Allergy and Oral Mucosal Disease

Shiona Rachel Rees
B.D.S. F.D.S. R.C.P.S.

A thesis presented for the degree of Doctor of Dental Surgery of the University of Glasgow

Faculty of Medicine
University of Glasgow

Glasgow Dental Hospital & School
May 2001

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

SUMMARY

The purpose of this study was to assess the prevalence of positive results to cutaneous patch testing in patients with oral mucosal diseases and to assess the relevance of exclusion of identified allergens to the disease process. It was also attempted to identify microscopic features that were related to a hypersensitivity aetiology in patients with oral lichenoid eruptions.

The analysis was carried out retrospectively in the Departments of Oral Medicine and Oral Pathology in Glasgow Dental Hospital And School and the Contact Dermatitis Investigation Unit in the Royal Infirmary, Glasgow. A total of 1,252 patients with oral mucosal diseases who had been referred to the Contact Dermatitis Unit were assessed, and the prevalence of positive reactions to patch testing and contact urticaria testing in each disease cohort was compared to the prevalence of positive reactions in 100 control volunteers. Sections of specimens from patients with oral lichenoid eruptions were analysed using photographic standards and by counting cells and measuring the sections.

The results indicated that patients with oral mucosal diseases were significantly more likely to have demonstrable hypersensitivity to food additives, especially benzoic acid, and perfumes and flavourings, especially cinnamaldehyde, than controls. Dietary avoidance therapy to identified allergens caused improvement in the majority. Patients with oral lichenoid eruptions were significantly more likely to react to mercurial allergens on patch testing than patients with recurrent aphthous stomatitis or orofacial

granulomatosis. Microscopic examination revealed that the density of the inflammatory infiltrate was higher in those patients with oral lichenoid eruptions who had one or more positive patch tests or contact urticaria tests. They also had more disruption of the basal cell layer though this was of borderline significance.

It was concluded that patch testing and contact urticaria testing, together with the resultant allergen avoidance therapy, are useful adjuncts in the management of oral mucosal diseases. The presence of a florid (in terms of thickness and density) inflammatory infiltrate and disruption of the basal cell layer in cases of oral lichenoid eruptions, suggested that an allergic aetiology was more likely.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF PUBLICATIONS

Works published by the author during the course of this thesis are as follows;

Rees, S. R. & Gibson, J. 1997, "Angioedema and swellings of the orofacial region.", *Oral Diseases*, vol. 3, pp. 39-42.

Rees, S. R., Gibson, J., Forsyth, A., & Wray, D. 1997, "Thiomersal sensitivity in health care workers.", *BDJ*, vol. 183, pp. 395-395. [Letter]

Rees, S. R., Gibson, J., Forsyth, A., & Wray, D. 1998, "Prevalence of food and environmental allergy in oral mucosal disease." Journal of Dental Research 77, 895. [Abstract]

Flemming, C. J., Lucke, T., Forsyth, A., Rees, S. R., Lever, R., Wray, D., Aldridge, R., & MacKie, R. 1998, "A controlled study of gold contact hypersensitivity", *Contact Dermatitis*, vol. 38, pp. 137-139.

Wray, D., Rees, S. R., Gibson, J., & Forsyth, A. 2000, "The Role of Allergy in Oral Mucosal Diseases", *Quarterly Journal of Medicine,* vol. 93, pp. 507-511.

GLOSSARY OF ABBREVIATIONS

AE	angioedema
ACD	allergic contact dermatitis
BP	bullous pemphigoid
CDIU	Contact Dermatitis Investigation Unit
CG	cheilitis granulomatosis
CUT	contact urticaria testing
DBPC	double blind placebo controlled
DHT	delayed hypersensitivity testing
DILR	drug induced lichenoid reactions
EM	erythema multiforme
FA	food additives
FS	food substances (i.e. food additives, perfumes & flavourings and chocolate)
GDH	Glasgow Dental Hospital
GRI	Glasgow Royal Infirmary
MRS	Melkersson Rosenthal syndrome
MMP	mucous membrane pemphigoid
NRL	natural rubber latex
OAS	oral allergy syndrome
OCD	oral Crohn's disease
OFG	orofacial granulomatosis
OLE	oral lichenoid eruption
OLP	oral lichen planus
NICU	non-immunologic contact urticaria

P&F perfumes and flavourings

PV pemphigus vulgaris

RAS recurrent aphthous stomatitis

ACKNOWLEDGMENTS

My grateful thanks firstly go to my husband Paul, without whose love, support, and willingness to swap lifestyles, this could have never been achieved. To our children, Nathan, Amy and Bethany, my thanks for putting up with my absence and to my parents for all the housing, childminding and encouragement to keep going, all of which made it all possible.

I wish to thank Professor David Wray for keeping in touch, for proof reading, encouragement and advice, and for believing it could be finished.

My grateful thanks to Angela Forsyth (consultant dermatologist at Glasgow Royal Infirmary) and her team carried out the patch testing and the contact urticaria testing on all the patients at the Contact Dermatitis Investigation Unit (CDIU). For your friendship, training, advice and laughs, I am very grateful

My thanks are due to Professor D.G. MacDonald (Professor of Oral Pathology, Glasgow Dental Hospital And School) for allowing me to use the facilities of the Oral Pathology Department and for his advice.

For the diligent patient care at the CDIU, my thanks go to Dr. John Gibson (consultant and lecturer in Oral Medicine, Glasgow Dental Hospital and School), who runs the joint (dental/contact dermatitis) clinic there on behalf of the Oral Medicine Department together with Dr Angela Forsyth, and who

arranged the follow up care and support for patients with severe symptoms.
Thanks are due to the staff at the CDIU, for teaching me the ropes of patch testing and to Karen Milligan (senior dietician at Glasgow Royal Infirmary) gave skilled written and verbal dietary advice to the patients.
To the librarians at Glasgow Dental Hospital and School, Beverly Rankin and Christine Leitch, my grateful thanks for your cheerfulness and willingness to help.
My thanks are also due to Siobhan McHugh (research statistician) for teaching me statistics and ensuring I was on the right track, and to Digby James for unlocking the computer database at the start.

Thanks also to the extra childminders whose care has been superb and whose help invaluable; Eilidh Shannon, Kerry Shannon, Rosanne Bertram and Maura Edwards.

Finally my thanks are due to the patients and staff of the Oral Medicine clinic and to the 114 volunteers who willingly gave of their time, arms and backs and without whom, this study couldn't have happened.

CHAPTER 1 LITERATURE REVIEW

1.1. Allergy: Historical Review and Basic Mechanisms

1.1.1. Historical Review

Although doubtless many thousands of people in past generations suffered and indeed may have died from allergic diseases, it has only been in the last 200 years that allergic processes have been identified as causing clinical disorders.

> "All diseases occur at all seasons, but some diseases are more apt to occur and to be aggravated at certain seasons."
>
> Hypocrites Aphorisms III 19 (Guthrie 1958)

It is very unlikely that Hypocrites when he wrote these words was referring to allergic diseases, however the first discovery of ailments mediated by allergic processes was of what we now term 'hay fever', to which the above quotation certainly applies.

A doctor, John Bostock in 1819 described his own symptoms while speaking to the Royal Medical Society of London. He suffered from a 'periodical affection of the eyes and chest' to which he gave the name *Catarrhus aestivus* or 'summer catarrh' (Avenberg & Harper 1982). Later in the 19th century, Charles Blackley another doctor also afflicted with hay fever discovered that pollen was able to cause hay fever, conjunctivitis, rhinitis and asthma, and, when rubbed into a scratch on his arm a reaction became visible. He furthered these observations with studies relating the

amount of pollen in the air to his symptoms. He used sticky microscope slides to count pollen grains and even sent up a kite to determine that pollen was airborne to a height of 500 m above ground level.

Other 'allergic' diseases recorded in the 19th century were *vasomotor rhinitis* (recorded in 1881 by Herzog) and *Quinke oedema* (angioedema) which was described by Dr Heinrich Quinke (Mattingly, Rodu, & Alling 1993). At this time the mechanisms underlying the disease processes were not known although it was understood that the exogenous materials e.g. pollen were not noxious to mankind *per se* but only to certain individuals (Mygind et al. 1996). Jadassohn introduced what we now know as allergic contact dermatitis in 1895 by reproducing a reaction to iodoform on the skins of five individuals (Jadassohn 1895).

Scientists in the early 20th century began to investigate further the effects of toxic substances on humans and whether repeated dosing of small amounts of toxins could induce some sort of tolerance. This idea had been tried as early as in the 1st century BC by the Greek King Mithradates who upon noticing strange tastes in his food suspected poison and for the remainder of his long life took a daily dose of both various antidotes and poisons. That he succeeded in rendering himself immune to one of the poisons was proved after he failed to die from taking a lethal dose to end his own life (Duggan 1974).

The scientists involved were the Frenchmen, Charles Richet and Paul Portier, who in 1901 injected repeated doses of the toxin gathered from the jellyfish the Portuguese man-of-war, into an unfortunate large dog. Twenty-two days after the first injection, a further injection of one tenth of the fatal

dose was given which resulted in the rapid death of the dog within minutes. They used the word *anaphylaxis* to describe the reaction as it had had the opposite effect of *prophylaxis.* The next year Maurice Arthus demonstrated that anaphylaxis could be triggered using a substance that was not usually toxic to humans. He used horse serum injected into rabbits – the first dose showing no effect and the repeated dose giving rise to local inflammation and in some cases necrosis (Arthus 1903).

In 1905, an Austrian scientist Clemens Von Pirquet coined the word 'allergy' to describe the 'changed reactivity' of the subject to the provoking substance (from the Greek words 'allos' meaning altered and 'ergos' meaning work). He had been working in the fledgling discipline of immunology, trying to find vaccines for the common diseases of the day and discovered the paradoxical situation in that some individuals developed immunity to the disease, while in others, a reaction (what he termed a supersensitive response) deleterious to the patient occurred.

"The vaccinated person behaves towards vaccine lymph, the syphilitic towards the virus of syphilis, the tuberculous patient towards tuberculin, the person injected with serum towards this serum, in a different manner from him who has not previously been in contact with such an agent. Yet he is not insensitive to it. We can only say of him that his power to react has undergone a change." (von Pirquet 1906)

Von Pirquet also refers to episodes of acute urticaria following the ingestion of foods such as egg white and buckwheat though these are case reports rather than controlled clinical experiments. He gave the name 'anergy' (lack of reactivity) to what had been termed antianaphylaxis (decrease in

sensitivity following repeated doses of antigen) and 'allergen' to describe an antigen that provoked an allergic reaction (von Pirquet 1911).

In 1923, Cooke and Coca named the clinical forms of allergy 'atopy'. They defined those who suffered thus as;

"the individuals as a group possess a peculiar capacity to become sensitive to certain proteins to which their environment and habits of life frequently expose them." (Coca & Grove 1924)

They also realised that atopic subjects had an inherited predisposition to become sensitised. Other features of allergy were the ability to transfer the 'supersensitivity' to another by the transfer of serum. Prausnitz and Küstner in 1921 conducted the classic experiment to prove that passive transfer of allergy was possible (Prausnitz & Küstner 1921). They obtained some serum from Küstner who had a severe allergy to cooked fish and injected this intradermally into the abdominal skin of Prausnitz. The next day they injected the same area with fish extract and he elicited a marked reaction to it, similar to the reaction that Küstner had from the fish extract. Coca and Cooke named the 'transfer factor' 'reagin'.

Later it became clear that reagin was associated with antibody but with distinctive features; it could not be demonstrated in serum by the usual precipitation reaction, was heat labile and had the ability to become fixed to the skin for prolonged periods. Reagin was also capable of producing the wheal and flare response.

Developments in the field of allergology continued apace with the discovery of the two main immunological pathways of response to an allergen, the humoral and cellular mechanisms. Developing this further, in 1962 Coombs

and Gell in their book 'Clinical Aspects of Immunology', gave a simplified view of four main allergopathological mechanisms. They based this classification on the circumstances of the initial antigen-antibody reaction and stressed that it was merely a classification of the initiating mechanisms of the allergic response which were secondarily classified by other differences.

"Again it must be emphasised that the pattern seen in any one human disease is often complex, involving not just one but several of the above pathways or responses" (Gell & Coombs 1968)

Considered in this classification were types of allergic reaction that firstly, resulted in tissue damage and secondly, involved the sensitisation of host cells. Therefore excluded were immune tolerance reactions and allogenic reactions. The authors were well aware of the variety of ways that allergies could be grouped e.g. by allergen type or source, by drug reactions, autoallergies, time and duration of response after allergen contact, but were successful in choosing a basic classification that is still helpful today (Gell & Coombs 1968). The types of allergic reactions as originally described are outlined below:

Type I Reaction (anaphylactic, reagin-dependent)

Initiated by the allergen reacting with tissue cells that have been passively sensitised by antibody that was produced elsewhere. This leads to the release of vasoactive hormones such as histamine.

Type II Reaction (cytotoxic)

Here the antibody reacts with either a) an antigenic component of a cell or tissue element or b) antigen or hapten that is closely linked with these. Complement is usually necessary to effect tissue damage.

Type III Reaction (damage by toxic complexes)

This starts when the antigen reacts with potentially precipitating antibody in the tissue spaces, forming microprecipitates in and around the small vessels which in turn causes cellular damage; or when antigen in excessive quantities reacts with potentially precipitating antibody in the blood stream, forming soluble circulating antigen-antibody complexes which are deposited in the blood vessel walls or basement membrane and cause damage by local inflammation.

Type IV Reaction (delayed, tuberculin-type, cell-mediated)

This reaction is initiated by the reaction of specifically modified mononuclear cells (previously sensitised) containing a substance or mechanism capable of responding specifically to an allergen deposited at a local site. The exact mechanism of this type of reaction is still uncertain, but it is manifested by the infiltration of cells, at the site where that antigen is, without the necessary participation of free antibody.
(Gell & Coombs 1968)

Bendixen in 1966 attempted a classification of allergy based on the clinical diseases that the different mechanisms produced. He divided hypersensitivity (note that he thought that the word 'allergy' had already lost its meaning and used 'hypersensitivity' to describe what Von Pirquet

had by 'allergy'!) into two parts between which he thought there was a clear distinction. Humoral (immediate) type and the cellular (delayed) type. He based the distinctions primarily on the method by which passive transfer of hypersensitivity could be done (serum and reagin compared with the injection of killed micro-organisms), on the time of onset of symptoms after allergenic challenge (minutes compared with hours and days) and by the different histological pictures produced by e.g. a local anaphylactic response (essentially a vascular reaction) and the tuberculin hypersensitivity response (antigen containing tissue invaded by mononuclear cells). He further divided the humoral hypersensitivities into four main types; Arthus, anaphylactic, reagin, and cytotoxic types, and the cellular hypersensitivities into five groups; infection, transient, contact, transplantation and organ-specific types. He was however aware of the provisional nature of his classification and of the amount of information that was lacking about these mechanisms and diseases (Bendixen 1966).

In 1967, reagin was identified to be IgE and allergology became integrated into the discipline of clinical immunology. Teruko and Kimishige Ishizaka, a husband and wife team, did this by eliminating anti-IgA, IgD, IgM and IgG antibodies from the serum (obtained from a rabbit which had been previously inoculated with the serum of a person with an extreme allergy to ragweed pollen) by precipitation with human IgA, IgD, IgM and IgG and found that a substance capable of transferring sensitivity to a particular allergen was still there. Thus they discovered that reagin antibody belonged to the same class of immunoglobulins and named it gamma E globulin (Ishizaka, Ishizaka, & Hornbrook 1966). At the same time, though

independently, Johansson and Bennich isolated IgE though it was more by luck while working with a patient whose disease processes (myeloma) caused excessive production of reagin which they isolated and named IgND after the patient's initials. They demonstrated by radioimunoassay that IgND is present in very small quantities in human serum and discovered also that the level of IgND was raised in atopic patients. The two teams met in 1967 and agreed to call it IgE (Mygind et al. 1996).

Allergy definition: Hypersensitivity caused by exposure to a particular antigen (allergen) resulting in a marked increase in reactivity to that antigen upon subsequent exposure, sometimes resulting in harmful immunologic consequences (Stedman's Medical Dictionary 2000).

1.1.2. Basic Mechanisms and Oral Mucosal Immunity

Although the allergic mechanisms are often still classified according to the Gell and Coombs definition, the groups often overlap or exist simultaneously (Krogh & Maibach 1982). Much more is now known about the individual processes involved and there are elements of both the humoral and the cell mediated pathways in most allergopathogenic mechanisms.

1.1.2.1.Saliva

The oral cavity has physical and immunological defence mechanisms to cope with the exogenous immunogenic challenge that presents itself in food stuffs, liquids and airborne materials. Potential allergens are washed away through the cleansing effect of saliva minimising contact time. The average unstimulated flow rate of saliva in healthy individuals is 0.3ml/minute (Colin Dawes 1996). The average bacterial load alone in 1ml of saliva is 10^9 so the swallowing action removes a considerable antigenic load from the oral mucosa (Bowen 1996). The saliva also contains digestive enzymes and many types of proteins including immunoglobulins (predominantly secretory IgA), which commence the breakdown of food stuffs and other carbohydrates, and remove some antigens, particularly viral ones, respectively (Mandel 1987). The role of IgA in the serum may be detrimental to the host against some capsulated bacteria such as gonococci,

since it may block the bactericidal activity mediated by complement, IgG and IgM though this has only been shown in serum and not in saliva as yet (Croitoru & Bienenstock 1991).

1.1.2.2.Mucosa

The mucosa of the gastrointestinal tract has to maintain a fine balance between defence of the host and attacking and neutralising noxious chemicals and harmful bacteria, viruses and fungi. Its immune systems have to be selective to avoid immune mediated damage to itself, while at the same time the function of much of the gastrointestinal tract is to absorb nutrients.

The oral mucosa consists of keratinized (hard palate and alveolar ridges) and non-keratinized stratified squamous epithelium (all the rest except the dorsum of the tongue which is covered with keratinized, specialised oral epithelium). Protective mechanisms such as a high epithelial turnover and the presence of a lipid permeability barrier in the superficial epithelium assist in guarding the epithelium even though the oral mucosal permeability is much lower than that of abdominal skin (Healy et al. 2000). Despite the fact that the non-keratinized oral epithelium doesn't have the protective layer of keratin as the skin does, the ability of the oral mucosa to become sensitised to an antigen is less than that of the skin, indeed irritant reactions to chemicals are rare (de Groot, Weyland, & Nater 1994; Jones & Beltrani 1997). This is because when an allergen is absorbed through the mucosa, the dense vascularity underlying the oral epithelium ensures rapid clearance

of allergens away from the local area and into the blood stream (Andersen 1978). However this can lead to systemic effects occurring; exacerbation of asthma was reported after exposure to toothpaste (Subiza et al. 1992) and extra-oral contact dermatitis was reported after a nickel plated fixed orthodontic appliance was fitted in a 12 year old boy who developed marked perioral and periorbital eczema with involvement of the anterior scalp and loss of hair. A nickel patch test elicited a positive reaction and the eczema resolved after removal of the metal appliances (de Silva & Doherty 2000). The Langerhan's cell density in oral mucosa is reduced compared to that of skin: 84-308 mm^{-2} in oral mucosa compared to 4500 mm^{-2} in skin, which reduces the sensitising potential in oral mucosa (Kaaber 1990).

1.1.2.3.Cells

Antigen Presenting Cells

Much work has been done on the functions and structures of antigen presenting cells. In the human oral mucosa, the main antigen presenting cells (APC) are the Langerhan's cells (LC) which express major histocompatibility (MHC) class II antigen on their cell surfaces. However, the presence of MHC class II molecules on the cell surfaces of oral keratinocytes and the fact that there is, in allergic inflammation, a significant presence of intraepithelial T lymphocytes, suggests that they too have a role to play in antigen presentation (Eversole 1994). The numbers of LCs in the skin are depleted markedly when exposed to UVA light and

correspondingly reaction to noted sensitisers such as dinitrofluorobenzene (DNFB) decreases rapidly. This has been shown to be a local rather than a systemic response in a murine model (Toews et al. 1980). Crutchley et al found a regional variation in Langerhan's cell distribution in normal oral mucosa with the highest to lowest concentration areas as follows; dorsum of the tongue, buccal mucosa, lip mucosa, lateral border of tongue/hard palate and floor of mouth (Cruchley et al. 1989). Langerhan's cell numbers have been found to be increased in human contact dermatitis lesions of the skin, and in the early stages of erythema multiforme lesions (Farthing, Matear, & Cruchley 1990; Lombardi, Hauser, & Budtz Jorgensen 1993).

Lymphocytes

The so called cell mediated response of delayed hypersensitivity is one in which the following must happen; the antigen must penetrate the stratum corneum, interact with dermal or epidermal cells, interact with the immune system and finally an inflammatory response occurs (Thestrup-Pedersen, Larsen, & Ronnevig 1989). The primary cell involved here is the T lymphocyte although in concert with a host of other cells and mediators. The T cell response is now known to exist as two different and mutually repressive systems, one subset of T helper cells (Th1) leading to a Type IV hypersensitivity reaction and the other subset of T helper cells (Th2) leading to a Type I reaction. Naïve T helper cells (Th0) are influenced by either interleukin 12 (IL-12) or IL-4. IL-12 is produced by the action of microbial antigens stimulating macrophages. It stimulates Th1 to produce gamma

interferon (IFN-g) which both inhibits the stimulation on Th2 cells and attracts macrophages, and IL-2 which is chemotactic to other T cells. IL-4 is produced by an as yet unknown monocytic antigen presenting cell and switches Th0 to produce IL-10 which inhibits the Th1 pathway, IL-4 which acts on B cells to produce IgE and IL-5 which attracts eosinophils (Mygind et al. 1996).

Eosinophils

In 1879 Paul Erlich noticed for the first time a mononuclear cell, in the circulatory system. He named it Eos after the Greek goddess of the dawn as it could be stained bright red with the histological stain eosin (Mygind et al. 1996). Tissue eosinophilia has been used as a marker for allergic responsiveness and atopy.

Mast cells and Basophils

Mast cells and their granules were described by Paul Erlich in 1877 (Avenberg & Harper 1982). Mast cells and basophils are the main cells involved in a Type 1 hypersensitivity reaction mediated by IgE. Mast cells and basophils are often considered together despite the difference in their maturation, development and site of action. Mast cell progenitor cells differentiate from stem cells in the bone marrow and enter the circulatory system to migrate into the tissue in which they develop into mature mast cells. Basophils develop along a common pathway with eosinophils from myeloid progenitor cells and it is the action of interleukin 5 (IL-5) that

determines which is the ultimate cell type. Basophils remain in the circulatory system throughout their lifetime (Mygind et al. 1996). However, they share many common features; both possess high affinity IgE receptors which when activated stimulate both cells to release mediators from granules contained within their cytoplasm, both also manufacture secondary mediators such as eicosanoids (Barrett 1991). Most of these chemical mediators are shared, though both manufacture different ones too.

Mast cells can be divided into two groups; those found primarily in the connective tissue of the skin and containing the enzymes tryptase and chymase, and those found in mucosal tissues such as lungs and gastrointestinal mucosa which contain the enzyme tryptase only (Irani et al. 1986). These are classed as MC_{TC} and MC_T respectively. The relative proportions of each vary in different tissues and in different disease states (Mygind et al. 1996).

1.1.2.4.Cytokines and Mediators

Cytokines are small soluble proteins that act as the messengers of the immune system, produced by cells to have an influence on other cells. Their known number is growing rapidly as more research is carried out and more are discovered. Cytokines have a crucial role to play in controlling the T cell differentiation as has already been described.

Histamine remains the most important of the chemical mediators as can be realised from the amount of antihistamine preparations available to treat some allergic disorders (British Medical Association & Royal

Pharmaceutical Society of Great Britain 2000a). It is released from both mast cells and basophils following degranulation and is widely used as a marker of mast cell activation (Barrett 1991).

1.1.2.5.Humoral Mechanisms in Oral Mucosa

IgE has been termed the 'master hypocrite of our body's defence system'. Though it exists in minute quantities in the human serum and performs useful functions in the host response to antigens, it is also capable of inflicting harmful and sometime severe effects on many individuals in our society today (Katz 1984). Type I reactions, though essentially immediate and short lasting, may also have a late phase response occurring hours after the immediate response (Solley et al. 1976). Type I reactions occur in some angioedema and urticarial reactions and in some drug reactions. The effect of Type I reactions on the oral mucosa is usually localised erythema, oedema and smooth muscle spasm (Spouge & Diamond 1963).

Oral allergy syndrome (OAS) has been described in the last 12 years comprising a number of IgE mediated hypersensitivity reactions localised in the oral cavity and sometimes followed by systemic symptoms. It is elicited upon exposure to food allergens related to pollens such as fruits and nuts e.g. papaya, avocado, banana, melon, peanut, chestnut, passion fruit, kiwi fruit, tomato, mango ,pineapple and peach, and is often associated with latex allergy – the 'latex-fruit syndrome' (Brehler et al. 1997). These are also often associated with pollen allergy (particularly birch, ragweed and grass) due to the presence of cross reacting allergens. Reactions may be severe

and require emergency medical treatment as in one case of OAS to chestnut (Antico 1996). Two separate reports of OAS to uncooked pork have been described suggesting that this syndrome has a wider aetiology than fruit and latex, though one patient had a family history of pollinosis and herself had experienced rhinoconjuctivitis to horse dander while the other had allergy to *Dermatophagoides* species (Asero, Mistrello, & Falagiani 1997; Liccardi, D'Amato, & D'Amato 1996).

Type II or cytotoxic reactions are not usually seen in the oral cavity though they may exert secondary effects such as thrombocytopenic purpura as a result of thrombcytopenia (Mygind et al. 1996).

Type III or immune complex reactions are seen in the oral cavity in erythema multiforme (EM) where in nearly half of cases the antigen is estimated to be of pharmacological origin. The other major antigen associated with EM is herpes simplex virus (Manganaro 1996). Circulating immune complexes may also act directly on blood vessels and precipitate angioedema (Kao & Zeitz 1993).

1.1.2.6.Cellular Mechanisms in Oral Mucosa

As has already been stated, the oral mucosa is more resistant to contact sensitivities than the skin and this is shown by the relatively small number of patients that present with allergic contact stomatitis (ACS). However Type IV hypersensitivity reactions or contact sensitivities have been found

in a number of cases, though the prevalence of contact stomatitis among the general population is at present unknown. Type IV reactions are characterised by the death of individual cells which in epithelium may lead to vesiculation and/or ulceration (Spouge & Diamond 1963). On a review of the literature pertaining to ACS, Jones and Beltrani found that a wide range of materials have been implicated as allergens in these cases (Jones & Beltrani 1997). It is recognised that ACS occurs less frequently than allergic contact dermatitis (ACD) and this may be due to the fact that the skin contains proteins that more readily combine with simple chemicals to form allergens (Rietschel & Fowler 1997). In contrast, Cawson and Odell consider that contact stomatitis is rarely if ever seen (Cawson & Odell 1998).

There is some overlap with humoral immunity and Types I and IV have been identified to coexist in some cases of allergy to castor bean (Kanerva, Estlander, & Jolanki 1990) and latex (Placucci et al. 1996). Absorption of an allergen through the skin may not only result in a Type IV hypersensitivity reaction, but occasionally also a Type I or III reaction (Friedman & Perry 1985).

1.1.3. Antigens and Allergy Testing

1.1.3.1.Antigens and the Oral Mucosa

Allergic contact dermatitis is by definition a disease of the skin and is often diagnosed by patch testing. However, other epithelial structures such as the oral mucosa may be involved in a similar way and these patients are less likely to be seen in a patch testing clinic. Allergic contact stomatitis presents primarily by the subjective symptoms experienced by the patient (burning, itching, loss of taste, soreness) rather on the physical signs which may be less prominent but include erythema, oedema, and rarely vesiculation (de Groot, Weyland, & Nater 1994). The pathological mechanisms of many oral diseases have been linked to allergic processes. These are such diseases as lichenoid reactions of the oral mucosa, recurrent aphthous stomatitis, erythema multiforme, angioedema, desquamative gingivitis, plasma cell gingivitis, oral dysaesthesia and orofacial granulomatosis (Lamey & Lewis 1990; Lewis et al. 1989; McGivern et al. 2000; Rosen et al. 1993; Silverman & Lozada 1977; Staines, Felix, & Forsyth 1998; Whitley, Shepherd, & Ferguson 1991; Wray, Vlagopolous, & Siraganian 1982). Some have a very strong link, for example in the case of OFG (Rees 1999), and some, such as angioedema, have a weaker link where the role of allergopathologic mechanisms have a major contribution only in certain subtypes of the disease and play a lesser part in the pathogenesis of the other types (Rees & Gibson 1997).

The antigens involved in stimulating the allergic processes in the above diseases can be complete or incomplete such as those acting as haptens, organic e.g. viral, or inorganic e.g. nickel.

Potentially, all elements and compounds have the ability to elicit an allergic response from a human being. Foods stuffs have by far the most potential to elicit hypersensitivity reactions given that it has been estimated that the average person's gastrointestinal tract will process more than 100 tons of food during a lifetime (Sampson & Metcalfe 1991). However, most substances humans interact with do not provoke an adverse immune response. Fortunately the immune system usually copes with the onslaught of potentially immunopathogenic material with no resultant clinical problems and though the prevalence of allergy to ingested materials is at present unknown, it is estimated to be in the region of 1-2% of the general population (Anderson 1997b). This figure takes into account the much higher incidence among infants of food intolerance and allergy which may be as high as 8% in some groups (Anderson 1997b).

As well as food stuffs themselves, food additives (substances with no nutritional value) are added to foods to alter their chemical properties. Modern Western civilisation demands pre-prepared foods with long shelf lives, enhanced food colours and flavours, and high yield farming that ensures that most foods are available all year round. It is estimated that between 2,000 and 20,000 types of food additives are available for incorporation into foods (Bosso & Simon 1991). Some foods and substances added to enhance, preserve or stabilise foods are known to be

more likely than others to elicit a response from the immune system though most have little or no history of provoking adverse reactions.

The antigenic agents commonly involved in stimulating allergic responses in the oral cavity can be divided into seven groups:-

Dental home care products

Dental materials and medicaments

Metals used in dentistry

Rubber products used in dentistry

Foods

Food additives

Cosmetics

(Fisher 1995; Jones & Beltrani 1997; Lewis, Shah & Gawkrodger 1995).

It is of course to be remembered that many other materials are habitually placed in the mouth. A case of desquamative gingivitis resolved after a patient changed her type of nail varnish. She was patch tested which elicited a positive result to formaldehyde resin and this was found in the patient's nail varnish (Staines, Felix, & Forsyth 1998).

The standard procedure for allergy testing involves: a history of exposure to the allergen, a positive allergy test, allergen avoidance leading to resolution of the symptoms and/or signs and a double-blind placebo controlled allergen rechallenge leading to recurrence of the symptoms and/or signs (Sicherer & Sampson 1999; Williams & Bock 1999). In the diagnosis of food allergy, the double-blind placebo controlled food challenge is considered the gold standard of allergy testing, often used without any other positive test results

(Sicherer & Sampson 1999). Unfortunately all these steps are rarely carried out and much of the literature includes anecdotal case reports.

Dental home care products

In a study involving 16 patients who had allergic reactions to toothpastes, Lamey et al found that the compound most likely to have caused these was cinnamaldehyde (Lamey et al. 1990). Cinnamaldehyde was identified by patch testing to be the cause of oral symptoms in 7 patients in another study (Kirton & Wilkinson 1975) and another study reported one patient reacting to cinnamaldehyde in a toothpaste (Downs, Lear, & Sansom 1998). Mint oil constituents are found in toothpastes and mouthwashes as well as confectionery, cosmetics etc, and have been reported as causing allergic manifestations (Downs, Lear, & Sansom 1998; Smith 1968; Worm et al. 1998). Though most authors have reported local effects, systemic effects have been noted after oral contact with toothpastes. There has been a report of asthma being provoked by the mint flavours in toothpastes and confectionery, though the mechanism for this was considered by the authors to be idiosyncratic as skin prick tests were negative and specific IgE could not be demonstrated (Subiza et al. 1992). A Danish study found that allergic contact dermatitis (ACD) of the skin was aggravated by the oral contact. Three children aged between 2 and 3 years had vaccination granulomas following the aluminium hydroxide containing triple vaccination programme and in each, patch testing gave a positive reaction to aluminium chloride. The lesions had failed to respond to corticosteroids and questioning revealed that each child used a brand of toothpaste that utilises aluminium oxide as its abrasive agent, the lesions resolved upon

ceasing use of the aluminium containing brand and in two out of the three cases, the ACD reappeared within four days after rechallenge with the toothpaste (Veien, Hattel, & Laurberg 1996b).

A Finnish study was carried out in 1995 to assess the pH of all available toothpastes on the market in Finland. They found that as far as the pH is concerned toothpastes are unlikely to cause irritant reactions as the pH was fairly neutral in all of the 48 toothpastes studied (pH 5.5-8.9). On an extensive review of the literature the authors found that most of the constituents in most types of dentifrices have in the past been reported to have caused allergic reactions. They found that the most common allergens were identified as cinnamaldehyde, cinnamon oil and peppermint (Sainio & Kanerva 1995). Anethole is another toothpaste flavouring agent that has been reported to cause adverse reactions in certain people, in the case reported giving rise to both extraoral (cheilitis and perioral eczema) and intraoral (erythema and desquamation of the mucosa) manifestations (Franks 1998). Mouthwashes also can contain flavourings such as eugenol and peppermint which have been reported as causing contact dermatitis and intraoral oedema respectively (Dooms-Goossens et al. 1977).

Dental materials and medicaments

That dental materials are of importance in causing allergic reactions is shown by the fact that a standard list of patch test allergens common in dentistry has been drawn up (Axéll et al. 1979).

Materials used in dental products such as instruments, medicaments and medicines contain a wide variety of compounds and in order to elucidate

sensitivity information more easily from patients with suspected allergy to dental materials, dental screening series of allergens have been developed (Axéll, Bjorkner, Fregert, & Niklasson 1979). Prophylactic paste contains similar ingredients to toothpastes and therefore has been dealt with in the previous paragraph.

A peppermint containing antiseptic spray used in the oral cavity of a patient who was later found to be allergic to some of the ingredients of peppermint oil, caused intraoral oedema and a burning sensation (Dooms-Goossens et al. 1977).

Eugenol

Eugenol is a constituent of many dental preparations including temporary and intermediate tooth dressings which often combine zinc oxide with eugenol, periodontal and endodontic dressings, denture base material and impression material (Wiltshire, Ferreira, & Ligthelm 1996). Eugenol has been reported as causing allergic contact dermatitis after occupational exposure in a dental nurse (Kanerva, Estlander, & Jolanki 1998), and acute allergic reactions in the oral cavity of a patient after a temporary dressing was placed and again after a small amount of eugenol-containing endodontic sealer was used (Barkin, Boyd, & Cohen 1984).

Colophony

Colophony is used together with eugenol in many periodontal dressings (Wiltshire, Ferreira, & Ligthelm 1996), and has been shown to cause allergic reactions. It is also a component of cavity varnishes and other resin based formulations. In a study of 18 patients with a history of reacting to

dental materials, 16 had a positive patch test to either colophony, eugenol or both. It was likely that these patients had become sensitised to these ingredients during dental treatment (placement of periodontal dressings was thought the most likely procedure) (Koch, Magnusson, & Nyquist 1971).

Methyl methacrylate

Methyl methacrylate has been suspected of causing many allergic reactions in the mouth particularly when patients complain of soreness or burning in the denture bearing area. However many of the seen incidences of denture stomatitis are a direct result of infection by *Candida albicans* of the palate particularly under a complete upper denture (Brunelle et al. 1997). This having been said, methacrylate has been shown to have caused a cutaneous allergic contact dermatitis which clinically and histologically had a lichen-planus like appearance (Kawamura et al. 1996) which lends credence to the possible aetiology of methacrylate allergy in some acrylic denture wearers as has been suggested by the following authors; one patient (Lamey et al. 1994), one patient (Stenman & Bergman 1989), one patient (van Joosst, van Ulsen, & van Loon 1988) and two patients (Kaaber & Nielsen 1979). Out of 690 patients referred for patch testing with suspected methacrylate allergy, only 3.6% (n=25) had a positive result on patch testing (Franz 1982), thus indicating that the numbers of true methyl methacrylate allergies are fairly small.

Thiomersal

Though not specifically used in dentistry, thiomersal sensitisation is found in increased numbers among medical and dental personnel. The cause of

this is likely to be the vaccination courses administered to those in contact with blood and blood products against Hepatitis B Virus.

Metals used in dentistry

Allergic reactions have been shown to many of the metals that are used in the manufacture of various dental alloys. Several patients react to up to six different metals and the term 'dental restoration metal intolerance syndrome' has been suggested for those patients (Hay & Ormerod 1998; Koch & Bahmer 1995).

Mercury

Mercury is used in amalgam which has been in use for over 150 years (Kaaber1990) and has been the subject of much speculation and research regarding its effect on oral tissues and the body as a whole. Oral disease related to mercury hypersensitivity is usually in the form of lichenoid reactions, though intraoral bullae and urticaria affecting the skin of the head and neck has been reported following a repair to an amalgam restoration (McGivern et al. 2000). A more detailed review is dealt with in section 1.2.5.2.

Nickel

Nickel allergy is the most common cause of allergic contact dermatitis (ACD) and this has been attributed in the main to the increase in body piercing (mainly ear) and using non-precious metal jewellery for the studs or rings used (McDonagh et al. 1992). Jones et al found a 20% and 2% incidence of nickel sensitivity among 50 women and men respectively, while Prystowsky found that 9% of 698 women and 0.9% of 360 men gave

positive reactions to a nickel patch test (Jones et al. 1986 ; Prystowsky et al. 1979). The differences between the sexes in part may be due to the fact that more women (82%) than men (0.6%) are likely to have their ears pierced (McDonagh et al. 1992), though with the increase of body piercing in males, the incidence of nickel sensitivity has also increased (Meijer et al. 1995). Nickel is found in the environment in many other ways: metal clasps, studs and buttons on clothing, personal items such as keys, spectacle frames and household items such as scissors, paperclips, screws nails etc. Cooking with stainless steel pots can contaminate foods as small amounts of nickel can leach out. Nickel reactions in the oral cavity are fortunately rare considering the amount of nickel in the environment and placed in the mouth in the form of fixed and removable prostheses, nickel plated pins, needles, metal lipstick holders and mouthpieces of musical instruments (Fisher 2000). Moffa et al (1977) exposed ten subjects with cutaneous positive reactions to nickel and ten control subjects to nickel chromium alloy on the skin and oral mucosa (using a removable acrylic palatal appliance). It was found that 80% of the nickel sensitive group responded positively to the cutaneous application of alloy and 30% to the intraoral alloy; all of the controls were negative (Moffa, Beck, & Hoke 1977). van Loon tested five subjects who had demonstrated a positive patch test to nickel sulphate with an intraoral nickel foil patch test for one week. The areas of mucosa adjacent were examined and biopsied revealing clinical and histological evidence of contact stomatitis. In five subjects not sensitive to nickel on patch testing, the same test gave no response (van Loon et al. 1984). Reported cases of intraoral reactions to nickel in subjects who have

had a positive cutaneous patch test to 5% nickel sulphate have involved crowns and bridges, and orthodontic appliances (de Silva & Doherty 2000; Lamster et al. 1986; Lyzak et al. 1994). One publication reported on a case where the 14 year old patient, in active orthodontic treatment utilising a metal face bow, developed systemic contact dermatitis affecting limbs, trunk, face and scalp. The patient had a positive patch test reaction to nickel and his symptoms resolved after removal of all the metal components from his mouth and face (Kerosuo & Kanerva 1997). Many nickel sensitive (cutaneous) people are able to tolerate nickel in relation to the oral mucosa, however, as was demonstrated in studies of ; ten patients (Spiechowicz et al. 1984), ten patients (Jones et al. 1986) and one patient (Basker 1981). The availability of nickel ions, their form and concentration seem to affect the ability of the mucosa to respond. In a study of 1,085 consecutive females in active orthodontic treatment or retention, none had any symptoms of nickel hypersensitivity in the oral cavity (Staerkjaer & Menné 1990).

Contact urticaria/angioedema has also been the sequelae of nickel contact in hypersensitive patients (Fernandez-Redondo, Gomez-Centeno, & Toribio 1998).

Oral tolerance specific to nickel has been shown to be able to be induced by early oral exposure to nickel via orthodontic braces prior to ear piercing leading to specific unresponsiveness in some patients (van-Hoogstraten et al. 1991). In guinea pigs, oral tolerance to nickel and chromium was induced by oral feeding prior to cutaneous sensitisation (van Hoogstraten et al. 1992). One nickel sensitive individual experienced resolution of long

standing forearm and hand eczema after placement of four intraoral nickel containing crowns (Spiechowicz et al. 1984).

New developments to decrease the exposure of nickel to mucosa and skin include the manufacture of metals bonded to resins, new nickel-free alloys and metals coated with titanium oxide (Vilaplana & Romaguera 1998).

Cobalt-Chrome

Cobalt-chrome is a common metal used in cast partial dentures primarily and has been reported as precipitating allergic contact dermatitis in a small number of patients (Fisher 2000).

Gold, Palladium and Copper

Gold hypersensitivity has been reported as being as high as 13% in 100 patients referred for routine patch testing at a contact dermatitis clinic (Sabroe, Sharp, & Peachey 1996) yet ten years earlier it was considered very rare (Rapson 1985). This also may be due to the increase of ear piercing as Sabroe et al (1996) considered that ear piercing might be a risk factor for gold hypersensitivity and found that 92% of the 13 with positive patch tests to gold had had their ears pierced. An intraoral contact lesion to gold in a dental crown was reported in 1984 which was confirmed by patch testing (Wiesenfeld et al. 1984).

The incidence of palladium allergy has increased in recent years and will probably continue to do so given that manufacturers are using it in more alloys as they develop more nickel-free products (Vilaplana & Romaguera 1998). Palladium was reported causing an intraoral reaction in a patient who had four successive bridge prostheses made using palladium containing

alloys (Koch & Baum 1996), though van Loon et al had found that in five patients who had positive reactions to palladium in a cutaneous patch test, none reacted to palladium foil when placed intraorally, next to the mucosa for one week (van Loon et al. 1984). One study found that the frequencies of gold, palladium, nickel and chromium allergy was significantly elevated in patients referred with oral symptoms compared to eczema sufferers (Marcusson 1996).

Copper is much less likely to elicit allergic responses but has been reported as a "possible cause of oral lesions of lichen planus" (Fryholm et al. 1969).

Electrogalvanism

Intraoral currents with saliva acting as an electrolyte between different metals used in dental restorations have been suspected of causing lichen-planus like reactions (Bánóczy, Roed-Petersen, & Pindborg 1979), symptoms of pain and altered taste, and increasing the corrosion rate thus providing free metallic ions that may act as sensitisers of the oral mucosa. However no correlation has been found between high electric potentials between metallic contacts in the mouth and oral disease (Hugoson 1986) and a study investigating the metal ions present in saliva found that there was no correlation between oral galvanic activity and metal ions in saliva or burning mouth symptoms, though the study group was small (Nilner & Glantz 1982). Lind et al (1984) reported a case of lichen planus-like lesions of the oral mucosa related to corroded amalgams and suspected that the corrosion of metals increased by galvanism with the cathode being a cobalt –chrome partial denture and the anode the amalgam restorations. This led to mucosal sensitisation to mercury (the patient tested positive to

mercury on cutaneous patch testing and to the lymphocyte transformation test) (Lind, Hurlen, & Stromme-Koppang 1984).

Rubber products used in dentistry

With the increased awareness of viral infections such as HIV and Hepatitis, gloves manufactured from natural rubber latex (NRL) are being increasingly used by healthcare personnel. Accordingly, there has been an increase in the reports of adverse reactions to them with the prevalence of adverse reactions among dentists in the UK being between seven and ten percent (Field 1998). NRL is also used in dental dam and orthodontic elastics and Type I reactions to dental dam in particular have been reported (Field et al. 1997). There are copious references in the literature regarding allergy to NRL and special care has to be taken with affected patients as the sequelae of an encounter with the allergen can be fatal (Placucci et al. 1996; Rosen et al. 1993). Concurrent allergy to peanut, fruits such as banana and melon and others associated with OAS, or a history of repeated exposure to NRL are all risk factors for developing NRL allergy (Field et al. 1998). Contact with NRL in sensitive individuals can also elicit contact dermatitis without the usual IgE mediated pathways (Shaffrali & Gawkrodger 1999). Coexistence of Types I and IV hypersensitivity reactions to NRL has been reported (Placucci et al. 1996).

Rubber products also contain vulcanising and antioxidising agents such as thiuram, carba and mercapto chemicals that have the potential to give rise to delayed type hypersensitivity reactions.

Foods

"One man's meat is another man's poison"

Lucretius (1st century B.C.) (Avenberg & Harper 1982)

The prevalence of food allergies appears to be on the increase in recent years with the prevalence among an American population estimated at 1.5% of the general population, and 5% of children under 3 years (Sampson 1997). In Gran Canaria, the prevalence is also estimated to be under 1.6 % among adults (Castillo et al. 1996), while in the UK a prevalence rate of 1.4% has been reported in the general population (all ages) (Rance et al. 1999). Food allergies have been implicated as a causative or complicating factor in many and sometimes diverse diseases such as coeliac disease, allergic eosinophilic gastro-enteritis, dermatitis herpetiformis (Sampson 1997), asthma (Bruijnzeel-Koomen et al. 1995) cystic fibrosis (Lucarelli et al. 1994) and migraine (Grant 1979). Atopic dermatitis has been linked to IgE mediated food allergies particularly in children (Eigenmann et al. 1998) though the link with food allergy in adults to atopic dermatitis was not shown by Castillo (Castillo et al. 1996) and is considered to be controversial (Wuthrich 1998).

In the area of adverse reactions to foods, the terminology used has been confused in the past and efforts to standardise nomenclature have been attempted (Bruijnzeel-Koomen et al. 1995). A summary of the classification given by the European Academy of Allergology and Clinical Immunology subcommittee is given here, to which I shall endeavour to adhere in this thesis.

Adverse reactions to foods can be divided up into toxic (dose dependant and affect potentially all individuals) and non toxic (depend on the susceptibility of a certain individual). Non toxic adverse reactions to foods can be either immunologically mediated (food allergy) or non-immunologically mediated (food intolerance). Food allergy can be further subdivided into IgE-mediated and non-IgE-mediated reactions and food intolerance into enzyme, pharmacologic and undefined intolerances (Bruijnzeel-Koomen et al. 1995). IgE-mediated or Type I reactions are the most common reactions associated with food allergy, with various clinical manifestations such as itching, urticaria/angioedema, rhinoconjunctivitis, asthma, oral allergy syndrome, allergic eosinophilic gastro-enteritis and systemic anaphylaxis. The definition of anaphylaxis is usually regarded as, an IgE reaction involving three or more organs (Bruijnzeel-Koomen et al. 1995), with anaphylactic shock extending that definition to include a dramatic fall in blood pressure with its associated sequelae (Sampson 1997).

Non-IgE-mediated reactions involving Type II mechanisms have been implicated in a few reports of Type II antigen-antibody-dependant cytotoxic reactions such as antibody-dependant thrombocytopenia secondary to the ingestion of cows milk (Sampson 1997). Type III reactions have been incriminated in some patients with subjective symptoms and elevated levels of food antigen-antibody complexes though these levels have also been found in normal individuals (Sampson 1997).

Type IV hypersensitivity reactions to foods are classically seen in allergic contact dermatitis lesions on the hands of those who work in the food preparation industry with the lesions being exacerbated by ingestion of the

offending foods (Wuthrich 1998). Treatment of food allergies is based around identification and complete avoidance of the offending allergen (Sampson 1997). In some food allergies, this is extremely difficult to do, due to the pervasive nature of some food stuffs . Pharmaceutical therapy and immunomodification by the induction of oral tolerance or desensitisation are controversial as they have not been documented in carefully controlled studies (Bruijnzeel-Koomen et al. 1995). The relationship between atopy and the type of milk that a subject was fed as an infant has been extensively investigated and efforts made to hydrolyse milk proteins continue to ensure that modern infant milk formulas induce less sensitisation to cows milk. Currently, it is considered that breast feeding delays the onset of atopic dermatitis and other atopic diseases and may moderate the severity of these diseases. Delaying the introduction of solid food until six months is also considered to be beneficial in allowing the immune system to mature before coming into contact with potentially sensitising food allergens.

Food Additives And Flavouring Agents

Food additives are substances added to foods that have no inherent nutritional value and act as preservatives, stabilisers etc. The prevalence of allergies to food additives in the US population has been estimated at 0.1% in adults and 1% in children (Sampson 1997).

Non-immunologic contact urticaria (NICU) is a disease entity in which the precise mechanisms of its action are not known. Known urticariants that

cause NICU are trans-cinnamic acid (found in many foods as a flavouring agent) and benzoic acid (a food additive) (Basketter & Wilhelm 1996). It may be that most individuals could react in this way given a high enough dose as in toxic reactions (Basketter & Wilhelm 1996). It is not clear what the exact mechanism for these reactions are; histamine and prostaglandins may play a role or the urticant chemical may have a direct effect on the dermal vasculature (Basketter & Wilhelm 1996).

Sulphites

Sulphites occur naturally in many foods and have a long history of use as food additives and they are also used in pharmaceuticals. Different chemical formulas include bisulphites and metabisulphites.

There is a large array of symptoms attributed to the ingestion of sulphite, including localised angioedema, dysphagia, contact dermatitis and urticaria. Reactions to sulphites are thought to be IgE mediated and they can trigger asthma in a small number of sensitive individuals which may be severe and life threatening (Taylor, Bush, & Nordlee 1991).

Monosodium glutamate

One of the most widely used food additives in the world, monosodium glutamate (MSG), has been used for hundreds of years naturally occurring in seaweed and used extensively as a flavouring agent throughout Asia. It was only in 1908 that MSG was isolated from the seaweed as the active component. Glutamic acid is a natural component of proteins (20% of most proteins) and is present naturally in tomatoes and mushrooms. The so called

Chinese restaurant syndrome was first described in 1968 – headache, burning sensation, chest tightness, nausea and sweating all within hours of eating a Chinese meal. The prevalence in the normal population is estimated at 30%! The mechanisms of these symptoms are thought to be due to peripheral neuroexcitatory phenomenon rather than an immune mediated allergy. Also asthmatic attacks have also been reported to have followed exposure to MSG, these are also thought to be a secondary response to the neurone excitation of irritant receptors in the lungs which gives rise to reflex bronchoconstriction (Allen 1991). There have been a few reports of hypersensitivity reactions of an immediate IgE mediated type (Bosso & Simon 1991), and recurrent angioedema of the face and extremities was reported in a 50 year old man following ingestion of MSG (Squire 1987).

Tartrazine

One of the coal tar derived azo dyes and colourings available for use in foods, these have had great interest in the lay press in recent years in particular with reference to immediate hypersensitivity reactions and hyperactivity in children. Most of the studies making these claims are defective in design and adverse reactions to azo dyes are extremely rare (Stevenson 1991) though one patient has been reported as having a fixed drug eruption due to tartrazine (Orchard & Varigos 1997).

Benzoates and parabens

Benzoic acid and sodium benzoate are grouped as benzoates and the methyl, n-propyl, n-butyl and n-heptyl esters of parahydroxybenzoic acid are grouped together as parabens. Benzoates are widely used as antimycotic and antibacterial preservatives in food and beverages while parabens are used extensively in cosmetic and pharmaceutical preparations as well as in a limited number of food stuffs. The quantities of benzoates consumed world wide (10 million pounds) per year indicates that these are one of the most commonly used food additives. Incidences of benzoate hypersensitivity in patients with chronic urticaria have been suggested from 3% to 60% after oral provocation tests. Again many of these studies had no control groups and did not use standardised, double blind, cross over trial protocols. In studies with more stringent design parameters, the incidence is reported to be in the region of 1-20% of patients with chronic urticaria. Benzoic acid can also produce contact urticaria and contact dermatitis (Ortolani et al. 1999). Among asthmatics the incidence of benzoate induced asthma is estimated at 1-4% (Jacobsen 1991), and incidences of anaphylaxis are rare (Ortolani et al. 1999). Benzoic acid is one of the substances that is known to effect NICU in some individuals and in a study carried out among 200 unselected volunteers, 157 subjects had a visible reaction to application of 500mM benzoic acid in petrolatum though in many cases this was barely perceptible (Basketter & Wilhelm 1996). The mechanism for action in most sensitive patients is thought to be not mediated by histamine as antihistamines have little effect (Lahti 1980).

Sodium benzoate used as a preservative in a toothpaste has been reported to have caused perioral contact urticaria in a five year old boy (Munoz et al. 1996).

The effect on allergic contact dermatitis (ACD) lesions being exacerbated by oral challenge with the offending allergen (in this case parabens) was investigated in 14 patients using a placebo controlled oral challenge (not stated whether this was carried out single or double blind). Two patients experienced specific aggravations of their ACD sites in response to oral challenge with parabens but not to the placebo, two further patients had non specific reactions to parabens and eleven had no reactions to either placebo or parabens. The two patients with specific reactions showed no improvement on a parabens free diet for one to two months. The authors concluded that oral challenge was not useful as a test procedure for ACD and the lack of response to elimination diet cast some doubt on the significance of the result (Veien, Hattel, & Laurberg 1996a)

Cinnamon

Cinnamaldehyde and cinnamyl alcohol are related flavouring agents used in a wide variety of foods. Cinnamaldehyde can act as a hapten and cause contact allergy and urticaria under some conditions but has also been shown to cause irritant positive reactions too (Taylor & Dormedy 1998).

Balsam of Peru

Vanillin, the fragrant constituent of vanilla, is found in Balsam of Peru and as a constituent of many perfumes and cosmetics (Ferguson & Beck 1995).

Peppermint flavours

Peppermint oil constituents are commonly found in confectionery as well as in the previously mentioned oral preparations and have been reported as causing intraoral oedema after chewing mint flavoured gum in sensitive people (Sugarman 1950).

Cosmetics

Cosmetics used near the oral cavity are lipsticks, lip-salves, foundation and nail varnishes (in nail biters). Parabens have been often implicated in reactions to cosmetics given that they are a common preservative used in many cosmetic preparations and can cause severe contact dermatitis in susceptible individuals (Bosso & Simon 1991). Flavouring agents, antioxidants, dyes and colouring agents are also involved in the manufacture of cosmetics and there are reports of adverse reactions from each of those groups (Giordano-Labadie, Schwarze, & Bazex 2000; Maibach 1986; Ophaswongse & Maibach 1995). There are reports of allergic reactions to vanilla/Balsam of Peru in patients using lip salves (Downs, Lear, & Sansom 1998; Ferguson & Beck 1995).

1.1.3.2.Allergy Tests

The 'gold standard' for allergy testing is the double blind placebo control (DBPC) challenge (Bruijnzeel-Koomenet al. 1995; Sampson 1997).

Tests for IgE-mediated allergic reactions include *in vivo* methods such as skin prick tests, scratch tests and intradermal skin tests. Variations of the skin prick test include prick-by-prick testing to food stuffs where the lancet is used to prick the fruit or vegetable and then the same lancet is used on the patient (Antico 1996). This method is of particular use in patients suffering from oral allergy syndrome where the allergens implicated are particularly labile and the use of fresh foods give a more reliable result for the individual patient than the commercial preparations (Bock 2000). The scratch test offers no advantage over the skin prick test and is more technically difficult to perform (Bruijnzeel-Koomen et al. 1995). There is thought to be no place for intradermal testing since it may provoke severe systemic reactions and introduce a physical 'wheal' that may mimic a positive reaction (Williams & Bock 1999). Suspected food allergens have been tested by the use of a labial food challenge (food placed on the lower labial mucosa for 2 minutes and then removed) (Rance et al. 1999) though this type of test requires further research (Bock 2000).

In vitro testing has improved over the years and will no doubt continue to provide more accurate diagnostic information that will aid in the investigations of suspected allergies and may reduce the need for time consuming DBPC oral challenges for foods and additives (Bock 2000).

The mainstay of *in vitro* allergy testing has been radio allergosorbent tests (RAST) that give the specific IgE content of serum to a number of food allergens. The test is only as useful as the allergens that can be used; egg, milk, pollens and mite allergens have been identified and reasonable extracts compounded. A newer test that utilises fluorescein instead of a radioisotope as in the RAST, has been developed in recent years. The CAP system fluorescein-enzyme immunoassay quantifies the reaction result and serves as a predictor for positive DBPC food challenge (Eigenmann et al. 1998).

Testing in non-IgE-mediated reactions utilises various cutaneous patch testing techniques, usually closed patch testing (see next paragraph), though open testing and rub testing may also be used and all three may be used to detect allergens causing contact urticaria and contact urticaria syndrome (Wuthrich 1998).

Patch testing

The first datable skin test carried out under the auspices of a physician was by Pierre Borel in 1656, who confirmed a patient's hypersensitivity to egg by applying some to his skin, duly raising a blister (Avenberg & Harper 1982).

Patch testing as an investigative tool has developed alongside the increasing awareness of contact sensitivity over the last 100 years. Allergic contact dermatitis was first described in 1817 (Hjorth 1989) where eczema caused by exposure to mercury was demonstrated. Patch testing was initially used to try and treat mercury allergy (Jadassohn 1895) in 1896, and then

introduced as a diagnostic method in 1911 (Bloch 1911). As the techniques were expanded and the tests more widely used, the need to standardise the procedures, allergen vehicles and the types and concentrations of allergens became more obvious. In 1961, the Nordic Dermatological Societies decided to embark upon a joint Scandinavian study to develop a standard series of allergens and a standard technique. From this the European Standard Series was developed, though this has been modified over the years as contact sensitivities change and new allergens become important (Andersen et al. 1988; Bruynzeel et al. 1995; Gollhausen et al. 1988; ICDRG 1984). The effectiveness of the use of the European Standard Series was tested in 1992 in an international, multicenter study. It was found to detect contact sensitivities in, between 77% and 95% of the patients tested (Menné et al. 1992).

Techniques of application of tests varys between the Al test ™[1], Finn chambers ™[2] and the Leukotest™[3] though other types are available. In these the amount of test substance applied may vary between observers and even between the same observer from application to application (Antoine & Lachapelle 1988; Lachapelle & Antoine 1989). As this variation may result in false negatives if too little is used, or sensitisation or irritant reactions if too much is used, newer testing systems have been developed where the test strip is supplied with a ready dispensed, exact amount of test substance already in place. Examples of these are the Epiquick™[4] and the TRUE test

---

[1] Imeco, Stockholm, Sweden.
[2] Epitest, Hyrylä, Finland.
[3] Beiersdorf, Hamburg, Germany
[4] Hermal Chemie, Reinbek, Germany

TM[5]. Open testing where the allergen is applied in a low concentration to a specified, non occluded area, often repeatedly, is also carried out.

Patch testing has been used by clinicians to ascertain the cause or contributing factors in the pathogenesis of various diseases. Though the reading of patch tests depends upon a subjective assessment by the observer, the results have been relevant to many patients (Podmore, Burrows, & Bingham 1984). Contact dermatitis remains the major disease investigated in this way though many other (mainly dermatological) disorders have been usefully investigated by patch testing, and the patients helped by avoidance of the causative allergens.

Patch testing attempts to elicit a delayed hypersensitivity response from sensitised patients. Patch testing is usually carried out to identify exogenous allergens to which the patient is sensitive. The allergens may be in the environment, or in pharmacological or other preparations applied to the skin but patch testing can occasionally be used successfully in systemically administered drug sensitivities (Felix & Comaish 1974; Houwerzijl et al. 1977; Quirce et al. 1991). Testing in this manner is also used for reactions to foods and food additives in cases where the patient has no obvious skin symptoms (Bock 2000).

---

[5] Pharmacia, Uppsala, Sweden.

Patch testing is useful where a food or drug (Calkin & Maibach 1993) allergy is suspected provided that there are criteria in place to establish scientific validity. Suitable criteria are:

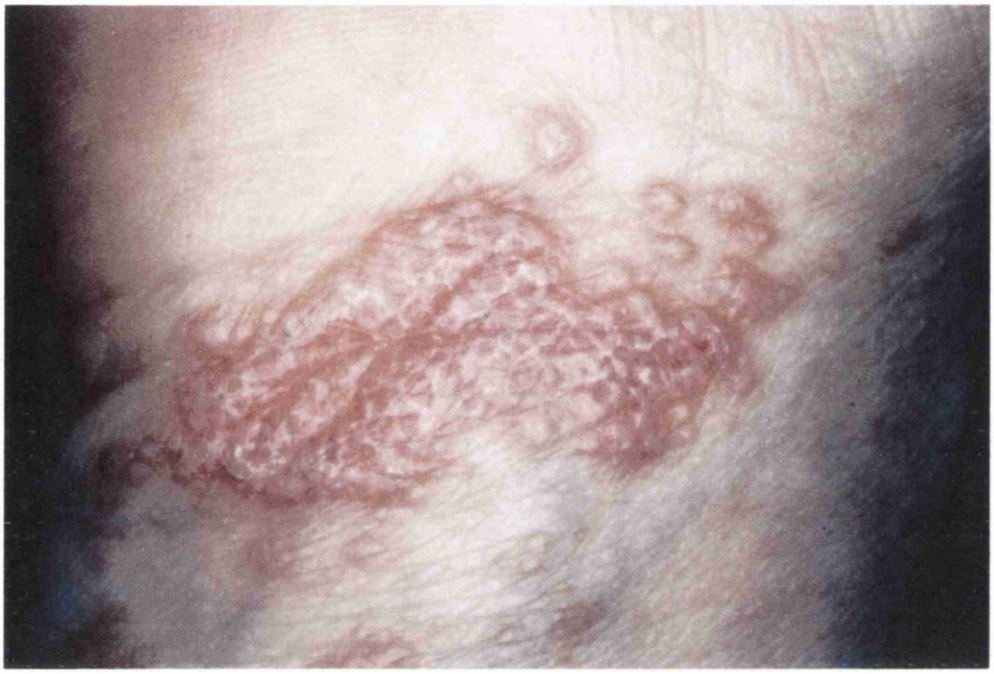
- History of food or drug exposure.
- The clinical morphology of the reaction.
- Positive patch test.
- Appropriate controls.
- Resolution when food or drug is discontinued.
- Recurrence of symptoms and signs upon allergen rechallenge.

1.2. Oral Lichenoid Eruption

1.2.1. Introduction and Historical Review

Oral lichenoid eruptions (OLE) are a common group of oral diseases that usually present with a clinical appearance of a lichenoid (i.e. lacy) pattern similar to the Wickham's striae found in cutaneous lichen planus an example of which is shown in Fig 1, (Boyd & Neldner 1991; Kramer et al. 1978). The term is designed to be descriptive only and does not attempt to give a clue to the aetiology of such conditions. OLE is a widely encompassing term that will include those diseases elsewhere termed; oral lichen planus (OLP), oral lichenoid reactions, oral lichenoid drug eruptions, oral contact lesions and oral delayed hypersensitivity reactions. Many authors use the term 'oral lichen planus' to include 'lichenoid reactions' and some suggest that the clinical and histological criteria used to define what most call OLP, may in fact be describing several different pathological entities (Holmstrup et al 1988). Thus I feel 'OLE' should be used as the umbrella term and 'OLP' kept separate from 'lichenoid reactions' due to the differing aetiologies. Eisenberg and Kritchkoff 1992 also prefer to keep the diagnosis of OLP only to a restricted pattern of clinical features or to within strict histological parameters when the clinical features are more varied. These guidelines specifically excluding lichenoid reactions (Eisenberg & Krutchkoff 1992). Other authors who differentiate OLP from other oral lichenoid reactions include Pecegueiro et al 1999, Scully et al 1998 and Bratel et al 1998.

Fig. 1. Photograph Of Cutaneous Lichen Planus Affecting The Flexor Surface Of The Forearm And Showing The Characteristic Wickham's Striae



Erasmus Wilson described cutaneous lichen planus in 1869 (Wilson 1869) and early remedies are to be found in medical text books dating back to 1904 where it was thought that appropriate treatment would consist of good food and cod-liver oil, and that "arsenic is of considerable value" (Stevens 1904). Early accounts of intraoral OLP are found in dermatology textbooks where it is stated that – "lichen planus affecting the mucous membranes is very obstinate and may last for years" (McKenna 1937). Lichen planus is a common mucocutaneous disease estimated to affect 0.9 –1.2% of the general population with an average disease duration of 8-18 months. In contrast, oral lesions can last for 20 years or more. Of those with cutaneous lesions as the primary sign, about 65% also have oral lesions (Strauss, Fattore, & Soltani 1989). OLP however more often occur on their own and reports of the percentage of OLP patients who have also cutaneous involvement range from 16% to 44% (Andreasen 1968; Silverman et al. 1991; Strauss, Fattore, & Soltani 1989; Vincent et al. 1990).

Controversy exists over whether OLE should be classified as a precancerous lesion. In 1978, the WHO Collaborating Centre for Oral Precancerous Lesions published a description of the lesions and diseases that they were considering as those that could be precancerous (Kramer et al. 1978). OLE was included though it was stated that there was "considerable uncertainty" about the frequency of malignant transformation in it. Eisenberg and Krutchkoff reviewed the literature and concluded that the reported malignant transformation of OLE figures were artificially high due to non consideration of carcinogen exposure and errors in missing histopathological signs of early dysplasia (Eisenberg & Krutchkoff 1992).

In a prospective Danish study of 611 OLE patients with well defined criteria for inclusion, 9 (1.5%) developed squamous cell carcinomas (SCC). The patients had all been followed up for at least 4.9 years prior to developing the SCC with no histological evidence of epithelial dysplasia on the biopsy taken at initial presentation. The authors calculated the estimated figure for development of oral SCC in the general population which was 0.18 (taking into consideration the age and sex of the patients) and found that there was a 50 fold increase over the expected oral SCC rate among the OLE patients (Holmstrup et al. 1988). There has also been a report of an increased incidence of oral SCC in patients with cutaneous lichen planus (Holmstrup 1992). Silverman and co-workers have carried out three prospective investigations of OLE and found that malignant transformation occurred in 1.2, 2.3 and 3.2% of 570, 214 and 95 patients (Silverman et al. 1991; Silverman & Bahl 1997; Silverman, Gorsky, & Lozada-Nur 1985). It should be noted that all but 19 of the 879 patients had mucosal biopsies and that the studies were not designed specifically to investigate SCC but to describe the clinical characteristics, patient profiles and treatment outcomes of OLE . A recent publication calls for stricter designed prospective studies to investigate the true incidence of SCC occurring in OLE patients bearing in mind other factors such as tobacco usage, alcohol consumption, diet, socio-economic status, and race (Lozada-Nur 2000).

1.2.2. Classification and Prevalence

OLE can be classified according to site and clinical appearance (Basker1981; Bays, Hamerlinck, & Cormane 1977). Andreason identified six different types: reticular, atrophic, plaque-like, bullous, erosive and ulcerated (Andreasen 1968). These are generally accepted though different authors may combine two or three of the classes into one; Silverman and co-workers use reticular, atrophic and erosive designations, while Bagán-Sebastián et al and Axéll used only two clinical classifications; those with exclusively white reticular lesions and those with atrophic or erosive lesions (Axéll & Rundquist 1987; Bagán-Sebastián et al. 1992; Silverman, Gorsky, & Lozada-Nur 1985). The lesions may be localised or generalised, unilateral or bilateral. Bilateral lesions are thought to be more likely to be idiopathic OLP whilst unilateral lesions are thought to be more often lichenoid eruptions appearing secondary to identifiable causes such as drug reactions. The lesions may be limited to the area adjacent to a possible cause such as an old corroded amalgam restoration or may be found as it were *ad hoc* in the mucosa (Becker & Schuppan 1995; Bergdahl, Anneroth, & Anneroth 1994; Bergman 1990).

The reported prevalence of OLE among the general population is difficult to estimate as most studies have been based on referred groups of patients and do not necessarily give, or are not able to estimate, the population using that referral centre. Most of the prevalence studies have been carried out in India (Axéll & Rundquist 1987). For a list of the reported prevalences of OLP, see Table 1. In the Indian subcontinent the estimated prevalences

have ranged between 0.02 and 1.5%, while in South East Asia they have been reported as higher at 2.1-3.8%. Few surveys have been carried out among Caucasian populations, one was in Sweden which yielded a prevalence rate of 1.9% (Axéll & Rundquist 1987). Most authors consider the prevalence rate to be in the region of 1-2% (Savin 1991; Strauss, Fattore, & Soltani 1989; Vincent et al. 1990).

For reported age, sex, type and site, see Table 2.

There is a female predilection of approximately 2:1 and the average age of disease onset is thought to be in the fifth and sixth decades. A few studies have found that males present on average ten years earlier (Lacy, Reade, & Hay 1983;)Andreasen 1968), though one investigation reported their highest prevalence of OLP to be among males in the 65-74 age band (3.8%) and females in the 55-64 age band (3.6%) (Axéll & Rundquist 1987).

OLE is not site-specific in the oral cavity though most patients (approx. 90%) have lesions affecting their buccal mucosa (Scully et al. 1998). The tongue is the next most common site with usually between 30 and 50 % of OLE patients experiencing tongue lesions (see Table 2), the alveolar ridges are affected less commonly though Silverman consistently found that this site was more prevalent than the tongue (Silverman et al. 1991; Silverman & Bahl 1997; Silverman, Gorsky, & Lozada-Nur 1985). The labial mucosa and other sites are less commonly affected. Gingival lesions may present a desquamative appearance and the term desquamative gingivitis is used, see section 1.7.2.

Table 1. Reported Prevalences of Oral Lichen Planus

Author and year	Geographical area	Population examined	Population selection	Prevalence
Pindborg 1972	Southern India	7,639	Over 15 years of age	1.5%
Axéll 1987	Sweden	20,333	Invited to participate, >15 years	1.9
Axéll 1990	Thailand	234	Consecutive dental outpatients	3.8%
Axéll 1990	Malaysia	233	Consecutive dental outpatients	2.1%
Mehta 1971	India (rural)	50,915	> 15 years	0.3%
Zachariah 1966	India (urban)	5,000	Consecutive admission clinic attenders	0.4%
Pindborg 1965	India (Uttar Pradesh)	10,000	Consecutive dental clinic attenders	0.19%
Pindborg 1965	India (Bombay)	10,000	Consecutive dental clinic attenders	0.22%
Pindborg 1966	India (Bangalore)	10,000	Consecutive dental clinic attenders	0.02%

(Pindborg et al. 1972 ; Axéll & Rundquist 1987 ; Axéll et al. 1990)

Table 2. Age, Sex, Type and Site of Lesions in Patients With OLP

Author and Year [No. of OLP patients in study]	Mean age [range] (years)	Female (%)	White lesions only (reticular, papular, plaque-like) (%)	Red lesions (atrophic, erosive, bullae, +/- white lesions) (%)	Buccal mucosa (%)	Tongue (%)	Alveolar ridges (%)
Andreasen 1968 [115]	65.2 -	65	57.4	42.6	99	38.3	-
Axéll 1987 [410]	[47.8% were aged 45-64]	62.4	77.3*	32.7#	92	28.8	13.2
Bagàn-Sebastiàn 1992 [205]	Approx 51	80	28	148	89.7	50.2	27.3
Pindborg 1972 [118]	[61% were aged 35-54]	54.2	-	-	84.3	5.2	-
Silverman 1985 [570]	52 [16-86]	67	31.7	68.2	87	45	60
Silverman 1991 [214]	54 [21-83]	71	28.5	71.4	86	46	68
Silverman 1997 [95]	60F 56M [33-92]	69	28.4	71.7	79	53	60
Thorn 1988 [611]	53 -	66.9	92*	44#	-	-	-
Vincent 1990 [100]	64.2 [18-90]	76	-	-	78	44	42

* Reticular only
# Atrophic only
(Andreasen 1968; Axéll & Rundquist 1987; Bagán-Sebastián et al. 1992; Pindborg et al. 1972; Silverman et al. 1991; Silverman & Bahl 1997; Silverman, Gorsky, & Lozada-Nur 1985; Thorn et al. 1988; Vincent et al. 1990)

The preponderances of the type of lesions found in OLE are varied between authors, and this may reflect variations in how rigidly the criteria were applied e.g. any hint of erythema should move a patient from 'white only' lesions to the 'red lesions' bracket. The variations may, to a certain extent, be accounted for by the selection bias of the patient groups. Axéll summoned 30,00 of the general population for examination, and found an approximately 2:1 ratio of 'white' only to 'red' lesions (Axéll & Rundquist 1987), whereas Silverman et al found the opposite ratio of 1:2 in their study of referred patients (Silverman et al. 1991). Patients with 'white' only lesions are more likely to be asymptomatic and therefore never present as patients to a specialist clinic, whereas patients with erythema, erosions or bullae will be likely to experience symptoms ranging from soreness to severe pain (Thorn et al. 1988) and thus present for treatment.

1.2.3. Aetiology, Features and Diagnosis

The aetiology of oral lichen planus is by definition unknown and once an allergic or traumatic or infectious cause has been found, the diagnosis is no longer OLP. 'Lichenoid reactions' is the name given to those lesions that have an identifiable allergic or drug induced aetiology (Pecegueiro et al. 1999; Scully et al. 1998). Idiopathic LP is the term that should be used for lesions of unknown aetiology (Femiano et al. 1999).

Medical conditions such as diabetes, chronic liver disease, hypertension and anxiety have all been implicated in the aetiology of OLE. Drugs that have been suggested as contributing to lichenoid reactions include oral

hypoglycaemics, penicillamine and anti-hypertensive drugs which may have clouded the issue of whether diseases, or the drugs being taken as treatment, cause lichenoid reactions (Scully et al. 1998).

Lacy et al found that 6% of their 108 OLE patients were also diabetic though they did not specify what drugs the patients were taking (Lacy, Reade, & Hay 1983). van Dis and Parks identified no difference in the prevalence of OLE between 273 patients with diabetes mellitus, and age, sex and race matched controls, taking into account the medications both controls and disease subjects were taking (van Dis & Parks 1995). In a larger study of 1600 diabetes patients and 617 healthy controls the authors also found no significant increase in the prevalence of OLE in the diabetic cohort, 1% of diabetic patients and none of the control subjects had clinical evidence of OLE (Albrecht et al. 1992). An association between chronic liver disease (CLD) and erosive OLE was found by Bagán et al who also noted a higher incidence of tongue lesions in the OLE patients with CLD than OLE alone (Bagán et al. 1994). Primary biliary cirrhosis has been linked with OLE as well (Strauss, Fattore, & Soltani 1989). Hepatitis C Virus (HCV) has been associated with OLE and recent studies showed that this association was not due to co-existent Hepatitis G Virus infection (Lodi et al. 1999).

Other viruses such as the Epstein Barr Virus (EBV) have been studied and Pedersen found that OLE was associated with an increased humoral immune response to EBV (Pedersen 1996). A Spanish study found that no relationship appeared to exist between OLE and the Human

Immunodeficiency Virus (HIV) (Ceballos-Salobreña, Aguirre-Urizar, & Bagan-Sebastian 1996).

Candidal infections have been found in a number of OLE patients, 25% of patients in one study (Vincent et al. 1990), but there was no difference in the cell mediated immune response to an intradermal injection of *Candida albicans* of OLE patients when compared to a control group (Simark-Mattsson et al. 1999). Silverman et al found no correlations with candidal infection and OLE (Silverman, Gorsky, & Lozada-Nur 1985).

Coeliac disease was not found to be commonly associated with OLE though one patient has been reported (Scully, Porter, & Eveson 1993).

The presence of a sub epithelial band of T lymphocytes in histological sections of OLE supports the possibility of the involvement of immune mechanisms in the pathogenesis of OLE. Many authors consider that a cell mediated hypersensitivity reaction to an exogenous drug or environmental allergen is responsible for the clinical entity of OLE , while others have suggested an auto-immune basis (Strauss, Fattore, & Soltani 1989; Sugarman et al. 1993). These will be further explored in sections 1.2.4 and 1.2.5.

The drugs that have been suggested as contributing to cutaneous lichenoid eruptions are captopril (Phillips et al. 1994), tetracycline (Fitzpatrick 1963), labatalol (Grange & Wilson Jones 1978) and methyldopa (Hay & Reade 1978; Holt & Navaratnam 1974). Other chemicals that are not drug related, such as para-phenylenediamine (black hair dye) are also capable of causing cutaneous lichenoid eruptions (Sharma et al. 1999).

Fenclofenac (Ferguson, Wiesenfeld, & MacDonald 1984) has been reported as contributing to the pathogenesis of OLE. See Table 3 for other types of drugs that have been implicated.

In a prospective study, in which the drugs that 49 patients with OLE took were noted, patients with erosive forms of OLE were nearly ten times more likely to be ingesting NSAIDs than patients with non-erosive OLE (Robertson & Wray 1992). Robertson and Wray also found that there was no increase in oral hypoglycaemic or psychotropic medication usage in the OLE group compared to a control group with non-OLE oral keratoses which does not contribute to the suggestion of a significant link with either diabetes or stress (Robertson & Wray 1992).

Stress was found to be an aggravating factor by Östman et al in that they found that more of their OLE patients had lifestyle reasons to have more stress – i.e. more were divorced/widowed (Östman et al. 1996). The role of stress in the aetiology of OLE has not been proven (Boyd & Neldner 1991) though an increase in both depressed mood and levels of circulating memory CD4+ cells was found in patients with erosive compared to non-erosive OLP compared to controls (Hietanen et al. 1987).

Tobacco usage in the form of cigarette smoking has been negatively associated with OLE (Axéll & Rundquist 1987), while subjects who chewed tobacco in the form of a betel quid had a higher prevalence of OLE lesions related to the site where the tobacco was chewed/placed (Daftary et al. 1980).

Table 3. Drugs Implicated In Lichenoid Drug Reactions

Drug Group	Drug
Antihypertensive	Methyldopa
	Oxyprenolol
	Practolol
	Propanolol
	Captopril
	Labetalol
Antiprotozoal	Chloroquine
	Dapsone
	Pyrimethamine
	Quinacrine
	Mepacrine
Antimicrobial	Ketoconazole
	Para-Aminosalicylic Acid
	Tetracycline
Metals	Bismuth/Arsenic
	Gold
NSAID	Fenclofenac
	Phenylbutazone
	Other Nsaids
Hypoglycaemic	Tolbutamide
	Chlorpropamide
Antirheumatics	Penicillamine
	Sulphasalazine
Antipsychotics	Phenothiazines
	Lithium
Miscellaneous	Allopurinol
	Amiphenazole
	Carbamazepine
	Cyanamide
	Levamisole
	Lorazepam
	Metopromazine
	Pyritinol
	Thiazides
	Thyroxine
	Triprolidine

Based on the tables in (McCartan 1997) and (Scully & Cawson 1993)

1.2.3.1.Other Diseases In Relation With OLE

Graft-versus-host-disease (GVHD) is an immunologically mediated disease that frequently complicates the transplant of allogeneic bone marrow (Nakamura et al. 1996). It is caused by immunologically active T cells being introduced into an immunocompromised, genetically disparate host (Mattsson et al. 1992). The clinical picture of chronic GVHD resembles that of spontaneously occurring autoimmune diseases such as; Sjögren's syndrome, primary biliary cirrhosis, scleroderma, systemic lupus erythematosus and dermatomyositis (Nakamura et al. 1996). A study measuring the lymphocytic infiltrate in chronic GVHD found that the density of the infiltrate related to the stage of the disease process (Nakamura et al. 1996). Historically the first link of OLE with an immune aetiology was the similarity of its histological appearance to GVHD (Strauss, Fattore, & Soltani 1989). Oral lesions of GVHD are clinically and histopathologically similar to those of OLE (Fujiwara et al. 1996; Walsh et al. 1990).

Lupus erythematosus and cutaneous LP have been described occurring together in what is known as the overlap syndrome (Boyd & Neldner 1991) and lichenoid oral mucosal lesions have been described as early manifestations of mixed connective tissue disease (Varga, Field, & Tyldesley 1990).

1.2.3.2.Histopathological Features of OLE Lesions

Some authors have found that the clinical appearance of OLE concurs with that of the histological appearance in 97% cases (Axéll & Rundquist 1987) though Ostman found concurrence in only 65% cases (Östman, Anneroth, & Skoglund 1994). However, while both the clinical appearance and the histological appearance are characteristic of OLE, they are not diagnostic (Holmstrup et al. 1988; Kramer et al. 1978) and the diagnosis has to be cautiously made. In some cases other techniques such as direct immunofluorescence or immunohistochemistry should be utilised (Boisnic et al. 1990; Ng, Ng, & Chng 1998). In cases where the gingival tissues are the only ones involved, the clinical appearance may be similar to that seen in linear IgA disease (Cohen et al. 1999), leukoplakia (Bánóczy, Roed-Petersen, & Pindborg 1979), lupus erythematosus and lichenoid dysplasia (Eisenberg & Krutchkoff 1992). The histological picture may be also confused with linear IgA disease and bears striking resemblance in some cases to epithelial dysplasia (Cohen et al. 1999; Vincent et al. 1990).

Biopsy specimens of OLE with a histological appearance consistent with the clinical diagnosis show a number of features. The most characteristic features of OLE are the subepithelial band of lymphocytes and the basal cell degeneration (Eisenberg & Krutchkoff 1992; Sugarman et al. 1993). Most authors also include as characteristic features an increased keratinohyalin granular layer and hyperkeratinisation (Farthing & Cruchley 1989; Hedberg, Ng, & Hunter 1986). Some authors have noted other features such as: early appearance and increased numbers of Langerhan's cells (Conklin &

Blasberg 1994; Lombardi, Hauser, & Budtz Jorgensen 1993), irregular acanthosis and an eosinophilic (fibrin) band adjacent to the basement membrane (Vincent et al. 1990) and apoptotic cells in the epithelium (Kramer et al. 1978). Saw-toothed rete ridges are regarded by some as characteristic features (Eisenberg & Krutchkoff 1992), but they are more commonly seen in cutaneous lichen planus than in the oral mucosa (Kramer et al. 1978).

A significant and positive correlation between the severity of the basal cell liquefaction and the density of the mononuclear infiltrate has been demonstrated in a study of the histology of specimens of 112 patients with OLE (Hedberg, Ng, & Hunter 1986).

The presence of parakeratosis is considered by some authors as one of the characteristic features (Eisenberg & Krutchkoff 1992) and Hedberg et al identified this in 93% of OLE sections examined (Hedberg, Ng, & Hunter 1986), though most would accept abnormal keratinisation with either ortho- or para-keratosis (Kramer et al. 1978).

Apoptotic cells are those which are undergoing programmed cell death, which may be physiological or pathological (Lindberg 1982). This process is extremely rapid and is estimated to take about three hours (Bloor et al. 1999). On histological examination, they appear with chromatin condensation at the periphery of the nucleus, a uniformly eosinophilic cytoplasm, nuclear fragmentation and pyknosis and nucleolar disintegration. The numbers of apoptotic cells have been found to be increased in sections of OLE tissue compared to normal oral mucosa and appear to be related to the inflammatory infiltrate (Bloor et al. 1999). They are probably related to

the Civatte, cytoid or colloid bodies often associated with OLE though these lack any nuclear fragments (Bloor et al. 1999; Kramer et al. 1978; Oliver, Winkelmann, & Muller 1989).

1.2.4. Pathogenesis

Though OLE has an as yet uncertain aetiology the presence of T lymphocytes in the superficial dermis indicates an aetiology originating in the immune system. Indeed the histopathology of Type IV hypersensitivity reactions such as contact dermatitis lesions, show a remarkable similarity to those of OLE (Conklin & Blasberg1994; Miller, Gould, & Bernstein 1992; Walsh et al. 1990).

1.2.4.1.Immune Pathogenesis

Studies investigating HLA types have identified genetic characteristics among different people groups that support an autoimmune mechanism in various diseases. HLA phenotypes vary considerably from patients of different genetic background and among patients with different types of disease.

HLA-DR antigens have been identified on the keratinocytes of OLE patients suggesting a role for antigen presenting capabilities of these keratinocytes and thus cell mediated immunity (Mattsson et al. 1992; Takeuchi et al. 1988). HLD-DR expression is thought to be induced by the action of interferon-γ, a cytokine produced by activated lymphocytes (Farthing, Matear, & Cruchley 1990). As has been stated previously Langerhan's cells have been found in increased numbers in OLE lesions (Boisnic et al. 1990). However, Farthing et al found that there was an increase in the activity but

not numbers of Langerhan's cells in OLE lesions when compared to normal controls (Farthing, Matear, & Cruchley 1990).

Recent publications have stressed that the pathogenesis of OLE is basically an immune reaction directed against the basal epithelial cells which is mediated by the cellular infiltrate composed mainly of T lymphocytes (Femiano et al. 1999; Walton, Thornhill, & Farthing 1996). The cells in the inflammatory infiltrate have been identified as mainly T lymphocytes and these have been isolated into specific T cell populations; T4 and T8 (Boisnic et al. 1990; Strauss, Fattore, & Soltani 1989). It is suggested that diverse exogenous agents upregulate the expression of proteins such as heat shock protein (HSP) by keratinocytes. Cytotoxic T lymphocytes then react against these activated keratinocytes and cause the tissue destruction (Sugarman et al. 1995). Keratinocytes in OLE have also been shown to produce more lymphocyte-chemotactic factors than those in normal oral mucosa (Yamammoto et al. 1994). However, some authors suggest that the T cells autoimmune reaction might not be primarily targeted towards the keratinocytes but to an unknown antigen in the epithelium (Becker & Schuppan 1995).

Mast cells are found in increased numbers in OLE (2-3 times that of normal oral mucosa), particularly in the layer immediately beneath the basal cell layer (Zhao et al. 1997) and their role is thought to be that of influencing the vascular endothelium (Zhao, Savage, & Walsh 1998). They may effect this via mast cell - nerve interactions as these have also been found in increased numbers in OLE tissues compared to normal oral mucosa (Zhao et al. 1997).

Though cell mediated immunity plays the major role in the pathogenesis of OLE, humoral immunity is involved. Anti-nuclear antibodies have been identified in both OLE and GVHD patients and anti-basal cell antibodies have been isolated in OLE patients (Sugarman et al. 1993; Sun et al. 1994). It has been postulated that the humoral response is a secondary event, after the basal layer has been damaged (Hedberg, Ng, & Hunter 1986).

It is most likely that a combined Type IV and III hypersensitivity reaction takes place in response to a locally released mucosal or epithelial antigen (Pedersen & Klausen 1984).

1.2.5. Role Of Allergy

1.2.5.1.General

It is considered that exogenous stimuli are capable of inducing changes in the skin or mucosa that make epithelial components antigenic, though no specific LP-antigen has been identified as yet (Pedersen & Klausen 1984). In cases where an allergen has been identified, it is likely that this antigenic stimulus is enough to promote the lesion (Hedberg, Ng, & Hunter 1986). Yiannias et al found in a recent study that 40% of patients with OLE who were referred for patch testing (25% of all OLP patients attending their clinic), had a clinically relevant positive reaction upon patch testing (Yiannias et al. 2000). Todd et al found a similar percentage (39.6%) of clinically relevant reactions in their study of 53 patients with OLE (Todd et al. 1990). The common allergens identified among these groups were, gold derivatives, mercury compounds, silver, nickel, acrylic resin monomer, vanillin, cinnamic aldehyde, fragrance mix, balsam of Peru, benzoic acid, rubber chemicals and colophony (Todd et al. 1990; Yiannias et al. 2000). Benzoic acid has been held responsible for causing OLE (de Groot, Weyland, & Nater 1994) as have metals used in dentistry such as cobalt, palladium and gold (Koch & Bahmer 1999). The role of mercury in amalgam in the aetiology of OLE is covered in the next section.

1.2.5.2. Mercury

Mercury in amalgam has been a cause for concern regarding its well known toxic properties and the effects on the body have been well documented as well as being a topic for scaremongering and media hype to a certain extent (Ziff & Ziff 1995). It has been established that mercury is taken up by lesional (lichenoid) oral mucosa and that it can also be found in intact oral epithelium (Bolewska et al. 1990b). Its allergy sensitising potential has come under scrutiny in more recent times and it is now fairly established that hypersensitivity to mercury and mercuric salts is responsible for causing lichenoid reactions in the mouth in some individuals (Finne, Goransson, & Winckler 1982). Other symptoms that have been reported in and around the oral cavity in relation to mercury hypersensitivity are, perioral eczema, aphthous ulceration, gingivitis and burning sensations of the mouth (Brehler et al. 1993).

Hypersensitivity to metallic mercury usually manifests as a localised, Type IV delayed hypersensitivity reaction and is uncommon (Eley & Cox 1993). Some authors deny that it occurs at all, and state that allergy to mercury causes no intraoral problems in patients with amalgam restorations in their teeth even in those patients with demonstrable sensitisation to mercury (Cawson & Odell 1998). Old and corroded amalgams seem to be responsible for more allergic reactions than newly placed restorations, though once a patient is sensitised, they may even react to the amalgam in the hours and days following dental treatment using amalgam (Bleiker & English 1998; McGivern et al. 2000). Rarely a more acute and generalised

reaction may occur involving pruritus and an urticarial rash within hours of exposure to mercury (McGivern et al. 2000).

There have been many studies carried out to investigate the relationship of OLE with amalgam and the effect of replacement of amalgam restorations with a non mercury substitute, (Table 4). The patients were tested to a variety of mercury compounds including, mercuric oxide, mercuric chloride, phenyl mercuric acetate, metallic mercury, amalgams, ammoniated mercury, phenyl mercuric nitrate, thiomersal, and phenyl mercuric borate. The number of patients with patch test results positive to mercurials varied widely between studies from 24.5%-100%, which may represent the differing referral patterns for patch testing, e.g. some would only refer those with a high risk of mercury allergy, whereas others referred all their OLE patients who had a possibility of hypersensitivity. This, however, was significantly more than the 3.5% reported in 2,300 eczema patients (Finne, Goransson, & Winckler 1982). The difference may also be due to reading by different dermatologists, different ethnic groups among the patients, variations in the patch test procedure (time of allergen exposure was 24-48 hours, and readings were carried out on days 1-17, Finne suggesting that late reading of the test sites is valuable in picking up further positive results (Finne, Goransson, & Winckler 1982)). The different types of mercury allergens that the patients were exposed to would also have affected the results. Most lesions in patients with positive patch test results improved after replacement of their amalgams, the percentages showing complete remission varying between 37.5% and 94.1%. Many more reported marked improvement in the lesions, for example, in one study a total 88.7% of 56

Table 4. Patch testing to mercury in patient with OLE lesions in relation to amalgam restorations*

No. OLE patients*	No. (%) positive to mercury compounds	No. (%) PT +ve patients having all amalgams removed	No. (%) of PT +ve patients showing complete improvement	No. (%) PT -ve patients having all amalgams removed	No. (%) of PT -ve patients showing complete improvement
118[a]	76 (64.4)	56 (73.7)	25 (45.2)	6 (40)	1 (20)
12[b]	5 (41.7)	-	-	-	-
33[c†]	15 (45.5)	15 (100)	7 (46.7)	18 (100)	8 (44.4)
53[d]	13 (24.5)	7 (53.8)	-	-	-
19[e]	15 (78.9)	15 (100)	9 (60)	3 (75)	0 (0)
65[f]	17 (26)	17 (100)	16 (94.1)‡	4	3 (75)‡
52[g] #	17 (33)	13 (76.5)	11 (85)	-	-
19[h]	19 (100)	16 (84)	13 (81.25)	-	-
12[j]	5 (42)	-	-	-	-
41[k]	12 (29.2)	-	-	-	-
33#[l]	18 (54.5%)	10 (55.6)	7 (70)	-	-
49[m]	17 (35)	17 (100)	14 (82.3)	31	19 (61.3)
11[n]	5 (45.5)	-	-	-	-
24[o]	8 (33)	8 (100)	3 (37.5)	-	-
29#[p]	18 (62)	4 (22)	3 (75)	-	-
29[q]	10 (34)	6 (60)	4 (66.7)	-	-

* Lesions topographically related to amalgam restoration(s).
\# All OLE patients tested
‡ Improvement but may not be complete (77.2% of all patients with replaced amalgams had complete resolution).
† Though clinically, the lesions were of lichenoid character, up to 7 of these patients had a histological diagnosis that was not indicative of OLE.

[a] (Laine, Kalimo, & Happonen 1997)
[b] (Pecegueiro et al. 1999)
[c] (Skoglund 1994)
[d] (Todd et al. 1990)
[e] (Koch & Bahmer 1999)
[f] (Ibbotson et al. 1996)
[g] (Smart, Macleod, & Lawrence 1995)
[h] (Pang & Freeman 1995)
[j] (Nordlind & Liden 1992)
[k] (Bolewska et al. 1990a)
[l] (Laine et al. 1992)
[m] (Östman, Anneroth, & Skoglund 1996)
[n] (Koch & Bahmer 1995)
[o] (Skoglund & Egelrud 1991)
[p] (Finne, Goransson, & Winckler 1982)
[q] (James et al. 1987)

patients, experienced improvement of some kind upon replacement of amalgam dental restorations with a non mercury restoration even though only 45.2% experienced complete remission (Laine, Kalimo, & Happonen 1997).

The percentages of those with negative patch test results to mercury who experience complete resolutions of their lesions ranged from 0 – 75%. Some authors found that the number of patients who showed clinical resolution following amalgam replacement in the patch test negative group being similar enough to the number in the patch test positive group to warrant the recommendation of amalgam removal and replacement in all patients who had lesions with a geographical relationship to amalgam restorations (Ibbotson et al. 1996; Östman, Anneroth, & Skoglund 1996; Skoglund 1994). Other authors found a marked difference in resolution of lesions between the patch test positive and negative groups (Koch & Bahmer 1999).

Bratel et al investigated the effect of replacement of amalgams with other dental materials in 142 patients with OLE lesions related to amalgam restorations and 19 patients with both OLE lesions related and unrelated to amalgam restorations. They found that 95% of the lesions in the first group considerably improved or resolved after replacement whereas 63% of the lesions related to amalgam restorations in the second group improved and

none of the lesions unrelated to amalgam restorations improved (Bratel, Hakeberg, & Jontell 1996).

Most authors found that the lesions resolved in under 3 months following amalgam removal (Camisa et al. 1999).

Garioch et al found that 14 out of 53 patients with OLE had clinically relevant positive patch test reactions to mercury or mercuric salts. In all these patients, clinical improvement was noted after replacement of amalgams with other materials or changing their thimerosal (thiomersal) containing contact lens cleaning fluid (Garioch et al. 1990). Other studies have found that only three out of 46, and one out of 12 OLE patients reacted to metallic mercury. (Hietanen et al. 1987; Yiannias et al. 2000).

In summary, contact sensitivity to mercurials as determined by patch testing seems to be fairly common among OLE patients who have amalgam restorations and that replacement is beneficial in these cases and also to a lesser extent in patients with OLE without a demonstrable mercury allergy.

Thiomersal is a mercurial that is used as a preservative in vaccines and sensitisation to it has been increasing most probably due to the increase in vaccination programmes (Aberer 1991). Thiomersal sensitivity has been found to be as high as 16% among eczema patients referred for patch testing (Aberer 1991). However, the minute amounts of thiomersal in vaccines (usually 0.05mg) are considered to be enough to sensitise an individual, but

have been shown not to provoke clinical symptoms upon vaccination if given intramuscularly rather that subcutaneously and so this is probably not of clinical relevance for further vaccinations, but only in those who have had problems using mercurial containing contact lens cleaning solutions (Aberer 1991; Cox & Forsyth 1988).

1.2.5.3.Comparison Of 'Lichenoid' and Drug Induced Lichenoid and 'Idiopathic LP' Lesions

McCullough and Radden suggest that one of the most difficult tasks in the diagnosis of oral mucosal diseases is the differentiation between the three lichenoid lesions; classic/idiopathic LP, drug related and other lichenoid type lesions and lesions which also show dysplastic epithelial changes (McCullough & Radden 1992). Making clear clinical and histological definitions of these lichenoid diseases will enable progress in aetiology and treatment and in particular will aid in discovering which are correlated with malignant potential (Lozada-Nur 2000).

Oliver et al (1989) investigated the histological characteristics of cutaneous LP (3 patients), cutaneous drug induced lichenoid reactions (DILR) (14 patients) and allergic contact dermatitis (ACD) (6 patients). They found that in cutaneous DILR sections, the most distinctive feature was the presence of a mixed cell infiltrate. Apoptosis and hyperkeratosis were commonly seen. The cutaneous LP sections demonstrated features indistinguishable from lupus erythematosus with significant numbers of apoptotic cells in the dermis, abnormal keratinisation was rare and spongiosis was absent. The ACD sections showed little distinguishing features apart from the mildness of the inflammatory reaction at the epithelial-dermal interface and the infrequency of apoptosis (Oliver, Winkelmann, & Muller 1989). The numbers however in each group were small so the significance was debatable.

Koch and Bahmer also distinguished between patients that had lichenoid lesions related to metal dental restorations and those with OLP (not related to metal restorations), by a lessening of the inflammatory infiltrate in the lichenoid group. A biopsy was taken from the positive patch test reactions to metal salts, and these, in contrast to the ACD patients reported by Oliver et al showed a marked dermal reaction with perivascular infiltrates, vacuolar changes and necrotic keratinocytes in the epithelium, as well as features of ACD; spongiosis of the epithelium and lymphohistiocytic infiltrates perivascularly in the dermis (Koch & Bahmer 1999).

A number of studies have compared the histopathology of both OLP lesions and lichenoid lesions to determine whether it is possible to establish a diagnosis of one against the other from the histological appearance. Some authors have even considered it possible that the reaction to a specific antigen (cinnamon) can be suggested by the histological appearance alone. Their histopathological criteria were; hyperkeratosis, chronic lichenoid mucositis with plasmacytic infiltration and marked chronic perivasculitis (Miller, Gould, & Bernstein 1992) but these were not quantified in any way.

van den Haute et al studied the histological appearance of cutaneous LP and found that while not pathognomonic of DILR, a drug aetiology could be suggested when the following criteria were present; focal para-keratosis, focal interruption of the granular layer, cytoid bodies in the cornified and granular layers (van den Haute, Antoine, & Lachapelle 1989).

Pecegueiro et al in 1999 retrospectively analysed 21 patient's case records and histopathology specimens. They noted the presence or absence of the following histological features; erosion, acanthosis, atrophy, granulosis,

keratosis (ortho or para), degeneration of the basal layer, Civatte bodies and lymphoid infiltrate. Dividing the patients into two groups, those with metallic restorations in their mouth or with a history of such, i.e. more likely to have a lichenoid eruption and those without, i.e. more likely to have idiopathic LP, they noted that those in the first group were more likely to react positively to patch testing to mercurials and potassium dichromate (six out of twelve patients had a positive patch test result), however they could identify no clinical or histological differences between the two groups. No statistical analysis of the results or drug histories of the patients were given (Pecegueiro et al. 1999). Bratel et al (1998) stated that it was not possible to reveal the difference between lichenoid contact lesions (LCL) and OLP lesions histologically. They compared T cell receptor V families and could identify no differences between the two groups (Bratel et al. 1998). Hietianen et al likewise could identify no histological or immunofluorescence alterations between the OLE lesions in contact with amalgams and those not (Hietanen et al. 1987). Another parameter that has been studied is the density of eosinophils in the two groups. No significant differences were found between sections from patients with OLP and DILR (Firth & Reade 1990). Others have distinguished DILR from OLP histologically but found no clinical differences between the two groups, though it was not stated upon what histological criteria these distinctions were made (Hamburger, Lawrence, & Oakes 1995). Involucrin, a marker for the normal maturation of the keratinocytes, has been postulated as an identifying feature for lichenoid reactions particularly in lichenoid dysplasia (Eisenberg, Murphy, & Krutchkoff 1987). McCullough and Radden tested

this claim and found no differences between specimens of patients with DILR and OLP (McCullough & Radden 1992).

McCartan and Lamey found, by indirect immunofluorescence, that there were circulating IgG basal cell cytoplasmic antibodies in patients with idiopathic OLP (3%) but they were associated more often with oral lichenoid drug eruptions (31%) suggesting that these are a potentially useful marker to distinguish between the two (McCartan & Lamey 1998). They also found that there was a significant increase in unilaterality in the lichenoid lesion (Lamey et al. 1995). Ingafou et al by contrast did not succeed in isolating any basal cell cytoplasmic antibodies from either patients with idiopathic OLP or DILR lesions but their sample size was very small (Ingafou et al. 1997). McCartan and Lamey also found differences in the expression of CD1+ and HLA DR antigens by Langerhan's cells in idiopathic OLP and DILR lesions and suggested that these diseases differed in the way that antigens were presented (McCartan & Lamey 1997). This, they postulated was due to the fact that systemically ingested drugs would be processed by antigen presenting cells elsewhere in the body, whereas, in cases of topically applied drugs and contact lesions with amalgams, the antigen crosses the oral epithelium and is processed there (McCartan & Lamey 1997). HLA DR antigens were only found in a third of all OLE patients studied in another publication, and no difference was found whether amalgam was in contact with the lesions or not, though the numbers of Langerhan's cells found was increased compared to normal oral mucosa (Bolewska & Reibel 1989).

The difference between the OLP and DILR seems to be regarded by most authors as the more frequent presence of the following in DILR: subepithelial infiltrate containing eosinophils and plasma cells, which is more diffuse and extends more deeply than in idiopathic LP, a perivascular infiltrate, and increased tendency to parakeratinisation and the presence of increased numbers of colloid bodies in the epithelium (McCartan & Lamey 1997; Savage 1997; van den Haute, Antoine, & Lachapelle 1989). These features can also be found in sections of idiopathic LP, so the histopathological diagnosis cannot be certain without other clinical data (McCartan 1997).

1.2.6. Treatment

Treatment of OLE involves removing aggravating trauma and infection by smoothing rough restorations and teeth, improving oral hygiene (Holmstrup, Schiotz, & Westergaard 1990) and treating any candidal infection present (Holmstrup et al. 1988; Thorn et al. 1988; Vincent et al. 1990). Both topical and systemic antifungal preparations have also be utilised though the use of griseofulvin is controversial (Bagán et al. 1991b; Eisen 1993). Careful history taking and examination of the patient may lead to the suspicion of a drug or allergen aetiology and this should be dealt with by communication with the medical specialists involved in prescribing the suspected drugs and/or by appropriate allergy testing and follow up. Stopping smoking was not found to have beneficial effects on OLE lesions and a negative correlation of the incidence of OLE with cigarette smoking was found in one large study (Axéll & Rundquist 1987; Savin 1991). The mainstay of symptomatic treatment revolves around immunosuppressive therapy in the shape of topical, local or systemic steroids (Silverman & Bahl 1997). Gingival lesions can be treated with steroid ointments held against the lesions in preformed Wenvac splints (Scully & Porter 1997). Steroids can also be contained in and applied to the mucosa in Orabase (sodium carboxymethylcellulose, pectin, gelatin and plasticized hydrocarbon gel which adheres to mucosa) preparations[6] (Silverman et al. 1991), tablets held

[6] Triamcinalone in orabase, clobestasol or fluocinonide.

against the mucosa while they dissolve[7], soluble tablets added to water to be used as a mouth wash[8] and metered dose inhalers containing beclomethasone which can be used as sprays[9]. Triamcinalone may be injected intralesionally or sublesionally in small areas of recalcitrant, symptomatic OLE. When systemic steroids are used, steroid sparing agents such as azathioprine (non-steroidal potent immunosuppressor) can be usefully employed (Silverman et al. 1991).

The use of other immunomodulators such as levamisole has been shown to remove anti basal cell antibody (ABA) from the serum of three out of six OLE patients positive for ABA. No mention of any resultant improvement in either symptoms or clinical appearance was made. The size and the 'open' nature of the trial, make it impossible to assess the clinical efficacy of this treatment from this study (Sun et al. 1994).

Retinoids such as Tretinoin, Isotretinoin, Etretinate and Tremarotene have been formulated in topical preparations to good effect and also used systemically though there is still a need for carefully designed, double blind, placebo controlled studies to evaluate their usefulness (Eisen 1993). Regezi et al found that topical isotretinoin had an antikeratinising and an immunomodulating effect on OLE lesions when assessed histologically (Regezi et al. 1986). These have to be prescribed carefully as the side effects can be troublesome or severe; dry mouth, hair loss, cheilitis, pruritus and desquamation of hands and feet have all occurred after retinoid therapy and these effects are often dose related (Eisen 1993).

---

[7] Corlan tablets – 0.2mg hydrocortisone
[8] Betnesol tablets –0.5mg betamethasone and Prednesol tablets –5mg prednisolone
[9] Becotide metered dose inhaler

Cyclosporine is a potent immunosuppressant and therefore need careful monitoring and although topical use minimises systemic effects while retaining clinical efficacy, reduced HLA-DR and ICAM-1 have been shown to be a result of topical (mouthwash) cyclosporine treatment (Eisen 1993). Surgical procedures such as conventional surgery, cryosurgery and carbon dioxide laser surgery have also been used. Other experimental treatments that have been tried require further investigation before being widely accepted and include; phenytoin, tetracycline, doxycycline, dapsone, and an antiviral – human fibroblast Interferon-B. Ultraviolet light therapy with or without a photosensitiser (psoralens) has yielded good results in some cases, though the link with UV light and malignancy needs to be borne in mind (Eisen 1993; Savin 1991).

The fact that treatments involving immunosuppressive and immunomodulating medications and UVA light are efficacious underlines the immune system involvement in the pathogenesis of OLE.

1.3. Recurrent Aphthous Stomatitis

1.3.1. Introduction

Hippocrates (460 – 370 BC) was the first to record the word 'aphthai' though he may well have been referring to thrush (Rogers III 1977). The first clear description of RAS was by Miculicz in 1898 (Savage et al. 1988). Recurrent aphthous stomatitis (RAS) is a common condition affecting both males and females and is found in all age groups. The ulceration almost inevitably presents as pain ranging from mild discomfort that the patient is just aware of to severe pain that debilitates the patient to the extent that even taking fluids orally becomes difficult and the patient has to rely on intravenous nutrition. The severity of pain not only depends on the size of the area of ulceration, but on the site. The different areas of the oral cavity have different sensory outputs, are exposed to differing amounts of trauma during mastication or speech for example and have varying degrees of mobility. And this means that an ulcer on the tip of the tongue is usually particularly painful even though it may be small in size. This is due to the fact that it is an extremely sensitive area, exposed to trauma repeatedly and being on purely a muscle base, has high mobility.

'Recurrence' is defined in different ways by various authors; Sun et al consider RAS as having at least one lesion per month (Sun et al. 1994) though others include those with recurrences of over three month intervals (Bagán et al. 1991a; Graykowski et al. 1966). Ship utilises more inclusive criteria with recurrence defined as two or

more episodes in a three year period (Ship 1965). Field notes that the some patients can identify a predictable, regular cyclic pattern while others have irregular recurrences of lesions (Field, Brookes, & Tyldesley 1992).

1.3.2. Classification and Features

RAS is thought to affect 10-20% of the general population (Field, Brookes, & Tyldesley 1992) though higher prevalences have been found in students and in younger age groups and great variation has been found in the prevalence in different population groups (Rogers III 1977). Bagán found the highest prevalence in the third and fourth decade (Bagán et al. 1991a) but many authors have found that most RAS patients experience ulceration in the first and second decades (Eversole, Shopper, & Chambers 1982). Patients with herpetiform ulceration present more often in the third decade (Field et al. 1987). Three clinical types of RAS have been identified; minor, major and herpetiform aphthae (Cooke 1960). Histologically the features are of non-specific ulceration (Porter, Scully, & Pedersen 1998) with a lymphocytic infiltration in the subepithelium initially which migrates intraepithelially as the lesions progress (Savage et al. 1988). The mononuclear infiltration seen in histopathological specimens of RAS lesions, is similar to that in delayed hypersensitivity (Lehner 1969b) as described by Coe et al (Coe, Feldman, & Lee 1966).

1.3.2.1.Minor Aphthae

Minor oral ulcers present typically as round or oval grey/yellow, shallow lesions surrounded by an erythematous halo. Their size is between 2-4 mm in diameter and heal spontaneously in 7-14 days. These commonly affect

the non-keratinised mucosa and tongue but may affect all intraoral sites (Field, Brookes, & Tyldesley 1992).

1.3.2.2.Major Aphthae

The major type of RAS is very similar to the minor except that the lesions are larger, often exceeding 1cm and due to this, take much longer to heal (up to six weeks) and scarring may occur. Again any part of the oral mucosa can be affected but the ulcers are commonly found on the soft palate, pillars of fauces and the lips (Field, Brookes, & Tyldesley 1992).

1.3.2.3.Herpetiform Ulceration

The appearance of herpetiform ulceration, first described by Cooke has been likened to that herpetic stomatitis, hence the nomenclature (Cooke 1960). Some have regarded these lesions as viral in nature as herpetic stomatitis may look clinically similar (Lehner 1967) but herpetiform ulceration is now considered part of the clinical spectrum of RAS (Field, Brookes, & Tyldesley 1992). The ulcers are very small, (about 1mm in diameter) and may occur in large quantities of up to 100 at one time, some of which may coalesce to form an ulcer with a ragged edge. Usually the anterior part of the mouth is affected, the average duration of lesions is more difficult to estimate but is thought to be several weeks (Field, Brookes, & Tyldesley 1992).

1.3.2.4.Behçet's Syndrome

Behçet's Syndrome is classified as a severe variant of RAS by some authors (Rogers III 1977) and regarded as a different though related entity by others (Porter, Scully, & Pedersen 1998). Behçet's Syndrome is a multisystem disease which is characterised by ulceration of the oral and genital mucosa and often ocular lesions such as uveitis as well as sometimes musculoskeletal, neurological, gastrointestinal and haematological problems (Rogers III 1977). In the early stages the lesions in the mouth may be indistinguishable from those of RAS (Lombardi, Hauser, & Budtz Jorgensen 1993). An immune pathogenesis for the disease is supported by the fact that increased numbers of Langerhan's cells can be induced by exposure to trauma in affected patients and that an autoimmune pathogenesis may be involved is suggested by the appearance of the macrophages and lymphocytes invading the epithelium (Lombardi, Hauser, & Budtz Jorgensen 1993). Antigenic cross reactivity may help to explain the involvement of many different tissues in Behçet's Syndrome (Lehner 1969a). Behçet's Syndrome is also characterised by human leukocyte antigens (HLA) B5 and B27 (Challacombe et al. 1977).

1.3.2.5.Other Systemic Diseases Associated With RAS

Gluten-sensitive enteropathy (GSE, Coeliac disease) has been associated with RAS to varying degrees by different authors. There seems to be no doubt that the prevalence of GSE is increased in patients with RAS, with different authors demonstrating that 4%, 24%, 1% and 0.5% of patients with RAS, had GSE (Wray et al. 1975 ; Ferguson et al. 1980; Ferguson et al. 1976; Hunter et al. 1993). Ferguson suggested that jejunal biopsy be carried out on all RAS patients (Ferguson et al. 1976), however most other authors recommend that only those with gastrointestinal symptoms or low folate or ferritin levels on haematological examination, be referred for jejunal biopsy (Ferguson et al. 1980). Field et al referred seven children with RAS and nutritional deficiencies for jejunal biopsy and found only one had evidence of GSE and recommended that children not be referred for jejunal biopsy unless the nutritional deficiency was accompanied by gastrointestinal symptoms and/or failure to thrive (Field et al. 1987). In all eight cases of GSE related RAS, there was complete remission of ulceration on commencing a gluten-free diet (Ferguson et al. 1980; Ferguson et al. 1976), however further studies have shown that 25% (n=5) (Wray 1981) and 25% (n=3) (Wright et al. 1986) of RAS patients with normal jejunal morphology, experienced complete remission on a gluten-free diet. Hunter et al investigated the effect of a gluten-free diet and also studied the effects on a blinded control group given gluten capsules and a gluten free diet. They found no significant differences between the two groups though all had a reduction in RAS symptoms indicating that a placebo effect may be at work (Hunter et al. 1993).

Other diseases that may have RAS as part of their clinical features are cyclic neutropenia (Gorlin & Chaudhry 1960), Sweet's syndrome (Von-den-Driesch 1994) and some immunodeficiency states including human immunodeficiency virus infection (Porter, Scully, & Pedersen 1998).

1.3.3. Aetiology

Traumatic insult to the oral mucosa is thought to precipitate RAS lesions in susceptible subjects (and frank traumatic ulceration if the trauma is severe or prolonged enough) (Eversole, Shopper, & Chambers 1982). This may be due to the oral mucosa being more vulnerable to mild trauma as the oral mucosa of RAS patients has been shown to be less keratinised than that of healthy patients (Bánóczy & Sallay 1968). Some authors consider that smoking is thought to have a protective role against the precipitation of ulceration in the oral cavity and this may be due to increased keratinisation of the oral epithelia in smokers that mitigates against minor trauma causing the ulcer (Bánóczy & Sallay 1968).

Genetic factors are strongly suggested (Ship 1965) and though the exact mode of inheritance has not been outlined, a recessive susceptibility gene has been suggested (Wray et al. 1981). HLA A2 and Bw44 were shown to be correlated to disease activity (Wray et al. 1981) and HLA A2 was found in RAS patients in another study along with HLA B12 (Challacombe et al. 1977). However, these results have not been confirmed by other studies (Dolby et al. 1977).

Nutritional deficiencies of iron, folic acid and vitamin B12 were found in 14.2% (n=47) of 330 patients with RAS and in 21% of 100 children with RAS (Field et al. 1987; Wray et al. 1978) and Nolan et al identified vitamin B_1, B_2 and B_6 deficiencies in 28% of 60 RAS patients (Nolan, McIntosh, & Lamey 1991).

Evidence for a psychogenic basis for RAS is not compelling though some have found that anxiety levels have been higher in RAS patients (Ship 1960). It may be that anxious people have a lower pain threshold and therefore present with RAS more often (Field, Brookes, & Tyldesley 1992). The role of exogenous antigens has been considered by many authors (Savage & Seymour 1994) and possible bacterial or viral antigens have been suggested. The role of streptococcal antigens is unclear. Some studies have found a possible involvement of *Streptococcus sanguis* strain 2A (Donatsky 1978) though this was not substantiated by a further study (Hoover, Olson, & Greenspan 1986) and Riggio et al found no association of RAS with *Streptococcus oralis* (Riggio et al. 1999). There is a possibility of antigenic cross reactivity between L form bacteria and oral mucosa (Lehner 1967). The role that viruses may play is yet to be established and adenoviruses and herpes simplex viruses have been implicated (Scully 1993).

An allergic basis for RAS has been postulated though this is considered uncommon by some authors (Field, Brookes, & Tyldesley 1992). See section 1.3.4.

The onset of RAS does not seem to coincide with puberty though up to 62% of female patients experience recurrence premenstrually (Eversole, Shopper, & Chambers 1982) and this is probably due to the decrease in keratinisation associated with low oestrogen levels which increases the susceptibility to ulcer formation (Main & Ritchie 1967).

1.3.4. Pathogenesis

Histologically the lesions of RAS show features of T cell lymphomas i.e. a lymphomonocytic infiltrate in the epithelium and it is well accepted that the pathogenesis of RAS involves immune mechanisms (Savage, Seymour, & Kruger 1986). It is thought that the lymphocytes interact with the keratinocytes in the epithelium and so mediate the damage (Lombardi, Hauser, & Budtz Jorgensen 1993). Savage and Seymour found that both CD4+ and CD8+ are capable of destroying oral mucosal epithelial cells that express both class I and II major histocompatibility (MHC) antigens (Savage & Seymour 1994). Gamma interferon (γ-IFN) is responsible for the increased expression of class I MHC antigens and the *de novo* synthesis of class II MHC antigens (Savage, Seymour, & Kruger 1986). It is not clear whether antigen cross reactivity exists between antigens of the oral mucosa and those of environmental or dietary origins, or whether chemicals such as some dietary antigens conjugate with epithelial proteins and act as sensitisers that way (Hay & Reade 1984). Once the lesion is established, polymorphonuclear neutrophils (PMN) are the predominant cell type and their increased adherence compared to controls may assist in the perpetuation of the ulcer (Wray & Charon 1991).

An autoimmune mechanism has been suggested because antibodies (residing in the IgG and IgM fraction) to foetal oral mucosa have been found in patients with RAS and Behçet's Syndrome, though they were not specific to oral mucosa (Lehner 1967).

1.3.5. Role of Allergy

In a survey of 338 patients attending a hospital for reasons other than RAS and allergic conditions, 84% of those who admitted suffering from RAS (n=69), also had a positive history of allergy, and 63% of those with allergic conditions (n=92), also had a positive history of RAS. These correlations were highly significant (Spouge & Diamond 1963). However, Wray found no increased incidence of atopy in RAS patients compared to the general population (Wray, Vlagopolous, & Siraganian 1982).

A study investigating the mast cell populations in RAS patients' oral mucosa, found that the role of a Type I hypersensitivity reaction was unlikely though histamine did have some role to play (Dolby & Allison 1969). The possibility of a Type IV hypersensitivity reaction in the aetiology of RAS lesions is supported but not proven by IgD positive cells in aphthous lesions similar to those in the acute phase of ACD (Bays, Hamerlinck, & Cormane 1977), and all types of RAS show histological features of a delayed type hypersensitivity reaction (Lehner 1972).

While Wray found that an empirical gluten-free diet resulted in complete resolution in 5 out of 20 RAS patients, the previously found low folate levels also were increased back to normal levels thus allergy to gluten was not the only mechanism involved (Wray 1981). However, RAS was induced by a variety of foods including gluten in five out of 12 patients who underwent an elimination diet followed by the staggered introduction of foods until a normal diet was achieved (Hay & Reade 1984). The foods eliciting RAS upon reintroduction were: tomatoes, figs, cheese, vinegar,

lemon, pineapple, French mustard, wheat flour and cow milk. The ulceration appeared in 8-48 hours after ingestion of the offending food item, this latent period being consistent with a Type IV hypersensitivity reaction (Hay & Reade 1984). Another study found that six out of 12 patients experienced complete remission from RAS after avoiding the following foods; gluten (n=3), food additives (tartrazine, benzoic acid, sunset yellow, and new coccine) (n=2), and cows milk products (n=1) (Wright et al. 1986). Six out of seven patients had no recurrence of RAS during a 'non-allergenic' dietary regime (Ship 1960).

The response to challenges to 15 food allergens and 10 environmental allergens was correlated with in vitro histamine release from leukocytes in 30% of RAS patients thus investigated but none of the patients experienced complete resolution upon avoidance. This indicated that both food allergens and histamine do have minor roles to play in the pathogenesis of RAS (Wray, Vlagopolous, & Siraganian 1982).

However some authors found no link between RAS and foods that patients thought were instrumental in precipitating lesions; walnuts, strawberries and tomatoes (Eversole, Shopper, & Chambers 1982). It was likely that the acidic and astringent nature of these foods caused pain in subjects already with RAS lesions rather than causing the ulcer formation itself.

A prospective study of 21 RAS patients utilised patch testing to identify allergens and 20 of these had one or more positive results. Of these, eight experienced compete remission on allergen avoidance and many others reported an 80% improvement (Nolan et al. 1991). This study clearly indicated that allergy testing and skilled allergen avoidance advice was

clinically efficacious in many patients with RAS though there was no control group tested. Another study found that one out of five RAS patients patch tested had a clinically relevant positive reaction (to menthol) and resolution upon allergen avoidance though again no healthy control group was studied (Shah, Lewis, & Gawkrodger 1996).

1.3.6. Management and Treatment

Clinical management of the patient with RAS involves history, examination and investigations (usually haematological) to check for the possibilities of underlying systemic disease and patients may require correction of haematinic deficiencies.

A total of 23 out of 47 patients identified as having one or more nutritional deficiencies experienced complete remission on replacement therapy (Wray et al. 1978). Peripheral blood examination (haemoglobin concentration, mean corpuscular volume, mean corpuscular haemoglobin and examination of blood film) alone would have missed 16 patients in this study and it was recommended that estimation of serum iron content, total iron binding capacity, whole blood folate and vitamin B_{12} assay should also be carried out in RAS patients (Hutcheon et al. 1978). The value of haematological screening in children aged 7-16 with RAS, was shown in a retrospective study of 100 children, 21 of whom were found to have a deficiency of one of the above mentioned nutritional factors (Field et al. 1987). Nolan et al suggested including vitamins B_1, B_2 and B_6 in the haematological screening as 28% of 60 RAS patients were found to be deficient in one or more of these vitamins and in a controlled but not blinded study, patients with a deficiency improved after replacement therapy (Nolan, McIntosh, & Lamey 1991). In a further study of a group of 47 RAS patients each having a single haematinic deficiency, 70% showed considerable subjective improvement in their symptoms when replacement regimes were instituted (Porter et al. 1992).

Avoidance of relevant allergens is efficacious in a proportion of patients. Treatment is generally focussed on controlling symptoms and preventing secondary infection and includes the types listed in Table 5. A placebo effect has been noted by some authors and few medicines actually reduce the recurrences of the lesions without notable side effects (Porter, Scully, & Pedersen 1998). The use of corticosteroids is of benefit in many cases, where they are thought to inhibit effector B and T cells and T helper cells (Pedersen & Klausen 1984) though a recent publication calls for more rigorous scientific study in this area (Kalmar 2000). The immunomodulator levamisole has been shown to have a number of effects in both humoral and cellular immune mechanisms of RAS patients. These include normalisation of the CD4+/CD8+ ratio, IgM and IgA levels, and the disappearance of serum antinuclear antibodies, giving rise to both subjective and objective clinical improvement in symptoms though long term (1-22 months) treatment was required (Sun et al. 1994).

Table 5. Some Reported Therapies of RAS

Preparation Types	Medicament
Mouthrinses	Chlorhexidine gluconate
	Benzydamine hydrochloride
	Carbenoxolon disodium
	Betadine
Topical corticosteroids	Hydrocortisone hemisuccinate
	Triamcinalone acetonide (in adhesive paste)
	Fluocinonide (cream)
	Betamethasone valerate (mouthrinse)
	Betamethasone-17-benzoate (mouthrinse)
	Flumethasone pivolate (spray)
	Beclomathasone dipropionate (spray)
Antibiotics	Topical tetracyclines
Immunomodulators	Levamisole
	Transfer factor
	Colchicine
	Gammaglobulins
	Aza thioprine
	Dapsone
	Thalidomide
	Pentoxifylline
	Prednisolone
	Azelastine
	Alpha-2-interferon
	Cyclosporin
	Amlexanox
	5-amino salicylic acid
Others	Systemic zinc sulphate
	Monoamine-oxidase inhibitors
	Sodium cromoglycate
	Deglycirrhizinated liquorice
	Sucralphate
	Etreninate
	Low-energy laser

Based on the table reproduced in (Porter, Scully, & Pedersen 1998).

1.4. Angioedema

1.4.1. Introduction

Quinke oedema was described by Dr Heinrich Quinke in 1881 and the hereditary version of this was reported seven years later (Mattingly, Rodu, & Alling 1993; Oltivai et al. 1991).

Hereditary (Ruddy 1988), acquired (Oltivaiet al. 1991; Postlethwaite & Parry 1988) and idiopathic forms of angioedema have been well documented in the literature in recent years. Patients with angioedema (AE) often experience orofacial symptoms such as tongue and lip swelling and thus may present first to their dental surgeon, though due to the sudden onset and severity of symptoms especially if pharyngeal and laryngeal swelling are present, patients often present to accident and emergency facilities (Guo & Dick 1999; Ruddy 1988). The condition was formerly known as angioneurotic oedema, due to patients complaining of a choking sensation and being labelled as neurotic, prior to the nature of the condition being fully known. The "neurotic" component has since been dropped as there is no marked contributing psychological overlay to this condition (Sim & Grant 1990). Dental treatment procedures, particularly surgical procedures, may aggravate or precipitate an angioedematous response (Degroote, Smith, & Huttula 1985; Ruddy 1988).

AE refers to localised swelling of skin or mucous membranes often associated with urticaria. It may occur as part of an IgE-mediated reaction (Sussman, Yang, & Steinberg 1992). AE is characterised by recurrent, non-

pruritic oedema of the subepithelium or submucosa (Wong 1990). The face, tongue, pharynx and larynx are commonly affected as are the small bowel and extremities. As well as being distressing to the patient, tongue, pharyngeal and laryngeal swelling can lead to respiratory embarrassment (Thompson & Frable 1993) and can be fatal (Ulmer & Garvey 1992). Small bowel involvement can give rise to acute abdominal pain and other symptoms which may mimic inflammatory bowel disease (Eck et al. 1993; Jacobs, Hoberman, & Goldstein 1993).

1.4.2. Classification

1.4.2.1.Hereditary Angioedema

Hereditary angioedema (HAE) is a rare, autosomal dominant genetic disorder affecting 1:50,000 of the population in the UK (Postlethwaite & Parry 1988). The genetic abnormality affects the coding for C_1 esterase inhibitor (C1-INH) which results in the formation of a null allele (Ishi, Kawaguchi, & Nakajima 1996; Ruddy 1988; Verpy et al. 1996). Two types have been recognised (Oltivai et al. 1991), type 1 which makes up 85% of cases and type 2 making up the other 15%. In type 1, affected patients have a biochemical deficiency of C_1 esterase inhibitor (C1-INH) which results in low circulating levels of this important regulator of the complement cascade. In type 2, affected patients have normal circulating levels of C1-INH but the protein is dysfunctional, causing a decrease in its activity. Without the regulating influence of C1-INH, patients are susceptible to a massive, escalating inflammatory response due to the unimpeded action of C1, C2 and C4 (Oltivai et al. 1991). Such a response may be triggered by a number of precipitants such as stress, oestrogen containing drugs, allergy or trauma (Degroote, Smith, & Huttula 1985; Ruddy 1988; Seidman et al. 1990; Sim & Grant 1990; Wilson 1996) and has considerable morbidity and may even be fatal. HAE is indeed the most severe form of AE (Ruddy 1988). Clinical features of hereditary AE are the absence of accompanied urticaria with the AE which suggests a minor role for histamine in its

pathogenesis (Sim & Grant 1990) and a positive family history though this is only found in 75-85% of cases (Ruddy 1988).

1.4.2.2.Acquired Angioedema - (1) Acquired C1-INH Deficiency

The acquired form of AE was first described in 1972 (Caldwell et al. 1972) and is recognised in patients presenting at a later age, a negative family history and low serum C1q (C1q levels are normal in HAE). Affected patients have a normal C1-INH gene and normal amount of functioning C1-INH protein secreted into the plasma. However, once in the plasma, C1-INH is bound by circulating antibodies and consequently its functioning capacity is reduced (Markovic et al. 2000). Two types have been recognised according to the types of antibodies involved.

In most cases, there is an associated benign or malignant lymphoproliferative disorder such as large cell lymphoma, chronic lymphocytic leukaemia, or monoclonal gammopathy (Eck et al. 1993; Markovic et al. 2000). Hodgkins disease and primary systemic amyloidosis have also been associated (Markovic et al. 2000). Antibodies against the monoclonal B-cell immunoglobulins cross react with the C1-INH protein and the resulting antigen-antibody complex is eliminated. C1q components are also affected by a similar mechanism.

Rarer forms of C1-INH deficiency arise in patients suffering from autoimmune diseases. These patients have autoantibodies that react with the C1-INH molecule and decrease the levels of C1-INH (Markovic et al. 2000).

1.4.2.3.Acquired Angioedema - (2) Drug and Allergy Related Angioedema and Idiopathic Angioedema

AE may occur in patients with no demonstrable decrease in the quantity or function of C1-INH. There is considerable debate regarding the aetiology of both urticaria and AE as evidenced by the correspondence between some authors (Dolovich 1992; Knight 1993; Singh 1992). These reactions may be induced by drugs, food, or contact allergies; stress; physical factors such as trauma, heat and cold; infections; systemic diseases such as systemic lupus erythematosus or be idiopathic (Kao & Zeitz 1993). The precipitating factors may operate together, for example trauma in a patient taking drugs that have been known to cause angioedema (Kharesh 1992). Some physical causes are found in combination as in cases where food intake together with a rise in body temperature results in AE (Zuberbier, Bohm, & Czarnetzki 1993). A helpful classification by mechanism has been tabled by Miller and Zeiss and is reproduced in Table 6 (Miller & Zeiss 1993). Urticaria is closely related to AE and the most common clinical finding is urticaria without AE. The next most common is urticaria and AE together and the least common

Table 6. Classification of Urticaria and Angioedema

I. Immunologic	IgE mediated	Foods Chemicals and therapeutic agents Foreign proteins (venom, latex, insulin)
	Immune complex and complement mediated	Blood and blood products, cuprophane haemodialysis membranes
II. Direct histamine release and/or uncertain mechanisms		Opiates, radiographic contrast media, vancomycin, pentamidine, dextran, aspirin, other NSAIDs
III. Nonimmunologic	Physical stimuli	Cold, cholinergic, solar urticarias, pressure and exercise urticaria/AE and dermatographism
	Underlying medical disease	Urticaria pigmentosa (systemic mastocytosis), cutaneous vasculitis, serum sickness, malignancy, infections (viral, parasitic), acquired CI inhibitor deficiency
	Hereditary	Hereditary AE, hereditary vibratory AE, familial cold urticaria, C3b complement deficiency,
	Papular urticaria	
IV. Idiopathic		

(Miller & Zeiss 1993)

is AE alone. Urticaria is characterised by cutaneous wheals and symptoms of intense pruritus and is designated acute or chronic if the lesions last less or more than six weeks (Kao & Zeitz 1993). Urticaria involves the superficial portion of the dermis while AE affects primarily the deeper dermal layers and the subcutaneous tissues with the most likely symptom being pain rather that pruritus (Cooper 1991). Urticaria and AE have a peak incidence in the third and fourth decades (Kao & Zeitz 1993).

The agents causing AE may be those acting directly with blood vessels such as circulating immune complexes (found in autoimmune diseases and in Type III hypersensitivity), chemicals (e.g. cocaine), systemic diseases and microorganisms, or on the mast cells. Those acting on mast cells may utilise an IgE mediated mechanism as in anaphylactic reactions or be mediated through substances such as vasoactive proteins e.g. histamine, bradykinin, prostaglandin D, leukotriene C and D and platelet activating factor. These mediators of the inflammatory response cause an increase in vascular permeability which gives rise to an increase in plasma kinin production which in turn leads to a further increase in vascular permeability and so starts a positive feedback mechanism (Davidson et al. 1992). Complement components play a major role as promoters of histamine release from basophils and mast cells as well as being chemotactic for components of the inflammatory response (Davidson et al. 1992).

Various substances have been reported as precipitating angioedema by allergic mechanisms and some of these are shown in Table 7. Contact urticaria has been reported after the use of a formaldehyde containing dental

Table 7. Allergens Implicated In Angioedema and Urticaria

Allergen	Reference
Tomato	(Thompson & Frable 1993)
Hazel nut	(Mattingly, Rodu, & Alling1993)
Peanut	(Sicherer, Burks, & Sampson 1998; Tariq et al. 1996)
Monosodium glutamate	(Squire 1987)
Food additives*	(de Martino et al. 1992)
Food additives#	(Malanin & Kalimo 1989)
β-lactam antibiotics	(Thompson & Frable 1993)
Bovine fibrin in haemostatic sponge	(Wuthrich, Bianchi-Kusch, & Johansson 1996)
Black rubber in dental dam	(Grattan & Kennedy 1985)
Latex	(Rosen et al. 1993)

* The following food additives resulted in positive reactions following oral challenge in 56 children with urticaria/AE: sunset yellow (E110), annatto (E160b), sodium benzoate (E211), tartrazine (E102), aspartamine, erythrosine (E127) and acetyl-salicylic acid.

The following food additives gave positive, reproducible reactions on skin prick testing: benzoic acid, propionic acid and patent blue

root canal paste (el Sayed et al. 1995). Recurrent facial swelling has been rarely reported as the clinical feature of a Type IV hypersensitivity reaction to rubber chemicals and formaldehyde (Lamey & Forsyth 1986).

The most common drugs associated with angioedema are the angiotensin converting enzyme (ACE) inhibitors which are used in the treatment of hypertension ("Medicines Resource Centre" 1994). All types of ACE inhibitors have the potential to cause AE although they may have different molecular configurations (Slater, Merrill, & Guess 1988). The most common types reported as precipitating AE, in order of frequency are lisinopril, enalapril and captopril, and reactions to these have been well documented (Giannoccaro et al. 1989; Rees, Bergman, & Ramirez-Alexander 1992; Thompson & Frable 1993; Ulmer & Garvey 1992). Most cases of AE occur in the first seven days of treatment with ACE inhibitors though late onset AE has been described occurring sometimes years after commencement of therapy (Guo & Dick 1999; Slater, Merrill, & Guess 1988). The precipitation of AE by ACE inhibitors is a mechanism based side effect of the drug involving the inhibition of ACE, which is the same substance as kininase 2, which may cause blockade of bradykinin metabolism which in turn leads to increased action of this vasoactive peptide. The conversion of angiotensin I to angiotensin II (a potent vasoconstrictor) is also blocked which significantly decreases peripheral vascular resistance (Gannon & Eby 1990). There may also be increased synthesis of bradykinin or related kinins. Some other pharmacological drug reactions may also contribute towards this phenomenon as some patients react to one type of ACE inhibitor but not to another. However, if a patient

has had a reaction to a particular ACE inhibitor they are more likely to have a reaction to another and so all ACE inhibitors should henceforth be avoided in these patients (Slater, Merrill, & Guess 1988). The incidence of ACE inhibitor-induced AE is estimated to be 0.1% - 0.2% of the population taking ACE inhibitor drugs (Gannon & Eby 1990).

The black population in America has been identified as being at increased (4.5 times) risk of ACE inhibitor induced AE than white Americans (Brown et al. 1996), and this may be due to increased sensitivity to bradykinin in black Americans (Gainer et al. 1996).

Other precipitating drugs include NSAIDs such as ketorolac (Shapiro 1994) and aspirin (Davidson et al. 1992) (NSAIDs are thought to cause allergy-like reactions mediated by vasoactive mediator release rather that true Type I allergic reactions (Anderson 1997a)), and angiotensin II receptor antagonists such as Cozaar (Boxer 1996).

1.4.3. Treatment

The treatment and management of angioedema can be divided into three stages :

(1) management of the acute attack;

(2) chronic prevention; and

(3) prophylaxis prior to surgery

In all types of angioedema, management of the acute attack centres around maintenance of the airway with in-patient care often being required.

1.4.3.1.Hereditary Angioedema and Acquired Deficiency of C1 INH

(1) Any patient with a history of HAE or with an acquired deficiency of C1 INH showing any signs of an angioedematous episode should be transferred as a matter of urgency to hospital for further management and observation as either endotracheal intubation or a surgical airway may be required (Thompson & Frable 1993). Episodes of angioedema may last 24-48 hours, often with increasing severity and so during significant episodes in-patient care is usually required (Giannoccaro et al. 1989). Patients who have bowel involvement may require re-hydration and narcotic analgesics as the bowel symptoms may be severe (Sim & Grant 1990).

(2) In the long term, prevention of attacks is of prime importance as, once an attack has started, it can be extremely difficult to control despite intensive medical management with antihistamines, corticosteroids and adrenaline (Sim & Grant 1990). Prophylaxis is usually achieved by attenuated androgens such as danazol or stanozolol (Madanes & Farber 1982). Patients can be maintained on low doses of these steroids for long periods of time with little or no side effects (Cicardi et al. 1991). These anabolic steroids increase the plasma levels of C1-INH as well as some other proteins (Cicardi et al. 1991). Pregnancy and menstruation increase HAE activity and prophylaxis with fresh frozen plasma and/or careful use of androgens during pregnancy has been useful (Hawthorne 1996; Sim & Grant 1990).

In patients with acquired C1-INH, the most effective treatment is diagnosis and treatment of the underlying disorder, however the AE often precedes the discovery of the underlying disease by up to seven years so anabolic steroids may have to be used for a period of time (Markovic et al. 2000).

(3) Prophylaxis prior to surgical procedures involving the oral cavity is necessary in patients who have HAE or acquired C1-INH deficiency. In some patients, the administration of a local anaesthetic may cause sufficient trauma to trigger an attack while in others, the stress of dental treatment contributes to their angioedema (Degroote, Smith, & Huttula 1985). The use of intravenous sedation is prudent to avoid further anxiety in these patients as the trauma of endotracheal intubation during a general

anaesthetic has been shown to precipitate attacks (Kharesh 1992). Fresh frozen plasma can be administered to increase the levels of C1-INH. Two units given 8 hours prior to treatment ensures adequate tissue distribution of the protein. Preparations of purified C1-INH can also be used which reduces the risk of cross infection from plasma transfusions. These preparations have been shown to significantly reduce the number and severity of attacks (Atkinson & Frank 1991; Degroote, Smith, & Huttula 1985).

1.4.3.2.Acquired Angioedema - Drug and Allergy-Related and Idiopathic Angioedema

(1) Although a patient with respiratory embarrassment secondary to AE would be unlikely to present to the dental surgeon, there is always the possibility that this could develop during a consultation or treatment in susceptible individuals (Grattan & Kennedy 1985). If there is respiratory distress or severe facial or lingual swelling, the patient should be transferred to hospital for further management as above. Administration of hydrocortisone and antihistamines such as chlorpheniramine, either intravenously or intramuscularly, is useful in the management of these cases as is the intramuscular administration of adrenaline (Wong 1990).

(2) Patients who are likely to suffer from severe or recurrent episodes are instructed on the use of a self-administration system of intramuscular adrenaline, Epipen®, which delivers 300 micrograms of adrenaline (British Medical Association & Royal Pharmaceutical Society of Great Britain 2000b).

Identification of the causative factor in the angioedema often provides the treatment regimen. This may require changing the drug regime or avoidance of identified allergens or physical factors . If food or environmental allergens are suspected, circulating IgE levels to putative allergens (RAST test) (Wuthrich, Bianchi-Kusch, & Johansson 1996) should be assessed and skin testing such as prick or patch tests should be carried out in a specialist centre (Lamey & Forsyth 1986; Tariq et al. 1996). In some cases, patients have been controlled on long term antihistamine therapy, while anticholinergics such as Pirenzepine have been useful in AE precipitated by physical factors (Ciprandi et al. 1989; Zuberbier, Bohm, & Czarnetzki 1993). An empirical, additive free diet was suggested by Malanin and Kalimo who found that skin testing was beneficial in predicting good responders to avoidance diets (Malanin & Kalimo 1989).

(3) In severe cases, steroid or antihistamine cover should be considered prior to undertaking dental surgery. Patients with a history of severe reactions may require referral for hospital management of certain dental procedures (Atkinson & Frank 1991).

1.5. Erythema Multiforme

1.5.1. Introduction

Erythema multiforme (EM) is thus named after its various clinical presentations which include macular, papular, vesiculo-bullous and ulcerative lesions and which may affect the skin, mucous membranes and conjunctiva (Schofield, Tatnall, & Leigh 1993). The disease is an uncommon mucocutaneous disorder that may represent a transient autoimmune defect (Lozada-Nur, Gorsky, & Silverman 1989). The age at onset is usually in the second and third decade (Farthing et al. 1995) and most initial presentations affect either the skin alone or the skin and the oral cavity though subsequent attacks were more likely to involve other sites as well (Farthing et al. 1995). The frequency of recurrence was 1-3 times per year in 34% of 82 EM patients investigated (Farthing et al. 1995) and a mean of 6 times per year in another study of 65 patients (Schofield, Tatnall, & Leigh 1993).

1.5.2. Classification and Features

The clinical spectrum of EM can be classified by the severity into EM minor - one mucous membrane affected with or without cutaneous manifestations and major - more than one mucous membrane involved with severe generalised skin lesions (Huff, Weston, & Tonnesen 1983). Major EM is also termed Stevens-Johnson syndrome (SJS) (Anderson 1997a; Eversole 1994). Some authors consider that toxic epidermal necrolysis (TEN, Lyell's disease, toxic epidermolysis), a rare, life threatening disorder characterised by widespread desquamation of skin and mucosa and multi organ-system failure, is part of the EM spectrum of diseases (Anderson 1997a).

EM may also be classified by its periodicity, either recurrent and self limiting or chronic and continuous (Eversole 1994; Manganaro 1996). The recurrent pattern lasts for usually 21 days while the chronic form if untreated may persist for years (Lozada-Nur, Gorsky, & Silverman 1989).

A characteristic feature of EM is vermilion haemorrhagic ulceration (Eversole 1994). Other clinical features include oral lesions in 25-50% of EM cases, and the classical target lesions of the skin which are found in 25-38% of cases (Lozada-Nur, Gorsky, & Silverman 1989; Lozada & Silverman 1978). More severe types may also be accompanied by headaches and elevated temperatures (Lozada-Nur, Gorsky, & Silverman 1989).

Diagnosis is by exclusion together with the clinical features and history as the features of EM are characteristic rather than pathognomic (Manganaro 1996). Clinically especially in the absence of cutaneous or ocular

involvement, the lesions may mimic those of RAS and primary herpes (Farthing et al. 1995). EM may be differentiated from minor RAS by the fact that EM lesions more often affect keratinised mucosa and areas of confluent ulceration can often be seen, major RAS by the predilection of the fauces in this case, from herpetiform ulceration by the size of the ulcers, and from primary herpes by the fact that this is not recurrent and typically affects the hard palate and gingivae (Farthing et al. 1995). Microscopic examination aids in eliminating other diseases that may present a similar clinical appearance such as pemphigus vulgaris, benign mucous membrane pemphigoid and erosive lichen planus (Manganaro 1996). The histological appearance of EM is fairly non-specific and consists of intracellular oedema of the stratum spinosum, intra and subepithelial vesicle formation and a primarily chronic inflammatory cell infiltrate of varying intensity (Staretz & DeBoom 1990).

1.5.3. Aetiology And Pathogenesis

EM is an acute dermatitis of unknown aetiology (Lombardi, Hauser, & Budtz Jorgensen 1993), nevertheless pharmacologic involvement is thought to be responsible for half of all cases, with circulating immune complexes consisting of antibody and drug antigenic component (Eversole 1994). The sulpha group of drugs have been implicated as causative agents in the majority of drug related EM (Eversole 1994) but many others have been recorded as precipitating the disease, such as the pharmacological preparations shown in Table 8.

Herpes simplex virus (HSV) infection accounts for many of the other cases particularly in recurrent EM and, though only one third of patients had detectable HSV by the polymerase chain reaction in this study, perhaps in most EM cases (Darragh et al. 1991). EM was preceded by HSV infection in 61% of 82 EM patients with the delay between HSV infection and EM being between 1 and 15 days in 97% of cases (Farthing et al. 1995).

EM can develop after a cutaneous delayed hypersensitivity reaction (Gil Mateo et al. 1995).

EM has also been associated with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease and the mechanism for this is thought to be a Type III or IV hypersensitivity reaction (Chapman, Forsyth, & MacQueen 1977).

Table 8. Drugs Suspected In the Aetiology OF Erythema Multiforme

Antimalarials	NSAIDs
Barbituates	Penicillin
Bisulphan	Phenylbutasone
Carbamazepine	Phenytoin
Chlorpromide	Salicylates
Clindamycin	Sulphonamides
Codeine	Tetracyclines

(Staretz & DeBoom 1990; Wolkenstein et al. 1996; Wright 1984; Yusin, Crawford, & Klaustermeyer 1999)

T lymphocytes are the dominant part of the cell infiltrate and many bear the CD8+ phenotype (Lombardi, Hauser, & Budtz Jorgensen 1993), with CD4+ T cells being predominant in the peripheral tissues of a typical cutaneous target lesion (Puig et al. 1995). Langerhan's cells are found to be increased in size and number in the early stages of the lesions (Lombardi, Hauser, & Budtz Jorgensen 1993). Anderson however states that no immune reaction has been identified in EM and refers to the disease as an 'allergic-like reaction' though he doesn't state the mechanism of this response (Anderson 1997a). Many reactions to topically applied agents have been termed EM-like reactions rather than EM though the histological picture, and more importantly the immunohistochemical characterisations of the two are very similar (Puig et al. 1995).

Eversole postulates that the mechanism behind EM involves immune complex vasculitis or the direct action of immunologic factors on the keratinocytes themselves resulting in necrosis (Eversole 1994). Puig et al consider that the epidermal expression of ICAM-1 and HLA-DR might be involved in the regulation of an immunologic process mediated by CD4+ lymphocytes which would give rise to the EM clinical and histological picture regardless of aetiology (Puig et al. 1995). In cases where HSV is suspected, the mechanism is likely to be an immune reaction to HSV rather than a pathologic effect of HSV itself (Scully 1993).

1.5.4. **Role of Allergy**

As has already been stated, the immune pathogenesis of EM involves reaction to an antigen be it viral, drug or other type (Eversole 1994). Indeed EM has been described as a possible morphological pattern of ACD (Rietschel 1989), as a sequelae of ACD in some patients (Gil Mateo et al. 1995) and others have suggested that EM may be a manifestation of an allergic contact sensitivity giving rise to a Type III reaction (Friedman & Perry 1985). Some however have been unable to identify any regularly associated factors with the onset of EM, drug, HSV or food/environmental hypersensitivities (Lozada-Nur, Gorsky, & Silverman 1989).

Other substances that have been reported as eliciting EM as a result of cutaneous or mucosal contact include: primula (Hjorth 1966), vitamin E (Saperstein, Rapaport, & Rietschel 1984), nickel (Friedman & Perry 1985), benzoic acid (Lewis et al. 1989), colophony and fragrance mix (O'Donnell & Tan 1997), sesquiterpene lactones (Gil Mateo et al. 1995) and bufexamac (Kurumaji 1998). It is most likely that a Type III hypersensitivity reaction is mainly responsible for the clinical features of EM though the close relationship with ACD suggests some role for a cell mediated role (Pedersen & Klausen 1984).

1.5.5. Management and Treatment

Testing for HSV is usually carried out by attempting to culture the virus though this is often unsuccessful (Scully 1993) and questioning the patient may elicit information about previous episodes of herpes labialis (Farthing et al. 1995). However, in cases where the history of the disease includes recent HSV infection, continuous treatment with aciclovir 400mg twice daily has been shown to be more effective than short courses of the drug (Schofield, Tatnall, & Leigh 1993).

A careful history will indicate what, if any drugs were being used at the time of and prior to the initial eruption. Patch testing to drugs implicated in EM were useful in testing a topical preparation (Kurumaji 1998) but showed weak sensitivity to systemically administered drugs thought to precipitate SJS (Wolkenstein et al. 1996). Treatment of the lesions is largely symptomatic and involves pain relief, fluid replacement (Wright 984) (intravenously if required) (Farthing et al. 1995) and antimicrobial therapy to prevent or treat secondary infections (Roleau 1999). Corticosteroids are used to both prevent, and modulate the severity of lesions in minor EM but have been shown to be deleterious in severe SJS and TEN (Roleau 1999). Levamisole may be used as a steroid potentiator or as treatment in its own right and both regimes have shown good results in a double blind cross over trial in 14 patients (Lozada 1982). Dapsone and antimalarials have also been utilised with a small degree of success (Schofield, Tatnall, & Leigh 1993). Azathioprine is recommended by some authors (Farthing et al. 1995).

Early withdrawal of the offending medication in drug-induced SJS/TEN is vital as this may save lives (Roleau 1999) and treatment of these severe cases is thought to be best undertaken in either specialised intensive care units or burns units and the symptomatic therapy should be the same as for major burns (warming of the environment, correction of fluid and electrolyte losses, high calorie intake and the prevention of sepsis) (Roleau 1999).

1.6. Orofacial Granulomatosis

1.6.1. Introduction

Oral granulomatous lesions were identified as part of the clinical picture of Crohn's disease in 1969 (Dudeney 1969). In 1985, Wiesenfield introduced the term orofacial granulomatosis (OFG) as an umbrella term for diseases of the oral cavity that are characterised by persistent oedema of the lips and/or orofacial regions, and that present a granulomatous histological appearance (Wiesenfeld et al. 1985).

The term 'granulomatous' implies that a histological examination has been performed and that granulomas have been identified. However, some authors use the term to describe a clinical picture as well, whether granulomas were found on biopsy or not (Wiesenfeld et al. 1985). Gibson recommends the use of the term orofacial lymphoedema to describe the clinical picture as granulomas are not always identified in specimens from these patients (Gibson 1998).

OFG includes Melkersson Rosenthal Syndrome (MRS), oral Crohn's disease (OCD), cheilitis granulomatosis (CG), sarcoidosis and Miescher's granulomatous cheilitis. Unfortunately some of the definitions of these diseases have been applied very loosely in some publications (Sussman, Yang, & Steinberg 1992) for instance CG is regarded by some as an oligosymptomatic form of MRS (Worsaae et al. 1982). Clinically, some cases of angioedema have been confused with OFG (Rees 1999).

1.6.2. Classification and Features

1.6.2.1.Orofacial Granulomatosis

The clinical feature of OFG as described by Wiesenfield are: facial swelling, lip swelling, mucosal oedema (lobulated or cobblestone appearance) , mucosal tags, gingival lesions (full thickness erythema and swelling), angular cheilitis, oral ulceration (usually irregular or linear in shape and affects 30-40% of patients with OFG (Armstrong & Burrows 1995)), geographic tongue, fissured tongue and unilateral facial nerve palsy (Wiesenfeld et al. 1985). The observed histological features were: oedema of the superficial corium with prominent dilated lymphatic vessels, granuloma formation in 47/57 patients and occasional intracellular birefringent material observed in some granulomas (which was not considered to be of aetiological significance). The granulomas varied considerably consisting of cells such as epithelioid histiocytes, multinucleated cells, lymphocytes and macrophages (Wiesenfeld et al. 1985). Six out of 60 OFG patients were diagnosed with definite Crohn's disease while two patients were diagnosed with sarcoidosis (Wiesenfeld et al. 1985).

OFG is a disease of primarily young adults and children, younger subjects being more likely to have, or to develop, CD (Sainsbury et al. 1987) and the distribution among the sexes is equal (James et al. 1986).

OFG patients with pyostomatitis vegetans are more likely to have OCD as it is associated with inflammatory bowel diseases and thus they should be

referred for gastrointestinal investigation (Rees 1999). Sanderson et al (1996) found a much higher incidence of OCD in patients manifesting signs of OFG. Ten patients who had no gastrointestinal symptoms were investigated for CD by colonoscopy, and eight of then had macroscopic or microscopic evidence of inflammation with seven showing granuloma formation (Sanderson et al. 1996).

1.6.2.2.Melkersson-Rosenthal Syndrome

The earliest references to this disorder were in 1859 by Märt (Wiesenfeld et al. 1985). Melkersson described the association of facial paralysis with facial oedema in 1928 and in 1931 Rosenthal added the finding of *lingua plicata* (also termed 'fissured', 'scrotal' or preferably 'furrowed' tongue (Fisher 1990)) as another associated sign and the triad was termed MRS in 1949 (Sussman, Yang, & Steinberg 1992). Many authors have since attempted to describe 'mono-symptomatic' MRS (Sussman, Yang, & Steinberg 1992). It is considered that lip swelling occurs in 66% of MRS patients (Hernandez, Hernandez, & Lucas 1986), though Hornstein includes this as by far the predominant feature (Hornstein 1997) and Sussman et al states the definitive diagnosis of MRS is only possible after a lip biopsy which suggests that they consider the diagnosis to stand even if no other symptoms are present (Sussman, Yang, & Steinberg 1992). Facial palsy occurs in 30% of cases and fissured tongue occurs in 20-40% of cases (Podmore & Burrows 1986). Some authors found that facial oedema was

present in 50% of MRS patients (Zimmer et al. 1992). This variation in presenting signs and symptoms makes the strict diagnosis of MRS as a triad of symptoms, tenuous at best in the majority of patients thus labelled however some of the difficulty in diagnosis is due to the fact that there may be a delay in the appearance of some of the symptoms for months or years (Hornstein 1997). Some authors include other clinical signs that are often found in MRS such as sclerosing macroglossitis, palsies of other cranial nerves, transitory encephalopathic disturbances and eyelid, facial or intraoral swelling (Hornstein 1997). As well as the intraoral swelling that may affect the labial, buccal, gingival, sublingual and palatal mucosa (Worsaae et al. 1982) and the tongue (Zimmer et al. 1992), further signs that have been reported are gingivitis, gingival and buccal erosions and buccal erythema (Zimmer et al. 1992). The signs of fissuring of the lips, angular cheilitis and excoriation of the lips are direct consequences of the lip oedema (Vistnes & Kernahan 1971). Several authors include a wide variety of 'minor' accompanying signs as part of the clinical picture of MRS such as the extensive list of nineteen neurological signs described by Hornstein (Hornstein 1997). The systemic or more generalised symptoms that have been associated with MRS are pyrexia, chills, migraine headaches, premenstrual tension, nausea, vomiting, epiglottic dysphagia, bronchospasm, acrocyanosis of hands and feet and factitious urticaria (Alexander & James 1972; Hornstein 1997; Ingram 1993; Worsaae et al. 1982).

There is an equal sex distribution and MRS commonly occurs in the second and third decades (Worsaae et al. 1982).

Histological examination shows the presence of noncaseating granulomas in many cases though it is not considered an obligatory characteristic by some authors (Hornstein 1997). The granulomas often consist of epithelioid giant cells and are perivascularly situated (Podmore & Burrows 1986). Other common features are non specific inflammation, the presence of lymphocytes and plasma cells in the granulomas and oedematous connective tissue (Worsaae & Pindborg 1980).

Cheilitis granulomatosa (CG) has been described as mono-symptomatic MRS as patients present with only swelling affecting one or both lips (Podmore & Burrows 1986). CG also usually affects young adults and is also called Miescher's granulomatous cheilitis. Clinically, the picture is of diffuse, non-tender swelling of one or both lips and the histological features are of non-necrotising granulomas and oedema, lymphangiectasia and perivascular infiltration (Allen et al. 1990). CG is probably identical to what is termed OFG (Field & Tyldesley 1989).

Rees considers that the diagnosis of classic (triad present) or mono-symptomatic MRS should be considered as a default diagnosis once Crohn's disease, sarcoidosis and allergic stomatitis have been ruled out, with OFG being the running diagnosis while investigations are going on (Rees 1999).

1.6.2.3.Oral Crohn's Disease

OCD and OFG have been shown to be closely linked and many authors have use the terms synonymously as the difference between them is still considered to be controversial (Ivanyi, Kirby, & Zakrzewska 1993). It is estimated that oral lesions have been found in 0-20% of patients with CD (Rees 1999), while among OFG patients, 6% (n=6) (Gibson, Forsyth, & Milligan 1995), 10% (n=6) (Wiesenfeld et al. 1985), 17% (n=13) (James et al. 1986), 37% (n=7) (Scully et al. 1982) and 48% (n= 14) (Williams, Wray, & Ferguson 1991) have later developed CD.

Early OCD is held to be difficult to distinguish from oligosymptomatic MRS (Hornstein 1997).

1.6.2.4.Sarcoidosis

Sarcoidosis is a chronic multisystem disease of unknown origin whose onset is in young adulthood and which may be life-threatening if the lungs or other vital organs are involved (Rees 1999). It has clinical and histological features as in the facial/lip swelling of OFG but the swelling is also associated with evidence of more systemic involvement (Armstrong & Burrows 1995). Rarely, a patient with sarcoidosis may initially present with tongue swelling alone (Mendelsohn, Field, & Woolgar 1992). Symptoms may include weight loss, fatigue, cough and bone or joint pain (Frieden et

al. 1989). It has been estimated that up to 3% of OFG patients also have signs and symptoms of sarcoidosis (Wiesenfeld et al. 1985).

1.6.3. Aetiology

The histological features of granulomas have prompted some to consider that the lip swelling may be composed of lymphoedema due to blockage of the lymphatics by the granulomas (Hernandez, Hernandez, & Lucas 1986).

1.6.3.1.Orofacial granulomatosis

No hereditary predisposition was found in 60 cases (Wiesenfeld et al. 1985) and hereditary factors are not considered to be of much importance by other authors (Armstrong & Burrows 1995).

The presence of mycobacterial infection has been investigated in 60 cases of OFG with entirely negative results after Ziehl-Neelson staining of lesional tissue samples (Wiesenfeld et al. 1985). One patient presented with cervical lymphadenopathy that had granulomas on histological examination that was diagnosed and treated as tuberculosis though Zeehl-Neelson stains showed no acid-alcohol-fast bacilli and a chest radiograph was normal. Three years later the patient represented with lip swelling and classical OFG features demonstrating that granulomatous cervical lymphadenopathy may be an early sign of OFG (James & Ferguson 1986).

1.6.3.2.Melkersson-Rosenthal Syndrome

The three most likely aetiologies are hereditary, allergic or infectious factors (Alexander & James 1972) and Meisel-Stosiek et al suggest a multifactorial origin including a genetic basis (Meisel-Stosiek, Hornstein, & Stosiek 1990).

MRS is held to be inherited as an incomplete, autosomal dominant trait with variable penetrance (Alexander & James 1972). Lygidakis identified MRS in seven family members spanning four generations (Lygidakis, Tsakamarakas, & Illias 1979). 42 patients with MRS and 171 of their relatives were examined in another study and were found to have an increased incidence of furrowed tongue (62% compared to the 15% incidence in the German population). This was the most striking inherited pattern as, precluding the tongue lesions the relative risk for MRS in first degree relatives was only 7% (estimated). It is therefore doubtful that the known hereditary anomaly of furrowed tongue can be extended to include all the symptoms of MRS. Nevertheless, the close association of furrowed tongue as part of MRS does suggest some genetic factors (Meisel-Stosiek, Hornstein, & Stosiek 1990). A possible location of the responsible gene is at 9p11 (Smeets, Fryns, & van den 1994).

Allergy to food additives (Pachor, Urbani, & Cortina 1989), flavourings (McKenna, Walsh, & Burrows 1994) and food stuffs (nuts) (Hernandez, Hernandez, & Lucas 1986) have been advocated, (see section 1.6.4.).

Viral aetiologies as herpetiform eruptions have preceded the lip swelling (Alexander & James 1972) and mycobacterial infection produces a similar histological picture (Sussman, Yang, & Steinberg 1992).

Stress, emotional turmoil, cold and trauma have all been proposed as precipitating factors (Nally 1970).

The generally held suggested pathogenesis of MRS is that of an abnormal reactivity of the cranial neurovascular system which causes intermittent orofacial oedema (the palsy is caused by nerve compression of the facial nerve or by direct granulomatous infiltration of the nerve sheath (Henry 1994)). The regional mucocutaneous tissues are therefore more susceptible to inflammatory reactions to noxious (allergic/infectious) stimuli (Meisel-Stosiek, Hornstein, & Stosiek 1990).

1.6.3.3.Oral Crohn's disease

Mycobacterial infection has been suspected to be involved in the aetiology of CD for some time and IgG antibodies to mycobacterial stress protein (mSP65) have been shown to be raised in some CD patients (Elsaghier et al. 1992) though certain epitopes of stress proteins are shared by several bacterial genera so other bacteria may be responsible. The mSP65 levels were measured in ten patients with OFG and were found to be significantly elevated in four of them who had OCD, and in three (these three had no CD at the time) out of the remaining six patients, compared to a control group (Ivanyi, Kirby, & Zakrzewska 1993). *Mycobacterium paratuberculosis* has been identified as the causative factor in provoking a delayed hypersensitivity reaction in Johne's disease, the ruminant equivalent of human CD (Morgan 1987). IgG antibodies to *M. paratuberculosis* were measured prior to and after dapsone therapy of CD and were significantly

higher in those patients that responded well to the treatment suggesting that either mycobacteria or a cross reacting species, sensitive to dapsone, are responsible for the development of CD (Prantera et al. 1989). The polymerase chain reaction technique was used to identify *M. paratuberculosis* in fresh frozen tissue from CD patients and was successful in two thirds of CD cases and 12.5% of normal controls (Sanderson et al. 1992). A further study using similar techniques in OCD and OFG lesional tissue (paraffin wax embedded) samples failed to isolate *M. paratuberculosis* in either of the disease groups though the use of paraffin wax embedded tissue may have been a factor in the negative results (Riggio et al. 1997).

The granulomatous reactions seen in CD has been postulated to be a result of a foreign body reaction against the silicates ingested through using toothpaste (Sullivan 1990).

1.6.4. Role of Allergy

Atopy has been suggested to coincide with OFG in 12% (n=1), 20%(n=29) and 60% (n=45) of cases in various studies (James et al. 1986; Sainsbury et al. 1987; Williams, Wray, & Ferguson 1991).

A Type IV allergic response to either an unidentified, non-degradable, particulate dental allergen or to an infectious agent was considered to be a possibility in some patients (Sussman, Yang, & Steinberg 1992). Analysis of T cell receptor V gene usage in an OFG patient suggested that delayed hypersensitivity was involved in the pathogenesis of the disease (Lim et al. 1997) and cellular immunity was also supported by a case with a decreased CD4:CD8 ratio (Henry 1994). Allen et al considered that the presence of the perivascular infiltrate and the granulomatous reaction in CG suggested that an immune response to some antigen/pathogen was involved (Allen et al. 1990).

Alexander and James consider that the possible role of allergy in OGD is inconsistent with the localised nature of the lesions (Alexander & James 1972) though they do not state what type of allergy they mean here.

One patient with CG who had extensive dental restorations was patch tested to dental materials with negative results (Sussman, Yang, & Steinberg 1992). Pachor et al described a case of MRS without the neurological involvement of the facial nerves (Pachor, Urbani, & Cortina 1989). This patient had positive reactions on double blind food challenge after elimination diet therapy to sodium benzoate and tartrazine and experienced complete remission of his facial swelling upon avoidance of these additives.

In a report of a case, Hernandez et al found that the patient with CG tested positive to almonds, hazelnuts, lactalbumin and rye on allergy testing (Hernandez, Hernandez, & Lucas 1986); on allergen avoidance of these foods, the patient experienced resolution of the lip swelling. In other isolated case reports, several authors had demonstrated the allergic nature of OFG to various allergens such as cobalt (Pryce & King 1990), monosodium glutamate (Oliver et al. 1991) carmosine and sunset yellow (Sweatman et al. 1986).

Several series of OFG patients most of whom who underwent patch testing with various allergens have been presented. 14 of 80 OFG patients (18%) were deemed to have an allergic response to foods or food additives though it was not stated how many of the 80 were patch tested and a very limited range of allergens were tested (cocoa, cinnamaldehyde, cinnamon and piperitone) (Patton et al. 1985). In another study 100 OFG patients were all tested to the Standard European Series and to food additives (FA), flavourings and dental materials. Immediate contact urticaria testing (20 minutes) was also carried out with the FA and flavourings. Overall 93 were positive to one or more allergens with the most common allergens being; benzoates (45), cinnamon (45), chocolate (19) and nickel (14) (Gibson, Forsyth, & Milligan 1995). Armstrong et al reported a series of 48 OFG patients who were all patch tested to a similar battery of allergens (with immediate contact urticaria testing as well) as the previous series of 100 patients. However only 20 (42%) had positive reactions to the standard patch tests with the most common allergens being nickel (4 patients) and fragrance mix (3). Ten patients had 14 positive responses to the FA and

flavouring allergens and out of this group, seven reported improvement on allergen avoidance. A further 18 (38%) had positives to the contact urticaria tests; benzoic acid (18), sorbic acid (15) and cinnamaldehyde (15) (Armstrong et al. 1997). It was not stated whether there was any crossover between the three groups listed and how many (if any) were negative, or if the contact urticaria reaction was read at the end of the 20 minutes only or evaluated after six hours. This could have a marked effect on the number of false positives reported as benzoic acid in particular can give rise to transient irritant reactions (Lahti 1980).

In all of these reports, no control groups were patch tested and this lack has been noted by others who have called for control populations particularly in relation to reactions to cinnamaldehyde (Challacombe 1997).

1.6.5. Management and Treatment

Appropriate treatment of OFG involves primarily investigations leading to a more specific diagnosis if possible (AE, OCD, sarcoidosis). Once these diseases have been excluded, appropriate allergy testing may identify a further section who can be treated effectively by allergen avoidance. This leaves patients with MRS on which a multiplicity of treatments have been tried with various results.

Investigations include questioning the patient for a history of gastrointestinal disturbance, symptoms of sarcoidosis or precipitating allergens. The nutritional status of patients should be checked at regular intervals to pick up asymptomatic gastrointestinal disease (Field & Tyldesley 1989; Scully et al. 1982). Radiographic examination (chest and barium meal series of the intestine) will assist in the diagnosis of sarcoidosis and CD (Field & Tyldesley 1989). Haematological and biochemical parameters such as serum ACE, C1 esterase inhibitor, complement, liver function tests, urea and electrolytes, serum calcium, phosphate, zinc, magnesium and immunoglobulin concentrations and erythrocyte sedimentation rate should also be measured (Scully et al. 1982). A biopsy of affected tissues should include the deep subcutaneous layers as some granulomas are located next to minor salivary glands and even into the facial musculature (Wiesenfeld et al. 1985). If CD or sarcoidosis are suspected, the patient should also be referred for further evaluation and

treatment as required. Some have proposed that serum IgA may prove to be a marker of OFG and/or OCD as this immunoglobulin has been found in increased quantities in these diseases (Challacombe et al. 1997). Patch testing to include food additives, flavourings and constituents of dental prophylactic preparations are appropriate allergy tests as it is a Type IV reaction that is suspected (Rees 1999).

Swelling of the lips has been treated with intralesional steroid injections, oral prednisolone, oral hydroxychloroquine and surgical reduction (Allen et al. 1990). Surgical reduction has yielded good initial results in some cases but recurrence is common and scar tissue formation may require further surgical intervention (Henry 1994) and is thought overall to be not warranted in most cases (Editorial 1991). As well as anti-malarial drugs, the anti-leprous drug clofazimine has been reported to have been clinically effective in one case of classic MRS and three cases of CG. The mechanism of action in these cases was thought to be of increased macrophage phagocytosis (Podmore & Burrows 1986). The intralesional steroids seem to be the most efficacious but spontaneous remission has been reported (Allen et al. 1990; Sakuntabhai, Macleod, & Lawrence 1992; Worsaae et al. 1982) and it is hard to know what brought about the resolution especially when some have claimed that intralesional injection of boiled water has given good results (Vistnes & Kernahan 1971). Removal of dental foci of infection has improved the lip swelling in some cases (Nally 1970) and laser beam acupuncture has been described as a promising treatment by others (Hornstein 1997). Many authors have tried various treatments, including

glucocorticoids, antihistamines, radiotherapy, sulphasalazine, co-trimoxazole, metronidazole, azathioprine all to no avail (Editorial 1991; Morales et al. 1995; Vistnes & Kernahan 1971; Wiesenfeld et al. 1985; Worsaae et al. 1982). Fisher found that a combination of tetracycline and prednisolone reduced lip swelling and prevented further recurrences of facial palsy (Fisher 1990).

The facial nerve palsy of MRS is considered to be self limiting, usually lasting about eight weeks and thus no treatment is offered in the majority of cases (Alexander & James 1972) though some advocate the use of systemic steroids (Zimmer et al. 1992). Though electrical stimulation of the nerve during the period of palsy has been suggested, its efficacy is debatable (Vistnes & Kernahan 1971). However, complete resolution does not occur in a small number (Zimmer et al. 1992) and residual weakness can be markedly disfiguring (Alexander & James 1972). Treatment that can then be offered consists of surgical decompression of the affected nerve (Vistnes & Kernahan 1971).

Where allergy is suspected, and an allergen identified by appropriate testing, allergen avoidance has been shown to give resolution in 55% (complete) and 37% (partial) patients (Gibson, Forsyth, & Milligan 1995). One patient improved only after commencing on an elemental diet with staggered introduction of different foods though she had shown positive reactions to some food additives, it was considered that other food stuffs not included in the allergy testing procedure must also be provoking her immune system to respond (Sweatman et al. 1986).

Compliance with dietary advice is improved when it is given by a dietitian or senior clinician (Gibson, Forsyth, & Milligan 1995).

1.7. Other Oral Diseases And Allergy

1.7.1. Plasma Cell Gingivitis

Plasma cell gingivitis has been described as a syndrome consisting of a triad of signs; gingivitis, cheilitis and glossitis, with early reports attributing the signs to a hypersensitivity reaction to micro-organisms or constituents of toothpastes or chewing gum (Silverman & Lozada 1977). It is now termed allergic gingivostomatitis (Wray et al. 1999). The pathognomonic histology consists of diffuse sheets of plasma cells replacing normal connective tissue structure. Silverman and Lozada in 1977 on review of the literature and from their own experience concluded that this syndrome was a transient disease occurring between approximately 1966 and1973 and affecting few persons and titled their publication 'An epilogue to plasma-cell gingivitis' accordingly. As a total of 12 patient's lesions resolved on systemic prednisolone therapy and two responded to discontinued use of chewing gum or toothpaste, they postulated that it was caused by allergy to an unidentified allergen present in substances such as chewing gums and toothpastes, though no allergy testing or oral rechallenge with the suspected agents were carried out. In all patients, the cheilitis component completely resolved with an antifungal cream (Silverman & Lozada 1977).
Unfortunately for the title, further cases of plasma cell gingivitis have been described in the subsequent years. Palmer and Eveson found no evidence of allergy in two cases with full thickness gingivitis which histologically contained a predominantly plasma cell infiltrate but there were no signs of

glossitis or cheilitis. Again there were no allergy tests done and the immunogenic component was discounted merely because the patients did not chew gum and had no resolution on discontinuance of their toothpaste. Interestingly one of the patients was treated with triamcinalone in orabase with a resultant slight improvement, but this was not followed with a stronger steroid and in both patients, the lesions persisted (Palmer & Eveson 1981). Further case reports have described one case related to use of a herbal toothpaste despite a negative patch test to the suspected paste (Macleod & Ellis 1989). In two cases reported in 1992 no causative allergen was discovered despite one patient reporting her symptoms starting with the use of a mouth wash preparation and undergoing no allergy tests, and the other's (what the authors refer to as) 'extensive allergy testing' being confined to selected inhaled allergens and eight foods all of which have been associated with IgE mediated reactions. No allergens associated with delayed type hypersensitivity reactions were tested (Sollecito & Greenberg 1992). Other case reports have related plasma cell gingivitis to the use of a mint flavoured confectionery and to spices though no allergy tests were carried out (Lubow et al. 1984; Reed et al. 1993).

A few authors have noted the psoriasiform appearance to the histological appearance of the affected epithelium, and the fact that two patients concomitantly suffered from psoriasis (Lubow et al. 1984; Palmer & Eveson 1981).

1.7.2. Desquamative Gingivitis

Desquamative gingivitis is a term that has been used for many years to describe erythematous, desquamating appearance of the marginal and attached gingivae that bleeds upon mild trauma. The condition is sore if not painful and as a result of this often has superimposed marginal gingivitis due to the pain and bleeding on tooth brushing (Jandinski & Shklar 1976). Desquamative gingivitis (DG) is a clinical description rather than a diagnosis. In a study of 453 patients attending a dermatology clinic, the percentages of each of the disease groups with which DG was associated were; mucous membrane pemphigoid (MMP) 63.6%, lichen planus (LP) 25%, pemphigus vulgaris (PV) 18.4% and bullous pemphigoid (BP) 3.2%. The definitive diagnosis was made from a biopsy of non-lesional mucosa with both histological and immunological examination (Sklavounou & Laskaris 1983). Markopoulos 13 years later found that the percentages of patients in different disease groups presenting with DG were slightly different: MMP 41.6%, PV 9.1% and OLP 6.8% (Markopoulos et al. 1996). In a study of 49 cases of DG they found that two had no histological evidence of MMP, PV or OLP and classed this group as idiopathic (Markopoulos et al. 1996). Recently Staines et al (1998) described a case of idiopathic DG that was related to an allergic response to formaldehyde in nail varnish (the patient was a habitual nail biter). No biopsy was taken but indirect immunofluorescence was carried out to exclude some immunological diseases before the patient was referred for cutaneous patch testing. The authors suggest that idiopathic DG is the same condition as

plasma cell gingivitis, which is more often associated with allergic mechanisms (Staines, Felix, & Forsyth 1998). The same year, Yih et al widened the collection of diseases that may present as DG to comprise: erosive OLP, lichenoid mucositis, MMP, PV, paraneoplastic pemphigus, linear IgA disease and BP, as an immunological group and an idiopathic group consisting of chronic bacterial, fungal or viral infections and other factors of a non autoimmune nature capable of causing irritation or inflammation (Yih et al. 1998). In 72 patients with DG Yih et al found that the most common underlying disease was erosive OLP and lichenoid mucositis, together comprising 42% of patients. They describe lichenoid mucositis as possibly being a result of a hypersensitivity reaction to drugs, dental materials or foods (Yih et al. 1998).

Treatment of DG not due to pemphigus is often difficult and involves oral hygiene measures, topical steroid preparations held against the gingivae with a Wenvac splint, and systemic steroids in persistent cases (Scully & Porter 1997). Some authors found that dapsone therapy met with some success (Matthews, Pinkney, & Scully 1981).

1.7.3. Oral Dysaesthesia

Also termed burning mouth syndrome and glossodynia, oral dysaesthesia (OD) is a complex issue in that a wide variety of aetiological factors have been implicated. This state of affairs stems in part from the fact that in OD, no clinical or histological evidence of disease can be observed and the disorder is based on the subjective symptoms experienced by the patient. Three types have been described by Lamey and Lamb: in type 1, the burning is not present on waking and appears and worsens as the day progresses; in type 2, the burning sensation is constant and unremitting and in type 3 the symptoms are intermittent (Lamey et al. 1994). OD primarily affects post climacteric females and the age of onset is usually in the fifth decade (Helton & Storrs 1994). The symptoms of patients who experienced burning sensations intraorally were noted in a prospective study of 25 patients (eight of whom who also had visible oral mucosal lesions so not all had OD) (Bergdahl, Anneroth, & Anneroth 1994). Most (24) complained of a wide variety of extraoral symptoms as well such as musculo-skeletal disorders, headache, dizziness, skin problems, insomnia, stress, fatigue and anxiety (Bergdahl, Anneroth, & Anneroth 1994).

The aetiology of OD is thought to reside in three main groups: local factors such as xerostomia, candidiasis, tongue dysfunction and hypersensitivity reactions; systemic factors such as anaemia, drug side effects and hormonal disturbances and psychogenic factors such as depression, anxiety and phobias (Bergdahl, Anneroth, & Anneroth 1994). Type 1 OD is thought to be often related to systemic factors, type 2 to psychogenic factors and type 3

to local factors particularly hypersensitivity (Lamey et al. 1994). In patients with type 3 OD who had no demonstrable allergy on patch testing, significantly higher levels of psychiatric illness were found compared to those with an identifiable allergen when using the General Health Questionnaire but this was not confirmed by using the Hospital Anxiety and Depression scale (Lamey et al. 1994). Treatment for those identified as having a psychogenic basis for the burning sensations includes reassurance, anxiolytic and antidepressant medication, and cognitive-behaviour therapy (Humphris, Longman, & Field 1996).

1.7.3.1. Role of allergy

A wide variety of allergens have been implicated in causing a hypersensitivity response giving rise to OD. These include: acrylic monomer, benzoyl peroxide, butyl methacrylate, cobalt chloride, *N,N*-dimethyl-4-toluidine, formaldehyde, glycol dimethacrylate, gold chloride, nickel sulphate, oligoacrylate, *p*-phenylenediamine, polyethyl methacrylate, potassium bichromate, 4-tolydiethanolamine, and food additives such as sorbic acid and propylene glycol (de Groot, Weyland, & Nater 1994).
21 patients in a different study were patch tested to a dental series and two (9.5%) showed a positive response to mercury with resolution of the burning sensation after their amalgam fillings were removed (one of these had a positive result to patch testing with gold also and this restorative material was also replaced). This was higher than the previously reported

prevalence of 0% of 24 Swedish patients though the numbers were small in both studies (Skoglund & Egelrud 1991).

In this group, 30% of patients had a deficiency of iron though no patients with iron deficiency alone were cured with replacement therapy (one patient with vitamin B_{12} and iron deficiency had complete resolution of the burning symptoms after replacement therapy) (Bergdahl, Anneroth, & Anneroth 1994). In a further study of 33 OD patients, 23 (65%) were found to have positive results to patch testing and of these 10 patients experienced complete symptomatic resolution upon allergen avoidance (Lamey et al. 1994). The allergens implicated were acrylics, epoxy resin, benzoic acid, propylene glycol, cinnamon, cinnamaldehyde, cinnamyl alcohol, fragrances, sorbic acid, cobalt and nickel and in nine patients, the burning recommenced on rechallenge (Lamey, Lamb, et al. 1994)}. Nickel allergy was found to be more prevalent in OD patients (21%) than OLP patients (3%) in a study in which 24 patients in each disease group were patch tested (Skoglund & Egelrud 1991). In a Finnish study, four patients with OD had positive results on patch testing with a dental series of allergens, three to gold and one to mercury; however none of these reactions were considered clinically relevant to their oral symptoms (Alanko et al. 1996). 22 patients with OD (though the authors stated that some had a mild erythematous appearance to the oral mucosa) were investigated by patch testing to a routine, dental and a spice series of allergens and a high proportion had relevant, positive reactions to materials used in the manufacture of acrylic dentures (27%) and to metals used in dentistry (27%) (Dutrée-Meulenberg, Kozel, & van Joosst 1992). Other positive reactions were elicited to carba mix,

phenylenediamine, formaldehyde, fragrance mix, balsam of peru, wood tar mix, primin, nutmeg, coriander, cinnamon, celery and curry (Dutrée-Meulenberg, Kozel, & van Joosst 1992).

Of 53 other OD patients, 23% had relevant positive patch test reactions to materials used in the manufacture of denture bases (Kaaber & Nielsen 1979) and van Joost described a further four patients all with positive reactions to denture materials (van Joosst, van Ulsen, & van Loon 1988).

Peanut sensitivity has been implicated in a patient with OD (Whitley, Shepherd, & Ferguson 1991) though food additives and flavourings have been reported more frequently (Lamey et al. 1994; Lamey, Lamb, & Forsyth 1987).

An American study found none of eight OD patients had positive reactions to patch tests using dental allergens though two had a non-immunologic contact urticaria reaction to cinnamic aldehyde and also had decreased symptoms after avoiding the agent (Helton & Storrs 1994).

CHAPTER 2 AIMS AND HYPOTHESES

2.1. Aims

Reactions to food additives and flavourings have been documented in OLE, (Todd et al. 1990; Yiannias et al. 2000), RAS (Wray, Vlagopolous, & Siraganian 1982; Wright et al. 1986), AE (de Martino et al. 1992; Squire 1987), EM (Lewis et al. 1989; O'Donnell & Tan 1997) and OFG (Gibson, Forsyth, & Milligan 1995; Oliver et al. 1991; Pachor, Urbani, & Cortina 1989). In none of the above publications were healthy controls also tested. It was therefore deemed of importance to patch test a healthy (without any of the oral mucosal diseases mentioned above) group of control subjects. From 1980 to 1996, patients from Glasgow Dental Hospital & School were referred to the Contact Dermatitis Investigation Unit (CDIU) at Belvidere Hospital (until 1994) and then at Glasgow Royal Infirmary, in order to investigate the role that allergy played in the oral mucosal diseases from which they suffered. The results of these tests were entered into a computer database.

A total of 1252 patients were tested (patch testing or delayed hypersensitivity testing, and contact urticaria testing) over the 16 year period and though various case reports and some larger studies utilised some of these results[10], no comprehensive or total analysis had been carried out to investigate this large group of patients. It was considered to be of good clinical and economical sense to categorically state the clinical benefit, if any of these referrals.

To this end, investigation into subjective clinical improvement experienced by the patients themselves, following the utilisation of avoidance diets (in cases of allergy to food substances), was considered important.

For some years it had been considered that there were differences in the histological appearance of sections from patients with OLE who had lesions and who also had amalgam dental restorations, and those who had OLE lesions in amalgam-free mouths. The differences that had been subjectively noted to be associated with amalgam related OLE were an increased number of apoptotic cells, an increase in the disruption of the basal cell layers of the epithelium, and an increased thickness and density of the inflammatory infiltrate. Likewise, the microscopic appearance of OLE lesions that were

---

[10] The results of studies on some of these patients have been published in previous papers (Garioch et al. 1990; Gibson, Forsyth, & Milligan 1995; James et al. 1987; Lamey et al. 1990; Lamey et al. 1994; Lamey & Forsyth 1986; Lamey, Lamb, & Forsyth 1987; Lamey & Lewis 1990; Lewis et al. 1989; McCartan & Lamey 1998; Nolan et al. 1991; Nolan, McIntosh, & Lamey 1991; Patton et al. 1985; Petrucci et al. 1995; Rees et al. 1998; Rees & Gibson 1997; Riggio et al. 1997; Riggio et al. 1999; Staines, Felix, & Forsyth 1998; Todd et al. 1990; Wiesenfeld et al. 1985).

associated with other topical allergens such as food additives and flavourings were also considered to have a particularly florid inflammatory cell infiltrate and marked degeneration of the basal cell layers of the epithelium.

It had also been noted that OLE lesions that were associated with systemic medications, drug induced lichenoid reactions (DILR), commonly presented one of two alternate histological appearances. Some were associated with a sparse inflammatory infiltrate together with a florid epithelial reaction, while others were associated with a florid inflammatory infiltrate with a relatively unaffected epithelium.

During the investigation, some other areas of interest were also explored such as the prevalence of allergy to mercurials in OLE patients.

The aims are summarized below;

1. Analyse computer data from the Contact Dermatitis Investigation Unit.

2. Test a group of healthy controls.

3. Ascertain the clinical results from the patients point of view.

4. Investigate the histological differences between sections of oral lichen planus and lichenoid reactions secondary to hypersensitivity responses.

2.2. Hypotheses

1. That the prevalence of positive patch test reactions in patients with recurrent aphthous stomatitis (RAS), oral lichenoid eruptions (OLE), orofacial granulomatosis (OFG), erythema multiforme (EM), and angioedema (AE) will be different from the normal population.
   The null hypothesis is stated: there are no differences in the prevalence of contact allergic reactions to food additives and flavourings and to environmental allergens between healthy subjects and those with OLE, RAS, AE, EM and OFG.

2. That these patient groups: OLE, RAS, AE, EM and OFG will have different allergy profiles in terms of the amount of positive reactions and what the test substances are that elicit these reactions.
   The null hypothesis is stated: there are no differences in the 'allergic profiles' of patients with OLE, RAS, AE, EM and OFG.

3. That the patients with positive reactions to food additives and flavourings upon patch testing will experience improvement in symptoms after following an allergen avoidance diet.
   The null hypothesis is stated: there is no symptomatic improvement upon following an allergen free diet in those with positive patch test reactions to food additives and flavourings.

4. That there are histological differences between specimens from patients with OLE lesions in patients with amalgam restorations and those with no amalgam present, and between those with positive and negative patch test results. More specifically, that in the amalgam related and patch test positive related lesions, the number of apoptotic cells will be increased, the inflammatory cell infiltrate will be thicker and denser and that the amount of basal cell disruption will be increased compared to the appearance of the lesions with no amalgam relationship or with negative patch test results.

The null hypotheses are stated:-

There are no differences in the number of apoptotic cells between OLE lesions related to amalgam and those that are not, and between OLE lesions that are associated with positive or negative results to patch testing.

There is no difference in the amount of inflammatory infiltrate as determined by thickness (distance extending into the lamina propria from the epithelium) and density between OLE lesions related to amalgam and those that are not, and between OLE lesions that are associated with positive or negative results to patch testing.

There is no difference in the amount of disruption of the basal layer between OLE lesions related to amalgam and those that are not, and between OLE lesions that are associated with positive or negative results to patch testing.

In regard to DILR, the null hypothesis is stated: that there are no distinguishing patterns in the histological appearance of specimens from patients that may have a drug related aetiology to their OLE. Specifically, there is not an increase among histological appearances of specimens showing a mild inflammatory infiltrate together with a florid epithelial reaction (increased epithelial tropism, increased numbers of apoptotic cells and increased basal cell disruption), or specimens showing an increased thickness and density of the inflammatory infiltrate together with a mild epithelial reaction (determined by none or small amounts of apoptotic cells, epithelial tropism and basal cell layer disruption).

CHAPTER 3 CLINICAL ALLERGY STUDIES

3.1. Introduction

Since 1980, patients from Glasgow Dental Hospital & School were referred to the Contact Dermatitis Investigation Unit (CDIU) at Belvidere Hospital (until 1994) and then at Glasgow Royal Infirmary, in order to investigate the role that allergy played in the oral diseases from which they suffered. As patients who tested positive to food additives began experiencing relief from their symptoms after following dietary advice on avoidance of the appropriate allergens, more patients were sent for testing. It became apparent that patients with some diseases affecting the oral cavity seemed to yield more positive reactions to these tests and to gain greater benefit from the dietary avoidance than others. However, during this time, little was known about the prevalence of allergy to food additives and food substances in the normal population. It was therefore decided to patch test a healthy group of control subjects to the same allergens that the group with oral diseases were exposed.

The patients who had been sent for patch testing as part of the investigation into their oral disease were then contacted to ascertain the outcome of any dietary modifications that they had carried out as a consequence of the patch test results.

3.2. Subjects

3.2.1. Disease population

The patients were all referred from the Oral Medicine Department at Glasgow Dental Hospital & School and were patch tested between 1980 and 1996 at the Contact Dermatitis Investigation Unit (CDIU) in Glasgow which is a regional referral centre covering the West of Scotland. The computer database at the CDIU in Glasgow Royal Infirmary was an old program (Delta 4 software based on an Apricot system) and was accessed by Digby James of MAPEJ (PCD)[11] and converted into a ASCII format. The file was then converted into Microsoft Access. The patient records at the CDIU and in some cases at GDH also, were referred to for further information. All referred patients were included in the study but particular attention was paid to those patients with: oral lichenoid eruption (OLE), recurrent aphthous stomatitis (RAS), orofacial granulomatosis (OFG), erythema multiforme (EM) and angioedema (AE). The criteria for the above diagnoses were as follows;

OLE – White papules or striae, forming reticular, linear or annular patterns; white plaque-like lesions with papules or striae at the margins; some patients also had areas of atrophy, erosions or bullae (Kramer, Lucas, Pindborg, & Sobin 1978), see Figs 2-5, and if a biopsy was carried out (as it was on most patients) a histological appearance consistent with OLE.

---

[11] MAPEJ (PCD), Digby James, Quinta Cres, Oswestry, Shropshire, SY10 7RN

Fig. 2. Photograph Of Reticular OLE Affecting Left Buccal Mucosa

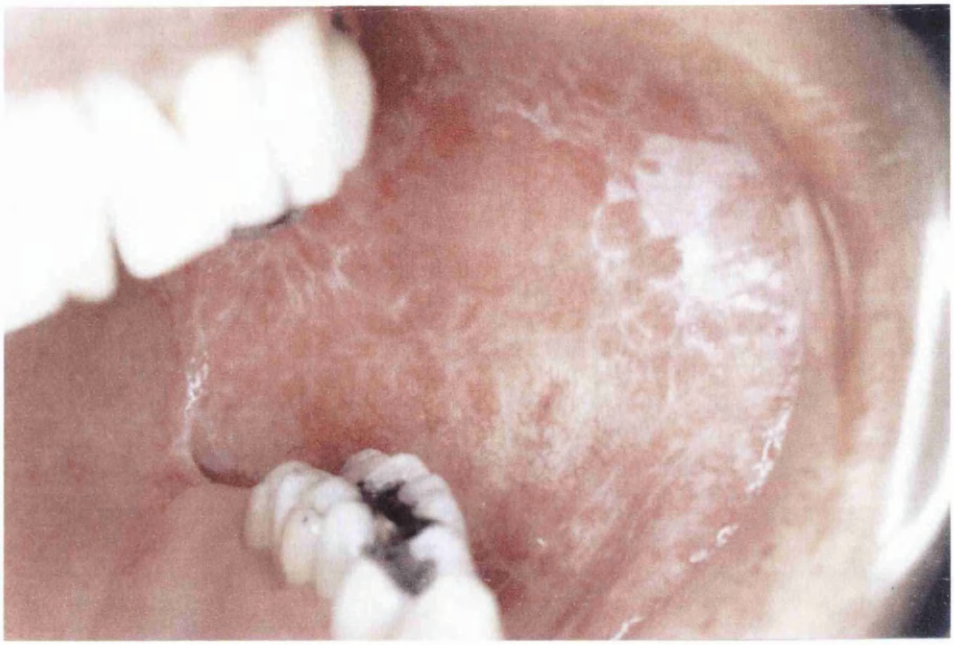


Fig. 3. Photograph Of Papular OLE Affecting Right Buccal Mucosa

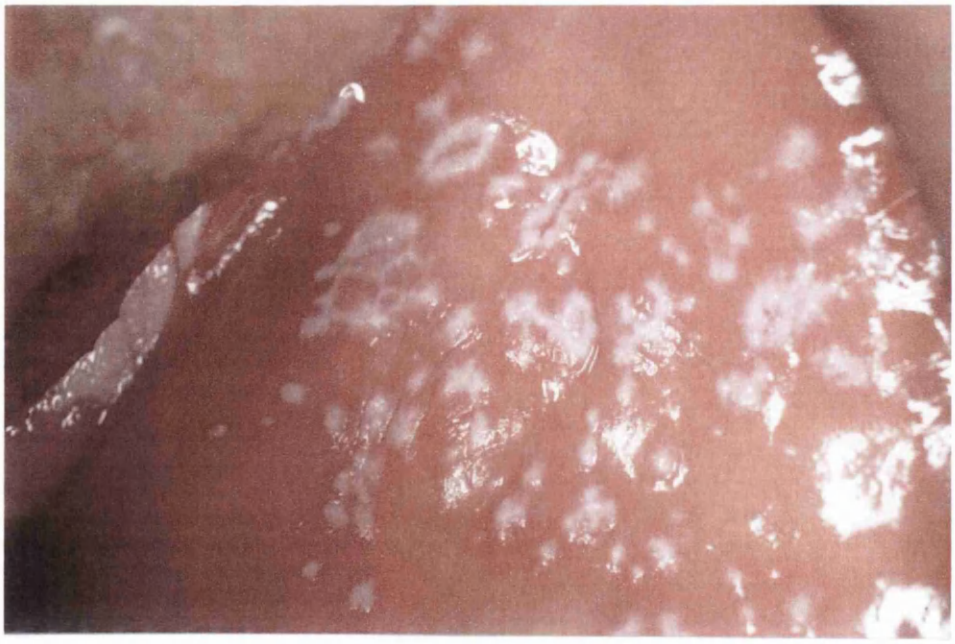


Fig. 4. Photograph Of Erosive OLE Affecting Left Buccal Mucosa

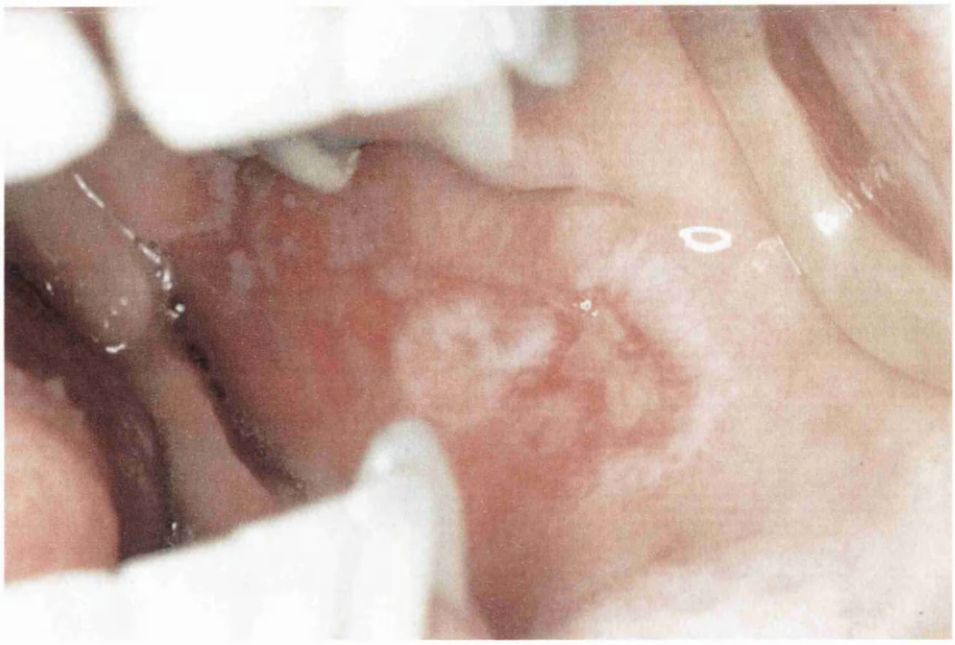
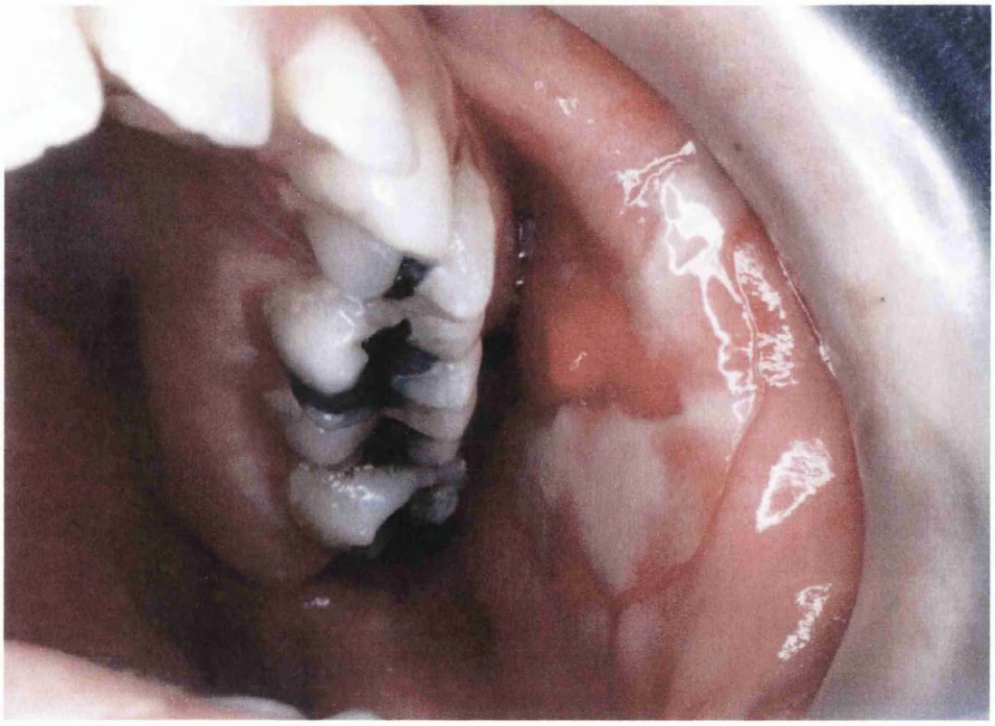


Fig. 5. Photograph Of Severe Erosive OLE Affecting Left Buccal Mucosa



RAS – Episodes of oral ulceration which recurred more that twice per year and that were not overtly traumatic in origin (Graykowski et al. 1966). See Figs 6-8.

AE – One or more episodes of sudden and rapid facial, laryngeal or oral swelling. See fig 9.

EM – A history of persistent or recurrent oral ulcerations with or without lip and skin lesions; clinically, diffuse oral erythema and irregular ulcerations frequently covered by pseudomembranes, ulceration and crusting of the lips, skin macules and papules (characteristically 'target' lesions) often with crusting, and a histological appearance consistent with EM, i.e. ruled out other oral mucocutaneous ulcerative diseases and often showed a perivascular lymphocytic cellular infiltrate (Lozada & Silverman 1978). See figs 10 and 11

OFG – Patients had at least two major criteria or had one major criterion plus three minor criteria. Major criteria were defined as chronic upper or lower lip swelling, mucosal oedema and cobblestoning, aphthous ulceration, mucosal tags and full thickness gingivitis. Minor criteria were defined as chronic facial swelling, angular cheilitis, fissured tongue, non-aphthous ulceration and papillary hyperplasia (Gibson 1998). See figs 12 and 13.

Fig. 6. Photograph of Minor RAS Lesion

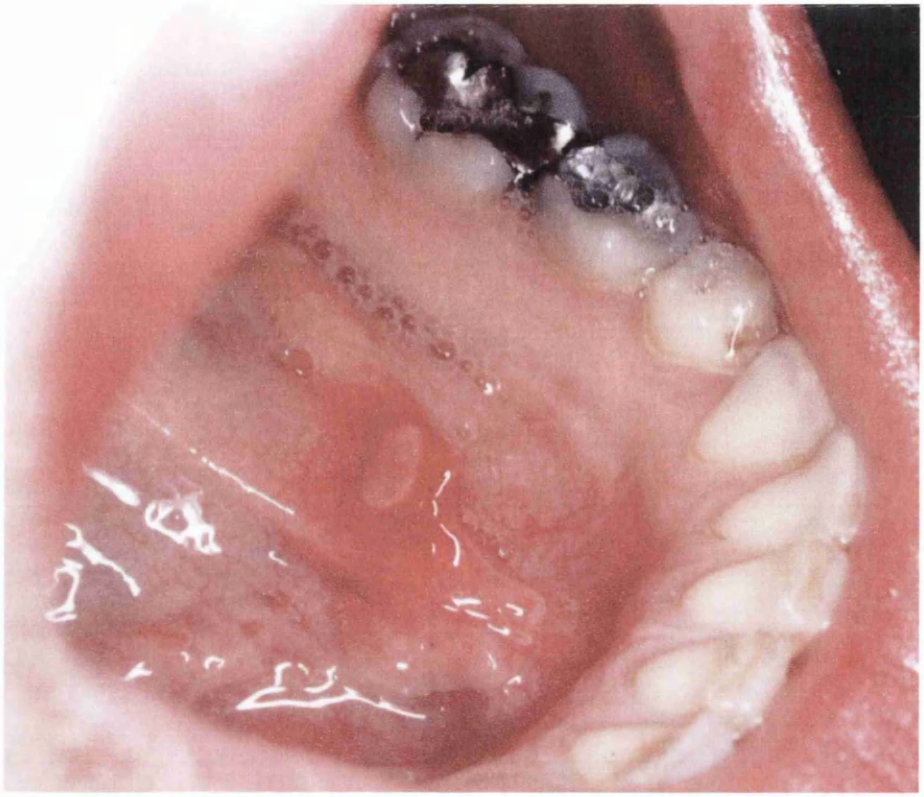


Fig. 7. Photograph of Major RAS Lesion

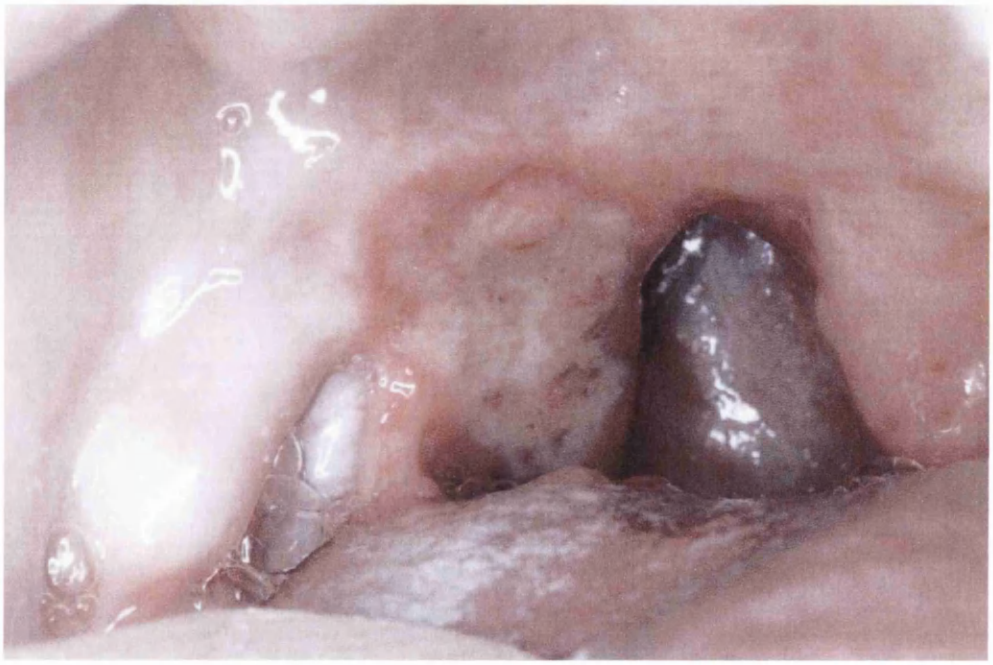


Fig. 8. Photograph of Herpetiform RAS Lesions

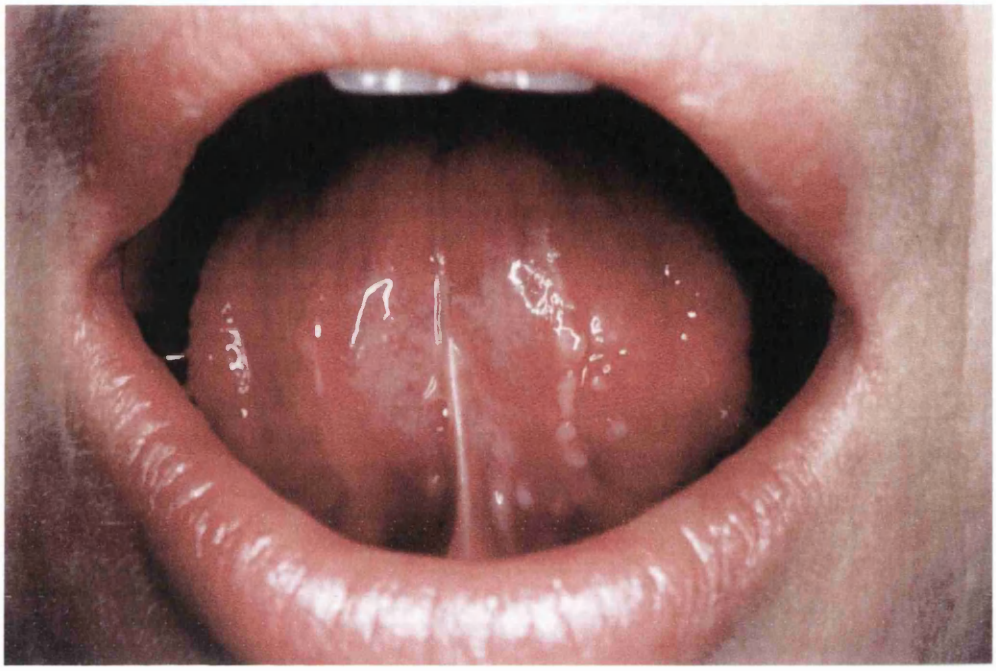


Fig. 9. Photograph Of Localised AE/Urticaria

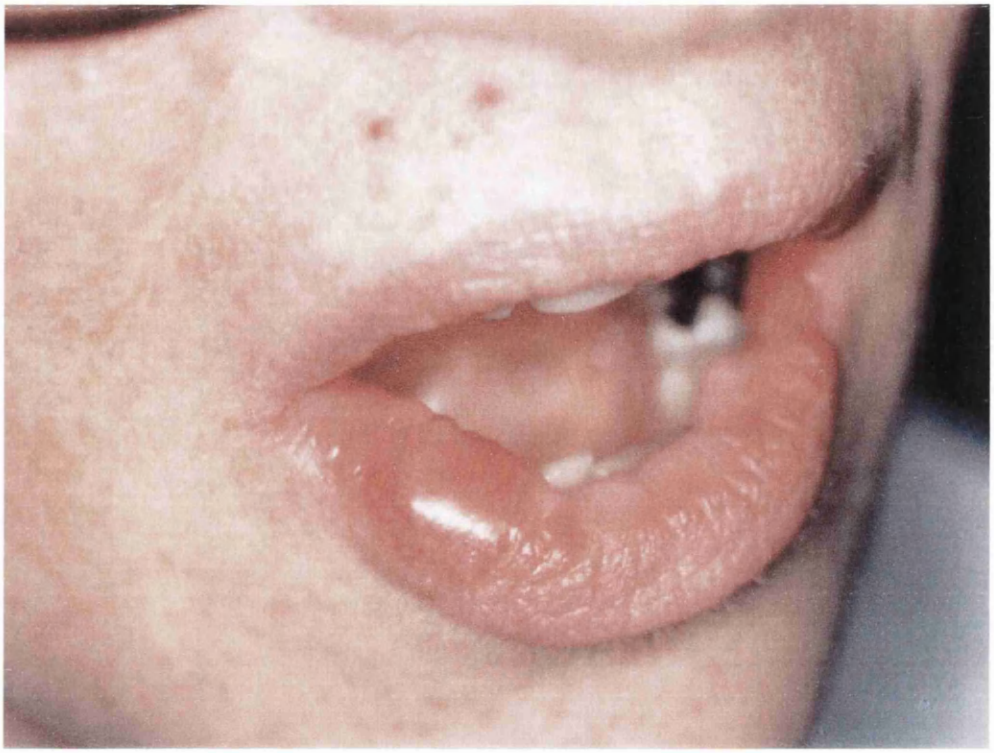


Fig. 10. Photograph Of EM Target Lesions And Lip Crusting

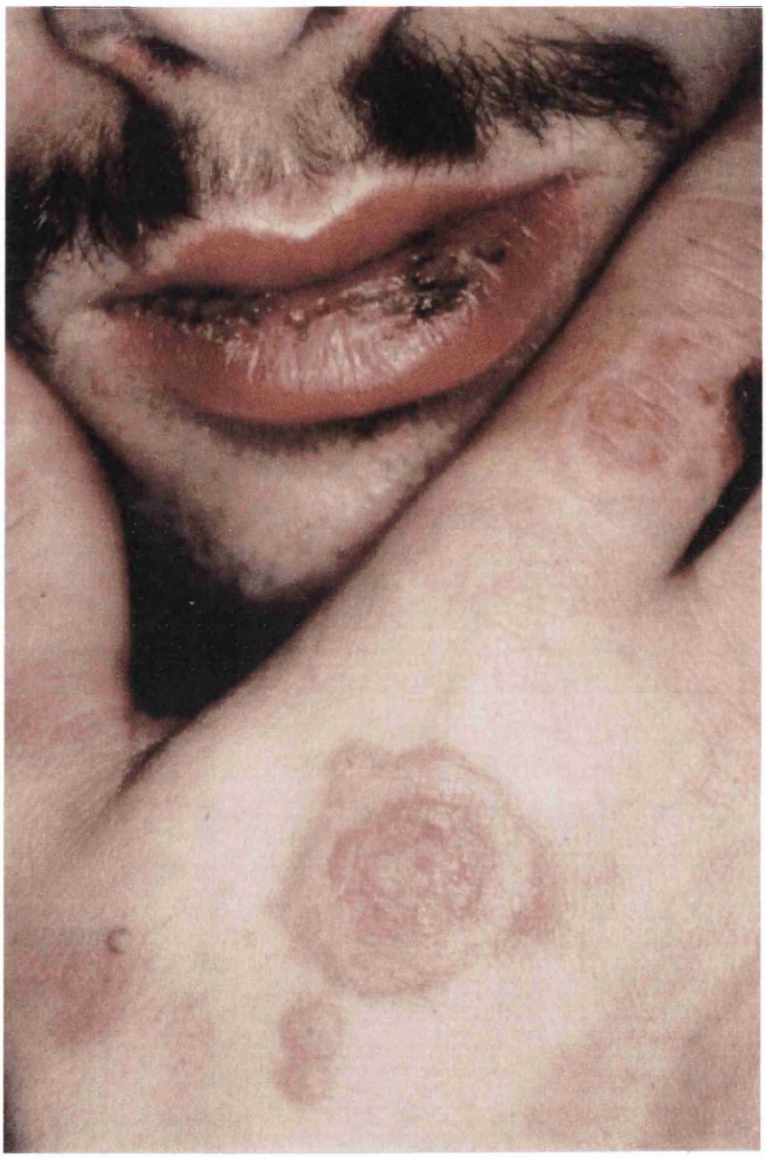


Fig. 11. Photograph Of Intraoral EM

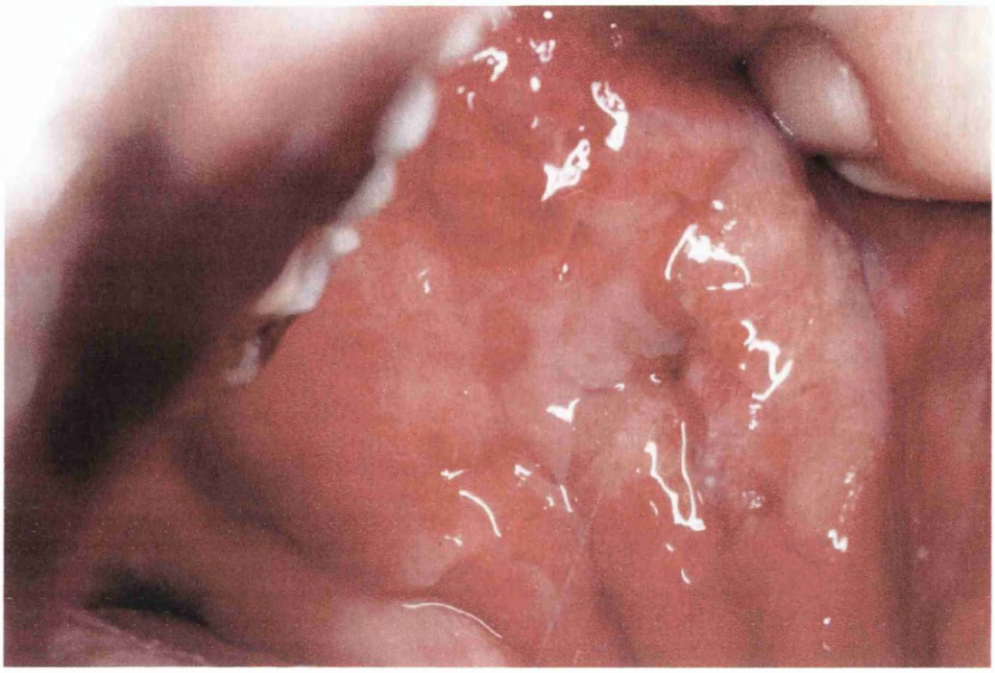


Fig. 12. Photograph Of Extraoral Appearance Of OFG

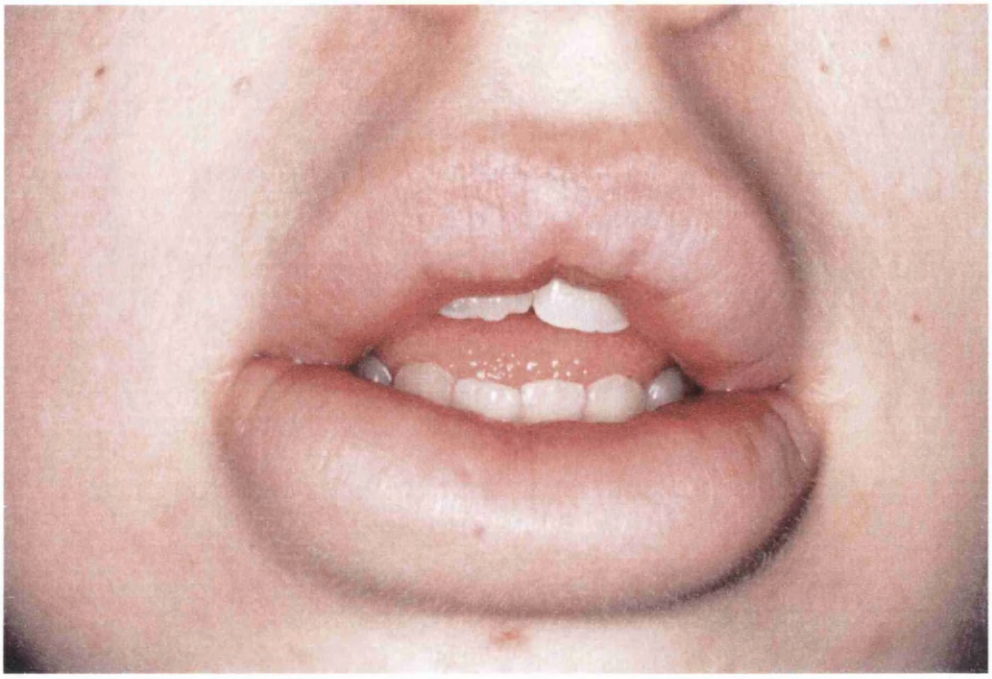
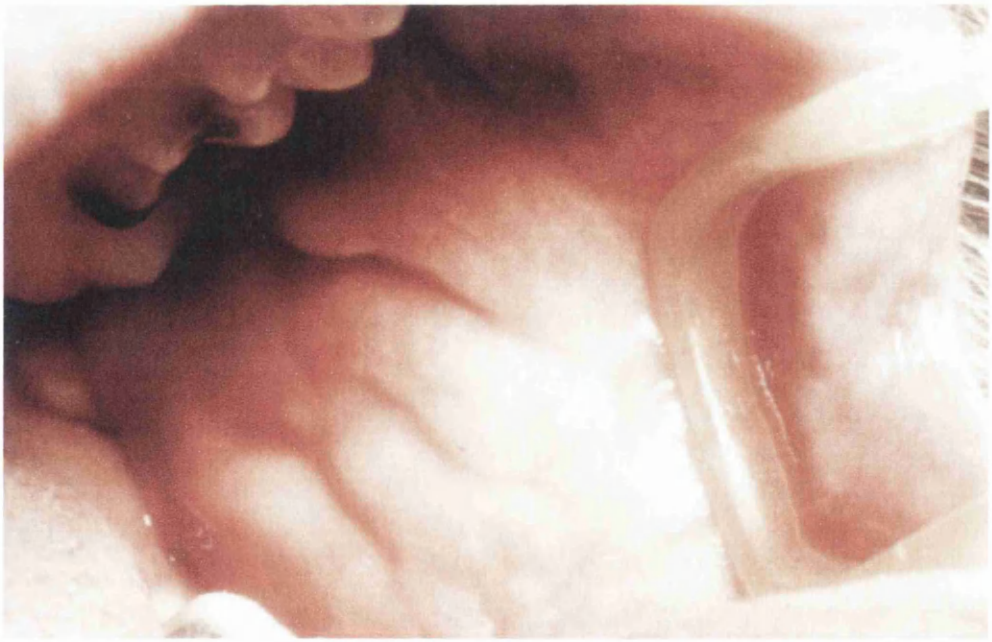


Fig. 13. Photograph Of Intraoral Appearance Of OFG



3.2.2. Control population

Permission from the local Area Dental Ethics Committee was sought and gained prior to this part of the study commencing. 100 people made up of volunteers from the following groups were patch tested: staff working at Glasgow Dental Hospital & School, students studying at Glasgow Dental Hospital & School and friends/family of the above. All were patch tested at Glasgow Dental Hospital from July to December 1996. A short series of questions were asked of all the control subjects and informed consent obtained prior to the tests commencing. The questions sought information on age, sex, geographical area, occupation, medical history and what type of milk (breast or formula) they were fed on as infants. See appendix A-E for the information sheets that all control subjects were given, questionnaire, consent form and working sheets.

Exclusion criteria:

Control subjects who had been patch tested for any reason previously or who had been referred for patch testing.

Control subjects who had a history or clinical evidence of any of the diseases outlined in section 3.2.1. according to the diagnostic criteria as previously outlined.

Exclusion From The Study:

114 people volunteered for the study. Six were excluded on the grounds that they had previously been patch tested and two had clinical evidence of a

mild oral lichenoid reaction. A further five gave a history of recurrent aphthous stomatitis and one had a history of angioedema. There remained 100 who were included in the control group.

3.3. Methods

3.3.1. Reading Of Patch Tests

3.3.1.1. Grading Systems

It is generally accepted that patch test sites should be viewed both at 48 hrs and at a later date (between 3 and 7 days on), which reduces the number of both false positive and false negative results (Brasch, Geier, & Henseler 1995; Rietschel et al. 1988).

There are a number of well used and accepted grading systems: the International Contact Dermatitis Research Group (ICDRG) original system, the ICDRG modified system, the North American Contact Dermatitis Group (NCDG) system and the Swedish Multicenter Study (SMCS) system. These scoring systems require various morphological features to be present at any one test site in order for a diagnosis of a positive allergic reaction to be made. All the systems require erythema and infiltration of the test site for a grade 1 allergic reaction and most require the presence of at least a few papules as well. All require the presence of papules in addition to the erythema and infiltration for a grade 2 reaction, and for a grade 3 reaction all require the presence of vesicles or bullae or both. The scoring system chosen for both the disease patients and the control subjects was the SMCS system which doesn't rely so heavily on the presence of papules which are the most difficult to assess (Bruze et al. 1995). This system, uses scores of 0, E, and 4 to indicate negative, equivocal, and irritant reactions and 1, 2,

and 3, to indicate allergic responses: 1 with erythema, 2 plus oedema and papules and 3, plus vesicles. Irritant reactions were defined as having a morphology composed of a) a smooth glazed appearance or slight erythema, or b) sharp borders confined to the patch test site, or c) a 'cracked' superficial surface, or d) minimal or no induration (Klas et al. 1996).

3.5.1.2. Irritant Responses

Irritant reactions to cutaneous patch tests can confuse the observer into treating these reactions as allergic in nature (Nater & Hoedemaker 1976). Grading patch test reactions by visual inspection and palpation is a subjective process and techniques to help objectively decide if a reaction is allergic or irritant are available. They include laser Doppler flowmetry (Gowkrodger, McDonagh, & Wright 1991; Staberg, Klemp, & Serup 1984) and skin reflectance measurements (Mendelow et al. 1986) to quantify the amount of erythema involved in a positive reaction, infra-red thermography to quantify the changing temperature of an allergic response (Baillie et al. 1990), measuring changes in skin-barrier function by transepidermal water loss measurements (Serup & Staberg 1987a; van der Valk et al. 1985) and measuring the associated oedema by ultrasonic methods (Serup & Staberg 1987b). Although these methods are more objective, good correlation has been shown to exist between many of the objective and visual/palpation methods (Berardesca & Maibach 1988; Willis, Stephens, & Wilkinson 1988) and the visual/palpation scoring of reactions takes far less time to complete so is generally used in clinical practice.

3.3.1.3. Other Techniques Used In Patch Testing

Due to differences between oral mucosal and cutaneous anatomy, it may be supposed that food substances and other materials ingested orally, may affect the mouth and not show positive results on cutaneous patch testing. However, Fisher believes that if the oral mucosa is sensitised, the skin is too (Fisher 1995) and other authors also believe that a positive patch test reaction is a fairly reliable sign of generalised sensitivity reaction (Skoglund & Egelrud 1991). It is also possible that the chemicals could have no effect on oral mucosa but after being absorbed from the gastro-intestinal tract may give rise to an allergic reaction that manifests itself in the skin. Materials used in the manufacture of dental appliances, used during dental treatment or used by the patient for dental home care purposes may also produce these phenomena. The techniques of intraoral patch testing are more complicated than cutaneous methods as the adherence of the suspected allergen to the mucosal surface is difficult to maintain and because of the presence of saliva, the histological differences of the epidermal surfaces and the differences in the microflora of the different areas, the results are not directly comparable to cutaneous patch testing (Axéll et al. 1986). However, methods that have been used are useful in a number of cases where cutaneous patch tests have given negative results and a reaction to a dental material is strongly suspected. The methods of attachment require either adhesive pastes and bandages or the use of suction cups to hold the allergen in place, all of which can only be used for a very short time. Alternatively, individual intraoral appliances can be constructed which hold

the allergen in a solid form next to the mucosa for longer periods of time (Fisher 1974; Fisher 1995; von Nielsen & Klaschka 1971). Positive test reactions on oral mucosa are only elicited when the test concentration of the allergen is 5-10 times greater than that of the test concentration used for skin (Kaaber 1990).

3.3.2. Factors To Consider When Patch Testing

3.3.2.1. Angry Back Syndrome

A single strong positive reaction at a test site can lead to a series of false positives elsewhere in the testing area due to a state of hypersensitivity (Mitchell 1975). The patch test chemical is absorbed into the blood stream and may be carried to any part of the skin. It is also absorbed by lymphatics which may carry the chemical to local parts of the skin, often to other patch test sites. The presence of a strong positive reaction may exaggerate adjacent weak irritant and allergic responses (Mitchell 1977).

3.3.2.2. Sensitisation

Sensitisation to allergens applied during the patch testing process has been a cause for concern. The risk is negligible (Meneghini, Rantuccio, & Lomuto 1972) and is minimised by using non-irritant vehicles for the test substances (Mendelow et al. 1985), avoiding placement of test strips on eczematous or otherwise compromised skin and by using the correct concentration of test substance (Kligman & Epstein 1975) in preparations that have been thoroughly mixed (Sulzberger 1975). The avoidance of patch testing during acutely active phases of disease states, no matter which part of the body is affected also minimises the risk of sensitisation.

3.3.2.3. Adverse Reactions

Systemic reactions to the applications of allergens in patch tests are rare but erythema multiforme has been reported after patch testing with colophony and fragrance mix (O'Donnell & Tan 1997), and nickel (Friedman & Perry 1985). Strong patch test reactions may last for up to three weeks especially in atopic individuals (Mancuso, Berdondini, & Cavrini 1999).

3.3.3. Patient variance

3.3.3.1. Age

Differences in the incidence of positive patch test results exist between populations of differing ages. Most studies detect the highest prevalence in the second to fifth decades (Husain 1977) with some showing a bimodal pattern giving a decrease in the forth decade, in both male and females according to some authors (Sugai et al. 1979) and in females only according to others (Walton, Nayagam, & Keczkes 1986). When tested with multivariate statistical analysis, the differences in positive reactions between the ages vary as to which allergen is being tested e.g. nickel cause positive reactions among younger people in the first to third decades, while fragrances tend to cause more positives among those in the seventh decade (Christophersen et al. 1989). However, among a normal population, while doing sensitisation studies with dinitrochlorobenzene, no significant differences were found between 165 subjects in the age range 23- 69 years (Friedmann et al. 1983).

Patch testing in young children has been shown to be effective giving a high incidence of positive and relevant reactions (Rademaker & Forsyth 1989; Wantke et al. 1996). There are however, inherent problems in patch testing in children. Their size can make application of tests difficult and their excessive mobility can affect the adherence of the tests. The skin of infants and young children is more likely to exhibit non specific irritant reactions which may manifest as false-positives. To avoid this many substances

should be tested in children in reduced concentrations (Fisher 1994; Fisher 1995).

The elderly skin has been said to be less able to mount an inflammatory response (Giannini & Sloan 1957). This may be due to a decrease in both epidermal Langerhan's cells (Gilchrest, Murphy, & Soter 1982), circulating T-lymphocytes (Augener et al. 1974) and in the function of different subsets of T-lymphocytes (Weksler 1982). However, there is considerable conflicting evidence for the incidence of the susceptibility of the elderly to contact sensitisation and to the ability to elicit a reaction via patch testing once sensitised (Kwangsukstith & Maibach 1995). One study found a steadily increasing prevalence of contact sensitivity with age (Goh 1986). It may be that with the increased dryness of the skin, together with an often increased exposure to toiletries and topical medications, that the decreased reactivity of the skin is compensated for in part (Fisher 1995). Despite the conflicting data, it is generally accepted that the elderly have a decreased incidence of delayed hypersensitivity, a decrease in sensitisation to new allergens and are less likely to react to substances to which they were previously sensitised.

3.3.3.2. Sex

Again there is controversy as to what influence gender has on the induction and elicitation of allergic contact dermatitis (ACD). The induction of sensitivity to dinitrochlorobenzene showed no differences between the sexes when carried out on 165 healthy subjects. However, in one study, sex

hormones were shown to have an effect on the induction of sensitivity with progesterone increasing the sensitisation and oestrogen decreasing it (Gerretsen et al. 1975). The differences in positive reactions between the sexes do however vary depending on what allergen is being tested e.g. testing with nickel sulphate yields a higher rate of positive reactions whereas there were no significant differences between the sexes with neomycin (Edman & Möller 1982). Most authors would agree however that the differences in induction of ACD can be accounted for by differing occupations, exposure to cosmetics and jewellery, culture and hormonal influence by the sexes (Kwangsukstith & Maibach 1995). Most studies conclude that females are patch tested for suspected allergens more often than males and that they have a higher incidence of positive results.

3.3.3.3. Atopy

The decision whether or not to patch test those with cutaneous or respiratory atopy has aroused interest because of a number of factors. The immune system of atopics is altered in that the local cell mediated immunity in the skin is suppressed due to a functional decrease in T-cells (Bos et al. 1992). However, this is not a severe systemic suppression as atopics are not predisposed to opportunistic infections (Bos et al. 1992). As a result of this, there has been a reported decrease in contact sensitivity among this group (Uehara & Sawai 1989). In some studies this has been shown to mainly exist in atopics with severe atopic dermatitis, with normal sensitisation rates occurring among those with mild or moderate atopic disease (Uehara &

Sawai 1989), while in others the rate of inducing sensitisation to dinitrochlorobenzene was decreased in patients with only minimal atopic dermatitis (Rees, Friedmann, & Matthews 1990). There is evidence of an increased irritant response in those with atopic dermatitis and this may be due to impaired skin barrier function (Klas et al. 1996). This defective cutaneous barrier together with an increased exposure to chemicals through skin care preparations offsets the mild immunological suppression so atopic patients may have a greater, equal or lesser incidence of allergic contact dermatitis which depends both on the severity of their atopic disease and on the activity of their atopic dermatitis at the time of testing (Mitchell 1975; Whitmore 1994).

3.3.3.4. Race

The effect of race on the elicitation of positive patch test results is complicated by the difficulty in visually reading the amount of erythema on the skin of people whose skin is very dark in colour (Fisher 1995). Possibly, partly due to this difficulty, it has often been concluded that the skin of blacks is more resistant to contact sensitivity and to irritants than that of Caucasians (Kligman & Epstein 1975). This has been further backed up by studies showing that black skin has more layers of stratum corneum than Caucasoid skin and that these layers are also more compact, as shown in density experiments (Weigand, Haygood, & Gaylor 1974). However, many studies have shown an equal ratio of allergic contact dermatitis between blacks and whites (Berardesca & Maibach 1988).

When studied in Singapore, no difference was found in the prevalence of contact sensitivity between Indian, Chinese and Malaysian subpopulations. (Goh 1986).

3.3.3.5. UV Radiation Exposure

Exposure to strong sunlight diminishes the numbers of Langerhan's cells present in the epidermis (Fyad, Masmoudi, & Lachapelle 1987; Zelickson & Mottaz 1970). This loss of antigen presenting ability consequently has an effect on both the induction and the elicitation of allergic responses during patch testing (Toews et al. 1980). To minimise this effect, patients and control subjects were not tested within four weeks of a prolonged period of UV radiation exposure by which time the Langerhan's cells would have returned to a normal state both qualitatively and quantitatively (Toews et al. 1980).

3.3.3.6. Observation Time

The period in history in which a patient is tested may be crucial in affecting the results of that patient's sensitivities (Aberer & Holub 1992). Humans can develop sensitivities to various new allergens at any time in their lives and by the same token, lose contact sensitivity to substances, though most will retain contact sensitivities for long periods of time if not for life (Ayala et al. 1996; Keczkes, Basheer, & Wyatt 1982; Meneghini & Angelini 1977).

Particular allergens may evolve as especially problematic during one period or another due to changing environmental conditions and industrial working practices (Edman & Möller 1982).

3.3.4. Patch Testing Procedure

For patch testing to be effective both in the diagnosis of contact sensitivity and in the treatment of such patients, the patch testing procedure should take the form of three parts: a) history and examination; b) application of the patch tests and, c) advising the patients on how to avoid the relevant allergens.

The words 'patch test' refer in relation to the patient groups and the control group in this investigation, to both delayed hypersensitivity testing (DHT) and to contact urticaria testing (CUT).

All patients when attending for patch testing were asked detailed questions about their symptoms and exposure to various food and environmental allergens. They were asked questions about their general medical history with particular attention paid to any skin or mucosal problems that they may have had. Their age, sex, where they lived, occupation, and whether they considered that their disease was related to their occupation was ascertained. An examination of any signs of the disease present at the time was carried out. Informed consent was given by each subject prior to the tests beginning.

The selection and application of appropriate test substances to the patient's requirements was then done.

Upon receiving a positive result, patients were given skilled advice, both verbal and written, on the steps they should take to avoid the causative allergens in their environment. This sometimes necessitated a visit to the

patient's home and/or workplace to aid in the education of the patient with regard to their environment.

3.3.4.1. 48 Hour Patch Test

Immunologically mediated reactions can be classified by the Gell and Coombs method (Gell & Coombs 1968). The type IV or delayed hypersensitivity reaction is mediated by T lymphocytes and classically takes 2 days to develop (Rietschel 1989).

Petrolatum was used as the carrying medium of choice where possible as this facilitates ease of handling and avoids the "edge effect" that can complicate the reading of patch tests carried out with solutions (Fyad, Masmoudi, & Lachapelle 1987). The test substances that were suspended in petrolatum were dispensed from plastic disposable syringes and placed in Finn chambers ™[12] (8mm aluminium wells) arranged on Scanpor[13] surgical tape. A 4mm length of the test substance carried in petrolatum from the containing syringe was expressed into the aluminium well (Antoine & Lachapelle 1988; Hjorth 1989; Rietschel 1989). Those carried in an aqueous solution were dispensed from plastic dropper bottles and placed on a 5mm disc of filter paper[14] that was sitting in the aluminium well. One drop was used to wet the filter paper immediately prior to the placement of the tests. On day 1, the tapes were applied to the upper back, avoiding the

---

[12] Epitest, Hyrylä, Finland.
[13] Scanpor, Norgesplaster, Oslo, Norway
[14] Filter paper discs supplied by Bio Diagnostics Ltd.

vertebral column, and a hypoallergenic skin marker[15] was used to denote the test sites. See Figs 14 and 15. The tapes remained in place for 48 hours. On day 3, approximately 1 hour after removal, the test sites were examined by the clinician and given a score as outlined below. The test sites were re-examined and scored on day 5, a total of 96 hours after initial exposure to the allergen via the test sites, see Figs 16 and 17.

A total of 48 different allergens were placed on the backs of control subjects on day 1 of the study and the results read on days 3 and 5. The allergens were suspended in petrolatum (n=46) or in an aqueous solution (n=2) and were the same as the basic 48 used on most of the disease population (modified European Standard Series, food additives, perfumes and flavourings, and chocolate). The patch testing procedure was carried out with the patients and with the control subjects in as similar a way possible to minimise any variance in the results due to differing patch testing and examining techniques.

[15] Supplied by Crawford Pharmaceuticals.

Fig. 14. Photograph Of Allergens Arranged On Tape Prior To Applying To The Volunteer's Back

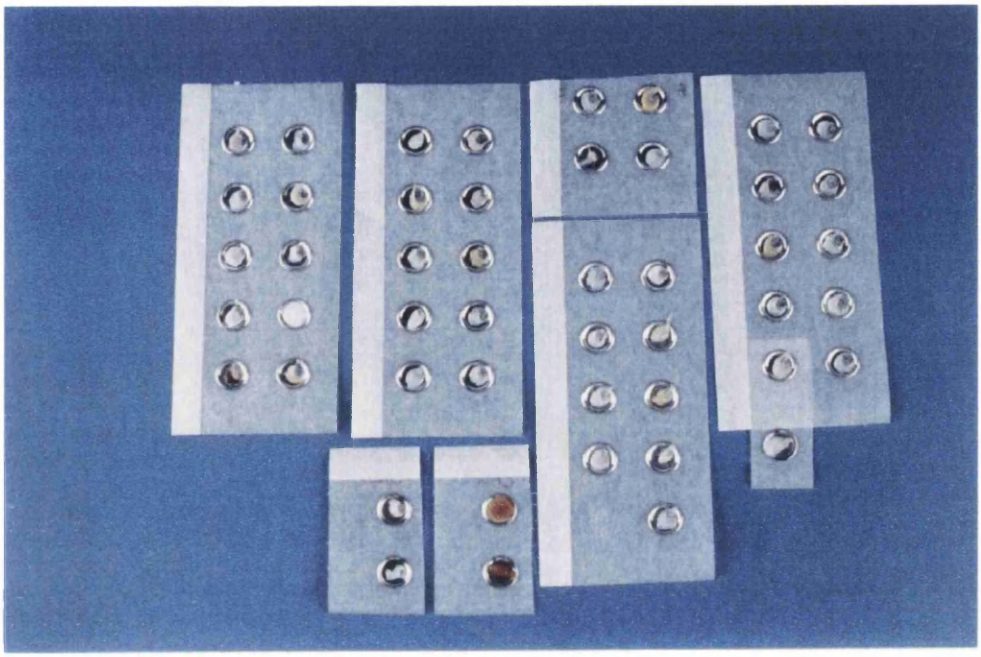


Fig. 15. Photograph Of Tapes With Allergens Applied To The Upper Back

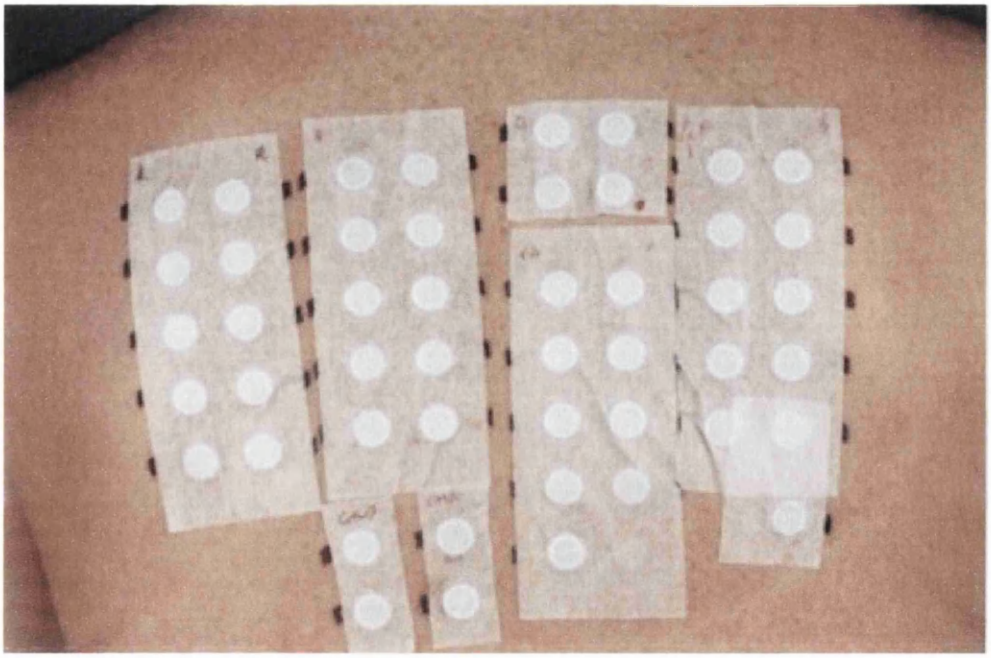


Fig. 16. Photograph Of Day 5 Results

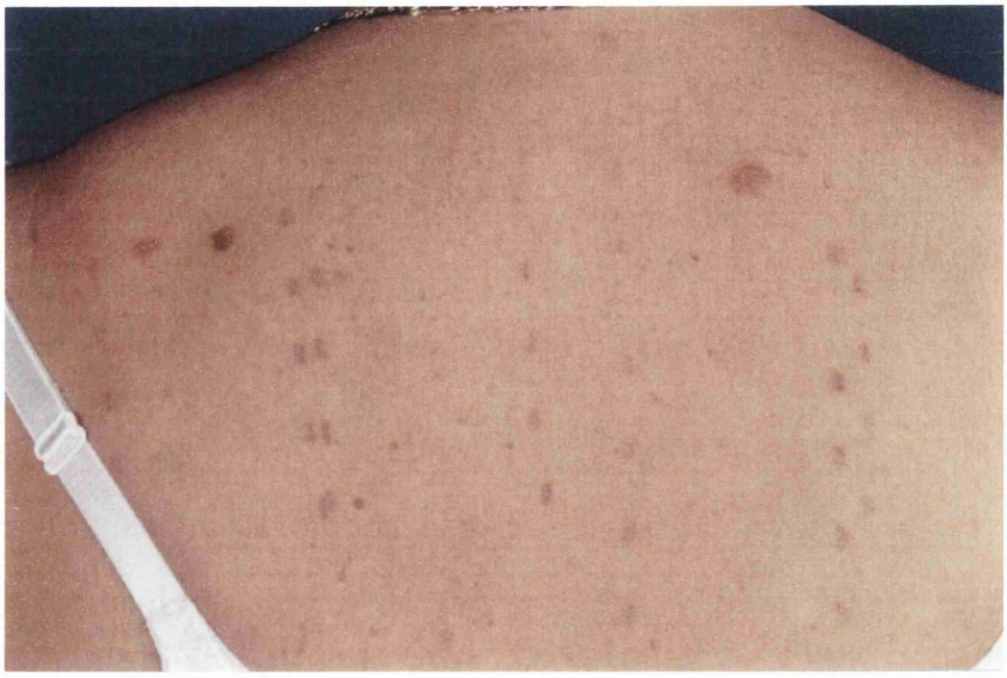
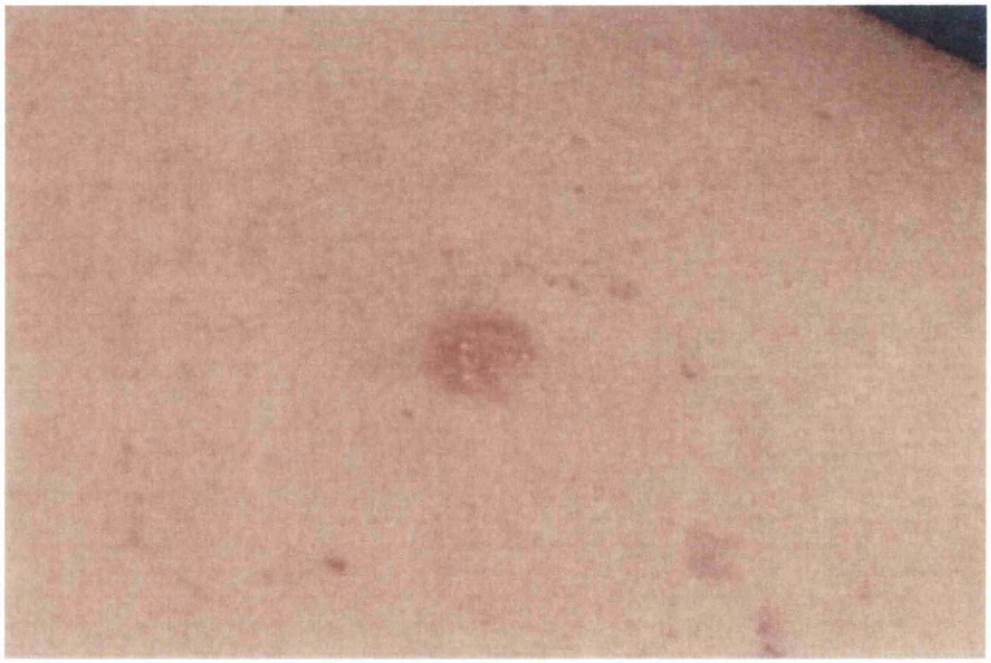


Fig. 17. Photograph Of Positive Reaction Showing Vesicles (Day 5)



3.3.4.2. Contact Urticaria Test

Epicutaneous testing can also be used to elicit Type I hypersensitivity reactions and non-immunologic contact urticaria (NICU) reactions in sensitised patients.

On day 1, the test substances (food additives, chocolate and all the perfumes and flavourings bar sorbitan sesquiolate) were placed on the subjects forearms where they were clearly visible to the subject. See Figs 18 and 19. On the skin next to each site, a number was clearly marked with a pen to identify each individual test. After 20 minutes, the Scanpor tapes with the test substances were removed and the test sites examined by the clinician. A score of 0 (no reaction) or 1 (reaction clearly visible, ie palpable, pruritic erythema) was given for each test site. See Fig 20. The subject was instructed to observe the test sites at hourly intervals over the subsequent 6 hours and record any changes or sensations of pruritus associated with any of the sites. At the following visit, the subjects records of the test were examined and a further score given.

Fig. 18. Photograph of allergens ready for contact urticaria testing

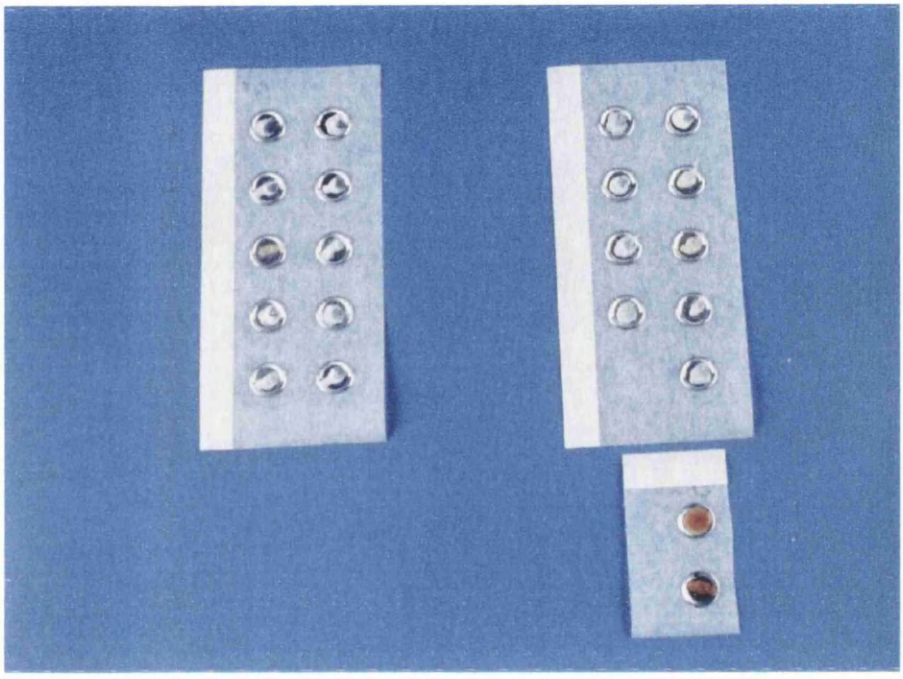


Fig. 19. Photograph of allergens *in situ* on flexor surfaces of forearms

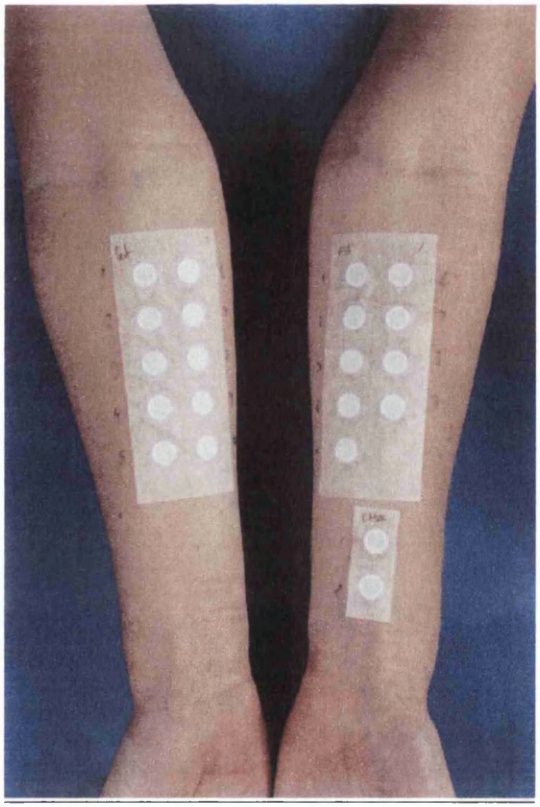
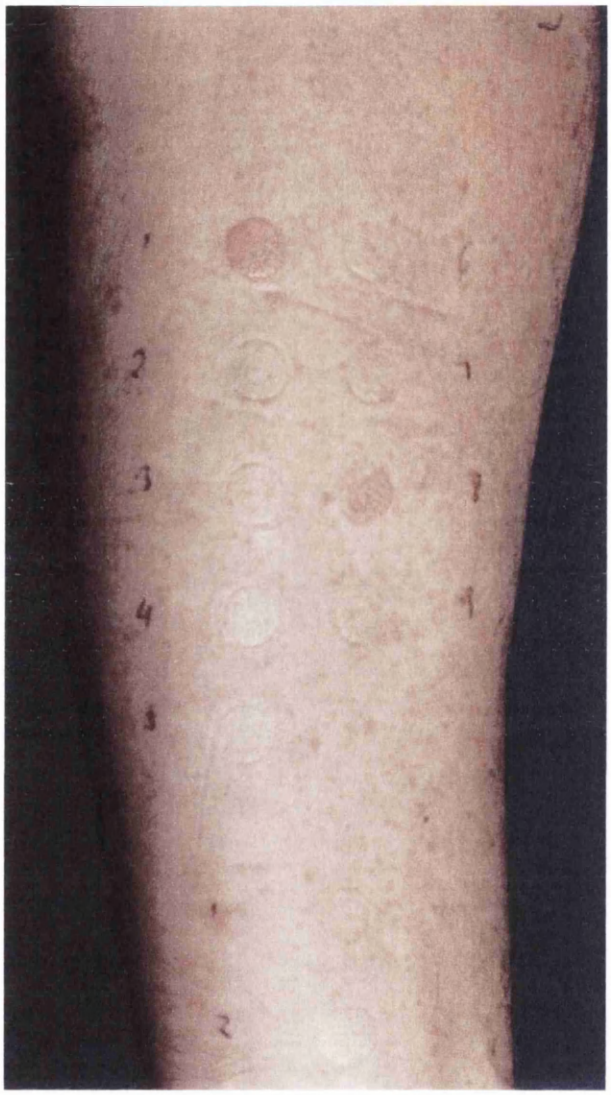


Fig. 20. Photograph Of Positive Result After 20 Minutes



3.3.5. Observer Calibration

It has been said that the preparing and placement of patch tests can be done by an amateur but the reading and interpretation requires an expert (Hjorth 1989; Sulzberger 1975). In order to gain the necessary training and experience, the research observer spent 3 months training in patch test techniques and in the reading of patch test reactions alongside the expert dermatologist. Most of the patients involved in the study were examined by the same clinician (consultant dermatologist) when attending for patch testing at the CDIU Dept. The control subjects were all examined by the research clinician at Glasgow Dental Hospital and School . In order to minimise inter-rater variation, a study was carried out to test the accordance in reading patch test reactions between the two observers. At the end of the training period and prior to the research project commencing, consecutive patients attending for their 96 hour delayed hypersensitivity reading were examined by both observers and the results compared. Patch test reactions were graded as outlined previously. This process was repeated during the period of patch testing the normal population sample, with both patients and healthy control subjects examined by both observers at the two different test locations. Each patient was examined individually by each observer in turn and there was no communication between the observers during the reading period. Both observers had access to the identity of the allergens on each patch and to the results of the 48 hour readings.

The disease subjects had between 48 and 111 patches to be read (all of which had been placed on their upper back), which averaged at 72.5 per subject.

3.3.6. Outcome Of Dietary Avoidance Of Relevant Allergens

Avoidance of allergens to which the patient is sensitive, minimises the immune response of the patient to that allergen and may enable the immune system to lose its sensitivity or at least its detectable sensitivity entirely (Keczkes, Basheer, & Wyatt 1982; Meneghini & Angelini 1977).

Patients who attended the CDIU for patch testing and who had a positive skin sensitivity to a dietary allergen were given diet avoidance advice with respect to the particular allergen. This was both verbally given usually by a senior dietician and in the form of written instructions. Examples of the dietary advice sheets for patients sensitive to benzoic acid and cinnamaldehyde are given in Appendix F. These were prepared by the senior dietician K.A. Milligan at Glasgow Royal Infirmary. These patients were contacted by means of a postal questionnaire with an accompanying letter and a post paid reply envelope. The letter and questionnaire are shown in Appendices G and H. The purpose was to ascertain the following:

- did they understand the diet advice
- how successful were they in maintaining the dietary changes/ restrictions
- whether their symptoms had changed in any way since receiving the advice
- whether they knew of any other contributing factors to their improvement or otherwise

Linear analogue scales were used to ascertain the levels of compliance with the dietary avoidance advice and the pre and post testing symptoms

(Huskisson 1974). The patients were asked to mark a cross on a 10cm line. The results were calculated by measuring with a ruler the distance along the line that the mark had been placed. A score of 0 was given if the score was at the beginning of the line, a score of 1 if the measurement was between 0 and 0.9cm from the beginning, 2 if the measurement was between 1 and 1.9cm, etc. A score of 10 was given when the cross was marked at the end of the line.

A total of 476 patients were sent a letter enclosing a questionnaire and a reply paid envelope with which to return it. The patients receiving the letter were selected by taking the disease group and selecting only patients with any of the 5 diseases under consideration and who also had a positive reaction to a food substance. 50 further patients' addresses were not available so letters were not sent. The letter and questionnaire can be found in Appendices F and G.

3.3.7. Statistical Analysis

Inter-rater agreement was calculated using the chance-corrected measure of agreement, known as *Kappa* (Campbell & Machin 1999) and this was carried out using SPSS computer software[16].

The statistics computer package, Minitab version 12[17] was used to compute the rest of the statistical analysis. Statistical significance was conceded at the 5% level. For age comparisons between different groups, the two sample t test was utilised and two proportions test was used in comparing the sex of different groups.

Categorical data were analysed by the Chi Squared test. The number of patients positive to the patch testing and contact urticaria testing was compared to the control group using the two proportions test, except where indicated.

The paired t test was used in the comparison between the pre post testing symptom scores in the analysis of the questionnaire results. The difference in symptom improvement between patients with different dietary compliance levels was calculated using one way analysis of variance.

---

[16] SPSS Science Software UK Ltd., The Research Park, Vincent Drive, Birmingham, B15 2SQ. UK Tel : (0121) 471 4199. Fax : (0121) 471 5169.
[17] Minitab Inc., 3081 Enterprise Drive, State College, PA 16801-3008

3.4. Materials

The patients attending the CDIU were tested to allergens that were likely to be contributing to their disease process in some way. The selection of allergens was based on the patients' signs, symptoms and history of exposure to various materials. Nearly all were tested with the modified European Standard Series and most of the patients were tested to food additives, perfumes and flavourings and to chocolate. As the testing period was over a long time period, some of the allergens or concentrations changed in the different series over the years and these changes have been explained in the text or taken into account in the computing of results, i.e. the percentages of positive results have been calculated from the number of patients who were tested to each allergen. Most patients were also tested to other allergens as well e.g. series of dental materials, cosmetic and pharmaceutical vehicles, rubber chemicals, medicaments or other foods thought to play a part in the patients' disease process. These other allergens are not included in this study except where specifically mentioned. The control subjects were tested to the same basic sets of allergens to which patients referred from the dental hospital were exposed, i.e. the modified European Standard Series of environmental allergens, food additives, perfumes and flavourings and to chocolate.

All the allergens were mixed with petrolatum as the carrying vehicle, except for formaldehyde and one of the chocolate essence preparations which were carried in aqueous solution. Both the carrying vehicles have low irritant and

sensitisation potential and a petrolatum test site was included on all subjects as a control (Mendelow et al. 1985).

3.4.1. Food Additives

The food additives that were used as test allergens for both the control subjects and the patients were: benzoic acid, salicylic acid, tartrazine, glutamic acid, butylated hydroxytoluene, butylated hydroxyanisole, propylene glycol, sorbic acid and sodium metabisulphite. These substances were tested in the delayed hypersensitivity reaction and in the contact urticaria tests. See Table 9 for the concentrations, carrying media and manufacturers of the various allergens.

Table 9. Concentration And Carrying Media Of The Food Related Allergens Used

ALLERGEN	CONCENTRATION [%]	MEDIUM	MANUFAC-TURER
Food Additives			
Benzoic Acid	5	Petrolatum	Crawford[18]
Salicylic Acid	1	Petrolatum	GRI[19]
Tartrazine	0.1	Petrolatum	GRI
Glutamic Acid	2	Petrolatum	GRI
Butylated Hydroxytoluene	2	Petrolatum	Trolab ®[20]
Butylated Hydroxyanisole	2	Petrolatum	Trolab ®
Propylene Glycol	5	Petrolatum	Crawford
Sorbic Acid	2	Petrolatum	Trolab ®
Sodium Metabisulphite	1	Petrolatum	Trolab ®
Perfumes and Flavourings			
Cinnamyl Alcohol	1	Petrolatum	Trolab ®
Cinnamaldehyde	1	Petrolatum	Trolab ®
Eugenol	1	Petrolatum	Trolab ®
Amylcinnamaldehyde	1	Petrolatum	Trolab ®
Hydroxycitraonellal	1	Petrolatum	Trolab ®
Geraniol	1	Petrolatum	Trolab ®
Isoeugenol	1	Petrolatum	Trolab ®
Oak Moss Absolute	1	Petrolatum	Trolab ®
Benzyl Alcohol	1	Petrolatum	Crawford
Musk Ambrette	5	Petrolatum	Trolab ®
Sorbitan Sesquiolate	20	Petrolatum	Trolab ®
Chocolate[A]			
Essence of Chocolate	5	Aqueous	GRI
Essence of Chocolate	5	Petrolatum	GRI

[A] The chocolate allergen used between 1980-1985 was 'creamy chocolate colour', 5% and 10%.

---

[18] Crawford — Crawford Pharmaceuticals, 71a High Street, Stony Stratford, Milton Keynes, MK11 1BA

[19] GRI — Glasgow Royal Infirmary
84 Castle Street, Glasgow, G4 OSF
Allergens prepared by the hospital pharmacy.

[20] Trolab® — Trolab Patch Test Allergens
HERMAL Diagnostics Dept., D-21462 Reinbek, Germany

3.4.2. Perfumes And Flavourings

The perfumes and flavourings that were tested were: cinnamyl alcohol, cinnamaldehyde, eugenol, amylcinnamaldehyde, hydroxycitraonellal, geraniol, isoeugenol, oak moss absolute, benzyl alcohol, and musk ambrette, (see Table 9). Sorbitan sesquiolate being added as an emulsifier to the fragrance mix in the European Standard Series, was included in the testing (Frosch et al. 1995). All were tested in the delayed hypersensitivity test and all but sorbitan sesquiolate were tested in the contact urticaria test.

3.4.3. Chocolate

Essence of chocolate was tested with the two different carrying media (petrolatum and water) in both the delayed hypersensitivity test and contact urticaria test, (see Table 9).

3.4.4. European Standard Series

The control subjects were tested to a series of common environmental allergens, which was the same as that of the disease patients. A modified European Standard Series was used consisting of 23 test allergens and a control (PMF). See Tables 10 and 11 for details of the concentrations, carrying media and manufacturers of these allergens.

Table 10. Concentrations And Carrying Media Of The Environmental Allergens Used (Modified European Standard Series)

ALLERGEN	CONCENT-RATION [%]	MEDIUM	MANUFAC-TURER
Nickel Sulphate	5[A]	Petrolatum	Trolab ®[21]
Colophony	20	Petrolatum	Trolab ®
Cobalt Chloride	1	Petrolatum	Trolab ®
Formaldehyde	1[B]	Aqueous	Trolab ®
Potassium Dichromate	0.5	Petrolatum	Trolab ®
PPD•	1[C]	Petrolatum	Trolab ®
Mercapto-mix[a]	2[C]	Petrolatum	See page 198
Neomycin	20	Petrolatum	Trolab ®
Paraben mix[b]	16	Petrolatum	See page 198
Balsam of Peru	25	Petrolatum	Trolab ®
Thiuram-mix[c]	1	Petrolatum	See page 198
PPD-mix[d]	0.6	Petrolatum	See page 198
Fragrance-mix[e]	8[D]	Petrolatum	See page 199
Primin	0.01	Petrolatum	Trolab ®
Quaternium 15	1	Petrolatum	Trolab ®
Carba-mix[f]	3	Petrolatum	See page 199
Wool Alcohols	30	Petrolatum	Trolab ®
PTBP# Formaldehyde Resin	1	Petrolatum	Trolab ®
Caine-mix[g]	5[E]	Petrolatum	See page 199
Epoxy Resin	1	Petrolatum	Trolab ®
Quinoline	6	Petrolatum	Trolab ®
Ethylene Diamine	1	Petrolatum	Trolab ®
Thiomersal	0.1	Petrolatum	Trolab ®
Control (Petrolatum)	100		DePuy[22]

Concentrations prior to August 1984:

[A] 2.5%

[B] 2%

[C] 0.5%

[D] 16%

[E] 8%

Abbreviations: • Paraphenylenediamine, # Paratertiarybutyl phenol

---

Suppliers and Manufacturers:

[21] Trolab® Trolab Patch Test Allergens
HERMAL Diagnostics Dept., D-21462 Reinbek, Germany.

[22] DePuy DePuy Healthcare, Leeds LS25 2JY, England.

Table 11. Mix Constituents:

All mixes prepared using equal quantities of each of the individual ingredients.

Allergen	Concentration [%]	Medium	Manufacturer
[a] Mercapto-mix supplied by Trolab ® ready mixed.			
Dibenzothiazyl disulphide	1	Petrolatum	Trolab ®
N-Cyclohexylbenzothiazyl Sulphenamide	1	Petrolatum	Trolab ®
Morpholinylmercatobenzothiazole	0.5	Petrolatum	Trolab ®
[b] Paraben mix supplied by Trolab ® ready mixed.			
Methyl Parahydroxybenzoate	3	Petrolatum	Trolab ®
Ethyl Parahydroxybenzoate	3	Petrolatum	Trolab ®
Propyl Parahydroxbenzoate	3	Petrolatum	Trolab ®
Butyl Parahydroxbenzoate	3	Petrolatum	Trolab ®
[c] Thiuram-mix supplied by Trolab ® ready mixed.			
Tetramethylthiuram Disulphide	0.25	Petrolatum	Trolab ®
Tetraethylthiuram Disulphide	0.25	Petrolatum	Trolab ®
Tetramethylthiuram Monosulphide	0.25	Petrolatum	Trolab ®
Dipentamethylenethiuram Disulphide	0.25	Petrolatum	Trolab ®
[d] PPD-mix prepared by GRI[23] pharmacy.			
Cyclohexlyphenyl PPD	1	Petrolatum	Crawford [24]
Diphenyl PPD	0.25	Petrolatum	Trolab ®
Isopropylphenyl PPD	1	Petrolatum	Trolab ®

[23] GRI Glasgow Royal Infirmary
84 Castle Street, Glasgow, G4 OSF
Allergens prepared by the hospital pharmacy.

[24] Crawford Crawford Pharmaceuticals, 71a High Street, Stony Stratford, Milton Keynes, MK11 1BA

Table 11 Continued

Allergen	Concentration [%]	Medium	Manufacturer
[e] Fragrance-mix supplied by Trolab ® ready mixed.			
Cinnamyl Alcohol	1	Petrolatum	Trolab ®
Cinnamonaldehyde	1	Petrolatum	Trolab ®
Eugenol	1	Petrolatum	Trolab ®
Amylcinnamaldehyde	1	Petrolatum	Trolab ®
Hydroxycitraonellal	1	Petrolatum	Trolab ®
Geraniol	1	Petrolatum	Trolab ®
Isoeugenol	1	Petrolatum	Trolab ®
Oak Moss Absolute	1	Petrolatum	Trolab ®
Sorbitan sesquiolate	20	Petrolatum	Trolab ®
[f] Carba-mix prepared by GRI pharmacy.			
Diphenylguanidine	1	Petrolatum	Trolab ®
Diethyldithiocarbamol	1	Petrolatum	Trolab ®
Dibutyldithiocarbamol	1	Petrolatum	Trolab ®
[g] Caine-mix prepared by GRI pharmacy.			
Lignocaine	15	Petrolatum	Trolab ®
Cinchocaine	5	Petrolatum	Trolab ®
Benzocaine	5	Petrolatum	Trolab ®
Tetracaine	1	Petrolatum	Trolab ®

3.4.5. Mercurials

There is a well established link in some patients with OLE to a positive reaction to mercurials (Laine, Kalimo, & Happonen 1997). An example of the improvement in the OLE in a patient sensitive to mercurials following amalgam replacement with non metal restorations is shown in Figs 21 and 22. To investigate this further, the results of all patients who had been tested with various mercurials were analysed.

Fig. 21. Photograph Of OLE Related To Old Corroded Amalgam Restoration

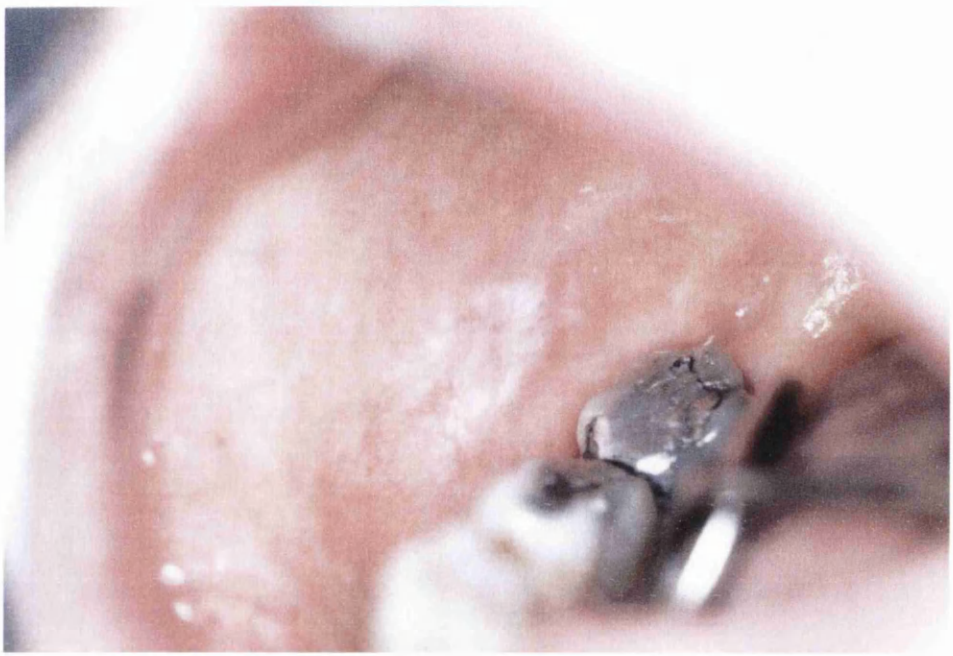
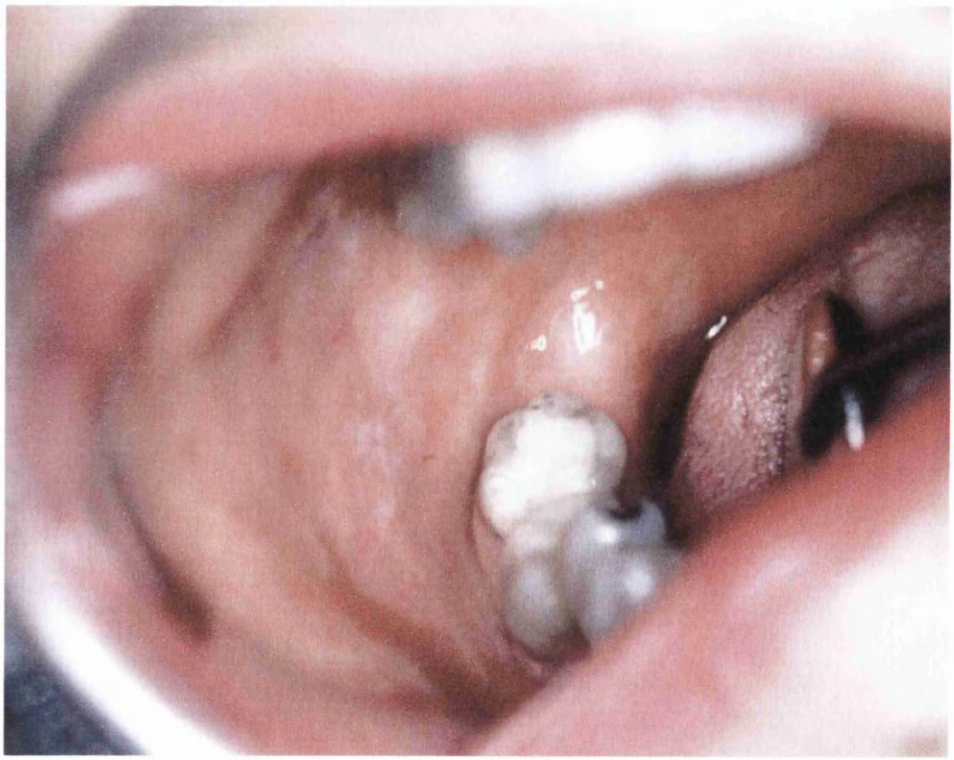


Fig. 22. Photograph Of OLE Following Replacement Of Amalgam Restorations (same patient as in Fig 2)



3.5. Results

3.5.1. Observer Calibration

The kappa statistic for the inter-rater agreement assessment prior to the commencement of the patch testing of the control sample was 0.60. The figure for the assessment obtained in the middle of the testing procedure was 0.73. These figures correlate well with inter-rater agreements when examining other subjectively determined parameters such as caries incidence in teeth (Fyffe et al. 2000).

3.5.2. Demographics Of Patients And Controls

A total of 1,252 patients were referred to the CDIU from Glasgow Dental Hospital in the time from 5th December 1980 to the 14th October 1996 and all were included in the study. One hundred controls were examined.

3.5.2.1. Diagnosis

A total of 889 of the patients were diagnosed as having one of the five main categories of disease under consideration, i.e. angioedema (AE), erythema multiforme (EM), oral lichenoid reactions (OLE), orofacial granulomatosis (OFG) and recurrent aphthous stomatitis (RAS). The categories and the number of patients in each are as shown in Table 12.

Among the rest of the patients, 162 were referred for oral dysaesthesia (OD), 17 were referred with desquamative gingivitis and two were referred with plasma cell gingivitis. The remainder (n=182), were referred for other

reasons such as: lip swelling which was not thought to be OFG or AE, facial eczema, suspected allergy to local anaesthetics, geographic tongue, gingivitis related to porcelain bonded crown, migraine, Sjögrens syndrome, median rhomboid glossitis, nasal congestion, dry mouth and suspected allergy to denture materials.

Table 12. Main Disease Categories of Patients Referred to the CDIU

Disease Category	Number of Patients
OLE	261
RAS	277
AE	45
EM	42
OFG	264

3.5.2.2. Age

The age of the total number of patients by decade is listed for every year in Table 13. A large proportion of the patients were tested in the years 1991,1992, 1994 and 1995. The normality of the age distribution is shown in Fig. 23 and the ages of the patients in each of the disease categories is shown in Fig. 24.

The average age of patients at the time of patch testing was 39 years (mean was 39.46, S.D. = 19.25) and the range was from 2 (n=1) to 94 (n=1) years.

The average age of OLE patients at the time of patch testing was 52 years (mean was 51.5, S.D. = 12.9) and the range was from 2 (n=1) to 79 (n=1) years.

The average age of RAS patients at the time of patch testing was 31 years (mean was 31.3, S.D. = 16.6) and the range was from 3 (n=1) to 83 (n=1) years.

The number of patients in the AE group was 45. The average age of patients at the time of patch testing was 48 years (mean was 47.8, S.D. = 18.25) and the range was from 13 (n=2) to 73 (n=2) years.

The number of patients in the EM group was 42. The average age of patients at the time of patch testing was 33 years (mean was 32.5, S.D. =14.31) and the range was from 12 (n=1) to 65 (n=1) years.

Table 13. Age by Year of Examination

Year	DECADE										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
1980			1				1				2
1981		5	2	2	3	0	2				13
1982	1	4	6	4	2	5	2	1			25
1983		2	2	1	6	16	1	4			42
1984		5	3	8	3	9	8	6			42
1985		5	5	8	3	9	10	5			45
1986	2	4	7	8	7	8	9	1			46
1987	6	10	8	11	10	14	5	2			66
1988	3	14	15	7	12	12	9	2	1		75
1989	3	10	23	14	14	15	16	1			96
1990	5	16	11	14	8	13	5	3	1		76
1991	9	26	15	21	15	23	11	5	1		126
1992	10	41	23	31	17	20	18	6			166
1993	5	5	10	15	8	12	11	3		1	70
1994	7	22	16	33	24	26	21	6	1		156
1995	5	16	12	32	29	19	18	9	1		141
1996	1	9	6	9	18	10	9	3			65
Total	**57**	**194**	**163**	**218**	**180**	**211**	**166**	**57**	**5**	**1**	**1252**

Fig. 23. Histogram of the Age of Total Number of Patients at the Time of Examination

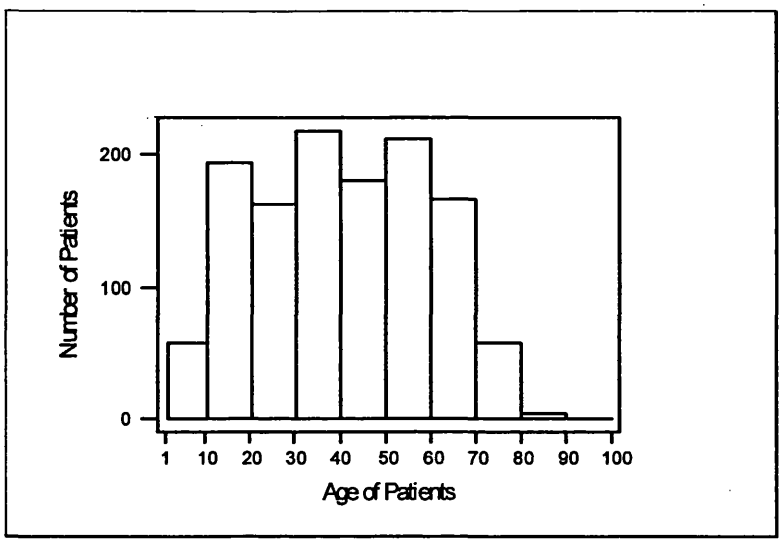
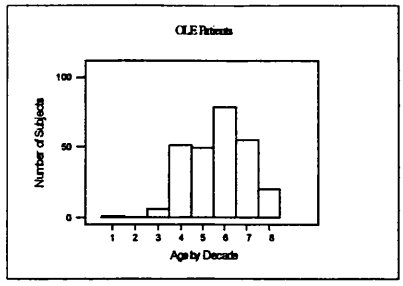
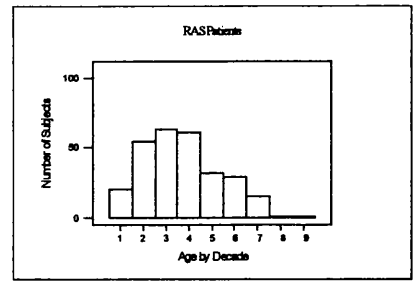
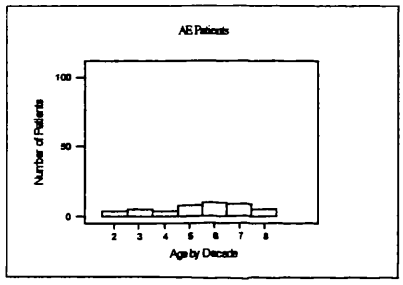
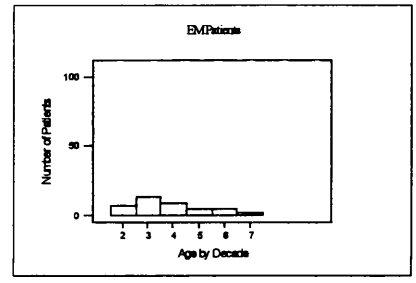


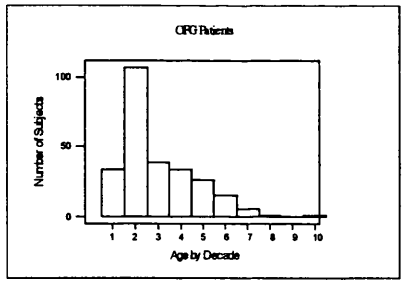
Fig. 24. Histograms of the Age of Patients and Controls

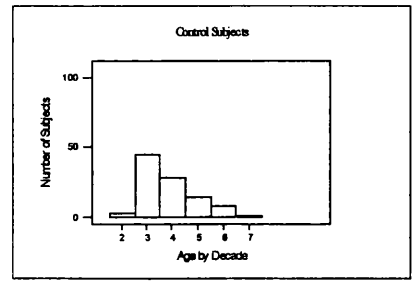












The average age of OFG patients at the time of patch testing was 24 years (mean was 24.3, S.D. = 16.13) and the range was from 3 (n=1) to 94 (n=1) years.

The ages of control subjects ranged from 19 (n=3) to 60 (n=1) with the mean at 33.33 years, S.D. = 10.57. However the most common age band that the control subjects were included in, was the third decade, 20–29 (n=45). The control group was comparable with the RAS and EM groups of patients, significantly younger than the OLE and AE groups and significantly older than the OFG group. See Table 14. and Fig. 25.

Table 14. Comparison Of The Age Of Controls And Disease Groups

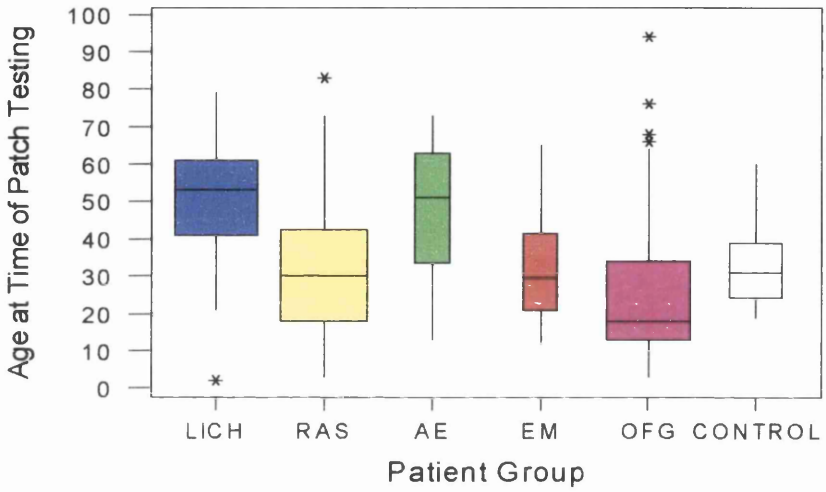
[Statistically significant results in bold italics]

Disease Group	Mean Age (Standard Deviation)	95% CI*
OLE	51.5 (12.9)	***15.5, 20.8***
RAS	31.3 (16.6)	-4.9, 0.8
AE	47.8 (18.3)	***8.6, 20.3***
EM	32.5 (14.3)	-5.8, 4.0
OFG	24.3 (16.1)	***-11.84, -6.1***
CONTROL	33.3 (10.6)	-

* 95% confidence interval for the ages of the patients (disease group minus the age of the control group).

Fig. 25. Boxplot of Age of Subjects at the Time of Examination: by Disease Group

[Width of box corresponds to sample size.]



3.5.2.3. Sex

Of all the patients that were sent for patch testing, 33.6% were male (n=420) and 66.4% were female (n=832).

When observed by disease category, 24.1% (n=63) of the patients with OLE were male and 75.9% (n=198) were female. Of the patients with RAS, 33.9% (n=94) were male and 66.1% (n=183) were female. The male : female ratio of those patients with AE was close to equal being 49% (n=22) : 51% (n=23). 45% (n=19) of the patients with EM who were referred for patch testing were male and 55% (n=23) were female. Of the patients with OFG who were referred for patch testing, 57% (n=151) were male and 43% (n=113) were female.

29% of the control subjects were male and 71% were female.

The numbers of males in each of the disease groups was compared with the number of males in the control group. The results are shown in Table 15. and in Fig. 26. There was a statistically significant higher proportion of males in the AE and OFG groups of patients when compared to the controls.

Table 15. Comparison Between Sex Of Controls And Disease Groups

[Statistically significant results in bold italics]

Disease Group	Sex % Male	Sex % Female	95% CI*
OLE	24.1	75.9	-15.1, 5.4
RAS	33.9	66.1	-56.0, 15.4
AE	48.9	51.1	***2.8, 37.0***
EM	45.2	54.8	*-1.2, 33.7*
OFG	57.2	42.8	***17.5, 38.9***
CONTROL	29.0	71.0	-

* 95% confidence interval for the percentage difference of the number of males (disease group minus the control group).

3.5.2.4. Geographical Area

840 patients came from either Glasgow itself (n=501) or the central belt of Scotland. One patient came from the north of Scotland and one other from the north of England. The addresses of the other 5 patients were not known. All the control subjects lived within commuting distance of Glasgow as they all worked or studied at Glasgow Dental Hospital & School .

3.5.2.5. Ethnic Origin

The ethnic origin of the patients referred for patch testing was not known as it had not been recorded at the time of examination either in the CDIU or GDH.

The majority of control subjects were of Caucasian origin (n=94), four were Asian, and two were African. The numbers of Asian and African subjects were too small to warrant separate analysis of the patch test results.

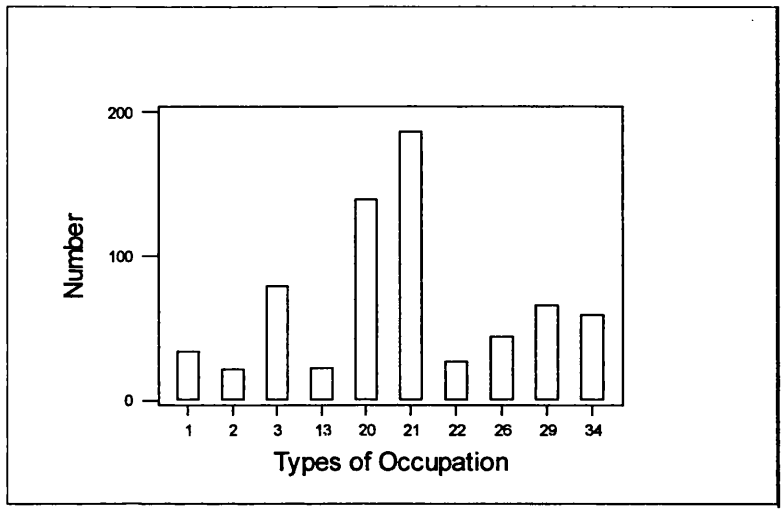
3.5.2.6. Occupation

A wide variety of occupations were represented in this group. See figs 27-29. The most common types of occupational status were; school pupils (n=186), housewives (n=139), secretarial/clerk (n=79) and retired (n=59).

In 21 (1.7%) of the 1,252 patients, the allergic reaction was considered to be of occupational significance. In a further 20 (1.6%) patients, the occupational relevance was possible but questionable.
70.4% (n=882) of the patients had no occupational relevance to their disease and in 26.3% (n=329) cases this was not recorded.

The main occupations among control subjects were dental surgeons (n=35), dental students (n=13) and nursing staff and dental surgery assistants (n=13). The proportions of these and the other occupations among the control group are shown in Fig. 30.

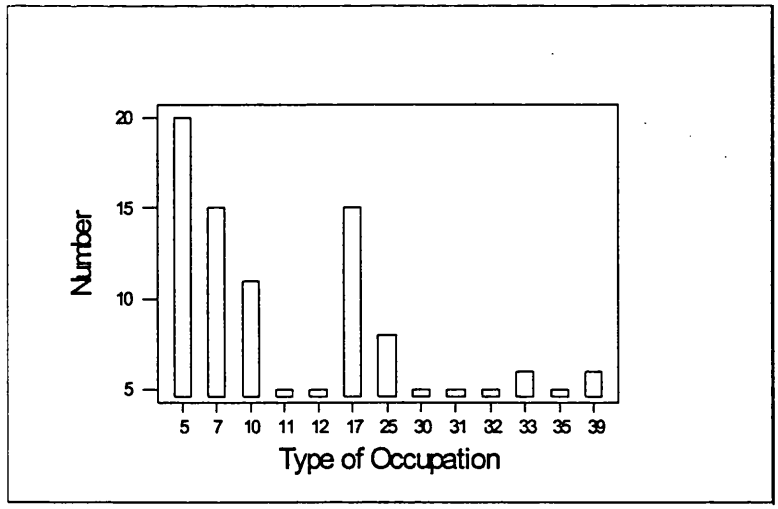
Fig. 27. Bar Chart of the Most Common Types of Occupation Among Patients



Key to Types of Occupation:

1	Teacher/Lecturer	21	School pupil
2	Shop Assistant	22	Student
3	Secretarial	26	Unemployed
13	Manager	29	Retired
20	Housewife	34	Miscellaneous

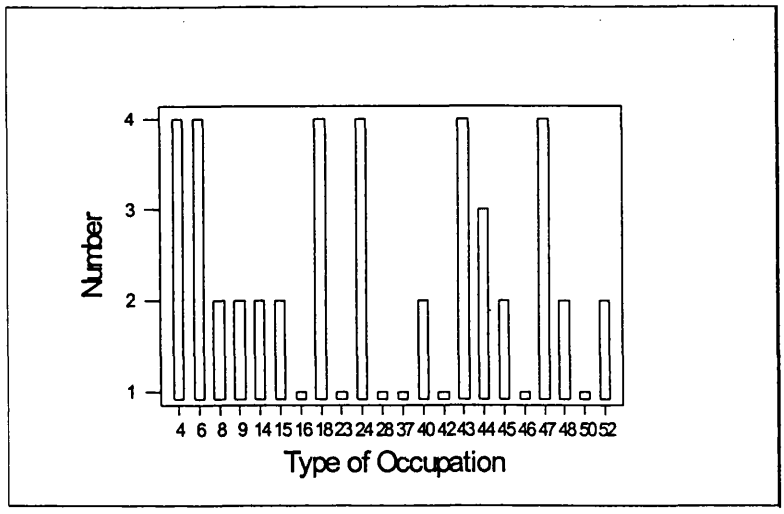
Fig. 28. Bar Chart of Types of Occupation Among Patients



Key to Types of Occupation:

5	Nurse/Dental Nurse	30	Paramedical worker
7	Factory worker	31	Auxiliary Nurse
10	Domestic	32	Welder/Tool maker
11	Catering	33	Salesman
12	Mechanic	35	Dentist/Doctor
17	Engineer	39	Architect/Surveyor
25	Driver		

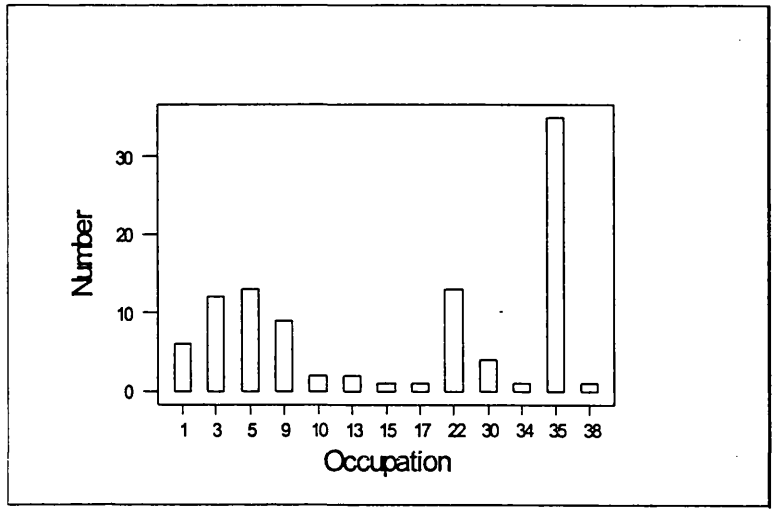
Fig. 29. Bar Chart of The Least Common Types of Occupation Among Patients



Key to Types of Occupation:

4	Hairdresser	40	Farmer/Gardener
6	Waiter	42	Postman
8	Building trade	43	Storeman
9	Technician	44	Printer
14	Electrician	45	Tailor
15	Plumber	46	Carpet fitter
16	Joiner	47	Journalist
18	Painter/Decorator	48	Foreman
23	Porter	50	Pre school age child
24	Labourer	52	Civil servant
28	Steel worker		
37	Laundrette assistant		

Fig. 30. Types of Occupation Among Control Subjects



Key to occupations:

1	Lecturer	17	Engineer
3	Secretary	22	Dental Student
5	Nurse/Dental Nurse	30	Medical photographer
9	Dental Technician	34	Miscellaneous
10	Cleaner	35	Dentist/Doctor
13	Manager	38	Science Officer
15	Plumber		

3.5.2.7. Further Characterisations of the Control Group

Skin Disease

Ten control subjects gave a history of past skin disease, which included childhood eczema (n=3), fungal infections (n=3), psoriasis (n=2) and itchy rashes on exposure to the sun (n=2).

Twenty eight gave a history of skin problems that had recently or currently affected them. Of these, eight gave a history of eczema (2 with their hands affected), another 11 described an itchy rash to unknown stimulus (3 of whom had their hands involved), four gave a history of irritation of the skin or rash produced by wearing examination gloves (3 dentists, 1 dental technician), two described an itchy rash to some soap powders, two had urticaria and one had dermatitis.

Known Intolerances

Medications - 11 control subjects gave a history of allergy to medications; six were allergic to penicillin, one to septrin, one to chloroquine, one to tetracycline, one to aspirin and one to 'Difflam' cream.

Elastoplasts – 11 control subjects gave a history of a skin reaction to elastoplasts.

Jewellery – 29 gave a history of skin reactions to this, with 28 reporting reactions to costume jewellery and one to gold. Of the 28

reacting to costume jewellery, five only had problems while wearing earrings in pierced ears.

Cosmetics/Toiletries – 13 control subjects experienced problems with these; five had skin reactions to perfumes and two to other cosmetic products.

Chemicals – five including two reporting skin problems with soap powders and one with detergents.

Fifty control subjects gave no history of skin reactions to any of the above categories.

Atopy

A total of 23 control subjects gave a history of atopy (criteria being asthma, severe childhood or adult eczema, or hay fever severe enough to warrant the use of antihistamine therapy). A further 14 control subjects had an atopic tendency (criteria being mild childhood or adult eczema, mild hay fever or migraine).

Infant Feeding Status

Forty nine control subjects had been fed from birth on infant formula and 49 were fed breast milk for a varying period of time; five for under one month, 35 for 1-6 months and nine for an unknown period of time. The remaining two control subjects were unsure of their infant feeding status.

3.5.3. Patch Test Results

The irritant reactions were not considered in this thesis, and "positive" refers to a positive allergic reaction. All positive reactions, graded 1, 2 or 3 according to the accepted scoring for patch tests as outlined earlier, were combined together in analysing the results. Equivocal test sites were considered a negative result. The percentage of positive reactions were calculated out of the number of patients tested for each allergen in each disease group. When calculating the percentages of positive reactions to the whole of a series of allergens, the maximum number of patients tested to at least one of the allergens in the series was used to avoid artificially inflating the number of positive results.

3.5.3.1. Atopy And Infant Feeding In The Control Group

There were no significant differences in the patch test results between subjects who had been bottle fed and those who had been breast fed from birth.

There were no significant differences in the patch test results between those who were atopics or had an atopic tendency and those who did not.

However, the proportion of subjects who had been bottle fed from birth was increased in the atopic group (23 out of 37 were bottle fed,

p=0.04, the 95% confidence interval for the difference in the proportions of those who were bottle fed minus the proportion of those who were breast fed was 0.011, 0.407).

3.5.3.2. Patch Test Results In The Total Number Of Referred Patients

The total number of patients who had one or more positive allergic reaction during the testing was 988 (78.9%) out of the group of 1,252. Most of these reactions (n=891, 71.2%) were to the modified European Standard Series or to the food additives, perfumes and flavourings or chocolate.

The total number of patients with OLE who had one or more positive allergic reactions during the testing was 212 (81.2%) out of the 261 patients in this group.

The total number of patients with RAS who had one or more positive allergic reactions during the testing was 230 (83.0%) out of 277 in this group.

The total number of patients with AE who had one or more positive allergic reactions during the testing was 36 (80.0%) out of the 45 patients in this group.

The total number of patients with EM who had one or more positive allergic reactions during the testing was 33 (78.6%) out of the 42 in this group.

The total number of patients with OFG who had one or more positive allergic reactions during the testing was 203 (76.7%) out of the 264 patients in this group.

Seventy out of the control group reacted positively to one or more of the allergens tested.

3.5.3.3. Notes on abbreviations, formatting and symbols used in Tables 5-14.

Abbreviations: DHT – delayed hypersensitivity test.

CUT – contact urticaria test.

95% CI – the 95% confidence interval for the difference in the number of positive reactions (disease group minus control group).

Total no. +ve – the total number of patients that had a positive reaction to the allergen.

Formatting: ***Bold italics*** indicate a significant result (p=<0.05).

Results in *italics* indicate borderline significance (p=>0.05 and <0.085).

Symbols: * indicates that the statistical results may be invalid due to the small sizes of some of the results.

3.5.3.4. Food Additives

The results of the patch tests for patients and controls for all the food additives are shown in Tables 16-18. Thirty three control subjects had one or more reactions to food additives (section 3.4.1 lists the food additives in this category). Of these, 11 had reactions to the delayed hypersensitivity tests (DHT) only and 20 reacted only to the contact urticaria tests (CUT). The other two control subjects had reactions to both types of tests but in each case to different food additives. No-one had a reaction to the same substance in both types of test.

Only three of the nine food additives elicited responses in the control subjects. These were benzoic acid, sorbic acid and sodium metabisulphite. The reaction rate between the two types of tests was 28%, 3% and 6% respectively.

Most of the positive reactions in the disease groups were also to benzoic acid (n=446), sorbic acid (n=87) and sodium metabisulphite (n=38).

Of the 222 patients with OLE who were tested to benzoic acid (in one or both of the DH and CU tests), 29.7% (n=66) had a positive reaction but this was not significantly different from the controls. 7.1% (n=15) reacted to sorbic acid in the CUT which was significant though the numbers were small enough to cast doubt on the validity of the statistical analysis.

Table 16 Positive Results to the Food Additives Series – A

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Benzoic DHT	124 (11.5)	-0.8, 9.9	*29 (13.1)*	*-0.6, 12.7*	31 (11.6)	-1.7, 10.9	***9 (25.0)***	***3.0, 33.0***	6 (14.6)	-4.3, 19.6	17 (7.1)	-5.9, 6.1	7
Benzoic CUT	***366 (33.8)***	***4.4, 21,3***	46 (20.7)	-9.9, 9.3	***106 (38.8)***	***8.0, 27.7***	10 (29.4)	-8.9, 25.7	***17 (40.5)***	***2.6, 36.3***	***110 (47.2)***	***16.0, 36.4***	21
Total no. +ve	***446 (41.5)***	***4.2, 22.8***	66 (29.7)	-8.9, 12.4	***126 (46.2)***	***7.6, 28.8***	15 (41.7)	-4.7, 32.0	***20 (47.6)***	***2.1, 37.1***	***122 (51.0)***	***12.2, 33.9***	28
Salicylic DHT	5 (0.5)	-	2 (0.9)	-	0	-	0	-	0	-	1 (0.4)	-	0
Salicylic CUT	2 (0.2)	-	0	-	0	-	1 (2.9)	-	0	-	1 (0.4)	-	0
Total no. +ve	7 (0.6)	-	2 (0.9)	-	0	-	1 (2.9)	-	0	-	2 (0.9)	-	0
Tartrazine DHT	3 (0.3)	-	0	-	0	-	0	-	0	-	1 (0.4)	-	0
Tartrazine CUT	2 (0.2)	-	0	-	1 (0.4)	-	0	-	0	-	1 (0.4)	-	0
Total no. +ve	5 (0.5)	-	0	-	1 (0.4)	-	0	-	0	-	2 (0.9)	-	0

Table 17 Positive Results to the Food Additives Series – B

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Glutamic Acid* CUT	1 (0.1)	-	0	-	0	-	0	-	0	-	1 (0.4)	-	0
BHT‡ DHT	1 (0.1)	-	0	-	0	-	0	-	0)	-	1 (0.5)	-	0
BHT CUT	1 (0.1)	-	0	-	1 (0.4)	-	0	-	0	-	0	-	0
Total no. +ve	2 (0.2)	-	0	-	1 (0.4)	-	0	-	0	-	1 (0.5)	-	0
BHA† DHT	1 (0.1)	-	0	-	1 (0.4)	-	0	-	0	-	0	-	0
BHA CUT	1 (0.1)	-	0	-	0	-	0	-	0	-	1 (0.5)	-	0
Total no. +ve	2 (0.2)	-	0	-	1 (0.4)	-	0	-	0	-	1 (0.5)	-	0

* The delayed hypersensitivity tests were negative and are not shown.
‡ Butylated hydroxytoluene
† Butylated hydroxyanisole

Table 18 Positive Results to the Food Additives Series – C

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Propylene Glycol DHT	5 (0.5)	-	1 (0.5)	-	2 (0.8)	-	0	-	0	-	1 (0.5)	-	0
Propylene Glycol CUT	1 (0.1)	-	0	-	1 (0.4)	-	0	-	0	-	1 (0.5)	-	0
Total no. +ve	5 (0.5)	-	1 (0.5)	-	1 (0.4)	-	0	-	0	-	2 (0.9)	-	0
Sorbic acid DHT	*6 (0.6)*	*-2.4, 1.6**	0	-	2 (0.8)	-2.5, 2.0*	0	-	0	-	2 (0.9)	-2.4, 2.3*	1
Sorbic acid CUT	***83 (8.1)***	*2.9, 9.3**	***15 (7.1)***	*0.7, 9.5**	***23 (8.6)***	*2.2, 10.9**	2 (6.1)	-4.5, 12.7*	*5 (12.5)*	*-0.1, 21.1**	***22 (10.3)***	*3.4, 13.3**	2
Total no. +ve	***87 (8.5)***	*1.7, 9.2**	15 (7.1)	-0.7, 8.9*	***24 (9.0)***	*1.2, 10.7**	2 (5.7)	-5.7, 11.1*	*5 (12.5)*	-1.3, 20.3*	***24 (11.1)***	*2.7, 13.5**	3
Sodium metabisulphite DHT	37 (4.7)	-4.8, 4.2	10 (5.5)	-4.9, 5.9	9 (4.6)	-5.6, 4.7	5 (17.2)	-2.2, 26.6	0	-	4 (2.5)	-7.4, 2.4*	5
Sodium metabisulphite CUT	2 (0.3)	-2.7, 1.2*	0	-	1 (0.5)	-2.7, 1.7*	0	-	0	-	1 (0.6)	-2.7, 1.9*	1
Total no. +ve	38 (4.8)	-6.1, 3.7	10 (5.4)	-6.3, 5.1	10 (5.0)	-6.5, 4.6	5 (17.2)	-3.3, 25.8	0	-	4 (2.5)	-8.8, 1.7*	6

The significant results in the RAS group of patients when compared to the 100 controls were, that there were many more reactions to CUT and to both CUT and DHT, with benzoic acid. 46.2% (n=126) had positive reactions out of a maximum of 273 tested to this allergen, compared to 28% controls. There was also a significant difference in the number of positive reactions to RAS patients tested to sorbic acid in the CUT when compared to controls though the small amount of positive reactions in the control group may have affected the validity of the statistical analysis.

Amongst the AE patients 25.0% (n=9) reacted positively to benzoic acid in the DHT which was significant compared to controls (7%).

Nearly half of the EM patients reacted to benzoic acid and this was significant in the CUT when compared to controls. The numbers of patients in this group 12.5% (5) reacting to sorbic acid yielded a result of borderline significance (p=0.052) though again the size of the positive group in the controls (2) was small which may invalidate the result.

Of the 240 patients with OFG, 47.2% (n=110) had a positive reaction to CUT with benzoic acid which was highly significant when compared to the controls. A significant number also reacted to sorbic acid.

The percentage of positive reactions to the food additives and benzoic acid in particular, across all disease groups are shown in Figs 31 and 32.

Fig. 31. Bar Chart of Positive Reactions to Food Additive Series

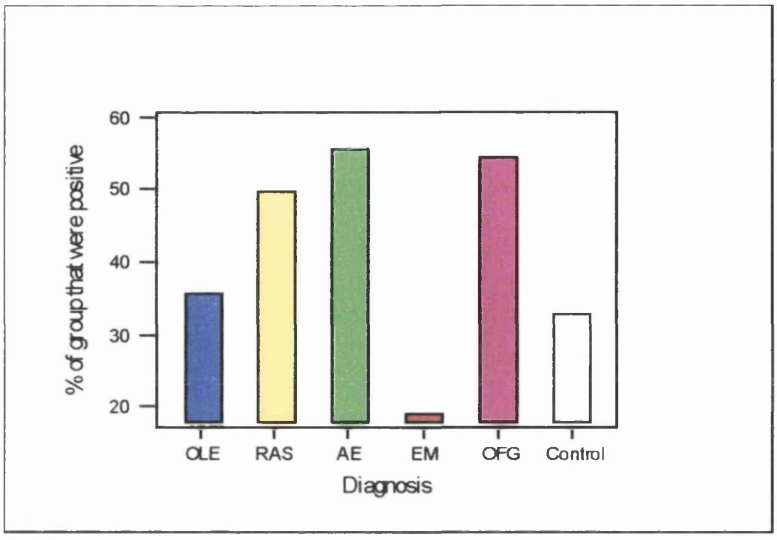
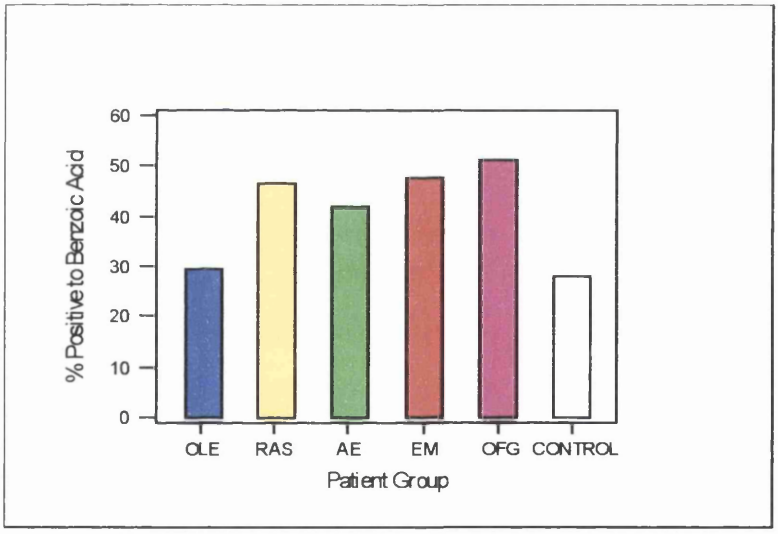


Fig. 32. Bar Chart of Positive Reactions to Benzoic Acid



As some of the patients who tested positive to some allergens in this series, also tested positive to others the total number of patients who had one or more reactions to one or more of the allergens in this series was calculated and are shown in Table 19.

In all patients, over one third had a positive reaction to one or more of the food additives tested in the CUT and nearly half when both tests were taken into account. These results were significantly higher than controls though it should be borne in mind that the control group size of 100 was small compared to the 1,082 patients who were tested to these allergens.

The RAS and OFG groups of patients had significantly more positives to the CUT compared to the control group, and the AE group had a significantly greater number of positives to the DHT.

Table 19 Positive Results Of Patients And Controls to Food Substances

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Food additives DHT	166 (15.4)	-4.5, 9.4	39 (17.6)	-3.7, 12.8	43 (16.0)	-4.9, 12.0	***14 (38.9)***	*8.7, 43.1*	5 (12.2)	-12.8, 11.2	23 (9.7)	-10.9, 4.3	13
Food additives CUT	***381 (35.2)***	*4.6, 21.8*	48 (21.6)	-10.1, 9.4	***111 (40.7)***	*8.7, 28.6*	10 (29.4)	-9.9, 24.7	5 (11.9)	-22.8, 2.6	***116 (49.8)***	*17.4, 38.1*	22
Total no. +ve	***488 (45.1)***	*2.4, 21.8*	79 (35.6)	-8.5, 13.7	***136 (49.8)***	*5.9, 27.8*	***20 (55.6)***	*3.9, 41.2*	*8 (19.0)*	*-29.0, 1.1*	***129 (54.4)***	*10.2, 32.6*	33
Perfumes and flavourings DHT	***148 (12.7)***	*4.5, 13.0**	***30 (12.9)***	*3.1, 14.6**	***30 (11.0)***	*1.6, 12.3**	***8 (19.0)***	*2.6, 27.5**	***7 (17.1)***	*0.9, 25.2**	17 (6.7)	-2.2, 7.6*	4
Perfumes and flavourings CUT	***331 (29.1)***	*17.8, 28.5*	***47 (20.1)***	*7.2, 21.0*	***92 (33.5)***	*20.2, 34.7*	***9 (23.7)***	*3.4, 32.0*	***10 (23.8)***	*4.1, 31.5*	***99 (41.3)***	*27.5, 43.0*	6
Total no. +ve	***429 (37.0)***	*21.7, 34.2*	***69 (29.5)***	*12.4, 28.6*	***112 (40.7)***	*23.7, 39.8*	***15 (35.7)***	*11.1, 42.3*	***15 (35.7)***	*11.2, 42.3*	***108 (42.7)***	*25.4, 42.0*	9
Chocolate DHT	***42 (3.9)***	*0.6, 5.1**	6 (2.7)	-1.2, 4.7*	7 (2.6)	-1.1, 4.3*	1 (2.9)	-4.0, 7.7*	2 (4.9)	-3.0, 10.7*	***17 (7.0)***	*7.0, 1.0**	1
Chocolate CUT	9 (0.8)	-	1 (0.5)	-	4 (1.5)	-	0	-	0	-	4 (1.6)	-	0
Total no. +ve	***49 (4.5)***	*1.2, 5.8**	7 (3.2)	-0.8, 5.2*	10 (3.7)	-0.3, 5.6*	1 (2.9)	-4.0, 7.7*	2 (4.8)	-3.0, 10.5*	***20 (8.2)***	*3.2, 11.2**	1

3.5.3.5. Perfumes And Flavourings

See Tables 20-23 for the results of the patch testing to these allergens. In the control group, only three out of the 11 substances elicited a response (see section 3.4.2 for listing of perfumes and flavourings in this category). Seven of the control subjects reacted to cinnamaldehyde. Of these, five had a positive reaction to the CUT only, one only to the DHT and one reacted to both. Two further patients had a positive reaction, one to geraniol and the other to oak moss absolute.

Of all the patients tested to these allergens (maximum number tested was 1161), 28.6% (n=327) reacted to cinnamaldehyde (nearly all in the CUT) and 4.2% (n=49) reacted to oak moss absolute (mostly in the DHT). As only one of the control group had a positive reaction to oak moss absolute, formal statistical analysis was not possible. Of the 234 OLE patients tested to these allergens, 16.2% (n=38) reacted to cinnamaldehyde in the CUT which was significant when compared to the control group. 6% (n=14) reacted to oak moss absolute though for the reasons outlined above, formal statistical comparison was not possible.

Table 20 Positive Results to the Perfumes and Flavourings Series A

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Cinnamyl alcohol DHT	22 (1.9)	-	4 (1.7)	-	5 (1.8)	-	1 (2.4)	-	1 (2.4)	-	5 (2.0)	-	0
Cinnamyl alcohol CUT	21 (1.8)	-	2 (0.9)	-	6 (2.2)	-	2 (5.3)	-	0	-	7 (2.9)	-	0
Total no. +ve	42 (3.7)	-	6 (2.6)	-	11 (4.0)	-	3 (7.9)	-	1 (2.4)	-	12 (5.0)	-	0
Cinnamaldehyde DHT	44 (3.8)	-1.2, 4.7*	7 (3.0)	-2.5, 4.5*	7 (2.6)	-2.8, 3.9*	4 (9.5)	-1.8, 16.8*	1 (2.4)	-5.0, 5.9*	9 (3.6)	-2.0, 5.1*	2
Cinnamaldehyde CUT	***300 (26.4)***	*15.1, 25.7*	***38 (16.2)***	*3.6, 16.9*	***86 (31.3)***	*18.1, 32.5*	***8 (21.1)***	*1.3, 28.8*	***9 (21.4)***	*2.2, 28.7*	***90 (37.5)***	*23.8, 39.2*	6
Total no. +ve	***327 (28.6)***	*16.0, 27.3*	***43 (18.4)***	*4.3, 18.4*	***89 (32.4)***	*17.9, 32.8*	***12 (28.6)***	*7.0, 36.1*	***10 (23.8)***	*3.0, 30.6*	***97 (38.3)***	*23.5, 39.1*	7
Eugenol DHT	36 (3.1)	-	9 (3.9)	-	6 (2.2)	-	2 (4.8)	-	2 (4.9)	-	4 (1.6)	-	0
Eugenol CUT	5 (0.4)	-	1 (0.4)	-	1 (0.4)	-	1 (2.6)	-	0	-	2 (0.8)	-	0
Total no. +ve	42 (3.7)	-	6 (2.6)	-	11 (4.0)	-	3 (7.9)	-	1 (2.4)	-	11 (4.6)	-	0

Table 21 Positive Results to the Perfumes and Flavourings Series B

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95 % CI	AE	95 % CI	EM	95 % CI	OFG	95% CI	Controls
Amylcinnamaldehyde DHT	8 (0.7)	-	2 (0.9)	-	1 (0.4)	-	1 (2.4)	-	1 (2.4)	-	0	-	0
Amylcinnamaldehyde CUT	7 (0.6)	-	1 (0.4)	-	3 (1.1)	-	1 (2.6)	-	0	-	1 (0.4)	-	0
Total no. +ve	14 (1.2)	-	3 (1.3)	-	4 (1.5)	-	2 (5.3)	-	1 (2.4)	-	1 (0.4)	-	0
Hydroxycitraonellal DHT	5 (0.4)	-	0	-	2 (0.7)	-	0	-	1 (2.4)	-	0	-	0
Hydroxycitraonellal CUT	2 (0.2)	-	1 (0.4)	-	0	-	1 (2.6)	-	0	-	0	-	0
Total no. +ve	7 (0.6)	-	1 (0.4)	-	2 (0.7)	-	1 (2.6)	-	1 (2.4)	-	0	-	0
Geraniol DHT	3 (0.3)	-2.7, 1.2*	0	-	0	-	0	-	0	-	0	-	1
Geraniol CUT	2 (0.2)	-	1 (0.4)	-	0	-	0	-	0	-	1 (0.4)	-	0
Total no. +ve	5 (0.4)	-2.6, 1.4*	1 (0.4)	-2.7, 1.5*	0	-	0	-	0	-	1 (0.4)	-2.7, 1.5*	1

Table 22 Positive Results to the Perfumes and Flavourings Series C

[See notes in section 3.5.3.3.]

Allergen	All patients	95 % CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95 % CI	Controls
Isoeugenol DHT	27 (2.3)	-	4 (1.7)	-	6 (2.2)	-	2 (4.8)	-	2 (4.9)	-	1 (0.4)	-	0
Isoeugenol CUT	1 (0.1)	-	0	-	0	-	0	-	0	-	0	-	0
Total no. +ve	27 (2.4)	-	0.4 (2.2)	-	6 (2.2)	-	2 (5.3)	-	2 (4.8)	-	1 (0.4)	-	0
Oak Moss Absolute DHT	***47 (4.0)***	*0.8, 5.3**	***14 (6.0)***	*1.4, 8.6**	8 (2.9)	-0.9, 4.7*	2 (4.8)	-3.0, 10.5*	0	-	5 (2.0)	-1.6, 3.6*	1
Oak Moss Absolute CUT	6 (0.5)	-	2 (0.9)	-	1 (0.4)	-	2 (5.3)	-	0	-	0	-	0
Total no. +ve	***49 (4.2)***	*1.0, 5.5**	***14 (6.0)***	*1.4, 8.6**	8 (2.9)	-0.9, 4.7*	*4 (9.5)*	*-0.6, 17.6**	0	-	5 (2.0)	-1.6, 3.6*	1

Table 23 Positive Results to the Perfumes and Flavourings Series D

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Benzyl Alcohol DHT	2 (0.2)	-	0	-	1 (0.4)	-	0	-	0	-	0	-	0
Benzyl Alcohol CUT	2 (0.2)	-	0	-	0	-	2 (5.3)	-	0	-	0	-	0
Total no. +ve	4 (0.4)	-	0	-	1 (0.4)	-	2 (5.3)	-	0	-	0	-	0
Musk Ambrette DHT	7 (0.6)	-	2 (0.9)	-	0	-	0	-	1 (2.4)	-	2 (0.8)	-	0
Musk Ambrette CUT	0	-	0	-	0	-	0	-	0	-	0	-	0
Total no. +ve	6 (0.5)	-	2 (0.9)	-	0	-	0	-	1 (2.4)	-	2 (0.8)	-	0

The only significant result in the other four disease groups was to cinnamaldehyde in the CUT, with the results from the RAS and OFG patients being highly significant.

The percentage of positive reactions to the perfumes and flavourings and to cinnamaldehyde in particular, across the disease groups are shown in Figs 33 and 34.

The reactions to the whole series of perfume and flavouring allergens (shown in Table 19) were significantly higher in all disease groups compared to controls in both types of tests (except for the DHT in the OFG group). The number of positives in the control group to the DHT in this series was small (n=4), and this should be borne in mind when considering the validity of the statistical analysis.

Fig. 33. Bar Chart of Positive Reactions to the Perfume and Flavouring Series

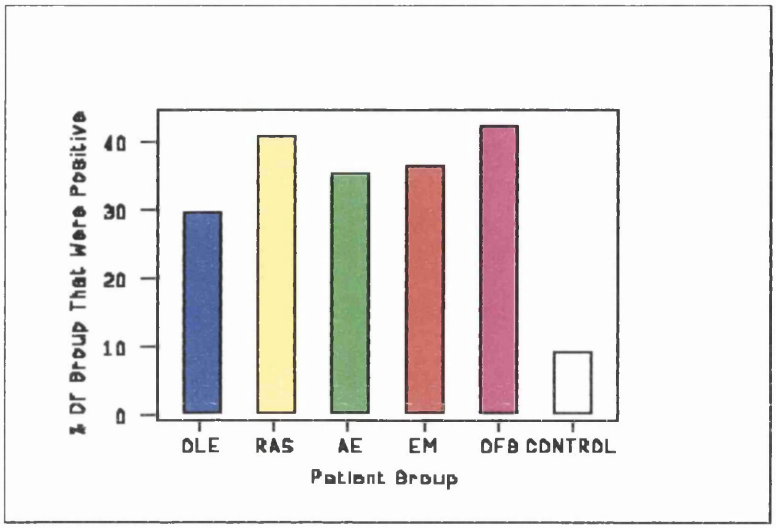
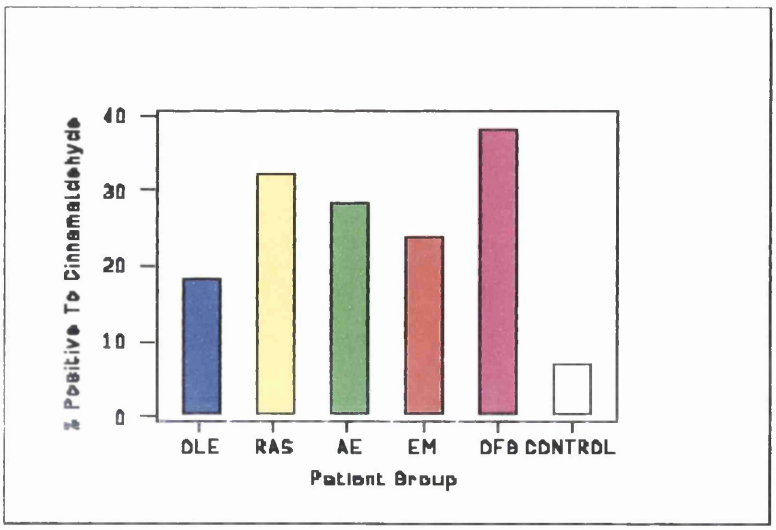


Fig. 34. Bar Chart of Positive Reactions to Cinnamaldehyde



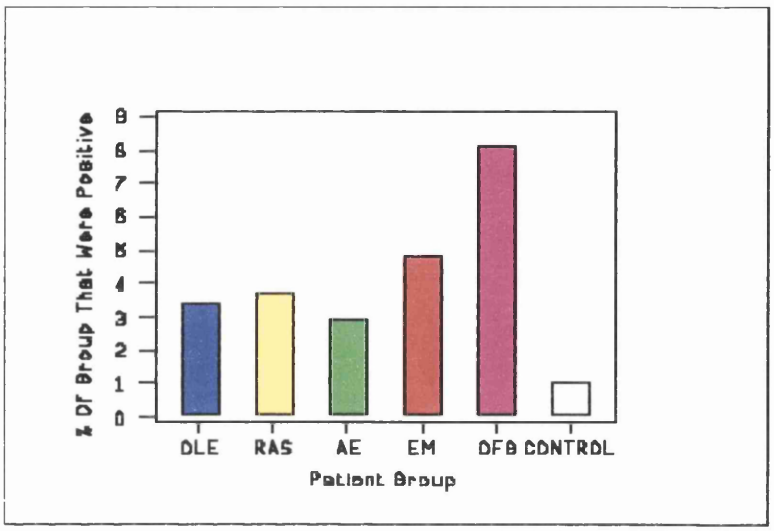
3.5.3.6. Chocolate

The results of patch testing with the chocolate allergens are shown in Table 19. together with the results to the food additive and perfumes and flavourings series as a whole.

Because of the small number of positive reactions to chocolate in the control group (one volunteer reacted to chocolate essence (in petrolatum) in the delayed hypersensitivity test), the validity of the statistical analysis must be questioned. However, of the total number of 49 who tested positive to chocolate (42 to the DHT), about 40% were in the OFG group.

The percentage of positive reactions in each group to the chocolate allergens are shown in Fig. 35.

Fig. 35. Bar Chart of Positive Reactions to Chocolate



3.5.3.7. All food substances

Table 24 shows the combined result of testing with all food substances in all the disease groups and controls.

Twenty three control subjects reacted positively to only benzoic acid, one reacted only to sorbic acid and three reacted only to sodium metabisulphite. Only two control subjects reacted only to cinnamaldehyde and the volunteer who reacted to chocolate only had that positive result. Of those who reacted to benzoic acid, most had only that reaction, whereas of those who reacted to cinnamaldehyde, most reacted to one of the food additives as well.

In total, 37 of the control subjects had a reaction to one or more food substances.

The results for the food substance (FS) allergens (food additive series, perfume and flavouring series and chocolate allergens) as a whole were significantly higher than the number of positives found among the controls. The 95% confidence interval for the difference in the percentage of positives in the disease minus the controls was over 20% in all the disease groups.

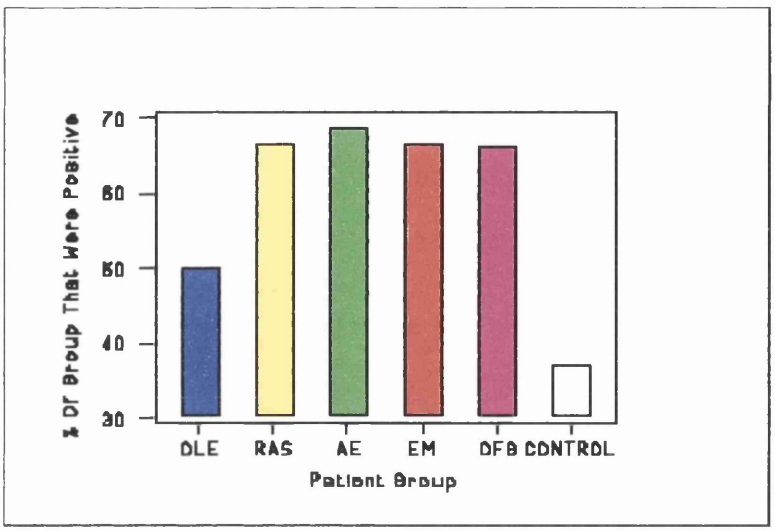
The percentage of positive reactions all of the food substances tested, are shown in Fig. 36.

Table 24 Positive Results of Patients with Oral Disease and Controls to Standard and Food Allergens

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
All Food Substances	*692 (59.6)*	*12.7, 32.5*	*117 (50.0)*	*1.6, 24.4*	*184 (66.9)*	*18.9, 40.9*	*29 (69.0)*	*15.2, 48.9*	*28 (66.7)*	*12.6, 46.8*	*168 (66.4)*	*18.3, 40.5*	37
Modified Standard European Series	*470 (37.7)*	*-21.5, -1.2*	109 (41.9)	-18.6, 4.4	*101 (36.6)*	*-23.7, -1.1*	15 (33.3)	-32.6, 1.2	*10 (24.4)*	*-41.0, -8.2*	*68 (25.9)*	*-34.3, -12.0*	49
Modified Standard European Series and Food Substances	891 (71.5)	-7.9, 10.8	169 (65.0)	-15.7, 5.7	*220 (79.7)*	*-0.4, 19.9*	35 (77.8)	-7.3, 22.9	30 (73.2)	-13.1, 19.4	194 (73.8)	-6.7, 14.2	70

Fig. 36. Bar Chart of Positive Reactions to All Food Allergens



3.5.3.8. Modified European Standard Series

The results are summarised in Table 24 and Fig. 37 and are tabulated in detail in Tables 25-30. The proportion of controls reacting to this series was significantly greater than the proportion of the RAS, EM and OFG patients and was similar to the proportion of the OLE group.

Fig. 38. shows the distribution between the disease groups of those who tested positive to the modified European Standard Series and/or the food substances.

When taken together with the FS allergens, there were no significant differences between the disease and control groups.

Seventy out of the control group reacted positively to one or more of the allergens tested. One had only an irritant reaction (to cobalt) and only 26 of the control subjects had no reactions at all.

The petrolatum test was negative in all 1,252 patients and controls.

Fig. 37. Bar Chart of Positive Reactions to the Modified Standard Series

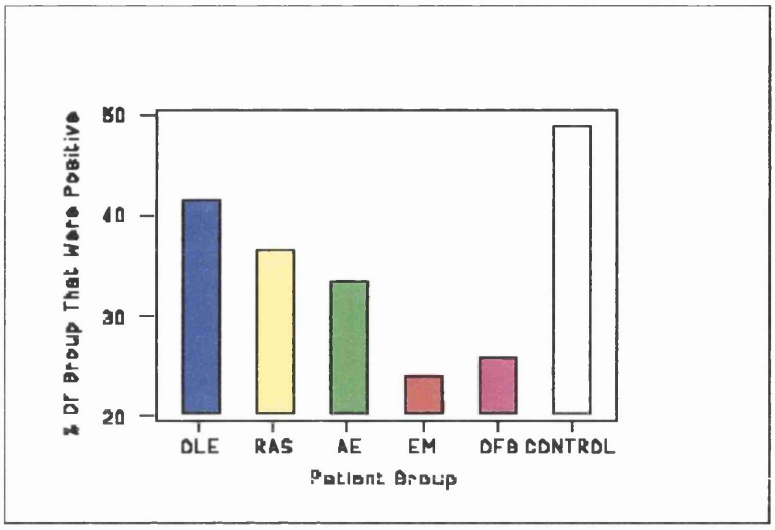


Fig. 38. Bar Chart of the Number of Patients with Positive Reactions to the Modified Standard Series and/or to Food Allergens

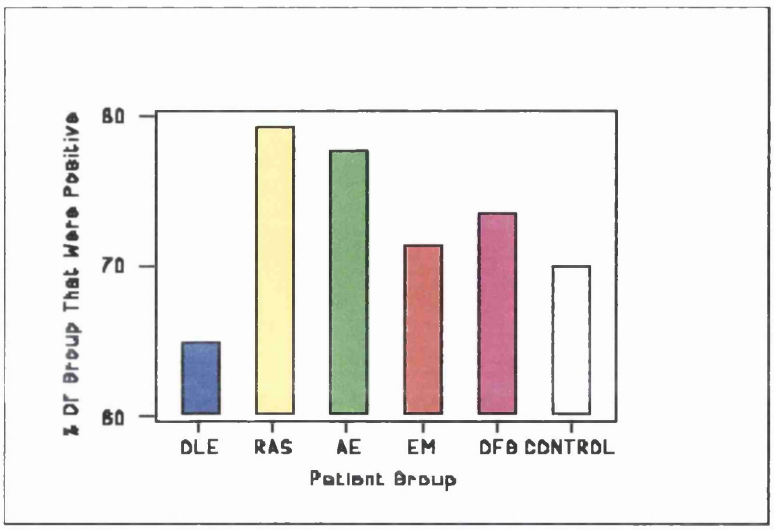


Table 25. Reactions of the Total Number of Patients to the Modified European Standard Series

Test Substance	Number patients tested	Positive Reactions	
		No.	(%)
Nickel Sulphate	1247	195	15.6
Colophony	1244	39	3.1
Cobalt Chloride	1245	40	3.2
Formaldehyde	1246	18	1.4
Potassium Dichromate	1245	16	1.3
PPD†	1244	16	1.3
Mercapto-mix	1245	7	0.6
Neomycin	1245	30	2.4
Paraben mix	1245	14	1.1
Balsam of Peru	1245	56	4.5
Thiuram-mix	1242	22	1.8
PPD†-mix	1244	1	0.08
Fragrance-mix	1230	128	10.4
Primin	1138	3	0.3
Quaternium 15	1138	7	0.6
Carba-mix	1244	8	0.6
Wool Alcohols	1246	16	1.3
PTPB# Formaldehyde Resin	1138	7	0.6
Caine-mix	1240	9	7.2
Epoxy Resin	1245	8	0.6
Quinoline	1138	8	0.7
Ethylene Diamine	1245	4	0.3
Thiomersal	1245	44	3.5
Control (Petrolatum)	1252	0	0
All of the above	1247*	470	37.7

† Paraphenylenediamine
# Paratertiarybutylphenol
* Some of these patients were not tested to all of the allergens in the series.

Table 26. Reactions Of OLE Patients And Controls To The Modified European Standard Series

[See notes in section 3.5.3.3.]

Test Substance	OLE Patients			Positive reactions in control group	p value	95% CI
	No. tested	Positive Reactions No.	%			
Nickel Sulphate	260	34	13.1	23	***0.035***	***-0.191, -0.007***
Colophony	259	1	0.4	5	***0.037****	***-0.90, -0.003***
Cobalt Chloride	260	8	3.1	3	0.97*	
Formaldehyde	260	6	2.3	0		
Potassium Dichromate	260	3	1.2	2	0.585*	
PPD†	260	4	1.5	1	0.668*	
Mercapto-mix	260	1	0.4	0		
Neomycin	260	7	2.7	1	0.231*	
Paraben mix	260	3	1.2	0		
Balsam of Peru	260	19	7.3	4	0.25	
Thiuram-mix	260	2	0.8	1	0.839*	
PPD†-mix	260	1	0.4	0		
Fragrance-mix	260	35	13.5	6	***0.019***	***0.012, 0.137***
Primin	235	0	0.0	0		
Quaternium 15	235	0	0.0	0		
Carba-mix	260	0	0.0	0		
Wool Alcohols	260	6	2.3	0		
PTPB resin#	235	1	0.4	0		
Caine-mix	260	2	0.8	0		
Epoxy Resin	260	0	0.0	1		
Quinoline	235	1	0.4	0		
Ethylene Diamine	260	1	0.4	0		
Thiomersal	260	20	7.7	21	***0.002***	***-0.219, -0.047***
Control (Petrolatum)	261	0	0.0	0		
All	260§	109	41.9	49	0.227	

† Paraphenylenediamine
# Paratertiarybutylphenol formaldehyde resin
§ Some of these patients were not tested to all of the allergens in the series. Chi Squared Test used.
* Small numbers may make test invalid.

Table 27. Reactions Of RAS Patients And Controls To The Modified European Standard Series

[See notes in section 3.5.3.3.]

Test Substance	RAS patients			Positive reactions in control group	p value	95% CI
	No. tested	Positive Reactions No.	%			
Nickel Sulphate	276	54	19.6	23	0.478	
Colophony	276	9	3.3	5	0.474	
Cobalt Chloride	276	10	3.6	3	0.76	
Formaldehyde	276	5	1.8	0		
Potassium Dichromate	276	4	1.45	2	0.726*	
PPD†	276	0	0	1		
Mercapto-mix	276	0	0	0		
Neomycin	276	5	1.8	1	0.526*	
Paraben mix	276	6	1.2	0		
Balsam of Peru	276	11	4.0	4	0.995	
Thiuram-mix	276	3	1.1	1	0.941*	
PPD†-mix	276	0	0	0		
Fragrance-mix	276	25	9.1	6	0.298	
Primin	273	0	0	0		
Quaternium 15	273	3	1.1	0		
Carba-mix	276	0	0	0		
Wool Alcohols	276	2	0.72	0		
PTPB# Resin	273	1	3.7	0		
Caine-mix	276	2	0.72	0		
Epoxy Resin	276	1	3.6	1	0.547*	
Quinoline	273	2	0.73	0		
Ethylene Diamine	276	2	0.72	0		
Thiomersal	276	10	3.6	21	***0.000***	***-0.257, -0.091***
Control (Petrolatum)	277	0	0	0		
All	276§	88	31.9	49	***0.005***	***-0.284, -0.059***

† Paraphenylenediamine
# Paratertiarybutylphenol formaldehyde resin
§ Some of these patients were not tested to all of the allergens in the series. Chi Squared Test used.
* Small numbers may make test invalid.

Table 28. Reactions Of AE Patients And Controls To The Modified European Standard Series

[See notes in section 3.5.3.3.]

Test Substance	AE patients			Positive reactions in control group	p value	95% CI
	No. tested	Positive Reactions No.	%			
Nickel Sulphate	45	9	20.0	23	0.681	
Colophony	45	1	2.2	5	0.369	
Cobalt Chloride	45	2	4.4	3	0.681	
Formaldehyde	45	0	0.0	0		
Potassium Dichromate	45	0	0.0	2		
PPD†	44	2	4.5	1	0.282*	
Mercapto-mix	45	0	0.0	0		
Neomycin	45	0	0.0	1		
Paraben mix	45	0	0.0	0		
Balsam of Peru	45	2	4.4	4	0.903*	
Thiuram-mix	45	1	2.2	1	0.612*	
PPD†-mix	45	0	0.0	0		
Fragrance-mix	44	5	11.4	6	0.264	
Primin	37	0	0.0	0		
Quaternium 15	37	0	0.0	0		
Carba-mix	45	0	0.0	0		
Wool Alcohols	45	0	0.0	0		
PTPB# Resin	37	1	2.7	0		
Caine-mix	44	0	0.0	0		
Epoxy Resin	45	0	0.0	1		
Quinoline	45	0	0.0	0		
Ethylene Diamine	45	5	0.0	0		
Thiomersal	45	0	0.0	21		
Control (Petrolatum)	45	0	0.0	0		
All	45§	15	33.3	49	*0.069*	*-0.326, 0.012*

† Paraphenylenediamine
# Paratertiarybutylphenol formaldehyde resin
§ Some of these patients were not tested to all of the allergens in the series. Chi Squared Test used.
* Small numbers may make test invalid.

Table 29. Reactions Of EM Patients And Controls To The Modified European Standard Series

[See notes in section 3.5.3.3.]

Test Substance	EM patients			Positive reactions in control group	p value	95% CI
	No. tested	Positive Reactions No.	%			
Nickel Sulphate	41	5	12.2	23	0.103	
Colophony	41	1	2.4	5	0.431*	
Cobalt Chloride	41	1	2.4	3	0.849*	
Formaldehyde	41	0	0.0	0		
Potassium Dichromate	41	0	0.0	2		
PPD†	41	0	0.0	1		
Mercapto-mix	41	0	0.0	0		
Neomycin	41	1	2.4	1	0.581*	
Paraben mix	41	0	0.0	0		
Balsam of Peru	41	0	0.0	4		
Thiuram-mix	41	2	4.9	1	0.269*	
PPD†-mix	41	0	0.0	0		
Fragrance-mix	41	2	4.9	6	0.785*	
Primin	41	0	0.0	0		
Quaternium 15	41	1	2.4	0		
Carba-mix	41	0	0.0	0		
Wool Alcohols	41	0	0.0	0		
PTPB# Resin	41	0	0.0	0		
Caine-mix	41	1	2.4	0		
Epoxy Resin	41	0	0.0	1		
Quinoline	41	0	0.0	0		
Ethylene Diamine	41	0	0.0	0		
Thiomersal	41	0	0.0	21		
Control (Petrolatum)	42	0	0.0	0		
All	41	10	24.4	49	***0.003***	***-0.410, -0.082***

† Paraphenylenediamine
# Paratertiarybutylphenol formaldehyde resin
* Small numbers may make test invalid.

Table 30. Reactions Of OFG Patients And Controls To The Modified European Standard Series

[See notes in section 3.5.3.3.]

Test Substance	OFG patients			Positive reactions in control group	p value	95% CI
	No. tested	Positive Reactions No.	%			
Nickel Sulphate	263	28	10.6	23	***0.007***	***-0.214, -0.033***
Colophony	261	7	2.7	5	0.337	
Cobalt Chloride	261	1	0.4	3	0.134*	
Formaldehyde	262	4	1.5	0		
Potassium Dichromate	261	1	0.4	2	0.265*	
PPD†	261	4	1.5	1	0.671*	
Mercapto-mix	261	1	0.4	0		
Neomycin	261	4	1.5	1	0.671*	
Paraben mix	261	2	0.8	0		
Balsam of Peru	261	9	3.4	4	0.807*	
Thiuram-mix	261	4	1.5	1	0.671*	
PPD†-mix	261	0	0.0	0		
Fragrance-mix	254	7	2.8	6	0.13	
Primin	232	0	0.0	0		
Quaternium 15	232	2	0.9	0		
Carba-mix	261	2	0.8	0		
Wool Alcohols	262	5	1.9	0		
PTPB# Resin	232	1	0.4	0		
Caine-mix	261	1	0.4	0		
Epoxy Resin	261	4	1.5	1	0.671*	
Quinoline	232	0	0.0	0		
Ethylene Diamine	261	0	0.0	0		
Thiomersal	261	7	2.7	21	***0.000***	***-0.265, -0.101***
Control (Petrolatum)	264	0	0.0	0		
All	263	68	25.9	49	***0.000***	***-0.343, -0.120***

† Paraphenylenediamine
# Paratertiarybutylphenol formaldehyde resin
Chi Squared Test used.
* Small numbers may make test invalid.

Out of the total number of patients, 195 reacted positively to nickel, 12 (6.2%) were male and 183 (93.8%) were female. The sex distribution of those patients who had a positive reaction to nickel according to diagnosis is shown in Table 31, and the percentages of each disease group with positive reactions to nickel are shown in Fig 39.

Significantly more control subjects than patients in the OLE group reacted to nickel, colophony and to thiomersal, though the numbers were small to colophony and valid statistical comparison was impossible. The proportion of positive reactions to the fragrance mix was in the opposite direction with 13.5% of OLE patients to 6% of controls. Positives to thiomersal were significantly more prevalent in controls than in RAS and OFG patients, see Fig 40. Because of the high incidence of thiomersal allergy in the control sample group (21%) which skewed the totals, these totals were calculated without the thiomersal results being considered. The results of these are shown in Table 32. This changed the results considerably, in that only the OFG group had more positives to the modified European Standard Series compared to the control group ($p=0.043$). When the results of the tests to the modified European Standard Series and FS allergens were combined, RAS, AE and OFG patients all showed a significantly greater proportion of positive reactions than control subjects with the 95% confidence interval being greater than 20% in each case.

There were no significant differences between the numbers of positive reactions to individual allergens in AE or EM patients when compared to controls, though the total number of positives in the EM group was significantly less than the total in the control group.

Table 31. Sex Distribution of Patients With Positive Reactions to Nickel

Disease Group	No. (%) Male	No. (%) Female
OLE	2 (5.9)	32 (94.1)
RAS	5 (9.3)	49 (90.7)
AE	0	8 (100)
EM	0	5 (100)
OFG	4 (14.3)	24 (85.7)
All patients	12 (6.2)	183 (93.8)
Controls	1 (4.3)	22 (95.7)

Fig. 39. Bar Chart Of Positive Reactions To Nickel

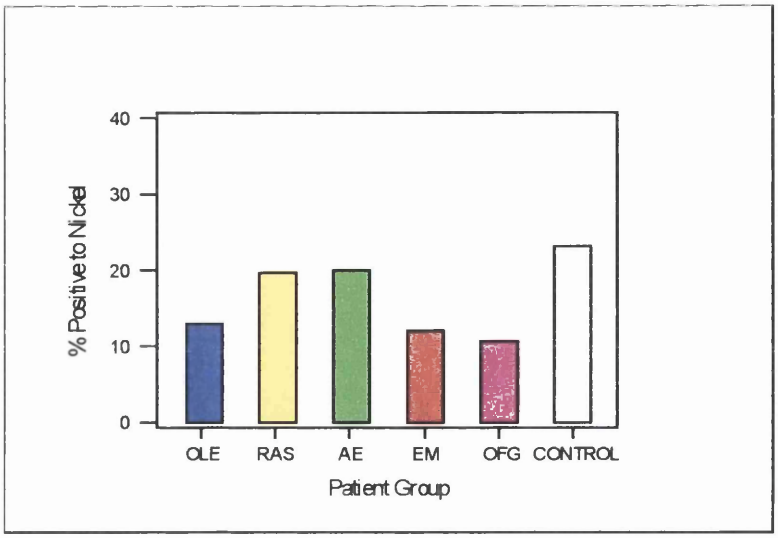


Fig. 40. Bar Chart Of Positive Reactions To Thiomersal

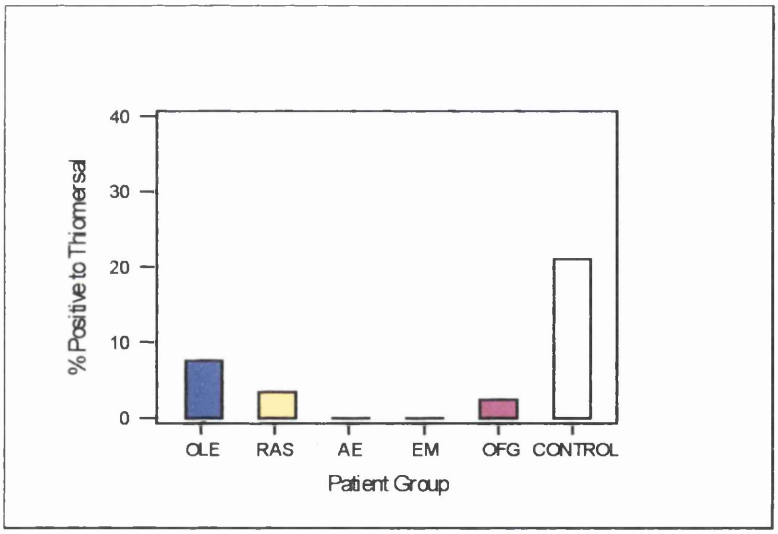


Table 32 Positive Results to the Modified European Standard Series Except Thiomersal

[See notes in section 3.5.3.3.]

Allergen	All patients	95% CI	OLE	95% CI	RAS	95% CI	AE	95% CI	EM	95% CI	OFG	95% CI	Controls
Modified Standard European Series excluding thiomersal	446 (35.8)	-9.0, 10.5	102 (39.2)	-6.8, 15.3	98 (35.5)	-10.4, 11.4	15 (33.3)	-18.3, 15.0	10 (24.4)	-26.7, 5.5	***63 (24.0)***	*-21.7, -0.4*	35
Modified Standard European Series excluding thiomersal and food substances	***879 (70.5)***	*0.6, 20.4*	162 (62.3)	-9.0, 13.6	***219 (79.3)***	*8.6, 30.1*	***35 (77.8)***	*2.3, 33.3*	30 (73.2)	-3.4, 29.8	***192 (73.0)***	*2.0, 24.0*	60

3.5.3.9. Results of Testing With Mercurials

Of the total number of patients (n=1,252), 1,244 were tested to thiomersal in the modified European Standard Series. A total of 241 were tested to the organic mercurials series which included mercury 0.5%, ammoniated mercury 1%, phenyl mercuric nitrate 0.05% and thiosalicylic acid 0.1%. Sixty of these and 226 further patients were tested to crushed amalgam 30% and ammoniated mercury 2%. These two series are referred to as the mercury and amalgam series. Phenyl mercuric acetate 0.05% was included in a number of different allergen series and out of 1,114 patients tested, 16 (1.4%) had a positive reaction to it. A total of 1,166 patients were tested to one or more other (not including thiomersal) mercurial allergens though most of these were only tested with thiomersal and phenyl mercuric acetate. Because of the different mercurials that patients were tested to, the results are differentiated into two groups of mercurials: those mercurials that act as preservatives, thiomersal and phenyl mercuric acetate, and those more closely related to amalgam restorations (the rest). The results are shown in Table 33 (thiomersal, phenyl mercuric acetate and the total all mercurials) and Table 34 (mercury and amalgam series). The OLE patients were statistically more likely to have a positive patch test to thiomersal or to allergens in the mercury and amalgam series than RAS and OFG patients (the numbers of positives in AE and EM patients were too small to analyse).

Table 33. Positive Reactions to Thiomersal and Phenyl Mercuric Acetate

[significant results indicated by bold italics ($p<0.05$)]

Disease Group	Thiomersal No. +ve (%)[#]	Phenyl mercuric acetate No. +ve (%)[#]	All mercurials No. (%)[#]
OLE	20 (7.7)	10 (4.2)	99 (8.0)
RAS	***10 (3.6)*** ***p=0.042***[a]	2 (0.80)	22 (1.8)
AE	0	0	0
EM	0	0	4 (0.3)
OFG	***7 (2.7)*** ***p=0.01***[b]	2 (1.0)	14 (1.1)
ALL PATIENTS	44 (3.2)	16 (1.4)	166 (13.3)

[#] Of those tested

Statistical analysis compared RAS, AE, EM and OFG groups to the OLE group

[a] 95% confidence interval for the difference in the proportion (%) of positive reactions (OLE group minus RAS group) (0.2, 8.0%).

[b] 95% confidence interval for the difference in the proportion (%) of positive reactions (OLE group minus OFG group) (1.2, 8.8%).

Table 34. Positive Reactions to Mercury and Amalgam Series'

[significant results indicated by bold italics ($p<0.05$)]

Disease Group	Mercury/Amalgam Series'	
	No. Tested[#]	No. patients positive (%)
OLE	201	91 (45.3)
RAS	80	***15 (18.8)***[a] ***p=<0.000***
AE	7	0
EM	15	4 (26.7) p=0.12*
OFG	53	***8 (15.1)***[b] ***p=<0.000***
ALL PATIENTS	467	140 (30.0)

[#] To one or more of these allergens.
Statistical analysis compared RAS, AE, EM and OFG groups to the OLE group
* The normal approximation may be inaccurate for small samples.
[a] 95% confidence interval for the difference in the proportion (%) of positive reactions (OLE group minus RAS group) (15.5, 37.5%).
[b] 95% confidence interval for the difference in the proportion (%) of positive reactions (OLE group minus OFG group) (18.3, 42.0%).

There was also a statistically significant difference in the number of positives in the OLE group when compared to all other patients (p=002, 95% confidence interval for the difference in the proportion (%) of positive reactions (OLE group minus the 'all other patients' group) was (1.9, 8.6))

3.5.4. Outcome Of Dietary Avoidance Of Relevant Allergens.

3.5.4.1. Analysis Of Responses

Number Of Responses

Of the 476 questionnaires that were sent out to patients, 275 (57.8%) questionnaires were returned to the department. Of these, 44 were returned by the postal service marked "not at this address", one couldn't remember much of the details of the clinic attendances and results as she had attended over 7 years previously, and one patient had died in the intervening period since patch testing. There were no significant differences between the age ($p=0.53$) and sex ($p=0.396$) of those who responded and those who did not respond to the questionnaire.

Number Filled Out Correctly

Of the 229 patients that did fill out the form, 214 (83.6%) completed the form correctly. Three patients only filled out one side of the questionnaire and a further 43 had incorrectly completed one or more of the linear analogue scales. However some of these ($n=18$) had indicated their answer by writing at the side of the scale and these were allocated an estimate based on that information.

Diet Advice

A total of 24 patients responded that they had never received written diet advice from the dietician at the CDIU department though they all would

have received verbal advice by a trained nurse at the clinic on their last visit. Fourteen of these patients went on to claim that they attempted to follow the advice given, presumably the verbally given diet advice, to a greater or lesser extent. The other 10 patients indicated that the question was not applicable to them or left it blank.

Estimate Of Cooperation With Diet Advice

Fifiteen patients left this blank. Of the 204 that answered this part, the scores were graded into 5 categories according to how well they complied with the diet advice;

0 = Not at all,

1-3 = Poor,

4-6 = Moderate,

7-9 = Good

10 = Fully.

The results were that most patients considered that they had shown good or full compliance with the diet advice and are shown in Table 35. There were no significant differences in the ages or sex of patients that indicated poor, moderate or full – good compliance with the diet advice (95% confidence intervals not shown).

Table 35. The Dietary Advice Compliance Scores For All Patients

Diagnosis	Total Number	Left blank	COMPLIANCE				
			No	Poor	Moderate	Good	Full
OLE	67	6	0	6	9	24	22
RAS	87	4	2	6	19	29	27
AE	5	0	2	0	1	0	2
EM	6	1	0	0	2	2	1
OFG	64	4	0	3	5	20	32
TOTAL	229	15	4	15	36	75	84

Estimate Of Pre-Testing Symptoms

A total of 231 patients completed this part correctly and again the scores were divided into 5 categories according to their symptoms:

0 = None,

1-3 = mild,

4-6 = moderate,

7-9 = severe

10 = most severe.

Most patients recorded scores of severe symptoms or above for their pre patch testing score with the median score being 8.21. The results are shown in more detail in Table 36.

Estimate Of Post-Testing Symptoms

A total of 224 patients answered this part and the scores were divided into 5 categories according to their symptoms as described above. The majority of patients recorded a lower score for their symptoms after their patch testing and subsequent dietary changes. The results are shown in Table 37.

Table 36. The Pre Patch Testing Symptom Scores

Diagnosis	Left	Pre Patch Testing Symptoms				
	blank	None	Mild	Moderate	Severe	Most severe
OLE	3	0	8	6	25	25
RAS	1	0	3	5	24	54
AE	0	0	0	2	2	1
EM	0	0	0	0	1	5
OFG	2	0	2	8	20	32
TOTAL	6	0	13	21	72	117

Table 37. The Post Patch Testing Symptom Scores

Diagnosis	Left	Post Patch Testing Symptoms				
	blank	None	Mild	Moderate	Severe	Most severe
OLE	3	2	27	12	15	8
RAS	4	1	32	26	15	9
AE	1	1	0	2	0	1
EM	1	0	1	1	1	2
OFG	3	3	32	13	6	7
TOTAL	12	7	92	54	37	27

Change in symptoms

This was calculated by subtracting the post testing symptom score from the pre testing score and the results were divided into 8 categories;

-9 - -7 = symptoms much worse

-6 - -4 = symptoms moderately worse

-3 - -1 = symptoms slightly worse

0 = no change

1–3 = slight improvement

4-6 = moderate improvement

7-9 = marked improvement

10 = maximum improvement

In 44 patients, the change could not be calculated because there was not enough information. Most patients had an improvement in their symptoms after patch testing with the average symptom score improving by 4.31. The results are shown in Table 38.

44 patients were concurrently taking medication(s) that could have caused OLE reactions in the mouth. Only 22 of these had OLE and none of these patients attributed any of their improvement to changing their medications. In those who experienced marked to maximum improvement (n=63), some patients attributed other factors as well as the dietary change. These were: replacement of amalgam restorations (n=8), steroid therapy (n=2), replacement of denture (n=2), changing toothpaste brand (n=1), avoiding certain metals (n=1), iron replacement therapy (n=1) and taking antihistamine therapy (n=1).

Table 38. Change in Symptom Scores

Diagnosis	Left	Change In Symptoms							
	blank	-9- -7	-6 - -4	-3 - -1	0	1 - 3	4 - 6	7 - 9	10
OLE	5	2	3	2	13	15	11	14	2
RAS	4	0	0	4	12	17	29	20	1
AE	0	0	0	1	2	0	0	1	0
EM	1	0	0	0	2	1	1	1	0
OFG	3	0	2	0	10	11	14	22	2
TOTAL	14	2	5	7	39	34	55	58	5

Results Of Dietary Avoidance Among Those Who Showed Good To Full Compliance With Advice.

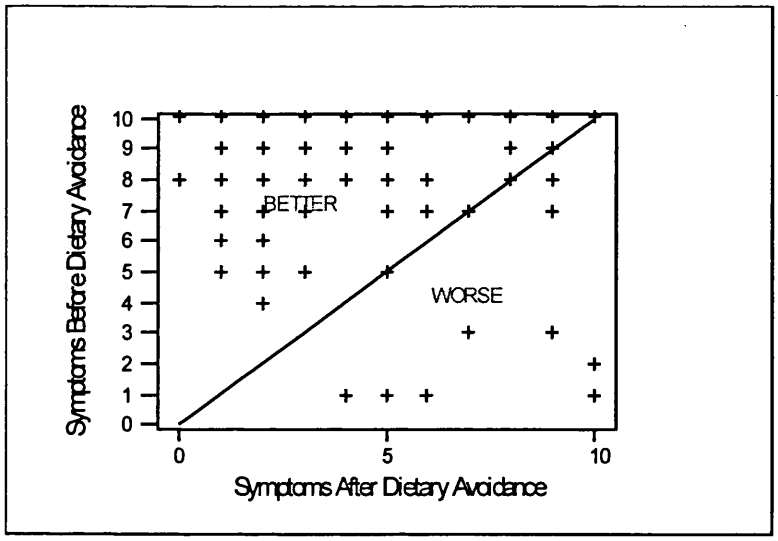
A total of 159 patients indicated by a score of 7 – 10 that they had complied with the dietary avoidance advice given. The mean pre testing score of symptoms was 8.7 and the mean post testing score was 4.7. Thus the mean improvement in this motivated group was 4.0. The improvement scores by disease category are shown in Table 38, and these are illustrated by plotting the pre testing symptom scores against the post testing symptom scores in Fig 41.

The pre testing symptom scores were significantly higher than the symptom scores after dietary advice, p=0.04.

Table 39. Response to avoidance therapy among patients with oral mucosal disease who showed good compliance

Disease Group	Number Replying	Good compliance n (%)	Average pre-test score	Average post- diet score	Average change in symptoms
OLE	52	46 (68.7)	7.8	5.0	2.8
RAS	85	56 (64.4)	9.4	4.9	4.5
AE	4	2 (40.0)	7.5	7.5	0
EM	6	3 (33.3)	9.7	7.3	2.4
OFG	61	52 (81.3)	8.8	3.9	4.9

Fig. 41. Results Of Dietary Avoidance In Patients With Good Compliance



Results Of Dietary Avoidance Among Those Who Showed Poor And Moderate Compliance

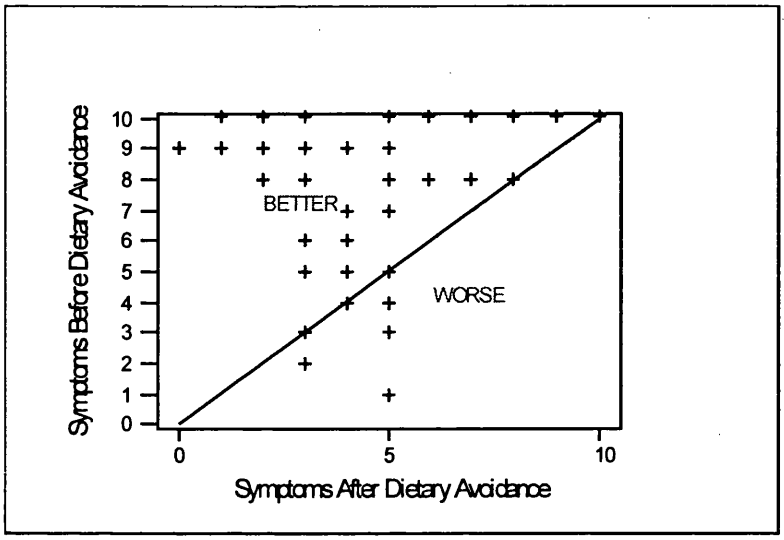
The response to the dietary advice in those who had indicated poor compliance (scores 0 – 3) and those who had indicated moderate compliance (scores 4-6) to the dietary advice are shown in Table 39. Moderate compliance results are shown in square brackets. The pre testing symptom scores were higher than the post dietary advice symptoms in the moderate compliance group (p=0.021) and also higher in those with poor compliance to dietary advice though this was of borderline significance (p=0.068). The results of dietary avoidance are shown in Fig 42. Though the numbers of patients were small especially in the AE and EM categories, most improvement was in the region of a decrease of the symptom score of between 2 - 3.5.

There were no significant differences in the improvement scores between those with good, moderate or poor compliance, in the three patient groups with large enough numbers to analyse. The p values for the analysis of variance for each of the three groups were; OLE p=0.94, RAS p=0.473 and OFG p=0.172.

Table 40. Response to avoidance therapy among patients with oral mucosal disease who showed poor and [moderate] compliance

Disease Group	Number Replying	Poor [moderate] compliance n (%)	Average pre-test score	Average post- diet score	Average change in symptoms
OLE	67	6 (9.0) [9 (13.4)]	6.8 [7.6]	5.3 [4.8]	1.5 [2.8]
RAS	87	6 (6.9) [19 (21.8)]	9.7 [7.6]	5.4 [4.2]	4.3 [3.4]
AE	5	0 [1 (20.0)]	- [4.0]	- [5.0]	- [-1.0]
EM	6	0 [2 (33.3)]	- [10.0]	- [6.5]	- [3.5]
OFG	64	3 (4.7) [5 (7.8)]	8.3 [6.6]	5.3 [4.6]	3.0 [2.0]

Fig. 42. Results Of Dietary Avoidance In Patients With Poor Or Moderate Compliance



3.5.4.2. Analysis by disease category

Oral lichenoid eruption

Of those who experienced moderate to maximum symptomatic improvement (improvement score 4-10, n=25), 8 patients (50%) attributed the improvement to the removal of their amalgam restorations as well as to the diet. This figure was much higher than the only other disease group that had a patient attribute the improvement to amalgam replacement, one out of the RAS group (2.3%). The value for this difference was. p=0.002 (the 95% confidence interval for the difference in the percentage of OLE patients attributing amalgam minus the percentage of RAS patients attributing their improvement to amalgam was; 10.8%, 48.5%).

Of those who showed good to full compliance (score 7-10), the improvement is shown in Table 39 and Fig 43.

Recurrent aphthous stomatitis

Questionnaires were received back from 87 patients with RAS and 56 (65.9%) showed good to full compliance. The average improvement in symptom scores for this group was of 4.3, with most of the patients starting with severe symptoms that after dietary modifications, were scored as mild symptoms. See Tables 39 and 40, and Fig 44.

Fig. 43. Results Of Dietary Avoidance In OLE Patients With Good Compliance

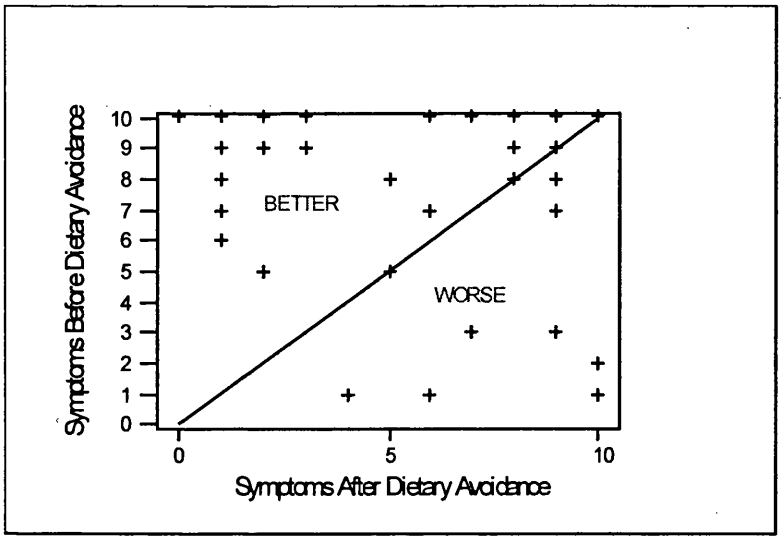
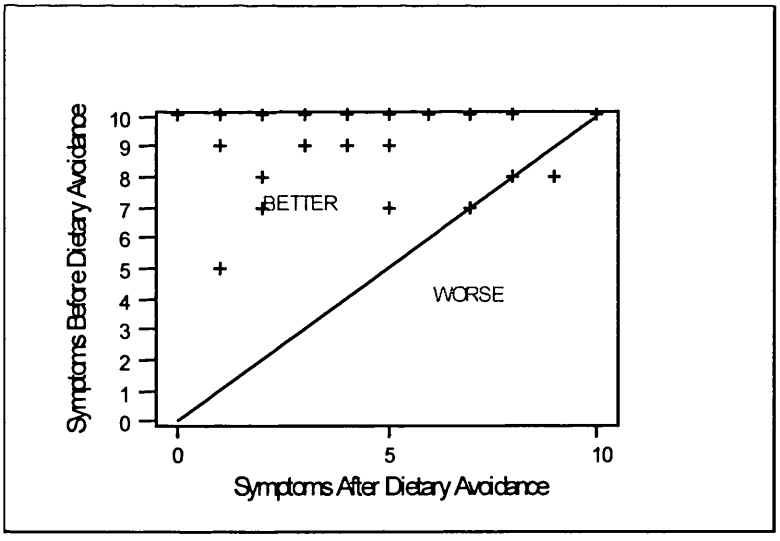


Fig. 44. Results Of Dietary Avoidance In RAS Patients With Good Compliance



Angioedema

Five questionnaires were received from patients with AE and of these, two indicated that they complied well with advice given (score 7-10). However their pre and post testing symptom scores showed no change (average of 7.5) so no improvement was noted. However, the numbers of received questionnaires were so small as to question the meaning of any analysis.

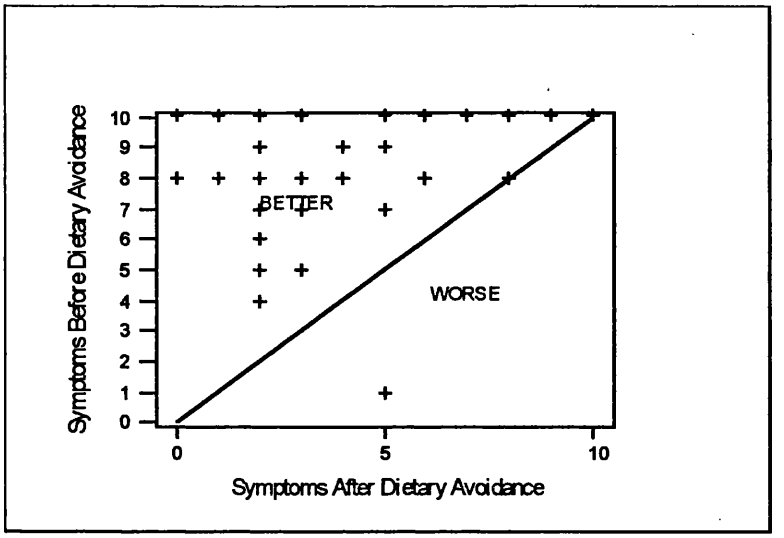
Erythema multiforme

Of the six questionnaires received, three patients showed good to full compliance but only one indicated improvement and the other two reported no change in their symptoms. It should be noted here that 10 of the 42 EM patients were also taking medications that could cause EM eruptions. These drugs were: aspirin, indocid, feldine, naproxin, carbamazepine, phenytoin and dihydrocoedine. Two of the EM patients who replied to the questionnaire were in this category though none claimed that their improvements was due to drug change or avoidance. However, the numbers of questionnaires received from the patients in this group were so small that analysis is meaningless.

Oro-facial granulomatosis

A total of 64 questionnaires were received and 52 (81.3%) of these showed good to full compliance. The average pre and post testing scores were 8.5 and 4.0 respectively and overall the average improvement was by a score of 4.5, see Tables 39 and 40 and Fig 45.

Fig. 45. Results Of Dietary Avoidance In OFG Patients With Good Compliance



CHAPTER 4: HISTOPATHOLOGY STUDIES

4.1. Introduction

Histopathology is essentially a subjective art that is brought to excellence by years of experience and gain in knowledge of the microscopic findings of various diseases. While variation in classifications of various microscopic findings between examiners is expected due to the subjective nature of the discipline, variation in the findings of the same examiner looking at the same section is also common (Smith & Pindborg 1969). In order to minimise this and to assist in increasing the reproducibility of findings between different examiners and between repeated examinations of the same section by the same examiner, some authors have devised photographic standards of histological and cellular features that aid in both identifying and grading the features found (Smith & Pindborg 1969). The aim in using these is to focus attention on one microscopic feature at a time and using photographic standards, to visually assess which of the photographs (showing a range of different appearances of individual features that are ordered in severity) is most like the field in question.

A subgroup of the oral lichenoid eruption (OLE) patients investigated in Chapter 3 were also investigated by histological examination. Specimens obtained from OLE patients were examined to see if it was possible to assess by histological examination, whether there were any differences in the microscopic appearance of specimens from patients whose OLE could have been caused by a variety of factors. Those factors that were investigated were: the presence of amalgam dental restorations, taking

medications that are associated with the development of OLE, and hypersensitivity to food additives and flavourings, mercurials and other allergens. As iron deficiency anaemia results in atrophy of the oral epithelium (Ranasinghe et al. 1983), the ferritin levels were also assessed as an atrophic epithelium would increase the likelihood of antigen penetration of the epithelium and hence sensitisation. Normal ferritin levels are found between 25 and 300ng/ml and a level of under 25ng/ml was considered to indicate latent or actual iron deficiency.

4.2. Patients

Consecutive patients from Glasgow Dental Hospital and School, Oral Medicine Clinic, who fulfilled the following criteria:

- clinical diagnosis of an oral lichenoid reaction
- biopsy from buccal mucosa, avoiding the occlusal line
- histological diagnosis of an oral lichenoid eruption
- attended CDIU at Belvidere/GRI for patch testing

The number of patients fulfilling the above criteria was 42. All pathological slides made from the specimens of buccal mucosa from each patient, were examined and the slide showing the most florid lichenoid reaction (as determined by disruption of normal histological appearance) was selected for histological grading. At the time of the histological grading the results of the patch tests were not known by the observer.

4.3. Methods

All slides were stained with haematoxylin and eosin and where there was a suspicion of candidal species involvement, further sections (n=30) were stained with periodic acid Schiff following diastase digestion (PASD).

A pilot study of 15 haematoxylin and eosin stained histology sections, each from a different OLE patient, was carried out to enable standardisation of the grading methods and to provide reference views for the visual grading procedure. The histological characteristics that were examined and graded were keratin layer thickness, epithelial thickness, the thickness and density of the inflammatory cell infiltrate and the degree of basal cell layer disruption. The presence or absence of structures consistent with candida, hypergranulomatosis, acanthosis, cellular tropism, germinal centres, perivascular infiltrate and marginating polymorphonuclear neutrophils was noted as was the number of mast cells, plasma cells and eosinophils present in each specimen.

From this, views of thin, medium and thick keratin layers, epidermal layers and inflammatory infiltrate layers were photographed along with views of sparse, medium and dense infiltrate layers. These reference views are shown in Figs. 45-50. The photographs served as a visual guide and the score was worked out by choosing the reference view that most closely resembled the section under scrutiny (Smith & Pindborg 1969). The grades for the other parameters were also worked out and standardised during the examination of the pilot study sections.

As the results of the histological assessment were not being compared with those made by any other observer, no inter-observer calibration was necessary. However, an experienced senior pathologist gave training and advice during the grading proceedure.

The patch test results of the patients were obtained after the grading had been completed and the results analysed to discover whether there was any differences between the histological appearances of specimens from patients having amalgam restorations in their mouths (group A) and those without any amalgam restorations (group B), between patients on drugs known to have caused OLE (group C) and those not on any drugs known to have caused OLE (group D) and patients with positive (group E) or negative (group F) patch test results.

Each patient's Dental Hospital records were examined to ascertain the ferritin levels from blood samples taken in the Oral Medicine Clinic, and dental information regarding the presence of amalgam restorations in the mouth. No ethical committee approval was required as the blood samples had all been collected prior to the study commencing and as part of the patients' clinical investigations.

4.3.1. Statistical Analysis

The categorical data were analysed using the Chi Squared test, combining some of the grades together where the expected values were less than two. Sets of (Bonferroni-corrected) 95% confidence intervals were computed for the difference between the proportions in each category of the two multinomial distributions. Multiple comparison analysis was not carried out on the data because the sample size was too small for the results to be valid. The continuous data was analysed using the 2 sample t-test and the binary data, using the 2 proportions test.

The ages of the various groups were compared after normality was demonstrated by the use of plots.

4.3.2. Histopathological Examination

Areas of ulceration in the specimens were not used in the assessment and a margin of one x20 microscope field adjacent to these areas was also avoided. Likewise areas of normal mucosa were excluded. No repeat examinations were made unless specified.

The different histological features of the specimens were graded as follows.

4.3.2.1. Histological Parameters Arranged Into Ordered Categories

Keratin Layer Thickness

This was measured at a magnification of x10 using the reference figures 45-47. As the thickness of the keratin layer varied along the length of some specimens, the thickest area was used in any given section for the assessment.

Epithelial Thickness

This was assessed at x10 again using reference figs. 45-47, taking the assessment from the thickest area of the section but not including the rete ridges in the assessment.

Inflammatory Cell Infiltrate Layer Thickness

The sections were assessed at x10 and the field with the thickest layer chosen for the grading. The reference figs 45-47 were used as a guide and

Fig. 46. Reference View Of Epidermis Showing Thin Keratin Epithelial And Infiltrate Layers (x10)

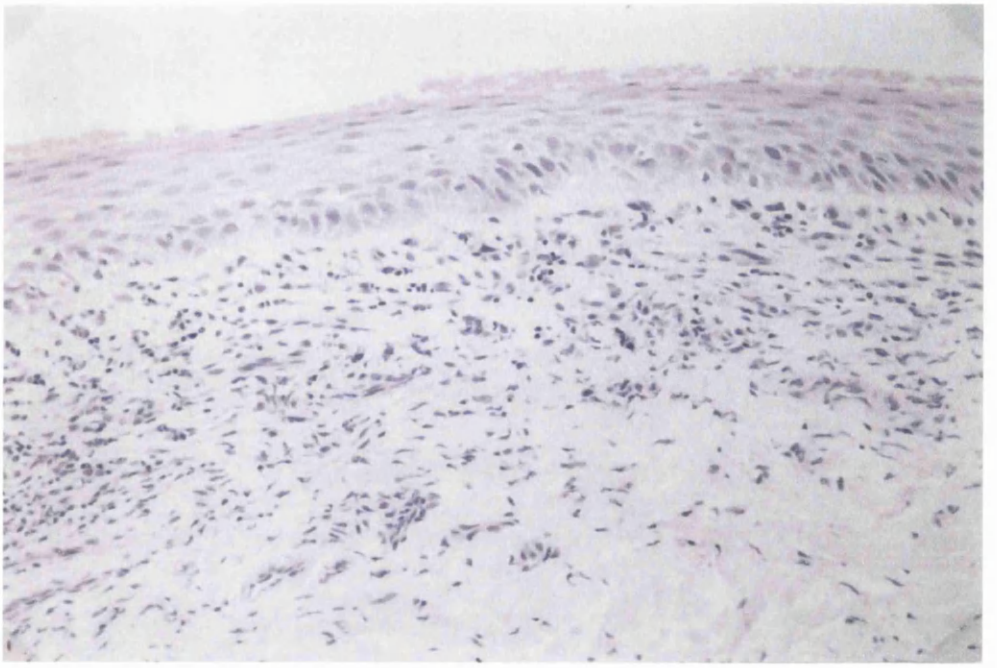


Fig. 47. Reference View Of Epidermis Showing Medium Thickness Of Keratin, Epithelial And Infiltrate Layers (x10)

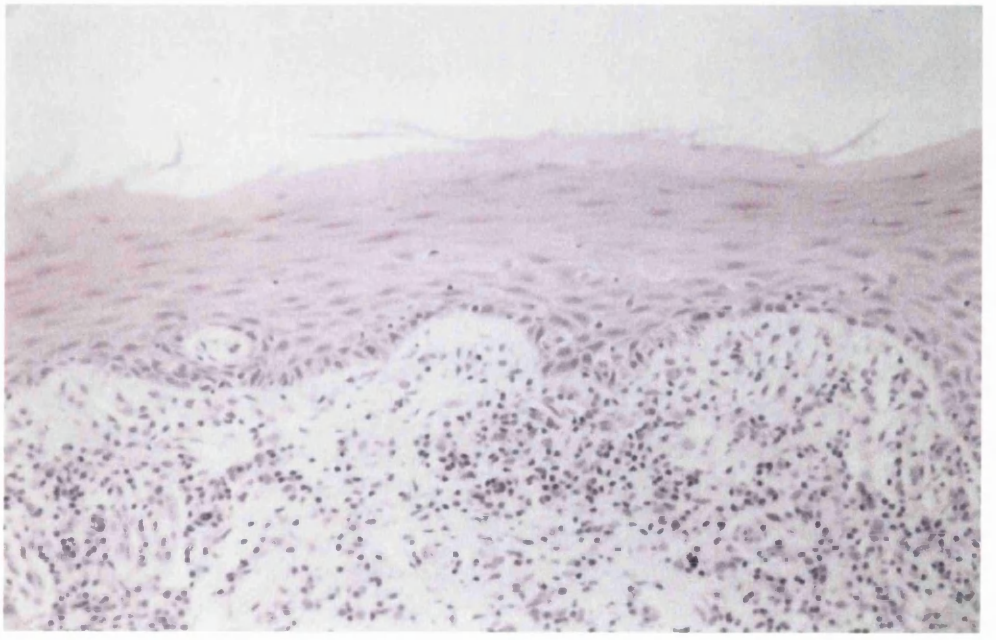
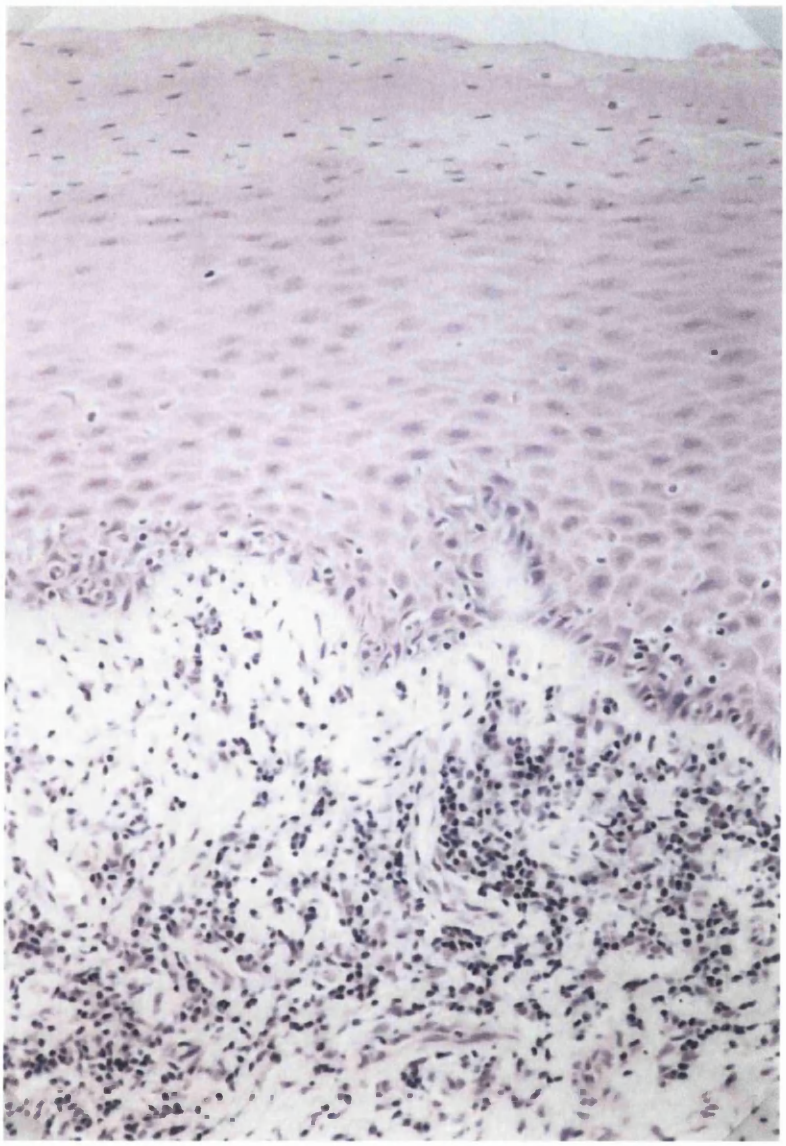


Fig. 48. Reference View Of Epidermis Showing Thick Keratin, Epithelial and Infiltrate Layers (x10)



the scoring was as follows; a score of 1 indicated a thin infiltrate layer (approximately one fifth of the field width), 2 indicated a medium thickness of infiltrate layer (approximately one third of the field width) and a score of 3 indicated a thick infiltrate layer (approximately one half of the field width).

Inflammatory Cell Infiltrate Layer Density

Reference figs. 48-50 were used to assess the density which was viewed at x10 and using the field with the densest area of infiltrate. This often but not necessarily corresponded with the thickest area of infiltrate on the section.

Basal Cell Layer Disruption

At a magnification of x10, the field width with the most evidence of disruption of the basal cell layer on each specimen was assessed. A grade of 1 was given if 0-33% of the length of the basal layer was affected by liquefaction, 2 if 33-66% was affected and 3 if over 66% of the area in the field was affected.

Cellular Tropism

This was assessed at x10 and graded 1-3 for mild, moderate and severe degrees of cellular tropism. The number of cells passing through the basement membrane was used rather that the height that they were seen to have reached in the epidermis. Again the field showing the most cells invading the epidermis was chosen for the assessment.

Fig. 49. Reference View Of Epidermis Showing A Sparse Inflammatory Cell Infiltrate Layer (x10)

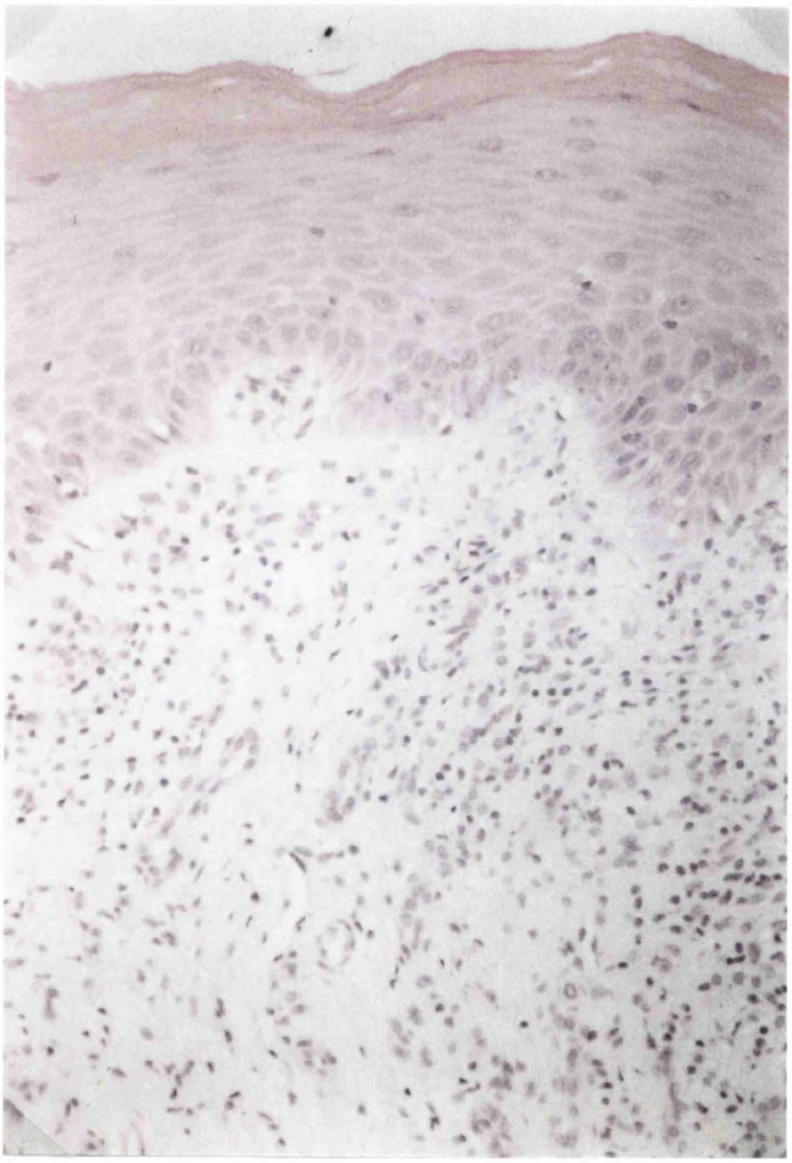


Fig. 50. Reference View Of Epidermis Showing An Inflammatory Cell Infiltrate Layer With Moderate Density (x10)

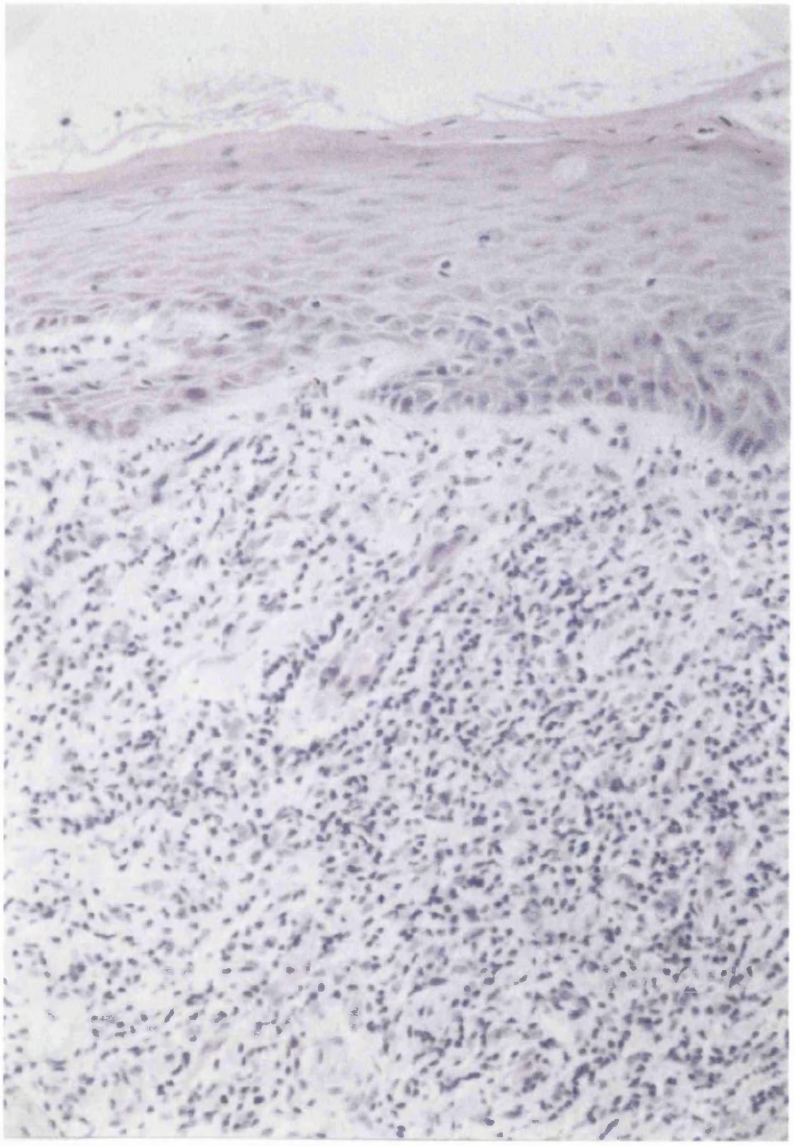
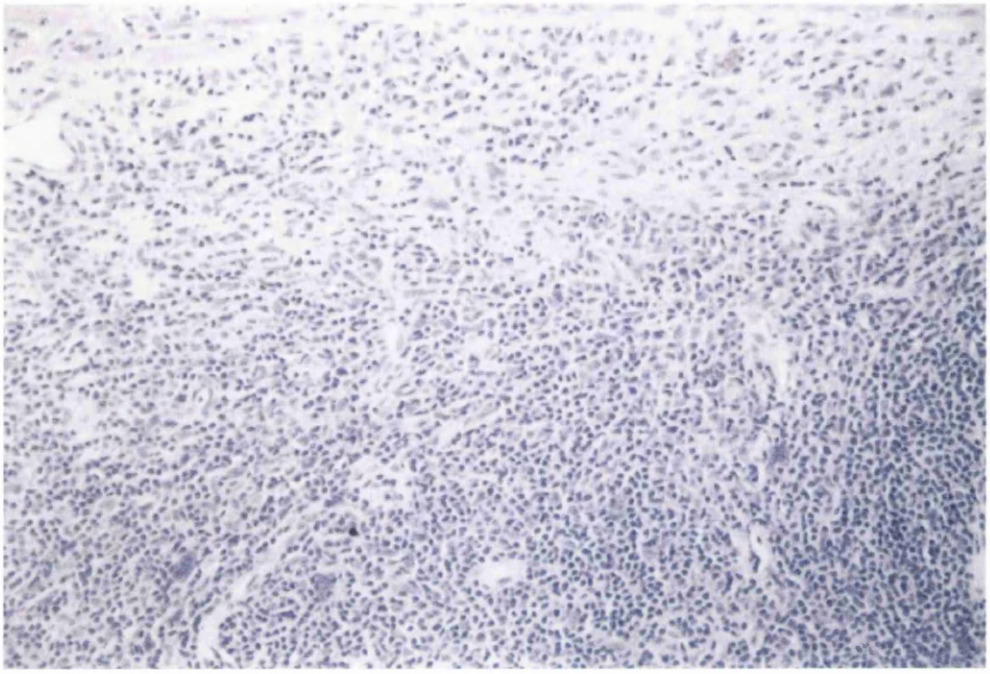


Fig. 51. Reference View Of Epidermis Showing A Dense Inflammatory Cell Infiltrate Layer (x10)



The following three parameters were assessed in a similar manner to that of Firth and Reade (Firth & Reade 1990).

Mast Cells

This was assessed at x20 and the depth of section examined shown in fig 51. Three field widths closest to the lesion, or the most florid part of the lesion were examined and the mast cells counted. The score of the section was taken to be the average of these three scores. Each section was assigned a grade according to the numbers of mast cells found: none = 1, 1-10 = 2, >10 = 3.

Plasma Cells

This was assessed at x20 and the depth of section examined shown in fig 52. Three field widths closest to the lesion or the most florid part of the lesion were examined and the mast cells counted. The score of the section was taken to be the average of these three scores. Each section was assigned a grade according to the numbers of plasma cells found: none = 1, 1-15 = 2, >15 = 3.

Eosinophils

This was assessed at x20 and the depth of section examined shown in fig 51. Three field widths closest to the lesion or the most florid part of the lesion were examined and the mast cells counted. The score of the section was taken to be the average of these three scores. Each section was assigned a grade according to the numbers of eosinophils found: none = 1, 1-10 = 2, >10 = 3.

Fig. 52. Diagram Of Epithelium Showing Field Placement For Assessment Of Mast Cells And Eosinophils

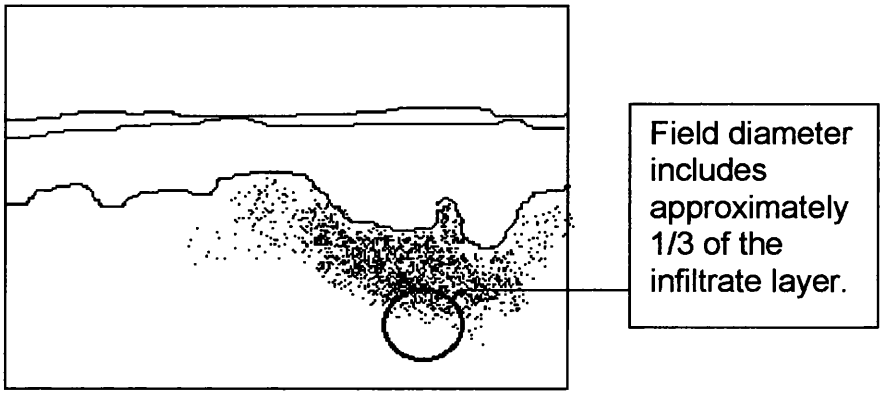
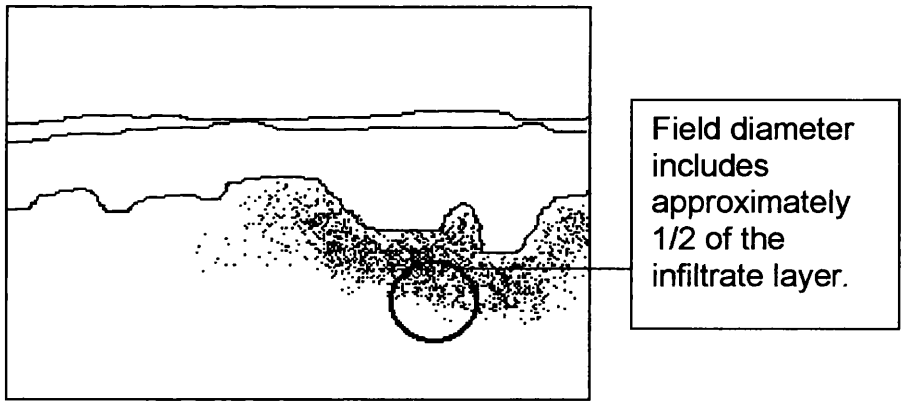


Fig. 53. Diagram Of Epithelium Showing Field Placement For Assessment Of Plasma Cells



4.3.2.2. Histological Parameters Arranged Into Binary Data

Acanthosis

Acanthosis was defined as a thickened spinous layer that was often but not always associated with rete ridge formation. The sections were assessed at x10 and the presence of acanthosis recorded.

Hypergranulomatosis

This was assessed at x 20. An increased thickness in the granular layer of the epidermis is usually found in specimens of patients with lichen planus (Ackerman 1978). This increased thickness was often arranged in regularly spaced clumps giving a 'zig-zag' appearance to the layer. The presence of hypergranulomatosis was taken as positive when the thickest point of the granular layer exceeded one third of the epidermal thickness.

Germinal Centres

This was assessed at x10 and was recorded positive if any germinal centres (focal concentration of inflammatory cells) were seen.

Marginating Polymorphonuclear Lymphocytes

The sections were examined at x20 and the three blood vessels that could be clearly seen closest to the most florid area were assessed for the presence of marginating polymorphonuclear leukocytes, i.e. neutrophils seen to be in contact with the vessel lumen walls.

Perivascular Infiltrate

This was assessed at x10 and was recorded as positive if any of the dermal blood vessels had a distinct inflammatory infiltrate associated with them.

4.3.2.3. Histological Parameters - Continuous Data

Apoptosis

Apoptosis was defined as cells with chromatin condensation at the periphery of the nucleus, a uniformly eosinophilic cytoplasm, nuclear fragmentation and pyknosis and nucleolar disintegration. The basal cell layer and the immediate suprabasal layers (3-4 cells thick) were assessed at a magnification of x10 for cells that were undergoing apoptosis and these were counted. The length of the basal cell layer was measured using a computer programme linked to a microscope. The basement membrane was traced, field by field on the computer monitor using a mouse and the length was returned by the computer in microns. From this, an estimate of the number of apoptotic cells per micron of basement membrane length could be determined.

4.4. Results

All the sections from the biopsy specimens taken from 42 patients were examined and the section showing the most florid disease process chosen. Table 41 shows the patient demographics and ferritin levels and Table 42 shows the possible aetiological factors which was the way in which the patients were divided up for further study. A total of 14 patients had low ferritin (<25mmol/l) but this did not correlate with atrophy of the epithelium, (p=0.166).

A total of 28 patients had one or more amalgam dental restoration in their mouth (group A) and 14 had no amalgam restorations (group B).

The same group of patients were divided up according to whether they were on medications that could cause OLE, 12 were taking medication that may have caused the OLE (group C) and 30 were not (group D). The medications that may have caused OLE and that were being taken by this group of patients were aspirin, sulphasalazine, diclofenac, thyroxine, diuretics, β-blockers and allopurinol.

The same group was again split up according to the results of the patch tests (delayed hypersensitivity (DHT) and contact urticaria tests (CUT)). A total of 28 patients had positive reactions to one or more patch tests (group E) and 14 patients were negative (group F).

Only two patients (patient number 5 and number 26) did not have any identified aetiological factor but this sample was too small to compare with the 40 that had identifiable possible aetiological factors. The age and sex

Table 41. Patient Demographics and Relevant Dental Information

Patients Number	Age	Sex	Ferritin levels [ng/ml]
1	52	F	137
2	59	F	NT[a]
3	43	M	148
4	45	M	176
5	37	F	64*
6	30	F	2
7	48	F	2
8	43	F	NT
9	59	F	183
10	47	F	1
11	40	F	13
12	57	F	90
13	62	M	NT
14	58	M	21
15	39	M	138
16	52	F	117
17	55	F	55
18	61	F	28
19	56	F	98
20	48	M	695
21	57	M	NT
22	61	F	30*
23	43	F	7
24	58	M	110
25	36	M	118
26	65	F	112
27	48	F	43
28	57	F	294
29	55	F	136
30	62	F	49
31	42	F	15
32	35	F	93
33	61	F	55
34	68	F	35
35	67	F	55
36	39	M	47
37	69	F	NT
38	48	F	6
39	37	F	156
40	44	F	NT
41	66	F	94
42	49	M	132

[a] Not tested

* Sample was not taken at the same time as the biopsy.

Table 42. Patients With OLE Lesions And Possible Aetiological Factors

[Y = Yes/positive, blank = no/negative]

Patient number	Amalgams in mouth	Contact With Amalgam	OLE associated drugs	One or more positive patch tests	Positive to FS/M[a]
1			Y		
2			Y		
3	Y	Y			
4	Y	Y			
5					
6	Y	Y			
7	Y			Y	M
8	Y		Y	Y	FS/M
9				Y	FS
10	Y	Y		Y	M
11	Y	Y		Y	M
12			Y	Y	
13			Y	Y	
14	Y			Y	FS
15	Y			Y	FS
16	Y			Y	FS/M
17	Y	Y		Y	FS/M
18	Y	Y	Y	Y	M
19	Y		Y	Y	FS
20			Y		
21	Y			Y	FS/M
22			Y	Y	
23	Y	Y		Y	M
24	Y	Y	Y	Y	M
25				Y	FS
26					
27	Y	Y		Y	
28			Y	Y	FS
29	Y	Y		Y	
30				Y	FS
31	Y	Y		Y	
32	Y	Y		Y	M
33				Y	FS
34	Y		Y	Y	M
35	Y	Y		Y	M
36	Y			Y	FS/M
37	Y			Y	M
38	Y			Y	M
39	Y	Y			
40				Y	
41	Y			Y	M
42	Y	Y		Y	M

[a] FS – Food substances, M - mercurials

distribution of these groups are shown in Table 43. There was a significant difference between the ages of groups C and D with those in group C being an average of 7 years older than those in group D. There were no significant differences in the sex ratio between group C and group D or in the age and sex distribution of groups A and B, and groups E and F.

Table 43. Age And Sex Distribution Of Patients

	Mean Age (SD) [years]	Age Range [years]	Significance	No. (%) Male	Significance
Group A and B					
Amalgams in mouth (n=28)	49.9 (10.6)	30 -69	p=0.19 CI[a] (-11.0, 2.2)	8 (28.6)	p=0.89* CI[b] (-2.9, 0.25)
No amalgam in mouth (n=14)	54.3 (9.5)	36 -65		3 (21.4)	
Group C and D					
Taking medications[c] (n=12)	56.8 (6.6)	43 -68	p=0.009 CI[a] (2.0, 13.2)	3 (25)	p=0.911 CI[b] (-0.31, 0.27)
Not taking medications (n=30)	49.2 (10.8)	30 -69		8 (66.7)	
Group E and F					
Positive patch test (n=32)	52.5 (9.8)	35 - 69	p=0.27 CI[a] (-4.1, 13.5)	7 (21.9)	p=0.29 CI[b] (-51.7, 15.4)
Negative patch tests (n=10)	47.8 (11.6)	30 -65		4 (40.0)	

* Numbers were small, statistical analysis may be invalid.

[a] 95% confidence interval for the difference in age (A minus B)/(C minus D)/(E minus F).

[b] 95% confidence interval for the difference in the proportions of male patients (A minus B)/(C minus D)/(E minus F).

[c] Medications that could cause OLE.

The positive reactions from the patch tests which were recorded in the 42 patients are shown in Tables 44 and 45. The patients were all tested to the European Standard Series of environmental allergens, the food additives, chocolate, and perfumes and flavourings series as outlined in Chapter 3 (both DHT and CUT in the latter three series). In addition 36 were tested to organic mercurials, 41 to peppermint (1% in petrolatum) and menthol (5% in petrolatum), and 30 to a series that included gold sodium thiosulphate (0.5% in aqueous solution). A total of 50% of the 42 patients tested positive to one or more of the organic mercurials which is similar to the 45% recorded for all the OLE patients in Chapter 3. The sample size was too small to consider analysing the rest of the positive reactions individually. Out of the 11 patients with positive reactions to one or more of the food additive series, nine were positive to benzoic acid (four had positives on DHT only, three had positives on CUT only, and two had positives to both tests). The other food additives which elicited positives were sodium metabisulphite (two patients – DHT) and sorbic acid (two patients – CUT). Most of these patients reacted positively to more than one food additive. Of the five patients who reacted to the individual components of the perfumes and flavourings series the results were as follows; three patients reacted to cinnamaldehyde (CUT), one to isoeugenol (DHT) and one to oak moss absolute (DHT). A further two patients reacted to the fragrance mix in the European Standard Series of allergens. The small numbers involved precluded analysing those with DHT positive reactions and CUT positive reactions, separately.

Table 44. Patch Test Results – to Testing with Food Additives, Perfumes And Flavourings And Organic Mercurials

[Y = Yes/positive, blank = no/negative]

Patient Number	P&F	CU P&F	FA	CU FA	Mint	Organic mercurials
1						
2						
3						NT[a]
4						
5						NT
6						
7						Y
8				Y		Y
9			Y			
10						Y
11						Y
12						
13					NT	NT
14	Y					NT
15				Y		
16	Y		Y			NT
17			Y			Y
18						Y
19		Y		Y		NT
20						
21	Y					Y
22						NT
23						Y
24						Y
25			Y	Y		NT
26						
27						
28		Y		Y		NT
29						
30		Y	Y			
31					Y	
32						Y
33			Y			
34						Y
35						Y
36			Y			Y
37						Y
38						Y
39						
40						
41						Y
42						Y
Total	**3**	**3**	**7**	**5**	**1**	**18**

[a] Not tested

Table 45. Patch Test Results – Environmental Allergens

[Y = Yes/positive, blank = no/negative]

Patient number	Para-bens	Frag-rance mix	Colo-phony	Cobalt	Nickel	Thiom-ersal	PPD	Balsam of peru	Lanolin	Gold
1										
2										
3										
4										
5										
6										
7										
8						Y				
9			Y							
10										
11										
12			Y							
13										
14	Y	Y								
15										
16		Y	Y					Y		
17										
18				Y						
19										
20										
21										
22									Y	
23										
24										
25										
26										
27										
28										
29					Y					
30										
31					Y					
32					Y					
33		Y								
34						Y				
35										
36										
37										
38							Y			
39										
40				Y	Y					
41										
42										Y
Total	**1**	**3**	**3**	**2**	**3**	**2**	**1**	**1**	**1**	**1**

The number of patients with a positive reaction to one or more food substances was 13 and those with a positive reaction to one or more mercurial allergens amounted to 18 patients. These are shown in Table 42. The microscopy results for all patients are shown in Tables 46 to 48.

Table 46. Histopathology Results – Ordinal Data

Patient number	Ker.	Epith.	Infil. Thick-ness	Infil. density	Basal cell layer disruption	Cellular tropism	Mast cells	Plasma cells	Eosin-ophils
1	1	1	2	2	1	1	2	2	2
2	2	1	2	3	3	3	2	3	2
3	2	2	1	2	1	1	3	2	2
4	2	2	2	2	2	3	3	3	3
5	2	2	2	2	1	2	3	3	2
6	3	2	2	2	1	2	3	2	2
7	3	2	2	2	2	1	3	2	2
8	1	1	2	2	1	2	2	3	2
9	2	2	3	3	3	2	3	3	2
10	2	2	3	3	2	3	2	3	1
11	3	3	3	3	3	3	2	3	2
12	2	1	2	3	3	3	2	1	1
13	3	3	2	2	2	1	2	2	1
14	2	2	2	2	3	3	3	2	2
15	3	3	2	3	3	2	2	2	1
16	3	2	2	2	3	2	2	2	1
17	2	2	2	2	3	1	3	3	2
18	3	3	2	2	2	1	3	2	1
19	2	2	2	3	1	1	2	2	1
20	2	3	1	2	1	1	2	2	2
21	1	1	2	2	1	1	3	3	2
22	2	1	3	3	3	3	3	3	2
23	3	3	3	3	1	1	3	2	2
24	1	1	3	3	2	2	3	2	1
25	3	2	2	3	1	1	3	2	1
26	3	2	2	2	2	1	3	2	2
27	2	2	2	3	1	2	3	2	3
28	2	2	2	3	3	2	3	2	2
29	3	3	3	3	2	3	3	2	1
30	3	3	2	2	3	3	3	3	2
31	3	2	2	2	1	1	3	2	1
32	1	3	3	3	2	2	2	3	1
33	1	1	2	2	3	2	2	2	1
34	2	2	2	3	2	3	3	2	2
35	2	1	3	3	3	3	2	3	2
36	3	2	1	2	3	2	2	2	2
37	2	2	2	3	3	2	3	2	2
38	2	2	2	3	3	2	2	2	2
39	2	2	1	2	1	2	3	2	3
40	2	3	2	2	1	2	2	2	1
41	2	1	3	2	1	2	2	2	1
42	2	3	2	2	2	2	2	1	1

Table 47. Histopathology Results – Binary Data

Patient number	*Candida*	Acan-thosis	Hyper-granulosis	Germinal centres	Marginating PMNL's	Perivascular infiltrate
1						Y
2				Y	Y	Y
3	Y				Y	
4	Y	Y	Y			Y
5		Y	Y			
6		Y	Y		Y	
7		Y	Y		Y	
8		Y				Y
9	Y				Y	Y
10		Y			Y	Y
11		Y	Y			Y
12		Y			Y	
13		Y	Y		Y	
14		Y	Y			Y
15			Y			
16		Y	Y			Y
17	Y	Y	Y			
18			Y			
19		Y	Y			
20			Y		Y	Y
21	Y	Y				Y
22	Y		Y			Y
23		Y	Y	Y		Y
24		Y				
25		Y	Y			Y
26			Y			
27		Y	Y			
28						Y
29		Y	Y			Y
30		Y	Y			
31		Y	Y			
32			Y			Y
33		Y			Y	Y
34		Y	Y		Y	Y
35		Y		Y	Y	Y
36		Y	Y		Y	
37		Y				
38			Y	Y		Y
39		Y	Y		Y	
40		Y	Y			
41		Y			Y	Y
42		Y	Y			

Table 48. Histopathology Results – Number of Apoptotic Cells

Patients Number	Number of apoptotic cells	length of section [microns]	Apoptotic cells per mm
1	0	546	0
2	17	2292	7.42
3	15	5915	2.54
4	11	1799	6.11
5	3	6292	0.47
6	17	9065	1.9
7	18	20565	0.88
8	5	4016	1.25
9	6	19043	0.32
10	7	7888	0.89
11	9	9873	0.91
12	12	4471	2.68
13	16	8330	1.92
14	9	8579	1.05
15	7	4465	1.57
16	18	6714	2.68
17	9	5333	1.69
18	3	3265	0.92
19	5	7179	0.7
20	4	3969	1.01
21	2	6979	0.5
22	4	3079	1.3
23	4	3502	0.22
24	6	2630	2.28
25	8	9582	0.83
26	15	18478	0.8
27	5	8329	0.75
28	7	13840	0.51
29	19	3836	4.95
30	39	12428	3.14
31	5	7876	0.63
32	2	4705	0.57
33	11	1167	9.43
34	14	9373	1.49
35	9	2091	4.3
36	4	3897	1.03
37	22	15271	1.44
38	25	22826	1.1
39	22	4283	9.64
40	13	4270	3.05
41	2	5008	0.4
42	2	3631	0.55

As in the previous chapter, the tables that follow utilise the following abbreviations: the use of ***bold italics*** indicates a significant result (p=<0.05), results in *italics* indicate borderline significance (p=>0.05 and <0.085) and '*' indicates that the statistical results may be invalid due to the small sizes of some of the results.

4.4.1. Histology Results – Groups A and B

The results are shown in Tables 49 and 50. There were no significant differences between those with amalgam dental restorations present and those without in the microscopic findings except for the presence of acanthosis which was found in more of the patients who had amalgam restorations than those without.

Table 49. Results Of Patient Groups A And B, - Ordinal Data

3.2.2. Histological parameters	Grade	Patients with amalgam [A] (=28)	%	Patients without amalgam [B] (=14)	%	Statistical Analysis p value
Keratin Thickness	1	4	14.3	2	14.3	0.89
	2	14	50.0	8	57.1	
	3	10	35.7	4	28.6	
Epithelial thickness	1	5	17.9	5	35.7	0.34
	2	16	57.1	5	35.7	
	3	7	25.0	4	28.6	
Infiltrate thickness	1	3	10.7	1	7.1	0.31 (Grades 1 and 2 combined)
	2	17	60.7	11	78.6	
	3	8	28.6	2	14.3	
Infiltrate density	1	0	0	0	0	0.83
	2	15	53.6	8	57.1	
	3	13	46.4	6	42.9	
Basal cell layer disruption	1	10	35.7	5	35.7	0.38
	2	9	32.1	2	14.3	
	3	9	32.1	7	50.0	
Cellular tropism	1	8	28.6	5	35.7	0.80
	2	13	46.4	5	35.7	
	3	7	25.0	4	28.6	
Mast cells	1	0	0	0	0	0.66
	2	12	42.9	7	50.0	
	3	16	57.1	7	50.0	
Plasma cells	1	1	3.6	1	7.1	0.64 (Grades 1 and 2 combined)
	2	19	67.9	8	57.1	
	3	8	28.6	5	35.7	
Eosinophils	1	11	39.3	5	35.7	0.82 (Grades 2 and 3 combined)
	2	14	50.0	9	64.3	
	3	3	10.7	0	0	

Table 50. Results Of Patient Groups A And B – Binary And Continuous Data

Histological Parameters	Score	Patients with amalgam [A] (=28)	%	Patients without amalgam [B] (=14)	%	Statistical Analysis (P value)
***Candidal sp.* present**	Present	4	14.3	3	21.4	0.58*
Acanthosis	Present	23	82.1	7	50.0	***0.034***[a]
Hypergranulosis	Present	20	71.4	8	57.1	0.36
Germinal centres	Present	3	10.7	1	7.1	0.69*
Marginating PMNL's	Present	9	32.1	6	42.9	0.50
Perivascular infiltrate	Present	14	50.0	8	57.1	0.66
Apoptotic cells [per mm]	Range	0.4 - 9.6		0 - 9.4		0.61
	Mean	1.9		2.3		

[a] The (Bonferroni corrected) 95% confidence interval for the difference in the proportions of the two groups (amalgam minus no amalgam) was, (2.4, 61.9%)

4.4.2. Histology Results – Groups C and D

The results are shown in Tables 51 and 52. Patients taking medications were more likely to have a thin oral epithelium and those not taking medications were more likely to have a medium thickness of oral epithelium, these were statistically significant. The presence of acanthosis was more likely in group D though this was of borderline significance ($p=0.064$). None of the other histological parameters investigated were statistically significant.

Table 51. Results of Patient Groups C and D – Ordinal Data

3.2.3. Histological parameters	Grade	Patients taking medications [C] (=12)	%	Patients not taking medications [D] (=30)	%	Statistical Analysis
Keratin Thickness	1	3	25.0	3	10.0	0.15 (Grades 1 and 2 combined)
	2	7	58.3	15	50.0	
	3	2	16.7	12	40.0	
Epithelial thickness	1	6	50.0	4	13.3	***0.031***[a]
	2	3	25.0	18	60.0	
	3	3	25.0	8	26.7	
Infiltrate thickness	1	1	8.3	3	10.0	0.46 (Grades 1 and 2 combined)
	2	9	75.0	19	63.6	
	3	2	16.7	8	26.7	
Infiltrate density	1	0	0	0	0	0.28
	2	5	41.7	18	60.0	
	3	7	58.3	12	40.0	
Basal cell layer disruption	1	4	33.3	11	36.7	0.80
	2	4	33.3	7	23.3	
	3	4	33.3	12	40.0	
Cellular tropism	1	5	41.7	8	26.7	0.33
	2	3	25.0	15	50.0	
	3	4	33.3	7	23.3	
Mast cells	1	0	0	0	0	0.25
	2	7	58.3	12	40.0	
	3	5	41.7	18	60.0	
Plasma cells	1	1	8.3	1	3.3	0.60 (Grades 1 and 2 combined)
	2	8	66.7	19	63.6	
	3	3	25.0	10	33.3	
Eosinophils	1	5	41.7	11	36.7	0.76 (Grades 2 and 3combined)
	2	7	58.3	16	53.5	
	3	0	0	3	10.0	

[a] The (Bonferroni corrected) 95% confidence intervals for the differences between the population proportions in each grade (C minus D) were; ***grade 1 (21.7, 50.9%), grade 2 (-52.6, -21.1%)*** and grade 3 (-14.1, 15.3%).

Table 52. Results of Patient Groups C And D - Binary And Continuous Data

Histological Parameters	Score	Patients taking medications [C] (=12)	%	Patients not taking medications [D] (=30)	%	Statistical Analysis
***Candidal sp.* present**	Present	1	8.3	5	16.7	0.43
Acanthosis	Present	6	50.0	24	80.0	*0.064*[a]
Hypergranulosis	Present	6	50.0	22	73.3	0.16
Germinal centres	Present	1	8.3	3	10.0	0.86
Marginating PMNL's	Present	5	50.0	10	33.3	0.62
Perivascular infiltrate	Present	7	58.3	15	50.0	0.62

Apoptotic cells	Range	0 – 7.42	0.32 – 9.64	0.60
[per mm]	Mean	1.79	2.17	

[a] The (Bonferroni corrected) 95% confidence interval for the difference in the percentage of positive results (C minus D) was *(-61.7, 1.7%)*.

4.4.3. Histology Results – Groups E and F

The results of the histopathological grading of these specimens are shown in Tables 53 and 54.

The difference between the grades given for the infiltrate density was statistically significant between the two groups of patients, with those with a negative patch test result more likely to have a moderately dense inflammatory infiltrate, and those with positive patch tests more likely to have a dense infiltrate.

Over half of the specimens from patients who had had positive patch tests exhibited a high degree of basal cell layer disruption whilst over half of those from negative patients exhibited a low degree of basal cell layer disruption, though these results were of borderline statistical significance.

The number of eosinophils in the negative group was higher than that of the positive group, with over three quarters of the negative group having eosinophils visible in the section whereas just under half of the positive group had no demonstrable eosinophils present.

There was a significantly higher proportion of specimens in the negative group that had marginating PMNL's in the dermal vessels.

Table 53. Results of Patient Groups E And F, - Ordinal Data

3.2.4. Histological parameters	Grade	Patients with positive patch test results (=32)		Patients with negative patch test results (=10)		Statistical Analysis
		n	%	n	%	
Keratin Thickness	1	5	15.6	1	10.0	p=0.80 (Grades 1 and 2 combined)
	2	16	50.0	6	60.0	
	3	11	34.4	3	30.0	
Epithelial thickness	1	8	25.0	2	20.0	p=0.76
	2	15	46.9	6	60.0	
	3	9	28.1	2	20.0	
Infiltrate thickness	1	1	3.1	3	30.0	***p=0.043*** (Grades 1 and 2 combined)
	2	21	65.6	7	70.0	
	3	10	31.3	0	0	
Infiltrate density	1	0	0	0	0	***p=0.006*** [b] (Grades 1 and 2 combined)
	2	13	40.6	9	90.0	
	3	19	59.4	1	10.0	
Basal cell layer disruption	1	9	28.1	6	60.0	*p=0.084*[c]
	2	8	25.0	3	30.0	
	3	15	46.9	1	10.0	
Cellular tropism	1	8	25.0	5	50.0	p=0.33
	2	15	46.9	3	30.0	
	3	9	28.1	2	20.0	
Mast cells	1	0	0	0	0	p=0.70 (Grades 1 and 2 combined)
	2	15	46.9	4	40.0	
	3	17	53.1	6	60.0	
Plasma cells	1	0	6.2	0	0	p=0.94 (Grades 1 and 2 combined)
	2	20	62.5	7	70.0	
	3	10	31.3	3	30.0	
Eosinophils	1	15	46.9	1	10.0	***p=0.036*** [d] (Grades 2 and 3 combined)
	2	16	50.0	7	70.0	
	3	1	3.1	2		

[a] The (Bonferroni corrected) 95% confidence intervals for the difference in the percentage of positive results (E minus F) were; ***grades 1 and 2 (-49.6, -12.9%), grade 3 (12.9, 49.6%).***

[b] The (Bonferroni corrected) 95% confidence intervals for the difference in the percentage of positive results (E minus F) were; ***grades 1 and 2 (-78.2, -20.6%), grade 3 (20.6, 78.2%).***

c The (Bonferroni corrected) 95% confidence intervals for the difference in the percentage of positive results (E minus F) were; *grade 1 (-73.6, 9.8%)*, grade 2 (-44.2, 34.2) and ***grade 3 (5.9, 67.9%).***

[d] The (Bonferroni corrected) 95% confidence intervals for the difference in the percentage of positive results (E minus F) were; **grade 1 (7.8, 65.9%), grades 2 and 3 (-65.9, -7.8)**

Table 54. Results of Patient Groups E And F – Binary And Continuous Data

Histological Parameters	Score	Patients with positive patch test results (=32) n	%	Patients with negative patch test results (=10) n	%	Statistical Analysis
***Candidal sp.* present**	Present	4	12.5	2	20.0	p=0.59
Acanthosis	Present	25	78.1	6	60.0	p=0.29
Hypergranulosis	Present	21	65.6	8	80.0	p=0.34
Germinal centres	Present	3	9.4	1	10.0	p=0.95
Marginating PMNL's	Present	10	31.3	7	70.0	***p=0.02***[a]
Perivascular infiltrate	Present	18	56.3	4	40.0	p=0.36
Apoptotic cells	Range	[0 - 9.6]		[0.2 - 9.4]		p=0.21
[per mm]	Mean	[2.9]		[1.7]		

[a] The (Bonferroni corrected) 95% confidence interval for the difference in the percentage of positive results (E minus F) was *(6.1, 71.4%)*.

4.4.4. Correlations With Apoptosis

The infiltrate thickness and density were correlated to the number of apoptotic cells found. There was no significant correlation between the thickness or the density of the inflammatory infiltrate with the number of apoptotic cells per mm of basal cell layer length (thickness $p=0.67$, density $p=0.57$).

CHAPTER 5 DISCUSSION

5.1. Clinical Allergy Studies

5.1.1. Comparability Of Patients And Controls

The patient group was tested over a 16 year period which could have affected the results when comparing these patients to the control group tested in 1996. However, over half of the patients were in fact tested within 5 years of the control group (724 were tested between 1991 and 1996). The control population, by necessity only had one mean age and one sex distribution, whereas the disease groups all differed because individual diseases affect different sections of the population. This effect where there is in fact no overlap in the inter-quartile range between the control group and the OLE group, would have been minimised by a wider age range in the control group. The difference that the age discrepancy could possibly make is that the OLE group would be more likely to react to fragrances and less likely to react to nickel than the control group. This in fact proved to be the case with the percentage of OLE patients reacting to fragrance mix and nickel was 13 5% and 13.1%, while the corresponding results for the control group was 6% and 23%.

Likewise the sex ratio of the control group (71% were female) was comparable to the OLE and RAS groups whose percentages of females were 76% and 66% respectively, but differed from the AE (49% were female) and OFG (43% were female) groups. This also could have affected some of the comparisons between the control and disease populations in that while

some allergens seem to elicit positive responses equally in males and females, positive reactions to others such as nickel and fragrances are more frequent in females than males.

The geographical spread of patients and controls was similar though individual home and background environments may have been shown to be considerably different if social class and/or years lived in the West of Scotland had been taken into account.

There was a far higher percentage of medical/health workers in the control group (61% compared to 5.2% of the patient group) which may have affected the results. The high incidence of thiomersal allergy detected in the control group could be related to the differences in occupation, in that medical personnel involved in clinical work are vaccinated against Hepatitis B Virus, with a vaccine that contains thiomersal. Although other vaccines also contain thiomersal this group would have had greater exposure than the general population with at least three injections for the vaccination programme, plus any boosters that may have been administered. The increased incidence of thiomersal allergy so affected the results, that the positive reactions to thiomersal were discounted in the control and patient groups and the totals separately computed. There may have been other, less obvious differences in reaction between the two groups because of the selected nature of the control group.

The size of the control group was greater than the numbers in the AE and EM groups but less than the others, though still valid statistically. The same control group was used for each of the disease groups.

Bearing all these factors in mind, the control group was comparable to the different disease populations.

5.1.2. Patch Test Results

The control population self-volunteered by responding to a poster display. Therefore, there was perhaps a bias towards those who thought that they may have allergies and wanted to find out what they were allergic to. This was minimised by excluding those who had been referred for patch testing for medical reasons but there may have been some who had low levels of inconvenience caused by allergic dermatitis and had not sought medical help for it but who wanted to come forward for patch testing to investigate it themselves. The high prevalence of allergic reactions during the patch testing in the control group would tend to indicate that this could have been the case. This would tend to minimise the differences between the results of the disease groups when compared to the control group. Thus if there is a significant difference it is not contradicted by this fact but likely to be more so, likewise, results with no significant differences may in fact have been significant, if a more random control sample had been used.

There are significant difficulties in enrolling appropriate control subjects to voluntarily participate in studies and this study has been no exception. Ideally, a much larger number of control subjects with a wider base of education, occupation and age range should have been sought. This group could then have been divided up into age and sex matched groups to be compared individually to the different disease groups. This would minimise the age and sex differences between disease and control group and also the differences between the sizes of the disease and control groups.

A total of 50% of RAS and 55% of OFG patients reacted to the food additive series which was significantly more than controls (to CUT and to the food additive testing as a whole). A total of 55% of the 45 AE patients also reacted to this series though half (n=10) reacted to food additives upon CUT and two thirds (n=14) to DHT. These reactions consisted mainly of positives to benzoic acid and when considered as an individual allergen, benzoic acid elicited significantly more reactions in RAS, EM and OFG patients on CUT and to AE patients on DHT, than controls. The significant percentages compared to the control group, of the positive reactions among different patient groups involved, when considering both types of tests were, RAS 46%, EM 48% and OFG 51%.

Sorbic acid is another allergen that provoked significantly greater numbers of positive reactions than controls, in this case in RAS, OFG and OLE patients.

Of the number of positives to the perfumes and flavourings series, most reactions were caused by one allergen, cinnamaldehyde. This flavouring agent elicited positive reactions in 18-38% of the patient groups and mostly to CUT. Oak moss absolute was the perfume agent most likely to provoke a positive reaction (to the DHT) and given a larger control group, this would probably have been a significant result.

OFG patients reacted to chocolate more than other patients or controls and this would probably have been significant again if the control group had been larger.

Taking all the food substances as a whole, over two thirds of patients with RAS, AE, EM and OFG, and half of the patients with OLE had one or more positive reaction to a food substance.

The control group reacted to the modified European Standard Series significantly more than RAS, EM and OFG patients did. The allergens that most commonly elicited positives were nickel, cobalt, fragrance mix, neomycin, colophony, balsam of Peru and thiomersal. Balsam of Peru and fragrance mix are related allergens and are found in perfumed products. Cobalt and nickel are often positive together partly because it has been suggested that it is almost impossible to obtain nickel-free cobalt and cobalt-free nickel (Dotterud & Flak 1994). The 15.6% positive to nickel in this patient group correlates well with reported nickel allergy prevalences of 9% (Prystowsky et al. 1979) and 17.2% (Dotterud & Flak 1994). The female preponderance of 93.8% in patients and 95.7% in the control group, is also in accord with a previously published figure of 98.8% female in nickel positive patients (Gollhausen et al. 1988).

The high incidence of thiomersal sensitivity can be explained by the thiomersal containing vaccines used among health professionals to protect against Hepatitis B Vaccine. When the thiomersal results are excluded from the analysis, the numbers of patients and controls who had positive reactions to the modified European Standard Series were not significantly different, except for the OFG patients who had significantly less positives than controls. This was probably due to the younger age of these patients (the age of most of the group was in the first to third decades), while it is

considered that the highest numbers of positive reactions are found in those from the second to fifth decades (Husain 1977).

The null hypotheses that patients with OLE, RAS, AE, EM and OFG have no greater number of positive reactions is is proven to be false in relation to food additives, perfumes and flavouings and chocolate, and true in relation to environmental allergens.

The null hypotheses that patients with OLE, RAS, AE, EM and OFG have different allergy profiles is shown to be true as OFG patients reacted more to chocolate and OLE patients to mercurials, however all the patient groups had similar reactions in that most reacted to the benzoic acid and to cinnamaldhyde.

OLE. The percentages of positives reactions in the total group (Table 32) would be artifically low as the number tested to different mercurials differed i.e. most were tested to thiomersal but not to other mercurials. However, it was shown that a greater percentage of the OLE group were positive to one or more mercurial allergen when compared to RAS or OLE patients.

5.1.4. RAS Patients

It is likely that RAS is provoked by contact with food additives such as benzoic acid and sorbic acid, and flavourings such as cinnamaldehyde in susceptible patients. From the results presented here, the type of reaction involved is less likely to be a Type IV reaction, but either a Type I hypersensitivity reaction or a non immunologic contact urticarial (NICU) reaction. The mechanism for this is uncertain as inconclusive findings regarding the role of histamine in RAS lesions have been published (Dolby & Allison 1969; Wray, Vlagopolous, & Siraganian 1982) and to date, no specific circulating antibodies have been isolated in these patients. Again, not all RAS patients attending the Oral Medicine clinic were referred for patch testing so the results have been artificially increased by the selection process. However, patients did benefit from dietary advice and avoidance of the allergens that they were sensitive to. A total of 77.0% of RAS patients who responded had experienced an improvement in their symptoms following an avoidance diet.

5.1.5. AE Patients

The results found for the AE patients showed that a significant proportion of those referred for patch testing had positive reactions to delayed hypersensitivity testing with benzoic acid (25%) compared to 7% of controls. This may have been an incidental finding and given a larger disease group may not have been statistically significant. AE is characterised by the immediacy of the reaction and so the relevance of positive delayed hypersensitivity reactions is debatable. AE patients did however, react significantly more readily than controls to CUT with cinnamaldehyde. The numbers of patients with AE responding to the questionnaire were too low to analyse meaningfully.

5.1.6. EM Patients

Nearly half of the EM patients that were referred for patch testing had a positive reaction to benzoic acid, and this was mostly in response to the CUT. Significantly more EM patients than controls reacted to cinnamaldehyde. Overall, two thirds of this group of patients (compared to just over one third of controls) reacted to one or more food substance which suggests that these substances may act as triggers to the episodes of EM in susceptible patients. 23.8% (n=10) were concurrently taking mediations that could cause EM eruptions and six of these also had positive reactions to one or more food substance.

No investigation into the HSV status of these patients was undertaken.

5.1.7. OFG Patients

OFG patients were more likely to react to food additives, particularly benzoic acid and sorbic acid, perfumes and flavourings, particularly cinnamaldehyde and chocolate than controls. A total of 51% reacted to benzoic acid, mostly on CUT (47%) which was the highest percentage of positive reactions out of the different disease groups. All patients diagnosed with OFG in the Oral Medicine clinic at Glasgow Dental Hospital were routinely sent for patch testing so this high percentage was a true representation of the frequency of positive patch test results among OFG sufferers in the West of Scotland. This group of patients indicated the greatest relief of symptoms following dietary avoidance out of all the disease groups (of those who showed good to full compliance with the dietary advice). It is clear that Type I hypersensitivity or NICU reactions to food additives, and Type IV hypersensitivity to chocolate, play a major role in the progression of OFG. This is likely to be due to the allergic reaction in the tissues superimposed on the granuloma formation, blocking the lymphatic drainage to the area, leading in turn to lymphoedema.

5.1.8. Outcome Of Dietary Avoidance

The response rate to the questionnaire was low (48%), but considering but considering that the time difference between the patch testing and avoidance diet and receiving the questionnaire was up to 15 years in a few patients, this was hardly surprising. There were no significant differences in the age and sex of responders and non responders. The outcome measure took no account of spontaneous remission that could have occurred in all disease groups, though less likely in the OLE group where the disease often persists for years. The patients were sent the questionnaire and had to work out the linear analogue scale with only brief written instructions which may have affected some of the responses as these may not be clear to some without skilled help (Huskisson 1974). Though the patients record of symptoms is necessarily subjective, the patients own testimony has been shown to be reliable, especially when comparing pain before and after treatment in the same patient (Huskisson 1974). The time delay (years in some patients) also could have affected the results, and outcome measures closer to the time of treatment would have been more accurate. The accuracy of such recall information offered by some of these patients could indeed be questionable. Though over two thirds of the responders had been patch tested within five years of receiving the questionnaire, even this length of time could have clouded the subjective assessment given by the patients. There may have been a bias among responders of those who felt strongly (positive or negative) about their treatment and its outcome.

Assuming the worst case scenario, that all non-responders experienced no benefit (as they were unlikely to experience worsening of their symptoms due to the diet alone) there would still be a subjective benefit ascertained from the pre and post testing symptom scores in 37.8% of OLE patients, 38.7% of RAS patients, and 32.8% of OFG patients. These figures are calculated assuming accuracy of patients' recall over the years and accuracy in filling in the questionnaire, so are a rough indication only. However, given these provisos it is clear that a significant number of patients with OLE, RAS and OFG did improve with allergen avoidance therapy. The results of the AE and EM groups were not calculated, as the numbers responding were so small.

Thus the null hypothesis that there would be no subjective benefit from following dietary avoidance advice was proven to be false in the disease groups that could be analysed, i.e., OLE, RAS and OFG.

5.2. Histopathology Studies

No obvious patterns that involved a variety of histological features, emerged during this study that could relate the microscopic features to different causes of OLE. This may be either because there are no actual differences in the histological features of OLE lesions arising from hypersensitivity to different substances and those with no hypersensitivity component, or, that the sample size and methods used were insufficient to demonstrate these results. Koch and Bahmer also found when studying the histology of specimens from positive patch test reactions to various metal salts, that there was a wide variation in the microscopic features observed and that they could detect no clear relationships between the histology and the different metals tested (Koch & Bahmer 1999).

However, the fact that the experienced pathologist can recognise different patterns, indicates that they do exist and the fact that some of the features did seem to differ between groups supports this. In a larger sample size, more features may have been recognised that were associated with certain groups. The sample size in this study was very small and only one section was examined from each specimen which may have resulted in some missed features. As the features may exist in groups, the sample size would need to be large enough to analyse the results using multiple comparison analysis between the different variables.

The basic principle was that of a hypersensitivity response being a likely aetiological factor in the pathogenesis of OLE. In both the amalgam group, drug group and the group who had identifiable allergens after patch testing,

similar allergic processes are taking place. It is therefore perhaps not surprising that only a few differences were found in the groups examined. Unfortunately, the sample size was such that only two patients had no identifiable causative factors and therefore these could not be analysed in the same way or compared to the 40 with suspected aetiological factors. Given that half of all OLE patients in the larger group described in chapter 3, had one or more positive reactions to a food substance and that 65% had one or more positive reactions on patch testing to a larger range of allergens, the likelihood of OLE being caused by a Type IV hypersensitivity reaction which may or may not be modulated by Type I or non immunologic contact urticaria reaction, is very high. This is also borne out by the fact that when comparing groups of patients with positive and negative responses to patch testing an increase in the density of the inflammatory infiltrate was found in the positive group. Given a larger sample size, the basal cell layer disruption scores may have shown that severe basal cell layer disruption was also correlated with allergy in this group.

The increase in inflammatory infiltrate in the lamina propria of OLE lesions indicates an aetiology originating in the immune system. The histopathology of Type IV hypersensitivity reactions elicited by patch testing, show a remarkable similarity to those of OLE, and certainly the predominantly T cell infiltrate in close apposition to the epithelium, the disruption of the basal cell layer and the degrees of cellular tropism (the grading for this did not include a 'none' category which may have downplayed the effect that this feature may have had in these sections)

indicate that they are reacting to either antigens in the epithelium or to the activated keratinocytes there.

The null hypothesis relating to the number of apoptotic cells was proven true in both the patients with amalgam restorations and in those with positive patch tests. No differences were found.

The null hypothesis relating to the amount of inflammatory infiltrate was proved to be true in the patients with amalgam restorations but was not proven in those with positive patch test results.

The null hypothesis relating to the amount of disruption of the basal cell layer of the epithelium was proved to be true in the amalgam patients but not in those with positive reactions to patch testing though this result was of borderline statistical significance.

When considering the possibility of DILR, the patients isolated as having their medication as a possible aetiological factor were not actually proven to have DILR, i.e. they did not undergo drug withdrawal followed by (preferably double blind, placebo) controlled rechallenge to the suspected drug agent. The null hypothesis that there were no distinguishing features was proven and there was no correlation between a mild reaction in the lamina propria with a florid epithelial reaction, nor was the vice versa situation noted. However, for the reason stated above, these results may not be valid.

5.3. Conclusions

Patients attending Glasgow Dental Hospital and School with RAS and OFG were significantly more likely to be suffering from hypersensitivity reactions or intolerances to food additives, perfumes and flavourings and chocolate, than controls. Dietary advice given to these patients, was efficacious in that compliance to the dietary avoidance of appropriate allergens resulted in subjective improvement in three quarters of all patients with OFG and three quarters of those patients with RAS who were referred for patch testing. In addition, OLE patients were significantly more likely to be sensitised to mercurials than patients in other disease groups, which could be detected by patch testing. These patients also had significantly more positive reactions to cinnamaldehyde on CUT and to which dietary avoidance resulted in improvement in symptoms in nearly two thirds of patients.

Regarding the results of dietary avoidance of appropriate allergens, even if it is assumed that the non responders experienced no subjective benefits at all, still a significant proportion improved (around one third of patients with OLE, RAS and OFG).

The AE and EM groups were small but the results did indicate some definate trends. Just over one quarter of AE patients reacted to cinnamaldehyde on CUT which suggests that this allergen may cause angioedematous reactions in certain subjects. Benzoic acid and to a lesser extent cinnamaldehyde seem to be important allergens in the aetiology of EM.

The numbers of responders to the questionnaire in the AE and EM groups were too small to analyse.

Density of inflammatory infiltrate was shown to be associated with patients who had positive reactions on patch testing and contact urticaria testing and given a larger patient group, the amount of disruption to the basal cell layer may have proved significant too.

5.4. Future Studies

A prospective study that continued to investigate the response to dietary modification in patients with positive contact urticaria tests and/or positive patch tests would be useful. It would be interesting to measure the clinically observed benefit to the patient in terms of improvement in the oral mucosa as well as the subjective benefit experienced by the patients themselves. It would also be of benefit to monitor the effects of dietary avoidance in patients closer to the dietary changes taking place. Double blind, placebo controlled, allergen rechallenge would also be of great value in identifying the exact mechanisms of hypersensitivity involvement in disease processes, as it would help to isolate the allergen involved in provoking the reaction in patients who reacted to more than one allergen.

In regard to the histopathology studies, it is possible that given a larger sample size, and one in which there were a greater proportion of patients with OLE with negative patch test results, no amalgam association and not on medications that could cause OLE, differences would be seen at a microscopic level that could be evaluated and categorised, between that 'allergic' group and those with no obvious causative factors involved. It is also likely that differences between sections from patients in contact with relevant topical allergens (mercury in amalgam and food stuffs particularly those kept in contact with the oral mucosa for longer periods of time such as flavouring in toothpastes, hard candy and chewing gum), and those ingesting allergens systemically (medications), would be found. A more clinically correlated study would be more useful, in terms of isolating patients with not just a suspicion of allergen involvement but a clinically

observed response to allergen withdrawal and preferably, difficult though it is to achieve, a recurrence on double blind placebo controlled exposure to the offending allergen.

APPENDICES

Appendix A Volunteer Information Sheet 1

STUDY OF THE PREVALENCE OF SKIN REACTIVITY TO PATCH TESTING

This is a joint project on behalf of the Department of Oral Medicine and the Contact Dermatitis Unit in the Royal Infirmary, Glasgow. We are studying the prevalence of skin reactivity to various patch test substances in a "normal" population. At present we extensively use this test to identify potential allergens in individuals who suffer from a number of oral diseases, but we do not know how the skin of normal individuals without these diseases reacts.

In order to participate in this study you will be given an appointment to visit the Oral Medicine Department on either a Monday, Wednesday or Friday, where a sticking plaster with a number of substances will be placed on the skin of your back and left there for 48 hours when you will be reviewed. You will then be reviewed two days thereafter to assess the response of your skin to these substances. This test will reveal for us how your skin reacts and does not necessarily imply that you are allergic to these substances, and in the absence of any symptoms the substances to which you react are probably not important. We will however, if you so wish, give you a list of the positive results. The process is painless and the only potential risk is that of sensitising yourself to one of the substances, although this is extremely unlikely if you do not have an open dermatitis, in which case you would be excluded from the study. Also you will need to keep your back dry for the period of the testing.

We hope that you will freely and voluntarily agree to take part in this project. If you wish to decline, however, this will not affect any future care that you receive in Glasgow Dental Hospital and will not be to your prejudice.

If you wish to discuss the project please do not hesitate to contact Mrs Shiona Rees in the Oral Medicine Clinic.

During your patch testing you may call at any time for information or advice at the numbers given below:

Mrs Shiona Rees: Day -
Night -

Professor David Wray: Day -
Night -

APPENDIX B VOLUNTEER INFORMATION SHEET 2

Thank you for taking the time and effort for this project.

It is important that you keep all three appointments this week, if there is a problem and you need to adjust the times of your appointment, please phone 9642 (oral medicine reception).

The tests on your arms should be kept dry for 6 hours during which you should observe at hourly intervals what, if anything, happens to the test sites. After the 6 hours are over you can wash the pen marks off and treat as normal skin.

The tests on your back will remain on for 48 hours. These should be removed 1 hour prior to the 2nd visit. It is important that you keep the test area dry at all times during the 5 days.

APPENDIX C VOLUNTEER HISTORY SHEET

CONTACT DERMATITIS RESEARCH PROJECT
Glasgow Dental Hospital

Name..... Occupation.....

DOB.....Sex: M \ F Dept.....

GDH number.....

HISTORY

Skin:Past_____Present_____

_____

_____

_____

Allergies: Asthma Hay fever Conjunctivitis Rhinitis
Migraine Travel sickness

Family History ..... **Atopic/ Healthy**

Medications: Antihistamines_____
Others_____
Intolerance Yes\No

Intolerant of: Elastoplasts Jewellery Cosmetics\Toiletries Chemicals

Disease State: RAS OFG
Lichenoid eruption Clinically Yes/No
Erythema multiforme Angioedema

Infant Feeding Status: Breastfed Yes/No
If yes, for how long? _____

Appendix D Consent Form

STUDY OF THE PREVALENCE OF SKIN REACTIVITY TO PATCH TESTING

I ..... freely and voluntarily agree to participate in the clinical research study on the prevalence of skin reactivity to patch testing. The nature and the purpose of this study has been explained to me by ..... I have had the opportunity to ask questions and I understand fully what is proposed.

I recognise that I may receive no benefit from this study. I accept that there are other risks associated with the procedure which are not directly attributed to negligence on the part of those undertaking the procedures.

I understand that I am free to withdraw my consent at any time without prejudice.

I have been reassured that any information obtained from me will not be disclosed without my permission to any other party in a manner that will reveal my identity.

Signature .....
Date .....

I confirm that I, ... have explained the nature and purpose of the clinical research study and the procedure in respect of which consent has been given by the above named.

Signature .....
Date .....

APPENDIX E VOLUNTEER WORKING SHEET

Contact Dermatitis Research

CDIU No. .....

Ref diagnosis.....

PT diagnosis.....

DELAYED HYPERSENSITIVITY

	ALLERGEN	48 hrs	96 hrs
	Food Additives		
1	Benzoic acid		
2	Salicylic acid		
3	Tartrazine		
4	Glutamic acid		
5	BHT		
6	BHA		
7	Propylene glycol		
8	Sorbic acid		
9	Sodium metabisulphite		
1	Essence of Choc(soln)		
2	Essence of Choc(PMF)		

	Perfumes and Flavours		
1	Cinnamyl alcohol		
2	Cinnamaldehyde		
3	Eugenol		
4	Amylcinnamaldehyde		
5	Hydroxycitraonellal		
6	Geraniol		
7	Isoeugenol		
8	Oak moss absolute		
9	Benzyl alcohol		
10	Musk ambrette		
11	Sorbitan sesquiolate		

CONTACT URTICARIA

	ALLERGEN	0	48 hrs
	Food Additives		
1	Benzoic acid		
2	Salicylic acid		
3	Tartrazine		
4	Glutamic acid		
5	BHT		
6	BHA		
7	Propylene glycol		
8	Sorbic acid		
9	Sodium metabisulphite		
1	Essence of Choc. (soln)		
2	Essence of Choc. (PMF)		

	Perfumes and Flavours		
1	Cinnamyl alcohol		
2	Cinnamaldehyde		
3	Eugenol		
4	Amylcinnamaldehyde		
5	Hydroxycitraonellal		
6	Geraniol		
7	Isoeugenol		
8	Oak moss absolute		
9	Benzyl alcohol		
10	Musk ambrette		

Key: BHT = Butylated Hydroxytoluene
BHA = Butylated Hydroxyanisole

Appendix F Benzoate And Cinnamaldehyde Diet Sheets

GLASGOW ROYAL INFIRMARY UNIVERSITY NHS TRUST

DEPARTMENT OF NUTRITION & DIETETICS

CINNAMON FREE DIET

You have been found to be allergic to cinnamon. This is a natural substance which does not require to be stated on food labels. Therefore, always look for the term 'spices' on food labels which are not included in the Manufactured Products List here.

Foods to be avoided

Soup: Tinned or packet soup with tomato or spices on the label

Meat: Canned meat in spicy sauce. Cold meat containing spices. Avoid spice for beef ham.

Fish: Canned fish in spicy sauce. Avoid made up meat or fish dishes containing spices e.g. pies. bridies, fish pie, lasagne. pizza.

AVOID curries and chinese food. Curry pastes, curry sauces.

Spices: Mixed spice, cinnamon, curry powder. Allspice. Check labels on any other spice mixes.

Baked beans in tomato sauce. ravioli, spaghetti in tomato sauce. "Invaders". Pork sauces and beans. Spaghetti Hoops.

Manufactured cakes and biscuits on list overleaf - and those containing spice. Check label. Gingerbread. Coffee Buns. Rich Fruit Cake. Keep to home-baking whenever possible.

Pickles and ketchup - see list.

Nuts - Dry Roasted type. Bombay Mix, Spicy Nut Mixes.

Crisps – Snacks - avoid spices. Check labels and Products List.

Mincemeat and Christmas pudding. Mincemeat pies and Christmas cake. Apple Strudel. Apple cake tart with cinnamon or spices.

Soft drinks: Coca Cola, Red cola, Vimto, Pepsi Cola, Dr. Peppers.

Alcoholic drinks: Red wine, gin, red and white Martini and Cinzano. Avoid the perfumed type of alcoholic drinks, e.g. Dubonnet, Malibu, Dark Rum, Tia Maria etc. Mulled wine.

Toothpaste: All others apart from on Allowed List.. No "Tartar Controlled" toothpaste. **AVOID MOUTHWASHES ALSO,** unless otherwise stated on Manufactured Products List.

Cola sweets: Cola cubes, Cola Chewits, cinnamon sticks. cola chews, etc.

Also see list of manufactured products containing cinnamon.

Foods Allowed

Soup:	Homemade or tinned or packet soup **not** containing spices or tomato.
Meat:	All fresh or frozen.
Fish:	All fresh or frozen.
Eggs:	All types.
Dairy Produce:	Milk - all types. Yoghurt. Butter. cheese, cream - all types. Ice cream.
Fats & Oils:	Margarine, cooking oils, lard.
Fruit:	All types.
Vegetables:	All types including potatoes, salad vegetables.
Bread:	All types.

Rice. pasta. pulses (peas. beans. barley, lentils), nuts (avoid dry roasted type).

Cereals:	All cereals. Breakfast cereals. porridge. Also flour, tapioca, sago, custard powder. cornflour.
Cakes & Biscuits:	Homemade. Shopbought cakes and biscuits avoiding spices on label.
Drinks:	Tea. coffee, Oxo, Bovril, Marmite, Bournvita. Cocoa, Drinking Chocolate, Horlicks. Squashes, lemonade and any other fizzy drinks apart from those on the 'Avoid List'. Soda water. Appletise, fresh fruit juices. Spring waters.
Alcoholic Drinks:	White wine, cider, lager, beer, whisky, vodka.
Miscellaneous:	Sugar, salt, pepper, herbs, spices not mentioned on 'Avoid List', e.g. nutmeg, chilli powder, ginger etc. Jams.marmalade. honey, lemon curd, peanut butter, saccharin and other artificial sweeteners.

KAM/RS
12.12.95.

MANUFACTURED PRODUCTS INFORMATION FOR CINNAMON

ASDA: No information available.

BARR: Strike Cola only product containing cinnamon.

BATCHELORS: No information available.

BERNARD MATTHEWS: Turkey Tikka only product containing cinnamon.

CADBURY:(INCL. SWEPPES) Chocolate Cream, Old Jamaica only products containing cinnamon.

CAMPBELLS: Avoid Tomato Soup only

COLMANS: **Products containing cinnamon:**

OK Fruit Sauce, Wholegrain Mustard, French Mustard, Dijon Mustard, Tikka Masala Dry Sauce Mix. Traditional Herb Mustard.
ANY Curry Sauce or Products.

CO-OP PRODUCTS CONTAINING CINNAMON:

Frozen;
American Style Double Cream Apple Pie Ice Cream
Apple Strudel
Summer Fruit Strudel

Canned Traditional Rice Pudding
Apple, Sultana & Cinnamon Custard Style Yoghurt
Apple & Cinnamon Fruit Filled Biscuits
Plain Chocolate Ginger Rings
Milk Chocolate Ginger Rings
Ground Mixed Spice
Ground Cinnamon

It is also recommended to avoid any product with **SPICES** in the ingredients.

DAIRY CREST: No products containing cinnamon

FARLEY'S: No products containing cinnamon

GOLDEN WONDER: **Products free from Cinnamon:**

Crisps	Ready Salted		Spring Onion
	Salt & Vinegar		Steak & Onion
	Cheese & Onion		Pickled Onion
	Smokey Bacon		Roast Chicken
Ringos	Salt & Vinegar		Cheese & Onion
Wotsits	Bacon	Cheese	Barbequed Beef
Golden Lights	Lightly Salted		Grilled Chicken
Pot Noodles	Chicken & Mushroom		Chicken Curry
	Bolognaise		Spicy Chicken
	Vegetable Korma		

HALLS:	Fruit Pudding)	
	Economy Black Pudding)	**ALL CONTAIN**
	Puritan Black Pudding)	**CINNAMON**
	Marks & Spencer Black Pudding)	

HEINZ: See attached list for products free from cinnamon.

H.P. FOODS: See attached list for products free from cinnamon

JACOBS: Fruit & Nut Crunch only product containing cinnamon

KELLOGS: Apple Pop Tarts and also Chocos contain cinnamon

KRAFT: Tomato Ketchup contains cinnamon

LYONS TETLEY: No products containing cinnamon

MARS: Honey flavoured Tunes only product containing cinnamon

MARKS & SPENCER: No information available.

MR. KIPLING; **Products containing cinnamon;**

Mr. Kipling Country Fruit Lemon Tart
" " Country Slices
" " Mince Pies
" " Luxury Mince Pies
" " Glazed Mince Tartlets
" " Mince + Brandy Sauce Pies
" " Country Fruit Cake
" " Christmas Slices
" " Christmas Cake
" " Stölen Slices

NESTLE; **Ice Cream Division;** No products containing cinnamon

Food Division: – Creamola Foam - Raspberry flavour
Pan Yan Sandwich Piccalilli
Pan Yan Original Pickle

NESTLE(incl. ROWNTREE CONFECTIONERY): Rowntree's Fruit Gums only product containing cinnamon

ROWATS OR ROTHWELL; **Products containing cinnamon:**

Tomato Ketchup
Family Sauce
Pickles Silverskin & Cocktail Onions
Pickled Chip Onions
Pickled Red Cabbage
Piccalilli
Hamburger Relish

SAFEWAY: No information available at present

SAINSBURY; **Products containing cinnamon:**

Soft Drinks: All products free from cinnamon

Confectionery: Milk chocolate covered almonds dusted with cinnamon

SAINSBURY - Cont'd.

Cakes & Biscuits:
1) Chocolate hearts - spicy jam filled Lebkuchen
2) Lebkuchen
3) Lebkuchen Gingerbread Men
4) Milk/Plain Chocolate Continental biscuit assortment
5) Pfeffernusse
6) Plum Pudding
7) Alcohol-free Christmas Pudding
8) Raisin & Walnut Malt Loaf.

ST. IVEL: No products containing cinnamon

TESCO: Follow general guidelines - avoid coke, baked beans, sauces, curried and spicy foods. Fresh Chicken Korma (in chilled cabinet) and Barbeque Sauce are free from cinnamon.

TREBOR BASSETT: No products containing cinnamon

THORNTONS: No products containing cinnamon

THOMAS TUNNOCK: Chocolate Perkins and Perkins contain cinnamon.

WALLS: 'Country Fair' Vermont Apple Cinnamon Pie contains cinnamon

FOX'S BISCUITS: Fruit Shrewsbury are only products containing cinnamon

WRIGLEY: Big Red and Juicy Fruit are only products containing cinnamon

TOOTHPASTE: **Colgate/Palmolive - Products containing cinnamon**

Colgate Blue Minty Gel
Colgate Plax
Colgate Actibrush

Stafford Miller - Search Dental Rinse contains cinnamon. All other products suitable for use.

Smith Kline Beecham - All products free from cinnamon

Procter & Gamble - All products free from cinnamon i.e. Crest.

KAM RS
20.12.95.

NB. The above information is believed to be correct at time of production.

The following Heinz products are free from Cinnamon

WEIGHT WATCHERS FROM HEINZ PRODUCTS

SAUCES, SALADS & PICKLES

Cooking Sauce, French White Wine & Dill
Cooking Sauce, Indian Korma
Cooking Sauce, Italian Tomato & Onion
Cooking Sauce, Oriental Sweet & Sour
Low Fat Dressing
Low Fat Dressing, Mild Mustard
Low Fat Dressing, Thousand Island
Low Fat Dressing, Yogurt & Herb
Mayonnaise Reduced Calorie

PASTA

Italiana Bolognese Shells
Italiana Pasta Tubes in Cheese Sauce with Bacon
Italiana Tortellini
Italiana Tuna Twists
Italiana Vegetable Ravioli with Tomato Sauce
Spaghetti in Tomato Sauce, No Added Sugar

DAIRY PRODUCTS

Cheese Slices, Reduced Fat
Dairy Spread with Cheese & Ham, Reduced Fat
Dairy Spread with Cheese, Reduced Fat
Dairy Spread ,Cheese, Onions & Chives, Reduced Fat
Hard Cheese Reduced Fat

FRENCH BREAD PIZZAS

French Bread Pizza, Cheese & Tomato
French Bread Pizza, Ham & Mushroom
French Bread Pizza, Ham & Pineapple
French Bread Pizza, Pepperoni

WEIGHT WATCHERS FROM HEINZ PRODUCTS Cont'd.

FROZEN READY MEALS

Beef Lasagne
Beef Oriental with Rice
Big Deal, Beef Goulash with Parsley Rice
Big Deal, Cajun Chicken
Big Deal, Chilli Con Carne with Rice
Big Deal, Keema Curry with Cumin Rice
Cannelloni Filled with Vegetables
Cauliflower Cheese
Chicken & Broccoli Pasta Bake
Chicken Chasseur with Rice
Chicken Curry with Rice
Chicken Marengo with Rice
Chicken Supreme
Fish Provincale with Noodles
Mediterranean Chicken
Pasta Bolognese
Pasta Shells with Vegetables & Prawns
Salmon & Prawn Fricasse
Salmon Mornay
Seafood Bake with Broccoli
Smoked Fish with Pasta Bows
Spaghetti Bolognese
Sweet & Sour Chicken with Rice
Sweet & Sour Vegetables
Tagliatelle Carbonara
Vegetable au Gratin
Vegetable Chilli with Rice
Vegetable Hotpot
Vegetable Lasagne
Vegetable Moussaka

DESSERTS

Cheesecake. Blackcurrant
Cheesecake. Strawberry
Dairy Ice Cream, Chocolate Ripple
Dairy Ice Cream, Neapolitan
Dairy Ice Cream, Strawberry
Dairy Ice Cream, Vanilla
Dessert Bombes, Chocolate with Orange Liqueur
Dessert Bombes, Lemon
Dessert Bombes, Mint Chocolate
Dessert Bombes, Tropical Fruit
Premium Ice Cream. Lemon Meringue
Premium Ice Cream. Strawberries & Cream
Premium Ice Cream. Triple Chocolate Fudge
Premium Ice Cream. Triple Toffee Fudge
Rice Pudding, No Added Sugar, Low Fat
Torte. Orange & Lemon
Torte. Peach & Apricot
Torte. Raspberry

JAMS & MARMALADES

Apricot Jam. Reduced Sugar
Blackcurrant Jam, Reduced Sugar
Fruits of the Forest Jam, Reduced Sugar
Marmalade. Reduced Sugar
Morello Cherry Jam. Reduced Sugar
Raspberry Jam, Reduced Sugar
Strawberry Jam, Reduced Sugar

BREAD & ROLLS

Brown Bread
Danish Brown Bread
Danish Malted Softgrain Bread
Danish White Bread
Oat Danish Bread
Soft Brown Rolls
Soft White Rolls
White Bread

CANNED SOUPS

Chicken & Ham with Rice Soup
Chicken Noodle Soup
Chicken Soup
Country Vegetable & Beef Soup
Country Vegetable Soup
Lentil & Carrot Soup
Mushroom Soup
Vegetable Soup
Wholesome Soup, Lentil & Chicken
Wholesome Soup, Winter Vegetable

INSTANT SOUPS

Asparagus & Leek Soup, 40kcal
Chicken & Sweetcorn Soup, 60kcal
Chicken & Vegetable Soup with Noodles, 60kcal
Chicken & Vegetable Soup, 40kcals
Chicken Soup, 40kcal
Minestrone Soup, 60kcal
Mushroom Soup, 40kcal
Mushroom Soup, 60kcal
Tomato Soup, 40kcal
Tomato Soup, 60kcal
Vegetable Soup with Croutons, 60kcal
Vegetable Soup, 40kcal

BISCUITS & SNACKS

Cookies, Dark Treacle
Cookies, Real Chocolate Chip
Cookies, Stem Ginger

The following Heinz products are free from Cinnamon

CORE PRODUCTS

BAKED BEANS

Barbecue Beans
Curried Beans with Sultanas

LUNCH BOWLS

Beef Curry with Rice
Beef Goulash with Noodles
Chicken Curry with Rice
Chilli Con Carne with Rice
Lamb and Vegetable Casserole

PASTA

Chef's Specials, Chicken Ravioli in Tomato Sauce
Chef's Specials, Macaroni Cheese
Chef's Specials, Pasta Pipes with Tuna & Bacon
Chef's Specials, Ravioli in Spicy Sauce
Chef's Specials, Sausage Hotpot with Pasta
Chef's Specials, Spicy Beef Pasta Twists
Dinosaurs with Mini Meat Boulders
Dinosaurs, Pasta Shapes in Tomato Sauce
Magic Roundabout, Spaghetti Shapes in Tomato Sauce
Noodle Doodles, Spaghetti Shapes in Tomato Sauce
Spaghetti Hoops in Tomato Sauce
Spaghetti in Tomato Sauce
Spaghetti with Sausages
Super Mario, Spaghetti Shapes in Tomato Sauce
Thomas the Tank Engine, Spaghetti in Tomato Sauce

SAUCES, SALADS & PICKLES

Apple Sauce
Coleslaw Salad
Coronation Sauce
Mayonnaise
Mixed Bean Salad
Pasta Salad
Ploughman's Piccalilli
Ploughman's Pickle
Ploughman's Tangy Sandwich Pickle

CINNAMON FREE PRODUCTS

HEINZ CORE PRODUCTS Cont'd.

SAUCES, SALADS & PICKLES Cont'd.

Ploughman's Tomato Pickle
Potato Salad
Salad Cream
Salad Cream, Spoonable
Salsa, Medium-Hot
Salsa, Mild-Medium
Sandwich Spread, Cucumber
Sandwich Spread, Spicy
Sandwich Spread, Sweetcorn & Red Pepper
Silverskin Onions
Vegetable Salad

SPONGE PUDDINGS

Sponge Pudding, Banana with Toffee Sauce
Sponge Pudding, Chocolate with Chocolate Sauce
Sponge Pudding, Lemon
Sponge Pudding, Mixed Fruit
Sponge Pudding, Strawberry Jam
Sponge Pudding, Treacle

READY TO SERVE SOUPS

Beef Soup
Big Soup, Beef & Bacon Hotpot
Big Soup, Beef & Vegetable
Big Soup, Beef Broth
Big Soup, Chicken & Ham
Big Soup, Chicken & Vegetable
Big Soup, Chicken, Leek & Potato
Big Soup, Giant Minestrone
Big Soup, Spicy Tomato with Beef Pasta Parcels
Big Soup, Thick Country Vegetable with Ham
Chicken & Mushroom Soup
Cream of Asparagus Soup
Cream of Celery Soup
Cream of Chicken Soup
Cream of Mushroom Soup
Farmhouse Beef & Vegetable Soup
Farmhouse Beef Broth

CINNAMON FREE PRODUCTS Cont'd.

READY TO SERVE SOUPS Cont'd.

Farmhouse Chicken & Vegetable Soup
Farmhouse Potato & Leek Soup
Farmhouse Scotch Broth
Mulligatawny Soup
Oxtail Soup
Pasta Soup, Beef & Tomato Bolognese
Pasta Soup, Chicken Pastini
Pasta Soup, Minestrone
Pasta Soup, Mushroom Carbonara
Pasta Soup, Tomato Napoli
Premium Soup, Beef, Potato & Red Pepper
Premium Soup, Carrot, Potato & Coriander
Premium Soup, Chicken Sweet Pepper & Dill
Premium Soup, Chicken, Sweetcorn & Asparagus
Premium Soup, Country Bean with Mushroom
Premium Soup, Seven Vegetable
Scottish Vegetable Soup with Lentils
Spicy Soup, Chilli Bean & Beef
Spicy Soup, Curried Chicken with Rice
Spring Vegetable Soup
Vegetable Soup
Wholesoup, Farmhouse Vegetable
Wholesoup, Ham & Butter Bean
Wholesoup, Lentil
Wholesoup, Pea & Ham
Wholesoup, Winter Vegetable

TOPPERS

Toast Toppers, Chicken & Mushroom
Toast Toppers, Ham & Cheese
Toast Toppers, Mushroom & Bacon

CANNED TUNA

Tuna Chunks, Canned in Brine
Tuna Chunks, Canned in Vegetable Oil
Tuna Steak, Canned in Brine
Tuna Steak, Canned in Vegetable Oil

HP FOODS LTD NUTRITION INFORMATION: CINNAMON CONTENT

21/03/94

	PRESENT	ABSENT
HP SAUCE		✓
HP FRUITY SAUCE		✓
HP TOMATO KETCHUP	✓	
HP SPICY TOMATO SAUCE		✓
HP CHILLI SAUCE	✓	
HP CURRY SAUCE		✓
HP FRUITY BARBECUE SAUCE	✓	
HP SWEET & SOUR SAUCE		✓
HP ORIGINAL BARBECUE SAUCE	✓	
HP MEXICAN SPICY BARBECUE SAUCE		✓
HP RICH JAMAICAN BARBECUE SAUCE		✓
HP MINT SAUCE		✓
HP MAYONNAISE (BULK)		✓
HP MALT VINEGAR		✓
HP BEANS IN TOMATO SAUCE	✓	
HP HEALTHY BEANS	✓	
HP BAKED BEANS IN TOMATO SAUCE (CATERING)	✓	
HP HEALTHY BEANS IN TOMATO SAUCE (CATERING)	✓	
HP BEANS AND BEEFBURGERS	✓	
HP BEANS AND SAUSAGE	✓	
HP SAUCY BEANS	✓	
HP BIG BREAKFAST BIG BEANS IN TOMATO SAUCE		✓
HP BIG BREAKFAST BIG BEANS & JUMBO SAUSAGES		✓
HP BATMAN BOLOGNESE		✓
HP PASTA SHAPESIN TOMATO SAUCE		✓
HP SPAGHETTI IN TOMATO SAUCE		✓
HP GLADIATORS IN TOMATO SAUCE (REDUCED SUGAR)		✓
HP GLADIATORS IN SMOKEY BACON SAUCE		✓
HP GLADIATORS IN PIZZA PIZZA SAUCE WITH PEPPERONI		✓
HP SONIC AND SAUSAGES IN TOMATO SAUCE		✓
HP SONIC RAVIOLI SHAPES IN TOMATO SAUCE		✓
HP CHICKEN KORMA BISTRO BREAK	✓	
HP SWEET & SOUR BISTRO BREAK		✓
HP CANNELLONI BISTRO BREAK		✓
HP LASAGNE BOLOGNESE BISTRO BREAK		✓
DADDIES TOMATO KETCHUP		✓
DADDIES BROWN SAUCE		✓
DADDIES BURGER RELISH		✓
DADDIES SALAD CREAM		✓
FLETCHERS TIGER SAUCE		✓
FLETCHERS TITBITS SAUCE		✓
FLETCHERS BROWN SAUCE		✓
FLETCHERS TOMATO KETCHUP	✓	
FLETCHERS BAKED BEANS IN TOMATO SAUCE	✓	
FLETCHERS SHORT CUT SPAGHETTI IN TOMATO SAUCE		✓

L & P	WORCESTERSHIRE SAUCE	✓
L & P	CHILLI & GARLIC SAUCE	✓
L & P	GINGER & ORANGE SAUCE	✓
L & P	GARLIC & SPRING ONION SAUCE	✓
L & P	HOT PEPPER SAUCE	✓
L & P	MUSTARD & PEPPERCORN SAUCE	✓
L & P	GARLIC SAUCE	✓
L & P	FRUIT SAUCE	✓
L & P	WORCESTER KETCHUP	✓
L & P	TOMATO KETCHUP WITH MILD CURRY SPICES	✓
L & P	SOY & GARLIC	✓
L & P	HOT PEPPER & LIME	✓
L & P	SOY & FIVE SPICE	✓
L & P	CURRY CONCENTRATE	✓
L & P	ITALIAN VINAIGRETTE MAKER	✓
L & P	WHITE WINE & GARLIC VINAIGRETTE MAKER	✓
L & P	CLASSIC FRENCH VINAIGRETTE MAKER	✓
L & P	PICKLE WITH WORCESTER SAUCE	✓
L & P	SWEET PEPPERS WITH CHILLI SAUCE	✓
L & P	GINGER SAUCE	✓
L & P	GREEN JALAPEÑO SAUCE	✓

IF YOU HAVE ANY QUERIES REGARDING THE DIETARY INFORMATION OR IF YOU WOULD LIKE AN APPOINTMENT TO DISCUSS THE DIET IN MORE DETAIL PLEASE CONTACT :

DIETITIAN: Karen Milligan

HOSPITAL: Glasgow Royal Infirmary

TELEPHONE NUMBER: _____ (Mon-Wed)

OR

_____

PAGE NO : _____

GLASGOW ROYAL INFIRMARY

DEPARTMENT OF NUTRITION & DIETETICS

MENU PLAN FOR BENZOATE + CINNAMON FREE DIETS

Fruit juice or tinned/fresh grapefruit (p.f.)

Breakfasts:
Any breakfast cereal milk, sugar, banana.
Egg/bacon/grilled tomatoes/mushrooms.
Wholemeal or unbleached white bread or rolls.
Spread or butter.
Jam, marmalade or honey (p.f.)

Lunches:

Sandwiches:
Wholemeal or unbleached white bread sandwiches or rolls.
Spread or butter

Sandwich fillings:
Cheese, egg, mayonnaise (Hellmans) onion + tomato
Chicken mayonnaise
Tuna mayonnaise
Salmon and blackpepper
* Cold ham, roast meat, tongue, corned beef (+ tomato/salad)
Peanut butter
Banana
Cold meat + homemade coleslaw
Cottage cheese
Sardines
Cold bacon
Edam cheese

N.B. Any item marked (p.f.) - please check for preservatives E210 - E219
* Do not use meat loaf, haslet or any spicy meats e.g. Chicken tikka, Italian and German sausage

Other Lunch Ideas:

Toasties - Cheese and onion
Cheese and bacon
Cheese and tuna

Baked potatoes and any sandwich fillings
Fish fingers
Homemade thick soup with bread and butter
Scrambled egg and cheese. French toast
Omelette - cheese, ham, mushroom, tomato

Main Meal Suggestions:

Starters:
Homemade soup, fruit juice, (p.f.) grapefruit segments (p.f.),
Grilled grapefruit (no cinnamon)
Prawn cocktail (homemade sauce - Hellmans mayonnaise + tomato puree (p.f.)
Egg mayonnaise - Hellmans mayonnaise
Melon

MENU PLAN FOR BENZOATE + CINNAMON FREE DIETS

Main Course: Stewed beef, stewed lamb, pork stew, chicken stew, rabbit stew
(Make into casserole by adding different vegetables, p.f. tomato puree, herbs, garlic,onion, mushrooms and allowed spices.

Egg Dishes - Omelette, fried egg, scrambled egg, baked egg

Salads - Tuna, salmon, cold meat, corned beef, cottage cheese, egg

Mince - Minced beef, cottage pie, mince cobbler (Mince + savoury scone on top)

Spag Bolog mix - garlic,onion, mushrooms, add tinned tomatoes (p.f.), tomato paste (p.f.) Black pepper, salt, bay leaves, mixed herbs.
Use as a base with spaghetti, in lasagne, cannelloni, mock moussaka with potato and cheese sauce/real moussaka with aubergines. Make spag. bolog. mix add in chilli powder and tinned kidney beans.

Pizza - buy bases from supermarket, use p.f. tomato paste/puree. Add on ham, tuna, anchovy (p.f.), cheese, mushrooms. fresh tomatoes.

Beefburgers - make with mince, onion, breadcrumbs, egg. Grill or fry

Sausages - Bernard Matthews sausages are free from cinnamon: use in casseroles with mix as for spag. bolog.

Gammon Steaks / with pineapple (p.f.)

Lamb or pork chops

Pork or beef steaks

Chicken in homemade white sauce with vegetables as Lasagne.

Pasta - 1. Boil pasta - make homemade Spag Bolog. mix sauce add cheese if wished.

2. Make white sauce - add bacon/ham, cheese, mushrooms, onions etc.

3. Cabonara type pasta - using bacon, eggs, cream and cheese to mix.

Fish - All types of fresh fish including smoked, oily fish and seafood. Poach, steam, grill or fry.
Use with a homemade white, mushroom or cheese sauce.
Fish finger. Haddock in batter.

MENU PLAN FOR BENZOATE + CINNAMON FREE DIETS

Vegetables:

All fresh or frozen vegetables are suitable
Potatoes - boiled, mashed, sauté, chips

Desserts:

Fresh fruit
Yoghurt - check for p.f.
Tinned fruit - check for preservatives
Milk puddings - custard, rice semolina, tapioca
Ice Cream - check for preservatives, -
No fruit or fruit sauce
Jelly - No lime or blackcurrant jellies
Fruit crumbles - using fresh fruit or p.f. tinned/ bottles fruit
Sponge puddings - Eve's pudding using fresh fruit or tinned fruit
Sponge puddings with dried fruit - check dried fruit for p.f.

KAM/EMT. FEB 95

SOFT DRINKS FREE FROM BENZOATES, CINNAMON AND SORBIC ACID

Fizzy Drinks

7-Up - ordinary and diet (bottles & cans)
Piermont
Rio Riva - (cans only)
Britvic Citrus Spring - (cans only)

Diet Kiri
Kiri
Apletise
Orangina - Diet and ordinary (cans only)

Schweppes Indian Tonic - slimline and ordinary (bottles)

Canada Dry - Ordinary Ginger Ale (not diet)

Asda - Soda Water

Diluting Drinks

Sainsbury Ruby Red Grapefruit Squash

St. Clements High Juice Orange Squash

Sunquick

Robinsons - Lemon Barley Squash

Wells - Orange Squash with Vitamins added

KAM/RS.
23.6.94.

CINNAMON FREE PRODUCTS

The following Heinz products are free from Cinnamon

CORE PRODUCTS

BAKED BEANS

Barbecue Beans
Curried Beans with Sultanas

LUNCH BOWLS

Beef Curry with Rice
Beef Goulash with Noodles
Chicken Curry with Rice
Chilli Con Carne with Rice
Lamb and Vegetable Casserole

PASTA

Chef's Specials, Chicken Ravioli in Tomato Sauce
Chef's Specials, Macaroni Cheese
Chef's Specials, Pasta Pipes with Tuna & Bacon
Chef's Specials, Ravioli in Spicy Sauce
Chef's Specials, Sausage Hotpot with Pasta
Chef's Specials, Spicy Beef Pasta Twists
Dinosaurs with Mini Meat Boulders
Dinosaurs, Pasta Shapes in Tomato Sauce
Flintstones, Spaghetti Shapes in Tomato Sauce
Magic Roundabout, Spaghetti Shapes in Tomato Sauce
Noodle Doodles, Spaghetti Shapes in Tomato Sauce
Spaghetti Hoops in Tomato Sauce
Spaghetti in Tomato Sauce
Spaghetti with Sausages
Super Mario, Spaghetti Shapes in Tomato Sauce
Thomas the Tank Engine, Spaghetti in Tomato Sauce

SAUCES, SALADS & PICKLES

Apple Sauce
Coleslaw Salad
Coronation sauce
Mayonnaise
Mixed Bean Salad
Pasta Salad
Ploughman's Piccalilli
Ploughman's Pickle
Ploughman's Tangy Sandwich Pickle
Ploughman's Tomato Pickle
Potato Salad
Salad Cream
Salad Cream, Spoonable
Salsa, Medium-Hot

Salsa, Mild-Medium
Sandwich Spread, Cucumber
Sandwich Spread, Spicy
Sandwich Spread, Sweetcorn & Red Pepper
Silverskin Onions
Vegetable Salad

SPONGE PUDDINGS

Sponge Pudding, Banana with Toffee Sauce
Sponge Pudding, Chocolate with Chocolate Sauce
Sponge Pudding, Lemon
Sponge Pudding, Mixed Fruit
Sponge Pudding, Strawberry Jam
Sponge Pudding, Treacle

READY TO SERVE SOUPS

Beef Soup
Big Soup, Beef & Bacon Hotpot
Big Soup, Beef & Vegetable
Big Soup, Beef Broth
Big Soup, Chicken & Ham
Big Soup, Chicken & Vegetable
Big Soup, Chicken, Leek & Potato
Big Soup, Giant Minestrone
Big Soup, Spicy Tomato with Beef Pasta Parcels
Big Soup, Thick Country Vegetable with Ham
Chicken & Mushroom Soup
Cream of Asparagus Soup
Cream of Celery Soup
Cream of Chicken Soup
Cream of Mushroom Soup
Farmhouse Beef & Vegetable Soup
Farmhouse Beef Broth
Farmhouse Chicken & Vegetable Soup
Farmhouse Potato & Leek Soup
Farmhouse Scotch Broth
Mulligatawny Soup
Oxtail Soup
Pasta Soup, Beef & Tomato Bolognese
Pasta Soup, Chicken Pastini
Pasta Soup, Minestrone
Pasta Soup, Mushroom Carbonara
Pasta Soup, Tomato Napoli
Premium Soup, Beef, Potato & Red Pepper
Premium Soup, Carrot, Potato & Coriander
Premium Soup, Chicken, Sweet Pepper & Dill
Premium Soup, Chicken, Sweetcorn & Asparagus
Premium Soup, Country Bean with Mushroom
Premium Soup, Seven Vegetable

CINNAMON FREE PRODUCTS - CONTINUED

Scottish Vegetable Soup with Lentils
Spicy Soup, Chilli Bean & Beef
Spicy Soup, Curried Chicken with Rice
Spring Vegetable Soup
Vegetable Soup
Wholesoup, Farmhouse Vegetable
Wholesoup, Ham & Butter Bean
Wholesoup, Lentil
Wholesoup, Pea & Ham
Wholesoup, Winter Vegetable

TOPPERS

Toast Toppers, Chicken & Mushroom
Toast Toppers, Ham & Cheese
Toast Toppers, Mushroom & Bacon

CANNED TUNA

Tuna Chunks, Canned in Brine
Tuna Chunks, Canned in Vegetable Oil
Tuna Steak, Canned in Brine
Tuna Steak, Canned in Vegetable Oil

CINNAMON FREE PRODUCTS - CONTINUED

BREAD & ROLLS

Brown Bread
Danish Brown Bread
Danish Malted Softgrain Bread
Danish White Bread
Oat Danish Bread
Soft Brown Rolls
Soft White Rolls
White Bread

CANNED SOUPS

Chicken & Ham with Rice Soup
Chicken Noodle Soup
Chicken Soup
Country Vegetable & Beef Soup
Country Vegetable Soup
Lentil & Carrot Soup
Mushroom Soup
Vegetable Soup
Wholesome Soup, Lentil & Chicken
Wholesome Soup, Winter Vegetable

INSTANT SOUPS

Asparagus & Leek Soup, 40 kcal
Chicken & Sweetcorn Soup, 60 kcal
Chicken & Vegetable Soup with Noodles, 60 kcal
Chicken & Vegetable Soup, 40 kcal
Chicken Soup, 40 kcal
Minestrone Soup, 60 kcal
Mushroom Soup, 40 kcal
Mushroom Soup, 60 kcal
Tomato Soup, 40 kcal
Tomato Soup, 60 kcal
Vegetable Soup with Croutons, 60 kcal
Vegetable Soup, 40 kcal

BISCUITS & SNACKS

Cookies, Dark Treacle
Cookies, Real Chocolate Chip
Cookies, Stem Ginger

BENZOATE AND CINNAMON AVOIDANCE

Foods Allowed	Foods to check labels for E210-E219	Foods to be avoided
Meat - Cook from fresh whenever possible. Fresh and frozen meats.		Canned meat in a spicy sauce. Cold meats containing spices. Commercially made meat dishes containing spices, eg lasagne, pizza. Pizza. Curries. Chinese meals. Avoid "spice" on beef ham. Some sausages, pies, bridies, etc MAY contain spices - check labels.
Fish - Cook from fresh wherever possible. All types of fresh, frozen, tinned fish (not in sauce), shell fish allowed.		Commercially made fish dishes containing spices. Canned fish in spicy sauce. Prawn cocktail. Prawn Marie Rose.
Spices - Nutmeg, ginger, cumin, coriander, chilli powder, turmeric and all other spices apart from those on Avoid list.		Spices - Cinnamon, mixed spice, allspice, Curry powder. Check labels on any other spice mixes. e.g. Garam Masala.
Herbs - all herbs including garlic. Salt, pepper, black pepper.		
Soup - Most soups - homemade, tinned, packet - apart from those on avoid list.		Tinned or packet soup containing tomato, spices, tomato purée.
Sugar - Tablet artificial sweetener.	Liquid artificial sweetener	

BENZOATE AND CINNAMON AVOIDANCE

Foods Allowed	Foods to check labels for E210-E219	Foods to be avoided
Crisps - Check Products List for those free from cinnamon. In general keep to salt & vinegar, ready salted, cheese & onion.		Crisps and snacks which contain spices, eg prawn cocktail, tomato, barbeque beef flavours.
Nuts - most types		Dry Roasted nuts. Bombay mix. Spicy nut mixes.
Vegetables - all types including potatoes, chips, salad vegetables, fresh and tinned tomatoes.	Tomato purée.	Commercially made foods containing tomato purée if not marked "preservative free", eg pizza, lasagne, pasta dishes.
Bread - Use brown breads, wholemeal bread, brown or wheaten rolls. White bread made with UNBLEACHED white flour (check label on loaf).		White rolls. } may cause a problem only. French bread. } White bread made with BLEACHED white flour. Check labels on loaves for type of flour used.
Fruit: Fresh fruit - all types.	Any preserved fruit in any form, eg Fruit based dessert sauces. Fruit toppings for ice cream. Gateaux containing fruit. Apple pies - fruit pies in general. Fruit pie fillings. Toppings for cheese cakes. Crystalised or glacé fruit. Dried fruit. Tins of fruit or fruit purée.	Preserved fruit in any form if it is not known to be free from E210-E219.

BENZOATE AND CINNAMON AVOIDANCE

Foods Allowed	Foods to check labels for E210-E219	Foods to be avoided
Milk, cream, butter, cheese, margarine	Yoghurt Flavoured milk drinks. Milk shake syrup Artificial cream	Ice cream with fruit or fruit syrup in it, eg Raspberry Ripple, Tutti Frutti. "Raspberry" sauce for ice cream.
Cooking oils and lard. Salad oils		
Eggs		
Pasta - all types	Made up pasta dishes.	Commercially made pasta dishes with spices on the label. All pasta tinned in tomato sauce.
Rice - all types		Commercially made rice dishes with spices on the label.
Breakfast cereals - all types including porridge, bran.		
Peas, beans, lentils		Baked beans in tomato sauce, spaghetti in tomato sauce, ravioli in tomato sauce. Any similar products tinned in tomato sauce.
Custard powder, custard, rice, semolina, tapioca, sago, cremola, cornflour, arrowroot. Tinned milk puddings.		

BENZOATE AND CINNAMON AVOIDANCE

FOODS ALLOWED	FOODS TO CHECK LABELS FOR E210-E219	FOODS TO BE AVOIDED
Alcohol: White wine,whisky,vodka, white rum,sherry,brandy,cider,lager, beer,Tennant's "LA" in cans.	Be careful that any mixers are preservative free.	Red wine,gin,dark rum,Tia Maria, Martini N.V.Many liqueurs may contain spices - be aware of this if any reaction occurs. Cinzano,Dubonnet and similar products. Tennant's "LA" on draught.
Pickles,sauces,chutneys NOT on Manufactured Products List and NOT containing E210-E219.	All pickles,sauces,chutneys,pickled foods (e.g. herring,onions,beetroot),vinegar,mustard,tomato sauce,brown sauce.Mayonnaise,salad cream,salad dressings. REMEMBER to check Manufactured Products List to see if they contain cinnamon.	Tomato sauce. ALL pickles etc.,on Manufactured Products List,i.e.containing cinnamon, or if containing E210-E219.
Hot Drinks: Tea,coffee,hot chocolate, cocoa,Ovaltine,Horlicks,Bournvita, Oxo,Marmite,Bovril.	"Camp" liquid coffee. Chocolate drinks.	
Jams and marmalade: Home made jam and marmalade. Honey,syrup,treacle, peanut butter.	Lemon curd. Diabetic jam.	Preserves containing E210-E219.
Home Baking: Use unbleached flour for baking. Check labels on packet for this.	Dried fruit,mixed peel,glace cherries. Pie fillings.	Cinnamon,allspice,mixed spice, mincemeat.

BENZOATE AND CINNAMON AVOIDANCE

FOODS ALLOWED

Cakes and biscuits: Keep to home baked goods as much as possible.

Soft Drinks: 7-Up (not diet). St.Clements canned drinks-not coke. Appletise,Kiri. Orangina (cans only), Sunquick squash,Robinsons High Juice Squashes and Barley Squashes, Robinson's "R" reduced sugar drinks, Perrier water and other natural spring water.

Fudge,toffee,tablet,chocolate, liquorice,boiled sweets (no cola sweets).

Toothpaste: Colgate Regular, Crest Regular, Kingfisher,
MACLEANS FRESHMINT,
" " MILDTASTE
" " SENSITIVE
" " MOUTHGUARD

See also Manufactured Food Products List

FOODS TO CHECK LABELS FOR E210-E219

Check labels on ALL squashes,fizzy drinks, soft drinks,bottled shandy,non-alcoholic grape juice drinks,e.g.Schloer. Ice lollies, Ice Poles, "Tip Tops",Slush Puppies. Soda waters.

FOODS TO BE AVOIDED

Mincemeat pies and tarts. Bought fruit pies,Danish pastries,coffee cuns,gingerbread. Rich fruit cake.Christmas cake/ pudding. Black Bun. Biscuits containing large quantities of dried fruit.

Any soft drinks containing E210-E219 also avoid Coca Cola, Irn Bru,Vimto,Dr. Peppers,Pepsi Cola.

Cinnamon sticks,cola cubes, cola sweets,cola chews,etc. Irn Bru chews.

All other toothpastes. NO tartar controlled toothpastes.
COLGATE MAX
COLGATE ARTBRUSH.
COLGATE BLUE MINTGEL.
Aquafresh Fresh & Minty
" " Mild & Minty
MACLEANS MILDMINT.

Glasgow Royal Infirmary

Dietetic Department

Benzoate Free Diet

As most of the Benzoates in the diet are added to foods as a PRESERVATIVE it is very important that you read the labels of any manufactured or prepared foods you consume. If Benzoates are added to the food, the manufacturer may name the particular Benzoate a serial number known as an E number, avoid those from E210 - E219 inclusive. If you are unsure whether a food / drink may contain Benzoate it is best to avoid it.

Avoid any food which just lists the word "Preservative" or "Permitted Preservative" as an ingredient.

The Benzoates used in foods are :

E210 - Benzoic acid.
E211 - Sodium Benzoate.
E212 - Potassium Benzoate.
E213 - Calcium Benzoate.
E214 - Ethyl 4-hydroxybenzoate.
E215 - Ethyl 4-hydroxybenzoate sodium salt.
E216 - Propyl 4-hydroxybenzoate.
E217 - Propyl 4-hydroxybenzoate sodium salt.
E218 - Methyl 4-hydroxybenzoate.
E219 - Methyl 4-hydroxybenzoate sodium salt.

AVOID ANY ITEM CONTAINING THESE

In general - **AVOID**

Commercially prepared meat and fish dishes of which the exact composition is not known - lasagne, pizza, curry, Chinese foods, flans, quiches. Keep to fresh or home cooked food wherever possible.

Check Labels On

1. Squashes. cordials and diluting drinks.
2. Fizzy drinks.
3. Glucose drinks. e.g. Lucozade.
4. Non alcoholic grape juice drinks. e.g. Schloer.
5. Slush puppies. ice poles. ice lollies. Tip Top.
6. Bottles shandy. Avoid Tennants 'L.A.' on draught.
7. Chocolate drinks.
8. Liquid coffee and chicory drinks e.g. Camp coffee.
9. Flavoured milk drinks and milk shake syrup.
10. Yoghurt.
11. Colourings and flavourings used in home baking.
12. Jams. marmalades. chocolate spreads and also diabetic jam.
13. Liquid artificial sweetener. e.g. Sweetex liquid.
14. Pickled products. e.g. herring, onions. beetroot. pickles. Canned fish in tomato sauce. pickled herring.
15. Also check sauces - horseradish. brown sauce. tomato sauce. mustard and vinegar.
16. Mayonnaise. salad cream. and salad dressings. Coleslaw and any salads in Delicatessen counters. Potato salad.
17. Dried fruit. Tins or jars of fruit or fruit puree. Avoid ice cream with fruit / fruit sauce in it.
18. White bread. Avoid bread made with bleached flour - check labels.
19. Fruit sauces. toppings on cheesecakes. gateaux etc.
    Fruit pie fillings. Dessert sauces. Bought dessert cakes and gateaux.
    Fruit pies.
20. Crystallised or glace fruit. Any preserved fruits.

The recommended toothpastes are :

1. Kingfisher.
2. Colgate Regular. Colgate Junior. Colgate Tartar Control. Ultrabrite. Colgate Blue Minty Gel.
3. Crest - all types.
4. Macleans Original. Macleans Sensitive. Macleans Milk Teeth. Aquafresh.

Any queries please contact your Dietitian :
Name :
Hospital :
Telephone No :

K.A.M. Dec 1995

Coffee

ASDA
- Ground Coffee - all varieties
- Instant coffee - all varieties

Cafe Hag
- Decaffeinated coffee

Kenco
- Coffee

Maxpax
- Black instant coffee
- Kenco Smooth blend white instant coffee
- White instant coffee

Maxwell House
- Cappuccino Instant cappuccino
- Instant coffee

Mellow Bird's
- Instant coffee

Nestle
- Espresso
- Nescafe Instant Cappuccino - original, and unsweetened
- Nescafe Nescafe Instant Coffee - all varieties

Fruit Drinks (including squashes and concentrates)

ASDA
- Apple C drink - UHT
- Grapefruit C drink - UHT
- Hi juice mange crush 3x 250ml
- Orange & apricot juice drink (no added sugar) - UHT - 3x 250ml
- Orange C drink - UHT
- Orange juice drink (no added sugar) - UHT - 3x 250ml
- Ready to drink lemon juice drink 3x 250ml

Bird's
- Apeel Orange drink mix

C-Vit
- Ready-to-drink multi-vitamin fruit drinks - all varieties

Five Alive
- Diet drink
- Drink

Fruitopia
- Drink

Kia-Ora
- Ready to Drink Mixed fruit drink
- Ready to Drink Orange & pineapple drink
- Ready to Drink Orange drink
- Ready to Drink Pear and blackcurrant drink

Maxpax
- Countrytime Blackcurrant flavour drink mix
- Countrytime Lemon flavour drink mix
- Countrytime Orange flavour drink mix

Ribena
- Ready-to-drink - all tetra pack varieties

Robinsons
- Apple and blackcurrant - in tetrapak RTD
- Apple and raspberry - concentrated

Fruit Drinks (including squashes and concentrates)

Robinsons
- Apple and strawberry concentated soft drink
- Citrus cordial
- Fruit and barley
- Lemon and lime - no added sugar
- Lemon barley water - concentrated
- Lime juice cordial - concentrated
- Mediterranean cordial
- Orange barley water - concentrated
- Premium lemon drink
- Premium orange drink
- Ready Drink Blueberry
- Special R Orange and pineapple concentated soft drink
- Special R Orange drink concentrated
- Special R Orange drink RTD in tetrapack

Robinsons
- Special R Summer fruit drink - concentrated
- Special R Tropical RTD
- Whole grapefruit and pinapple - no added sugar
- Whole grapefruit drink - concentrated
- Whole lemon - no added sugar
- Whole orange drink - concentrated

Rose's
- Diabetic Fruit squashes
- Lime juice cordial

Schweppes
- Blackcurrant flavour cordial
- Lime flavour cordial
- Peppermint cordial

Fruit Juices

ASDA
- All chilled and UHT pure fruit juices
- Apple & Blackcurrant juice drink (no added sugar) - 3x 250ml

Britvic
- Fruit juices - bottles, cans, Tetrapaks
- Orange juice - draught

Copella
- Freshly pressed English apple and blackcurrant juice - bottles and cartons
- Freshly pressed English apple and orange - bottles
- Freshly pressed English apple and strawberry juice - bottles and cartons

Copella
- Freshly pressed English apple juice - bottles and cartons
- Freshly pressed English pear and apple juice - bottles

Libby
- "C" fruit juice drinks - all varieties
- Fruit juices, unsweetened
- Tomato juice - canned or glass or carton
- Um Bongo mixed fruit juice drink

Meridian
- Fruit juice concentrates

Robinsons
- Blackcurrant juice - in tetrapack RTD

Carbonated Drinks

ASDA
Soda water

Britvic
Citrus Spring Cans
Citrus Spring Glass bottles

Cherry Coke
Drink

Coca-Cola
Drink

Ribena
Spring All varieties - bottled

Schweppes
American ginger ale

Schweppes
Canada Dry Ginger ale
Dry ginger ale
Ginger beer - in bottles
Indian tonic water
Schizan Sparkling drink with fruit and plant extracts
Slimline American ginger ale - low calorie
Slimline Indian tonic water - low calorie
Soda water

St Clements
All sparkling fruit drinks - in cans

Chocolate and Malt Drinks

ASDA
Drinking chocolate - 250g and 500g
Fat reduced drinking chocolate granules 500g
Instant hot chocolate - 400g

Cadburys
Bournvita
Bournvita Break Instant malted chocolate drink
Choc-a-shake
Chocolate Break Milk chocolate beverage
Cocoa
Drinking chocolate
High Lights Low calorie chocolate beverage - all varieties
Milk drink

Fussells
Instant Hot Chocolate Drink

Horlicks
Low fat instant All varieties
Malted food drink

Jubilee
Hot chocolate mix

Mars
Milk drink

Maxpax
Chocolate drink mix
Malted milk drink mix

Nestle
Chococino hot chocolate drink - standard & light all types

NATLETTE
Kiz.1

Please check products periodically as composition may change

APPENDIX G LETTER ACCOMPANYING FOLLOW UP QUESTIONNAIRE

Glasgow Dental Hospital & School
378 Sauchiehall St.
Glasgow
G2 3JZ

20 January 1997

Dear Sir/Madam,

I would be very grateful if you could take time to help me in my research study.

I am looking at the benefits of following advice in avoiding food allergens after being patch tested.

Enclosed is a short questionnaire. Please could you complete it as soon as possible and return it using the reply paid envelope. There is no need to put your name on the returned questionnaire and the results will be treated in the strictest confidence.

Thank you for your time in answering these questions. Your involvement will help us provide better care in the future.

Yours faithfully,

Shiona R Rees
(Senior House Officer and Clinical Research Assistant in Oral Medicine)

Appendix H Patient Follow Up Questionnaire

No. .....

[linear analogue line. not to scale]

QUESTIONNAIRE

REASON FOR PATCH TESTING

1. What was the reason you were sent for patch testing?

Please circle all that apply to you

Mouth ulcers? White patches? Angioedema? Erythema multiforme?
Orofacial Granulomatosis? Other? Please explain .....
.....
.....

DIET ADVICE

2. Did you understand the written dietary avoidance sheets? Yes / No / Didn't receive
Please circle the answer that most applies to you.

3. How closely did you follow the dietary avoidance advice?

Didn't follow it at all	———	Followed the diet advice completely

Please indicate with a 'x' on the line where best indicates your answer.

SYMPTOMS PRIOR TO PATCH TESTING

4. How bad were your symptoms prior to attending for patch testing?

No symptoms	———	Symptoms as bad as they could be

Please indicate with a 'x' on the line where best indicates your answer.

SYMPTOMS AFTER RECIEVING DIET ADVICE

5. How bad were your symptoms after receiving dietary avoidance advice?

No symptoms	———	Symptoms as bad as they could be

Please indicate with a 'x' on the line where best indicates your answer.

PLEASE TURN OVER

OTHER FACTORS

6. Were there any other factors that may have influenced any change in symptoms?

Removal of amalgam fillings? Yes / No Change of denture? Yes / No

Change of crowns? Yes / No

Medications? Yes / No .....please specify

Other? Yes / No.....please specify

7. Do you have any medical conditions? Yes / No

If yes, please specify.....

.....

8. What medications do you take?

.....

.....

9. Do you smoke? Yes / No / In the past

If yes, how many per day? .....

THANK YOU FOR ANSWERING THESE QUESTIONS
PLEASE POST TODAY

BIBLIOGRAPHY

"Medicines Resource Centre" 1994, "Angiotensin-converting enzyme inhibitors.", *International Pharmacy Journal*, vol. 8, no. 2, pp. 58-62.

2000, *Stedman's Medical Dictionary*, 27th edn, Lippincott, Williams and Wilkins, Philadelphia.

Aberer, W. 1991, "Vaccination despite thimerosal sensitivity.", *Contact Dermatitis*, vol. 24, pp. 6-10.

Aberer, W. & Holub, H. 1992, "Multicentre studies and conflicting prevalence data.", *Contact Dermatitis*, vol. 27, pp. 133-135.

Ackerman, A. B. 1978, *Histologic Diagnosis of Inflammatory Skin Diseases*, Lea & Febiger, Philadelphia.

Alanko, K., Kanerva, L., Jolanki, R., Kannas, L., & Estlander, T. 1996, "Oral mucosal diseases investigated by patch testing with a dental screening series.", *Contact Dermatitis*, vol. 34, pp. 263-267.

Albrecht, M., Bánóczy, J., Dinya, E., & Tamás, Gy. Jr. 1992, "Occurrence of oral leukoplakia and lichen planus in diabetes mellitus", *Journal of Oral Pathology and Medicine*, vol. 21, no. 364, p. 366.

Alexander, R. W. & James, R. B. 1972, "Melkersson-Rosenthal syndrome:Review of the literature and report of a case", *Journal of Oral Surgery*, vol. 30, pp. 599-604.

Allen, C. M., Camisa, C., Hamzeh, S., & Stephens, L. 1990, "Cheilitis granulomatosa: Report of six cases and review of the literature", *Journal of the American Academy of Dermatology*, vol. 23, pp. 444-450.

Allen, D. H. 1991, "Monosodium glutamate," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, pp. 260-266.

Andersen, K. E. 1978, "Contact allergy to toothpaste flavors", *Contact Dermatitis*, vol. 4, pp. 195-198.

Andersen, K. E., Burrows, D., Cronin, E., & Dooms-Goossens, A. 1988, "Recommended changes to standard series.", *Contact Dermatitis*, vol. 19, pp. 389-391.

Anderson, J. A. 1997a, "Allergic and allergic-like reactions to drugs and other therapeutic agents," in *Allergic Diseases: Diagnosis and Treatment*, P. Lieberman & J. A. Anderson, eds., Humana Press Inc., Totowa, New Jersey, pp. 275-292.

Anderson, J. A. 1997b, "Food allergy and intolerance," in *Allergic Diseases: Diagnosis and Treatment*, P. Lieberman & J. A. Anderson, eds., Humana Press, Totowa,New Jersey, pp. 255-274.

Andreasen, J. O. 1968, "Oral lichen planus: A clinical evaluation of 115 cases", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 25, no. 1, pp. 31-42.

Antico, A. 1996, "Oral allergy syndrome induced by chestnut (Castanea sativa)", *Annals of Allergy, Asthma and Immunology*, vol. 76, pp. 37-40.

Antoine, J. L. & Lachapelle, J. M. 1988, "Variations in the quantities of petrolatum applied in patch testing.", *Dermatosen in Beruf und Umwelt*, vol. 36, no. 6, pp. 191-194.

Armstrong, D. K. B., Biagioni, P., Lamey, P. J., & Burrows, D. 1997, "Contact Hypersensitivity in Patients with Orofacial Granulomatosis", *American Journal of Contact Dermatology*, vol. 8, no. 1, pp. 35-38.

Armstrong, D. K. B. & Burrows, D. 1995, "Orofacial granulomatosis", *International Journal of Dermatology*, vol. 34, pp. 830-833.

Arthus, M. 1903, "Injections repetées de sérum de cheval chez le lapin", *Comptes Rendus des Seances de la Societe de Biologie (Paris)*, vol. 55, pp. 817-820.

Asero, R., Mistrello, G., & Falagiani, P. 1997, "Oral allergy syndrome from pork", *Allergy*, vol. 52, no. 6, pp. 684-686.

Atkinson, J. C. & Frank, M. M. 1991, "Oral manifestations and dental management of patients with hereditary angioedema.", *Journal of Oral Pathology and Medicine*, vol. 20, pp. 139-142.

Augener, W., Cohen, G., Reuter, A., & Brittinger, G. 1974, "Decrease of T lymphocytes during ageing.", *Lancet*, vol. 1, p. 1164.

Avenberg, K. M. & Harper, D. S. 1982, *Footnotes on Allergy,* Pharmacia AB, Uppsala, Sweden.

Axéll, T., Bjorkner, B., Fregert, S., & Niklasson, B. 1979, "Standard patch test series for screening of contact allergy to dental materials", *Contact Dermatitis*, vol. 9, no. 1, pp. 82-84.

Axéll, T. & Rundquist, L. 1987, "Oral lichen planus - a demographic study", *Community Dental and Oral Epidemiology*, vol. 15, pp. 52-56.

Axéll, T., Spiechowicz, E., Glantz, P.-O., Andersson, G., & Larsson, Å. 1986, "A new method for intraoral patch testing.", *Contact Dermatitis*, vol. 15, pp. 58-62.

Axéll, T., Zain, R. B., Siwamogstham, P., Tantiniran, D., & Thampipit, J. 1990, "Prevalence of oral soft tissue lesions in out-patients at two Malaysian and Thai dental schools", *Community Dental and Oral Epidemiology*, vol. 18, pp. 95-99.

Ayala, F., Balato, N., Lembo, G., Patruno, C., Fabbrocini, G., Nofroni, I., Magliocchetti, N., Schena, D., Rafanelli, A., Seidenari, S., Motolese, A., Angelini, G., Tosti, A., Saccabusi, S., Pigatto, P., & Lisi, P. 1996, "Statistical evaluation of the persistence of acquired hypersensitivity by standardized patch tests.", *Contact Dermatitis*, vol. 34, pp. 354-358.

Bagán-Sebastián, J. V., Milián-Masanet, M. A., Peñarrocha-Diago, M., & Jiménez, Y. 1992, "A clinical study of 205 patients with oral lichen planus.", *Journal of Oral and Maxillofacial Surgery*, vol. 50, pp. 116-118.

Bagán, J. V., Aguirre, J. M., Olmo, J. A., Milián, A., Penarrocha, M., Rodrigo, J. M., & Cardona, F. 1994, "Oral lichen planus and chronic liver disease: A clinical and morphometric study of the oral lesions in relation to transaminase elevation.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 78, pp. 337-342.

Bagán, J. V., Sanchis, J. M., Milián, M. A., Peñarrocha-Diago, M., & Silvestre, F. J. 1991a, "Recurrent aphthous stomatitis. A study of the clinical characteristics of lesions in 93 cases.", *Journal of Oral Pathology and Medicine*, vol. 20, pp. 395-397.

Bagán, J. V., Silvestre, F. J., Mestre, S., Gisbert, C., Bermejo, A., & Agramunt, J. 1991b, "Treatment of lichen planus with griseofulvin.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 60, pp. 608-610.

Baillie, A. J., Biagioni, P. A., Forsyth, A., Garioch, J. J., & Mcpherson, D. 1990, "Thermographic assessment of patch-test responses", *British Journal of Dermatologyatol*, vol. 122, no. 3, pp. 351-360.

Barkin, M. E., Boyd, J. P., & Cohen, S. 1984, "Acute allergic reaction to eugenol.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 57, pp. 441-442.

Barrett, K. E. 1991, "Mast cells, basophils, and immunoglobulin E," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, pp. 13-35.

Basker, R. M. 1981, "Nickel sensitivity.", *British Dental Journal*, vol. 151, pp. 414-415.

Basketter, D. A. & Wilhelm, K. P. 1996, "Studies on non-immune immediate contact reactions in an unselected population", *Contact Dermatitis*, vol. 35, pp. 237-240.

Bays, R. A., Hamerlinck, F., & Cormane, R. H. 1977, "Immunoglobulin bearing lymphocytes and polymorphonuclear leucocytes in recurrent aphthous ulcers in man.", *Archives of Oral Biology*, vol. 22, pp. 147-153.

Bánóczy, J., Roed-Petersen, B., & Pindborg, J. J. 1979, "Clinical and histologic studies on electrogalvanically induced oral white lesions", *Oral Surgery*, vol. 48, pp. 319-328.

Bánóczy, J. & Sallay, K. 1968, "Comparative cytologic studies in patients with recurrent aphthae and leukoplakia", *Journal of Dental Research*, vol. 48, no. 2, pp. 271-273.

Becker, J. & Schuppan, D. 1995, "Altered expression of extracellular matrix proteins and integrins in oral lichen planus.", *Journal of Oral Pathology and Medicine*, vol. 24(4), pp. 159-164.

Bendixen, G. 1966, "Classification of hypersensitivity in relation to clinical disease", *Annals of Internal Medicine*, vol. 64, no. 3, pp. 669-686.

Berardesca, E. & Maibach, H. I. 1988, "Racial differences in sodium lauryl sulphate induced cutaneous irritation: black and white.", *Contact Dermatitis*, vol. 18, pp. 65-70.

Bergdahl, B. J., Anneroth, G., & Anneroth, I. 1994, "Clinical study of patients with burning mouth.", *Scandinavian Journal of Dental Research*, vol. 102(5), pp. 299-305.

Bergman, M. 1990, "Side-effects of amalgam and its alternatives: local, systemic and environmental", *International Dental Journal*, vol. 40, no. 1, pp. 4-10.

Bleiker, T. O. & English, J. S. 1998, "Acute contact allergy to dental amalgam", *Contact Dermatitis*, vol. 38, no. 2, p. 112.

Bloch, B. 1911, "Diasthesen in der dermatologie", *Verhandlungen des Deutschen Kongress für Innere Medizen*, pp. 86-106.

Bloor, B. K., Malik, F. K., Odell, E. W., & Morgan, P. R. 1999, "Quantitative assessment of apoptosis in oral lichen planus", *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics*, vol. 88, no. 2, pp. 187-195.

Bock, S. A. 2000, "Evaluation of IgE-mediated food hypersensitivities", *Journal Of Paediatric Gastroenterology and Nutrition*, vol. 30, no. Suppl, pp. s20-s27.

Boisnic, S., Frances, C., Branchet, M.-C., Szpirglas, H., & Le Charpentier, Y. 1990, "Immunohistochemical study of oral lesions of lichen planus: diagnostic and pathophysiologic aspects", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 70, pp. 462-465.

Bolewska, J., Hansen, H. J., Holmstrup, P., Pindborg, J. J., & Stangerup, M. 1990a, "Oral mucosal lesions related to silver amalgam restorations", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 70, pp. 55-58.

Bolewska, J., Holmstrup, P., Møller-Madsen, B., Kenrad, B., & Danscher, G. 1990b, "Amalgam associated mercury accumulations in normal oral mucosa, oral mucosal lesions of lichen planus and contact lesions associated with amalgam", *Journal of Oral Pathology and Medicine*, vol. 19, pp. 39-42.

Bolewska, J. & Reibel, J. 1989, "T lymphocytes, Langerhan's cells and HLA-DR expression on keratinocytes in oral lesions associated with amalgam restorations", *Journal of Oral Pathology and Medicine*, vol. 18, no. 9, pp. 525-528.

Bos, J. D., Wierenga, E. A., Smitt, H. S., van der Heijden, F. L., & Kapsenberg, M. L. 1992, "Immune dysregulation in atopic eczema.", *Archives of Dermatology*, vol. 128, pp. 1209-1512.

Bosso, J. V. & Simon, R. A. 1991, "Urticaria, angioedema and anaphylaxis provoked by food additives," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, pp. 288-300.

Bowen, W. H. 1996, "Salivary influences on the oral microflora," in *Saliva and Oral Health*, 2nd edn, W. M. Edgar & D. M. O'Mullane, eds., British Dental Association, London, pp. 95-103.

Boxer, M. 1996, "Acupril- and Cozaar-induced angioedema in the same patient.", *The Journal of Allergy and Clinical Immunology*, vol. 98, p. 471.

Boyd, A. S. & Neldner, K. H. 1991, "Lichen planus.", *Journal of the American Academy of Dermatology*, vol. 25, no. 4, pp. 593-619.

Brasch, J., Geier, J., & Henseler, T. 1995, "Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the Information Network of Departments of Dermatology (IVDK).", *Contact Dermatitis*, vol. 33, pp. 375-380.

Bratel, J., Dahlgren, U., Simark, M. C., & Jontell, M. 1998, "The frequency of different T-cell receptor V-families in oral lichen planus and lichenoid contact lesions: an

immunohistochemical study", *Journal of Oral Pathology and Medicine*, vol. 27, no. 9, pp. 415-419.

Bratel, J., Hakeberg, M., & Jontell, M. 1996, "Effect of replacement of dental amalgam on oral lichenoid reactions.", *Journal of Dentistry*, vol. 24, no. 1-2, pp. 41-45.

Brehler, R., Panzer, B., Forck, G., & Bertram, H. P. 1993, "Mercury sensitization in amalgam fillings. Assessment from a dermatologic viewpoint.", *Deutsche medizinische Wochenschrift*, vol. 118(13), pp. 451-456.

Brehler, R., Theissen, U., Mohr, C., & Luger, T. 1997, ""Latex-fruit syndrome": frequency of cross-reacting IgE antibodies", *Allergy*, vol. 52, no. 4, pp. 404-410.

British Medical Association & Royal Pharmaceutical Society of Great Britain 2000a. British National Formulary. Joint Formulary Committee. *British National Formulary*, 39, 149-153, 161-162, 198-199, 476, 490 & 505.

British Medical Association & Royal Pharmaceutical Society of Great Britain 2000b. British National Formulary. Joint Formulary Committee. *British National Formulary*, 39, 155-156.

Brown, N. J., Ray, W. A., Snowden, M., & Griffin, M. R. 1996, "Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema.", *Clinical Pharmacology and Theraputics*, vol. 60, pp. 8-13.

Bruijnzeel-Koomen, C., Ortolani, C., Aas, K., Bindslev-Jensen, C., Björkstén, B., Moneret-Vautrin, D., & Wuthrich, B. 1995, "Adverse reactions to food.", *Allergy*, vol. 50, pp. 623-635.

Brunelle, J. A., Streckfus, C. F., Klienman, D. V., Winn, D., & Swango, P. A. 1997, "Denture-related oral mucosal lerions in U.S. adults", *Journal of Dental Research*, vol. 76, p. 142.

Bruynzeel, D. R., Andersen, K. E., Camarasa, J. G., Lachapelle, J. M., Menné, T., & White, I. R. 1995, "The European Standard Series.", *Contact Dermatitis*, vol. 33, pp. 145-148.

Bruze, M., Isaksson, M., Edman, B., Björkner, B., Fregert, S., & Möller, H. 1995, "A study on expert reading of patch test reactions: inter-individual accordance.", *Contact Dermatitis*, vol. 32, pp. 331-337.

Caldwell, J. R., Ruddy, S., Schur, P. H., & Austen, K. F. 1972, "Acquired C1 inhibitor deficiency in lymphosarcoma.", *Clinical Immunology and Immunopathology*, vol. 1, pp. 39-52.

Calkin, J. M. & Maibach, H. I. 1993, "Delayed hypersensitivity drug reactions diagnosed by patch testing.", *Contact Dermatitis*, vol. 29, pp. 223-233.

Camisa, C., Taylor, J. S., Bernat, J. R., Jr., & Helm, T. N. 1999, "Contact hypersensitivity to mercury in amalgam restorations may mimic oral lichen planus", *CUTIS; Cutaneous Medicine for the Practitioner*, vol. 63, no. 3, pp. 189-192.

Campbell, M. J. & Machin, D. 1999, *Medical Statistics: A Commonsense Approach*, 3rd edn, John Wiley & Sons, Ltd, Chichester.

Castillo, R., Delgado, J., Quiralte, J., Blanco, C., & Carrillo, T. 1996, "Food hypersensitivity among adult patients: epidemiological and clinical aspects", *Allergology and Immunopathology (Madrid)*, vol. 24, no. 3, pp. 93-97.

Cawson, R. A. & Odell, E. W. 1998, *Essentials of Oral Pathology and Oral Medicine*, 6th edn, Churchill Livingstone, Edinburgh.

Ceballos-Salobreña, A., Aguirre-Urizar, J. M., & Bagan-Sebastian, J. V. 1996, "Oral manifestations associated with human imunodeficiency virus infection in a Spanish population", *Journal of Oral Pathology and Medicine*, vol. 25, pp. 523-526.

Challacombe, S. J. 1997, "Orofacial granulomatosis and oral Crohns diease: are they specific diseases and do they predict sustemic Crohns disease", *Oral Diseases*, vol. 3, pp. 127-129.

Challacombe, S. J., Batchelor, J. R., Kennedy, L. A., & Lehner, T. 1977, "HLA antigens in recurrent oral ulceration", *Dermatology*, vol. 113, pp. 1717-1719.

Challacombe, S. J., Savage, N. W., Barnard, K., Rahman, D., Mistry, M., & Sanderson, J. 1997, "A comparison of systemic and mucosal antibody responses in oro-facial granulomatosis and Crohn's Disease", *Journal of Dental Research*, vol. 76, p. 142.

Chapman, R. S., Forsyth, A., & MacQueen, A. 1977, "Erythema multiforme in association with active ulcerative colitis and Crohn's disease", *Dermatologica*, vol. 154, no. 1, pp. 32-38.

Christophersen, J., Menné, T., Andersen, K. E., Brandrup, F., Kaaber, K., Osmundsen, P. E., Thestrup-Pedersen, K., & Veien, N. K. 1989, "Clinical patch test data evaluated by multivariate analysis.", *Contact Dermatitis*, vol. 21, pp. 291-299.

Cicardi, M., Bergamaschini, L., Cugno, M., Hack, E., & Agostoni, G. 1991, "Long-term treatment of hereditary angioedema with attenuated androgens: A surgey of a 13-year experience", *The Journal of Allergy and Clinical Immunology*, vol. 87, pp. 768-773.

Ciprandi, G., Perasso, A., Marenco, G., Santucci, R., Buffa, P., Cheli, R., & Canonica, G. W. 1989, "Pirenzipine treatment in urticaria-angioedema syndrome caused by adverse reactions to foods.", *Allergology et Immunopathology.*

Coca, A. F. & Grove, E. F. 1924, "Studies in hypersensitiveness", *Journal of Immunology*, vol. 10, pp. 445-464.

Coe, J. E., Feldman, J. D., & Lee, S. 1966, "Immunologic competence of thoracic duct cells: I. Delayed hypersensitivity", *Journal of Experimental Medicine*, vol. 123, pp. 267-282.

Cohen, D. M., Bhattacharyya, I., Zunt, S. L., & Tomich, C. E. 1999, "Linear IgA disease histopathologically and clinically masquerading as lichen planus", *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, vol. 88, no. 2, pp. 196-201.

Colin Dawes 1996, "Factors influencing salivary flow rate and composition," in *Saliva And Oral Health*, 2nd edn, W. M. Edgar & D. M. O'Mullane, eds., British Dental Association, London, pp. 27-41.

Conklin, R. J. & Blasberg, B. 1994, "Oral lichen planus.", *Dermatology Clinics*, vol. 5, no. 4, pp. 663-673.

Cooke, B. E. D. 1960, "The diagnosis of bullous lesions affecting the oral mucosa", *British Dental Journal*, vol. 109, no. 3, pp. 83-89.

Cooper, K. D. 1991, "Urticaria and angioedema: diagnosis and evaluation", *Journal of the American Academy of Dermatology*, vol. 25, pp. 166-176.

Cox, N. H. & Forsyth, A. 1988, "Thiomersal allergy and vaccination reactions.", *Contact Dermatitis*, vol. 18, no. 4, pp. 229-233.

Croitoru, K. & Bienenstock, J. 1991, "Mucosal Immunity," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, pp. 1-12.

Cruchley, A. T., Williams, D. M., Farthing, P. M., Lesch, C. A., & Squier, C. A. 1989, "Regional variation in Langerhan's cell distribution and density in normal human oral mucosa determined using monoclonal antibodies against CD1, HLADR, HLADQ and HLADP", *Journal of Oral Pathology and Medicine*, vol. 18, no. 9, pp. 510-516.

Daftary, D. K., Bhonsie, R. B., Musti, R. B., Pindborg, J. J., & Mehta, F. S. 1980, "An oral lichen planus-like lesion in Indian betel tobacco chewers", *Scandinavian Journal of Dentistry*, vol. 88, pp. 244-245.

Darragh, T. M., Egbert, B. M., Berger, T. G., & Yen, T. S. B. 1991, "Identification of herpes simplex virus DNA in lesions of erythema multifome by the polymerase chain reaction", *Journal of the American Academy of Dermatology*, vol. 24, pp. 23-26.

Davidson, A. E., Miller, S. D., Settipane, G., & Klein, D. 1992, "Urticaria and angioedema.", *Cleveland Clinic Journal of Medicine*, vol. 59(5), pp. 529-534.

de Groot, A. C., Weyland, J. W., & Nater, J. P. 1994, *Unwanted Effects of Cosmetics and Drugs Used in Dermatology*, 3rd edn, Elsevier, Amsterdam.

de Martino, M., Peruzzi, M., Galli, L., Lega, L., Zammarchi, E., & Vierucci, A. 1992, "Food-additive intolerance and its correlation with atopy in children with recurrent or intermittent urticaria-angioedema", *Paediatric Allergy and Immunology*, vol. 3 (1), pp. 33-38.

de Silva, B. D. & Doherty, V. R. 2000, "Nickel allergy from orthodontic appliances", *Contact Dermatitis*, vol. 42, pp. 102-103.

Degroote, D. F., Smith, G. L., & Huttula, G. S. 1985, "Acute airway obstruction following tooth extraction in hereditary angioedema.", *Journal of Oral and Maxillofacial Surgery*, vol. 43, pp. 52-54.

Dolby, A. E. & Allison, R. T. 1969, "Quantitative changes in the mast cell population in Mikulcz's recurrent oral aphthae.", *Journal of Dental Research*, vol. 48, pp. 901-903.

Dolby, A. E., Walker, D. M., Slade, M., & Allan, C. 1977, "HLA histocompatibility antigens in recurrent aphthous ulceration.", *Journal of Dental Research*, vol. 56, pp. 105-107.

Dolovich, J. 1992, "Diagnostic testing in chronic urticaria and angioedema.", *Canadian Medical Association Journal*, vol. 146, no. 9, p. 1528.

Donatsky, O. 1978, "Cell-mediated and humoral immunity against oral streptococci, neisseria, staphylococci, and adult human oral mucosa antigens in recurrent aphthous stomatitis.", *Scandinavian Journal of Dental Research*, vol. 86, pp. 25-34.

Dooms-Goossens, A., Degreef, H., Holvoet, C., & Maertiens, M. 1977, "Turpentine-induced hypersensitivity to pettermint oil.", *Contact Dermatitis*, vol. 3, pp. 304-308.

Dotterud, L. K. & Flak, E. S. 1994, "Metal allergy in north Norwegian school children and its relationship with ear piercing and atopy.", *Contact Dermatitis*, vol. 31, pp. 308-313.

Downs, A. M., Lear, J. T., & Sansom, J. E. 1998, "Contact sensitivity in patients with oral symptoms", *Contact Dermatitis*, vol. 39, no. 5, pp. 258-259.

Dudeney, T. P. 1969, "Crohn's disease of the mouth", *Proceedings of the Royal Society of Medicine*, vol. 62, no. 12, p. 1237.

Duggan, A. 1974, *He Died Old*, 2nd edn, Peter Davies, London.

Dutrée-Meulenberg, R. O. G. M., Kozel, M. M. A., & van Joosst, Th. 1992, "Burning mouth syndrome: a possible etiologic role ofr local contact hypersensitivity", *Journal of the American Academy of Dermatology*, vol. 26, pp. 935-940.

Eck, S. L., Morse, J. H., Janssen, D. A., Emerson, S. G., & Markovitz, D. M. 1993, "Angioedema presenting as chronic gastrointestinal symptoms.", *American Journal of Gastroenterology*, vol. 88, no. 3, pp. 436-439.

Editorial 1991, "Orofacial granulomatosis", *Lancet*, vol. 338, pp. 20-21.

Edman, B. & Möller, H. 1982, "Trends and forecasts for standard allergens in a 12-year patch test material.", *Contact Dermatitis*, vol. 8, pp. 95-104.

Eigenmann, P. A., Sicherer, S. H., Borkowski, T. A., Cohen, B. A., & Sampson, H. A. 1998, "Prevalence of IgE-mediated food allergy among children with atopic dermatitis", *Pediatrics*, vol. 101, no. 3, p. E8.

Eisen, D. 1993, "The therapy of oral lichen planus.", *Critical Reviews in Oral Biology and Medicine*, vol. 4, no. 2, pp. 141-158.

Eisenberg, E. & Krutchkoff, D. J. 1992, "Lichenoid lesions of oral mucosa", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 73, pp. 699-704.

Eisenberg, E., Murphy, G. F., & Krutchkoff, D. J. 1987, "Involucrin as a diagnostic marker on oral lichenoid lesions", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 64, pp. 313-319.

el Sayed, F., Seite-Bellezza, D., Sans, B., Bayle-Lebey, P., Marguery, M. C., & Bazex, J. 1995, "Contact urticaria from formaldehyde in a root-canal dental paste.", *Contact Dermatitis*, vol. 33, p. 353.

Eley, B. M. & Cox, S. W. 1993, "The release, absorption and possible health effects of mercury from dental amalgam: a review of recent findings.", *British Dental Journal*, vol. 175, pp. 161-168.

Elsaghier, A., Prantera, C., Bothamley, G., Wilkins, E., Jindal, S., & Ivanyi, J. 1992, "Disease association of antibodies to human and mycobacterial hsp70 and hsp60 stress proteins", *Clinical and Experimental Immmunology*, vol. 89, pp. 305-309.

Eversole, R. L. 1994, "Immunopathology of oral mucosal ulcerative, desquamative, and bullous diseases.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 77(6), pp. 555-571.

Eversole, R. L., Shopper, T. P., & Chambers, D. W. 1982, "Effects of suspected foodstuff challenging agents in the etilogy of recurrent aphthous stomatitis", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 54, no. 1, pp. 33-38.

Farthing, P. M. & Cruchley, A. T. 1989, "Expression of MHC class II antigens (HLA DR, DP and DQ) by keratinocytes in oral lichen planus", *Journal of Oral Pathology and Medicine*, vol. 18, no. 5, pp. 305-309.

Farthing, P. M., Maragou, P., Coates, M., Tatnall, F., Leigh, I. M., & Williams, D. M. 1995, "Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme", *Journal of Oral Pathology and Medicine*, vol. 24, no. 1, pp. 9-13.

Farthing, P. M., Matear, P., & Cruchley, A. T. 1990, "The activation of Langerhan's cells in oral lichen planus", *Journal of Oral Pathology and Medicine*, vol. 19, no. 2, pp. 81-85.

Felix, R. H. & Comaish, J. S. 1974, "The value of patch and other skin tests in drug eruptions.", *Lancet*, vol. 1, pp. 1017-1019.

Femiano, F., Cozzolino, F., Gaeta, G. M., De Luca, P., Perfetto, B., & Baroni, A. 1999, "Recent advances on the pathogenesis of oral lichen planus (OLP). The adhesion molecules", *Minerva Stomatologica*, vol. 48, no. 4, pp. 151-159.

Ferguson, J. E. & Beck, M. H. 1995, "Contact sensitivity to vanilla in a lip salve.", *Contact Dermatitis*, vol. 33, p. 352.

Ferguson, M. M., Wiesenfeld, D., & MacDonald, D. G. 1984, "Oral mucosal lichenoid eruption due to fenclofenac.", *Journal of Oral Medicine*, vol. 39, pp. 39-40.

Ferguson, M. M., Wray, D., Carmichael, H. A., Russell, R. I., & Lee, F. D. 1980, "Coeliac disease associated with recurrent aphthae", *Gut*, vol. 21, no. 3, pp. 223-226.

Ferguson, R., Basu, M. K., Asquith, P., & Cooke, W. T. 1976, "Jejunal mucosal abnormalities in patients with recurrent aphthous ulceration.", *British Medical Journal*, vol. i, pp. 11-13.

Fernandez-Redondo, V., Gomez-Centeno, P., & Toribio, J. 1998, "Chronic urticaria from a dental bridge", *Contact Dermatitis*, vol. 38, no. 3, pp. 178-179.

Field, E. A. 1998, "Atopy and other risk factors for UK dentists reporting an adverse reaction to latex gloves", *Contact Dermatitis*, vol. 38, no. 3, pp. 132-136.

Field, E. A., Brookes, V., & Tyldesley, W. R. 1992, "Recurrent aphthous ulceration in children--a review", *International Journal of Paediatric Dentistry*, vol. 2, no. 1, pp. 1-10.

Field, E. A., Longman, L. P., Al Sharkawi, M., & King, C. M. 1997, "An immediate (type I) hypersensitivity reaction during placement of a dental rubber dam", *European Journal of Prosthodontic and Restorative Dentistry*, vol. 5, no. 2, pp. 75-78.

Field, E. A., Longman, L. P., Al Sharkawi, M., Perrin, L., & Davies, M. 1998, "The dental management of patients with natural rubber latex allergy", *British Dental Journal*, vol. 185, no. 2, pp. 65-69.

Field, E. A., Rotter, E., Speechley, J. A., & Tyldesley, W. R. 1987, "Clinical and haematological assessment of children with recurrent aphthous ulceration", *British Dental Journal*, vol. 163, no. 1, pp. 19-22.

Field, E. A. & Tyldesley, W. R. 1989, "Oral Crohn's Disease Revisited - A 10-year-review", *British Journal of Oral and Maxillofacial Surgery*, vol. 27, pp. 114-123.

Finne, K., Goransson, K., & Winckler, L. 1982, "Oral lichen planus and contact allergy to mercury", *International Journal of Oral Surgery*, vol. 11, pp. 236-239.

Firth, N. A. & Reade, P. C. 1990, "Comparison of eosinophil densities in oral mucosal lichen planus and lichenoid drug reactions", *Journal of Oral Pathology and Medicine*, vol. 19, no. 2, pp. 86-88.

Fisher, A. A. 1974, "Contact stomatitis, glossitis and cheilitis", *Otolaryngologic Clinics of North America*, vol. 7, no. 3, pp. 827-843.

Fisher, A. A. 1990, "Chronic Lip Edema with Particular Reference to the Melkersson-Rosenthal Syndrome (MRS)", *CUTIS; Cutaneous Medicine for the Practitioner*, vol. 45, pp. 144-146.

Fisher, A. A. 1994, "Patch testing in children including early infancy.", *CUTIS; Cutaneous Medicine for the Practitioner*, vol. 54, pp. 387-388.

Fisher, A. A. 1995, *Contact Dermatitis.*, 4th edn, Williams and Watkins, Baltimore, pp. 885-919.

Fisher, A. A. 2000, "Allergic reactions due to metals used in dentistry", *CUTIS; Cutaneous Medicine for the Practitioner*, vol. 14, pp. 797-800.

Fitzpatrick, T. B. 1963, "Lichen planus-like drug eruption", *Archives of Dermatology*, vol. 88, p. 352.

Franks, A. 1998, "Contact allergy to anethole in toothpaste associated with loss of taste", *Contact Dermatitis*, vol. 38, no. 6, pp. 354-355.

Franz, G. 1982, "The frequency of allergy to dental materials", *Journal of the Dental Association of South Africa*, vol. 37, no. 12, pp. 805-810.

Frieden, I. J., Prose, N. S., Fletcher, V., & Turner, M. L. 1989, "Granulomatous perioral dermatitis.", *Archives of Dermatology*, vol. 125, pp. 369-373.

Friedman, S. J. & Perry, H. O. 1985, "Erythema multiforme associated with contact dermatitis", *Contact Dermatitis*, vol. 12, no. 1, pp. 21-23.

Friedmann, P. S., Moss, C., Shuster, S., & Simpson, J. M. 1983, "Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects.", *Clinical and Experimental Immmunology*, vol. 53, pp. 709-715.

Frosch, P. J., Pilz, B., Burrows, D., Camarasa, J. G., Lachapelle, J. M., Lahti, A., Menné, T., & Wilkinson, J. D. 1995, "Testing with fragrance mix.", *Contact Dermatitis*, vol. 32, pp. 266-272.

Fryholm, K. O., Frithiofi, L., Fernstron, A., Moberger, G., Blohm, S. G., & Bjorn, E. 1969, "Allergy to copper derived from dental alloys as a possible cause of oral lesions of lichen planus", *Acta Dermato-Venereologica*, vol. 49, pp. 268-281.

Fujiwara, K., Sakai, Y., Sugiura, J., Yamasaki, A., & . 1996, "Oral mucosal lesions in experimental graft-versus-host disease: morphological and immunohistochemical characterization of infiltrating cells", *Journal of Oral Pathology and Medicine*, vol. 25, pp. 314-319.

Fyad, A., Masmoudi, M. L., & Lachapelle, J. M. 1987, "The "edge effect" with patch test materials.", *Contact Dermatitis*, vol. 16, pp. 147-151.

Fyffe, H. E., Deery, C., Nugent, Z. J., Nuttall, N. M., & Pitts, N. B. 2000, "Effect of diagnostic threshold on the validity and reliability of epidemiological caries diagnosis using the Dundee Selectable Threshold Method for caries diagnosis (DSTM)", *Community Dental and Oral Epidemiology*, vol. 28, pp. 42-51.

Gainer, J. V., Nadeau, J. H., Ryder, D., & Brown, N. J. 1996, "Increased sensitivity to bradykinin among African Americans.", *The Journal of Allergy and Clinical Immunology*, vol. 98, pp. 283-287.

Gannon, T. H. & Eby, T. L. 1990, "Angioedema from angiotensin converting enzyme inhibitors: a cause of upper airway obstruction", *Laryngoscope*, vol. 100, pp. 1156-1160.

Garioch, J. J., Todd, P., Lamey, P.-J., Lewis, M. A. O., Forsyth, A., & Rademaker, M. 1990, "The significance of a positive patch test to mercury in oral disease", *Contact Dermatitis*, vol. 23, p. 301.

Gell, P. G. H. & Coombs, R. R. A. 1968, *Clinical Aspects of Immunology*, 2 edn, Blackwell Scientific, Oxford, pp. 575-596.

Gerretsen, G., Kremer, J., Bleumink, E., & Nater, J. P. 1975, "Dinitrochlorobenzene sensitisation test in women on hormonal contraceptives.", *Lancet*, vol. 2, pp. 347-349.

Giannini, D. & Sloan, R. S. 1957, "A tuberculin survey of 1285 adults with special reference to the elderly.", *Lancet*, vol. 1, pp. 525-527.

Giannoccaro, P. J., Wallace, G. J., Higginson, L. A. J., & Williams, W. L. 1989, "Fatal angioedema associated with enalapril.", *Canadian Journal of Cardiology*, vol. 5, no. 7, pp. 335-336.

Gibson, J. 1998, *Orofacial Granulomatosis: Clinical And Immunological Aspects*, PhD, University of Glasgow.

Gibson, J., Forsyth, A., & Milligan, K. A. 1995, "Orofacial granulomatosis - the role of patch testing.", *British Journal of Dermatology*, vol. 133, p. 25.

Gil Mateo, M. P., Velasco, M., Miquel, F. J., & de la Cuadra, J. 1995, "Erythema-multifome-like eruption following allergic contact dermatitis from sesquiterpene lactones in herbal medicine.", *Contact Dermatitis*, vol. 33, pp. 449-450.

Gilchrest, B. A., Murphy, G. F., & Soter, N. A. 1982, "Effect of chronologic aging and ultraviolet irradiation on Langerhan's cells in human epidermis.", *The Journal of Investigative Dermatology*, vol. 79, no. 2, pp. 85-88.

Giordano-Labadie, F., Schwarze, H. P., & Bazex, J. 2000, "Allergic contact dermatitis from octyl gallate in lipstick", *Contact Dermatitis*, vol. 42, no. 1, p. 51.

Goh, C. L. 1986, "Prevalence of contact allergy by sex, race and age.", *Contact Dermatitis*, vol. 14, pp. 237-240.

Gollhausen, R., Enders, F., Przybilla, B., Burg, G., & Ring, J. 1988, "Trends in allergic contact sensitization.", *Contact Dermatitis*, vol. 18, pp. 147-154.

Gorlin, R. J. & Chaudhry, A. P. 1960, "The oral manifestations of cuclic (periodic) neutropenia", *Archives of Dermatology*, vol. 82, pp. 344-348.

Gowkrodger, D. J., McDonagh, A. J. G., & Wright, A. L. 1991, "Quantification of allergic and irritant patch test reactions using laser-doppler flowmetry and erythema index.", *Contact Dermatitis*, vol. 24, no. 3, pp. 172-177.

Grange, R. W. & Wilson Jones, W. 1978, "Bullous lichen planus caused by labetalol.", *British Medical Journal*, vol. 1, pp. 816-817.

Grant, E. C. G. 1979, "Food allergies and migraine.", *Lancet*, vol. i, pp. 966-968.

Grattan, C. E. H. & Kennedy, C. T. C. 1985, "Angioedema during dental treatment.", *Contact Dermatitis*, vol. 13, pp. 333-349.

Graykowski, E. A., Barile, M. F., Lee, W. B., & Stanley, H. R. 1966, "Recurrent aphthous stomatitis: clinical, therapeutic, histopathologic, and hypersensitivity aspects", *Journal of the American Medical Association*, vol. 196, pp. 637-644.

Guo, X. & Dick, L. 1999, "Late onset angiotensin-converting enzyme induced angioedema: case report and review of the literature", *Journal - Oklahoma State Medical Association.* pp. 71-73.

Guthrie, D. 1958, *A History of Medicine* Thomas Nelson and Sons Ltd., London.

Hamburger, J., Lawrence, C. M., & Oakes, R. 1995, "Clinical features of lichenoid drug reactions.", *Journal of Dental Research*, vol. 74, no. 3, p. 834.

Hawthorne, L. A. 1996, "Hereditary angioedema: prophylaxis management in the puerperium.", *Anaesthesia*, vol. 51, pp. 283-284.

Hay, I. C. & Ormerod, A. D. 1998, "Severe oral and facial reaction to 6 metals in restorative dentistry", *Contact Dermatitis* , vol. 38, no. 4, p. 216.

Hay, K. D. & Reade, P. C. 1978, "Methyldopa as a cause of oral mucous membrane reactions.", *British Dental Journal* , vol. 145, pp. 195-203.

Hay, K. D. & Reade, P. C. 1984, "The use of an elimination diet in the treatment of recurrent aphthous ulceration of the oral cavity", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 57, no. 5, pp. 504-507.

Healy, C. M., Cruchley, A. T., Thornhill, M. H., & Williams, D. M. 2000, "The effect of sodium lauryl sulphate, triclosan and zinc on the permeabiblity of normal oral mucosa", *Oral Diseases*, vol. 6, pp. 118-123.

Hedberg, N., Ng, A., & Hunter, N. 1986, "A semi-quantitative assessment of the histopathology of oral lichen planus", *Journal of Oral Pathology*, vol. 15, pp. 268-272.

Helton, J. & Storrs, F. 1994, "The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis", *Journal of the American Academy of Dermatology*, vol. 31, no. 2 Pt 1, pp. 201-205.

Henry, C. H. 1994, "Orofacial Granulomatosis: Report of a case with decreased CD4/CD8 ratio", *Journal of Oral and Maxillofacial Surgery*, vol. 52, pp. 317-322.

Hernandez, G., Hernandez, F., & Lucas, M. 1986, "Miescher's granulomatous cheilitis : Literature review and report of a case", *Journal of Oral and Maxillofacial Surgery*, vol. 44, pp. 474-478.

Hietanen, J., Pihlman, K., Förström, L., Linder, E., & Reunala, T. 1987, "No evidence of hypersensitivity to dental restorative metals in oral lichen planus", *Scandinavian Journal oof Dental Research*, vol. 95, pp. 320-327.

Hjorth, N. 1966, "Primula Dermatitis: sources of error in patch testing and patch test sensitization", *Transactions of the St John's Hospital Dermatological Society*, vol. 52, pp. 207-219.

Hjorth, N. 1989, "The development of the patch testing procedure and working for consistency.", *Journal of the American Academy of Dermatology*, vol. 21, pp. 855-857.

Holmstrup, P. 1992, "The contoversy of a premalignant potential of oral lichen planus is over", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 73, pp. 704-706.

Holmstrup, P., Schiotz, A. W., & Westergaard, J. 1990, "Effect of dental plaque control on gingival lichen planus.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 69, pp. 585-590.

Holmstrup, P., Thorn, J. J., Rindum, J., & Pindborg, J. J. 1988, "Malignant development of lichen planus-affected oral mucosa,", *Journal of Oral Pathology*, vol. 17, pp. 219-225.

Holt, P. J. A. & Navaratnam, A. 1974, "Lichenoid eruption due to methyldopa.", *British Medical Journal*, vol. 3, pp. 234-244.

Hoover, C. I., Olson, J. A., & Greenspan, J. S. 1986, "Humoral responses and cross-reactivity to viridans streptococci in recurrent aphthous ulceration", *Journal of Dental Research*, vol. 65, no. 8, pp. 1101-1104.

Hornstein, O. P. 1997, "Melkersson-Rosenthal Syndrome - A Challenge for Dermatologists to Participate in the Field of Oral Medicine", *Journal of Dermatology*, vol. 24, pp. 281-296.

Houwerzijl, J., de Gast, G. C., Nater, J. P., Esselink, M. T., & Niewig, H. O. 1977, "Lymphocyte-stimulation tests and patch tests in carbamazepine hypersensitivity.", *Clinical and Experimental Immunolgy*, vol. 29, pp. 272-277.

Huff, J. C., Weston, M. D., & Tonnesen, M. G. 1983, "Erythema Multiforme: A critical review of characteristics, diagnostic criteria, and causes", *Journal of the American Academy of Dermatology*, vol. 8, pp. 763-775.

Hugoson, A. 1986, "Results obtained from patients referred for the investigation of complaints related to oral galvanism.", *Swedish Dental Journal*, vol. 10(1-2), pp. 15-28.

Humphris, G. M., Longman, L. P., & Field, E. A. 1996, "Cognitive-behavioural therapy for idiopathic burning mouth syndrome: a report of two cases", *British Dental Journal*, vol. 181, no. 6, pp. 204-208.

Hunter, I. P., Ferguson, M. M., Scully, C., Galloway, A. R., Main, A. N., & Russell, R. I. 1993, "Effects of dietary gluten elimination in patients with recurrent minor aphthous stomatitis and no detectable gluten enteropathy", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 75, no. 5, pp. 595-598.

Husain, S. L. 1977, "Contact dermatitis in the West of Scotland.", *Contact Dermatitis*, vol. 3, pp. 327-332.

Huskisson, E. C. 1974, "Measurement of pain", *Lancet*, vol. 2, no. 7889, pp. 1127-1131.

Hutcheon, A. W., Wray, D., Ferguson, M. M., Dagg, J. H., Mason, D. K., & Lucie, N. P. 1978, "Clinical and haematological screening in recurrent aphthae", *Postgraduate Medical Journal*, vol. 54, pp. 779-783.

Ibbotson, S. H., Speight, E. L., Macleod, R. I., Smart, E. R., & Lawrence, C. M. 1996, "The relevance and effect of amalgam replacement in subjects with oral lichenoid reactions", *British Journal of Dermatology*, vol. 134, no. 3, pp. 420-423.

ICDRG 1984, "European Standard Series.", *Contact Dermatitis*, vol. 11, pp. 63-64.

Ingafou, M., Lodi, G., Olsen, I., & Porter, S. 1997, "Lichen planus is not associated with IgG circulating components to epithelial antigens", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 84, no. 2, pp. 175-178.

Ingram, C. S. 1993, "Melkersson-Rosenthal Syndrome - Orofacial granulomatosis", *Journal of the New Zealand Society of Periodontology*, vol. 75, pp. 29-32.

Irani, A. A., Schechter, N. M., Craig, S. S., DeBlois, G., & Schwartz, L. B. 1986, "Two types of human mast cells that have distict neutral protease compositions", *Proceedings of the National Academy of Science of the USA*, vol. 83, pp. 4464-4468.

Ishi, N., Kawaguchi, H., & Nakajima, H. 1996, "Hereditary angioedema caused by a point mutation of exon 7 in the C1 inhibitor gene.", *British Journal of Dermatology*, vol. 134, pp. 731-733.

Ishizaka, K., Ishizaka, T., & Hornbrook, M. M. 1966, "Physico-chemical properties of human reaginic antibody", *Journal of Immunology*, vol. 97, no. 1, pp. 75-85.

Ivanyi, L., Kirby, A., & Zakrzewska, J. M. 1993, "Antibodies to mycobacterial stress protein in patients with orofacial granulomatosis", *Journal of Oral Pathology and Medicine*, vol. 22, pp. 320-322.

Jacobs, R. L., Hoberman, L. J., & Goldstein, H. M. 1993, "Angioedema of the small bowel caused by an angiotensin- converting enzyme inhibitor", *American Journal of Gastroenterology*, vol. 89(1), pp. 127-128.

Jacobsen, D. W. 1991, "Adverse reactions to benzoates and parabens," in *Food Allergy: Adverse Reactions to Foods And Food Additives*, 1st edn, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific, Cambridge, Massachusetts, pp. 276-287.

Jadassohn, J. 1895 *"Zur kenntnis der medikamentösen dermatosen"*, Austria, pp. 103-129.

James, J. & Ferguson, M. M. 1986, "Orofacial granulomatosis presenting clinically as tuberculosis of cervical lymph nodes", *British Dental Journal*, vol. 161, pp. 17-19.

James, J., Ferguson, M. M., Forsyth, A., Tulloch, N., & Lamey, P.-J. 1987, "Oral lichenoid reactions related to mercury sensitivity", *The British Journal of Oral And Maxillofacial Surgery*, vol. 25, no. 6, pp. 474-480.

James, J., Patton, D. W., Lewis, C. J., Kirkwood, E. M., & Ferguson, M. M. 1986, "Oro-Facial Granulomatosis and Clinical Atopy", *Journal of Oral Medicine*, vol. 41, No 1, pp. 29-30.

Jandinski, N. J. & Shklar, G. 1976, "Lichen planus of the gingiva.", *Journal of Periodontology*, vol. 47, no. 12, pp. 724-733.

Jones, D. H. & Beltrani, V. S. 1997, "Oral mucous membrane contact dermatitis", *Immunology and Allergy Clinics of North America*, vol. 17, no. 3, pp. 471-487.

Jones, T. K., Hansen, C. A., Singer, M. T., & Kessler, H. P. 1986, "Dental implications of nickel hypersensitivity.", *Journal of Prosthetic Dentistry*, vol. 56, pp. 507-509.

Kaaber, S. 1990, "Allergy to dental materials with special reference to the use of amalgan and polymethylmethacrylate.", *International Dental Journal*, vol. 40(6), pp. 359-365.

Kaaber, S. & Nielsen, E. 1979, "Skin sensitivity to denture base materials in the burning mouth syndrome", *Contact Dermatitis*, vol. 5, pp. 90-96.

Kalmar, J. R. 2000, "Topical corticosteroids and oral vesiculo-erosive disease: where's the beef", *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, vol. 89, no. 4, pp. 395-396.

Kanerva, L., Estlander, T., & Jolanki, R. 1990, "Long-lasting contact urticaria.", *Contact Dermatitis*, vol. 8, no. 1, pp. 181-188.

Kanerva, L., Estlander, T., & Jolanki, R. 1998, "Dental nurse's occupational allergic contact dermatitis from eugenol used as a restorative dental material with polymethylmethacrylate", *Contact Dermatitis*, vol. 38, no. 6, pp. 339-340.

Kao, N. L. & Zeitz, H. J. 1993, "Etiology of urticaria and angioedema in the elderly.", *Allergy Clinics of North America*, vol. 13(3), pp. 613-626.

Katz, D. H. 1984, "Regulation of the immune system: experimental and clinical aspects.", *Allergy*, vol. 39, pp. 81-106.

Kawamura, T., Fukuda, S., Ohtake, N., Furue, M., & Tamaki, K. 1996, "Lichen planus-like contact dermatitis due to methacrylic acid esters", *British Journal of Dermatology*, vol. 134, no. 2, pp. 358-360.

Keczkes, K., Basheer, A. M., & Wyatt, E. H. 1982, "The persistence of allergic contact sensitivity: a 10-year follow-up in 100 patients", *British Journal of Dermatology*, vol. 107, pp. 461-465.

Kerosuo, H. & Kanerva, L. 1997, "Systemic contact dermatitis caused by nickel in a stainless steel orthodontic appliance", *Contact Dermatitis*, vol. 36, pp. 112-113.

Kharesh, E. D. 1992, "Angiotensin-converting enzyme inhibitor-induced angioedema associated with endotracheal intubation", *Anesthesia and Analgesia*, vol. 74, pp. 602-604.

Kirton, V. & Wilkinson, D. S. 1975, "Sensitivity to cinnamic aldehyde in a toothpaste 2.", *Contact Dermatitis*, vol. 1, pp. 77-80.

Klas, P. A., Corey, G., Storrs, F. J., Chan, S. C., & Hanifin, J. M. 1996, "Allergic and irritant patch test reactions and atopic disease", *Contact Dermatitis*, vol. 34, pp. 121-124.

Kligman, A. M. & Epstein, W. 1975, "Updating the maximization test for identifying contact allergens", *Contact Dermatitis*, vol. 1, pp. 231-239.

Knight, A. 1993, "Diagnostic testing in chronic urticaria and angioedema", *Canadian Medical Association Journal*, vol. 148, no. 3, p. 375.

Koch, G., Magnusson, B., & Nyquist, G. 1971, "Contact allergy to medicaments and materials used in dentistry. II. Sensitivity to eugenol and colophony", *Odontology Review*, vol. 22, no. 3, pp. 275-289.

Koch, P. & Bahmer, F. A. 1995, "Oral lichenoid lesions, mercury hypersensitivity and combined hypersensitivity to mercury and other metals: histologically-proven reproduction of the reaction by patch testing with metal salts", *Contact Dermatitis*, vol. 33, pp. 323-328.

Koch, P. & Bahmer, F. A. 1999, "Oral lesions and symptoms related to metals used in dental restorations: a clinical, allergological, and histologic study", *Journal of the American Academy of Dermatology*, vol. 41, no. 3 Pt 1, pp. 422-430.

Koch, P. & Baum, H.-P. 1996, "Contact stomatitis due to palladium and platinum in dental alloys", *Contact Dermatitis*, vol. 34, pp. 253-257.

Kramer, I. R. H., Lucas, R. B., Pindborg, J. J., & Sobin, L. H. 1978, "Definition of leukoplakia and related lesions: An aid to studies on oral precancer", *Oral Surgery*, vol. 46, no. 4, pp. 518-539.

Krogh, G. V. & Maibach, H. I. 1982, "The contact urticaria syndrome-1982", *Seminars in Dermatology*, vol. 1, no. 1, pp. 59-66.

Kurumaji, Y. 1998, "Photo koebner phenomenon in erythema-multiforme-like eruption induced by contact dermatitis due to bufexamac", *Dermatology*, vol. 197, pp. 183-186.

Kwangsukstith, C. & Maibach, H. I. 1995, "Effect of age and sex on the induction and elicitation of allergic contact dermatitis", *Contact Dermatitis*, vol. 33, pp. 289-298.

Lachapelle, J. M. & Antoine, J. L. 1989, "Problems raised by the simultaneous reproducibility of positive allergic patch test reactions in man", *Dermatology*, vol. 21, no. 4(2), pp. 850-854.

Lacy, M. F., Reade, P. C., & Hay, K. D. 1983, "Lichen planus: A theory of pathogenesis", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 56, pp. 521-526.

Lahti, A. 1980, "Non-immunologic contact urticaria", *Acta Dermato-Venereologica Supplement (Stockholm)*, vol. 60, no. 91, pp. 1-49.

Laine, J., Kalimo, K., Forssill, H., & Happonen, R. P. 1992, "Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds", *British Journal of Dermatology*, vol. 126(1), pp. 10-15.

Laine, J., Kalimo, K., & Happonen, R. P. 1997, "Contact allergy to dental restorative materials in patients with oral lichenoid lesions", *Contact Dermatitis*, vol. 36, no. 3, pp. 141-146.

Lamey, P.-J. & Forsyth, A. 1986, "An unusual cause of facial swelling [letter]", *British Dental Journal*, vol. 160, no. 6, p. 189.

Lamey, P.-J., Lamb, A. B., & Forsyth, A. 1987, "Atypical burning mouth syndrome", *Contact Dermatitis*, vol. 17, no. 4, pp. 242-243.

Lamey, P.-J., Lamb, A. B., Hughes, A., Milligan, K. A., & Forsyth, A. 1994, "Type 3 burning mouth syndrome: psychologcal and allergic aspects", *Journal of Oral Pathology and Medicine*, vol. 23(5), pp. 216-219.

Lamey, P.-J. & Lewis, M. A. O. 1990, "Oral medicine in practice: orofacial allergic reactions", *British Dental Journal*, vol. 168, pp. 59-63.

Lamey, P.-J., Lewis, M. A. O., Rees, T. D., Fowler, C., Binnie, W. H., & Forsyth, A. 1990, "Sensitivity reaction to the cinnamonaldehyde component of toothpaste", *British Dental Journal*, vol. 168, no. 3, pp. 115-118.

Lamey, P.-J., McCartan, B. E., MacDonald, D. G., & Mackie, R. M. 1995, "Basal cell cytoplasmic autoantibodies in oral lichenoid reactions", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 79, pp. 44-49.

Lamster, I. B., Kalfus, D. I., Steigerwald, P. J., & Chasens, A. I. 1986, "Rapid loss of alveolar bone associated with nonprecious alloy crowns in two patients with nickel hypersensitivity", *Journal of Periodontology*, vol. 58, no. 7, pp. 486-492.

Lehner, T. 1967, "Autoimmunity and management of recurrent oral ulceration", *British Dental Journal*, vol. 122, pp. 15-20.

Lehner, T. 1969a, "Characterization of mucosal antibodies in recurrent aphthous ulceration and Behcet's syndrome", *Archives of Oral Biology*, vol. 14, pp. 843-853.

Lehner, T. 1969b, "Pathology of recurrent oral ulceration and oral ulceration in Behcet's synndrome: light, electron and fluorescence microscopy", *Journal of Pathology*, vol. 97, pp. 481-494.

Lehner, T. 1972, "Immunologic aspects of recurrent oral ulcers", *Oral Surgery*, vol. 33, pp. 80-85.

Lewis, F. M., Shah, M., & Gawkrodger, D. J. 1995, "Contact sensitivity to food additives can cause oral and perioral symptoms", *Contact Dermatitis,* vol. 33, pp. 429-430.

Lewis, M. A. O., Lamey, P.-J., Forsyth, A., & Gall, J. 1989, "Recurrent erythema multiforme: a possible role of foodstuffs", *British Dental Journal*, vol. 166, no. 10, pp. 371-373.

Liccardi, G., D'Amato, M., & D'Amato, G. 1996, "Oral allergy syndrome after ingestion of salami in a subject with monosensitization to mite allergens", *The Journal of Allergy and Clinical Immunology*, vol. 98, pp. 850-852.

Lim, S. H., Stephens, S. H., Cao, Q., Coleman, S., & Thomas, D. W. 1997, "Molecular analysis of T cell receptor ? variability in a patient with orofacial granulomatosis", *Gut*, vol. 40, pp. 683-686.

Lind, P. O., Hurlen, B., & Stromme-Koppang, H. 1984, "Electrogalvanically-induced contact allergy of the oral mucosa. Report of a case", *International Journal of Oral Surgery*, vol. 13(4), pp. 339-345.

Lindberg, M. 1982, "Studies on the cellular and subcellular reactions in epidermis at irritant and allergic dermatitis", *Acta Dermato-Venereologica Supplement (Stockholm)*, vol. 105, pp. 9.

Lodi, G., Carrozzo, M., Harris, K., Piattelli, A., Teo, C. G., Gandolfo, S., Scully, C., & Porter, S. 1999, "Hepatitis C virus-associated oral lichen planus: no influence from hepatits G virus co-infection", *Journal of Oral Pathology and Medicine*, vol. 29, pp. 39-42.

Lombardi, T., Hauser, C., & Budtz Jorgensen, E. 1993, "Langerhan's cells: structure, function and role in oral pathological conditions", *Journal of Oral Pathology and Medicine*, vol. 22, no. 5, pp. 193-202.

Lozada-Nur, F. 2000, "Oral lichen planus and oral cancer: Is there enough epidemiologic evidence", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 89, no. 3, pp. 265-266.

Lozada-Nur, F., Gorsky, M., & Silverman, S. 1989, "Oral erythema multiforme: clinical observations and treatment of 95 patients", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 67, pp. 36-40.

Lozada, F. 1982, "Levamisole in the tratment of erythema multiforme: a double-blind trial in fourteen patients", *Oral Surgery*, vol. 53, pp. 28-31.

Lozada, F. & Silverman, S. 1978, "Erythema multiforme", *Oral Surgery*, vol. 46, pp. 628-636.

Lubow, R. M., Cooley, R. L., Hartman, K. S., & McDaniel, R. K. 1984, "Plasma-cell gingivitis", *Journal of Periodontology*, vol. 55, no. 4, pp. 235-241.

Lucarelli, S., Quattrucci, S., Zingoni, A. M., Frediani, T., Diamanti, S., Quintieri, F., Barbato, M., Cardi, E., & Antonelli, M. 1994, "Food allergy in cystic fibrosis", *Minerva Pediatrica,* vol. 46, pp. 543-548.

Lygidakis, C., Tsakamarakas, C., & Illias, A. 1979, "Melkersson-Rosenthal syndrome in four generations", *Clinical Genetics*, vol. 15, pp. 189-190.

Lyzak, W. A., Flaitz, C. M., McGuckin, R. S., Eichmiller, F., & Brown, R. S. 1994, "Diagnosis and treatment of an oral base-metal contact lesion following negative Dermatologic Patch Tests", *Annals of Allergy*, vol. 73, pp. 161-165.

Macleod, R. I. & Ellis, J. E. 1989, "Plasma cell gingivitis related to the use of herbal toothpaste", *British Dental Journal*, vol. 166, pp. 375-376.

Madanes, A. E. & Farber, M. 1982, "Danazol", *Annals of Internal Medicine*, vol. 96, pp. 625-630.

Maibach, H. I. 1986, "Cheilitis: occult allergy to cinnamic aldehyde", *Contact Dermatitis*, vol. 15, pp. 106-107.

Main, D. M. G. & Ritchie, G. M. 1967, "Cyclic changes in oral smears from young menstruating women", *British Journal of Dermatology*, vol. 79, pp. 20-30.

Malanin, G. & Kalimo, K. 1989, "The results of skin testing with food additives and the effect of an elimination diet in chronic and recurrent urticaria and recurrent angioedema", *Clinical and Experimental Allergy*, vol. 19, pp. 539-543.

Mancuso, G., Berdondini, R. M., & Cavrini, G. 1999, "Long-lasting allergic patch test reactions: a study of patients with positive standard patch tests", *Contact Dermatitis*, vol. 41, pp. 35-39.

Mandel, I. D. 1987, "The functions of saliva", *Journal of Dental Research*, vol. 66, no. Spec Iss, pp. 623-627.

Manganaro, M. 1996, "Erythema multiforme", *General Dentistry*, vol. 44, pp. 164-166.

Marcusson, J. A. 1996, "Contact allergies to nickel sulfate, gold sodium thiosulfate and palladium chloride in patients claiming side-effects from dental alloy components", *Contact Dermatitis*, vol. 34, pp. 320-323.

Markopoulos, K., Antoniades, D., Papanayotou, P. & Trigonidis, G. 1996, "Desquamative gingivitis: a clinical, histopathologic, and immunologic study", *Quintessence International*, vol. 27, pp. 763-767.

Markovic, S. N., Inwards, D. J., Frigas, E. A. & Phyliky, R. P. 2000, "Acquired C1 esterase inhibitor deficiency", *Annals of Internal Medicine*, vol. 132, no. 2, pp. 144-150.

Matthews, R. W., Pinkney, R. C. & Scully, C. 1981, "The management of desquamative gingivitis with dapsone", *Annals of Dentistry*, vol. 48, pp. 41-43.

Mattingly, G., Rodu, B. & Alling, R. 1993, "Quincke's disease: nonhereditary angioneurotic edema of the uvula", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 75, no. 3, pp. 292-295.

Mattsson, T., Sunqvist, K. G., Heimdahl, A., Dahllöf, G., Ljungman, P., & Ringdén, O. 1992, "A comparative immunological analysis of the oral mucosa in chronic graft-versus-host disease and oral lichen planus", *Archives of Oral Biology*, vol. 37, no. 7, pp. 539-547.

McCartan, B. & Lamey, P. J. 1998, "Antibodies in oral lichen planus [letter; comment]", *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, vol. 85, no. 5, pp. 493-494.

McCartan, B. E. 1997, "Oral lichenoid drug eruptions", *Oral Diseases*, vol. 3, pp. 58-63.

McCartan, B. E. & Lamey, P.-J. 1997, "Expression of CD1 and HLA-DR by Langerhan's cells (LC) in oral lichenoid drug eruptions (LDE) and idiopathic oral lichen planus (LP)", *Journal of Oral Pathology and Medicine*, vol. 26, pp. 176-180.

McCullough, M. J. & Radden, B. G. 1992, "Involucrin expression in some oral lichenoid lesions", *Journal of Oral Pathology and Medicine*, vol. 21, pp. 367-369.

McDonagh, A. J. G., Wright, A. L., Cork, M. J. & Gawkrodger, D. J. 1992, "Nickel sensitivity: the influence of ear piercing and atopy", *British Journal of Dermatology*, vol. 126, pp. 16-18.

McGivern, B., Pemberton, M., Theaker, E. D., Buchanan, J. A. G. & Thornhill, M. H. 2000, "Delayed and immediate hypersensitivity reactions associated with the use of amalgam", *British Dental Journal*, vol. 188, no. 2, pp. 73-76.

McKenna, K. E., Walsh, M. Y. & Burrows, D. 1994, "The Melkersson-Rosenthal syndrome and food additive hypersensitivity", *British Journal of Dermatology*, vol. 131, pp. 921-922.

McKenna, R. W. 1937, *Diseases of the skin*, 4th edn, Baillière, Tindall and Cox, London.

Meijer, C., Bredberg, M., Fisher, T. & Widström, L. 1995, "Ear piercing, and nickel and cobalt sensitisation, in 520 young Swedish men doing compulsory military service", *Contact Dermatitis*, vol. 32, pp. 147-149.

Meisel-Stosiek, M., Hornstein, O. P. & Stosiek, N. 1990, "Family study on Melkersson-Rosenthal Syndrome. Some hereditary aspects of the disease and review of the literature", *Acta Dermato-Venereologica Supplement (Stockholm)*, vol. 70, pp. 221-226.

Mendelow, A. Y., Forsyth, A., Feather, J. W., Baillie, A. J. & Florence, A. T. 1986, "Skin reflectance measurements of patch test responses", *Contact Dermatitis*, vol. 15, pp. 73-78.

Mendelow, A. Y., Forsyth, A., Florence, A. T. & Baillie, A. J. 1985, "Patch test for nickel allergy", *Contact Dermatitis*, vol. 3, pp. 29-33.

Mendelsohn, S. S., Field, E. A. & Woolgar, J. 1992, "Sarcoidosis of the tongue", *Clinical and Experimental Dermatology*, vol. 17, pp. 47-48.

Meneghini, C. L. & Angelini, G. 1977, "Behaviour of contact allergy and new sensitivities on subsequent patch tests", *Contact Dermatitis*, vol. 3, pp. 138-142.

Meneghini, C. L., Rantuccio, F. & Lomuto, M. 1972, "A propos de réactions de sensibilisation active aprés l'éxecution des tests diagnostiques épicutanés: observations sur 281 cas", *Annales de Dermatologie et de Syphiligraphie*, vol. 99, p. 161.

Menné, T., Dooms-Goossens, A., Wahlberg, J. E., White, I. R. & Shaw, S. 1992, "How large a proportion of contact sensitivities are diagnosed with the European Standard Series?", *Contact Dermatitis*, vol. 26, pp. 201-202.

Miller, R. L., Gould, A. R. & Bernstein, M. L. 1992, "Cinnamon-induced stomatits venenata", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 73, pp. 708-716.

Miller, T. P. & Zeiss, C. R. 1993, "Urticaria and angioedema", *Allergy Procedures*, vol. 14, no. 2, pp. 1313-132.

Mitchell, J. C. 1975, "The angry back sydrome:eczema creates eczema", *Contact Dermatitis*, vol. 1, pp. 193-194.

Mitchell, J. C. 1977, "Multiple concomitant positive patch test reactions", *Contact Dermatitis*, vol. 3, pp. 315-320.

Moffa, J. P., Beck, W. D. & Hoke, A. W. 1977, "Allergic response to nickel containing dental alloys", *Journal of Dental Research*, vol. 56, p. 104.

Morales, C., Penarrocha, M., Bagan, J. V., Burches, E. & Pelaez, A. 1995, "Immunological study of Melkersson-Rosenthal syndrome. Lack of response to food additive challenge", *Clinical and Experimental Allergy*, vol. 25, no. 3, pp. 260-264.

Morgan, K. L. 1987, "Johne's and Crohn's. Chronic inflammatory bowel diseases of infectious aetiology?", *Lancet*, vol. i, pp. 1017-1021.

Munoz, F. J., Bellido, J., Moyano, J. C., Alvarez, M. & Fonseca, J. L. 1996, "Perioral contact urticaria from sodium benzoate in a toothpaste", *Contact Dermatitis*, vol. 35, no. 1, p. 51.

Mygind, N., Dahl, R., Pedersen, S. & Thestrup-Pedersen, K. 1996, "Basic Mechanisms," in *Essential Allergy*, 2nd edn, Blackwell Scientific Publications, Oxford, pp. 1-60.

Nakamura, S., Hiroki, A., Shinohara, M., Gondo, H., Ohyama, Y., Mouri, T., Sasaki, M., Shirasuna, K., Harada, M. & Niho, Y. 1996, "Oral involvement in chronic graft-versus-host disease after allogenic bone marrow transplantation", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 82, pp. 556-563.

Nally, F. F. 1970, "Melkersson-Rosenthal syndrome", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 29, pp. 694-703.

Nater, J. P. & Hoedemaker, Ph. J. 1976, "Histological differences between irritant and allergic patch test reactions in man", *Contact Dermatitis*, vol. 2, pp. 247-253.

Ng, P. P., Ng, S. K., & Chng, H. H. 1998, "Pemphigus foliaceus and oral lichen planus in a patient with systemic lupus erythematosus and thymoma", *Clinical and Experimental Dermatology*, vol. 23, no. 4, pp. 181-184.

Nilner, K. & Glantz, P.-O. 1982, "The prevalence of copper-, silver-, tin-, mercury- and zinc-ions human saliva", *Swedish Dental Journal*, vol. 6, pp. 71-77.

Nolan, A., Lamey, P.-J., Milligan, K. A., & Forsyth, A. 1991, "Recurrent aphthous ulceration and food sensitivity.", *Journal of Oral Pathology and Medicine*, vol. 20, pp. 473-475.

Nolan, A., McIntosh, W. B., & Lamey, P.-J. 1991, "Recurrent apthous ulceration: vitamin B1, B2 and B6 status and response to replacement therapy", *Journal of Oral Pathology and Medicine*, vol. 20, pp. 389-391.

Nordlind, K. & Liden, S. 1992, "Patch test reactions to metal salts in patients with oral mucosal lesions associated with amalgam restorations", *Contact Dermatitis*, vol. 27, no. 3, pp. 157-160.

O'Donnell, B. F. & Tan, C. Y. 1997, "Erythema multiforme reaction to patch testing", *Contact Dermatitis*, vol. 27, pp. 230-234.

Oliver, A. J., Reade, P. C., Varigos, G. A., & Radden, B. G. 1991, "Monosodium glutamate-related orofacial granulomatosis", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 71, pp. 560-564.

Oliver, G. F., Winkelmann, R. K., & Muller, S. A. 1989, "Lichenoid dermatitis: a clinicopathologic and immunopathologic review of sixty-two cases", *Journal of the American Academy of Dermatology*, vol. 21, pp. 284-292.

Oltivai, Z. N., Wong, E. C. C., Atkinson, J. P., & Tung, K. S. K. 1991, "C1 inhibitor deficiency: molecular and immunologic basis of hereditary and acquired angioedema", *Laboratory Investigation*, vol. 65(4), pp. 381-388.

Ophaswongse, S. & Maibach, H. I. 1995, "Allergic contact cheilitis", *Contact Dermatitis*, vol. 33, pp. 365-370.

Orchard, D. C. & Varigos, G. A. 1997, "Fixed drug eruption to tartrazine", *Australian Journal of Dermatology*, vol. 38, no. 4, pp. 212-214.

Ortolani, C., Bruijnzeel-Koomen, C., Bengtsson, U., Bindslev-Jensen, C., Bjorksten, B., Host, A., Ispano, M., Jarish, R., Madsen, C., Nekam, K., Paganelli, R., Poulsen, L. K., & Wuthrich, B. 1999, "Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) Reactions to Food Subcommittee", *Allergy*, vol. 54, no. 1, pp. 27-45.

Östman, P. O., Anneroth, G., Johansson, I., Stegmayr, B., & Skoglund, A. 1996, "Life-style survey of patients with oral lichenoid reactions", *Acta Odontologica Scandinavica*, vol. 54, no. 2, pp. 96-101.

Östman, P. O., Anneroth, G., & Skoglund, A. 1994, "Oral lichen planus lesions in contact with amalgam fillings: a clinical, histologic, and immunohistochemical study", *Scandinavian Journal of Dental Research*, vol. 102(3), pp. 172-179.

Östman, P. O., Anneroth, G., & Skoglund, A. 1996, "Amalgam-associated oral lichenoid reactions", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 81, pp. 459-465.

Pachor, M. L., Urbani, G., & Cortina, P. 1989, "Is the Melkersson-Rosenthal syndrome related to the exposure to food additives?", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 67, pp. 393-396.

Palmer, R. M. & Eveson, J. W. 1981, "Plasma-cell gingivitis", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 51, pp. 187-189.

Pang, B. K. & Freeman, S. 1995, "Oral lichenoid lesions caused by allergy to mercury in amalgam fillings", *Contact Dermatitis*, vol. 33, pp. 423-427.

Patton, D. W., Ferguson, M. M., Forsyth, A., & James, J. 1985, "Oro-Facial Granulomatosis: A possible allergic basis", *The British Journal of Oral and Maxillofacial Surgery*, vol. 23, pp. 235-242.

Pecegueiro, M., Sachse, M. F., Amaro, J., Farinha, P., & Fonseca, I. 1999, "Oral lichen planus versus oral lichenoid eruption as a manifestation of contact allergy", *Contact Dermatitis*, vol. 40, pp. 333-334.

Pedersen, A. 1996, "Abnormal EBV immune status in oral lichen planus", *Oral Diseases*, vol. 2, pp. 125-128.

Pedersen, A. & Klausen, B. 1984, "Glucocorticosteroids and oral medicine", *Journal of Oral Pathology*, vol. 13, pp. 1-15.

Petrucci, D. I., Felix, D. H., MacDonald, D. G., & Wray, D. 1995, "Associations of lichenoid reactions with exposure to environmental and dietary allergens", *Journal of Dental Research*, vol. 74, no. 3, p. 834.

Phillips, W. G., Vaughan-Jones, S., Jenkins, R., & Breathnach, S. M. 1994, "Captopril-induced lichenoid eruption", *Clinical and Experimental Dermatology*, vol. 19, pp. 317-320.

Pindborg, J. J., Mehta, F. S., Daftary, D. K., Gupta, R. C., & Bhonsle, R. B. 1972, "Prevalence of oral lichen planus among 7639 Indian villagers in Kerala, South India", *Acta Dermato-Venereologica*, vol. 52, pp. 216-220.

Placucci, F., Vincenzi, C., Ghedini, G., Piana, G., & Tosti, A. 1996, "Coexistence of type I and type IV allergy to rubber latex", *Contact Dermatitis*, vol. 34, p. 76.

Podmore, P. & Burrows, D. 1986, "Clofazimine - an effective treatment for Melkersson-Rosenthal syndrome or Miescher's cheilitis", *Clinical and Experimental Dermatology*, vol. 11, pp. 173-178.

Podmore, P., Burrows, D., & Bingham, E. A. 1984, "Prediction of patch test results", *Contact Dermatitis*, vol. 11, pp. 283-284.

Porter, S., Flint, S., Scully, C., & Keith, O. 1992, "Recurrent aphthous stomatitis: the efficacy of replacement therapy in patients with underlying hematinic deficiencies", *Annals of Dentistry*, vol. 51, no. 2, pp. 14-16.

Porter, S., Scully, C., & Pedersen, A. 1998, "Recurrent Aphthous Stomatits", *Critical Reviews in Oral Biology and Medicine*, vol. 9, no. 3, pp. 306-321.

Postlethwaite, K. R. & Parry, D. H. 1988, "Acquired angioedema", *The British Journal of Oral and Maxillofacial Surgery*, vol. 26, pp. 499-502.

Prantera, C., Bothamley, G., Levenstein, S., Mangiarotti, R., & Argentieri, R. 1989, "Crohn's disease and mycobacteria : two cases of Crohn's disease with high anti-mycobacterial antibody levels cured by dapsone therapy", *Biomedicine and Pharmacotherapy*, vol. 43, pp. 295-299.

Prausnitz, C. & Küstner, H. 1921, "Studies on sensitivity", *Centralblatt fur Bakteriologie. 1. Abt. Originale*, vol. 86, pp. 160-169.

Pryce, D. W. & King, C. M. 1990, "Orofacial granulomatosis associated with delayed hypersensitivity to cobalt", *Clinical and Experimental Dermatology*, vol. 15, pp. 384-386.

Prystowsky, S. D., Allen, A. M., Smith, R. W., Nonomura, J. H., Odom, R. B., & Akers, W. A. 1979, "Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. Relationships between age, sex, history of exposure, and reactivity to standard patch tests and use tests in a general population", *Archives of Dermatology*, vol. 115, no. 8, pp. 959-962.

Puig, L., Fernandez-Figueras, M.-T., Montero, M.-A., Ferrándiz, C., & Alomar, A. 1995, "Erythema-multiforme-like eruption due to topical contactants: expression of adhesion molecules and their ligands and characterization of the infiltrate", *Contact Dermatitis*, vol. 33, pp. 329-332.

Quirce, S., Parra, F., Lázaro, M., Gómez, M. I., & Cano, M. S. 1991, "Generalized dermatitis due to oral nystatin", *Contact Dermatitis*, vol. 25, pp. 197-198.

Rademaker, M. & Forsyth, A. 1989, "Contact dermatitis in children", *Contact Dermatitis*, vol. 20, no. 2, pp. 104-107.

Ranasinghe, A. W., Warnakulasuriya, K. A. A. S., Tennekoon, G. E., & Seneviratna, B. 1983, "Oral mucosal changes in iron deficiency anaemia in a Sri Lankan female population", *Oral Surgery*, vol. 55, no. 1, pp. 29-32.

Rance, F., Kanny, G., Dutau, G., & Moneret-Vautrin, D. A. 1999, "Food hypersensitivity in children: clinical aspects and distribution of allergens", *Pediatric Allergy and Immunology*, vol. 10, pp. 33-38.

Rapson, W. S. 1985, "Skin contact with gold and gold alloys", *Contact Dermatitis*, vol. 13, pp. 56-65.

Reed, B. E., Barrett, A. P., Katelaris, C., & Bilous, M. 1993, "Orofacial sensitivity reactions and the role of dietary components. Case reports", *Australian Dental Journal*, vol. 38 (4), pp. 287-291.

Rees, J., Friedmann, P. S., & Matthews, J. N. S. 1990, "Contact sensitivity to dinitrochlorobenzene in impaired in atopic subjects", *Archives of Dermatology*, vol. 126, pp. 1173-1175.

Rees, R. S., Bergman, J., & Ramirez-Alexander, R. 1992, "Angiodema associated with Lisinopril", *American Journal of Emergency Medicine*, vol. 10, pp. 321-322.

Rees, S. R. & Gibson, J. 1997, "Angioedema and swellings of the orofacial region", *Oral Diseases*, vol. 3, pp. 39-42.

Rees, S. R., Gibson, J., Forsyth, A., & Wray, D. "Prevalence of food and environmental allergy in oral mucosal disease", *Journal of Dental Research,* 77, 895. 1998.

Rees, T. D. 1999, "Orofacial granulomatosis and related conditions", *Periodontology 2000*, vol. 21, pp. 145-157.

Regezi, J., Ellis, C. N., Stewart, J. C. B., & Giustina, T. A. 1986, "Histologic changes associated with the topical use of isotretinoin on oral lichen planus", *Oral Oncology, European Journal of Cancer*, vol. 61, no. 5, pp. 479-483.

Rietschel, R. L. 1989, "Contact dermatitis and diagnostic techniques", *Allergy Procedures*, vol. 10, no. 6, pp. 403-411.

Rietschel, R. L., Adams, R. M., Maibach, H. I., Storrs, F. J., & Rosenthal, L. E. 1988, "The case for patch test readings beyond day 2", *Journal of the American Academy of Dermatology*, vol. 18, no. 1, pp. 42-45.

Rietschel, R. L. & Fowler, J. F. 1997, "Contact Stomatitis and Cheilitis," in *Fisher's Contact Dermatitis*, 4th edn, R. L. Rietschel & J. F. Fowler, eds., Williams and Wilkin, Baltimore, pp. 886-919.

Riggio, M. P., Gibson, J., Lennon, A., Wray, D., & MacDonald, D. G. 1997, "Search for Mycobacterium paratuberculosis DNA in orofacial granulomatosis and oral Crohn's disease tissue by polymerase chain reaction", *Gut*, vol. 41, pp. 646-650.

Riggio, M. P., Lennon, A., Ghodratnama, F., & Wray, D. 1999, "Lack of association between Streptococcus Oralis and recurrent aphthous stomatitis", *Journal of Oral Pathology and Medicine*, vol. 29, pp. 26-32.

Robertson, W. D. & Wray, D. 1992, "Ingestion of medication among patients with oral keratoses including lichen planus", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 74, pp. 183-185.

Rogers, R. S., III 1977, "Recurrent aphthous stomatitis: clinical characteristics and evidence for an immunopathogenesis", *The Journal of Investigative Dermatology*, vol. 69, no. 6, pp. 499-509.

Roleau, J.-C. 1999, "Treatment of severe drug eruptions", *Journal of Dermatology*, vol. 26, pp. 718-722.

Rosen, A., Isaacson, D., Brady, M., & Corey, J. P. 1993, "Hypersensitivity to latex in health care workers: report of five cases", *Otolaryngology and Head and Neck Surgery*, vol. 109, pp. 731-734.

Ruddy, S. 1988, "Hereditary Angioedema undersuspected, underdiagnosed", *Hospital Practitioner*, vol. 23(8), pp. 91-106.

Sabroe, R. A., Sharp, L. A., & Peachey, R. D. G. 1996, "Contact allergy to gold sodium thiosulfate", *Contact Dermatitis*, vol. 34, pp. 345-348.

Sainio, E.-L. & Kanerva, L. 1995, "Contact allergens in toothpastes and a review of their hypersensitivity", *Contact Dermatitis*, vol. 33, pp. 100-105.

Sainsbury, C. P. Q., Dodge, J. A., Walker, D. M., & Aldred, M. J. 1987, "Orofacial granulomatosis in childhood", *British Dental Journal* , vol. 163, pp. 154-157.

Sakuntabhai, A., Macleod, R. I., & Lawrence, C. M. 1992, "Intralesional steroid injection after nerve-block in orofacial granulomatosis", *Lancet*, vol. 340, p. 969.

Sampson, H. A. 1997, "Food Allergy", *Journal of the American Medical Association;* vol. 278, pp. 1888-1894.

Sampson, H. A. & Metcalfe, D. D. 1991, "Immediate reactions to foods," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, p. 101.

Sanderson, J. D., Barnard, K. M., Lucas, S., & Challacombe, S. J. 1996, "Oro-facial granulomatosis and crohn's disease; results of ileo-colonoscopy", *Gut*, vol. 39, no. suppl 1, p. A37.

Sanderson, J. D., Moss, M. T., Tizard, M. L. V., & Hermon-Taylor, J. 1992, "Mycobacterium paratuberculosis DNA in Crohn's disease tissue", *Gut*, vol. 33, pp. 890-896.

Saperstein, H., Rapaport, M., & Rietschel, R. L. 1984, "Topical vitamen E as a cause of erythema multiforme-like eruption", *Archives of Dermatology*, vol. 120, pp. 906-908.

Savage, N. W. 1997, "Oral lichenoid drug eruptions", *Oral Diseases*, vol. 3, pp. 55-57.

Savage, N. W., Mahanonda, R., Seymour, G. J., Bryson, G. J., & Collins, R. J. 1988, "The proportion of suppressor-inducer T-lymphocytes is reduced in recurrent aphthous stomatitis", *Journal of Oral Pathology*, vol. 17(6), pp. 293-297.

Savage, N. W. & Seymour, G. J. 1994, "Specific lymphocytotoxic destruction of autologous epithelial cell targets in recurrent aphthous stomatitis", *Australian Dental Journal*, vol. 39(2), pp. 98-104.

Savage, N. W., Seymour, G. J., & Kruger, B. J. 1986, "Expression of class I and class II major histocompatibility complex antigens on epithelial cells in recurrent aphthous stomatitis", *Journal of Oral Pathology*, vol. 15(4), pp. 191-195.

Savin, J. A. 1991, "Oral lichen planus, not rare-and not easily treated", *British Medical Journal*, vol. 302, pp. 544-545.

Schofield, J. K., Tatnall, F. M., & Leigh, I. M. 1993, "Recurrent erythema multiforme: clinical features and treatment in a large series of patients", *British Journal of Dermatology*, vol. 128, pp. 542-545.

Scully, C. 1993, "Are viruses associated with aphthae and oral vesiculo-erosive disorders?", *The British Journal Of Oral And Maxillofacial Surgery*, vol. 31, no. 3, pp. 173-177.

Scully, C., Beyli, M., Ferreiro, M. C., Ficarra, G., Gill, Y., Griffiths, M., Holmstrup, P., Mutlu, S., Porter, S., & Wray, D. 1998, "Update on oral lichen planus: etiopathogenesis and management", *Critical Reviews in Oral Biology and Medicine*, vol. 9, no. 1, pp. 86-122.

Scully, C. & Cawson, R. A. 1993, *Medical Problems in Dentistry*, 3rd edn, Wright, Oxford.

Scully, C., Cochran, K. M., Russell, R. I., Ferguson, M. M., Ghouri, M. A. K., Lee, F. D., MacDonald, D. G., & McIntyre, P. B. 1982, "Crohn's disease of the mouth: an indicator of intestinal involvement", *Gut*, vol. 23, pp. 198-201.

Scully, C. & Porter, S. 1997, "The clinical spectrum of desquamative gingivitis", *Seminars in Cutaneous Medicine and Surgery*, vol. 16, no. 4, pp. 308-313.

Scully, C., Porter, S., & Eveson, J. W. 1993, "Oral lichen planus and coeliac disease", *Lancet*, vol. 341, p. 1660.

Seidman, M. D., Lewandowski, C. A., Sarpa, J. R., Potesta, E., & Schwietzer, V. G. 1990, "Angioedema related to angiotensin-converting enzyme inhibitors", *Otolaryngology and Head and Neck Surgery*, vol. 102, pp. 727-731.

Serup, J. & Staberg, B. 1987a, "Differentiation of allergic and irritant reactions by transepidermal water loss", *Contact Dermatitis*, vol. 16, pp. 129-132.

Serup, J. & Staberg, B. 1987b, "Ultrasound for assessment of allergic and irritant patch test reactions", *Contact Dermatitis*, vol. 17, pp. 80-84.

Shaffrali, F. C. & Gawkrodger, D. J. 1999, "Allergic contact dermatitis from natural rubber latex without immediate hypersensitivity", *Contact Dermatitis*, vol. 40, no. 6, pp. 325-326.

Shah, M., Lewis, F. M., & Gawkrodger, D. J. 1996, "Contact allergy in patients with oral symptoms: a study of 47 patients", *American Journal of Contact Dermatitis*, vol. 7, no. 3, pp. 146-151.

Shapiro, N. 1994, "Acute angioedema after ketorolac ingestion", *Journal of Oral and Maxillofacial Surgery*, vol. 52, pp. 626-627.

Sharma, V. K., Mandal, S. K., Sethuraman, G., & Bakshi, N. A. 1999, "Para-phenylenediamine-induced lichenoid eruptions", *Contact Dermatitis*, vol. 41, no. 1, pp. 40-41.

Ship, I. I. 1960, "The etiology of recurrent aphthous stomatitis", *Journal of Dental Research*, vol. 39, p. 748.

Ship, I. I. 1965, "Inheritance of aphthous ulcers in the mouth", *Journal of Dental Research*, vol. 44, pp. 837-844.

Sicherer, S. H., Burks, A. W., & Sampson, H. A. 1998, "Clinical features of acute allergic reactions to peanut and tree nuts in children", *Pediatrics*, vol. 102, no. 1, pp. e6.

Sicherer, S. H., & Sampson, H. A. 1999, "Food hypersensitivity and atopic dermatitis: Pathophysiology, epidemiology, diagnosis, and management", *Journal of Allergy and Clinical Immunology,* vol. 104, no. 3 (2), pp. S114-S122.

Silverman, S. & Lozada, F. 1977, "An epilogue to plasme-cell gingivostomatitis (allergic gingivostomatitis)", *Oral Surgery*, vol. 43, no. 2, pp. 211-217.

Silverman, S. Jr. & Bahl, S. 1997, "Oral lichen planus update: clinical characteristics, treatment responses, and malignant transformation", *American Journal of Dentistry*, vol. 10, pp. 259-263.

Silverman, S. Jr., Gorsky, M., & Lozada-Nur, F. 1985, "A prospective follw-up study of 570 patients with oral lichen planus: Persistence, remission, and malignant association", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 60, pp. 30-34.

Silverman, S. Jr., Gorsky, M., Lozada-Nur, F., & Giannotti, K. 1991, "A prospective study of findings and management in 214 patients with oral lichen planus", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 72, pp. 665-670.

Sim, T. C. & Grant, J. A. 1990, "Hereditary angioedema: Its diagnostic and management perspectives.", *The American Journal of Medicine*, vol. 88, pp. 656-664.

Simark-Mattsson, C., Jontell, M., Bergenholtz, G., & Dahlgren, U. I. 1999, "Reduced in vivo cell-mediated immune responses to mumps, tuberculin, and streptokinase/streptodornase but not to Candida albicans in oral lichen planus", *Journal of Dental Research*, vol. 78, no. 11, pp. 1704-1710.

Singh, J. N. 1992, "Diagnostic testing in chronic urticaria and angioedema.", *Canadian Medical Association Journal*, vol. 147, no. 9, pp. 1303-1304.

Sklavounou, A. & Laskaris, G. 1983, "Frequency of desquamative gingivitis in skin diseases.", *Oral Surgery*, vol. 56, no. 2, pp. 141-144.

Skoglund, A. 1994, "Value of epicutaneous patch testing in patients with oral, mucosal lesions of lichenoid character", *Scandinavian Journal Of Dental Research*, vol. 102(4), pp. 216-222.

Skoglund, A. & Egelrud, T. 1991, "Hypersensitivity reactions to dental materials in patients with lichenoid oral mucosal lesions and in patients with burning mouth syndrome.", *Scandinavian Journal Of Dental Research*, vol. 99, pp. 320-328.

Slater, E. E., Merrill, D. D., & Guess, H. A. 1988, "Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition", *Journal of the American Medical Association*, vol. 260, pp. 967-970.

Smart, E. R., Macleod, R. I., & Lawrence, C. M. 1995, "Resolution of lichen planus following removal of amalgam restorations in patients with proven allergy to mercury salts: a pilot study.", *British Dental Journal*, vol. 178, pp. 108-112.

Smeets, E., Fryns, J. P., & van den, B. H. 1994, "Melkersson-Rosenthal syndrome and de novo autosomal t(9; 21)(p11;p11) translocation", *Clinical Genetics*, vol. 45, pp. 323-324.

Smith, C. & Pindborg, J. J. 1969, *"Histological Grading of Oral Epithelial Atypia by the use of Photographic Standards"*, C. Hamburgers Bogtrykkeri, Copenhagen.

Smith, I. L. F. 1968, "Acute allergic reaction following the use of toothpaste", *British Dental Journal*, vol. 125, pp. 304-305.

Sollecito, T. P. & Greenberg, M. S. 1992, "Plasma cell gingivitis", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 73, pp. 690-693.

Solley, G. O., Gleich, G. J., Jordon, R. E., & Schroeter, A. L. 1976, "The late phase of the immediate wheal and flare skin reaction", *The Journal of Clinical Investigation*, vol. 58, pp. 408-420.

Spiechowicz, E., Glantz, P.-O., Axéll, T., & Chmielewski, W. 1984, "Oral exposure to a nickel-containing dental alloy of persons with hypersensitive skin reactions to nickel.", *Contact Dermatitis*, vol. 10, pp. 206-211.

Spouge, J. D. & Diamond, B. A. 1963, "Hypersensitivity reactions in mucous membranes.", *Oral Surgery*, vol. 16, pp. 412-421.

Squire, E. N. Jr. 1987, "Angio-edema and monosodium glutamate", *Lancet*, vol. 8539, no. 1, p. 988.

Staberg, B., Klemp, P., & Serup, J. 1984, "Patch test responses evaluated by cutaneous blood flow measurements.", *Archives of Dermatology*, vol. 120, no. 6, pp. 741-743.

Staerkjaer, L. & Menné, T. 1990, "Nickel allergy and orthodontic treatment.", *European Journal of Orthodontics*, vol. 12(3), pp. 284-289.

Staines, K. S., Felix, D. H., & Forsyth, A. 1998, "Desquamative gingivitis, sole manifestation of tosylamide/formaldehyde resin allergy", *Contact Dermatitis*, vol. 39, no. 2, p. 90.

Staretz, L. R. & DeBoom, G. W. 1990, "Multiple oral and skin lesions occurring after treatment with penicillin", *Journal of the American Dental Association*, vol. 121, no. 3, pp. 436-437.

Stenman, E. & Bergman, M. 1989, "Hypersensitivity reactions to dental materials in a referred group of patients", *Scandinavian Journal of Dental Research*, vol. 97, no. 1, pp. 76-83.

Stevens, A. A. 1904, *A Manual of the Practice of Medicine*, 6th edn, W.B. Saunders and Co., Philadelphia, New York and London.

Stevenson, D. D. 1991, "Tartrazine, azo, and nonazo dyes.," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, pp. 267-275.

Strauss, R. A., Fattore, L., & Soltani, K. 1989, "The association of mucocutaneous lichen planus and chronic liver disease", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 68, pp. 406-410.

Subiza, J., Subiza, J. L., Valdivieso, R., Escribano, P. M., Garcia, R., & Jerez, M. 1992, "Toothpaste flavor-induced asthma", *The Journal of Allergy and Clinical Immunology*, vol. 90, no. 6, pp. 1004-1006.

Sugai, T., Takagi, T., Yamamoto, T., & Takahashi, Y. 1979, "Age distribution of the incidence of contact sensitivity to standard allergens.", *Contact Dermatitis*, vol. 5, pp. 383-388.

Sugarman, M. M. 1950, "Contact allergy due to mint chewing gum", *Oral Surgery*, vol. 3, pp. 1145-1147.

Sugarman, P. B., Savage, N. W., Walsh, L. J., & Seymour, G. J. 1993, "Disease mechanisms in oral lichen planus. A possible role for autoimmunity.", *Australian Journal of Dermatology*, vol. 34(2), pp. 63-69.

Sugarman, P. B., Savage, N. W., Xu, L. J., Walsh, L. J., & Seymour, G. J. 1995, "Heat shock protein expression in oral lichen planus.", *Journal of Oral Pathology and Medicine*, vol. 24(1), pp. 1-8.

Sullivan, S. N. 1990, "Hyposthesis revisited: toothpaste and the cause of Crohn's disease", *Lancet*, vol. 336, pp. 1096-1197.

Sulzberger, M. B. 1975, "The patch test - who should and should not use it and why.", *Contact Dermatitis*, vol. 1, pp. 117-119.

Sun, A., Chiang, C. P., Chiou, P. S., Wang, J. T., Liu, B. Y., & Wu, Y. C. 1994, "Immunomodulation by levamisole in patients with recurrent aphthous ulcers or oral lichen planus", *Journal of Oral Pathology and Medicine (JRF)*, vol. 4, pp. 172-177.

Sussman, G. L., Yang, W. H., & Steinberg, S. 1992, "Melkersson-Rosenthal syndrome: clinical, pathologic, and therapeutic considerations", *Annals of Allergy*, vol. 69, pp. 187-194.

Sweatman, M. C., Tasker, R., Warner, J. O., Ferguson, M. M., & Mitchell, D. N. 1986, "Oro-facial granulomatosis. Response to elemental diet and provacation by food additives", *Clinical Allergy*, vol. 16, pp. 331-338.

Takeuchi, Y., Tohnai, I., Kaneda, T., & Nagura, H. 1988, "Immunohistochemical analysis of cells in mucosal lesions of oral lichen planus.", *Journal of Oral Pathology*, vol. 17, pp. 367-373.

Tariq, S. M., Stevens, M., Matthews, S., Ridout, S., Twiselton, R., & Hide, D. W. 1996, "Cohort study of peanut and tree nut sensitisation by age of 4 years.", *British Medical Journal*, vol. 313, pp. 513-514.

Taylor, S. L., Bush, R. K., & Nordlee, J. A. 1991, "Sulphites," in *Food Allergy: Adverse Reactions to Foods and Food Additives*, D. D. Metcalfe, H. A. Sampson, & R. A. Simon, eds., Blackwell Scientific Publications, Cambridge, Massachusetts, pp. 239-259.

Taylor, S. L. & Dormedy, E. S. 1998, "The role of flavoring substances in food allergy and intolerance", *Advances in Food and Nutrition Research*, vol. 42, pp. 1-44.

Thestrup-Pedersen, K., Larsen, C. G., & Ronnevig, J. 1989, "The immunology of contact dermatitis.", *Contact Dermatitis*, vol. 20, pp. 81-92.

Thompson, T. & Frable, M. A. S. 1993, "Drug-induced, life-threatening angioedema revisited", *Laryngoscope*, vol. 103, pp. 10-12.

Thorn, J. J., Holmstrup, P., Rindum, J., & Pindborg, J. J. 1988, "Couse of various clinical forms of oral lichen planus. A prospective follow-up study of 611 patients.", *Journal of Oral Pathology*, vol. 17, pp. 213-218.

Todd, P., Garioch, J. J., Lamey, P.-J., Lewis, M. A. O., Forsyth, A., & Rademaker, M. 1990, "Patch testing in lichenoid reactions of the mouth and oral lichen planus", *Contact Dermatitis*, vol. 23, pp. 300-301.

Toews, G. B., Bergstresser, P. R., Streilein, J. W., & Sullivan, S. 1980, "Epidermal Langerhan's cell density determines whether contact hypersensitivity or unresponsivenes follows skin painting with DNFB.", *Journal of Immunology*, vol. 124, no. 1, pp. 445-453.

Uehara, M. & Sawai, T. 1989, "A longitudinal study of contact sensitivity in patients with atopic dermatitis.", *Archives of Dermatology*, vol. 125, pp. 366-368.

Ulmer, J. L. & Garvey, M. J. 1992, "Fatal angioedema associated with lisinopril.", *The Annals of Pharmacotherapy*, vol. 26, pp. 1245-1246.

van-Hoogstraten, I. M. W., Andersen, K. E., von Blomberg, B. M. E., Boden, D., Bruynzeel, D. P., Burrows, D., Camarasa, J. G., Dooms-Goossens, A., Kraal, G., Lahti, A., Menne, T., Rycroft, R. J. G., Shaw, S., & Todd, D. 1991, "Reduced frequency of nickel allergy upon oral nickel contact at an early age", *Clinical and Experimental Immmunology*, vol. 85, pp. 441-445.

van den Haute, V., Antoine, J. L., & Lachapelle, J. M. 1989, "Histopathological discriminant criteria between lichenoid drug eruption and idiopathic lichen planus: retrospective study on selected samples", *Dermatologica*, vol. 179, pp. 10-13.

van der Valk, P. G. M., Kruis-de Vries, M. H., Nater, J. P., Bleumink, E., & de Jong, M. C. J. M. 1985, "Eczematous (irritant and allergic) reactions of the skin and barrier function as determined by water vapour loss.", *Clinical and Experimental Dermatology*, vol. 10, pp. 185-193.

van Dis, M. L. & Parks, E. T. 1995, "Prevalence of oral lichen planus in patients with diabetes mellitus.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 79, pp. 696-700.

van Hoogstraten, I. M., Boden, D., von Blomberg, M. E., Kraal, G., & Scheper, R. J. 1992, "Persistent immune tolerance to nickel and chromium by oral administration prior to cutaneous sensitization", *The Journal of Investigative Dermatology*, vol. 99, no. 5, pp. 608-616.

van Joosst, Th., van Ulsen, J., & van Loon, L. A. J. 1988, "Contact allergy to denture materials in the burning mouth syndrome", *Contact Dermatitis*, vol. 18, pp. 97-99.

van Loon, L. A. J., van Elsas, P. W., van Joosst, Th., & Davidson, C. L. 1984, "Contact stomatitis and dermatitis to nickel and palladium.", *Contact Dermatitis*, vol. 11, pp. 294-297.

Varga, E., Field, E. A., & Tyldesley, W. R. 1990, "Orofacial manifestations of mixed connective tissue disease", *British Dental Journal* , vol. 168, no. 8, pp. 330-331.

Veien, N. K., Hattel, T., & Laurberg, G. 1996a, "Oral challenge with parabens in paraben-sensitive patients", *Contact Dermatitis*, vol. 34, no. 6, p. 433.

Veien, N. K., Hattel, T., & Laurberg, G. 1996b, "Systemically aggravated contact dermatitis caused by aluminium in toothpaste", *Contact Dermatitis*, vol. 28, pp. 199-200.

Verpy, E., Biasotto, M., Brai, M., Misiano, G., Meo, T., & Tosi, M. 1996, "Exhaustive mutation scanning by fluorescence-assisted mismatch analysis discloses new genotype-phenotype correlations in angioedema.", *American Journal of Human Genetics*, vol. 59, pp. 308-319.

Vilaplana, J. & Romaguera, C. 1998, "New developments in jewellery and dental materials", *Contact Dermatitis*, vol. 39, no. 2, pp. 55-57.

Vincent, S. D., Fotos, P. G., Baker, K. A., & Williams, T. P. 1990, "Oral lichen planus: The clinical, historical and therapeutic features of 100 cases.", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 70, pp. 165-171.

Vistnes, L. M. & Kernahan, D. A. 1971, "The Melkersson-Rosenthal syndrome", *Plastic and Reconstructive Surgery*, vol. 48, pp. 126-134.

Von-den-Driesch, P. 1994, "Sweet's syndrome (acute febrile neutrophilic dermatosis).", *Journal of the American Academy of Dermatology*, vol. 31(4), pp. 535-560.

von Nielsen, Ch. & Klaschka, F. 1971, "Teststudien an der mundschleimhaut bei ekzemallergikern", *Deutsche Zahn-, Mund-, und Kieferheilkunde mit Zentralblatt*, vol. 57, no. 7/8, pp. 201-218.

von Pirquet, C. E. 1906, "Allergy", *Munchener medizinische Wochenschrift*, vol. 30, p. 1457.

von Pirquet, C. E. 1911, "Allergy", *Archives of Internal Medicine*, vol. 7, pp. 258-288.

Walsh, L. J., Savage, N. W., Ishii, T., & Seymour, G. J. 1990, "Immunopathogenesis of oral lichen planus.", *Journal of Oral Pathology and Medicine*, vol. 19(9), pp. 389-396.

Walton, L. J., Thornhill, M. H., & Farthing, P. M. 1996, "T cell antigen receptor expresion by intra-epithelial lymphocytes in oral lichen planus", *Journal of Oral Pathology and Medicine*, vol. 25, pp. 534-537.

Walton, S., Nayagam, A. T., & Keczkes, K. 1986, "Age and sex incidence of allergic contact dermatitis.", *Contact Dermatitis*, vol. 15, pp. 136-139.

Wantke, F., Hemmer, W., Jarisch, R., & Götz, M. 1996, "Patch test reactions in children, adults and the elderly. A comparative study on patients with suspected allergic contact dermatitis.", *Contact Dermatitis*, vol. 34, pp. 316-319.

Weigand, D. A., Haygood, C., & Gaylor, J. R. 1974, "Cell layers and density of negro and caucasian stratum corneum.", *The Journal of Investigative Dermatology*, vol. 62, no. 6, pp. 563-568.

Weksler, M. E. 1982, "Age-associated changes in the immune response.", *Journal of the American Geriatrics Society*, vol. 30, pp. 718-723.

Whitley, B. D., Shepherd, M. G., & Ferguson, M. M. 1991, "Peanut sensitivity as a cause of burning mouth", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 72 (6), pp. 671-674.

Whitmore, S. E. 1994, "Should atopic individuals be patch tested?", *Dermatology Clinics*, vol. 12, no. 3, pp. 491-499.

Wiesenfeld, D., Ferguson, M. M., Forsyth, A., & MacDonald, D. G. 1984, "Allergy to dental gold", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 57, no. 2, pp. 158-160.

Wiesenfeld, D., Ferguson, M. M., Mitchell, D. N., MacDonald, D. G., Scully, C., Cochran, K., & Russell, R. I. 1985, "Oro-Facial Granulomatosis - a Clinical and Pathological Analysis", *Quarterly Journal of Medicine*, vol. 213, pp. 101-113.

Williams, A. J. K., Wray, D., & Ferguson, A. 1991, "The clinical entity of orofacial Crohn's disease", *Quarterly Journal of Medicine*, vol. 289, pp. 451-458.

Williams, L. W. & Bock, S. A. 1999, "Skin testing and food challenges in allergy and immunology practice", *Clinical Reviews in Allergy and Immunology*, vol. 17, pp. 323-338.

Willis, C. M., Stephens, C. J. M., & Wilkinson, J. D. 1988, "Assessment of erythema in irritant contact dermatitis.", *Contact Dermatitis*, vol. 18, pp. 138-142.

Wilson, C. L. 1996, "Hereditary angioedema: a potential clinical emergency.", *The Clinical Forum for Nurse Anaesthetists*, vol. 2, pp. 108-109.

Wilson, E. 1869, "On leichen planus", *Journal of Cutaneous Medical Diseases of the Skin*, vol. 3, pp. 117-132.

Wiltshire, W. A., Ferreira, M. R., & Ligthelm, A. J. 1996, "Allergies to dental materials", *Quintessence International*, vol. 27, no. 8, pp. 513-520.

Wolkenstein, P., Chosidow, O., Flechet, M. L., Robbiola, O., Paul, M., Dume, L., Revuz, J., & Roujeau, J. C. 1996, "Patch testing in severe cutaneous adverse drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis", *Contact Dermatitis*, vol. 35, pp. 234-236.

Wong, S. 1990, "Angioedema.", *Allergy Procedures*, vol. 11, no. 4, pp. 163-164.

Worm, M., Jeep, S., Sterry, W., & Zuberbier, T. 1998, "Perioral contact dermatitis caused by L-carvone in toothpaste", *Contact Dermatitis*, vol. 38, no. 6, p. 338.

Worsaae, N., Christensen, K. C., Schiodt, M., & Reibel, J. 1982, "Melkersson-Rosenthal syndrome and cheilitis granulomatosa", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 54, pp. 404-413.

Worsaae, N. & Pindborg, J. J. 1980, "Granulomatous gingival manifestations of Melkersson-Rosenthal syndrome", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 49, pp. 131-138.

Wray, D. 1981, "Gluten-sensitive recurrent aphthous stomatitis", *Digestive Diseases and Sciences*, vol. 26, no. 8, pp. 737-740.

Wray, D. & Charon, J. 1991, "Polymorphonuclear neutrophil function in recurrent aphthous stomatitis.", *Journal of Oral Pathology and Medicine*, vol. 20, pp. 392-394.

Wray, D., Ferguson, M. M., Hutcheon, A. W., & Dagg, J. H. 1978, "Nutritional deficiencies in recurrent aphthae", *Journal of Oral Pathology*, vol. 7, no. 6, pp. 418-423.

Wray, D., Ferguson, M. M., Mason, D. K., Hutcheon, A. W., & Dagg, J. H. 1975, "Recurrent aphthae: treatment with vitamin B_{12}, folic acid and iron", *British Medical Journal*, vol. 2, pp. 490-493.

Wray, D., Lowe, G. D. O., Dagg, J. H., Felix, D. H., & Scully, C. 1999, "*Textbook of General and Oral Medicine*", Churchill Livingstone, Edinbugh.

Wray, D., Rubinstein, P., Walker, M., & Notkins, A. 1981, "Inheritance and HLA markers in recurrent aphthous stomatitis (RAS)", *Journal of Dental Research*, vol. 60, pp. 378.

Wray, D., Vlagopolous, T., & Siraganian, R. 1982, "The role of food allergens and basophil histamine release in recurrent aphthous stomatitis.", *Oral Surgery*, vol. 54, pp. 388-395.

Wright, A., Ryan, F. P., Willingham, S. E., Holt, S., Page, A. C., Hindle, M. O., & Franklin, C. D. 1986, "Food allergy or intolerance in severe recurrent aphthous ulceration of the mouth", *British Medical Journal (Clinical Research Ed.)*, vol. 292, no. 6530, pp. 1237-1238.

Wright, J. M. 1984, "Oral manifestations of drug reactions", *Dental Clinics of North America*, vol. 28, no. 3, pp. 529-543.

Wuthrich, B. 1998, "Food-induced cutaneous adverse reactions", *Allergy*, vol. 53, no. 46 Suppl, pp. 131-135.

Wuthrich, B., Bianchi-Kusch, E., & Johansson, S. G. O. 1996, "Allergic urticaria and angioedema caused by a hemostatic sponge of bovine fibrin used in tooth extraction.", *Allergy*, vol. 51, pp. 49-51.

Yamammoto, T., Osaki, T., Yoneda, K., & Ueta, E. 1994, "Cytokine production by keratinocytes and mononuclear infiltrates in oral lichen planus", *Journal of Oral Pathology and Medicine*, vol. 23(7), pp. 309-315.

Yiannias, J. A., el Azhary, R. A., Hand, J. H., Pakzad, S. Y., & Rogers, R. S., III 2000, "Relevant contact sensitivities in patients with the diagnosis of oral lichen planus", *Journal of the American Academy of Dermatology*, vol. 42, pp. 177-182.

Yih, W. Y., Maier, T., Kratochvil, F. J., & Zieper, M. B. 1998, "Analysis of desquamative gingivitis using direct immunofluorescence in conjunction with histology", *Journal of Periodontology*, vol. 69, no. 6, pp. 678-685.

Yusin, J. S., Crawford, W. W., & Klaustermeyer, W. B. 1999, "Facial edema, oral ulcers and a cutaneous eruption following a dental procedure utilizing diflusal and mepivicaine", *Annals of Allergy, Asthma and Immunology*, vol. 83, pp. 353-355.

Zelickson, A. S. & Mottaz, J. 1970, "The effect of sunlight on human epidermis.", *Archives of Dermatology*, vol. 101, pp. 312-315.

Zhao, Z. Z., Savage, N. W., Pujic, Z., & Walsh, L. J. 1997, "Immunohistochemical localization of mast cells and mast cell-nerve interactions in oral lichen planus", *Oral Diseases*, vol. 3, pp. 71-76.

Zhao, Z. Z., Savage, N. W., & Walsh, L. J. 1998, "Associations between mast cells and laminin in oral lichen planus", *Journal of Oral Pathology and Medicine.*, vol. 27, no. 4, pp. 163-167.

Ziff, S. & Ziff, M. F. 1995, *Dentistry without mercury* Bio-Probe, Inc., Orlando, Florida.

Zimmer, W. M., Rogers III, R. S., Reeve, C. M., & Sheridan, P. J. 1992, "Orofacial manifestations of Melkersson-Rosenthal Syndrome", *Oral Surgery, Oral Medicine and Oral Pathology*, vol. 74, pp. 610-619.

Zuberbier, T., Bohm, M., & Czarnetzki, B. M. 1993, "Food intake in combination with a rise in body temperature: a newly identified couse of angioedema.", *The Journal of Allergy and Clinical Immunology*, vol. 91, no. 6, pp. 1226-1227.