	(< 0.35 KU/ℓ)	3	27.3	0.24 ± 0.54	0.00	1.78
↑ RAST – Mango	(< 0.35 KU/ℓ)	4	36.4	0.33 ± 0.67	0.00	2.25
↑ RAST – Banana	(< 0.35 KU/ℓ)	4	36.4	0.40 ± 0.64	0.00	1.82
↑ RAST – Avocado	(< 0.35 KU/ℓ)	7	63.6	0.91 ± 1.36	0.00	4.39

Table 13 (continued)

	Reference range	n	%	Mean	Min	Max
↑ RAST – Chestnut	(< 0.35 KU/ℓ)	3	27.3	0.40 ± 0.82	0.00	2.14
Only done on patients with negative latex-specific IgE negative who have work-related and ≥ 2 severe symptoms on questionnaire (n = 25)						
SPT	Positive	12	48.0			
	Negative	13	52.0			

4.3. CONTROL GROUP

The control group comprised 50 persons working in areas with no or low latex exposure at TBH. The mean age of the control group was 37.92 ± 9.20 years and the range 21 – 57 years.

Table 14: Demographic Data of Control Group (n = 50)

		n	%
Ethnic group:	Caucasian	23	46.0
	Mixed Race	25	50.0
	Black	2	4.0
Gender:	Male	8	16.0
	Female	42	84.0
Occupation:	Administration	31	62.0
	Housekeeper	3	6.0
	Porter	4	8.0
	Radiographer	1	2.0
	Secretary / Typist	10	20.0
	Social Worker	1	2.0
Personal history of Atopy:	Eczema	2	4.0
	Asthma	2	4.0
	Hay Fever	14	28.0
	Rhinitis	3	6.0
Family history of Atopy:	Yes	24	48.0
	No	26	52.0
Other allergies:	Medicine	4	8.0
	Food	3	6.0
	Other	5	10.0

Table 15: Past / Present Latex Exposure of Control Group (n = 50)

		n	%	Mean	Min	Max
Wear latex gloves:	Yes	2	4.0			
	No	48	96.0			
Suspect LH:	Yes	0	0.0			
	No	45	90.0			
	Don't know	5	10.0			
Previous operations:	Yes	36	72.0			
	No	14	28.0			
	Side-effects	2	4.0			

Table 16: Clinical Signs of Control Group (n = 50)

		n	%
Conjunctivitis:	Absent	41	82.0
	Mild	1	2.0
	Moderate	7	14.0
	Severe	1	2.0
Nasal congestion:	Absent	34	68.0
	Mild	5	10.0
	Moderate	10	20.0
	Severe	1	2.0
Rhinitis:	Absent	34	68.0
	Mild	3	6.0
	Moderate	11	22.0
	Severe	2	4.00
Shortness of breath:	Absent	45	90.0
	Mild	2	4.0
	Moderate	3	6.0
	Severe	0	0.0
Bronchospasm:	Absent	44	88.0
	Mild	3	6.0
	Moderate	3	6.0
	Severe	0	0.0
Urticaria:	Absent	47	94.0
	Mild	1	2.0
	Moderate	2	4.0
	Severe	0	0.0
Angioedema:	Absent	48	96.0
	Mild	1	2.0
	Moderate	1	2.0
	Severe	0	0.0
Anaphylaxis:	Absent	50	100.0
	Mild	0	0.0
	Moderate	0	0.0
	Severe	0	0.0
Pruritus:	Absent	46	92.0
	Mild	2	4.0
	Moderate	1	2.0
	Severe	1	2.0
Skin Rash:	Absent	38	76.0
	Mild	7	14.0
	Moderate	4	8.0
	Severe	1	2.0
Hand eczema:	Absent	46	92.0
	Mild	3	6.0
	Moderate	1	2.0
	Severe	0	0.0
Other*:	Absent	45	90.0
	Mild	1	2.0
	Moderate	3	6.0
	Severe	1	2.0

The control group generated a mean allergy score of 2.64 ± 3.71 with a range of 0 – 15.

* Includes additional symptoms not related to LH: acne vulgaris (2), plantar callus (1) and xeroderma (1)

Table 17: Clinical / Dermatological Examination of Control Group (n = 50)

		n	%	Mean	Min	Max
Blood Pressure (mmHg):	Systolic			121.98 ± 10.23	100	151
	Diastolic			75.94 ± 7.71	60	97
Pulse (beats per minute)				76.32 ± 5.84	67	90
Lowered hairline		1	2.0			
Hertoche's sign		8	16.0			
Infraorbital hyperpigmentation		6	12.0			
Photosensitivity		5	10.0			
Cataracts		0	0.0			
Geographical tongue		0	0.0			
Facial erythema		0	0.0			
Facial pallor		6	12.0			
Cutaneous pallor		2	4.0			
White dermographism		1	2.0			
Pityriasis alba		0	0.0			
Dennie Morgan lines		13	26.0			
Keratoconus		0	0.0			
Cheilitis		0	0.0			
Anterior neckfolds		1	2.0			
Eczema		8	16.0			
Pruritus		6	12.0			
Polished nails		0	0.0			
Periostitis		0	0.0			
Areolar dermatitis		1	2.0			
Xeroderma		23	46.0			
Ichthyosis vulgaris		0	0.0			
Dirty neck		2	4.0			
Hyperlinear palms		7	14.0			
Hand / foot dermatitis		0	0.0			
Prominent perifollicular areas		1	2.0			
Cutaneous infections		0	0.0			
Keratosis pilaris		0	0.0			
Keratosis punctata		0	0.0			
Pruritus with sweat		3	6.0			
Subungual haemorrhage		0	0.0			
Shortened body length		0	0.0			
External triggers		0	0.0			
Other		0	0.0			

Table 18: Special Investigations of Control Group (n = 50)

	Reference range	n	%	Mean	Min	Max
White blood cells	(4.1 - 10.9 x $10^9/\ell$)			6.86 ± 1.60	4.00	11.00
Red blood cells	(3.82 – 5.78 x $10^{12}/\ell$)			4.57 ± 0.45	3.76	5.51
Haemoglobin (Hb)	(M: 13.05 – 17.95 g/dℓ)					
	(F: 11.55 – 16.45 g/dℓ)			13.22 ± 1.42	9.00	16.20

Table 18 (continued)

	Reference range	n	%	Mean	Min	Max
Haematocrit (Hct)	(M: 40.14 – 53.86%) (F: 37.10 – 46.90%)			40.05 ± 3.80	28.50	48.70
Mean corpuscular volume (MCV)	(M: 80.14 – 93.86 fℓ) (F: 76.20 – 95.80 fℓ)			87.85 ± 5.97	66.80	101.60
Mean corpuscular haemoglobin (MCH)	(27.05 - 31.95 pg)			29.02 ± 2.40	21.20	32.30
Mean corpuscular Haemoglobin concentration (MCHC)	(29.56 – 35.44%)			33.00 ± 1.20	29.90	35.7
Red cell distribution width	(11.60 – 14.00)			12.97 ± 1.29	11.70	19.20
Platelets	(152.5 – 397.5 x 10^9/ℓ)			250.06 ± 60.85	144.00	400.00
Mean platelet volume (MPV)	(6.1 – 8.9 μm^3)			8.83 ± 0.77	6.90	10.50
Neutrophils	(2.06 – 7.45 x 10^9/ℓ)			3.94 ± 1.23	1.52	7.78
Lymphocytes	(1.52 – 3.97 x 10^9/ℓ)			2.14 ± 0.63	0.83	3.98
Monocytes	(0.21 – 0.79 x 10^0/ℓ)			0.45 ± 0.17	0.23	1.04
Eosinophils	(0.05 – 0.45 x 10^9/ℓ)			0.16 ± 0.15	0.03	0.07
Basophils	(0.04 – 0.16 x 10^9/ℓ)			0.05 ± 0.03	0.00	0.18
Large unstained cells				0.12 ± 0.09	0.00	0.39
Plasma viscosity	(1.49 – 1.73 cP)			1.67 ± 0.11	1.47	2.00
Total IgE	(Caucasian: <100 KU/ℓ, Mixed race: <200 KU/ℓ, Black:< 500 KU/ℓ)			137.04 ± 204.37	0.00>	1000.0
↑ Latex-specific IgE	(< 0.35 IU/ℓ)	3	6.0	4.13 ± 4.37	<0.35	9.10
Only done on patients with ↑ Latex-specific IgE (n = 3)						
↑ RAST – Carrot	(< 0.35 KU/ℓ)	2	66.7	7.84 ± 9.02	0.00	17.70
↑ RAST – Potato	(< 0.35 KU/ℓ)	2	66.7	8.59 ± 12.32	0.00	22.7
↑ RAST – Kiwi fruit	(< 0.35 KU/ℓ)	1	33.3	N/A	0.00	4.31
↑ RAST – Mango	(< 0.35 KU/ℓ)	2	66.7	2.53 ± 3.23	0.00	6.17
↑ RAST – Banana	(< 0.35 KU/ℓ)	2	66.7	7.69 ± 12.15	0.00	21.70
↑ RAST – Avocado	(< 0.35 KU/ℓ)	2	66.7	3.21 ± 3.82	0.00	7.43
↑ RAST – Chestnut	(< 0.35 KU/ℓ)	2	66.7	1.78 ± 1.62	0.00	3.16

4.4. STATISTICAL COMPARISONS

The experimental group was compared to the study group on all parameters. Two additional groups were formed according to the latex-specific IgE and SPT results. The LH positive group (n = 26) included patients with positive latex-specific IgE (n = 14) or positive SPT against latex extracts (n = 12), and LH negative group (n = 99) where both parameters were negative or SPT was not done.

In cases of severe skewed distribution curves it was necessary to use the logarithm of the observations in order to calculate representative p values. Confidence intervals of 95% have been applied throughout and p values less than 0.05 are being regarded as statistically significant.

Table 19: p-Values for Statistical Comparison of Clinical signs

	Experimental vs Control Groups		LH Positive vs LH Negative Groups	
	Trend	**Overall**	**Trend**	**Overall**
Hand eczema	0.000007	0.000266	0.000000	0.000000
Conjunctivitis	0.002092	0.012678	0.000000	0.000003
Bronchospasm	0.179459	0.420248	0.000021	0.000210
Pruritus	0.000001	0.000042	0.000032	0.000280
Skin rash	0.005248	0.053715	0.001722	0.000325
Shortness of breath	0.469656	0.728899	0.006982	0.014209
Urticaria	0.009592	0.126713	0.020815	0.020095
Nasal congestion	0.085619	0.114006	0.028076	0.092462
Rhinitis	0.103418	0.191725	0.007289	0.097739
Angioedema	0.359215	0.846796	0.034785	0.152046

Table 20: Statistical Comparison of Demographic Information, Latex Exposure and Special Investigations

	Experimental vs Control Group			LH Positive vs LH Negative Group		
	(n=75) Mean	**(n=50) Mean**	**p value**	**(n=26) Mean**	**(n=99) Mean**	**p value**
Age	35.24	37.92	0.08779	35.77	36.45	0.71912
Systolic blood pressure	118.15	121.57	0.03368	120.36	119.28	0.58460
Diastolic blood pressure	74.14	75.94	0.21788	75.92	74.58	0.45320
Pulse	74.39	76.10	0.07013	75.81	74.90	0.43470
Allergy score	6.13	2.64	0.00030	9.92	3.37	0.00000
Exposure to latex						
Number of years	9.73	9.50	0.96293	11.02	9.19	0.29920
Hours per week	23.63			20.30	25.29	0.09879
Pairs of gloves per week	25.79			26.70	25.47	0.85013
Total operations / person	1.36	1.94	0.09187	1.54	1.61	0.87144
Special investigations						
WBC	7.25	6.69	0.07828	7.21	6.97	0.54333
RBC	4.43	4.55	0.10182	4.44	4.48	0.60167
Hb	12.73	13.22	0.04916	12.81	12.96	0.61267
Hct	38.35	40.05	0.00805	38.23	39.24	0.19912
MCV	86.54	87.85	0.21933	86.14	87.30	0.36968
MCH	28.74	29.02	0.54307	28.88	28.84	0.93793
MCHC	33.17	33.00	0.50487	33.45	33.01	0.13811
RDW	12.92	12.91	0.95966	13.04	12.89	0.54233
Platelets	247.76	243.14	0.65793	270.37	239.85	0.01816

Table 20 (continued)	Mean	Mean	p value	Mean	Mean	p value
MPV	8.68	8.83	0.30118	8.65	8.76	0.52930
Neutrophils	4.12	3.77	0.14612	4.20	3.92	0.35244
Lymphocytes	2.33	2.14	0.16186	2.22	2.26	0.82279
Monocytes	0.48	0.42	0.02919	0.40	0.46	0.79997
Eosinophils	0.12	0.13	0.51784	0.15	0.12	0.10782
Basophils	0.04	0.05	0.21847	0.04	0.04	0.21305
Large unstained cells	0.10	0.12	0.20282	0.09	0.11	0.23393
Plasma viscosity	1.62	1.66	0.01909	1.64	1.64	0.87143
Total IgE	39.27	43.21	0.75546	50.68	38.54	0.46014
Latex-specific IgE	3.83	2.68	0.69563			

Table 21: Statistical Comparison of Atopy and Dermatological Features

	Number Positive	Experimental vs Control Groups p value	LH Positive vs LH Negative Groups p value
Atopy (in the order of appearance on data capture form)			
History of eczema	15	0.024619	0.050815
History of asthma	9	0.258432	0.069646
History of hay fever	41	0.350656	0.245919
History of allergic rhinitis	9	0.671719	0.069649
Family history of atopy	54	0.376386	0.218172
Allergy to medicine	7	0.340648	0.138913
Food allergy	13	0.188240	0.001927
Other allergies	16	0.444227	0.002058
Dermatology (in order of significance in LH groups)			
Hand and foot dermatitis	4	0.096962	0.000073
Photosensitivity	14	0.728324	0.004282
Dennie Morgan lines	38	0.382546	0.014630
Cutaneous pallor	10	0.178317	0.017697
Facial pallor	19	0.415843	0.061362
Xeroderma	57	0.941556	0.066723
Hyperlinear palms	24	0.228129	0.261242
Eczema	20	1.000000	0.268711
Dirty Neck	4	0.678185	0.297530
Lowered hairline	6	0.231807	0.438205
Pruritus with sweat	10	0.500962	0.454878
Infraorbital hyperpigmentation	22	0.179471	0.806181
Pruritus	15	1.000000	0.935142
Hertoche's sign	23	0.571792	0.902231
The following had too few positive individuals for valid statistical comparison			
Facial erythema	3		
White dermographism	3		
Cheilitis	2		

Table 21 (continued)	Number Positive	p value	p value
Anterior neckfolds	2		
Ichthyosis vulgaris	1		
Areolar dermatitis	1		
Prominent perifollicular areas	1		
External trigger	1		
Keratosis pilaris	1		
Shortened body length	1		

4.5. SUMMARY

All clinical and laboratory results of the study group were within the 95% confidence intervals for the population group.

The experimental and control groups ($p = 0.0878$) were comparable with respect to age. Similarly, the LH positive and negative groups ($p = 0.7191$) did not differ significantly with respect to age. Although the mean systolic blood pressure of the control group (121.57 mmHg, left cubital fossa with patients lying horizontally for 10 minutes) was significantly higher ($p = 0.0337$) than that of the experimental group (mean 118.15 mmHg, left cubital fossa with patients lying horizontally for 10 minutes), this finding is not regarded as biologically meaningful.

A personal history of eczema was significantly higher in the experimental than control group ($p = 0.0246$). When the LH positive and LH negative groups were compared, food ($p = 0.0019$) and other allergies ($p = 0.0021$) were prominent findings in the LH positive group.

In the LH positive group ($n = 26$), only 1 patient (4%) reported none of the 11 specified symptoms on the questionnaire, as opposed to 13 patients (17%) in the experimental ($n = 75$) and 23 patients (46%) in the control ($n = 50$) groups. Anaphylaxis was present in only 1 patient and was thus unsuitable for statistical analysis. Definite increasing trends (p values varying from 0.03 to < 0.00001) in the severity of all clinical signs could be demonstrated in the LH positive group. In the experimental group these trends were also evident for conjunctivitis, urticaria, pruritus, skin rash and hand eczema.

Twenty-six patients (21%) reported a definite connection between work and symptoms. The experimental group showed a mean allergy score of 6.13, as opposed to 2.64 in the control group ($p = 0.0003$). The mean allergy score of the LH positive group was 9.92, and that of the LH negative group 3.37 ($p < 0.0001$).

No statistical differences could be detected in dermatological findings when comparing the experimental and control groups, but when comparing the LH positive and LH negative groups, Dennie Morgan lines ($p = 0.0146$), cutaneous pallor ($p = 0.0178$), photosensitivity ($p = 0.0042$) and hand / foot dermatitis ($p = 0.0001$) were significantly more prominent in the LH positive group. No further statistical comparisons were done where 3 or fewer persons were positive, which would lead to invalid comparisons. Dermatological features absent in all four groups included pityriasis alba, keratoconus, subungual haemorrhage, keratosis punctata, cataracts, geographical tongue, cutaneous infections, polished nails and distal phalangeal periostitis.

In the LH positive group, 7 patients (27%) had elevated total serum IgE values when measured against the normal values for the individual ethnic groups in the Western Cape. Three (12%) of these patients reached values of > 1 000 KU/ℓ. Elevated total serum IgE values were reported in 14 (19%) patients in the experimental group and 15 (30%) patients in the control group, with 2 (3%) and 1 (2%) patients reaching values of > 1 000 KU/ℓ respectively.

Latex-specific serum IgE values for the total group ranged from < 0.35 IU/mℓ to 23.9 IU/mℓ. Values greater than 0.35 IU/mℓ were considered to be positive according to the manufacturer's specifications (Weiss, 1995). In the experimental group, 11 (15%) and only 3 (6%) in the control group tested positive *in vitro*. A further 25 patients from the experimental group were subjected to subcutaneous SPT. These patients had negative *in vitro* results, but more than one severe symptom on the questionnaire or indicated that their symptoms were work-related. Twelve patients in this group (48%) had positive SPT. Final prevalence of LH in the experimental group reached 31% (n = 23).

Only 7 of the 14 (50%) patients who thought they were allergic, 6 of the 82 (7%) who did not suspect an allergy and 13 of the 28 (46%) who did not know, were proven to be LH positive by *in vitro* or subcutaneous SPT. The odds ratio of those that knew their allergy status (n = 96) was 12.67 (95% CI: 2.80 – 60.67, p value = 0.0003). This would indicate that persons suspecting that they are allergic, are in fact more liable to be allergic.

CHAPTER V

Discussion

5.1. IMMUNOLOGICAL BACKGROUND OF LATEX HYPERSENSITIVITY

The pathogenesis of LH classically illustrates the three levels of defence, i.e. surface barriers, innate and acquired immunity (Delves & Riott, 2000a).

Breaching of surface barriers targets the respiratory tract, the gastrointestinal system or skin via percutaneous penetration. Atopic patients classically have impaired function of the skin barrier system. These patients most probably have similar restricted function in the gastrointestinal and respiratory barriers. Patients known with LH have not been investigated for barrier function disruption. An interesting field of possible future research could address the penetration of high MW latex molecules through the surface barriers of these three systems. *In vitro* technology is available to label latex particles with isotopes, e.g. tritium (Van der Bijl *et al,* 2000), and to evaluate the penetration thereof through these three barriers in atopic and non-atopic patients.

The finer details of the cascade leading to LH reactions have not been clarified to date. *In vivo* and *in vitro* techniques could be employed to clarify the role of the key cellular components of innate immunity. The effect of the carbohydrate activating components of latex on interdigitating dendritic cells should be investigated. Evaluating the expression of CD 80 and CD 86 molecules on dendritic cells after exposure to latex would furthermore clarify the role of latex composition and the role of these cells in LH.

B and T lymphocytes process antigens via receptor mechanisms as part of the acquired (adaptive) immunologic response. These receptors have small binding sites of only 600 Å to 1 700 Å and can only recognise a small part of complex antigens, such as latex, via the antigenic epitope. Splitting of latex molecules with high hypersensitivity indexes by using proteolytic enzymes could further clarify these specific antigenic epitopes. These chemical markers could be used to identify latex with a high sensitivity index and lead to the elimination of these molecules from the manufacturing process. Industry could be helped to improve the final product and limit exposure of the general public to allergenic latex.

An antigen is recognised on the basis of shape. These molecules bind to antibodies by way of an undulating surface after recognition of a continuous peptide sequence. AA are

brought together to form discontinuous epitopes (the peptide sequence) when the protein folds into its native structure. These antigenic epitopes fit with the B-cell receptor or the population of antibodies developed against the epitopes. Depending on the epitopes, it is therefore possible to speculate that the larger latex molecules would initiate a polyclonal antibody reaction against a latex antigen leading to higher hypersensitivity. Polysaccharides, like those contained in latex, can furthermore stimulate B-cells without the help of T-cells. B-cell dependent antigen reactions are limited due to the minimal formation of memory B-cells. Most antigens are however unable to stimulate B-cells without assistance from CD 4 T-cells. It is therefore possible to speculate that the complex protein and polysaccharide molecules of latex could induce B-cell activation either without the help of T-cells or with the help of CD 4 T-cells. This is referred to as T-cell dependent antigen reactions. Set against this background it would seem that an important part of the LH cascade forms by way of a T-cell dependent antigen reaction where protein molecules are bound to B-cell receptors, internalised, processed and brought to the cell surface by major histocompatibility complex (MHC) class II molecules. These molecules are recognised by CD 4 T-cells, lead to activation and binding to the CD 40 receptor on B-cells and stimulate immunoglobulin production. This cascade is mediated by background production of interleukin 2, 4 and 5 from CD 4 cells leading to further dendritic cell and macrophage activation (Delves & Riott, 2000b).

This pre-primed immune system is stimulated by latex immunogenic epitopes, leading to additional epitope recognition on the antigen due to general upregulation of antigen processing and presentation. This is known as epitope spreading and may spill over to other antigens. Interestingly, patients with LH may exhibit intermolecular spreading and become sensitive to numerous fruits and vegetables. These results therefore further underline the danger of chronic latex exposure as can be seen in the present LH positive group. Protection of workers and the reduction of exposure to latex in the work environment are therefore imperative.

5.2. PREVALENCE OF LATEX HYPERSENSITIVITY

The findings of this study are in keeping, or marginally higher than results of previously published studies world-wide (see Table 4). Due to financial constraints, only a small, statistically planned, cohort was tested. The individual groups were representative of the respective populations, i.e. 2.7% of workers in high exposure areas and 2.3% of workers in low exposure areas.

Prevalences found in this study were 14.7% for the experimental group, 6% for the control group and an overall LH prevalence of 21% for the study group. To extrapolate the results to the study population, the experimental group may be compared to persons with high latex exposure, e.g. HCW, and the control group to persons with no or low latex exposure, e.g. the general population.

With 95% confidence intervals, the projected LH prevalences are as follows:

High exposure (all known high risk groups):	21 – 42%
Low / no exposure (general population):	1 – 17%

The difference in the projected and reported figures in this study was probably caused by the relatively small sample size of the respective populations. The prevalence of LH in the general population is increasing due to a variety of non-occupational exposure, e.g. surgery, clothes, food, condoms, sanitary pads, balloons, plaster, etc. Although the study prevalences were lower than the projected figures, the latter could be regarded as a true reflection of the respective populations.

5.3. OCCUPATIONAL EXPOSURE

All subjects in the experimental group were regularly exposed to latex, as opposed to only 4% of the control group, who only experienced occasional exposure, e.g. rubber kitchen gloves. In the LH positive group, 88.5% wore gloves on a daily basis. A highly significant correlation between the wearing of latex gloves and positive latex results was demonstrated when the experimental group was compared to the control group ($p = 0.0009$). This confirms the importance of exposure as a major contributing factor in the development of LH.

The questionnaire proved to be a satisfactory screening tool for LH. Of the patients who thought they were allergic ($n = 14$) or was not sure ($n = 28$), 48% ($n = 20$) were confirmed to be LH positive. However, it should not be seen as the ultimate screening method for LH, as some leading questions could not be avoided. Patients might also have been biased while completing the form, e.g. 12 of 20 patients (60%) who thought they were allergic or reported work-related symptoms, were negative on both *in vitro* and SPT.

When assessing patients with possible LH, the questionnaire could be used together with the calculated allergy score (refer to Chapter 3) and primary and / or secondary criteria for atopic eczema (Hanifin & Rajka, 1980; Mar & Marks, 1999). Specific prominent criteria were statistically confirmed in this study (Table 22). Additional information from the patient

should always be considered, e.g. suspicion of LH (which was confirmed by an odds ratio of 12.67), work-related symptoms and primary allergies to food known to cross-react with latex. This method may limit the possibility of anaphylaxis or any other untoward reaction when patients are exposed to latex occupationally or by means of SPT.

Table 22: Prominent Clinical Findings in Patients with Latex Hypersensitivity (n = 26)

		n	%	p value
Atopy	Personal history	16	61.5	0.020464
	Family history	14	53.8	0.218172
	Personal and family history	14	53.8	0.280328
Bronchospasm		11	42.3	0.000210
Conjunctivitis		19	73.1	0.000003
Cutaneous pallor		5	19.2	0.017697
Dennie Morgan lines		13	50.0	0.014630
Food allergies		7	26.9	0.001927
Hand and foot dermatitis		4	15.4	0.000073
Hand eczema		18	69.2	0.000000
Photosensitivity		7	26.9	0.004282
Pruritus		16	61.5	0.000280
Shortness of breath		6	23.1	0.014209
Skin rash		14	53.8	0.000325
Urticaria		7	26.9	0.020095

Similarly, the allergy score should not be used independently in deciding when to use *in vitro* latex-specific IgE and when to use SPT for diagnosis. Significant differences in the allergy score were recorded between the experimental and control groups ($p = 0.0003$) and LH positive and negative groups ($p < 0.0001$). Furthermore, the mean values for the *in vitro* positive ($n = 16$) (10.50 ± 7.94) and SPT positive groups ($n = 12$) (9.25 ± 5.40) were higher than the SPT negative group ($n = 13$) (6.77 ± 3.35) and those not subjected to SPT ($n = 86$) (2.86 ± 3.87). However, the ranges of the groups (0-29, 2-19, 2-14 and 0-15 respectively) and especially the minimum values, did not provide a conclusive platform for such a decision. One should rather look at the severity of the individual symptoms and if they are work-related with possible improvement over weekends or holidays. If there are any indication of life-threatening reactions, such as anaphylaxis or severe bronchospasm, it is advisable to rather use the *in vitro* method. Furthermore, it is noteworthy that 7 of the 11 predefined LH symptoms, i.e. bronchospasm, conjunctivitis, hand eczema, pruritus, shortness of breath, skin rash and urticaria, were significantly higher in the LH positive

than LH negative groups. The selection of these symptoms could thus be regarded as representative for the evaluation of the condition.

5.4. ATOPY CRITERIA

Atopic eczema is an exaggerated cutaneous immune response to environmental antigens. Patients with this disorder have a humoral response characterised by IgE antibodies associated with T-cells that produce Th_2 cytokines. Allergen-specific T-cells in patients with atopic eczema are preferentially induced to develop into cutaneous lymphocyte antigen (CLA) positive T-cells producing Th_2 cytokines. CLA positive CD 4 memory T-cells specific to allergens are found in blood from patients with atopic eczema. Although these cells are intermediately involved in the final production of atopic eczema, Th_2 cytokine production promote growth and activate dendritic cells, lead to IgE production and a reduction in cell mediated immunity (Robert & Kupper, 1999).

Clinical assessment of atopic eczema has improved since the publications of Rajka (1975), Rajka & Langeland (1989) and Hanifin & Rajka (1980). A set of primary and secondary criteria had been used to grade atopic eczema (Costa *et al,* 1989). This led to the development of the ADSI (Atopic Dermatitis Severity Index) (De Rie *et al,* 1991). Refined by Bahmer & Schubert (1991), the area of cutaneous involvement was calculated using a grid technique with the severity of itching. Numerous other scoring systems for atopic dermatitis are available, e.g. SASSAD Index (Six-Area, Six-Sign, Atopic Dermatitis), ADASI (Atopic Dermatitis Area and Severity Index), Rajka and Langeland Scoring System, SSS (Simple Scoring System), BCSS (Basic Clinical Scoring System), SIS (Skin Intensity Score) and ADAM (Atopic Dermatitis Assessment Measure) (Charman & Williams, 2000). These clinical assessment modules make it possible to compare different publication results. At present the Working Party assessment module and the EASI (Eczema Area and Severity Index) clinical assessment programs are extensively used, although both have limitations.

Patients in the current study were evaluated for atopy according to the guidelines published by Hanifin & Rajka (1980) and Mar & Marks (1999). However, when rigorously applying the Hanifin criteria, requiring 3 primary criteria (e.g. pruritus, flexural lichenification, chronic dermatitis and personal or family history of atopy), in combination with 3 or more secondary criteria, the group was insignificantly small. Only 24 patients fulfilled the 3 primary criteria alone and a mere 17 had a combination of 3 primary and 3 secondary criteria for atopy. It was therefore decided to use the less stringent criteria of

Mar & Marks (1999) in order to compile a group, unique for atopy. In the study group, a total of 64 patients had pruritus, the primary criterion, and 3 or more secondary criteria for atopy and these patients formed the atopy group. This group was not statistically compared to any of the other groups and only frequencies within the group are reported. Forty-three patients (67%) were in the experimental group and 21 (33%) in the control group. Although only 23 (36%) atopic patients were LH positive, 23 of 26 (89%) LH positive patients were atopic. The finding most frequently reported in the atopy group was xeroderma in 45 patients (70%). This was followed by a personal history of atopy in 43 (67%) patients, conjunctivitis in 38 (59%), nasal congestion in 37 (58%), rhinitis and family history of atopy in 36 each (56%), pruritus and skin rash in 35 each (55%), hay fever in 34 (53%), Dennie Morgan lines in 33 (52%), hand eczema in 32 (50%) and a combination of personal and family history of atopy in 28 (44%). Only 22 (34%) patients in this group had elevated serum IgE values when compared to the individual reference ranges for the different ethnic groups. The mean allergy score for this group was 8.00 ± 5.67, which was lower than that of the LH positive group and higher than the LH negative group, but the range (0-29) was once again inconclusive.

No distinct clinical or laboratory features could be identified in the atopy group to distinguish it from any of the other groups in the study. The current findings supported the theories of Moneret-Vautrin *et al* (1993) that a combination of exposure and atopy considerably increases the risk of LH, and that of Lebenbom-Mansour *et al* (1997) that atopy might be predisposing factor for LH, rather than an independent risk factor. The 89% frequency of atopy among the LH positive group, was comparable with several other investigators who reported 60-80% frequency (Heese *et al,* 1992; Pecquet *et al,* 1990; Turjanmaa, 1987). The current study found that 69% of LH positive patients had hand eczema, compared to the 60% in a Finnish survey published by Turjanmaa (1987).

When assessing personal or family history of atopy as individually, the LH positive group reported a 62% personal history of atopy (6/26 eczema, 4/26 asthma, 11/26 hay fever and 4/26 rhinitis), compared to 45% in the experimental group (13/75 eczema, 7/75 asthma, 27/75 hay fever and 6/75 rhinitis) and 36% in the control group (2/50 eczema, 2/50 asthma, 14/50 hay fever and 3/50 rhinitis). The prevalence of family history of atopy alone did not seem to be very important and was present in 54%, 40% and 48% in the three groups respectively. However, although not statistically significant ($p = 0.280328$), a combination of personal and family history of atopy were present at a much higher

percentage in the LH positive group (14/26, 54%) than in the experimental (29%) or control groups (18%).

Pruritus was a significant feature in the LH positive group ($p = 0.00028$) where 16 of 26 patients (61.5%) confirmed symptoms.

Secondary criteria confirmed in the LH positive group include food intolerance, hand and foot dermatitis, conjunctivitis and Dennie Morgan lines. Significantly more LH positive than LH negative patients reported food ($n = 7$, $p = 0.0019$) and other allergies ($n = 8$, $p = 0.0021$). Hand and foot dermatitis was present in 4/26 LH positive patients ($p = 0.000073$) and conjunctivitis was present in 19/26 patients ($p = 0.000003$). Dennie Morgan lines was reported in 13 (50%) of the LH positive patients ($p = 0.014630$). Although not statistically significant ($p = 0.0667$), xeroderma was the most prominent atopic feature in 62% of the LH positive group.

Hand eczema is an important factor in the course of LH and is very often one of the first and most cumbersome symptoms as well. Different reasons could be postulated for this. A pre-existing hand eczema, as seen in most atopic patients, implies a disrupted skin barrier, facilitating percutaneous absorption of latex proteins from gloves. The mechanical irritation of gloves on eczematous lesions, will undoubtedly aggravate the existing condition, leading to accelerated absorption. Even when hand eczema is not a pre-existing condition, scrubbing of hands with harsh antiseptic solutions before putting on gloves, which is standard practise for HCW, can compromise the skin barrier. Moreover, hands are never completely dry when putting on gloves and together with the production of sweat within the gloves, a very wet and humid environment quickly arises. Most latex allergens are soluble C-serum proteins and this humid environment within gloves will promote absorption of these allergens.

Hand eczema is usually a manifestation of an acute phase type I hypersensitivity reaction, with the subsequent production of inflammatory cytokines by neutrophils, macrophages and plasma cells. However, it can also present as part of a chronic late phase reaction, initiated by T-cells and mediated by lymphokines (Chapel & Haene, 1993). This reaction is characterised by a dense cellular infiltrate and is more oedematous than the early reaction. More research is warranted to clarify the exact mechanisms, and sophisticated techniques, such as *in situ* hybridisation, could be utilised. Assessment of the skin barrier function could be done, using transepidermal water loss (TEWL) technology.

ACD is a T-cell dependent skin disease with the kinetics of delayed type hypersensitivity response. Offending antigens are introduced epicutaneously leading to a cascade of reactions that include dendritic cells and CLA positive T-cells. The present system could therefore be modified to study the cytokine and dendritic cascade during the production of allergic contact dermatitis (Robert & Kupper, 1999).

The role of T-cells in chronic reactions to LH has not been clarified. It is difficult to understand why the present group of patients, although showing low grade atopy of skin surfaces, presented only with hand eczema. Results however show that memory T-cells appear to remember the anatomical sight where they first encountered antigen. There is a identifiable subgroup of memory T-cells with the ability to circulate preferentially to the skin. These memory T-cells are identified by a marker known as CLA. These cells are produced in lymph nodes draining skin and are recruited back to the skin during inflammation. The CLA positive T-cells are implicated in targeted areas of ACD and atopic eczema. T-cells recognise antigens as fragments of macro molecules on antigen presenting cells and migrate to specific areas by the activation of adhesion molecules and chemokines on specialised post-capillary venules (Robert & Kupper, 1999). The complexity of latex molecules could speculatively activate T-cells by binding of class I and class II MHC molecules to peptide antigen fractions of latex, while CD 1 molecules bind the non-peptide antigens of these latex molecules. It would therefore be possible to use an *in vitro* model to evaluate the role of epidermal production of interleukin 1 and tumour necrosis factor α after presentation to latex molecules. Activation of the nuclear factor NF-κ ß pathway and the production of E-selectin and numerous chemokines could be evaluated. Plant-like material, such as latex, further induce Toll-like receptors on T-cells and could play a role in signal transduction of these complex molecules. The role of latex to induce Toll-like receptors and initiate a chemokine cascade should therefore be investigated. This *in vitro* or *in vivo* evaluation system could be developed to identify highly sensitisable latex molecules (Robert & Kupper, 1999; Delves & Riott, 2000a).

5.5. PHYSICAL EXAMINATION

The diastolic blood pressure and pulse rates of the experimental and control groups were within normal reference ranges. The higher systolic blood pressure of the control group should not be regarded as biologically meaningful. It could possibly be explained by the fact that the group was slightly older and definitely more inactive than the experimental group. However, there is no relationship between LH and blood pressure.

5.6. EXPOSURE VIA SURGERY

Reported LH cases have increased dramatically since 1980 and surgical procedures before and after 1980 were recorded separately on the questionnaire. Theoretically, it should have an effect on the development of LH, but the sample size of this study was not large enough to draw any significant conclusion. Other factors should also be considered before meaningful conclusions can be drawn, e.g. site and duration of each procedure, possible concomitant medication such as immunosuppressants, steroids or H_1 / H_2 blockers, etc.

5.7. SPECIAL INVESTIGATIONS

The full blood counts served as a parameter of overall health. Isolated abnormal values were found, mostly decreased haemoglobin or haematocrit values, suggestive only of slight anaemia and / or iron deficiency. These values were not group-specific and patients were followed up and treatment was instituted. The platelet count was significantly higher in the LH positive than LH negative group ($p = 0.0182$) and it could be ascribed to a chronic, underlying inflammation, infection or irritation of the respiratory tract (Griesshammer *et al,* 1999), which is common in conditions such as LH. However, it would not seem as if any individual haematological parameter or combination plays a role in the development or course of LH. An interesting finding in this study was the marginally decreased, although not statistically significant ($p = 0.213$), mean basophil count of the LH positive group. While the mean values of the rest of the haematogram were well within the individual normal parameters, almost 50% of the group had individually decreased basophil values with a mean value equal to the lower limit of the reference range. One can speculate that the release of histamine from basophils, caused by latex-specific IgE degranulation in this group, could have been a contributing factor thus leading to lower basophil numbers.

The plasma viscosity value of a patient reflects the level of proteins and acute phase molecule production at a specific stage of a disease. The few elevated values were marginal and it is not possible to draw any meaningful conclusion from that. Although it was statistically higher in the experimental than control group ($p = 0.0191$), no difference was noted between the LH positive and negative groups. The reason can be twofold. Firstly, plasma viscosity is not significantly influenced by a condition such as LH. Secondly, no patient was in an acute stage of the disease at the time of testing.

The gene for atopy is believed to be on the long arm of chromosome 11 (Chapel & Haene, 1993). An elevated serum IgE level usually implies a familial tendency to produce high levels of IgE antibodies against one or more common allergens. Twenty-two of 64 (34%) patients in the atopy group had elevated IgE levels when measured against the normal values for the individual ethnic groups. In the study group, only 7 of the 29 patients (24%) with elevated total serum IgE levels were LH positive. The mean total serum IgE value of the LH positive group was also higher than that of the experimental and control groups. However, it was still within the normal reference range and no statistical differences could be demonstrated. The independent value of the total IgE in the current study was questionable, because it was not a clear indicator for atopy or LH. It can also not be linked to the value of latex-specific IgE and the elevated IgE levels in these 7 LH positive patients may indicate atopy, rather than allergy.

5.8. LATEX-SPECIFIC IgE

Two reactions to latex were identified in the present research group. These were a type I hypersensitivity, mediated by the IgE mast cell system, and a type IV T-cell mediated reaction. When B-cells undergo terminal differentiation into plasma cells, they acquire the ability to produce and secrete high levels of antibodies. Pre-primed latex-specific IgE is available intravascularly and on mast cells in the extravascular space. This study identified IgE molecules against latex in the intravascular component. It is noteworthy that most of the body's IgE is found outside the vascular system. This could explain the patients with low or negative latex-specific IgE in serum, but positive SPT. The mast cell degranulation process leads to acute phase reactions in the respiratory, gastrointestinal and skin systems. Patients who had positive SPT showed acute urticarial reactions with significant late phase reactions still present after 24 hours. Latex application to dermal skin could be used as an *in vivo* model to identify the acute phase reaction and late phase mediators in these patients. Alternatively the role of the complement system, classically triggered by protein molecules, should be investigated to clarify this secondary system during the urticarial reaction of latex sensitive patients.

The *in vitro* test for latex-specific IgE is a rather expensive method, but was chosen because of the potential danger of exposing an already sensitised patient to latex by means of SPT. According to the manufacturer, this method is 97% sensitive and 81% specific (Weiss, 1995). It is safe for the patient, easy to perform and produces absolute values with definite reference ranges. However, it measures IgE-mediated latex sensitivity

and not irritation or delayed reaction to latex. Patients with only type IV allergy to latex would be likely to have a negative *in vitro* latex-specific IgE test result. This was possibly the reason why 12 *in vitro* negative patients had positive SPT results in the current study, and does not necessarily reflect a decreased sensitivity with this method. No direct correlation was found between the severity of symptoms and latex-specific IgE. Anaphylaxis can also occur in patients with marginally elevated values.

5.9. RAST FOR CROSS-REACTIVE FOODS

Due to financial constraints, RAST for cross-reactive foods were only done on *in vitro* positive patients. A selection was made, which was representative of previously reported cross-reactions (see Table 7), and only those were tested. For all the individual tests, at least 28.6% of the *in vitro* positive patients already have antibodies against these foods, although clinical symptoms may be absent.

When evaluating a patient, a history of food allergies in general may be a very good indicator of possible LH ($p = 0.001927$ in LH positive group). Allergies or sensitivity to specific food, as depicted in Table 7, undoubtedly warrant further investigation. Because specific latex proteins are present in cross-reactive food, possibly as a result of wound-repair or defence-related proteins, a primary food allergy to one of these can result in LH.

CHAPTER VI

Conclusions

Hypersensitivity to latex is a very serious problem world-wide and it cannot be ignored. The production of latex-specific IgE is a cumulative process. Therefore, LH and subsequent sensitisation to latex proteins are not reversible processes. The only way of preventing further sensitisation is to avoid exposure of any kind to latex proteins. This can either be achieved by totally eliminating latex from the environment (latex-free environment), or by producing latex products of such quality that no leachable proteins are present in the final product (latex-safe environment).

However, the reality is that latex exposure over the past 20 years has definitely left its mark on society. One of the important observations in this study was that certain individuals already have high latex-specific IgE concentrations without realising it, and it is possible that their next exposure to latex proteins might be fatal. Fortunate individuals might never develop any symptoms or encounter any untoward reaction to latex, but there are definitely those who will react against, or might even die as a result of latex proteins.

Until the ultimate goal of creating a latex-safe environment is realised, it is imperative to manage the current problems. At least 20 years of intensive research made it possible to compile guidelines to enable the clinician, or even the informed patient, to recognise various warning signs of possible LH. Application of these guidelines in a clinical setting should undoubtedly contribute to limit adverse reactions and subsequent sensitisation to latex, not only in HCW, but also in all patients.

6.1. WHAT TO LOOK FOR WHEN EVALUATING PATIENTS WITH POSSIBLE LATEX HYPERSENSITIVITY

- Occupational latex exposure (e.g. HCW) or frequent mucosal contact with latex (e.g. surgical or dental procedures)
- Personal and / or family history of atopy
- Clinical manifestations as identified in Table 22 (page 73)
- Elevated allergy score or progressively worsening symptoms
- Hand eczema, caused or aggravated by wearing latex gloves

- Xeroderma and dishydrosis
- Work-related symptoms in persons working with latex
- Upper respiratory symptoms or aggravation thereof in the presence of latex gloves, due to airborne allergens on glove powder
- Food allergies, especially those known to cross-react with latex (Table 7, page 45)
- Other allergies, as part of an overall allergy expression
- Female gender
- Increased latex-specific IgE and / or total IgE
- History of anaphylaxis with latex contact

6.2. FOR THE PATIENT AND / OR CLINICIAN

- All patients should be advised to wear a Medic-Alert disc / bracelet
- Avoid all latex and latex-containing devices (hypoallergenic is **NOT** latex-free!)
- Inform all healthcare providers, e.g. general practitioner, dentist, gynaecologist, anaesthetist, surgeon, hospital, etc.
- Always carry antihistamine, bronchodilator and self-injectable adrenaline for emergencies
- Avoid known cross-reactive food and be alert to any reaction against other food, even if previously unconfirmed as cross-reactive
- All patients, regardless of risk group status, should be questioned about a history of LH
- All high risk patients should be offered testing for LH
- Education about and familiarisation with latex-free alternatives, both in home and work environments
- Inform Commissioner for Occupational Health and follow up at regular intervals
- In case of hospitalisation, clearly identify patient as LH positive
- Procedures on all patients with LH or SB should be performed in a latex-free environment – one in which no latex gloves are used by any personnel, and

where no latex accessories (catheters, adhesives, tourniquets, anaesthesia equipment) can come into direct contact with the patient

- Schedule patient for first on theatre list to limit contamination from other patients
- Pre-treat patient with H_1 and H_2 blockers and steroids if necessary
- Provide private room if possible to limit contamination via glove powder
- Make sure that all masks, intravenous tubing, syringes, catheters, etc., used on the patient are latex-free
- Remove rubber stoppers from multidose vials and draw medication directly from vial
- When in doubt about a patient's LH status, perform a diagnostic test or in an emergency, apply the necessary precautions and handle patient as if LH positive

6.3. GENERAL RECOMMENDATIONS

NRL is ubiquitous and elimination of the use thereof is not a viable option. Latex awareness is currently growing, but the lifestyles of people already suffering from LH have been changed drastically, because LH is neither treatable, nor curable. The only management for a person with LH is total avoidance of all latex. In a hospital setting this is extremely difficult, since more than 50% of hospital devices contain latex (Warshaw, 1988). Latex–free substitutes must be made available to affected persons and manufacturers of latex products should adopt a uniform cautionary statement on the labelling of all latex-containing devices. Since 30 September 1997 the FDA compelled all manufacturers by law to label all latex devices with the statement: "Caution: This product contains NRL which may cause allergic reactions" (ALERT, 1998; Cohen *et al,* 1998).

The strongest therapy approach is to inform patients well through detailed counselling and guidance.

Unfortunately, the cost of latex-free gloves makes total elimination of latex, especially in high exposure areas such as laboratories and theatres, not a viable option. Other temporary safety measures can be instituted, e.g. changing the electrostatic charge of all wall and working surfaces in high exposure areas and regular testing and cleaning of air and extractor filters. The ultimate goal still remains prevention of exposure to latex and subsequent sensitisation.

6.4. FURTHER RESEARCH

- Acute phase vs late phase hypersensitivity reactions
- The role of cytokines, lymphokines, T-cells and interleukins in the acute and late phase hypersensitivity processes
- Contact urticaria as part of LH with release of specific inflammatory mediators
- TEWL as an indicator of xeroderma and / or atopy
- Transepidermal permeability of specific latex proteins
- Identification of protein bands in specific food and latex products
- The role of histamine and histidine in cross-reactive foods
- Possible contamination of airconditioning and extractor systems via glove powder

BIBLIOGRAPHY

1. Agner T, Dam P, Skouby SO. *Menstrual cycle and skin reactivity.* **J Am Acad Dermatol 1991;24:4:566-570.**

2. Akasawa A, Hsieh L-S, Lin Y. *Serum reactivities to latex proteins (Hevea brasiliensis).* **J Allergy Clin Immunol 1995;95:1196-1205.**

3. Akasawa A, Hsieh L-S, Lin Y. *Comparison of latex-specific IgE binding among non-ammoniated latex, ammoniated latex, and latex glove allergenic extracts by ELISA and immunoblot inhibition.* **J Allergy Clin Immunol 1996;97:1116-1120.**

4. Alenius H, Turjanmaa K, Palosuo T, Mäkinen-Kiljunen S, Reunala T. *Surgical latex glove allergy: characterization of rubber protein allergens by immunoblotting.* **Int Arch Allergy Appl Immunol 1991;96:376-380.**

5. Alenius H, Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Palosuo T. *IgE immune response to rubber proteins in adult patients with latex allergy.* **J Allergy Clin Immunol 1994;93:859-863.**

6. Alenius H, Kalkkinen N, Reunala T, Turjanmaa K, Palosuo T. *The main IgE-binding epitope of a major latex allergen, prohevein, is present in its N-terminal 43-amino acid fragment, hevein.* **J Immunol 1996;156:1618-1625.**

7. Añibarro B, García-Ara MC, Pascual C. *Associated sensitization to latex and chestnut.* **Allergy 1993;48:130-131.**

8. Archer BL. *The proteins of Hevea brasiliensis latex.* **Biochem J 1960;75:236-240.**

9. Arreguin B, Lara P, Rodríguez R. *Comparative study of electrophoretic patterns of latex proteins from clones of Hevea brasiliensis.* **Electrophoresis 1988;9:323-326.**

10. Axelsson JGK, Johansson SGO, Wrangsjö K. *IgE-mediated anaphylactoid reactions to rubber.* **Allergy 1987;42:46-50.**

11. Bahmer FA, Schubert HJ. *Quantification of the extent and severity of atopic dermatitis: the ADASI score.* **Arch Dermatol 1991;127:1239-1240.**

12. Baur X, Jäger D. *Airborne antigens from latex gloves.* **Lancet 1990;335:912.**

13. Baur X, Ammon J, Chen Z, Beckmann U, Czuppon AB. *Health risk in hospitals through airborne allergens for patients presensitised to latex.* **Lancet 1993;342:1148-1149.**

14. Beezhold D, Beck WC. *Surgical glove powders bind latex antigens.* **Arch Surg 1992;127:1354-1357.**

15. Beezhold D. *Measurement of latex proteins by chemical and immunological methods.* **Regent Review 1993;1:1:1-4.**

16. Beezhold DH, Kostyal DA, Wiseman J. *The Transfer of Protein Allergens From Latex Gloves.* **AORN Journal 1994a;59:3:605-613.**

17. Beezhold DH, Sussman GL, Kostyal DA, Chang N-S. *Identification of a 46-kD latex protein allergen in healthcare workers.* **Clin Exp Immunol 1994b;98:408-413.**

18. Beezhold DH, Sussman GL, Liss GM, Chang N-S. *Latex allergy can induce clinical reactions to specific foods.* **J Clin Exp Allergy 1996;26:416-422.**

19. Belsito DV. *Contact urticaria caused by rubber. Analysis of seven cases.* **Dermatol Clin 1990;8:1:61-66.**

20. Beuers U, Baur X, Schraudolph M, Richter WO. *Anaphylactic shock after game of squash in atopic woman with latex allergy.* **Lancet 1990;335:1095.**

21. Bowles DJ. *Defense-related proteins in higher plants.* **Ann Rev Biochem 1990;59:873-907.**

22. Brehler R, Kolling R, Webb M, Wastell C. *Glove powder – a risk factor for the development of latex allergy?* **Eur J Surg 1997a;Suppl 579:23-25.**

23. Brehler R, Tehissern U, Mohr C, Luger T. *"Latex-fruit syndrome": frequency of cross-reacting IgE antibodies.* **Allergy 1997b;52:404-410.**

24. Bubak ME, Reed CE, Fransway F, Yunginger JW, Jones RT, Carlson CA, Hunt LW. *Allergic reactions to latex among health-care workers.* **Mayo Clin Proc 1992;67:1075-1079.**

25. Büyüköztürk S, Kardeş, Erden S, Çolakoglu B, Dal M, Akkor A. *Latex allergy in a glove plant.* **Allergy 2000;55:2:196-197.**

26. Carrillo T, Cuevas M, Muñoz T, Hinojosa M, Moneo I. *Contact urticaria and rhinitis from latex surgical gloves.* **Contact Dermatitis 1986;15:69-72.**

27. Chambeyron C, Dry J, Leynadier F, Pecquet C, Thao TX. *Study of the allergenic fractions of latex.* **Allergy 1992;47:92-97.**

28. Chapel H, Haene M. *Techniques in Clinical Immunology.* **In: Essentials of Clinical Immunology. 3rd Edition. Eds: Blackwell Scientific Publications. 1993.**

29. Charman C, Williams H. *Outcome measures of disease severity in atopic dermatitis.* **Arch Dermatol 2000;136:763-769.**

30. Chen Z, Cremer R, Baur X. *Latex allergy correlates with operation.* **Allergy 1997a;52:8:873.**

31. Chen Z, Posch A, Lohaus C, Raulf-Heimsoth M, Meyer HE, Baur X. *Isolation and identification of hevein as a major IgE-binding polypeptide in hevea latex.* **J Allergy Clin Immunol 1997b;99:402-409.**

32. Cilliers J. *Atopic dermatitis – new perspectives in clinical assessment.* **Int J Dermatol 1993;32:12:860-862.**

33. Cohen DE, Scheman A, Stewart L, Taylor J, Pratt M, Trotter K, Prawer S, Warshaw E, Rietschel R, Watsky K, Schwarzenberger K, Zug K, Shama S, Godwin L, Kosann MK, Wilson BA. *American Academy of Dermatology's position paper on latex allergy.* **J Am Acad Dermatol 1998;39:98-106.**

34. Committee report. *Task force on allergic reactions to latex.* **J Allergy Clin Immunol 1993;92:16-18.**

35. Costa C, Rilliet A, Nicolet M, Saurat JH. *Scoring atopic dermatitis: The simpler the better?* **Acta Derm Venereol Suppl 1989;69:1:41-45.**

36. Cronin E. *Rubber.* In: **Contact Dermatitis. Churchill Livingstone 1980:714-770.**

37. Czuppon AB, Chen Z, Rennert S, Engelke T, Meyer HE, Heber M, Baur X. *Allergens, IgE, mediators, inflammatory mechanisms. The rubber elongation factor of rubber trees (Hevea brasiliensis) is the major allergen in latex.* **J Allergy Clin Immunol 1993;92:690-697.**

38. Delves PJ, Roitt IM. *Advances in immunology: The immune system. Part I.* **New Engl J Med 2000a;343:37-49.**

39. Delves PJ, Roitt IM. *Advances in immunology: The immune system. Part II.* **New Engl J Med 2000b;343:108-117.**

40. Dennis MS, Henzel WJ, Bell J, Kohr W, Light DR. *Amino acid sequence of rubber elongation factor protein associated with rubber particles in Hevea latex.* **J Biol Chem 1989a;264:31:18618-18626.**

41. Dennis MS, Light DR. *Rubber elongation factor from Hevea brasiliensis. Identification, characterization and role in rubber synthesis.* **J Biol Chem 1989b;264:31:18608-18617.**

42. D'Epiro NW. *Latex allergy: potentially disabling.* **Patient Care 1995;Feb 15:32-41.**

43. De Rie MA, Meinardi MM, Bos JD. *Lack of efficacy of topical cyclosporin A in atopic dermatitis and allergic contact dermatitis.* **Acta Derm Venereol 1991;71:5:452-454.**

44. Downing JG. *Dermatitis from rubber gloves.* **New Engl J Med 1933;208:4:196-198.**

45. Ellis H. *The hazards of surgical glove dusting powders.* **Surg Gynecol Obstet 1990;171:521-527.**

46. Ellis H. *Hazards from surgical gloves.* **Ann R Coll Surg Engl 1997;79:161-163.**

47. Fisher AA. *Contact urticaria and anaphylactoid reaction due to cornstarch surgical glove powder.* **Contact Dermatitis 1987;16:224-225.**

48. Fisher AA. *Standard and special tests for the barrier integrity of medical gloves. Part 1: The use and abuse of vinyl gloves by health care workers allergic to latex.* **Cutis 1997a;59:61-62.**

49. Fisher AA. *The diagnosis and management of health personnel allergic to natural rubber latex gloves. Part II.* **Cutis 1997b;59:168-170.**

50. Forster J. *The hazards of working in health care.* **Patient Care 1996;Feb 15:94-98.**

51. Fuchs T. *Latex allergy.* **J Allergy Clin Immunol 1994;93:5:951-952.**

52. Fuchs T, Spitzauer S, Vente C, Hevler J, Kapiotis S, Rumpold H, Kraft D, Valenta R. *Natural latex, grass pollen, and weed pollen share IgE epitopes.* **J Allergy Clin Immunol 1997;100:356-364.**

53. Garred P, Vage DI, Mollnes TE, Harboe M. *Latex gloves as a cause of inflammation and eczema.* **Lancet 1990;335:1469.**

54. Giercksky K-E. *Misdiagnosis of cancer due to multiple glove powder granulomas.* **Eur J Surg 1997;Suppl 579:11-14.**

55. Griesshammer M, Bangerter M, Sauer T, Wennauer R, Bergmann L, Heimpel H. *Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count.* **J Int Med 1999;245:295-300.**

56. Grote M, Mahler V, Spitzauer S, Fuchs T, Valenta R, Reichelt R. *In situ localization of latex allergens in 3 different brands of latex gloves by means of immunogold field emission*

scanning and transmission electron microscopy. **J Allergy Clin Immunol 2000;105:561-569.**

57. Grzybowski M, Ownby DR, Peyser PA, Johnson CC, Schork MA. *The prevalence of anti-latex IgE antibodies among registered nurses.* **J Allergy Clin Immunol 1996;98:535-544.**

58. Guin JD. *The doctor's surgical / examination gloves – Problems with and without them.* **Int J Dermatol 1992;31:12:853-855.**

59. Gurman RW, Siu S, Sussman GL. *Latex allergy: cost to the health care system.* **Source to Surgery 1995;3:12.**

60. Hadjiliadis D, Khan K, Tarlo SM. *Skin test responses to latex in an allergy and asthma clinic.* **J Allergy Clin Immunol 1995;96:431-432.**

61. Hadjiliadis D, Banks DE, Tarlo SM. *The relationship between latex skin prick test responses and clinical allergic responses.* **J Allergy Clin Immunol 1996;97:1202-1206.**

62. Hamilton RG, Adkinson NF. *Natural rubber latex skin testing reagents: Safety and diagnostic accuracy of non-ammoniated latex, ammoniated latex, and latex rubber glove extracts.* **J Allergy Clin Immunol 1996;98:872-883.**

63. Hanifin JM, Rajka G. *Diagnostic features of atopic dermatitis.* **Acta Dermatovener (Stockholm) Suppl 1980;92:44-47.**

64. Heese A, Van Hintzenstern J, Peters K-P, Koch HU, Hornstein OP. *Allergic and irritant reactions to rubber gloves in medical health services. Spectrum, diagnostic approach, and therapy.* **J Am Acad Dermatol 1991;25:831-839.**

65. Heese A, Peters K-P, Koch HU. *Type I allergies to latex and the aeroallergenic problem.* **Eur J Surg 1997;Suppl 579:19-22.**

66. Heilman DK, Jones RT, Swanson MC, Yunginger JW. *A prospective, controlled study showing that rubber gloves are the major contributor to latex aeroallergen levels in the operating room.* **J Allergy Clin Immunol 1996;98:325-330.**

67. Holme SA, Lever RS. *Latex allergy in atopic children.* **Br J Dermatol 1999;140:919-921.**

68. Hunt LW, Fransway AF, Reed CE, Miller LK, Jones RT, Swanson MC, Yunginger JW. *An epidemic of occupational allergy to latex involving health care workers.* **J Occup Environ Med 1995;37:10:1204-1209.**

69. Hunt LW, Boone-Orke JL, Fransway AF, Fremstad CE, Jones RT, Swanson MC, McEvoy MT, Miller LK, Majerus ET, Luker PA, Scheppmann DL, Webb MJ, Yunginger JW. *A medical-center-wide, multidisciplinary approach to the problem of natural rubber latex allergy.* **J Occup Environ Med 1996;38:8:765-770.**

70. Jackson WF, Cerio R. *Allergy to drugs.* **In: A Colour Atlas of Allergy. Eds: Wolfe Medical Publications Ltd, 1988.**

71. Jaeger D, Kleinhans D, Czuppon AB, Baur X. *Latex-specific proteins causing immediate-type cutaneous, nasal, bronchial, and systemic reactions.* **J Allergy Clin Immunol 1992;89:759-768.**

72. Jekel PA, Hartman BH, Beintema JJ. *The primary structure of hevamine, an enzyme with lysozyme/chitinase activity from Hevea brasiliensis.* **Eur J Biochem 1991;200:123-130.**

73. Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I. *The influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen.* **Clin Exp Allergy 1995;5:461-466.**

74. Katelaris KC, Widmer RP, Lazarus RM. *Prevalence of latex allergy in a dental school.* **Med J Austr 1996;164:711-714.**

75. Kelly KJ, Kurup VP, Reijula KE, Fink JN. *The diagnosis of natural rubber latex allergy.* **J Allergy Clin Immunol 1994;93:5:813-816.**

76. Kelly KJ. *Stop the sensitization.* **Source to Surgery 1995;3:11-12.**

77. Kelly KJ, Sussman G, Fink JN. *Stop the sensitization.* **J Allergy Clin Immunol 1996;98:857-858.**

78. Konrad C, Fieber T, Gerber H, Schuepfer G, Muellner G. *The prevalence of latex sensitivity among anesthesiology staff.* **Anesth Analg 1997;84:629-633.**

79. Kostyal DA, Kickey, VL, Noti JD, Sussman GL, Beezhold DH. *Cloning and characterization of a latex allergen (Hev b 7): homology to patatin, a plant PLA_2.* **Clin Exp Immunol 1998;112:355-362.**

80. Kurup VP, Kumar A, Kelly KJ, Fink JN. *Characterization of a monoclonal antibody against latex protein associated with latex allergy.* **J Allergy Clin Immunol 1993;92:638-643.**

81. Lagier F, Baier M, Martigny J, Charpin D, Vervloet D. *Latex as aeroallergen.* **Lancet 1990;336:516-517.**

82. Lagier F, Vervloet D, Lhermet I, Poyen D, Charpin D. *Prevalence of latex allergy in operating room nurses.* **J Allergy Clin Immunol 1992;90:3:319-322.**

83. Latex allergy: *Prevention and Management in the Workplace.* **Surveillance of Occupational Respiratory Diseases in South Africa ALERT:September 1998.**

84. Laurent J, Malet R, Smiejan JM, Madelenat P, Herman D. *Latex hypersensitivity after natural delivery.* **J Allergy Clin Immunol 1992;89:3:779-780.**

85. Lavaud F, Prevost A, Cossart C, Guerin L, Bernard J, Kochman S. *Allergy to latex, avocado pear, and banana: Evidence for a 30 kD antigen in immunoblotting.* **J Allergy Clin Immunol 1995;95:557-564.**

86. Lebenbom-Mansour MH, Oesterle JR, Ownby DR, Jennett MK, Post SK, Zaglaniczy K. *The incidence of latex sensitivity in ambulatory surgical patients: a correlation of historical factors with positive serum immunoglobulin E levels.* **Anest Analg 1997;85:44-49.**

87. Levy DA, Charpin D, Pecquet C, Leynadier F, Vervloet D. *Allergy to latex.* **Allergy 1992;47:579-587.**

88. Light DR, Dennis MS. *Purification of a prenyltransferase that elongates cis-polyisoprene rubber from the latex of Hevea brasiliensis.* **J Biol Chem 1989;264:31:18589-18597.**

89. Lipozencic J, Milavec-Puretic V, Štulhofer Buzina D, Kotrulja L, Sajatovic B. *Allergy to latex in Croatia.* **Allergy 1998;53:43:52 (Abst P127).**

90. Lu L, Kurup VP, Hoffman DR, Kelly KJ, Murali PS, Fink JN. *Characterization of a major latex allergen associated with hypersensitivity in spina bifida patients.* **J Immunol 1995;155:2721-2728.**

91. Lundberg M, Wrangsjö K, Johansson SGO. *Latex allergens in glove-powdering slurries.* **Allergy 1995;50:378-380.**

92. Lundberg M, Wrangsjö K, Van Hage-Hamsten M. *Diagnosis of latex allergy.* **Allergy 1997;52:1042-1043.**

93. Lyttle L. *Are your workers allergic to latex?* **Journal of the Ontario Occupational Health Nurses Association 1994:27-28.**

94. M'Raihi L, Charpin D, Pons A, Bongrand P, Vervloet D. *Cross-reactivity between latex and banana.* **J Allergy Clin Immunol 1991;87:129-130.**

95. Maillard H, Machet L, Meurisse Y, Garot D, Toledano C, Jan V, Vaillant L. *Cross-reactivity to latex and spinach.* **Acta Derm Venereol 2000;80:51.**

96. Mäkinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T. *Characterization of latex antigens and allergens in surgical gloves and natural rubber by immunoelectrophoretic methods.* **J Allergy Clin Immunol 1992;90:2:230-235.**

97. Mäkinen-Kiljunen S, Reunala T, Turjanmaa K, Cacioli P. *Is cows' milk casein an allergen in latex-rubber gloves?* **Lancet 1993;342:863-864.**

98. Manjra A. *Anaphylaxis.* **Specialist Medicine 1994;XVI:9:17-24.**

99. Mar A, Marks R. *The descriptive epidemiology of atopic dermatitis in the community.* **Australas J Dermatol 1999;40:75-78.**

100. Marais GI, Fletcher JM, Potter PC. *In vivo and in vitro diagnosis of latex allergy at Groote Schuur Hospital.* **S Afr Med J 1997;87:8:1004-1008.**

101. Marcos C, Lázaro M, Fraj J, Quirce S, De la Hoz B, Fernandez-Rivas M, Losada E. *Occupational asthma due to latex surgical gloves.* **Ann Allergy 1991;67:319-323.**

102. Mazón A, Nieto A, Estornell F, Nieto A, Reig C, García-Ibarra F. *Factors that influence the presence of symptoms caused by latex allergy in children with spina bifida.* **J Allergy Clin Immunol 1997;99:600-604.**

103. McCaskell L. *Protein transfer from using latex gloves.* **The ONA News 1995;13-14.**

104. Miguel AG, Cass GR, Weiss J, Glovsky MM. *Latex allergens in tire dust and airborne particles.* **Environ Health Perspect 1996;104:11:1180-1186.**

105. Moneret-Vautrin D-A, Beaudouin E, Widmer S, Mouton C, Kanny G, Prestat F, Kohler C, Feldmann L. *Prospective study of risk factors in natural rubber latex hypersensitivity.* **J Allergy Clin Immunol 1993;92:668-677.**

106. Newsom SWB, Shaw P. *Airborne particles from latex gloves in the hospital environment.* **Eur J Surg 1997;Suppl 579:31-33.**

107. Nieto A, Estornell F, Mazón A, Reig C, Nieto A, García-Ibarra F. *Allergy to latex in spina bifida: A multivariate study of associated factors in 100 consecutive patients.* **J Allergy Clin Immunol 1996;98:501-507.**

108. Niggeman B. *The prevalence of latex allergy in children seen in a university hospital allergy clinic.* **Allergy 1997;52:670.**

109. Novembre E, Bernardini R, Brizzi I, Bertini G, Mugnaini L, Azzari C, Vierucci A. *The prevalence of latex allergy in children seen in a university hospital allergy clinic.* **Allergy 1997;52:101-105.**

110. Nutter AF. *Contact urticaria to rubber.* **Br J Dermatol 1979;101:597-598.**

111. Ownby DR. *Is rubber elongation factor the major allergen of latex?* **J Allergy Clin Immunol 1993;92:633-635.**

112. Ownby DR, Ownby HE, McCullough J, Shafer AW. *The prevalence of anti-latex IgE antibodies in 1 000 volunteer blood donors.* **J Allergy Clin Immunol 1996;97:1188-1192.**

113. Palczynski C, Walusiak J, Hanke W, Wittczak T, Górski P. *Latex allergy in Polish nurses.* **Allergy 1998;53:43:53 (Abst P131).**

114. Palczynski C, Walusiak J, Ruta U, Gorski P. *Nasal provocation test in the diagnosis of natural rubber latex allergy.* **Allergy 2000;55:34-41.**

115. Pastorello EA, Pravettoni V, Ispano M, Farioli L, Ansaloni R, Rotondo F, Incorvaia C, Åsman I, Bengtsson A, Ortolani C. *Identification of the allergenic components of kiwi fruit and evaluation of their cross-reactivity with timothy and birch pollens.* **J Allergy Clin Immunol 1996;98:601-610.**

116. Pecquet C, Leynadier F, Dry J. *Contact urticaria and anaphylaxis to natural rubber.* **J Am Acad Dermatol 1990;22:4:631-633.**

117. Phillips AM, Birch NC, Ribbans WJ. *Protective gloves for use in high-risk patients: how much do they affect the dexterity of the surgeon?* **Ann R Coll Surg Engl 1997;79:124-127.**

118. Porri F, Pradal M, Rud C, Charpin D, Alazia M, Gouin F, Vervloet D. *Is systematic preoperative screening for muscle relaxant and latex allergy advisable?* **Allergy 1995;50:374-377.**

119. Posch A, Chen Z, Dunn MJ, Wheeler CH, Petersen A, Leubner-Metzger G, Baur X. *Latex allergen database.* **Electrophoresis 1997a;18:2803-2810.**

120. Posch A, Chen Z, Wheeler C, Dunn MJ, Raulf-Heimsoth M, Baur X. *Characterization and identification of latex allergens by two-dimensional electrophoresis and protein microsequencing.* **J Allergy Clin Immunol 1997b;99:385-395.**

121. Potter PC, Berman D, Toerien A, Malherbe D, Weinberg EG. *Clinical significance of aero-allergen identification in the Western Cape.* **S Afr Med J 1991;79:80-84.**

122. Potter PC. *Allergy and the skin.* **Diseases of the Skin 1994a;Oct:5-6.**

123. Potter PC. *Latex allergy – an emerging problem.* **Specialist Medicine 1994b;XVI:9:10-16.**

124. Potter PC. *Latex allergy – wide implications for health care providers.* **Specialist Medicine 1996a;XVIII:8:32-36.**

125. Potter PC. *Latex allergy.* **MIMS Prescribing Power 1996b;3:21a-23a.**

126. Potter PC. *Advances in the understanding of the allergic response.* **Specialist Medicine 1997a;XIX:2:2.**

127. Potter PC. *Update on allergen immunotherapy.* **Specialist Medicine 1997b;XIX:2:4-12.**

128. Potter PC. *Latex allergy – a major problem in South African hospitals.* **Curr Allergy Clin Immunol 1998a;11:1:4-5.**

129. Potter PC. *Latex allergy – a major problem in South African hospitals.* **Professional Nursing Today 1998b;2:2:3-6.**

130. Potter PC. *Latex allergy and the law.* **Curr Allergy Clin Immunol 1998c;11:1:2.**

131. Pretorius I. *The South African Blood Transfusion Service – taking the initiative addressing problems associated with powdered gloves.* **Curr Allergy Clin Immunol 1999;12:1:12.**

132. Pumphrey RSH. *Allergy to Hevea latex.* **Clin Exp Dermatol 1994;98:358-360.**

133. Rajka G. *Atopic dermatitis.* **In: Major problems in Dermatology, Vol 3, 1975. WB Saunders London.**

134. Rajka G, Langeland T. *Grading of the severity of atopic dermatitis.* **Acta Derm Venereol Suppl 1989;144:13-14.**

135. Robert C, Kupper TS. *Inflammatory skin diseases, T-cells, and immune surveillance.* **New Engl J Med 1999;341:24:1817-1828.**

136. Raulf-Heimsoth M, Chen Z, Liebers V, Allmers H, Baur X. *Lymphocyte proliferation response to extracts from different latex materials and to the purified latex allergen Hev b 1 (rubber elongation factor).* **J Allergy Clin Immunol 1996;98:640-651.**

137. Rawlins D, Smith S, Tyndall J. *The unsuspected allergy.* **Canadian Operating Room Nursing Journal 1992;6-9.**

138. Ross BD, McCullough J, Ownby DR. *Partial cross-reactivity between latex and banana allergens.* **J Allergy Clin Immunol 1992;90:3:409-410.**

139. Schnuch A, Uter W, Geier J, Frosch PJ, Rustemeyer T. *Contact allergies in healthcare workers. Results from the IVDK.* **Acta Derm Venereol (Stockh) 1998;78:358-363.**

140. Senna G, Agostini E, Crocco I, Crivellaro M, Dama A, Bonadonna, Caputo M, Roata C, Zanini M, Aprili G. *Latex-specific IgE antibodies in volunteer blood donors: An Italian study.* **Allergy 1998;53:43:51 (Abst P126).**

141. Seppälä U, Palosuo T, Seppälä U, Kalkkinen N, Ylitalo L, Reunala T, Turjanmaa K, Reunala T. *IgE reactivity to patatin-like latex allergen, Hev b 7, and to patatin of potato tuber, Sol t 1, in adults and children allergic to natural rubber latex.* **Allergy 2000;55:266-273.**

142. Siler DJ, Cornish K. *Measurement of protein in natural rubber latex.* **Anal Biochem 1995;229:278-281.**

143. Siler DJ, Cornish K, Hamilton RG. *Absence of cross-reactivity of IgE antibodies from subjects allergic to Hevea brasiliensis latex with a new source of natural rubber latex from guayule (Parthenium argentatum).* **J Allergy Clin Immunol 1996;98:895-902.**

144. Slater JE, Chhabra SK. *Latex antigens.* **J Allergy Clin Immunol 1992a;89:673-678.**

145. Slater JE. *Latex allergy - what do we know?* **J Allergy Clin Immunol 1992b;90:3:279-281.**

146. Slater JE, Trybul DE. *Immunodetection of latex antigens.* **J Allergy Clin Immunol 1994a;93:825-830.**

147. Slater JE. *Latex allergy.* **J Allergy Clin Immunol 1994b;93:139-149.**

148. Smith S, Tyndall J, Young A. *Do you have a Latex Protocol?* **Canadian Operating Room Nursing Journal 1993:26-29.**

149. Spaner D, Dolovich J, Tarlo S, Sussman G, Buttoo K. *Hypersensitivity to natural latex.* **J Allergy Clin Immunol 1989;83:1135-1137.**

150. Sussman GL, Beezhold DH. *Allergy to latex rubber.* **Ann Intern Med 1995;122:43-46.**

151. Sussman GL. *Allergy Session. Chairman's conclusion.* **Eur J Surg 1997;Suppl 579:29-30.**

152. Swanson MC, Bubak ME, Hunt LW, Yunginger JW, Warner MA, Reed CE. *Quantification of occupational latex aeroallergens in a medical center.* **J Allergy Clin Immunol 1994;93:445-451.**

153. Tarlo SM, Wong L, Roos R, Booth N. *Occupational asthma caused by latex in a surgical glove manufacturing plant.* **J Allergy Clin Immunol 1990;85:626-631.**

154. Tarlo SM, Sussman G, Contala A, Swanson MC. *Control of airborne latex by use of powder-free latex gloves.* **J Allergy Clin Immunol 1994;93:985-989.**

155. Tarlo SM, Sussman GL, Holness DL. *Latex sensitivity in dental students and staff: A cross-sectional study.* **J Allergy Clin Immunol 1997;99:396-401.**

156. Taylor JS, Cassettari J, Wagner W, Helm T. *Contact urticaria and anaphylaxis to latex.* **J Am Acad Dermatol 1989;21:4:874-877.**

157. Taylor JS, Praditsuwan P. *Latex allergy. Review of 44 cases including outcome and frequent association with allergic hand eczema.* **Arch Dermatol 1996;132:265-271.**

158. Taylor M. *Cost of latex device-related occupational illness, workmen's compensation and legal issues.* **Eur J Surg 1997;Suppl 579:49-51.**

159. Taylor JS, Wattanakrai P, Charous BL, Ownby DR. *Latex allergy.* **The Year Book of Dermatology and Dermatologic Surgery 1999:1-44.**

160. Terrados S, Blanca M, Justicia JL, Moreno F, Mayorga C. *The presence of latex can induce false-positive skin tests in subjects tested with penicillin determinants.* **Allergy 1997;52:200-204.**

161. Tomazic VJ, Withrow TJ, Hamilton RG. *Allergens, IgE, mediators, inflammatory mechanisms. Characterization of the allergen(s) in latex protein extracts.* **J Allergy Clin Immunol 1995;96:635-642.**

162. Turjanmaa K. *Incidence of immediate allergy to latex gloves in hospital personnel.* **Contact Dermatitis 1987;17:270-275.**

163. Turjanmaa K, Laurila K, Mäkinen-Kiljunen S, Reunala T. *Rubber contact urticaria. Allergenic properties of 19 brands of latex gloves.* **Contact Dermatitis 1988a;19:362-367.**

164. Turjanmaa K, Reunala T, Räsänen L. *Comparison of diagnostic methods in latex surgical glove contact urticaria.* **Contact Dermatitis 1988b;19:241-247.**

165. Turjanmaa K, Reunala T. *Contact Urticaria from Rubber Gloves.* **Dermatol Clin 1988c;6:1:47-51.**

166. Turjanmaa K, Reunala T, Alenius H, Brummer-Korvenkontio H, Palosuo T. *Allergens in latex surgical gloves and glove powder.* **Lancet 1990;336:1588.**

167. Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, Reunala T, Palosuo T. *Natural rubber latex allergy.* **Allergy 1996;51:593-602.**

168. Turjanmaa K, Palosuo T, Alenius H, Leynadier F, Autegarden J-E, André C, Sicard H, Hrabina M, Tran TX. *Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract.* **Allergy 1997;52:41-50.**

169. Turner P. *Latex glove allergy.* **Occup Health (Lond) 1997;49:2:57-60.**

170. Valentine JP, Kurinczuk JJ, Loh RKS, Chauvel PJ. *Latex allergy in an Australian population of children and adolescents with spinal dysfunction.* **Med J Aust 1999;170:15-18.**

171. Van der Bijl P, Van Eyk A, Cilliers J, Stander IA. *Diffusion of water across human skin in the presence of two barrier creams.* **Skin Pharmacol Appl Skin Physiol 2000;13:104-110.**

172. Wakelin SH, White IR. *Natural rubber latex allergy.* **Clin Exp Dermatol 1999;24:245-248.**

173. Walker M. *Rubber trouble. If latex brings you out in a rash try this shrub.* **New Scientist 11 December 1999;9.**

174. Walls RS. *Latex allergy: a real problem.* **Med J Austr 1996;164:707-708.**

175. Warshaw EM. *Latex allergy.* **J Am Acad Dermatol 1998;39:1-24.**

176. Weiss J. *Latex allergy.* **DPC Technical Report 1995:1-7.**

177. White IR. *Setting standards for product selection: Allergy prevention.* **Eur J Surg 1997;Suppl 579:27-28.**

178. Wilkinson SM, Burd R. *Latex: a cause of allergic contact eczema in users of natural rubber gloves.* **J Am Acad Dermatol 1998;38:36-42.**

179. Williams PB, Dolen WK, Koepke JW, Selner JC. *Comparison of skin testing and three in vitro assays for specific IgE in the clinical evaluation of immediate hypersensitivity.* **Ann Allergy 1992;68:35-45.**

180. Wrangsjö K, Mellström G, Axelsson G. *Discomfort from rubber gloves indicating contact urticaria.* **Contact Dermatitis 1986;15:79-84.**

181. Wrangsjö K, Lundberg M. *Prevention of latex allergy.* **Allergy 1996;51:1:65-67.**

182. Yagami T, Sato M, Nakamura A, Shono M. *One of the rubber latex allergens is a lysozyme.* **J Allergy Clin Immunol 1995;96:677-686.**

183. Yeang HY, Cheong KF, Sunderasan E, Hamzah S, Chew NP, Hamid S, Hamilton RG, Cardosa MJ. *The 14.6 kD rubber elongation factor (Hev b 1) and 24 kD (Hev b 3) rubber particle proteins are recognized by IgE from patients with spina bifida and latex allergy.* **J Allergy Clin Immunol 1996;98:628-639.**

184. Yunginger JW, Jones RT, Fransway AF, Kelso JM, Warner MA, Hunt LW. *Extractable latex allergens and proteins in disposable medical gloves and other rubber products.* **J Allergy Clin Immunol 1994;93:836-842.**

185. Zerin JM, McLaughlin K, Kerchner S. *Latex allergy in patients with myelomeningocele presenting for imaging studies of the urinary tract.* **Pediatr Radiol 1996;26:450-454.**

ADDENDUM 1

ETHICAL APPROVAL

UNIVERSITEIT VAN STELLENBOSCH
UNIVERSITY OF STELLENBOSCH

14 Mei 1998

Prof J Cilliers
Departement Dermatologie
TYGERBERGKAMPUS

Geagte prof Cilliers

NAVORSINGSPROJEK: **"HIPERSENSITIWITEIT TEEN LATEX PROTEÏENE IN HOSPITAALWERKERS IN 'N AKADEMIESE HOSPITAAL"**
PROJEKNOMMER: **98/046**

Dit is vir my aangenaam om u mee te deel dat Subkomitee C van die Navorsingskomitee bogenoemde projek goedgekeur het, ook wat die etiese aspekte daarvan betref.

Die projek is nou geregistreer en u kan voortgaan met die werk. U moet asseblief in verdere korrespondensie na bogenoemde projeknommer verwys.

Ek vestig graag u aandag daarop dat pasiënte wat deelneem aan 'n navorsingsprojek in Tygerberg-hospitaal nie gratis behandeling sal ontvang nie aangesien die PAWK nie navorsing finansieël ondersteun nie.

Die verpleegkorps van die Tygerberg-hospitaal kan ook nie omvattende verpleeghulp met navorsingsprojekte lewer nie weens die swaar werkslading waaronder hulle reeds gebuk gaan. Dit kan dus van 'n navorser verwag word om in sulke gevalle privaat verpleegkundiges te verkry.

Die uwe

C J VAN TONDER
ns ADJUNKREGISTRATEUR (TYGERBERGKAMPUS)

CJVT/II

C:\WANTONDER\NAVORSING\NAVCVAFR-GOED97-1.DOC

Cape
Kaapse
Technikon

P.O. Box 652 Cape Town 8000 Keizergracht Cape Town 8001
Posbus 652 Kaapstad 8000 Keizergracht Kaapstad 8001
Tel. (021) 460 3911 Fax (021)

FAX (021) 460-3217

FACULTY OFFICE: NATURAL SCIENCES
FAKULTEITSKANTOOR: NATUURWETENSKAPPE

Life Sciences/Lewenswetenskappe 4603176/4603153
Hotel & Catering/Hotel & Spyseniering 4603176
Mechanical & Process Eng./Meganies & Proses Ing. 4603175

1998-08-20

MS C DE BEER
P O BOX 19065
TYGERBERG
7505

DEAR MS DE BEER

RESEARCH PROJECT FOR THE MASTERS DEGREE: BIOMEDICAL TECHNOLOGY

It is my pleasure to inform you that your Research Project has been approved by the Academic Board of the Technikon.

We would appreciate it if you could complete the attached application form and forward the registration fee of R50,00 as soon as possible (if not already done). I would like to draw your attention to the fact that the abovementioned approval will lapse if you do not register and pay the necessary fees within 12 months of the date of this letter. The fees for the Masters Degree are currently R2 000-00 per annum.

You are advised to keep in touch with your supervisors to ensure that your research is progressing according to plan. Biannual progress reports (preferably typed) must be handed in to your supervisors during May and September. A few copies of this form are included.

Please note that it will be expected of you to hold a seminar on your research to interested members of staff on completion of your dissertation.

We wish you well with your studies.

Yours faithfully

REGISTRAR

PF/hap

ADDENDUM 2

PERMISSION FROM TYGERBERG HOSPITAL MANAGEMENT

ENQUIRIES / NAVRAE: Dr A K M M Rahman
TELEPHONE / TELEFOON: 938-4136
REFERENCE / VERWYSING:
DATE / DATUM: 19 May 1999

PROVINCIAL ADMINISTRATION : WESTERN CAPE
Department of Health
PROVINSIALE ADMINISTRASIE : WES-KAAP
Departement van Gesondheid

Mrs C de Beer
Chief Medical Technologist
Department of Dermatology
TYGERBERG HOSPITAL

LATEX HYPERSENSITIVITY STUDY AT TYGERBERG HOSPITAL

Your letter dated 17 May 1999 refers.

As discussed with Prof J Cilliers on 19 May 1999, permission is granted to continue with the allergy test in the Department of Dermatology as requested.

Please inform this office of your findings and recommendations.

CHIEF MEDICAL SUPERINTENDENT
[rahman/debeer-latex-study]
19.05.99

TYGERBERG HOSPITAAL
Privaatsak X3
Tygerberg 7505
Faks (021) 931 1451

TYGERBERG HOSPITAL
Private Bag X3
Tygerberg 7505
Fax (021) 931 1451

ENQUIRIES
NAVRAE Dr A K M M Rahman
TELEPHONE
TELEFOON 938-4136
REFERENCE
VERWYSING H196/H/14
DATE
DATUM 22 July 1998

PROVINCIAL ADMINISTRATION : WESTERN CAPE
Department of Health
PROVINSIALE ADMINISTRASIE : WES-KAAP
Departement van Gesondheid

Professor J Cilliers
Department of Dermatology
Faculty of Medicine
UNIVERSITY OF STELLENBOSCH

Dear Professor Cilliers

LATEX HYPERSENSITIVITY STUDY

I wish to acknowledge receipt of your letter of 15 July 1998 and advise that you have Management's consent to undertake the Latex Hypersensitivity Study in our hospital as requested.

I will be interested to see the final results of your investigation of this potentially life threatening condition when available.

Yours sincerely

CHIEF MEDICAL SUPERINTENDENT

TYGERBERG HOSPITAAL
Privaatsak X3
Tygerberg 7505
Faks (021) 931 1451

TYGERBERG HOSPITAL
Private Bag X3
Tygerberg 7505
Fax (021) 931 1451

ADDENDUM 3

INFORMED CONSENT

Informed Consent - Latex Hypersensitivity Study

I, the undersigned, ... (name)

of ..... (address)

confirm that:

1. I was invited to take part in a Latex Hypersensitivity Study, conducted by the Department of Dermatology, University of Stellenbosch.
2. I was informed that:
   - 2.1. repeated exposure to latex (e.g. surgical gloves and other medical equipment) can result in the development of a specific allergic reaction due to specific antibodies which form in the blood
   - 2.2. my personal risk profile will be determined by means of:
     - 2.2.1. completion of a questionnaire
     - 2.2.2. clinical examination
     - 2.2.3. special laboratory investigations - dermatoscopy, immunological serum assays (± 20 ml blood) and clinical and histological (3 mm punch biopsy on the medial aspect of the hand) evaluation of the skin barrier function
   - 2.3. the study group will consist of 100 health care workers in Tygerberg Hospital
   - 2.4. a single visit will be necessary for obtaining all the relevant information and specimens
3. I was informed that all the information I supplied will be regarded as strictly confidential, but might be used for possible publications by means of an identification code.
4. If any allergic or other medical condition is identified during this examination, I will be informed immediately to plan treatment or management thereof.
5. I may refuse to participate in the study and such refusal will not in any way influence my current / future treatment at this institution.
6. Participation in this study will not imply any additional costs for myself.
7. If I have any problems or queries, I can contact Prof Jacques Cilliers at Tel 938 5433 (or 938 4911 all hours) or Mrs Corena de Beer at Tel 938 9453.
8. I have read and understand this consent form. My questions have been answered and I voluntarily consent to participate.

.....	.....
(Signature of Volunteer)	(Date)
.....	.....
(Signature of Investigator)	(Date)
.....	.....
(Signature of Witness)	(Date)

ADDENDUM 4

QUESTIONNAIRE

Questionnaire - Latex Hypersensitivity Study

Date: _____ **Patient Name:** _____
Date of Birth: _____ **R/S:** _____
TBH Folder Number: _____

Age: _____ Sex: _____ Occupation: _____

Department: _____ Short job description: _____

Do you use latex **GLOVES?** _____ How many years? _____ Are you allergic to latex? _____

How many hours per week: _____ How many pairs of gloves per week? _____

History of **ATOPY** (Eczema / Asthma / Hay fever / Rhinitis)**:** _____ Family History: _____

ALLERGIES: Drugs _____
Food _____
Other _____

Previous **OPERATIONS (general anaesthesia / epidural / spinal block):** _____
Name all procedures and year: _____
_____
_____

Side effects from anaesthesia: _____

CURRENT SYMPTOMS:	**Absent**	**Mild**	**Moderate**	**Severe**	**Better outside work**	**Duration of symptoms**
Conjunctivitis:	☐	☐	☐	☐	☐	_____
Nasal congestion:	☐	☐	☐	☐	☐	_____
Rhinitis:	☐	☐	☐	☐	☐	_____
Shortness of breath:	☐	☐	☐	☐	☐	_____
Bronchospasm:	☐	☐	☐	☐	☐	_____
Urticaria:	☐	☐	☐	☐	☐	_____
Angioedema:	☐	☐	☐	☐	☐	_____
Anaphylactic shock:	☐	☐	☐	☐	☐	_____
Pruritus:	☐	☐	☐	☐	☐	_____
Skin rash:	☐	☐	☐	☐	☐	_____
Hand eczema:	☐	☐	☐	☐	☐	_____
Other:	☐	☐	☐	☐	☐	_____

ADDENDUM 5

LATEX ALLERGY QUESTIONNAIRE
GROOTE SCHUUR HOSPITAL

GROOTE SCHUUR HOSPITAL

LATEX ALLERGY QUESTIONNAIRE

1. **NAME:** .....

2. **AGE:** ..... years

3. **SEX:**
   Male [ ]
   Female [ ]

4. **DATE OF BIRTH:** .....

5. **WORK LOCATION:**
   Theatre [ ] Specify .....
   Ward [ ] Specify .....
   Laboratory [ ] Specify .....
   Admin [ ] Specify .....
   ICU [ ] Specify .....
   OPD [ ] Specify .....
   Other [ ] Specify .....

6. **NAME OF DEPARTMENT:** .....

7. **JOB DESCRIPTION:**
   Doctor [ ]
   Nursing [ ]
   Technical [ ]
   Paramedical [ ]
   Administrative [ ]
   Cleaning [ ]
   Other [ ] Specify .....

8. **HOW LONG HAVE YOU WORKED AT GROOTE SCHUUR HOSPITAL:** ..... years

9. **WHAT SORT OF WORK DO YOU DO AT GROOTE SCHUUR (1 LINE):**

   .....

10. **GIVE A BRIEF OUTLINE OF YOUR WORKING LIFE – LIST PREVIOUS JOBS AND YEARS OF SERVICE**

11. **HAVE YOU BEEN IN CONTACT WITH RUBBER / LATEX IN ANY OF YOUR PREVIOUS JOBS?**
    Yes [ ]
    No [ ]

12. **WHAT ARE YOUR HOBBIES?**

13. **DO YOUR HOBBIES INVOLVE EXPOSURE TO LATEX / RUBBER? (DESCRIBE)**

14. **DO YOU HAVE ANY OF THE FOLLOWING DISEASES?**
IF SO, TICK THE BOX BELOW:

Asthma	[ ]
Anaphylaxis	[ ]
Seasonal hay fever	[ ]
Insect allergies	[ ]
Eczema	[ ]
Urticaria (hives)	[ ]
Chronic rhinitis	[ ]
Drug allergies	[ ]
Food allergies	[ ]
Swelling of the mouth after eating any foods	[ ]
Conjunctivitis	[ ]
Other occupational allergies	[ ]

15. **ARE YOU ALLERGIC TO ANY OF THE FOLLOWING?**

Kiwi fruit	[ ]
Chestnut	[ ]
Bananas	[ ]
Avocado	[ ]
Latex	[ ]

16. **HAVE YOU EVER HAD ANY SKIN IRRITATION OR SKIN DISEASE RESULTING FROM CONTACT WITH THE WORK ENVIRONMENT?**

Yes	[ ]
No	[ ]

17. **IF ANSWER TO THE ABOVE IS "YES", PLEASE GIVE DETAILS BELOW:**

.....
.....
.....
.....

18. **HAVE YOU EVER BEEN DIAGNOSED AS HAVING AN ALLERGY?**

Yes	[ ]
No	[ ]

19. **IF SO, HAVE YOU EVER HAD SKIN PRICK TESTS OR RAST (BLOOD) TESTS TO INVESTIGATE YOUR ALLERGIES?**

Yes	[ ]
No	[ ]

20. **WHERE WERE THESE TESTS PERFORMED AND WHICH OF THE ABOVE TEST RESULTS WERE POSITIVE?**

.....
.....
.....
.....
.....

21. **DO YOU WEAR RUBBER GLOVESDO YOU WEAR RUBBER GLOVES:**

Yes	[ ]
No	[ ]

22. **IF YES, HOW FREQUENTLY DO YOU WEAR RUBBER GLOVES?**

Every working day during the week	[ ]
Most working days during the week	[ ]
A few working days during the week	[ ]
Infrequently	[ ]
Very infrequently	[ ]
Never	[ ]

23. **ON DAYS THAT YOU WEAR GLOVES, HOW MANY TIMES PER DAY DO YOU CHANGES GLOVES?**

..... times per day

24. **DO YOU WORK IN AN ENVIRONMENT WHERE GLOVES ARE WORN BY OTHER STAFF MEMBERS?**

Yes	[ ]
No	[ ]

25. **DO YOU HAVE ANY OF THE FOLLOWING SYMPTOMS IN THE WORK ENVIRONMENT?**

Itchy eyes	[ ]
Runny or blocked nose	[ ]
Coughing	[ ]
Wheezing	[ ]
Itchy skin	[ ]
Skin rashes	[ ]
Dizziness	[ ]

26. **IF SO, TICK THE CORRECT BOX BELOW:**

(Specify symptoms and indicate how often you get them)

Often	[ ]
Sometimes	[ ]
Occasionally	[ ]

27. **SPECIFY WHEN YOU GET YOUR SYMPTOMS TYPICALLY:**

(Specify symptoms and indicate how often you get them)

At work	[ ]
At home	[ ]
At night	[ ]
In bed	[ ]
On holiday	[ ]
All of these	[ ]

28. **DO YOU THINK YOUR WORK ENVIRONMENT IS CAUSING YOU TO DEVELOP ALLERGIC SYMPTOMS?**

Yes	[ ]
No	[ ]

29. **DO YOU USE GLOVES IN YOUR WORK ENVIRONMENT?**

Yes	[ ]
No	[ ]

30. **IF YOU ARE A GLOVE USER, DO YOU FIND THAT WEARING RUBBER GLOVES IRRITATE YOUR:**

Skin	[ ]
Eyes	[ ]
Nose	[ ]
Chest	[ ]

31. **WHAT BRANDS OF GLOVES DO YOU USUALLY USE IN THE HOSPITAL ENVIRONMENT?**

Specify .....

.....

.....

Uncertain [ ]

32. **HAVE YOU EVER REQUESTED THE USE OF ALTERNATIVE GLOVES?**

Yes [ ]
No [ ]

33. **HAVE YOU EVER DEVELOPED ANY ALLERGIC SYMPTOMS (E.G. ITCHY EYES, RUNNY OR BLOCKED NOSE, WHEEZING, RASHES) WHEN HANDLING OTHER EQUIPMENT (E.G. RUBBER TUBING, INJECTION AMPOULES, ANAESTHETIC APPARATUS, CATHETERS, SCOPES)?**

Yes [ ]
No [ ]

34. **WERE YOU AWARE THAT THE USE OF LATEX GLOVES CAN CAUSE ALLERGIES IN CERTAIN INDIVIDUALS?**

Yes [ ]
No [ ]

35. **HAS LATEX ALLERGY EVER BEEN DIAGNOSED IN YOU?**

Yes [ ]
No [ ]

36. **IF YES, BY WHOM?**

.....

37. **ARE YOU EXPOSED TO LATEX IN THE HOME OR SPORTING ENVIRONMENT THROUGH THE REGULAR USE OF RUBBER GLOVES, CONDOMS OR RUBBERED SPORTING EQUIPMENT (E.G. TENNIS GRIPS)?**

Yes [ ]
No [ ]
Describe details .....
.....
.....

38. **PLEASE SUPPLY YOUR WORK POSTAL ADDRESS (INTERNAL) AND CONTACT TELEPHONE NUMBER SO THAT WE CAN FOLLOW YOU UP AFTER EVALUATING YOUR QUESTIONNAIRE**

Work address: .....
.....
.....
.....

Telephone number (Work): .....
Telephone number (Home): .....
E-mail address: .....

PLEASE COMPLETE THE QUESTIONNAIRE IN FULL AND POST IN THE INTERNAL MAIL TO THE FOLLOWING ADDRESS:

Mrs Jacqui Higgins
Allergology Unit
Department of Immunology
UCT Medical School

(Contact No: 406-6147)

ADDENDUM 6

CLINICAL EXAMINATION

Clinical Examination - Latex Hypersensitivity Study

Date: _____ Code Number: _____

Patient Sticker:

Department: _____

Blood Pressure: _____ Pulse: _____

Pruritus: _____ Eczema: _____

Hyperlinear palmar surfaces: _____ Xeroderma: _____

Ichthyosis vulgaris: _____ Prominent perifollicular areas: _____

Lowered hairline: _____ Hertoche's sign: _____

Keratosis pilaris: _____ Keratosis punctata: _____

Facial erythema: _____ Facial pallor: _____

White dermographism: _____ Cutaneous pallor: _____

Pityriasis alba: _____ Photosensitivity: _____

Dennie Morgan folds: _____ Infraorbital hyperpigmentation: _____

Keratoconus: _____ Cataracts: _____

Cheilitis: _____ Geographical tongue: _____

Anterior neck folds: _____ Cutaneous infections: _____

Areolar dermatitis: _____ Hand / foot dermatitis: _____

Pruritus during sweat: _____ Polished nails: _____

Subungual haemorrhage: _____ Periostitis: _____

Shortened body length: _____ Environmental / emotional triggers: _____

ADDENDUM 7

LABORATORY REQUEST FORMS

Tygerberg Hospitaal

Hematologie & Bloedgroepering

Saal/Kliniek Ward/Clinic	Vir Lab. gebruik For Lab use
BEROEPSGESONDH 4261 BYLYN 5171	

PASIëNT GEGEWENS / PATIENT DETAILS

Van/Surname			
Voornaam/Name			
Voorl./Initials	Geslag/Sex M F	Ras/Race	
Pasiëntlêer- of klinieknr./Patient folder or clinic no.		Geb. Datum/DOB	

MONSTER / SPECIMEN

Datum/Date:	
Tyd geneem/Time taken:	
Tipe/Type:	5ml EDTA

Dokter: Doctor:	Voorl./Initial	Van/Surname	Tel. Nr./Phone No.:	Sakradio Bleeper:
	D	E L O F F 4 0 8 6 3 1 0	5171	–

Diagnose: Diagnosis:	Allergie	Terapie: Therapy:		Warfarin / Heparien

Hematologie

ROETINE
- [X] VBT (P)
- [X] DIFF WST (P)
- [X] Viskositeit (P)
- [ ] Morfologie (P)
- [ ] Retiktelling (P)
- [ ] BBS (S)
- [ ] Vog seltelling (P)

STOLLING
- [ ] GTT (B)
- [ ] INR (B)
- [ ] Fibrinogeen (B)
- [ ] XDP (B)
- [ ] Monomere (B)
- [ ] ATIII (B)
- [ ] Prot C & S (B)
- [ ] APC Weerstand (B)
- [ ] Bloeityd (pasiënt)
- [ ] LUPUS Antikoag (B)

HEMOLITIES
- [ ] Coombs (R)
- [ ] Hapto & Hemopeksin (R)
- [ ] Hb Elektroforese (P)
- [ ] Malaria (P)
- [ ] Muramidase (P & U)
- [ ] NAF (pasiënt)
- [ ] Sekelsel toets (P)
- [ ] PNH sifting (B)
- [ ] Osmotiese fragiliteit (P)

- [ ] G6PD sifting (P)
- [ ] Kleihauer (P)

ANEMIE
- [ ] Ferritien (R)
- [ ] Vit B12 & Folaat (R)
- [ ] RBS Folaat (P)

ANDER
- [ ] Buffie laag (P)
- [ ] SSV Sitospin
- [ ] Hemosiderien (U)

Ander toetse : ....

*Versamelbuis kodes: B = Blou prop (sitraat) P = Pers prop (EDTA) R = Rooi prop (steriel) S = Swart prop U = Urine monster

BLOEDGROEPERING / BLOOD GROUPING

Departement Hematologie, **Tygerberg Hospitaal**, C9A Wes, Kamer 205.
Department of Haematology, **Tygerberg Hospital**, C9A West, Room 205. Tel./Phone: 938-6081/2

Kliniek/Clinic, Hospitaal/Hospital óf Privaat/Private Dr.: posadres/postal address

Tel. No.: **Poskode/Postal code:**

PRIVAAT PAS. ALLEENLIK/PRIVATE PAT. ONLY

Med. Fonds/Aid:
Med. Fonds Nr./Aid No.
Rek. aan:
Acc. to:

VOORGEBOORTELIKE TOETSE: ANTENATAL TESTS: UXILONGO LWABAKHULELWEYO:
- [ ] 1ste besoek / 1st visit
- [ ] Herhaal monster / Repeat specimen — Perm. No.

NAGEBOORTELIKE TOETSE: POSTNATAL TESTS: UXILONGO EMVA KOBELEKO:
- [ ] Moeder / Mother
- [ ] Naelstring / Cord Blood

ANDER TOETSE: OTHER TESTS: EZINYE IZINGULO:
- [ ] Kordosintese (1-2 ml EDTA bloed) / Cordosinthesis (1-2 ml EDTA blood)
- [ ] Amniosintese (10 ml amniovog in 'n lig-digte buis) / Amniosinthesis (10 ml amniotic fluid in a dark tube - protected from light)

PASIëNT GEGEWENS: PATIENT DETAILS: INCUKACHA NGEZINGULANE:

Vorige van/Previous surname:

Verwagte bevallingsdatum: Exp. Delivery date:

Taal Voorkeur: Afr. / Language Preference: Eng.

VOLTOOI INDIEN BEKEND: Moeder se bloedgroep
COMPLETE IF AVAILABLE: Mother's blood group

5 ml EDTA bloed word benodig vir al bogenoemde toetse. / 5 ml EDTA blood is required for all above-mentioned tests.

Alle post partum pasiënte se Rh bepaling moet bekend wees voor ontslag sodat IgG Anti-D toegedien kan word, indien nodig.
Confirm Rh status before discharing post natal patients in case IgG Anti-D should be administered.

Tygerberg Hospitaal

Laboratorium aanvraagvorm

Saal/Kliniek Ward/Clinic	Vir Lab. gebruik/For Lab use
	BEROEPSGESONDH 4261 BYLYN 5171

PASIËNT GEGEWENS / PATIENT DETAILS

Van/Surname			
Voornaam/Name			
Voorl./Initials		Geslag/Sex M F	Ras/Race
Pasiëntlêer- of klinieknr./Patient folder or clinic no.		Geb. Datum/DOB	

MONSTER / SPECIMEN

Datum/Date:	
Tyd geneem/Time taken:	
Tipe/Type:	10ml SST

Dokter: Doctor:	Voorl./Initial	Van/Surname	Tel. Nr./Phone No.:	Sakradio/Bleeper:
	D	ELOFF 4086310	5171	–

Diagnose: Diagnosis:	Allergie	Terapie: Therapy:		Warfarin	
				Heparien	

Laboratoriums(☑) Chem Pat (x) Mikrobiol/Immunol ( ) Virologie ( ) Farmakologie/Toks ( )

ONDERSOEK VERLANG: (Reël spoedondersoeke asb. telefonies)

Chemiese Patologie

VASTEND: ☐ Ja ☐ Nee

NIER / ALGEMEEN
- ☐ pH (KAP)
- ☐ OSMOLALITEIT
- ☐ BLOEDGASSE (H, *)
- ☐ Na, K, Cl
- ☐ UREUM / STIKSTOF
- ☐ KREATINIEN
- ☐ KREAT OPRUIMING
- ☐ GLUKOSE (G)
- ☐ HbA1c (P, *)
- ☐ URIENSUUR

LEWER
- ☐ Tot BILIRUBIEN
- ☐ Gek&Ong BILI

ENSIEME
- ☐ AST
- ☐ ALT
- ☐ LD
- ☐ GGT
- ☐ ALP
- ☐ CK
- ☐ CK-MB
- ☐ AMILASE
- ☐ SUURFOSFATASE (*)
- ☐ PChE

MINERALE / METALE
- ☐ KALSIUM
- ☐ FOSFAAT
- ☐ MAGNESIUM
- ☐ YSTERSTUDIES
- ☐ KOPER (O)
- ☐ SINK (O)
- ☐ LITHIUM

LIPIEDE
- ☐ *LIPOGRAM*
- ☐ Tot CHOLESTEROL
- ☐ TRIGLISERIEDE

PROTEÏENE
- ☐ Tot PROTEÏENE
- ☐ ALBUMIEN
- ☐ MIKRO-ALBUMIEN
- ☐ ELEKTROFORESE
- ☐ IgG, IgA, IgM
- ☐ BENCE-JONES
- ☒ IgE

ENDOKRIEN
- ☐ LH
- ☐ FSH
- ☐ ESTRADIOL
- ☐ PROGESTEROON
- ☐ TESTOSTEROON
- ☐ SHBG
- ☐ DHEAS
- ☐ 17-OH PROG
- ☐ β-MCG
- ☐ PROLAKTIEN
- ☐ KORTISOL
- ☐ ACTH (P, *)
- ☐ GROEIHORMOON
- ☐ TSH
- ☐ T4
- ☐ URINE SWANGERSKAP
- ☐ INSULIEN
- ☐ PTH (P)

TUMORMERKERS
- ☐ PSA
- ☐ α-FETO PROT
- ☐ CEA

VOGTE
- ☐ SSV - CHEMIE
- ☐ IgG INDEKS
- ☐ ASPIRAAT - CHEMIE
- ☐ ADA

ANDER
- ☐ REDUS STOWWE
- ☐ AMINOSUUR SIF
- ☐ PORFIRIE SIF (O)
- ☐ VMA / HVA / NORMET
- ☐ FEKALE VET

Mikrobiologie

AANVANG VAN INFEKSIE BINNE 72 h NA TOELATING: ☐ Ja ☐ Nee

- ☐ MKS
- ☐ MIKROSKOPIE
- ☐ ZN
- ☐ TB KULTUUR
- ☐ GONOKOK
- ☐ PARASIETE
- ☐ SWAMME
- ☐ ANAEROBE
- ☐ MYCO-/UREAPLASMA
- ☐ CRYPTOSPORIDIUM

Mikrobiologie Immunol / Serologie

OUTO IMMUNOLOGIE
- ☐ KOLLAGEEN SIF
- ☐ ANF
- ☐ ANCA
- ☐ ACA
- ☐ TIROÏED
- ☐ ANTI JO-1
- ☐ ANTI SCL- 70
- ☐ ANTI Ro/La
- ☐ Rh FACTOR
- ☐ CRP
- ☐ TOT.KOMPLEMENT (*)
- ☐ C3/C4
- ☐ SIRK. IMM KOMPL.
- ☐ ASOT
- ☐ C1 ESTERASE INHIB
- ☐ C3 NEFRITIESE FAK (Δ)

CELLULAR IMMUNOLOGIE
- ☐ CD4/CD8 TELLINGS
- ☐ LIMFOSIET STIM
- ☐ NEUTROFIL FUNC (Δ)
- ☐ HLA B27

SEROLOGIE
- ☐ RPR/VDRL
- ☐ FTA
- ☐ WIDAL
- ☐ BILHARZIA
- ☐ BRUCELLA
- ☐ CHLAMYDIA
- ☐ COXIELLA
- ☐ CYSTICERCUS
- ☐ ECHINOLOCCUS
- ☐ ENTAMOEBA
- ☐ LEGIONELLA
- ☐ LEPTOSPIRA
- ☐ MYCOPLASMA
- ☐ PNEUMOCYSTIS
- ☐ RICKETTSIA
- ☐ TOXOCARD
- ☐ TOXOPLASMA
- ☐ VERSINIA
- ☐ SWAM AL. PRESIP
- ☐ VOëL AL PRESIP
- ☐ LAL ENDOTOXIN (Δ)

Virologie

AANVANGSDATUM VAN SIMPTOME: _____

SEROLOGIE
- ☐ HIV (R)
- ☐ HTLV I/II (R)
- ☐ HEPATITIS B (R)
- ☐ HEPATITIS A (R)
- ☐ HEPATITIS C (R)
- ☐ RUBELLA IgM (R)
- ☐ RUBELLA IgG (R)
- ☐ PARVO (R)
- ☐ SMV (R)
- ☐ EBV (R)
- ☐ HSV (R)
- ☐ MASELS (R)
- ☐ PAMPOENTJIES (R)
- ☐ VZV (R)

VIRUS KWEKING
- ☐ ADENO
- ☐ SMV
- ☐ HSV
- ☐ VZV
- ☐ ENTERO
- ☐ RUBELLA
- ☐ PARAINFLU. 1-3
- ☐ RSV
- ☐ INFLUENZA A/B
- ☐ PAMPOENTJIES
- ☐ MASELS

GASTRO ENTERITIS
- ☐ ROTA (Stg)
- ☐ ADENO 40/41 (Stg)

SPOED TOETSE
- ☐ RSV SPOED (NFA/TA)(1h)
- ☐ RESP. PANEEL(NFA/TA)(24h)
- ☐ SMV VIREMIE (P)(24h)
- ☐ SMV VROEë IMF (48h)

Stg = stoelgang NFA = nasofaringeale aspiraat TA = trageale aspiraat

Farm / Toksikologie

Inname / Toediening: DAT._____ TYD._____
Monsterneming: DAT._____ TYD._____

L.W.: TYE VAN TOEDIENING EN MONSTERNEMING MOET AANGEDUI WORD.

SIFTING (urine)
- ☐ BARBITURATE
- ☐ BENSODIASEPIENE
- ☐ AMFETAMIENE
- ☐ OPIATE
- ☐ FENSIKLIDIEN
- ☐ METADOON
- ☐ PARAQUAT
- ☐ MANDRAX
- ☐ CANNABIS
- ☐ KOKAïEN

KWANTITATIEF (bloed)
- ☐ METOTREKSAAT
- ☐ KINIDIEN
- ☐ DIGOKSIEN
- ☐ SIKLOSPORIEN (P)
- ☐ ETANOL
- ☐ PARASETAMOL
- ☐ SALISILAAT
- ☐ TRISIKL ANTIDEP
- ☐ TEOFILLIEN
- ☐ KARBAMASEPIEN
- ☐ VALPROAAT
- ☐ ETOSUKSIMIED
- ☐ PRIMIDOON
- ☐ FENOBARBITOON
- ☐ FENITOïEN (DPH)

MELD: Pre ☐ Post ☐
- ☐ AMIKASIEN
- ☐ GENTAMISIEN
- ☐ NETILMISIEN
- ☐ TOBRAMISIEN
- ☐ VANKOMISIEN

Ander toetse

SPESIFISEER:

Versamelbuis kodes: Gebruik SST (Gel) buise vir alle bloedmonsters tensy anders vermeld:

P = Pers prop (EDTA) S = Swart prop (sitraat) R = Rooi prop (steriel) H = Heparien spuit Δ = Bespreek telefonies
B = Blou prop (sitraat) G = Grys prop (fluoried) O = Oranje skroefdop (Li-heparien) * = Op ys