currence is probable; alopecia is generally permanent. The seborrhœas of the body are more easily controlled. The same is true of *crusta lactea* in infants. *Pre-epitheliomatous seborrhœa* is not so unfavorable since the introduction of the *x*-ray as a therapeutic measure in skin diseases. In Kaposi's forms the prognosis is undoubtedly grave.

Stelwagon calls attention to the frequent presence of hypertrichosis in those suffering from seborrhœa of the face. It should be remembered that the prolonged use of greasy applications is certain to add to the hair growth already present. *Ernest Lewis McEwen.*

SECRETIN.—It has long been known that the introduction of acid into the intestine (duodenum) provokes a flow of pancreatic juice. Popielski and Wertheimer and Lépage demonstrated that this result may follow even after the exclusion of nervous impulses from without these organs. The secretion has therefore been attributed to the effects of a peripheral reflex brought about independently of central nervous influences. Since this flow of pancreatic juice will apparently follow even after inhibition of all nervous elements by atropine, it has been ascribed to a chemical stimulation of the pancreatic gland cells. The name *secretin* has been given by Bayliss and Starling to the chemical substance, as yet not isolated and identified, which is the direct stimulant to the gland. Wertheimer does not believe, however, that secretin acts independently of any nervous relations; and like Pflüger he points out the difficulty in obtaining complete isolation of an organ from nervous elements. The specific substance is obtained by extracting the mucous coat of the jejunum with 0.4 per cent. HCl. A very small portion of such an extract injected into the circulation suffices to call forth a copious flow of pancreatic juice. The active agent is not the HCl, since this alone does not provoke secretion when introduced directly into the blood current. Secretin is not present as such in the intestine, but is formed from a precursor, *prosecretin*, by the action of the acid. The transformation of prosecretin into secretin can also be accomplished by the action of boiling water or salt solution. The acid secretin solutions can be boiled and neutralized without undergoing a diminution in activity. The active substance thus does not behave like an enzyme. It is not precipitated by alcohol or ether; and presumably further investigation will demonstrate it to be a definite chemical individual of relatively low molecular weight. Camus has found that secretin may be formed in all animals examined by him, viz., the dog, cat, rabbit, guinea-pig, pig, pigeon, and frog. *Lafayette B. Mendel*

REFERENCES.

Bayliss and Starling: Centralblatt für Physiologie, 1901, xv., p. 682.—Proceedings of the Royal Society, London, 1902, lxix., p. 352.—Journal of Physiology, 1902, xxviii., p. 325.
Camus and Gley: Comptes rendus de la Société de Biologie, 1902, liv., pp. 242, 465.
Wertheimer: *Ibid.*, 1902. liv., pp. 472, 474.
Pflüger: Archiv für die gesammte Physiologie, 1902, xc., p. 32.
Camus: Comptes rendus de la Société de Biologie, 1902, liv., pp. 442, 513.
Herzen and Radzikowski: *Ibid.*, 1902, liv., p. 507.
Fleig: Centralblatt f. Physiologie, 1903, xvi., p. 681.

SECRETION, PHYSIOLOGY OF.—By secretions we mean the products of the activity of gland cells. Usually these products are liquid or semi-liquid in character. In recent years a distinction has been made between internal and external secretions. By the latter term we designate a secretion that is discharged upon a free epithelial surface that communicates with the exterior. Such, for example, are the secretions of the glands of the skin or of the mucous membrane of the alimentary or respiratory tract. The name internal secretion is used to designate those secretions that are discharged into the blood or the lymph. The term is used especially in connection with the so-called ductless glands, such as the thyroids or the adrenal bodies, but it happens that in some cases a gland possessing a duct may form an internal as well as an external secretion. A good example of this combination of functions is found in the case of the pancreas. The external secretion of the pancreas, the pancreatic juice, is emptied through its duct into the duodenum, while its internal secretion, of an unknown character chemically, is discharged into the blood. As will be described later, the two secretions in this case are formed in all probability by two different kinds of gland cells. It will be convenient to consider these two kinds of secretion separately.

EXTERNAL SECRETIONS.

The composition of the external secretions varies greatly, but in general we may say that they consist of water, inorganic salts, and certain organic constituents. The organic elements in the secretions have aroused the greatest interest since they may be characteristic of the secretion. They are found in some instances (for example, the urea of the urine) preformed in the blood, and the function of the gland cell is a selective one, picking out this particular constituent and discharging it into the lumen of the gland. In other cases the organic element is not present in the blood or lymph, and must therefore be formed within the substance of the gland cell. In both cases there is a general agreement, speaking broadly, that the gland cells take an active part in the secretion and that the production or elimination of the organic products involves the expenditure of energy on the part of these cells. We picture this energy as dependent upon the chemical changes, the metabolism within the gland protoplasm, and naturally the character of these changes may vary greatly. General theories of secretion have concerned themselves chiefly with the physiological mechanisms by which the secretion is excited, and the means by which the inorganic constituents of the secretion are produced, whether in response to purely physical forces such as filtration, osmosis, and diffusion, or by means of unknown activities of the living protoplasm. The general nature of the theories proposed and the modifications suggested for the different secretions can be given best by describing the physiology of the most important secretions.

SECRETION OF THE SALIVARY GLANDS.—Under the designation salivary glands we must include all the glands whose ducts open into the mouth cavity and whose secretions contribute to the formation of the saliva. Ordinarily, however, the term is applied to the three large pairs of glands, the parotid, the submaxillary, and the sublingual. The duct of the parotid, duct of Stenson, opens opposite the second molar tooth of the upper jaw; the duct of the submaxillary, duct of Wharton, opens at the side of the frænum of the tongue; the duct or rather ducts of the sublingual, open into the floor of the mouth and are usually known as the ducts of Rivinus; although in some animals, and sometimes it is said in man, one of these ducts, the duct of Bartholin, may be especially conspicuous and runs parallel with the duct of Wharton. The portion of this gland which empties into the mouth by the duct of Bartholin is designated by Ranvier by the separate name of the retrolingual gland. Histologically these large glands show certain differences in structure. The secreting cells of the alveoli may belong either to the albuminous or to the mucous type. In the former the cells are relatively small and densely granular in appearance, so that in fresh sections of the living gland the outlines of the individual cells cannot be distinguished readily. In the mucous type the secreting cells are larger and much clearer. In the living condition they present a homogeneous ground-glass appearance, but on appropriate treatment display a few large granules much less opaque than those in the albuminous cells. These two types of cells may be found in the same gland or even in the same alveolus; but, speaking generally, the parotid in man contains chiefly albuminous cells, and the submaxillary and especially the sublingual, chiefly mucous cells. This difference in histological structure is associated with

a chemical difference in the secretion. The saliva from the submaxillary and the sublingual contains mucin and is thick and stringy, while the parotid saliva, although it contains some albumin, is free from mucin and is thin and limpid. Each of these glands receives a double nerve supply one set of fibres coming from the cervical,

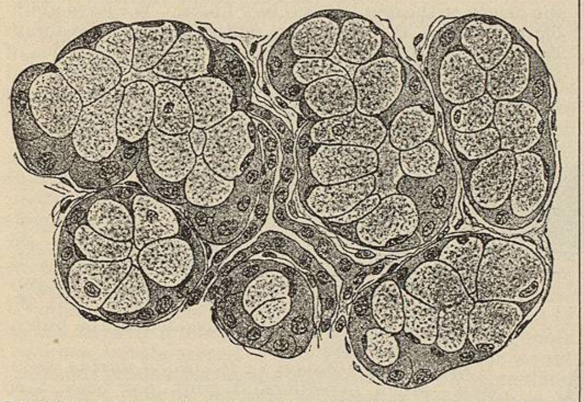

FIG. 4164.—A Section Through the Human Sublingual Gland. (Böhm-Davidoff.)

sympathetic and the other directly from the cranial nerves. The parotid receives its cranial nerve fibres by a very indirect path. In the dog in which their course has been worked out experimentally the fibres arise from the brain in the glossopharyngeal, pass into the tympanic branch of this nerve, also known as the nerve of Jacobson, and thence to the small superficial petrosal through which they reach the otic ganglion. In branches from this ganglion they pass to the auriculo-temporal branch of the inferior maxillary, and thence by several small branches to the gland. This path is supposed to involve two nerve units, the first which may be designated as the cranial or preganglionic neurone ending in the otic ganglion; the second, the sympathetic or postganglionic neurone, arising in the otic ganglion and ending in contact with the gland cells. The cranial fibres for the submaxillary and sublingual are found in the chorda tympani nerve. They arise with this nerve from the facial and pass with it to join the lingual branch of the inferior maxillary. After running in the lingual for a short distance the secretory (and vaso-dilator) fibres branch off in several small strands which pass toward the hilus of each gland following the course of the ducts. This path also involves two nerve units. The cranial or preganglionic neurone ends in nerve cells of the sympathetic type, which, in the case of the submaxillary, are found in its hilus or along the duct, while in the sublingual they form a collection, conspicuous enough to be seen with the eye, and located in the angle made by the strands of fibres as they leave the lingual nerve. This collection of nerve cells was formerly designated as the submaxillary ganglion, but since Langley has shown by the use of the nicotine method that they are intercalated in the course of the nerve path to the sublingual gland, it is more appropriately named the sublingual ganglion. These sympathetic cells constitute the second or postganglionic neurone which ends in the gland cells. The sympathetic nerve supply to the three glands is in general the same. The fibres emerge from the spinal cord in the upper thoracic nerves, pass over to the sympathetic chain in the corresponding rami communicantes, ascend in the neck in the cervical sympathetic, and terminate, so far as the first neurone is concerned, in the cells of the superior cervical ganglion. From this ganglion sympathetic neurones pass out in strands that form a plexus in the coats of the arteries supplying the glands. These fibres are usually stimulated while in the cervical sympathetic or by applying the electrodes to the superior cervical ganglion.

Composition of the Saliva.—The saliva of the mouth consists, or may consist, of the mixed secretions from the large salivary glands together with the secretions of the small unnamed glands of the buccal mucous membrane. In addition to accidental constituents, such as epithelial cells, it contains mucin, a small proportion of albumin, an amylolytic enzyme known as ptyalin, and inorganic salts. The saliva of each gland may be collected separately by inserting a cannula into its duct. By this means it can be shown that the secretion of each gland has its own characteristics, the parotid saliva, for instance, being free from mucin, while the sublingual and the submaxillary saliva have varying proportions of this substance, but contain little or none of the ptyalin. Experiments by Pawlow indicate that the secretion of each gland may be excited differently under normal conditions. He found that in dogs the submaxillary secretion is readily excited by sapid bodies in the mouth, or by the sight or smell of food, while the flow of parotid saliva is especially marked when dry substances are placed in the mouth.

Secretory Nerves.—The discovery that these glands are supplied by secretory nerve fibres, we owe to Ludwig. In 1851 he found that stimulation of the lingual nerve causes a flow of saliva from the submaxillary gland. Bernard showed that the fibres in question belong to the chorda tympani, and discovered in addition that during the stimulation of this nerve there is a greater flow of blood through the gland. We now know that the chorda tympani conveys both secretory and vaso-dilator fibres to the submaxillary and sublingual. The natural suggestion that the increased secretion on stimulation of this nerve is due to the greater blood flow has been disproved by a series of experiments. It has been found, for instance, that after administration of atropine stimulation of the nerve is followed by a vascular dilatation without any secretion, and, on the other hand, that injection of quinine may cause a dilatation of the vessels without a secretion, which, however, is readily obtained if the nerve is stimulated. Evidently the glands possess true secretory fibres capable of starting and maintaining a secretion from the gland cells. It was found, subsequently, that stimulation of the cervical sympathetic nerve gives a small flow of saliva which is characterized by its large amount of solids and by the fact that during the stimulation the blood flow through the gland is diminished in consequence of the simultaneous stimulation of vaso-constrictor fibres. Corresponding to these facts, Heidenhain found for the parotid gland that stimulation of the cranial nerve fibres in the nerve of Jacobson, gives an abundant secretion of thin saliva, while stimulation of the cervical sympathetic gives little, or, in the case of the dog, no secretion. In the latter case, however, it was discovered that stimulation of the sympathetic fibres has an effect on the gland, although no visible secretion is produced. Sections of the gland, for instance, after

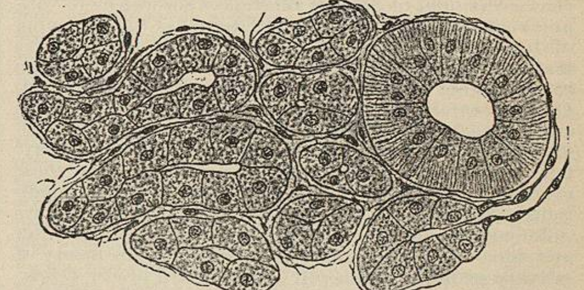

FIG. 4165.—A Section Through the Human Parotid Gland. (Böhm-Davidoff.)

such a stimulation show that the lumina of the alveoli and the ducts are distended with secretion, and if the cranial fibres are stimulated simultaneously with or subsequently to that of the sympathetic fibres, the secretion that forms instead of being thin and watery is thick, and on chemical examination shows a much larger percentage of solid matter. We are justified therefore in stating for all the salivary glands that each receives a double nerve supply, and that the sympathetic saliva, as it is called, is much smaller in amount and much richer in solids than that obtained by stimulation of the cranial fibres, the chorda or tympanic saliva. The physiological significance of this double supply of secretory fibres is not understood at present. The evidence that we have shows that reflex stimulation of these glands takes place through the cranial fibres alone, and, on the other hand, that injury to or experimental section of the cranial fibres is followed by a loss of function of the glands. In what way the sympathetic nerve supply participates in their functional activity is not explained.

Relation of the Secretion to the Strength of the Stimulus.—As in the case of the neuromuscular apparatus, it is found that the extent of the secretion varies with the intensity of the stimulus, or, in other words, we can get a series of submaximal secretions by varying the stimulation. The experiments upon this relationship have been made in connection with the cranial nerve supply. According to Heidenhain, the quantity of water and the percentage amount of inorganic salts increase as the stimulus increases up to a certain maximum, while the percentage amount of organic substances shows a more variable relation. If the gland is unfatigued at the beginning of the experiment the proportion of organic substances increases rapidly as the stimulus grows, but the maximum reached is not maintained if the stimulation is continued. On the contrary, continued stimulation may give a saliva containing less and less of the organic constituents, although the water and salts may continue to show a maximal proportion. The absence of parallelism under these conditions led Heidenhain to conclude that the conditions controlling the secretion of the organic material are different from those governing the formation of the water and salts. This conclusion is expressed in his theory of salivary secretion which will be mentioned briefly below.

Normal Mechanism of the Secretion of Saliva.—The secretion of saliva may be excited reflexly by stimulation of various sensory nerves, particularly those of the mouth. The action in this case is, of course, reflex, and, as said above, the efferent path to the glands is through the cranial fibres, for if these fibres are cut a reflex secretion cannot be obtained. Although this reflex secretion may be obtained by electrical stimulation of the sensory nerves of the mouth, it may be produced most easily and abundantly by the chemical stimulation caused by sapid substances. We may assume therefore that under normal conditions the sapid substances of the food stimulate the sensory endings of the lingual and glossopharyngeal nerves in the mouth cavity and start afferent impulses to the medulla which reflexly stimulate the motor cells giving origin to the cranial secretory fibres. We have abundant evidence that the same motor cells may be stimulated reflexly through other sensory paths. The idea of food, for instance, or the sight or smell of agreeable food to a hungry person may make the mouth water, and, on the other hand, gastric irritation may give the same reaction, as is shown by the disagreeable flow of saliva that accompanies an attack of nausea. Under normal conditions the large salivary glands in man secrete only when reflexly stimulated; the secretion, in other words, is not continuous but is dependent on stimulation through the nerves. Since, however, the mouth cavity is always more or less moist even in sleep, it is probable that there is a continuous secretion from the smaller unnamed glands embedded in the buccal mucous membrane.

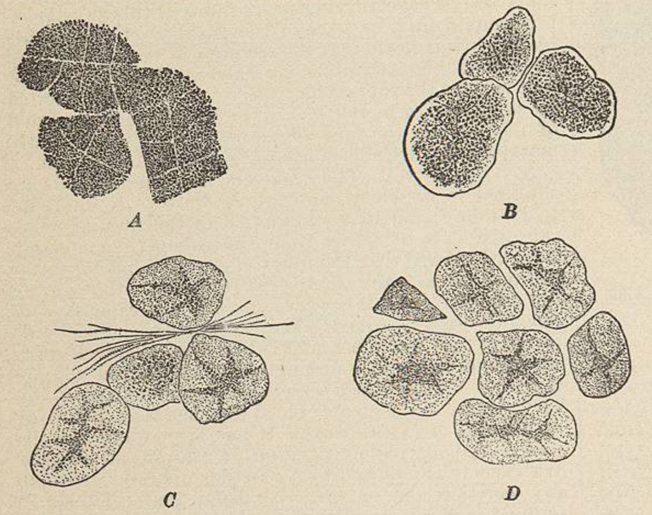

Fig. 4166.—Parotid Gland of the Rabbit in a Fresh State, showing Portions of the Secreting Tubules. *A*, In a resting condition; *B*, after secretion caused by pilocarpine; *C*, after stronger secretion, pilocarpine and stimulation of the sympathetic; *D*, after long-continued stimulation of the sympathetic. (Langley.)

Histological Changes in the Gland during Secretion.—Much experimental work has been done upon the changes in microscopic appearance of the gland cells during secretion. This work was of great importance in proving that the gland cells take an active part in the secretion. Sections made of the fresh or of the hardened gland show that after prolonged secretion the gland cells are smaller than in the resting state. Moreover, in the gland at rest granules are formed within the cells, and during active secretion these granules slowly disappear. The most interesting observations are those made by Langley on sections from the living gland. He finds that in the parotid gland the cells during the resting stage are densely granular throughout. As the gland is made to secrete the granules begin to disappear first from the outer border, and after prolonged stimulation they may disappear almost entirely, the few that are left being clustered round the margin of the cells bordering on the lumen. In the mucous glands the granules are larger and clearer and much less numerous. They swell and disappear on the addition of water, and it may be assumed that they represent the mucin found in the secretion, or a preparatory material which during secretion is dissolved by the water formed, and is thus discharged from the cell.

Action of Atropin, Pilocarpin, and Nicotin on the Salivary Glands.—The three alkaloids named exert an interesting and typical action on the secretion of the salivary glands. Atropin injected into the circulation or into the gland directly through its duct will destroy its power of secretion. The gland cannot be made to secrete either by direct or by reflex stimulation. Inasmuch as the gland refuses to secrete when the stimulus is applied directly to the hilus, we may conclude that the action of the drug is either upon the gland cells themselves or upon the ending of the nerve fibres in their cells. Since stimulation of the sympathetic nerve supply may produce the usual flow of sympathetic saliva, we may conclude that the gland cells are still functional, and that the effect of the atropin is to paralyze the endings of the cranial secretory fibres. Pilocarpin or muscarin has a directly opposite effect. In proper doses each sets up a continuous secretion of saliva, and this effect may be prolonged by repeated injections of the drugs. It is assumed that these alkaloids stimulate chemically the endings of the nerve fibres in the gland cells. Atropin and pilocarpin exhibit toward these and many other glands the same antagonistic action that they exert upon the inhibitory nerve fibres of the heart. The action of nicotin has been studied chiefly by Langley. He finds that injection of this alkaloid causes first a slight stimulating effect followed soon by a temporary paralysis of both the cranial and the sym-

pathetic fibres. After the stage of paralysis is reached it is found that stimulation of the second or post-ganglionic neurone of each path will give the customary secretion. It would seem from this result that the nicotin paralyzes the connection between the first or preganglionic and the second or post-ganglionic neurone. This action of nicotin takes place for other kinds of nerve fibres in which the path involves the union of a cerebrospinal with a sympathetic neurone.

Paralytic Secretion.—After section of their cranial nerve supply, chorda tympani and nerve of Jacobson, the salivary glands give a slow continuous secretion which may keep up for several weeks. Eventually, however, the glands undergo atrophy and lose their normal structure in spite of the fact that they still possess a connection with the central nervous system by way of the sympathetic nerve fibres. This paralytic secretion occurs only when the cranial secretory fibres are destroyed, injury to the sympathetic supply alone has no such effect. The cause of the continuous secretion is not evident. Langley is inclined to the view that it is dependent upon a continuous excitation of the nerve cells within the gland, the post-ganglionic neurone. Section of the chorda, or the nerve of Jacobson, would be followed in a few days by a total degeneration of the pre-ganglionic neurone, but the second or post-ganglionic neurone would probably retain its structure and irritability for some time. Langley's view is not very satisfactory, inasmuch as it throws no light on the nature and origin of the supposed excitation.

Theory of Salivary Secretion.—Some of the constituents of saliva, *e.g.*, mucin and ptyalin, do not occur in the blood and must therefore be formed within the gland cells as a result of a special metabolism. The histological changes in the gland cells during secretion corroborate this conclusion. Heidenhain has suggested the hypothesis that the metabolism giving rise to the organic products in the secretion is under the control of a special variety of the secretory fibres for which he proposed the name of trophic fibres. A second set of fibres which he designated as secretory fibres proper control the formation of the water and salts. The action of the trophic fibres is readily understood. Like the motor fibres to the muscles, their impulses set up katabolic changes which result in the formation of mucin, ptyalin, and the peculiar proteid found in the secretion. The action of the fibres supposed to control the production of the water and salts is more difficult to explain. When the gland is at rest there is no flow of water through the gland cells from the blood and lymph. In this condition therefore the protoplasm of the cells is impermeable to the water and salts. When the secretory fibres are stimulated the flow begins promptly, and we might suppose that the action of the impulses conveyed by the nerve fibres causes a physical alteration in the gland cells, in consequence of which they become permeable to the water and salts. Since, however, under continuous stimulation of the secretory fibres the hydrostatic pressure in the occluded ducts may exceed the pressure in the capillaries and arteries, it is evident that mere filtration through the cells will not explain the flow of water. There must be some substance within the gland cells possessing a high osmotic pressure and capable therefore, if we may use the expression, of attracting the water. Heidenhain makes such an hypothesis. He assumes that normally the gland cell at rest contains water under tension in consequence of the osmotic pressure of its substance, but that this water cannot escape into the ducts in consequence of the impermeability of the limiting layer of the cells bordering upon the lumen of the alveolus. The effect of the secretory impulses is to alter the structure of this limiting layer so as to make it permeable, and the stream of water and salts will continue as long as this permeability is maintained. It would seem necessary for the completeness of the hypothesis to assume that the border of the cells resting upon the basement membrane is constantly permeable to the water, but only in one direction, that is, from the lymph toward the interior of the cells. Langley is inclined to believe that the hypothesis of two kinds of nerve fibres is unnecessary, and that it is preferable to assume that one and the same set of fibres may cause the katabolic changes leading to the formation of the organic products and at the same time control the flow of water and salts. On the histological side it may be said that there is no indication of two kinds of fibres or two sets of nerve endings in the gland.

The Secretion of the Pancreas.—The pancreas has much the same general histological structure as the salivary glands. The alveoli contain granular cells belonging to the albuminous type, but characterized in the resting stage by a clear non-granular zone on the basal side. The histological changes during secretion are especially distinct and resemble those described for the parotid gland. During active secretion the size of the cells is diminished, the granules disappear from the basal side, and the non-granular zone extends farther toward the inner margin of the cells. In the resting stage, on the contrary, granules are again formed within the cells, and the non-granular zone is reduced in size. Physiological evidence indicates that the granules within the cells consist of a preparatory material from which the several enzymes of the secretion are formed, and they are therefore designated usually as zymogen granules. In addition to this type of cell, which is undoubtedly responsible for the formation of the pancreatic secretion, the pancreas contains an entirely different kind of cell found in groups that are known as the islands of Langerhans. These cells seem to be connected with the production of the internal secretion of the pancreas, and will be described more fully under that head. The chief duct of the pancreas in man, the duct of Wirsung, opens into the duodenum together with the common bile duct at a distance of 8–10 cm. below the pyloric orifice. The nerves of the pancreas are derived from the solar plexus, but physiological experiments indicate that ultimately the gland receives nerve fibres from two sources, the vagus and the sympathetic nerves.

Composition of the Secretion.—The pancreatic secretion is an alkaline liquid, which in some animals is clear and limpid and in others thick and glairy. From a physiological standpoint the most important constituents are the enzymes of which three or four have been described. These are trypsin, a proteid-splitting enzyme; lipase, a fat-splitting enzyme; amylopsin, a starch-splitting enzyme, and in some animals chymosin, a milk-curdling enzyme. The strong alkaline reaction of the secretion is due to sodium carbonate. A number of organic substances may also be present in small amounts, such as albumin, peptones, leucin, tyrosin, xanthin, soaps, and fats.

Secretory Nerve Fibres.—Direct observations on animals like the dog, in which the processes of digestion are not continuous, have shown that the flow of pancreatic juice is intermittent and related to the periods of digestion. This fact would indicate that its secretion, like that of the salivary glands, is caused by reflex stimulation. Direct experimental attempts to prove the existence of secretory fibres were unsuccessful until the beautiful work done by Pawlow and his pupils. These workers found that stimulation of the peripheral end of the cut vagus or splanchnic under proper conditions causes a secretion of the juice. The latent period between the stimulation and the beginning of the flow from the pancreatic duct is quite long, from three to five minutes, and has been explained on the hypothesis that the nerves stimulated carry secretory as well as inhibitory fibres, both of which would be stimulated by the method used. The existence of inhibitory fibres is made probable also by the fact that when a secretion is in progress stimulation of the peripheral end of the cut vagus may bring the flow to a standstill. If the existence of both secretory and inhibitory fibres to the gland be accepted, recent work, which will be described in the following paragraph, makes it probable that these nerve fibres have only a regulating control over the secretion. Even when all the extensive nerve connections are severed the gland may secrete in connection with the digestive processes. Unlike the salivary gland the secretory fibres from the central nervous system are not apparently essential to secretion, but regulate it after the manner that the extrinsic nerves regulate the movements of the stomach or the heart.

Normal Mechanism of the Pancreatic Secretion.—After Pawlow's discovery of the secretory fibres to the pancreas the natural supposition was that the mechanism of secretion is analogous to that of the salivary glands, that is, some peripheral sensory stimulus in the intestines stimulates these secretory fibres reflexly. It was supposed, in fact, that the acid chyme ejected from the stomach acts upon the sensory fibres of the mucous membrane of the duodenum and sets going the normal reflex that causes the pancreatic secretion. This view was founded upon the fact, demonstrated by several observers, that acids applied to the duodenal membrane will start the pancreatic secretion. Popielski, however, asserts that the same reaction is obtained when the vagi and sympathetic are cut on both sides, so that if the reaction is effected by a nervous reflex this reflex does not involve the central nervous system. More recently an entirely new light has been thrown upon the subject by some most interesting investigations made by Bayliss and Starling. These authors find in the first place that acid (0.4 per cent. HCl) placed in the duodenum or jejunum will cause a secretion of the pancreatic juice when the loop of the intestine used (jejunum) has all of its nervous connections severed. Moreover, if the mucous membrane from the duodenum or jejunum is scraped off and treated with the acid, the solution so obtained when injected into a vein causes an active secretion by the pancreas, although the acid alone or the extract of the mucous membrane without treatment by acid is ineffective. The authors apparently have proved that normally the acid from the stomach or the acid formed (lactic) during digestion acts upon the mucous membrane and produces a substance which they designate as secretin. The secretin is absorbed, carried to the pancreas, and either stimulates the pancreatic cells directly, or, possibly, acts upon the intrinsic nerves of the gland. Secretin is not an enzyme; boiling or the action of absolute alcohol does not destroy it. According to this new and interesting discovery the secreting nerves play no necessary part in the normal mechanism of pancreatic secretion, and if this turns out to be the case we shall have to attribute to them merely a regulating influence upon the secretion. The flow of pancreatic juice caused by secretin is characterized by the fact that it does not contain an active trypsin, but recent experiments go to indicate that any normal flow of pancreatic juice possesses the same peculiarity. It would seem that in the normal secretion the trypsin is contained in the form of zymogen or pro-enzyme, and that it becomes converted to the active enzyme when it comes in contact with the intestinal mucous membrane. The conversion is made by the peculiar enzyme found in the intestinal secretion by Schepowalnikow and to which Pawlow has given the name of enterokinase (see heading of Intestinal Secretion). The normal sequence of events, then, in the secretion of pancreatic juice is, first, the formation of secretin by the action of the acid of the gastric juice on the mucous membrane of the small intestine; second, the action of this secretin, after absorption into the blood, upon the pancreatic cells; third, the conversion of the zymogen of the secretion into the active enzyme by the enterokinase of the succus entericus. This last act may be necessary only for the trypsin.

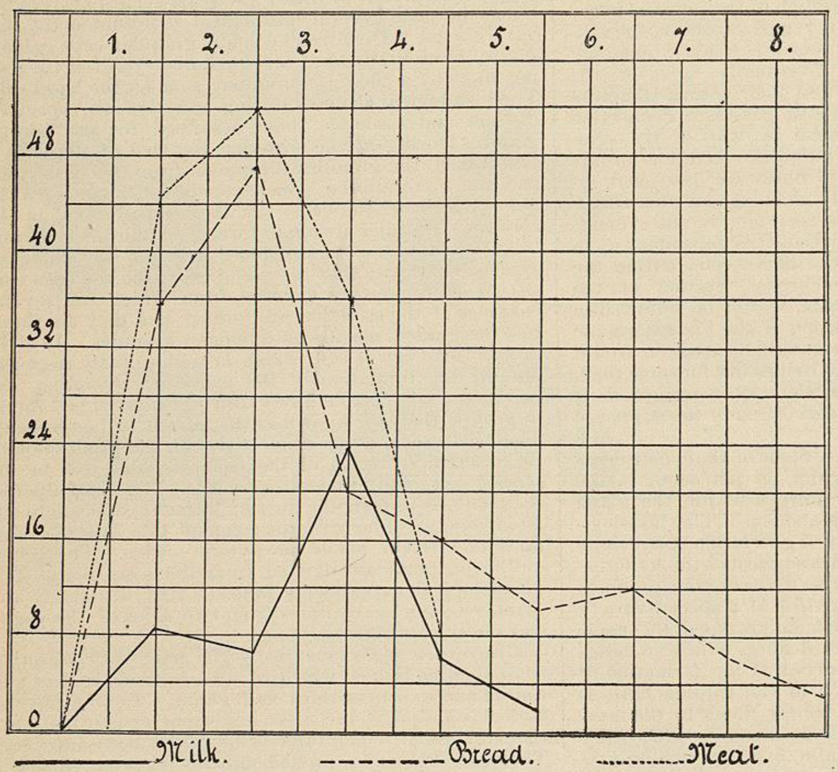

FIG. 4167.—Three Curves showing the Secretion of Pancreatic Juice upon a Diet (1) of 600 c.c. of milk; (2) of 250 gm. of bread; (3) of 100 gm. of meat. The divisions along the abscissa represent hours after the beginning of the meal; the figures along the ordinate represent the quantity of the secretion in cubic centimetres. (Walter.)

The curve of secretion of the pancreatic juice has been determined with care in the case of dogs. According to experiments made upon animals with a pancreatic fistula, the secretion begins shortly after the introduction of food into the stomach, and increases in volume to a maximum, which is reached between the first and the third hours. The curve then falls again more slowly to the base line, although there may be a second smaller rise from the fifth to the tenth hour. The general character of the curve is shown by the accompanying figure (Fig. 4167).

Relation of the Composition of the Secretion to the Character of the Food.—The work from Pawlow's laboratory indicates that the composition of the secretion varies somewhat with the character of the food, and that the variation has the appearance of a beneficial adaptation. That is, proteid foods cause in some way the secretion of a juice rich in proteolytic enzyme, and oily foods a secretion with an increased amount of lipase. This statement needs further experimental confirmation. , If correct it shows a kind of biological reaction between the food and the secretion which it is difficult to explain satisfactorily. Pawlow maintains that similar specific stimuli in the food influence or control the composition of the gastric and salivary secretions. We have here a relationship which, when more fully investigated, may prove to be of much practical importance in dietetics.

SECRETION OF THE GASTRIC GLANDS.—The accepted method of obtaining the gastric secretion dates from the famous work of Beaumont. His use of an accidental fistula in the case of St. Martin indicated at once that similar fistulas might be established upon animals for experimental purposes. Operations of this kind were performed first by Basson and by Blondlot in 1842, and were used subsequently by many investigators. At first, metal cannulas were placed in the fistulous openings to facilitate the collection of the secretion, but modern surgical technique has enabled experimenters to avoid this clumsy and often injurious device by converting a portion of the reflected mucous membrane into a tube opening on the surface of the skin. With a fistula of this character the stomach contents cannot escape to the exterior and yet can be drawn off at any time by the insertion of the catheter. The difficulty in such experiments is that the secretion becomes contaminated with the food, and its analysis is therefore difficult or impossible. Heidenhain obviated this difficulty and opened the way to successful investigation of the secretion by his device of cutting off a portion of the stomach, especially the fundic end, so as to form an isolated sac opening to the exterior. The remainder of the stomach was closed off by sutures so as to maintain the continuity of the alimentary canal. In such animals the food does not enter the isolated fundic sac, but nevertheless starts a secretion in it which may be obtained through its fistulous opening entirely free from mixture with the food. By this means the quantity, rate of flow, and composition of the secretion may be studied satisfactorily under various conditions. This operation was subsequently improved by Pawlow, who introduced a variation by means of which the nervous supply, as well as the vascular supply of the isolated sac, was maintained intact. The character of this operation is shown in the accompanying diagram (Fig. 4168). Pawlow devised also a secondary operation which in his hands has led to important results. In this operation the œsophagus was divided in the throat, and both upper and lower ends were brought to the surface of the skin to form permanent fistulas. After such an operation the food that the animal chewed and swallowed did not enter the stomach, but escaped to the exterior through the upper œsophageal fistula. By this means the effect of the act of eating upon the gastric secretion was determined. It was found that a fictitious meal of this character causes an abundant secretion of gastric juice in spite of the fact that none of the food enters the stomach, and this fact in turn led to the discovery of secretory nerves to the gastric glands.

Composition of the Secretion.—In addition to the mucus formed by the columnar epithelium on the surface of the mucous membrane, the secretion as collected contains water, inorganic salts, hydrochloric acid, pepsin, rennin, and usually a trace of peptones. The amount of the hydrochloric acid may be as great as 0.56 per cent. in the dog, but in the human gastric juice is usually given as 0.2–0.3 per cent. The secretion does not decompose easily—in fact, specimens may be kept for long periods without undergoing any putrefaction and without losing their digestive action. Evidently the secretion has marked antiseptic properties which are doubtless due to the free hydrochloric acid it contains. There has been considerable discussion as to the composition of the secretion from different parts of the stomach. The marked difference in histological structure between the glands of the cardiac and those of the pyloric end would suggest that their respective secretions might vary in character. According to most observers, the pyloric mucous membrane, when isolated from the rest of the stomach, gives a secretion that is alkaline in reaction but contains some pepsin and rennin. The hydrochloric acid, therefore, must be formed in the glands of the cardiac end. As far as is known, the glands of the pyloric end add nothing that is characteristic or essential to the secretion.

Nervous Control of the Secretion.—Much experimental work has been done to ascertain whether or not the flow of gastric juice is under the control of secretory nerves. The earlier experiments were inconclusive and need not be recalled, since in recent years Pawlow has obtained positive evidence of secretory nerve fibres. With the aid of his pupils and co-workers he has demonstrated the following facts: When a dog is given a fictitious meal by means of the œsophageal fistulas described above, there is a flow, often an abundant flow, of gastric juice, although no food gets into the stomach. If, however, the two vagi are cut previously, the fictitious meal does not cause a secretion. Evidently, therefore, the act of eating must occasion a reflex secretion of gastric juice, and the efferent paths in this reflex must pass to the stomach by way of the vagi. By the same means it was shown that the sight or smell of food will cause a reflex secretion in a hungry animal. After these preliminary experiments had indicated the existence of secretory fibres positive proof of their existence was obtained by direct stimulation of the peripheral end of a cut vagus. Under proper conditions of stimulation a flow of gastric juice can be obtained in this way, although the latent period of the secretion is unusually long, from four to ten minutes.

Normal Mechanism of the Gastric Secretion.—Beaumont and later observers held that mechanical irritation of the gastric mucous membrane is capable of provoking a secretion, and that the food therefore acts in part, especially in the beginning of digestion, as a mechanical stimulus. Pawlow, however, states positively that this belief is erroneous, and that mechanical stimuli are entirely ineffective. Heidenhain gave convincing evidence that the normal stimulus is a chemical one derived from the food, and this fact was afterward confirmed by the more detailed and satisfactory experiments made by Pawlow, who has given us a nearly complete account of the means by which the flow of gastric juice is started and maintained during digestion. According to this author, the first flow of the gastric juice is caused reflexly by the sight or smell of food, or more especially by the act of eating, and constitutes what he calls the psychical secretion. This term is used because the sensory nerves stimulated are the gustatory, olfactory, or optic nerves, and the reflex is accompanied by the conscious and agreeable sensations associated with eating. The term seems to imply also that the reflex arc involves the cerebral cortex, and is thence continued to the secretory fibres in the vagus. The secretion produced in this way appears promptly, and under favorable conditions may be abundant in quantity. In one experiment in which the fictitious feeding was continued for several hours, it is stated that about 700 c.c. of pure gastric juice were obtained. A further flow of the secretion is caused by the action of

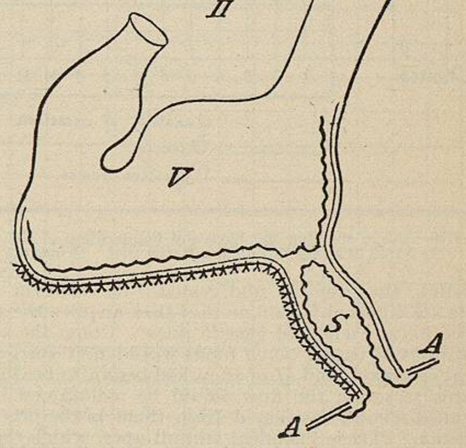

FIG. 4168.—Figure from Pawlow to show the Operation of Forming an Isolated Fundic Sac (*S*) and its Opening at the Abdominal Wall, *A*, *A*; *V*, cavity of the stomach.