EFFICACY OF SALIVA ORTHANA IN THE MANAGEMENT OF XEROSTOMIA IN HOSPICE PATIENTS

by

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For my parents

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PREFACE

The work in this thesis was carried out at the ACCORD Hospice and in the Department of Oral Sciences, Glasgow Dental Hospital and School, from March 1994 to September 1996, under the supervision of Dr Jeremy Bagg.

These studies represent original work carried out by the author, except for the processing of the microbiological specimens which was undertaken by the Oral Microbiology Unit of Glasgow Dental Hospital and School, and have not been submitted in any form to any other university.

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DECLARATION

This thesis is the original work of the author

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SUMMARY

Oral disease has been reported as a common feature in patients with advanced malignancy, although this area has been poorly researched. The development of appropriate mouth care régimes, particularly for use by nursing staff, is therefore a priority. Dryness of the mouth, often secondary to the use of xerogenic medication or previous radiotherapy, affects up to 70% of terminally ill cancer patients, but there have been no formal studies of its treatment in this group.

This thesis describes a placebo-controlled, double-blind clinical trial of a mucin-based salivary substitute spray, among 70 hospice patients (25 male and 45 female; age range 42 - 88 [mean 66] years) complaining of xerostomia. At baseline, demographic data and details of symptomatology were recorded, and the mouth fully examined for clinical abnormalities. Imprint cultures were collected from the tongue and, in denture wearers, from the palate and denture fitting surface. These were cultured for yeasts, coliforms and staphylococci. A swab was collected for culture of herpes simplex virus. Sixty eight patients (97%) complained of oral dryness during the day, 21 (30%) indicating that it was a severe problem and 35 (50%) that it was a moderately severe problem. Fifty nine patients (84%) also complained of oral dryness at night. Soreness of the mouth was reported by 22 patients (31%). Forty six patients (66%) had difficulty talking and 36 (51%) reported difficulty eating. Of the 56 denture wearers, 23 (41%) complained of denture problems. On examination, 63 (90%) of the patients had clinical evidence of xerostomia. Oral mucosal abnormalities were detected in 45 patients (65%), most commonly erythema (20%), coated tongue (20%), atrophic glossitis (17%), angular cheilitis (11%) and pseudomembranous candidosis (9%). Forty seven (67%) of the patients carried yeasts in the mouth, 18 (26%) were carriers of *Staphylococcus aureus* and 13 (19%) carried coliforms. Herpes simplex virus was isolated from five patients, of whom two had herpetic stomatitis. These significant oral complications and abnormalities of the oral microflora confirmed previous reports on oral health in cancer patients.

The clinical trial examined effectiveness of the mucin-containing mouth spray, Saliva Orthana (Nycomed [UK]), against a mucin-free version of the same preparation in this group of 70 patients. Each preparation was used for 14 days

and the participants were interviewed, examined and specimens collected as described above, at days 7 and 14. The trial was complicated by reports from some of the earlier-enrolled patients of a burning sensation of the oral mucosa. On investigation, all of those affected were using active spray, and the trial was halted at Patient 35. Although chemical analysis revealed no abnormalities in the first spray batch, when the trial re-commenced three months later a new batch of active and placebo sprays was used for the remaining 35 patients.

For the first 35 patients, 8/16 on Saliva Orthana and 6/13 on placebo felt by Day 7 that the respective sprays had been beneficial in relation to dryness during the day. For dryness at night the corresponding figures were 6/16 for Saliva Orthana and 5/13 for placebo. None of these differences between preparations were statistically significantly different. Similarly, with the exception of 'oral soreness', there were no significant differences between the active and placebo sprays for any of the other symptoms recorded. This pattern of results was repeated at Day14. Significantly more patients on Saliva Orthana complained of soreness of the oral mucosa between days 1 and 7 ($p=0.04$).

For the second 35 patients, relief of oral dryness during the day was reported by 9/15 on Saliva Orthana and 10/16 patients on placebo by Day 7, with a similar degree of improvement maintained to Day 14. The corresponding figures by Day 7 for relief of dryness at night were 8/15 for Saliva Orthana and 8/16 for placebo. There were no statistically significant differences between those on active and those on placebo spray for any of the oral symptoms recorded. Neither spray had any major impact on the oral microflora. However, the majority of patients in both treatment groups wished to continue using a mouth spray at the end of their involvement in the trial.

Whilst the data from this study provide no evidence for increased benefit of a mucin-containing spray over a mucin-free placebo among xerostomic hospice patients, it was clear that both sprays provided worthwhile symptomatic relief of oral dryness for many of the participants. Further studies are required to determine the optimum saliva substitute for use by patients with advanced cancer.

CHAPTER 1

INTRODUCTION AND REVIEW OF THE LITERATURE

1.1 GENERAL INTRODUCTION

In recent years there has been an increased awareness of oral disease among patients with systemic illness. The responsibility for mouth care in such patients frequently falls to medical and nursing staff, many of whom have little formal training in oral health and oral hygiene measures. It is, therefore, important that professional dental staff interact with other health care workers to devise appropriate mouth care protocols for use by specific patient groups. As far as possible, these protocols should be evidence-based.

Oral dryness is known to be a common problem among terminally ill cancer patients, and its management should be an important element of the mouth care process. However, no clinical trials of saliva substitutes or other approaches to treatment of xerostomia in this patient group have been reported in the literature. This thesis describes a clinical trial of a mucin-containing mouth spray among cancer patients attending the bedded-unit and day-unit of a Scottish Hospice. It was carried out with the cooperation of the Medical Director and nursing staff of the hospice.

1.2 ORAL PROBLEMS IN PATIENTS WITH ADVANCED CANCER

From the few published studies to date, it is clear that patients suffering from advanced cancer at any primary site are liable to present with symptoms and signs of oral disease (Pople and Oliver, 1986; Clarke *et al*, 1987; de Conno *et al*, 1989; Jobbins *et al*, 1992b; Aldred *et al*, 1991). The extent of the need for oral and dental care among cancer patients is frequently underestimated and there has been a reported failure by many hospice administrators to appreciate the problem (Gordon, Berkey and Call,

1985). Patients may not complain spontaneously of what they believe to be inevitable discomfort in their mouths, or they may be physically or mentally unable to do so. It is important, therefore, that such patients are specifically questioned about mouth problems and that their mouths are regularly examined to reveal signs of treatable oral pathology. The terminally ill need, by definition, palliative and not necessarily curative care. Any therapeutic measures used should, therefore, relieve distressing symptoms and, if possible, delay progression of the disease process, but should not worsen the prognosis. The predominant oral problems experienced by those with advanced cancer will now be described.

1.2.1 Xerostomia

Oral dryness is one of the most upsetting and common symptoms affecting patients with terminal cancer (Clarke *et al*, 1987; Gordon, Berkey and Call, 1985; Jobbins *et al*, 1992b) and is covered in detail in Section 1.4. In one study, 77% of 197 terminally ill cancer patients complained of xerostomia (Jobbins *et al,* 1992). In addition to the distressing nature of this problem for the patients, the lack of saliva also predisposes to other types of oral pathology, for example candidosis (Section 1.2.2). There are many general causes of xerostomia as discussed in Section 1.4.2. Several of these are relevant to xerostomia in the terminally ill but drug therapies are probably the most important (de Conno *et al*, 1989). Many of the drugs used in palliative medicine, for example opioids, phenothiazines and anti-depressants (Sreebny and Schwarz, 1986) reduce salivary flow. Permanent damage to salivary glands occurs in patients given local radiotherapy for treatment of tumours of the oral cavity or the oropharynx (de Conno *et al*, 1989). The effects of xerostomia on patients' symptoms are varied. They

may complain of a burning mouth (de Conno *et al*, 1989). Soreness of the mouth may also result from mucosal infections secondary to xerostomia, for example candidosis (Pople and Oliver, 1986; Clarke *et al*, 1987; Finlay, 1986; Jobbins *et al*, 1992b). The absence of the protective effect of saliva on the oral mucosa is an important factor in facilitating spread of these infections and of permitting colonisation by exogenous bacteria (Jobbins *et al*, 1992c). The loss of lubrication makes chewing and swallowing difficult and painful, contributing to anorexia. Alteration in taste discrimination is another feature of xerostomia which can affect appetite and is discussed below. Dry mouth may also seriously affect speech, leading to further discomfort, difficulty in communication and subsequent frustration and embarrassment for patients, relatives and carers (de Conno et al, 1989).

Finally, in addition to protecting the oral mucosa, saliva plays an important role in preventing loss of tooth substance by both direct and antimicrobial activity and by buffering (Mandel, 1989). Therefore it is not surprising that dental caries and dental erosion may become problematic in terminally ill patients with xerostomia.

1.2.2 Oral Candidosis

1.2.2.1 Introduction

The mouth contains a diverse commensal microbial flora. About 40% of healthy adults harbour yeasts in their mouths as commensals, with no evidence of mucosal disease (Arendorf and Walker, 1979). *Candida albicans* is one of many candidal species found in the oral cavity and this organism is responsible for most oral candidal infections (Samaranayake and Lamey, 1988a). A minority of infections are caused by at least 12 other species including *C.glabrata*, *C.tropicalis*, *C.parapsilosis* and *C.krusei* (Samaranayake and Lamey, 1988a). During pregnancy, in tobacco-smokers and among denture-wearers the density of yeasts in saliva is increased (Arendorf and Walker, 1979). Candida species are also found as commensals in the throat, large bowel and the vagina. Candida species are notorious opportunistic pathogens. Both general factors, such as diabetes mellitus, and local predisposing factors, for example poor denture hygiene, are important in the pathogenesis of oral candidal infections (Samaranayake and Lamey, 1988a). Debilitated patients, such as those receiving antibiotic, steroid or cytotoxic therapy, are particularly susceptible to oral candidosis (Samaranayake and Lamey,1988a). Xerostomia, from whatever cause, is a further important predisposing factor (Sreebny and Valdini, 1987).

High levels of candidal carriage have been reported among the terminally ill (Pople and Oliver, 1986; Clarke *et al*, 1987; Finlay, 1986; Jobbins *et al*, 1992b; Jobbins *et al*, 1992c) with correspondingly high levels of mucosal disease.

1.2.2.2 Classification and clinical features

Oral candidosis can be classified into acute and chronic types. Acute oral candidosis can be further subdivided into acute pseudomembranous candidosis and acute atrophic (erythematous) candidosis. The chronic forms include chronic atrophic (erythematous) candidosis and chronic hyperplastic candidosis. Apart from these four types, there are a number of related conditions in which oral yeasts are implicated. These include angular cheilitis, in which there may also be a staphylococcal element, and median rhomboid glossitis which is now believed to be a low-grade chronic candidal infection.

(i) Acute pseudomembranous candidosis (Thrush)

The development of thrush is usually associated with some local disturbance or systemic illness, for example the extremes of age, broad-spectrum antibiotics, systemic or local steroids, cytotoxic therapy, HIV infection, diabetes mellitus or advanced malignancy.

It presents clinically as a thick white coating (pseudomembrane) on the affected mucosa which can be rubbed off to reveal a granular, erythematous base. Lesions may occur on any mucosal surface of the mouth and can vary from isolated patches to large confluent areas.

(ii) Acute atrophic (erythematous) candidosis

This occurs most commonly on the dorsum of the tongue following the use of broad-spectrum antibiotics, or in patients undergoing prolonged corticosteroid therapy. Antibiotic therapy alters the commensal oral flora thus allowing resistant organisms

such as *Candida* species to flourish. The condition is often referred to as `antibiotic sore tongue' and presents as a red, painful area of oral mucosa, usually on the tongue. More recently, erythematous candidosis has been described as a feature of HIV infection (Samaranayake and Lamey, 1988a).

(iii) Chronic atrophic (erythematous) candidosis (Denture stomatitis)

This is a common condition in denture wearers although it is rarely seen under a lower denture. The characteristic picture is of an area of erythema and oedema corresponding exactly to the fitting surface of the upper denture. Clinically three patterns of inflammation have been described, namely pin-point areas of erythema (localised inflammation), diffuse areas of erythema (generalised inflammation) and erythema associated with a granular mucosal surface (papillary hyperplasia).

Poor denture hygiene, continuous wearing of dentures and tobacco smoking are thought to be contributory factors, as is a high carbohydrate diet which favours candidal growth. The presence of xerostomia, iron or folate deficiency, or underlying endocrine disorders such as diabetes mellitus should also be considered.

(iv) Chronic hyperplastic candidosis (Candidal leukoplakia)

This presents as persistent white patches on the oral mucosa which are clinically indistinguishable from leukoplakia. These plaques are adherent unlike those of thrush which can be rubbed off. In some cases there are areas of erythema within the plaque producing a speckled leukoplakia. Typical sites are the buccal mucosa just within the commissures, or the dorsum of the tongue. The lesions are often bilateral. Long-standing angular cheilitis and denture stomatitis may be associated. In many patients

there is a long history of tobacco smoking and denture wearing. Diagnosis depends on biopsy. The lesion is premalignant with epithelial dysplasia seen in 50% of cases.

(v) Angular cheilitis

This is frequently associated with intra-oral candidosis, particularly with denture stomatitis. It may be a mixed infection with *Staphylococcus aureus* or less frequently beta-haemolytic streptococci (MacFarlane and Helnarska, 1976). Clinically, angular cheilitis may affect one or both angles of the mouth and presents as painful, cracked, erythematous fissures at the corners of the mouth. It can occur in dentate patients, edentulous or partially dentate patients and is the result of organisms from the oral cavity and anterior nares colonising the angles. Nutritional deficiencies, especially of iron, folate and vitamin B12, are recognised predisposing factors.

1.2.2.3 Diagnosis of oral candidosis

Routine methods available for diagnosis include swabs, imprint cultures or oral rinses for culture, direct smears and biopsy for chronic hyperplastic candidosis. In the research setting quantitation of yeasts may be important. Swabs and smears, although useful for assessing the presence or absence of *Candida* species, cannot provide a quantitative estimate of oral yeast carriage. Both oral rinse culture and imprint culture techniques permit quantification and can be used for differentiating commensal yeast carriage and clinical candidal infection. (Samaranayake and Lamey, 1988b).

1.2.2.4 Treatment of oral candidosis

Treatment of intra-oral candidal infections involves both non-specific and specific measures.

(i) Non-specific measures

It is important that denture wearers remove their prostheses overnight and soak them in a suitable cleansing solution, since the fitting surface of the denture is the main reservoir for *Candida* species (Arendorf and Walker, 1979). It is also important to check that patients with oral candidosis are haematologically normal, do not have diabetes mellitus and to check concurrent drug therapy, especially antibiotics and steroids.

(ii) Specific measures

Specific antifungal treatment may be provided either topically or systemically.

The main topical treatments are nystatin and amphotericin, neither of which is absorbed systemically. Nystatin is available in the form of tablets, oral suspension, pastilles, cream and ointment. Duration of therapy is based on clinical response and should be continued for at least two weeks after clinical resolution. Amphotericin B is also available in tablet form, as lozenges or as an ointment. Miconazole oral gel is particularly useful for the management of angular cheilitis, which often has a mixed aetiology (fungal and bacterial), as it has activity against Gram positive cocci as well as yeasts.

There are three main drugs available for systemic treatment of oral candidosis. Ketoconazole is available in a number of oral and topical forms. The oral form is well absorbed but should be used with caution owing to recognised side-effects, notably liver toxicity. Fluconazole, a newer triazole antifungal agent, is available in both oral and parenteral forms and has a broad spectrum of action. It is useful in mucosal and cutaneous forms of candidosis and is well tolerated, but some resistant strains of *Candida albicans* are emerging following long term treatment (Warnock, 1992). Itraconazole, another triazole antifungal drug, is available in oral capsule form and has a broad spectrum of action. It is useful for deep forms of oral candidosis and is well tolerated. A cyclodextrin solution of itraconazole is currently undergoing clinical trials (Blatchford, 1990) and has shown potential in the treatment of oropharyngeal candidosis among immunocompromised patients. It has a dual topical and systemic action and may prove of great value in hospice patients in due course.

Appropriate treatment is important for two reasons. First, it will improve the patient's comfort and second, oral candidosis may be a source of disseminated candidosis, a potential cause of death in patients with cancer (de Conno *et al*, 1989).

1.2.3 Oral Viral Infections

Herpes simplex virus (HSV) is the commonest cause of viral infection of the oral mucosa. Like all herpes viruses, following resolution of the primary infection HSV establishes latent infections, which may become reactivated at a later date. Whilst reactivation may occur in health, typically as herpes labialis, among immunocompromised hosts the reaction may be atypical, often intraoral, and severe. Such reactivations have been described in up to 65% of patients with leukaemia (Barrett, 1986; Barrett, 1987), although others describe a much lower incidence (Dreizen *et al*, 1982). Another group showed that HSV culture was positive in 85% of patients with chemotherapy-induced stomatitis (Rand *et al*, 1982). It is likely that the incidence of HSV infections among the immunocompromised is underestimated, because of the wide range of possible clinical presentations (Barrett, 1986; Barrett, 1987). Laboratory diagnosis by culture or rapid antigen detection (Bagg *et al*, 1989) is therefore essential for confirmation of the clinical diagnosis. Treatment is with acyclovir. No data are available on either asymptomatic shedding of HSV or on oral mucosal infection with this virus in patients with terminal cancer.

1.2.4 Cytotoxic Drugs and Stomatitis

1.2.4.1 Introduction

Cancer patients, like any others, are susceptible to the side-effects of drugs they are prescribed. For example, treatment with phenothiazines or antidepressants commonly results in xerostomia and associated oral disease. In addition, cancer patients are liable to suffer from specific adverse effects of the treatment for their malignant disease.

These effects are due to direct toxic damage to the tissues of the mouth. Cytotoxic drugs are, by definition, designed to destroy malignant cells, but when they are given in adequate doses, normal healthy cells will always be vulnerable and adverse effects are virtually inevitable. Some anti-cancer drugs are especially liable to result in stomatitis, and it is important to minimise damage by avoiding concomitant treatment with drugs of other classes which may result in xerostomia or have other adverse interactive effects.

Inhibition of stomatitis is important for a number of reasons, the most obvious of which is prevention of pain and thus improvement in the quality of life. In addition it may help to maintain compliance with treatment regimes, thus permitting higher chemotherapy dose intensity and improving the likelihood of treatment success (Nguyen, 1992). Severe ulceration of the oral cavity can limit nutritional intake, hinder proper oral hygiene, increase the risk of local and systemic infection and cause serious pain and bleeding, Appropriate management is, therefore, essential. (Childers *et al*, 1993)

1.2.4.2. Clinical features of chemotherapy-induced stomatitis

The stomatitis may, in fortunate patients, be mild. On the other hand it may be so severe as to be life-threatening, thus requiring cessation of chemotherapy. In order to grade the level of toxicity associated with certain drug regimes, the Southwest Oncology Group, in conjunction with the U.S. National Cancer Insititute and others have co-operated in the development of new toxicity criteria for reporting the results of

clinical cancer trials objectives (Green and Weiss, 1992) and resultant demands for greater rigour in definitions of response and endpoint.

The standard gradings for mucositis are as follows:

GRADE O ..... no symptoms

GRADE 1 ..... painless ulcers, erythema, mild soreness

GRADE 2 ..... painful erythema, oedema or ulcers but can eat.

GRADE 3 ..... painful erythema, oedema or ulcers and cannot eat

GRADE 4 ..... requires parenteral or enteral support

Gradings also exist for other mucosal surfaces, in particular the pharynx and vagina. Damage to the oral mucosa is associated with the use of both cytotoxic agents and ionising radiation, which impair cell division and disrupt normal replacement of superficial epithelium by basal layers. Mucosal damage is generally dose-related, with increased risk of mucosal toxicity accompanying high dose induction therapy, escalating dosage patterns, continuous infusion (versus bolus doses) and combination chemotherapy/radiotherapy treatments.

Oral mucositis starts with erythema and oedema then progresses to painful ulcerations. Ulceration is most prominent on non-keratinised tissue including the floor of the mouth, buccal mucosae and soft palate. Loss of epithelium as a protective barrier may result in local infections and provide a portal of entry for microorganisms into the systemic circulation. This may result in life-threatening septicaemia in patients who are immunosuppressed (Landsaat *et al*, 1995). The incidence of oral infections is also

influenced by antibiotic use during prolonged neutropenia which alters the flora of the mouth and creates a favourable environment for fungal super-infections. Bleeding of the gingivae may also occur, especially in the presence of thrombocytopenia.

Other serious complications of oral mucositis include pain, haemorrhage, airway obstruction and nutritional deficiencies. The pain that accompanies oral mucositis is considered a major problem for the cancer patient and often requires continuous intravenous infusion as well as bolus doses of analgesia (Zerbe *et al*, 1992).

1.2.4.3 Cytotoxic drugs implicated in stomatitis

By their nature, many anti-cancer drugs have significant effects on rapidly dividing cells such as oral epithelium. Often these drugs are used in combination, increasing the likehood of mucosal damage. Five of the most important drugs used in the treatment of cancer, which are known to cause stomatitis individually or in combination, will now be discussed.

(i) 5 Fluorouracil

5 Fluorouracil (5FU), administered as a single agent or in combination with other drugs, is widely used to treat several types of malignancy, especially within the gastro-intestinal tract. The drug inhibits DNA synthesis. Introduced as a treatment for cancer in the 1960s, it was soon evident that stomatitis was a common, if not inevitable, side-effect. In fact, oral mucositis is one of the major dose-limiting toxicities of 5FU. The first sign of stomatitis is a contra-indication for continuing treatment (ABPI Data Sheet

Compendium, 1995-96). This toxicity is particularly prominent when 5FU is administered with concomitant leucovirin (Rocke *et al*, 1993).

The action of 5FU on rapidly dividing tissue is responsible for its toxic effects on bone marrow and oral and intestinal mucosa. Thus, mucositis is an extremely common complication of 5FU-containing protocols and can greatly affect the quality of life of the patients treated for malignancy, interfering with dietary intake and leading to a discontinuation of treatment (Porta, Moroni and Nastasi, 1994). A potential synergy between 5FU and interferon-alpha (IFN alpha 2α) has been demonstrated in the treatment of colorectal cancer but clinical trials reported substantial toxicity, most commonly mucositis (John *et al*, 1993). A study on elderly gastric cancer patients using a combined regime of etoposide, leucovirin, 5FU and IFN alpha 2α again found that mucositis was the most common toxicity encountered (Cascinu, Fedeli and Catalano, 1994). Previously untreated patients with metastatic colorectal cancer were enrolled in a phase II study of combined 5FU and folinic acid (FA). Substantial to severe side-effects occurred in 39% of patients. Mucositis was one of the main dose-limiting toxicities with 73% of patients exhibiting some degree of toxicity and 15% of patients exhibiting Grade 3 or 4 (Rosso *et al*, 1994).

(ii) Methotrexate

Methotrexate is a folic acid analogue that inhibits folate metabolism by its effects on dihydrofolate reductase. The result is reduced formation of DNA and RNA. Major toxicities include bone-marrow suppression and gastro-intestinal mucositis (Adverse Drug Reaction Advisory Committee,1994).

(iii) Dactinomycin

Dactinomycin inhibits cell proliferation by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis. It is particularly potent on rapidly proliferating cells and in the oropharynx may cause cheilitis, dysphagia, oesophagitis, pharyngitis and ulcerative stomatitis (ABPI Data Sheet Compendium, 1995-1996). If stomatitis appears during therapy then the drug should be discontinued until the oral mucosa has recovered.

(iv) Cytosine arabinoside

This drug is an analogue of the naturally occurring nucleoside 2'deoxycytidine. It is phosphorylated within the cell to the triphosphate form, which then inhibits DNA polymerase. The main side-effects are on bone marrow and the gastro-intestinal tract, the latter including oral inflammation or ulceration (ABPI Data Sheet Compendium, 1995-1996)

(v) Vinblastine

This is one of the vinca alkaloids, which acts by binding to tubulin and thus inhibiting mitosis. It is generally relatively non-toxic, but side-effects include pharyngitis and ulceration of the mouth and skin (ABPI Data Sheet Compendium, 1995-1996).

1.2.5 Alteration in Taste Sensation

Changes in taste sensation may be of three types. There may be a reduction (hypogeusia), distortion (dysgeusia) or absence (ageusia) of normal taste sensation. Between 25% and 50% of cancer patients are reported to experience taste disturbances (Twycross and Lack 1986). As noted earlier, xerostomia may contribute to taste disturbances. However, zinc deficiency has been linked with abnormalities in taste sensation (Cohen, Schechter and Henkin, 1973) and it is of interest that zinc levels may be reduced in patients with malignant disease (Davies, Musa and Dormandy, 1986). Drugs administered to treat cancer patients may also alter taste sensation (Willoughby, 1983), for example, etoposide.

1.2.6 Dental Hard Tissue Pathology

The majority of the clinical problems related to the teeth in patients with advanced cancer are a consequence of xerostomia. These are dealt with in Section 1.4.3.

1.3 NORMAL SALIVARY PHYSIOLOGY

1.3.1 General Introduction

Saliva is a complex biological fluid, essential for healthy bodily function. In particular, it aids mastication and swallowing and protects the oral and pharyngeal mucosa. Its composition varies according to glandular source, with serous secretions from the parotid and mucous secretions from the submandibular and sublingual glands. To secretion from these three main pairs of glands is added that from numerous smaller mucous glands in the oral mucosa (labial, lingual, buccal and palatal). The composition also varies according to the stimulus for secretion. Furthermore, the properties of saliva alter after it has been expressed into the mouth, including the addition of fluid and cells from the gingival crevice. The greatest flow under resting conditions comes from the submandibular glands, which produce approximately three times that of the parotids. However this relationship is reversed when flow is stimulated.

Secretion is controlled by the autonomic nervous system. The parotid gland receives its secreto-motor supply via parasympathetic fibres from the auriculotemporal branch of the Glossopharyngeal nerve (IX). The submandibular and sublingual glands are supplied by the chorda tympani branch of the Facial nerve (VII) via the submandibular ganglion. Sympathetic supply arises between the first and fourth thoracic segments and relays in the superior sympathetic ganglion.

There is diurnal variation in both volume and composition, as well as wide individual variation. Estimation of total daily volume is difficult because of the problems of reproducing the physiological conditions during collection but an average daily secretion of about 600ml is accepted. A resting flow rate of 0.3 ml / minute is taken as normal and this can increase up to ten fold during stimulation, giving a flow rate of 2-3 ml / minute. A resting saliva of less than 0.1 ml / minute is considered abnormal as is a stimulated rate of less than 0.7 ml / minute. Secretion during sleep is negligible, presumably due to lack of stimulation.

1.3.2 The Constituents of Saliva

Saliva is a viscous, aqueous fluid with a varying organic and inorganic mix of constituents depending on origin. Electrophoresis has demonstrated that salivary secretions are highly complex fluids (Beeley *et al*, 1991). More than 40 proteins have been identified so far (Levine *et al*, 1987). A summary of the key constituents will follow.

1.3.2.1 The proteins of parotid and submandibular saliva

Table 1.1 summarises some of the major proteins in saliva. A selection of the more important groups of salivary proteins will now be discussed in detail.

Table 1.1 Proteins of parotid and submandibular saliva

Salivary protein families	
1. Proline-rich	Acid, basic, basic glycoprotein
2. Histidine-rich	Neutral, basic
3. Cysteine-containing	Cystatin S, cystatin SN
4. Tyrosine-rich	Statherin
5. Amylase	Glycosylated, non-glycosylated
6. Mucin	MG 1 ($>10^6$)*, MG2 ($>2x10^5$)*
7. Salivary peroxidase	(SAPX 1, 2 and 3)
Other acinar proteins	
1. Lactoferrin	
2. Secretory component	
3. Zinc-binding protein - gustin	
4. Parotid-aggregating glycoproteins	
High-molecular weight (440 000)	
Low-molecular weight (60 000)	
5. Epidermal growth factor	
6. Antileukoprotease	
Ductal, stromal or origin unknown	
1. Lysozyme	7. Nerve growth factor
2. Secretory IgA	8. Lipase
3. Kallikrein	9. Ribonuclease
4. Vitamin B12-binding protein	10. Carbohydrates
5. Vitamin D-binding protein	11. Esterases
6. Fibronectin	12. Amino peptidases
	13. Phosphatases
Serum proteins	
1. Albumin	2. IgG

From: Mandel I.D. (1989) The role of saliva in maintaining oral homeostasis.

***Journal of the American Dental Association*, 119, 298-304.**

* molecular weight

(i) Proline-rich proteins (PRP)

Between 60 and 70% of the total protein in saliva is PRP. Proline alone accounts for up to 42% of the amino acids in PRP's, while proline, glycine and glutamine together constitute 70-88% of the amino acids in PRP's (Bennick, 1982)

PRP's can be roughly sub-divided into three groups, glycosylated, basic and acidic accounting for approximately 17%, 23% and 30% respectively of the total protein in parotid saliva. The major parotid glycoprotein is a basic PRP (Bennick, 1982). Both acidic and basic PRP's are important in inhibiting the precipitation of calcium-phosphate salts in the salivary glands, in the oral cavity and onto tooth surfaces. Acidic PRP's bind to calcium and maintain it in the supersaturated state, thus avoiding precipitation in the ducts or in the mouth. PRP's bind to hydroxyapatite and thereby form part of the dental pellicle (Bennick, 1982). The basic PRP's when combined with albumin can be extremely effective as a lubricant (Hatton *et al*, 1985).

(ii) Histidine-rich proteins

These proteins may be neutral or basic (MacKay *et al*, 1984a). Histidine-rich proteins form an important part of the non-immune host defence system. They have an antimicrobial effect by inhibiting both the growth and viability of several strains of *Streptococcus mutans* (MacKay *et al*, 1984b). They also have an antifungal effect, causing complete growth inhibition of *Candida albicans* by means of membrane damage.

(iii) Cysteine-rich proteins

These proteins, also known as cystatins, are important contributors to enamel pellicle (Shomers *et al*, 1982)

(iv) Tyrosine-rich proteins (Statherin)

These proteins have a unique activity compared with all the other serum and salivary proteins in that at concentrations at which they occur naturally they will inhibit spontaneous (primary) precipitation of calcium-phosphate salts from a supersaturated solution (Hay, 1973). This is important within the glands themselves as precipitation of calcium phosphate in a microcrystalline form could potentially damage the gland acini and duct system. Statherin also inhibits secondary precipitation (crystal growth).

(v) Amylase

Amylase is the most abundant and best characterised enzyme found in saliva. It has two main family branches, glycosylated and non-glycosylated and 6-8 isoenzymes. Alpha-amylase is a calcium-requiring metalloenzyme which is responsible for the enzymatic hydrolysis of glycosidic linkages in starch, glycogen and glucose polymers (Kauffman *et al*, 1970).

(vi) Mucins

Mucins are the principal organic constituents of mucus, the visco-elastic material that coats mucosal surfaces. In saliva, mucins are contributed by the submandibular, sublingual and numerous minor salivary glands. The minor salivary glands contribute

up to 70% of the total mucin found in saliva (Milne and Dawes, 1973) although they only contribute about 10% to the total volume of saliva produced.

Mucins are high molecular weight glycoproteins which usually contain greater than 50% carbohydrate. The carbohydrate is in the form of oligosaccharide chains linked to threonine or serine. The chains are formed from various combinations of five monosaccharides, namely galactose (GAL), fucose (FUC), N-acetyl-galactosamine(GAL NAc), N-acetyl-glucosamine (GLcNAc) and sialic acids (SA). Sulphate linked to GAL or GLcNAc may also be present. (Spiro, 1973).

Current evidence suggests that two mucins exist within submandibular and sublingual saliva, a high molecular weight MG1 ($>10^6$) and a lower molecular weight MG2 ($2x10^5$) (Prakobphol *et al*, 1982). MG1 consists of multiple disulphide linked subunits. The protein core contains less then 15% of the total weight. In the protein core approximately 43% of the total amino acid residues are threonine, serine, proline and alanine. Glycine constitutes 8.6% of the total amino acids. There are also covalently linked fatty acids. The major oligosaccharides of MG1 range in size from 4-16 sugar residues and are responsible for 78% of the total weight of the molecule, with sulphate adding another 7%. The glycopeptide linkage of MG1 involves 0-glycosidic bonds between GAL-NAc and threonine and serine.

MG2 is a molecule of approximately 200-250kDA. It is a single peptide chain accounting for roughly 30% of the total weight. About 75% of the total amino acids are threonine, serine, proline and alanine while glycine contributes only 1.4%. The

carbohydrate content of MG2 is approximately 68% and consists of carbohydrate units 2-7 residues in length. With an estimated molecular weight of 250,000kDA, about 170 oligosaccharide chains are spread over the single polypeptide chain of MG2. There is evidence which suggests that MG2 displays little organised secondary structure, existing primarily as a random coil (Cohen and Levine, 1989).

Recent studies have localised each of the salivary mucins to mucous acini within human submandibular gland tissues. The studies also demonstrate that there are two different distinct cell subpopulations of MG1- and MG2-secreting acini within the glands. This suggests that the two mucins are authentic cell products (Cohen *et al*, 1987). The salivary mucins provide protection in two ways. First, by covering the mucosal surfaces, mucin functions both as a lubricant and a selective permeability barrier which guards against drying out of the mucosa and protects against harmful environmental factors. (Tabak *et al*, 1982). Second, mucin can modulate the oral microflora by favouring attachment and subsequent proliferation of certain microorganisms and/or by promoting the clearance of others (Gibbons and Querishi, 1976).

(vii) Salivary peroxidase

The salivary peroxidase system consists of the peroxidase enzyme, the thiocyanate ion (SCN-) and hydrogen peroxide (H_2O_2). This system catalyses the oxidation of salivary thiocyanate by hydrogen peroxide produced by oral bacteria such as *Streptococcus sanguis* to generate highly reactive oxidising agents, most prominently hypothiocyanite and hypothiocyanous acid. These oxidise sulfhydryl groups in bacterial enzyme

systems involved in glucose transport and glycolysis, thus seriously affecting acid production and growth (Morrison and Allen, 1963; Morrison *et al*, 1965). The antimicrobial activity of salivary peroxidase against *Streptococcus mutans* is enhanced by interaction with secretory IgA.

(viii) Lactoferrin

This protein has been shown to possess bacteriostatic properties for various aerobic and facultative organisms. These are attributed to the ability of the unsaturated protein to bind two atoms of iron per molecule, thus withholding iron from invading bacteria, a form of nutritional immunity. Nutritional immunity is an important protective mechanism against bacteria that require ferric iron for metabolism as it can effectively compete with the bacterial iron-binding molecules (Mandel, 1989).

(ix) Lysozyme (Muramidase)

This enzyme can cause lysis of oral bacterial cells, especially *Streptococcus mutans* and *Veillonella* species. It splits the 1-4 links between N-acetylmuramic acid and N-acetylglucosamine present in the walls of the bacteria, thus causing death and disintegration. If these polysaccharides are absent from a species of bacteria then it is not destroyed by lysozyme. The effectiveness of lysozyme in saliva is reduced by the presence of mucin which inhibits its action (Simmons, 1952). Lysozyme also exerts an antibacterial effect by inhibiting growth and dechaining as well as by reducing glucose incorporation and lactic acid production (Mandel, 1989).

(x) Secretory IgA

This is the predominant immunoglobulin in saliva and is produced by plasma cells within the salivary glands. They produce mainly dimeric IgA, not the conventional monomeric IgA of serum. Only dimeric IgA complexes with secretory component (SC) an epithelial glycoprotein.

Secretory IgA has two functional advantages. First, it is preferentially transferred from the gland to the mucosal surface by virtue of SC, which may have special receptors on duct epithelial cells. Secondly, secretory IgA is more resistant to proteolytic degradation by bacterial and digestive hydrolases than are other immunoglobulins, so it is particularly suited to its function on mucous membranes which are either colonised by a variety of microorganisms or covered by potent digestive juices (Lehner, 1992).

(xi) Kallikrein

This enzyme has the ability to liberate vasoactive peptides (kinins) from their inactive precursors (kininogens). Kallikrein has also been reported to activate contraction of myoepithelial cells of salivary glands, which expel saliva (Makinen, 1989).

1.3.2.2 Other nitrogenous constituents of saliva

(i) Amino acids

Eighteen amino acids have been detected in whole saliva (Jenkins, 1978).

(ii) Peptides

These may act as cofactors in the metabolism of salivary bacteria (Molan and Hartles, 1971; Kleinberg *et al*, 1978).

(iii) Urea, creatinine, uric acid and ammonia

The concentration of urea in saliva is virtually identical to plasma levels. Virtually all the ammonia is formed by bacteria from urea and amino acid (Kopstein and Wrong, 1977).

1.3.2.3 Glucose

Lindqvist (1952) showed sugars in free form to be present only in traces in fasting saliva (0.5-1.0 mg / 100ml)

1.3.2.4 Other organic constituents

(i) Lactate

Saliva contains variable quantities of lactate since it is one of the main products of bacterial degradation of carbohydrates by salivary bacteria (Jenkins, 1978).

(ii) Agglutinogens ABO

These blood group antigens are polysaccharides found in the saliva of approximately 80% of the population. Those individuals whose saliva contains ABO blood group antigens are referred to as "secretors" (Jenkins, 1978).

(iii) Lipids

Chromatography has detected the presence of many lipids including cholesterol, cholesterol esters, fatty acids, glycerides and phospholipids in variable concentrations (Dirksen, 1963).

1.3.2.5 Inorganic constituents of saliva

Saliva contains a wide range of electrolytes (Söderling, 1989), and there have been many audits of their normal concentrations in saliva. These studies show wide variations between subjects, but also within the same subject, and factors such as salivary flow rate are known to significantly affect concentrations of salivary electrolytes (Dawes, 1969). Circadian rhythms may also have substantial effects on electrolyte content of saliva, although their influence is less than that due to variations in flow rate (Dawes and Chebib, 1972). Effects of diet (Dawes, 1970) and exercise (Dawes, 1981) on electrolyte concentrations have also been studied, but appear to have little effect.

(i) Electrolyte composition and oral disease

Although salivary concentrations of electrolytes such as calcium may be anticipated to affect the natural history of dental caries, no consistent variations in salivary electrolyte concentrations have been observed in subjects who are caries-free or caries-susceptible (Mandel, 1974a). Similarly, there is no consistent correlation of salivary electrolyte pattern with periodontal disease (Mandel, 1974b).

Significant increases in salivary sodium and chloride concentrations have been described in patients with acute sialadenitis (Mandel and Baurmash, 1980), while potassium and phosphate concentrations were low under the same conditions. Another scenario in which damage to salivary glands causes alteration in salivary electrolytes is that following radiation exposure. These changes are relevant to cancer patients and to the terminally ill. One group has described reduced unstimulated salivary flow rates and an increase in sodium concentration (Ben-Aryeh *et al*, 1975). A second group studied stimulated whole saliva and described markedly increased concentrations of sodium, chloride, calcium and magnesium, with a concomitant decrease in bicarbonate concentration following radiotherapy (Dreizen *et al*, 1976). However, the overwhelming feature of radiation-induced damage is reduction in flow rate and the true clinical significance of the changes in electrolyte levels is unclear.

Finally, patients with Sjögrens syndrome demonstrate markedly increased concentrations of sodium and chloride and a reduced concentration of phosphate in stimulated parotid saliva (Mandel and Baurmash, 1976), features consistent with the ongoing glandular damage.

(ii) Electrolyte composition and pharmacological agents

Terminally ill patients are on multiple forms of medication. Any drugs which affect sympathetic or parasympathetic activity will affect salivary secretion (Section 1.3.1). However, any effects on electrolytes are usually non-specific and result from the effects of the drugs on salivary flow rate (Mandel, 1980).

(iii) Individual ion species

There is a wide range of ion species in saliva and a comprehensive review of the field is outwith the scope of this thesis. The normal concentrations of ionic species in whole saliva are summarised in Table 1.2. A small number of the more important electrolytes will be discussed in the following sections.

Table 1.2 Concentrations (mmol/l) of some of the principal electrolytes in whole saliva

Electrolyte	Unstimulated		Stimulated	
	Mean ± s.d.	Range	Mean ± s.d.	Range
Sodium	7.7 ± 3.0	2 - 26	32 ± 20	13 - 80
Potassium	21 ± 4	13 - 40	22 ± 12	13 - 38
Calcium	1.35 ± 0.45	0.5 - 2.8	1.7 ± 1.0	0.2 - 4.7
Magnesium	0.31 ± 0.22	0.15 - 0.6	0.18 ± 0.15	
Chloride				10 -56
Hydrogen carbonate	24 ± 8		25 ± 18	
Phosphate	2.9 ± 2.4		2.0 ± 0.8	1.5 - 2.5
Iodide	5.5 ± 4.2	2 - 22	10 ± 7	
Fluoride (umol / l)			68 ± 11	

From: Ferguson D.B. (1989) Salivary electrolytes. In: *Human Saliva: Clinical Chemistry and Microbiology, Volume 1.* Ed: J.O. Tenovuo, CRC Press, Boca Ratan, Florida, pp 75-99.

Sodium and chloride

Physiologically, the transportation of these two ions into saliva is closely linked. Two active transport processes are involved for transportation of these ions across the basolateral walls of the acinar cells, thus creating an osmotic gradient and ensuring flow of water. The final concentrations of Na^+ and Cl^- in saliva depend on the extent of their reabsorption in the striated ducts, hence the sensitivity to flow rate (Ferguson, 1989). Thus, sodium and chloride concentrations give useful information on the efficiency of ductal transport systems.

Potassium

Potassium concentrations are five to ten times as high as in plasma. However, the mechanisms by which K^+ reaches saliva are not fully understood. Active transport processes are believed to be involved in both acini and ducts, and potassium concentrations are relatively flow-rate dependent (Schneyer, Young and Schneyer, 1972).

Calcium

Calcium reaches saliva in the acinus by active transport and by movement in association with protein during exocytosis (Wallach and Schramm, 1971). Calcium concentrations in acinar saliva increase with flow rate but plateau at higher rates of flow. However, in whole saliva concentrations fall as flow rate increases, because of the smaller proportion of the secretion contributed by the submandibular gland, whose saliva contains more calcium.

Hydrogen carbonate (bicarbonate)

Bicarbonate is produced in cells of salivary glands by metabolic production of carbon dioxide and its hydration in the presence of the enzyme carbonic anhydrase. It is actively secreted into saliva largely in the ducts, and its concentration increases with the rate of flow. Its concentration gives an indication of buffering capacity and gland activity (Ferguson, 1989).

Phosphate

Salivary phosphate concentrations are higher than in blood. Phosphate is actively transported into saliva, and the concentration decreases as flow rate increases. Although there is no clear relationship between salivary phosphate levels and dental calculus formations, more recent evidence suggests that high salivary phosphate levels may be associated with a lower caries rate (Shaw *et al*, 1983).

Fluoride

Levels of fluoride in gland saliva follow plasma fluoride levels (Ericsson, 1969). Fluoride is believed to reach saliva by passive diffusion in the acini (Shannon, 1977) and there is no variation in concentration with rate of flow. Peak concentrations of fluoride in gland saliva occur 30-60 minutes after ingestion of a fluoride dose (Ferguson, 1989).

1.3.3 Overview of the Functions of Saliva

The complexity of saliva has been increasingly recognised in the last decade or so. The various organic and inorganic constituents have overlapping functions which are perhaps not fully worked out. Some of these have been mentioned already in the previous sections.

Saliva, in the short term at least, is not essential to life, but its prolonged absence leads inevitably to damage to the oral and pharyngeal mucosa and to the teeth. Eventually this damage will result in malnutrition, infection and chronic discomfort.

The principal functions of saliva are as follows

- Lubrication
- Antimicrobial activity
- Remineralisation
- Buffering
- Cleansing
- Digestion

Mucosal integrity is ensured by the efficient working and overlapping of these qualities of saliva in maintaining homeostasis (Mandel, 1989). The more important activities of saliva will now be covered in detail.

1.3.3.1 Lubrication

The viscous nature of saliva and its low-friction quality is due mainly to the mucin glycoproteins and also to the basic proline-rich glycoproteins of parotid saliva when complexed with albumin. Lactoferrin, amylase and SIgA also possess lubricating abilities.

The moistening of food is important for bolus formation and facilitates mastication and swallowing. Coating the mucous membranes also provides smooth tissue surfaces with minimal friction thus making tongue movements easier and aiding speech (Hatton *et al,* 1988). Salivary mucins possess rheologic properties which enable them to concentrate on oral mucosal surfaces, where they provide an effective barrier against desiccation and exogenous factors (Tabak *et al*, 1982), for example irritants and toxins in food and tobacco smoke. The protective potential of all the anti-bacterial proteins can be extended by interaction with each other and with high molecular weight mucin MG1.

1.3.3.2 Antimicrobial effects

Many of the salivary families contribute to the antimicrobial effect of saliva. Specific antimicrobial effects are mediated by enzymes such as lysozyme, lactoferrin and lactoperoxidase and by mucins, histatins, cystatins and specific antimicrobial immunoglobins.

Secretory IgA antibodies act in a "first line" of mucosal defence, principally by simple binding to soluble or particulate antigens (Hansol and Brandtzaeg, 1988). This

function of immune exclusion is probably enhanced by cooperation of SIgA with non-specific defence factors. In addition to effective binding and complexing of antigens, SIgA causes aggregation of bacteria and may inhibit colonisation of microorganisms on epithelial cells

Lysozymes, histidine-rich peptides, lactoferrin and salivary peroxidase working in conjunction with other components of saliva can have an immediate effect on oral bacteria, interfering with their ability to produce acid and multiply, or killing them directly (Mandel,1989).

As well as antibacterial activity, saliva has also been shown to possess antifungal (Pollock *et al*, 1984) and antiviral (Heineman and Greenberg, 1980) properties. Parotid fluid has an antifungal capacity reflecting properties of both the neutral and basic histidine-rich peptides (Pollock *et al*, 1984). It has been shown that the basic peptides could cause a 99% loss of viability of *Candida albicans* at levels of 25 g/ml, levels commensurate with salivary concentrations (Pollock *et al*, 1984). Secretory IgA can directly neutralise viruses, and mucins are also effective antiviral molecules.

1.3.3.3 Maintenance of pH

Saliva helps maintain a relatively neutral pH in the mouth, in bacterial plaque and during swallowing in the oesophagus as well (Helm *et al*, 1982). In plaque, saliva regulates pH by means of bicarbonate, phosphate and histidine-rich peptides. Urea from saliva is converted by bacterial urease to ammonia which neutralises acid.

1.3.3.4 Digestion

The digestive function of saliva seems secondary, as only cooked starch is shown to be affected by amylase, the main digestive protein (Jenkins, 1978). However, digestion presumably continues in the food bolus for some time after leaving the mouth.

1.3.3.5 Other protective activities

Saliva protects teeth in several ways. The flow of saliva aids in the clearance of sugars and carbohydrate remnants. Small decreases in the resting salivary flow rate can greatly prolong sugar clearance time (Dawes, 1983) and are an important factor in the destructive caries often seen in xerostomia. By constantly replenishing the pellicle/film surrounding the teeth, saliva provides a protective barrier (of phosphoproteins, albumin and MG1 and neutral lipids, glycolipids and phospholids) against acid penetration and a limitation against mineral egress (Zahradnik, Propas and Moreno, 1977; Slomiany *et al*, 1986).

Oral homeostasis exists without unwanted precipitation of calcium phosphate salts within glands, mouth or onto tooth surfaces and this is regulated mainly by statherin (tyrosine-rich peptide) which inhibits spontaneous precipitation from supersaturated solutions until remineralisation is appropriate. Anionic PRP's, neutral histidine-rich peptides and cystatin S also contribute to this regulation.

1.3.3.6 Summary of salivary functions

Much about the interlinking functions of saliva remains obscure and awaits further research but to summarise, the functions of saliva include lubrication, facilitation of

speech, mastication, deglutition and digestion and protection from microorganisms for both hard and soft tissues. Its buffering power, dependent largely on the bicarbonate content, maintains an optimal pH while the calcium and phosphorus ion concentrations influence the development of caries and plaque. Deficiency in, or lack of, saliva adversely affects all these functions.

1.4 XEROSTOMIA

1.4.1 General Introduction

Xerostomia (dry mouth) is the subjective feeling of oral dryness (Sreebny and Valdini, 1987; Fox *et al*, 1985; Crocket, 1993; Fox, Busch and Baum, 1987). Use of the term xerostomia does not necessarily indicate that the mouth is objectively dry. Thus xerostomia, which can have many causes, may be a complaint even when salivary flow is normal. In spite of the importance of xerostomia, patients rarely complain, either because they accept it as inevitable or because other symptoms overshadow it. More usually, though, the symptom is related to a physical lack of moisture affecting the oral mucous membranes. There are many causes of xerostomia and these will be detailed in the next section.

1.4.2 Causes of Xerostomia

The principal causes of xerostomia are shown in Table 1.3. Dry mouth is usually associated with a decrease in salivary secretion. Most frequently it is induced by drugs that inhibit the flow of saliva, for which the term "xerogenic medication" has been used.

Table 1.3 The principal causes of xerostomia

Normal salivary flow
Anxiety states
Reduced salivary flow
Drug-induced
Anticholinergic
Antihistamine
Anti-hypertensive
Dehydration
Diabetes mellitus
Diarrhoea, vomiting, haemorrhage
Reduced fluid intake
Salivary gland disease
Radiotherapy
Sjögren's syndrome
Calculi
Mumps
Sarcoidosis
Parotid agenesis

1.4.2.1 Drugs and medications

Many classes of drugs are implicated in xerostomia. Sreebny and Schwartz (1986) listed 315 medications that had been documented as inducing varying degrees of xerostomia.

Drug-induced xerostomia is always reversible, although it is often not possible to find a suitable alternative drug for treatment of the primary disease. The anti-cholinergic drugs are, by definition, bound to cause a degree of xerostomia. Generally speaking these drugs are used in the short-term but may be used longer-term in certain chronic illnesses such as Parkinson's disease. Xerostomia is also a side-effect of drugs in other categories, for example some antidepressants, antihistamines, antihypertensives, sedatives and hypnotics. Diuretics, by their nature, are liable to cause xerostomia if not accompanied by sufficient fluid intake.

1.4.2.2 Therapeutic irradiation

Irradiation of the head and neck damages both the salivary acini and the vascular supply to some extent, depending on the dose. (Sreebny *et al*, 1992). The earliest effects are probably caused by vascular damage and interference with nerve transmission. Xerostomia can occur within a short period and may be irreversible, particularly if bilateral exposure of the glands is unavoidable. Since the serous cells are more sensitive to radiation than are the mucus-secreting cells, the residual secretion after irradiation tends to be reduced in amount and is more viscous (Sreebny *et al*, 1992).

1.4.2.3 Systemic disease

Xerostomia is frequently a feature of systemic disease (Sreebny *et al*, 1992) but is seldom the presenting symptom. Any process which disturbs the body's electrolyte balance may cause xerostomia at some stage, for example diabetes mellitus, AIDS and other multisystem diseases. Connective tissue diseases such as rheumatoid disease, systemic lupus erythematosus (SLE), primary biliary cirrhosis and systemic sclerosis may all be associated with Sjögrens syndrome. In view of the importance of Sjögrens syndrome in the differential diagnosis of dry mouth, it will now be dealt with in some detail.

1.4.2.4 Sjögrens syndrome

(i) Introduction

Sjögrens syndrome, first described in the medical literature as early as 1888, takes its name from the Swedish ophthalmologist Henrik Sjögrens who was the first to recognise the systemic nature of the disease in 1933 (Greenspan and Daniels, 1990). It consists of a triad of clinical features notably xerophthalmia (dry eyes), xerostomia and a connective tissue disease - most commonly rheumatoid arthritis (50-75%) though SLE, polyarteritis nodosa, progressive systemic sclerosis, polymyositis and dermatomyositis may all be associated (Bloch *et al*,1965)

Only two of the three major components of the disease need to be present for a diagnosis to be made and the condition is further classified into primary and secondary Sjögrens syndrome. Primary Sjögrens syndrome has no connective tissue component, only dry eyes and dry mouth, while in secondary Sjögrens syndrome a connective

tissue disease is present. This classification was introduced by Frost-Larson, Isager and Manthorpe (1978) and is now widely accepted.

Most patients with Sjögrens syndrome are women (80-90%) and it usually presents in patients over the age of 50 years. Sjögrens syndrome is a relatively common condition affecting an estimated 25% of patients with rheumatoid arthritis (Greenspan and Daniels, 1990). Although many patients do not develop further problems, in others the course of the disease is progressive and can lead to multi-organ involvement and very occasionally malignant transformation, for example parotid lymphoma (Scully and Cawson, 1987).

Sjögrens syndrome is a systemic autoimmune disease. It is characterised by an intense infiltration of the lacrimal, salivary and other exocrine glands by lymphocytes and plasma cells, with progressive acinar destruction. The parotid glands are mainly affected but the changes are also evident in the minor labial glands.

The cause of Sjögrens syndrome is unknown, but recent evidence suggests an interplay between viruses and the immune system. Epstein Barr virus has been proposed as a trigger for Sjögrens syndrome in individuals with an appropriate immunogenetic background but the results of studies of this association have been conflicting. (Flescher and Talal, 1991). More recently there have been reports of retroviruses in salivary glands of patients with Sjögrens syndrome. (Garry *et al*, 1990). Retroviral infection could cause significant changes in the behaviour of epithelial cells of exocrine glands, which may contribute to development of a localised immune response. In

addition, the retroviral agents may possess epitopes that are similar to epitopes of self antigens, thus converting an immune defence process into an autoimmune response. The most recently proposed candidate virus in Sjögrens syndrome is hepatitis C virus (HCV). An elevated prevalence of anti-HCV antibodies has been reported in Sjögrens syndrome (Garson *et al*, 1991), and an association has been reported between HCV infection and sialadenitis similar to that seen in Sjögrens syndrome (Haddad *et al*, 1992).

(ii) Diagnosis and clinical features

Since Sjögrens syndrome is a multisystem disorder, diagnosis is often delayed because full development of the syndrome over a length of time may result in undue concentration on one aspect of the disease. Specialists from many fields may be involved in management but referral to the most appropriate physician, usually a rheumatologist, may be delayed as may treatment of the ocular damage which is most urgent.

As many patients suffer from rheumatoid arthritis, the clinical picture may include any of the other manifestations of rheumatoid disease but those peculiar to the syndrome include keratoconjunctivitis sicca, decreased salivation with obvious dryness of the oral mucosa and fissuring of the tongue. Swelling of the parotid glands, present in approximately 30% of patients, is usually bilateral and may be painful.

The dryness of the mucosa predisposes to candidal and other infections. There may be a disturbance of taste and an increased susceptibility to caries and periodontal disease.

Patients may complain of swallowing difficulty and also of problems with denture retention.

The symptoms may be slow in onset with periods of remission. Diagnosis cannot be made by simple clinical examination of the mouth because, as stated earlier, xerostomia is a subjective condition and the picture of xerostomia in Sjögrens syndrome is often identical to that in xerostomia from other causes. Confirmatory diagnosis depends largely on objective evidence from histopathological and immunopathological investigation. The main abnormalities are hypergammaglobulinaemia, mainly as a result of the presence of rheumatoid factor, antinuclear factors and frequently of other autoantibodies. Rheumatoid factor is present in the serum of most patients with primary or secondary Sjögrens syndrome, often in high titre. Antinuclear antibody (ANA) is present in the serum of a majority of patients with Sjögrens syndrome. Antibodies against nuclear antigens SS-A (Ro) and SS-B (La) are found in some Sjögrens patients but their presence is not specific to Sjögrens syndrome.

More specific diagnostic information can be gained from a labial gland biopsy. This shows a primary lymphocytic infiltrate in otherwise normal-appearing glands and includes focal aggregates of 50 or more lymphocytes adjacent to normal acini, plus the consistent presence of these foci in all or most of the glands in the specimen. A labial gland biopsy is the best diagnostic criterion in terms of disease specificity, convenience, availability and low risk. (Greenspan and Daniels, 1990).

(iii) Management

Sjögrens syndrome is not curable but should be treated both to reduce symptoms and to prevent further damage to teeth and eyes. The first aspect is to take a clear history and remove, if possible, any extraneous causes of oral dryness, particularly drugs whose side-effects include this symptom. Patients who are dentate should receive both preventive and dietary advice as well as treatment of any caries present.

Relieving the symptoms of mucosal dryness is very difficult and, as yet, no single satisfactory method has emerged. At present two approaches are used, either stimulation of additional salivary secretion or use of salivary substitutes. Gustatory and masticatory stimulation achieved by sucking hard/soft sweets (which should be sugar-free) or chewing sugar-free gum, can increase saliva flow but only in the short-term. The increased salivation only lasts as long as the stimulus is present. Use of the parasympathomimetic drug pilocarpine can help patients with severe xerostomia by increasing saliva production both in the long and short term (Greenspan and Daniels, 1990). Many patients find that frequent sips of water or water sprayed from a pump dispenser are the most effective and best tolerated ways of dealing with their problem. However, several saliva substitutes are now commercially available, some fluoridated, both in spray and lozenge form. These and the other treatment options already mentioned will be discussed more fully in Sections 1.4.4.3 and 1.4.4.4.

1.4.2.5 Pyschogenic disorders

Some patients complain of xerostomia when there is no objective evidence of dryness or any salivary gland dysfunction whatever. There is often an associated complaint of

taste alteration. Usually no definable psychiatric illness is evident but the condition sometimes responds to antidepressants, provided these drugs do not themselves cause dryness of the mucosa.

1.4.2.6 Ageing

Ageing itself is not now thought to be a primary factor in xerostomia, (Tylenda *et al*, 1988) but the condition may be commoner in older people because of their increased liability to disease and exposure to medication.

1.4.3 Effects of Xerostomia on Oral Tissues

Saliva has a vital role to play in protecting the tissues of the mouth. In its absence both the hard and soft tissues may be severely damaged. The caries rate increases and erosion of the dental hard tissues may occur. The oral mucosa becomes prone to infection, for example candidosis, and the mastication and digestion of food may be impaired (Sreebny and Valdini, 1988). Patients may complain of severe dryness of the mouth, throat and lips. Eating is difficult, they have to sip water continually as they chew and it is hard to swallow. Denture retention is difficult and patients may complain of burning mouth, abnormal taste sensation and difficulty with speech. There may be lobulation and fissuring of the tongue (Sreebny *et al*, 1992).

1.4.4 Diagnosis of Xerostomia

Diagnosis of salivary gland hypofunction is based on the findings obtained from the patient's general history, from symptoms associated with his disease, from data derived

from clinical examination of the patient and from laboratory tests (Sreebny *et al*, 1992). These will now be described in detail.

1.4.4.1 Clinical signs of xerostomia and salivary gland hypofunction

Dry, sticky oral mucosa is a common finding in salivary gland hypofunction. The mucosa may appear atrophic and feel sticky to touch. In fact a mouth mirror or tongue depressor may adhere to the mucosa if the xerostomia is severe. An increase in dental caries is almost inevitable with new cavities developing rapidly, often in sites not usually affected by caries, for example incisal tips or lower anterior teeth. In long-standing cases, the tongue becomes fissured, lobulated and atrophic and in particularly severe cases there may be swelling of the salivary glands. Intra-oral infections are common, especially erythematous and pseudomembranous candidosis.

1.4.4.2 Methods for measuring salivary flow rates

Although many believe that the diagnosis of xerostomia should be based on a subjective complaint of oral dryness, as described earlier, accurate measurement of flow can be useful as a confirmatory aid to diagnosis. The measurement of salivary flow rates is also an important element of research projects, particularly in the fields of oral physiology and therapeutics. Regardless of the collection method used, salivary flow rates are known to be influenced by a range of exogenous factors including time of day (Jenkins, 1978), recent food intake (Jenkins, 1978) or exercise (Dawes, 1981) and, in the case of stimulated flow rates, the choice of stimulus. It is important that, in the planning of experiments, these variables are controlled as far as possible. The methods available for collecting saliva are as follows:

(i) Whole salivary flow rate

Whole saliva can be collected directly into a receptacle such as a conical plastic collection tube (Heft and Baum, 1984). Collection is made over a standard period of time. The flow may be either unstimulated or stimulated with a chemical stimulus such as citric acid (Heft and Baum, 1984) or a physical stimulus, for example paraffin wax (Parvinen and Larmas, 1981). The value of whole unstimulated salivary flow rates in the diagnosis of Sjögrens syndrome has recently been reported by Speight and co-workers (Speight, Kaul and Melsom, 1992), who showed that a whole unstimulated salivary flow of 0.1ml/minute or less was highly specific for xerostomia.

(ii) Flow rates from individual glands

Parotid flow rates - Segregated parotid saliva is the easiest of the individual glandular secretions to collect. Saliva is collected through the parotid papilla using a Carlson Crittendon cup (Carlson and Crittenden, 1910). An inner chamber is placed over the parotid papilla and the device is held in place through a vacuum created in an outer ring. Saliva is transported from the central chamber to a collecting receptacle via a narrow bore plastic tube. As with whole saliva, the secretion may be collected under resting conditions or following chemical stimulation.

Submandibular flow rates - Collection of saliva from the submandibular gland is difficult because of the complex anatomy of the floor of the mouth. The first device to be described for collection of submandibular and sublingual salivas was that of Schneyer (Schneyer, 1955). This was a custom-made acrylic device which was

retained over the lower anterior teeth and was extended over the floor of the mouth to cover the submandibular papilla and the sublingual glands. In an attempt to overcome the need for custom-made devices, a "universal" submandibular saliva collector was described (Truelove, Bixler and Merritt, 1967), but in practice this was unreliable. Subsequent workers have described other customised devices including an acrylic collector retained by clasps on the lower premolars or first molars (Stephen, Lamb and McCrossan, 1978) and a collector based on an overextended lower silicone impression (McCarthy and Bagg, 1987). Regardless of the device chosen for the collection of submandibular saliva, the mobility of the floor of the mouth can easily result in loss of peripheral seal around the collecting chamber with subsequent contamination of the collected secretion. Use of an indicator dye, for example plaque-disclosing solution, placed in the mouth after insertion of the collector, alerts the clinician to contamination of the fluid leaving the tube (McCarthy and Bagg, 1987). Another approach has been the use of a micropipette to collect saliva directly from the ducts of the submandibular and sublingual salivary glands (Fox *et al*, 1985)

Minor salivary gland secretions - The minor salivary glands produce less than 10% of the volume of whole saliva (Dawes and Wood, 1973). These secretions may also be of particular relevance to denture retention (Niedermeier and Kramer, 1992). Measurement of the overall flow rate from the minor glands is difficult, but one method is based on measuring the volume of fluid absorbed by a "Periopaper" placed on the base of a well-sealed maxillary denture for one minute (Niedermeier and Kramer, 1992).

(iii) The Saxon Test

This method is described as an oral equivalent of the Schirmer Test for ocular dryness (Kohler and Winter, 1985). The patient vigorously chews a pre-weighed dry gauze (5 x 5 cm) for 2 minutes. The gauze is re-weighed and the amount of saliva derived by subtraction.

(iv) Salivette™

The Salivette™ (Sarstedt, Leicester, UK) is a device designed for the collection of saliva for use in analytical tests, including the measurement of drug levels (Haeckel, 1989) and antiviral antibodies (Parry, 1993) in saliva. However, if the fibre roll is placed in the mouth for a standard period of time, and the volume of saliva absorbed by the roll then measured, this can be used as a measure of salivary flow rate (Lamey and Nolan, 1994)

(v) Other methods

In view of the difficulties in standardising methods for measuring salivary flow rates, a number of other techniques have been described, although their applicability to the clinical situation is dubious. Examples include light microscopy of dried saliva for the pattern of crystallised mucus (Andonopoulos, Tzanakaks and Christophidou, 1992) and measurement of oral mucosal sliding friction (Nederfors *et al*, 1993)

1.4.4.3 Pharmaceutical agents used in the treatment of xerostomia

A simple approach to the management of patients with salivary gland dysfunction is to attempt to increase the flow of saliva by use of sialogogues. These may be mechanical

and/or gustatory, for example sugar-free chewing gum with sustained flavour release, or pharmacologic. In the past, a variety of systemic pharmaceutical agents have been employed to promote salivation but pilocarpine has been used the most extensively. This section will summarise details of the pharmaceutical agents so far studied for the promotion of salivation.

(i) Pilocarpine

Pilocarpine is an alkaloid, first isolated from South American plants of the genus Pilocarpus in the 19th century. It functions primarily as a muscarinic-cholinergic agonist and has potent effects on both smooth muscle and exocrine tissue, for example salivary and sweat glands (Fox *et al*, 1986). Historically, pilocarpine was first used to treat xerostomia by Blackman at the end of the nineteenth century, using a 3-6mg dose systemically (Ferguson, 1993). It has since been used to combat xerostomia appearing as a side-effect of drug treatment, for example antihypertensives and tricyclic antidepressants. Thus, Prutting (1965) used an oral dose of 2.5-5mg qid to alleviate xerostomia in a group of patients receiving either imipramine or amitryptilline for depression. The main side-effect noted was sweating, which can be minimised by decreasing the dose of pilocarpine. Ferguson *et al* (1991), treated 100 patients with xerostomia and administered pilocarpine for up to 2 years in doses ranging from 1-15mg qid. He used the drug in solution and started with a low dose, gradually increasing it to minimise side-effects such as sweating, nausea and diarrhoea.. There was a marked individual variation in therapeutic dosage, but no apparent change in response over the period of observation (Ferguson *et al*, 1991).

In persons with normal salivary function, low dosages of pilocarpine result in transient but marked increases in salivary flow (Mandel and Katz, 1971). Pilocarpine is not the treatment of choice for all patients with xerostomia as some residual gland function must be present. Fox *et al* (1986) used the criterion that it might be effective therapy for patients with diminished salivary function who responded to citrate stimulation. For people with documented salivary gland disease who have some functional salivary gland tissue, orally administered systemic pilocarpine is effective in relieving xerostomia and increasing salivary output (Fox et al, 1986). Stimulation of gland function may also help to prevent ascending infections of salivary glands and retard the formation of mucous plugs.

Whilst none of the studies to date document serious side-effects on cardiovascular or respiratory systems, Ferguson recommends caution in the use of pilocarpine in patients with disorders of these systems (Ferguson, 1993). For appropriately selected patients, pilocarpine is an effective, easily administered and safe therapy for oral dryness that accompanies salivary gland hypofunction.

(ii) Bromhexine

Initial studies using bromhexine treatment to alleviate eye and mouth dryness were encouraging, but a later study found no difference between the effects of bromhexine and placebo on salivary function (Tapper-Jones *et al*, 1980).

(iii) Sialor (Anetholetrithione)

The use of Sialor in the treatment of dry mouth associated with psychotropic medication was first reported by Debuch *et al* (1973). Sialor acts by increasing the number and concentration of salivary gland receptor sites for neurostimuli (Ukai *et al*, 1984). Epstein, Decoteau and Wilkinson (1983) reported that an increased output of whole saliva was observed in 75% of patients studied. A later study (Epstein and Schubert, 1987) suggested a synergistic effect between pilocarpine and Sialor. Some authors report that Sialor is not as effective in those patients whose xerostomia is induced by radiation as in those whose xerostomia is secondary to Sjögrens syndrome. (Epstein, Decoteau and Wilkinson, 1983).

(iv) Pyridostygmine bromide

Pyridostygmine bromide is a cholinesterase inhibitor which also possesses both muscarinic and nicotinic activity (Navazesh and Ship, 1983). In a trial carried out by Ferguson *et al* (1991) the starting dose was 3mg, gradually increasing in steps until a salivary response was obtained or side-effects became prominent. The authors pointed out that there was a considerable variation between patients. Teichman *et al* (1985) administered 180-540 mg pyridostygmine per day and found that it was possible to counteract the anticholinergic effects of disopyramide (a cardiac anti-arrhythmic drug). Subsequently it was found that 180mg of pyridostygmine bromide every 12 hours significantly reduced the xerostomia caused by disopyramide, though the measured increase in salivary flow did not reach significance (Teichman *et al*, 1987). There was, however, a definite increase in tear production.

(v) Bethanechol chloride

Bethanecol chloride is an analogue of acetyl choline that possesses both muscarinic and some nicotinic cholinergic activity. It has been reported to counter successfully xerostomia resulting from administration of tricyclic antidepressants and phenothiazines. In a report of 20 patients taking imipramine and amitryptilline and experiencing xerostomia, all reported Bethanechol to be effective at a dose of 25mg tds (Everett, 1975).

(vi) Interferon alpha

Levels of circulating interferon alpha, as well as the content of interferon alpha in the salivary gland tissue itself, are decreased in Sjögrens syndrome. Shiozawa *et al* (1993), therefore, studied the therapeutic effect of interferon alpha on the xerostomia of Sjögrens syndrome by injecting 1×10^6 international units intramuscularly once per week. Six out of 10 patients showed a statistically significant increase in saliva production.

1.4.4.4 Saliva stimulants and substitutes

(i) Saliva stimulants

A range of agents has been suggested for stimulation of salivary flow. Citric acid was one of the earliest preparations to be recommended (Watanube and Dawes, 1988). It has been used in the form of sweets and chewing gum but, in view of the potential adverse effects on the dental hard tissues its use has been supplanted by newer agents. Many of the recent trials of these newer agents have been undertaken in Scandinavia.

In a recent study, five saliva stimulants - Salivin, V6 chewing gum, Mucidan, Nicotinamide and Ascoxall T - plus three saliva substitutes - Saliment, Salisynt and an ex tempore solution - were compared in a 10 centre clinical trial (Bjornstrom, Axell and Birkhed, 1990). The trial involved 106 patients complaining of dry mouth and who had reduced whole salivary flow rates. Each patient used the eight products for periods of 14 days in a randomised order, with intervening washout periods of one week. All the products relieved the symptoms to some extent, but, in general, saliva stimulants were preferred to the saliva substitutes. V6 chewing gum (carbamide-containing gum flavoured with sorbitol) and Salivin lozenges (malic acid and sorbitol) were ranked as the best two products by the patients. There were no long term effects on measured salivary flow rates. (Bjornstrom, Axell and Birkhed, 1990).

In a recent two week cross-over trial of salivary stimulation by chewing gum and lozenges, 18 patients with dry mouth and reduced salivary flow rates were recruited (Risheim and Arneberg, 1993). The two preparations examined were Dentirol gum (sweetened with xylitol) and Profylin lozenges (carboxymethylcellulose with xylitol and sorbitol). One third of the patients reported relief with both agents, though reduction in symptoms was not always accompanied by increased salivary flow rates. In addition, neither preparation influenced buffering capacity, counts of cariogenic bacteria or candida and oral sugar clearance time. (Risheim and Arneberg, 1993).

Olsson and co-workers (Olsson, Spak and Axell, 1991) studied the effectiveness of a new xylitol and sorbitol chewing gum (PTC) which provided prolonged release (at least 30 minutes or more) of flavouring agent. The new gum was compared with V6

gum in a blinded, randomised cross-over trial. PTC gave consistently higher mean values of saliva secretion and lower oral mucosal friction values. PTC gum was also significantly better with regard to saliva stimulating ability and taste, as reported by the patients in the trial (Olsson, Spak and Axell, 1991).

V6 chewing gum has also been compared with a mucin-containing chewing gum in a placebo-controlled, double-blind, cross-over trial (Aagard *et al*, 1992). Forty three patients complaining of a subjective dry mouth used each preparation for two weeks in a randomised order. Outcome was measured by interview and also by determining changes in stimulated and unstimulated salivary flow rates. Subjectively, 64% of the patients reported a positive effect with the mucin gum, 44% a positive effect with the V6 and 26% with placebo. In terms of patient preference, 61% favoured the mucin gum, 21% the V6 and only 5% the placebo. Half of the participants had an increased unstimulated salivary flow rate after use of each of the stimulants for 14 days (Aagard *et al*, 1992). This long-term mechanical stimulating effect of mastication has been reported previously (Jenkins and Edgar, 1989).

The effectiveness of salivary stimulants in patients with Sjögrens syndrome has also been investigated. In a recent double-blind cross-over trial among 42 patients, a mucin- containing lozenge was used against placebo for a period of 14 days (s'Gravenmade and Vissink, 1993). Assessment of effectiveness was based on self-administered questionnaires completed before and after use of each lozenge. Seventy six per cent preferred the mucin-containing lozenges, 10% the placebo and 14% had no preference. Mucin lozenges were better at reducing the total pattern of complaints and

the sensation of oral dryness. The lozenge preparation acts as a time-release vehicle for mucin which can effectively maintain a high concentration of mucin in the mouth over a longer period. In addition, the lozenges are easier and more convenient to use than fluids in public places.

(ii) Saliva substitutes

As indicated earlier, a clear-cut distinction cannot always be drawn between salivary stimulants and salivary substitutes. For example, mucin-containing lozenges (see above) function in both capacities. This section will deal solely with artificial saliva preparations. Saliva substitutes were reviewed by Levine *et al* (1987). There are currently no saliva substitutes which are entirely ideal. Their effects are of limited duration and they may have unpleasant tastes or textures.

Most preparations available at present are based on carboxymethylcellulose (CMC) or mucin (Levine *et al*, 1987). CMC imparts lubrication and viscosity and the preparations usually contain sorbitol or xylitol to act as a sweetener and provide surface activity. However they tend to be very viscous. As a result animal mucins have been employed to produce substitutes with a viscosity and surface tension similar to that of human saliva. A number of clinical trials (see below) have compared the effectiveness of these two types of saliva substitutes and, in general, the mucin-containing preparations are preferred by patients.

One of the earliest reports of an open trial of mucin-containing artificial saliva involved 18 patients suffering from radiotherapy-induced xerostomia (s'Gravenmade, Roukema

and Panders, 1974). The patients who had previously used a CMC preparation without success used a bovine salivary gland extract prepared by the authors. Whilst the evaluation of the preparation was not rigorous, most of the patients responded favourably and preferred the mucin to the CMC substitute (s'Gravenmade, Roukema and Panders, 1974).

Since then there have been several properly designed clinical trials examining mucin-based saliva substitutes. In one such study, a double-blind cross-over trial compared a mucin-based artificial saliva (Saliva Orthana) with its non-mucin base and water (Duxbury, Thakker and Wastell, 1989). Thirty two patients with xerostomia participated, of whom thirty completed the trial. Overall, 60% of the patients obtained a degree of relief of xerostomia using Saliva Orthana, compared with 49% using the non-mucin base and 40% with flavoured water. However, there were no significant differences in the length of time patients experienced relief, all preparations providing relief for about one hour. Overall, Saliva Orthana offered significantly greater relief than its non-mucin base (Duxbury, Thakker and Wastell, 1989).

Some studies have directly compared the efficacy of CMC and mucin-based saliva substitutes. In one small study (6 patients) the lubrication properties of mucin-containing and CMC-containing saliva substitutes were evaluated in a double-blind trial (Olssen and Axell, 1991). The outcome was based on both subjective feeling of the patient and objective measurement using a friction probe (Henricsson *et al*, 1990). In summary, the oral mucosal lubricating effects of CMC and mucin-containing substitutes were very similar and better than water. In a larger double-blind crossover

trial conducted among 42 patients with xerostomia (Visch *et al*, 1986), the effectiveness of a CMC and a mucin-containing substitute were compared. The value of each preparation was based on a questionnaire and an objective measure of salivary flow was made by sweeping the mouth with a pre-weighed gauze and then re-weighing. There were few major differences between the two preparations but in general patients preferred the mucin-based preparation. Thirty-eight per cent of the patients did not wish to continue with application of a saliva substitute at the end of the study. The data also suggested that the effectiveness of the saliva substitute was dependent on the aetiology of the xerostomia (Visch *et al*, 1986).

When one considers the complexity of natural saliva it is perhaps not surprising that none of the currently available saliva substitutes are ideal. However, great advances are being made in our understanding of salivary biochemistry (Beeley, 1993). The genes that code for some of the bioactive proteins in saliva are now being cloned and there is no reason why they should not be produced in due course (Gibson and Beeley, 1994).

In the next few years it is likely that completely new preparations will be available which have increased bioactivity. The use of lactoperoxidase-containing toothpaste in those with radiation-induced xerostomia, as reported recently (van Steenberghe *et al*, 1994), is a good example of this new generation of saliva substitutes.

CHAPTER 2

PATIENTS, MATERIALS AND METHODS

2.1 PATIENTS

The study was conducted among 70 patients associated with the ACCORD Hospice, Paisley, Scotland. The hospice occupies a rebuilt, custom-designed ward in Paisley's once celebrated 1930's Infectious Diseases Hospital. The Royal Alexandra Hospital Trust has responsibility for approximately 30% of the funding, the remainder being raised by voluntary effort.

The hospice caters almost exclusively for terminal cancer patients, providing symptom and drug control as well as respite and terminal care. Admission from home or hospital is on medical recommendation. The Hospice is staffed by a Medical Director, a Nursing Director, a Nursing Sister and a team of staff nurses. Four Home-care Sisters are based at the Hospice and a Physiotherapist, a Community Dentist and several visiting General Medical Practitioners attend on a regular basis.

Both in-patients resident in the Bedded Unit and day care patients attending the Day Unit were studied. The patients were attending the hospice for a variety of reasons, including symptom control, respite care or terminal care. Many of the visits to the patients during the trial were, therefore, domiciliary visits since there was a constant flux of patients from their homes to the hospice.

2.1.1. Enrolment

Medical and nursing staff sought details of dry mouth from all patients receiving care at the hospice. Those patients complaining of a dry mouth were referred to the author to be considered for enrolment into the study.

2.1.1.1 Enrolment criteria

All patients were over the age of 18 years and complaining of a dry mouth. They were all suffering from advanced malignant disease, with the exception of one patient with motor neurone disease. Those enrolled had to be conscious, cooperative and able to give consent at the time of admission.

2.1.1.2 Exclusion criterion

Patients who were unwilling or too unwell (including life expectancy of less than seven days) to participate were excluded. There were no other specific exclusion criteria.

2.2 TRIAL SPRAYS

Sprays were supplied free of charge by Nycomed (UK) Ltd., Sheldon, Birmingham. The trial was divided into two sections, each involving 35 patients. This was necessary because a small number of the earlier patients complained of a burning sensation when using the spray. When the code was examined by the supplying company, it became clear that all of the patients with a burning sensation were using active spray. Although chemical analysis revealed no abnormalities in the trial batch of active sprays, it was considered inappropriate to continue using them. A separate batch of both active and placebo sprays was employed for the second group of 35 patients.

2.2.1. Active Spray

The active spray was Saliva Orthana, a mucin-based artificial saliva substitute which is commercially available. The constituents of the spray are listed in Table 2.1.

Table 2.1 The constituents of the active, mucin-containing spray

CONSTITUENT	PER 100 ML
Gastric mucin NNR53	**3.5 g**
Xylitol FCC81	**2.0 g**
Menthae piperitae aetheroleum Ph Eur	**5.0 mg**
Spearmint oil USNF	**5.0 mg**
Methylis parahydroxybenzoas Ph Eur	**100.0 mg**
Benzalkonium chloride USNF	**2.0 mg**
EDTA-disodium BP	**50.0 mg**
Aqua purificata Ph Eur	**ad 100 ml**

2.2.2 Placebo spray

The placebo spray contained all the constituents of the active spray, with the exception of the gastric mucin.

2.2.3 Packaging of sprays

Both the active and the placebo preparations were dispensed in pump spray bottles identical with the packaging of the commercial product, except for the absence of labelling.

Six bottles of spray (A-F) were provided per patient. Each set was numbered and supplied in a labelled box.

2.3 CLINICAL TRIAL

2.3.1 Ethical approval

Ethical approval for the study was obtained from the Ethics Panel of the Royal Alexandra Hospital NHS Trust, Paisley.

2.3.2 Trial design

The trial was performed as a double blind, placebo-controlled, parallel study, with greater efficacy of the active spray as the parameter to be evaluated. Patients were seen at enrolment, after 7 days and after 14 days of entry to the trial.

2.3.3 Randomisation and coding of sprays

Randomisation and coding details for the active and placebo sprays were prepared and held by Nycomed (UK) Ltd. Details of the randomisation code were also held in a sealed envelope by the Principal Pharmacist at the Royal Alexandra Hospital, in case the code needed to be broken urgently in response to an adverse reaction.

The numbered mouth sprays were delivered in batches by courier to the ACCORD Hospice.

2.3.4 Case Record Forms

The design of the Case Record Form (CRF) is shown in Appendix I. Demographic details, details of symptoms (based on visual analogue scales) and the results of clinical examination were all collected onto the CRF.

2.3.5 Trial visits

2.3.5.1 Enrolment (Visit 1, Day 1)

Patients complaining of a dry mouth were referred by the hospice staff to the author. The purpose of the study and the nature of patient involvement was explained and those who wished to participate gave written consent. A copy of the consent form is shown in Appendix II.

The following categories of information were gathered during the enrolment visit:

(i) General clerking information

Demographic details, diagnosis of the underlying disease and details of previous and current treatments were obtained from the individual patients and from the medical records.

(ii) Symptoms

Baseline assessment of the following symptoms was collected on visual analogue scales graded from 0 (no problem) to 3 (severe problem):

- Dry mouth during the day
- Dry mouth at night
- Sore mouth
- Bad or altered taste
- Difficulty talking
- Difficulty eating
- Denture problems

(iii) Clinical examination

A subjective assessment of the degree of oral dryness was made by the author and recorded on a visual analogue scale from 0 (absent) to 3 (severe).

For dentate patients, the teeth were charted and visible caries was recorded. Oral hygiene was assessed by a modification of the Debris Index (Greene and Vermillion, 1960). Thus, plaque deposits were subjectively scored on the buccal surfaces of all remaining natural teeth, where 0 = no visible plaque, 1 = minimal plaque, 2 = moderate plaque and 3 = severe plaque.

The types of dentures owned and worn were recorded, together with details of denture fit and cleanliness. The latter were categorised as 'good', 'acceptable', 'poor' or 'very poor'.

The oral mucosa was carefully examined for pathological changes, particularly erythema, plaques, atrophic glossitis, thrush, denture stomatitis and angular cheilitis.

(iv) Specimen collection

Salivette™

The Salivette™ has been described in Section 1.4.4.2. The insert from a sterile Salivette™ (Sarstedt Ltd, Leicester, England) was placed beneath the tongue for 30 seconds, replaced in the inner tube, and sealed. The specimen was then transported immediately to the laboratory for processing.

Viral swab

The floor of the mouth was sampled with a dry swab (Sterilin Ltd, Feltham, Middlesex, England) which was then broken off into 2 ml of virus transport medium (Gibco BRL, Life Technologies, Paisley, Scotland). Any vesicular lesions present on the oral mucosa were also sampled. The specimens were transported to the laboratory within three hours of collection.

Imprint cultures

The method was adapted from that described by Arendorf and Walker (1979) and as used in a previous study of geriatric patients (Sweeney *et al*, 1995).

The sites sampled were the dorsum of the tongue and, among denture wearers, the hard palate and the fitting surface of the upper denture. Foam pads (1cm x 1cm), packed and sterilised in groups of three, were removed individually with sterile, disposable forceps and applied for 5 seconds to the sample site. The pad was then used to inoculate sequentially individual plates of Sabouraud's agar (Life Technologies, Paisley, Scotland), mannitol salt agar (Life Technologies, Paisley, Scotland), MacConkey agar (Life Technologies, Paisley, Scotland) and Pagano Levin agar (Samaranayake, MacFarlane and Williamson, 1987). The plates were transported to the laboratory within three hours for incubation and processing.

(v) Provision of spray

At the enrolment visit, each participant was provided with a box of 6 sprays. The sprays were allocated on a strictly numerical basis. The patients were shown how to

operate the spray bottles and told to use the spray whenever their mouths felt dry and at least twice per day. In-patients were informed that the nursing staff would operate the sprays for them, in case of difficulty.

Patients and nursing staff were instructed not to discard used spray bottles, since they were to be collected for weighing, as a measure of compliance.

Nursing staff were provided with an information sheet on use of the spray (Appendix III) to act as an *aide memoire*.

2.3.5.2 Follow-up : Visit 2, Day 7

Participants were re-visited after they had been using the spray for 7 days. Many of these visits were on a domiciliary basis. A note was taken of whether the patients had been using the spray themselves or whether they had required assistance from a nurse.

Changes in oral symptoms were then recorded, using a modification of the visual analogue scales employed at the baseline visit. These are illustrated on the Case Record Forms in Appendix I.

The clinical examination and collection of specimens followed the same pattern as for the baseline visit described above (Section 2.3.5.1)

Finally, the patients were asked to estimate for how long the spray had provided relief, and whether or not they would wish to continue using the spray. If participants withdrew from the study at this stage, the reason for their withdrawal, for example a sudden deterioration in health, was recorded.

2.3.5.3 Follow-up : Visit 3, Day 14

The format of Visit 3 was identical with that for Visit 2. However, the box of trial sprays was retrieved for subsequent weighing. If the patient had found the mouth spray

beneficial, then he/she was provided with a supply of Saliva Orthana (commercial product) to use thereafter.

2.4 LABORATORY PROCESSING OF SPECIMENS

2.4.1 Salivette™

Each Salivette™ was centrifuged (4000 rpm, 10 min) in a bench top centrifuge (Centaur 1, Fisons, Crawley, Sussex). The volume of saliva which collected in the outer tube was measured by means of a Hamilton syringe and the volume recorded.

2.4.2 Culture from Viral Swab

The viral transport medium containing the swab was vortex mixed for five seconds. For the first fifteen patients, specimens were inoculated directly into tissue culture tubes containing fungizone but this method resulted in many tubes becoming contaminated with yeasts. Subsequently the viral transport medium was filtered through a Sartorius Minisart 0.2 μm disposable syringe filter (Sartorius AG, D-3400 Göttingen, Germany) prior to inoculation of the cell line.

2.4.2.1 Cell line

Culture for herpes simplex virus type 1 was performed in a human embryonic lung fibroblast cell line (HEL 299; ECACC No. 87042207). Details of the growth and maintenance media are given in Appendix V.

To subculture a confluent monolayer of cells the growth medium was decanted and the monolayer washed carefully twice with sterile Hanks Balanced Salt Solution. Trypsin EDTA mixture (1-2 ml) was added for 10 seconds, then decanted and the flask incubated at 37^0C until the cell sheet became detached (4-10 minutes). The detached cells were resuspended in 5-10 ml growth medium and centrifuged (500 rpm; 10 min) in a bench top centrifuge (Centaur 2, Fisons, Crawley, Sussex). The supernate was discarded and the cells resuspended in 10 ml growth medium. The suspension was then inoculated into flasks or tubes at the following dilutions:

- 25 cm^2 flask : 2.5 ml cells + 7.5 ml growth medium
- 50 cm^2 flask : 5.0 ml cells + 15 ml growth medium
- Tissue culture tube : 0.25 ml cells + 0.7 ml growth medium

The cultures were incubated at 37^0C in 5% CO_2 in a LEEC CO_2 Incubator. When the monolayers reached confluence, the growth medium was replaced with maintenance medium.

2.4.2.2 Inoculation of monolayers with specimen

Two tubes containing intact monolayers of HEL299 cells were inoculated with 0.1 ml and 0.2 ml of specimen respectively. The tubes were sub-cultured after 18 hours, and examined under an inverted microscope (Leitz Labovert) every other day for a maximum of 14 days for evidence of cytopathic effect (CPE). Any tubes suggestive of a positive CPE were examined by direct immunofluorescence (see Section 2.4.2.3). Cells in all of the tubes were examined by immunofluorescence before they were discarded, even in the absence of a CPE.

2.4.2.3 Immunofluorescence for confirmation of herpes simplex virus type 1 in tissue culture

On appearance of a CPE, or after 14 days, whichever was the sooner, the cell monolayer was detached from the tube by aspiration. The cell suspension was decanted into a centrifuge tube and spun at 1000 rpm for 15 minutes (Centaur 2 Centrifuge, Fisons, Crawley, Sussex). The supernatant was removed carefully and the cell pellet suspended in 0.2 ml PBS.

From this suspension, three spot smears were prepared on Hendley slides, dried in air and fixed immediately in cold acetone. A positive HSV Type 1 control was set up simultaneously. To spot smears 1 and 2 were added a small volume of HSV1 and HSV2 Direct Specimen Reagent (Syva Microtrak), and to spot smear 3 a small volume of PBS. The smears were incubated in a moist chamber at 37^0C for 20 minutes, then the excess reagents were washed off in three changes of PBS. The smears were

mounted and examined (x 20) under a fluorescence microscope. Positive smears showed strong green or yellow fluorescence.

2.4.3 Imprint Cultures

The culture plates were inoculated aerobically for 48 hours. The plates were then examined for the presence of yeasts (Sabouraud's and Pagano-Levin agar), staphylococci (mannitol salt agar) and coliforms (MacConkey agar).

2.4.3.1 Quantitation

In all cases, the number of colonies over the area inoculated with the foam pad was counted. If growth were too heavy to permit accurate counting, the amount of growth was recorded as semi-confluent or confluent.

2.4.3.2 Identification of isolates

(i) Yeasts

A germ tube test was undertaken on all yeasts isolated. A small portion of a yeast colony was emulsified into 0.5 ml horse serum and incubated for 4 h at 37^0C. Evidence of germ tube formation was obtained by microscopy (x 40) of a wet film. Germ tube positive yeasts were identified as *Candida albicans*.

Germ tube negative yeasts were identified by sugar assimilation tests. Basal agar was melted and cooled to 45^0C. One colony of the yeast for identification was added to 5 ml of distilled water and 5 drops of this suspension added to the molten agar. The seeded agar was poured into a petri dish and allowed to set. Paper discs saturated with individual carbohydrates were placed around the periphery of the plate. The carbohydrates used were glucose, sucrose, lactose, trehalose, cellobiose, and raffinose. The plates were incubated at 30^0C for 24-48 hours and they were then examined for growth around the discs to provide an assimilation pattern. The yeasts were identified by comparing this pattern with a key table.

Any yeasts which could not be identified on the basis of a germ tube test and sugar assimilation tests were inoculated into an API32C strip (Bio Merieux SA, Marcy l'Etoile, France) for identification.

(ii) *Staphylococcus aureus*

Staphylococcus aureus produces yellow colonies on mannitol salt agar. Representative yellow colonies were subcultured onto blood agar purity plates. Isolates which were catalase positive, Gram positive cocci were tested for coagulase production (Slidex Staph-Kit, Biomerieux, SA, Marcy l'Etoile, France). Coagulase positive isolates were identified as *Staphylococcus aureus*.

(iii) Coliforms

Aerobic Gram negative rods isolated from MacConkey's agar were tested for the presence of oxidase (Dry Slide Oxidase, Difco Laboratories, Detroit, Michigan). Oxidase positive organisms were identified by their API 20NE profile (Biomerieux SA, Marcy l'Etoile, France) and oxidase negative organisms by their API 20E profile (Biomerieux SA, Marcy l'Etoile, France).

2.4.4 Spray Weights

Each returned bottle of spray was weighed and the total weight determined for the six sprays returned by each patient.

2.5 DATA PROCESSING

Data contained in the Case Record Form for each patient were transferred to a coding form. The design of the coding form and the details of the coding sheet are shown in Appendix IV.

2.6 STATISTICAL ANALYSIS

The data were analysed using the Minitab Statistical Programme, Release 10 for Windows.

Comparisons between the two treatment groups (Saliva Orthana and placebo) were carried out by means of two-sample t-tests and confidence intervals for the continuous variables. The latter were the pre-treatment values, the changes from start to Day 7 and from start to Day 14 for each of the seven subjective assessments by visual analogue scales, the Salivette™ volume and the degree of oral dryness based on clinical appearance.

The maximum concentrations (on a scale of 'low', 'medium' or 'high') of all yeast species present at each of the three sites (tongue, palate and, if appropriate, denture) were recorded at the start of treatment and at 7 and 14 days respectively into the study. Comparisons between the two treatment groups were then carried out by means of chi-square tests on the start concentrations as well as the changes from start to Day 7 and start to Day 14 respectively. Coliforms and *Staphylococcus aureus* were not isolated with sufficient frequency to permit meaningful statistical analysis

CHAPTER 3

RESULTS

As discussed in the Materials and Methods section, because of the reports by several patients of possible adverse reactions to the active preparation, the trial was stopped at Patient 35 and re-started with a new batch of 35 sprays. This in effect means that two trials were undertaken. As a reflection of this problem, the results will be presented in three sections. The first will give a detailed baseline description of the 70 patients enrolled. The second section will describe the results for Trial 1 (Patients 1 - 35) and the final section will describe the results for Trial 2 (Patients 36 - 70).

3.1 DESCRIPTION OF THE STUDY POPULATION

3.1.1 Age and Sex Distribution

Seventy patients (25 male and 45 female) were enrolled in the study. Their ages ranged from 42 - 88 years (mean age 66 years).

3.1.2 Primary Diagnosis

With the exception of one patient, who had motor neurone disease, all of those studied were suffering from advanced malignant disease. The types and sites of the primary tumours are shown in Tables 3.1 and 3.2 respectively. The vast majority of the tumours were carcinomas, with lung and breast the commonest sites. Only two patients enrolled had oral carcinoma.

Table 3.1 Summary of primary tumour types

TUMOUR TYPE	NUMBER OF PATIENTS
CARCINOMA	57
ADENOCARCINOMA	5
MELANOMA	1
MESOTHELIOMA	1
ANGIOMEIOLYOMA	1
[MOTOR NEURONE DISEASE]	1
OLIGODENDROGLIOMA	1
OSTEOGENIC SARCOMA	1
MERKEL CELL TUMOUR	1
UNKNOWN PRIMARY	1
TOTAL	**70**

Table 3.2 Summary of primary tumour sites

TUMOUR SITE	NUMBER OF PATIENTS
LUNG	23
BREAST	10
KIDNEY	6
COLON	5
BLADDER	4
PROSTATE	4
OVARY	3
PANCREAS	2
RECTUM	2
MOUTH	2
MEDIASTINUM	1
BRAIN	1
FEMUR	1
CERVIX	1
SKIN	1
STOMACH	1
UNKNOWN	3
TOTAL	**70**

3.1.3 Previous Treatment for Malignancy

Forty one of those enrolled had received surgical treatment for their malignant disease, 39 had been treated with radiotherapy and 20 had undergone chemotherapy. Clearly, some of the patients had received multiple forms of treatment.

3.1.4 Current Drug Treatment

The 70 patients examined in this study were all on complex and customised drug régimes, which made it impossible to undertake a meaningful analysis in relation to their oral symptoms. Table 3.3 gives an indication of the main categories of drugs prescribed to the study population and it should be noted that every patient was taking at least one form of medication known to induce xerostomia.

Table 3.3 Summary table of main types of medication

MEDICATION	NUMBER OF PATIENTS
ORAL OPIOIDS	48
LAXATIVES	39
CORTICOSTEROIDS	37
DIURETICS	29
BENZODIAZEPINES	28
H2 RECEPTOR ANTAGONISTS	19
NON STEROIDAL ANTI-INFLAMMATORY DRUGS	18
MORPHINE	8
PHENOTHIAZINES	6
TRICYCLIC ANTIDEPRESSANTS	4
CYCLIZINE	4
HALOPERIDOL	2

3.1.5 Place of Enrolment

Of the 70 patients enrolled, 37 (53%) were in-patients at the Bedded Unit of the ACCORD Hospice, 25 (36%) were attending the Day Unit of the Hospice and 8 (11%) were visited at home.

3.1.6 Oral Symptoms

Since a subjective complaint of oral dryness was one of the enrolment criteria, all of the patients complained of xerostomia either during the day or the night. The overall prevalence of symptoms is summarised in Table 3.4.

Table 3.4 Summary of symptoms at enrolment

SYMPTOM	NUMBER (%)
Dryness during day	68 (97%)
Dryness at night	59 (84%)
Altered taste	40 (57%)
Soreness	22 (31%)
Difficulty talking	46 (66%)
Difficulty eating	36 (51%)
Denture problems (n = 55)	22 (40%)

The degree of severity of each symptom was graded on a visual analogue scale from 0 (no problem) to 6 (severe problem). The numerical gradings are shown for the major symptoms in Figures 3.1 to 3.6 inclusive. Whilst few of the patients complained of oral soreness as a severe problem, significant numbers of the participants were seriously troubled by an unpleasant taste sensation, difficulty talking and difficulty eating.

Figure 3.1

Bar chart illustrating the visual analogue scores for the severity of oral dryness during the day.

(0 = no problem, 2 = mild problem, 4 = moderate problem, 6 = severe problem)

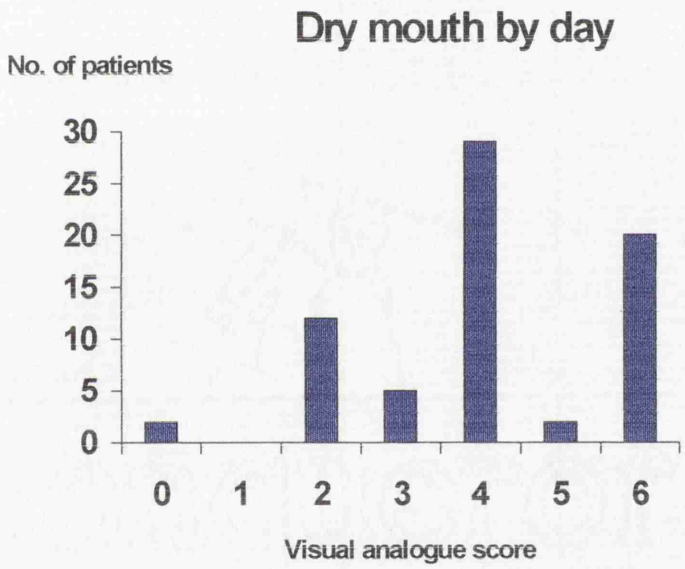


Figure 3.2

Bar chart illustrating the visual analogue scores for the severity of oral dryness during the night.

(0 = no problem, 2 = mild problem, 4 = moderate problem, 6 = severe problem)

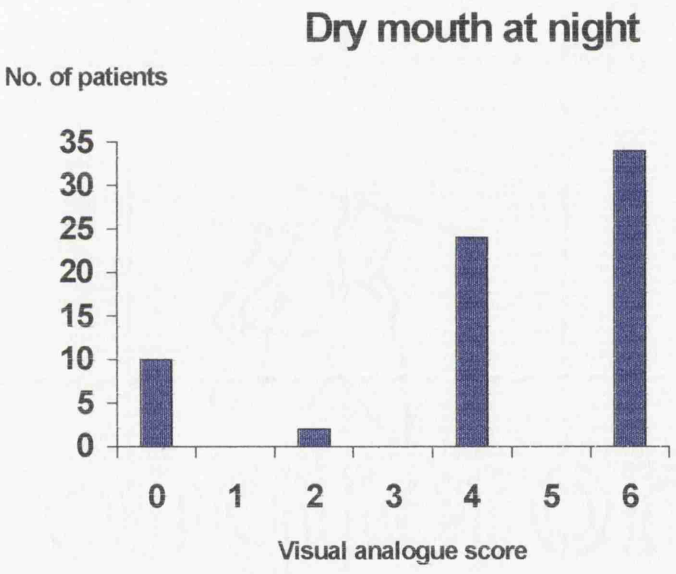


Figure 3.3

Bar chart illustrating the visual analogue scores for the severity of soreness of the oral mucosa.

(0 = no problem, 2 = mild problem, 4 = moderate problem, 6 = severe problem)

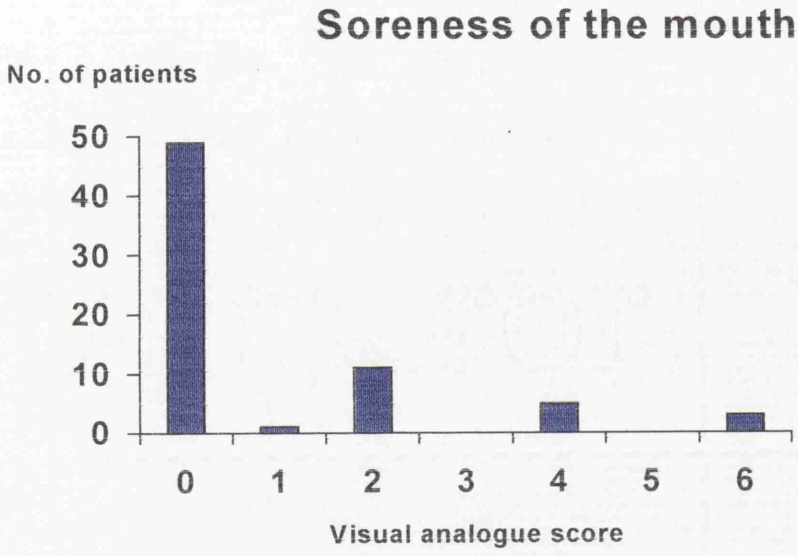


Figure 3.4

Bar chart illustrating the visual analogue scores for the severity of unpleasant taste sensation.

(0 = no problem, 2 = mild problem, 4 = moderate problem, 6 = severe problem)

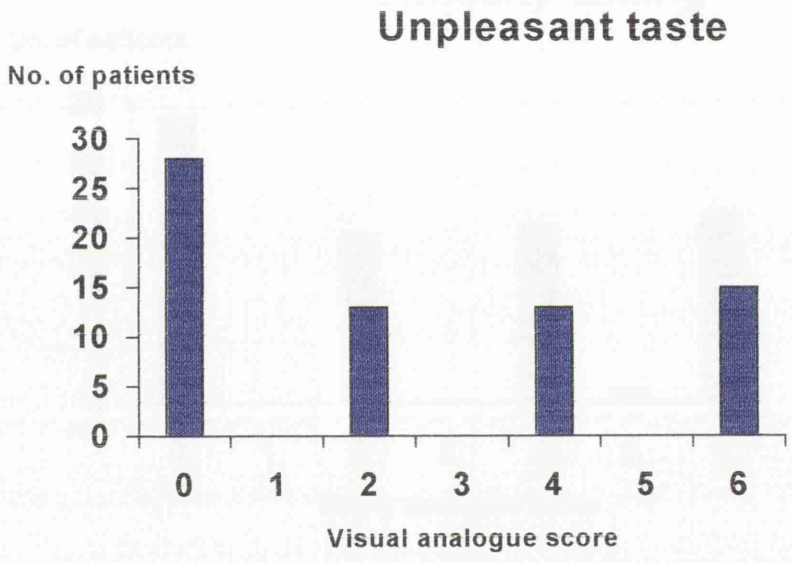


Figure 3.5

Bar chart illustrating the visual analogue scores for the severity of difficulty talking.

(0 = no problem, 2 = mild problem, 4 = moderate problem, 6 = severe problem)

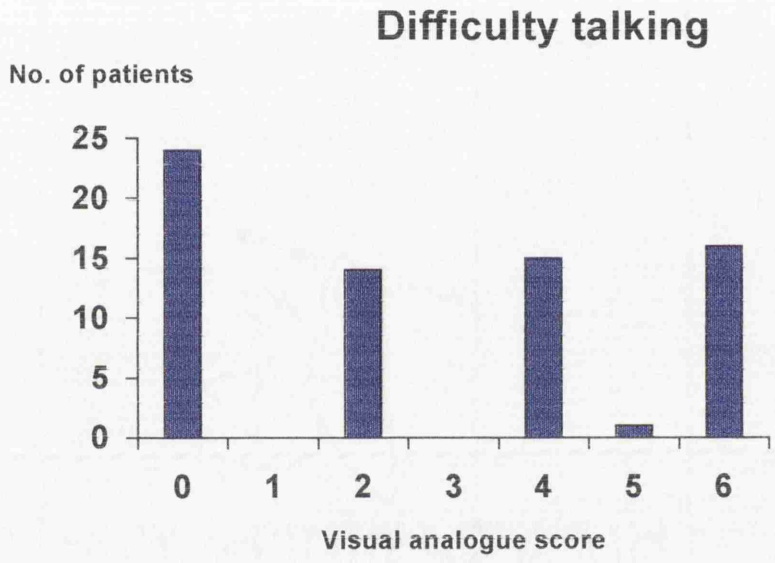
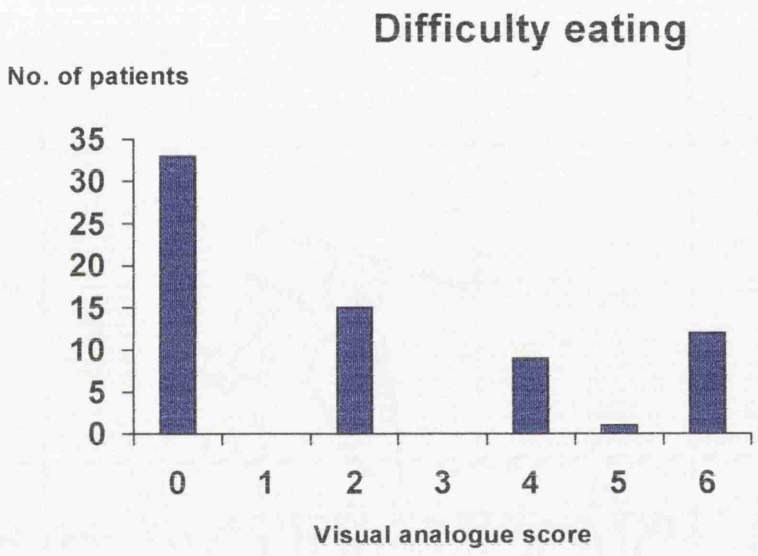


Figure 3.6

Bar chart illustrating the visual analogue scores for the severity of difficulty eating.

(0 = no problem, 2 = mild problem, 4 = moderate problem, 6 = severe problem)



3.1.7 Dental Status

Twenty one of the patients had remaining natural teeth. The oral hygiene was generally good, with mean plaque scores ranging from 0.0 - 3.0 . Only seven patients had clinically evident dental caries.

Fifty six of the patients were denture wearers. Details of denture fit and cleanliness are given in Table 3.5.

Table 3.5 Summary of denture fit and denture hygiene

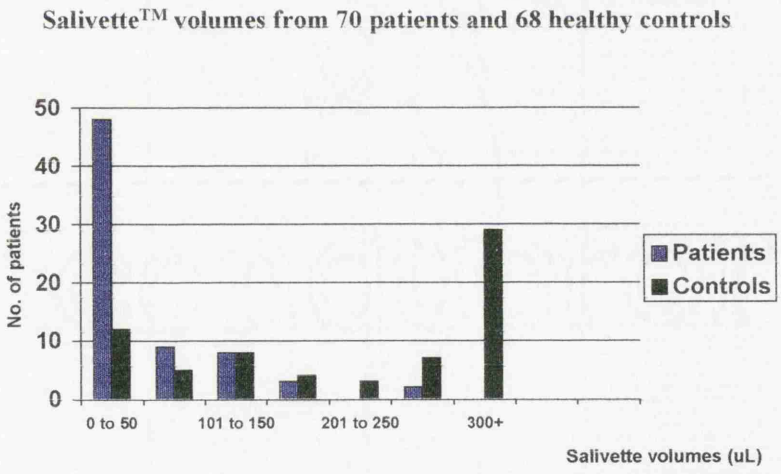
UPPER DENTURE		
GRADING	**FIT**	**CLEANLINESS**
Good	24	27
Acceptable	23	22
Poor	4	3
Very poor	1	0
LOWER DENTURE		
GRADING	**FIT**	**CLEANLINESS**
Good	10	22
Acceptable	21	14
Poor	7	3
Very poor	1	0

3.1.8 Oral Signs

On examination, 63 patients (90%) had visual evidence of xerostomia. This visual impression was reinforced by the Salivette™ volumes. The median Salivette™ volume for the 70 patients was 25 uL and for the 68 healthy controls was 250 uL. These figures are plotted in Figure 3.7.

Figure 3.7

Bar chart illustrating the range of Salivette™ volumes for the 70 patients and for 68 healthy control subjects.



Median volume for patients = 25 uL
Median volume for controls = 250ul

Forty five patients (65%) demonstrated abnormalities of the oral mucosa. The most frequent abnormalities are summarised in Table 3.6.

Table 3.6 Summary of common oral mucosal abnormalities

SIGN	NUMBER (%)
Erythema	14 (20%)
Coated tongue	14 (20%)
Atrophic glossitis	12 (17%)
Angular cheilitis	8 (11%)
Pseudomembranous candidosis	6 (9%)
Total with mucosal abnormalities	**45 (65%)**

3.1.9 Oral Microbiology

The overall carriage rates of yeasts, *Staphylococcus aureus* and coliforms are shown in Table 3.7

Table 3.7 Oral carriage rates of yeasts, staphylococci and coliforms

ORGANISM	NUMBER (%)
Yeasts	47 (67%)
Staphylococcus aureus	18 (26%)
Coliforms	13 (19%)

In relation to the yeasts, five patients were colonised with more than one species. *Candida albicans* was the commonest isolate as illustrated in Table 3.8.

Table 3.8 The species of yeast isolated from the study population

SPECIES	NUMBER OF TIMES ISOLATED
Candida albicans	23
Candida glabrata	13
Candida parapsilosis	2
Candida tropicalis	1
Candida krusei	1
Saccharomyces cerevisiae	1

Only a small number of patients were colonised with coliforms. However, two patients were colonised with more than one species. The various species isolated are summarised in Table 3.9.

Table 3.9 The species of coliforms isolated from the study population

SPECIES	NUMBER OF TIMES ISOLATED
Enterobacter cloacae	4
Escherichia coli	3
Enterobacter aerogenes	2
Klebsiella pneumoniae	2
Acinetobacter calcoaceticus	1
Proteus mirabilis	1
Pseudomonas maltophilia	1
Citrobacter spp	1
Klebsiella oxytoca	1

3.2 SALIVA ORTHANA TRIAL I : PATIENTS 1 - 35

The baseline description of all the patients participating in both Trial I (Section 3.2) and Trial II (Section 3.3) has been provided in the previous section. Statistical analysis has revealed no significant differences in the baseline data for the groups of patients entering Trials I and II respectively. Detailed baseline figures will not, therefore, be reiterated in Sections 3.2 and 3.3.

3.2.1 Study Population

Thirty five patients, 15 male and 20 female, were enrolled. Their ages ranged from 42-88 years (mean age 68 years).

The number of patients allocated the active and placebo sprays, together with the number reaching each stage of the trial are summarised in Table 3.10.

Table 3.10 Number of patients in each group reaching Day 7 and Day 14

	BASELINE	DAY 7	DAY 14
Saliva Orthana	18	16	9
Placebo	17	13	10

3.2.2 Initial Symptoms

The differences in initial symptoms between those randomised to receive active and placebo were compared, to ensure that there were no major differences between the groups at the start of the study. The relevant figures are presented in Table 3.11.

Two-sample t-tests showed that none of the differences between the groups were statistically significant. The study design has, therefore, produced two groups that are comparable to within the limits of random assignment.

Table 3.11 **Breakdown of the severity of baseline symptoms and clinical appearance of xerostomia for those randomised to active and placebo sprays.**

Variable	Saliva Orthana			Placebo		
	No Problem	Mild Problem	Severe Problem	No Problem	Mild Problem	Severe Problem
Dry mouth during day	0	9	9	0	11	6
Dry mouth during night	2	6	10	4	5	8
Sore mouth	10	8	0	9	5	3
Bad taste	8	9	1	6	6	5
Difficulty talking	6	7	5	5	8	4
Difficulty eating	8	7	3	6	6	5
Denture problems*	14	2	0	10	4	0
Clinical appearance of xerostomia	1	16	1	3	14	0

* Not all patients wore dentures

3.2.3 Changes in Symptoms from Baseline to Day 7

The changes in symptoms, clinical appearance of xerostomia and the Salivette™ volumes for the 29 patients examined on Day 7 are summarised in Table 3.12.

For the symptom of 'dry mouth during the day', 8/16 patients on Saliva Orthana and 6/13 on placebo felt that the treatment had been beneficial. The corresponding figures for 'dry mouth at night' showed improvement for 6/16 patients on Saliva Orthana and for 5/13 patients on placebo. Two-sample t-tests revealed no statistically significant differences between active and placebo for these two parameters.

Similarly, no statistically significant differences were detected between active and placebo for 'unpleasant taste', 'difficulty talking' or 'difficulty eating'. However, for 'difficulty talking' and 'difficulty eating' the performance of the Saliva Orthana was disappointing compared with the placebo.

The results for 'soreness of the oral mucosa' revealed that four patients using Saliva Orthana developed a sore mouth between Days 1 and 7. By contrast, none of the patients on placebo developed oral soreness, while six improved. A two-sample t-test showed this difference between Saliva Orthana and placebo to be statistically significant ($p = 0.04$). Whilst this could not, with confidence, be directly attributed to the Saliva Orthana spray, and may have been related to other pathology, it was this finding, together with the withdrawal of several patients complaining of a burning sensation from use of the active preparation (Section 3.2.9), which finally resulted in the trial being halted at Patient 35.

Table 3.12 Summary of changes in symptoms, appearance of xerostomia and Salivette™ volume from Baseline to Day 7 of the trial

Variable	Saliva Orthana			Placebo		
	Worse	No change	Better	Worse	No change	Better
Dry mouth during day	2	6	8	1	6	6
Dry mouth during night	1	9	6	1	7	5
Sore mouth	4	11	1	0	7	6
Bad taste	1	11	4	1	9	3
Difficulty talking	3	10	3	2	4	7
Difficulty eating	5	9	2	1	6	6
Denture problems	1	13	1	0	10	1
Clinical appearance of xerostomia	6	3	7	3	5	5
Salivette volume	6	4	6	5	0	8

3.2.4 Changes in Symptoms from Day 7 to Day 14

The table of changes from Day 7 to Day 14 (Table 3.13) shows that for those receiving placebo spray, more patients improved than deteriorated for every symptom studied. Far fewer patients showed improvements with Saliva Orthana, and in relation to the symptom 'difficulty talking' the placebo was significantly better ($p = 0.05$) than the active preparation.

Table 3.13 Summary of changes in symptoms, appearance of xerostomia and Salivette™ volume from Day 7 to Day 14 of the trial

Variable	Saliva Orthana			Placebo		
	Worse	No change	Better	Worse	No change	Better
Dry mouth during day	1	6	2	0	5	5
Dry mouth during night	4	4	1	1	4	5
Sore mouth	1	6	2	1	5	4
Bad taste	1	7	1	0	6	4
Difficulty talking	3	5	1	0	5	5
Difficulty eating	0	7	2	2	4	4
Denture problems	1	7	1	0	8	0
Clinical appearance of xerostomia	4	2	3	0	5	5
Salivette volume	5	2	2	6	1	3

3.2.5 Effect of the Sprays on the Oral Microflora

The small numbers of patients in each group who were colonised with coliforms and *Staphylococcus aureus* made it impossible to undertake a formal statistical analysis of the changes in numbers occurring during the trial.However, Table 3.14 gives a comparison of the concentrations of yeasts across the study.

Table 3.14 Summary of yeast concentrations pre-treatment and the changes in concentration by Day 7 and by Day 14.

Pre-treatment	Saliva Orthana				Placebo			
	None	Low	Medium	High	None	Low	Medium	High
Tongue	5	3	6	4	6	0	3	8
Palate	8	5	2	3	7	3	1	6
Denture	11	2	2	2	8	0	0	5
Change by Day 7	**Saliva Orthana**				**Placebo**			
	Higher at Day 7	Same or none	Lower at Day 7		Higher at Day 7	Same or none	Lower at Day 7	
Tongue	5	5	6		4	6	3	
Palate	4	7	5		3	8	2	
Denture	4	9	2		1	6	4	
Change by Day 14	**Saliva Orthana**				**Placebo**			
	Higher at Day 14	Same or none	Lower at Day 14		Higher at Day 14	Same or none	Lower at Day 14	
Tongue	1	7	1		4	4	2	
Palate	2	6	1		6	4	0	
Denture	2	5	1		1	7	0	

3.2.6 Administration of the Spray

At Day 7, 24 of the 29 participants remaining in the study reported that they had been using the spray themselves. One had required nursing staff to administer the spray exclusively and in four cases administration had been a combination of self and nursing support. The distribution was similar at Day 14, with 17 self-administering, two being treated by a nurse and one receiving some nursing input.

3.2.7 Length of Time Sprays Provided Relief

Many of the patients found it very difficult to give a period of time for which the sprays provided relief and the accuracy of these data are therefore questionable.

At Day 7 the responses ranged from zero to 30 minutes (median 10 minutes) for Saliva Orthana and from two to 60 minutes (median 22.5 minutes) for the placebo

At Day 14 the responses ranged from one minute to 30 minutes (median 3 minutes) for Saliva Orthana and from three minutes to 90 minutes (median 10 minutes) for the placebo preparation.

3.2.8 Patients Wishing to Continue with Use of the Spray

By Day 7 of the trial, 12 /16 of those using Saliva Orthana and 11/13 of those on placebo wished to continue using the respective sprays. This difference was not significant by the Fisher exact test. The corresponding figures by Day 14 were 3/9 of those on Saliva Orthana and 10 /11 of the participants allocated placebo. In this case there was a statistically significant difference (Fisher exact test; $P<0.01$) in favour of the placebo.

3.2.9 Reasons for Withdrawal

Two patients, one on Saliva Orthana and one on placebo, had both withdrawn by Day 7 because of increasing mental confusion. One further patient on placebo had become too ill by Day 7 to continue. Three patients, all on Saliva Orthana, withdrew by Day 7 on account of a burning sensation of the oral mucosa.
Four patients, two on placebo and two on Saliva Orthana, died between Days 7 and 14. A further four patients (three on Saliva Orthana) become too unwell to participate during this period and a further two, both on placebo, were withdrawn because of mental confusion. A final patient on Saliva Orthana withdrew because he believed the spray was traumatising his oral mucosa.

3.2.10 Weights of Residual Sprays

The mean residual weight of the Saliva Orthana sprays was 365 $\pm$ 35g and of the placebo sprays 316 $\pm$ 88g. The difference between these weights just achieved statistical significance (2-sample t-test; P=0.06), indicating greater use of the placebo preparation.

3.3 SALIVA ORTHANA TRIAL II : PATIENTS 36-70

3.3.1 Study Population

Thirty five patients, 10 male and 25 female, were enrolled. Their ages ranged from 49-83 years (mean age 65 years).

The number of patients allocated the active and placebo sprays, together with the number reaching each stage of the trial are summarised in Table 3.15.

Table 3.15 Number of patients in each group reaching Day 7 and Day 14

	BASELINE	DAY 7	DAY 14
Saliva Orthana	18	15	13
Placebo	17	16	13

3.3.2 Initial Symptoms

The differences in initial symptoms between those randomised to receive active and placebo were compared, to ensure that there were no major differences between the groups at the start of the study. The relevant figures are presented in Table 3.16.

Two-sample t-tests showed that none of the differences between the groups were statistically significant. There were also no significant differences in Salivette™ volumes between the two groups. The study design had, therefore, produced two groups that were comparable to within the limits of random assignment.

Table 3.16 **Breakdown of the severity of baseline symptoms and clinical appearance of xerostomia for those randomised to active and placebo sprays.**

Variable	Saliva Orthana			Placebo		
	No Problem	Mild Problem	Severe Problem	No Problem	Mild Problem	Severe Problem
Dry mouth during day	0	15	3	2	12	3
Dry mouth during night	4	5	9	1	9	7
Sore mouth	15	3	0	14	3	0
Bad taste	6	4	8	8	7	2
Difficulty talking	7	8	3	6	7	4
Difficulty eating	9	6	2	10	5	2
Denture problems*	5	6	1	5	8	1
Clinical appearance of xerostomia	2	14	1	2	14	1

* Not all patients wore dentures

3.3.3 Changes in Symptoms from Baseline to Day 7

The changes in symptoms, clinical appearance of xerostomia and the Salivette™ volumes for the 31 patients examined on Day 7 are summarised in Table 3.17.

For the symptom of 'dry mouth during the day', 9/15 patients on Saliva Orthana and 10/16 on placebo felt that the treatment had been beneficial. The corresponding figures for 'dry mouth at night' showed improvement for 8/15 patients on Saliva Orthana and for 8/16 patients on placebo. Thus, both the active and placebo sprays relieved oral dryness for many of the participants, but appropriate two-sample t-tests revealed no statistically significant differences between the two preparations. Most of the remaining patients in both groups claimed no change in their symptoms of dry mouth. For the other symptoms, namely sore mouth, bad taste, difficulty talking and difficulty eating, most patients reported no change in either treatment group, though more patients improved than deteriorated.

Table 3.17 **Summary of changes in symptoms, appearance of xerostomia and Salivette™ volume from Baseline to Day 7 of the trial**

Variable	Saliva Orthana			Placebo		
	Worse	No change	Better	Worse	No change	Better
Dry mouth during day	1	5	9	0	6	10
Dry mouth during night	1	6	8	0	8	8
Sore mouth	1	12	1	1	11	2
Bad taste	0	12	3	0	12	4
Difficulty talking	1	11	3	1	10	5
Difficulty eating	0	15	0	2	11	3
Denture problems	0	8	1	1	12	0
Clinical appearance of xerostomia	4	7	3	5	7	4
Salivette volume	2	6	5	6	5	5

Missing values reflect difficulties in collection of histories and clinical samples in terminally ill patients

3.3.4 Changes in Symptoms from Day 7 to Day 14

The changes from Day 7 to Day 14 are shown in Table 3.18. Of the 26 patients remaining in the study to Day 14, the majority claimed no change in their symptoms on either spray. However, for most of the variables studied, for those who did report change, the majority were improving rather than deteriorating. There was some indication that Saliva Orthana improved dryness marginally more than the placebo.The changes in Salivette™ volume also appeared to favour the active spray ($P = 0.08$ in a two-sample t-test), though there is no evidence to suggest that use of Saliva Orthana increases natural production of saliva. However, none of the differences between Saliva Orthana and placebo illustrated in Table 3.18 achieved statistical significance.

Plots of the changes at Day 7 against the changes at Day 14 showed that across most of the symptoms there was a reassuring pattern that any initial improvement by Day 7 was generally maintained from Day 7 to Day 14.

Table 3.18 **Summary of changes in symptoms, appearance of xerostomia and Salivette™ volume from Day 7 to Day 14 of the trial**

Variable	Saliva Orthana			Placebo		
	Worse	No change	Better	Worse	No change	Better
Dry mouth during day	0	7	6	1	6	5
Dry mouth during night	0	8	5	1	7	4
Sore mouth	2	10	1	2	9	1
Bad taste	0	9	3	0	8	4
Difficulty talking	1	9	2	0	10	2
Difficulty eating	0	12	0	1	8	2
Denture problems	1	7	1	1	8	0
Clinical appearance of xerostomia	5	6	1	2	9	2
Salivette Volume	3	2	7	5	3	4

Missing values reflect difficulties in collection of histories and clinical samples in terminally ill patients

3.3.5 Effect of the Sprays on the Oral Microflora

The small numbers of patients in each group who were colonised with coliforms and *Staphylococcus aureus* made it impossible to undertake a formal statistical analysis of the changes in numbers occurring during the trial.

However, Table 3.19 gives a comparison of the concentrations of yeasts across the study. There were slightly higher numbers of yeasts in the placebo group compared with the Saliva Orthana group at baseline, but this difference did not achieve statistical significance. Overall, the results showed no significant effects of either spray on the oral candidal load.

Table 3.19 Summary of yeast concentrations pre-treatment and the changes in concentration by Day 7 and by Day 14.

Pre-treatment	**Saliva Orthana**				**Placebo**			
Site	None	Low	Medium	High	None	Low	Medium	High
Tongue	6	4	4	4	6	3	4	4
Palate	10	6	1	1	9	4	1	3
Denture	7	2	1	2	7	4	0	3
Change by Day 7	**Saliva Orthana**				**Placebo**			
	Higher at Day 7	Same or none	Lower at Day 7		Higher at Day 7	Same or none	Lower at Day 7	
Tongue	7	7	1		5	6	5	
Palate	3	8	4		4	9	3	
Denture	2	5	2		3	6	4	
Change by Day 14	**Saliva Orthana**				**Placebo**			
	Higher at Day 14	Same or none	Lower at Day 14		Higher at Day 14	Same or none	Lower at Day 14	
Tongue	5	4	4		4	5	4	
Palate	2	11	0		1	5	6	
Denture	3	4	2		3	1	5	

3.3.6 Administration of the Spray

At Day 7, 22 of the 31 participants remaining in the study reported that they had been using the spray themselves. Three had required nursing staff to administer the spray exclusively and in six cases administration had been a combination of self and nursing support. The distribution was similar at Day 14, with 18 self-administering, six being treated by a nurse and two receiving some nursing input.

3.3.7 Length of Time Sprays Provided Relief

As in Trial I, many of the patients found it difficult to give a period of time for which the sprays provided relief and the accuracy of these data are therefore questionable.

At Day 7 the responses for Saliva Orthana ranged from zero to 180 minutes (median 10 minutes) and for placebo from zero to 240 minutes (median 15 minutes).

At Day 14 the responses ranged from less than one minute to 180 minutes (median 20 minutes) for Saliva Orthana and from less than one minute to 240 minutes (median 15 minutes) for the placebo preparation.

3.3.8 Patients Wishing to Continue with Use of the Spray

By Day 7 of the trial, 14 /15 of those using Saliva Orthana and 14/16 of those on placebo wished to continue using the respective sprays. The corresponding figures by Day 14 were 11/13 of those on Saliva Orthana and 7/13 of the participants allocated placebo. Whilst these figures show a trend in favour of Saliva Orthana at Day 14, the difference was not statistically significant ($P = 0.14$; chi-square test).

3.3.9 Reasons for Withdrawal

By Day 7 one patient, on Saliva Orthana, had withdrawn himself from the trial because he disliked the spray. A second patient, on placebo, also withdrew because he believed the spray was causing a sore throat. A third patient died prior to Day 7 of the study.

By Day 14 three patients, all on Saliva Orthana, had withdrawn because they had become too unwell to cooperate. Two further patients, both on placebo, died between Day 7 and Day 14.

3.3.10 Weights of Residual Sprays

The mean residual weight of the Saliva Orthana sprays was 326 $\pm$ 54g and of the placebo sprays 322 $\pm$ 59g. There was no significant difference between these values (2-sample t-test; P=0.85).

CHAPTER 4

DISCUSSION

Oral problems are common in patients with cancer (Aldred *et al*, 1991; Jobbins *et al*, 1992b; de Conno *et al*, 1989). The present study has confirmed the findings of these earlier authors. The oral complications in cancer patients are frequently a result of treatment, but may be a feature of the disease itself in the case of primary oral malignancy or secondary tumour deposits in the jaws. Obviously the clinical problems are likely to be most severe and difficult to treat in patients with primary oral malignancy, of which squamous cell carcinoma is the commonest (Soames and Southam, 1993). Palliative treatment of disease in the oral cavity presents special difficulties as the mouth is central to so many functions, such as eating, speaking and swallowing. Even when the mouth is surgically by-passed to facilitate these functions, for example with a Percutaneous Endoscopic Gastrostomy (PEG) tube, the procedure seldom improves oral health and indeed may exacerbate the problems (Bagg *et al*, 1995).

One major problem for cancer patients is xerostomia. Approximately 70% of all terminal cancer patients suffer from the sensation of dry mouth (Jobbins *et al*, 1992b) but many do not report the symptoms, or indeed many other oral problems, unless specifically asked. Dryness may be caused by a direct effect of the disease process on the salivary glands, by medication, either specific or symptomatic, or by radiotherapy. Indeed, in the present study, every patient enrolled was taking at least one drug which is recognised to cause dry mouth. There may also be a psychological component. There is evidence that xerostomia is not considered a major problem by the medical profession and that unless specifically complained of by patients it is often ignored

(Gordon, Berkey and Call, 1985). In fact, the current study and others have shown that xerostomia is a principal cause of distress to these patients (Jobbins *et al*, 1992b) as it interferes with speech and swallowing (including the swallowing of medication) and can lead to secondary mouth infections.

The group of patients described in the present study was selected on the basis of a complaint of xerostomia. The severity of the dryness, both during the day and at night, was reported as moderate to severe by a majority of the patients. This is a distressing additional problem for patients who are already seriously ill and study of its treatment should be a priority. The dryness is also likely to contribute to other symptoms such as difficulty with talking and eating and can affect denture retention. This is also compromised in many cases by the loss of bulk of the facial musculature that occurs in cachectic cancer patients.

The oral and denture hygiene among this group of patients was generally good, reflecting the strong emphasis on mouth care at the hospice where the study was undertaken. In the author's experience, less attention is paid to mouth care for cancer patients being nursed in acute hospitals or in the community (Sweeney *et al*, in press). This is an area, therefore, in which the dental profession can play a significant educational role.

The prevalence of oral mucosal abnormalities (65%), though high, was lower than that described in a previous study (82%) (Jobbins *et al*, 1992b) This may again

reflect the level of oral care provided. Much of the mucosal disease noted was fungal in nature and yeasts were isolated from the mouths of 67% of the patients. Oral candidosis is a well recognised complication among cancer patients (Finlay, 1986), in whom it can present in many forms including plaques, areas of erythema, or angular cheilitis. All of these various forms of oral candidosis were detected in the current patient group.

The isolation rate of *Staphylococcus aureus* (26%) was very similar to that described for oral carriage in terminally ill cancer patients (28%) by a previous study (Jobbins *et al*, 1992c). There is increasing interest *in Staphylococcus aureus* in the mouth, since it has recently been described as a cause of mucositis in some clinical situations (Bagg et al, 1995). It also plays a role in many cases of angular cheilitis (MacFarlane and Helnarska, 1976), a relatively common problem in the terminally ill.

Coliforms were isolated from only 19% of patients, compared with 49% in an earlier study (Jobbins *et al*, 1992c). The role, if any, of coliforms in mediating oral disease is uncertain, and the relatively low prevalence of oral carriage in the present group may again reflect the high level of oral care they were receiving at the hospice.

Oral shedding of herpes simplex virus was studied because of recent evidence that such shedding is more frequent among the immunocompromised (Kameyama *et al*, 1988) In addition, intra-oral reactivation lesions are more common in such patients

and are often clinically atypical. The number of individuals who were shedding the virus was relatively low and it would be of interest to repeat this work using more sensitive molecular biological methods, for example the polymerase chain reaction, for detection. Nevertheless, the culture results were very helpful in establishing the diagnosis for the two patients with herpetic stomatitis. In recent months we have seen and treated several cancer patients with unusual forms of oral ulceration which have proved on culture to be caused by herpes simplex virus. This diagnosis should always be considered in immunocompromised patients with atypical oral ulceration.

Treatment of xerostomia in all patient groups has never been completely satisfactory, though various approaches have been tried (Levine *et al*, 1987). An obvious first step is to consider reducing or discontinuing , where practicable, drugs or other treatments which may be causing or exacerbating the dryness. This, however, rarely occurs partly because the symptom is often not reported to or appreciated by the doctor in charge of the treatment but also because frequently the xerogenic medication is central to the patient's overall care. This is particularly true of terminally ill cancer patients.

The second logical line of treatment for dry mouth is to provide regular hydration, preferably by way of sips of water, self-administered if possible. An aqueous spray is a slightly more complicated method of delivery, often requiring nursing assistance in the later stages of disease. However, in practice the relief provided is so short-lived that the patient soon tires of the constant sipping or spraying and often accepts xerostomia as an inevitable consequence of terminal illness.

The next step is to apply specific anti-xerostomic substances by mouthwash, spray or gel, at frequent intervals. Among the compounds already tested and marketed are the carboxymethyl cellulose based sprays and the mucin-based products (Levine *et al*, 1987). However, despite the frequent occurrence of xerostomia among terminally ill cancer patients, there have been no formal trials of saliva substitutes in this group. The current study has investigated the effects of treatment with a mucin-containing spray (Saliva Orthana; Nycomed [UK] Ltd.) on a cohort of 35 terminally ill cancer patients complaining of xerostomia, against a placebo spray containing no mucin used by a further 35 xerostomic cancer patients. This was a double-blind trial, but it was technically impossible to conduct a cross-over study as the expected life span of most of the patients involved was not sufficiently long.

The trial was further complicated as a result of several apparent adverse reactions to the active spray. At Patient 35 the trial was stopped, after two consecutive reports of severe burning mouth were received. When the trial code was broken by the responsible pharmacist it was discovered that both patients had used the active product. Furthermore, a retrospective examination of the case record forms showed that several of the patients had complained of similar mild symptoms and all were using the active spray. Discussions took place with the manufacturers, who in turn searched their records for previous reports of this problem with the mucin-containing spray. The manufacturers stated that a burning sensation had never been reported as a side-effect of the spray.

The manufacturers next checked whether there were any abnormalities in the formulation of the trial product. The chemical analysis of the relevant batch of Saliva Orthana included high pressure liquid chromatography, but all parameters were found to be within normal limits. At the end of the entire study, it became clear that the two trials exhibited differences in the desire of the patients to continue using the respective preparations. In Trial I, by Day 14, 10 out of 11 patients remaining on placebo wished to continue using it, while only 3 out of 9 remaining on Saliva Orthana wished to do so. This difference was statistically significant. In contrast, in Trial II, 11out of 13 patients on Saliva Orthana wished to continue as opposed to only 7 out of 13 on placebo, showing a trend in favour of Saliva Orthana. On the assumption that both batches of spray were chemically identical, it is difficult to explain this difference between the two trials. One may speculate that there was a difference between the batches of Saliva Orthana which was not identified by the analytical methods used. In retrospect it would have been useful to have the sprays analysed independently. Whilst this was considered at the time, the necessary resources and facilities were unfortunately not available.

The undertaking of these chemical analyses caused a considerable time-delay. Following receipt of the results, further discussions took place with the hospice staff and the manufacturers to decided if it would be appropriate to re-start the trial and whether any changes should be made in trial design. The decision was taken jointly to start a completely new trial of a further 35 patients with a new batch of active and

placebo sprays. It was unfortunate that the overall size of the trial was now limited to 35 patients, since the use of new batches of spray meant that the data from the two groups could not be merged to give a total of 70 patients.

Some of the hospice staff were obviously unconvinced about the ethics of this decision, even though the re-commencement had been approved by the local Ethics Committee. There have been few clinical trials of mouth care products and régimes involving patients who are terminally ill. This is unfortunate, since terminal cancer patients represent a group for whom much research is required to find the best palliative treatments that will ensure these patients end their lives with as much comfort and dignity as possible. Nevertheless, many people regard the involvement of such patients in a clinical trial as unethical and even cruel, a sentiment which was met by the author on more than one occasion. Terminal illness is an extremely emotive subject and even though ethical approval is obtained for a trial, this is no guarantee that the study will carry the support of the family and carers.

The overall outcome of the trial was disappointing in that no statistically significant benefit was demonstrated for the mucin treatment when compared to the placebo spray. This was in direct contrast to earlier trials with mucin-containing sprays in Sjögrens Syndrome patients (Duxbury *et al*, 1989). Nevertheless, it is important to note that most patients obtained some relief from using both types of spray. The finding that cancer patients with xerostomia may derive benefit from use of even a pharmacologically inactive mouth spray has been reported by others (Jobbins *et al*,

1992a)

One explanation of these disappointing results when compared to those for patients with Sjögrens Syndrome may relate to fundamental differences between the patient groups. Thus, whilst Sjögrens Syndrome patients have a serious problem with dry mouth and dry eyes, it is rarely a life-threatening condition. Although they may also suffer from a disabling connective tissue disease, these patients are generally able to look after themselves and administer their own medication. On the other hand the patient group participating in this trial was more severely medically compromised. All of the patients were terminally ill, some in the last few weeks or days of life and most were very tired and emotionally labile. Often the severity of their pain required control with high dose opiates, leading to a degree of sedation and confusion which called into question the eligibility of the subjective responses to certain questions.

The complexity of the patients' medication could also have contributed to the poor performance of the Saliva Orthana. A note of all medication was taken at the baseline visit. However, it was often impossible to record all the changes which took place in the patients' individual drug regimes - both dosage and type - during the course of their involvement. Some patients were taking as many as ten different preparations and these altered frequently, with antifungals, narcotic analgesics, phenothiazines and anti-emetics being introduced, or the dose modified, as required. Since many of these drugs can increase oral dryness (Sreebny and Schwarz ,1986), it was difficult for the patients to assess, in isolation, the ability of the Saliva Orthana to reduce the extent of the initial

dryness. In turn, this will have made it more difficult for the Saliva Orthana to demonstrate a significant advantage .

Poor memory between baseline and Day 14 also gave cause for concern. Sometimes patients could not remember starting the trial, and / or their initial responses and could not accurately remember the state of their mouths seven days previously, let alone 14 days before. Some patients could not even remember meeting the author at the previous visit. It was often very difficult to avoid leading the patients into providing the answers they thought the author expected to hear and time had to be taken to talk them carefully through the questions at each visit. This proved a problem in itself, as the patients were often so tired and debilitated that they were unable to communicate for more than a few minutes. Indeed, some patients deteriorated so rapidly after enrolment that they were unable to answer any questions at one or both of the subsequent visits and were withdrawn from the trial.

Another problem encountered within the trial included the patients' obvious confusion with, and mistrust of , the visual analogue scales used to measure the subjective responses. This sometimes resulted in a lack of consistency in the responses from week to week. At first the author did not refer to the previous week's answers when questioning at Day 7 and Day 14, but it quickly became apparent that the patients were unable to remember the condition of their mouths from the earlier visit and had been unable to assess accurately their initial level of discomfort. Often responses were received at Day 7 and Day 14 that contradicted the baseline responses. This lack of

consistency of response was due only in part to the patient's poor memory or sedated state. Perhaps of more importance was the fact that the baseline data were collected shortly after the patient's admission to the hospice, at a time when other more worrying symptoms and fears had not been brought under control. It is not surprising that the symptoms of a dry, uncomfortable mouth may be overshadowed by those of uncontrolled pain of a rapidly growing primary or secondary tumour.

There were a number of problems associated with the active spray itself. Frequent complaints were received about the consistency of the spray. Some patients thought it too sticky and compounded the xerostomia. The stickiness of the Saliva Orthana was described as unpleasant by some patients, who complained that it actually made swallowing and speaking more difficult. Since 66% of the patients complained of 'difficulty talking' at baseline, it is perhaps understandable that many wished to discontinue use of Saliva Orthana. The presence of mucin in the Saliva Orthana allows it to remain on the surface of the mucosa for longer than water, and this feeling was described by some as " ...having something else to contend with". Others felt that the spray was too watery and was not retained for long enough in the mouth. The flavour was criticised as being both too 'minty' by some and too weak by others. Clearly, in a group of patients as seriously ill as those in this study, it is difficult to find a preparation which will suit everybody's needs.

The design of the spray bottles led to many reported difficulties. First, the clear plastic top on each spray bottle was a tight fit and some of the participants found difficulty

removing it. Secondly, the bottles were pump-action and thus had to be primed before use, again a procedure which required more strength than many of these patients possessed. This could also be a problem for other groups of patients, such as those with rheumatoid arthritis. The position of the nozzle was confusing, since the neck and nozzle were all white and the spray aperture was difficult to distinguish. This design of spray, coupled with poor spatial orientation in many of these patients, often made delivery of the preparation into the mouth a 'hit-or-miss' procedure. It is clear that far more attention should be paid to the design of the spray bottle, if it is to be used successfully by weak and debilitated patients.

Other problems emerged in relation to some of the nursing staff caring for the patients in the hospice. Nurses have their own management structure and it was necessary to work within the constraints imposed by that structure during this trial. This required working by consent of the nurses rather than by request to the nurses and the control of the trial was, therefore, effectively in the hands of the nursing staff. For reasons now to be discussed, this may have an important bearing on the inability to demonstrate a significant benefit of the active over the placebo spray.

Since some of the more debilitated patients encountered problems using the spray, nursing assistance was requested for each patient who was unable to cope alone. In fact, only a minority of patients throughout both trials had extensive nursing assistance, despite the obvious inability of several patients to self-administer. Many of the nursing staff were not enthusiastic about discussing individual patients or the progress of the

trial as a whole. The feedback received from several of the nursing staff indicated at best a negative approach and at worst an antagonistic attitude towards the whole concept of the study. This negativity was disappointing, as meetings had been held with all staff likely to be involved in the trial before the final protocol had been drawn up, the study was fully explained to them and all questions answered. Special information sheets were also printed and distributed to the staff members to ensure they were fully informed of what was involved. Despite these initiatives, staff would generally only administer the spray on direct patient request, though as previously stated these patients were often unable to remember spontaneously that they had a spray to use and talking was sometimes too much of an effort. They relied on the nursing staff to remind them and assist them frequently, support which appears not to have been readily forthcoming. This was uncharacteristic in view of the usually high standard of overall care in this hospice. With hindsight, it would perhaps have been better to make the nursing staff fully responsible for administering the spray, at least on two occasions daily, to all those participants who were in-patients at the hospice.

It is always difficult to achieve a meaningful result with a small study group. The inherent variability of response from subjects in the Life Sciences is so great that the smaller the group the less likely one is to gain a significant result. This is less of a problem in Physical Sciences. The initial intention was to use a cohort of 100 patients for the trial. Enrolling suitable patients proved a slow process, since not all of the patients in the hospice complained of a dry mouth or were able to give consent. Patients were also excluded if their life expectancy was less than seven days, though

this was often difficult to predict. Often, patients were referred to the author for inclusion in the trial, but on direct questioning were found not to be currently suffering from xerostomia and were therefore ineligible.

The logistics of this trial caused several problems. As the Bedded Unit of the hospice concerned contained only eight beds, some patients were seen at the Day Care centre or in their homes. Since the hospice serves a large geographical area this often meant much travelling. Not all patients admitted to the hospice were within the last few weeks of life - some were admitted for symptom control or for respite and thus were in the Bedded Unit for only a short time. This meant that the baseline information was obtained in the Bedded Unit but that the follow-up visits could have been at home, while the patient was visiting Day Care, or even in a ward of an acute hospital to which they had been admitted since the previous visit.

The provision of oral care in palliative medicine has been poorly researched and much current nursing practice appears to be anecdotal, rather than being evidence-based. Patient non-cooperation and / or lack of knowledge, training and cooperation of nurses and doctors in mouth care are further complicating factors (Sweeney *et al*, in press). At best, therefore, mouth care for these patients is often suboptimal and the need for clinical research in this area is evident. This study has highlighted some of the major difficulties encountered with any clinical trial involving terminally ill patients. Some of these are ethical, including the question of whether one should undertake research among dying patients. The latter is relevant to the potential problem of hostility among

other staff to the trial itself. The physical and emotional health of the patients may result in poor cooperation and unreliable responses, whilst the short life-expectancy has an impact on the number of participants likely to complete the trial period.

Despite the many problems encountered during this trial, one fact emerged - that hydration of the mouth by use of a spray was generally welcomed by these patients. This supports previous research on a similar patient group (Jobbins *et al*, 1992a). Although Saliva Orthana has not performed significantly better than the placebo under the conditions of test described, the results strongly suggest that regular use of a mouth spray should be considered as part of all mouth care protocols for terminally ill cancer patients. As new saliva substitutes become available (Gibson and Beeley, 1994), their value to this important group of patients should be carefully examined.

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APPENDIX I

CASE REPORT FORM

Patient No.: |_|_|_|_|

CASE REPORT FORM

EFFICACY OF SALIVA ORTHANA IN THE MANAGEMENT OF XEROSTOMIA IN HOSPICE PATIENTS

TRIAL NUMBER: SSGB901

ure	:	University of Glasgow, Department of Oral Sciences
ble Investigator	:	Dr Jeremy Bagg, Lecturer/Honorary Consultant in Oral Microbiology
igator(s)	:	Mrs Petrina Sweeney, Dental Surgeon Dr Wendy Baxter, Medical Director, Accord Hospice

tient withdrawn? No ☐ Yes ☐ If, Yes, why? .....

.....

signed, certify that all the data included in this C.R.F. have been reviewed, are valid and actual.

Date: ___/___/___ (Day Mth Year)

_____
Signature, Responsible Investigator

Patient No.: ___ ___ ___

INITIALS: _____

BIRTH: ____/____/____/
Day Mth Year

SEX: Female ☐ Male ☐

ATION:

FIRST EXAMINATION: _____

IS / SITE (PRIMARY TUMOUR) : _____

☐ NON-SMOKER ☐ EX-SMOKER ☐

S TREATMENT(S):

Date of the most recent:

URGERY ☐ _____

ADIOTHERAPY ☐ _____

HEMOTHERAPY ☐ _____

T DRUG TREAMENT:

ARENTERAL MORPHINE / DIAMORPHINE ☐

RAL OPIOID ☐

ORTICOSTEROID ☐

RECEPTOR ANTAGONIST ☐

IURETIC ☐

HENOTHIAZINE ☐

RICYCLIC ☐

ON-STEROIDAL ANTI-INFLAMMATORY ☐

YCLIZINE ☐

ALOPERIDOL ☐

AXATIVE (specify) ☐

THER (specify) ☐

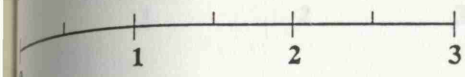
Patient No.: ___ ___ ___

C ASSESSMENT

MS:

RY MOUTH DURING DAY

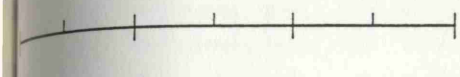
Mild Moderate Severe



☐ ☐ ☐

RY MOUTH AT NIGHT

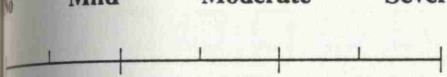
Mild Moderate Severe



☐ ☐ ☐

ORE MOUTH

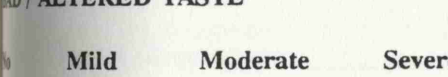
Mild Moderate Severe



☐ ☐ ☐

AD / ALTERED TASTE

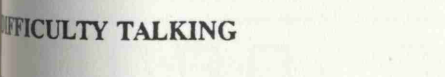
Mild Moderate Severe



☐ ☐ ☐

FFICULTY TALKING

Mild Moderate Severe



☐ ☐ ☐

FFICULTY EATING

Mild Moderate Severe

☐ ☐ ☐

NTURE PROBLEMS

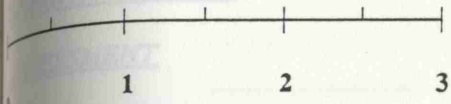
Mild Moderate Severe

☐ ☐ ☐

MENT OF XEROSTOMIA:

CLINICAL APPEARANCE

Absent Mild Moderate Severe



☐☐☐

VOLUME OF SALIVA FROM SALIVETTE (µL)

☐☐☐☐

Patient No.: ____

EXAMINATION

...L ASSESSMENT

...STATUS:

...ent:

8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8

...ore:

8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8

Overall plaque score: _____

...ries:

8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8

...tus:

	Owned	Worn		Owned	Worn
...mplete upper	☐	☐	Complete lower	☐	☐
...rtial upper	☐	☐	Partial lower	☐	☐

	GOOD	ACCEPTABLE	POOR	VERY POOR
...E FIT				
...E ...NESS				

☐ _____

☐ _____

☐ _____ ossitis

☐ _____

☐ _____ matitis

☐ R _____ eilitis

☐ L _____

☐ _____

OLOGICAL SPECIMENS

☐

☐

_____

_____

_____

__/__/__/
Mth Year

_____
Investigator signature

DAY 7

ADMINISTRATION

SE ☐ SELF ☐

DRY MOUTH DURING DAY

No Mild Moderate Severe

0 1 2 3 ☐ ☐ ☐

DRY MOUTH AT NIGHT

No Mild Moderate Severe

0 1 2 3 ☐ ☐ ☐

SORE MOUTH

No Mild Moderate Severe

0 1 2 3 ☐ ☐ ☐

BAD / ALTERED TASTE

No Mild Moderate Severe

0 1 2 3 ☐ ☐ ☐

DIFFICULTY TALKING

No Mild Moderate Severe

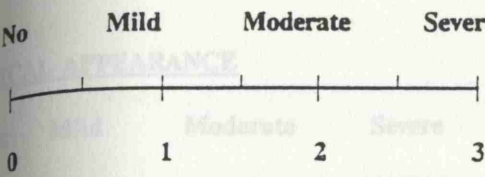
0 1 2 3 ☐ ☐ ☐

DIFFICULTY EATING

No Mild Moderate Severe

0 1 2 3 ☐ ☐ ☐

DENTURE PROBLEMS

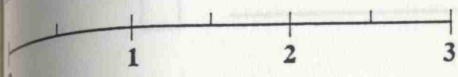


Patient No.: ☐☐☐

...MENT OF XEROSTOMIA:

CLINICAL APPEARANCE

Absent Mild Moderate Severe



☐☐☐

VOLUME OF SALIVA FROM SALIVETTE (µL)

☐☐☐☐

...AMINATION

...core	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8

Overall plaque score: _____

...ES

	GOOD	ACCEPTABLE	POOR	VERY POOR
...RE FIT				
...RE ...LINESS				

☐ _____

☐ _____

glossitis ☐ _____

☐ _____

stomatitis ☐ _____

cheilitis ☐ R _____

☐ L _____

☐ _____

BIOLOGICAL SPECIMENS

☐

☐

_____

_____

_____

Patient No.: ___

PATIENT ASSESSMENT (1)

FOR HOW LONG DOES A SPRAY PROVIDE RELIEF (MINUTES)?

☐☐☐

WOULD YOU WISH TO CONTINUE USING THE SPRAY?

☐ Yes

☐ No

PLEASE GIVE REASON: _____

_____

REASON FOR WITHDRAWAL (IF APPROPRIATE)

_____

_____

___/___/___/
Day Mth Year

_____
Investigator signature

DAY 14

DAY ADMINISTRATION

DOSE ☐ SELF ☐

DRY MOUTH DURING DAY

No Mild Moderate Severe

0 1 2 3 ☐☐☐

DRY MOUTH AT NIGHT

No Mild Moderate Severe

0 1 2 3 ☐☐☐

SORE MOUTH

No Mild Moderate Severe

0 1 2 3 ☐☐☐

BAD / ALTERED TASTE

No Mild Moderate Severe

0 1 2 3 ☐☐☐

DIFFICULTY TALKING

No Mild Moderate Severe

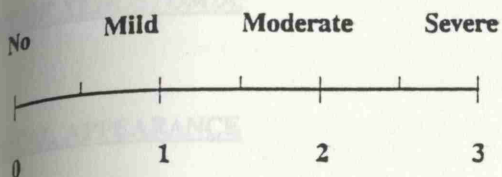
0 1 2 3 ☐☐☐

DIFFICULTY EATING

No Mild Moderate Severe

0 1 2 3 ☐☐☐

DENTURE PROBLEMS



☐ ☐ ☐

Patient No.: ☐☐☐☐

...MENT OF XEROSTOMIA:

...CLINICAL APPEARANCE

Absent Mild Moderate Severe

0 1 2 3

☐☐☐

...VOLUME OF SALIVA FROM SALIVETTE (µL)

☐☐☐☐

...EXAMINATION

Score	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8

Overall plaque score: _____

...ES

	GOOD	ACCEPTABLE	POOR	VERY POOR
...RE FIT				
...RE ...LINESS				

☐ _____

☐ _____

glossitis ☐ _____

☐ _____

stomatitis ☐ _____

cheilitis ☐ R _____

☐ L _____

☐ _____

IOLOGICAL SPECIMENS

☐

☐

PATIENT ASSESSMENT (2)

FOR HOW LONG DOES A SPRAY PROVIDE RELIEF (MINUTES)?

☐☐☐

WOULD YOU WISH TO CONTINUE USING THE SPRAY?

☐

☐

PLEASE GIVE REASON: _____

_____

REASON FOR WITHDRAWAL (IF APPROPRIATE)

_____

_____

ys collected by investigator ☐

returned sprays : _____

__/__/__/ _____

ay Mth Year Investigator signature

APPENDIX II

PATIENT CONSENT FORM

Patient No.: |_|_|_|_|

ARGYLL & CLYDE HEALTH BOARD
RENFREW GENERAL ACUTE UNIT ETHICAL COMMITTEE
FORM OF CONSENT FOR PATIENT VOLUNTEERS IN CLINICAL RESEARCH PROJECT

...ITLE OF PROJECT: Clinical trial of Saliva Orthana spray in hospice patients.

...TS SUMMARY (Purpose of study, nature of procedure, discomfort and possible risks in terms which the patient ...eer can understand)

...ients who are being cared for in a hospice complain of dryness of the mouth. Frequently this is a result of the ...ich are prescribed as part of their treatment. We are, therefore, investigating the effectiveness of two mouth sprays ...ing mouth dryness. One may be more effective than the other and some patients may derive no benefit from either.

...ree to participate you will be allocated a spray for your personal use. You may use it yourself, or ask a nurse to ...r you. The spray may be used as often as you wish, but should be used at least twice a day. You will be visited ...ist on three occasions to see how effective you are finding the spray and she will also quickly examine your mouth. ...o risk or pain associated with taking part and you are free to withdraw at any time.

APPENDIX III

INFORMATION SHEET FOR NURSING STAFF

...NT

_____ of _____

...nsent to the research procedures described above, the nature, purpose and possible consequences of which have ...ribed to me by

_____ Date_____

_____

APPENDIX III

INFORMATION SHEET FOR NURSING STAFF

CLINICAL TRIAL OF SALIVA ORTHANA SPRAY
ACCORD HOSPICE, PAISLEY

NOTES FOR NURSING STAFF

Saliva Orthana spray is a saliva substitute. In this study we are assessing its value in the care of terminally ill cancer patients, many of whom experience distressing dryness of the mouth.

One hundred patients will be enrolled and will use the spray for 2 weeks. Each patient will be allocated 6 numbered bottles of spray supplied in a box labelled with their trial number. Each set of 6 bottles is for the personal use of ONE PATIENT ONLY - patients must NOT SHARE SPRAYS. It is suggested that the name of each patient be written on their box of sprays and the box stored in the relevant bedside lockers.

If participants return home before the end of their involvement in the trial, the sprays MUST go with them to their home for continued use and Mrs Sweeney must be informed.

ALL empty bottles of spray MUST be kept after use and returned to the box for collection by Mrs Sweeney, so that we can subsequently assess the amount of spray used by each patient.

The Saliva Orthana spray is not a medicine and is entirely safe. It may be used as frequently as required and MUST be used AT LEAST TWICE DAILY to conform to the trial protocol. When the mouth feels dry or uncomfortable, patients are asked to use the spray. Some patients may be too unwell to spray their own mouths, in which case we would ask the nursing staff to assist. Denture wearers may find it helpful if their dentures are sprayed on both sides before insertion into the mouth.

We are very grateful to you for your assistance. If you run into any difficulties relating to this study the principal investigators are available as follows:

Dr Wendy Baxter	:	Accord Hospice 889 8169
Mrs M Petrina Sweeney	:	(work) 649 4545 ext 6540 (Mon, Wed, Fri) (home) 637 8188
Dr J Bagg	:	(work) 332 7020, ext 202 , page 01 (home) 334 7013

APPENDIX IV

CODING FORM AND CODING SHEET

SALIVA ORTHANA STUDY

ACCORD HOSPICE TRIAL

RESULTS

STUDY NUMBER ☐☐☐

DATE OF BIRTH ☐☐ ☐☐ ☐☐

AGE ☐☐

SEX ☐

PRIMARY TUMOUR (TYPE) ☐☐

PRIMARY TUMOUR (SITE) ☐☐

SMOKING HISTORY ☐

✦ *PREVIOUS TREATMENT*

SURGERY ☐

RADIOTHERAPY ☐

CHEMOTHERAPY ☐

✦ *CURRENT DRUG TREATMENT*

PARENTERAL MORPHINE/DIAMORPHINE ☐

ORAL OPIOID ☐

CORTICOSTEROID ☐

H_2 RECEPTOR ANTAGONIST ☐

DIURETIC ☐

PHENOTHIAZINE ☐

TRICYCLIC ANTIDEPRESSANT ☐

BENZODIAZEPINE ☐

NON-STEROIDAL ANTI-INFLAMMATORY ☐

CYCLIZINE ☐

HALOPERIDOL ☐

LAXATIVE ☐

OTHER ☐

IF YES, OTHER DRUGS: ☐

☐

☐

☐

☐

☐

✦ *BASIC ASSESSMENT*

PLACE OF VISIT ☐

SYMPTOMS

DRY MOUTH DURING DAY ☐.☐

DRY MOUTH AT NIGHT ☐.☐

SORE MOUTH ---------- ☐.☐

BAD/ALTERED TASTE ---------- ☐.☐

DIFFICULTY TALKING ---------- ☐.☐

DIFFICULTY EATING ---------- ☐.☐

DENTURE PROBLEMS ---------- ☐.☐

✦ *ASSESSMENT OF XEROSTOMIA*

CLINICAL APPEARANCE ---------- ☐.☐

SALIVETTE VOLUME ---------- ☐ ☐ ☐ ☐

✦ *CLINICAL ASSESSMENT*

DENTAL STATUS ---------- ☐

NO. OF TEETH PRESENT ---------- ☐ ☐

MEAN PLAQUE SCORE ---------- ☐.☐

NO. OF CARIOUS LESIONS ---------- ☐ ☐

✦ *DENTURE STATUS*

UPPER DENTURE TYPE ---------- ☐

UPPER DENTURE WORN ---------- ☐

LOWER DENTURE TYPE ---------- ☐

LOWER DENTURE WORN ---------- ☐

UPPER DENTURE FIT ---------- ☐

LOWER DENTURE FIT ☐

UPPER DENTURE CLEANLINESS ☐

LOWER DENTURE CLEANLINESS ☐

✦ *ORAL MUCOSA*

NO ABNORMALITIES ☐

ERYTHEMA ☐

VESICLES ☐

EROSIONS ☐

PLAQUES ☐

ATROPHIC GLOSSITIS ☐

THRUSH ☐

DENTURE STOMATITIS ☐

ANGULAR CHEILITIS ☐

OTHER ☐

IF YES, QUALIFY ☐

☐

✦ *MICROBIOLOGY*

ICT TONGUE

SPECIMEN COLLECTED ☐

YEAST 1 ☐ ☐

YEAST 2 ☐ ☐

YEAST 3 ☐ ☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐ ☐

COLIFORM 3 ☐ ☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

ICT PALATE

SPECIMEN COLLECTED ☐

YEAST 1 ☐ ☐

YEAST 2 ☐ ☐

YEAST 3 ☐ ☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐☐

COLIFORM 3 ☐☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

ICT DENTURE

SPECIMEN COLLECTED ☐

YEAST 1 ☐☐

YEAST 2 ☐☐

YEAST 3 ☐☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐☐

COLIFORM 2 ☐☐

COLIFORM 3 ☐☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

HERPES SIMPLEX VIRUS ISOLATED ---------- ☐

DAY 7

PATIENT AVAILABLE FOR EXAMINATION ---------- ☐

PLACE OF VISIT ---------- ☐

SPRAY ADMINISTRATION ---------- ☐

SYMPTOMS

DRY MOUTH DURING DAY ---------- ☐☐.☐

DRY MOUTH AT NIGHT ---------- ☐☐.☐

SORE MOUTH ---------- ☐☐.☐

BAD/ALTERED TASTE ---------- ☐☐.☐

DIFFICULTY TALKING ---------- ☐☐.☐

DIFFICULTY EATING ---------- ☐☐.☐

DENTURE PROBLEMS ---------- ☐☐.☐

ASSESSMENT OF XEROSTOMIA

CLINICAL APPEARANCE ---------- ☐ . ☐

VOLUME OF SALIVA FROM SALIVETTE ---------- ☐☐☐☐

ORAL EXAMINATION

MEAN PLAQUE SCORE ---------- ☐ . ☐

DENTURE STATUS

UPPER DENTURE FIT ☐

LOWER DENTURE FIT ☐

UPPER DENTURE CLEANLINESS ☐

LOWER DENTURE CLEANLINESS ☐

UPPER DENTURE WORN ☐

LOWER DENTURE WORN ☐

ORAL MUCOSA

NO ABNORMALITIES ☐

ERYTHEMA ☐

VESICLES ☐

EROSIONS ☐

PLAQUES ☐

ATROPHIC GLOSSITIS ☐

THRUSH ☐

DENTURE STOMATITIS ☐

ANGULAR CHEILITIS ☐

OTHERS ☐

IF YES, QUALIFY ☐

☐

MICROBIOLOGICAL SPECIMENS

ICT TONGUE

SPECIMEN COLLECTED ☐

YEAST 1 ☐☐

YEAST 2 ☐☐

YEAST 3 ☐☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐☐

COLIFORM 2 ☐☐

COLIFORM 3 ☐☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

ICT PALATE

SPECIMEN COLLECTED ☐

YEAST 1 ☐☐

YEAST 2 ☐☐

YEAST 3 ☐☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐ ☐

COLIFORM 3 ☐ ☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

ICT DENTURE

SPECIMEN COLLECTED ☐

YEAST 1 ☐ ☐

YEAST 2 ☐ ☐

YEAST 3 ☐ ☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐ ☐

COLIFORM 3 ☐ ☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

HERPES SIMPLEX VIRUS ISOLATED ☐

PATIENT ASSESSMENT (1)

LENGTH OF TIME SPRAY PROVIDES RELIEF ☐ ☐ ☐

WISH TO CONTINUE WITH SPRAY ☐

WITHDRAWN ☐

REASON FOR WITHDRAWAL ☐

DAY 14

PATIENT AVAILABLE FOR EXAMINATION ☐

PLACE OF VISIT ☐

SPRAY ADMINISTRATION ☐

SYMPTOMS

DRY MOUTH DURING DAY ☐☐.☐

DRY MOUTH AT NIGHT ☐☐.☐

SORE MOUTH ☐☐.☐

BAD/ALTERED TASTE ☐☐.☐

DIFFICULTY TALKING ☐☐.☐

DIFFICULTY EATING ☐☐.☐

DENTURE PROBLEMS ☐☐.☐

ASSESSMENT OF XEROSTOMIA

CLINICAL APPEARANCE ☐.☐

VOLUME OF SALIVA FROM SALIVETTE ☐☐☐☐

ORAL EXAMINATION

MEAN PLAQUE SCORE ☐.☐

DENTURE STATUS

UPPER DENTURE FIT ☐

LOWER DENTURE FIT ☐

UPPER DENTURE CLEANLINESS ☐

LOWER DENTURE CLEANLINESS ☐

UPPER DENTURE WORN ☐

LOWER DENTURE WORN ☐

ORAL MUCOSA

NO ABNORMALITIES ☐

ERYTHEMA ☐

VESICLES ☐

EROSIONS ☐

PLAQUES ☐

ATROPHIC GLOSSITIS ☐

THRUSH ☐

DENTURE STOMATITIS ☐

ANGULAR CHEILITIS ☐

OTHERS ☐

IF YES, QUALIFY ☐

MICROBIOLOGICAL SPECIMENS

ICT TONGUE

SPECIMEN COLLECTED ☐

YEAST 1 ☐ ☐

YEAST 2 ☐ ☐

YEAST 3 ☐ ☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐ ☐

COLIFORM 3 ☐ ☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

ICT PALATE

SPECIMEN COLLECTED ☐

YEAST 1 ☐ ☐

YEAST 2 ☐ ☐

YEAST 3 ☐ ☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐ ☐

COLIFORM 3 ☐ ☐

COLIFORM COUNT 1 ☐

COLIFORM COUNT 2 ☐

COLIFORM COUNT 3 ☐

STAPHYLOCOCCUS AUREUS COUNT ☐

ICT DENTURE

SPECIMEN COLLECTED ☐

YEAST 1 ☐ ☐

YEAST 2 ☐ ☐

YEAST 3 ☐ ☐

YEAST COUNT 1 ☐

YEAST COUNT 2 ☐

YEAST COUNT 3 ☐

COLIFORM 1 ☐ ☐

COLIFORM 2 ☐ ☐

COLIFORM 3 ---------- ☐ ☐

COLIFORM COUNT 1 ---------- ☐

COLIFORM COUNT 2 ---------- ☐

COLIFORM COUNT 3 ---------- ☐

STAPHYLOCOCCUS AUREUS COUNT ---------- ☐

HERPES SIMPLEX VIRUS ISOLATED ---------- ☐

PATIENT ASSESSMENT (2)

LENGTH OF TIME SPRAY PROVIDES RELIEF ---------- ☐ ☐ ☐

WISH TO CONTINUE WITH SPRAY ---------- ☐

WITHDRAWN ---------- ☐

REASON FOR WITHDRAWAL ---------- ☐

USED SPRAYS COLLECTED ---------- ☐

WEIGHT OF RETURNED SPRAYS..... ☐ ☐ ☐.☐

SALIVA ORTHANA STUDY - CODING SHEET

MISSING VALUES — Blank = not applicable; 9 = not done/not known

PATIENT NO. — As charted

DATE OF BIRTH — As charted

AGE — Years

SEX — 1 = M; 2 = F

PRIMARY TUMOUR (TYPE)

1 = Carcinoma
2 = Adeno carcinoma
3 = Lymphoma
4 = Melanoma
5 = Mesothelioma
6 = Angiomeiolyoma
7 = Motor neurone disease
8 = Oligodendroglioma
10 = Osteogenic sarcoma
11 = Merkel cell tumour

PRIMARY TUMOUR (SITE)

1 = Bladder
2 = Lung
3 = Prostate
4 = Kidney
5 = Breast
6 = Ovary
7 = Colon
8 = Pancreas
10 = Rectum
11 = Oral
12 = Mediastinum
13 = Brain
14 = Femur
15 = Cervix
16 = Skin
17 = Stomach

SMOKING HISTORY

0 = Non-smoker
1 = Ex-smoker
2 = Regular smoker

PREVIOUS TREATMENTS

SURGERY — 1 = Yes; 0 = No
RADIOTHERAPY — 1 = Yes; 0 = No
CHEMOTHERAPY — 1 = Yes; 0 = No

CURRENT DRUG TREATMENT

PARENTERAL MORPHINE/DIAMORPHINE — 1 = Yes; 0 = No
ORAL OPIOID — 1 = Yes; 0 = No
CORTICOSTEROID — 1 = Yes; 0 = No

H_2 RECEPTOR ANTAGONIST	1 = Yes; 0 = No
DIURETIC	1 = Yes; 0 = No
PHENOTHIAZINE	1 = Yes; 0 = No
TRICYCLIC ANTIDEPRESSANT	1 = Yes; 0 = No
NON-STEROIDAL ANTI-INFLAMMATORY	1 = Yes; 0 = No
CYCLIZINE	1 = Yes; 0 = No
HALOPERIDOL	1 = Yes; 0 = No
LAXATIVE	1 = Yes; 0 = No
OTHER:	1 = Yes; 0 = No

1 = Baclofen
2 = Fluoxetine
3 = Coproxamol
4 = Tryptizol (Amitryptilline)
5 = Fluconazole
6 = Antiemetic
7 = Ditropan
8 = Merbentyl
10 = Current chemotherapy
11 = Danazol
12 = ACE inhibitor
13 = Quinine sulphate
14 = Benzodiazepines
15 = Oral hypoglycaemic agent
16 = Ca^{2+} channel blocker
17 = Zimovane
18 = Epanutin
19 = Mianserin
20 = Loperamide
21 = Atarax

BASIC ASSESSMENT

PLACE OF VISIT

1 = Bedded Unit
2 = Day Unit
3 = Home

SYMPTOMS

DRY MOUTH DURING DAY	Length (cm)
DRY MOUTH AT NIGHT	Length (cm)
SORE MOUTH	Length (cm)
BAD/ALTERED TASTE	Length (cm)
DIFFICULTY TALKING	Length (cm)
DIFFICULTY EATING	Length (cm)
DENTURE PROBLEMS	Length (cm)

ASSESSMENT OF XEROSTOMIA

CLINICAL APPEARANCE	Length (cm)
SALIVETTE VOLUME	No of μL

CLINICAL ASSESSMENT

DENTAL STATUS	0 = Dentate 1 = Dentate and dentures 2 = Edentulous
NO. OF TEETH PRESENT	As charted
MEAN PLAQUE SCORE	As calculated
NO. OF CARIOUS LESIONS	As charted
UPPER DENTURE TYPE	0 = None 1 = Partial 2 = Full
UPPER DENTURE WORN	1 = Yes; 0 = No
LOWER DENTURE TYPE	0 = None 1 = Partial 2 = Full
LOWER DENTURE WORN	1 = Yes; 0 = No
UPPER DENTURE FIT	4 = Good 3 = Acceptable 2 = Poor 1 = Very poor
LOWER DENTURE FIT	4 = Good 3 = Acceptable 2 = Poor 1 = Very poor
DENTURE CLEANLINESS - UPPER	4 = Good 3 = Acceptable 2 = Poor 1 = Very poor
DENTURE CLEANLINESS - LOWER	4 = Good 3 = Acceptable 2 = Poor 1 = Very poor

ORAL MUCOSA

NO ABNORMALITIES	1 = Yes; 0 = No
ERYTHEMA	1 = Yes; 0 = No
VESICLES	1 = Yes; 0 = No
EROSIONS	1 = Yes; 0 = No
PLAQUES	1 = Yes; 0 = No
ATROPHIC GLOSSITIS	1 = Yes; 0 = No

THRUSH 1 = Yes; 0 = No

DENTURE STOMATITIS 1 = Yes; 0 = No

ANGULAR CHEILITIS 1 = Yes; 0 = No

OTHERS 1 = Yes; 0 = No

1 = Lichen planus
2 = Oral ulcers
3 = Herpetic stomatitis
4 = Hairy tongue
5 = Coated tongue
6 = Geographic tongue
7 = Denture induced hyperplasia
8 = Papillary hyperplasia
10 = Cold sore
11 = Frictional keratosis

MICROBIOLOGICAL CODING

SPECIMEN COLLECTED 1 = Yes; 0 = No

COLONY COUNTS

1 = Scanty (1-5 colonies)
2 = Light (6-15 colonies)
3 = Moderate (> 15 but countable)
4 = Heavy (semi-confluent)
5 = V. heavy (confluent)

YEAST IDENTIFICATIONS

1 = *Candida albicans*
2 = *Candida tropicalis*
3 = *Candida glabrata*
4 = *Saccharomyces cerevisiae*
5 = *Candida guilliermondii*
6 = *Candida parapsilosis*
7 = *Candida krusei*

COLIFORM IDENTIFICATIONS

1 = *Enterobacter aerogenes*
2 = *Enterobacter cloacae*
3 = *Klebsiella pneumoniae*
4 = *Serratia forticola*
5 = *Acinetobacter calcoaceticus*
6 = *Escherichia coli*
7 = *Proteus mirabilis*
8 = *Pseudomonas maltophilia*
10 = *Hafnia alvei*
11 = *Citrobacter spp*
12 = *Enterobacter agglomerans*
13 = *Klebsiella oxytoca*

HERPES SIMPLEX VIRUS

1 = Positive
0 = Negative

DAY 7

PATIENT AVAILABLE FOR EXAMINATION	1 = Yes; 0 = No
PLACE OF VISIT	1 = Bedded Unit 2 = Day Unit 3 = Home
SPRAY ADMINISTRATION	1 = Nurse 2 = Self 3 = Both

SYMPTOMS

DRY MOUTH DURING DAY	Length (cm)
DRY MOUTH AT NIGHT	Length (cm)
SORE MOUTH	Length (cm)
BAD/ALTERED TASTE	Length (cm)
DIFFICULTY TALKING	Length (cm)
DIFFICULTY EATING	Length (cm)
DENTURE PROBLEMS	Length (cm)

ASSESSMENT OF XEROSTOMIA

CLINICAL APPEARANCE	Length (cm)
VOLUME OF SALIVA FROM SALIVETTE	No of μL

ORAL EXAMINATION

MEAN PLAQUE SCORE	As calculated

DENTURES

UPPER DENTURE FIT	4 = Good 3 = Acceptable 2 = Poor 1 = Very poor
LOWER DENTURE FIT	4 = Good 3 = Acceptable 2 = Poor 1 = Very poor

DENTURE CLEANLINESS - UPPER

4 = Good
3 = Acceptable
2 = Poor
1 = Very poor

DENTURE CLEANLINESS - LOWER

4 = Good
3 = Acceptable
2 = Poor
1 = Very poor

UPPER DENTURE WORN

1 = Yes
0 = No

LOWER DENTURE WORN

1 = Yes
0 = No

ORAL MUCOSA

NO ABNORMALITIES — 1 = Yes; 0 = No

ERYTHEMA — 1 = Yes; 0 = No

VESICLES — 1 = Yes; 0 = No

EROSIONS — 1 = Yes; 0 = No

PLAQUES — 1 = Yes; 0 = No

ATROPHIC GLOSSITIS — 1 = Yes; 0 = No

THRUSH — 1 = Yes; 0 = No

DENTURE STOMATITIS — 1 = Yes; 0 = No

ANGULAR CHEILITIS — 1 = Yes; 0 = No

OTHERS — 1 = Yes; 0 = No

1 = Lichen planus
2 = Oral ulcers
3 = Herpetic stomatitis
4 = Hairy tongue
5 = Coated tongue
6 = Geographic tongue
7 = Denture induced hyperplasia
8 = Papillary hyperplasia
10 = Cold sore
11 = Frictional keratosis

MICROBIOLOGICAL SPECIMENS

SPECIMEN COLLECTED — 1 = Yes; 0 = No

COLONY COUNTS

1 = Scanty (1-5 colonies)
2 = Light (6-15 colonies)
3 = Moderate (> 15 but countable)
4 = Heavy (semi-confluent)
5 = V. heavy (confluent)

YEAST IDENTIFICATIONS

1 = *C. albicans*
2 = *C. tropicalis*
3 = *C. glabrata*
4 = *S. cerevisiae*
5 = *C. guilliermondii*
6 = *C. parapsilosis*
7 = *C. krusei*

COLIFORM IDENTIFICATIONS

1 = *Enterobacter aerogenes*
2 = *Enterobacter cloacae*
3 = *Klebsiella pneumoniae*
4 = *Serratia forticola*
5 = *Acinetobacter calcoaceticus*
6 = *Escherichia coli*
7 = *Proteus mirabilis*
8 = *Pseudomonas maltophilia*
10 = *Hafnia alvei*
11 = *Citrobacter spp*
12 = *Enterobacter agglomerans*
13 = *Klebsiella oxytoca*

HERPES SIMPLEX VIRUS

1 = Positive
0 = Negative

PATIENT ASSESSMENT (1)

SPRAY RELIEF - HOW LONG — As charted; minutes

WOULD YOU CONTINUE WITH SPRAY — 1 = Yes; 0 = No

WITHDRAWN — 1 = Yes; 0 = No

REASON FOR WITHDRAWAL

1 = Death
2 = Confusion
3 = Too unwell
4 = Possible allergic response to spray
5 = Believed spray caused mucosal trauma (denture related)
6 = Disliked spray
7 = Believed spray was causing a sore throat

DAY 14

PATIENT AVAILABLE FOR EXAMINATION 1 = Yes; 0 = No

PLACE OF VISIT

1 = Bedded Unit
2 = Day Unit
3 = Home
4 = Hospital

SPRAY ADMINISTRATION

1 = Nurse
2 = Self
3 = Both

SYMPTOMS

DRY MOUTH DURING DAY Length (cm)

DRY MOUTH AT NIGHT Length (cm)

SORE MOUTH Length (cm)

BAD/ALTERED TASTE Length (cm)

DIFFICULTY TALKING Length (cm)

DIFFICULTY EATING Length (cm)

DENTURE PROBLEMS Length (cm)

ASSESSMENT OF XEROSTOMIA

CLINICAL APPEARANCE Length (cm)

VOLUME OF SALIVA FROM SALIVETTE No of μL

ORAL EXAMINATION

MEAN PLAQUE SCORE As calculated

DENTURES

UPPER DENTURE FIT

4 = Good
3 = Acceptable
2 = Poor
1 = Very poor

LOWER DENTURE FIT

4 = Good
3 = Acceptable
2 = Poor
1 = Very poor

DENTURE CLEANLINESS - UPPER

4 = Good
3 = Acceptable
2 = Poor
1 = Very poor

DENTURE CLEANLINESS - LOWER

4 = Good
3 = Acceptable
2 = Poor
1 = Very poor

UPPER DENTURE WORN

1 = Yes
0 = No

LOWER DENTURE WORN

1 = Yes
0 = No

ORAL MUCOSA

NO ABNORMALITIES — 1 = Yes; 0 = No

ERYTHEMA — 1 = Yes; 0 = No

VESICLES — 1 = Yes; 0 = No

EROSIONS — 1 = Yes; 0 = No

PLAQUES — 1 = Yes; 0 = No

ATROPHIC GLOSSITIS — 1 = Yes; 0 = No

THRUSH — 1 = Yes; 0 = No

DENTURE STOMATITIS — 1 = Yes; 0 = No

ANGULAR CHEILITIS — 1 = Yes; 0 = No

OTHERS — 1 = Yes; 0 = No

1 = Lichen planus
2 = Oral ulcers
3 = Herpetic stomatitis
4 = Hairy tongue
5 = Coated tongue
6 = Geographic tongue
10 = Cold sore
11 = Frictional keratosis

7 = Denture induced hyperplasia
8 = Papillary hyperplasia

MICROBIOLOGICAL SPECIMENS

SPECIMEN COLLECTED — 1 = Yes; 0 = No

COLONY COUNTS

1 = Scanty (1-5 colonies)
2 = Light (6-15 colonies)
3 = Moderate (> 15 but countable)
4 = Heavy (semi-confluent)
5 = V. heavy (confluent)

YEAST IDENTIFICATIONS

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COLIFORM IDENTIFICATIONS

1 = *Enterobacter aerogenes*
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5 = *Acinetobacter calcoaceticus*
6 = *Escherichia coli*
7 = *Proteus mirabilis*
8 = *Pseudomonas maltophilia*
10 = *Hafnia alvei*
11 = *Citrobacter spp*
12 = *Enterobacter agglomerans*
13 = *Klebsiella oxytoca*

HERPES SIMPLEX VIRUS

1 = Positive
0 = Negative

PATIENT ASSESSMENT (2)

SPRAY RELIEF - HOW LONG — As charted; minutes

WOULD YOU CONTINUE WITH SPRAY — 1 = Yes; 0 = No

WITHDRAWN — 1 = Yes; 0 = No

REASON FOR WITHDRAWAL

1 = Death
2 = Confusion
3 = Too unwell
4 = Possible allergic response to spray
5 = Believed spray caused mucosal trauma (denture related)
6 = Disliked spray
7 = Believed spray was causing a sore throat

USED SPRAYS COLLECTED — 1 = Yes; 0 = No

WEIGHT OF RETURNED SPRAYS — Weight in grams

APPENDIX V

VIRAL GROWTH AND MAINTENANCE MEDIA

GROWTH MEDIUM

Eagle's Minimal Essential Medium with Glutamax-1 and Earle's salts	88 ml
Foetal bovine serum	10 ml
Penicillin / streptomycin mixture	1 ml
MEM amino acids	1 ml

MAINTENANCE MEDIUM

Eagle's Minimal Essential Medium with Glutamax-1 and Earle's salts	96 ml
Foetal bovine serum	1 ml
Penicillin / streptomycin mixture	1 ml
MEM amino acids	1 ml