Chapter 9: Anatomy and physiology of the salivary glands

O. H. Shaheen

Every textbook of human physiology includes a section on the salivary glands but rarely does this provide an insight into how disturbances of function affect the individual. This is hardly surprising in view of our limited knowledge, but an awareness of the importance of the salivary glands to the health and sense of well-being of the individual is increasingly evident.

Investigations into recurrent parotitis and the sicca syndrome are but one example of how an appreciation of the mechanics of disordered function can clarify the pathological sequences, but it would not be surprising if, in the future, other subclinical entities having their basis in a physiological disturbance were to come to light.

In spite of an ever-increasing literature on the subject, much of it seemingly esoteric, our understanding of the relation of salivary physiology to disease processes remains somewhat limited. The preoccupation with tumours at the expense of non-neoplastic pathology has possibly now rebounded to the detriment of the patient; attention must, therefore, be redirected towards gaining a better understanding of the salivary glands in health and in disease.

Development of the salivary glands

All the salivary glands, both major and minor, develop along the same pattern, namely as sophisticated diverticula originating from oral epithelium. The first steps in the process are a proliferation and budding of epithelium in the form of a solid cord which migrates into the subjacent mesenchyme. Subsequently, extensive branching of this diverticulum occurs and forms the template of the embryonic gland. The acquisition of a lumen proceeds through this branching system, the final arborizations representing the future acini and the principal cord linking the structure to the surface epithelium, the excretory duct. All the major glands are ectodermal in origin, but some of the minor glands, which have their origin distal to the site of the stomatodeal plate, arise from endoderm.

The first gland to make its appearance between the fourth and sixth weeks is the parotid. As it grows back, the parotid engulfs mesenchymal structures, of which the most important will be the facial nerve, but which also include lymph follicles.

The submandibular gland arises in the sixth week and the sublingual in the eighth, the latter developing as a series of independent secretory units which ultimately fuse, while retaining their individual ducts.

Developmental anomalies relating to the salivary glands are uncommon and include congenital absences or hypoplasia, as in the Melkersson-Rosenthal syndrome, as well as ectopic collections at unusual sites.
Anomalies such as congenital cysts or fistulae, which may have an intimate relationship to structures such as the facial nerve, are of branchial origin and do not therefore represent true malformations of salivary gland development.

The parotid gland

In appearance, the lateral aspect of the parotid gland is not unlike a Welsh harp, possessing as it does a forward prolongation which overlies the masseter muscle to give off the duct, a sliver which insinuates itself into the gap between the condyle of the mandible and external meatus, and a downward extension which fills the retromandibular sulcus. In horizontal section, the parotid gland is broadly triangular and exhibits an external aspect, an anteromedial surface and a posteromedial surface.

The outer aspect of the gland is covered by an extension of the deep cervical fascia which is continuous posteriorly with the fascial envelope of the sternomastoid muscle, and anteriorly with the fascia covering the masseter muscle. This fascial covering is for the most part thick, tough and inelastic, although further forwards, where it blends with the masseteric fascia, its thickness varies and in places becomes quite thin. It sends off fibrous septa into the substance of the parotid and some of these are continuous with the fine fascial envelope surrounding the facial nerve. Superiorly, the external layer of parotid fascia is bound firmly to the zygomatic arch, while inferiorly, it blends with the deep cervical fascia anterior to the sternomastoid muscle. At the anterior and posterior borders of the gland there is a medial extension of the outer fascial covering which becomes progressively thinner the further inwards it passes, until it is no more than fine areolar tissue. The posteromedial deep extension blends with the styloid apparatus, and deep to that with the carotid sheath; however, from the styloid process to the angle of the mandible, it condenses into a tough unyielding band called the stylomandibular ligament.

The inelastic nature of the outer layer of fascia accounts for the severe pain of which sufferers of parotitis complain, and also for the long period of time before parotid swellings become significantly obvious.

The partial absence of a definite fascial barrier on the deep aspect of the gland means that parotid suppuration may ultimately spread to the parapharyngeal space, with all the sinister connotations that such an eventuality holds for the patient. On the other hand, the presence of the tough stylomandibular ligament acts as a very definite barrier to medial extension of tumours located in the outer part of the gland, while tumours originating immediately lateral to, or in, the stylomandibular tunnel - that is between the ligament and mandible - may grow unimpeded towards the pharynx across the parapharyngeal space. If the tumours actually pass through this tunnel, they may assume a dumb-bell appearance.

A horizontal section of the gland shows that most of the gland is lodged in the retromandibular sulcus; the forward tongue of glandular tissue which overlies the masseter is but a small part of the overall volume.

The facial nerve traverses the retromandibular portion in a medial to lateral direction to subdivide the gland into a large superficial component and a small subfacial or deep lobe, although it has been suggested that their weights are in fact roughly comparable.
The upper part of the outer aspect of the parotid gland is covered with skin and subcutaneous tissue, while the lower half of the gland is also covered with the platysma. The anteromedial surface of the gland is intimately related to the masseter, to the posterior edge of the ascending mandibular ramus, and the back edge of the medial pterygoid muscle. Tumours arising from the deep aspect of the parotid gland and growing across the parapharyngeal space are inevitably covered on their anterior aspect with the stretched out fibers of the medial pterygoid, which are commonly mistaken for those of the superior constrictor.

The posteromedial aspect of the parotid is related to the sternomastoid, digastric, and styloid muscles, and to the bony process of the same name. At a point higher up, the relationship is with the mastoid process, cartilaginous meatus and deep meatus to which the enveloping fascia is loosely attached. There is invariably an extension of the gland back into the tympanomastoid sulcus which needs to be displaced forwards when a search is being made for the main trunk of the facial nerve.

**Nerves**

Nerves of sensation include the great auricular and auriculotemporal nerve.

The great auricular nerve runs upwards and slightly forwards on the deep cervical fascia covering the outer aspect of the sternomastoid to innervate the skin and fascia overlying the parotid gland. Just before it leaves the sternomastoid to enter the parotid compartment, it gives off a slender posterior branch which passes up into the postauricular region. Much is made of the need to preserve this branch during parotidectomy, as a means of trying to lessen the sensory loss, but it is by no means certain that such an objective is in fact achieved.

Loss of the great auricular nerve results in anaesthesia of the parotid area and the lower half of the pinna, which may turn into an unpleasant form of hyperaesthesia as the nerve regenerates. It is useful to preserve as much of the trunk as possible in case a graft is required, such as after parotid resection of the facial nerve.

The great auricular nerve is routinely transected during parotidectomy at the point where it leaves the sternomastoid to enter the parotid area, and it is here that an amputation neuroma may subsequently arise.

The auriculotemporal nerve which is mainly sensory to the upper pinna and side of the scalp, also carries postganglionic secretomotor fibres from the otic ganglion to the parotid. It comes into contact with the gland as it winds its way round the neck of the mandibular condyle, and then ascends anterior to the external auditory canal just behind the superficial temporal vessels. It is said to give off an anastomotic connection to the uppermost branches of the facial nerve. Its destruction does not invariably cure the syndrome of Frey, otherwise known as gustatory sweating.

This condition, which commonly occurs some months after parotidectomy, manifests itself during meals as sweating and erythema in the preauricular and subparotid areas. It is alleged to be a consequence of transected secretomotor fibres growing into the cut ends of
cutaneous nerves and reinnervating sweat glands, thereby triggering off the sweating sequence when food is taken. This explanation, although currently very popular, does not accord with the fact that proximal division of the parasympathetic nerve supply fails to cure the syndrome in question.

The facial nerve exits from the stylomastoid foramen in the apex of the bony tympanomastoid sulcus some 3-4 mm deep to the rolled edge of the bony external canal. It passes forwards, downwards and outwards to bisect the sulcus, and lies in that situation immediately above the leading edge of the digastric muscle, posterolateral to the styloid process. It is enmeshed in this position by fibroareolar strands which have to be teased out at operation to reveal the trunk of the nerve. Immediately below and lateral to the facial nerve is the posterior auricular artery.

The extraparotid segment of the nerve is short, no more than 1 cm or less, but then it enters the posteromedial surface of the gland to travel in the same direction for a short distance before dividing into its two main divisions, each of which diverges sharply from the other.

The upper division proceeds upwards, forwards and very much outwards to give off temporal, upper zygomatic, lower zygomatic and buccal branches. It is stouter than the lower division and therefore better withstands handling, although the fact that its branches tend to be very sinuous in elderly or corpulent individuals means that they are more vulnerable to damage unless put on the stretch by suitable retraction.

The number of listed branches is subject to considerable variation, and no one pattern of branching prevails. However, good facial function may still be preserved even when one or two branches are eliminated because of the extensive network of fine interlacing peripheral anastomoses, although this is frequently absent between upper zygomatic and temporal fibres.

The lower zygomatic nerve has a constant relationship to the parotid duct which lies immediately below it; care must, therefore, be taken not to injure this nerve when operating to remove a calculus from the duct.

The lower division passes downwards and forwards at a deeper level to give origin to a variable number of buccal branches, a mandibular and a cervical branch. The last two emerge at the very apex of the gland, at which point the mandibular branch lies immediately anterior to the posterior facial or retromandibular vein. This constant relationship is employed when for any reason the main trunk of the facial nerve cannot be found. Once the mandibular branch is located at its point of emergence from the parotid, it can be traced cephalad to the point where it comes off into the lower division and further still to the main trunk of the nerve. In only 5% of cases does the mandibular branch have peripheral connections with the lowest buccal branch; hence damage to it is rarely compatible with spontaneous recovery of the depressor anguli oris which it supplied.

Care must always be exercised when working close to the facial nerve, but the slenderness of the lower division and its mandibular branch makes it especially vulnerable to surgical insults. It is noteworthy that the branches which are least likely to recover after injury or grafting are those to the frontalis and the depressor of the lower lip.
The sympathetic nerve supply reaches the parotid gland from the superior cervical ganglion by way of the external carotid artery.

**Blood supply**

The external carotid artery enters the deep aspect of the gland just above the point where it is covered by the stylohyoid muscle. It passes vertically upwards in the deepest part of the gland, giving off the transverse facial, internal maxillary and, finally, the superficial temporal artery.

The venous drainage is mainly by means of the retromandibular or posterior facial vein which is formed by the merging of the superficial temporal and maxillary veins. This has the same direction as the artery but lies superficial to it and immediately deep to the facial nerve. It exits at the tail of the gland, at which point the mandibular branch of the facial nerve crosses immediately superficial to it before passing downwards and forwards into the submandibular triangle.

**Lymphatic nodes**

There are basically two groups of lymphatic tissue aggregates, namely a series of superficial nodes lying under the external parotid fascia, and about 15-20 lymph follicles embedded in the gland, superficial to the facial nerve. The deep lobe may contain one or at the very most two of these follicles.

**The parotid duct**

The parotid duct runs forwards from the forward prolongation of the gland along a line which is roughly equidistant from the upper and lower jaws. At the anterior border of the masseter, it curves inwards and then obliquely forwards through the buccinator to end adjacent to the second upper premolar tooth.

**The submandibular gland**

When viewed from the external aspect, the submandibular gland appears ovoid. However, its configuration in horizontal section is in fact that of an uneven U, with the limb representing the more superficial part of the gland, being considerably larger than the deep component. The gland fills the submandibular triangle and overlaps its lower boundaries, namely both bellies of the digastric muscle; but the upper edge is itself tucked away beneath the horizontal ramus of the mandible.

The superficial part of the gland is related inwardly to the mylohyoid muscle, while the junction between the deep and superficial lobes curls round the posterior free edge of that muscle. The deep part of the gland which lies sandwiched between the inner aspect of the mylohyoid and the hyoglossus muscle gives rise to the submandibular duct at its anterior extremity. The duct runs medially, forwards and upwards beneath the mucous membrane of the floor of the mouth to end at the sublingual papilla close to the midline. It has on its anterolateral aspect the sublingual salivary gland, some ducts of which drain directly into it.
The submandibular gland is covered with skin, superficial fascia, platysma, and deep cervical fascia, from which it receives a loose fine capsule. Surgical excision of the gland should always be carried out within the confines of this fine envelope in order to ensure that adjacent structures are not damaged.

**Nerves**

The mandibular branch of the seventh nerve, which innervates the depressor anguli oris, lies plastered to the outer aspect of the deep cervical fascia overlying the submandibular triangle; it divides into several subsidiary filaments which spread out over the whole of this compartment before heading towards the corner of the mouth. One of these filaments is often larger than the rest and would appear to provide the dominant or definitive innervation of the depressor muscle and should be safeguarded as much as possible. Incisions for the purpose of exposing and removing the submandibular gland should always, therefore, be sited over its lower border, just above the line of the hyoid bone. Elevation of the upper flap should be carried out in the plane between the gland and its surgical capsule to ensure that the mandibular branches of the facial nerve are not compromised.

The hypoglossal nerve is separated from the deep aspect of the deep lobe of the gland by a potential space and is only really vulnerable if pathological processes cause fusion of the gland and the hyoglossus on which the nerve lies.

The lingual nerve arches gently downwards just above the upper edge of the deep part of the gland to which it is attached by a ganglion. It subsequently passes forwards below the duct and curves round its outer aspect before reaching its final destination in the mucous membrane of the tongue. That part of the nerve which is closely related to the duct is very much at risk when resorting to intraoral operations for the removal of ductal calculi.

The lingual nerve carries taste and secretomotor fibres, the latter synapsing in the ganglion which lies above the deep part of the gland, and from which postganglionic fibres originate to innervate the gland. The nerve also carries tactile, thermal and pain fibres from the oral cavity, and its division therefore results in anaesthesia, ageusia, parageusia and diminished salivary secretion. Sympathetic nerve fibres are carried to the submandibular gland along the facial and lingual arteries.

**Blood supply**

The principal arterial supply is from the facial artery which approaches the posterior edge of the gland just deep to the posterior belly of the digastric and stylohyoid muscle. This artery climbs vertically along the posterior border of the gland, or is buried within it, to reach the upper edge where it curves before finally turning upwards over the lower border of the mandible.

The facial artery may be as large as the external carotid and should therefore be ligated with double ties.
**Lymph nodes**

A small number of nodes are present on the outer aspect of the submandibular gland, and a couple at its upper border in relation to the facial vessels. These pre- and postvascular nodes represent an important station in the lymphatic drainage of the oral cavity, and are apt to be overlooked in radical neck dissections for mouth cancer.

**The sublingual gland**

The sublingual gland is also ovoid in shape and roughly twice the size of an almond kernel. It lies above the mylohyoid between the inner aspect of the mandible and the genioglossus, lateral to the submandibular duct and the lingual nerve.

As many as 20 ducts may emerge from this gland, of which about half empty directly into the oral cavity and the remainder into the submandibular duct. Its nerve supply is essentially the same as for the submandibular gland, and it receives arterial blood from the sublingual branch of the facial artery.

Its lymphatics drain into the submental and submandibular lymph nodes.

**The minor or accessory salivary glands**

These glands, which number anything between 600 and 1000, are small, isolated and mainly numerous; each gland has its own minuscule duct. They are to be found anywhere in the mouth, but are especially concentrated in the mucous membrane of the floor of the mouth, palate and buccal areas.

**Saliva**

Saliva is made up of the secretion of all the aforementioned glands together with other constituents which might appropriately be regarded as contaminants. Most of the secretion comes from the parotid, submandibular and sublingual glands, but a small contribution originates in the so-called minor or accessory salivary glands.

Gingival, or as it is sometimes called crevicular fluid, forms a minuscule part of the total liquid volume of saliva, while a solid element is provided by cells of various types, notably desquamated epithelium, leucocytes, and bacteria of one kind or another.

The viscosity of saliva depends, in essence, on the interplay of the volume and rate of secretion, the relative contribution of each of the independent gland entities, and the amount of solid constituents. Recent investigations have suggested that former estimates of saliva production of 1.5 litres over 24 hours were almost certainly too high, and that a volume of between 500 and 700 mL is much more realistic. Almost half of this is produced constantly, as a so-called steady state, while the remainder appears in response to specific, although not always clearly defined, stimuli. The time of day and the nature and intensity of stimuli are important factors in determining the relative contributions of the individual glands to whole or mixed saliva.
A reasonably good assessment of the volume of resting saliva during waking hours can be arrived at by asking subjects to spit at regular intervals into a container, hence the figure of 20 mL/h. By cannulating the ducts of the major glands, the relative contribution of each can be ascertained. The submandibular gland would appear to be responsible for three-quarters of the total output, the parotid for one-fifth, and other sources for the rest.

During sleep, production of saliva by the parotid virtually ceases, whereas secretion by the submandibular gland continues as before, and the sublingual gland makes up most of the shortfall.

Under the effect of chemical stimuli, the parotid gland increases its contribution to match that of the submandibular gland, while under the influence of mechanical stimuli, the volume of parotid output may even outstrip that of the submandibular.

The contribution of the accessory glands amounts to between 6 and 7.5% of the total, depending on the absence or presence of stimulation.

**Microscopical anatomy of the salivary glands**

A gland such as the parotid or submandibular is subdivided into lobes and lobules, comprising a multitude of basic secreting units, namely the acini and their immediate associated ducts.

Each acinus is composed of a circular grouping of cells surrounding a potential space which in turn leads into an intercalated duct. Beyond this is found a striated duct which joins with its counterparts from adjacent secreting units so that a succession of excretory ducts of increasing size and width are eventually formed. These ultimately merge to form the main duct of the gland.

The cells comprising the acini are backed by a basement membrane, outside of which other cells may be found; these latter cells are either secretory as in the case of the submandibular gland, or myoepithelial as those cells which surround the acini of the major glands.

The cells making up the acini are classified into two types depending on their staining characteristics with haematoxylin and eosin. Pink staining cells, which show a granular or vacuolated appearance, are found predominantly in the submandibular and sublingual glands, and are considered to be mucus secreting. Finely granulated cells, which stain blue, are seen mainly in the parotid but may also be seen abutting against the outer aspect of the pink-staining mucus-secreting acini of the submandibular gland.

The secretion of the parotid gland, while containing some mucoproteins and the starch-splitting enzyme amylase, is much less viscous than that produced by the other glands, hence its designation as a serous gland.

The intercalated ducts leading off the acini are short in length and lined with squat cuboidal cells with large nuclei; the striated ducts, on the other hand, are made up of taller
cells exhibiting a typically striated appearance. Outside both types of duct are more of the stellate myoepithelial cells mentioned in connection with the secretory acini.

The excretory ducts are thicker than the striated ducts by virtue of an increase in the number of cell layers forming the lining epithelium, a trend culminating in the appearance of a stratified squamous epithelium in the distal part of the main duct.

**Microneurohistology**

Staining techniques, which permit the mapping out of nerve distributions within the salivary glands, reveal both sympathetic and parasympathetic plexus in relation to the striated and intercalated ducts, and the surface of the acini. The principal nerve trunks which activate these plexus travel along main ducts in company with blood vessels.

Electron microscopy shows both types of secretomotor fibres penetrating between individual secretory cells and also at the junction of the acini and intercalated ducts. As the fibres approach their final point of innervation, they are seen to have shed their sheaths to reveal bare axons in the immediate proximity of acinar and ductal cells.

**The mechanism of secretion**

**Afferent stimulatory pathways**

The salivary glands secrete a certain minimal volume of saliva - the so-called steady or resting state - but respond to a variety of stimuli by an outpouring of saliva. It is not clear whether or not the resting state is dependent on a background of subtle stimulation from tactile sensors within the oral cavity, but it is evident that a number of afferent pathways may be involved in the secretion of saliva.

**Psychic stimuli**

The thought and sight of food, or the sounds and smells associated with cooking, may be responsible for a real increase in the secretion of saliva, while, conversely, thoughts about unrelished foods may have the opposite effect. Certainly, the consequence of fear is a drying of the mouth and this cannot be exclusively a humoral effect. It is commonly believed that in some parts of the world the psychosalivatory reflex was used in courts of law to determine whether or not the accused was telling the truth.

**Smell**

It may be difficult to isolate purely olfactory stimuli from psychic stimuli as the one may influence the other, but experiments carried out under controlled conditions have established a relationship between olfaction and salivation. This is to be distinguished from the salivary reflex initiated by exposure of the nose to olfactory irritants.
Taste

Profuse salivation is induced by various taste stimuli, of which the most potent seems to be a mixture of acid and sugar, followed by acid, sweet and salt.

Tactile stimulation

Chewing and mastication are potent initiators of salivary production and excretion. There is some evidence to suggest that the greater the impact of touch or stretch, the greater will be the salivary response. Apart from the normal sensory endings in the oral and oropharyngeal mucosa, there are pressure sensors in the periodontal membranes of the teeth which respond to biting and chewing, and which initiate saliva production in a quantity which is related to the logarithm of the weight of the bolus. Proprioceptors in the muscles of mastication and in the temporomandibular joints also seem to activate the secretion of saliva and, together with the movements of swallowing, assist in synchronizing the ejection of saliva from the various duct orifices. By connecting a manometer to Stenson's duct, for instance, the pressure of salivary outflow is seen to rise simultaneously with swallowing, a phenomenon which is much less apparent with gustatory stimulation.

The tactile stimulating zone is very extensive for not only is the oral cavity a significant area in this respect, but the oro- and hypopharynx are both involved. Jets of saliva may be seen, for example, when the tongue is forcibly extracted or depressed, and when an oesophagoscope is passed. Equally painful conditions arising in the oral cavity, such as aphthous ulcers, toothache and quinsy, may also be responsible for salivation.

Interorgan stimuli

These stimuli are not altogether well-defined and are not thought to provide a significant stimulus to salivation. The oesophagosalivary reflex results from irritation of the distal oesophagus and has little to do with the nausea-vomiting reflex which causes much salivation. It is thought, however, that the stomach, and indeed other abdominal organs such as the liver, gallbladder and appendix, may influence salivary production using the vagus nerve as the afferent pathway.

Afferent neural pathways

The pathways thought to be at the heart of the stimulatory sequence of salivation belong in the first, fifth, seventh and ninth cranial nerves. These eventually connect through a series of synaptic links with the salivary nuclei which are responsible for the effector side of the cycle.

Central control of salivation

The cell bodies of preganglionic secretomotor neurons are the points at which incoming stimuli initiate the efferent responses to the salivary glands.

The parasympathetic salivary nuclei are located in the pons close to the nucleus of the facial nerve, and also in the medulla near the nucleus of the glossopharyngeal nerve. They
are referred to as the superior and inferior salivary nuclei respectively, and are part of the reticular formation. The former is responsible for stimulating the submandibular and sublingual glands, and the latter for stimulating the parotid. In addition to receiving impulses from the various cranial nerves subserving the afferent side of the pathway, these nuclei are subject to influences from other parts of the brain. In this way, as mentioned before, psychic influences may either increase or decrease salivation, which will also diminish during sleep.

Certain pathological processes are known to increase salivation - for instance, rabies, encephalitis lethargica, tabes, epilepsy, and parkinsonism - whereas rarely the reverse may occur (Rauch and McCleve, 1961).

Stimulation of the hypothalamus causes hypersialism, and may explain why excessive salivation is so often associated with nausea and vomiting.

The cell bodies of the sympathetic system lie in the lateral columns of the spinal cord, mainly at the level of the second thoracic nerve, and are under the control of fibres passing from the hypothalamus and medulla.

The efferent pathway

The neural control of the salivary glands is effected mainly through the parasympathetic system with preganglionic fibres being carried by the seventh and ninth cranial nerves. The facial fibres leave the seventh nerve by way of the chorda tympani and synapse in the ganglion which lies close to the submandibular and sublingual glands; their postganglionic fibres run a short course before reaching the salivary gland.

The glossopharyngeal fibres travel by way of the tympanic and lesser superficial petrosal nerves to synapse in the otic ganglion. The postganglionic fibres leaving the otic ganglion join the auriculotemporal nerve from which they eventually separate to innervate the parotid. The neurotransmitter released in the ganglia and at the nerve endings in the glands is acetylcholine, and it can therefore be blocked by atropine.

Sympathetic nerves also exert some control over the salivary glands. The nerve fibres in the cervical sympathetic pathway synapse in the superior cervical ganglion, whence postganglionic fibres travel in company with the nearest blood vessels to reach the salivary glands. The neurotransmitter in the superior cervical ganglion is acetylcholine, but at the glandular nerve endings it is noradrenaline.

Nerve stimulation is responsible, in general terms, for secretory activity, the rate of blood flow and the contraction of myoepithelial cells.

So far as secretion is concerned, the parasympathetic pathway would appear to play the major part although the sympathetic may also be involved. When both are employed simultaneously, the effect on secretion appears to be synergistic. It is assumed, however, that changes in the composition of saliva may be influenced by the degree of activity of each of the two neural systems at any one time.
In experimental animals, stimulation of the cervical sympathetic fibres elicits a flow of saliva from the submandibular gland exclusively, but injection of adrenaline into the ducts of all the glands produces the same effect.

The fact that large doses of atropine injected into man fail to abolish submandibular secretion supports the view that the sympathetic pathway has a secretomotor role, at least in the case of this gland.

Electron microscopical observations in man reveal the presence of parasympathetic and sympathetic fibres in proximity to the acini of both the submandibular and parotid glands, a finding which is difficult to reconcile with the view that the sympathetic has a secretory role only in the submandibular gland.

In the case of the blood supply, the parasympathetic fibres are vasodilatory whereas the sympathetic fibres have the opposite effect. Once secretion has started, bradykinin is released and causes further vasodilatation by overriding the neural mechanism.

It is not altogether clear which of the two systems is responsible for contraction of the myoepithelial cells, although there is evidence that taste stimuli may trigger off their contraction by way of the sympathetic pathway (Babkin, 1943).

**Disturbances of the efferent pathways**

The consequences of interrupting the parasympathetic pathways do not always accord with the predicted outcome, a situation which would seem to indicate that accepted accounts of the pathways in question may be incomplete or incorrect.

In certain instances, for example, preganglionic section of the ninth cranial nerve not only restricts parotid secretion but also causes submandibular and sublingual asialia (Dandy, 1927). One possible explanation for this invokes the existence of an anastomotic connection between Jacobson's nerve and the geniculate ganglion.

Interruption of the parasympathetic fibres at a peripheral level, such as occurs during parotidectomy, supposedly causes gustatory sweating or Frey's syndrome in consequence of the misrouting of regenerating secretomotor fibres into the cutaneous nerves which activate the sweat glands.

There are, however, reasons to doubt such a supposition. In the first place, if parasympathetic fibres transected at operation were capable of regeneration, the same would surely have to be true of the sympathetic, whose fibres are, if anything, capable of reaching the sweat glands first.

It would also appear that a condition not unlike Frey's syndrome may occur after a cervical sympathectomy and that anaesthesia or resection of the stellate ganglion will abolish it (Ashby, 1960). The fact that the division of Jacobson's nerve or of the auriculotemporal nerve fails to cure the syndrome is perhaps the strongest argument in favour of rejecting the current popular explanation for gustatory sweating.
On the other hand, it seems much more likely that the regeneration of active sympathetic fibres may be responsible for the poorly controlled or vicarious sweating which characterizes the condition.

**Formation of saliva**

Saliva is the end product of a process of secretion which commences in the acinus and is then modified by the activity of the intercalated and striated ducts.

The hydrostatic pressure in the capillaries surrounding the acini leads to the escape of a number of moieties from the blood stream to the adjacent interstices. These are principally water, ions, glucose, urea, amino acids and proteins of lower molecular weight.

Migration of interstitial fluid across the basement membrane of the acinar epithelium occurs by a process of diffusion resulting from the pressure gradient which exists between the capillaries and the acinar lumen. A rise in the capillary hydrostatic pressure in response to vasodilatation inevitably increases the pressure gradient and, therefore, secretion.

The acinar epithelium is freely permeable to water- and lipid-soluble substances, but less so to other products such as amino acids and glucose which can gain entry only by active diffusion.

The concentration of sodium and chloride ions within the acini is similar to that of interstitial fluid, and is important to the osmotic movement of water through these cells.

Stimulation of the secretomotor nerves causes the release of transmitter substances at the neuroepithelial termini, namely acetylcholine for the parasympathetic fibres, and noradrenaline for the sympathetic. Circulating adrenaline within local blood vessels also affects the blood supply and the functioning of the salivary glands.

The neurotransmitters act on receptors located in the surface membrane of the acini and neighbouring ductal cells, and at the same time influence the degree of contractibility of the local blood vessels. Neutralization of neurochemical mediators is brought about by specific enzymes such as acetylcholinesterase and monoamine oxidases.

The exact sequence of events which takes place within the acinus and its effluent duct in response to stimulation is the subject of controversy, but in the case of the submandibular gland it seems likely that stimulation of either the sympathetic or parasympathetic pathway increases the potential across the basal cell membrane and enhances its permeability. The immediate consequence of this is a migration of potassium ions in conjunction with interstitial fluid through the acini to their respective lumina, with a resultant increase in the level of intracellular potassium.

In the case of the parotid, however, it is possibly only the parasympathetic pathway which is capable of eliciting this sequence of events.
Salivary proteins, which are an important constituent of saliva, are synthesized by ribosomes before being assimilated into the endoplasmic reticulum from which 'granules' or 'vacuoles' are formed during the resting phase of metabolism.

A high level of intracellular calcium would appear to be necessary for the mobilization of these granules or vacuoles and their extrusion into the acinar lumen. This is brought about by a rise in the cell concentration of calcium, in response to the increased basement membrane permeability induced by acetylcholine. Calcium ions attach themselves to the secretory granules and help them to fuse with the apical or luminal membrane before their extrusion into the acinar lumen.

It is likely that the intercalated ducts modify the acinar fluid by adding further potassium ions, but major alterations occur principally in the striated ducts and result in the conversion of acinar fluid from a slightly hypertonic to a low sodium chloride hypotonic solution. Sodium ions are actively transported back from the lumen into the cells, accompanied in the process by a passive diffusion of chloride ions, while potassium ions and bicarbonate permeate in the reverse direction.

Water, on the other hand, is not reabsorbed and helps to preserve the hypotonicity of the intraluminal fluid.

Stimulation of either the sympathetic or parasympathetic pathway influences the activity of the striated ducts, in the former case by producing a small volume of saliva rich in potassium and poor in sodium.

Finally, as a result of the passage of water and potassium back into the extracellular compartment, the concentration of ions in the saliva in the excretory ducts once again begins to approach that of plasma.

**Composition of saliva**

Ninety-nine per cent of saliva is in the form of water, the solute being a mixture of inorganic ions and organic molecules (Table 9.1).

Sodium appears in the acinar fluid at about the same concentration as interstitial fluid, that is to say 140-150 mm/L, but subsequently passes back through the striated ducts to leave a saliva low in sodium. However, as flow rates increase, so the concentration of sodium in saliva begins to approach that of plasma.

The concentration of extracellular potassium is low at 4-5 mmol/L, whereas in the acini and duct systems (excluding the terminal duct) is considerably higher, and varies between 20 and 80 mm/L depending on the flow rate. Stimulation brings about a sudden sharp increase in intracellular potassium with a concomitant discharge into the salivary secretion.

The reabsorption of sodium which takes place in the striated ducts is accompanied by a passive diffusion of chloride in the same direction. As the rate of secretion increases, so bicarbonate is actively expelled into the saliva, and there is a simultaneous increase in the rate
of reabsorption of chloride ions to adjust the requisite ionic balance. As the flow rate increases still further, the time available for reabsorption diminishes and the concentration of chloride in saliva begins to rise again.

Table 9.1 Principal contents of saliva

<table>
<thead>
<tr>
<th>Inorganic constituents</th>
<th>Organic constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Mucoproteins</td>
</tr>
<tr>
<td>Potassium</td>
<td>Serum proteins</td>
</tr>
<tr>
<td>Chloride</td>
<td>Enzymes</td>
</tr>
<tr>
<td>Calcium</td>
<td>amylase</td>
</tr>
<tr>
<td>Phosphate</td>
<td>lysozyme</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Glycoproteins</td>
</tr>
<tr>
<td>Thiocyanate</td>
<td>fucose</td>
</tr>
<tr>
<td>Iodine</td>
<td>neuraminic acid</td>
</tr>
<tr>
<td>Bromide</td>
<td>mannose</td>
</tr>
<tr>
<td>Fluoride</td>
<td>galactose</td>
</tr>
<tr>
<td>Copper</td>
<td>Free sugars</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Blood group substances</td>
</tr>
<tr>
<td></td>
<td>Lipids</td>
</tr>
<tr>
<td></td>
<td>Amino acids</td>
</tr>
<tr>
<td></td>
<td>Urea</td>
</tr>
</tbody>
</table>

The pH of saliva is low when the glands are not actively secreting, but rises with faster flow rates in consequence of the outpouring of bicarbonate.

The calcium content of saliva is lowest in the parotid and highest in the accessory glands. In the resting secretion of the submandibular gland, the calcium content exceeds that of plasma; however, as the flow rate increases, it begins initially to fall, only to return gradually to a level approaching the concentration in resting saliva (3.7 mm/L). However, the amount of calcium present in mixed saliva diminishes when the flow rate increases, probably because of the dilution induced by an outpouring of low-calcium parotid secretion.

Between one-tenth and one-third of the calcium content of saliva is bound to proteins in the form of complexes, of which amylase comprises a significant proportion.

Salivary secretion involves the active transport of iodide from the plasma, so that its concentration in the glands is always higher than that of the blood stream, and the same effect is observed with the isotope technetium-99 and fluoride.

Similarly, thiocyanate is found in saliva in a higher concentration than in plasma, and this is much more apparent in smokers. The association of thiocyanate with one of the salivary proteins results in a complex which possesses some degree of bacteriostatic activity.
Salivary proteins are a mixture of glycoproteins, mucoproteins, enzymes, blood group substances and serum proteins, the sum total of which rises together with the increase in flow rates.

The gamma-globulins in saliva have received much attention in recent years because of the possibility that they may protect the host against caries and oral inflammatory disease, but this line of investigation has proved disappointing so far.

In the case of the proteins synthesized within the parotid gland, about one-third appear in the form of amylase, the enzyme by means of which starch is broken down into maltose. The proportion in submandibular or sublingual saliva is, in fact, much less and is virtually non-existent in accessory gland secretion. The concentration of amylase, particularly that of the parotid gland, increases as the flow rate goes up, but its activity in general is shortlived, and has virtually ceased by the time the food bolus has reached the stomach.

Lysozyme is an enzyme which is effective against the carbohydrate components of the cell wall of certain bacteria. It constitutes about 10% of the protein content of parotid saliva, and is found mostly in the submandibular gland.

A variety of other enzymes - including acid phosphatase, cholinesterase, ribonuclease, lipase, peroxidase and many others - is also present in saliva. Kallikrein, from which bradykinin is derived, is also an enzymatic product of the salivary glands and helps to maintain an increased blood supply following the vasodilatation induced by nerve stimulation.

Much of the protein content of saliva appears in the form of mucoproteins. For instance, 35% of parotid protein contains an appreciable quantity of associated carbohydrate, while in the case of the submandibular gland the figure is even higher. Such mucoproteins may be protective against certain viruses, but in the case of the rabies virus the role is reversed and they appear to aid its survival. They are suspected of being intimately involved in the formation of salivary calculi, by providing a matrix for the precipitation of minerals, the final product of which appears as a succession of concentric layers of salts.

Carbohydrate-protein substances corresponding to the blood group antigens are secreted by all the glands, with the exception of the parotid. Their concentration is highest in the accessory glands, followed by the sublingual and then the submandibular.

Persons harbouring blood group B seem to be the most prone to developing salivary tumours; 85% of all adenocarcinomata occur in men belonging to this blood group, and pleomorphic adenomata and papillary cystadenomata are to be found especially in people of this blood group.

A substance of protein origin, which has been given the name parotin, has been isolated from parotid saliva and is alleged to possess hormonal activity. However, its role, which appears to be directed mainly towards the maintenance of blood calcium, requires further clarification.

A number of blood-borne products - including cortisone, pilocarpine, physostigmine and even sodium and potassium chloride - may influence the function of the salivary glands.
The effect of disordered volume and composition is best illustrated by the condition of recurrent parotitis in which patients experience intermittent bouts of parotid enlargement, sometimes associated with pain.

Diminution of the secretory rate of the parotid is evident not only in the affected gland but also on the uninvolved contralateral side. In addition, the viscosity of parotid secretion will be increased, as a result of a higher concentration of proteins of all types together with the overt appearance of mucus. The net result is a significant tendency towards stasis, a state of affairs which predisposes to bacterial infection and the establishment of a progressively destructive vicious circle which can be monitored by sialography.

**Hormonal influences**

The reabsorption of sodium in the striated duct, in conjunction with the movement of potassium in the reverse direction, is said to be under the influence of aldosterone, whereas the reabsorption of water is affected by the antidiuretic hormone.

Salivation increases with pregnancy, testosterone and thyroxine, and decreases at the time of the menopause.

**Other influences**

Starvation leads to massive enlargement of the salivary glands, as seen in Greece towards the end of the Second World War. Hypoproteinaemia from other causes may also predispose to a similar hypertrophy, one example being of the farmers in the Nile valley who are subject to chronic infestation by bilharzia or ankylostoma.

People on high protein-low carbohydrate diets are found to produce a saliva which has increased buffering power but which is deficient in amylase.

**Functions of saliva**

Saliva, by virtue of its glycoprotein and mucoprotein content, acts as a lubricant for ingested food. It thus serves to protect the mucous membrane from trauma caused by the food bolus while, at the same time, assisting the latter's passage into the oro- and hypopharynx.

In the absence of food in the mouth, saliva keeps the oral mucosa constantly moistened, which thereby precludes the ill-effects, namely inflammation, ulceration, hyperkeratinization, and general discomfort, resulting from dryness.

Saliva has a bacteriostatic function by virtue of the presence of lysozyme, and possibly also gamma-globulins which act against some oral bacteria. A globulin which reacts with thiocyanate is considered to be part of this protective system.

The buffering effect of saliva counters the dissolution of dental enamel by acid, and provides a source of calcium ions for recalcification.
The digestive function of saliva is limited, as amylase works best at a pH of 6.8, and after the food bolus has been swallowed, the acid environment of the stomach renders the saliva ineffective.

The role of the salivary glands in the maintenance of water balance is restricted in adults, but is possibly of greater importance in infants in whom vomiting or diarrhoea may lead to life-threatening dehydration. Antidiuretic hormone, which influences the permeability of the striated ducts to the reabsorption of water, may thus help to restrict the loss of water in saliva by producing a less hypotonic saliva.

Saliva serves as a solvent for food substances, and by virtue of its viscosity acts as an effective spreading agent, so that food is exposed to a maximum of taste buds.

Saliva also acts incidentally as an excretory organ for urea and other substances such as iodine, fluoride, thiocyanate, and bacteria. The characteristic fetor of uraemics is thus produced by the excretion of urea in saliva.

Tubercle bacilli are excreted in saliva and almost certainly account for the rare instances of cold abscess which occur in the parotid gland of both the very young and the very old.

The possible role of saliva in the aetiology of dental disease has been the subject of many investigations. However, no effect, other than that of a possible synergism with plaque formation has yet been demonstrated.