GASTRO-INTESTINAL PHYSIOLOGY

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PREFACE

It is hoped that this book will be of value to medical students and to medical practitioners. There are fashions in Physiology just as there are in dress and speech. The gastro-intestinal canal has not been a fashion leader for a number of years and for that reason many not engaged in active research in the field have found it difficult to acquire understanding of recent developments. Many of these developments have considerable practical importance. It is hoped that this text will enable readers to obtain a basic understanding of the subject as it is today and also to gain some idea of the directions in which research is currently proceeding.

There are various reasons advanced to explain why gastro-intestinal physiology has remained behind the fashion front for such a long time, but the upshot has been that we lack knowledge of many seemingly very simple problems. This will be obvious to all in chapter after chapter. It may frustrate some but it is hoped that the curiosity and interest of many others will be aroused.

Since it is not intended that this be a reference book but rather a textbook, the reference lists at the end of each chapter are not exhaustive and whenever possible contain recent reviews in which those interested in further reading will find complete reference lists.

ACKNOWLEDGMENTS

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D. F. M.

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Chapter 1

THE MOUTH AND SALIVA

DIGESTION is usually considered as starting in the mouth. In certain animals, including man, this is clearly the case. Food is chewed and reduced thereby to a finer state of division. It is at the same time mixed with saliva which in these animals contains amylase, a digestive enzyme which splits starch to disaccharides. This enzyme is identical, as far as has been determined, with pancreatic amylase. It will be dealt with in the chapter on the pancreas. In many other animals, carnivores and ruminants for the most part, the saliva contains no digestive enzymes, but acts merely as a lubricant.

In practically all rodents the saliva contains proteases as well as amylase but the importance of this in digestion has not been assessed.

Without saliva, swallowing of dry foods would be difficult or impossible; lubrication is essential. Lubrication is provided by the secretions of not only the salivary glands, but also by smaller glands present in the buccal mucosa. Without saliva, we could not taste dry materials since we taste substances which are in solution. This does not apply to flavors and aromas which are appreciated as a result of stimulation of olfactory endings in the nose. Only very few tastes can be appreciated. Most of the differences between foods depend on olfactory stimulation.

The major salivary glands are paired. In man they are the parotids lying in front of and below the ear. Their ducts enter the mouth on the inside of the cheek at the level of the 2nd molar tooth. The other two pairs secrete into a duct which enters the mouth under the tongue close to the frenulum. The sublinguals lie in the anterior part of the mouth floor in a superficial position. They are inside the muscles forming the floor of the mouth. The submandibulars lie outside the mouth under the middle third of the mandible. In the common experimental animals the major salivary glands are all placed close together in the region of the angle of the mandible. The gland most like the human submandibular is known as the submaxillary. Like the submandibular it shares its duct with the sublingual and empties sublingually in the anterior part of the mouth. In addition to these major glands there are many small mucin secreting glands throughout the mouth and pharynx.

Taste buds are scattered over the anterior tip and over the base of the tongue in the region of the very large circumvallate papillae and more sparsely over the soft palate and epiglottis. They are most plentiful in the grooves surrounding the circumvallate papillae and on the fungiform papillae on the tip of the tongue. In cross-section, the taste buds look like an onion which has been cut vertically. There are two types of cells in these buds. The inner ones are the neuro-epithelial cells which are responsible for the sensation of taste. The non-nervous cells are longer than the nervous elements and thus the taste bud is hollow. This hollow communicates with the mouth through a small pore. The neuro-epithelial cells extend into the central hollow. Substances which are tasted pass in solution into the taste bud and come in contact with the hairs of the neuro-epithelial cells. With advancing age the number of taste buds decreases. The only sensations which are truly tastes are those giving impressions of saltiness, sweetness, bitterness and sourness or acidity. It has been claimed that metallic and alkaline tastes are truly tastes, that is, that they are appreciated solely by stimulation of taste buds. Strong acids and alkalis and other substances will, of course, produce simple irritation of the buccal cavity. The astringent properties of acids and the slippery feel of alkalis are well known and these can be appreciated within the mouth. However, all these sensations including touch, pain, heat and cold are carried over afferents in the lingual nerve and do not give rise to impulses which can be picked up in the chorda tympani or glossopharyngeal nerves in which the taste afferents travel.

The ultimate method by which it can be determined whether or not a given substance stimulates a taste ending is by recording electrically from the chorda tympani. By isolating single fibres in this nerve one can determine whether or not there are specific endings for each of the basic tastes (Fig. 1). Quinine, sodium chloride, hydrochloric acid and sucrose will, when dropped on the tongue in high enough concentrations, produce volleys of discharges in the chorda tympani. They will produce discharge in the lingual nerve but at much higher concentrations. The magnitude of the chorda tympani response increases exponentially to a plateau with the concentration of the test substance applied. The threshold concentrations, the concentrations required to produce a plateau and the potency of various substances as taste producers vary from substance to substance and from animal to animal. Quinine, for example, has the lowest and sucrose the highest threshold in the rat. In the rat also, NaCl is much more potent than KCl and less potent than LiCl. Taste thresholds are greatly influenced by temperature; at temperatures below 0·5°C taste is absent. To drink iced water, therefore, with one's meal could logically be considered an insult by one's host; and to ice one's whisky is unassailable evidence of dislike for its taste. The optimal temperature for taste is between 20 and 40°C.

Recently Swedish workers have shown the existence of water fibres in cats and also discrete salt and quinine fibres. In rats it is claimed that salt fibres are stimulated by acid, but separate sweet and bitter fibres exist. It is likely in this species that the bitter taste endings are situated at the base of the tongue and

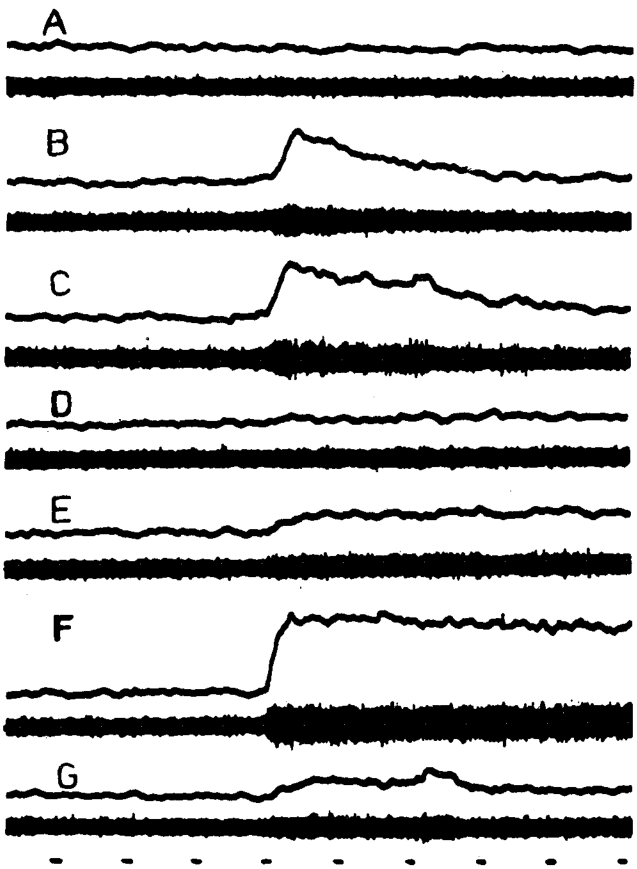

Fig. 1. Records from the whole chorda tympani nerve of a cat when applying to the tongue. (A) Ringer at 28°C. (B) Ringer at 35°C. (C) Distilled water. (D, E and F) Ringer's solutions with sodium hydroxide added to pH 11.7, (D) 11.9, (E), (F) 12.2, (G) Distilled water five minutes later. Upper tracing integrated response. Time in seconds. All test solutions but (B) at 28°C. (From Liljestrand, G. and Zotteman, Y.: *Acta. Physiol. Scand.*, 35:380, 1955.)

that their afferents travel over the glossopharyngeal nerve. In man also, there is evidence that different tastes are appreciated by different parts of the tongue; sweet and sour by the anterior and lateral and salt and bitter by the posterior parts. Naturally it has not been possible to work out the specificity of taste receptors in man, but there is considerable overlap in rats and cats; e.g., acid and salt in the former, while in the latter alkali will stimulate water, salt and bitter fibres and sometimes in man alkali may taste sweet or salty. In man, there is some evidence that both salt and sour may be mediated by the same ending since on application of cocaine to the tongue salt and sour are the last sensations to go. The leaves of the plant Gymnema sylvestre abolish sweet and bitter but leave salt and sour unchanged. No naturally occurring cases of loss of one taste without the others have been described. Electrophysiological data does not substantiate the idea therefore that there is one taste bud for each taste sensation which has been implied by mapping experiments. In these the subjective response to the application of test solutions with a fine brush is determined for various parts of the tongue in man.

The taste buds in man are sensitive to some blood-borne substances. The classic example is sodium dehydrocholate which is used to determine circulation time. It is injected into the cubital vein. When it reaches the tongue, it can be tasted. Secretion into the mouth cannot be eliminated, however. Taste buds are said to react to changes in blood chemistry. The taste of salt is enhanced in persons with low plasma NaCl. This fact has been used to explain salt hunger in animals and man. An interesting phenomenon seen in man is the ability of one taste to mask or enhance another. Salt may mask sweet and bitter tastes may overcome all others. This may be a matter of central interpretation, a matter of the magnitude of the afferent discharge or if, as seems likely, substances tasted combine with the taste bud then some substances may interfere or facilitate the ability of others to combine. Differences in combining power have been thought to explain the observed threshold differences of various mono and divalent chlorides, but this is not a complete explanation since many of these can be distinguished from sodium chloride, i.e., not only do they taste more or less intensely, but they may taste differently.

The sensation of taste has proved an accessible area in which to study the combination between chemical substances and receptors. The results have been disappointing. Electrolytes alone produce the sensation of saltiness. Sourness is produced only by acids and the intensity of the taste depends on the titratable acidity. Sweetness and bitterness, however, present difficulty since they can be produced by a great variety of substances including electrolytes. There are a few remarkable examples of specificity, an l-amino acid tastes quite differently from its d-isomer. It is easy to distinguish between the o, m and p forms of tolylurea. Then remarkably enough, some people have an inherited trait which enables them to taste phenylthiourea while to others it is tasteless.

Taste is represented in the sensory cortex in the tongue area. Cells have been picked up in the sensory cortex which will respond to the application of taste producing substances to the dorsum of the tongue and not to nonspecific stimuli. Some specificity for single basic tastes has been discovered in these cells in that all do not respond to all the basic tastes. Nutritionally taste and smell, which tend to be regarded as trivial sensations, are very important, they determine whether or not a food is appetizing. This in turn determines the intensity of the cephalic or psychic responses of the whole digestive tract.

Saliva Oral Hygiene

A third function of saliva of great importance pertains to oral hygiene. If for some reason all salivary secretion stops, oral infection occurs. Even if salivation stops or is diminished for a short time, an hour or so, fetid breath undoubtedly from bacterial multiplication, is the result. It has been suggested that saliva contains some antimicrobial agent since infection in the normally salivating mouth after oral surgery or injury is very rare even though aseptic procedures are impossible in the buccal cavity. Simple mechanical flushing in all likelihood plays an important part in maintaining a clean mouth. Offending substances or organisms are washed away and swallowed or expectorated. Complete removal of the salivary glands has been effected in a number of experimental animals. This procedure normally increases the incidence of dental caries.

Saliva does not normally dissolve teeth because its pH is around neutrality. The average value in man is 6.7 and furthermore it is saturated with calcium and phosphate ions. However, a rise in salivary pH with precipitation of calcium salts is held by some to be responsible for the deposition of inorganic plaques on teeth. The continuous flow of saliva during the waking state and the buffering by its contained bicarbonate ensure that, even after acid or alkali mouth washes, the pH returns to normal in minutes. The futility of attempts to change oral pH by using buffered toothpastes will be evident to everyone.

Stimuli for Secretion of Saliva

We can from these considerations say that saliva has functions connected directly with eating and functions related to oral hygiene and the appreciation of taste. We would anticipate, therefore, continuous salivary secretion increasing in association with food. This is exactly what occurs. The normal stimuli for salivary secretion are both intraoral and extraoral. In the latter category are the sight, smell or thought of appetizing food or anything connected with it. In the former category are taste, i.e., sour substances, mechanical stimulation of the oral mucosa and chewing movements. A tasteless substance like paraffin wax for example, will cause some secretion. The intraoral stimuli do not need to be appetizing. The impedimenta of the dentist are far from appetizing yet they cause salivation. To evoke an extraoral or conditioned response an appetizing foodstuff must be involved. Nausea produces profuse salivation probably largely of central origin.

Only during sleep can we say that secretion unassociated with food is taking place since only then are the extraoral factors completely eliminated. During sleep stimuli of all sorts are reduced and as a result the total amount of saliva is diminished; in fact, in man, of the major glands, only the sublinguals and perhaps the submandibulars to a lesser extent, secrete during sleep. The small mucosal glands likewise secrete. These glands and the sublinguals produce a mucinous secretion which contains no amylase. Factors associated with food result in a profuse secretion from the parotids, the submaxillaries and an increase in the secretion of the sublinguals and mucosal glands.

Histology of Salivary Glands

The parotids in man secrete amylase and almost no mucin. The submaxillaries (or submandibulars in man) produce more mucin and almost no amylase, while the sublinguals are largely mucin producing glands. There is histological basis (Fig. 2) for the differences in the nature of the secretion of the individual salivary glands. The parotids contain few mucin cells. Their secretion is therefore thin and watery, containing only a little protein. The parotid is mainly a serous gland. The sub-

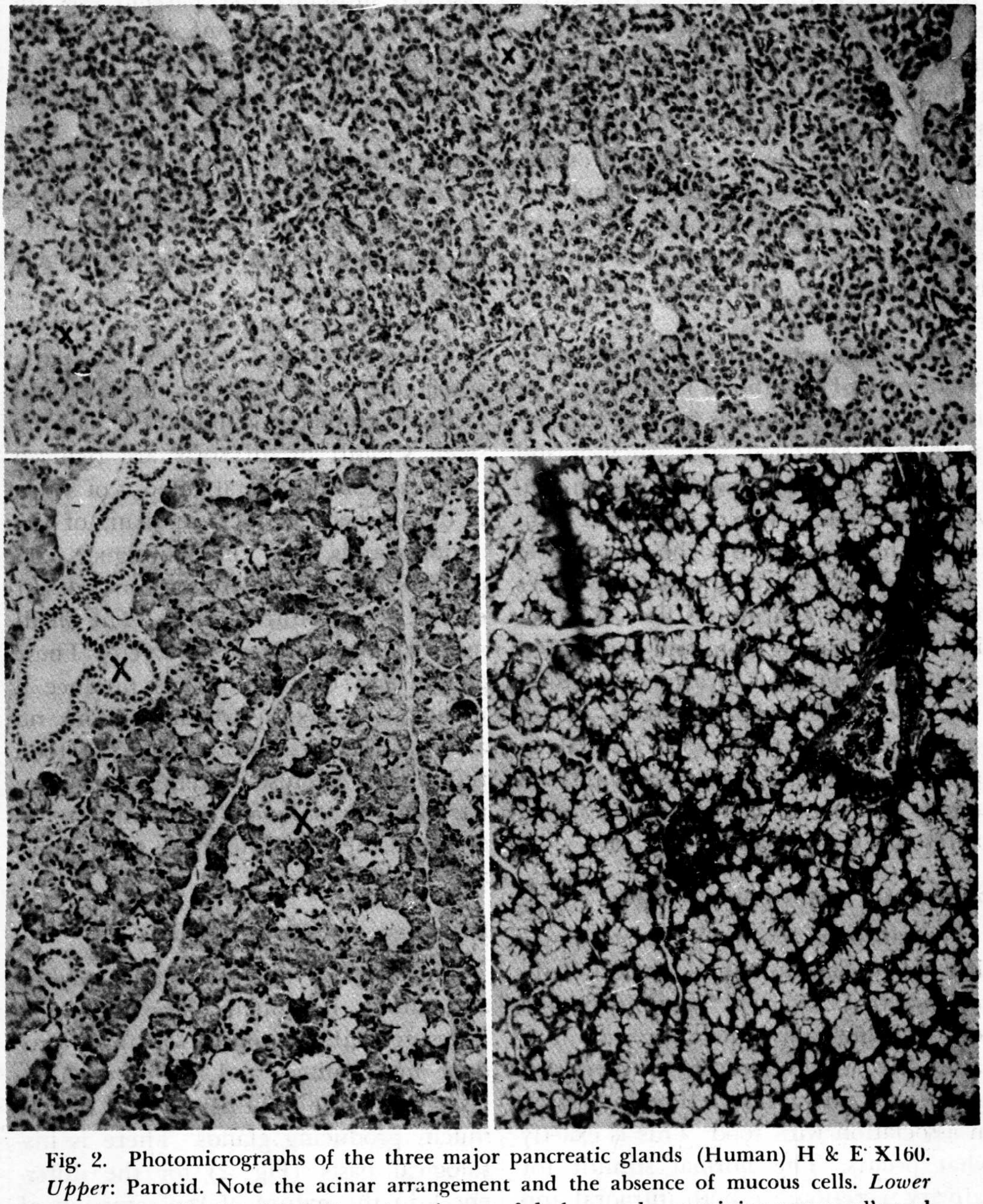

Fig. 2. Photomicrographs of the three major pancreatic glands (Human) H & E X160. *Upper*: Parotid. Note the acinar arrangement and the absence of mucous cells. *Lower left*: Submandibular gland. Note the mixture of dark granule containing serous cells and clear mucinous cells. These two types are often seen in the same acinus. *Lower right*: Sublingual gland. Here there are no serous cells. In the parotid and submandibular glands a number of small ducts (X) with their characteristic cuboidal epithelium are present.

maxillary is mixed, containing both mucin and serous cells. The sublinguals are mixed but contain far fewer serous cells than the submaxillaries. In animals in which the saliva contains no amylase, these same serous cells are seen. They secrete the watery electrolyte containing secretion which will be discussed further. The serous cells are very like pancreatic acinar cells in that they contain much basophilic material and have a granular cytoplasm; they do not stain for mucin. In stimulated glands the granules decrease in number. In the submaxillary and sublingual glands the serous cells sit as half-moon shaped caps on the largely mucinous acini. These are called the demilune cells. They are nothing more than serous cells which have been as it were, squeezed out by the overwhelming numbers of the mucinous cells. There are no demilunes in the parotid because there are few mucous cells. The small buccal glands contain no demilune cells. They are entirely mucinous.

The ducts which drain the acini directly, have a low cuboidal epithelium. These join to form the intralobular ducts which have a high columnar epithelium with a rodded or striated cytoplasm. The striations are at right angles to the direction of the duct. The granules which make up these rods are reduced in the stimulated gland. It is held, as will be mentioned later on, that these cells are responsible for the change in electrolyte concentrations which occur as the secretory rate changes.

In man a little over a litre of saliva is secreted per day. Two-thirds of it originates from the submandibular glands. Between 5 and 10% is contributed by the sublinguals and by the small buccal glands. The rest is produced by the parotids. Carnivores have relatively smaller daily secretory volumes while herbivores secrete vast amounts of saliva estimated as up to from 50-100 litres daily in cattle.

Regulation of Secretion

As one moves down the intestine, one finds that digestive functions become more and more independent of extrinsic nerves, that is, they become more dependent upon hormonal regulation or become autonomous. The salivary glands including the small buccal glands at the top of the alimentary canal are completely dependent upon extrinsic nerves for secretory activity. Each gland receives a dual nerve supply. The sympathetic fibres supplying the gland travel along the arteries to the gland having synapsed in the superior cervical ganglion. The parasympathetic fibres to the parotids and submandibular glands travel in easily distinguishable trunks. The auriculo-temporal nerve carries those that go to the parotid and the chorda tympani, which runs with the lingual nerve, those that go to the submandibular gland.

For years attempts have been made to show the existence of some hormonal regulation of salivary secretion. Not one of these attempts has provided any satisfactory evidence except to the contrary. Intravenous administration of mouth washings and of buccal digestion products have not increased salivary flow. Quite a large number of workers have shown that "denervated" glands will secrete in response to feeding. The fact that these same glands will show development of conditioned responses indicates that they were not in fact, denervated.

Role of Autonomic Nerves

For years the part played by these two sets of fibres has been in dispute. It was felt that one supplied the serous and the other the mucinous cells because stimulation of the parasympathetic fibres produces a copious secretion of saliva of low viscosity, while stimulation of the sympathetic results in a small amount of viscous secretion, in some animals at least (the cat does not show this). Against this argument is the fact that the parotid has dual nerve supply, to both of which it responds and in the main only one cell type. Indirect evidence from electrophysiological studies has been taken to prove that all cells innervated by the sympathetics are also innervated by the chorda (Fig. 3). This evidence has been obtained from cats in which potential changes were studied in the submaxillary gland with reference to the rest of the body during sympathetic and parasympathetic nerve stimulation and during injections of acetylcholine and epinephrine. During chorda stimulation added sympathetic stimulation did not change the external current flow as it should if additional cells were being stimulated. Intracellular records show that both sympathetic and chorda stimulation produce secretory potentials sometimes of equal magnitude but often the sympathetic potentials were smaller than those of the chorda. In all cells simultaneous chorda and sympathetic stimulation gave a potential equal to that seen after chorda stimulation alone. If fibres from the two branches of the autonomic nervous system supplied separate cells one would expect that stimulation of both branches simultaneously would give a greater volume of secretion than stimulation of the chorda alone, provided the decreased blood flow produced by the sympathetic is eliminated. Such an additive effect is not seen and there is no antagonism. This is a unique situation since the usual state of affairs is that sympathetics and parasympathetics act as antagonists. Some of the consequences of this are discussed below.

What the physiological role of the sympathetic supply is in conscious animals is not clear. It is well known in man at least, that fright or apprehension or epinephrine will result in a dry mouth. This seems inconsistent with the experimental findings. The explanation, however, may be found in the fact that the sympathetics do supply vasco-constrictor

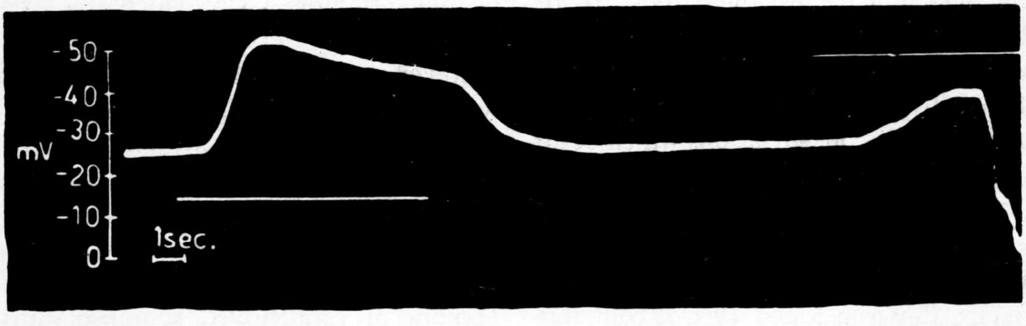

Fig. 3. Intracellular record from sublingual gland cell with secretory potentials resulting both on stimulation of the chorda (left) and the sympathetic nerve (right), (From Lundberg: A., *Acta. Physiol. Scand., 40*:21, 1957).

fibres to the gland which may be the prime cause of dry mouth in man. Furthermore anatomical or pharmacological removal (atropine) of the parasympathetics to the glands will also produce dry mouth and abolition of the normal reflex salivation following adequate stimulation. This leads to the conclusion that the parasympathetics are without doubt the main secretory nerves of the salivary glands in conscious animals.

Paralytic Secretion

In anesthetized animals several days following section of the chorda tympani the phenomenon of paralytic secretion is seen from the submaxillary gland. This secretion is small in amount. Its occurrence has been used as an argument to support the notion that the chorda and the sympathetics supply different cells since the submaxillary has two types. It is not seen in the parotid which has only one cell type. It has now been shown that the reason for paralytic secretion is that the gland has become hypersensitive to adrenaline. The phenomenon can be decreased by adrenalectomy or by the administration of adrenaline antagonists. It can be produced even without section of the chorda if the activity of the nerve is prevented by the administration of atropine for a few days prior to the experiment. This is a very curious phenomenon, but not a unique one, since usually structures exhibit sensitization to adrenaline after section of the sympathetic, but here it occurs after section of the parasympathetics. Section of the chorda will sensitize in addition as expected, to pilocarpine and acetylcholine.

It would be wrong to imagine that no sensitization follows section of the sympathetics. It does, but the effect is much less than after parasympathetic section. One might imagine that the presence of adrenergic nerves in the chorda might provide the explanation. This, however, appears not to be the case since the effect of sympathetic section is less than that of chorda section. If the sympathetics are cut following chorda section there is no further increase in paralytic secretion. It is unlikely, therefore, that the phenomenon can be considered as providing evidence for separate innervation of the two types of cells. Whether or not the phenomenon appears in the unanesthetized animal or in man is not clear. It would be expected in circumstances where adrenaline is released after chorda section.

Augmented Secretion

It appears from the foregoing discussion that the sympathetics and parasympathetics have no separate function as far as secretion is concerned. There is no evidence that they supply separate cells and any differences in the nature of their secretion may be accounted for by different vascular effects within the gland. The phenomenon of augmented secretion described by Babkin fits well with the notion that all cells have a dual innervation with perhaps 10 fibres supplying each cell as suggested by others. Augmented secretion is seen if following sympathetic or chorda stimulation the same or the other nerve is stimulated. It consists in the secretion of a volume greater than that which would result from stimulation of either nerve once. An explanation is that one has produced a change in cellular excitability resulting from the potentiation of one of the neuro humoral agents by more of the