RESEARCH ON NICKEL ALLOY SENSITIVITY

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SIGNED STATEMENT

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any other university and that, to the best of my belief, it contains no material previously published or written by another person, except where due reference is made in the test.

Itone Muteba 16 April 1999

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SECTION ONE

Introduction

1. INTRODUCTION

Nickel plays a part in almost all our daily lives. As in the air we breathe, the cooking utensils, the coins we handle and indeed from some of the food we eat. Nickel has been observed in human tissues at birth and remains at approximately constant levels throughout life (McNeely et al., 1972). The daily intake of nickel has been observed to vary from 300 to 600 μg with the mean daily excretion of 2.5 to 28μg (Schroeder et al., 1962).

Nickel sensitivity was first observed and reported in 1889 by Prystovsky et al. Scientific knowledge and the available technology prevented the full investigation into the material. With the development of new technology into metal alloy analysis, more and more allergens are being identified. Therefore, the need for detailed evaluation of the toxicity, carcinogenicity and allergy-inducing properties of these alloys is necessary. Whatever causes these reactions during contact with these alloys needs to be analysed in detail.

The aim of this study was to collect information about numbers of dental workers who are sensitive or allergic to nickel which is a common metal used in jewellery and in some types of dental treatment.

We know from overseas studies that about 30 percent of young people are likely to be sensitive to nickel and that in some countries 20 percent of all the people show some

kind of reaction to nickel. Despite this, great attention has not been paid to nickel allergy and its long term consequences have not been fully considered.

Most commonly, people who are sensitive to nickel develop a rash in areas that come into contact with the metal, but there are rare cases where nickel has been shown to cause a range of other health problems.

In this study we are also using a simple questionnaire to help identify signs which might predict those people who are most likely to be sensitive to nickel and using a standard patch test to identify sensitive subjects.

SECTION TWO

Literature Review

2.1. DENTAL ALLOYS

An alloy is defined as a metal containing two or more elements that are soluble in the molten state (Phillips, 1996). The difference between pure metal and alloy is the point at which pure metals solidify. Most alloys solidify over a range of temperatures rather than at a single temperature, as seen in pure metals. Within this range, it can exist in two phases, solid and liquid.

The composition of an alloy varies and depends on its uses. In some instances, the combination is complex and on occasions is a manufacturer's secret. In dentistry, the main purpose of the alloys is to enhance the properties necessary for prostheses construction.

An alloy system is an aggregate of two or more metals in all-possible combinations (Phillips, 1996). For example, in gold-silver systems, one can have all the possible concentrations of gold with silver containing anything up to 100 percent of gold to 100 percent of silver. The composition of an alloy is defined by either by weight per cent (w/o) of each element or by atomic fraction percent (a/o). For instance, $AuCu_3$ alloy has 51 percent by weight but only 25 percent by atomic fraction of gold. Some alloys vary in their atomic weight composition. The properties of an alloy relate more to the atomic percent and not weight percent of each element.

Alloys are classified according to how many elements are present in an alloy. If there are two elements, it is a binary alloy and if there are three elements, it is known as ternary alloy. They can also be classified on the basis of the miscibility of the atoms in a solid

state. When the atoms of two metals intermingle randomly in a common sphere, the grains resemble that of pure metal, although the structure is homogenous. The metals are soluble in each other and are called solid solution. Sometimes these metals may not be completely soluble in each other and they are then termed as being in an intermediate phase.

In dentistry, there are many different types of alloys used. In 1984, the American Dental Assocaition adopted a simple classification for dental casting alloys:

High noble metal

- Contains > 40% wt gold and <60% wt of noble metals (gold, platinum, palladium, rhodium, ruthenium, iridium, osmium). These include gold-platinum-palladium (Au-Pt-Pd), gold-palladium-silver (Au-Pd-Ag) and gold-palladium (Au-Pd)

Noble metal

- contains > 25% wt of noble metals. These include palladium-based alloys, (eg. palladium-silver, palladium-copper)

Predominantly base metal

- contains < 25% wt of noble metals, or > 75% wt of base metals. The most common alloys in this class include nickel-chromium (Ni-Cr) and chrome-cobalt (Cr-Co).

The composition of base metal alloys varies. Usually, the content for nickel is of the order of 80% with 13 to 22% for chromium. Their physical workability has often been enhanced by the addition of 2% by weight of beryllium, which makes it easy to cast and finish.

Cobalt-chromium alloys have been widely used in dentistry for removable partial denture frames. They contain 55 to 68 % of cobalt and up to 25 to 27 % of chromium. They contain no beryllium, which makes them oxidise more easily than the alloys containing beryllium.

Nickel and cobalt are often considered interchangeable in alloys. As the content of nickel increase, the strength, hardness, modulus of elasticity and fusion temperature decreases, while ductility increases. In most alloys chromium acts as solid solution hardener and provides passivity and resistance to corrosion

The introduction of beryllium reduces fusion temperature, increases fluidity, improves casting performance and controls surface oxidation. Berylium is not, however, without its disadvantages. Gelman (1936) reported the first case of beryllium poisoning and Van Orstrand (1945) is attributed with having established its toxicity. The delayed beryllium poisoning was first reported by Hardy and Tabershaw (1946).

Beryllium adversely affects different organs in humans, such as skin, eyes, lungs and nasal passages, in either acute or chronic form. Acute forms include acute dermatitis, conjunctivitis and bronchitis. In case of beryllium-induced acute respiratory reactions, the effects range from inflammation of the nasal mucosa, pharynx and tracheo-bronchial system to severe chemical pneumonitis (Tepper et al., 1961). Chronic signs of the disease may take time to show. Symptoms range from coughing, chest pain and general weakness to pulmonary dysfunction. It becomes evident only after a series of laboratory tests and documentation of beryllium exposure. During this period, a number of organic damages to liver could have occurred, such as changes in serum proteins, uric acid, and urinary calcium levels.

2.2 CARCINOGENICITY OF ALLOYS

The most serious concerns about the safety of materials involves questions of their carcinogenicity.

Nickel has been ranked as one of the most carcinogenic metallic elements (Heuper and Conway, 1964). As most experiments have been done on animals (Heuper, 1958; Mitchell et al., 1960), there is more information on carcinogenic effects on them, than there is on human beings.

Nickel carbonyl ($Ni(CO_4)$), nickel subsulphide (Ni_3S_2), and nickel sulphide (NiS) have been shown to produce tumours (Schottenfield and Haas, 1978) presumably because they are soluble in lipids. There has been no scientific evidence in the literature to prove the relationship between cancer and metal alloys in humans.

Nickel subsulphide has been found as a potential inducer of cancer in rats and mice (Gilman et al., 1966). The estimated latent period of nickel is 22 years and the target organ is the lung (Heuper and Conway, 1964). Laboratory investigations have found response towards nickel chloride salt. In mice, nickel accumulates in the skin, central nervous system, lungs, and kidney (Woody et al., 1977).

Though nickel has been reported to induce cancer in rats, no direct relationship between carcinogenicity in human and dental restorations containing nickel has been established. On the contrary, Vreeburg et al (1984) suggested that exposure to dental base metal alloys might result in tolerance towards the metal alloys.

The first cancer of the respiratory tract involving chromium was reported as early as 1932 by Lehmann. Since then, there have been several experiments on animals confirming the carcinogenic effect (eg Sunderman, 1971). Despite having great biological value in its minute ionic form, chromium has the ability to penetrate cells easily by oxidising organic compounds, and is known to be a potent mutagen and carcinogenic agent at low concentration (Roe and Carter, 1969).

In 1971, Schroeder and Michener, found 13 tumours, eleven of which were malignant, after feeding palladium chloride to 100 mice. From these results, they concluded slight carcinogenic activity of palladium in mice. Pillai and Nandi (1977), found evidence of palladium interacting with the phosphates and bases of DNA, thereby implicating this metal as a potential mutagen, though no mutation of DNA was reported.

In 1977 the National Research Council in the United States reported several Japanese studies which found tumours in seven of the fourteen rats implanted with silver-palladium. Primary carcinomas from implanted prostheses have been reported (McDougall, 1956). although very few have been reported as having carcinomas found near dental alloys (Kinnebrew, 1984).

People who need protection are those within the metal alloy environment, such as dental technicians, blacksmiths and dentists. There are reports that lung cancer occurred four times more often in dental technicians, though such studies did not take into account other causative factors of cancer such as smoking (Menck and Henderson, 1976). In modern laboratories with good ventilation, the problem of fine alloy particles causing cancer is almost nil. This may not apply to people working in big factories, mines and to ordinary blacksmiths working in unfavourable conditions. It is of primary importance to note that, in regions such as Eastern Europe with uncontrolled heavy industries, cause of cancer from such alloys can not be ruled out. An example of such a place is Cracow in Poland, where chest infection and child mortality is higher than any other towns in the country (Jedyrchowski, 1995).

When considering the mechanisms of action of various metals acting as toxins or carcionogens there are important differences between the oral mucosa and the skin. Among the differences, the most important one is the rapid and complete formation of salivary glycoprotein films on exposed oral surfaces. This protects the oral cavity from allergens as it acts as a diffusion barrier (Baier and Glantz, 1978).

Kaaber (1978) experimented with the water flow, and found that it was 10 to 100 times faster through the oral mucosa than through the skin, both inward and outward. Further

information was obtained from the research by Covington et al (1985). They obtained unstimulated saliva from volunteers and studied the effect of this saliva at various pH levels over a period of 20 days, during which time they analysed for the dissolution of nickel and beryllium. They found that dissolution was not dependent on time and concluded that the combination of nickel and beryllium in an alloy potentiates the dissolution of both in acidic media.

Once in the blood stream, the nickel is found to form complexes with alpha-macro-globulin and turn into nickel plasmin (Nomoto et al., 1971). This serves as a micronutrient to the cells and can lead to complications as it is capable of depolymerising RNA and proteins as well as disrupting muscle and enzyme function. This general systemic effect could explain reports of patients with oral rehabilitation using nickel alloy prostheses developing skin eczema.

2.3 SENSITIVITY TO DENTAL ALLOYS

Every so often after inserting a denture. the dentist is confronted with ulceration in the oral cavity of a patient which is not related to any past medical history or dental causes. Therefore, the dentist tries to treat the effect without success. In some cases, the dentist removes the prostheses and the patient is relieved from the pain or any symptoms. The prostheses might be questioned, but still, the causative factor is unknown. The difficult part is that, no alloy is used in isolation. There is always a combination of one or more components, to achieve the desired mechanical and physical properties. So, a thorough analysis is required in order to separate the individual alloy components. It has been estimated that 2 - 8% of the population have some kinds of allergy to metal alloys (Moffa, 1983).

Hypersensitivity is a general term used to describe the various types of immune reactions to an antigen. It can be divided into four general types and a reaction to a specific antigen may involve one or more types. These reactions are described as:

Type I Reaction

- Immediate hypersensitivity reaction
- Involves the recognition of an antigen by IgE

Type II Reaction

- IgE antibody - dependent cytotoxicity
- Directed against specific cell-surface antigen or tissues

Type III Reaction

- Similar to type II reaction, except that it is directed to widely distributed antigens that may be soluble.

Type IV Reaction

- Referred to as delayed type (of at least 12 hours) reaction.
- Unlike type I to III, antibody is not required
- Can only be mediated by T-cells, in response to an antigen
- Release inflammatory mediators and lymphokines
- These mediators, in turn, cause macrophages to release mediators, resulting in local tissue reaction.

All four types of hypersensitivity have been found to occur in the oral cavity and may play a role in the development or control of various oral diseases. In dentistry our most common concern is more with Type IV, rather than with the other three types.

Allergenic contact dermatitis is considered a prototype of delayed hypersensitivity reaction (Woody et al., 1977). It can be divided into two phases: the induction phase and the elicitation phase. During the induction phase, the lymphocytes take some time to recognise and respond to the chemical following initial exposure. Subsequent re-exposure and development of dermatitis constitutes the elicitation phase.

There are several principles that metal alloys follow in order for them to interact with our body systems. With metals, the biochemical form of the element significantly affects its biological properties (Dahl, 1981). Metal can exist in the metallic state, or ionic state. For example, elemental mercury has a significant vapour pressure, is lipid soluble, and can pass from inspired air to the bloodstream. In this form it has an affinity for red blood cells and nervous tissues. In its ionic form, mercury has no vapour pressure and is water soluble, which limits its absorption and penetration across the lipid membranes of the intestinal epithelium (Vreeburg et al., 1984).

In general the toxicity of metal salts follows their water solubility (water solubility in itself does not imply toxicity) Lipid solubility, usually via an organic-metal complex,

allows the metal to gain access to the cells through the lipid membrane and can contribute to the toxic effect. The route of exposure can signficantly influence the effects of metals. Intravenous exposure (eg. during dialysis) is usually the most damaging route of exposure. Inhalation and intra-tracheal exposure less potent and oral ingestion is generally the least toxic route of exposure. This is important, as with dental casting alloys, any dissolved metals are exposing the body through the oral route

Several authors (Aas, 1971; Peer and Dockhom, 1973; Gell and Combs, 1973) agree that there are a great variety of factors that can influence the development of hypersensitivity. The most important are mechanical irritation, skin maceration, individual susceptibility, temperature, climate and intensity and duration of exposure. The high temperature causes increased sweating and the chloride present in perspiration ionises metals such as nickel present. In this way, nickel salts are formed which can induce skin hypersensitivity reactions (Rostenburg and Perkins, 1951).

In general, the rate of elimination will determine how much metal will accumulate in the body and the route of elimination will determine the organ systems which are at risk of toxic effects. Elimination rates and routes are complex and depend upon the ingestion rate, diet, disease states, exposure to other metals and other factors (Goyer, 1986).

The most common allergens that have brought the world to question base materials in dental prostheses are nickel, chromium, beryllium and cobalt (Mitchell, 1959; Kallus, 1984). However, there are other components of dental alloys (eg palladium) that need more investigation and in recent time gold has been questioned (Bjorkner, 1994). Menne et al. (1982) reported a case of permanent disability in Denmark as a result of nickel-induced hand eczema. These are complications, which can lead the patient to consult a dermatologist, who may not know the intraoral source of the problems (Andersen at al., 1984). There are important reasons for questioning patients in relation to metal alloy allergy and, if need be testing the alleged allergens and finally obtaining informed consent from the patient prior to the use of suspected materials.

2.4. SENSITIVITY TESTS

Diagnosis of allergy is often based on patient history, clinical findings and results of sensitivity tests (Fisher, 1973). Sometimes, it is not easy to isolate the allergen, as dental alloys usually contain more than one metal. In some cases, there could be more than one allergen in a given alloy.

The most common methods employed to determine allergies are standard patch tests, skin-prick methods and subcutaneous implantation.

The most common used method is by standard patch tests. This test is used routinely by dermatologists and allergists to determine allergic responses. It is a well-stabilised and approved method for detection of sensitivity to different substances (Fisher, 1973; Engelman and Blecher, 1978; Blanco-Dalmau, 1982).

Depending on what material is thought or suspected of being an allergen, the test series can be in the form of a group standard series, a metal salt series, or a dental restorative metal series. The test patch or patches are then placed on the forearm or in an alternative selected site as follows:

- the test solution or salt is placed in the centre of the test patch free from sensitisers
- the test patch should provide air tight occlusion
- a site such as the medial aspect of upper arm is cleaned with alcohol before placement of the test patch
- a control patch, without the reagent, is placed next to the test patch
- skin that is infected or macerated or shows any signs of rash should be avoided.
- the test patch is left for at least 48 hours before the reading is taken
- the subjects are instructed not to wash or remove the patch during this period, with exception of those who develop extreme itchiness or pain.

If there is any reaction, one is able to see signs of oedema, erythema, papules, vesicles alone, or a combination of responses. Mild itching and erythema are inadequate to be considered as primary criteria for patch test reactions. This is to eliminate false positive results. Erythema combined with other signs is regarded as positive reactions.

In the skin-prick method, the skin is scratched and the alleged sensitisers applied. The readings are done 48 hours later, as in the standard test patch. The prick test is evaluated on the basis of erythema and oedema by visual means and the reactions are ranked either from very negative (---) to very positive signs (+++) (Beradesca, 1992).

When there are problems distinguishing between positive (+) and negative (-) readings, a non-invasive quantitiative technique such as remittance spectroscopy and ultrasound can be employed.

The quantitative information provided can be evaluated, compared and analysed statistically which can be difficult with data obtained with the visual scoring method. This provides an objective tool to study skin function.

2.5. SENSITIVITY TO NICKEL

Presently, base metal alloys are widely used in the dental industry, as well as in non-dental industrial applications. Base metal alloys with a high percentage of nickel have been available for many years. The first base metal alloys to be used as the framework of prostheses were manufactured in the United States as far back as 1950. These alloys include combinations of nickel, beryllium, chromium and cobalt. In the United States, the use of these alloys has climbed from merely a small percentage to 80% (Morris, 1977). Their success was due entirely to their strength and low cost. Clinically, the alloys have performed just as well as gold-based alloys. However, laboratory studies have shown that the dust from these metallic alloys is toxic and injurious to health. They have also been reported by the American Dental Association Council on Dental Materials (1982) to have potential allergic, carcinogenic and toxic reactions in living organisms.

Nickel has been found to be the most common metallic contact sensitisers among all other metals (see above). Nickel sensitivity has a long history. The first case of nickel dermatitis was reported by Blaschko as far back as 1889. At that time, they advised the personnel working in proximity with the metal to wear gloves and apply protective cream on their hands to reduce eczema. It was not until 1933 that Goldman came across a specific skin disease related to nickel compounds sensitivity. In the early fifties, the sensitivity towards nickel was observed as common occurrence. Originally, nickel dermatitis was just a secular disease emanating from a few people such as miners, smelters, refiners, and electroplaters working in industrial surrounding. During that period of time, it was called 'nickel-itch' as it attacked the hands, mostly between the fingers, wrists and forearms. The symptoms were characterised by burning sensation and papular erythema.

A second form of nickel dermatitis was described as papular or papulo-vesicular dermatitis with a tendency to lichenification. With the present environmental developments, daily contact with nickel has become difficult to avoid. The prevalence of

nickel contact has now shifted from nickel-workers to the whole population. The people at highest risk are those in heavy industrial areas, where nickel is the main product. The other sources of daily contact is from coins, which were said to contain about 25% nickel and 75% copper, and from coat-plated ornaments.

There have also been questions unanswered in respect to the biologic safety of nickel alloys for our patients, as well as for those who handle the alloys, such as dentists and technicians. The sensitivity to nickel was found to be ten times greater in women than men (Peltonen, 1979) varying from 0.8% to 20% in men and 9% to 31.9% in women (Prystovsky et al., 1979). The difference has been reported to be due to more frequent contact with the alloys in women (Moffa et al., 1983). However, there could be a change of thought concerning the gender-related difference in the frequency of allergy as more young men are piercing their ears and other parts of the body with different types of metal alloys.

It has been shown that 81.1% of subjects with a history of allergy to jewellery were tested positive to nickel hypersensitivity (Blanco-Dalmau et al., 1984) and 80% of nickel-sensitive patients also reacted positively to dental Ni-Cr alloy. In these subjects, 30% had allergic reactions within 48 hours (Moffa et al., 1977).

Contact with nickel is ever present. The human body is full of minute elements of different kinds, of which nickel is one of them. Schroeder et al. (1962) estimated that our daily intake of nickel is between 300 to 600 μg. Nickel can be found in human saliva in quantities that vary from 0.8 to 4.5 μg/l (Catalano et al., 1977).

Previous reviews have not gone so far as to pinpoint the focal issue of safety and generally fall short of recommending what level of nickel concentration (if any) is safe. Jacobsen (1977) demonstrated that nickel concentration as low as 2.5 mg/ml were toxic to human gingival cells in tissue culture. Woody et al (1977) also confirmed the cytotoxicity of nickel-containing dental alloys under experimental conditions although this study lacked specificity as the reaction could have been any metal in the alloy. However, it does demonstrate that nickel alloys are not "tissue friendly" as tissue

reactions to foreign materials vary from person to person, depending on specific body receptors.

Blanco-Dalmau (1982) investigated the nickel sensitivity by using a standard patch test. He used 5% nickel sulphate with or without a petroleum base. In this study, good quality, square Band-Aids (Johnson & Johnson Products Inc., New Brunswick, N.J.), on which the solution was placed was chosen. He placed the patch on the medial aspect of the upper arm pre-cleaned with alcohol swab, and left it for 48 hours. He also used a Band-Aid without reagent as a control.

The overall aims of Blanco-Dalmau's study were:

- To determine the incidence of an allergic response to nickel by patch testing in a group of students, faculty members, and employees of a Medical Science campus
- To investigate if differences exist in the incidence of nickel hypersensitivity between sexes.
- To determine if there is a relationship between incidence of nickel hypersensitivity and age.
- To determine if there is a relationship between previous allergic history and nickel hypersensitivity.

The details of this study are summarised in Tables I-VII. The distribution on subjects in the study population is described in Table I.

Table I. Distribution of study population

Department	Absolute frequency	Relative frequency (%)
Public Health	82	20.3
School of Dentistry	52	12.9
Pharmacy	24	6.0
School of Medicine	6	1.5
Allied Health Professions	20	5.0
Non students	219	54.3
Total	403	100

The incidence of a positive patch test reaction to nickel in this study was 28.5% (Table II and III). The incidence of nickel hypersensitivity in females (31.9%) was higher than in males (20.7%) (Table IV).

Table II. Patch test results of allergic reaction to nickel

Reaction	Absolute frequency	Relative frequency (%)
Negative	288	71.5
Positive	115	28.5
Total	403	100

Table III. Patch test results of allergic reaction to nickel according to degree of reaction

Degree of reaction	Absolute frequency	Relative frequency (%)
No reaction	263	65.3
Erythema	25	6.2
Erythema and papules	76	18.9
Erythema, papules and vesicles	32	7.9
Marked oedema with vesicles	7	1.7
Total	403	100

Table IV. Classification of allergic reaction to nickel according to sex.

Sex	Negative	Positive	Relative frequency (%)
Men	96	25	20.7
Women	192	90	31.9
Total	288	115	52.6

Chi Square = 5.26, $p < .05$

Table V shows relationship between a history of allergy to jewellery and nickel hypersensitivity. A total of 81.8% with history of allergy to jewellery were also sensitive to nickel. There was a statistically significant relationship ($p<0.001$) between a history of allergy to jewellery and nickel hypersensitivity.

Table V. Relationship of previous allergic history and reaction to nickel

Reaction to nickel	No allergic history	Jewellery	Penicillin	Aspirin	Others	Raw total
Negative	201	7	26	6	48	288
Positive	58	30	10	2	15	115
Total	259	37	36	8	63	403

Chi Square = 55.63; $p < 0.001$

This study demonstrated that females are far more likely to have a history of allergies than males (Table VI) but that there was no significant relationship between age and nickel sensitivity.

Table VI. Classification of previous allergic history according to sex in subjects with positive patch reaction to nickel.

Sex	No allergic history	Allergy history	Relative frequency (%)
Men	19	6	10.5
Women	39	51	89.5
Column total	58	57	100

Chi Square = 8.35; $p < .01$

In a series of patch tests of different materials including nickel by a Magnusson et al. (1968) found that of the 5558 patients tested the following rates of sensitivity:

Chromate	7.4%
Balsam of Peru	6.9%
Nickel	5.9%
Cobalt	5.0%
Neomycin	4.5%
P-phenylendiamine	4.5%
Wood tars	3.8%
Oil of turpentine	3.3%
Coal tar	3.1%
Formaldehyde	2.8%
N-phenyl-N-Cyclohexyl-phenylenediamine	2.8%
Tetramethylthiauramdisulphide	2.5%
Vioform +Sterosan	2.4%
Mercuric Chloride	2.3%
Colophony	2.3%
Primula	2.3%
Benzocaine	2.1%
N.N-di phenyl-p-phenylenediamine	1.9%
Mercaptobenzothiazole	1.9%
Lanoline	1.5%

In this study it was also observed that there was a high frequency of allergy in females than males for almost all the allergens.

While sufficient evidence exists to indicate that exposure to metals should be controlled, "safe" levels have not been established. However, Roschin (1984) proposed the following levels for base metals in air:.

	Level (mg/m^3)
Beryllium	0.002
Nickel	1.0
Chromium	0.5
Cobalt	0.1
Copper	1.0
Silver	0.01
Indium	0.1

In Sweden, the National Board of Health and Welfare has discouraged the use of more than 1% of nickel in any alloy (Bergman, 1980). The U.S. Department of Health, Education, and Welfare environment concentration standard (U.S.D.H.W., 1977) recommended that no employee should be exposed to nickel concentration greater than $15\mu g/cm^3$ of air for up to 10-hour working time or 40-hour per week.

SECTION THREE

Aims

3. AIMS

The aim of this study was to collect information about the incidence of nickel sensitivity among dental workers who, because of their exposure to nickel containing alloys, are at risk of developing nickel sensitivity.

We know from the studies described above that as many as 30 percent of young adults are likely to be sensitive to nickel and that in some countries 20 percent of all people show some reaction to nickel. In spite of this, nickel allergy has not been paid great attention nor has its long term consequences been fully investigated. Most commonly people who are sensitive to nickel develop a rash in areas which come into contact with the metal but there are rare situations where nickel has been shown to cause a range of other health problems.

The specific aims of this study were to:

- describe the variation in nickel sensitivity between male and females
- describe variations in nickel sensitivity with age
- identify factors which might be associated with sensitivity to nickel.

SECTION FOUR

Material and Methods

4. MATERIALS AND METHODS

4.1 Subjects

The subjects included in this study were self-selected volunteers from among the staff and students of the Faculty of Dentistry, The University of Adelaide and the Adelaide Dental Hospital. The final sample consisted of 38 males and 53 females . The age distribution of the sample is summarised in Table VII.

Table VII: Age distribution of male and female samples

	Males		Females	
	Number	Percent	Number	Percent
< 30 years	18	47.4	30	56.6
30-39 years	5	13.2	12	22.6
40-49 years	11	28.9	9	17.0
>50 years	4	10.5	2	3.8
Total	38	100.0	53	100.0

Each subject was enrolled in the study according to a protocol approved by the Human Ethics Committee of The University of Adelaide (Approval H/12/98) and were

provided with a printed information sheet (Appendix One). All subjects provided written consent for their involvement in the study (Appendix Two). The subjects were informed that they were free to withdraw at anytime if they so wished. Each subject provided personal details and details of allergy, sensitivity and jewellery use (Appendix Three).

4.2 Methods

A standard patch test consisting of 5% nickel sulphate was prepared and administered according to the method described by Blanco- Dalmau (1982). This involved applying nickel sulphate in petrolatum base to the skin of the upper, inner forearm. Adhesive hypoallergenic, water repellent "Transparent Spots" (Beirsdorf Australia Ltd Lot no.76334) were used to apply the test material. An additional "Transparent Spot" with petrolatum base alone served as the control. Test and control patches were assessed after 48 hours and scored as positive (any sign of inflammation) or negative. Examples of typical positive reactions are shown in Figure I.

Age, gender, allergy history and patch test results were analysed by standard descriptive statistics, chi-square analysis and un-paired t-tests using the Statview 512+ program (Abacus Concepts, Calabasas, CA, USA) for the Macintosh computer.

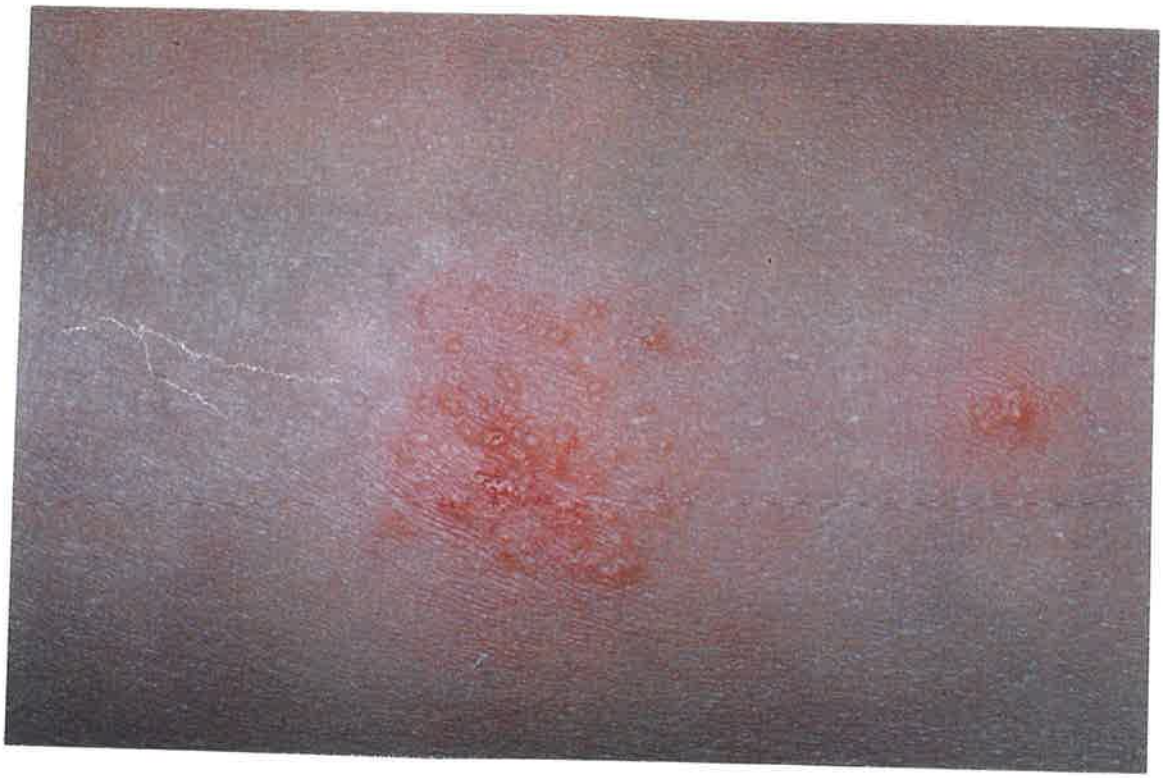

Figure I: Positive skin reactions to patch testing

SECTION FIVE

Results

5. RESULTS

A total of 8 subjects (8.8 percent) tested positive to nickel using the patch test. There were no significant differences (p=0.21) in the incidence of sensitivity between males and females (Table VIII).

Table VIII: Incidence and frequency of nickel sensitivity in males and females.

	Males		Females	
	Number	Percent	Number	Percent
Positive	5	13.2	3	5.7
Negative	33	86.8	50	94.3
Total	38	100	53	100

There was no strong evidence of a relationship between age and nickel sensitivity. The mean age of sensitive subjects (29.0 years, s.d.=9.7) did not differ significantly from the mean age for non-sensitive subjects (32.0 years, s.d.=10.4).

The skewed distribution of ages makes this data difficult to interpret however. Considering the sample with ages grouped (less than 31 years, and over 31 years) suggests a tendency for younger subjects to show a higher frequency of sensitivity (Table IX).

Table IX: Frequencies of patch test results in subjects grouped by age

	Age <31 years		Age 31 + years		Combined	
	Number	Percent	Number	Percent	Number	Percent
Positive	6	12.5	2	4.7	8	8.8
Negative	42	87.5	41	95.3	83	91.2
Total	48	100.0	43	100.0	91	100.0

The frequencies of responses to each of the questions assessing history of allergy, jewellery use and body piercing are summarised in Tables X - XVI.

A total of 39 (42.8 percent) subjects reported a history of some type of allergic reaction (Table X). The frequencies of reactions did not differ significantly between males and females ($p=0.33$)

Of the subjects reporting allergies, sensitivity to plants were most common in males while multiple allergies tended to be more common in females (Table XI).

Table X: Frequencies of male and female subjects with any history of allergic reaction

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Allergy	14	36.8	25	47.2	39	42.8
No Allergy	24	63.2	28	52.8	52	57.2
Total	38	100.0	53	100.0	91	100

Table XI: Frequencies of types of allergy in male and female subjects

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Drugs	1	7.1	4	16.0	5	12.8
Food	1	7.1	2	8.0	3	7.7
Plants	7	50.0	3	12.0	10	25.6
Insects	0	0.0	1	4.0	1	2.6
Metal	0	0.0	1	4.0	1	2.6
Other	2	14.3	5	20.0	7	17.9
Multiple	3	21.4	9	36.0	12	30.8
Total	14	100.0	25	100.0	39	100.0

Forty-seven subjects (51.7 percent) reported a history of some form of allergy-related medical condition (Table XII). The observed differences between males and females did not differ significantly from zero (p=0.31)

Table XII: Frequencies of types of allergy related medical conditions in males and females

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Allergic condition	22	57.9	25	47.2	47	51.7
No allergic conditions	16	42.1	28	52.8	44	48.4
Total	38	100.0	53	100.0	91	100.0

Of the conditions considered, hayfever was reported most frequently in both males and females (Table XIII).

Table XIII: Frequencies of types of allergy-related medical conditions in male and female subjects

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Asthma	0	0.0	1	4.0	1	2.2
Dermatitis	1	4.5	2	8.0	3	6.7
Eczema	1	4.5	1	4.0	2	4.4
Hayfever	10	45.5	14	56.0	24	53.3
Hives	1	4.5	0	0.0	1	2.2
Multiple	9	40.9	7	28.0	16	35.6
Total	22	100.0	25	100.0	45	100.0

A total of 41.8 percent of subject reported some systemic symptoms (itchy eyes, running nose, sneezing, upset stomach) which might be attributable to allergy (Table XIV). The observed frequencies did not differ significantly between males and females ($p=0.22$).

Table XIV: Frequencies of allergy related symptoms in male and female subjects

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Symptoms	13	34.2	25	47.2	38	41.8
No symptoms	25	65.8	28	52.8	53	58.2
Total	38	100.0	53	100.0	91	100.0

Of the symptoms reported, eyes symptoms were common in both males and females and stomach symptoms were also commonly reported in females (Table XV).

The frequencies of body piercing differed significantly between males and females ($p<0.001$) with 5.3 percent of males reported some form of body piercing compares with 71.7 percent of females (Table XVII).

All subjects with body piercing used gold jewellery except for one female who used something other than gold or stainless steel.

Of the subject with body piercing 100 percent of the males (ie 2 of 2) and 23 of the 38 females (61 percent) had experienced associated infection or inflammation at some time.

Table XV: Frequencies of types of allergy-related symptoms in male and female subjects

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Eye	4	18.2	4	16.0	8	17.0
Nose	0	0.0	2	8.8	2	4.3
Sneeze	1	4.5	1	4.0	2	4.3
Stomach	1	4.5	4	16.0	5	10.6
Multiple	7	31.8	14	56.0	21	44.7
Total	22	100.0	25	100.0	47	100.0

Table XVI: Frequencies of body piercing in male and female subjects

	Males		Females		Combined	
	Number	Percent	Number	Percent	Number	Percent
Piercing	2	5.3	38	71.7	40	44.0
No piercing	36	94.7	15	28.3	51	56.0
Total	38	100.0	53	100.0	91	100.0

Because the ages of the sample were not normally distributed, subjects were grouped according to age (less than 31 years and over 31 years) and the responses to the allergy and piercing questions compared between the two groups.

Table XVII: Frequencies of allergy in subjects grouped by age

	Age <31 years		Age 31 + years		Combined	
	Number	Percent	Number	Percent	Number	Percent
Allergy	20	41.7	19	47.2	39	44.2
No allergy	28	58.3	24	52.8	52	55.8
Total	48	100.0	43	100.0	91	100.0

Table XVIII: Frequencies of allergy related medical conditions in subjects grouped by age

	Age <31 years		Age 31 + years		Combined	
	Number	Percent	Number	Percent	Number	Percent
Condition	26	54.2	21	48.8	47	51.6
No condition	22	45.8	22	51.2	44	48.4
Total	48	100.0	43	100.0	91	100.0

Table XIX: Frequencies of allergy related symptoms in subjects grouped by age

	Age <31 years		Age 31 + years		Combined	
	Number	Percent	Number	Percent	Number	Percent
Symptoms	21	43.8	17	39.5	38	41.8
No symptoms	27	56.2	26	60.5	53	58.2
Total	48	100.0	43	100.0	91	100.0

Table XX: Frequencies of body piercing in subjects grouped by age

	Age <31 years		Age 31 + years		Combined	
	Number	Percent	Number	Percent	Number	Percent
Piercing	24	50	16	37.2	40	44.0
No piercing	24	50	27	62.8	51	56.0
Total	48	100.0	43	100.0	91	100.0

Table XXI: Frequencies of inflammation associated with body piercing in subjects grouped by age

	Age <31 years		Age 31 + years		Combined	
	Number	Percent	Number	Percent	Number	Percent
Inflammation	13	27.1	12	27.9	25	27.5
No inflammation	35	72.9	31	72.0	66	72.5
Total	48	100.0	43	100.0	91	100.0

In no cases did the frequencies of responses differ significantly between the age groups ($p>0.05$).

The data obtained in this study were unable ato demosnstrate significant relationships between patch test results and any of the information obtained form the subjects history of allergy related conditions or body piercing.

Table XXII: Frequencies of allergy in subjects grouped patch test results

	Positive Patch Test		Negative Patch test		Combined	
	Number	Percent	Number	Percent	Number	Percent
Allergy	3	37.5	36	43.4	39	42.9
No Allergy	5	62.5	47	56.6	52	57.1
Total	8	100.0	83	100.0	91	100.0

Table XXII: Frequencies of allergy related medical conditions in subjects grouped by patch test result

	Positive Patch Test		Negative Patch test		Combined	
	Number	Percent	Number	Percent	Number	Percent
Condition	4	50.0	43	51.8	47	51.6
No Condition	4	50.0	40	48.2	44	48.4
Total	8	100.0	83	100.0	91	100.0

Table XXIII: Frequencies of allergy related symptoms in subjects grouped by patch test results

	Positive Patch Test		Negative Patch test		Combined	
	Number	Percent	Number	Percent	Number	Percent
Symptoms	2	25.0	36	43.4	38	41.8
No Symptoms	6	75.0	47	56.6	53	58.2
Total	8	100.0	83	100.0	91	100.0

Table XXIV: Frequencies of body piecing in subjects grouped by patch test results

	Positive Patch Test		Negative Patch test		Combined	
	Number	Percent	Number	Percent	Number	Percent
Piercing	3	37.5	37	44.6	40	43.9
No Piercing	5	62.5	46	55.4	51	56.1
Total	8	100.0	83	100.0	91	100.0

Table XXV: Frequencies of inflammation associated with body piercing in subjects grouped by patch test results

	Positive Patch Test		Negative Patch test		Combined	
	Number	Percent	Number	Percent	Number	Percent
Inflammation	3	37.5	24	28.9	27	29.7
No Inflammation	5	62.5	59	71.1	64	70.3
Total	8	100.0	83	100.0	91	100

SECTION SIX

Discussion and Conclusions

6.1. DISCUSSION

The results of this study suggest that the frequency of nickel sensitivity in this sample of dental workers is lower than that reported in other samples. In addition, there was no significant difference between the frequency of sensitivity in males and females. Previous studies (Bjorkner et al., 1994; Peltonen, 1979; Moffa et al., 1983) have found higher frequencies in females than in males. Blanco-Dalmau (1982) found the incidence of nickel sensitivity was in the region of 28.5% and that the occurrence of nickel sensitivity was more in females than in males. However, in different research by Magnusson et al. (1968) on the distribution of allergy from individual metal alloys nickel was ranked third in the metal series at 5.95 in sensitivity. At the other extreme, Koch and Baum (1996) revealed a signficantly higher incidence of nickel sulphate sensitivity in the range between 93 and 100 percent.

While this study provides no indication of the reason for the relatively low frequency of nickel sensitivity in this sample of people who would be exposed to nickel, it is interesting to speculate on possible reasons. These might include:

- a generally higher level of awareness of the dangers of nickel in the selected sample of dental workers resulting in a lower level of exposure and lower risk.
- a combination of socio-economic factors which might result of this sample being exposed to lower level of nickel in the general environment

- although this study provided no evidence of a relationship between age and sensitivity, the age profile of the sample (almost half of the sample less than 30 years of age) would limit any cumulative effect of exposure and could result in a lower than expected frequency of sensitivity.

There is no evidence in this study of a strong relationship between age and nickel sensitivity. The tendency for younger subjects to show a slightly higher frequency may well have arisen by chance because of the relatively small sample size. In addition, there was a tendency for more younger subjects to have some form of body piercing which (if this is a factor which contributes to sensitivity) might explain the higher frequency in younger subject and the lower frequency in older subject where piercing was less common. The fact that sensitivity is not more common in females who show a significantly higher incidence of body piercing complicates the interpretation of this information. A complete understanding of these factors would require a examination of a much larger sample.

While the possibility of reliably predicating individuals who might be more likely to be sensitive to nickel from personal information, history of allergy-related condition and from history of body piercing would be desirable from a clinical perspective, the data collected in this study did not provide any evidence that this is likely to be possible.

6.2 CONCLUSIONS

In conclusion, this study has demonstrated:

- a relatively low incidence (8%) of nickel sensitivity in dental workers in this sample
- no evidence of a relationship between sex and sensitivity
- no clear evidence of a relationship between age and sensitivity
- no clearly identifiable predictors of sensitivity to nickel

APPENDICES

APPENDIX ONE

THE UNIVERSITY OF ADELAIDE

Department of Dentistry

About the Nickel Sensitivity Study

The aim of this study is to collect information about numbers of people in our community who are sensitive or allergic to nickel which is a common metal used in jewellery and in some types of dental treatment.

We know from some overseas studies that about 30 percent of young women are likely to be sensitive to nickel and that in some countries 20 percent of all people show some reaction to nickel. Most commonly people who are sensitive to nickel develop a rash in the areas which come into contact with the metal but there are rare cases where nickel has been shown to cause a range of other health problems.

In our study we are also using a simple questionnaire to identify things which might help us predict those people who are most likely to be sensitive to nickel.

You might not benefit directly from agreeing to be in the study other than by finding out for sure whether or not you are sensitive to nickel. However, what you will be doing is helping us develop methods for identifying those people who do react badly to nickel.

What will we do if you agree to be in the study? First we will ask you to fill out a questionnaire which asks about whether you are allergic to other things or have any other health problems which might be associated with allergy. Then we will be placing two "Band-Aids" on the top part of your arm. One will contain some nickel (in the form of 5% nickel sulphate) and the other will be a "control" to see if you are allergic to the Band-Aid even if it contains no nickel. We will ask you to keep the "Band-Aids" in place for 48 hours. Then either we will remove them for you if it is a day when you will be in the Dental School of we will ask you to remove them and see if there is any reaction. If you remove them yourself and there is a reaction we will ask you to contact us. If not we will ask you what happened at your next visit.

If you get a reaction to the nickel patch you will probably be aware of some "itchiness" which will be gone within about a day of removing the patch. Occasionally, very sensitive people get some small blisters which will also clear up quickly. Very rarely the reactions are slow to go away in which case we will provide appropriate treatment. If the patch gets very uncomfortable you can remove it at any time and contact the staff involved in the study for advice. If you need to do this nothing about your clinical treatment if you are a patient, your employment (if you are a staff member) or your academic progress (if your are a student) will be affected.

The staff involved in this study are:

Dr Itone Muteba
Assoc. Professor Lindsay Richards

After hours these staff can be contacted on [redacted] if you have an questions or problems.

APPENDIX TWO

THE UNIVERSITY OF ADELAIDE

Department of Dentistry

CONSENT FORM

1. I _____ (please print) hereby consent to take part in the "Nickel Sensitivity Study"

2. I acknowledge that I have read the Information Sheet which describes the study

3. I have had the project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is given freely.

4. Although I understand that the purpose of this research project is to improve the quality of dental care, it has also been explained that my involvement may not be of any benefit to me.

5. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

6. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.

7. I understand that I am free to withdraw from the project at any time and that this will not affect me in any way, now or in the future.

8. I am aware that I should retain a copy of this Consent Form, when completed, and the relevant Information Sheet.

SIGNED ..... DATE.....

NAME OF WITNESS..... SIGNED.....
(Please print)

DATE.....

I, Itone Muteba / Lindsay Richards *(delete not applicable names)* have described to the person named above the nature of the procedures to be carried out. In my opinion she/he understood the explanation.

SIGNED..... DATE.....

STATUS IN PROJECT: Investigator

See also Information Sheet attached

APPENDIX THREE

ALLERGY ASSESSMENT

Name: .....

Date of Birth: .....

The following information will be used to develop methods for predicting whether or not people are likely to allergic to nickel.

The information will be regarded as strictly confidential and will not be revealed without your consent.

1. Do you have any known allergies?

- ☐ No (please go to Part 2)
- ☐ Yes, I think that I am allergic to the following things:
  - ☐ drugs or medicine (details: .....)
  - ☐ foods (details: .....)
  - ☐ plants or pollen (details: .....)
  - ☐ insect bites (details: .....)
  - ☐ metals (details: .....)
  - ☐ plastics or rubber (details: .....)
  - ☐ other things (details: .....)

2. Have you suffered from any of the following conditions:

Asthma	☐ yes	☐ no
Dermatitis	☐ yes	☐ no
Eczema	☐ yes	☐ no
Hayfever	☐ yes	☐ no
Hives	☐ yes	☐ no

3. Would you say that you are often affected by:

Itchy or sore eyes	☐ yes	☐ no
Running nose	☐ yes	☐ no
Sneezing	☐ yes	☐ no
Upset stomach	☐ yes	☐ no

4. Do you have pierced ears or any other body piercing?

- ☐ no (Go to Part 5)
- ☐ yes What types of jewellery do you wear? ☐ gold ☐ stainless steel ☐ other

Have you ever had an infection or painful swelling associated with wearing jewellery?

☐ yes ☐ no

5. Thank you for your help.

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