The angle formed by the submandibular duct as it turns in an inferior direction at the posterior border of the mylohyoid muscle is commonly $90^\circ$ or greater. Inferior to the angle of the duct a slight narrowing in the duct lumen may occur. Also a secondary duct is sometimes observed joining the main duct below its angle. This secondary duct drains the portion of the submandibular gland above the mylohyoid muscle\textsuperscript{134} (vide supra: Gross anatomy of the salivary glands, p. 5).

**Intraglandular duct pattern**

Second order ducts in the submandibular gland are generally larger in diameter and shorter in length than second order ducts in the parotid gland. The secondary ducts of the submandibular gland often appear to end abruptly, with third order ducts being ill-defined or even absent\textsuperscript{125,134} [see Fig. 18 (A) to (C)].

The submandibular sialogram may show little or no duct pattern, instead a "soft" lobulated effect called acinar clouding is produced [see Fig. 18 (D) to (F)].

Some of the above variations in the normal sialographic appearance of the parotid and submandibular glands is due to the use of a fixed quantity of contrast medium. Small glands may be overfilled and larger glands underfilled if a fixed amount of contrast medium is used during sialography (vide supra: The quantity of contrast medium used, p. 86).

Present sialographic techniques do not fill every salivary gland to the same degree with contrast medium. Therefore, the descriptions of underfilled and overfilled glands are of practical value.
Fig. 18. Types of intraglandular pattern seen in lateral oblique projection of submaxillary sialogram.

ACINAR CLOUDING

Contrast medium filling the acini of the salivary gland produces a "cloud-like" opacity of the gland on a sialogram. This opacity is referred to as "acinar clouding". Acinar clouding occurs frequently when water soluble contrast media are used for sialography. This appearance is expected when using soluble contrast media as these media are absorbed by the salivary gland following injection (vide supra: Contrast media in sialography, p. 89). Acinar clouding on sialograms of salivary glands which contain fat soluble contrast media is probably due to overfilling of the gland.

Ollerenshaw and Rose (1951) stated that acinar clouding is a normal finding on a sialogram. The absence of the clouding effect indicates incomplete filling of the gland. Incomplete filling may result from an inadequate quantity of contrast medium or from debris such as pus or desquamated epithelial cells preventing complete filling of the acini. Rankow and Polayes (1976) concluded that acinar clouding is not significant since its presence depends upon the pressure used to inject the contrast medium, the type of contrast medium used, the structure of the gland, and the existence of pathosis in the gland under examination. The submandibular gland shows acinar clouding more often than the parotid gland. The wider ducts of the submandibular gland probably render the submandibular acini more accessible to the contrast medium.

Deliberate overfilling of a salivary gland with contrast medium may aid the determination of the intraglandular or extraglandular position of a suspected lesion. Calculi can also be better defined by deliberate production of acinar clouding. It is recommended that if acinar clouding is desired then water soluble contrast media are used for sialography. Overfilling of a gland with a fat soluble
medium may result in retention of some of the medium with harmful effects (vide supra: Fat soluble contrast media, p. 90).

ULTRASOUND AND RADIOISOTOPES IN THE DIAGNOSIS OF SALIVARY GLAND DISORDERS

The use and interpretation of ultrasound and radioisotopes is highly specialized and only basic concepts are reviewed.

ULTRASOUND

Ultrasonic diagnostic equipment consists of a transducer which converts electrical energy into mechanical vibrations called ultrasound. When transmitted into a patient's tissues the ultrasound is reflected back to the transducer with acoustic changes that are characteristic for the tissues reflecting the sound. The reflected sound is received by a signal processor linked to a recorder. The recorder produces a "picture" or echogram of the tissue under examination. Ultrasonic techniques used in the diagnosis of salivary gland disorders involve transmitting acoustic energy into the salivary tissue; monitoring the energy reflected by the tissues, and then recording this energy to allow interpretation.

In diseases of the major salivary glands ultrasound with its resultant echogram may be specially useful in the diagnosis of space occupying lesions.

RADIOISOTOPE SCANNING

Sialography is useful to demonstrate the salivary gland ducts whereas radioisotope scanning or scintigraphy is used to evaluate the gland parenchyma and the level of function of the gland. In the scintigraphic examination of the salivary glands the artificial
radioisotope technetium is injected intravenously in the form of technetium pertechnate. Fifteen to twenty minutes following injection of the isotope the emission of gamma radiation from the salivary glands is recorded by a scintillation camera. The resultant scintigraph can be seen on an oscilloscope and recorded on film\textsuperscript{145,146}. The most significant limitation of scintigraphy is its failure to evaluate tumours less than 1 to 2 cm in size\textsuperscript{125}.

Space occupying lesions are designated "hot", "warm" or "cold" lesions depending on their uptake of radioisotope. Warthin's tumour is the only salivary tumour which shows consistently as a "hot" lesion due to a high uptake of radioisotope. Carcinomas and cysts appear as cold lesions with low uptake of radioisotope. These lesions probably appear cold because they almost completely replace normal parenchymal cells. Mixed tumours vary in their scintigraphic appearance depending upon histological composition. Most mixed tumours appear as "warm" lesions with an isotope uptake similar to that of normal gland tissue. Acute staphylococcal parotitis and the early stage of mumps show increased isotope uptake because of hyperaemia and oedema within the affected glands. In the late stage of mumps epithelial necrosis and lymphocytic infiltration of the interstitial tissue reduces isotope uptake. In chronic recurrent parotitis the affected gland has a generalized decrease in isotope uptake\textsuperscript{125}.

Hausler, N'Guyen, Ritschard and Montandon (1977)\textsuperscript{146} described a scintigraphic method for use in the differential diagnosis of xerostomia. This method compares the uptake of pertechnate by the salivary glands with the uptake of pertechnate by a standard reference area in the neck. The measurements taken of these two areas allow an index of salivary gland activity to be formulated. In Sjögren's syndrome the loss of functioning salivary parenchymal cells is shown
by a reduced index of gland activity. Sialosis occurring in hormonal and metabolic disorders as well as sialosis associated with the use of drugs result in an increased index of gland activity with this method of scintigraphy.
DECREASED SALIVARY FLOW

11. CONDITIONS IN WHICH XEROSTOMIA MAY BE A SYMPTOM

PHYSIOLOGICAL DECREASE IN SALIVARY FLOW DURING SLEEP AND MOUTHBREATHING

Most people have experienced a sensation of a dry mouth following a period of sleep. This dryness follows a marked reduction in salivary flow which occurs during sleep and during periods of darkness\(^7^3\). Schneyer, Pigman, Hanahan and Gilmore (1956)\(^1^4^7\) reported a marked decrease in the volume of saliva secreted during sleep. Kerr (1961)\(^1^4^8\) and Mandel and Wotman (1976)\(^1^4^9\) noted that at night secretion from the major salivary glands and salivary antibacterial activity virtually cease. Usually the minor salivary glands keep the mucous membrane adequately moist.

Ferguson and Port (1974)\(^1^5^0\) demonstrated a circadian rhythm for unstimulated salivary flow. Maximum flow rates occurred during the day and fell to minimum rates during the night. The lowest rates were observed at approximately 4 a.m. Dawes and Ong (1973)\(^1^5^1\) demonstrated circadian rhythms in the flow of saliva from the parotid gland. They reported that the flow of both whole saliva and parotid saliva falls during the night to a lowest value at about 4 a.m.

Central nervous system depression by depressing the autonomic nervous system is the probable cause of the reduction in salivary flow during sleep\(^1^5^2\) (vide infra: Drugs which depress the central nervous system, p. 174).

Clinical use can be made of the knowledge of reduced salivary flow during sleep. The patient who reports a dry mouth immediately on
waking but a moist mouth at other times can be reassured that this is physiological.

Patients may be advised of the value in cleaning plaque from their teeth before going to sleep. The plaque may still be producing acids following a late meal and a reduction in both salivary flow and salivary antibacterial activity leaves the teeth less protected against caries (vide supra: Saliva and the loss of tooth substance, p. 50).

The subjective sensation of a dry mouth may occur temporarily even in the presence of normal salivary gland function. People whose work requires that they speak constantly and mouthbreathers may develop a dry mouth and frequently sip water for relief\textsuperscript{152,153}. Allington (1950)\textsuperscript{153} reported a young female patient developing xerostomia. She was a telephonist who talked constantly in her job taking advertisements for a newspaper.

Mouthbreathing due to nasal obstruction or habit is a further cause of xerostomia. In children enlarged adenoids and respiratory infections most frequently cause mouthbreathing. While in adults any cause of nasal obstruction such as a deviated nasal septum, nasal polyps or hypertrophic rhinitis will force the patient to breathe through the mouth\textsuperscript{152}.

These patients may also be "snorers" who, by sleeping on their back, are prone to have the nasal airway obstructed by the soft palate. This forces them to breathe through the mouth with drying of the mucosa occurring at a time the major salivary glands are secreting very little or no saliva\textsuperscript{152}.

The typical Angle's Class II division I malocclusion patient with protruding upper incisors and weak or incompetent lip seal is also often a mouthbreather. Treatment and correction of the malocclusion and lip seal will often stimulate normal breathing and
resolve the dry mouth\textsuperscript{154}.

Irrespective of the cause of nasal obstruction, the result is a dry mouth and often a gingival hyperplasia on the labial aspect of the upper anterior teeth\textsuperscript{152}.

Once it has been determined if the patient does breathe through the mouth or not, treatment can be planned. The services of an E.N.T. surgeon or an orthodontist may be required. Habitual mouth-breathing may be overcome by constructing an oral screen from acrylic or a soft plastic mouthguard to make breathing, other than through the nose, difficult.
PSYCHOGENIC FACTORS AND REDUCED SALIVARY FLOW

The reduction in salivary flow in response to fear, anxiety and depression has been mentioned previously (vide supra: The variability in the flow rate of saliva, p. 72). Bates and Adams (1968) reported a reduction in the stimulated flow of saliva in students thirty minutes prior to sitting for examinations. The psychic response to nervous tension is probably a decrease in the efferent stimuli to salivary glands (vide supra: The efferent pathway from salivary centres, p. 25). Morris (1967) considered that the dry mouth accompanying fear was caused by central inhibition of parasympathetic secretomotor activity. Some people respond to any emotion, including fear, with a decrease in salivary secretion. In other people the response to fear may be an increased salivary flow.

Bogdanoff, Bogdanoff and Wolf (1961) studied the effect of stress on the secretion of saliva from the parotid gland. Stress was induced in dental patients by bringing a rotating dental drill up to their mouths. They found that patients rated as aggressive on psychometric scales showed increased salivary flow. Those patients rated as defensive showed decreased salivary flow rates. One subject with an unaltered salivary flow reported that the dental drill was not unpleasant.

Brown (1970) reviewed the literature on salivary output in psychopathologic states. Manic depressives, early schizophrenics and the endogenously depressed were shown to have salivary flow rates which were significantly reduced. The low salivary flow in these conditions was attributed to hypofunction of the autonomic nervous system causing a reduction in neural stimulation of the salivary glands. Other symptoms related to hypofunction of the autonomic nervous system such as sexual impotence, decreased sexual desire in
females and constipation\textsuperscript{157} are associated with depressed states. Strongin and Hinsie's (1938)\textsuperscript{158} early study showed that in the depressed phase, manic-depressive patients secrete much less parotid saliva than do normal subjects. The pH of this saliva was low correlating with the increase in the concentration of hydrogen ions as the flow rate of saliva decreases (vide supra: Hydrogen ions, p.41). The secretion of saliva in manic-depressive patients in the manic phase was little different to the salivary flow in normal individuals.

Busfield, Wechsler and Barnum (1961)\textsuperscript{159} reported that the flow of whole saliva is abnormally low in endogenous depressives and manic-depressives. Exogenous depressive patients do not show a reduced salivary flow. No significant difference in salivary flow was seen between mild, moderate and severely endogenous depressed patients. Davies and Gurland (1961)\textsuperscript{160} concluded that the rate of flow of whole saliva in schizophrenics is significantly less than the flow in normal subjects under resting conditions. Busfield and Wechsler (1961)\textsuperscript{161} reported that schizophrenic patients secrete more whole saliva than depressed patients but less saliva than normal patients.

Brown (1970)\textsuperscript{115} stimulated salivation in depressed patients with a weak solution of citric acid. The reflex flow of saliva produced was not significantly different in quantity to the flow of saliva in normal subjects under the same conditions. This fact was presented as evidence that the inhibition of resting flow of saliva in depressive states is functional and not resulting from damage to the salivary glands.

The reduction in salivary flow in patients with depressive illness is confirmed by numerous investigations\textsuperscript{115,157,158,160}. 
However, it should be noted that in these patients subjective complaints of xerostomia are not always reflected by a measured reduction in saliva.\textsuperscript{155,159} Busfield and Wechsler (1962)\textsuperscript{161} investigated salivary flow in 68 depressed patients before and after antidepressant drug therapy. The results showed that a relatively high pre-treatment salivary flow was prognostic that treatment would be successful. They confirmed that a subjective complaint of xerostomia may not be accompanied by any obvious reduction in salivary flow. However, patients may have an average salivary flow rate but still complain of xerostomia because their "normal" flow rate is higher than the accepted average. Successful treatment of depressive illness may result in an improvement in a patient's xerostomia. During the period of reduced salivary flow special attention should be given to preventive dental care to reduce both the soft tissue trauma and the increased caries incidence accompanying xerostomia (vide infra: Effect of xerostomia on the oral tissues, p. 259, 260 and 267).
REDUCTION IN SALIVARY FLOW FOLLOWING CHANGES IN BODY FLUID AND ELECTROLYTE BALANCE

Morris (1967)\textsuperscript{155} considered a dry mouth to be a useful clinical sign of depletion of body fluids. Kerr (1961)\textsuperscript{148} stated that the level of hydration of the body is the most important factor affecting salivation. A dry mouth can be related to an excessive loss of body fluid and a loss of body fluids is related to thirst. However a dry mouth is not always coincident with thirst. In animal experiments where a dry mouth was produced by blocking the secretion of the salivary glands, the animals only drank more than normal when eating\textsuperscript{162}. Steggerda (1941)\textsuperscript{163} showed by recording the fluid intake of a man who had no major salivary glands that a dry mouth does not always result in a high fluid intake. The theory first conceived by Walter Canon (1918)\textsuperscript{164} that a dry mouth is the cause of thirst is clearly incorrect. The thirst centre in the hypothalamus is stimulated by a reduction in the volume of the intracellular fluid and not by a dry mouth. This intracellular dehydration is probably also responsible for the reduced salivary flow seen accompanying thirst\textsuperscript{162,165}.

Holmes (1964)\textsuperscript{165} suggested that the following have a role in reducing salivary flow through body fluid and electrolyte disturbances:

(a) Changes in intracellular hydration.

(b) Changes in the metabolic composition of intra- and extra-cellular fluids.

(c) Changes in blood flow through the salivary glands.

Saliva is an ultrafiltrate of plasma relying on transport of ions, principally sodium and potassium ions, for its secretion into the lumena of salivary gland acini. A nerve mediated increase of pressure in local blood vessels and an increase in osmotic pressure are also important in the production of acinar fluid (vide supra:}
Salivary fluid and electrolyte secretion, p. 30). Therefore it is probable that changes in body fluid and electrolyte balance and changes in blood flow through salivary glands will affect the production of saliva. Dehydration, haemorrhage, low cardiac output, oedema or renal failure may disturb body fluids, sufficient to cause a dry mouth.

DEHYDRATION

Dehydration is the state resulting from an abnormally low quantity of water in the body. Water can be removed from the body by evaporation from the skin or lungs, or by water loss from the gut and kidneys.

DEHYDRATION PATHWAYS

Dehydration results when the sum of water intake plus water derived from metabolism is insufficient to balance water lost from the body. Dehydration may take place in three ways:

(i) Decreased water intake. This may follow coma, psychosis, lack of available drinking water and hypodipsia.

(ii) Increased loss of water via skin, lungs, gut and kidneys. Loss of water may be seen in burns, fever with sweating, severe vomiting for example in pyloric stenosis, and severe diarrhoea such as occurs in cholera. This water loss is accompanied by loss of electrolytes, especially sodium and potassium.

(iii) Excessive excretion of urinary solutes with obligate polyuria. Loss of urinary solutes occurs in uncontrolled diabetes, Addison's disease, certain forms of chronic renal failure, sodium depletion, potassium depletion and hypercalcaemia.
Cheraskin, Ringsdorf and White (1964)\textsuperscript{169} investigated the relationship between xerostomia and carbohydrate metabolism. Their results showed that xerostomia was associated with both high and low blood glucose concentrations. Hyper- and hypoglycaemia probably decrease salivary flow by both dehydration and interference with the osmotic transfer of fluid across salivary cells and ducts. Conner, Iranpour and Mills (1970)\textsuperscript{170} reported the mean parotid flow in 30 diabetics was one-fourth the flow in 30 non-diabetic controls (\(P<0.01\)).

**SIGNS AND SYMPTOMS OF DEHYDRATION**

The anatomic changes accompanying body water depletion are usually minimal. The small quantity of free fluid normally present in the pleural, peritoneal and pericardial spaces may be absent. Excessive dryness of serosal membranes may manifest as a loss of their glistening appearance. The body tissues as a whole show slight contraction and the blood becomes more viscous (increased haematocrit value). Where dehydration is the result of water loss alone then thirst becomes intense. Where sodium loss results in dehydration abnormal thirst is not a feature. A low sodium concentration in extracellular fluid programmes the thirst centre to respond as though the body were adequately hydrated\textsuperscript{162,166} (vide infra: Dehydration and the secretion of saliva, p.114).

**Equilibrium between extracellular fluid and intracellular fluid**

Any body water loss from the extracellular fluid is followed immediately by an osmotic shift of water from the intracellular fluid (ICF) into the extracellular fluid (ECF). In this way the ECF and ICF are maintained in osmotic equilibrium\textsuperscript{171}.
DEHYDRATION AND THE SECRETION OF SALIVA

The probable cause of xerostomia in dehydrated subjects is intracellular dehydration\textsuperscript{162,165}. Dehydration of the salivary gland parenchymal cells must increase the concentration of intracellular solutes. The increased concentration of solutes increases the osmotic pressure across the acinar lumen. Secretion of the hypotonic acinar fluid must then be against an increased osmotic pressure.

In conditions such as severe vomiting, diarrhoea and profuse sweating there is a loss of electrolytes, mainly sodium, from the body. Enough body water can be lost in this way to produce a profound state of dehydration. The loss of electrolytes results in a marked fall in extracellular fluid volume. Since a loss of water from the ECF results in a loss of water from the ICF a decrease in salivary flow can be anticipated. The reduction in ECF volume stimulates the release of antidiuretic hormone (ADH) from the posterior pituitary gland. The response of the kidney to an increase in the blood level of ADH is the excretion of a decreased quantity of urine which is more concentrated\textsuperscript{162,166}.

Xerostomia in the dehydrated subject may be compounded by the secretion of ADH in response to an abnormally high concentration of the ECF following body water loss. According to Lavelle (1975)\textsuperscript{6} ADH caused an increase in the permeability of the striated ducts of the salivary glands to water. The striated ducts absorb more water than usual and a decreased quantity of a less hypo-osmotic saliva is produced.

Excess secretion of ADH may also cause xerostomia. For example, a female patient aged 57 was admitted to hospital in a coma. The patient became conscious and exhibited features of "inappropriate ADH syndrome". The patient had hypernatraemia and other signs
consistent with the syndrome such as restlessness, muscle twitching and confusion. The probable explanation for the patient's xerostomia is the effect of ADH on the striated ducts and the body fluid changes associated with hyponatraemia. The reduced sodium concentration of the ECF promotes a transfer of fluid from the ECF to the ICF to balance the osmolalities of the two fluid compartments. A continuing loss of sodium from the ECF increases the degree of intracellular hydration so the osmotic force is against the secretion of fluid from salivary acinar cells into the acinar lumen.

HAEMORRHAGE AND REDUCED SALIVARY FLOW

It has been considered that a decrease in salivary flow during periods of dehydration could be related to a reduction in blood flow to the salivary glands. Gesell (1918) measured a 90% reduction in salivary flow in animals who exhibited a decrease of less than 10% of blood volume. Gregersen and Bullock (1933) showed that subjects deprived of water for two days lost approximately 25% of their blood volume and salivary flow fell from 5 cc in five minutes to 0.7 cc in five minutes. The lower flow rate of saliva could cause dryness of the mouth in some patients.

Holmes (1964) measured the salivary flow in blood donors prior to and following a loss of between 6% and 11% of their total blood volume. His results indicated that in the majority of subjects no significant alteration in salivary flow occurs following loss of about one tenth of the total blood volume. In two subjects a marked fall in salivary flow coincided with a drop in blood pressure and significant vasoconstriction. It was suggested that a reduction in salivary flow accompanied by thirst will follow haemorrhage only when the patient has significant vasoconstriction. The reduction in
salivary flow under these conditions was attributed to a reduced flow of blood through the salivary glands.

The early concepts \(^{164,172,173}\) of a 10% loss in total blood volume causing a significant reduction in salivary flow cannot be dismissed completely. Following a 10% loss of total blood volume there is a marked increase in the blood ADH concentration. The effect of ADH, in increasing the resorption of water by the striated ducts, has been noted above. Haemorrhage causes a loss of ECF resulting in a transfer of body water from ICF to the ECF compartment \(^{162}\). The loss of water from the ICF may contribute to a reduction in salivary flow.

LOW CARDIAC OUTPUT AND OEDEMA

Thirst is a complaint of many patients who have cardiac failure with co-existing oedema \(^{162,165}\). Holmes (1964) \(^{165}\) selected three cardiac failure patients who complained of thirst. He reported that thirst was a complaint during periods of reduced salivary flow. A complex series of events follows cardiac failure and some of the following may contribute to a reduction in salivary flow:

(i) Retention of fluid by the kidney due to decreased glomerular filtration, activation of the renin-angiotensin system and increased secretion of aldosterone. The release of ADH is stimulated by angiotensin and by an increase in the concentration of sodium in the blood in response to the release of aldosterone. The result is an increase in the ECF volume \(^{168,174}\).

(ii) A reduction in the flow of blood through the salivary glands reducing the secretion of saliva.

(iii) A decrease in the quantity of nutrients reaching the salivary parenchyma due to a reduced blood flow to the salivary glands. This "cellular malnutrition" causes loss of cell potassium.
which results in intracellular dehydration\textsuperscript{162}. Holmes (1964)\textsuperscript{165} described fluid retention in a group of women where no organic cause of the oedema could be found. Some women in the group showed increased fluid intake during periods of fluid retention. A decrease in salivary flow was observed during the periods of fluid retention. A number of patients had persistently dry mouths with many of the consequences of xerostomia.

Fitzsimons (1976)\textsuperscript{168} stated that thirst in oedematous conditions results from the mechanisms controlling water intake receiving incorrect information about the state of hydration of the body. Oedema results when excess fluid intake, insufficient fluid loss or both are not corrected by an increased renal excretion of excess fluid and electrolytes.

It would appear that in patients with fluid retention the kidney retains body fluid by the same mechanisms operating during cardiac failure, where the release of ADH in response to release of angiotensin and aldosterone limits the secretion of saliva.

RENNAL FAILURE

Therapy during acute renal failure is aimed at restricting fluid intake and keeping the patient mildly dehydrated\textsuperscript{165}. The effect of dehydration is a decrease in salivary flow.

During chronic renal failure a range of metabolic disturbances occur. Some of these disturbances may result in a reduction in salivary flow\textsuperscript{165}. The derangement of kidney function in chronic renal failure will result in\textsuperscript{175}:

(i) Defective fluid volume regulation, leading to dehydration or to retention of salt and water with resultant oedema.

(ii) Loss of control of acid-base balance leading to metabolic
acidosis. The acidosis disturbs intracellular metabolism throughout the body contributing to secondary derangements in carbohydrate and protein metabolism.

(iii) Electrolyte imbalances of which hyperkalaemia and hypocalcaemia produce the most detrimental effects.

(iv) Retention of nitrogenous wastes seen as increases in blood urea nitrogen and blood creatinine levels.

The implication is that the marked changes in the ECF and ICF following renal failure disrupt salivary gland function sufficiently to cause xerostomia. Holmes (1964)\textsuperscript{165} showed that the sodium, potassium and chloride ion concentration in saliva increased markedly during renal failure. Increases in sodium and chloride ion concentration usually occur with increased not decreased salivary flow (vide supra: Inorganic constituents of saliva, p. 38 and p. 40).

The systemic changes and abnormal concentration of ions in saliva during renal failure suggest that disruption to the metabolism of the salivary glands is responsible for the reduction in salivary flow.
RADIOThERAPY - ITS EFFECT ON THE SALIVARY GLANDS

The general term 'radiation' refers to energy derived from either electromagnetic or particle radiation. Radiation which has sufficient energy to produce ions in matter, including living tissues, is called 'ionizing radiation'. Ionizing radiation causes electrically stable atoms and molecules to become electrically unstable. The effects of this instability are alterations in molecular structure and the creation of new chemicals. One example of these alterations in irradiated cells is the conversion of water to hydrogen peroxide. It is the hydrogen peroxide and not the radiation per se which causes cellular dysfunction. Thus ionizing radiation can alter the chemical composition of cellular components such as enzymes, enzyme inhibitors and hormones causing them to be partially or totally ineffective. Hence the phenomenon of ionization is believed to be the cause of cell injury and tissue change in irradiated tissue. The cell nucleus is very sensitive to the effects produced by the ionization of molecules caused by radiation and both reversible and irreversible changes occur in the cell. The results of these changes may be: delay or inhibition of mitosis, cell death before or after division, chromosome breakage and functional deficiencies in the cell.

Alpha particles (positively charged helium nuclei) and beta particles (electrons) directly ionize atoms and molecules of matter with which they collide. These particles have little penetrating power and have little use in medical therapy. Their importance is in the hazards they constitute during radiotherapy when they are produced as unwanted radiation. Uncharged neutron particles produced by the cyclotron have been used experimentally in treatment and they appear to be a promising addition to radiotherapy.
Electromagnetic radiation such as X-rays and gamma rays have sufficient energy to penetrate atoms and displace electrons from their orbits to produce ions. The displaced electrons then ionize other atoms. Radiotherapy is the therapeutic irradiation of tissues for the treatment of malignant diseases and it includes the use of ionizing radiations such as neutron particles, gamma rays and X-rays. The effect of radiotherapy depends on the type of radiation and the magnitude of the dose, the size of the area irradiated, the time over which the dose is administered and the susceptibility of the individual or the particular tissue. Radiation may cause cell death, delayed cell death, permanent cell injury or transient cell injury in both healthy and diseased tissues. Irradiation of the salivary glands during the course of radiotherapy may damage the parenchyma thus decreasing the output of saliva and causing a transient or permanent xerostomia.

RADIATION FACTORS AND THE EXTENT OF TISSUE DAMAGE

1. SOURCE AND TYPE OF RADIATION

Irradiation of the body may be applied from an external, an internal or a combined internal and external source. Teletherapy is the term used when the external source of radiation is more than a few centimeters from the tissue. Plesiotherapy is external or internal irradiation from a source which is within 2 cm of tissue being treated. External plesiotherapy utilizes moulds adapted to the tissues to be irradiated. The moulds contain radium needles as a source of radiation. Internal radiotherapy is the use of a source of radiation within the body to irradiate tissues. The source can be within tissues
or in a natural body cavity such as the maxillary sinus. The advantage of internal radiotherapy is in its ability to deliver high doses of radiation to a tumour without applying high doses to surrounding tissues. This type of radiotherapy is unlikely to damage all of the major salivary glands in a patient as its affect is limited beyond 1 or 2 cm into the surrounding tissue. Therefore xerostomia is less likely to result from internal radiotherapy than from external radiotherapy.

The most extensively used sources for external radiotherapy are:

Orthovoltage

The conventional oil-cooled cathode ray tube which produces orthovoltage radiation emits low voltage X-rays in the range of 150 kilo volts peak (kvp) to 250 kvp. The cell damage at this relatively low energy level is caused by both the photoelectric effect and the Compton effect. The photoelectric effect produces a transfer of energy from X-rays to tissues in relation to the tissue’s atomic number. Bone has almost twice the atomic number of fat or muscle, so if bone is irradiated with orthovoltage it receives approximately eight times the energy that the soft tissues receive at the same dose.

The Compton effect (scattering of free photons by free electrons with a resulting increase in the wavelength of the photons) transfers radiant energy depending on the electron density of the matter being irradiated. Since all body tissues have almost equal electron density they absorb equal amounts of energy when irradiated.

Orthovoltage radiation is useful for treating lesions that are superficial such as those on the lips or near the parotid glands. Bone metastases may be treated with orthovoltage X-rays because bone
is heavily irradiated due to the photoelectric effect.

Cobalt 60

The natural radioactive element cobalt 60 emits gamma rays and has a half-life of 5.3 years. The cobalt 60 is stored within a machine of lead or tungsten which has a variable aperture to control the size of the gamma ray beam for therapeutic use. The gamma rays emitted are photons with an average energy of approximately 1.2 million electron volts (mev). Radiant energy from 500 kev (thousand electron volts) to 8 mev is termed supervoltage and energy above this level megavoltage. Therefore radiation from cobalt 60 is in the supervoltage energy range.

The biological effect of cobalt 60 results almost entirely from the Compton effect. Thus when bone is irradiated with cobalt it is spared the over-irradiation that occurs with orthovoltage therapy. The 'bone sparing' phenomenon of super and megavoltage radiation is important when there is no need to irradiate bone during radiotherapy.

Linear accelerators

Linear accelerators are machines which utilize high frequency radiowaves to accelerate electrons to high speeds. These high energy electrons are either focused directly onto tissues or are converted to X-rays via a tungsten-copper target. These machines are capable of producing ionizing radiation of higher energy than cobalt 60 and so linear accelerators are especially useful to irradiate large fields and tumours.

The sources used more extensively for internal radiation are:
Radium needles

These straight needles contain radium and are usually 2 cm or 4.2 cm in length. Radium, which emits a gamma ray, has a half-life of 1,620 years and so there is no appreciable loss in radiation intensity from a radium needle. Depending on the quantity of radium in a needle, daily doses between 100 roentgens (r) and 1200 r (delivered dose) can be delivered to a lesion. More than one needle can be used in treatment. Radium needles are used in treating tumours of the maxillary sinus, lips, floor of mouth, buccal mucosa and the anterior two-thirds of the tongue. The needles can be embedded in moulds adapted to the palate for treating tumours in the floor of the nose and nasopalatine canal.

Radon seeds

Radon seeds are small capsules 4 mm by 1.5 mm in size which contain radon gas as a source of gamma rays. The seeds are inserted beneath the tissue surface and they can be left in place permanently because the half-life of radon is only 3.8 days. The dose of the seeds is such that one millicurie delivers a total of 1000 rads (roentgen absorbed dose). The radiation is effective up to 1 cm from the seed and beyond this distance the dose falls off rapidly. Radon seeds can be used in locations where radium needles are impractical because of their larger size. Areas such as the base of the tongue, tonsillar pillars and pharynx are treated with radon seeds.

Other radioactive sources used for internal radiotherapy include the radioactive isotopes tantalum (\(^{182}\text{Ta}\)) half-life 115 days, iridium (\(^{192}\text{Ir}\)) wires half-life 74.4 days, cesium (\(^{137}\text{Cs}\)) half-life 30 years and radioactive gold (\(^{198}\text{Au}\)) with a half-life of 2.7 days.
2. DOSE OF RADIATION

The extent of the damage caused by radiotherapy is proportional to the total dose of radiation\textsuperscript{178}. The dose used to treat a tumour is assessed depending upon the location and type of malignancy and upon whether the radiotherapy is used curatively or as a pre- or post-surgical aid. A curative dose of radiation for oral carcinoma is between 5000 rads and 7000 rads. External radiotherapy is usually administered over four to six weeks at 1000 rads each week or 200 rads on five days of a week. This division of the total dose is referred to as fractionated radiotherapy. The advantages of fractionated therapy is in providing time between doses to allow normal tissue to repair itself and to allow the tumour to 'shrink' slowly which enables better oxygenation of tumour cells and thus gives more effective treatment\textsuperscript{180}. Pre-operative irradiation with doses approximating 4000 rads is often applied to tumours of the head and neck\textsuperscript{182}.

3. TISSUE SUSCEPTIBILITY

Certain tissues are less susceptible to damage by radiation and these recover more rapidly than the more radiosensitive tissues. Traumatized, diseased, poorly vascularized and fast growing tissues are generally the most radiosensitive\textsuperscript{178}. The following tissues and organs are listed in the order of decreasing susceptibility to radiation\textsuperscript{177}:

(i) Bone-forming tissues and reproductive cells.

(ii) Young bone, gland tissue and epithelium of the alimentary canal.

(iii) Skin and muscle.

(iv) Nerve tissue and adult bone.

Salivary gland tissue despite its relative stability as
expressed by a low mitotic index is quite sensitive to ionizing radiation. Human salivary glands are so sensitive to radiation that their secretion may be reduced or abolished by irradiation of tumours in close proximity to them. Even the infusion of radioactive iodine for the treatment of thyroid disease may temporarily, and following repeated doses permanently, reduce salivary flow. Schneyer and Tanchester (1954) reported that xerostomia was the first clinical effect of radioactive iodine therapy.

4. TISSUE ABSORPTION

This factor varies with the volume of tissue, the density of tissue and with the source of radiation. When a given dose of radiation is applied to a small volume of tissue its effect will be more severe than if a larger volume of tissue receives the same amount of radiation. More dense tissue such as adult bone is generally less affected by ionizing radiation than less dense tissue such as gland tissue. This infers that the more dense tissue can absorb more energy before damage occurs.

The excessive irradiation of bone by orthovoltage X-rays in comparison to cobalt 60 gamma rays is an example of tissue absorption varying with the source of radiation.

5. FIELD SIZE

The size of the area to be irradiated is the field size and it directly affects the amount of secondary or scatter radiation produced during radiotherapy. The greater the field size then the greater the damage that can result to surrounding tissues. The field size in irradiation of head and neck tumours will determine the proportion of salivary tissue affected by radiation. The more
salivary tissue irradiated then the greater will be the reduction in salivary flow. For instance, radiotherapy for lesions of the tongue or retromolar trigone will induce a more rapid and profound xerostomia than will radiotherapy for lesions in the larynx\textsuperscript{184}.

CELL AND TISSUE RESPONSE TO RADIOThERAPY FOR ORAL CARCINOMA

The morbidity associated with external radiotherapy of the oral cavity includes mucositis, epidermitis, xerostomia, gustatory alteration, radiation caries, pulpal damage, trismus and a reduced ability of the tissues to resist trauma or infection\textsuperscript{180}.

EPIDERMITIS

During radiotherapy most patients develop a tan or burn of the skin in the area being irradiated\textsuperscript{185}. The tan or burn represents an inflammatory process called epidermitis and its intensity varies between patients. Epidermitis lasts longer than the inflammatory response of the mucosa to radiation because epidermis has a slower turnover of cells\textsuperscript{180}. Hair growth is also suppressed by radiation\textsuperscript{185}.

MUCOSITIS

In the mouth a painful mucositis may follow as little as 1000 rads of radiation\textsuperscript{178}. This mucosal inflammation usually begins in the second week of a five week course of fractionated radiotherapy. The mucositis progresses or persists until irradiation is discontinued or until shortly thereafter. The pain associated with mucositis may cause difficulty in mastication and dysphagia if the pharynx is involved preventing adequate nutrition\textsuperscript{180,185}.
ALTERATION IN TASTE

Change in taste sensation is an early response to radiation proceeding both mucositis and xerostomia. Taste sensitivity may be heightened or depressed by radiation and normal taste returns gradually over a one year period if less than 6000 rads has been received\(^{180}\). Stein, James and King (1970)\(^{186}\) stated that a radiation dose of 6000 rads causes a permanent loss of taste. Gustatory change following radiation is thought to result from oedema of the taste buds and changes in saliva and the oral mucosa\(^{180}\).

TRISMUS

Limitation of jaw movement is an occasional effect of radiotherapy. Trismus due to fibrosis and scarring of the temporomandibular joint or muscles of mastication follows direct irradiation of these structures\(^{180}\).

VASCULAR AND BONE CHANGES

Rubin and Doku (1976)\(^ {180}\) described vascular changes following therapeutic radiation as an initial periarteritis and endarteritis progressing to thickening of the tunica intima with fibrosis. Eventually obliteration of the lumina of blood vessels occurs.

The major effect of irradiation on bone is the damage rendered to its vascular supply. The numbers of osteoblasts and osteocytes in bone may be reduced. Therefore irradiation of bone in an actively growing stage will prevent full bone growth\(^{180}\).

EARLY CHANGES IN THE SALIVARY GLANDS DURING RADIOTHERAPY

Patients undergoing radiotherapy for head and neck malignancy may develop reduced salivary secretion resulting in xerostomia. This
xerostomia will be usually noticed during the third week of fractionated radiotherapy and follows radiation damage to the salivary glands. The severity of xerostomia is directly proportional to the dose of radiation and to the proportion of salivary gland tissue irradiated.\(^{180}\)

**ACUTE POST-IRRADIATION SIALADENITIS**

Kashima, Kirkham and Andrew (1965)\(^{187}\) reported on the acute reaction of the salivary glands to a single dose of pre-operative supervoltage radiation of between 1000 r and 2000 r. They described post-irradiation sialadenitis as a syndrome of acute swelling, tenderness and pain related to the salivary glands. In this form of sialadenitis the earliest complaints are of dryness of the mouth occurring simultaneously with swelling of the parotid and submandibular salivary glands. The swelling is often of gross proportions reaching a maximum twelve to twenty-four hours following irradiation and then subsiding rapidly. Other symptoms are sensations of tingling and burning over the major salivary glands and a general tightness of facial skin. The salivary glands are firm without obvious oedema and very tender to palpation. Usually elevations in temperature do not occur with this type of acute sialadenitis.

Kashima et al (1965)\(^{187}\) described the histopathological changes of salivary glands that were subjected to single doses of pre-operative irradiation. The parotid glands of irradiated patients showed acute inflammatory and degenerative changes. The inflammatory cell infiltrate consisted of polymorphonuclear leukocytes, eosinophilic leukocytes and a few plasma cells. Inflammatory cells aggregated along interlobular septa outlining acini, and also among the granules of degenerating serous cells. A zone of suppuration developed along the interlobular septa of some glands. The presence of a purulent
exudate in intercalated, interlobular and excretory ducts was a constant finding in acute post-irradiation sialadenitis. All intraglandular ducts showed some dilation. Excretory ducts were only moderately dilated and contained less exudate than the smaller ducts.

In many of the salivary glands examined the outlines of the acini were difficult to distinguish. Serous cells appeared to be separated from the basement membrane by large vacuoles or spaces. Some glands showed zymogen granules, without a cytoplasmic membrane, pooled in the acini. In other glands there was a marked reduction in the number of zymogen granules in the acinar cells.

Irradiated submandibular salivary glands showed changes similar to the acute inflammatory and degenerative changes seen in the parotid gland after irradiation. However the mucous cells in the submandibular glands showed little if any microscopic changes following irradiation.

The reaction to irradiation of the sublingual and minor salivary glands varies depending on the ratio of serous to mucous cells in the gland affected (vide infra: Arrangement of cells in terminal secretory units, p.18). Glands composed entirely of mucous cells show little or no inflammatory response to irradiation. In irradiated mixed salivary glands acute inflammation and degeneration affects serous acini and an inflammatory exudate fills the small ducts.

Even though severe tissue damage and suppuration may follow irradiation of the salivary glands, pyrexia and leukocytosis are uncommon. Acute post-irradiation sialadenitis subsides rapidly without specific therapy although almost total cessation of salivary flow occurs after single doses of radiation of 1000 rad and greater. Subsequent partial recovery of salivary flow occurs several months post-irradiation. English, Wheatcroft, Lyon and Miller (1955)
reported recovery of salivary flow in dogs following at least 1000 r of radiation to the head. One dog had salivary glands which were almost normal 15 months after a single dose of 1750 r of radiation.

LATE CHANGES IN THE SALIVARY GLANDS FOLLOWING IRRADIATION

Irradiated salivary glands exhibit fibrosis and acinar atrophy which is still seen long after the radiotherapy is completed. These atrophic changes, by definition reduce the amount of functional parenchymal tissue within the irradiated gland and xerostomia is a consequence.\(^\text{187}\)

Frank, Herdly and Philippe (1965)\(^\text{181}\) described the histopathological lesions characteristic of submandibular and parotid glands treated with 5000 r to 6000 r of cobalt 60 radiation. Structural changes reported for both these salivary glands were similar when the time interval following treatment and the dose of radiation received by each gland were the same. The changes described evolved over about eight months and then remained virtually static.

Between one and a half and three months post-irradiation the submandibular and parotid glands became more dense and firm in consistency. After degeneration of the tuncia media of gland arterioles the interlobular connective tissue became thickened and oedematous. Intralobular connective tissue developed a loose fibrosis which became infiltrated by mononuclear cells. These cells were mainly plasma cell type. About one-third of gland acini were reduced in size and showed necrosis of single serous cells or degeneration of entire acini. Excretory ducts became more prominent probably because of the reduced size of many acini. Polymorphonuclear leukocytes and necrotic material filled many gland ducts and the lumena of acini.

At three and a half to four months after radiotherapy the
salivary glands were firmly fixed to the adjacent tissues. Inter-lobular fibrosis and intralobular adiposis became evident and intralobular fibrosis was well advanced. The inflammatory cell infiltrate was predominantly lymphoid cells with some macrophages. Some acini continued to undergo necrosis and involution. Mucous acini remained easily identifiable but with a tendency to hypoplasia.

Between four and a half and eight months following irradiation, the salivary glands showed a reduction in size. A pronounced interlobular fibrosis rich in collagen and hyperplastic Schwann cells was present. The well developed intralobular fibrosis contained areas of adiposity, and granulomatous and necrotic foci.

By eleven months to two and a half years, post-irradiation salivary gland changes were static. The interlobular fibrosis contained thick walled veins and Schwann cell hyperplasias. Lobular adiposis surrounded atrophic acini which were centred around excretory ducts. Lymphocyte infiltration was still associated with the areas of fibrosis. A reduction in the numbers of both serous and mucous acini was evident.

Histological changes in salivary glands affected by radiation from radium implants and external X-rays are similar to, although more slowly developing and less extensive than, histological changes in salivary glands irradiated with cobalt.

English, Wheatcroft, Lyon and Miller (1955) observed that irradiated salivary glands in dogs showed a marked reduction in the quantity of parenchymal tissue. The occurrence of alterations in gland and cell structure and the presence of fibrosis is described. Mucous cells were reported to suffer less from radiation damage than did serous cells.

Rubin and Doku (1976) reported an increased capillary
permeability followed by interstitial oedema and inflammatory infiltrates during the initial period of salivary gland irradiation. Later histological changes were progressive interstitial fibrosis and gland atrophy followed by acinar degeneration and fibrosis and degeneration of small blood vessels. Again serous cells were reported to degenerate more rapidly than the mucous cells following irradiation of salivary glands.

Brown, Dreizen, Rider and Johnston (1967) monitored radiotherapy-induced changes in the saliva of thirty patients who had radiosensitive malignancies of the head or neck. Following 5000 rads of fractionated radiotherapy the changes in the saliva indicated that there were a greater number of functional mucous cells remaining compared with functional serous cells.

SIALOGRAMS OF IRRADIATED SALIVARY GLANDS

Kashima, Kirkham and Andrews (1965) considered that the sialographic appearance of irradiated salivary glands was consistent with the histological features of late stage atrophy in other salivary glands also subjected to high doses of radiation. The chronic and apparently permanent damage sustained by an irradiated salivary gland is seen sialographically by incomplete filling of the gland, smaller gland volume and an absence of acinar patterns. Eneroth, Henrikson and Jakobsson (1971) stated that irradiated salivary glands examined one year and more after radiotherapy were significantly smaller than non-irradiated salivary glands or salivary glands examined immediately following completion of radiotherapy.
QUALITATIVE AND QUANTITATIVE CHANGES IN SALIVA FOLLOWING IRRADIATION OF THE SALIVARY GLANDS

Whole saliva in healthy subjects has a fluid consistency with a clear or slightly cloudy appearance. The pH of whole saliva has a small range above and below neutral \(^{181}\) (vide supra: Hydrogen ions, p. 41). Irradiated salivary glands produce a saliva which shows marked changes both quantitative and qualitative in character \(^{181,184,189,190}\).

The degree of the reduction in salivary flow and the resultant xerostomia is related directly to the extent of radiation damage sustained by the salivary glands. Shannon, Starcke and Wescott (1977) \(^{184}\) reported a continual decrease in salivary flow in ten patients receiving six weeks of fractionated cobalt 60 radiation for primary malignancy in the head and neck. Measuring from the end of week one to the completion of therapy at week six, the average weekly decreases from patient's initial salivary flow were: 40, 29, 24, 19, 9 and 5%.

Stein, James and King's (1970) \(^{186}\) survey of radiotherapists aimed to define the dose of radiation at which certain complications arose. The results showed that a dose of 6000 rads produced a permanent loss of taste. A dose of 2000 rads to 3000 rads produced a temporary dry mouth and 4000 rads to 6000 rads predisposed a patient to the development of radiation caries. A permanent xerostomia will result from doses of radiation to the salivary glands of more than 4000 rads to 6000 rads \(^{186,191}\). Osteoradionecrosis is considered a possible complication in bone which has received 6000 rads to 7000 rads or more of radiation \(^{186}\).

Wescott, Mira, Starke, Shannon and Thornby (1978) \(^{191}\) investigated the alterations in whole salivary flow induced by fractionated cobalt 60 radiation at doses between 4500 rads and 6300 rads. They
recorded wide variations in the doses at which different patients developed xerostomia. Generally patients with high initial salivary flows required higher radiation doses to reduce salivary flow. The study showed that a permanent reduction in salivary flow occurred when all the major salivary glands were in the field of radiation and received a dose of 4500 rad or more. However, in time subjective improvement in the xerostomia was occasionally reported.

Frank, Herdly and Philippe (1965)\(^{181}\) commented on individual patient reaction to irradiation of salivary glands and considered that in some patients the salivary flow increased at two to six months post-irradiation. They also noted that while reduction in salivary flow occurred in the majority of patients following radiotherapy affecting the salivary glands not all patients showed such a reduction. The dose of radiation given to patients who showed minimal or no decrease in salivary flow was not recorded.

The saliva secreted by irradiated salivary glands is usually viscous and white or yellow to brown in colour. Any saliva that can be collected foams intensely\(^{180,181}\). There is a definite fall in the pH of saliva from irradiated glands. Frank, Herdly and Philippe (1965)\(^{181}\) compared the pH of saliva from irradiated patients with the pH of saliva from patients who had not been irradiated. The mean pH of saliva from irradiated salivary glands was 5.88, while the mean pH of saliva from the non-irradiated patients was 6.54. A trend for the pH of saliva to rise between two and six years following radiotherapy was noted\(^{181}\).

Brown, Dreizen, Rider and Johnston (1976)\(^{188}\) studied the effect of radiation on the lysozyme and immunoglobulin levels in saliva and serum. Cancer patients prior to radiotherapy had significantly higher concentrations of lysozyme, total protein and serum
immunoglobulins in their saliva than did control patients without cancer. During radiotherapy the cancer patients showed further pronounced increases in the concentration of all immunoproteins in saliva, except IgA. The patients also showed a marked reduction in the aqueous component of whole saliva during radiotherapy. The increased protein content of whole saliva in xerostomia patients in this study was attributed to the impaired function of the major salivary glands and to an increase in protein contributed exogenously. This increase in exogenous protein in saliva probably arose from serum transudate from inflamed gingiva and mucosa, ulceration and cell exfoliation of the mucosa, leukocyte degeneration, and debris retention, all of which probably stem from radiation mucositis. Slow clearance of saliva from the mouth further contributed to the increase in exogenous protein in whole saliva. The saliva of the xerostomic radiotherapy patients was considered to be more viscous than the pre-treatment saliva in the same patients. Once radiotherapy was completed the protein concentration in saliva reverted towards the pre-irradiation concentration. The increase in salivary immunoprotein concentration following radiotherapy did not reduce the predisposition to rampant caries which was caused by the reduced salivary flow.

Tarbet and Barrickman (1968) measured the concentration of sodium, potassium, chloride and calcium ions, as well as phosphate, amylase, esterase and acid phosphatase in the saliva of patients prior to and following irradiation of all the major salivary glands. In all cases the results showed that the salivary components measured increased in concentration following radiotherapy. The increases were moderate for the inorganic components but very marked for the organic fractions and especially notable with amylase concentrations.

Kashima, Kirkham and Andrews (1965) investigated the
effects of irradiation of salivary glands in stimulating an elevated serum concentration of amylase. The degree of hyperamylasaemia was directly related to the quantity of salivary gland tissue irradiated and the dose received. Hyperamylasaemia accompanies inflammation of the salivary glands. Epidemic parotitis and calculi obstructing salivary gland ducts are accompanied by inflammation and also by hyperamylasaemia. Early inflammatory changes in the salivary glands, such as increased papillary permeability and interstitial oedema probably allow diffusion of salivary amylase from the glands into the blood resulting in hyperamylasaemia. The elevated serum concentration of amylase fell after repeated irradiation of the salivary glands.

The increase in the viscosity of saliva in patients with radiation-induced xerostomia is probably caused by the high concentration of inorganic and organic components of the saliva. Also the greater resistance of mucous cells to irradiation compared to serous cells must also increase the viscosity of saliva in irradiated xerostomia patients.

IRRADIATION OF THE TEETH

Del Regato (1939)\textsuperscript{192} reviewed early studies on the effect of orthovoltage radiation on the teeth. Orthovoltage radiation was reported to cause destruction of odontoblasts, a reticular atrophy of pulp tissue and cystic degeneration around the roots of irradiated teeth.

Meyer, Shklar and Turner (1962)\textsuperscript{193} contrasted the damage to rat's teeth caused by a single 2040 r dose of orthovoltage radiation against damage caused by 2040 r of cobalt 60 (Co 60) supervoltage radiation. The orthovoltage radiation reduced the number of odontoblasts, damaged the remaining odontoblast layer, caused severe
alterations in both pulp and periodontal tissues and damaged bone and connective tissue. The teeth, bone and connective tissue in rats subjected to Co 60 radiation were relatively normal. Some of the minor alterations in pulp tissue were a thickening in the walls of blood vessels, and occasionally a little degeneration in the connective tissue, ground substance and odontoblasts.

Walker (1975)\textsuperscript{194} reported experiments that showed single 3500 rads dose of Co 60 radiation did not alter the solubility of human teeth in vitro. These experiments did not exclude other possible effects of Co 60 radiation such as increased tooth fragility caused by protein degradation.

Frank, Hendly and Philippe (1965)\textsuperscript{181} reported that the dental defects acquired after irradiation in teeth both inside and outside the field of irradiation, have the histological characteristics of dental caries. Evidence suggested that dental caries following irradiation of the salivary glands resulted from changes in the composition and quantity of saliva. For example, "radiation caries" is known to develop in the teeth in areas of patient's mouths which have not been irradiated\textsuperscript{181}. Animals subjected to removal or ligation of their major salivary glands show a dramatic increase in the incidence of dental caries. The extensive destruction of teeth by caries often found in patients with Sjögren's syndrome is similar to the dental caries seen following irradiation of the salivary glands\textsuperscript{60}.

Caries seen in patients following irradiation of their salivary glands usually occurs within one year\textsuperscript{180}. Frank, Hendly and Philippe (1965)\textsuperscript{181} reported the shortest interval between commencing radiotherapy and the appearance of dental defects was one month in a man with a squamous cell carcinoma of the nasopharynx. The dental defects referred to as "radiation caries" are typified by cervical
caries that progresses either slowly or rapidly to the stage of causing amputation of the clinical crowns of teeth.\textsuperscript{180}

\textbf{DENTISTRY AND THE RADIOThERAPY PATIENT}

Xerostomia, acute mucositis and a danger of osteomyelitis are part of the morbidity associated with radiotherapy of the head and neck. A combination of xerostomia and inadequate oral hygiene predisposes the irradiated patient to a rampant dental caries. Therefore any patient about to undergo irradiation of the head or neck should be assessed to determine the need for corrective and preventive dental treatment. The possibility of rampant caries and osteomyelitis in irradiated patients can be reduced by meticulous oral hygiene, patient education and long term dental follow up.
OBSTRUCTION TO THE SECRETION OF SALIVA

Obstruction of a salivary gland may be caused by:

a) Sialoliths (salivary calculi or stones).
b) Mucus plugs.
c) Stenosis of a duct orifice.
d) Stricture along the course of a duct, or
e) Congenital absence or occlusion of ducts.

a) SIALOLITHS

Salivary calculi may occur at any age but are most common in middle aged adults and rare in children. They are found very rarely in minor salivary glands. In major salivary glands, 80% occur within the submandibular duct and about 20% within the parotid duct. Intraglandular calculi are most frequently found within the deep part of the submandibular gland, only a small number are found in the sublingual gland and only rarely is a calculus found within the parotid gland. Langlais and Kasle (1975) reported that sialolithiasis affected the parotid more frequently than the submandibular gland but their conclusion was based on a small study of thirty patients.

Sialoliths are usually round to ovoid in shape, have a smooth or irregular surface, vary in size from a small grain to the size of a peach stone and are yellowish in colour. However, unusually large sialoliths up to 6 cm in size have been reported. They are composed of inorganic and organic constituents. The inorganic portion is mainly apatite crystals of calcium phosphates and calcium carbonates. The organic portion is composed of proteins, fatty acids and mucopolysaccharides. Blatt, Denning, Zumberge et al (1958) reported a uric acid stone formed in a parotid gland which
secreted saliva with a low pH and twice the normal level of uric acid.

It is generally accepted that a nidus, probably mucoid in nature, initiates formation of salivary calculi. The nidus enlarges by apposition of alternating layers of organic and inorganic substances 196,198,202,203. This would produce a lamellar structure of alternate bands of high and low mineral content. Anneroth, Eneroth and Isacsson (1975) 203 showed that some calculi are homogenous, some are only partly lamellar in structure and mineralised nuclei are not a constant finding. They suggested that the variation in morphology results from varying pathogenesis of salivary calculi.

Stasis of saliva is a probable factor in the initial nidus formation and development of sialoliths. A reduction in salivary flow increases the local concentration of calcium and phosphate ions, their solubility product is exceeded thus favouring the precipitation of calcium, phosphate and carbonate complexes 202,203.

Stasis of saliva may occur more frequently in the submandibular gland because of the upward inclination of the duct and the small size of the orifice. Submandibular saliva has a higher pH, higher mucin content and approximately twice the calcium content of parotid secretion. Hence the greater frequency of sialolith formation in submandibular glands and ducts 203.

Frequently, symptoms are not experienced until the calculus reaches a size which prevents the free flow of saliva from the affected gland. Then sudden swelling and pain occur, usually at meal times. The more complete the obstruction the greater the swelling and pain. The rate of salivary secretion falls after meals and a small leakage of saliva past the obstruction is sufficient to drain the affected gland and temporarily resolve the swelling 196,198,204.

Small calculi produce symptoms if they impact in narrow
parts of a duct or at the duct orifice. When these calculi move obstructive symptoms resolve\textsuperscript{204}. Patients occasionally report spontaneous extrusion of small calculi from a salivary duct\textsuperscript{93}.

A history of intermittent, progressive and usually painful swelling of a salivary gland, often following gustatory stimulation, indicates sialolithiasis\textsuperscript{196}. Diagnosis may be confirmed visually, by palpation or by radiography although approximately 20\% of sialoliths are radiolucent\textsuperscript{196,198,202,205}.

Occlusal view radiographs are useful to demonstrate radiopaque calculi in the submandibular duct. In the parotid duct, an antero-posterior view of the cheek puffed out by the patient or a lateral view with the mouth wide open may demonstrate calculi\textsuperscript{125}. Radiolucent calculi are demonstrated by sialography\textsuperscript{197}.

Sialograms may show partial or complete filling defects in the duct system and retention of contrast medium on evacuation sialograms\textsuperscript{93}. Partially obstructed salivary glands show a general uniform underfilling proximal to the obstruction. A sialogram of a completely obstructed gland outlines the duct only to the point of blockage. If calculi have eroded through the duct epithelium within the gland a sialogram will show a pool of contrast medium within the affected gland or if the calculi pass outside the gland the sialogram shows contrast medium filling a salivary fistula\textsuperscript{125}. Sialograms may also demonstrate that a calcified mass is a sialolith and not extra- ductal or extraglandular pathology\textsuperscript{195}. Excessive resistance to injection of contrast medium into an obstructed gland will be detected by the clinician\textsuperscript{143}.

Complications of sialolithiasis include conditions such as sialochitis (duct inflammation), retrograde sialadenitis, acute suppurative abscess with sinus tract or salivary fistula formation.
Ulceration of a salivary duct by a calculus may cause granulation with subsequent scarring and stricture of the affected duct\textsuperscript{125,196,206}. Sialolithiasis which causes partial or intermittent obstruction produces atrophic, inflammatory and regenerative changes and the gland may still secrete saliva\textsuperscript{155}.

Histological features of a chronically obstructed salivary gland are interstitial lymphocyte infiltration and atrophy of acinar cells followed by formation of multiple abscesses and eventually fibrosis\textsuperscript{93}.

The treatment of sialolithiasis is removal of the calculus or calculi. The anatomy and surgical techniques for treatment of a sialolith are presented in detail by Seward (1968)\textsuperscript{204,206,207,208,209,210,211}. A conservative or radical approach (involving complete or partial removal of the gland) is determined by the location of the calculus, the condition of the affected gland parenchyma and the presence of acute infection\textsuperscript{196,198}. Therapy following removal of a calculus involves antibiotics, heat, gland massage, salivary flow stimulation and sialography.

b) MUCUS PLUGS

Mucus plugs and incompletely mineralized sialoliths cause similar although less severe signs and symptoms to fully developed sialoliths. Sialadenitis as a result of the presence of mucus plugs of incompletely mineralized sialoliths is unlikely to occur\textsuperscript{196}. The pathogenesis of mucus plug formation is not known although in some instances the plugs may be the result of an allergic reaction\textsuperscript{91} (vide supra: Bacteriological culture and smear, p.66).

Pearson (1961)\textsuperscript{212} described recurrent swellings of the parotid glands and attributed these swellings to food allergy. The
obstruction of salivary ducts is caused by mucus plugs infiltrated with eosinophil leukocytes.

Kussmaul's disease or sialodochitis fibrinosis is a condition caused by mucus plugs in one or more of the excretory ducts of salivary glands. The disease typically occurs in dehydrated patients such as those undergoing intense fluid restriction for cardiac or renal disease. Recurrent salivary gland swelling which may be extremely painful during meals is common. Sialodochitis fibrinosis should be suspected when patients give a history a periodic salivary gland swelling and dehydration or fluid restriction.

c) STENOSIS OF A DUCT ORIFICE

Trauma is the most frequent cause of obstruction at the papilla or papillary stenosis of a salivary gland. Papillary trauma may be caused by maloccluded, malposed or sharp teeth, faulty restorations, projecting denture retainers, over extended denture flanges and by dentures with high occlusal planes. Inflamed oedematous ulcers in close proximity to salivary papillae may cause compression and acute obstruction of their ducts. Foreign bodies such as toothbrush bristles, grass, wheat, fish bone, straw, portion of a fingernail, wood splinter, thorn and feather have been reported as obstructions at papillae causing infection of salivary glands.

Seward (1968) classified papillary obstruction as either acute ulcerative obstruction or chronic fibrotic stenosis. The former features a sudden onset of symptoms of obstruction which are of short duration. Treatment is conservative with saline rinses, gland massage and removal of the cause of the ulceration. The ulceration usually heals and symptoms subside within a few days. In chronic fibrotic papillary obstruction recurrent irritation of a papilla
produces scarring and stricture. The symptoms are identical to those
of sialolithiasis and retrograde sialadenitis of the affected gland is
common. Investigation of chronic papillary stenosis by probing or
sialography is difficult due to the duct constriction at the orifice.
The duct orifice may be difficult to locate and resist insertion of a
probe. Sialograms demonstrate the degree of narrowing of the duct in
the region of the papilla and dilation of the duct behind the stenosis.
The presence of sialadenitis may also be revealed by sialograms of a
duct stenosis (vide infra: Sialadenitis and reduced salivary flow,
p.152). Treatment of chronic papillary obstruction involves papillotomy
and suturing of the duct lining to the oral mucosa. The affected
salivary gland is removed if irreversible destructive changes are
found 196,198.

d) DUCT STRicture 93,196,198

Obstruction to flow may result from stricture along the
course of a salivary gland duct. Ulceration of a duct around a sub-
mandibular sialolith with subsequent scar contraction of the duct is
a cause of stricture. Duct stricture may also follow traumatic
injuries, neoplasms, infections and congenital failure of duct develop-
ment. Ill-fitting dentures should be examined as a cause of trauma to
salivary ducts. Benign neoplasms may obstruct a duct by simple
compression whereas malignant neoplasms may both compress a duct and
infiltrate the duct wall and obstruct salivary flow. Trauma to the
parotid duct may result from chronic friction against the coronoid
process and masseter muscle. Seward (1968) 204 reported that this
frictional trauma has caused bilateral strictures where the parotid
duct crosses in front of the coronoid process.

A differential diagnosis of duct stenosis includes
sialolithiasis, acute parotitis and chronic recurring sialadenitis. The signs and symptoms of duct stenosis are similar to those in sialolithiasis and acute infection of the affected salivary gland may occur.

Sialograms are useful in locating a duct stricture and in evaluating the health of the affected gland. The stricture will appear as an obvious narrowing of the salivary duct with dilatation of ducts proximal to the constriction\textsuperscript{125}. A sialogram of saccular dilatation of a duct resembles a string of sausages. Smooth muscle atonicity may account for saccular dilatation in the parotid duct [see Plate\textsuperscript{2E}, p.156]. This form of dilatation does not occur in the submandibular duct possibly because of the absence of a muscle layer\textsuperscript{143}.

Treatment of a duct stricture in a healthy salivary gland involves progressive and frequent dilatations of the duct using lacrimal probe dilators with local or topical analgesia. When duct dilatation fails to relieve the obstruction caused by a stricture then a ductoplasty, which involves deliberate fistulization of a salivary duct into the mouth proximal to the stricture, is indicated. Where recurrent infection is considered to have irreversibly damaged a salivary gland affected by a duct stricture then excision of the gland is indicated.

e) ATRESIA

Atresia is the congenital occlusion or absence of one or more of the major salivary gland ducts. The condition is exceedingly rare and when it does occur may result in the formation of a retention cyst or produce a relatively severe xerostomia\textsuperscript{213,214}. Orban (1957)\textsuperscript{215} reported that atresia is found more commonly in the floor of the mouth in association with the sublingual and submandibular glands.

The possible sequelae to obstruction of salivary flow
includes infection of the gland, development of a ranula or mucocele, formation of a salivary fistula and pressure atrophy of gland parenchyma.  

OBSTRUCTION AND XEROSTOMIA

Obstruction to the flow of saliva from a salivary gland is often listed as a cause of xerostomia\textsuperscript{84,152,198}. Shafer, Hine and Levy (1974)\textsuperscript{213} however, stated that obstruction of one salivary gland seldom causes notable changes in the oral mucosa and Bertram (1967)\textsuperscript{216} Furstenberg (1945)\textsuperscript{217} and Allington (1950)\textsuperscript{153} considered that local conditions, such as obstruction affecting salivary glands, are most unlikely to cause xerostomia. Obstruction of more than one major salivary gland at any one time is a rare occurrence\textsuperscript{202}.

Perrotta, Williams and Sefie (1978)\textsuperscript{202} reported a female of 57 years with simultaneous bilateral parotid and submandibular calculi and complaining of a "dry mouth with a bad taste and spitting white particles".

Eisenbud and Cranin (1963)\textsuperscript{143} reported 8 of 87 patients with chronic obstructive sialadenitis in whom more than one major salivary gland was involved. Five had chronic obstruction of both parotid glands, one had bilateral submandibular gland involvement and there were two patients with combined submandibular and parotid gland involvement. In this study there was complete loss of salivary flow from 61% of obstructed submandibular glands and from 32% of obstructed parotid glands. Other affected salivary glands showed a marked reduction in flow.

Gayford and Haskell (1971)\textsuperscript{152} stated that the secretion of saliva from both submandibular glands may cease and not cause undue symptoms. However, loss of secretion from one parotid gland causes
some dryness and transient xerostomia. This observation appears
contradictory since the submandibular glands contribute 60 to 70% of
total saliva flow.\textsuperscript{110}

The importance of parotid gland secretion in causing xerostomia
may be the lower viscosity in comparison with submandibular secretion.
The serous parotid saliva, aided by gravity, wets a larger area of
oral mucosa than does mucus submandibular saliva which is spread by
the tongue. In addition, the parotid duct orifices are separated by
the width of the maxillary arch whereas the submandibular ducts open
in close proximity. One functioning parotid gland cannot fully wet
the buccal mucosa of the opposite side whereas one functioning sub-
mandibular gland may lubricate all the floor of the mouth.

Sialolithiasis or atresia may involve more than one major
salivary gland concurrently, obstructing the flow of saliva and
causings xerostomia. Papillary stenosis and duct stricture are less
likely to cause xerostomia as the predominately traumatic origin tends
to affect only one major salivary gland at a time.

In considering obstruction as a cause of xerostomia the
variation in resting salivary flow between individuals may be signifi-
cant. Patients with low resting flow rates of saliva are more likely
to be aware of any reduction or loss of secretion.
SIALADENITIS AND REDUCED SALIVARY FLOW

The following classification of inflammatory salivary gland diseases has been adapted from Epker (1972)\textsuperscript{196}.

a) Bacterial, viral and allergic diseases

Bacterial sialadenitis - Acute

- Chronic

Sialodochitis

Allergic sialadenitis

Viral sialadenitis - Epidemic parotitis

- Cytomegalic inclusion disease

- Other viruses

b) Specific granulomatous diseases

Sarcoidosis - Heerfordt's syndrome

Actinomycosis

Other granulomatous diseases: tuberculosis, syphilis and

Fungal diseases

ACUTE SIALADENITIS

Acute sialadenitis is usually a self-limiting disease but it can lead to abscess formation\textsuperscript{218}. Acute pyogenic or suppurative sialadenitis is the term used when pus forms within a salivary gland\textsuperscript{93}.

Acute pyogenic sialadenitis most often affects the parotid glands and is unilateral in all but 20% of cases. Occasionally both parotid and submandibular glands are affected\textsuperscript{196}. A marked reduction in the incidence of acute parotitis followed the introduction of antibiotics. However the emergence of penicillin resistant staphylococcus
 aureus has resulted in an increase in the incidence of acute parotitis.\textsuperscript{219}

Reduced secretion of saliva is the predisposing factor in the etiology of bacterial sialadenitis.\textsuperscript{93,219,220} Approximately one-third of cases of acute sialadenitis occur post-operatively especially after abdominal surgery when debilitation and dehydration reduce salivary flow.\textsuperscript{93,219} Acute parotitis may follow the use of drugs which have a xerostomic side effect. Chronic non-specific sialadenitis may have acute episodes.\textsuperscript{219}

Clinical onset of acute sialadenitis is marked by a sudden painful swelling of the affected salivary gland and the adjacent soft tissues. The skin overlying the gland is erythemic and palpation shows the gland to be very tender and indurated. A purulent discharge can often be expressed from the inflamed duct orifice using digital pressure. Other signs and symptoms of acute sialadenitis are a low grade fever, generalised malaise, headaches, occasionally trismus, an elevated ESR and leukocytosis.\textsuperscript{93,219}

The micro-organisms most frequently involved in acute sialadenitis are the coagulase positive staphylococci. Streptococcus pneumoniae and haemolytic streptococci are occasionally cultured. Immediately acute sialadenitis is suspected a specimen for culture should be obtained from the duct of the affected gland. Blood cultures are advisable because septicaemia can predispose to or result from acute sialadenitis.\textsuperscript{93}

The histological features of acute sialadenitis are typical of acute inflammation. An acute inflammatory cell infiltrate is present throughout the fibroadipose stroma and polymorphonuclear leukocytes are present within the duct lumen.\textsuperscript{219} The parotid gland seldom forms a discrete fluctuant abscess because it has dense fascial
septa. The submandibular gland is more likely to form a fluctuant abscess.\textsuperscript{93}

The treatment of acute sialadenitis includes rest, body fluid maintenance, antibiotic therapy and surgical drainage where necessary. Travis and Heght (1977)\textsuperscript{93} summarized the treatment for acute sialadenitis in a review of inflammatory salivary gland disease.

**CHRONIC RECURRENT SIALADENITIS**

Chronic disease can be classified as recurrent or progressive. Chronic progressive sialadenitis is caused by the specific granulomatous diseases and by autoimmune diseases affecting salivary glands.

Chronic recurrent sialadenitis often follows obstruction of salivary glands and the aetiological factors are similar to causes of acute sialadenitis shown in Figure 19\textsuperscript{196,218,219}. Patey (1965)\textsuperscript{221} considered that the sicca syndrome is at least as frequent a cause of chronic parotitis as is obstruction.

Chronic inflammatory diseases usually involve only one major salivary gland, most frequently the parotid gland, although bilateral involvement does occur\textsuperscript{93}.

The symptoms of chronic recurrent sialadenitis include a history of recurring mildly painful swelling of one or more salivary glands which often occurs during meals. Palpation of the affected salivary gland reveals a swollen, indurated and tender gland. The affected duct orifice will be erythemic and it may be possible to express a purulent salty tasting discharge from the gland. Tabak, Mandel, Karlan and Baurmash (1978)\textsuperscript{222} included a complaint of a dry mouth as characteristics of chronic recurrent parotitis. Patey (1965)\textsuperscript{221}
Fig. 19  The relationship of acute and chronic sialadenitis.

reported that dryness of the mouth occurs in some cases of chronic sialadenitis.

Sialograms cannot be used during acute inflammatory episodes but the changes due to chronic sialadenitis can be displayed by sialography. Sialectasis or sialoanectasis is the term used to describe the sialographic appearance produced by chronic recurrent sialadenitis. Sialectasis has been likened to an apple tree in blossom, to a snowstorm and to bunches of grapes [see Plate 2C]. The appearance of sialectasis has been explained as due to the breakdown and confluence of acini with pooling of contrast medium in the pathological spaces. Maynard (1965) considered that chronic sialadenitis weakens intralobular duct walls and that during sialography contrast medium escapes into the stroma through the weakened ducts. It was suggested that sialectasis is only one stage in the damage to salivary glands caused by chronic recurrent sialadenitis. Table 2 lists the progressive abnormalities shown by sialograms in chronic recurrent sialadenitis and Figure 2 shows these changes diagrammatically. The sialographic changes caused by chronic recurrent sialadenitis are accompanied by decreases in salivary flow from the affected gland. In general, the decrease in salivary flow reflects the severity of gland destruction shown by a sialogram [see Plates 2A to 2F].

The histological features of chronic recurrent sialadenitis are initially hyperplasia of duct epithelium and periductal lymphocytic infiltration. As the disease advances atrophy and fibrosis lead to eventual disappearance of acini.

The treatment for chronic sialadenitis should be conservative and consists of appropriate antibiotic therapy, analgesics, heat, gland massage and salivary flow stimulation. When a cause for the
Table 2. Normal gland
Branch duct changes
Sialectasis and branch duct changes
Sialectasis and main duct changes
Main duct changes
Complete gland disorientation

Fig. 20

Table 2 & Fig. 20
Progressive sialographic abnormalities caused by recurrent sialadenitis.

From: Maynard, J.D., Recurrent parotid enlargement.
Plates 2A to 2F: Examples of sialograms representing changes shown in Figure 20. (From: Maynard, J.D., Recurrent parotid enlargement. Brit.J.Surg., 52:784-789, 1965)

Plate 2A. Normal gland

Plate 2B. Branch duct changes
Plate 2C. Sialectasis and branch duct changes

Plate 2D. Sialectasis and main duct changes
Plate 2E. Main duct changes

Plate 2F. Complete glandular disorganization
inflammation is found such as sialolithiasis or duct stricture then these must be treated\textsuperscript{93,196,205}.

Whinnery (1973)\textsuperscript{131} reported treating recurrent parotitis utilising sialography with oil-soluble contrast medium followed by gland massage. This therapeutic effect of sialography may result from the distension of the salivary gland ducts by the viscous contrast medium. The distention of the ducts should allow drainage of the inflammatory products. When conservative management of chronic sialadenitis fails superficial parotidectomy or excision of the sub-mandibular gland seems the only effective treatment. Acute exacerbations of chronic sialadenitis should be treated as acute suppurative sialadenitis\textsuperscript{93}.

**CHRONIC RECURRENT PAROTITIS IN CHILDREN**

Chronic recurrent parotitis is not common in children, however, certain features distinguish it from the chronic parotitis seen in adults. In children males are affected with twice the frequency of females, whereas in middle-aged adults the ratio is reversed\textsuperscript{224}. Brook (1969)\textsuperscript{224} reported that recurrent parotitis in children has an uncertain etiology. Factors suggested as responsible in addition to those which occur in adults are: plugging by mucus from mucous cells found in the parotid glands of the newborn infant but not found in adults, allergy and pre-existing foci of infection such as tonsillitis and otitis media.

The swelling of recurrent parotitis in children lasts for hours, days or even weeks and may affect one or both parotid glands. The duct orifice of the affected gland is usually erythemic. Pressure over the tense gland may produce a flow of purulent, fibrinous or gelatinous saliva. The systemic reaction of children with recurrent
parotitis is usually minimal but it may be severe. The affected
gland may remain slightly enlarged between exacerbations which vary
from once every few weeks to once or twice a year \(^{219,224}\).

There is a tendency for this condition to resolve after
puberty especially in patients with sialograms showing little or no
duct distortion or dilation and who have salivary flow rates within
normal limits. Children whose sialograms show salivary glands with
main duct dilation tend to have chronic recurrent parotitis persisting
into adult life [see Fig. 21].

Chronic recurrent sialadenitis in children is given the
same conservative treatment as it receives in adults. Surgical
intervention is to be avoided in view of the possibility of spontaneous
recovery from this disease after puberty \(^{219,224}\).

SIALODOCHITIS

Sialodochitis is the acute inflammation of a major salivary
duct. The disease usually occurs secondarily to gland obstruction or
infections. However, primary bacterial or viral sialodochitis may
occur \(^{196,218}\).

The signs and symptoms of sialodochitis are the same as those
in obstructive salivary gland disease. Palpation of the involved duct
will show it to be tender and patients often think that they have a
toothache or an abscess. A patient with a purulent sialodochitis
should receive a course of antibiotics to prevent the development of
a retrograde sialadenitis developing in the affected gland \(^{196,218}\).

Sialodochitis causes inflammatory changes in duct epithelium.
Dilation of a main duct may follow epithelial atrophy while irregular
duct narrowing is caused by reparative fibrosis. Early in the course
of sialodochitis excretory ducts may be uniformly dilated. Advanced
Abnormally low secretion rate

→ Retrograde infection

→ Excess mucus and symptoms

Duct growth

→ Duct growth

→ Spontaneous recovery

→ Main duct changes

→ Irreversible disease

Fig. 21. Suggested sequence of events in children with chronic recurrent parotitis.

sialodochitis is associated with segmental stricture and dilation of larger ducts giving a sausage string appearance [see Plate 2E].

The sialographic appearance of sialodochitis correlates with the changes seen histologically. In emptying phase sialograms of glands affected by sialodochitis with strictures, elimination of contrast medium may be delayed. Sialograms demonstrating sialodochitis differ from sialograms of sialadenitis in the absence of dilation of terminal ducts and acini.\textsuperscript{125}

SIALOCHEMISTRY AND SIALADENITIS

Sialochemistry has received little attention as an aid in the differential diagnosis of salivary gland disease. Mandel and Wotman (1976)\textsuperscript{149} reported that it was possible to differentiate between inflammatory (sialadenitis) and non-inflammatory (sialadenosis) salivary gland disease on the basis of electrolyte concentrations in saliva.

In acute sialadenitis the concentration of sodium ions in resting saliva from involved glands is between two and ten times the normal value. The sialadenoses are accompanied by elevations in the potassium ion concentration of resting saliva from involved glands but concentrations of sodium and chloride ions are low or normal.

Resolution of acute sialadenitis is followed by a decrease in the concentration of sodium, chloride and phosphate ions to approach normal. In less severe chronic sialadenitis the salivary electrolyte concentration will be close to normal during quiescent periods. Acute exacerbations of chronic recurrent parotitis show elevations of salivary albumin and the immunoglobulins A, G and M. The increase in these constituents of saliva is between three and ten times normal salivary concentrations.\textsuperscript{149}
Tabak, Mandel, Karlan and Baurmash (1978) reported increases between two and twenty fold in salivary lactoferrin concentration during episodes of recurrent sialadenitis. The increase in lactoferrin was most marked during the acute phases of the disease but remains elevated between recurrences.

**ALLERGIC SIALADENITIS**

Sialadenitis as an allergic response does not appear to be a frequent occurrence. Allergens reported responsible for sialadenitis include various foods, some pollens, heavy metals, medications containing high concentrations of iodine and drugs such as chloramphenicol, oxytetracycline and griseofulvin. The probable allergic basis of mucus plugs in salivary glands has been noted (vide supra: Mucus plugs, p. 142).

Sialadenitis due to allergy is frequently multiglandular in nature. Cohen (1965) reported cases of allergic sialadenitis affecting submandibular and parotid glands simultaneously. Affected patients complain of pain and are often aware of a relationship between ingestion of a particular food or a drug and a recurrent salivary gland swelling. The latent period between ingestion of the allergen and gland swelling may be only minutes. The affected glands remain enlarged for several hours after which the swelling subsides. Expression of mucus plugs may occur as a feature of allergic sialadenitis.

Pearson (1961) and Hall (1969) suggested that eosinophils in saliva or in mucus plugs and a high blood eosinophil count suggest a diagnosis of allergic sialadenitis.

Banks (1967) reported a patient with a convincing case of allergic sialadenitis which eventually affected all the major
salivary glands. Six years after the onset of the allergy there was clinical evidence of fibrosis and permanent salivary gland enlarge-
ment. At this time the glands were secreting a clear saliva but the flow rate was too low for measurement. Presumably the patient suffered some oral dryness.

The histopathological features of allergic sialadenitis include acute inflammation and parenchymal degeneration.$^{219}$

The treatment of this form of sialadenitis should be conservative and includes gland massage, maintenance and hydration, antibiotic therapy where suppuration is evident and advice to avoid the allergenic food or drug in the future.$^{225}$ Steroids should be used only where conservative treatment fails to prevent or control recurrent attacks. Cohen (1965)$^{226}$ and Banks (1967)$^{223}$ found that anti-histamines were of little value in treating cases of allergic sialadenitis.

VIRAL SIALADENITIS

EPIDEMIC PAROTITIS (MUMPS)

Mumps is caused by a myxovirus which has an affinity for mammalian salivary glands.$^{155,224}$ This myxovirus is highly contagious and is transmitted by direct contact or in droplets of saliva. The incubation period for the disease is two to three weeks. Epidemic parotitis most frequently affects children of either sex in the 5 to 15 years of age group.$^{196,219}$ The parotid glands are usually affected and in 70% of patients involvement is bilateral. The submandibular glands are affected in 10% of cases of mumps.$^{219,224}$

The prodromal period for mumps is one or two days during which a moderate pyrexia, malaise and headache are experienced.

Clinical examination of a patient during the acute phase of
mumps reveals diffusely enlarged, painful salivary glands that are both tense and warm to touch. Trismus is often present because of the enlargement of the deep portion of the parotid gland. Intra-orally the papillae of the affected salivary glands are oedematous and a red to purple colour. Pus is usually absent from the ducts of the affected gland. The gland swelling reaches a maximum within two or three days and diminishes over an additional week. A lasting immunity results following a mumps infection and it is unlikely that it can be contracted more than once\textsuperscript{196,219,224,225}.

The diagnosis of mumps is made from the clinical history of an acute salivary gland swelling and exposure to a person with the disease during the previous two or three weeks\textsuperscript{196,224,225}. Confirmation of the diagnosis can be made by demonstrating a rise in serum antibodies to the two S and V antigens characteristic of mumps. When a blood specimen taken early in the disease does not show an increased antibody titre then a second specimen should be taken ten to fifteen days later\textsuperscript{196,223}. Serum amylase is elevated during the acute stage of mumps because a mild pancreatitis develops\textsuperscript{225}.

Mason (1976)\textsuperscript{219} considered the histology of mumps to be a diffuse infiltration of the gland parenchyma by mononuclear cells accompanied by acinar degeneration. Epker (1972)\textsuperscript{196} and Ritter (1977)\textsuperscript{225} described the inflammation caused by mumps as being primarily of the interstitial tissues. The gross enlargement of the salivary glands was considered to be due to cellular oedema of the interlobular connective tissue and not due to acinar changes. Morris (1967)\textsuperscript{155} noted that salivary glands affected by mumps recovered fully in time.

The treatment for a mumps infection is symptomatic and requires isolation of the patient for between six and ten days\textsuperscript{219}. Analgesics, fluid maintenance, bed rest and cold applied to the
swollen glands are useful in treatment. Serious complications such as orchitis and oophoritis, although rarely sterility, may occur in adults who contract mumps. Other organs which may be affected are the pancreas, liver, kidneys or nervous system.

Gayford and Haskell (1971) stated that a short period of xerostomia may occur in severe cases of bilateral mumps. Faber (1943) reported the case of an adult with epidemic parotitis whose salivary secretion was moderately reduced. Banks (1967) stated that viral parotitis causes a profound xerostomia. The most serious salivary gland complication of mumps is the development of chronic recurrent sialadenitis and sometimes acute suppurative sialadenitis.

The acute stage of mumps has features which could produce xerostomia. Fever may cause dehydration and dehydration causes xerostomia (vide supra: Reduction in salivary flow following changes in body fluid and electrolyte balance, p.111). Oedema of interstitial salivary gland tissue may obstruct salivary flow by compression and obstruction of small ducts. Acinar degeneration, if it occurs in mumps, would reduce the quantity of saliva produced and secreted. Therefore, xerostomia could be expected during the course of epidemic parotitis.

CYTOMEGALIC INCLUSION DISEASE (SALIVARY GLAND INCLUSION DISEASE)

Cytomegalic inclusion disease is a rare condition caused by the cytomegalovirus. The disease primarily affects newborn infants. Adults are rarely affected by the disease although 80% of adults possess serum antibodies against the cytomegalovirus. Adults who
develop cytomegalic inclusion disease usually have severe debilitating diseases such as leukaemia or are in an immunosuppressed state.

Transplacental infection with the cytomegalovirus may occur in a foetus even in the absence of clinical infection in the mother. Infants who develop the disease usually die within a few days of birth suffering from splenomegaly, hepatomegaly and jaundice, anaemia, thrombocytopenic purpura and petechiae. Those infants that do survive usually show a retardation in mental and motor development.

There are no specific signs and symptoms of cytomegalic inclusion disease. The most frequent clinical manifestations are fever, hepatosplenomegaly and lymphocytosis during the infection. Diagnosis depends on the detection of characteristic cells in the saliva, sputum or urine. These cells contain intranuclear and cytoplasmic inclusions which are pathognomonic.

Histologically the disease is characterized by the inclusion bodies in the cells of various organs including the kidneys, liver, pancreas, lungs, adrenals, intestines and brain. Infection of the salivary glands by the cytomegalovirus produces greatly enlarged cells containing numerous inclusion bodies within the acini and ducts of parotid and submandibular glands. The extent of destruction of the salivary glands by the virus is variable.

OTHER VIRAL INFECTIONS

It should be remembered that salivary glands can be infected by other viruses including coxsackie type A virus, echo virus, choriomeningitis virus and parainfluenza viruses 1 and 3\(^219\). These viruses may produce a clinical parotitis (or sialadenitis) and account for some unexplained negative serological results in "mumps". Isolation of the virus and examination of acute and convalescent sera
for viral particles and allergens may confirm the diagnosis.  

GRANULOMATOUS INFILTRATIVE DISEASES

SARCOID INVOLVEMENT OF THE SALIVARY GLANDS -
HEERFORDT'S SYNDROME (UVEOPAROTID FEVER)

Sarcoidosis is a chronic, benign, systemic granulomatous disease of underdetermined etiology which may involve the lungs, liver, spleen, heart, lymph nodes, eyes, skin, mucous membranes, bone and salivary glands. Parotid gland and parotid lymph node involvement are estimated to occur in approximately 6% of cases of sarcoidosis. Sarcoidosis occurs most frequently in young to middle aged adults of the negro race. It has been suggested that a complex hereditary trait is a factor in the pathogenesis of sarcoidosis. An immunodeficiency involving impairment of T-lymphocyte but not B-lymphocyte cell function has also been associated with this disease. Sarcoidosis has some features that are similar to tuberculosis such as histology and sites affected, and it has been suggested that sarcoidosis is an atypical form of tuberculosis.

Heerfordt in 1909 described a syndrome of parotid enlargement, uveitis and facial paralysis in patients with sarcoidosis. It is now known that sarcoid involvement of the uveal tract of the eye, salivary glands and lacrimal glands is the cause of Heerfordt's syndrome.

Patients affected by Heerfordt's syndrome usually experience a prodromal period of between one week and several months, during which they may experience fever, lassitude, malaise, vague gastrointestinal disturbances and ill-defined cerebral symptoms.

The first specific symptom of the syndrome is usually a firm, painless and often bilateral enlargement of the parotid glands.
The submandibular, sublingual and even the lacrimal glands may also be swollen and xerostomia is frequent\textsuperscript{231}. Chisholm, Lyell, Haroon, Mason and Beeley (1971)\textsuperscript{232} discussed the salivary gland function in patients with sarcoidosis. They presented the case of a male patient who had bilateral parotid swelling, xerostomia, loss of taste sensation and dry eyes. Later the patient developed sarcoid lesions involving the skin. Chisholm et al (1971)\textsuperscript{232} confirmed that salivary flow volumes and enzyme content are reduced in patients with sarcoidosis. Inflammation of the uveal tracts of the eyes and other ocular lesions can lead to permanent pupillary changes and alterations in visual acuity\textsuperscript{196,231}. Cranial nerve involvement in 50\% of cases of Heerfordt's syndrome occurs as unilateral or bilateral facial nerve paralysis. Involvement of other cranial nerves and central nervous system may also occur in the syndrome\textsuperscript{196}.

The typical case of uveoparotid fever is accompanied by sarcoid lesions in the lungs, viscera and skin. A patchy, erythematous skin rash may present early in the course of the disease. Enlargement of cervical lymph nodes is seen in some patients with Heerfordt's syndrome\textsuperscript{231,232}.

The diagnosis of Heerfordt's syndrome is made on the basis of clinical signs and symptoms, biopsy and on the results of the Kveim antigen test\textsuperscript{196}.

A biopsy site can be easily selected when lymphadenopathy or palpable skin lesions are present. If there is no clinically obvious site of sarcoid involvement then a random biopsy site is selected. Biopsy sites currently employed include lung, mediastinal lymph nodes, liver, scalene fat pad, gastrocnemius muscle and bone marrow. Biopsy of some of these sites involves significant risk as well as patient discomfort\textsuperscript{233}. Tarpley, Anderson, Lightbody and
Sheagren (1972) proposed a biopsy of minor salivary glands in the submucosa of the lower lip as a safe alternative means of establishing a diagnosis of sarcoidosis. This biopsy procedure is not diagnostic in every case but it seems to be reliable enough to perform prior to taking a biopsy from a less accessible site (vide supra: Biopsy of minor salivary glands, p.68).

The Kveim test requires an intracutaneous injection of a suspension of known sarcoid tissue. Then after four to six weeks a biopsy is taken from the injection site. A positive test results in the development of microscopic epitheloid tubercles which are seen in the biopsy specimen. The Kveim test is positive in 60 to 80% of patients with active sarcoidosis and the test's reactivity falls appreciably as the disease becomes more chronic or resolves.

The histology of sarcoid lesions is characterized by the formation of non-necrotizing epithelioid granulomas. Caseation is not a feature of sarcoidosis. A number of other agents and conditions may cause granulomas similar to sarcoidosis and among these are tuberculosis, atypical myco-bacterial infections, leprosy, syphilis, mycoses, neoplasms, viruses and some metals. The causes can be excluded by a history, special histological stains and the use of polarised light microscopy.

The treatment of sarcoidosis is non-specific and symptomatic as the disease is usually self-limiting and reversible. However, Chisholm et al (1971) and Epker (1972) reported successful treatment of sarcoidosis with corticosteroids and as permanent eye damage can occur in patients with Heerfordt's syndrome a course of steroid therapy should be considered.
ACTINOMYCOSIS IN SALIVARY GLANDS

Actinomycosis affecting the parotid gland is considered rare and as a primary infection actinomycotic sialadenitis is very rare\textsuperscript{234}. Most cases of actinomycosis affecting salivary glands result through spread from adjacent tissues\textsuperscript{234,235}. The features and treatment of actinomycosis affecting the parotid gland are reviewed in case reports by Hopkins (1973)\textsuperscript{234} and Sazama (1965)\textsuperscript{236}.

OTHER GRANULOMATOUS DISEASES\textsuperscript{196,219}

Granulomatous diseases such as tuberculosis, syphilis, histoplasmosis, leprosy, rhinosporidiosis, blastomycosis and lympho-granuloma venerum rarely affect salivary glands but should be remembered in making a differential diagnosis of chronic diseases involving the salivary glands.

XEROSTOMIA AND SIALADENITIS

Gayford and Haskell (1971)\textsuperscript{152} considered that apart from autoimmune diseases, diseases affecting the salivary glands rarely cause xerostomia. Shklar and McCarthy (1976)\textsuperscript{84} included inflammation of the salivary glands in the etiology of xerostomia.

Acute sialadenitis may result from a reduced salivary flow, but it seems unlikely that acute sialadenitis could be a primary cause of xerostomia.

A dry mouth or a significant reduction in salivary flow have been reported with sufficient frequency in chronic, allergic and viral sialadenitis to list these conditions with the causes of xerostomia.

Of the granulomatous diseases Heerfordt's syndrome has the potential to involve all major salivary glands and cause xerostomia.
The considerations given to obstruction of one major salivary gland as a cause of xerostomia also apply where inflammation causes the loss of salivary flow from one major salivary gland. The parotid glands are considered most essential to maintaining normal lubrication of the mouth by saliva (vide supra: Obstruction and xerostomia, p. 146).
DRUGS AND REDUCED SALIVARY SECRETION

Considering the various neural influences acting on the salivary glands it is not surprising that numerous pharmacological agents affect salivary flow. The drug groups which have been reported to have a xerostomic effect are set out below.\(^{149,152,237}\).

DRUGS WITH XEROSTOMIC POTENTIAL

a) DRUGS WHICH DEPRESS THE CENTRAL NERVOUS SYSTEM

Narcotics

Hypno-sedatives: barbiturates, benzodiazepines, others

Antipsychotics: phenothiazines

Antidepressants

Antihistamines

Antihypertensives with central actions: methyldopa, clonidine.

b) DRUGS ACTING ON AUTONOMIC GANGLIA

Antihypertensives

Nicotine

c) DRUGS BLOCKING PARASYMPATHETIC NEURO-EFFECTORS

Atropine-like drugs: belladonna alkaloids and related synthetics

Antispasmodics

Antiparkinson's

Antipsychotics

Antihistamines

Antiemetics

Antiarrhythmic: disopyramide
d) DRUGS ACTING ON ADRENERGIC NEURO-EFFECTORS

Decongestants
Expectorants
Appetite suppressants

e) DRUGS AFFECTING BODY WATER AND ELECTROLYTE BALANCE

Diuretics
Antidiuretics
Laxatives - Cathartics
Antibiotics: clindamycin, griseofulvin, carindacillin

f) DRUGS DIRECTLY AFFECTING SALIVARY GLAND CELLS

Antineoplastics

The drugs which most often produce xerostomia are those which disrupt the transmission of nerve impulses to the salivary glands. These drugs either block the physiological action of acetylcholine (Ach) or stimulate the activity of neurotransmitters such as noradrenaline (NA). The distribution of neurotransmitters within the autonomic nervous system is shown in Figure 22. The ganglia of both the sympathetic and parasympathetic nervous systems contain acetylcholine. The parasympathetic system releases only acetylcholine at post-ganglionic nerve endings while the sympathetic system may release either noradrenaline or adrenaline.\(^{238}\)

Although the nerve supply to the salivary glands in various animals has been intensively studied, far less is known about the innervation of the salivary glands in man. Animal experiments cannot be directly extrapolated to man because salivary gland physiology varies widely between different species.\(^{239}\) Significant features of
Fig. 22 Neurotransmitters of the autonomic nervous system.

the neural supply to salivary glands in man are $^{239,240}$:

i) Both parasympathetic and sympathetic nerves supply salivary secretory cells. Secretory cells may receive a 'double' nerve supply from both parts of the autonomic nervous system. Alternatively mucous cells may receive sympathetic nerves and serous cells parasympathetic nerves.

ii) Salivary gland blood vessels receive sympathetic constrictor nerve fibres and parasympathetic dilator fibres.

iii) Myoepithelial cells contract in response to neural stimulation and expel saliva which has already been formed.

In general it is reasonable to regard parasympathetic nerves as stimulating a serous or watery secretion from the salivary glands while sympathetic nerves stimulate an increase in the protein content of saliva making it more viscous. By reducing blood flow, sympathetic vasoconstriction of salivary gland blood vessels may reduce the secretion of saliva.

DRUGS WHICH DEPRESS THE CENTRAL NERVOUS SYSTEM

Drugs which depress the central nervous system (CNS) will also depress the autonomic nervous system (ANS). Depression of the ANS which innervates the salivary glands reduces the flow of saliva causing a dry mouth$^{152}$. The reduction in salivary flow during sleep is probably also due to depression of the ANS (vide supra: Physiological decrease in salivary flow during sleep and mouthbreathing, p.105).

Narcotic drugs reduce salivary flow and cause xerostomia. This decrease in salivary flow is a factor in the development of rampant caries often seen in narcotic addicts. Neglect of oral hygiene is another factor$^{241}$. Opium and its derivatives such as morphine, codeine, heroin as well as synthetic opioids like
levorphanol, meperidine and fentanyl result in xerostomia as a side effect of their use.\textsuperscript{242}

The primary action of the opiates is on the CNS and bowel but their mechanism of action remains uncertain. It does appear that they act on more than one of the body's neurotransmitters. The release of Ach from some peripheral and central cholinergic neurones is decreased but overall the level of Ach in the brain increases. Thus the net effect of opiates on the brain is an increase in the release, synthesis and turnover of Ach. Morphine and most other narcotics also stimulate the release of antidiuretic hormone (vide supra: Dehydration and the secretion of saliva, p.114). The central depression produced by the opiates causes drowsiness which is followed by dryness of the mouth.\textsuperscript{242}

A number of actions of the opiates on the salivary glands may combine to produce xerostomia -

i) A selective peripheral anticholinergic action affecting the salivary glands.

ii) Release of ADH.

iii) Depression of the CNS causing drowsiness similar to sleep.

Narcotic addicts often present with rampant caries similar to that observed in non-addict patients who have xerostomia. These addicts also tend to have a craving for refined carbohydrates which in combination with xerostomia and poor oral hygiene accelerates dental caries.\textsuperscript{241,243}

Hypno-sedatives include drugs of various classes, among these are the barbiturates, benzodiazepines, piperidinediones, and methaqualone. The principal use of the hypno-sedatives is to induce drowsiness and the barbiturates are used in general anaesthesia for this purpose. Most of the modern hypno-sedatives are general
depressants affecting a wide range of cellular functions in many vital organs. Barbiturates are usually classified as long acting, short to intermediate acting and ultra short acting drugs. Examples of these classes are phenobarbitone, amylobarbitone, sodium thiopentone respectively. The barbiturates can produce CNS depression ranging from mild sedation to coma and so it can be expected that salivary flow may be reduced by these drugs.

Transmission of nerve impulses across autonomic neuroeffectors is interfered with by barbiturates. Mandel and Wotman (1976) classified barbiturates as parasympatholytic in their inhibitory effect on salivation. The response of the submandibular gland to both Ach and stimulation of the chorda tympani is inhibited by amylobarbitone. Gastric secretions may in general be decreased by barbiturates.

The benzodiazepines classified as hypnotics are flurazepam, nitrazepam and flunitrazepam. Other drugs in this class referred to as anti-anxiety agents are chlordiazepoxide, diazepam, clorazepate, oxazepam, lorazepam and medazepam. Clonazepam is a benzodiazepine used for its anticonvulsant effect. There is a complex relationship between the different benzodiazepines and many are metabolites of others in the group. Thus these drugs have similar pharmacological activities, their main difference being in duration of action. Benzodiazepines have no anticholinergic activity and if they produce xerostomia at all then it is related to a sedative action. In fact, diazepam may increase salivary and bronchial secretion in children.

The piperidinediones are represented by glutethimide and methylprylyone. Glutethimide exhibits pronounced anticholinergic activity which is manifest by the dilation of the iris and the inhibition of salivary secretion. Methylprylyone apparently lacks the
anticholinergic activity of glutethimide\textsuperscript{244}.

The single quinazalinone used in drug therapy is methaqualone. In addition to a hypno-sedative action methaqualone possesses antispasmodic, weak antihistaminic, local analgesic and anticonvulsant properties\textsuperscript{244}. Both the sedative and anticholinergic activity associated with this drug could be responsible for its xerostomic side effect.

Antihistamines, antidepressants and antipsychotics may all cause sedation which may contribute to a reduction in salivary flow. However, the greatest reduction in salivary flow produced by these drugs probably results from their anticholinergic effect\textsuperscript{149,152}.

Methyldopa (Aldomet) is an antihypertensive agent which apparently acts on the CNS. Johnson, Kitchin, Lowther and Turner (1966)\textsuperscript{247} reviewed reports on the efficacy and side effects of methyldopa. Drowsiness and a dry mouth were the most frequent side effects. Nickerson and Ruedy (1975)\textsuperscript{248} reported that dry mouth and nasal congestion associated with methyldopa therapy may originate in the CNS. Retention of sodium and water are further side effects of this drug and reference to oedema and decreased salivary flow has been made (vide supra: Low cardiac output and oedema, p.116). Mardh, Belfrage and Naversten (1974)\textsuperscript{249} reported three cases of sialadenitis following treatment with methyldopa. The patients were thoroughly investigated and allergic, viral and bacterial causes were excluded. Nevertheless, the descriptions of the patients' signs and symptoms are suggestive of an infective retrograde sialadenitis secondary to a decrease in the flow of saliva.

Clonidine is an antihypertensive drug which has diverse actions including effects on the CNS, such as sedation\textsuperscript{238,248}. Rand, Rush and Wilson (1969)\textsuperscript{250} investigated the inhibitory effect of
clonidine upon salivary flow and ruled out sedation, anticholinergic
and ganglion blockade as the cause of salivary inhibition. By
elimination the most likely site of action for clonidine in depress-
ing salivation was suggested to be the salivatory nucleus in the
brain. Putzeys and Hoobler (1972)\textsuperscript{251} reported that the occurrence
of a dry mouth was frequent in patients taking clonidine but rarely
observed in those taking methyldopa. Davies, Wing, Reid, Neil,
Tippet and Dollery (1977)\textsuperscript{252} noted that following a 900 \textmu g dose of
oral clonidine all of the subjects in their study reported considerable
dryness of the mouth in the proceeding eight hours. It was considered
that not only the sedation but also the dry mouth was caused by
actions on the CNS.

DRUGS ACTING ON AUTONOMIC GANGLIA

Ganglion blocking drugs are used mainly now in the control
of hypertensive crises. Trimethapam, an extremely short acting drug,
and the longer acting pentolinium and mecamylamine are representative
of the ganglion blocking agents\textsuperscript{253}. These drugs have been replaced
by newer agents in the long term control of hypertension because the
ganglion blockers have a wide range of side effects including xero-
ostomia\textsuperscript{152}.

The ganglion blockers act by occupying receptor sites on
postsynaptic nerve terminals. This stabilizes the postsynaptic
membrane against the action of acetylcholine released from presynaptic
nerve endings. Because ganglion blockers are non-selective in their
action both sympathetic and parasympathetic nerves are inhibited\textsuperscript{253}.
The effect of blockage of nerve impulses to the salivary glands is
a failure to secrete saliva resulting in xerostomia. Pentolinium has
been shown to produce almost total inhibition of parotid secretion
and almost 90% inhibition of submandibular secretion.\textsuperscript{254}

Nicotine contained in tobacco is a ganglion stimulating drug which has numerous complex actions both centrally and peripherally. The most significant peripheral action of nicotine is its initial transient stimulation and subsequent more persistent depression of all autonomic ganglia. Small doses of nicotine stimulate ganglion cells directly and facilitate nerve impulse transmission. Larger doses of the drug cause initial stimulation followed rapidly by a blockade of nerve impulses. Thus nicotine produces initial neural stimulation of salivary secretion followed by inhibition of secretion. Nicotine also stimulates the release of antidiuretic hormone from the neurohypophysis and this hormone may further reduce salivary flow (vide supra: Dehydration and the secretion of saliva, p.114).

Therefore theoretically and from clinical impressions heavy smokers may suffer from xerostomia\textsuperscript{152,253}.

**DRUGS BLOCKING PARASYMPATHETIC NEUROEFFECTORS**

The drugs grouped under this heading are those reported as having anticholinergic activity, which may be a therapeutic action or an unwanted side effect. Anticholinergic drugs act as competitive antagonists at muscarinic receptors. At these receptors the attachment of acetylcholine and other muscarinic agonists is inhibited thus preventing stimulation of the neuroeffectors.\textsuperscript{238} The majority of drugs which may cause xerostomia come from this group with anticholinergic activity\textsuperscript{152}.

**ATROPINE-LIKE DRUGS**

Atropine and scopolamine (hyoscine) are the most important of the alkaloids from the belladonna plant.\textsuperscript{255} Atropine and related
alkaloids have a high degree of specificity for muscarinic receptors and high concentrations are required to produce nicotinic receptor blockade \(^{238}\).

Salivary secretion is especially sensitive to inhibition by antimuscarinic agents which can cause sufficient oral dryness to make talking and swallowing difficult \(^{255}\).

Atropine-like drugs are used for:

i) Treatment of smooth muscle spasm in the GIT and ureters by reduction of parasympathetic overactivity.

ii) Reduction of acid secretion from the stomach in treating peptic ulcers.

iii) Premedication prior to general anaesthesia to protect the heart from vagal inhibition and to reduce bronchial secretions.

iv) Prevention of motion sickness (scopolamine).

v) Control of Parkinsonian rigidity.

vi) Ophthalmology as topical agents to produce mydriasis to aid retinal examination (will not lead to xerostomia).

In relation to dosage 0.5 mg of atropine causes some oral dryness, 1.0 mg definite dryness, 2.0 mg marked dryness and 5.0 mg dryness which causes difficulty in swallowing.

Because the antimuscarinic effect of the belladonna alkaloids is non-specific, attempts have been made to produce drugs with more selective antimuscarinic actions. Success has been limited and at therapeutic doses synthetic and semi-synthetic antimuscarinic drugs have similar, although weaker, side effects to the belladonna alkaloids. See Table 3 for a list of synthetic and semi-synthetic antimuscarinic drugs \(^{255}\).

Dicyclomine hydrochloride and adiphenine hydrochloride are
<table>
<thead>
<tr>
<th>SYNTHETIC QUATERNARY AMMONIUM ANTIMUSCARINICS</th>
<th>SEMISYNTHETIC SUBSTITUTES FOR BELLADONNA ALKALOIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>antisotropine methylbromide</td>
<td>atropine methylnitrate</td>
</tr>
<tr>
<td>diphenamid methylsulphate</td>
<td>methscopolamine bromide</td>
</tr>
<tr>
<td>glycopyrrolate</td>
<td>homatropine methylbromide</td>
</tr>
<tr>
<td>hexocyclium methylsulphate</td>
<td>homatropine (ophthalmic)</td>
</tr>
<tr>
<td>methantheline</td>
<td></td>
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<tr>
<td>propatheline</td>
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<tr>
<td>oxyphenonium</td>
<td></td>
</tr>
<tr>
<td>isopropanide iodide</td>
<td></td>
</tr>
<tr>
<td>mepenzolate bromide</td>
<td></td>
</tr>
<tr>
<td>poldine methylsulphate</td>
<td></td>
</tr>
<tr>
<td>tridihexethylene chloride</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>OTHER SYNTHETIC ANTIMUSCARINICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclopentolate hydrochloride (HCl)</td>
</tr>
<tr>
<td>eucatropine (HCl)</td>
</tr>
<tr>
<td>oxyphencyclidine (HCl)</td>
</tr>
<tr>
<td>piperidolate (HCl)</td>
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<tr>
<td>thiphenamid (HCl)</td>
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Table 3. Synthetic and semisynthetic antimuscarinic drugs.
anti-spasmotic drugs which have little anti-muscarinic activity. Large doses of these drugs would probably be required before any atropine-like effects such as xerostomia could occur\textsuperscript{255}.

LEVODOPA AND AMANTADINE

The introduction of levodopa has been a major advance in the treatment of Parkinsonism although other anticholinergic drugs are still useful. In large doses levodopa once decarboxylated to dopamine acts centrally. Dopamine is a pharmacologically active catecholamine with prominent effects on $\alpha$- and $\beta$-adrenergic receptors. Contrary to expectations levodopa can produce orthostatic hypotension. This hypotension plus the vasoconstrictor effect of dopamine may reduce salivary gland blood flow sufficiently to reduce the flow of saliva and cause a dry mouth. However, tolerance to the side effects of levodopa develops and so xerostomia is unlikely to be more than a transient patient complaint\textsuperscript{256}.

Amantadine is a drug used both in treating Parkinsonism and as an antiviral agent. Although this drug is more effective than the anticholinergic drugs it does not match levodopa in efficacy. Amantadine appears to act by stimulating the release of dopamine from central and peripheral sites in the body. Xerostomia has been occasionally reported with the use of this drug\textsuperscript{256,257}.

ANTIPSYCHOTICS, ANTIHISTAMINES, ANTIEMETICS

This group of drugs is closely related in that many of the antihistamines are phenothiazine antipsychotics and many of the antiemetics are also antihistamine or antipsychotic drugs\textsuperscript{152}. The sedative effect of antihistamines and antipsychotics has been noted.

The major representatives of the antipsychotic drugs are the
phenothiazines and butyrophenones. The butyrophenones have minimal
effect on the autonomic nervous system, although they have a weak
anticholinergic activity which extends to little more than occasional
blurring of vision. Butyrophenones are used primarily in the treat-
ment of psychiatric disorders\(^{258}\).

Chlorpromazine is the prototype of the phenothiazine drugs
and as such has been more extensively studied than other drugs in this
category. Among its complex effects is a peripheral cholinergic
blocking activity. The side effects of therapeutic doses of chlor-
promazine and other phenothiazines include faintness, palpitations,
nasal congestion, slight constipation and xerostomia\(^{258}\). Scopp,
Heyman, Goldberg and Croy (1965)\(^{259}\) investigated the effect of chlor-
promazine in causing dryness of the mouth. The clinical observations
of oral dryness in the patients medicated with this drug were supported
by quantitative measurements showing reduced salivary flow. Curry
(1974)\(^{260}\) noted a dramatic fall in the secretion of saliva at the
beginning and throughout a six week multidose course of chlorpromazine.
The reduction in salivary flow was maintained throughout the six week
period.

Phenothiazines are used in treating psychiatric disorders
such as anxiety and endogenous depression. It should be remembered
that the disorders for which they are used may also reduce salivary
flow (vide supra: Psychogenic factors and reduced salivary flow,
p.108). Thus xerostomia in a patient taking a phenothiazine drug may
be caused by both the condition under treatment and the therapy pre-
scribed. The following drugs are representative of the more than two
dozen phenothiazines used in therapy\(^{258}\): chlorpromazine, trifluo-
promazine, prochlorperazine, promethazine, thiethylperazine, thiori-
dazine, perphenazine, fluphenazine and trifluoperazine.
Antihistamines are very useful in the symptomatic treatment of various allergic responses such as urticaria. In addition some antihistamines possess central actions which suppress motion sickness. Most of the current histamine antagonists exert their actions on specific $H_1$ type histamine receptors. In therapeutic doses all $H_1$ antagonists elicit side effects including anticholinergic activity. This anticholinergic activity is probably primarily responsible for the dryness of the mouth experienced by some patients prescribed antihistamines $^{152,261}$.

The classes of $H_1$ receptor antagonists and examples of them are as follows $^{261}$:

(i) Ethanolamines - diphenhydramine, dimenhydrinate, carbin-oxamine.
(ii) Ethylenediamines - antazoline, methpyrilene.
(iii) Alkylamines - chlorpheniramine.
(iv) Piperodines - diphenylpyraline.
(v) Piperazines - cyclizine, meclizine.
(vi) Phenothiazines - promethazine.

ANTIDEPRESSANTS (TRICYCLIC ANTIDEPRESSANTS, MONOAMINE OXIDASE INHIBITORS)

Depression is a frequent disorder and in its more severe and recurrent forms has a prevalence of between 1% and 2% in the population. The prevalence of all types of depressive illness in the community may be as high as 8 to 10%. The availability of antidepressant drugs has meant that patients who in the past may have been hospitalized are now treated as outpatients $^{262}$. Therefore it is not unusual to find patients presenting for dental treatment who are taking antidepressant drugs. Currently the tricyclic antidepressants are the
drugs of choice in treating depressive illness. Monoamine oxidase inhibitors (MAOI's) are being reserved for patients resistant to treatment with the tricyclics\textsuperscript{262}.

The most frequently encountered adverse reactions caused by antidepressant drugs are those attributed to anticholinergic effects including urinary retention, constipation, dizziness, tachycardia, palpitations, blurred vision and xerostomia\textsuperscript{258,263}. However, it has been noted that tolerance to the side effects of tricyclic antidepressants may develop with continued use\textsuperscript{262}.

Although it has been accepted that tricyclic antidepressants have an anticholinergic action doubts have been raised. Bein (1977)\textsuperscript{264} reported that special investigations have not been made to evaluate typical antimuscarinic effects of these drugs in man. He suggested that clinical observation of symptoms referred to as "atropine-like" have been accepted as proof of the antimuscarinic action of tricyclic antidepressants. It was stated that in evaluating functional neural changes in an organ under both sympathetic and parasympathetic control it could be difficult to decide which of the two systems was responsible for the changes. Dryness of the mouth was cited as a symptom typical of stimulation of the salivary glands by adrenergic neuroeffectors of the sympathetic nervous system. Inhibition of the parasympathetic system leading to dominance by the sympathetic system was not excluded. These hypotheses were proposed to explain the reports of xerostomia following use of the newer tricyclic drugs supposedly devoid of anticholinergic activity. Because the knowledge of the neurophysiology of the salivary glands is uncertain, Bein's (1977)\textsuperscript{264} assumption can neither be completely accepted nor refuted at present.

Imipramine and amitriptyline are the most widely used
tricyclic antidepressants. Other drugs in this group include doxepin, desipramine, nortriptyline and protriptyline\textsuperscript{258}.

Monoamine oxidase inhibitors (MAOI's) have received much attention because of their potentially fatal interaction with numerous other drugs and with amines occurring naturally in foodstuffs. It is for this reason that the use of MAOI's is tending to be restricted unless considered especially beneficial. The group of MAOI's available for treating psychiatric depression are - isocarboxazid (Marplan), phebazine (Nardil), tranylcypromine (Parnate) and nialamide (Niamid)\textsuperscript{258}.

MAOI drugs inhibit not only the enzyme after which they are named but also many other enzymes. They have numerous other effects which are probably unrelated to enzyme inhibition. Both MAO and catechol-O-methyl transferase (COMT) are of major importance in the metabolic degradation of adrenaline, noradrenaline, dopamine and 5-hydroxytryptamine. It is thought that MAO plays a significant role in the degradation of intracellular biologic amines while COMT is more important in the breakdown of circulating catecholamines. MAOI's are likely to prevent both the breakdown and release of noradrenaline from nerve endings resulting in an increase in the concentration of intracellular noradrenaline. Indirectly acting sympathomimetic amines such as amphetamine or tyramine will cause the release of the intracellular noradrenaline resulting in a marked increase in blood pressure. Therefore, MAOI drugs disrupt processes necessary to the proper function of the autonomic nervous system\textsuperscript{258}. The xerostomia reported as a less serious side effect of this group of drugs\textsuperscript{265} can probably be attributed to a disruption of the autonomic nerve supply to the salivary glands with a resultant decrease in salivary flow.
ANTIARRHYTHMIC (DISOPYRAMIDE)

Disopyramide is a relatively new drug with an antiarrhythmic action similar to that of quinidine sulphate. Side effects related to disopyramide include hepatotoxicity and cardiotoxicity but the highest incidence of adverse reactions is due to anticholinergic activity. These reactions are typically blurred vision, gastrointestinal disturbances, difficulty in micturition and xerostomia.  

DRUGS Acting ON ADRENERGIC NEUROEFFECTORS

The role of the sympathetic nervous system in the innervation of the salivary glands is not completely understood. Therefore it is difficult to be certain of the mechanisms by which drugs affecting adrenergic neuroeffectors influence salivary flow. An important factor in determining the effect of drugs on adrenergic neuroeffectors is the presence of two major types of receptors termed α and β. The β receptors are further classified β₁ and β₂ in type.  

β₁ receptors are located mainly in the heart and gastrointestinal tract while β₂ receptors are found in smooth muscle, lungs, liver and blood vessels. The parenchymal cells of the salivary glands probably contain mostly β type receptors and the blood vessels α receptors to mediate vasoconstriction. Vasodilation of salivary gland blood vessels may be effected through both β₂ adrenergic receptors and cholinergic receptors.  

Adrenaline seems to have a variable stimulatory effect on both α and β receptors depending on where these are located. The effect of adrenaline on secretory glands is not pronounced. However, the secretion from most glands is somewhat reduced following the vasoconstriction and decreased blood flow caused by adrenaline.  

The effect of the neurotransmitter noradrenaline when
released from sympathetic nerves in the salivary glands is to increase the total protein concentration of whole saliva\(^\text{258}\). The resulting increase in the viscosity of this saliva may result in a subjective impression of a dry mouth. As a drug, noradrenaline acts predominantly on \(\alpha\) receptors and probably does not significantly alter the secretory rate of saliva\(^\text{267}\).

Drugs with actions on \(\alpha\) and \(\beta\) receptors similar to adrenaline or noradrenaline are called sympathomimetics. Sympathomimetics may act by a direct action on effector cells or by stimulating the release of noradrenaline from adrenergic nerves\(^\text{267}\).

Amphetamine and its numerous derivatives which are used as CNS stimulants or even as appetite suppressants will reduce salivary flow to a limited degree\(^\text{152}\). Drugs related to amphetamine include methamphetamine, hydroxyamphetamine, methoxamine and methoxyphenamine\(^\text{267}\).

Ephedrine is a natural sympathomimetic which stimulates both \(\alpha\) and \(\beta\) receptors. This drug has direct effects on receptors and also stimulates the release of noradrenaline from adrenergic nerves. Among the other sympathomimetic drugs pseudoephedrine, phenylpropanolamine and phenylephrine are frequently used as expectorants and decongestants as well as bronchospasm relaxants\(^\text{152,265}\). These drugs are often compounded with antihistamines which have already been noted for their role in causing oral dryness. Fortunately bronchodilators are now being used which seem to have a more specific \(\beta_2\) stimulatory effect and less inhibitory action on salivary glands. Isoproterenol and salbutamol are examples of the \(\beta_2\) specific drugs\(^\text{238,268}\).

Non-selective \(\beta\) adrenergic blocking drugs such as alprenolol have been reported as causing dryness of the mouth\(^\text{265}\). If \(\beta\) blockers inhibit salivary gland secretion it could be expected that
other glands may be similarly affected. In fact, the pancreas shows a decrease in the volume and protein concentration of its exocrine secretion as a result of \( \beta \) adrenergic blockade\(^{269} \).

The decrease in salivary flow caused by either sympathetic stimulating or inhibiting drugs may be less contradictory than it would appear. The effect of sympathomimetic drugs on salivary glands could be explained by a predominance of \( \alpha \) receptor stimulation over \( \beta \) stimulation. The vasoconstriction produced by the \( \alpha \) receptors may be the cause of the reduction in salivary flow (vide supra: Haemorrhage and reduced salivary flow, p.115). \( \beta \) adrenergic blockers may result in reduced salivary flow by allowing unopposed \( \alpha \) receptor vasoconstriction in salivary glands.

DRUGS AFFECTING BODY WATER AND ELECTROLYTE BALANCE

**DIURETICS AND LAXATIVES**

Diuretics are agents that increase the rate of urine formation. The maintenance of an adequate urine volume may be sought in an attempt to prevent extensive renal damage during acute renal failure. The most important use of diuretics is for the removal of oedema fluid such as occurs in congestive cardiac failure. Most diuretics act directly on the kidney, affecting tubular rather than glomerular filtration. The actions of the different diuretic drugs can be found in pharmacology texts\(^{270}\).

Examples of the classes of diuretic agents are\(^{265,270}\):

(i) osmotic diuretics: mannitol.

(ii) inhibitors of carbonic anhydrase: azetilamide, ethoxzolamide.

(iii) benxothiadiazines: chlorothiazide, hydrochlorothiazide, cyclopethiazide, methylchlothiazide, cylothiazide, clorexolone (similar structure and actions to chlorothiazide
although not a benzo thiadiazine\(^{257}\).

(iv) high-ceiling diuretics: ethacrynic acid, frusemide.

(v) aldosterone antagonists: spironolactone.

(vi) potassium sparing diuretics: triamterene, amiloride.

Chlorothiazide and hydrochlorothiazide have been reported as causing a dry mouth\(^{271}\). These benzo thiadiazines have also been reported as causing sialadenitis\(^{265}\). This sialadenitis could be allergic in type but is more probably secondary to a reduction in salivary flow.

Theoretically the activity of carbonic anhydrase in salivary glands could be disrupted by the carbonic anhydrase inhibitors (vide supra: Modification of acinar fluid by striated ducts, p.32). However at therapeutic doses these drugs do not interfere with gastric or pancreatic secretions and it is unlikely that they affect salivary flow\(^{270}\). The other diuretics may alter body fluid and electrolyte balance sufficient to cause dehydration and then xerostomia (vide supra: Dehydration and the secretion of saliva, p.114). Although diuretic therapy does not appear to be a frequent cause of xerostomia it should be at least considered when a patient taking diuretics complains of a dry mouth.

Antidiuretics which mimic the actions of antidiuretic hormone may cause xerostomia and the effect of ADH has been noted (vide supra: Dehydration and the secretion of saliva, p.114).

Laxatives and cathartics are drugs that promote defecation. The distinction between the two is that laxatives cause elimination of soft formed stool whereas cathartics cause a more fluid evacuation. Excessive use of cathartics without adequate fluid replacement may lead to dehydration and to xerostomia. Cathartics may be saline in type, such as magnesium sulphate, sodium phosphate and potassium
tartrate or contact (stimulant) type, such as caster oil, phenolphthalein, bisacodyl, senna, danthron and cascara\textsuperscript{272}.

Some antibiotics may cause xerostomia probably as an indirect effect by causing diarrhoea and dehydration. Carindacillin, a semisynthetic antibiotic, and griseofulvin have been reported to have caused dry mouths\textsuperscript{273}. Clindamycin may also cause diarrhoea of sufficient severity to lead to dehydration and xerostomia\textsuperscript{265}.

**DRUGS DIRECTLY AFFECTING SALIVARY GLAND CELLS**

Antineoplastic or chemotherapeutic agents are used to destroy or suppress the growth and spread of malignant cells. The efficacy of antineoplastic agents results from their interference with the metabolism or the reproductive cycle of tumour cells. Antineoplastic agents are not selective in their action and they often damage and destroy normal as well as malignant tissues. This non-selectivity of action produces numerous side effects including bone marrow suppression, gastro-intestinal disturbances and hepatotoxicity. One of the less serious side effects of antineoplastic agents is reduced salivary gland secretion resulting in xerostomia\textsuperscript{274}. However one treatment in Sjögren's syndrome involves the use of antineoplastic agents (vide infra: Management of Sjögren's syndrome, p.250).

**DENTAL IMPLICATIONS OF DRUGS WITH XEROSTOMIC POTENTIAL**

A wide range of drugs can cause xerostomia. As most of these have a justifiable or essential role in medical treatment it is impractical to suggest that their use be discontinued for a relatively minor side effect. However, dental practitioners need to be aware of the xerostomic potential of medications because of the oral problems related to this side effect. Patients experience discomfort with a
dry mouth and are subjected to a significantly increased risk of
dental caries. A further complication of drugs causing reduced
salivary flow is the predisposition to ascending infection of salivary
glands (vide supra: Acute sialadenitis, p. 149). If medications are
found to be responsible for a patient's xerostomia then possible
alternatives should be discussed with the patient's physician.

According to Whaley, Williamson and Mason et al (1973)\textsuperscript{275}
patients with drug induced xerostomia have normal salivary flow rates
when stimulated with lemon juice. Therefore if drug therapy cannot
be altered reflex stimulation of salivary flow may be useful (vide
infra: Stimulation of salivary flow, p.281).

\textbf{NOTE:}

See Appendix for drugs with xerostomia as a reported or
potential side effect, p.289.
XEROSTOMIA IN NUTRITIONAL AND METABOLIC DISORDERS

Dietary and vitamin deficiencies may cause not only inflammatory and atrophic changes in mucous membranes but also atrophy in salivary and lacrimal glands resulting in a failure of secretion. In developed countries acute and severe vitamin deficiencies are rare. However, subclinical nutritional and vitamin deficiencies are more frequent and these may cause profound physiological disturbances. The most frequent cause of nutritional deficiency is a decreased intake of essential nutrients. Other factors contributing to deficiency states include: impaired absorption from the alimentary tract; failure of utilization by the tissues; inadequate storage; increased metabolism due to rapid growth, fever and pregnancy.

Vitamin A and the B complex vitamins, thiamine (B₁), riboflavin (B₂) and niacin (B₃) are of interest for their possible roles in reducing salivary flow and causing oral dryness. Although classical descriptions of individual B group deficiencies are given, nutritional disturbances tend to involve more than a single vitamin. For instance, niacin deficiency has been associated with deficiencies of thiamine, riboflavin and cyanocobalamin (B₁₂) as well as lack of protein.

Pernicious and iron deficiency anaemias have also been reported to cause sufficient disturbance of salivary gland function to produce a dry mouth. Also impaired liver and pancreatic function have been related to reduced activity of the salivary glands.

VITAMIN A DEFICIENCY

Vitamin A is necessary for the synthesis of rhodopsin, (visual purple) in the retina. Rhodopsin is formed by the attachment of vitamin A to a binding protein and when light acts upon this complex vitamin A is destroyed. Therefore a continual supply of
vitamin A is necessary for vision in subdued light\textsuperscript{279,280}. The other function of vitamin A is the maintenance of the structure and integrity of both covering and glandular epithelial tissue\textsuperscript{279}.

Vitamin A is found in foods such as the fats of dairy products, eggs, liver, kidney and marine liver oils and as carotenoids which are the yellow pigment of most fruit and vegetables\textsuperscript{279,281}. Carotenoids, converted to vitamin A in the intestine, are stored in the liver which contains the body's largest concentration of the vitamin. The liver synthesizes transport proteins which convey vitamin A throughout the body. Vitamin A deficiency may result from dietary lack, interference with intestinal absorption, or from disturbances in transport or storage\textsuperscript{277}.

One of the earliest symptoms of vitamin A deficiency is the inability to see in subdued light, often called night blindness. Other ophthalmological pathology may follow the reduction of lacrimal gland secretion causing xerophthalmia leading to corneal ulceration and possibly ultimately to blindness\textsuperscript{277}.

Epithelial tissues, primarily those which are non-keratinized, are affected by vitamin A deficiency, including the epithelium of the upper and lower respiratory tract, genitourinary tract, eye, pancreas, lacrimal and salivary glands. The cells in the affected tissues fail to differentiate normally and they revert to a stratified squamous epithelium with keratin production. This process is termed keratinizing squamous metaplasia. The basal cells in all areas retain their potential to revert to normal if the supply of vitamin A is restored\textsuperscript{277,280}.

Hyperkeratosis of the oral mucosa and various skin lesions with abnormal roughness and dryness may develop in chronic vitamin A deficiency. Darrier's disease or keratosis follicularis has been
associated with vitamin A deficiency in man\textsuperscript{279,280}.

Enamel hypoplasia from disturbed amelogenesis has been noted in an infant with vitamin A deficiency\textsuperscript{279}. Salley and Bryson (1957)\textsuperscript{282} confirmed that the changes in the odontogenic tissues of rats were squamous metaplasia of odontoblasts and irregular dentin formation. Significant developmental lesions in human tooth enamel cannot occur after six years of age because by this time the crowns of all permanent teeth, except the third molars, have formed\textsuperscript{280}.

\textbf{CHANGES IN SALIVARY GLANDS DUE TO VITAMIN A DEFICIENCY}

Salley and Bryson (1957)\textsuperscript{282} reported that hamsters deficient in vitamin A for fifteen weeks showed the most marked tissue changes in both the major and minor salivary glands. Complete degeneration of all or part of the major salivary glands was observed. The serous portion of the submandibular glands showed the earliest and most severe morphological changes; mucous acini were less severely affected. In the parotid glands, metaplasia and degeneration occurred but at a later time. Macroscopically the glands were replaced by sac-like structures full of purulent material. Microscopic changes consisted of epithelial metaplasia of ducts and acini characterised by a keratinized squamous epithelium. The ducts and acini were often filled with plugs of keratin. Sialadenitis and fibrosis were other features noted in the glands examined. Remarkably, although there were marked histopathological changes in the salivary glands the investigators reported that none of the vitamin A deficient hamsters showed xerostomia. The reliability of this observation of the lack of xerostomia must be questioned. Destruction of the glands was considered to be secondary to duct obstruction by keratin followed by retrograde infection.
Salley, Bryson and Eshleman (1959) described the changes in the salivary glands of hamsters deficient in vitamin A for thirty weeks. The histological findings were similar to those reported earlier by Salley and Bryson (1957). However, xerostomia was observed in the deficient animals during the course of the 1959 study. It was concluded that degenerative alterations in the salivary glands accounted for the xerostomia. Carious lesions were evident in the vitamin A deficient animals from both studies and these lesions were attributed to changes in the quality and quantity of saliva.

Trowbridge (1969) summarized the principal effects of vitamin A deficiency in rats to be acinar atrophy and proliferation, distention and squamous metaplasia of duct epithelium. Obstruction of excretory ducts frequently occurred when metaplasia resulted in the formation of keratinizing epithelium. Although much evidence of duct metaplasia was seen, keratinization was not a consistent feature. Inflammatory changes were related to degenerative alterations in the ducts or to infection in the glands, although the inflammatory changes were not seen in all of the salivary glands of all deficient animals. This tends to confirm that sialadenitis in vitamin A deficiency is secondary to degenerative gland alterations and is not a direct result of the deficiency.

Jolly (1964) noted that there were few reports on the histopathological changes in the salivary glands of humans deficient in vitamin A. This is still the case, probably because vitamin A deficiency is infrequently seen. Patients with vitamin A deficiency reported by Wilson and Dubois (1923) and by Blackfan and Wolbach (1933) showed histopathological changes in their salivary glands similar, although less marked, to those observed in vitamin A deficient animals. Areas of acinar atrophy, keratinizing squamous
metaplasia of ducts and areas of cellular inflammatory infiltrates were noted.

XEROSTOMIA AND VITAMIN A DEFICIENCY

Bertram (1967)\textsuperscript{278} and Allington (1950)\textsuperscript{153} cited early reports of vitamin A deficiency as a cause of xerostomia. Both authors appeared to question the diagnosis in some of these reports. Bertram (1967)\textsuperscript{278} stated that in two patients described in the literature other causes such as diabetes mellitus and connective tissue disease could have caused the xerostomia. The confusion over some of the early reports may have resulted from misdiagnosis because xerostomia and xerophthalmia are common to both vitamin A deficiency and Sjögren's syndrome. Nevertheless the alterations seen in the salivary glands of vitamin A deficient animals and humans suggests that the deficiency has the potential to produce xerostomia. As the histopathological features of salivary glands affected by vitamin A deficiency are quite specific diagnosis is possible following biopsy and histological examination of minor salivary glands (vide supra: A technique of labial salivary gland biopsy, p. 70).

SPECIFIC B COMPLEX VITAMINS

The literature contains few reports on the effect of B-complex vitamins on the structure and function of the salivary glands. However references have been made to the improvement of xerostomia following administration of riboflavin and niacin\textsuperscript{153,227,278,288}. Chronic deficiency of B-complex vitamins has been associated with the enlargement of the tongue, the parotids and at times, the submandibular glands\textsuperscript{279}.

The B-group vitamins, thiamine, niacin and riboflavin have
similar dietary sources and so it is not surprising that deficiencies of these tend to occur together. Milk, fish, eggs, liver and green leafy vegetables are rich in riboflavin. Thiamine is found in lean meats including pork and organ meats, legumes, green leafy vegetables and nuts. Niacin is most concentrated in liver, yeast, red muscle meats, fish, coffee, wheatgerm and nuts. Where protein intake is adequate deficiency of these three vitamins is unlikely to occur. Alcoholics are especially prone to B-complex vitamin deficiency due to inadequate protein intakes.

Thiamine is essential in carbohydrate metabolism; riboflavin affects ectodermal tissues and is required in cellular oxidation processes; and niacin is concerned with tissue respiration, fat synthesis and glycolysis.

DEFICIENCY SYMPTOMS

THIAMINE

Severe thiamine deficiency is referred to clinically as beri beri. The most pronounced symptom of severe thiamine deficiency is a multiple neuritis. Paraesthesiae with soreness and weakness of muscles may be severe enough to make walking difficult. Cardiac changes may accompany the neurological symptoms or they can appear alone. Dependent and pulmonary oedema and other signs of congestive cardiac failure are often present. Chronic diarrhoea with inflammatory lesions in the intestinal tract may complicate the nutritional state. Thiamine deficiency can also produce definite behavioural changes such as depression, agitation, anxiety and psychosis.

Thiamine deficiency alone rarely, if ever, causes severe oral symptoms. However, hypersensitivity and colour changes of the oral mucosa, enlargement of fungiform papilla of the tongue and small
fissures in the vermilion border of the lips have been described\textsuperscript{279}. Smith (1976)\textsuperscript{289} reviewed reports on the role of vitamin deficiencies in the development of cheilitis and angular cheilitis and found conflicting results. Cheilitis, angular cheilitis and atrophic glossitis caused by nutritional deficiencies could not be attributed to any specific nutrient factor.

RIBOFLAVIN

Deficiency of riboflavin primarily involves epidermal tissues with the mucous membranes of the mouth and cornea most frequently involved. The oral mucosa and the vermilion border of the lips may develop a magenta or purple colour similar to mild cyanosis. Angular cheilitis, cheilitis and a sore throat are early findings in this deficiency. Ocular changes may lead to visual impairment and photophobia. A seborrhoeic dermatitis of the face, especially the nasolabial folds and ala of the nose\textsuperscript{276}, and a generalized dermatitis of the trunk and extremities can occur.

Glossitis in riboflavin deficiency ranges from soreness and atrophy of filiform papillae to complete atrophy of all papillae giving the tongue a smooth glazed appearance. A normochromic, normocytic anaemia can be induced experimentally in primates by creating a deficiency of riboflavin. This riboflavin deficiency anaemia is linked to other types of anaemia such as iron deficiency and pernicious anaemias by the glossitis they can all produce.

Diagnosis of riboflavin deficiency can be difficult because its signs are not specific.

NIACIN

Pellagra is the name given to severe niacin deficiency.
Classically, pellagra has been characterized by the four "D's" of diarrhoea, dermatitis, dementia and death. Prior to any of these, patients may have vague complaints such as burning sensations, paraesthesiae, anorexia, lassitude, headaches and vertigo. The involvement of the skin in this deficiency consists of a symmetrical red scaly dermatitis of the neck, stocking and glove areas of the body.

The behavioural changes seen in thiamine deficiency can also occur in pellagra\(^ {281} \).

A sore mouth is often the initial complaint in niacin deficiency. The oral mucosa and tongue may become fiery red and complete atrophy of the tongue papillae may occur. These oral lesions frequently become secondarily infected and they are more varied and severe than the lesions occurring with deficiencies of other B vitamins.

VITAMIN B-GROUP DEFICIENCY AND XEROSTOMIA

It seems probable, but not certain, that deficiencies of some B-group vitamins will cause xerostomia. Firstly, the discomfort from the inflammatory involvement of the oral mucosa in these deficiencies could obscure patient assessment of the degree of oral dryness. Secondly, both salivation and lacrimation have been reported 153,276 in arboflavinosis and niacin deficiencies.

Faber (1943)\(^ {227} \) and Allington (1950)\(^ {153} \) reported patients with xerostomia who showed improvement in their condition when administered specific B vitamins or B-complex vitamin supplements. Faber (1943)\(^ {227} \) was certain that at least one of his patients with xerostomia was suffering from arboflavinosis and treatment with the vitamin was successful. Saphir (1940)\(^ {288} \) reported the case of a patient treated successfully for xerostomia with nicotinic acid. However it was noted that the patient lacked classic symptoms of
niacin deficiency. Stein and Gold (1955) showed that the serous glands of von Ebner in the tongue underwent degenerative or atrophic changes in response to nutritional deficiency. The tongue was said to be dry but no mention was made of any changes in the major salivary glands. If the tongue is dry it is probably reasonable to assume that the major salivary glands have a reduced secretion. Since the patients reviewed were terminal cancer sufferers factors such as protein and carbohydrate malnutrition could have influenced the oral changes.

Effects of thiamine, niacin and riboflavin deficiencies could indirectly disrupt salivary gland function. Lack of either thiamine or niacin may cause psychogenic changes such as anxiety, psychosis and depression which may cause xerostomia. These deficiencies can also cause diarrhoea with subsequent dehydration which reduces salivary flow. Congestive cardiac failure and oedema which may complicate thiamine deficiency may also cause xerostomia.

MALNUTRITION AND MALABSORPTION

Brief mention needs to be made of the role of malnutrition and malabsorption in the etiology of xerostomia. These conditions may cause a deficiency of vitamins and poor nutrition of salivary gland parenchyma which may reduce salivary flow.

In young animals, malnutrition has been shown to result in atrophy of salivary glands and a decrease in the salivary flow. As a result the caries rate of these malnourished animals was significantly greater than that of control animals.

Disorders of absorption have many causes and these have been reviewed by Greenberger and Isselbacher (1977). Decreased salivary secretion has been reported in cases of sprue. Also, steatorrhoea may occur in patients with endocrine disorders such as diabetes mellitus,
adrenal insufficiency and hyperthyroidism\textsuperscript{291}. Malabsorption may in part account for the reports of xerostomia related to these endocrine diseases\textsuperscript{84,152}. Endocrine disorders may also reduce salivary secretion by interfering with normal body fluid and electrolyte concentrations (\textit{vide supra}: Dehydration pathways, p. 112).

ANAEMIA

The term anaemia will be used to describe a reduction in the haemoglobin concentration of the circulating blood. Impaired tissue oxygenation is the major deficit caused by low haemoglobin concentration. The following list is a simple etiological classification of anaemia\textsuperscript{293}:

(i) Increased loss of red cells - haemorrhage causing iron deficiency anaemia.

(ii) Increased rate of red cell destruction - haemolytic anaemia.

(iii) Decreased red cell production - nutritional disorders, iron deficiency anaemia and pernicious anaemia.

- bone marrow failures.

Anaemia and its resultant tissue hypoxia is reflected in certain characteristic body changes. The skin becomes pale, thin and inelastic as the dermis and epidermis atrophy. The nails may become brittle and assume a concave spoon-shaped appearance (koilonychia). Cells especially susceptible to hypoxia may undergo fatty change or even ischaemic necrosis. Such damage is most frequently seen in heart muscle, epithelial cells in the proximal convoluted tubules of the kidney, centrilocular hepatic cells and in the ganglion cells of the cortex and basal ganglia. In addition to these hypoxic changes anaemic patients may suffer haemosiderosis\textsuperscript{293}. 
ORAL CHANGES IN ANAEMIA

Both iron deficiency and pernicious anaemias have been reported to produce xerostomia. Tyldesley (1975) reviewed the types of anaemia which may produce oral signs and symptoms and refers to iron deficiency and pernicious anaemias. The oral signs and symptoms of both these anaemias occur as a result of basic changes in the metabolism of oral epithelial cells which are susceptible to minor variations in the quality of their blood supply. These metabolic changes result in abnormalities of cell structure and keratinization which often result in atrophy of the oral mucosa. Atrophic changes affecting the filiform papillae of the tongue may cause their complete loss.

Jones (1973) considered that the tongue in iron deficiency anaemia is often painless but in appearance it may be bald, red and glazed. Pain was a feature in patients whose tongues showed vesicle or ulcer formation. Bertram and Hjørting-Hansen (1968) described the most frequent oral changes in pernicious anaemia as burning and itching sensations in the tongue; atrophy of filiform and later fungiform papillae lead to a smooth, fiery red dorsal surface (Hunter's glossitis). The tongue may show signs of fissuring but is more often lobulated as seen in xerostomia.

The oral changes in anaemia are not restricted to the tongue as an irregular red enanthema or frank ulceration and generalized soreness may occur. Anaemic patients are susceptible to angular cheilitis and to infection by Candida albicans. Disturbances in taste can develop and they are probably related to atrophy of the tongue epithelium causing disruption of underlying nerve endings. The taste changes may also be related to a reduction in the flow of saliva since saliva is involved in the taste process (vide supra: Functions
BIOCHEMICAL AND CELLULAR CHANGES IN ANAEMIA

Hypoxia causes tissue changes such as fatty degeneration in anaemic patients. Other changes seen in mucosal and epithelial tissue appear to be caused in part by biochemical lesions. Rose (1968) suggested that low plasma iron concentration would deprive cells of sufficient iron to synthesize iron-containing enzymes such as cytochrome, cytochrome oxidase, catalase and peroxidase. Both human and animal subjects deficient in iron have been shown also to be deficient in cytochrome oxidase.

In iron deficiency anaemia, keratin develops in normally non-keratinized epithelium, while in the megaloblastic anaemias binucleated cells are frequently seen in the epithelium. Changes such as these are unlikely to be a direct result of anaemia because they may occur in other conditions such as sideropenia and sprue in which there are normal haemoglobin concentrations. The cellular abnormalities are probably the result of multiple metabolic defects which result from iron and vitamin $B_{12}$ deficiencies.

GENERAL FEATURES OF IRON DEFICIENCY ANAEMIA

Iron deficiency anaemia is the type of anaemia most often encountered clinically, especially in females of child bearing age, and it is the sign of an underlying problem of iron metabolism. The deficiency of iron may result from inadequate absorption, physiological losses exceeding intake as in pregnancy and from pathological blood loss specifically haemorrhage.

Rose (1968) and Tyldesley (1975) described the typical stages of iron deficiency as:
Stage 1 - Health

Normal levels of: Iron stores (marrow, spleen)
Serum iron
Transferrin (iron transport protein in blood)

Stage 2 - Pre-latent iron deficiency

Decreased or depleted: Iron stores
Normal levels of: Serum iron
Transferrin
Haemoglobin

Stage 3 - Latent iron deficiency (sideropenia)

Decreased: Serum iron
Increased: Transferrin (this means that the percentage saturation of this protein is reduced)

Normal: Haemoglobin

Stage 4 - Iron deficiency anaemia

As for stage 3 except haemoglobin concentration is reduced below normal.

Oral symptoms can appear in the third and fourth stages of iron deficiency. This means that oral lesions caused by iron deficiency can occur in patients without the presence of anaemia but with sideropenia 295,297,298.

GENERAL FEATURES OF PERNICIOUS ANAEMIA (ADDISONIAN ANAEMIA)

This disease is the most frequent and important of the vitamin B₁₂ (cobalamin) deficiency syndromes. It usually occurs in middle aged patients who often have blue or grey-blue eyes and prematurely grey hair. The onset is classically insidious.
and patients affected may be extremely pale and severely anaemic without symptoms of anaemia. Occasionally a slight icterus of the skin and eyes may be found and often paraesthesia of the fingers and more seldom of the feet is present. Neurological complications may be severe enough to cause paresis and spasticity with difficulty in walking or inco-ordination of movement\textsuperscript{293,294}.

Pernicious anaemia is caused by a lack of intrinsic factor which is formed in the gastric mucosa and complexes with vitamin $B_{12}$ in the stomach. Intrinsic factor then facilitates the absorption of $B_{12}$ from the distal ileum\textsuperscript{293,295}.

An autoimmune reaction against antigens in the gastric mucosa causes a severe chronic atrophic gastritis which destroys gastric parietal cells. Because the parietal cells produce both hydrochloric acid and intrinsic factor their loss results in pernicious anaemia\textsuperscript{293,294}.

The major effect of a lack of cobalamin is delayed DNA synthesis in all proliferating cell systems throughout the body. Principally affected are the bone marrow, tongue, buccal mucosa and alimentary tract. The actively proliferating cells develop various morphological changes including increased cell and nuclear size. The effect on bone marrow is a derangement of erythropoiesis with transformation of erythroblasts to megaloblasts. Thus pernicious anaemia is classified as a macrocytic anaemia\textsuperscript{293,299}.

It should be noted that a deficiency of cobalamin may arise other than in pernicious anaemia from such as dietary deficiency, with total gastrectomy or severe gastritis, and from intestinal mal-absorption including sprue\textsuperscript{293}. 
FOLIC ACID (Pterygoglutamic acid [PGA]) DEFICIENCY

Folic acid is necessary for the normal function of the haemopoetic system. A deficiency of folic acid can cause a macrocytic anaemia with similar cytological affects as a deficiency of vitamin $B_{12}$. The most frequent cause of PGA deficiency is inadequate intake and so it is widespread among malnourished populations and alcoholics and among pregnant women who have an increased dietary requirement for this vitamin. Also any of the malabsorption syndromes or persistent vomiting may lead to a deficiency of folic acid. Drugs which may interfere with the absorption or utilization of PGA include methotrexate, mercaptopurine, 5 fluorouracil, diphenylhydantoin and some of the oral contraceptives. Rose (1971) reported angular cheilitis and atrophic changes in the tongue in two patients deficient in folic acid but not showing anaemia.

THE LIVER AND PANCREAS AND REDUCED SALIVARY FLOW

Nutritional and metabolic disturbances which are part of the morbidity of the liver and pancreatic disorders are apparently responsible for morphological changes in the parotid glands. Bertram (1967) noted that liver disease had been reported as a cause of xerostomia although few other reports have been published. The role of diabetes mellitus in reducing salivary flow through dehydration has been mentioned (vide supra: Dehydration pathways, p. 112). Chronic pancreatitis related to high alcohol consumption has been reported concurrent with reduced secretion of saliva. Sjögren's syndrome has been found in association with chronic active hepatitis (vide infra: Associated disorders, p. 220).
Enlargement of the parotid glands without involvement of other salivary glands has been reported in alcoholic cirrhosis by Mason and Chisholm (1972)\textsuperscript{302} and Rothbell and Duggan (1957)\textsuperscript{303}. Borsanyi and Blanchard (1960)\textsuperscript{304} noted parotid enlargement in Laennec's cirrhosis where chronic alcohol consumption is often a feature. While parotid enlargement occurs most frequently in alcoholics with cirrhosis it may also occur in alcoholics without cirrhosis\textsuperscript{302}. Malnutrition which is a contributing factor in the development of alcoholic cirrhosis has also been shown to induce a non-inflammatory enlargement of the parotid glands\textsuperscript{303,305}. Rothbell and Duggan (1960)\textsuperscript{303} considered that parotid enlargement in alcoholic cirrhosis had much the same significance as a fatty liver pointing to a disturbance in nutrition or metabolism but not defining that disturbance. Borsanyi and Blanchard (1960)\textsuperscript{304} described the characteristic histological changes of enlarged parotid glands of patients with alcohol cirrhosis as:

(i) hypertrophy of gland cells due to oedema of individual acinar cells.

(ii) increase in the numbers of secretory granules in acinar cells.

(iii) fatty infiltration.

(iv) a moderate degree of fibrosis.

Mason and Chisholm (1975)\textsuperscript{302} stated that chronic secondary infection is present in the glands of almost 50% of patients with parotid enlargement due to cirrhosis.

Minnaire, Descos and Lambert (1975)\textsuperscript{301} noted that the enlargement and histological changes that occurred in the parotid glands of alcoholic patients with chronic pancreatitis were similar to the changes in alcoholic patients with cirrhosis. The changes
affecting both types of patients were said to be due to the large alcohol intake rather than any specific process affecting the salivary glands, the liver or the pancreas. It was also suggested that a large alcohol intake decreases the sensitivity of the neural control of salivation resulting in a lower resting salivary flow rate without affecting the secretory capacity of the salivary glands. The resting flow rates of saliva in this study averaged 6.6 mls per 10 minutes. Previous studies indicate that this value would not be low enough to cause xerostomia (vide supra: Salivary flow rate in patients with xerostomia, p. 77).

Sialosis is the term used to describe a non-inflammatory, non-neoplastic and bilateral enlargement of salivary glands. When nutritional disorders, specifically as associated with alcoholism, affect the liver and pancreas, an asymptomatic enlargement of the parotid glands and occasionally other salivary glands may occur\(^{302, 303, 304}\). The salivary gland swelling associated with alcoholic cirrhosis and chronic pancreatitis fits into this general category of sialosis\(^{302}\). Sialosis, uncomplicated by acute infection, seems unlikely to exhibit xerostomia as a symptom.
AGENESIS OF SALIVARY GLANDS

Agenesis or aplasia of salivary glands refers to the congenital absence or rudimentary development of salivary gland structure.\(^{214,306}\)

Smith and Smith (1977)\(^{307}\) reviewed the reports of congenitally absent salivary glands in the literature and since 1885 only 16 cases had been presented. Eleven of these cases were living subjects and the remaining five were discovered following post-mortem examination. The salivary gland most frequently reported to be absent either singly or bilaterally was the parotid. The contribution of the parotid glands to the moistness of the mouth has been noted (vide supra: Obstruction and xerostomia, p. 146).

Ramsey (1924)\(^{308}\) reported a case of hereditary congenital absence of salivary glands in a three year old child. At no time was salivary secretion present in the child’s mouth and her father showed a similar xerostomia.

Smith and Smith (1977)\(^{307}\) reported the second recorded incidence of a patient showing congenital absence of salivary glands with a familial pattern in a five year old boy missing both right and left parotid and submandibular glands. The patient’s father was examined and was found to lack submandibular and parotid glands on the right side. Neither father nor son had detectable abnormalities other than absence of salivary glands.

Hereditary ectodermal dysplasia in its most frequent form is a syndrome displaying a sex-linked recessive inheritance seen in males. Signs of the syndrome include lack of normal hair and sweat glands, deformed nails, saddle-shaped nose, frontal bossing and protruberant lips. Affected people may find warm temperatures unbearable because they lack sweat glands. Oligodontia or anodontia
invariably manifest in the syndrome and any teeth present are usually a conical shape. A high vaulted palate or a cleft palate is another frequent feature\textsuperscript{309,310}. Besserman-Neilsen (1971)\textsuperscript{311} reported that both major and minor salivary glands may be hypoplastic in hereditary ectodermal dysplasia with xerostomia as a result. Labial salivary gland biopsy will readily confirm the absence of minor salivary glands. Faber (1942)\textsuperscript{312} reported that a notable reduction in salivary secretion from hypoplastic glands could be found in a few cases of hereditary ectodermal dysplasia.

Wood and Mitchell (1962)\textsuperscript{313} described the case of a fifteen year old boy with major salivary gland dysfunction where the salivary glands appeared to be present but no flow of saliva could be detected. Both Wharton's and Stensen's ducts also seemed to be present although their orifices could not be located. A provisional diagnosis of hereditary ectodermal dysplasia was made because of the patient's sparsity of hair and the suggestion of spooned nails. However, further examination failed to reveal other characteristics of the syndrome; none of the immediate relatives were affected and the patient was not particularly uncomfortable when hot.

McKenzie and Craig (1955)\textsuperscript{314} noted the absence of parotid glands following the autopsy of a child with Treacher Collins syndrome. This syndrome is often hereditary or familial and manifests a number of defects of the head and face including malformation of the eye-lids and of the external ear and other embryonic faults which contribute to the bird-like appearance of the face\textsuperscript{315}. Absence of salivary glands is probably not a frequent feature of Treacher Collins syndrome but the possibility exists.

In past reports\textsuperscript{313,316} of agenesis of major salivary glands palpation has been relied upon to determine the presence or absence
of individual glands. However, this method is not always reliable because non-diseased glands are not usually palpable. If necessary, patients suspected of lacking one or more of their parotid or sub-mandibular glands can be examined using radioisotope scans\textsuperscript{307} (vide supra: Radioisotope scanning, p. 102).
SJÖGREN'S SYNDROME

The various features of Sjögren's syndrome were described during the late nineteenth century but it was not until 1933 that a Swedish ophthalmologist, Henrik Sjögren gave a full description of the syndrome that carries his name.\(^{317}\)

There is general agreement that Sjögren's syndrome (SS) consists of a triad of keratoconjunctivitis sicca ("dry eyes"), xerostomia and rheumatoid arthritis or some other connective tissue disease. The diagnosis is made when any two of the three main components are present. The term sicca syndrome is used when only xerostomia and keratoconjunctivitis sicca are present\(^{55,318,319,320,321,322,323}\).

Sjögren's syndrome is the most significant systemic condition involving xerostomia and among the connective tissue diseases this syndrome ranks second in frequency to rheumatoid arthritis (RA). Between 11% and 20% of patients with RA have keratoconjunctivitis sicca (KCS), approximately 1% of RA patients have oral symptoms but up to 28% of RA patients may have subclinical SS. However, the frequency with which SS is recognised depends largely upon the awareness of the examiner who sees the patient.\(^{55,324,325}\).

The xerostomia of Sjögren's syndrome results from a destruction of the salivary glands by lymphocytic infiltration.\(^{322}\) Salivary gland enlargement frequently accompanies other signs of this disease.\(^{323}\)

AGE AND SEX DISTRIBUTION

Whaley, Williamson, Chisholm et al. (1973)\(^{317}\) studied the sicca components of 153 female and 18 male patients with SS and calculated their mean age to be 57.2 years. Bloch, Buchanan, Wohl
et al (1965)\textsuperscript{319} presented a study of 62 patients with SS and all but three of these were female. The majority of the female patients developed their first sicca symptoms during the fourth, fifth and sixth decades. Thus investigators examined an association between the menopause and the development of SS but no relationship was found. Other reports\textsuperscript{55,318,321,326} confirmed the predilection of SS for women and for those over forty years of age.

Athreya, Norman, Myers et al (1977)\textsuperscript{327} noted that although SS in children is a relatively infrequent condition it does occur. They described the features of SS in two females with onset at ages seven and twelve years and listed six reports of SS affecting children between four and twenty years of age.

Fraga, Gudino, Ramos-Niembro et al (1978)\textsuperscript{328} reported SS in three children at ten, twelve and fifteen years of age in association with mixed connective tissue disease (an entity characterized by the combination of the clinical and laboratory data of systemic lupus erythematosus, scleroderma and polymyositis).

**ETIOLOGY**

In a broad sense SS can be considered a chronic inflammatory disease with diverse features and involvement of many body systems\textsuperscript{321}. Although the cause of the syndrome remains unknown a number of factors, genetic, immunologic and viral, have been implicated. Kassan and Gardy (1978)\textsuperscript{318} considered that SS has evolved from a medical curiosity to a link between a number of major disorders including autoimmune disease, lymphoproliferative malignancies and the dysproteinaemias.

The role of hereditary factors in the etiology of SS was suggested following observations of familial incidence. Studies of blood relatives of patients with connective tissue diseases such as
RA, systemic lupus erythematosus (SLE), and progressive systemic sclerosis have indicated that the serological abnormalities found may be familial. Block, Buchanan, Wohl and Bunim (1965) found that the relatives of numerous patients in their study of SS had abnormalities which are often related to immune disorders. Two patient's mothers had symptoms suggestive of SS, one patient had a brother who died of lymphosarcoma. Six patients had a history of thyroid disease. Another nine patients had relatives with the following findings:

(i) possible or probable RA
(ii) decreased tear formation
(iii) antibodies reacting with thyroid or thymus components
(iv) elevated levels of gamma globulins.

The advent of histocompatibility tissue typing has emphasized the role of genetics in numerous disease states. The tissues of all animals including man possess histocompatibility (H) antigens, also called transplantation antigens, which are either bound to, or included in, the plasma membrane of the cells. These H antigens are responsible for the immune response when tissues or cells are transferred from one member of a species to another. The major histocompatibility system known at present in man is referred to as the human leukocyte antigen system (HLA). An analogy to the HLA system of tissue antigens is the ABO blood system where twenty or more different antigens have been discovered. However, only the ABO and Rh antigens are sufficiently strong to cause immunological reactions between blood donor and blood recipient. So perhaps the HLA system will be found to be the major immunological barrier in causing rejection of tissue and organ transplants.

However Kassan and Gardy (1977) indicated that the
HLA-DW3 and HLA-B8 tissue antigens are found almost exclusively in patients with sicca syndrome but not in those with Sjögren's syndrome involving a connective tissue disorder. They considered that sicca syndrome may have a different etiology to SS (which includes a connective disorder) because of differences in the HLA antigens and serological features of the two entities. Webb (1978)\textsuperscript{324} considered that the high frequency of rheumatoid factors in the serum of both sicca syndrome and SS may require clinical separation of these syndromes on the basis of inflammatory nodular polyarthritis in the latter but its absence in the former.

Lawley, Peck, Moutsopoulos et al (1977)\textsuperscript{331} described the development of Sjögren-like-syndrome in a patient who developed chronic graft-versus-host disease following a bone marrow transplant. The patient had acute myeloid leukaemia and received the marrow allograft from his brother who shared several identical antigens of the HLA system. The patient developed scleroderma, xerophthalmia and xerostomia in association with his chronic graft-versus-host disease despite methotrexate therapy. These findings give further evidence of the immunological and genetic factors in the development of SS.

Studies of inbred New Zealand black and white mice have shown that genetic, immunological and viral factors may all have a role in the development of SS\textsuperscript{318,320}. After the fourth month of life the mice spontaneously develop abnormalities and produce multiple auto-antibodies resembling those seen in SS. The abnormalities increase in severity with age, especially in females\textsuperscript{55}. Multiorgan involvement includes infiltration of the salivary glands by lymphocytes and plasma cells as well as development of lymphoid neoplasms\textsuperscript{320}.

New Zealand mice, like most other strains of mice, harbour the Gross leukaemia virus. One explanation of the abnormalities
exhibited by these mice is that they fail to tolerate this virus and produce antibodies to the viral antigens. They also have difficulty in developing and maintaining immunological tolerance to experimental antigens\textsuperscript{320}. These facts are relevant to the lack of immunological tolerance seen generally in autoimmune disease. A hypothetical concept of the pathogenesis of autoimmunity and malignancy in New Zealand mice is shown in Figure 23.

Virus-like particles similar to C-type murine oncogenic virus have been observed within endothelial cells and lymphocytes in the parotid glands and labial salivary glands of patients with SS\textsuperscript{332}. Kassan and Gardy (1978)\textsuperscript{318} gave several possible explanations for the etiology of SS:

(i) Disease due to genetic abnormalities of the immune system. The abnormality may affect B-lymphocytes in which there is spontaneous B-cell activation or it may be an abnormality of T-lymphocytes which fail to suppress the activation of B-cells.

(ii) Disease resulting from an acquired antigenic challenge, i.e. infection. The infection could be viral and result in alteration of the body's self antigens. This alteration may stimulate B-cell activation and auto-antibody formation.

(iii) A combination of the above factors leading to B-lymphocyte activation and then to lymphocytic infiltration of target organs such as salivary glands, kidneys and liver. This third hypothesis assumes interaction of an infectious antigenic challenge with a specific genetic susceptibility to the infection. Alternatively, an abnormal genetic control of the response to the infectious agent may be present in the host. Kassan and Gardy (1978)\textsuperscript{318} emphasized
Fig. 23 Hypothesis of the pathogenesis of autoimmunity and malignancy in New Zealand mice.

that the existence of a defect in the cellular immune system in SS is unproven.

CLINICAL FEATURES OF SJÖGREN'S SYNDROME

The systemic signs, symptoms, laboratory findings and radiographic changes in patients with rheumatoid arthritis complicated by SS closely resemble those of classic rheumatoid arthritis. Ropes, Bennett, Cobb et al (1958) defined the criteria accepted by the American Rheumatism Foundation for the diagnosis of rheumatoid arthritis. The criteria included features such as morning stiffness, pain on motion or tenderness in at least one joint, joint swelling, subcutaneous nodules in specified sites, radiographical, haematological and histological changes typical of the disease.

Systemic lupus erythematosus of which 30% to 40% of affected patients may show SS has had criteria established to enable its diagnosis. Cohen and Canoso (1972) described fourteen features of systemic lupus erythematosus of which the presence of four or more in one patient was accepted as diagnostic of the disease. The criteria included facial erythema (butterfly rash), discoid lupus, Raynaud's phenomenon, oral or nasopharyngeal ulceration, arthritis without deformity, LE cells and other haematological abnormalities as well as photosensitivity and alopecia, pericarditis and/or pleuritis.

Arthritis is the most frequent initial complaint of patients who subsequently develop SS. The ocular and oral signs of SS precede the development of rheumatoid arthritis and other connective tissue disease in approximately 10% of cases. Xerostomia and keratoconjunctivitis sicca have been noted up to several years prior to the development of rheumatoid arthritis.
ASSOCIATED DISORDERS

The majority of cases of SS include rheumatoid arthritis as part of the triad but instead of arthritis the connective tissue disease may be systemic lupus erythematosus, progressive systemic sclerosis, polyarteritis nodosa, polymyositis (dermatomyositis) or mixed connective tissue disease. Sapiro and Eisenberg (1978) considered that diseases which 'often replaced' the arthritis in SS included chronic active hepatitis, primary biliary cirrhosis, Hashimoto's thyroiditis, Behcet's syndrome, Reiter's syndrome and eosinophilia syndrome. Macfarlane, Wojcicka, Tsantolous et al (1976) discussed the association of chronic active hepatitis and primary biliary cirrhosis with sicca syndrome and concluded that an immunological reaction between antigens in the liver and other tissue antigens, such as in the lacrimal and salivary glands, was responsible for the sicca features of these diseases. Kassan and Gardy (1978) also found an association between primary biliary cirrhosis, chronic active hepatitis as well as renal tubular acidosis and SS. Patients initially diagnosed with only these conditions also showed features of the sicca syndrome.

Because SS is a part of a spectrum of connective tissue diseases clinical features in common with other disease entities must be expected.

OCULAR FEATURES

The term keratoconjunctivitis sicca (KCS) refers to inflammation of the conjunctiva at the border of the cornea associated with lacrimal deficiency. It has been estimated that between 11% and 20% of patients with rheumatoid arthritis develop KCS. Bloch et al (1965) diagnosed definite KCS in 57 of their 62 patients with SS,
probable KCS in a further 3 patients and possible KCS in the remaining 2 patients. Whaley et al (1973)\textsuperscript{317} diagnosed KCS in 163 of their group with SS.

Most of the individual symptoms of KCS are non-specific and may accompany other forms of conjunctivitis or keratitis or even be elicited in the absence of demonstrable eye disease [see Plate 3]. The symptoms of KCS in Sjögren's syndrome are often mild and may go undetected especially when patients have the distraction of a painful rheumatoid arthritis\textsuperscript{317,319,324}. Even though tear production is known to decline with advancing age, KCS can be recognised by its symptomology\textsuperscript{324}. The presence of several eye signs and symptoms combined with the results of ophthalmological tests (vide infra: Ophthalmological examination, p.246) confirm a diagnosis of KCS. The most frequent and distressing symptom of KCS appears to be a foreign body sensation or a grittiness in the eyes. A burning sensation is another frequent symptom, and a more specific although less frequent complaint was a lack of tears\textsuperscript{317,319,323}. The possible range of clinical signs and symptoms of KCS are listed in Table 4.

Block et al (1965)\textsuperscript{319} observed few ocular abnormalities in patients with uncomplicated KCS even when symptoms were severe. In a few cases there was a mild diffuse congestion of the conjunctiva or slight erythema of the lid margins. Occasionally whitish mucoid strands were seen in the inferior cul-de-sac or there was debris over the cornea. Lacrimal gland enlargement was seen in only 2 of the 62 patients with SS and both of these patients also had enlarged parotid glands. Whaley et al (1973)\textsuperscript{317} found only 7 patients with lacrimal gland enlargement out of 163 who had KCS and SS. Thus a low frequency of lacrimal gland enlargement can be expected in SS. Untreated filamentous conjunctivitis in close approximation to the
Plate 3. Minimal ocular changes in a patient with Sjögren's syndrome who experienced severe dryness, grittiness, recurrent conjunctivitis and blepharitis.
SYMPTOMS
1. Foreign body sensation
2. Burning
3. Tiring with or without difficulty in opening eyes
4. Inability to tear in response to irritants or emotions
5. Itching
6. Aches, soreness, pain
7. Photosensitivity and excess secretion appearing to be watery, ropy or a film over eye
8. Changes (decrease) in visual acuity

SIGNS
1. Irregularity of the corneal image
2. Photophobia
3. Dilation of bulbar conjunctival vessels (usually interpupillary).
4. Mild pericorneal injection
5. Dullness of conjunctiva and/or cornea
6. White and/or yellow frothy tenacious discharge
7. Ptosis
8. Redness

TABLE 4. Eye signs and symptoms in KCS (listed in order of decreasing frequency)

Adapted from:
cornea may cause ulceration, vascularization, perforation or scarring of the cornea as well as a marked susceptibility to infection\textsuperscript{323,338}.

**ORAL AND SALIVARY GLAND INVOLVEMENT**

The oral signs and symptoms reported in SS, which include mucosal changes and dental caries, are characteristic of xerostomia and cannot be directly related to the syndrome\textsuperscript{321,323} [see Plate 4]. Daniels et al (1975)\textsuperscript{321} reported an inverse relationship between the intensity and diversity of oral symptoms and the flow of parotid saliva. The features of xerostomia are discussed later (vide infra: Effect of xerostomia on the oral tissues, p.257). Oral candidiasis is related to the xerostomia and possibly to the abnormal immunological state which may occur in SS\textsuperscript{321,332,339}. Block et al (1965)\textsuperscript{319} reported dryness of the mouth and lips in 56 of their 62 patients with SS. Whaley et al (1973)\textsuperscript{317} reported that intermittent xerostomia was more frequent than persistent xerostomia in their patients with SS or sicca syndrome. The frequency of xerostomia was similar in each group, being 97% in SS (64 patients) and 100% in sicca syndrome (54 patients). Henkin, Talal, Larson et al. (1972)\textsuperscript{322} recorded a dry mouth reported by all of their 29 patients with SS. They reported that of oral, nasal and pharyngeal symptoms the oral symptoms occurred first.

Signs and symptoms, other than xerostomia, related to reduced exocrine secretions include hoarseness or deepening of the voice, an altered sensation of taste and smell and an increased rate of dental caries. Many patients with SS describe a cyclical course for the oral symptoms with periods of progression and remission\textsuperscript{321}.

An increase in fluid intake both with and often between meals has been noted in 25 to 80% of patients with xerostomia caused
Plate 4. Xerostomia and dental caries in a patient with Sjögren's syndrome
by either SS or sicca syndrome. Whaley et al (1973) considered that in sicca syndrome the increased fluid intake persisted throughout the day whereas in SS it occurred only in relation to meals. The assumption was that xerostomia was most severe in sicca syndrome.

An increased ingestion of water in an attempt to relieve oral dryness may lead to polyuria. This polyuria can be reduced by advising patients to rinse their mouths with water, without drinking it, whenever possible. However, the presence of polyuria and nocturia should alert suspicion of nephrogenic diabetes insipidus associated with gross renal tubular acidosis which is occasionally seen in patients with SS.

Salivary gland enlargement is often the most obvious sign of SS and its frequency is reported to be between 25% and 50% of patients. The glands affected are usually the parotid, mostly bilaterally, which gives the patient a typical "chipmunk face" [see Plate 5A and 5B]. The submandibular glands may be enlarged but usually only in association with the parotids. It should be recalled that the swelling in infective or obstructive salivary gland diseases is mostly unilateral and episodic rather than chronic and bilateral. A false impression of unilateral gland swelling may be gained from enlargement in which one gland is more swollen than the other. Patients may report recurrent swelling in the region of the affected salivary glands lasting from only a few weeks to several months. Since they may not present with this sign patients should be questioned specifically about any previous swelling.

In some patients the salivary gland enlargement associated with SS can only be detected by palpation. The consistency of the swelling is usually firm but not stony hard and it is confined to
Plate 5A and 5B. Bilateral parotid gland swelling in a patient with Sjögren's syndrome. Note a degree of ptosis and swelling over lacrimal glands.
the gland capsule. The surface may be lobulated or smooth but not craggly or irregular. Tenderness rather than pain is a feature unless secondary infection supervenes. Occasionally a patient may develop an acute suppurative sialadenitis which is probably due to retrograde infection by staphylococcus aureus$^{317,319}$.

Although enlargement of major salivary glands is frequently a feature of SS swelling of minor salivary glands does not usually occur$^{340}$. Cooper (1976)$^{340}$ reported the development of a diffuse spongy swelling arising from the posterior part of the hard palate and adjacent alveolus in a patient with SS (including xerostomia). The swelling was biopsied and the histological appearance was consistent with that of the major salivary glands in SS. Treatment of the lesion entailed cryosurgical destruction and follow-up for any signs of recurrence.

OTHER SYSTEMS AFFECTED IN SJÖGREN'S SYNDROME

Dermal, genital, gastrointestinal, hepatic, renal, pulmonary, vascular, neural, muscular and thyroid pathology have all been associated with SS. Some of these are related to the sicca features of the disease and others to the immunological abnormalities of the syndrome$^{318,319,324}$.

Dryness of the skin is a frequent complaint of patients with SS who may report the complete or partial absence of sweating. Hair and nail dystrophies may accompany the skin changes and persistent dandruff can be a problem$^{322,324}$.

Vaginal dryness with or without dyspareunia, pruritus and recurrent irritation often dismissed as infection are seen in numerous patients with SS. Although many of these patients are of menopausal age a sufficient number of younger patients reported these symptoms
to exclude menopause as the cause\textsuperscript{319,324}. Nasopharyngeal dryness, pruritis and crusting causing blockage of the eustachian tubes may result in hearing difficulties. Middle ear infection is a risk under these conditions\textsuperscript{319,324}. Henkin et al (1972)\textsuperscript{322} reported that 27 of their 29 patients with SS had complained of a dry nose and 13 complained of hyposmia.

Lower respiratory tract involvement in SS frequently causes pulmonary disorders. Recurrent tracheobronchitis and pneumonia follow the development of an abnormally viscous mucus in the respiratory tree which causes blockage and atelectasis. Submucous gland atrophy and lymphocyte and plasma cell infiltration at all levels of the respiratory tract combined with a fibrosing alveolitis cause restrictive ventilatory abnormalities associated with defective gas transfer\textsuperscript{318,319,324}.

Hepatic involvement appears to affect approximately 6% of patients. Cryptogenic cirrhosis, chronic active hepatitis and primary biliary cirrhosis are the most significant disorders. Also about 6% of SS patients have mitochondrial antibody which is the serological marker for primary biliary cirrhosis\textsuperscript{318,324}. Block et al (1965)\textsuperscript{319} reported 13 of his patients having hepatomegaly associated with hypergammaglobulinaemia which reflects changes in serum proteins rather than primary liver disease.

Latent renal tubular dysfunction of concentrating and acidifying mechanisms are demonstrable in up to 30% of patients with SS. The abnormalities involve renal tubular acidosis, chronic interstitial nephritis (mononuclear infiltrate) and occasionally nephrogenic diabetes insipidus. Kidney biopsy has shown focal glomerulitis and scarring of glomeruli which may be associated with the high levels of immune complexes in the blood\textsuperscript{318,324}. 
Acute and chronic pancreatitis with impaired pancreatic exocrine function and pancreatic calcification do occur in SS but are not frequent.\textsuperscript{319,324}

Vascular involvement may take the form of polyarteritis nodosa and Raynaud's phenomenon. Non-thrombocytopenic purpuric lesions have been observed in the syndrome and these may appear as recurrent crops of pink macules which may become confluent. These lesions may change colour and leave a brown stain which can persist for twelve months. Purpura hyperglobulinaemia and related Waldenstrom's macroglobulinaemia may be further manifestations of the immune disorder present in SS\textsuperscript{319,324}.

Patients affected by SS with polymyositis instead of rheumatoid arthritis show histological alterations in muscle fibres with infiltrates of mono-nuclear cells within and around damaged fibres and small blood vessels. Varying degrees of muscle weakness may be present.\textsuperscript{319} Webb (1978)\textsuperscript{324} noted that dermatopolymyositic patients show multisystem abnormalities including SS.

Autoimmune thyroid disease appears to have an association with SS but this has not yet proven significant.\textsuperscript{319,324}

LYMPHOPROLIFERATIVE AND NEOPLASTIC CHANGES IN SJÖGREN'S SYNDROME

The characteristic histopathological changes in SS is lymphoid cell infiltration and proliferation in salivary glands but any organ may be affected.\textsuperscript{321} The lymphoproliferation remains in a benign state in most patients but transformation along a spectrum of neoplasia to overtly malignant disease can occur.\textsuperscript{318,320,324,341,342} [see Fig. 24].

An autoimmune disorder, such as SS, may precede the develop-
Fig. 24. The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome.


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ment of lymphoma by intervals as long as twenty years\textsuperscript{342}. The incidence of malignant transformation of the lymphoproliferation in SS could be 6\% to 7\%\textsuperscript{332}.

SS is at the benign end of the lymphoproliferation spectrum with the lymphoid infiltrate confined mostly to secretory and glandular tissue in lacrimal and salivary glands as well as glands in the genital and respiratory tracts\textsuperscript{320}. The term pseudolymphoma describes tumour-like aggregates of lymphoid cells which do not meet histological criteria of malignancy. Pseudolymphoma represents an intermediate stage between benign and malignant lymphoproliferation which may regress with treatment or progress when untreated\textsuperscript{320,324}. The malignant end of the spectrum is represented by Waldenstrom's macroglobulinaemia, reticulum cell sarcoma and other lymphomas.

The lymphoid aggregates are malignant and the clinical course is often resistant to treatment and rapidly fatal\textsuperscript{320}. Progression from benign to malignant disease may occur over a number of years and this necessitates constant clinical and biopsy review and re-evaluation of patients with SS\textsuperscript{324}.

The development of lymphoproliferation in SS may be preceded by a marked fall in gammaglobulin synthesis in patients previously hypergammaglobulinaemic. A progressive decline in antibody titres, such as rheumatoid factor may accompany the fall in serum gammaglobulin concentration\textsuperscript{318,324}. Faguet, Webb, Agee et al (1978)\textsuperscript{341} reported the use of lymphocyte markers in the immunological diagnosis of the progression from benign to malignant disease in a patient with SS.

Initial immunological examination showed that although lymphoid proliferation was present the blood lymphocytes were of numerous immunological classes (referred to as polyclonal distribution of membrane immunoglobulins). However lymphocyte suspensions from lymph
node and lymphoid lung nodule showed an abnormal ratio of T-cell to B-cell lymphocytes as well as the proliferation of a single cell type (monoclonal marker). Twenty-two months later the patient developed a clinically and histologically classic malignant lymphoma. A repeat of lymphocyte marker studies on the malignant lymph node showed persistence of the monoclonal marker on most cells. It suggested that earlier immunological diagnosis of malignant transformation in SS will lead to an improved survival rate from earlier therapeutic intervention.

DIAGNOSTIC TECHNIQUES

The confirmation of salivary gland involvement and xerostomia in SS may be difficult since there are no pathognomonic criteria for either condition. As many parameters of salivary gland function as possible may need to be examined to establish salivary gland involvement including salivary flow rate, sialography, radioisotope scans, biopsy and sialochemistry.

SALIVARY FLOW RATE

The measurement of whole salivary flow rate as previously described (vide supra: A test of salivary gland function by assessing salivary flow rate, p. 78) could be used in the examination of patients with SS. However the measurement of stimulated parotid flow rate has been described as a more sensitive indicator of salivary gland function of 90% of patients with this disease. Reductions in parotid flow rate (PFR) have been measured in sufficiently large numbers of patients with Sjögren's and sicca syndromes for the reliability of this test to be accepted as indicative of the degree of salivary gland dysfunction. There is good correlation between a
low PFR and the presence of xerostomia.\textsuperscript{317,319,332} The PFR test is performed using a parotid saliva collector called a Carlson-Crittenden cup. The cup is placed over the orifice of Stensen's duct and held in place by suction while 5% citric acid is used to stimulate salivary flow\textsuperscript{317} [see Plate 6].

Chisholm and Mason (1973)\textsuperscript{332} and Daniels et al (1975)\textsuperscript{321} measured the PFR in SS with the parotid saliva collector and 5% citric acid painted for five seconds on the lateral borders of the tongue each thirty seconds. Their results indicated that a PFR of 5 mls per gland per ten minutes is the lowest value of normal for the test. Table 5 shows the variation in PFR as mls/min/gland in a large group of control, SS and sicca syndrome patients. The results from PFR tests should be examined keeping in mind the wide variation of salivary flow rates in "normal" individuals (vide supra: The flow rate of saliva, p. 75 and 76).

SIALOGRAPHY

Sialographic abnormalities related to narrowing of small ducts, dilation of main ducts, acinar atrophy and failure to secrete dye following stimulation may be seen together or alone in 50% or more of patients with SS\textsuperscript{317,319,343}. Generally the severity of the sialographic changes parallel the severity of xerostomia but the abnormalities are not specific and they may be seen in chronic sialadenitis from causes other than SS\textsuperscript{318,343} (vide supra: Chronic recurrent sialadenitis, p.150). Block et al (1965)\textsuperscript{317} noted a general correlation between xerostomia and sialographic changes but they also examined two patients with gross sialographic abnormalities and minimal complaints of xerostomia.

A frequent feature in the sialograms of patients with SS
Plate 6. Collection device for measuring PFR.

Adapted from:
<table>
<thead>
<tr>
<th>AGE RANGE (Years)</th>
<th>0 - 20</th>
<th>21 - 40</th>
<th>41 - 60</th>
<th>61 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.49 ± 0.09</td>
<td>1.73 ± 0.09</td>
<td>1.69 ± 0.11</td>
<td>1.58 ± 0.16</td>
</tr>
<tr>
<td>Female</td>
<td>1.99 ± 0.14</td>
<td>1.76 ± 0.09</td>
<td>1.36 ± 0.12</td>
<td>1.15 ± 0.08</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.43 ± 0.08</td>
</tr>
<tr>
<td>Female</td>
<td>-</td>
<td>-</td>
<td>0.24 ± 0.08</td>
<td>0.27 ± 0.05</td>
</tr>
<tr>
<td>Sjögren's syndrome + rheumatoid arthritis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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</table>

Table 5. Citric acid (5% solution) stimulated parotid flow rates (ml/min ± S.E.M.) in 171 control subjects, 32 patients with sicca syndrome and 86 patients with Sjögren's syndrome.

is the sialectasis associated with chronic sialadenitis$^{317,319,332}$. Chisholm, Blair, Low et al (1971)$^{343}$ described punctate, globular and cavitary sialectasis in SS and the defects were classified as less than 1 mm, 1 to 2 mm, and greater than 2 mm in diameter respectively [see Plate 7]. Atrophy of the duct system, defined as sparsity of duct branches and narrowing of lumena, as well as main duct dilation and complete atrophy of the duct system were also noted.

Correlation of sialographic changes with PFR in Sjögren's syndrome suggest the following$^{317,343}$:

(i) With increasing severity of sialectasis the PFR tends to decrease, that is, as the size of the sialectatic cavities increased.

(ii) Atrophy of the duct system is associated with considerable gland dysfunction reflected by decreased PFR.

(iii) Main duct changes are usually associated with more severe degrees of sialectasis and thus with decreased PFR.

(iv) Retention of contrast medium on evacuation sialograms is associated with more severe sialectasis.

(v) PFR is a more sensitive indicator of salivary gland dysfunction in SS than is sialography.

SCINTIGRAPHY

Salivary gland scintigraphy in relation to salivary gland disease and function has been discussed (vide supra: Radioisotope scanning, p.102). The technique has been cited as being promising for diagnosing the degree of salivary gland dysfunction in SS$^{55,317}$. However a low uptake of radioisotope by the salivary glands is not pathognomonic for SS as it may occur in conditions such as chronic recurrent sialadenitis, radiation sialadenitis and even in physio-
A. Punctate sialectasis

B. Globular sialectasis

C. Cavitary sialectasis

Plate 7A to 7C. Sialectasis in Sjögren's syndrome.

logical aging. Low radioisotope uptake in SS is associated with low PFR and lymphoid infiltration of the labial salivary glands especially in the most severely affected patients. Less severely affected patients may not show a good correlation between radioisotope uptake, PFR and labial salivary gland infiltration. Schmitt, Lehmann, Strotges et al (1976) showed that sialography was a more accurate technique than scintigraphy for the diagnosis of various salivary gland diseases in 169 patients. In order of diagnostic value in SS, scintigraphy follows PFR, labial salivary gland biopsy and sialography.

LABIAL SALIVARY GLAND BIOPSY

The technique of labial salivary gland biopsy has been discussed (vide supra: Biopsy of minor salivary glands, p.68), and one of its most valuable applications is in the diagnosis of SS.

A focal lymphocytic sialadenitis of labial salivary glands is estimated to occur in approximately 70% of patients with SS and in about 20% of patients with rheumatoid arthritis alone. It has been suggested that these arthritis patients have a subclinical form of SS. The histological appearance of the minor salivary glands in SS has been shown to correlate with the appearance of the major salivary glands in the same patient. Also the degree of lymphocytic infiltration into the labial salivary glands appears to be a good index of the severity of the disease. The biopsy appearance is relatively specific although not pathognomonic for SS. Whaley et al (1973) reported focal lymphocytic infiltrate in minor salivary glands of patients with psoriatic arthritis, ankylosing spondylitis, progressive systemic sclerosis and osteoarthritis but
with no other signs of SS.

The results of labial salivary gland biopsies have been expressed numerically as classes, grades or focus scores of lympho-cytic infiltration. There is some difficulty in comparing the different classifications because they are not completely standardized. However all classifications specify assessment of the lymphocyte, plasma cell and histiocyte infiltration into a 4 sq mm section representative of the biopsy specimen. Numbers from zero (normal) to four (most severe) are most frequently used to assess the severity of infiltration\(^{320,322,346}\) [see Plate 8A to 8D].

When fibrosis and marked infiltration with acinar destruction become evident in the biopsy specimen grades three and four are applied\(^{105,346}\). Focus scores are used to indicate the degree of infiltration in grade four biopsies. A focus is fifty or more round cells (lymphocytes, plasma cells, histiocytes) and the focus score is the number of foci in a 4 sq mm specimen. Usually a focus score of no more than ten can be counted and when foci are numerous enough to be confluent a score of twelve is assigned\(^{105}\). Greenspan, Daniels, Talal et al (1974)\(^{105}\) observed a marked variation in the degree of inflammation and destruction of minor salivary glands and gland lobules in individual patients with SS. Therefore several minor glands should be examined from each patient so that a representa-tive biopsy specimen is obtained for grading.

Histological features of biopsies

It must be emphasized that the differential diagnosis of salivary gland disease using labial salivary gland biopsy alone cannot be achieved, correlation with clinical examination and other tests is necessary\(^{346,347}\).
Plate 8A. Slight lymphocytic infiltration

Plate 8B. Multiple aggregates of lymphocytes

Plates 8A to 8D. Histological classification of lip biopsies from patients with Sjögren's syndrome.

Plate 8C. Generalized lymphocytic infiltration with atrophy of acinar cells.

Plate 8D. Extensive acinar destruction with round cell infiltrates replacing lobular architecture.
Block et al (1965)\textsuperscript{319} summarized the histological features of the major salivary glands in SS as parenchymal and ductal alterations, decrease or disappearance of acini, lymphocyte and plasma cell infiltration, hyperplasias of the lining cells of intraglandular ducts and formation of myoepithelial islands. Myoepithelial islands consist of epithelial and myoepithelial cells that proliferate to such an extent that they narrow and eventually obliterate striated ducts.

Myoepithelial islands are seen in only about 40% of patients with a clinical diagnosis of Sjögren's syndrome.

Tarpley, Anderson and White (1974)\textsuperscript{346} described an admixture of lymphocytes and plasma cells and their specific locations within the labial salivary glands in SS. Lymphocytes were mainly periductal although some periductal aggregates consisted primarily of plasma cells. The plasma cells were usually the predominant infiltrate throughout the gland stroma. A variety of round cells were found in close proximity to capillaries and small blood vessels.

Greenspan et al (1974)\textsuperscript{105} also reported periductal and perivascular lymphoid infiltrates in lip biopsies of SS. They suggested that the ducts appeared as though they had been engulfed by expansion of perivascular infiltrates. Germinal centres were seen in the middle of large lymphocytic foci in 11 out of 43 patients with SS. A decrease was noted in the numbers of plasma cells in lymphocytic foci as the size of the focus increased. Also the highest focus scores were recorded in patients with sicca syndrome without connective tissue disease. The location and distribution of inflammatory cells in this study were similar to those shown by Tarpley et al (1974)\textsuperscript{346}.

Friedman, Kilmar, Galletta et al (1979)\textsuperscript{347} noted the importance others had given to the presence of plasma cells in the
early lesions of SS. They suggested that the involvement of plasma cells in the early stage of the disease may indicate involvement of the humoral immune system in its pathogenesis. The lymphocyte infiltration (comprising a large proportion of B-cell lymphocytes) appears later as the disease progresses.

Duct changes in the labial salivary gland biopsy in SS have been described as being non-existent; as showing various degrees of dilation of intralobular and interlobular ducts with thinning of duct epithelium but with no appearance of myoepithelial islands and as duct changes consistent with or suggestive of myoepithelial islands. Myoepithelial islands appear to be a late feature of the disease process so, depending on when a biopsy is taken, varying descriptions could be expected.

Generally the increase in the size and number of lymphoid foci is related to loss or atrophy of salivary gland acini. However, even with massive lymphoid infiltration the integrity of the lobular structure is preserved. When fibrosis is present it is usually periductal but an increase of interseptal fibrosis occasionally occurs. This abnormal collagen deposition is a non-specific feature in several of the connective tissue diseases including systemic lupus erythematosus and scleroderma.

Less specific features have been noted in labial biopsy in SS including accumulations of hyaline material around altered ducts and blood vessels and increases in the numbers of fat cells and oncocytes. Fat cells and oncocytes may also be the result of age changes in salivary glands (vide supra: The salivary glands and age changes, p. 60), or changes secondary to diseases such as diabetes mellitus, obesity, alcoholism and malnutrition.
SIALOCHEMICAL EXAMINATION

Sialochemistry has been given little recognition as an aid in the differential diagnosis of salivary gland disease although it is of value in disease where salivary gland swelling is a feature. One problem is that sialochemical analysis of saliva may be difficult when insufficient saliva is secreted on which to perform tests. Testing is usually carried out on stimulated parotid saliva to avoid contamination from the materia alba and epithelial cells collected with whole saliva. Stimulated saliva is collected in an attempt to standardize results as the composition of saliva varies with flow rate and resting saliva differs markedly in different individuals (vide supra: The flow rate of saliva, p.75 & 76). The most significant changes in the saliva of patients with SS are in sodium, chloride and phosphate ion concentrations.

The concentration of sodium and chloride ions is up to three times the normal (23 ± 3 m Eq/l) concentration. Bendek-Spat (1978) recorded high sodium ion concentration only in those patients with SS where the salivary flow rate was less than 0.01 ml/minute. The results indicated that the salivary sodium ion concentration in chronic parotitis was higher than in SS. Other studies reported sodium ion elevations in SS as being greater than those in chronic parotitis. Differences in disease severity may explain these conflicting results. Apparently changes in the duct cells render them incapable of effectively resorbing sodium and chloride ions despite the reduced salivary flow. Therefore patients with less severe involvement of the salivary glands should not only show higher salivary flow rates but also lower sodium and chloride ion concentrations.

The phosphate ion concentration is reduced in SS and sial-
adenitis to between 30% and 50% of its usual value of 6.0 ± 0.7 m/Eq/l.

In advanced cases virtually no phosphate at all may be found in parotid saliva 149,349.

Elevations of IgA have also been recorded in SS although the increase has been reported as consistent with the concentrating effect of the reduction in salivary flow 349.

Tabak, Mandel, Karlan et al (1978) 222 showed that lactoferrin was markedly elevated in five out of six patients with SS. The patient with a normal lactoferrin level also had a normal salivary flow rate but severe lymphoid infiltrate of labial salivary glands. Lactoferrin concentration was also found to be elevated in patients with chronic recurrent parotitis but not elevated in patients with low salivary flow from other causes such as sarcoidosis.

Fischer, Whyshak and Weisberger (1968) 350 showed that the electrophoretic pattern of saliva was specific for SS. They also noted that anodal proteins increased in concentration with advancing severity of the syndrome. Chisholm, Beely and Mason (1973) 351 showed by a more sensitive electrophoretic technique that a number of protein bands specific for SS could be detected in saliva.

Other salivary constituents such as IgM, IgG, albumin and ions such as potassium and calcium have shown either no alterations in patients with SS or results have been conflicting 325,348,349.

OPHTHALMOLOGICAL EXAMINATION

After history and clinical examination the ophthalmologist has several techniques available to aid the diagnosis of keratoconjunctivitis sicca. These techniques include the Schirmer test, rose bengal fluorescein staining and slit lamp examination, as well as quantitative lysozyme tear assay 321,352.
The Schirmer test is a crude functional estimation of tear production using sterile standardized filter paper strips (Halberg, G.P. and Berens, C., New York City). The strips are 35 mm long and are folded 5 mm from their end so they can be hooked over the lower fornix of the eye at the junction of the middle and outer thirds. After 5 minutes the wetting of the filter paper is measured in millimeters, 15 mm or more of wetting is considered normal tear production, although for patients over 40 years of age, normal values may vary between 10 mm and 15 mm. Where equivocal results are obtained with this test the maximum tear production is measured using 10% ammonia, held below the patients nose, to stimulate lacrimation (Schirmer II test). Filter paper wetting should be 15 mm or more in 5 minutes for a normal result. Fifteen per cent false positive or negative results may occur with the Schirmer tests depending on such factors as the humidity, the degree of hydration, and the age of the patient\textsuperscript{317,318,338}.

One drop of rose bengal dye can be instilled into each conjunctival sac followed by immediate irrigation with normal saline to detect abnormalities of the cornea and conjunctival ulceration. A slit lamp can be used to verify the presence of mucous filaments on the conjunctiva and punctate or filamentary keratitis\textsuperscript{317,323}.

Positive results for either the Schirmer test or rose bengal dye staining are individually non-specific. When they occur together in one patient they are highly suggestive of Sjögren's syndrome\textsuperscript{318}. van Bijsterveld (1973)\textsuperscript{352} developed an agar diffusion method to determine the lysozyme content of human tears. This test was cited as the most sensitive ophthalmological test for the diagnosis of SS and sicca syndrome. The hallmark of these syndromes is a decrease in tear lysozyme with a test error of only 1%.
LABORATORY IMMUNOLOGICAL FEATURES

One of the most remarkable aspects of SS is the prevalence of abnormal immunological features including a wide range of serum autoantibodies. Only systemic lupus erythematosus shows a greater number of autoantibodies both organ specific and non-specific\textsuperscript{324,332}. Block et al (1965)\textsuperscript{319} showed the presence of abnormal proteins, rheumatoid factors, antinuclear factors and LE cells in their patients with SS. Tissue extracts were found to give false positive reactions to complement fixation test, precipitin reactions and passive cutaneous anaphylactic reactions.

Salivary duct autoantibody (an antibody to salivary duct cells) has been demonstrated by indirect immunofluorescence in SS. This autoantibody is found in approximately 15\% of patients with sicca syndrome, 65\% of those with SS and in 25\% of patients with rheumatoid arthritis alone. Study has shown that there is no correlation between salivary duct autoantibody and the development of focal lymphocytic infiltration of the salivary glands. The autoantibody is now considered to be associated with rheumatoid arthritis rather than with SS\textsuperscript{332}.

Berry, Bacon and Davis (1972)\textsuperscript{353} used the leukocyte migration test to investigate cell-mediated immunity to parotid and liver antigens in patients with SS and with rheumatoid arthritis alone. Ninety-three per cent of the patients with SS and 25\% of the patients with rheumatoid arthritis showed reactivity to the parotid extract antigen. There was a good correlation between the presence of lymphocytic infiltration of salivary glands and reactivity in the leukocyte migration test.

Anderson, Cummings, Asofsky et al (1972)\textsuperscript{354} showed in vitro, using labial biopsy specimens from SS, that some of the infiltrating
lymphoid cells synthesized large amounts of IgM and IgG while others showed anti-IgG and rheumatoid factor activity. The synthesis of IgM was at times so distinctive that it was suggestive of a primary macroglobulinaemia although serum proteins were normal in the patients from whom the tissue was taken. Rheumatoid factor was found in 18 of the 41 patients with SS and in 2 of 35 control subjects. The 2 control subjects had symptoms of dry eyes and dry mouth but the authors did not consider that they had SS.

Antinuclear antibodies (ANA) can be detected in up to 48% of patients with sicca syndrome and in somewhat fewer patients with either SS or rheumatoid arthritis. In rheumatoid arthritis alone, ANA's are low to moderate titre, 1:10 to 1:100, while in SS, patients may have a titre of 1:100 or greater. Antinuclear antibodies are specific for nucleoproteins (termed SS-A and SS-B) in sicca syndrome and for nucleoprotein (termed SS-C) in Sjögren's syndrome with connective tissue involvement. In systemic lupus erythematosus and mixed connective tissue disease the ANA are specific for different nucleoproteins. It has been suggested that differences in autoantibody specifications indicate further etiological differences between Sjögren's and sicca syndromes (vide supra: Etiology, p.214).

Numerous other autoantibodies including antibodies to thyroid microsomes, thyroglobulin and gastric parietal cells are found in SS but no apparent increase in the organ specific autoimmune diseases related to the autoantibodies seem to occur in the syndrome.

MANAGEMENT OF SJÖGREN'S SYNDROME

The chronic xerostomia suffered by patients with Sjögren's or sicca syndrome may be one of their most distressing symptoms. The management of this problem consists primarily of symptomatic
relief and prevention of both candidal infection and dental caries (vide infra: Treatment of xerostomia, p.276).

The systemic treatment of rheumatoid arthritis of any of the other connective tissue diseases associated with Sjögren's syndrome is the same as that given in the absence of the syndrome. Therapy for rheumatoid arthritis is aimed at reducing inflammation, pain, joint dysfunction and deformity.

Drug therapy includes the use of anti-inflammatory agents both steroids and non-steroids, gold salts and antimalarial drugs. Immunosuppressive drugs and antiviral agents, such as amantadine, have been found useful but they have not been fully evaluated. Some reports suggested that treatment of the systemic effects of SS with cyclophosphamide produced clinical improvement in up to 50% of patients treated. However because of the severity of their side effects immunosuppressive agents can only be justified in patients with severe systemic involvement and where concern exists over the possible development of lymphoid neoplasia in salivary glands.

Scott (1978) described the local treatment for rheumatoid arthritis as rest, exercise, heat, cold, local steroids, joint surgery and rehabilitation. The treatment available for other connective tissue diseases including systemic lupus erythematosus, polyarteritis nodosa, scleroderma and dermatomyositis was also described.

Systemic corticosteroids have a variable effect in the treatment of SS and generally no improvement in oral or ocular symptoms can be expected. Gegick and Levitin (1977) noted resolution of xerostomia in a patient with SS when a low dose of prednisone (20 mg) was given every alternate day. A 10 mg maintenance dose was required to keep the patient free of xerostomia. The validity of using steroids to treat oral and/or ocular symptoms must be
decided for each patient with these symptoms.

Salivary gland swellings in SS usually subside but they may become painful and persistent in which case analgesics and antibiotics should be prescribed. Irradiation of the enlarged salivary glands is contra-indicated in view of the predisposition to malignant change\textsuperscript{332}.

Webb (1978)\textsuperscript{324} recommended six-monthly clinical and serological review of patients with SS because of the danger of malignant transformation of lymphoid infiltrates.

Ophthalmological treatment for keratoconjunctivitis sicca is important if long term complications such as corneal ulceration are to be avoided. Whaley et al (1973)\textsuperscript{317} found that 0.5% carboxymethylcellulose eyedrops and tear conservation by nasolacrimal duct occlusion produced best results. Tenacious mucus may be broken up by mucolytics such as acetyl cysteine 20% but success is limited\textsuperscript{317,338}. 
MIKULICZ'S DISEASE

In 1888 Mikulicz described a man with "both lacrimal and all of the salivary glands changed into tumours". Since that time there appears to have been confusion and probably misdiagnosis of the entity he described. A number of cases reported as Mikulicz's disease, especially prior to 1933 when Sjögren's syndrome was described, were probably incorrect diagnoses \(^{358,359,360}\).

Mikulicz's disease, often referred to as benign lymphoepithelial lesion, is of unknown etiology and usually follows a benign course. A distinction must be made from Mikulicz's syndrome which is a symptom complex of salivary gland swelling caused by numerous systemic disorders including lymphoma, leukaemia, syphilis, tuberculosis and sarcoidosis \(^{360}\).

Clinically Mikulicz's disease is characterized by persistent salivary gland swelling which is usually bilateral but can be unilateral. The disease occurs most frequently in middle-aged females although more men seem to be affected than is the case in Sjögren's syndrome. The lesions are usually painless and widespread systemic involvement or immunological abnormalities are absent. It also appears that sicca components are not a feature in Mikulicz's disease \(^{360,361}\).

The histopathological appearance of benign lymphoepithelial lesion is the same as that of Sjögren's syndrome and the lymphoid infiltrate does not destroy the lobular architecture of the involved glands \(^{319,358,359}\). However the disease has been seen to undergo malignant transformation and this has been interpreted as evidence for an autoimmune etiology \(^{362}\).

Romero, Nesbitt and Ichinose (1977) \(^{361}\) reported the development of systemic lupus erythematosus in a 12 year old boy who had
Mikulicz's disease for 2 years prior to its onset. No evidence of joint involvement, KCS or xerostomia was noted but immunological abnormalities such as elevated anti-DNA antibodies and depressed serum C3 value were evident.

Although the etiology of Mikulicz's disease remains obscure it does seem to be related to the larger symptom-complex of Sjögren's syndrome\textsuperscript{319,358,361}. While the disease may not present the distressing eye, oral and systemic features of Sjögren's syndrome its potential for immunological aberration including malignant transformation makes its diagnosis and follow-up important.
XEROSTOMIA ASSOCIATED WITH NEUROLOGICAL PATHOLOGY

Neurology is a complex speciality and the neurologist is best equipped to diagnose and plan the overall treatment for a patient who develops xerostomia as part of a neurological disorder. However the dental practitioner should be aware that this type of patient may present with a dry mouth.

Mason and Chisholm (1975)\textsuperscript{363} included encephalitis, brain tumours and trauma, both accidental and neurosurgical, in the etiology of xerostomia. These causes are not discussed apparently because the authors do not consider them at all frequent.

Furstenburg and Crosby (1945)\textsuperscript{217} published a report on disturbance of the function of the salivary glands which although written over thirty years ago makes some pertinent comments on neurological causes of xerostomia. One group of patients referred to demonstrated some physiological disturbance in the end-organs of the nerves supplying the salivary glands. The pathological change could not be detected but evidence from the use of pilocarpine in these patients (a drug showing predilection for the end-organs of secretory nerves) indicated that the dysfunction was caused by defective secretory nerve function. The pilocarpine was prescribed as 10 mg orally three times a day and this dose was seen to restore normal salivary function in this group of patients.

Furstenburg et al (1945)\textsuperscript{217} discussed a further group of patients who demonstrated salivary gland dysfunction caused by interruption of the central pathways of the secretory nerves due to some organic lesion. They suggested that any lesion of the brain stem of sufficient proportions to irritate or block the nerve pathways to the salivary glands was certain to produce obvious paralysis of the cranial nerves. Destructive lesions in the brain stem would need
to be bilateral and of such extent to involve salivary centres in the lower pons and upper medulla before a dry mouth was produced. Such lesions would be exceedingly rare clinically and difficult to produce in experimental animals if their survival was a requisite.

Lesions which involve specific descending systems may cause at least a temporary xerostomia. Irritative bilateral lesions of the posterior end of the hypothalamus should cause a dry mouth due to decreased salivary flow and an inadequate blood supply to the glands. Destructive bilateral lesions of the rostral region of the hypothalamus would markedly decrease reflex salivary flow since a large part of the olfactory impulses to the hypothalamus would be removed. While the recognition of various odours would be impaired the salivary dysfunction might only be noted when the sense of smell is missed, such as at mealtimes. At other times different neural reflexes should stimulate salivation (vide supra: The stimulus to secretion of saliva, p. 24).

Tautin and Banasik (1974) reported an unusual case of xerostomia involving bilateral facial nerve palsy, caused by a brain stem glioma, and mouthbreathing. The dry mouth probably resulted from a number of factors including a drooping lower lip and mouthbreathing, tranquilizing drugs and scatter of therapeutic irradiation delivered to the pons and pre-pontine structures. The cholinergic nerve supply of the submandibular and sublingual glands was reported to be intact. Construction of a supporting device for the lower lip resulted in improvement of the xerostomia to the degree that methylcellulose mouthrinses could be discontinued.

Galil (1976) reported the development of xerostomia as a complication of vagotomy and pyloroplasty. The possibility of coincident occurrences was dismissed because of the dramatic development
of the xerostomia following surgery. No direct logical association between vagostomy and the development of xerostomia could be found. Perhaps that association lies in the interruption of the nausea-vomiting-salivation reflex although this does not seem highly probable.