SALIVARY GLAND DYSFUNCTION AND XEROSTOMIA

GRAYDON CHARLES SMITH, B.D.S.

University of Sydney

A treatise submitted in partial requirement
for the degree of Master of Dental Surgery

Department of Oral Medicine and Oral Surgery

Faculty of Dentistry

University of Sydney

1980
PREFACE

Xerostomia has been defined classically as a failure of the salivary glands either partial or complete with resultant dryness of the mouth (Butterworth's Medical Dictionary). However factors such as mouthbreathing or psychogenic states may cause oral dryness in which salivary gland function is not impaired. Therefore in this treatise the term xerostomia will be used with the more liberal meaning of dry mouth from an objective and/or a subjective viewpoint.

Salivary gland dysfunction leading to a decreased salivary flow results from either local salivary gland disorders or from systemic factors. Whatever the cause a deficiency of saliva alters the homeostasis of the oral cavity leading to pathological changes in the teeth, their supporting structures and the oral mucosa generally. The purpose of this treatise is to review the causes and possible consequences of xerostomia.

As a basis for understanding the pathology of the salivary glands, normal structure, physiology, function and the composition of saliva are discussed. Normal structure is described in terms of gross anatomical and histological features of the glands. The physiological mechanisms by which saliva is produced, modified and secreted are reviewed. The functions of the salivary glands and saliva, such as antibacterial and anticaries activity, as well as those of more obscure significance such as production of hormones, are considered. Age changes are discussed and xerostomia is shown not to be a feature of these changes.

Clinical examination, biopsy procedures and the assessment of the flow rate of saliva are discussed prior to a review of the radiographic examination of the salivary glands. Current sialographic
techniques and the sialographic appearance of normal salivary glands precede brief mention of the use of ultrasound and radioisotopes in diagnosis.

The underlying processes which may result in xerostomia are diverse and include developmental, physiological, inflammatory, obstructive, drug related, endocrine, nutritional, immunological and neurological states. These processes are discussed under headings which reflect their etiology.

Neoplasms of salivary glands which are usually confined to one salivary gland and are therefore unlikely to exhibit xerostomia as a symptom have not been included.

The signs and symptoms of xerostomia and the pathological alterations in the teeth and oral mucosa caused by a deficiency of saliva are extensively reviewed. A discussion of both symptomatic and preventive treatment for the patient with intractable xerostomia concludes the treatise.
CONTENTS

THE SALIVARY GLANDS AND SALIVA

1. GROSS ANATOMY OF THE SALIVARY GLANDS  
2. HISTOLOGY OF SALIVARY GLANDS  
3. THE SECRETORY PROCESS IN SALIVARY GLANDS  
4. THE COMPOSITION OF SALIVA  
5. FUNCTIONS OF SALIVA  
6. AGE CHANGE

Page  
1  
11  
24  
38  
49  
58

DIAGNOSIS

7. CLINICAL EXAMINATION OF THE SALIVARY GLANDS  
8. BIOPSY OF SALIVARY GLANDS  
9. THE FLOW RATE OF SALIVA  
10. RADIOLOGY OF THE SALIVARY GLANDS

Page  
62  
67  
71  
80

DECREASED SALIVARY FLOW

11. CONDITIONS IN WHICH XEROSTOMIA MAY BE A SYMPTOM

- Physiological decrease in salivary flow  
  during sleep and mouthbreathing  
- Psychogenic factors and reduced salivary flow  
- Reduction in salivary flow following changes  
  in body fluid and electrolyte balance  
- Radiotherapy - its effect on the salivary glands  
- Obstruction to the secretion of saliva  
- Sialadenitis and reduced salivary flow  
- Drugs and reduced salivary secretion  
- Xerostomia in nutritional and metabolic disorders

Page  
105  
108  
111  
119  
139  
148  
171  
193
11. CONDITIONS IN WHICH XEROSTOMIA MAY BE A SYMPTOM (Continued)

. Agenesis of salivary glands 210
. Sjögren's syndrome 213
. Mikulicz's disease 252
. Xerostomia associated with neurological pathology 254

12. EFFECT OF XEROSTOMIA ON THE ORAL TISSUES 257

13. TREATMENT OF XEROSTOMIA 276

CONCLUSION 287

APPENDIX 289

REFERENCES 302
THE SALIVARY GLANDS AND SALIVA

Saliva is a composite fluid produced by three pairs of major glands: the parotid, the submandibular and the sublingual salivary glands. Minor salivary glands found in the cheeks, lips, hard and soft palate and tongue also contribute to this fluid. The gingival tissues may be the source of a fluid which is added to saliva\(^1,2,3\). However, the volume of this fluid from normal non-inflamed gingiva is probably too small\(^4\) to be of significance in its contribution to total saliva.

1. GROSS ANATOMY OF THE SALIVARY GLANDS

RELATIONS \(^5,6,7,8\)

(a) The Parotid glands [Fig. 1 and 2] are pyramidal shaped glands with the base of the pyramid lying immediately beneath the skin. They are the largest of the salivary glands, each weighing between 14 g and 28 g in the adult\(^5\). The parotid is separated from its confining structures by a fascial capsule of varying thickness. The gland lies below the zygomatic arch, in front of the external auditory meatus, mastoid process and sternomastoid muscle; and behind the posterior border of the ascending ramus. Medially the gland extends into the space between the ascending ramus anteriorly, and the sternomastoid muscle posteriorly, to reach the styloid process and styloid muscles. The lateral surface of the parotid is separated from the skin by its capsule and by superficial fascia.

The isthmus of the parotid gland is a narrow portion which joins the superficial and deep parts of the gland. An accessory part of the parotid extends for a variable distance over the masseter
Fig. 1. Lateral view of relations of parotid gland.

Fig. 2. Horizontal cross section of parotid gland at level of occlusal surfaces of lower teeth.

Fig. 1 and Fig. 2 from:
muscle and the ramus of the mandible.

The main excretory duct of the parotid, Stenson's duct, lies over the masseter muscle and mandibular ramus. The accessory part of the parotid lies above the duct. At the anterior border of the masseter muscle the duct turns medially and penetrates the buccinator muscle. Opposite the upper first or second molar tooth, the duct opens into the oral cavity. The duct is about 5 cm in length with an internal diameter of 3 mm.

The facial nerve passes through the parotid gland and divides into branches within the gland. The major branches of the facial nerve within the parotid are the temporo-facial and cervico-facial. From these branches stem the temporal, zygomatic, buccal, marginal mandibular and cervical branches of the facial nerve.

The external carotid artery passes through the parotid gland and emerges posterior to the neck of the mandible. Behind the neck of the mandible the external carotid artery divides into the maxillary and superficial temporal arteries. The retromandibular vein passes through the parotid superficial to the external carotid artery.

Lymph nodes embedded in the parotid gland are concentrated near the superficial surface of the gland.

(b) The Submandibular glands [Fig. 3 and 4] are the second largest of the salivary glands and are half the size of the parotid and weigh 10 g to 15 g in the adult. The glands are an irregular shape and consist of superficial and deep portions.

The superficial portion of each gland lies between the body of the mandible in the submandibular fovea and the mylohyoid muscle. Superiorly the gland reaches the mylohyoid line on the medial aspect
Fig. 3. Lateral view of relations of sublingual and submandibular salivary glands.

Fig. 4. Coronal section of sublingual and submandibular salivary glands at the level of the first molar tooth.

Fig. 3 and Fig. 4 from:
of the mandible. Here mucosa lies above the gland where the stylo-
mandibular ligament separates the submandibular gland from the
parotid gland. The gland extends posteriorly, past the free margin
of the mylohyoid, to the angle of the mandible\(^8\). The submandibular
gland may extend anteriorly as far as the lower bicuspide teeth.

The small deep portion of the gland lies above the mylohyoid
and below the hyoglossus and styloglossus muscles. The deep part
extends antero-medially above the duct of the superficial part to
reach the posterior edge of the sublingual gland.

Wharton's duct is the main excretory duct. It emerges from
the supero-medial aspect of the superficial part of the gland. The
duct then courses over the hyoglossus muscle under cover of the
mylohyoid muscle, then passes on to the genioglossus muscle, where it
is separated from the mylohyoid by the sublingual gland. Here the
duct hooks around the lingual nerve superiorly\(^7\) to end at the summit
of the sublingual papilla, or caruncle, just lateral to the lingual
frenum. The duct is approximately 5 cm long.

(c) The Sublingual glands, the smallest of the major salivary
glands are about 3 cm long and weigh between 3 g and 4 g in the adult\(^6\).
[Fig. 3 and 4]. Each gland is anteriorly placed in the floor of the
mouth immediately beneath the oral mucosa. They lie between the
sublingual fovea of the mandible laterally, the genioglossus muscle
medially and the mylohyoid muscle inferiorly. The right and left
glands meet in the midline above the origin of the genioglossus
muscle; here the sublingual glands raise the mucosa covering their
superior surfaces, to form the sublingual folds.

Bartholin's duct, the major excretory duct of the sublingual
gland, may unite with the submandibular duct and share with it a
common orifice on the sublingual papilla. More frequently it will open independently on the papilla. Numerous small ducts, up to twenty in number, known as the ducts of Rivinus open onto the crest of the sublingual fold.

**BLOOD SUPPLY**

Parotid gland

Branches of the external carotid artery supply the parotid gland. These include the posterior auricular and maxillary arteries as well as the superficial temporal artery and its branch the transverse facial artery. Venous return is to the retromandibular vein.

Submandibular gland

Several small branches of the facial and submental arteries supply the submandibular gland. Submandibular gland venous drainage is to the common facial vein.

Sublingual gland

The sublingual artery and branches of the submental artery supply the sublingual gland.

**NERVE SUPPLY**

The salivary glands are innervated by autonomic nerves both sympathetic and parasympathetic, and by sensory nerves [Fig. 5 and 6].

(a) Parotid gland

Pre-ganglionic parasympathetic secretomotor nerves arising
Fig. 5. Parotid gland - autonomic nerve supply.

Fig. 6. Submandibular and sublingual glands - autonomic nerve supply.

from cell bodies in the inferior salivatory nucleus of the brain (medulla oblongata) travel via the glossopharyngeal nerve and its tympanic branch to the tympanic plexus. From this plexus fibres travel via the lesser petrosal nerve to the otic ganglion where they synapse. The post-ganglionic fibres then pass with the auriculotemporal nerve to the parotid gland.

Sympathetic nerve fibres originating in the superior cervical ganglion reach the gland from the plexus on the middle meningeal and external carotid arteries.

Sensory fibres from the parotid fascia pass via the great auricular nerve.

(b) Submandibular and sublingual glands

Pre-ganglionic parasympathetic secretomotor nerve fibres arising from cell bodies in the superior salivatory nucleus in the pons pass via nervus intermedius with the facial nerve. Just before the stylomastoid foramen these fibres branch from the facial nerve in the chorda tympani and leave the skull through the petro-tympanic fissure. The chorda tympani then runs antero-inferiorly to join the lingual nerve.

The original pre-ganglionic fibres then synapse, in the submandibular ganglion or in small ganglionic masses within the glands. The post-ganglionic fibres then innervate both submandibular and sublingual glands.

Sympathetic innervation arising from the superior cervical ganglia reaches both glands from a plexus surrounding the facial artery.

The nerve pathways, described above are the main pathways of the major salivary glands. It is probable that cross-innervation
between the chorda tympani and glossopharyngeal nerves occurs along with a contribution to innervation of the submandibular and sublingual glands by the cervical branch of the facial nerve.

THE MINOR SALIVARY GLANDS

The minor salivary glands may be found just beneath the mucosa in almost every part of the oral cavity. The exceptions are the gingiva and the anterior regions of the hard palate, (minor salivary glands are seldom found anterior to the first molars in the palate). The vermilion borders of the lips are also devoid of salivary glands.

Concentrations of minor glands do occur in certain positions, namely the labial mucosa of the middle portion of the upper and lower lips, posteriorly in the buccal tissue, linguually below the lower incisors, and in the tongue.

The minor glands in the tongue are concentrated in two areas: firstly, the anterior lingual glands (Gland of Blandin or Nuhn), at the most anterior portion of the ventral surface; and secondly, the dorsal group of lingual glands. The dorsal groups are of two types: the entirely serous von Ebner glands, which open into the crevicular trough of the vallate papilla, and the mucous posterior glands, which open into the lingual crypts at the base of the tongue.
2. HISTOLOGY OF SALIVARY GLANDS

Morphologically and physiologically salivary glands may be classified as being serous, mucous or mixed in nature. This classification derives from the relative proportions of serous, mucous or seromucous secretory units within the gland. The secretory units with cells arranged spherically around a small lumen are called acini, while those secretory units arranged cylindrically around a lumen are called secretory tubules\(^{14}\) [see Fig. 7].

The secretions from the acini or tubules flow from the lumina into intercalated ducts. The intercalated ducts empty into the larger striated ducts. The intercalated and striated ducts comprise the intralobular duct system which flows into the extralobular system of excretory ducts\(^{14,15}\) [see Fig. 9].

The appearance of the cells of the salivary glands may vary slightly from one gland type to the other. Also the morphology of the cells appears different during different phases of the secretory process. This is most marked following excretion of secretory granules\(^{14,15}\) where serous, mucous and some duct cells diminish in size\(^{14,15,16}\).

CONNECTIVE TISSUE

Partitions of connective tissue known as septa extend into the substance of the salivary glands and divide them into lobules [see Plate 1]\(^4\). The lobules are composed of groups of terminal secretory units and the intralobular ducts. The interlobular connective tissue septa contain the extralobular ducts\(^{14,15}\). Delicate connective tissue extends into the lobules around the intralobular ducts and secretory end-pieces\(^{14}\).
Fig. 7. Drawing of main features of parenchymal cells of salivary glands and their arrangement to form ducts and terminal secretory units.


Plate 1. Minor salivary gland from the lip showing the lobular structure and connective tissue arrangement of salivary glands.
The cells found in the connective tissue of the salivary glands are the same as those found in other connective tissues of the body. These cells include: fibroblasts, macrophages and mast cells, occasional leukocytes, fat cells and plasma cells. The connective tissue cells as well as collagen and reticular fibres are contained in a ground substance composed of proteoglycans and glycoproteins\textsuperscript{14,17}.

The vascular supply to the glands is within the connective tissue entering the glands alongside the excretory ducts and the vessels branch to follow the small ducts\textsuperscript{17}.

A dense capillary network extends to the level of the striated duct. A less extensive capillary plexus supplies the intercalated ducts and terminal secretory units\textsuperscript{14,15,17}.

CELL STRUCTURE

SEROUS CELLS\textsuperscript{16,17} [see Fig. 8]

The serous cells are specialized for the synthesis, storage and secretion of protein. Typically the serous cell is pyramidal in shape with a broad base which rests on a thin basal lamina. The nucleus is located in the basal third of the cell and it is surrounded by cytoplasm which stains darkly basophilic with haematoxylin and eosin\textsuperscript{17,18}.

The most prominent feature of the apical cytoplasm is secretory granules which may be seen under the electron-microscope to have a dense core surrounded by a lighter matrix. The matrix is surrounded by a limiting membrane\textsuperscript{14,17}.

In resting serous cells the secretory granules are dispersed. When a cell is stimulated the granules more closely appose one another and the plasma membrane of the lumen\textsuperscript{14}.

The basal cytoplasm is packed with rough endoplasmic
Fig. 8. Adapted from:

reticulum (RER). This RER is a closed system of membranous sacs, the outside of which are studded with ribosomes. The RER in the serous cell is arranged in parallel stacks mostly basal and lateral to the cell nucleus.

The function of the RER system is the synthesis of protein from amino acids, under the control of the cell nucleus. Serous cells have very well developed RER, a characteristic of cells producing large amounts of protein.$^{17,18}$

Golgi complexes are found apically or laterally in relation to the cell nucleus.$^{14}$ These complexes consist of membranous sacs consisting of from between 4 and 6 smooth surfaced saccules. The saccules are slightly cup-shaped with the concave aspect facing the secretory surface of the cell. The golgi complex is a packing and finishing organelle where protein transported from the RER is conjugated with carbohydrate residue to form glycoproteins. Glycoproteins form the bulk of the secretory protein formed in serous cells. The protein from the RER is carried in small vesicles to the golgi apparatus. Here the vesicles may fuse with the golgi saccules or with the vacuoles present on the concave aspect of the golgi complex. The vacuoles adjacent to the golgi complex are the immature secretory granules. They are smaller and less dense than the mature secretory granules. The size and density of immature secretory granules increases with maturation.$^{17,18}$

Other organelles

Serous cells contain other organelles which are found in most other salivary gland cells.

Free ribosomes are scattered throughout the cell cytoplasm. These unattached ribosomes produce non-secretory protein.$^{18}$
Mitochondria are found mostly between the RER, around the golgi complex and along the lateral and basal plasma membranes\textsuperscript{14}. The mitochondria supply the bulk of the high energy compounds required for synthetic and transport processes which take place within the cell\textsuperscript{18}.

The cell contains lysosomes, which are basically sacs of powerful hydrolytic enzymes. These enzymes remove intercellular debris such as worn out cell components or foreign material taken up by the cell\textsuperscript{17,18}.

Peroxisomes are small enzyme-storing microbodies. Catalase and other oxidative enzymes are contained in these peroxisomes\textsuperscript{18}. Currently their enzyme function is doubtful, although recent research indicates peroxisomes have a role in lipid metabolism\textsuperscript{20,21}.

Bundles of tonofilaments and microfilaments associated with desmosomes can be seen in the cell cytoplasm. It is thought that these filaments give the cell some degree of contractility\textsuperscript{18}.

Microtubules have been seen under the electron-microscope. These tubules are thought to be cytoskeletal structures which influence cell shape by imparting stiffness or rigidity to parts of the cell.

Microtubules may also be "pipelines" to direct a flow of cytoplasm or cell particles along cell processes\textsuperscript{18}.

MUCOUS CELLS\textsuperscript{16,17} [see Fig. 8]

The mucous cell, like the serous cell is specialized for synthesis, storage and secretion of a product. However, structurally mucous and serous cells are quite different.

A mucous cell is relatively large in size and is pyramidal in shape. In routine histological preparations the apical portion of
the cell contains thin strands of cytoplasm forming a trabecular network. Apart from this network the apical area of the cell appears empty. An oval or flattened nucleus with a thin rim of cytoplasm is compressed against the basement membrane of the cell.

Secretory granules, larger and more irregular in shape than those in serous cells, fill the remainder of the mucous cell. The secretory product of a mucous cell is different in two important aspects from the secretory product of the serous cell, namely;

i) it has little or no enzymic activity and probably serves mainly for lubrication and protection of the oral mucosa,

ii) its ratio of carbohydrate is greater and larger amounts of sialic acid and occasionally sulphated sugar residues are present.

RER is limited to the base and lateral borders of the cell with patches between the mucous droplets.

Mitochondria and other organelles are limited to the small basal and lateral band of cytoplasm.

The golgi complex is large (when compared to that of a serous cell), consisting of stacks of from ten to twelve saccules. The basally located complex has mucous droplets forming on its concave aspect. The golgi complex is an important organelle in the mucous cell because of the large quantity of carbohydrates it supplies to the mucous secretory granules.

MYOEPIThELIAL CELLS (or basket cells) [see Fig. 8]

These cells lie between the basal lamina and cell membranes of both secretory and intercalated duct cells. The body of the myoepithelial cell is small and filled mainly by a flattened nucleus.
This cell body often lies in the space where the bases of two or three parenchymal cells come together. Finger-like cytoplasmic processes radiate from the cell body and enfold the parenchymal cells. The processes contain longitudinally oriented filaments of approximately 50Å thickness. Aggregations of the filaments appear to form dense bodies within the cytoplasmic processes.

The plasma membranes of the myoepithelial and parenchymal cells are in close apposition and an occasional desmosome joins the two membranes.

Mitochondria, although not abundant, appear evenly distributed throughout the myoepithelial cell.

Other organelles are restricted to the perinuclear cytoplasm.

The function of myoepithelial cells is considered to be a contractile one. Contraction of these cells aids movement of secretion from the lumina of secretory acini and ducts. The myoepithelial cell may give support to acinal and intercalated duct cells to counteract distention during secretion.

Arrangement of cells in terminal secretory units. [see Fig. 9]

In the serous salivary glands, such as the parotid gland, terminal secretory units are acinar in structure. The acini are formed by serous cells clustered spherically around a central lumen. The lumen is separated from the intercellular spaces of the serous cells by junctional complexes. The junctional complexes consist of a tight junction (zonula occludens), an intermediate junction (zonula adherens), and one or more desmosomes (macula adherens).

Intercellular canaliculi, which are branches of the lumen
Fig. 9. The distribution of the salivary ducts in the various salivary glands. E.D. - excretory duct, S.D. - striated duct, I.D. - intercalated duct (absent from sublingual), A - alveolus containing serous cells (in the parotid) or serous and mucous cells (submandibular).

of an acinus, extend deeply between adjacent serous cells. These canaliculi increase the secretory surface area of the serous cell. Junctional complexes seal the canaliculi along their length. Mucous and mixed terminal secretory units possess a similar arrangement of intercellular canaliculi.

In mucous salivary glands, such as the minor buccal and labial glands, secretory cells are arranged in a tubular shape. The lumen of the secretory tubule is larger than the lumen of the acinus.

Mixed salivary glands vary in the relative proportions of serous to mucous cells. The submandibular gland contains mostly serous cells. The sublingual gland is predominantly composed of mucous cells. Three terminal cell arrangements exist in mixed salivary glands:

(i) serous acini (vide supra, p.11)
(ii) mucous tubules (vide supra, p.11)
(iii) mucous tubules capped by crescents of serous cells.

These crescents of serous cells are known as serous demilunes or "crescents of Gianuzzi".\(^{18}\)

The secretions of the serous demilunes reach the lumen of the mucous tubules via intercellular canaliculi.

DUCT CELLS\(^{17,18}\)

Intercalated ducts [see Fig. 10]

Intercalated ducts are present in serous and mixed salivary glands. However, in the predominantly mucous sublingual and labial salivary glands intercalated ducts are sparsely distributed [see Fig. 9].

The cells of the intercalated ducts form a low cuboidal epithelium resting on a basal lamina. These cells have a characteristic
Intercalated Duct Cell  

Fig. 10.  N - Nucleus;  M - Mitochondria;  
E - Endoplasmic reticulum;  
G - Golgi apparatus.

Striated Duct Cell

paucity of cytoplasmic organelles and a centrally placed nucleus.

Within the cell a variable amount of RER is located basally, and a golgi complex is found apically$^{14}$. A few small secretory granules may be found in duct cells which are near terminal secretory units. Limited numbers of stubby microvilli protrude into the lumina of intercalated ducts from the cells [see Fig. 10].

Striated ducts [see Fig. 10]

Striated duct cells are columnar in type. These cells have large, spherical, centrally placed nuclei surrounded by abundant cytoplasm.

At the basal end of the duct cell prominent striations can be seen. The striations are perpendicular to the basal lamina. This striated appearance is formed by deep infoldings of the plasma membrane. These infoldings greatly increase the surface area of the cell membrane. Mitochondria in a parallel arrangement fill the processes formed by the infoldings$^{14,17}$.

The intercellular membranes show extensive irregularities; they produce folds that interdigitate with the plasma membranes of adjacent cells. The folds presumably increase the firmness of contact between adjacent striated duct cells$^{14}$.

Around the nucleus of the duct cell short RER and a golgi complex are found. These organelles are generally poorly developed. Apically in the cell only a few small vesicles may be found. Basally located chains of vesicles are associated with the infoldings of the plasma membrane.

Numerous short microvilli protrude into the lumen of the striated duct from the duct cells$^{17}$. 
Excretory ducts

Excretory ducts lying within the lamina propria of the oral mucosa may be composed of pseudostratified or tall columnar cells. Excretory ducts within the oral epithelium are composed of stratified squamous cells.\textsuperscript{16}

There is no abrupt transition between any of the cells along the secretory and ductal portions of the salivary glands. Intercalated duct cells near the secretory end-pieces have features in common with acinar cells such as apically located secretory granules. Intercalated duct cells farther from the secretory end-pieces have fewer apical secretory granules and do not resemble acinar cells.

Similarly striated ducts merge into excretory ducts and as the excretory duct becomes larger its features in common with striated ducts become less pronounced.\textsuperscript{14, 17}
3. THE SECRETORY PROCESS IN SALIVARY GLANDS

The control over salivary gland secretion is entirely neural. In other glands of the alimentary system hormones as well as nerves control secretion. Hormones can alter the composition of saliva, but hormones cannot initiate the secretion of saliva.

THE STIMULUS TO SECRETION OF SALIVA

THE AFFERENT PATHWAY

External stimuli acting on salivary centres in the brain may be broadly classified into psychic, local and inter-organ stimuli.

Psychic stimuli are external influences on salivary centres. Conditioned reflexes are initiated by these stimuli. Reflex salivation can be caused by stimulation of the sight and hearing organs. The sight and sound of cooking or even listening to a description of food are examples of psychic stimuli.

Psychic stimuli may produce a sensation of mouthwatering. This sensation is not due to the small increase in salivary flow but probably to an increased awareness of the oral cavity.

Local stimuli are direct actions upon the salivary glands or upon adjacent related structures. These local stimuli include:

(a) Taste - acid taste is the most stimulating to salivation. Sweet and salt taste are moderately stimulating and bitter taste least stimulating to salivation.

(b) Smell - olfactory irritants and stimulants cause reflex salivation.

(c) Touch and irritation of the oral mucosa, including food.
Proprioceptive impulses from pressure sensors in the temporomandibular joint, masticatory muscles and in the periodontal membrane.

Inter-organ stimuli are actions upon part of the digestive tract, excluding the salivary glands, which produce a reflex salivation. Inter-organ stimulation of salivation has been reported for the oesophagus. Irritation of the oesophagus may cause salivation as part of the nausea-vomiting reflex. A similar response may follow irritation of the soft palate and posterior part of the tongue.

THE REFLEX PATHWAY

Efferent secretomotor nerve fibres and afferent taste nerve fibres pass within the same nerve trunks to the salivary glands. Taste sensation relayed by the glossopharyngeal nerve stimulates mainly parotid gland secretion, while taste sensation relayed by the chorda tympani nerve stimulates mainly submandibular and sublingual gland secretion. Cross-innervation between nerves in the area of the salivary glands occurs (vide supra: Nerve supply, p. 6). This cross-innervation makes the reflex pathway more complex than the above suggests.

THE EFFERENT PATHWAY FROM SALIVARY CENTRES

The parasympathetic nerves from salivary centres cause release of the neurotransmitter acetylcholine at post-ganglionic nerve terminals. Atropine blocks uptake of acetylcholine at post-ganglionic nerve terminals. Thus salivary flow can be reduced by administration of atropine to patients.

The sympathetic nerves from salivary centres cause release
of the neurotransmitter noradrenaline at post-ganglionic nerve terminals\(^28\).

Both sympathetic and parasympathetic nerves are found in the major salivary glands. Sympathetic stimulation of submandibular and sublingual glands produces a flow of saliva. However no flow of saliva is produced by sympathetic nerve stimulation of the parotid gland\(^6,26,30\), which indicates that the secretory cells of the parotid gland have no sympathetic innervation.

There are four possible effects of nerve impulses acting on salivary glands; these are\(^6\):

(i) Secretion from both serous and mucous cells. This indicates that common stimulus pathways exist for both cell types. Stimulation of both parasympathetic and sympathetic nerves has a synergistic effect on salivary secretion\(^26\).

(ii) Vasomotor changes, parasympathetic vasodilation and sympathetic vasoconstriction of blood vessels may occur. Once secretion is initiated bradykinin is produced by sympathetic nerves\(^24\). Bradykinin causes a vasodilation which overrides nervous control of salivary gland blood vessels.

(iii) Parasympathetic activity on salivary ducts is indicated by the presence of cholinesterase around salivary duct cells. This parasympathetic activity is in doubt\(^26\).

(iv) Myoepithelial cells contract in response to bradykinin\(^23\). It is not certain whether myoepithelial cells also respond to sympathetic and/or parasympathetic stimulation\(^6\). Garret\(^31\) suggests that myoepithelial cells do respond to autonomic nerve stimulation.
TRANSDUCTION OF THE NERVE IMPULSE

The neurotransmitters, acetylcholine and noradrenaline from autonomic nerves, and circulating adrenaline act on membrane receptor sites of acinar cells. These neurotransmitters also act on salivary gland blood vessels and possibly on some duct cells\(^6,26\).

Acetylcholine is inactivated by acetylcholinesterases. Noradrenaline and adrenaline are inactivated by monoamine oxidases. Monoamine oxidases are present in high concentration in salivary glands and probably inactivate all the catecholamines that normally circulate through the glands\(^28\).

Nervous stimulation of acinar cells is associated with:

(i) Hyperpolarization of cells.
(ii) Release of intercellular potassium ions \((K^+)^6\).
(iii) An increased intracellular cyclic 3,5 adenosine monophosphate \((\text{cyclic } 3,5 \text{ AMP})\) content.
(iv) An increased intracellular calcium ion \((Ca^{+})\) concentration.

HYPERPOLARIZATION OF ACINAR CELLS FOLLOWING NEURAL STIMULATION [see Fig. 11]

Cat acinar cells have a resting membrane potential between -20mV and -30mV inside negative. Following a nerve impulse the membrane potential across the basal cell membrane hyperpolarizes to about -56mV, inside negative\(^6,32\). This change in membrane potential approaches the equilibrium potential for potassium of -90mV inside negative. The sodium equilibrium potential is +32mV and chloride equilibrium potential is -15mV\(^6\). These figures, although from animal studies, suggest that the effect of neurotransmitters on acinar cell membranes is to increase permeability to \(K^+\)\(^30\).

This explains the net efflux of \(K^+\) into the acinar lumen
Fig. 11. Movement of ions across the acinar cells.

and tissue fluids at the commencement of salivary secretion. Later during secretion blood potassium crosses into acinar cells balancing the initial $K^+$ efflux $^6,30,32$.

INTRACELLULAR INCREASE IN CYCLIC 3,5 AMP AND IONIC CALCIUM FOLLOWING NEURAL STIMULATION

The relatively high concentration of calcium in salivary acinar cells is probably due to binding of calcium by sialate-containing compounds and other mucoid substances $^6$.

Acinar cell calcium concentration could be raised by three means $^6,33,34$:

(i) Acetylcholine (AcCh) increases cell membrane permeability to calcium. Evidence $^{35}$ seems against extracellular calcium being important in the initiation of secretory events.

(ii) AcCh acts on acinar cell membrane receptors that convert adenosine triphosphate (ATP) into cyclic 3,5 AMP. The adenosine triphosphate, found immediately beneath the cell membrane, releases calcium on breakdown to cyclic 3,5 AMP. It is now thought that the source of this calcium is intercellular, rather than extracellular $^{33}$.

(iii) Cyclic 3,5 AMP causes changes in cell membrane permeability to calcium or membrane-bound calcium is released by cyclic 3,5 AMP.

Irrespective of how a high intracellular calcium level is achieved it seems to allow for protein excretion from the acinar cell $^{30}$. Calcium probably acts as a binding agent between the secretory granule membrane and the acinar cell membrane, resulting in exocytosis. Calcium may be required to mediate the change in membrane
permeability to sodium and/or potassium that accompanies the response to nervous stimulation of acinar cells\textsuperscript{30}.

**SALIVARY FLUID AND ELECTROLYTE SECRETION**

The cells of the acini are the logical source for most of the salivary fluid with ductal cells modifying the composition of the fluid\textsuperscript{6,30,31,32,36}. It has been proposed that striated duct cells provide the bulk of salivary fluid\textsuperscript{24}. The suggested mechanism describing secretion of salivary fluid is similar, irrespective of which cell contributes most of the fluid. The acinar fluid contains water, ions, small molecules and secretory products from acinar cells. The bulk of acinar fluid is derived from blood in adjacent capillaries. The following description of secretion assumes that most of the salivary fluid crosses the acini [see Fig. 11].

A nerve-mediated increase in intramural vascular pressure starts the secretory process (vide supra: The Efferent Pathway from Salivary Centres, p.25). The high pressure difference across the capillary endothelium results in increased ultrafiltration of plasma. This increased ultrafiltration of plasma produces an elevation of the pressure and volume of the interstitial fluid. The interstitial fluid must now cross the basal cell membrane of the acinar cell and the cell itself or the intercellular spaces to reach the acinar lumen. Thus stimulation of salivary glands increases interstitial fluid pressure which creates a gradient of pressure towards the acinar lumen. During unstimulated salivary flow fluid crosses the acinar basal cell membrane by passive diffusion\textsuperscript{6}.

The sudden influx of interstitial fluid into the secretory cell rapidly elevates the concentration of intracellular electrolytes. Thus an increased intracellular concentration of sodium would be
present. This increased sodium level probably stimulates active transport, where sodium is extruded from the cell and potassium absorbed\textsuperscript{30,37}. Active transport of sodium and potassium ions operates with the Sodium-Potassium Adenosine Triphosphatase enzyme\textsuperscript{37}. Potassium ion uptake balances the earlier loss of potassium ions due to increased basal cell membrane permeability to potassium. The increased cell membrane permeability to $K^+$ follows release of acetylcholine (vide supra: Hyperpolarization of acinar cells following nervous stimulation, p.27).

Osmotic force accelerates fluid movement across acinar cells into the acinar lumen. The osmotic force is produced by active transport of sodium into the lumen of the acinus and into the extracellular fluid\textsuperscript{30}.

Acinar cells seem to be freely permeable to water- and lipid-soluble substances but the cells are not freely permeable to other, even small, molecules. The metabolic requirements of acinar cells are met by active transport of glucose and amino acids across the basal cell membrane. Serum proteins can probably pass between acinar cells. However, intercellular junctions would be expected to limit this movement of protein between acinar cells\textsuperscript{6,32}.

EXCRETION OF SECRETORY GRANULES

Synthesis and storage of secretory granules takes place when the acinar cells are not being stimulated. Stimulation of the cells produces a high intracellular calcium concentration. Fusion of secretory granules with the luminal membranes occurs and exocytosis follows. The rate of protein synthesis in the acinal cell does not appear to be influenced by nerve stimulation of the cell\textsuperscript{6}.

Secretion of the acinal product and contraction of
myoepithelial cells, around the acini, drive the secretory product towards the duct system\textsuperscript{23,31} (vide supra: Intracellular increase in cyclic 3,5 AMP and ionic calcium following neural stimulation, p. 29).

MODIFICATION OF THE ACINAR FLUID

MODIFICATION BY INTERCALATED DUCTS

The intercalated duct cells produce a fluid rich in potassium ions\textsuperscript{38}. This adds to the loss of potassium from acinar cells.

A small amount of protein is probably secreted by intercalated duct cells. Histologically these cells do not resemble those cells usually associated with protein secretion, but a few small secretory granules can be found in the luminal half of intercalated duct cells\textsuperscript{6,14}.

MODIFICATION OF ACINAR FLUID BY STRIATED DUCTS [see Fig. 12]

The major modification of acinar saliva occurs in the striated ducts\textsuperscript{35}. An isotonic or slightly hypotonic fluid is converted to a hypotonic fluid\textsuperscript{6}. This hypotonic fluid contains low sodium chloride ion concentration relative to plasma\textsuperscript{39}.

Nervous stimulation of the salivary glands produces a depolarization of the basal cell membranes of striated duct cells. These basal cell membranes have a resting potential of around -90mV, which on stimulation falls to between -20mV and -30mV. The high resting potential of the basal cell membrane indicates that this membrane is more permeable to potassium ions than to sodium ions\textsuperscript{35}.

A sodium-potassium pump actively transports sodium ions across the basal cell membrane of striated duct cells. The capacity of this sodium-potassium pump is quite large due to the large area of
Fig. 12. Movement of ions across the striated duct cells.

basal cell membrane of the striated ducts (vide supra: Striated ducts, p.22). A large number of sodium ions can be driven into the extracellular fluid, and potassium ions are driven into the lumina of the striated ducts.

Chloride ions diffuse from the duct lumina and across the duct cells into the extracellular fluid. This movement of chloride ions electrochemically balances the movement of sodium and potassium ions\(^{30,38}\).

Bicarbonate is excreted from the striated duct cells. The reaction of carbon dioxide and water catalysed by carbonic anhydrase produces the bicarbonate\(^{36}\) [see Fig. 12].

The luminal membrane of the striated duct cell operates as if it were largely impermeable to water. Therefore the resorption of sodium from the duct results in minimal osmotic loss of water from the fluid in the duct\(^{6,35}\).

Flow rate of saliva and ion transfer in striated duct\(^{30}\)

As the flow of saliva changes, the concentrations of various ions in that saliva change also. The striated duct is responsible for this flow-dependent change in ion levels. The concentration of sodium, chloride and bicarbonate ions rises to maximal values as salivary flow rate increases. Potassium concentration falls to a minimum as salivary flow rate rises\(^{36}\).

The more slowly saliva flows through the striated duct, the greater the time for resorption of sodium and chloride ions from the fluid in the duct. Similarly, at low salivary flow rates excretion of potassium ions into the slowly moving fluid will produce a high potassium concentration. As the flow rate of saliva increases the fluid passes the striated duct cells more rapidly. Thus both
resorption and excretion of ions into the fluid are less effective. Hence sodium and chloride ion concentration rises and potassium ion concentration falls in the fast flowing salivary fluid.

Salivary fluid flowing rapidly through the striated duct contains increasing concentrations of sodium and chloride ions and a decreasing potassium ion concentration. These concentrations approach but never reach the acinar fluid concentrations of sodium, potassium and chloride. There seems to be some balancing mechanism which holds ion transfer at a constant rate across the striated duct \(^{38}\).

With an increased flow rate of saliva the bicarbonate ion concentration in that saliva also increases. This probably results from an increased cellular metabolism in the striated duct cells producing more metabolic carbon dioxide \(^{36}\). Carbonic anhydrase in the striated duct cell then catalyses the production of bicarbonate ions. The concentration and rate of production of carbonic anhydrase in the cell would determine the maximum concentration of bicarbonate ions in fast flowing saliva [see Fig. 12].

Parasympathetic nerve stimulation of salivary glands produces a greater volume and flow of saliva than does sympathetic nerve stimulation. Sympathetic nerve stimulation has only approximately one-eighth the effect of parasympathetic nerve stimulation in initiating acinar saliva. Sympathetic stimulation of striated duct cells, however, has an almost equal effect to parasympathetic stimulation \(^{38,40}\). These facts are reflected in the difference in ion concentration between sympathetically and parasympathetically stimulated saliva. Sympathetically stimulated saliva shows the ionic characteristics of slow flowing saliva, while parasympathetically stimulated saliva shows the ionic characteristics of fast flowing saliva \(^{30}\).
Modification of acinar fluid by excretory ducts [see Fig. 13]

In the distal parts of the excretory ducts a passive diffusion of ions occurs down their concentration gradients. This diffusion of ions increases the ionic concentration of the duct fluid to more plasma-like levels\textsuperscript{6,30}. 
Fig. 13. Passive movement of ions across the cells of the excretory duct.

4. THE COMPOSITION OF SALIVA

Saliva consists of water, inorganic and organic constituents. The composition of mixed saliva will be reviewed. Mixed or whole saliva will be taken to be the products of the major and minor salivary glands, gingival crevice fluids, polymorphonuclear leukocytes, epithelial squames and commensal oral microflora.

The concentrations of the major inorganic constituents in saliva depend upon the rate at which saliva is secreted. The flow rate of saliva in turn depends upon the type and duration of stimuli affecting the salivary glands (vide supra: The stimulus to secretion of saliva, p.24). Also there are variations between the flow rates of saliva from the individual paired major salivary glands. Because the composition of the secretions from these glands is not identical, an increase in secretion from one pair of glands will alter the composition of the mixed saliva\(^{39}\).

WATER IN SALIVA

Over 99% of saliva is water\(^{40}\). Between 600 ml and 1500 ml of saliva is secreted each day. Thus saliva is an important part of total body water balance\(^6,27\) (vide infra: Saliva and body water balance, p.51).

INORGANIC CONSTITUENTS OF SALIVA

Sodium ions:

The concentration of sodium ions in acinar secretion is similar to the sodium ion concentration in extracellular fluids. The concentration is reduced by resorption of sodium in the striated ducts, (vide supra: Salivary fluid and electrolyte secretion, p.30).
With an increase in flow rate the concentration of sodium ions in saliva increases to approach the serum sodium ion concentration.\(^6\)

Potassium ions:

A low concentration of potassium ions is present in extracellular fluid. A high concentration of potassium ions is present in whole saliva due to active transport of these ions across acinar cells (vide supra: Salivary fluid and electrolyte secretion, p.30). Salivary potassium ion concentration remains relatively unchanged as the flow rate of saliva rises\(^6,27\).

Dawes (1974)\(^{41}\) reported a slight increase in potassium concentration of submandibular saliva with increasing flow rate, whereas parotid saliva showed a significant fall in potassium ion concentration with increasing flow rates.

Calcium ions:

Unstimulated submandibular saliva often contains a concentration of calcium ions in excess of serum calcium ion concentration\(^6\). Parotid saliva contains only about one half the calcium ion concentration of submandibular saliva\(^{42}\). The calcium ion concentration of parotid saliva remains approximately the same with increasing flow rate\(^{27}\). Dawes (1974)\(^{41}\) reported an increase in the concentration of ionic calcium with increasing flow rates of submandibular saliva.

In whole saliva as the flow rate increases so the calcium ion concentration falls. This reflects the greater proportion of fast flowing whole saliva that is contributed by the parotid gland\(^6\).
Phosphate ions:

Parotid and submandibular saliva contains similar amounts of inorganic phosphate. In both types of saliva an increase in flow rate produces a fall in inorganic ionic phosphate concentration. Mixed saliva, therefore, also shows a fall in inorganic phosphate concentration with increasing flow rate\textsuperscript{6,41}.

Chloride ions:

The acinar fluid of salivary glands contains a chloride ion concentration similar to that of plasma. In the striated duct chloride ions are passively resorbed from the lumen by diffusion down an electrochemical gradient. The gradient is created by active transport of sodium ions out of the duct lumen. Moderate increase in the flow rate of acinar fluid are followed by an increase in bicarbonate ion concentration in the striated duct lumen (vide infra: Bicarbonate ion, p.40). This excess of anions within the duct lumen appears to promote an increased resorption of chloride ions. Therefore as the flow rate of saliva changes from slow to moderate, salivary chloride ion concentration falls.

Large increases in the flow rate of saliva reduce the time available for chloride ion resorption in the striated duct. So in fast flowing whole saliva the chloride ion concentration rises again to approximate the plasma concentration\textsuperscript{6,40}.

Bicarbonate ion:

At resting, low flow rates of saliva, the concentration of bicarbonate ion is low. An increase in salivary flow rate produces an increase in salivary bicarbonate ion concentration\textsuperscript{41}. Increases in salivary flow rates are accompanied by higher levels of intracellular
carbon dioxide. The carbon dioxide is a product of a more rapid metabolism within the salivary gland cells. An intracellular enzyme, carbonic anhydrase, converts the carbon dioxide into bicarbonate ions (vide supra: Modification of acinar fluid by striated ducts, p. 34).

Thiocyanate ions:

There is a greater concentration of thiocyanate ions in saliva than in serum. Salivary glands may have an excretory function for thiocyanate. In combination with salivary protein, thiocyanate has a bacteriostatic, anti-bacterial action.

Iodide:

The salivary glands actively transport iodide and produce an iodide concentration in saliva between 20 and 100 times the plasma iodide concentration. The salivary gland acinal cell, unlike the thyroid acinal cell, does not retain iodide but transports it directly into saliva.

Fluoride ions:

The fluoride ion concentration in saliva is similar to that in plasma. It has been suggested that the fluoride ion is carried across the acinal cell in bulk flow with the fluid of secretion.

Hydrogen ions:

At low flow rates saliva has a pH of less than 7 units, usually between 5 and 7. The pH of fast flowing saliva may rise to pH 8 due to an increased concentration of bicarbonate ions (vide supra: Bicarbonate ions, p. 40).
Other ions found in saliva\textsuperscript{27,40}:

Small traces of sulphate, bromide, nitrate, copper and magnesium ions have been isolated from whole saliva.

**ORGANIC CONSTITUENTS OF SALIVA**

**PROTEINS IN SALIVA**

The protein in saliva is derived from both serum and from the salivary glands themselves\textsuperscript{46}. The total protein content of saliva is about 0.3\% but the percentage may fluctuate widely\textsuperscript{27}. Sublingual saliva contains the highest percentage of protein, followed by parotid saliva, with submandibular saliva containing the least protein.

Lavelle (1976)\textsuperscript{6} stated that salivary protein concentration in whole saliva is considered to increase with increasing flow rate. However Mandel, Thompson and Ellison (1965)\textsuperscript{45} have shown that the protein concentration in parotid saliva is not generally dependent on flow rate.

**SERUM PROTEIN IN SALIVA\textsuperscript{6,27}**

Serum protein can constitute one fifth of total salivary protein. Seven or eight proteins similar in antigenicity to blood proteins are known and these include:

- **serum albumin**
- $\gamma$-globulin G
- $\gamma$-globulin $\gamma$,M ($P_\gamma M$ globulin)
- $\gamma$-globulin $\gamma$,A ($P_\gamma A$ globulin)
- Plus some $\alpha$ and $\beta$ globulins.

The serum albumin content of whole saliva exceeds the total
amount of serum albumin secreted by the individual salivary glands. Possibly gingival fluid is the source of the additional albumin. Although the difficulty in assessing the contribution of albumin from minor salivary glands may account for the difference. Estimations of serum albumin range from between 1% and 10% of total salivary protein.

The concentration of \( \gamma \)-globulin in saliva is less than 0.5% of blood levels of \( \gamma \)-globulin. Unlike that in blood, salivary \( \gamma \)-globulin is mainly \( \gamma \), \( \alpha \)-globulin. Parotid saliva may contain four times as much of the large \( \gamma \)-globulin molecules as the smaller albumin molecules. Therefore diffusion is not considered to be important in the process by which most \( \gamma \)-globulin reaches saliva. Most \( \gamma \)-globulin is considered to be synthesized within the salivary glands.

PROTEIN SYNTHESIZED WITHIN SALIVARY GLANDS

a) Protein similar to serum \( \gamma \)-globulin

Analouges of serum clotting factors similar in function to factors VII, VIII, IX and a platelet factor are present in saliva\(^6\)

(vide infra: The effect of saliva on blood coagulation, p.53).

b) Enzymes

Salivary amylase\(^27\):

This enzyme is the only one in saliva sufficiently active to be able to aid digestion. Two types of amylases, \( \alpha \) and \( \beta \), are known. Human amylase is probably entirely \( \alpha \) in type. Salivary amylase is capable of breaking down molecules of cooked starch. The starch is first broken into dextrin molecules and then the dextrin into the disaccharide maltose. Amylase achieves its optimal activity at pH 6.8., although if chloride ions are added to saliva this optimal
pH falls to around 6 units.

A large variation in salivary amylase activity occurs between individuals. However, low salivary amylase activity is of little consequence because pancreatic juice contains amylase.

Food generally remains in the mouth for far too short a time to allow much digestion of starch. Following a large meal, food in the stomach remains at a neutral pH for up to thirty minutes. During this time salivary amylase activity may continue.

Lysozyme:

Lysozyme is present in most body secretions. In saliva the lysozyme concentration is about the same as that in blood. Lysozyme can split the cell walls of certain bacteria.

Peroxidase:

Parotid saliva contains a small amount of peroxidase as part of an antibacterial system.

Acid Phosphatase, Cholinesterase, Ribonuclease and a specific Lipase:

These enzymes are found as components in saliva.

Kallikrein:

The action of the enzyme kallikrein, splitting a serum Y-globulin, produces a polypeptide, bradykinin, which passes from the salivary gland cells to dilate the blood vessels in the glands (vide supra: The efferent pathway from salivary centres, p. 26).

Other enzymes:

Saliva contains a large number of other enzymes. Enzymes
are produced within the salivary glands and there are intra- and extracellular enzymes from living and dead leukocytes and bacteria\textsuperscript{6,27}.

c) Mucoprotein

The major protein component in saliva is conjugated with carbohydrate as mucoprotein which represents approximately one third of the total protein in parotid saliva. In submandibular saliva mucoprotein forms a higher proportion of the total protein.

The proportion of parotid secretion in whole saliva increases with flow rate. Due to the lower mucoprotein content of parotid saliva, increases in flow rate bring decreases in the mucoprotein content of whole saliva\textsuperscript{6}.

d) Blood group substances

The agglutinogens A, B, O, Lewis (a) and Lewis (b) are carbohydrate-protein complexes on the cell walls of erythrocytes. In about 80% of people, termed "secretors", these agglutinogens are present in tissue fluids and secretions. Secretory agglutinogens are present in submandibular and sublingual, but not parotid, saliva. Other blood group substances are not present in any salivary secretions. Minor salivary glands in the lip mucosa secrete up to thirty times the quantity of blood group substances as do the submandibular glands\textsuperscript{27,40}.

e) Hormones

Parotin is a protein component isolated from parotid saliva. This protein is said to lower blood calcium and increase the blood leukocyte count\textsuperscript{49}. As a hormone parotin is still of doubtful status\textsuperscript{50}.

Nerve growth factor is a protein isolated from saliva that
influences the growth of sympathetic ganglia and sensory nerves in mice. Higher than normal serum levels of nerve growth factors have been found in children with neuroblastomas. This fact suggests that nerve growth factor influences nerve growth in man as well as in mice. The salivary glands are thought to store nerve growth factor but not produce the hormone.\(^\text{49}\).

**NITROGEN COMPOUNDS IN SALIVA**

a) Amino acids:

Whole saliva contains a greater concentration of amino acids than the total secreted from the major salivary glands. The difference is accounted for by the proteolytic action of bacterial enzymes on the protein in whole saliva. Eighteen amino acids have been found in mixed saliva. Nine of these amino acids are found consistently and nine occasionally. Nine different amino acids have been found in parotid secretions and twelve in submandibular secretions.\(^\text{6}\).

\(\gamma\)-amino-butyric acid is present in whole saliva; however, it is absent from secretions of the major salivary glands. This acid may arise by enzymic action on salivary protein or from the minor accessory salivary glands.\(^\text{27}\).

b) Urea, creatinine, uric acid and ammonia:

The significance of these nitrogen compounds in saliva is unknown. Urea has its highest concentration in labial accessory gland secretion followed by its concentration in parotid and then sub- mandibular secretions. Urea crosses into the salivary gland by diffusion, so, as the flow rate of saliva increases, the concentration of urea falls. Absolute content of salivary urea is fairly constant.
Uric acid behaves similarly to urea with regard to flow rate. The concentration of both urea and uric acid is dependant on their respective blood levels.\textsuperscript{6} Ammonia is formed in saliva by bacterial breakdown of urea and to a lesser degree by de-amination of amino acids\textsuperscript{27}. Creatinine is present in whole saliva in very small amounts\textsuperscript{6}.

**FREE CARBOHYDRATES IN SALIVA**

Traces of free sugars (from 0.5 to 1.0 mg %) have been isolated from unstimulated saliva\textsuperscript{51}. Submandibular saliva contains more free carbohydrates than parotid saliva. In addition to glucose, submandibular saliva contains small amounts of hexose, fucose, hexosamine and sialic acid\textsuperscript{6}. Extremely accurate analysis has shown that changes in glucose concentrations in parotid saliva correspond to changes in blood glucose levels. Diabetics show a consistently higher than normal glucose level in their saliva\textsuperscript{27}.

**LIPIDS IN SALIVA**

Many lipids are present in saliva but not all of these are secreted by the salivary glands\textsuperscript{52}. Bacterial cell wall components, plaque and food debris contribute to the very low lipid concentration of whole saliva\textsuperscript{40}. Corticosteroids are present in parotid saliva at a much lower concentration than their concentration in blood\textsuperscript{40}. Salivary steroids occur as cortisone not cortisol as in serum. The concentration of salivary steroid is independant of the flow rate of saliva\textsuperscript{27}. 
ORGANIC ACIDS IN SALIVA$^{6,27}$

Citrate and lactate are present in saliva; both probably arise from bacterial breakdown of carbohydrates. Lactate concentration may increase as much as ten-fold following a meal.

VITAMINS IN SALIVA

Most of the water-soluble vitamins are present in saliva. Low levels of B complex and vitamin K are also present$^6$. However, little is known about the source of salivary vitamins$^{40}$. Oral bacteria and food debris may contribute some vitamins to saliva.
5. FUNCTIONS OF SALIVA

LUBRICATION AND WETTING OF THE ORAL MUCOSA

The oral mucosa is adapted to a fluid environment and does not withstand drying at all well. Saliva, by virtue of its mucoprotein content, protects the oral mucosa from a dry and abrasive environment. Adams (1975) describes an extraneous protective coating formed from saliva which covers oral epithelial surfaces. The lubrication of oral mucosa aids speech, deglutition and resistance to physical trauma.

DIGESTION OF FOOD

The most important digestive function of saliva is coating food stuffs with a mucous layer which assists chewing and swallowing. By moistening food, saliva assists bolus formation prior to deglutition.

Salivary amylase is the only important digestive enzyme present in saliva (vide supra: Hormones, p.45). The role of amylase is probably digestion of cooked starch residues remaining in the mouth following meals.

SALIVA AND TASTE

The sensation of taste is only perceived from substances in solution. Foods which contain little water are dissolved in saliva and carried to the taste papillae to contact the taste buds. In conjunction with the taste mechanism saliva makes eating more pleasant and helps in detection of unwholesome contaminants in food.

Saliva from the small salivary glands of the tongue removes dissolved substances from the taste buds, and prepares the taste buds
for further taste stimuli.$^{40}$

**SALIVA AND THE LOSS OF TOOTH SUBSTANCE**

Saliva maintains intact enamel surfaces in two ways. Firstly, saliva aids the maturation of newly erupted tooth enamel which is highly susceptible to dissolution in acidic conditions. The surface apatite crystals of immature enamel are saturated by the calcium and inorganic phosphate ions in saliva. This saturation produces an enamel surface more resistant to dissolution by acids.$^{6}$

Secondly, the buffering capacity of saliva protects tooth enamel from dissolution. Salivary buffers inhibit large falls in the pH of the oral environment. High levels of ionic calcium and inorganic phosphate in saliva ensure that the apatite in tooth enamel will not rapidly dissolve at a lowered pH.$^{6}$ Bicarbonate is the major buffer in saliva, although phosphate buffer extends the pH range over which saliva is an effective buffer.$^{56,57}$ The bicarbonate content of slow-flowing saliva is low. As the flow rate of saliva increases, such as during a meal, the bicarbonate concentration increases, thus the buffering power of saliva increases with flow rate.

The effect of salivary buffers has to be indirect since the bacterial plaques producing acid are in direct contact with tooth enamel.$^{57}$ Diffusion of buffering ions through the plaque matrix must precede any neutralization of plaque-produced acids. Recently, Edgar (1976)$^{58}$ has shown salivary pH to be a major determinant of plaque pH. The incorporation of urea, from saliva, into the plaque matrix may keep plaque pH higher than it would otherwise be and so restrict the dissolution of tooth substance.$^{59}$
SALIVA AND CALCULUS FORMATION

Lavelle (1976)\(^6\) summarised the role of saliva in the formation of calculus as:

(i) Producing an alkaline environment favouring the deposition of calcium salts.

(ii) Increasing the quantity of ionized and precipitable calcium in plaque.

(iii) Increasing the quantity of ionized phosphate in plaque. This results from the action of phosphatase on organic phosphates in saliva.

(iv) Supplying calcium-binding proteins that act as seeding substances to initiate calculus formation\(^6,60\).

Also of relevance is a correlation shown between a high concentration of calcium ions in saliva and susceptibility to heavy calculus formation\(^6,61\).

SALIVA AND BODY WATER BALANCE\(^6,27\)

Most of the saliva is swallowed so the role of the salivary glands in body water balance is limited\(^27\). The water from swallowed saliva is reabsorbed in the distal parts of the digestive tract. Loss of this water due to vomiting or diarrhoea will reduce total body water. Rarely is this a problem except in babies where digestive secretions form a large proportion of their extracellular fluid.

The result of a loss of body water is an increase in the osmotic pressure of the blood. The increased osmotic pressure is detected by the hypothalamus\(^40\). The hypothalamus operates on the posterior pituitary resulting in the release of anti-diuretic hormone. Anti-diuretic hormone reduces the permeability to water of the striated ducts of the salivary glands. A lower volume of a less
hypo-osmotic saliva is secreted\textsuperscript{6}.

**SALIVA AS A ROUTE FOR EXCRETION**

Saliva has been described as an excretory route for several blood components\textsuperscript{40}. Afonsky (1961)\textsuperscript{62} suggested that research indicated saliva is a route of excretion for antibiotics, alcohol, heavy metals, salicylates and other substances. However, since saliva is normally swallowed, it is not at all efficient as an excretory mechanism.

In abnormal states such as uraemia the high blood level of urea increases salivary urea to the degree that a characteristic odour appears in the breath. High circulating levels of heavy metals, such as lead and bismuth, may be excreted by saliva and be deposited in oral tissues\textsuperscript{6}.

**THE SECRETION OF HORMONES IN SALIVA**

It has been suggested that the salivary glands are activated by endocrine systems or are in part endocrine organs\textsuperscript{63}. Evidence for the endocrine dependence of the salivary glands has come from the operation of a hormonal axis between the pituitary, thyroid and salivary glands. In laboratory animals dysfunction of either the pituitary or thyroid gland resulted in structural and chemical changes in salivary gland cells\textsuperscript{64,65}.

As far as endocrine production by salivary glands is concerned most investigation has been into a substance termed parotin. Parotin activates the adrenocortical function of the pituitary, lowers blood calcium levels and promotes calcification\textsuperscript{6,63}. A nerve growth factor (vide supra: Hormones, p.45) and an extra-pancreatic source of a glucagon-like material have been isolated
from the salivary glands\textsuperscript{49,66}.

**THE EFFECT OF SALIVA ON BLOOD COAGULATION**

Only some of the serum clotting factors are produced in the salivary glands, yet Jenkins (1973)\textsuperscript{27} reported that all the serum clotting factors are present in whole saliva. For instance, Factor V does not appear in secretions obtained from the individual major gland ducts\textsuperscript{27}; therefore some serum clotting factors must have sources other than the major salivary glands.

Presumably by virtue of its clotting factors, saliva reduces the clotting time of freshly shed blood\textsuperscript{27,62}.

Saliva also contains activators of fibrinolysis which reduces the solidity of a blood clot. Early activation of fibrinolysis in oral wounds will cause early clot dissolution. Therefore it seems that saliva should be prevented from contaminating oral wounds which are to heal by organisation of a blood clot\textsuperscript{55}.

**THE ANTIBACTERIAL ACTION OF SALIVA**

A common observation in dentistry is the ability of the oral mucous membrane to resist infection. This resistance is effective even in the presence of potentially pathogenic bacteria in the oral flora. Saliva, in several ways, plays a significant role in the resistance to oral infection:

a) A mechanical washing action of saliva entraps bacteria, desquamated mucosal cells and food debris and conveys these via the oesophagus to the stomach\textsuperscript{67}. Bacteria conveyed to the stomach are killed by gastric secretions. The washing of food debris and mucosal cells from the mouth deprives remaining micro-organisms of one source
of substrates required for growth.\textsuperscript{40}

b) Saliva provides the environment in which oral micro-organisms function.\textsuperscript{47} The pH range in the mouth is determined by salivary buffers and the amount of carbon dioxide dissolved in saliva. Micro-organisms are adapted to restrict pH range and the effect of saliva which determines oral pH is to restrict the growth of some micro-organisms not adapted to that pH. Also the composition of saliva limits or promotes the growth of micro-organisms depending on their nutritional requirements.\textsuperscript{47} Therefore, the characteristics of saliva determine which micro-organisms survive in the oral cavity.

Micro-organisms that are well adapted to the oral environment may prevent the colonisation of the oral cavity by non-resident organisms. This is called bacterial antagonism and is partly responsible for restricting the range of micro-organisms inhabiting the mouth.\textsuperscript{68} The advantage in having a narrower range of oral flora is probably that local defence mechanisms can more easily cope with an infective threat from a small, rather than large, range of micro-organisms.

c) Lysozyme is an enzyme found in secretions from both major and minor salivary glands.\textsuperscript{69} Salivary lysozyme concentration is only 1/300th that of lacrimal fluid and 1/45th the concentration of nasal secretory lysozyme.\textsuperscript{47} Salivary lysozyme can induce lysis of many common bacteria through a hydrolytic action of the mucopeptide component of the bacterial cell wall.\textsuperscript{70} According to Gibbons, de Stopelaar and Harden (1966)\textsuperscript{70} lysozyme is ineffective against commensal oral micro-organisms.

Coleman, van de Rijn and Bleiweis (1971)\textsuperscript{48} have determined
that lysozyme on its own causes considerable disruption to the cell wall structure of oral bacteria. Mandel (1976)\textsuperscript{67} stated that lysozyme in conjunction with other natural substances, for example, complement and IgA, has the ability to kill and lyse bacteria.

The in vivo significance of salivary lysozyme is unclear. At the least lysozyme aids in the prevention of non-commensal micro-organism colonising the mouth\textsuperscript{49,71}.

d) Lactoferrin is an iron binding protein normally present in milk but also present in saliva and in the lysozomal granules of polymorphonuclear leukocytes. Lactoferrin chelates iron, depriving bacteria of a substrate required for growth. This is termed nutritional immunity against bacteria\textsuperscript{67}. Lactoferrin chelates copper as well as iron and may, by this action, enhance the function of salivary lysozyme. Both iron and copper are inhibitory to lysozyme\textsuperscript{67}.

e) Two separate antibacterial systems function in conjunction with the thiocyanate ion. The first consists of hydrogen peroxide, a peroxidative enzyme and thiocyanate ions. The second system consists of an unidentified salivary protein and thiocyanate ions. The peroxidative system operates aerobically and is inhibited by the enzyme catalase. The non-peroxidative system operates aerobically or anaerobically and is not inhibited by catalase\textsuperscript{48}. Since catalase is produced by many oral bacteria, the peroxidative system may not function in vivo\textsuperscript{72}.

The thiocyanate dependent factors appear to inhibit a growth factor essential to actively growing bacteria\textsuperscript{71}. The factors have been found active in vitro against oral micro-organisms including lactobacilli and bacteroides melaninogen\textsuperscript{70}. 
Immunoglobulins are recognised as being important in the protection of the oral mucosa from infection. Mixed human saliva contains IgA, IgM, IgE and IgG. The salivary glands produce only IgA and a small amount of IgM. The gingival crevice is a source of all four of these immunoglobulins.

Of the immune globulins found in saliva and other secretions IgA predominates. IgA in the oral cavity affords protection against bacterial and viral infection. The structure of this secretory IgA is unique in that two serum-type IgA molecules, synthesized by the salivary glands, are linked together by components called a secretory piece and J chain. The epithelium produces the secretory piece and J chain and as the secretory IgA molecules move across the epithelium two IgA molecules are joined. This action produces an immunoglobulin complex which is resistant to degradation in the changeable oral environment.

An example of the action of secretory IgA is the relatively high resistance of adult oral tissue to staphylococcal infection following mechanical trauma. The resistance to staphylococcal infection following mechanical trauma to infants' oral tissue is far lower. This difference in resistance between adult and infant is due in part to a locally acquired natural immunisation. The secretory IgA provides a first line of defence against staphylococcal infection by keeping staphylococcal colonisers to a low number. Non-secretory IgA and IgG provide a second line of defence by eliminating bacteria which penetrate the oral mucosa.

Secretory IgA present in the mucous coating on the oral mucosa alters the ability of bacteria to colonise the surface. This IgA can also aggregate bacteria into clumps which when large enough are washed into the stomach by saliva.
In contrast to the protective action of secretory IgA, agglutination of bacteria may aid plaque formation.
6. AGE CHANGE

DEFINITION OF AGING

Timiras (1972)\textsuperscript{75} defined aging as "the sum total of all changes that occur in a living organism with the passage of time leading to functional impairment and death". He made a further qualification that aging decreased the ability of an organism to survive stress.

Korenchevsky's (1961)\textsuperscript{76} opinion of aging was that of a physiological process which is rarely seen in present day humans. He stated that present day aging is a pathological syndrome.

ETIOLOGY OF AGING

The processes of aging are still largely conjectural. Nevertheless aging is commonly divided into physiological and pathological causes.

Physiological aging is seen as occurring in two forms during the maturation of an organism\textsuperscript{77}. The first type of physiological aging starts in organs which cannot renew their cells. The brain or eyes serve as examples where aging commences prior to completion of growth of the body. Neurones are lost from age 5 onwards and visual accommodation commences to decline between 8 and 50 years of age\textsuperscript{77}.

The second type of physiological aging starts in most organs when they reach the point of full growth. The functions of these organs becomes progressively impaired. The decline with increasing age of vital capacity, cardiac output, gastric juice secretion and muscle strength are examples of aging of tissue from a time of full growth\textsuperscript{77}.

Due to the interdependence of body organs and tissues if one
organ declines in function other organs and tissues are adversely affected. Korenchevsky (1961)\textsuperscript{76} stated that a functional decline in one organ sets up "vicious circles". Atrophy of a controlling organ impairs the function of organs under its control. Organs dependent on these controlled organs will be impaired in turn and so on.

Timiras (1972)\textsuperscript{75} described physiological aging as a consequence of growth cessation. He stated that a decline in the function of one part of an organism must produce age changes in the organism as a whole. He further suggested that the rate of aging of cells and cell components was dependent on a ratio between biologically important non-renewable and biologically important renewable materials. The change in this ratio over time would determine how rapidly an organism ages.

The exhaustion of biologically important non-renewable cell substrates may place a limit on the longevity of the single cell and all cells derived from it.

Hayflick (1965)\textsuperscript{78} has shown that a limit to the lifetime of in vitro strains of human cells exists. The finite lifetime of one cell was shown to be related to a finite number of cell doublings from that one cell. In vivo experiments indicated that the expected number of cell doublings from one cell of an organism, decreases with increasing age of the organism\textsuperscript{78}.

Hayflick (1965)\textsuperscript{78} also reported chromosomal abnormalities in old strains of human diploid cells. He suggested in vivo evidence of age associated chromosomal abnormalities may be involved in the limit to proliferation of human diploid cell strains in vitro.

Burnett (1970)\textsuperscript{79} related aging to the competence of the body's immune surveillance system. This system is thymus dependent and functions to destroy aberrant cells arising by mutation. These
aberrant cells may manifest as malignant or autoimmune disease. Exhaustion of the thymus dependent system was cited as a cause of aging in mammals and other vertebrates.

The thymic cortex has the most rapid cell turnover of any body organ. Accepting that there is a "Hayflick limit" in vivo, then the thymus must use up its quota of cells more rapidly than any other body organ. With a decreasingly competent thymus it follows that the immune surveillance system also becomes less competent. Therefore cellular aberrations may arise in body tissues and not be destroyed by the immune surveillance system.

Further it is known that any serious body stress such as trauma, infection or starvation causes very rapid atrophy of the thymic cortex. One result of serious stress on an individual is probably an increased aging rate.

THE SALIVARY GLANDS AND AGE CHANGES

Franks and Hedegard (1973) stated that a fall in production of saliva followed the pattern and rate of age changes in the salivary glands. They indicated that the volume of saliva secreted decreased with increasing age. From the minor salivary glands, at least, a decreased or sparse mucinous secretion follows involution of the glandular epithelium.

Normally aging does result in a diminution of the volume of saliva produced. However, rarely does this lack of saliva produce more than a transient feeling of dryness.

Waterhouse et al. (1973) examined a large group of hospital autopsy subjects and found that the fraction of total salivary gland volume occupied by parenchymal cells decreased gradually with age. The parenchymal cells were replaced by fat and
connective tissue. The study showed that between childhood and old age approximately one quarter of salivary gland parenchymal cells were lost. This loss of parenchymal cells would reduce the functional reserve normally present in the salivary glands and this lack of reserve may be associated with a reported reduction of salivary flow in senescence.81,84,85,86

Andrew (1952)87 summarized age change in submandibular and parotid salivary glands as follows:

a) fatty replacement of parenchymal cells

b) development of aberrant cells with nuclear and cytoplasmic changes

c) metaplasia of small salivary ducts

d) an accumulation of lymphoid tissue.

An increase in the number of large degenerate cells or oncocytes and fibrosis within salivary glands are common senile changes.

83,88
7. CLINICAL EXAMINATION OF THE SALIVARY GLANDS

A physical examination of the salivary glands involves examination of the whole cervico-facial region. Systematic use can be made of the following approaches:

- Inspection and palpation
  - Extra-oral
  - Intra-oral

- Exploration of the salivary ducts

- Bacteriological culture and smear, antibiotic sensitivity test.

INSPECTION AND PALPATION

The clinician should stand in front of the patient and note any change from the normal facial appearance. In particular, evidence of asymmetry, discolouration, visible pulsation or the presence of discharging sinuses should be sought. Enlargement of salivary glands may be unilateral or bilateral; and may involve one or all glands both major and minor.

THE PAROTID GLAND

Characteristic of generalized enlargement of the parotid gland is a swelling which when viewed full face overlaps the tragus of the ear. The swelling obliterates the depression normally present below and anterior to the lobe of the ear. Palpation of the parotid gland is recommended as follows:

a) Place the pulps of the fingers over the main body of the
gland. Ascertain the consistency of any swelling and whether or not tenderness or pain is produced on palpation.

b) Have the patient clench his teeth, raising the masseter muscle into relief. Then attempt to define the anterior extent of the gland.

c) Palpate the superior third of the gland. Any fulness here should be seen to be continuous with the main body of the gland. If the fulness is not continuous it may be from an adjacent structure. Note that a preauricular lymph node overlies the gland in this region. Hall (1969)\(^1\) warns that enlargement of a preauricular lymph node may simulate a neoplasm. If a neoplasm is suspected in the parotid gland then function of the facial muscles should be tested. A neoplasm in the parotid gland may cause paralysis of facial muscles by damaging branches of the facial nerve which pass through the gland (vide supra: Gross anatomy of the salivary glands, p. 3).

THE SUBMANDIBULAR AND SUBLINGUAL GLANDS

An enlargement of the submandibular gland causes a swelling just below and medial to the angle of the mandible. This swelling may be difficult to differentiate from enlarged submandibular lymph nodes. Swellings of salivary gland origin are generally single, larger and more smooth surfaced than swellings due to enlarged lymph nodes\(^9\). Swellings arising consistently just prior to or during meals are almost certainly from salivary glands\(^9\).

Bimanual palpation of a submandibular gland is performed with an index finger placed lateral to the tongue and posteriorly in the floor of the mouth. Pressure is applied downwards against the
fingers of the other hand, which are placed on the skin medially and anterior to the angle of the mandible. Moving the palpating fingers towards the midline and then posteriorly to the opposing side of the jaw completes palpation of the paired submandibular and sublingual glands. Experience is required to palpate abnormalities in the floor of the mouth as the normal consistency varies widely.

THE MINOR SALIVARY GLANDS

Examination of the labial and buccal minor salivary glands can be performed by bimanual palpation. Compression of palatal glands against the underlying bone enables their examination. The function of the minor salivary glands can be assessed by everting the lower lip and drying it with a gauze swab. Within a short time droplets of saliva should be expressed onto the labial mucosa.

In cheilitis glandularis apostematosa, a rare form of labial saladenitis, a thick viscous mucus can be expressed from the salivary glands in the lower lip.

Rarely one of the salivary glands of Blandin in the tongue may undergo cystic degeneration. Knowledge of the anatomical location of these two glands provides a diagnosis following the examination of the swelling (vide supra: The minor salivary glands, p.10).

EXAMINATION OF THE SALIVARY DUCTS

It is important to determine whether Stensen's and Wharton's ducts are patent and indeed if they are present at all. Eliciting a flow of saliva makes these observations simple.

Pressure exerted on the parotid or submandibular gland or along the course of their main ducts should express some saliva from the duct orifices. The saliva is normally watery, clear and easily
expressed from the ducts. Pathosis is evident when the saliva contains debris, plugs of mucus or pus\textsuperscript{89}.

When examining the submandibular gland ducts one duct opening should be covered with a gauze swab because the right and left glands open in close proximity. The mucosa around the duct orifice should be dried prior to examination. It can then be determined whether or not saliva is being excreted from this orifice\textsuperscript{91}.

Inflammation around the duct orifices aids diagnosis even if a discharge or purulent saliva cannot be elicited. Doubt about inflammation due to a minor erythema in the region of duct openings may be resolved by comparison with the duct orifice of the gland of the opposite side\textsuperscript{90}.

**PROBING OF DUCTS**

Probing of Stensen's and Wharton's ducts is indicated when a reduction in salivary flow or a palpable mass along the course of the ducts is noted\textsuperscript{92}. However, during periods of acute sialadenitis insertion of probes is contraindicated\textsuperscript{93}.

A lacrimal probe dilator of appropriate size is used to investigate the course of a duct\textsuperscript{89}. The mucosa over the duct orifice is dried with gauze which is held in place to cause saliva to backup in the duct. When the gauze is removed the duct orifice opens to emit a small flow of saliva. The probe is then gently inserted into the duct. The anatomy of the main salivary ducts is tortuous and care should be taken to prevent perforation of the relatively thin duct walls. Stensen's duct permits insertion of a probe for a distance of between 13 mm and 25 mm and Wharton's duct from 38 mm to 50 mm\textsuperscript{92}. Insertion of a probe may be aided by giving the patient a dilute solution of citric acid or a lemon to suck as these stimulate a copious
flow of saliva.

Interference with the insertion of a probe may indicate the presence of stenosis, salivary calculi, epithelial plugging and post-inflammatory or neoplastic constriction of a duct. Location of an obstruction of a duct can be aided by leaving a probe in the duct and taking appropriate soft tissue radiographs of the area. When the probe is removed any saliva expressed should be examined for salivary sand, pus, inspissated mucus or degenerate epithelial cells\textsuperscript{92}.

BACTERIOLOGICAL CULTURE AND SMEAR, ANTIBIOTIC SENSITIVITY TEST

If clinical findings are suggestive of infection some saliva should be collected from the affected gland and a culture and bacterial antibiotic sensitivity test performed\textsuperscript{92}. A gram stain of any pus excreted frequently provides immediate identification of the general type of organism involved in the infection. When the presence of actinomycosis or a true fungus is suspected, then a wet mount may reveal the organism involved. Examination of mucus plugs using a Wright blood stain may show an abundance of eosinophils consistent with an allergic reaction\textsuperscript{91}. 
8. BIOPSY OF SALIVARY GLANDS

In all cases of salivary gland disorders biopsy is the one procedure which routinely gives an indication of the nature of the disease process. A biopsy allows better assessment for further treatment and management of an individual case\(^{94,95}\).

BIOPSY OF MAJOR SALIVARY GLANDS

The two biopsy techniques used for major salivary glands are incision and needle biopsy.

Incision biopsy provides the most satisfactory tissue for histopathological examination. The more superficial parotid and sublingual glands are more easily biopsied than the submandibular glands\(^{91}\). The mass to be biopsied should be palpated and a readily accessible portion located\(^{95}\). Short incisions will provide adequate exposure and a skin incision in a line of election will produce a scar that is hardly noticeable. The facial nerve is embedded in the substance of the parotid gland and this dictates that a biopsy wedge should be no more than 3 mm to 4 mm in depth\(^{91}\).

Post-operative complications following incision biopsy may include: damage to important neurovascular structures, creation of salivary fistulas, and seeding of tissue planes with neoplastic cells. Also, scar tissue at the site of a biopsy can make later surgery more difficult\(^{95}\).

Adkin, Kreller and Walters (1975)\(^{96}\) have adapted the Seward technique for intra-oral removal of calculi from the extraglandular part of the parotid duct to obtain a biopsy specimen of the parotid gland. The technique involves tracing the parotid duct through the buccinator muscle to where the accessory parotid arises\(^{97}\). This
intra-oral approach removes the risk of external scarring and of creating an external salivary fistula. The risk of facial nerve damage is not reduced. Kraaijenhagen (1975)\textsuperscript{98} points out that the biopsy approach used by Adkin et al (1975)\textsuperscript{96} can only be used for the 20\% to 50\% of patients who have an accessory parotid gland. The presence of an accessory parotid gland can be determined by sialography (vide infra: Indications for sialography, p.80). Kraaijenhagen (1975)\textsuperscript{98} has described his technique of biopsy of the parotid gland from an incision just below the ear lobe.

Where malignancy is suspected an incisional biopsy of a major salivary gland should be placed within the area contemplated for resection. When malignancy is proven the initial biopsy site with an ellipse of normal skin should be included with the surgical specimen containing the malignancy\textsuperscript{99}.

The needle or aspiration biopsy has the advantage of being easily performed and leaving no visible scar. However, the biopsy specimen is often of insufficient size to provide a definitive diagnosis and may be misleading\textsuperscript{91,99}. Hall (1969)\textsuperscript{91} and Rankow and Polayes (1976)\textsuperscript{99} considered needle biopsy should not be used if a tumour is suspected because the needle track may be seeded with tumour cells. Mason and Chisholm (1975)\textsuperscript{95} stated that by allowing the pressure in the biopsy syringe to equalize before withdrawing the needle, aspiration of tumour cells into the needle track is prevented. Eneroth, Franzen and Zajicek (1967)\textsuperscript{100} using aspiration biopsy, showed positive tumour diagnosis in 92\% of 1,000 cases of proven salivary tumours.

**BIOPSY OF MINOR SALIVARY GLANDS**

Salivary gland tissue is readily available for biopsy from
minor salivary glands which are abundant beneath the oral mucosa (vide supra: The minor salivary glands, p.10). Biopsy of minor salivary glands may provide important information when these glands are involved in a generalized disease process.

Cahn, Eisenbud, Blake and Stern (1964)\textsuperscript{101} reported the experimental use of a punch biopsy for minor salivary glands in the palates of patients with known sarcoidosis. Eisenbud, Platt, Stern, D'Angelo and Sumner (1973)\textsuperscript{102} used a palatal punch biopsy of minor salivary glands in a study of connective tissue diseases including Sjögren's syndrome. They stated that the palatal biopsy is simple to perform, does not require suturing and provides tissue of diagnostic quality. The technique requires that the tissue is taken in close proximity to the greater palatine artery in an area where gagging can be troublesome. Persistent haemorrhage in two patients from their series of palatal biopsies is not surprising.

Minor salivary glands are abundant beneath the mucosa of the lower lip where a biopsy can be readily performed. Meskin, Bernard and Warwick (1964)\textsuperscript{103} used a biopsy punch to obtain salivary gland tissue from the lower lip. The technique is quick and simple but has the disadvantage of unreliability in obtaining salivary tissue in the specimen, especially when the minor salivary glands are atrophic. Also the biopsy specimen can be distorted during the punch biopsy procedure. The arterial supply to the lower lip is deep to the minor salivary glands and so haemorrhage is rarely a problem following biopsy of these glands.

Chisholm and Mason (1968)\textsuperscript{104} described the use of incisional biopsy for the minor salivary glands of the lower lip. The biopsy procedure entails removal of a wedge of the mucosa and the submucosa. In the lower lip the submucosa contains the minor salivary glands.
The wound is closed with fine black silk sutures and heals with little
evidence of fibrous contraction.

A TECHNIQUE OF LABIAL SALIVARY GLAND BIOPSY

Greenspan, Daniels, Talal and Sylvester (1974)\textsuperscript{105} described
a biopsy procedure of minor salivary glands of the lower lip where
the mucosa is incised but not removed. Local anaesthetic is injected
deep to the glandular tissue of the lower lip. A linear incision
1.5 cm to 2.0 cm in length is made parallel to the vermillion border
and lateral to the midline. The margins of the incision are bluntly
dissected and the salivary glands are removed individually and placed
in fixative. The mucosal incision is closed with sutures. Between
4 and 7 minor salivary glands can usually be obtained from the lower
lip using this biopsy procedure. These provide ample material for
electronmicroscopy, immunofluorescence and tissue culture as well as
providing a specimen for routine histopathological examination\textsuperscript{105}.
The advantages of this simple biopsy procedure are that salivary gland
tissue is certain to be obtained and minimal scarring of the labial
mucosa occurs.
9. THE FLOW RATE OF SALIVA

The diagnosis of xerostomia may be aided by comparing a patient's salivary flow against an experimentally determined mean salivary flow. Salivary flow rate has been dealt with in numerous studies\textsuperscript{85,106,107,108,109,110,111}. Not all studies measure total salivary flow and the methods and conditions of flow rate estimation vary greatly. Therefore, conflicting results appear in the literature. Estimation of whole salivary flow by simple clinically adaptable methods will be examined.

RESTING AND ACTIVATED SALIVARY FLOW RATE

The resting flow rate of saliva is the flow measured in a subject when there are no extra-oral and intra-oral stimuli acting on the salivary glands. This situation probably occurs during sleep but is difficult to simulate in the conscious patient\textsuperscript{85,112}.

Activated salivary flow is that flow of saliva produced by the direct or indirect action of extra-oral or intra-oral stimuli on the salivary glands (vide supra: The stimulus to secretion of saliva, p.24).

Measurement of the resting flow of saliva provides a baseline for diagnosis as it is more representative of the secretion throughout the day and night. Measuring the activated salivary flow and relating this to a patient's resting flow rate gives an indication of the functional reserve of the patient's salivary glands\textsuperscript{113}, in other words, determining whether a patient can produce more than their resting flow of saliva.
METHODS USED TO DETERMINE WHOLE SALIVARY FLOW RATE

Bertram (1967) \(^{111}\) and Kerr (1961) \(^{114}\) list the main methods to determine the resting flow rate of whole saliva as drainage, spitting and suction. In addition they describe an infrequently used technique employing cotton wool rolls to measure salivary flow rate. The main measurement techniques all require the patient to be placed with the head inclined forward so that saliva will collect anteriorly in the floor of the mouth \(^{111,114}\).

The drainage method entails the patient allowing the saliva to run out over the lower lip into a funnel connected to a graduated measuring glass for a specific period of time \(^{111}\).

The spitting method has the patient spit the pooled saliva into a collecting funnel once every unit of time, usually once a minute \(^{111}\).

The suction method employs a saliva ejector placed to the lingual of the lower incisors to collect the saliva. Kerr (1961) \(^{114}\) used a smooth glass tube, angled to fit over the lower incisors, coupled to a vacuum trap to collect saliva by suction. He does not use this method for collecting resting saliva as it stimulates salivary flow.

THE VARIABILITY IN THE FLOW RATE OF SALIVA

The conflicting results of many studies on the flow rate of saliva are probably due to variation in collection technique and conditions, and to variability in the salivary flow between individuals.
COLLECTION VARIABLES INCLUDE

(a) Collection time

A collection time of 10 to 15 minutes was suggested by Bertram (1967)\textsuperscript{111} as a useful interval. Kerr (1969)\textsuperscript{112} used 10 minutes for collection of resting whole saliva from 149 individuals. A collection time which is too brief can produce unduly high flow rate values, while a prolonged collection time may fatigue the patient and produce low flow rate values\textsuperscript{111}. However, Brown (1970)\textsuperscript{115} reported undiminished salivary flow during one hour while chewing gum.

(b) Circadian rhythm

Dawes (1972)\textsuperscript{109} has shown that the circadian rhythm found with human salivary flow has a 24 hour periodicity. As shown in Figure 14, salivary flow rates are lowest in the morning and highest in the afternoon.

![Graph showing circadian rhythm of unstimulated salivary flow rate](image)

**Fig. 14.** Adapted from: Dawes, C., Circadian rhythms in human salivary flow rate and composition. J. Physiol. 220:529-545. 1972
Malfunctioning salivary glands may not have the reserve capacity to increase their secretion in the afternoon, thus morning and afternoon measurements of salivary flow rate in a patient may have diagnostic use.

(c) The environment in which saliva is collected from a patient affects salivary flow rate

Agitation and noise can result in anxiety and a decrease in salivary flow. A dry mouth during periods of nervous tension, threat or fear has been experienced by most individuals. Bates and Adams (1968) demonstrated the influence of mental stress upon the stimulated flow of saliva in man. The stress that a dental environment places on many individuals must also be considered when measuring resting salivary flow.

Bertram (1967) reports that a room temperature greater than the usual 20°C-25°C lowers the secretory rate of saliva.

Shannon and Suddick (1975) showed that there is a pronounced fall in salivary flow from subjects in total darkness.

(d) Intra-oral stimuli

Intra-oral stimuli affect salivary flow rate and produce an activated, non-resting, secretion from the salivary glands. Shannon (1962) demonstrated that the flow rate of whole saliva increases significantly in subjects chewing rubber bands. Increasing the size of the bolus of bands being chewed led to proportional increases in parotid flow rate. Extra-parotid sources of saliva were far less sensitive to increases in bolus size. Jaw movements stimulating chewing also increase parotid secretion.

Kerr (1961) reported that increasing the stiffness of the
bolus chewed increased salivary secretion rate in his human subjects. Kerr (1961) concluded from numerous earlier studies that the greater the intra-oral disturbance caused by the collection of saliva the greater will be the amount of saliva collected. Therefore, a saliva ejector or any other device in the mouth will increase salivary flow rate.

Variation in salivary flow rate between individuals may result from:-

(a) Differences between sexes - males may have higher salivary flow rates than females. Bertram's (1967) experiments support this concept of higher salivary flow in males. Studies which Bertram (1967) quoted are equivocal. If any sex difference in flow rate exists it is certainly of a small amount.\textsuperscript{85,118}

(b) Age related changes in salivary flow rates occur (vide supra: The salivary glands and age changes, p.60). After approximately 29 years of age, salivary flow rate slowly decreases. Measurements of salivary flow rates in healthy, aged individuals should fall within the lower range of normal.\textsuperscript{85,111}

(c) The physical and mental condition of an individual influences his flow of saliva. Bertram (1967) reported that in a group of elderly people the secretion values of hospital patients were lower when compared to clinically healthy old people. Infection, fatigue, hunger, and also dehydration depress salivation.\textsuperscript{111,115} Kerr (1961)\textsuperscript{114} ensured that all subjects in his experiments were adequately hydrated prior to determination of salivary flow rates. Hydration was ensured by inviting subjects to drink water, if they desired, before collection of their saliva. Anxiety, stress and fear can reduce salivary flow and cause a dry mouth.\textsuperscript{108} Brown (1970)\textsuperscript{115}
<table>
<thead>
<tr>
<th>OUTPUT MEAN</th>
<th>COLLECTION TIME (MIN.)</th>
<th>METHOD OF COLLECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>* 2.43 ± 0.46 ml/5 min. (4.9 ± 0.9 ml/10 min.)</td>
<td>5</td>
<td>Draining for 5 minutes, spitting once to clear mouth at the end of the collection time.</td>
<td>Dawes (1972)\textsuperscript{109}</td>
</tr>
<tr>
<td>* 3.8 ml/15 min. (2.5 ml/10 min.)</td>
<td>15</td>
<td>Suction with negative pressure of 5 - 10 mm Hg. (Small group)</td>
<td>Bertram (1967)\textsuperscript{111}</td>
</tr>
<tr>
<td>* 19 ± 0.54 ml/hour (3.2 ml/10 min.)</td>
<td>15</td>
<td>Draining</td>
<td>Becks and Wainwright (1943)\textsuperscript{85}</td>
</tr>
<tr>
<td>* 0.65 ml/min. (6.5 ml/10 min.)</td>
<td>5 - 10</td>
<td>Suction</td>
<td>Schneyer and Levin (1955)\textsuperscript{120}</td>
</tr>
<tr>
<td>* 0.51 ml/min. (5.1 ml/10 min.)</td>
<td>10</td>
<td>Spitting at a rate of once per minute for 10 minutes.</td>
<td>Kerr (1961)\textsuperscript{112}</td>
</tr>
</tbody>
</table>

TABLE 1: The "normal" flow rate of saliva.  
* These figures are from the author's experimental results. Figures in parenthesis are approximations of flow rates per 10 minutes.
reviewed studies of lowered salivary flow in psycho-pathologic states. A group of psychotics whose main symptom was depression was studied. It was confirmed that a reduction in parotid saliva flow rate can be correlated to the depth of depression. No impairment of the salivary mechanism was present in these depressed states.

(d) Biological variability is a simple way of explaining the large range of salivary flow rates seen in normal individuals\textsuperscript{119}. The difference in the size and functional capacity between the salivary glands in different individuals must be a factor in the variation of their salivary flow rates.

**QUANTIFYING THE FLOW RATE OF SALIVA**

Factors which influence a "normal" salivary flow have been presented. These factors should be considered when estimating a patient's salivary flow rate. Table 1 presents a range of normal salivary flow rates and the method by which the rates were determined.

**SALIVARY FLOW RATE IN PATIENTS WITH XEROSTOMIA**

Bertram (1967)\textsuperscript{121} determined the median salivary flow rate in 50 patients referred because of xerostomia. The median flow rate for 7 men was 0.10 ml/15 minutes and for 43 women, 0.05 ml/15 minutes. The difference in these values between male and female was not statistically significant. The results for the patients were divided between those with most severe and those with least severe xerostomia. The least severely affected group had an average flow rate of 1.03 ml/15 minutes and a median of 0.513 ml/15 minutes. These values from the least severe group are just below Bertram's value for mean flow rate of saliva in normal individuals\textsuperscript{111}. 
A TEST OF SALIVARY GLAND FUNCTION BY ASSESSING SALIVARY FLOW RATE

Almost any form of intra-oral disturbance will produce an increase in the flow rate of saliva. A standard stimulus is required when comparing the salivary flow rate between individuals. Three main stimuli are used: parasympathomimetic drugs, mechanical (chewing) and gustatory stimuli\textsuperscript{107,113,115}.

The use of parasympathomimetic drugs, such as pilocarpine, to stimulate salivation is unwise in patients with some disease states; for example, the use of these drugs in patients with occult heart disease would be contra-indicated\textsuperscript{113}.

Chewing is too variable to be used as a standard method of activating salivation.

Kerr (1961)\textsuperscript{122} stated that the most effective method of producing a copious flow of saliva is to allow citric acid sugar candy to dissolve on the tongue.

A suitable gustatory stimulus to give activated salivary flow is 5\% citric acid dropped onto the tongue from a syringe\textsuperscript{113}.

Procedure for Test

1. Establish a base value for the patient's resting salivary flow.

2. Establish an activated or stimulated flow rate of saliva by dropping 5\% citric acid onto the patient's tongue.

Saliva can be collected by having the patient spit into a 10 ml measuring cylinder at the end of each 10 consecutive minutes. The cylinders should be graduated in 1/10th of a millilitre\textsuperscript{112}.

Schneyer and Levin (1955)\textsuperscript{120} reported a 2.4 fold increase of a group mean for the flow rate of whole saliva after painting 1\% acetic acid on the tongue.
Kerr (1961)\textsuperscript{122} using 0.5M citric acid obtained six times the increase in whole salivary flow rate to that obtained by Schneyer and Levin.

Therefore, in patients whose salivary glands have an adequate function reserve, 5% citric acid should at the lowest range of normal produce twice that patient's resting flow rate of saliva. Otherwise, a reduction in stimulated salivary flow may be due to gland dysfunction.
10. RADIOLOGY OF THE SALIVARY GLANDS

Sialography is the radiographic demonstration of a salivary gland and its ducts by means of the injection of radiopaque solution into the duct\(^ {123} \). Arcelin in 1913 is reported to have been the first to present a complete roentgenographic demonstration of a human salivary gland\(^ {124,125} \). Since the introduction of sialography the basic technique has remained little changed, although numerous modifications have been devised\(^ {126,127,128,129} \).

INDICATIONS FOR SIALOGRAPHY\(^ {125,130} \)

Detection or demonstration of the following in salivary glands may be aided by sialography:

(i) A calculus, calculi or foreign bodies whether these are radiopaque or radiolucent. Information as to the extent of destruction of a salivary gland following obstruction.

(ii) Fistulae, diverticulae or strictures.

(iii) Chronic inflammatory processes and recurrent swellings.

(iv) Neoplasms, including their location, size, origin and degree of malignancy.

(v) Site for biopsy.

(vi) Residual pathology following surgical procedures.

Whinery (1973)\(^ {131} \) reported the therapeutic value of sialography followed by gland massage in cases of recurrent parotitis (vide infra: Chronic recurrent sialadenitis, p.157).

CONTRA-INDICATIONS TO SIALOGRAPHY\(^ {125} \)

Sialography is usually contra-indicated in the following circumstances:

(i) Patients having or reporting a sensitivity to iodine
compounds including patients who have had severe asthma or anaphylaxis, following the administration of iodine containing compounds.

(ii) During a period of acute inflammation in the salivary gland to be radiographed.

(iii) Prior to thyroid function tests. Iodinated contrast media used in sialography may interfere with these tests. Thyroid function tests therefore should be performed prior to sialography.

(iv) In the presence of calculi placed anteriorly in the main duct of a salivary gland. Sialographic procedures can displace calculi posteriorly along a duct.

COMPLICATIONS OF SIALOGRAPHY

Complications arising following sialography are unusual. Overdistension of the gland may cause temporary swelling and discomfort for a few hours or a few days. The discomfort can be relieved with mild analgesics. Occasionally a chronic inflammatory process will be aggravated by sialography. In these cases an appropriate antibiotic will control and alleviate discomfort.

Perforation of the main duct of a salivary gland could result in constriction of the duct following fibrous repair and contraction of the defect.

Extra-ductal injection of contrast medium can incite a foreign body reaction in the extra-ductal tissues (vide infra: Contrast media in sialography, p. 89).

SIALOGRAPHIC TECHNIQUES

No one sialographic technique or its armamentarium are
entirely perfected as the many modifications testify. The two most frequently used techniques of injecting radiopaque solution in sialography are by hand injection and by hydrostatic or gravity-feed. The hand injection technique requires a syringe containing contrast media to be injected through a metal or plastic cannula into the gland undergoing sialographic examination.

Hydrostatic sialography is performed by allowing a water-soluble contrast medium to flow into a salivary duct from a reservoir at a fixed height above the duct orifice. The height of the reservoir produces a small positive pressure of contrast medium which forces its way into the gland being examined. Hydrostatic sialography is reported to be less painful for the patient than other techniques. Park and Bahn (1968) and Blair (1973) described techniques and equipment suitable to perform hydrostatic sialography.

Ferguson, Evans and Mason (1977) described continuous infusion pressure-monitored sialography and claim that it avoids the problems, principally pain and overfilling of the gland, encountered with either hand injection or hydrostatic sialography. The technique differs from others in using a continuous infusion pump and pressure recording apparatus to force the contrast medium into the gland to be radiographed. The continuous infusion technique requires more complex equipment than other techniques and its advantage of not overfilling a gland with aqueous contrast medium is not sufficient to recommend its routine use.

Two types of contrast media are used for sialography, water soluble and oil soluble. Both media contain iodine in some form (vide infra: Contrast media in sialography, p. 89).
ROUTINE PROCEDURES IN SIALOGRAPHY

Sialography may be carried out with the patient in a supine position or seated in a dental chair. Plain radiographs of the salivary gland to be examined are obtained. These films detect the presence of any calculi or calcification within the gland and allow positioning of the patient and exposure times to be checked prior to sialography.

PLAIN RADIOGRAPHIC VIEWS OF THE SUBMANDIBULAR GLAND

(a) Lateral oblique, neck hyperextended to project the submandibular gland below the mandible.
(b) Central true occlusal of the floor of the mouth.
(c) Posterior oblique occlusal of the gland itself.

PLAIN RADIOGRAPHIC VIEWS OF THE PAROTID GLAND

(a) Off centre antero-posterior view.
(b) Lateral view as for a lateral projection of the maxillary sinus.
(c) If indicated, a lateral oblique view, with the tube positioned under the contralateral ramus. Extension of the neck keeps the cervical spine clear of the parotid gland.
Rose (1950) criticised the lateral oblique view for the parotid gland stating that it unacceptably distorts the normal anatomy.

LOCALISING AND CANNULATING THE SALIVARY DUCT SYSTEM

The parotid duct opens at the apex of the parotid papilla in the buccal mucosa opposite the maxillary second molar tooth. Stensen's duct in the first part of its course runs submucosally and
posteriorly for 3 mm to 5 mm. The duct then turns laterally, passes through the buccinator muscle and crosses the anterior border of the masseter muscle. Finally the duct inclines downwards and medially. Seward (1961) and Archer (1975) stated that Stensen's duct should be cannulated for only a short distance to avoid perforation or impingement by the cannula when the duct turns sharply through the buccinator muscle. An acrylic stop 3 mm from the tip of the metal cannula restricts penetration of the duct and reduces backflow of contrast medium. A flexible cannula can be manipulated to give deeper penetration of Stensen's duct resulting in greater stability of the cannula and reduced backflow of contrast medium. A 23 gauge cannula is usually adequate for Stensen's duct. Where the orifice of Stensen's duct is difficult to locate, stroking the cheek or having the patient suck a lemon will elicit a flow of saliva which reveals the opening.

Lebowitz and Laskin (1978) described the use of an angiocatheter as a cannula for sialography. The angiocatheter is useful in that it can be placed over the lacrimal dilator used to gain entrance to the duct. Once the duct is entered the cannula can be slipped down the lacrimal dilator and into the duct. The lacrimal dilator is then removed from the duct to allow connection of extension tubing and a syringe containing contrast medium. The catheter can be held between the patient's teeth when ready to position the patient for radiographs. The various gauges of angiocatheter available allow selection of a catheter which fits tightly into the duct of the gland being examined.

The submandibular duct measures up to 5 mm in diameter but its orifice, situated on the tip of the mobile sublingual papilla, may be minute. From the papilla the submandibular duct runs
posteriorly and inferiorly on the lingual side of the sublingual fold. The duct diverges from the sublingual fold at an acute angle\textsuperscript{127}.

To enable cannulation of Wharton's duct the patient is instructed to curl the tongue upward. The floor of the mouth is dried and the sublingual papilla watched until the duct orifice becomes apparent with a flow of saliva. The mobile papilla may have to be fixed with toothed tissue forceps in which case local anaesthetic is infiltrated. As the orifice of the submandibular duct is small, lemon juice and lacrimal dilators are often needed to aid cannulation of the duct. Care is needed in using salivary stimulants as injection of contrast medium against fast flowing saliva may be painful for the patient. A 26 gauge cannula is usually small enough to negotiate the orifice of Wharton's duct\textsuperscript{127}.

When a cannula is introduced into the submandibular duct then the hub should be moved upwards, toward the midline, then downwards towards the opposite side of the mouth. These movements bring the tip of the cannula into line with the main part of the duct and the contrast medium can be injected\textsuperscript{127}. If the cannula fails to slip easily into the submandibular duct a small amount of contrast medium can be injected to dilate and lubricate the duct. It is important that the cannula be directed posteriorly and inferiorly otherwise the cannula may enter a sublingual gland duct near the sublingual papilla. If a sublingual duct is entered the cannula will meet resistance after 1 cm or less and injection of contrast medium will produce distention of the sublingual fold. The sublingual gland will fill with about 0.25 ml of contrast medium and if more medium is injected the patient may feel pain. When the cannula is stopped a short distance into the submandibular duct it should be withdrawn until its tip is just within the sublingual papilla. Some of the
contrast media will then reflux from the sublingual gland into Wharton's duct and the cannula will enter the duct more deeply if correctly directed. Seward (1961)\textsuperscript{127} recommended cannulating Wharton's duct for a distance of 2 cm.

Park and Mason (1966)\textsuperscript{136} suggested incision of the submandibular duct orifice where efforts to cannulate it have failed. This procedure can be advocated only in cases where sialographic information is essential for diagnosis because of the risk of subsequent scarring and obstruction of the duct.

**THE QUANTITY OF CONTRAST MEDIUM USED**

Underfilling a salivary gland during sialography will cause loss of the detailed structure of the duct system on the resultant sialogram. Conversely, overfilling with contrast medium produces a clouding of the gland on the sialogram which obscures detail and causes unnecessary pain for the patient\textsuperscript{127,132}. Under or overfilling of glands with contrast medium should be avoided if no preconceived quantity of medium is injected.

Blair (1973)\textsuperscript{124} reviewed the volume ranges of contrast medium used by different authors for parotid sialography between 1925 and 1970. The majority of volumes were between 0.5 ml and 2.0 ml. Cook and Pollack (1966)\textsuperscript{133} reported their best sialograms resulted when no more than 1.2 ml of contrast medium was injected into the parotid gland and not more than 1.0 ml injected into the submandibular gland. Lowman and Cheng (1976)\textsuperscript{125} and Ericson (1968)\textsuperscript{119} employed the production of pain as a guide to the quantity of contrast medium to inject into salivary glands. The development of pain as an endpoint to filling a gland may be unreliable due to a considerable difference in pain thresholds between patients. Seward (1966)\textsuperscript{127}
used 0.5 ml to 1.0 ml of contrast medium in submandibular sialography and 1.0 ml to 2.0 ml for parotid sialography. At the end of injection the submandibular gland should form an easily visible and palpable swelling in the submandibular triangle of the neck. Similarly the parotid gland becomes more visible and palpable following injection of contrast medium. The patient will experience a sensation of tightness near the endpoint of injection. Distention of the sublingual fold indicates filling of the sublingual gland by reflux. Park and Bahn (1968) commented that salivary gland capacity varies widely not only between adults and children but also when different pathological conditions are present. For example, in duct obstruction with dilation of the duct system, a gland may hold 2.5 ml to 3.0 ml of contrast medium. While in atrophied glands the duct system may be filled by 0.5 ml of contrast medium. The normal parotid gland will be filled adequately by about 1.5 ml of contrast medium and the submandibular gland by slightly less medium.

RADIOGRAPHS FOLLOWING INJECTION OF CONTRAST MEDIUM

The radiographic views used for the plain survey of the gland being examined are repeated when the gland has been filled with contrast medium (vide supra: Routine procedures in sialography, p.83). When the cannula used to inject contrast medium is left in the gland's duct backflow of medium into the mouth should be prevented. Contrast medium which overflows into the mouth should be removed with gauze swabs otherwise the opaque medium in the mouth will be confused with the medium within the gland rendering the sialogram useless.

When stenosis of the orifice of either the parotid or submandibular duct is suspected then the cannula should be removed after a first set of radiographs have been exposed and a further radiograph
showing the duct orifice obtained\textsuperscript{127}. Feldman (1965)\textsuperscript{129} recommended using image intensification fluoroscopy during sialography and cites these advantages: 

(i) Interstitial extraductal injections can be detected immediately. 

(ii) Filling of the ducts and gland and the endpoint of filling are directly controlled. 

(iii) Radiographs can be exposed at optimal positions. 

Additionally fluoroscopy allows spot radiographs to be exposed to provide views of the main duct and the partially and completely filled duct system. Goebel (1977)\textsuperscript{137} reported gradual filling of the gland under study and exposing spot sialograms assures better opportunity for studying the total duct structure. Small radiolucent non-obstructing stones could be overlooked without fractionated filling and spot filming steps. 

Ferguson, Evans and Mason (1977)\textsuperscript{132} suggested that the image intensifier does not have sufficient resolution to detect the filling of fine salivary gland ducts. This means that the endpoint of filling is not well controlled and also image intensification subjects a patient to considerably higher level of radiation than does a standard sialographic survey hence routine use of image intensification during sialography is not advisable. However, the development of higher resolution image intensifiers may prove very useful in sialography.

**EVACUATION OR SECRETORY PHASE RADIOGRAPHS**

Secretory sialography is the term used to describe the method of exposing radiographs after the contrast medium has been secreted or absorbed by the gland under examination. Following
filling-phase radiographs, the patient is given lemon juice to stimulate the evacuation of the contrast medium. If an obstruction is known to be present within the gland sialogogues should not be given as the patient may experience pain. Five minutes following stimulation of salivation radiographs can be exposed to assess the emptying of the glands. Should the radiographs show retention of contrast medium further radiographs at 1 hour and 24 hours later should be obtained.\textsuperscript{125,127,134,138}

Controversy exists over the length of time oil based contrast media are retained by normal salivary glands following sialography. Seward (1961)\textsuperscript{127} maintained that most of the contrast medium is ejected by the unobstructed gland within a few minutes. Park and Mason (1966)\textsuperscript{136} used water soluble contrast media for sialography and indicated that no residual contrast medium should be evident five minutes after stimulating salivation. Blair (1973)\textsuperscript{124} claimed that oil based contrast medium is retained for as short a period as ten to fifteen minutes and as long as 48 hours.

Retention of contrast medium following sialography can indicate obstruction, inflammation or neoplasia within a salivary gland.\textsuperscript{137}

CONTRAST MEDIA IN SIALOGRAPHY

Neustaeder, Ehrlich, Dubois and Blalock (1933)\textsuperscript{139} established the following criteria for an ideal contrast medium in uterosalpingography:

(i) Proper viscosity similar to oil.
(ii) Capable of rapid absorption and excretion.
(iii) Non-injurious when entering the circulation.
(iv) Freedom from injurious effect on the tissues.
(v) Sufficient radiopacity to render good delineation of the structure under examination. 

Lowman and Cheng's (1976)\textsuperscript{125} criteria for contrast media apply specifically to sialography and include in addition to the above:

(i) Physiological properties similar to saliva.

(ii) Miscibility with saliva.

(iii) Pharmacological inertness.

(iv) Low surface tension and low viscosity.

(v) Residual contrast medium should be absorbed by the salivary gland and detoxified by the liver or be excreted by the kidneys.

**FAT SOLUBLE CONTRAST MEDIA**\textsuperscript{125,140}

There are two types of fat soluble contrast media; iodized oils and insoluble organic iodide compounds. The oil derivatives include viscous media, like Lipiodol, and the more fluid media, like Ethiodol. Pantopaque represents the fat soluble organic iodide contrast media. The working time with these solutions is rapid as they require only minutes for injection and subsequent radiographing. Fat soluble contrast media provide good radiographic opacification\textsuperscript{137}.

Elimination of the fat soluble contrast media is primarily via the duct system. If the duct system is damaged by disease then the fat soluble media may be retained for a prolonged period of time. This retention of contrast medium in the salivary gland does provide diagnostic information but may further damage the gland by inciting a foreign body reaction\textsuperscript{130}. Extraductal injection of fat soluble contrast medium is reported to induce a foreign body reaction in the extraductal tissues\textsuperscript{141}. Patient response to sialography using fat
soluble contrast media varies from none to pain on injection, allergic reaction and foreign body reaction.

Ethiodol is probably the fat soluble contrast medium of choice as it is more fluid thus requiring a lower injection pressure than the other media. Also severe foreign body reaction or allergy has not been reported following the use of Ethiodol$^{125}$. 

WATER SOLUBLE CONTRAST MEDIA$^{125,140}$

The water soluble contrast media are principally iodinated benzene or pyridone derivatives. These media most closely satisfy the criteria for an ideal sialographic contrast medium. The water soluble media are miscible in body fluids including saliva. Elimination of these media from the salivary glands occurs primarily by reabsorption and they are then broken down and excreted by the kidneys. The working time with water soluble contrast media is very short because they are so rapidly eliminated from the salivary glands. Little, if any, pain on injection and no allergic reactions have been reported with the use of water soluble contrast media.

Goebel (1977)$^{137}$ stated that although water soluble contrast media can provide excellent diagnostic information, fluoroscopy, spot filling sialograms and 24 hour evacuation films cannot be employed when using these media. Lowman and Cheng (1976)$^{125}$ suggested that while water contrast media are less opaque than the oil soluble media, the more dense contrast of the latter can obscure debris and small non-opaque calculi. Spot filling sialograms overcome this objection to the oil soluble contrast media (vide supra: Radiographs following injection of contrast medium, p.87). Hypaque and Renografin are the water soluble contrast media of choice$^{125}$.

The choice of a contrast medium is governed by the technique
of sialography and the health of the gland under examination. Hydro-
static sialography requires a water soluble contrast medium. Fluoro-
scopy and spot filling sialograms require the more radiopaque oil
soluble media. Following hand injection of a contrast medium the
medium must remain in the salivary gland for sufficient time to allow
positioning of the patient and for exposure of radiographs. Hand
injection techniques of sialography are more easily performed using
oil soluble contrast media as these media are not absorbed by the
salivary gland.

When extensive destruction of a salivary gland is suspected
the escape of contrast medium into the tissues is a possibility. In
these cases water soluble contrast media are best employed as the
tissues may react adversely to oil soluble media. For the same reason
water soluble media are best used in demonstrating salivary fistulae.

Small salivary calculi may be displaced proximally down a
duct by oil soluble contrast media while the more fluid water soluble
media are less likely to displace these stones.

Patients who have a history of allergic reactions, without a
specific allergy to iodine, should be examined using water soluble
contrast media as allergic reactions with these media have not been
reported.

In older patients the flow rate of saliva may be lowered
(vide supra: The salivary glands and age changes, p.60). Because oil
soluble contrast media are excreted from the salivary glands via the
ducts the reduced flow of saliva in certain older patients may allow
prolonged retention of contrast media. In older patients with a
reduction in salivary flow a water soluble contrast medium for
sialography is indicated.
THE NORMAL SIALOGRAM

The size, shape and position of the major salivary glands vary in different individuals. Asymmetry between gland pairs in the same individual is seen\textsuperscript{134}. Schultz and Weisberger (1948)\textsuperscript{142} state that although considerable variation exists in minor sialographic details of the duct system the overall duct pattern is fairly constant. Eisenbud and Cranin (1963)\textsuperscript{143} note that sialography essentially only displays the duct system. Acini are seen coalesced on a sialogram and not individually since they are of microscopic size. Therefore it is the change in the relative size, shape and position of minor and major salivary ducts which indicate pathosis on a sialogram.

NORMAL PAROTID SIALOGRAM

Stensen's duct is relatively uniform in diameter with a lumen of approximately 1 mm to 3 mm \ldots This main duct branches with a gradual change to second and third order ducts\textsuperscript{125,134}. Hettwer and Folsom (1968)\textsuperscript{134} in their study of sialograms of hospital patients aged 19 years to 68 years described four basic normal configurations of Stensen's duct [see Fig. 15].

On lateral oblique sialograms nearly 50% of Stensen's ducts are classed as "modified curvilinear". These ducts show an S-shaped curve in the distal part of the duct as it courses around the anterior border of the masseter muscle. The central part of the duct is relatively straight while the proximal segment curves superiorly.

Twenty-five per cent of ducts are classed as "curvilinear" where the duct forms a gentle curve, concave superiorly. Seventeen per cent of ducts are described as "reverse sigmoid", being concave superiorly at the distal end and convex superiorly at the proximal portion. Less than ten per cent of ducts conform to an S-shaped or
Fig. 15. Basic configurations of Stenson's duct as seen on lateral oblique sialogram.

sigmoid pattern. It should be noted that the sialographic appearance of the distal part of a duct will be altered by the length, gauge and position of the cannula inserted into the duct.

When seen on a postero-anterior sialogram of the parotid gland, Stensen's duct should be no more than 2 cm lateral to the ramus of the mandible. Lateral displacement of the duct further than 2 cm suggests a mass may be present within the parotid gland\textsuperscript{125,134}.

An accessory lobe of the parotid gland is sometimes found superior to Stensen's duct (vide supra: Gross anatomy of the salivary glands, p. 3). The accessory lobe joins Stensen's duct at an acute angle anterior to the main part of the parotid gland\textsuperscript{125,134,142}.

Duct pattern within the parotid gland

Although there may be considerable individual variation in parotid duct pattern, similarities between patients do exist. Most parotid glands exhibit a tree-like branching of ducts posterior to the hilus\textsuperscript{142,143}. The general direction of the intraglandular ducts is postero-superior in close proximity to the mandibular ramus. These ducts show a gradual decrease in size as they approach the terminal acini. The intraglandular ducts of the parotid gland are smaller and more regular in size than the ducts within the submandibular gland\textsuperscript{134,142}.

Hettwer and Folsom (1968)\textsuperscript{134} described six patterns of intraglandular parotid ducts [see Fig. 16]. All glands examined were injected with approximately 1.5 ml of an oil soluble contrast medium for sialography. This resulted in the smaller glands, (A) to (C), being more fully filled than the larger glands (D) to (F). About 60% of parotid sialograms in the study showed the parallelism of second and third order ducts seen in (D) to (F). Patterns (B) to (C)
Fig. 16. Types of intraglandular pattern seen in lateral oblique projection sialogram.

do not show duct alignment but do illustrate the stretching of ducts postero-superiorly. Fifteen per cent of cases were similar to pattern (A) showing a small gland with poorly defined duct branches and gland outline.

Lowman and Cheng (1976)\textsuperscript{125} illustrated a postero-anterior sialogram of the parotid gland which shows stretching of the duct system across the isthmus joining the superficial and deep portions of the gland. This stretched appearance is normal and should not be interpreted as displacement of ducts by a tumour.

**THE SUBMANDIBULAR SIALOGRAM**

Wharton's duct is 2 mm to 4 mm in width and is usually wider than the parotid duct. The lumen of Wharton's duct may decrease in size as it courses from the angle at the posterior edge of the mylohyoid muscle to its orifice on the sublingual papilla\textsuperscript{125,134}. The submandibular duct merges into second and third order ducts which are wider than those in the parotid gland\textsuperscript{142}.

Hettwer and Folsom (1968)\textsuperscript{134} described three configurations, L- or S-shaped, of Wharton's duct on the lateral oblique sialogram [see Fig. 17]. Forty-five per cent of ducts are categorised as "curvilinear". These ducts follow a single gentle curve, concave superiorly, from the sublingual papilla to the sharp angle of the duct. Another 45% of Wharton's ducts are classified as "linear" where the horizontal arm of the duct is straight. The remaining 10% of submandibular ducts are classed as "sigmoid" being an elongated S-shape. No particular significance is given to the different shapes of Wharton's ducts on lateral oblique sialograms. The differences are attributed to variation in the tonus of the musculature of the floor of the mouth and of the position of the patient's neck during sialography\textsuperscript{134}.
Fig. 17. Basic configurations of Wharton's duct as seen on lateral oblique sialogram.