SECRETORY PROCESSES
OF THE
DIGESTIVE GLANDS

THESIS

THE RÔLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE SECRETORY PROCESSES OF THE DIGESTIVE GLANDS

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INTRODUCTION.

Very few definite facts are known concerning the rôle of the sympathetic nervous system in the secretory processes of the digestive glands. A certain amount of controversial data has been presented but a true understanding of the sympathetic innervation of the various digestive glands has not been reached. There are several reasons which may account for this. Investigation of the function of the sympathetic nerve supply to the digestive glands involves many experimental difficulties. In all experimental work involving stimulation of the sympathetic nerves, the characteristic vasoconstrictor action of these nerves is encountered. This must be overcome in one of several ways before the true secretory action of the sympathetic nervous system can be ascertained. Long continued rhythmic stimulation until the vasoconstrictor nerves become fatigued, previous aseptic section and partial degeneration of the sympathetic trunk, and the use of special types of stimulation such as Heidenhain's tetanomotor, are some of the methods used to overcome this problem. Furthermore, the inaccessibility of the abdominal sympathetic trunks, and their requirement of special shield electrodes, add another difficulty to the investigation of the secretory properties of these nerves.

The most thoroughly investigated of the digestive glands in regard to the secretory activity of their sympathetic nerve supply are the salivary glands, but in spite of a wealth of experimental data the exact rôle of the sympathetic nerve in the secretory pro-

:cesses of the salivary glands has been a subject of controversy. Recently, however, as the result of special researches performed in Dr. Babkin's laboratory, new and important facts have been reported. Accordingly no experimental work in this field has been included in this work.

Very little is known concerning the part played by the sympathetic nervous system in the digestive processes of the stomach. The need of a systematic investigation of this problem is therefore obvious. We have undertaken a combined physiologico-histological investigation, in order to determine not only the gross effect of sympathetic stimulation on the gastric secretion but also to identify if possible the individual cellular elements of the gastric mucosa activated by stimulation of the sympathetic nervous system. Acute and chronic experiments have been performed, as will be described below.

Physiological data regarding the effect of the sympathetic nervous system on the secretory processes of the pancreatic gland are also rather scanty. We have extended some of our previous observations (Baxter, 1931) and have also carried out a physiologico-histological research to determine the effect on the pancreatic a~~s~~cini of long continued rhythmic stimulation of the sympathetic nerve.

Concerning the action of the sympathetic nervous system on the secretory processes of the intestine, practically nothing is known. A summary of the available data with regard to this section of the digestive tract will be included in the general review of the literature to follow. No extensive experimentation on the intestine has been undertaken in this work, as, being of a special nature, it is reserved for a future investigation.

PART I.

REVIEW OF THE LITERATURE.

A review of the important literature on the relation of the sympathetic innervation to the secretory processes of the digestive glands is given below under the following headings:-

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A. Origin and Development of the Sympathetic Nervous System.

For the proper understanding of the functional activity of different autonomic nerves and the interrelations of parasympathetic and sympathetic nerves, as well as parasympathomimetic and sympathomimetic drugs, a study of the origin of this part of the nervous system is necessary. The sharp division of the autonomic nerves into parasympathetic and sympathetic, as proposed in the classic investigations of Gaskell and Langley, cannot be retained in its original form. As it is based chiefly on gross anatomical data, on the results of electrical stimulation of nerve trunks, and on the action of a few drugs such as pilocarpin, atropin, ergotamin, adrenalin, and others, it undoubtedly does not now cover all the known physiological data relating to the autonomic nervous system. Recent anatomical and embryological investigations have necessitated new conceptions regarding the origin and development of the autonomic nervous system. If these views are sustained by further investigation, they will aid greatly in the interpretation of physiological phenomena.

Concerning the origin and development of the sympathetic nervous system, several conflicting opinions have been stated, each backed by a certain amount of experimental work of different investigators. The theory that the sympathetic elements are of mesenchymal origin was inaugurated by Remak in 1847, but was not generally accepted. Recently Tello (1925) has supported this theory by attempting to show that an important part of the sympathetic nervous system arises from local differentiation of mesodermal elements. The majority of early investigators, however, supported the theory that the cells which go to make up the primordia of the ganglia of the sympathetic trunks and prevertebral plexuses are derived exclusively from the spinal ganglia or neural crests (Schenck and Birdsall, 1878; His, Sr., 1899; Marshall, 1893; Kohn, 1905, 1907).

Froriep (1907) traced cells of medullary origin into the primordia of the sympathetic trunks via the ventral nerve roots and communicating rami, and stated that it was mainly these cells which became differentiated into sympathetic ganglion cells. Kuntz (1909-1914) supported the view of Froriep, maintaining that these medullary cells did not migrate into plexuses functionally connected with the vagi (cardiac, pulmonary and enteric plexuses), but that cells composing these latter plexuses could be traced distally along the vagi and their branches. These findings were corroborated by numerous other investigators (Abel, 1912; Stewart, 1920; Rau and Johnson, 1923; and Uchida, 1927).

Contrary to these recent investigators, Müller (1920) and Müller and Ingvar (1923) supported the older theory that the primordia of the sympathetic trunks contain only cells which are derived from the spinal ganglia and neural crests. Recently Van Campenhout (1929, 1930 a, b and c, 1931) also reported experiments which corroborate the work of Müller. As a result of his experiments on frog and chick embryos, Van Campenhout claims that the enteric sympathetic system is derived from the neural crests, for if the dorsal half of the neural canal is removed sympathetic anlagen do not develop. Neither do the intestinal plexuses (Auerbach's and Meissner's) appear. On the other hand, if the hind brain is destroyed and the neural crests left intact, the visceral branch of the vagus does not develop but the sympathetic and intestinal plexuses are quite normal. Thus he claims that the visceral part of the vagus arises from the medullary neural crest and that the intestinal plexus is not related to the vagus in origin. According to him the vagus fibres grow down to an already formed sympathetic plexus. The mesenteric plexus of the stomach and oesophagus, however, originates from vagus elements, while the submucous plexus of these two parts of the digestive tract come from sympathetic anlagen. He also puts forward certain theories regarding the so-called antagonistic systems, parasympathetic and sympathetic, and the double innervation of glands and organs. The parasympathetic and sympathetic should be regarded as parts of one system and not as antagonistic, he states. If Van Campenhout's findings are corroborated by other investigators, they will throw a new light on the interrelations of the tissue and its nerve supply. The type of reaction with which the tissue responds to nerve stimulation will depend on the properties of the last neuron connecting the tissue with the central nervous system. The function of the connector neuron, e.g. the vagus or splanchnic nerves, would merely be to convey the impulses from the central nervous system to the final neuron. The latter is responsible for the reaction of the tissue in response to this particular stimulation. Similar reasoning could be applied also to the action of drugs. Van Campenhout's theory of the origin and development of the autonomic innervation of the gastro-intestinal tract is more acceptable from a physiological point of view than the purely anatomical conception of Kiss (1931). According to the latter, there is no anatomical foundation for the argument that there is a parasympathetic nervous system of the abdominal organs. The sympathetic fibres join the vagus nerve in its initial course and run with it to the abdominal organs. Therefore the so-called parasympathetic phenomena must be regarded as a "negative phase" of the sympathetic action. He concludes: "Par analogie avec la cavité abdominale, on n'a aucun droit d'admettre que les autres viscères aient une double innervation (sympathique et parasympathique). Aussi bien l'anatomie et l'histologie montrent que les viscères sont innervés par des branches sensitives cérébro-spinales et les branches motrices et sécrétoires sympathiques."

B. Salivary Glands.

(i) Sympathetic innervation - anatomical description.

All the salivary glands receive their sympathetic nerve supply from the cervical sympathetic nerve. The fibres for the parotid gland and the submaxillary and sublingual glands arise from the 1st to the 5th thoracic spinal nerves, pass through the stellate ganglion, and then by the ansa Vieussenii they reach the inferior cervical ganglion, from which they proceed to the superior cervical ganglion where the synapse occurs. The post-ganglionic fibres leave the superior cervical ganglion, travel to the exterior carotid artery, and follow its branches into the glands, where they are ultimately distributed to the gland cells and the walls of the arterioles.

Langendorff (1894) found that, four months after hemisection of the spinal cord in the upper cervical region, the cervical sympathetic nerve showed no signs of degeneration. He concluded therefore that the nerve cells of these fibres are situated in the corresponding segments of the spinal cord from which they emerge. Grützner and Chlapowski (1873) showed, however, that stimulation of the medulla oblongata produced a secretion from the submaxillary glands which was not completely abolished by section of the chorda tympani, and also that no response was obtained from the gland when the cervical sympathetic was severed. Therefore they assumed that the spinal sympathetic nerve cells are in some way associated with a higher medullary centre. Subsequent investigators (Kohnstamm, 1902, 1907; Yagita and Hayma, 1909; Yagita, 1910; Miller, 1913) confirmed the data of Grützner and Chlapowski.

(ii) Secretory effect of the cervical sympathetic nerve on the salivary secretion.

Direct stimulation.

Ludwig (1856) first discovered the secretory effect of the cervical sympathetic on the submaxillary gland of the dog, which was confirmed by Czermak (1857). Langley (1878) made a similar observation on the cat. Heidenhain (1878) demonstrated the analogous action of the cervical sympathetic on the submaxillary and parotid glands in the rabbit. All the investigators agree that stimulation of the vago-sympathetic nerve in the dog produces at most an extremely scanty secretion of saliva from the parotid gland, but frequently none at all. Thus Heidenhain (1878), on stimulating the cervical sympathetic of a dog with an induction current, obtained practically no secretion from the parotid gland. Langley (1879-80) observed, however, that in the same animal the ducts were sometimes free and sometimes filled with thick saliva, while in a few experiments several drops of thick saliva were excreted after stimulation of the cervical sympathetic.

In the dog the sympathetic saliva from the submaxillary gland is scanty, but even less is obtained from the parotid gland. Application of an induction current of moderate strength to the vago-sympathetic in the neck usually produces a few drops of thick viscous saliva from the submaxillary gland. Stimulation of the cervical sympathetic in the cat produces a more copious flow of saliva from the submaxillary gland, but much less than when the chorda tympani is stimulated.

The sympathetic saliva of the dog is rich in organic substances (Eckhard, 1860), while the saliva obtained from the submaxillary gland of the cat by sympathetic stimulation is poorer in organic material than that obtained by stimulation of the chorda tympani (Langley, 1878). Sympathetic saliva from the submaxillary and parotid glands of the dog, cat and rabbit contains less inorganic material than the saliva secreted under stimulation of the appropriate parasympathetic nerve, but considering the extremely slow rate of secretion of the sympathetic saliva the percentage of inorganic elements is remarkably high (Langley and Fletcher, 1890).

Reflex stimulation of the sympathetic.

The possibility of reflex stimulation of the salivary glands through the sympathetic is doubtful. Claude Bernard (1864) reported that section of the parasympathetic nerve abolished the reflex action from the mouth cavity to the mixed gland and produced a paralytic secretion. This fact has been observed and studied by subsequent investigators (Heidenhain, 1868; Langley, 1885; Bradford, 1888; and Miller, 1913). Thus it would seem that the sympathetic nerves do not possess the property of reflex transmission.

However, there are indications that secretory impulses may be transmitted to the salivary glands through the sympathetic nerve alone. In a dog with permanent fistulae of the mixed and parotid glands Maevsky (1923) observed that the secretion from the mixed glands after stimulation by pilocarpin was greatly increased when food was given or a $\frac{1}{4}$ p.c. solution of HCl poured into its mouth. After section of the cervical sympathetic nerve as well as the vagus on the corresponding side, this effect disappeared. Whether the greater outflow of saliva during reflex stimulation was due entirely to a true secretory action, as Maevsky believed, or to the pressing out of saliva by the contractile mechanism of the gland innervated by the sympathetic nerve, cannot be said without further investigation. If pilocarpin secretion was not initiated the reflexes from the mouth cavity were not relayed to the salivary glands through the intact sympathetic nerve.

Recently Andreeff and Podkopaeff (1928) have reported that, after section of Jacobson's and the auriculo-temporal nerves in a dog with permanent parotid fistulae, there was a secretory response to a meal of bread powder or to the introduction of $\frac{1}{2}$ p.c. HCl into the mouth. This response to reflex stimulation developed very gradually, reaching normal only after 8 months. The organic content of the saliva remained much lower than that of the secretion from the normal gland.

Surgical section of the sympathetic nerve, however, does not influence the reflex production of saliva to any great degree. Bradford,(1888) removed the superior cervical ganglion in a cat and found that after seven months the gland was normal in action and appearance. Langley (1898) did not observe any change in the histological appearances of the submaxillary glands of rabbits up to three years after removal of the superior cervical ganglion. Henri and Malloizel (1902), Babkin (1913) and H. Baxter (1931) demonstrated in dogs with permanent fistulae of the mixed and parotid glands that extirpation of the superior cervical ganglion caused practically no change in the volume of the saliva activated by the introduction of different substances into the mouth. The concentration of organic substances in such saliva was even slightly increased. Moreover, H. Baxter (1931) noted that after cervical sympathectomy and removal of the superior cervical ganglion in dogs with permanent parotid fistulae the output of organic material in the initial phase of reflex secretion was lower than before operation.

(iii) Motor effects of the cervical sympathetic nerve on the salivary secretion.

Augmented secretion.

Another phenomenon in which the sympathetic innervation plays an important part is the so-called augmented secretion. Langley (1889) demonstrated on both the submaxillary and parotid glands that previous stimulation of the parasympathetic nerves greatly augmented the effect of subsequent sympathetic stimulation. Langley concluded that this result was due to the increased nervous excitability of the gland, i.e., the impulses arising through the sympathetic encountered favourable conditions for their action initiated by the preceding parasympathetic stimulation. This phenomenon was designated by him "augmented salivary secretion". His view was shared by Bradford (1888), Maevsky (1923) and Goldenberg (1924).

Mathews (1898) opposed Langley's theory of augmented secretion. According to the former the cervical sympathetic does not send secretory fibres to the submaxillary, parotid and sublingual glands in the dog, but carries special motor fibres to the postulated muscular fibres of the ducts and alveoli of these glands. Thus he attributed the flow of saliva on sympathetic stimulation to a purely mechanical pressing out of saliva when the smooth muscle elements contracted. Experimental observation supported this view. If the ducts of the gland were filled by stimulation of the parasympathetic nerve or from the outside by blowing back saliva into the network of the ducts, the effect of sympathetic stimulation was much greater than when the sympathetic nerve was stimulated alone. Furthermore the sympathetic secretion is very scanty when the duct system is empty, and the amount of saliva obtained from successive sympathetic stimulation decreases rapidly. Mathews also claimed that the composition of the sympathetic saliva depended on the quality of the fluid present in the ducts.

Anrep (1922) also tried to demonstrate that augmented salivary secretion was a purely mechanical event, but at the same time he did not deny the presence of secretory fibres in the cervical sympathetic of the dog. He suggested that the augmented effect of the sympathetic nerve after chorda stimulation was due to the pressing out of saliva from the gland only, and repudiated Langley's theory of the varied excitability of the gland.

Babkin and McLarren (1927) in an attempt to clear up these conflicting theories concluded as a result of their experiments that there are two phases in the augmented sympathetic secretion, first, a mechanical phase due to the action of special motor fibres in the sympathetic nerve, and, second, a secretory phase which appears as a result of previous stimulation of the parasympathetic nerve. This latter effect is due to the presence of secretory fibres in the cervical sympathetic nerve supply to the submaxillary gland in the dog. The possibility of contraction of Wharton's duct in the dog and cat was excluded by perfusion experiments, in which it was found that neither stimulation of the sympathetic nor the addition of adrenalin or pituitrin to the perfusing fluid changed the rate of flow through the ducts. Thus they proved that the motor effects take place within the gland and not in the ducts.

MacKay (1927) showed that histamin possesses a motor as well as a secretory effect on the salivary glands. Subsequently (1929) she revealed the fact that the contractile mechanism is not paralysed by ergotoxin and may be activated by histamin, though not by stimulation of the sympathetic or by adrenalin. Stavraky (1931b) showed that moderate doses of atropin abolish the secretory response to histamin in the submaxillary gland of the dog, but do not affect the motor activity to any marked degree.

Thus it has been concluded that the cervical sympathetic nerve activates some contractile elements in the salivary glands, which elements are not of a muscular nature. Histologists long ago ascribed contractile properties to the special myoepithelial cells or basket cells found in the salivary glands. It is considered possible that these cells really have a contractile power and are under the control of the cervical sympathetic nerve, and that they play a part in the phenomena of augmented salivary secretion (Babkin & MacKay, 1930).

(iv) Vascular effects of the cervical sympathetic nerve on the salivary secretion.

The cervical sympathetic supplies all the salivary glands with vasoconstrictor fibres. This fact was first noted by Claude Bernard (1858) in the case of the submaxillary gland of the dog. Stimulation of this nerve produced vasoconstriction in the sublingual and parotid glands of the cat, while in the submaxillary gland it caused a brief vasoconstriction followed by a marked vasodilatation (Carlson, 1907; McLean, 1908). Barcroft (1914) and his co-workers considered that this vasodilatation was of a secondary nature, due to the formation and action of metabolites produced by the active gland.

The vasomotor effect disappears on the third day after section of the cervical sympathetic nerve in a dog (Carlson, Greer and Becht, 1907-08; Sinelnikoff, 1921), but the secretory effect may remain under certain conditions till the sixth day after section. Stavraky (1931 a) by the method of degeneration has been able to separate the vasoconstrictor and secretory fibres from the special motor fibres in the cervical sympathetic nerve to the submaxillary gland in the dog. Stimulation of the vagosympathetic nerve in the neck 90 hours after aseptic section produces no vasoconstriction and no secretion, but after stimulation of the chorda the phenomenon of augmented secretion is still observed. He considers that it is a purely motor phenomenon. Saliva which has been blown back into the gland is pressed out by stimulation of the degenerated nerve. Jurist and Rabinowitch (1924) found in the cat that both actions disappear from 41 to 48 hours after section of the cervical sympathetic nerve.

Babkin (1931), as a result of work carried out chiefly in his laboratory, concluded that the cervical sympathetic nerve contains the following types of fibres for the salivary glands: (1) secretory fibres, (2) motor fibres, (3) vasoconstrictor fibres.

C. Stomach.

(i) Sympathetic innervation - anatomical description.

(a) Extrinsic nerves.

The extrinsic nerves of the sympathetic supply to the stomach are derived entirely from the coeliac plexus. According to McCrae (1924) the following groups are to be distinguished:-

(a) Fibres of the coeliac plexus which pass with the left phrenic artery and so on to the stomach. They wind about the lower extremity of the oesophagus from left to right, communicate with branches of the anterior vagal trunk and are distributed to the region of the cardia and fundus.

(b) Fibres which follow the left gastric artery, of which three groups are recognised:- 1. A group which runs with the oesophageal and superior branches of the left gastric artery to the cardia and proximal part of the body of the stomach. Reinforcements are received from the fibres with the inferior phrenic artery. These twigs may be traced to the cardia and communicate with branches of the anterior and posterior vagal trunks. - 2. Fibres which pass with the main stem of the left gastric artery along the lesser curvature to supply both surfaces of the body of the stomach and pyloric antrum. - 3. Fibres which pass across between the layers of the lesser omentum towards the porta hepatis and communicate with the hepatic of the anterior vagal trunk in most cases.

(c) A group of fibres which go with the hepatic artery. They form several large branches and are distributed, along with the right gastric and right gastro-epiploic arteries to the pyloric region of the stomach.

One or two observers have described vagus fibres in the splanchnic nerves of the cat, dog and rabbit, but state that they are small and functionally insignificant (Rasmussen and Duncan, 1926; Duncan, 1928.)

The possibility of a connection between spinal sympathetic centres and higher autonomic centres has been demonstrated by the work of Beattie, Brow and Long (1930). Experimental lesions involving certain nuclei of the posterior part of the hypothalamus were followed by descending degeneration in the spinal cord. These fibres have been shown to play an important part in the control of the bulbar and spinal sympathetic nuclei. Beattie (1932) has demonstrated that stimulation of the tuber cinereum in cats produces gastric secretion and motility.

Enteric plexuses.

The extrinsic nerve fibres of the parasympathetic and sympathetic nerves form various anastomoses with the enteric plexuses. One of these plexuses - the myenteric or Auerbach's plexus lies between the longitudinal and circular layers of the intestine. Owing to the more complex arrangement of the musculature of the stomach, the position of the myenteric plexus is somewhat different. According to Müller (1924) the myenteric plexus in the stomach consists of a rich intermuscular mesh-work of nerve fibre bundles, in which groups of ganglion cells are incorporated. In the human stomach only relatively small numbers of ganglion cells are observed in the submucous plexus. The submucous or Meissner's plexus is situated between the muscularis mucosa and the submucous membrane.

Irwin (1931), using the methylene blue method of staining, investigated microscopically the myenteric plexus in the dog, cat, rabbit, rat, but chiefly in the guinea pig. He found a marked variability in the size and shape of the gastric ganglia and interganglionic fibres. In the region of the cardiac orifice there are very few ganglia and few interganglionic fibres. The ganglia are small and elongated, usually containing five to ten nerve cells. The nerve cells have a very loose arrangement. As the midgastric region is approached, the ganglia increase in size and number, becoming more compact and circular in outline. The nerve fibres of the interganglionic tracts also gradually increase in number as the midgastric region is approached. The average number of nerve cells per square centimetre at various levels of Auerbach's plexus in the stomach is as follows:

Cardia	3,500 nerve cells
Mid-zone	6,500 " "
Pyloric end	17,500 " "
Pylorus	20,000 " "

Except for the increased number of nerve cells, the plexus passes over the pylorus without change, and the branches of the interganglionic fibre bundles supply the smooth muscle of that region in the same way as elsewhere. In describing the connections of the myenteric plexus with the extrinsic nerves, Irwin explains that the main vagal branches on each side of the stomach, i.e. anteriorly and posteriorly, pass, one along the lesser curvature, and the other midway between the greater and lesser curvatures to the mid-zone. Each main branch in its course gives off several smaller branches. As these branches pass by adjacent ganglia they give off a few short fibres to each of them. The nerve gradually diminishes in size and at the mid-zone of the stomach it ends by anastomosis of the remaining fibres with a ganglion. The vagal branchings can frequently be followed through two or three ganglia as a fairly compact diminishing bundle before their identity is lost. Also bundles of non-medullated nerve fibres travelling by way of the mesentery and those lying in the adventitia of small arteries were seen to give off branches to the myenteric plexus of the intestine. These branches were given off either to a ganglion or bundle of interganglionic fibres. The same adventitial bundles could be seen to give off branches to the peri-vascular nerve network of the arterial wall. Irwin denies the interconnection of myenteric and submucous plexuses, saying: "No evidence was seen of direct communication between Auerbach's and Meissner's plexuses." This is contrary to what most of the investigators observed (cf. Kuntz, 1922). The structure of the submucous plexus in general resembles that of the myenteric plexus, with ganglia at nodal points and interganglionic nerve bundles. The submucous plexus in the small intestine gives fibres to the muscularis mucosae, mucous glands, muscular fibres of the villi and epithelial cells (Hill, 1927).

In general, however, the enteric plexuses, with some variations, chiefly of a quantitative nature, exhibit the same morphological arrangement throughout the whole intestinal tract.

Cell types in plexuses.

The data concerning the intimate structure of the enteric plexuses, which are of great value for the understanding of their function, are rather confused. Dogiel (1899) described two main types of cells in the enteric plexuses, namely, (1) multipolar cells, present only in the myenteric plexus, and (2) multipolar, bipolar and unipolar cells with long dendrites, found both in myenteric and submucous plexuses. Type I is a multipolar cell with short dendrites which end on Type II cells and is therefore believed to be of an associative nature. Type II cells are more numerous and their longer dendrites end in relationship with cells of I and II. Their axones end in connection with individual muscle cells. Hill (1927) confirmed Dogiel's classification, but does not support the findings of Kuntz (1913), Carpenter (1924) and Johnson (1925), who consider that all possible gradations of cells exist. As a result of her investigations, Hill considers Type I as associative and Type II as motor neurones. This view is also supported by the observations of Van Esveld (1928).

A problem which interested the investigators was the source of the fibres forming the so-called "interganglionic fibre complex" of the ganglia of enteric plexuses. In this connection Johnson (1925) carried out a series of experiments on cats. In the first group all nerves entering the gut from the outside by way of the mesentery and mesenteric vessels were cut and allowed to degenerate. In the second group the splanchnic nerves were cut just above the coeliac ganglia. In the third the vagi were severed immediately below the diaphragm. After allowing time for degeneration the myenteric plexuses were studied in silver pyridine preparations. Johnson found that in the first group the fine intercellular plexus completely disappeared. The remaining fibres he regarded as the processes of local ganglion cells. The results of the second set of experiments showed no appreciable change in the appearance of the myenteric plexus, indicating that the splanchnics take no part in the formation of the intercellular plexus. In the third type of experiment the myenteric plexus showed apparently complete degeneration of the fine intercellular plexus. The fibres of local ganglion cells still remained, and also a considerable number of fine non-medullated fibres, which Johnson regarded as the post-ganglionic fibres of the splanchnic nerves. Thus according to his findings the pericellular plexuses in the myenteric ganglia are made of up postganglionic fibres of the vagus. Also the postganglionic sympathetic fibres which enter the intestinal wall pass through the myenteric plexus but apparently take no part in the formation of the intercellular plexuses. This arrangement conforms to the parasympathetic and sympathetic relationships in other parts of the body, e.g. the coeliac and pulmonary plexuses. The data obtained by Johnson are in accordance with the current teaching concerning the structure of enteric plexuses. The vagus fibres are preganglionic and enter into synaptic relation with the enteric neurons,which are postganglionic, while the sympathetic fibres, which are post-ganglionic, go directly to the muscle cells without any synaptic connections with the enteric neurons. Johnson's findings were opposed by Hill (1927). According to her opinion the intercellular plexuses of the myenteric ganglia contain two types of fibres, namely, post-ganglionic vagus fibres and processes of the enteric neurons.

Another important question in connection with the anatomy of the enteric plexuses is whether the enteric neurons should be classified as parasympathetic or sympathetic. Müller (1908) stated that the myenteric plexus in the stomach includes only neurons of vagus origin and that in the intestine neurons of both vagus and sympathetic origin, while the submucous plexus in both stomach and intestine contains neurons of sympathetic origin only. Abel (1912) however claimed that the enteric neurons in the small intestine were of vagus origin. Abel (1919), Stewart (1920) and Kuntz (1920-1926) all believe that the cells which give rise to the enteric neurons in the stomach are displaced from the region of the hind brain along the vagi. Uchida (1927), as a result of embryological studies concluded that the primordia of the enteric ganglia in the intestine come chiefly from the sympathetic, but later receive cells derived from the vagus. On the other hand, the plexuses in the stomach and oesophagus are composed chiefly of cells of vagus origin.

The recent researches of Van Campenhout (1931) have shed a new light on this problem. As the result of numerous experiments on chick embryos, he concluded that the myenteric plexuses of the oesophagus and stomach derive their origin from vagus primordia, while the submucous plexuses originate from the sympathetic. The enteric plexuses of the intestine are derived solely from sympathetic elements before the vagus is sufficiently developed to reach the intestine.

(ii) Secretory action of the sympathetic nervous system on the stomach.

There are very few data regarding the secretory action of the sympathetic nervous system on the gastric glands. According to Bickel (1925), who reviewed his own work and that of his associates, the chief and parietal cells of the fundus glands are innervated by both parasympathetic and sympathetic fibres which excite, and by sympathetic fibres which inhibit secretory activity. The parasympathetic fibres exert the major influence in the secretion of water and hydrochloric acid in the fundus, while the sympathetic fibres play but a secondary part in this respect. On the other hand, the sympathetic fibres have the major rôle in the production of enzymes, and the parasympathetic fibres play a secondary part in this function. The sympathetic inhibitory fibres inhibit all secretory activity. The pyloric portion of the stomach is innervated solely by sympathetic fibres, some of which excite, others of which inhibit secretion. In this part of the stomach the sympathetic secretory fibres control both the secretion of water and enzymes, but water is secreted in relatively small quantities. According to Bickel, all nervous excitation and inhibition of gastric secretion is mediated through the extrinsic nerves, as he denies the presence of intramural ganglia. These conclusions are highly theoretical and are not entirely confirmed by experimental evidence.

Effect of section of splanchnics on gastric secretion.

The effect of section of the splanchnic nerves has been studied by a few investigators with conflicting results. Pavlov and Schumow-Simanowski (1895) reported that section of the splanchnics in the dog had no effect on the quantity of the secretion obtained by sham feeding. They noted however that the content of total solids in the secretion did not rise as sharply as in the normal dog. Gaultier (1907) found that stimulation of the splanchnic nerves had no effect on gastric acidity, whereas section of the splanchnics or removal of the coeliac plexus caused a constant and pronounced hyperchlorhydria. According to Foà (1927), section of the splanchnic nerves in dogs caused a great increase in the free and total hydrochloric acid. Section of the vagi below the diaphragm, on the other hand, produced a great diminution of HCl. In two clinical cases resection of the branches of the vagus on the lesser curvature and of the sympathetic elements of the pylorus produced a diminution of HCl secretion which was still apparent after 1½ years. Moll and Flint (1928) also reported hyperchlorhydria in dogs after section of both splanchnic nerves. The gastric secretion was stimulated by a test meal of gruel, and fractional specimens withdrawn through a gastric fistula. This problem was also investigated by Trinchera and Rindone (1930) in dogs. They reported that one-sided splanchnicotomy had no effect on gastric secretion. Double splanchnicotomy, however, produced an increase in HCl and pepsin which was still present after one month. The denervation of the coeliac trunk, after Leriche, or the treatment of the coeliac plexus with alcohol had no effect on gastric secretion. Double vagotomy below the diaphragm produced an increase in the secretion of HCl.

Hess and Faltitschek (1924 a and b, 1925) studied the effect of paravertebral nerve block of dorsal segments with novocain in normal and gastric patients. They found that injection of a 1 per cent novocain and epinephrin solution into the 7th and 8th right dorsal segments produced an increase in HCl secretion in healthy normal patients. Injection of saline into the same segments had no effect, nor had the injection of novocain-epinephrin solution into different areas of the body. However, when the same technique was employed on patients suffering with gastric ulcer, no increase in HCl secretion was observed.

Pieri and Tanferna (1932) repeated this work with entirely different results. They studied a series of normal and gastric patients, in whom the gastric secretion was stimulated by means of the Ewald test meal and histamin , after the blocking of various dorsal segments and also after section of sympathetic rami of various segments. These authors claim that paravertebral injection of the 4th and 5th dorsal segments blocks the sympathetic nerve supply to the body and fundus of the stomach, while blocking of the 6th 7th and 8th dorsal segments paralyses the sympathetic supply to the pylorus and antrum. They found that blocking of these dorsal segments produced in the great majority of cases (77 to 80 per cent) a diminution in the free and total acidity and peptic content of the gastric secretion, both when the secretion was stimulated by histamine and by the Ewald test meal. The diminution of acidity was more marked in patients with gastric disease, especially when histamine was used as a secretory stimulant. Resection of the sympathetic rami in the 7th and 8th dorsal segment gave similar results. They concluded therefore that the sympathetic has a stimulating effect on gastric secretion, not so much on the "psychic" secretion, which is chiefly under the control of the vagus, but on the chemical phase of the secretion, which they believe is under the control of the intramural innervation. In an earlier study (1930) these same authors reported that section of the vagi below the diaphragm in cases of gastric ulcer, for example, brought about a fall in HCl and pepsin, which, however, rose to the former level or higher shortly after operation.

Several investigators have studied the secretion of the pyloric part of the stomach in response to different drugs and nerve stimulation. According to Bickel (1925) the pyloric part receives sympathetic nerve fibres only. Here, too, conflicting data are reported. Kresteff (1899) found that pilocarpine activated a secretion from the isolated pylorus. Linghstone (1924) claimed that both acetyl choline and pilocarpine were without effect on the isolated pylorus. Epinephrine, however, produced a secretion. He suggested that the pyloric glands have a secretory as well as an inhibitory sympathetic innervation. Bickel (1925) demonstrated that vagotomy had no effect on the isolated pyloric pouch. Pilocarpin and acetyl cholin were without effect and adrenalin did not inhibit the pyloric secretion. He concluded therefore that the sympathetic possessed inhibitory and secretory fibres for the pyloric part of the stomach. Kreps and Savitsch (1925) made observations on the isolated pouch of the pylorus, following the method of Pavlov. They found that the injection of HCl solution into the pouch increased the secretion. If, however, the right vagus was severed in the neck or atropin given, then HCl had no effect. Small doses of pilocarpin increased the content of pepsin, whereas larger doses inhibited the secretion. Atropin inhibited the secretion and decreased the amount of pepsin. Stimulation of the vagi four days after aseptic section in the neck gave either no effect or an inhibition of the secretion from the Pavlov pouch of the pylorus.

Ivy and Oyama (1921) and Lim and Mott (1923) experimented on denervated and intact pyloric pouches. These investigators found that the denervated and intact pouches had a continuous secretion in the dog and that the taking of food and water into the large stomach had no effect on the secretion in either the denervated or intact pyloric pouch.

Thus the evidence of the action of the sympathetic and parasympathetic nerves on the pyloric secretion is contradictory and must be the subject of further research.

Effect of stimulation of the splanchnic nerves on the gastric glands.

Volborth and Kudriawzeff (1927) in a series of acute and semi-acute experiments investigated the effect of stimulation of the splanchnic nerves on the gastric glands. They used spinal dogs and in one series they stimulated the freshly sectioned splanchnic nerves, using shield electrodes. The vagi were cut in the neck and the oesophagus tied there also. According to their description "the cardiac part of the stomach on the boundary with the pylorus was sewed subserously and tied so that the passage to the pylorus was tightly closed;" thus the secretion of the pyloric part of the stomach was not collected as a fistula was placed in the fundus only. They stimulated the splanchnics alternately for 15-minute periods with a rhythmic tetanizing current giving 30 minutes' stimulation followed by 30 minutes' rest for as long as three hours. Using this procedure they obtained small quantities of gastric juice (.4 to 3.6 c.c. in 30 minutes) but did not state its composition.

They also performed experiments, using the degenerated nerve technique of Kudrewezky (1894). The left splanchnic nerve was severed aseptically 5 days before the experiment to allow degeneration of the vasoconstrictor fibres as well as of the fibres to the adrenal glands; thus stimulation of the nerve gave no rise in blood pressure. Stimulation of the degenerated splanchnic gave only a scanty secretion of "gastric juice" - 2.2 c.c. in 40 minutes.

The third set of experiments were combined acute and chronic. They used a dog with a Heidenhain pouch, and 5 days before the experiment sectioned the left splanchnic nerve aseptically. On the day of the experiment the wound was opened and under anaesthesia the degenerated nerve was placed in a shield electrode. The dog was placed in a frame and they waited until the secretion from the pouch subsided and the reaction was neutral. Now rhythmic stimulation was started as before. The secondary coil was placed at 24 cm. at the beginning of the experiment and gradually moved down to 10 cm. during the course of the experiment. The secretion obtained from the pouch varied from .4 to .8 c.c. during periods of stimulation (15 minutes) and was acid throughout the experiment. Free HCl was present only during the last half hour of experiment (no figures given). From the main stomach 5 to 10 c.c. of secretion were obtained during periods of stimulation.

From these experiments Volborth and Kudriazeff concluded that the sympathetic nervous system through the splanchnic nerves conveys excito-secretory impulses to the fundus glands of the stomach.

Action of epinephrin on the gastric secretion.

With regard to the action of epinephrin on the gastric secretion, conflicting data have been reported by several investigators. A strong inhibition of the gastric secretion in all its phases was reported by Hess and Hundlach (1920) and Rothlin (1920).

However, other observers have demonstrated an undoubted secretory response of the gastric glands to epinephrin. (Yukawa, 1908; Loeper and Verpy, 1917). Lim (1923) worked on anaesthetised cats and found that epinephrin provoked gastric secretion in a certain number of cases. Ivy and McIlvain (1923) experimented on dogs with Pavlov pouches and Thiry fistulae of the duodenum and jejunum. They reported that the introduction of epinephrin solution (1/50,000) into the duodenal-jejunum loop produced a definite secretion from the pouch. Sirotinin (1924) used dogs with Heidenhain pouches in his experiments. He noted that the subcutaneous injection of epinephrin simultaneously with the ingestion of 200 c.c. of Liebig's meat extract increased the amount and duration of the secretion to 1.5 to 2 times that obtained from the meat extract alone. Injection of epinephrin towards the end of the secretion from meat extract caused a slight but long continued elevation of the secretion. Finally the subcutaneous injection of epinephrin in a fasting dog activated a distinct secretion from the Heidenhain pouch. Moll and Flint (1928) found that epinephrin decreased the gastric acidity both in man and experimental dogs. They claimed also that clinical cases of hypertonia of the sympathetic nervous system (e.g. exophthalmic goitre) showed decreased gastric acidity.

Bickel (1925) and his associates investigated the action of epinephrin in dogs with Pavlov, Heidenhain and Bickel pouches. In fasting Pavlov pouch dogs the intravenous injection of epinephrin had no certain effect. If the animals were in a digesting state there was no increase but perhaps a slight inhibition. If, however, both vagi were sectioned below the diaphragm, the intravenous or intramuscular injection of epinephrin in fasting or almost fasting dogs gave a slight but definite increase in the secretion. The intravenous or intramuscular injection of epinephrin in dogs with Bickel pouches had no effect on the secretion either in the fasting or digestive state. Bickel therefore concluded that epinephrin has no effect on the normal stomach, increases the secretion slightly in Heidenhain pouches and has no effect on Bickel pouches. In the last epinephrin can act only on the nerve endings and must stimulate equally the endings of the sympathetic inhibitor and secretory fibres.

The general impression from the above review of the literature concerning the rôle played by the sympathetic nervous system is highly confusing. The results of the section and stimulation of the splanchnic nerves are contradictory. The same may be said of the action of epinephrin, if this drug can be looked on as a true substitute for sympathetic action. The explanation of this state of affairs must be sought in the manifold action of the sympathetic nervous system on an organ of such complicated structure as the stomach. A fresh experimental attack on the function of the sympathetic nerve in relation to the gastric mucous membrane was greatly to be desired.

(iii) Motor action of the sympathetic nervous system on the stomach in relation to secretion.

In a study of the secretory activity of the glandular structures innervated by the sympathetic nervous system it is necessary to consider the problem of the relation between the secretory and motor phenomena. A striking example of the confusion of two phenomena is the so-called "sympathetic after chorda augmented salivary secretion", where the motor function of the sympathetic nerve was taken for an increased secretory activity of the salivary glands. According to the modern conception, the sympathetic innervation of the muscular wall of the stomach and intestine conveys not only inhibitory but also motor impulses.

Moreover there are indications, as will be quoted later, that it may produce an excitatory as well as an inhibitory influence on the muscularis mucosae of these organs. It is clear that the phenomena of the motility of the gastro-intestinal wall and especially of the muscularis mucosae, which has such an intimate relation to the glandular structures situated in the mucosa, cannot be overlooked. Accordingly a short review of the "periodic work" of the gastro-intestinal tract, called by American authors "hunger contractions", will be presented, as well as a discussion of the influence of the sympathetic nervous system on the motility of the stomach.

The "periodic work" of the gastro-intestinal tract was first noticed by Schirokich (1901) and Tscheschkow (1902), and later emphasised by Klodnizki (1902), Edelmann (1906) and Boldyreff (1911). This periodic work is described as consisting of twenty to thirty minute long contractions of the stomach and small intestine which occur every 1½ to 2½ hours in the fasting state, the stomach being empty and completely at rest. These contractions are accompanied by pancreatic and biliary secretions as well as by the secretion of intestinal mucus. Neither the salivary glands nor the gastric glands produce any secretion during the periodic contractions. The phenomenon starts with contraction of the stomach, from which mucus is discharged, and contractions as well as secretion in the small intestine. Then follows secretion of pancreatic juice and bile. In the intervals between contractions, neither movements nor secretion occur. However, if gastric secretion commences, the periodic contractions cease immediately. The periodic activity can also be inhibited by the introduction of 0.1 to 0.5 HCl or other acid solution, or fat, into the stomach. The introduction of small amounts of fat or oleic acid solution does not interrupt the periodic activity (Babkin and Ishikawa, 1912). The periodic activity of the stomach may occur whether the reaction is alkaline or acid. In the latter case, the secretion becomes very scanty or practically ceases with the onset of the periodic contractions.

The hunger contractions of the human stomach were first studied by Cannon and Washburn (1912), and then by Carlson (1919) and his co-workers, and many other investigators.

The nature of the "periodic secretion" of the pancreas and intestine is not clear. It was regarded by Boldyreff (1911) and others as the result of a true secretory activity of the corresponding glands. However, Babkin and Ishikawa (1912) brought forward certain evidence in favour of the view that the pancreatic and intestinal secretions are secondary phenomena. Both secretions could be easily elicited, the one from the pancreatic ducts, the other from the intestinal folds, by the movements of the corresponding structures during the periods of hunger contraction. Although the problem of periodic secretion by the pancreas and small intestine cannot be regarded as definitely settled, we have good reason to believe that "true" gastric secretion does not accompany the hunger contractions, as Anitschkow (1924) and Nechoroschew (1925) attempted to prove. In most of such cases the gastric secretion was due to uncontrolled conditioned reflexes (Rabinkowa, 1926; Rabinkowa and Eberle, 1926).

The cause of the "periodic activity" of the gastrointestinal tract or of "hunger contractions" is not yet quite clear. The fact that a loop of the small intestine, when separated from the mesentery and transplanted into a skin graft, five months later showed hunger contractions and secreted succus entericus (Levin, 1926) suggests the possibility of humoral stimulation of its neuromuscular apparatus. The experiments of Carlson and his co-workers support this supposition. By lowering the blood sugar concentration about 25 per cent, using insulin, Bulatao and Carlson (1924) were able to intensify the hunger contractions in dogs. Intravenous injection of glucose abolished the contractions. Subsequently Quigley and Hallaran (1931) confirmed these observations. In their experiments insulin increased the periodic activity of the stomach and duodenum as well as the sensation of hunger. Introduction of glucose into the duodenum inhibited all these phenomena. It seems therefore that hypoglycemia stimulates the "periodic activity".

The point of application of the hypothetical hormonal stimulus of the hunger contractions is not clear. Thus Orbeli (1923) demonstrated that the inhibitory effect of fat on the periodic intestinal secretion disappeared after section of the vagi. Atropin also inhibited the periodic secretion. Therefore the importance of the parasympathetic innervation is indicated by these experiments. However, there are indications that the sympathetic nervous system (either directly or through the suprarenal glands) may influence the hunger contractions. Sinelnikoff (1926) showed that emotional states inhibited the periodic activity of the small intestine in the dog, but stimulated contractions when the intestine was in a period of rest.

In connection with the problem of the sympathetic innervation of the stomach, the investigation of the motility of the mucous membrane is of great importance. The work of Forsell and Thorell, which throws a new light on this problem, will be briefly discussed. Forsell (1913) from anatomical and x-ray observations reported that the folds of the gastric mucous membrane showed such marked variations that the existence of a motor mechanism could be assumed. In a further investigation (1921 and 1923) he showed that the great variations which take place in the folds of the gastric mucous membrane are under the control of the muscularis mucosae. He also (1925) demonstrated that a certain degree of contraction of the muscularis mucosae was necessary in order to form and maintain the folds of the gastric mucosa.

Thorell (1927) investigated this problem further. He studied the movements of isolated pieces of gastric mucosa with attached muscularis mucosae. By the use of pilocarpin, acetylcholin and epinephrin he obtained movements and tonic changes in his preparations. The results in the dog and cat with epinephrin only are cited here. <u>In the dog</u> the fornix (fundus), body and sinus (pyloric antrum) gave tonus positive reactions to epinephrin. A part of the sinus and canalis egestorius (pylorus) gave at first strong tonus negative reaction, which later changed to tonus positive. Atropin gave a reversal of epinephrin action on the fundus of the dog's stomach. *In the cat* the cardia was tonus positive to epinephrin. The rest of the mucous membrane of the cat except the border of the fundus was weakly tonus negative. Thorell noted that the excised strips showed small pendulum movements and longer rhythmic movements resembling peristalsis. The addition of calcium to the bath fluid often caused weak contractions and augmented the action of epinephrin, whereas calcium lack decreased the excitability of epinephrin.

Action of the sympathetic nervous system on the muscles of the gastric wall.

The older traditional view of the action of the sympathetic in this respect was that it was merely depresso-motor in function and it was regarded as the antagonist of the parasympathetic system (Langley, 1901; Elliott, 1905). Recently, however, on the basis of continued experimentation the opinion has been put forward that the sympathetic contains not only depresso-motor but also excito-motor fibres for the stomach. Oser (1892) found that a weak contraction of the stomach often resulted from stimulation of the splanchnics, this being followed by a relaxation of long duration, during which existing movements were inhibited. An increase in peristalsis was observed as an after-effect which could be arrested by further stimulation. Doyon (1895) noted that, if both vagi were cut and the stomach was then quiescent, stimulation of the splanchnics resulted in a single contraction, but that if the stomach was contracting stimulation produced inhibition. Botelli (1896) obtained confirmation of these results. Smith (1918) as a result of his experiments with epinephrin on isolated strips of muscularis mucosae came to the conclusion that in the cat the sympathetic contained depresso-motor fibres, while in the dog it contained in the fundus and body excito-motor and in the antrum and pylorus depresso-motor fibres for the muscularis mucosae.

Carlson, Boyd and Pearcey (1922) observed in the cat both motor and inhibitor responses and in the dog motor responses to the stimulation of the sympathetic. Thomas and Wheelon (1922) also recorded motor and inhibitor effects, which they associated with changes in blood pressure. Inhibitor effects were often associated with a rise in blood pressure and augmentor with only a slight rise in blood pressure. Carlson (1922, 1924) has postulated that the sympathetic and vagus contain excito-motor and also depresso-motor fibres for the stomach and that the state of contraction depends on the balance between these two sets of fibres. Thorell also suggested that the sympathetic and parasympathetic may have a different action on different sections of the same stomach.

Nolf (1925) confirmed in the domestic chicken the earlier findings of Doyon (1895). Nolf stated that stimulation of the sympathetic produced both inhibitor and motor effects depending on experimental conditions. All motor action of the sympathetic was abolished by the intravenous injection of sufficient doses of nicotin. Veach (1925) found that the degree of inhibition produced in the cat's stomach by stimulation of the major splanchnic nerves parallelled the degree of vasoconstriction. If the constriction was lacking or slight, contraction frequently occurred. He concluded therefore that the chief factor in the production of inhibition in the stomach of the cat by splanchnic stimulation was vasoconstriction. McCrea and McSwiney (1928) found that the effect of stimulation of the peripheral end of either splanchnic nerve depended on the existing state of gastric tonus. If the stomach was in a state of hypotonus, stimulation brought about an increase in tonus, while if the organ was initially in a state of hypertonus, stimulation caused a fall in tonus. Later Brown, McSwiney and Wadge (1930), working with spinal cats or dogs, the stomach being divided at the incisura, found that the results of stimulation were associated with the type of current employed. Stimulation at a frequency of one break shock per second caused contraction of the body of the stomach, while stimulation with a rapid tetanizing current brought about relaxation. The movements of the dog's antrum, usually inhibited by sympathetic stimulation, occasionally showed augmentor effects. The cat's antrum was inhibited by all forms of stimulation. The motor responses were usually inhibited by ergotoxin. Adrenalin, however, did not produce the effects of sympathetic stimulation. Brown and McSwiney (1932) have recently reported that sodium luminal injected in decapitate preparations permits any type of sympathetic stimulation to produce motor effects.

Recently McSwiney and Robson (1929 a and b) have been able to prepare strips of stomach innervated by periarterial sympathetic nerve supply. They have shown (1931 a) that the results of stimulation of the periarterial sympathetic nerves depends on the frequency of the faradic current used. The use of induction shocks with a frequency of from one to twelve shocks per second caused contraction of the muscle strip, while with twenty to fifty shocks per second relaxation occurred.- Reversal effects were also obtained by varying either the strength of the current or the duration of the faradic stimulation. The authors claim that these results prove that contraction and relaxation of the isolated strip on periarterial stimulation are not related to vasomotor changes or the existing state of tonus.

Interaction of sympathetic and vagus nerves in intact stomach and isolated strips.

Botelli (1896) and Oser (1892) found that simultaneous stimulation of the vagus and splanchnic nerves reduced the effects of exciting the vagi. Oser observed that the vagal action appeared first, but that if in place of stimultaneous stimulation the splanchnics were stimulated first so that inhibition was predominant, then a vagus effect was difficult to obtain. McCrea and McSwiney (1928) also confirmed this observation. McSwiney and Robson (1931 b) have also studied the interaction of the vagus and stimulation of the periarterial nerves. They found that stimulation of the sympathetic nerves alone with a low frequency induction current caused contraction. If, however, the sympathetic was stimulated with the same frequency during a contraction induced by tetanic stimulation of the vagus, relaxation occurred. Stimulation of the periarterial nerves during vagus stimulation also gave a reversal effect of the sympathetic response, but only after the lever had returned to the base line through apparent fatigue of the muscle to vagus stimulation. Stimulation of the periarterial nerves, which under ordinary conditions had no effect, frequently produced relaxation during vagus stimulation. Further relationship was demonstrated in the following experiments. Stimulation of the sympathetic caused contraction. If during the sympathetic stimulation the vagus was also stimulated, a further contraction occurred. Sympathetic stimulation was then discontinued and the vagal contraction immediately increased in magnitude.

Effect of removal of the sympathetic innervation on the motility of the stomach.

This question is related to the present investigation, since experiments were performed on cats with gastric fistula and oesophagotomy in which the splanchnic nerves were sectioned. It was hoped in this way to study the rôle of the sympathetic nervous system in the normal processes of gastric digestion. Besides this in many experimental animals the splanchnic nerves were severed two to four days before to permit degeneration of the vasoconstrictor and secretory fibres to the suprarenal glands. This was done in the hope of observing the action of the true secretory sympathetic fibres, if such existed.

The importance of the interrelation of the secretory and motor processes made it necessary to study the literature concerning the effects of sympathectomy on gastric motility. In his recent book, "The Wisdom of the Body" (1932), Cannon quotes Spadolini (1926) who declared that complete extirpation of the mesenteric nerves of the cat is incompatible with life. Among other disturbances Spadolini found "severe lesions of the gastro-intestinal tract". Cannon and his co-workers removed the abdominal sympathetic chain, with the splanchnic nerves, in cats, and in some of the animals the semilunar ganglia were also extirpated and the nerve strands stripped from the large branches of the abdominal aorta. They did not note any alarming symptoms resulting from these operations. "From these observations," concludes Cannon, "we are driven to the conclusion that the superior cervical and sympathetic ganglia and the sympathetic nerves distributed to the stomach and intestine are not essential for life."

Although the continued existence of animals after sympathectomy is possible, as Cannon and his co-workers showed and as we have ourselves observed, yet this operation has a definite influence on the function of the gastro-intestinal tract. It is true that in his earlier work Cannon (1911) declared that section of the splanchnic nerves on both sides did not affect the motility of the stomach. However, most of the recent investigators noted certain changes in the motor activity of the stomach after double splanchnectomy. Thus Koennecke and Meyer (1922) sectioned the splanchnics transperitoneally in dogs. When the immediate effect of the operation had passed, they observed increased tonus of the stomach and accelerated motility of the gastro-intestinal tract. Similar results were obtained by Watanabe (1924) and Bickel (1925) after bilateral intra-thoracic section of the sympathetic chains and splanchnic nerves. This initial increase in tonus and augmentation of the peristalsis was somewhat reduced during the subsequent existence of the dogs.

Alvarez and Hosoi (1929) studied the effect of degenerative section of the splanchnic nerves on the motility of the stomach in rabbits, They reported that the operation caused a high mortality in these animals (65%) with a large percentage of gastric ulcers

(35%). The animals that died usually had severe diarrhoea and inanition and the gut was abnormally empty. If animals recovered, the appearance of the stomach on opening the abdomen after several weeks to permit degeneration of fibres was essentially normal except that it showed abnormal sensitivity to stimulation and manipulation. Trinchera and Rindone (1930) reported increased tone and hyperperistalsis of the stomach after bilateral sub-diaphragmatic splanchnicotomy in dogs, which was still present after one month. Hess and Faltitschek (1924), using the technique of paravertebral injection of dorsal spinal segments in humans with a 1% novocain and epinephrin solution, previously described, found increased motility of the stomach on x-ray examination. These investigators attributed the result to removal of sympathetic impulses by anaesthesia, which they considered equal to sympathetic paralysis.

In the older as well as in the more recent literature there are indications that the extirpation of the coeliac ganglion has a greater effect on the motility of the gastro-intestinal tract than the mere section of post-ganglionic sympathetic fibres. Popielski (1903) after extirpation of the coeliac ganglion in dogs noted diarrhoea with blood or a foul odour. No such results were observed after section of the splanchnics and extirpation of long pieces of sympathetic chain. According to Magnus (1909) the section of post-ganglionic sympathetic fibres to the stomach and intestine in the cat produced mild disturbances and in a comparatively short time the function of the digestive tract returned to normal. Five weeks after the extirpation of the coeliac ganglion in dogs, Koennecke and Meyer (1922) by means of x-rays observed increased peristalsis and hypermotility of the stomach and intestine. In spite of their great appetite the animals lost weight. One of the dogs died, and another did not regain its previous state for a long time. Watanabe (1924) and Bickel (1925) made similar observations after extirpation of the coeliac ganglion. According to them the peristalsis was stronger and hypermotility could be noted. These phenomena gradually diminished and finally disappeared. Watanabe and Bickel ascribed the return of normal conditions to the gradually increasing activity of the sympathetic fibres contained in the vagus.

The effects observed in the gastro-intestinal tract after it has been deprived of sympathetic innervation are explained by most of the investigators as being due to unrestricted activity of the vagus. On the other hand section of the vagi, with the sympathetic nervous system left intact, diminishes but does not completely abolish the motility of the stomach. The effect of vagotomy is especially marked immediately after the operation. A somewhat different opinion is expressed by McSwiney in his recent review on the "Innervation of the stomach" (1931). In his opinion "the immediate effects of vagotomy, splanchnicotomy and denervation of the stomach are similar, namely retardation of function. After a period the peripheral intrinsic nervous mechanism assumes control of the denervated stomach, and only one permanent symptom of importance, i.e. a decrease in initial emptying time, is observed" (p. 493).

Effect of epinephrin on the motility of the stomach.

One of the most important questions which arise when different parasympathomimetic and sympathomimetic drugs are used is whether they are true substitutes for reflex or direct stimulation of the corresponding nerves. It seems that in the case of epinephrin and its effect on the stomach of warm-blooded animals this question may be answered in the affirmative. P. Trendelenburg (1927), one of the great pharmacologists and an authority on problems of gastro-intestinal motility, writes: "Bei der näheren Analyse der Magen- und Darmbewegungen der Warmblüter ergab sich, dass diese sich überall mit den Wirkungen einer Reizung der sympathischen Nervenfasern decken." This opinion is not entirely shared by McCrea and Macdonald (1928), according to whom there is a difference in the effects produced by nerve stimulation and epinephrin respectively. However, from a review of the literature it seems that in general the action of epinephrin duplicates more or less the result of stimulation of the sympathetic nerves to the stomach.

As stimulation of the splanchnic nerves produces not only inhibition but frequently an increase of the gastric motility, epinephrin acts similarly under certain conditions. The inhibitory action of this drug on the motility of the stomach, demonstrated by Elliot (1905) and a great many other experimenters, was shown to be not the only one which may be noted in this organ. Smith (1918) stated that the sympathetic nerve supply to the pylorus is motor in effect. Carlson, Boyd and Pearcey (1922) found that the action of epinephrin on the cardia was motor when the stomach generally was hypertonic, and inhibitor when the stomach was hypertonic. Thomas (1926) obtained similar results on the pylorus of the dog. McCrea and Macdonald (1928) have shown that epinephrin may produce both motor and inhibitor responses in the stomach of the dog and cat but its action is chiefly inhibitor. It is interesting to note that epinephrin stimulates the motility of the muscularis mucosae (Gunn and Underhill, 1914; Thorell, 1927).

Motility of the stomach in elasmobranch fishes.

The peculiarities of innervation in the stomach of elasmobranch fishes throw some light on the double function - motor and inhibitory - of the sympathetic nervous system of the mammalian stomach. The sympathetic nervous system in the elasmobranchs is in the initial stage of development. On each side of the vertebral column are one large and several small sympathetic ganglia. They send nerve branches to the gastrointestinal tract along the arteries. The first and largest ganglion is closely connected with the chromaffin body. A remarkable feature of the sympathetic nervous system to the abdominal viscera of elasmobranchs, such as the skate, is that there are no large sympathetic ganglia on the way from the lateral sympathetic ganglia to the abdominal organs. Botazzi (1902) thinks that most of the nerve fibres arising from the lateral ganglia are post-ganglionic. According to Daniels (1928) the lateral sympathetic ganglia in the shark are never connected in a chain. They are connected by many fibres, like the lateral ganglia in mammals, with the anterior spinal nerves.

Botazzi (1902) was the first to demonstrate that stimulation of both vagus and sympathetic nerves produces contractions of the stomach. His findings were confirmed by Müller and Liljestrand (1918), Lutz (1931) and Babkin and Sawyer (1931). Stimulation of the sympathetic nerves following the coeliac artery produced a contraction of the pyloric sphincter in ten seconds. In one to two minutes the contraction passed up the pyloric canal, spreading upward to the antrum pylori and finally into different parts of the fundic portion. The pyloric canal was completely contracted. The contractions of the stomach were of a slowly pulsating ring type. Stimulation of the different branches of the vagus gave the following results. The stimulation of the main visceral branch of the vagus produced an immediate contraction of the oesophagus and a few seconds later several rings of contraction in the middle part of the stomach. The dorsal branch of the vagus caused contraction of the oesophagus and of the pyloric canal, but no contractions of the body of the stomach were noted.

None of the above-named authors observed any inhibition of the motility of the stomach on stimulation of the sympathetic nerves; the effect was always positive. It must be added, however, that all the data concerning movements of the stomach were visual observations only, and that the interrelated effects of sympathetic and vagus stimulation were not studied.

Dreyer (1928) investigated the effect of different drugs on isolated strips taken from the ascending limb of the stomach and the spiral valve in the skate. His chief finding was that epinephrin stimulated the motility of both regions of the gastro-intestinal tract. On the other hand, pilocarpin and atropin had no effect. Nicholls (1932) also used isolated strips from different regions of the skate's stomach. He found that epinephrin in concentrations of 1:2,000,000 stimulated all parts of the stomach except the antral region near the pyloric canal, but caused inhibition in concentrations of 1:1,000,000 or less. Epinephrin given after pilocarpin had a synergic effect. The effect of epinephrin on the antral region may be explained by hypersensitivity of this region to adrenalin or double sympathetic innervation - inhibitory and motor- of this region. Pilocarpin and acetyl-cholin stimulated all parts of the stomach. Atropin had no effect on the normal contractions in any part of the stomach, but was antagonistic to the effect of pilocarpin and acetyl-cholin.

According to all these investigators therefore the sympathetic nervous system and the sympathomimetic drugs exert in the main a positive stimulating effect on the stomach of elasmobranch fishes. It is only in the region of the pyloric antrum that they produce inhibition. The elasmobranchs are in the direct line of evolutionary development of the mammals, and the above-mentioned findings may have some bearing on the motor innervation of the mammalian stomach. The positive motor innervation of the stomach may be looked on as a remnant of the periods of evolutionary history. It is possible that the limited region of inhibitory sympathetic innervation spread over the whole organ, and that the positive motor effect may only be demonstrated under special conditions.

(iv) Vascular effects of the sympathetic nervous system on the stomach.

Effect on secretion.

The stomach is of course like the other parts of the gastro-intestinal tract, supplied with vasoconstrictor sympathetic nerves. That the presence of these nerves modifies the responses of the stomach, secretory and motor, is undoubted. It has already been noted in the work of Volborth and Kudriazeff (1927) that vasoconstriction is a serious obstacle in experiments on the secretory action of the splanchnic nerves or gastric glands. Further observations will be presented in the experimental part of this thesis.

Effect on motor responses.

Several investigators have correlated the results which the effect of stimulation of the splanchnic nerves produced on the tone of the stomach and the degree of vasoconstriction engendered. Thus Thomas and Wheelon (1922) recorded inhibitor responses with marked vasoconstriction and augmentor with slight rises in blood pressure. This was corroborated by Veach (1925).

Epinephrin when injected intravenously constricts the blood vessels of the stomach. Its effect may be so strong that it inhibits the gastric secretion (Hess and Hundlach, 1920; Rothlin, 1920). The amount of blood flowing from the blood vessels of the mesentery is greatly diminished after the injection of epinephrin (Pick, 1899).

There is no certain evidence of the presence of vasodilator fibres for the stomach in the vagus. As every-day experience shows, the blood vessels of the stomach are dilated when the stomach is filled with food. This, however, is not due to the distention of the organ, since Burton-Opitz (1910) and Tomita (1906) showed that, when the stomach was inflated with air, the venous outflow was diminished. Therefore the vasodilatation of the active stomach must have some other explanation. By analogy with other secretory organs (e.g. the salivary glands) it may be supposed that during the activity of the peptic glands "metabolites" or "local hormones" are formed, which act as vasodilators on the gastric blood vessels. No experimental proof of this, however, could be found in the available literature.

An interesting finding was recently reported by Kuré, Ichiko and Ishikawa (1931 b) regarding the course of the parasympathetic fibres. According to these investigators some of the "spinal parasympathetic fibres", leaving the dorsal spinal roots, join the splanchnic nerves and supply the stomach and intestine with motor fibres. Kuré et al. (1931 a) also showed that these spinal parasympathetic fibres exerted a vasodilator action on the stomach and small intestine. The data presented by Kuré and his co-workers have not yet been confirmed, and McSwiney (1931) in his review does not accept their views unreservedly.

D. Pancreas.

(i) Sympathetic innervation - anatomical description.

The sympathetic innervation of the pancreatic gland comes via the splanchnic nerves to the coeliac plexus. From offsets of the hepatic, superior mesenteric and splenic plexuses networks of fibres reach the gland with the blood supply. The sympathetic nervous system is believed to supply the pancreatic gland with secretory, trophic and motor fibres to the ducts, as well as vasoconstrictor fibres. De Castro describes isolated nerve cells and ganglia in the pancreas which he regards as sympathetic.

(ii) Effect of the sympathetic innervation on the pancreatic secretion.

Early investigators found that the stimulation of the splanchnic nerves had a very slight effect on the pancreatic secretion. Kudrewezki (1890) used two methods to overcome the marked vasoconstriction produced by splanchnication to which the pancreatic gland is so sensitive. He used mechanical stimulation with Heidenhain's tetanomotor or stimulated the partially degenerated splanchnic nerve six to seven days after it had been aseptically sectioned. He obtained a scanty secretion very rich in organic material and enzymes. Savitsch (1909) with long continued stimulation of the freshly sectioned nerve obtained a scanty secretion similar to that obtained by Kudrewezki. According to Savitsch(1909) atropin inhibited the splanchnic secretion, while Modrakowski (1906) denied the inhibitory action of the drug. Recently however addition-

:al data have been added. The spontaneous secretion of the pancreatic gland of the rabbit was found to be most suitable for experiments of this type (Baxter, 1931 a and b). Using faradic stimulation of the freshly divided splanchnic nerves, the adrenal veins being ligated, we found that, after several periods of stimulation which gave decreasing inhibition, stimulation finally resulted in an augmented secretion during the period of excitation. The enzyme power of the juice secreted during the period of repeated sympathetic stimulation showed a marked increase, it being doubled or even trebled. The regularly repeated injection of epinephrin gave similar results. When the splanchnic nerves were severed below the diaphragm, there was a marked fall of several hours' duration in the enzyme content of the spontaneous secretion.

According to Yoshioka (1930) the ducts of the pancreatic gland are under the control of the sympathetic nervous system as well as the parasympathetic.

Thus it would appear that the sympathetic nervous system exerts a true secretory and "trophic" influence on the pancreatic gland.

(iii) Vascular effects of the sympathetic nerve supply on the pancreatic secretion.

That the pancreatic gland is extremely sensitive to changes in blood pressure has been shown by many investigators (Bernstein, 1869; Pavlov, 1893; Gottlieb, 1894; May, 1904). Edmunds (1909, 1910) showed that the pancreatic gland was especially sensitive to the vasoconstrictor action of epinephrin. The volume of the gland as shown by the plethysmograph remained decreased long after the systemic blood pressure returned to normal. Pemberton and Sweet (1908 a and b; 1910 a and b) also recorded inhibition of pancreatic secretion from the intravenous injection of epinephrin and regarded epinephrin as a specific inhibitor. They also noted a spontaneous secretion from the pancreatic gland after extirpation of the adrenals in the dog. However, these experiments are not conclusive, as the pylorus was not ligated. Mann and McLachlin (1917) also noted sensitivity of the pancreatic vessels to epinephrin. They gave minimal doses which, although they produced a fall in the systemic blood pressure, nevertheless caused slight vasoconstriction of the pancreatic gland and inhibition of the secretion. Babkin (1924) demonstrated that a slight and short contraction of the pancreatic blood vessels can inhibit or even stop the pancreatic secretion. In our experiments (Baxter, 1931 b) it was shown that the inhibitory effect of epinephrin and splanchnic stimulation on the spontaneous secretion of the pancreatic gland in the rabbit was only slight. The effect was even less marked when the adrenal veins were tied.

This review of the literature relating to the sympathetic innervation of the pancreas, especially to the secretory fibres of the sympathetic nerve, indicates that we are still very far from a complete understanding of its function. The problem of the sympathetic innervation was attacked in the present work from different angles, i.e. physiological and histo-physiological. The results obtained will be reported in the experimental part.

E. Intestine.

No experimental investigation of the part played by the sympathetic nervous system in the secretory function of the small and large intestine was performed during this work. However, it was felt that a review of the corresponding literature would be desirable. The structure and function of different parts of the gastro-intestinal tract, such as, for example, the stomach and small intestine, have much in common. Nevertheless they are morphologically as well as functionally different. It is always of advantage in an experimental investigation to compare the function of closely related organs. Some of the obscure phenomena of the activity of one organ may frequently be explained through the relatively simple functional relationships of another.

(i) Sympathetic innervation.

The anatomical description of the extrinsic and intrinsic nervous systems of the intestine has already been included in the corresponding sections of the literature on the stomach.

(ii) Secretory action of the sympathetic nervous system on the intestine.

That the intestinal secretion was activated by mechanical and chemical stimuli has been shown by many early investigators (Schepowalnikow, 1899; Glinski, 1891; Orbeli and Savitsch, 1916

-mechanical. - Leper, 1904; Schepowalnikow, 1898; London and Dobrowolskaja, 1910; Frouin, 1904; Orbeli and Savitsch, 1916, and others - chemical). Concerning the rôle of the nervous influences in the mechanism of intestinal secretion relatively little is known. Savitsch and Soshestwensky (1917, 1921) however have investigated the effect of vagal stimulation on the secretion of the small intestine. They found that rhythmic stimulation of the vagus with a gradually increasing induction current in spinal cats produced an intestinal secretion after a latent period of one to one and a half hours. Intestinal movements were also initiated which in some cases had the appearance of strong peristaltic waves. The authors however did not observe any relationship between movements and secretion in these experiments. On the other hand, Melik-Megrabow (1926) noted a gradual increase in the motility of the small intestine when he stimulated the vagi in exactly the same manner as Savitsch and Soshestwensky. Therefore, whether the motility and secretion run a parallel course, or whether the secretion depends on motility is not yet quite certain. According to Savitsch and Soshestwensky, atropin produced a strong inhibition or even complete cessation of the secretion. The intestinal movements were also reduced after atropin. These authors also noted that vagus stimulation increased the ferment content of the secretion independently of the rate of secretion. Atropin produced a decrease in the ferment power of the secretion. Pilocarpin also produced a secretion from the intestinal glands. These experiments then indicate that the parasympathetic nervous system has secretory and trophic fibres for the small intestine as well as motor.

Another experimental observation which indicates the influence of the autonomic nervous system on the intestinal secretion is the "paralytic secretion". If all the nerve fibres coming to an isolated loop of intestine are severed, about four hours later the loop begins to secrete in increasing quantities, which reach a maximum after about twelve hours. It gradually becomes slower and after twenty-four hours the paralytic secretion ceases altogether. The properties of the paralytic secretion resemble those of the normal secretion. (Mendel, 1896; Falloise, 1904). The paralytic secretion is regarded by Molnàr (1909) and Falloise (1904) to be due to the removal of inhibitory impulses. Starling (1906) however regarded the paralytic secretion as due to the hyperaemia induced by section of the sympathetic nerves. When the tone of the local blood vessels is restored, the secretion disappears. Savitsch (1921) is also of the opinion that not only secretory impulses reach the intestinal glands along the extrinsic nerves but also inhibitory impulses. On the other hand, section of all extrinsic nerves has no lasting effect on the production of enzymes by an isolated loop of the small intestine. Savitsch (1923) could observe no change in the entero-kinase content of the intestinal juice of a dog with two Thiry-Vella fistulae five years after the solar plexus and splanchnic nerves had been extirpated.

Brestkin and Savitsch (1927) came to the conclusion that under normal conditions the secretory and trophic functions of the intestinal glands are inhibited. These inhibitory impulses are abolished by local mechanical stimulation. When the intestine is denervated these inhibitory impulses are no longer received and the isolated loop secretes in response to local impulses.

All these investigations indirectly indicate the rôle which the sympathetic nerves play in the intestinal secretion. Regarding the direct action of the sympathetic nervous system itself in the production of intestinal secretion, very little is known. King and Arnold (1927) and King, Arnold and Church (1922) reported the appearance of whitish mucus on the surface of the small intestine after repeated splanchnic stimulation or intravenous injection of adrenalin. The appearance of this mucus was associated with contractions of the mucosa.

(iii) Motor effect of the sympathetic nervous system on the intestine with special reference to secretion.

Under the corresponding section of the literature on the stomach we have dealt with the so-called periodic activity of the digestive tract which occurs in fasting animals. That the intestine takes part in this activity has been pointed out. This activity is secretory as well as motor (Sinelnikoff, 1925). The intestinal secretion has properties similar to the normal secretion (Boldyreff, 1911). The same theoretical considerations apply here too, and the relationship between secretion and motility are significant. The experiments of Savitsch and Soshestwensky (1917), who showed that the vagus has a secretory effect on the intestinal glands, and their criticism of Melik-Megrabow (1926) were quoted above. The long latent period of the secretion[1] and the very insignificant motility of the intestine during the first 1½ to 2½ hours[2] were probably due to

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[1] Savitsch and Soshestwensky.

[2] Melik-Megrabow.

the very weak stimulation which all these investigators applied to the vagi at the beginning of their experiments. The current was only increased very gradually and the nerve stimulated in fresh places. The object of this method was to keep the nerve alive as long as possible. It is worthy of note that the greatest secretion was obtained by Savitsch and Soshestwensky at the end of the experiment, when the strongest currents were used. The same is true for the motility, as demonstrated by Melik-Megrabow. The structure of Lieberkühn's glands is so simple and their relation to the muscular layers of the intestine is so close that the conception regarding the dependence of certain of their functions on the motility of the organ seems to be justified. However, this supposition has yet to be proved and would not exclude the possibility of a "true" secretion of Lieberkühn's glands.

The researches of Forsell (1921-25) are also of importance in this connection. Forsell demonstrated the existence of spontaneous movements of the mucous membrane of the duodenum and small and large intestines which he attributed to contractions of the muscularis mucosae. He also pointed out that the formation of folds in the mucous membrane was due to tonic contraction of the muscularis mucosae. We have already referred to the work of Thorell (1927) who observed contraction of the muscularis mucosae in response to various drugs, epinephrin, pilocarpin, acetyl-cholin, etc. His observations were made on the gastric mucous membranes of the human, dog, cat, guinea pig, rabbit, pig, turtle and frog.

The experiments of King and Arnold (1922) and King, Arnold and Church (1922) gave important evidence concerning the relationship between motility and secretion in the small intestine. These authors worked on the intestine of the dog, which they observed under low magnification (25x). An incision 5 cm. long was made on the gut wall opposite the mesenteric attachment, the loop was then drawn through a slit in a small board and the edges pressed out flat. The animals were first etherised and then decerebrated. The action of various mechanical stimuli, drugs and electrical stimulation of the nerves was studied. They observed that the villi may manifest rhythmical shortening, lengthening or swaying singly or in groups. The mucosa as a whole also showed ridging, grooving and pitting movements. These two sets of movements were often associated with each other or could occur independently. Electrical stimulation of the splanchnic nerves below the diaphragm caused vigorous action of the whole mucosa, villi included. No rhythmic movements occurred during stimulation but frequently started after its cessation. This reaction to splanchnic stimulation was most marked in the duodenum and jejunum and almost negative in the ileum. In some animals the post-ganglionic mesenteric fibres were stimulated 4 to 17 days after sub-diaphragmatic section of the splanchnic nerves. Contractions resulted in response to electrical stimulation as well as to epinephrin. Simultaneous stimulation of the splanchnics and vagi together gave the effect of splanchnic stimulation alone. The intravenous injection of epinephrin gave quite similar results to nervous stimulation. Following repeated splanchnic stimulation or the intravenous injection of epinephrin, the surface of the mucosa epithelium became covered with a thick whitish mucus. Nicotin also gave sharp contractions of the mucosa and villi, frequently followed by a period of cessation and then by rhythmical movements. Repeated injections of nicotin often resulted in a secretion of thick whitish mucus on the surface of the gut.

These authors concluded that there is no definite correlation or interdependence between the motor movements of the outer and mucosal muscular layers. They regarded the submucous plexus as a terminal splanchnic mechanism with a local reflex tonus mechanism. Vagal impulses do not reach the mucosa. The motor reactions decrease in activity from the duodenum towards the large bowel, possibly in agreement with the gradients of Alvarez (1928). Finally they pointed out that there is a marked relationship between intestinal movements and the secretion, more especially the mucosal movements.

Excised strips of muscularis mucosae.

Exner (1902) reported local contraction of the muscularis mucosae in situ on mechanical stimulation, and considered that it exhibited only local contraction. Magnus (1904) first tried to register movements of the excised muscularis mucosae of the gut but did not obtain any real contraction either with circular or longitudinal registration. He believed that his results supported Exner's view. However, Gunn and Underhill (1915), using a modification of Magnus's method, found that excised strips of muscularis mucosae exhibited regular rhythmic contractions. Epinephrin increased the tone of the strips. They concluded that this slow rhythmic contraction of the muscularis mucosae served the function of accelerating the local circulation, mentioning the spleen as an analogy. King and Church (1923), using the technique of Gunn and Underhill (1915) also recorded rhythmic movements of the isolated muscularis mucosae of the dog. They studied in detail its reaction to various drugs, Epinephrin, pilocarpin and barium were found to be vigorous stimulants of the muscularis mucosae. Nicotin, pituitrin and strychnin were milder stimulants, while morphine, nitrites and cocain were depressant in their action on the excised muscularis mucosae.

Here again we have suggestive evidence for the existence of a certain relationship between motility and secretion, especially of the mucoid type.

(iv) Vascular action of the sympathetic nervous system on the intestine.

Here as elsewhere in the gastro-intestinal tract the sympathetic nervous system exerts a vasoconstrictor action on the blood vessels. King and Arnold (1922) noted blanching of the mucous membrane of the small intestine after the local application of epinephrin. This was followed by movements of the villi and mucosae. McSwiney (1931) thinks that the blanching of the mucous membrane during stimulation of the sympathetic nerves to the intact intestine may in some degree be due to the compressing of the arteries by contracting muscles. Starling (1906) explained the paralytic secretion resulting from denervation of the gut as due to the dilatation of the local blood vessels caused by section of the splanchnic fibres. The secretion stopped when the blood vessels recovered their tone.

PART II.

METHODS.

Acute Experiments:

The acute experiments on the stomach were performed on dogs and cats. These animals were fed on a diet of raw beef heart, porridge and milk, and the day preceding the experiment were given only milk and water. Thus the stomach was free from food residue and usually in a quiescent state. Anaesthesia was quickly induced with ether, and then a mixture of chloralose and urethane was given into the saphenous vein. (0.5 gram of urethane and 0.05 gram of chloralose per kilo weight, dissolved in normal saline solution, was found to be the best proportion).

In these experiments certain routine procedures were carried out. The vagi were either sectioned in the neck or below the diaphragm, or included in the subdiaphragmatic ligature of the oesophagus. The oesophagus and pylorus were always ligated. In most experiments the adrenal veins were ligated in order to avoid the secretion of epinephrin caused by splanchnic stimulation. A small metal fistula was inserted in the posterior wall of the stomach and brought out in the left flank through a stab wound. Warm saline towels were used to protect the intestine from undue exposure or manipulation.

The greater splanchnic nerves were identified and gently freed and tied. In some experiments the nerves were severed before being placed in shield electrodes, but in many they were left intact, the electrodes being placed peripherally to the ligatures. In the latter case it was noted that the nerves retained their excitability for much longer periods (8 - 10 hours). Specially constructed and designed shield electrodes were used which usually gave very satisfactory results. They consisted of an ivory bar about 6 cm. long and 0.5 cm. wide, which contained two embedded platinum electrode wires, 3 mm. apart. The wires were exposed in a small chamber at one end just large enough to admit the splanchnic nerve easily. The chamber was covered by a T-shaped bar which was operated by a small wire spring. This bar kept the nerve firmly in contact with the exposed portion of the wires and prevented other tissues from coming in contact with the exposed electrodes. By gradually increasing the strength of the current, splanchnic nerves placed in these electrodes retained their excitability for periods of 8-10 hours. Rhythmic stimulation was employed, a metronome being used to break the circuit. The induction coil used was the Baird type, and was calibrated to give the following currents for the corresponding readings on the centimetre scale: 11 cm., 0.20 milliamperes; 10 cm., 0.50 m.a.; 9 cm., 1.0 m.a.; 8 cm., 1.80 m.a.; 7 cm., 2.90 m.a., etc.

A number of experiments were also done using a Palmer induction coil of low frequency, 3-4 shocks per second. The splanchnic nerves were stimulated alternately, five minutes excitation and five minutes rest, thus each nerve was stimulated for fifteen minutes in the hour. The blood pressure was registered as an index of splanchnic stimulation.

Chronic Experiments:

Chronic experiments were performed on cats only. On these animals a gastric fistula was first performed and the cat allowed to recover completely. Then an oesophagotomy was done according to the technique described by Komaroff (1925), i.e., it was performed in two stages. First, the oesophagus was freed and brought out on the neck, the skin being closed underneath it. Care must be taken to sew up the fascial sheath of the oesophagus. After 5-6 days the oesophagus was severed and the ends trimmed down and sewn to the skin edges. In this way skin infection was avoided and possible mediastinal infection, which accounts for many fatalities of the one-stage operation.

Oesophagotamized cats proved extremely easy to keep in good condition. They were fed through the lower oesophageal fistula by means of a rubber tube and funnel. The diet consisted of minced raw beef heart, salt and milk, and in winter, cod liver oil. A certain amount of extra fluid was required to make up the water loss in the saliva. A definite set of experiments were performed on these animals and then the splanchnic nerves or the coeliac ganglia were removed through a bilateral lumbar incision. This technique is very simple in the cat, and is well sustained by the animals. Following post operative recovery, the experimental observations were repeated.

The pancreatic experiments were performed on rabbits and cats, and the details will be given in their respective sections.

Histological sections were taken from the stomach and pancreas in cats under varying experimental conditions. The experimental data of these investigations will also be dealt with later.

Biochemical Methods.

The samples of gastric juice were collected in graduated centrifuge tubes, and in most experiments filtered, and kept in the frigidaire if determinations were not made on them immediately.

The acidity was determined by titration with 0.01 N NaOH, using Topfer's reagent and phenolphthalein as indicators. The alkalinity of mucus samples was determined by back titration with 0.02 N HCl after 0.5 c.c. of the secretion had been boiled with 0.1 N. NaOH. The total chlorides were estimated according to the method of Wilson and Bald (1928). The peptic power of the gastric juice was determined by Christiansen's modification of Mett's method (1912). The results were rendered comparable by the use of a standard of dog's gastric juice kept on ice. The reducing power of the gastric secretions was determined by the method of Komaroff and Webster (1932).

PART III.

EXPERIMENTAL RESULTS.

I. Acute Gastric Experiments:

(i) Stimulation of Freshly Cut Splanchnic Nerves:

Long continued rhythmic stimulation of the splanchnic nerves resulted in the secretion of a thick whitish mucus, which was secreted at a fairly even rate. The reaction was usually alkaline. The ferment power of this secretion after acidification according to Mett's method was low. The total solids, at first high, progressively diminished towards the end of the secretion. The diminution in the concentration of solids was due to a progressive fall of organic material in the secretion. The mineral parts, on the other hand, were practically unchanged during the whole experiment. The reducing power, expressed as per cent. of glucose, according to the method of Komaroff and Webster (1932), was quite high, indicating probably a high content of mucoprotein. It was diminished somewhat towards the end of the experiment. The course of the secretion activated by splanchnic stimulation and beginning during complete rest of the gastric glands is illustrated in Table I.

TABLE I.

TABLE I.

Experiment April 1, 1930.

Dog, 5.4 k. Oesophagus tied in neck; adrenal veins ligated; vagi sectioned in neck; both splanchnic nerves in shield electrodes; fistula in posterior wall of stomach; stomach reaction neutral; stimulation right and left splanchnic nerves alternately 5 minutes stimulation and 5 minutes rest.

Sample No.	Time	Vol.	Alkalinity	Total Cl	Reducing Power	Peptic Power	Total Solids	Org.	Ash	B. P.	Remarks
	Min.	c.c.	Milli equiv.	Mg. %	Mg. % glucose	Mett's Units	Mg. %	Mg.%	Mg.%	Mm.Hg	
1	30	0									Control, no secretion
2	60	4.5	13.6	447	161.5	6.25	2100	1180	920	38-46	Stimulation R. & L. splanchnic coil, 10 cm. - 9 cm.
3	30	0.8								50	No stimulation
4	60	3.5	14.0	479	146	16.0	1860	900	960	50-55	Stim. R. & L. coil, 9 cm. - 8.5 cm.
5	60	3.5	11.6	499	124.5	36.0	1720	760	960	40-45	Stim. R. & L. coil, 8.5 cm.
6	60	3.0	11.2	501	108	16.0	1840	860	980	30-40	" " " 8.25 cm.
7	60	3.0	13.6	462	112	16.0	1640	720	920	30-35	" " " 8.0 cm.
8	30	0.5									No stimulation
9	60	3.0	13.6	510.4	114	16	1500	580	920	26-32	Stim. R. & L. coil, 8 cm.

At end of experiment whole stomach alkaline, surface covered with clear shiny mucus, more in pylorus than in fundus.

Occasionally if a strong acid reaction was present at the onset of the experiment it frequently required several hours of stimulation before the reaction turned alkaline. The peptic power of the acid secretion, which was high, fell precipitately at the change of reaction. This fact is demonstrated in Table No. II., shown on page 70.

Thus when the reaction became alkaline between the sixth and seventh periods, the peptic power of the secretion fell from 550 units to 16 units. The first five samples were a mixture of acid secretion and mucus secretion. The per cent of mucus gradually increased until the whole secretion was mucus.

TABLE II.

TABLE II.

Experiment March 11, 1931.

Dog, 13 K. Pylorus tied; oesophagus and vagi ligated below diaphragm; stomach reaction acid; stomach washed out with tepid water; adrenal veins ligated; both splanchnic nerves in shield electrodes; nerves stimulated alternately 5 minutes stimulation and 5 minutes rest.

Sample No.	Time	Vol.	Acidity milli equiv.		Alkalinity	Total Cl	Peptic Power	Mucus	B. P.	Remarks
			Free	Total						
	Min.	c.c.			milli equi.	Mg.%	Mett's Units	%	Mm.Hg	
1	30	1.3	52.8	58.4			121	7	110-120	R. & L. Spl. coil 11-10 cm. left nerve not responding
2	30	1.4	44.0	52.0			144	7	90-110	Rt. coil 11.5, lt. 9.5 cm. slight response.
3	30	0.1				448				No stimulation
4	60	1.7	28.0	36.8			320	17	90-110	Rt. 11.5-10.5; Lt.9.5-9.0 cm. Vagi cut in neck.
5	60	1.2	12.0	19.2			420	50	90-100	Rt. 10.25 - 10; Lt. 9.0 cm
6	60	3.0	0	8.8		419	550	120	80 -90	Rt. 10-9.25; Lt. 8.75-8.0.
7	60	3.4			8.0	388	16	100	80	Rt. 9.0; Lt. 8.0
8	60	5.0			12.8	411	7.8	100	40-45	No stimulation.

A series of control experiments were performed in which the animal was prepared as usual, only the stimulation was omitted. The animals were placed on the stand and the stomach secretion collected in hourly samples for a period of 6-7 hours.

It was found that during the first hour or two a slight acid secretion took place, probably stimulated by the anaesthetic manipulation, etc. Then this subsided, and a minimal secretion was recorded which after several hours frequently became neutral or alkaline. An example of this type of experiment on a cat is shown in shown in Table III. Analogous results were obtained in dogs.

TABLE III.

Experiment Feb. 15, 1932.

Cat, 4.2 Kilo. Vagi tied below diaphragm around oesophagus.
Pylorus ligated. Stomach reaction acid.

Sample No.	Time	Vol.	Body Temp.	B.P.	Reaction	Remarks
	Min.	c.c.				
1	60	0.7	37.4	140	Acid	Watery
2	60	0.15			Very faintly acid	Mucoid
3	60	0.15	37.0	130	Alkaline	Mucoid
4	60	0.2			"	"
5	60	0.2		135	"	"
6	60	0.3	38.0		"	"
7	60	0.2		135	"	"

Experiments were performed with low frequency as well as high frequency induction currents, since Brown, McSwiney and Wadge (1930) found that the motor responses of splanchnic stimulation depended on the type of current employed. Stimulation at a frequency of 1 - 12 break shocks per second caused a motor response, whereas stimulation with a tetanizing current (50 shocks per second) produced relaxation of the gastric musculature.

In our experiments we used induction shocks obtained from a Palmer coil at the rate of 3 - 4 per second. Regular stimulation with this type of current also produced an alkaline mucus secretion. The details of such an experiment are given in Table IV. In this experiment the peptic power and the Cl content were somewhat higher than in the experiments in which high frequency induction current was used. No particular significance is attached to the fact since the volume of the alkaline secretion was somewhat less than in the experiments quoted above.

TABLE IV.

TABLE IV.

Experiment Nov. 20, 1931.

Cat, 3.1 K. Vagi and oesophagus tied below diaphragm. Pylorus ligated and adrenal veins ligated. Stimulation - Palmer coil - 3-4 shocks per second. 5 minutes stimulation and 5 minutes rest.

No.	Time	Vol.	Reaction	Total Cl	Peptic Power	B.P.	Remarks
	Min.	c.c.		Mg.%	Metts Units		
1	30						No stimulation, no secretion.
2	90	1.0	Alkaline	513	64	90-100	Stim. Rt. coil, 10, Lt. 11.5 cm. for one hour.
3	60	1.0	"		144	80-90	Stim. Lt. nerve only responding coil. 11.25 cm.
4	90	1.0	"	536	120	68-74	Stim. Lt. Nerve coil. 11.0 cm.
5	60	0.5	"		144	66	Stim. Left N. coil 10.5 cm.

It was observed in some experiments that a high initial blood pressure was unfavourable to the secretion of mucus. In these experiments the secretion was very scanty and tenacious, and could be collected only with difficulty. Thus during a rest period the amount of secretion collected was often larger than that obtained during a period of stimulation. This phenomenon is demonstrated in Table V.

In this experiment the action of atropin on the sympathetic mucus secretion is also shown. During the seventh period of stimulation, 10 mg. of atropin were injected intravenously at 30 minute intervals. Stimulation during this period was performed for only 30 minutes and a small secretion resulted.

A good response was obtained during the following period of stimulation, when the animal was still under the effects of the drug. Thus in this and similar experiments we have noted that atropin has no inhibitory action on the sympathetic mucus secretion.

TABLE V.

TABLE V.

Experiment July 15, 1932.

Dog, 7.8 k. Vagi tied around oesophagus below diaphragm. Adrenal veins and pylorus ligated. Stomach empty; reaction faintly acid. Both splanchnic nerves in shield electrodes. Nerves ligated (not sectioned). Nerves stimulated alternately 5 minutes stimulation, 5 minutes rest.

No.	Time	Vol.	Reaction	B.P.	Remarks
	Min.	c.c.			
1	60	0.45	Very faintly acid		Control. No stimulation
2	60	none		110	Stim. nerves both responding well. Rt. & L. coil 11.75 - 11.5. B.P. during stimulation 144.
3	60	0.3	Alkaline mucus	120	Stim. R. & L. coil 11.5 cm. B.P. during stimulation 156-164.
4	30	2.0	" "	128	Rest period. No stimulation
5	120	0.7	" "		Stim. R. & L. coil 11.5-11.0 cm. B.P. during stimulation 160-182.
6	60	0.9	" "	120	Stim. R. & L. coil 11.0 - 10.5 cm. B.P. during stimulation 140-154.
7	90	0.5	" "	100	6 mg. atropine intravenously at beginning. 30 minutes later, 4 mg. atropine intravenously. Stim. 30 minutes only. Right and left coil 10.25 cm.
8	60	1.1	" "	110	Stim. R. & L. coil 10 cm. Pupils widely dilated. B.P. during stimulation 140-148.

Having established the effect of persistent rhythmic stimulation of the splanchnic nerves on the gastric mucosa, our next step was to ascertain the result of repeated injection of epinephrin solution. Essentially the same operative preparation was carried out, except that the splanchnic nerves were not sectioned and the adrenal veins left intact.

Epinephrin solution, 1/5000 or 1/10,000, was injected intravenously at regular intervals, 0.5 c.c. every five minutes. In this way stimulation comparable to the duration of the nervous excitation was obtained. The results of these experiments, as indicated in Table VI, show that the same type of secretion was activated as by nervous stimulation.

TABLE VI.

TABLE VI.

Experiment April 28, 1931.

Cat 3.5 k. Vagi sectioned and oesophagus ligated below diaphragm. Fistula in anterior wall of stomach. Splanchnic nerves and adrenal veins intact. Stomach reaction very faintly acid. At the end of the experiment the stomach was found to be covered with a layer of alkaline mucus more marked in pyloric region.

No.	Time	Vol.	Alkalinity	Total Cl	Peptic Power	Reaction	Remarks
	Min.	c.c.	Milli equiv.	Mg. %	Mett's Units		
1	60	0.6		487	4	Neutral	Control. Watery secretion
2	60	0.6				Alkaline mucus	0.5 c.c. 1/10,000 epinephrin sol. every 5 minutes.
3	60	0.2		541	16	" "	ditto
4	60	0.25				" "	Control. No stimulation.
5	60	0.7					Epinephrine as above
6	60	1.6	12.0	581	35	" "	" "
7	60	2.0	8.0	567	64	" "	" "
8	60	0.2	10.4	553	64	" "	Control. No stimulation
9	60	0.6					Epinephrine as above.
10	60	2.0	10.4	561	99	" "	ditto

In this experiment the peptic power of the secretion, which was low at first, rose considerably towards the end of the experiment. This coincided with a greater flow of the mucus. However, in this case too the peptic power was quite moderate if compared with the peptic power of gastric juice obtained by stimulation of the vagi. It reaches in the latter case the values of 800 to 1,000 Mett's units.

Thus in our hands both the rhythmic stimulation of the major splanchnic nerves and the repeated injection of epinephrin have activated a steady flow of alkaline mucus from the whole stomach of the dog and cat. The only other investigators who employed rhythmic stimulation of the splanchnic nerves, Volborth-Kudriazeff (1927), obtained small amounts of an acid secretion. In none of their experiments, however, did they give titration values of the acidity, or state the character of the secretion obtained. They did not stimulate the nerves for such long periods as is frequently necessary to obtain the characteristic result. Moreover, in their experiments they excluded the pyloric part of the stomach by means of a subserous ligature. This procedure greatly affected their results, as will be pointed out in a later section of this work.

(ii) Action of Cocain on the Stimulation of the Freshly Sectioned Splanchnic Nerves.

That cocain has the property of sensitizing the sympathetic nervous system has been recognized for some time. Thus Frohlich and Loewi (1910), Neubauer,(1913) Santesson (1919), MacGuigan and Atkinson (1921), and Tainter and Chang (1927) all noted that cocain increased the pressor action of epinephrin. Tatum (1920) reported that the previous injection of cocain increased the effect of splanchnic stimulation on the blood pressure.

Rosenblueth and Schlossberg (1931) have studied in detail the action of various reputed sensitizing agents on the sympathetic nervous system. They found that cocain was the only agent which regularly gave an increase in the pressor effect of epinephrin. They injected 3 - 10 mg. per kilo in a 1.0% solution intravenously in cats. They recorded a considerable fall in pulse rate at first, but after ten minutes the pulse became 12% faster. With the injection of smaller doses (2 mg. per kilo) there was a sharp rise in B. P., but with larger doses the B.P. fell, coinciding with the lowest pulse rate. When the heart recovered, the B.P. was usually slightly higher than before the injection.

We therefore considered it possible that cocain might sensitize the secretory fibres of the sympathetic nerves to the gastric glands. Following the technique of Rosenblueth and

Schlossberg, we injected cocain hydrochloride in a 1% solution slowly, judging the dosage from the reaction of the animals. We found that after the various experimental procedures had been carried out somewhat smaller doses had to be used, otherwise the animals succumbed to circulatory or respiratory paralysis.

After a control period of splanchnic stimulation cocain hydrochloride in a 1% solution was slowly injected intravenously, the dosage being determined by the reactions of B.P., pulse and respiration. Then splanchnic stimulation was resumed. Repeated smaller doses of cocain were given at intervals during the periods of stimulation, and in some cases subcutaneous injections were used to supply a slower steady source of cocain.

It was found that cocain in these experiments had a definite effect in augmenting the secretory response of the stomach to rhythmic stimulation of the splanchnic nerves. We also noted that the blood pressure response to splanchnic stimulation was increased. In certain cases it was observed that there was not a greater rise in B. P. than before the cocain injection but that the effect of splanchnic stimulation on the B. P. was better sustained throughout the 5 minute period of excitation. The results of this type of experiment are set forth in Table VII.

TABLE VII .

Experiment May 16, 1932.

Dog 8.1 k. Vagi and oesophagus tied below diaphragm; adrenal veins ligated; fistula in posterior wall brought out through a stab wound in the left flank; both splanchnic nerves placed in shielded electrodes; stomach reaction acid; fundus separated from body and pylorus by a strong ligature.

No.	Hour	Time	. Pylorus and Body			Reaction	B.P.	Remarks
			Vol.	Total Cl	Peptic Power			
		Min.	c.c.	mg.%	Mett's Units		mm. Hg.	
1	1.00-2.00	60	2.0	437	100	Very faintly acid		Control, no stimulation. Brownish mucus and debris.
2	2.00-3.00	60	3.9	519	35.2	alkaline	80	Stim. Rt. & Lt. splanchnics alternately 5 min. stim. & 5 min. rest; clear whitish mucus. Coil, Rt.11.5 cm., Lt. 12 cm.
3	3.00-4.00	60	1.8	528	16	alkaline mucus		Stim. Rt. nerve 12.0 cm., lt. N. 11.0 cm. Both responding well.
4	4.00-5.00	60	1.8		16	"	72	No stimulation
5	5.00-5.30	30	0.6			"		" "
6	5.30-6.30	60	3.0	505	35.2	"	86	Stim. Rt. N. 12.0 cm., Lt. N. 11.0 cm. 5.35, 15 mg. cocain HCl intravenously. B.P. rose to 100 and gradually subsided
7	6.30-7.30	60	3.0	462	16	"	94	Stim. Rt. N. coil 11.5, Lt. N. 10.5. Both nerves responding well.
8	7.30-8.30	60	0.4		8	"		No stim. At end of exp't. fundus covered with thick tenacious mucus, faintly acid. No secretion collected from duodenum during exp't. Pylorus and antrim alkaline, body neutral.

From this experiment it will be noted that during the sixth and seventh hours the injection of cocain intravenously distinctly increased the secretory response of the stomach (pylorus and body) to splanchnic stimulation. When stimulation was discontinued in the eighth period, the secretion practically stopped. Thus we feel justified in extending the sensitizing action of cocain to include the secretory function of the splanchnic nerves as well as the pressor reactions of epinephrin and splanchnic stimulation.

It is interesting to note in this connection that Rosenblueth and Schlossberg (1931) have demonstrated the sensitizing action of cocain on the vascular responses produced by the sympathetic hormone "sympathin".

(iii) Action of Epinephrin on Histamin Gastric Secretion.

The purpose of these experiments was to superimpose on the effect of sympathetic action that of histamin, which activates a secretion from inorganic substances, in order to clarify the rôle of the sympathetic system. Histamin was chosen as a secretagogue since it activates a secretion with characteristic properties, i.e., high acidity and diminishing peptic power and organic substances (Babkin, 1930; Vineberg and Babkin, 1931; Gilman and Cowgill, 1931), and low content of dissolved mucin (Webster, 1931).

Concerning the action of epinephrin on gastric secretion much contradictory evidence has been brought forward. Hess and Humdlach (1920), Rothlin (1920) and Moll and Flint (1928) all claimed that epinephrin had a depressing action on the gastric secretion.

On the other hand, Yukawa (1908), Loeper and Verpy (1917), Lim (1923), Ivy and McIlvain (1923), and Sirotinin (1924) all demonstrated that epinephrin stimulated the gastric glands. Bickel (1925) reported varying results in different types of gastric pouches. Epinephrin had no effect on the excretion from Pavlov or Bickel pouches, but produced a slight augmentation of the secretion in dogs with Heidenhain pouches.

In these experiments the following procedure was adopted. The animals were anaesthetized as previously described, the oesophagus and pylorus were ligated; the vagi were sectioned, while the splanchnic nerves and adrenal veins were left intact. A metal fistula was inserted into the posterior gastric wall and brought out through a stab wound in the left flank. Different results were obtained if epinephrin was injected intravenously during a profuse gastric secretion from the histamin (Table VIII),which averaged 10.5 c.c. in half an hour (samples 4 to 7), or during a slower secretion (TableIX), which measured only 2.8 c.c. in half an hour (samples 5 - 7). In the first case epinephrin had apparently no effect either on the course of histamin secretion or the composition of the juice. This is easily understood from the fact that the secretion activated by adrenalin is itself rather scanty.

TABLE VIII.

Experiment, April 19, 1932.

Cat 3.8 k. Oesophagus tied in neck; vagi cut in neck; splanchnic nerves and adrenal veins intact; fistula in posterior gastric wall.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Mett's Units	Remarks
	Mins	c.c.	mg.%	mg.%	mg.%	% glucose		
1	60	1.0				3.0		Control
2	45	4.1	37	216		1.0	2.5	1 mg. histamin subcutaneously
3	15	4.2	158	346	691	0.8	2.5	2 mg. histamin subcutaneously
4	15	5.0	264	434	682	9.2	2.5	
5	15	5.0	263	447	686	12.4	0.8	0.5 c.c. epinephrin every 5 minutes
6	15	5.8	324	488	672	10.2	2.5	
7	15	5.2	367	507	708	1.4	0.8	" " "
8	15	3.3	370	572		.0	0.8	
9	15	1.2	324	512	745	8.4	2.5	
10	15	1.8						
11	15	1.2	292	451		14.6	2.5	
12	15	1.8						

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In the case of less profuse gastric secretion epinephrin exhibited definite effects on the course of the histamine secretion. These facts are demonstrated in Table IX.

TABLE IX.

Experiment April 12, 1932.

Cat 3.4 k. Oesophagus ligated in neck; pylorus tied; vagus cut in neck; splanchnic nerves and adrenal veins intact; fistula in posterior gastric wall.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Mett's Units	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose		
1	60	1.0					16	1 mg. histamin subcutaneously
2	90	11.0	234	353	326	0	8	2 mg. histamin subcutaneously
3	15	3.0	256	371	794	7.4	8	
4	30	3.0				4.2	8	
5	30	2.5	358	339	709	18.2	8	
6	30	3.6	168	337	562	18.6	64	adrenalin, 0.5 c.c. 1/5000 each 5m.
7	30	1.6	219	409			64	ditto
8	30	1.6	424	528			64	ditto
9	30	0.5					100	

The effects of the injection of epinephrin in these experiments were as follows: increase in the volume of secretion during the first period of injection, a decrease in

the

the free and total acidity, decrease in the concentration of Cl, and an increase in the digestive power of the gastric juice. The latter reached the values which it usually has during splanchnic stimulation or action of epinephrin.

All these phenomena show that adrenalin activated a typical gastric secretion which modified the composition of the histamin gastric juice.

(iv) Effect of Stimulation of the Freshly Cut Splanchnic Nerves on Histamin Gastric Secretion.

It was interesting to compare the effect of epinephrin with the effect of splanchnic stimulation on the histamin secretion. Two such experiments were performed. In one of them (Table X) the secretion due to a larger dose of histamin (4 mg.) injected subcutaneously was extremely profuse (average 33.2 c.c. in 30 minutes at the heighth of the secretory period - see samples 7 to 10). The same experimental procedures were performed and the splanchnic stimulations were started during the course of the histamin secretion. The experimental data of these are set forth in Table X.

In this experiment the right splanchnic nerve was stimulated for 1 hour and 45 minutes, 5 minutes stimulation and 5 minutes rest during the course of the histamin secretion.

Stimulation of the splanchnics did not produce any marked changes in the course or composition of the gastric secretion when it was maximal (samples 8 to 10), but when it began to diminish (samples 11 to 13) two phenomena could be noted: diminution of the free and total acidity of the juice, and a more rapid diminution of the secretion of the fluid parts of the juice as compared with the dissolved mucin (expressed in per cent. of glucose). If we compare separately the relations between the volumes and glucose concentrations of each two samples 10, 11, 12 and 13, and express them in per cent, we find the following figures (the last three samples, Nos. 14, 15 and 16, were excluded since the volume of the secretion was very small):

Samples	Volumes	% Glucose
10 to 11	- 27 p.c.	+ 28 p.c.
11 to 12	- 26 "	- 6
12 to 13	- 30 "	- 19

This indicates that the volume of the secretion diminished from 26 to 30 per cent. in each consecutive sample. The glucose concentration at first rose in sample 11 as compared with sample 10, and then began to fall. The diminution, however, was much less pronounced than that of the fluid. In other words, stimulation of the splanchnic nerves did not greatly affect the course of the secretion of the liquid part of the juice, or its digestive power, but increased the production of dissolved mucin. The increase of the latter was presumably the cause of the lowering of the acidity of the juice.

The increase of glucose concentration could not have been due to the solution of surface mucus as all the samples were filtered immediately on collection. The specimens towards the end (12 to 16) contained jelly-like clumps of clear transparent mucus in increasing amounts. The filtered specimens were clear and homogeneous. The blood pressure varied between 70 and 80 mm. Hg throughout the experiment, and responded to splanchnic stimulation, rising to 100 - 104.

In another experiment of the same type free HCl disappeared entirely in the last two specimens following splanchnic stimulation accompanied by a rise in the amounts of dissolved mucin.

In ordinary experiments with subcutaneous histamin injection, the acidity of the secretion remains high throughout the experiment - Babkin (1930); Vineberg and Babkin (1931).

The conclusions which can be drawn from the experiments with combined activation of the gastric mucous membrane with histamin and epinephrin as well as splanchnic stimulation are as follows: If the secretion of the liquid parts of the juice is moderate then the secretion of alkaline fluid activated by epinephrin or splanchnic stimulation produces obvious changes in the composition of the juice, lowering its acidity and Cl content and slightly raising its digestive power and reducing power. On the other hand, the influence of sympathetic stimulation on the composition of the gastric juice is very slight, or even nil, if the secretion is profuse.

TABLE X.

Experiment Aug. 2, 1932.

Dog 5.9 k. Pylorus ligated; Vagi and oesophagus cut below diaphragm; splanchnic veins tied; splanchnic nerves in shield electrodes; fistula in posterior gastric wall. Suprarenal veins ligated.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Mett's Units	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% glucose		
1	60	7.5	70	168	556	21.2	16	
3	15 15 15	3.5 2.0 0.7	254	374	533	10	35.2	
4	15	2.9	298	438		12.2	16	4 mg. histamin subcutaneously
5	15	5.6	314	448	601	11.4	16	
6	15	13.5	431	524	604	20.6	4	
7	15	17.0	453	562	590	11.4	1	
8	15	20.0	482	569	598	14.0	1	Stim. Rt. splanchnic coil 11.5
9	15	21.0	446	569	610	11.0	1	"
10	15	18.5	454	561	533	7.2	0	" coil 11.25
11	15	13.5	402	534	584	10.0	0	" " 11.0
12	15	10.0	396	494	581	9.4	0	" " 10.75
13	15	7.0	321	478	573	7.6	0	" " 10.5
14	15	4.5	212	314	576	17.0	1	No stimulation
15	15	1.8	248	368		33.6	0	Coil 10.25
16	30	1.0						No stimulation

(v) Stimulation of the Splanchnic Nerves with Stomach Divided in Portions.

In performing post mortem examinations on the stomach of dogs and cats after long continued splanchnic stimulation, it was repeatedly noted that the greatest amount of mucus adhering to the mucous membrane was found in the pylorus and antrum of the stomach. This mucus formed a clear transparent jelly-like layer on the surface of the mucous membrane. The body of the stomach was also covered with mucus, but not so thickly as the pyloric part. The fundus usually contained the least amount of mucus which was often very dry and tenacious.

Again variations in the reaction of the mucous membrane were noted. In the experiments the pylorus and antrum were alkaline in reaction to litmus; the body usually so, and the fundus only occasionally alkaline. The fundus and upper margin of the body of the stomach were frequently faintly or distinctly acid.

These observations led us to believe that the response to sympathetic stimulation varied in quantity and quality from different parts of the stomach. Considered from a histological as well as a physiological point of view, this observation seemed quite logical. It is a well known fact that the quantity of the various cytological elements of the gastric mucosa varies considerably in different regions of the stomach. This is especially true of certain of the mucus-forming cells of the gastric glands.

Two types of mucus-producing cells are found in the gastric mucus membrane. One is the mucus goblet cell of the surface epithelium. These cells produce the visible mucus of the gastric secretion. The second type of mucoid cell is the "Nebenzellen" of Ellenberger (1911) and Zimmermann (1925), "mucoid cells" of Lim (1922), or "Zwischenzellen" of Aschoff (1923). According to Aschoff (1923), the stomach can be divided histologically into three distinct sections: (1) fundus, (2) pylorus proper, and (3) intermediate zone. In the fundus the gastric glands are composed, for the most part, of chief and parietal cells, and only a few "Nebenzellen" can be seen in the "Mündungstück" of the glands. Towards the pylorus the number of "Zwischenzellen" in the peptic glands gradually increases and finally they completely replace the chief cells, forming the "intermediate zone", where instead of three glandular elements, chief, parietal cells and "Zwischenzellen", we find only two - parietal cells and "Zwischenzellen".

In the intermediate zone which, according to Aschoff, in the dog is 1 to 1½ cm. wide, the gastric glands are not a mixture of pylorus and fundus glands, but are a third distinct variety which he calls "Zwischendrüsen". Towards the pyloric end of the stomach this zone ends more or less abruptly and the characteristic pyloric gland makes its appearance. In the true pyloric part of the stomach the glands are composed of the characteristic pyloric gland cells and only an occasional parietal cell.

The "Nebenzellen" are distinguished from the chief cells by the fact that they are stained by dyes which are absorbed by mucus-containing cells such as mucicarmin, muchaematin, etc. The Nebemzellen and the intermediate zone have been identified by Aschoff and co-workers in the human stomach also.

Thus the problem of the origin of the sympathetic mucus secretion is related to the identification of these types of mucus-producing cells in the gastric glands and their distribution in the gastric mucosa.

Experiments were performed in which the stomach was divided into three sections: (1) the true pylorus (4 cm. from the pyloro-duodenal junction in the dog and 2.5 cm. in the cat), (2) the body containing the intermediate zone, and (3) the fundus. The divisions were made in the following manner: strong ligatures were passed around the stomach at the site of the above mentioned divisions. Care was taken to avoid ligating any important blood vessels or nerve trunks at the attachments of the greater and lesser omenta. When the incision was made in the body of the stomach for the insertion of the metal cannula small rubber corks, with a shallow groove running around their circumference, were introduced and the ligatures tied tightly round them. In this way the stomach could be partitioned off exactly without any great interference to the blood or sympathetic nervous supply, and without the possibility of one section communicating with with another. Small metal fistulas were inserted into the posterior wall of the body and fundus pouches and brought out through separate stab wounds in the left flank. A glass cannula was tied in the pylorus by making a small incision in the first part of the duodenum. The mouth of this cannula was brought out through a small stab wound in the right flank. The usual preparation of the splanchnic nerves, etc. was completed, the electrodes adjusted, and the abdominal incision closed. The findings of these three section experiments are given in Table XI.

These experiments furnished data which explain several of the observations made on the whole stomach. The fundus secreted only very scanty amounts of mucus, which was acid throughout the whole experiment. The body of Stomac which at first was acid in reaction towards the end of the experiment produced an alkaline mucus in more abundant quantities. The pylorus, however, secreted a far greater amount than either of the other sections. The secretion was alkaline throughout, fluid at first, later becoming mucoid. When the volumes of the respective pouches are taken into account the results are more striking. The body pouch was twice as large as the fundus, and five times as large as the pylorus section, yet the pylorus secreted twice as much as the body and seven times as much as the fundus pouch during the whole experiment.

TABLE XI.

TABLE XI.

Experiment June 23, 1932.

Cat 4.4k. Oesophagus and Vagi tied below diaphragm. Stomach divided into three sections; pylorus ligated at pyloro-duodenal junction. Stomach reaction faintly acid. Right splanchnic nerve in shield electrodes, stimulated, five minutes stimulation and five minutes rest. Lt. nerve sectioned, not stimulated.

Sample No.	Hour	Time	Fundus of Stomach			Body of Stomach			Pylorus					Remarks
			Vol.	Peptic Power	Reaction	Vol.	Peptic Power	Reaction	Vol.	Total Cl	Reducing Power	Peptic Power	Reaction	
		Min.	c.c.	Mett's Units		c.c.	Mett's Units		c.c.	mg.%	% Glucose	Mett's Units		
1	11.30-12.30	60	0.4	16	acid watery	1.0	64	acid watery					alkaline	Control, no stimulation
2	12.30-1.30	60	0.1		acid	0.4	100	faintly acid	2.0	533	39.5	0	watery	" " "
3	1.30 - 2.30	60	0.1	35.2	acid mucus	0.4	64	acid mucus						Stim. rt. nerve coil 12.0 - 11.75 cm.
4	2.30 - 5.30	180	0.3		faintly acid mucus	1.3	100	alkaline mucus	2.0	542	23.5	0	alkaline mucus	Stim. Rt. nerve coil 11.75 - 9.5 cm.
5	5.30 ¾ 6.30	60	0.1		neutral mucus	0.5	64	alkaline mucus	3.0	536	15.0	0	alkaline mucus	No stimulation
			Vol. of fundus pouch, 10 c.c. Total secretion 1.0 c.c.			Vol. of Body pouch, 24 c.c. Total secretion 3.6 c.c.			Vol. of pyloric pouch, 4.5 c.c. Total secretion, 7.0 c.c.					

These results are interesting when considered in connection with the distribution of the mucoid cells in the mucosa according to Aschoff (1923), for the fundus, which contains relatively few "Nebenzellen", produced very small amounts of faintly acid mucus, whereas the body containing the intermediate zone, with many "Nebenzellendrusen", secreted much larger quantities of alkaline mucus.

These results also explain why in certain experiments on the whole stomach the secretion may remain acid for several hours, and why a greater amount of mucus is observed on the surface of the mucous membrane of the pylorus and body than in the fundus.

The pyloric secretion when acidified showed no peptic power. The total chlorides were slightly lower than in the gastric juice and the reducing power, at first moderately high, declined towards the end of the experiment. The peptic power of the body mucus was slightly higher than that of the fundus secretion, both however being fairly low.

The repeated injection of epinephrin solution gave quite similar results with the divided stomach technique. The results of one of these experiments in a dog are cited in Table XII.

TABLE XII.

TABLE XII.

Experiment June 1, 1932.

Dog 8.4 k. Oesophagus and vagi tied below diaphragm; pylorus ligated; splanchnic nerves sectioned; adrenal veins intact; stomach divided into three sections. Epinephrin injected, 0.5 c.c. 1/5000 every alternate five minutes.

No.	Time	Fundus		Body		Pylorus		Remarks
		Vol.	Reaction	Vol.	Reaction	Vol.	Reaction	
	Min.	c.c.		c.c.		c.c.		
1	60	0.25	Faintly acid mucus	1.3	Acid mucus & juice	2.4	Alkaline mucus	.5 c.c. 1/5000 epinephrin every alternate 5 minutes
2	60			1.6	faintly acid mucus			"
3	60							"
4	60			0.3	"	1.0	"	"
5	60							"
6	60			0.4	neutral mucus	1.0	"	"
7	60							No stimulation
		Vol. fundus pouch 26 c.c. Total sec. 0.25 c.c.		Vol. body pouch 45 c.c. Total sec. 3.6 c.c.		Vol. pylorus pouch 5 c.c. Total sec. 4.4 c.c.		

In this experiment the pylorus produced alkaline mucus, the body faintly acid mucus in smaller quantities, and the fundus practically no secretion at all. The volume of the body was 1½ times as large as the fundus, and 9 times as large as the pyloric part, yet the secretion from the pyloric pouch was 33% greater than that from the body. Thus the findings in the experiments with the repeated injection of epinephrin confirm the results obtained by splanchnic stimulation.

The above reported experiments lend strong support to the supposition that the source of the mucus secreted under sympathetic stimulation may be the "mucoid cells" ("Nebenzellen"; "Zwischenzellen"). The final conclusion, however, can only be obtained after a detailed histological examination of the gastric mucous membrane, which may show whether changes occurred in the mucous cells of surface epithelium or in the "mucoid cells".

If mucus comes from the surface cells, one would expect a more or less even secretion from the various segments of the stomach unless, of course, the innervation of different areas of the surface cells varies in different localities. On the other hand, if the Nebenzellen are the source of this mucus secretion one could expect a greater secretion of mucus from the body than from the fundus, a fact which is demonstrated in the above mentioned experiments.

(vi) Stimulation of Splanchnic Nerves in Animals with a glass window in the stomach

In an effort to observe the mucous membrane of the stomach during long-continued splanchnic stimulation, experiments were performed in which a glass window was sewn into the anterior surface of the stomach. The window consisted of a brass ring, one inch deep, one inch in diameter, one surface being covered with glass. In the edge of the brass part small holes were made to permit the walls of the stomach and skin edges to be closed securely around the window. In this way a considerable area of the gastric mucosa could be viewed without exposure to the air and other abnormal influences.

During rhythmic stimulation of the splanchnic nerves with a rapid induction current no movement of the mucosa could be observed with the naked eye or with a magnifying lens. Occasionally a peristaltic wave passed over the stomach, and if stimulation was begun during the peristaltic action the movements were completely inhibited. These results were in agreement with those of Brown and McSwiney and Wadge (1930) for induction currents of rapid frequency.

During the course of several hours stimulation, the surface of the mucous membrane was observed to become covered with a layer of clear transparent mucus. At first the surface was merely shiny and wet, then the hollows between the folds became filled with mucus and the whole surface became raised, due to the thick layer of jelly-like mucus which gradually and slowly was formed on it. Blanching of the mucosa was observed during stimulation, followed by a reactive hyperaemia when stimulation was stopped. The injection of epinephrin produced the same picture. Thus the formation of mucus on splanchnic stimulation is not associated with any visible movements of the mucosa or underlying musculature.

Discussion.

The data reported in this part of the thesis justify the following conclusions:

Rhythmic stimulation of the freshly cut splanchnic nerves with an induction current, as well as long-continued intravenous injections of small doses of epinephrin, activate a scanty secretion of alkaline mucoid fluid. The alkalinity of this secretion ranges between 8 and 14 milliequivalents. The concentration of Cl is somewhat lower than in the pure gastric juice, being from 388 to 581 mg. per cent. The total Cl content of the gastric juice is equal, according to Rosemann (1907), to 582 to 642 mg. per cent. During prolonged secretion the ash of the alkaline gastric secretion remains very constant, being about 920 mg. per cent. The concentration of the organic part of the juice, on the other hand, gradually diminishes almost to one half (from 1180 to 580 mg. per cent). High blood pressure, presumably due to the vasoconstriction, is not favourable to this secretion, just as it is not favourable for the activity of any of the digestive glands. Sensitization of the animal with cocain increases the secretory effect of the stimulation of splanchnic nerve, emphasizing the sympathetic origin of this secretion.

A combined

A combined activation of the secretory elements of the gastric mucous membrane with histamin and epinephrin or splanchnic stimulation affects the composition of the gastric juice, decreasing slightly its acidity and concentration of Cl, and increasing the peptic power of the juice only if the histamin gastric secretion is not very profuse.

By a method of separation of the stomach in three parts - fundus, body and pylorus - important data were obtained, suggesting that the alkaline sympathetic secretion is due to the activity of special "mucous cells" ("Nebenzellen", "Zwischenzellen") incorporated in the gastric glands, and not to the surface epithelium. This supposition was supported by a direct observation of the gastric mucous membrane through a glass window sewn into the wall of the stomach. Stimulation of the splanchnic nerves did not activate movements of the mucosa, and so could not press out the mucus from its folds.

Summary.

1. Long-continued rhythmic stimulation of the freshly sectioned splanchnic nerves with an induction current in cats and dogs activates a steady secretion of alkaline mucus. High and low frequency currents produce the same effects.

2. The repeated injection of a small dose of epinephrin has the same effect as splanchnic stimulation.

3. The secretion is scanty, mucoid and alkaline. The alkalinity ranges between 8 and 14 milliequivalents. The concentration of Cl is lower than that of gastric juice. The organic material in the secretion gradually diminishes, the ash remaining constant. The reducing power of the mucus is high, indicating a high content of mucoprotein.

4. High blood pressure is not favourable for the mucoid secretion.

5. Atropin in moderate doses does not inhibit the sympathetic mucus secretion.

6. Previous sensitization with cocain produces an increase in the secretory effect of splanchnic stimulation.

7. Stimulation of the splanchnic nerves, or the injection of epinephrin during the course of histamin gastric secretion modifies the composition of the juice, decreasing the acidity and concentration of Cl slightly and increasing the peptic power, only if the secretion is not too profuse.

8. Separation of the stomach into three parts - fundus, body and pylorus - seems to indicate that the alkaline sympathetic mucus secretion is produced by special mucoid cells, "Nebenzellen" or "Zwischenzellen", found in the gastric glands, and not to a secretion of surface mucus.

9. Direct observation of the gastric mucous membrane through

a glass window inserted into the anterior wall of the stomach showed that splanchnic stimulation did not activate any movements of the mucosa or musculature, but inhibited any existing peristaltic movements. The formation of a layer of mucus on the mucous membrane was observed.

II. EXPERIMENTS WITH PARTLY DEGENERATED SPLANCHNIC NERVES.

Previous investigators, Volborth and Kudriazell (1927), have used this technique of stimulation of partly degenerated splanchnic nerves in their experiments on gastric secretion. This method was employed by Kudrewezky (1890) in experiments on pancreatic secretion. Since the pancreatic secretion is easily inhibited by vaso-constriction, Kudrewezky stimulated the splanchnic nerves, which had been cut aseptically four to six days before the experiment. The vaso-constrictor fibres had degenerated during this time, but the secretory fibres still responded to electrical stimulation and activated a secretion of pancreatic juice.

In our experiments the splanchnic nerves were severed in cats and dogs under aseptic conditions below the diaphragm and above the coeliac ganglia, through bilateral lumbar incisions. The animals were allowed to recover and were experimented on at varying intervals after operation. It was noted that the vaso-constrictor fibres of the splanchnic nerves in the cat undergo degeneration more quickly than those of the dog. In many of our experiments performed forty-eight hours after section of the splanchnic nerves vaso-constriction was absent entirely, or a slight effect was noted during the first two or three periods of stimulation. Subsequent stimulation, even with very strong currents, failed to elicit any vaso-constrictor effects. a certain amount of individual variation in this respect was

noted

noted in different animals. Thus in some cats a few slight vaso-constrictor responses were obtained 96 hours after the section of the aplanchnic nerves.

The first interesting observation made on these animals was that after being prepared in the usual manner a spontaneous secretion of alkaline mucus was present. This spontaneous mucus secretion occurred at a regular rate and lasted for several hours. The peptic power of the secretion was low. These facts are demonstrated in Table No. XIII.

TABLE XIII.

Experiment March 17, 1932.

Cat 3.6 k. Splanchnic nerves severed 48 hours previously; Oesophagus tied below diaphragm. Vagi sectioned in the neck; pylorus ligated; stomach empty.

No.	Time	Vol.	Peptic Power	Reaction	B. P.	Remarks
	Min.	c.c.	Mett's Units			
1	60	2.4	8	Alkaline mucus	92	Slightly bile stained, watery.
2	60	1.0	8			
3	60	1.1	16	"	80	
4	60	0.9	35.2	"	74	
5	60	1.0	35.2	"	48	
6	60	1.1	35.2	"	36	

Whether

Whether the spontaneous secretion of alkaline mucus occurring after degenerative section of the splanchnic nerves can be regarded as a "sympathetic paralytic secretion" in the same sense as applied to the salivary and intestinal glands after denervation is difficult to state. Certainly it is a well established fact that the intestinal and salivary glands show a paralytic secretion after section of their respective extrinsic nerves. These facts have been pointed out in the review of the literature. A sort of paralytic secretion in the form of a hypersecretion from the Pavlov pouch in a dog after intrathoracic secretion of vagi was observed by Litthauer (1919-20). However, the section of the sympathetic chain between the eighth and ninth dorsal segments did not produce any marked changes in the secretion from a Pavlov's pouch, according to Ishido (1922). The discrepancy between Ishido's and our results could be due partly to the fact that we noted the secretion from the whole stomach, whereas he collected it from a pouch only. Therefore it is reasonable to assume by analogy that the spontaneous mucus secretion obtained from the stomach of the degeneration section of the splanchnic nerves is due to the same phenomena.

It is also interesting to note that the spontaneous secretion has the same physical characteristics, reaction and peptic power as the mucus obtained by sympathetic stimulation. On the other hand, it must be noted that in these animals the blood pressure was considerably reduced, due to vaso dilatation

of the

of the abdominal regions. (Table XIII). This dilatation of the vessels of the stomach very probably exerted an influence similar to that suggested by Starling (1906) as an explanation of the paralytic secretion of the intestine.

(i) Stimulation of the Partly Degenerated Splanchnic Nerves.

Electrical stimulation of the partly degenerated splanchnic nerves in the cat offered considerable technical difficulties. To begin with, the splanchnic nerves in this animal are rather delicate, and after section frequently become very soft and friable, so that extreme care had to be taken in adjusting the shield electrodes. Furthermore, if there was absolutely no response of the vaso-constriction fibres it was difficult to be certain that the nerves were being stimulated at all times. An added difficulty was the fact that in the majority of these experiments there was of course a certain amount of spontaneous secretion. However, in the majority of our experiments we noted a very moderate but definite increase in the secretion of the rhythmic stimulation of the partly degenerated splanchnic nerves. It was necessary in these experiments to obtain a control period of sufficient length to permit a definite comparison with the periods of stimulation The results shown in Table XIV are representative of this type of experiment.

TABLE XIV.

TABLE XIV.

Experiment March 5, 1932.

Cat 4.2 k. Both splanchnic nerves sectioned 72 hours previously; vagi and oesophagus ligated below diaphragm; pylorus tied; stomach empty; reaction acid.

No.	Time	Vol.	Peptic Power	Reducing Power	Reaction	B. P.	Remarks
	Min.	c.c.	Mett's Units	mg. % glucose		mm.Hg.	
1	60	0.6	320	53.4	acid	98	Mucoid
2	60	1.2	192		"		Spontaneous sec. no stimulation.
3	60	0.7			acid mucus	86	
4	60	0.5	320		Very slightly acid mucus		
5	60	0.8	320	56.0	"	90	Stim. splanchnic nerves, alternately 5 mins. stim., 5 mins. rest. Coil 11 - 11.5 cm.
6	60	0.8	192		"	76	Stim. coil 11.5 - 10 cm.
7	60	1.0			Neutral mucus	70	stim. coil 10 - 9.5 cm.
8	60	0.8	320		"	62	" coil 9.5-9 cm. A very slight rise in B.P. on stim. of rt. spl. nerve with current 9.5-9 cm.

A strong acid reaction was present in the stomach at the beginning of this experiment, and the peptic power of the

mucus

mucus was higher than usually noted. It is interesting to observe that as the current was increased the right splanchnic nerve gave a very slight vasoconstrictor response. The composition of the secretion before and after stimulation was essentially the same.

(ii) Partly Degenerated Splanchnic Nerves and the Action of Epinephrin.

The action of epinephrin on the stomach with partly degenerated splanchnic nerves was also studied. In these experiments the peripheral action of epinephrin was obtained alone as of course all central splanchnic impulses were removed. According to our view of available literature, this type of experiment has not been previously performed. The results of this type of experiment are illustrated in Table XV.

Several interesting facts regarding the action of epinephrin are brought out in the experiment. During the fourth hour of the experiment it will be noted that epinephrin caused a temporary inhibition of the secretion. This was probably due to vascular inhibition (B.P. rose to 210-215), as described by Hess and Hundlach (1920) and Rothlin (1920).

When in the succeeding periods a half hour of rest was coupled with a half hour of stimulation, the secretion increased markedly and remained at a constant level. It is also noteworthy that during the last four hours of the experiment the secretion became slightly acid and that the peptic power of the secretion increased moderately.

TABLE XV.

Experiment April 21, 1932.

Cat 4.1 k. Ether, chloralose and urethane. Splanchnic nerves sectioned 48 hours previously. Fed milk only day before. Oesophagus tied in neck; vagi sectioned in neck; pylorus ligated. Stomach reaction slightly acid.

No.	Time	Vol.	Peptic Power	Reaction	B. P.	Remarks
	Min.	c.c.	Mett's Units		mm.Hg.	
1	60	1.3	400	Neutral	110	Mucoid secretion
2	60	0.8	35.2	Alkaline mucus	80	Control, no stimulation
3	60	0.7	16	"	82	
4	60	0.3		"	80	0.5 c.c. 1/5000 epinephrin every 5 min. B. P. 210.
5	60	0.5	16	"	76	½ hr. rest, ½ hr. stimulation with epinephrin.
6	60	1.0	320	Very faintly acid mucus	68	½ hr. rest, ½ hr. stimulation
7	60	1.5	256	"	72	"
8	60	1.1	256	"	60	"
9	60	1.6	256	"	58	"

(iii)The Effect of Cocain on Stimulation of the Partly Degenerated Splanchnic Nerves.

The action of cocain on the stimulation of partly degenerated splanchnic nerves was also investigated. The literature concerning the action of cocain on the sympathetic nervous system has already been described in the foregoing section of this part of the thesis, as well as the effect of cocain on the stimulation of the freshly cut splanchnic nerve.

The sensitization of cocain was also noted in the stimulation of the partly degenerated nerve. As usual, a long-control period was recorded before the injection of cocain and the start of stimulation. In addition, cocain was injected during the hour preceding the electrical stimulation to observe its effect, if any, on the course of the secretion. The results of this experiment are tabulated in Table XVI .

TABLE XVI.

TABLE XVI.

Experiment April 28, 1932.

Cat 4.1 k. Splanchnic nerves sectioned 72 hours previously. Vagi sectioned in the neck; oesophagus and pylorus ligated; fistula in the posterior wall of the stomach brought out through a stab wound in the left flank. Stomach reaction faintly acid.

No.	Hour	Time	Vol.	Peptic Power	Reaction	B. P.	Remarks
		Min.	c.c.	Mett's Units		mg.Hg.	
1	a.m. 11 - 12	60	0.1		acid	140	Juice, no stim.
2	12 - 1 p.m.	60	0.15		"		" " "
3	p.m.						
3	1 - 3	120	0.5	64	faintly acid	120	Mucoid " "
4	3 - 4	60	0.2		Neutral		mucoid. 4 mg. cocain HCl intravenously
5	4 - 5	60	2.0	64	alkaline mucus	94	Stim. rt. splan. nerve 5 min. stim., 5 min. rest; coil 11.0 cm. 4.15, 1 mg. cocain intrav.
6	5 - 6	60	1.2	35.2	"	90	5 p.m. 1 mg. cocain intrav. 5.30, 1 mg. coc. Stim. rt. spl. nerve, coil 10.75 cm.
7	6 - 7	60	0.25	16	"	78	No stimulation
8	7 - 8	60	0.2		"	74	" "

In this experiment, then, cocain plus splanchnic stimulation produced a very marked increase in the mucus secretion, which diminished rapidly when stimulation was discontinued.

(iv) The action of ergotamin tartrate on the spontaneous mucus secretion.

The effect of ergotamin tartrate on the spontaneous mucus secretion which followed degenerative section of the splanchnic nerves in the cat was investigated. In these experiments it was usually noted that the injection of repeated small doses of ergotamin at first caused a sharp rise in B. P., followed in several minutes by a fall. The subsequent injections produced a decreasing effect on the B.P. until a slight fall in B.P. was noted. An example of these experiments is quoted in Table XVII.

In this experiment it is noted that the spontaneous mucus secretion reached a steady level of 1.2 c.c. per hour. The first injection of ergotamin produced a marked increase in B.P., the second a fall in B.P. The secretion during this hour was distinctly inhibited.

During the next hour repeated injections of small doses of ergotamin were given. The B.P. had reached a lower level, and the injections had only a slight pressor action. Dilatation of the pupil by stimulation of the cervical sympathetic, though not entirely abolished, yet was very slight, indicating that the animal was moderately well under the influence of the drug. During this period also, the secretion was inhibited. Another point of note is the fact that following the injection of ergotamin the mucus secretion which was previously alkaline became strongly acid and the peptic power increased greatly. In the hour following (i.e., No. 8) the secretion returned to its former level although it remained acid and showed a high ferment activity.

In a consideration of the factors responsible for the inhibitory action of ergotamin in this experiment, the rise in blood pressure must be taken into account. We have already noted that a high blood pressure was unfavourable for the production of the mucus secretion. However, it is highly suggestive when ergotamin, which is known to depress sympathetic activity, inhibits the spontaneous mucus secretion even if the blood pressure has returned to its previous level.

TABLE XVII.

TABLE XVII.

Experiment March 24, 1932.

Cat 4.2 K. Splanchnic nerves sectioned 48 hours previously. Vagi cut in the neck. Oesophagus and pylorus ligated; fistula in posterior wall of stomach brought out through stab wound in the left flank. Stomach reaction slightly acid.

No.	Hour	Time Min.	Vol. c.c.	Peptic Power Mett's Units	Reaction	B. P. mm.Hg	Remarks
	a.m.						
1	10.00-11.00	60	1.1	400	acid	106	Watery secretion
2	11.00-12.00	60	0.6	400	"		
3	12.00- 1.00	60	0.7	256	"	100	Mucoid secretion
	p.m.						3.05 - 2.5 mg. ergotamin intrav. B.P. 76-120, gradual fall.
4	1.00 - 2.00	60	1.2	16	Neutral mucus	78	3.20 - 1.5 mg. ergotamin intrav. B.P. gradually fell to 60. artificial respiration. B.P. returned to 110.
5	2.00 - 3.00	60	1.2	8	Alkaline mucus		
6	3.00 - 4.00	60	0.2	256	Neutral mucus	76	4.00 - Pupil dilated on stim. of central end of cervical sympathetic. 1.5 mg. ergotamin intrav. Slight rise in B.P.
7	4.00 - 5.00	60	0.35		Acid mucus	98 - 104	4.08 - 1.25 mg. ergotamin intrav. slight response of pupil to stimulation. 4.16 - " " " 4.29 - 1.25 mg. ergotamin intrav. Very slight response of pupil.
8	5.00 - 6.00	60	1.1	256	Acid mucus	80-84	No ergotamin

DISCUSSION.

The experiments with partly degenerated splanchnic nerves, in which the vaso-motor and secretory fibres to the suprarenal glands were destroyed, yielded important results. First of all must be noted the "paralytic secretion" of mucoid fluid from the stomach after bilateral section of the splanchnic nerves. Although it is very tempting to explain it by the paralytic state of the blood vessels in the gastric mucous membrane, it seems that such a simple explanation cannot cover all the facts observed in these experiments. Thus the stimulation of partly degenerated splanchnics, especially after administration of cocain, increased the secretion. Since the vaso-motor fibres were degenerated stimulation could not increase the vasodilation and diffusion of fluid from the capillaries. Again, in the experiments with ergotamin , which inhibited the spontaneous secretion of mucus, not only when the blood pressure rose, but also when the blood pressure fell, indicated that the vaso-motor mechanism alone cannot be responsible for the "paralytic secretion". Therefore, without denying altogether the participation of vascular phenomena in the mucoid secretion observed by us after the section of splanchnic nerves, we should like to emphasize the possibility of the pressure in the splanchnic nerves of special secretory fibres for mucus-forming glandular elements.

Another interesting fact noted in these experiments was the appearance of an acid secretion with a high digestive power after the injection of adrenalin (Table XV), which might be interpreted as a true secretory effect. However, at the present time we are not justified in drawing such a conclusion.

Summary.

1. Aseptic section of the splanchnic nerves in the cat and dog below the diaphragm produces a spontaneous secretion of mucus similar to the "paralytic secretion" observed in the salivary and intestinal glands after denervation.

2. Electrical stimulation of the partly degenerated splanchnic nerves (24 - 72 hours after section) causes a definite increase in the "paralytic mucus secretion".

3. The repeated injection of epinephrin solution also increases the volume of the spontaneous secretion and its peptic power.

4. Cocain sensitizes the partly degenerated splanchnic nerves also, electrical stimulation producing a marked increase in the volume of the secretion.

5. Ergotamin inhibits the "paralytic secretion".

III. STIMULATION OF THE VAGI.

It has recently been demonstrated by Vineberg (1931) that different types of gastric secretion could be obtained, on vagus stimulation by varying the strength of the induction current used. Thus with weaker currents (secondary coil 16 - 11 cm.) a flow of very faintly acid or faintly alkaline mucus was obtained. This mucus had a high digestive power when acidified according to Mett's method. According to Vineberg, this mucus secretion came chiefly from the body and fundus of the stomach, since when the pylorus and antrum were separated by a sub-mucous ligature from the remainder of the stomach a flow of mucus was obtained from the upper segment of the stomach. Stimulation with stronger currents (secondary coil 11-7 cm.) however, activated a flow of gastric juice with only a small mucus content. This secretion had all the properties of typical gastric secretion, high acidity, very high digestive powers, and normal chlorine content.

In one experiment a glass window was sewn into the anterior surface of the stomach. On subsequent stimulation of the vagi, a flow of gastric juice was observed as well as definite movements of the gastric mucous membrane.

Vineberg suggests the possibility that the vagus contains different fibres innervating different cytological elements of the gastric mucosa and that these fibres may be activated by induction currents of different strengths.

It was considered necessary to repeat this work on the cat for several reasons. Vineberg's experiments were all performed on dogs, and as in many of our experiments cats were used, it was advisable to confirm these results in this animal. Furthermore, the physical characteristics and the rate of secretion in the vagus experiments with stimulation, and in our experiments with splanchnic stimulation had several similarities, necessitating a further analysis.

In addition, several investigators - Kuré et al. (1931 - a), Kiss (1931) - have reported the presence of sympathetic fibres in the vagus, and there was therefore a possibility that the mucus secretion resulting from weak vagal stimulation could be due to stimulation of sympathetic fibres.

(i) Stimulation of the Vagi in the Cat.

The same technique of anaesthesia and operation as those used by Vineberg in similar experiments on dogs were employed in our experiments. A calibrated induction coil with a metronome interrupter was used to give rhythmic stimulation. The vagi were stimulated in the neck, shielded electrodes being used. The nerves were usually stimulated for five-minute periods alternately, five minutes rest intervening between each period of excitation. The results of weak vagus stimulation on the stomach of the cat are shown in Table XVIII. The secondary coil was started at 12 cm. and gradually increased.

TABLE XVIII.

TABLE XVIII.

Experiment April 27, 1932.

Cat 3.8 k. Oesophagus ligated below diaphragm. Pylorus tied; vagi sectioned high up in neck; fistula in posterior wall of stomach brought out through stab wound in left flank; stomach reaction slightly acid.

Sample No.	Time	Vol.	Free HCl	Total HCl	Peptic Power	Type of Secretion	B. P.	Remarks
	Min.	c.c.	gm.%	gm. %	Mett's Units		mm.Hg	
1	60	0.8			266	acid, watery	140	Control; no stimulation
2	60	0.7			96	"		
3	60	0.8			144	"		Stim. vagi alternately 5 min. stim. 5 min. rest. coil 12 cm.
4	60	0.7			266	acid, mucoid	136	Stim. coil 11.75 cm.
5	60	1.0	0.00	0.010	522	mucus		" coil " "
6	60	1.8	0.00	0.021	600	"	128	" " 11.75-11.5 cm.
7	60	1.8	0.00	0.032	522	"		" 11.5 cm.
8	30	0.2						No stimulation
9	60	1.7	0.010	0.034	600	"	110	" 11.0 cm.
10	60	1.8	0.015	0.036				" 11.0 cm.

It will be seen from this table that weak stimulation of the vagi in the cat produced a flow of musus having a low acidity and high digestive power, similar to that obtained in

analogous

analogous experiments on the dog. Accordingly, the vagus in the cat must contain the same type of fibres which respond to weak electrical stimulation.

The effect of strong vagus stimulation in the cat is shown in Table XIX. This experiment gives the typical picture of strong vagus stimulation after a long latent period of weaker stimulation (period No. 2). The properties of the secretion are those of the normal gastric juice - high acidity and peptic power, and normal chlorine content. The reducing power of the secretion was similar to that found in the gastric juice obtained by sham feeding or pilocarpin.

TABLE XIX.

TABLE XIX.

Experiment Feb. 19, 1932.

Cat 4.1 k. Oesophagus tied below diaphragm; pylorus ligated; vagi stimulated in the neck; stomach reaction acid.

Sample No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	B. P.	Type of Secretion	Stimulation
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose	Mett's Units			
1	30	0.1					202.5	140	acid, watery	No stimulation
2	240	0.6						130	acid watery	Stim. Rt. Vagus, coil 12-11.5 cm.
3	60	1.5	0.124	0.355			400	122	Mucus	Rt. vagus 11.5 - 10.5 cm.
4	60	2.0	0.190	0.399	613		516	126	Juice small am't. mucous	Rt. vagus 10.5 - 9.75 cm.
5	45	3.2	0.277	0.479	652	23	672	124	Juice	" " 9.75-8.5 cm.
6	45	3.2	0.329	0.482	641	25	785	112	"	" " 8.5- 8.0 cm.
7	60	2.6	0.348	0.495		35.6	785	100	"	" " 8.0 - 7.5 cm.

Having verified these experiments on the stomach of the cat, our next procedure was to investigate in more detail the origin of the mucus secretion activated by weak vagus stimulation. In other words, was it activated by stimulation of true vagus fibres or of sympathetic fibres contained in the vagus? To determine this point, we used two drugs in the experiments - atropin and ergotamin. After obtaining a uniform mucus secretion by weak vagus stimulation, atropin was given intravenously and the stimulation continued while the animal was deeply under the influence of the drug. Table XX. presents the results of this type of experiment. Here, it will be noted, stimulation of the vagi after a latent period of four hours, produced a secretion of faintly acid mucus. When this secretion was definitely established, 6 mg. of atropin were given intravenously, 4 mg. at the beginning of the period and 2 mg. 30 minutes later. Stimulation was carried on as before - a new place in the nerve was chosen and the current slightly increased. The pupil was widely dilated and stimulation produced no inhibition of the heart or any effect on blood pressure.

In the next hourly period, 6 mg. of atropin were given intravenously and the same technique of stimulation carried on.

During these two periods (8 and 9), and in the following hour, when no more atropin was given, it will be noted that there was a definite and significant inhibition of the secretion.

This

This would seem to indicate that paralysis of the endings of the vagus fibres had the result of inhibiting the secretion. The inhibition was not complete, however, and much of the secretion collected after the injection of atropin could be partly due to the slow expulsion of mucus already found during the previous periods of stimulation. This phenomenon has been noted repeatedly in connection with the secretion of a thick tenacious mucus.

Another explanation for the collection of small amounts of mucus from the stomach after after the atropinization of the animal could be an incomplete paralysis of the motor vagus fibres of the stomach. Bayliss and Starling (1899) noted a similar condition in the small intestine. After the effect of the vagus on the heart was abolished by atropin, stimulation of the nerve activated powerful concentrations in the intestine. The acidity, peptic activity and reducing power of the secretion were not affected by atropin.

TABLE XX.

TABLE XX.

Experiment March 2, 1932.

Cat 4.4 k. Oesophagus ligated below diaphragm; pylorus tied at pyloro-duodenal junction; fistula in posterior stomach wall empty; reaction acid. Vagi stimulated alternately 5 minutes stimulation and 5 minutes rest.

No.	Hour	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	Type of Secretion	B. P.	Remarks
		Min.	c.c.	mg.%	mg.%	mg.%	mg.% Glucose	Mett's Units		mm.Hg	
1	12.30-1.30	60	1.0					400	acid, watery	160	Control, no stimulation.
2	1.30 - 2.30	60	0.2						"		Stim. Rt. & Lt. vagi, coil 12 cm.
3	2.30 - 3.30	60	0.7					99.5	acid, mucoid	156	Stim. Rt. & Lt. vagi coil 11.5 cm.
4	3.30 - 4.30	60	0.3								" " " 11.25 cm.
5	4.30 - 5.30	60	0.4					256			" " " 11.25 cm.
6	5.30 - 6.30	60	2.8	0.00	0.012	0.457	75.6	256	acid mucus	146	" Rt. 11.0, Lt. 10.75 cm.
7	6.30 - 7.30	60	3.2	0.00	0.013	0.516	88.8	784	"		" " 10.75, Lt.10.5
8	7.30 - 8.30	60	1.5					576	"	140	7.30, 4mg. atrop. i.v. 8.00, 2mg. " " Stim. fresh place of nerve, Rt. 10.5, Lt. 10.25. No effect on B.P.
9	8.30 - 9.30	60	1.75	0.00	0.034	0.539	58.4	576	"		8.35, 3 mg. atropin intrav.; 9.10, 3 mg. atrop. i.v. Stim. no effect on B.P.
10	9.30 -10.30	60	1.4					656	"	124	Stim. Rt. & Lt. vagi coil 10 cm. No effect on B.P.

The action of ergotamin on the mucus secretion activated by weak vagus stimulation also gave interesting results. The same preparatory technique was carried out in these experiments as in the foregoing ones. These results of these experiments are indicated in Table XXI.

TABLE XXI.

Experiment March 10, 1932.

Cat 3.2 k. Ether, chloralose and urethane; fed milk day before; some debris in pylorus; stomach washed with tepid water; oesophagus tied below diaphragm; pylorus ligated at pyloro-duodenal junction; fistula in posterior wall of stomach; vagi stimulated in neck; stimulation of vagi alternately five minutes stimulation and five minutes rest.

No.	Hour	Time	Vol.	Peptic Power	B. P.	Type of Secretion	Remarks
		Min.	c.c.	Mett's Units	mg.Hg		
1	11-12.30	90	0		140		Control. No secretion.
2	1 - 3	120	0.7	576		Acid mucus	Stim. Rt. & Lt. vagi coil 11.0-10.75 cm.
3	3 - 4	60	1.0	576		"	" " 10.5 cm.
4	4 - 5	60	2.4	576	126	"	" " 10.5-10.25 cm.
5	5 - 6	60	3.2	784	124	"	5.00, 5 mg. ergotamine intrav. 5.15, 3 mg. ergotamin intrav. Stim. as before. Nerves still gave inhibition of heart.
6	6 - 7	60	3.5	576			6.00 stim. of peripheral cervical sympathetic. No dilatation of pupil Stim. Rt. & Lt. 10 - 9.75 cm.

In this experiment, after the usual latent period vagus stimulation activated a secretion of mucus. At the beginning of the fifth hourly period, 5 mg. of ergotamin were given intravenously. At first the B. P. rose from 120 to 160, and then gradually fell back to previous level. Fifteen minutes later 3.5 mg. were again given intravenously, and the blood pressure fell slightly, to 110. Stimulation of the vagi was carried on, the nerves producing the characteristic inhibition of the heart. The volume of the secretion during this and the following hour increased slightly. At 6 p.m. stimulation of the peripheral end of the cervical sympathetic caused no dilatation of the pupil, indicating that the animal was well under the influence of the drug. There was no change in the peptic power of secretion after the injection of ergotamin. The slight increase in the secretion after ergotamin was probably due to a certain amount of vaso dilatation caused by paralysis of the sympathetic vaso-constrictor fibres.

These experiments then give significant information concerning the nervous fibres involved in the production of the mucus secretion following weak stimulation of the vagus, and corroborate the atropin experiments. Consequently, from these experiments with atropin and ergotamin it must be concluded that weak stimulation of the vagi in the cat or dog activates a mucus secretion through stimulation of certain vagus fibres and not of sympathetic fibres contained in the vagus.

Summary.

1. Rhythmic stimulation of the vagi in the cat with a weak induction current produces a flow of faintly acid mucus having a high digestive power.

2. Strong stimulation activates a secretion of gastric juice with high acidity and digestive and reducing power, and normal Cl content. These results are similar to those obtained in dogs.

3. Atropin inhibits the mucus secretion activated by weak stimulation of the vagi.

4. Ergotamin has no effect on the mucus secretion resulting from weak stimulation of the vagi.

5. It is concluded that weak stimulation of the vagi produces a mucus secretion having characteristic properties by exciting vagus fibres which activate certain elements in the gastric mucosa, and not by stimulation of sympathetic fibres contained in the vagi.

IV. CHRONIC EXPERIMENTS ON CATS WITH GASTRIC FISTULAE AND OESOPHAGOTOMIES.

As previously stated, the investigation of the rôle of the sympathetic nervous system in the normal processes of digestion was studied in animals with gastric fistulae and oesophagotomies. These experiments were performed on cats and as far as we know they the first operations of this type reported on these animals. They were found to be very satisfactory animals for chronic experiments of this nature, quickly becoming accustomed to the gastric fistula and oesophagotomy. Fed on a diet of raw minced beef heart, milk, salt, and cod liver oil, they retained their weight and vitality very well.

A routine of experimental observations was carried out and then the splanchnic nerves were sectioned below the diaphragm, through bilateral lumbar incisions. The animals made a good recovery, the wounds healed rapidly, and several days afterwards they were lively and hungry. The experiment routine was then repeated.

Observations included experiments with sham feeding (15 minutes); histamin and sham feeding; histamin and epinephrin; and pilocarpin and sham feeding. Using these diverse stimuli, it was hoped that some information regarding the rôle of the sympathetic nervous system in secretory processes of the gastric glands would be obtained.

The

The relationship of the peptic power and content of dissolved mucin in the juice activated by sham feeding before and after section of the splanchnic nerves in cat No. 1 are shown in Figures I and II.

Fig. I. represents the comparison of the total output (concentration multiplied by volume of the secretion) of pepsin in ten-minute periods. Comparison is made between the average values of all experiments before operation, the first post operative experiment (4 days) and the average of all subsequent post operative experiments (1 month to 2½ months after operation). The average volumes for the corresponding ten-minute periods in these three sets of experiments are also shown.

It will be noted that in the case of the average pre-operative experiments the peptic power rose sharply until the maximum figure was reached in the fourth period; it then declined steadily to the end of the experiment. In the first post operative experiment the total output of pepsin was much reduced. From a comparison of the volume curves it will be seen that this was due partly to a smaller volume of secretion. Sham feeding was carried on for the usual length of time (15 minutes), the cat being hungry, but as the experiment was done on the fourth day after operation, the stomach possibly had not recovered from operative disturbances. Accordingly, too much emphasis cannot be placed on the result. The curve of the total output pepsin for the subsequent post operative experiments showed an interesting fact. It will be noted that the maximum output of pepsin was reached in the first period after sham feeding; it declined slowly until the third period and then rapidly to the end of the experiment. The average volume curve of this set of experiments presented no essential differences from that of the preoperative experiments. Accordingly it must be concluded that the peptic content of the "nervous" phase of gastric secretion reaches a maximum much sooner after section of the splanchnic nerves than it does in the normally innervated stomach. It also declines more quickly than in normal conditions.

Pavlov and Schumow-Simanowski (1895) carried out the same technique on dogs, and reported that section of the splanchnics had no effect on the quantity of gastric secretion. They noted, however, that the content of total solids did not rise as sharply as in the normal animal.

Trinchera and Rindone (1930) found that section of both splanchnic nerves in dogs caused an increase in the output of pepsin. Pieri and Tonferna, on the other hand, observed that blocking of the 6th, 7th and 8th dorsal root segment in humans produced a diminution in the peptic content of the gastric secretion.

In our experiments a decrease in total output of pepsin was noted only in the first experiment four days after section

of

of the splanchnic nerves, but as this result was associated with a decreased volume of secretion, no particular stress can be laid on it. In the subsequent experiments the main difference was found to be in the distribution of the output of pepsin during the course of the secretion. Instead of rising gradually to a maximum output in the fourth ten-minute period, as in the normal animal, after section of the splanchnic nerves the maximum output occurred in the first period, declined gradually during the next two periods and then fell sharply to the end of the experiment.

Fig. No. II shows a comparison of the total output of dissolved mucin in ten-minute periods (expressed as % glucose). In the preoperative experiments the highest value was obtained during the first ten-minute period and then a gradual decline towards the end of the experiment occurred. In the first experiment after section of the splanchnic nerves, while the initial value was practically the same it decreased abruptly, rising slightly in the last period. However, the same objections apply to this curve, i.e., the volume of the secretion was lower.

The average of the succeeding post operative experiments showed distinct changes; the initial value was much higher than in the preoperative experiments but it declined more rapidly. Thus practically the same relationships are found here as in the output of pepsin before and after section of the splanchnic nerves. Webster (1931) has reported a certain parallelism between the output of pepsin dissolved mucin and total nitrogen in the gastric juice of the dog in response to various stimuli. This parallelism has also been noted in our experiments before and after section of the splanchnic nerves.

Regarding the effect of section of the splanchnic nerves on gastric acidity, divergent opinions have been reported. Gaultier (1907), Foa (1927), Moll and Flint (1928), Trinchera and Rindone (1930), all reported that bilateral splanchnicotomy produced an increase in the free and total HCl of the gastric juice. Hess and Faltitschek (1924 and 1925) found that paravertebral block of the 7th and 8th dorsal segments in humans brought about an increase in free HCl in the gastric secretion.

Pieri and Tanferna (1930), on the other hand, repeating this work, reported that the paravertebral block of the 6th, 7th and 8th dorsal segments in humans caused a decrease in free and total acidity in a large percentage of cases (72-80%). However, these experiments on the human are open to several objections. Their results were possibly influenced by increased motility of the stomach induced by temporary paralysis of the sympathetic fibres. Another objection is the increased vascularity produced immediately after the removal of the splanchnic impulses to the stomach.

In our experiments we noted a slight diminution in the free and total acidity of the gastric juice after bilateral splanchnicotomy in the cat. The decline in all post operative experiments was: free HCl, average before operation 375 mg. %; after section of splanchnics, 335 mg. %, a decrease of 10.60%, and total HCl, average before operation 513 mg. %; after operation, 452 mg. %, a decrease of 11.9%. There was no significant change in the concentration of Cl in the gastric juice after section of the splanchnic nerves: average before operation, 593 mg. %; average after operation, 581 mg. %, a decrease of 2.0%.

Observations were also made on Cat No. 2 for evidence of the spontaneous mucus secretion noted in acute experiments on cats after section of the splanchnic nerves. It was found that when the animal was placed in the stand in a fasting condition and the fistula drained there was a small flow of mucoid secretion which occurred at an even rate for five to seven hours. This secretion was thick and slightly opaque. There was no free acidity and the peptic and reducing powers of the secretion were quite high. These facts are illustrated in Table XXII from an experiment on cat No. 2 four days after section of the splanchnic nerves.

TABLE XXII

TABLE XXII.

Experiment May 10, 1932.

Cat No. 2. 72 hours after section of both splanchnic nerves.

No.	Time	Vol.	Free HCl	Total HCl	Reducing Power	Peptic Power	Remarks
	Min.	c.c.	mg.%	mg.%	% Glucose	Mett's Units	
1	60	0.6				784	Mucoid secretion
2	60	0.9	0.00	88			" "
3	60	0.7			95	784	" "
4	60	0.9	0.00	89			" "
5	60	0.8				576	" "

This secretion, which was of a slightly acid reaction, had a much higher peptic content than that obtained in the acute experiments, but all the other characteristics were similar.

(i) Action of Epinephrin on Histamin Secretion.

The action of epinephrin on histamin gastric secretion in acute experiments has already been described in a preceding section of this part of the thesis.

This type of experiment was done also on a cat with gastric fistula and oesophagotomy. Epinephrin was injected intramuscularly and intravenously in dilute solution. Here too, as in the acute experiments, the result seemed to depend on the rate of histamin secretion. Modifications of the course of the histamin secretion were noted only when its rate was slower. The positive effects noted were slight increase in the peptic power and slight to marked increase in the reducing power. An inhibition action on the concentration of free HCl was present in several experiments. Table XXIII. demonstrates these effects.

Here it will be noted that the free acidity diminished 10.4% in the first period and 16.6% in the second period after the intravenous injection of epinephrin. The total acidity remained unchanged. There was a slight increase in the reducing power and the peptic power in the first period after the epinephrin was injected.

TABLE XXIII.

TABLE XXIII.

Experiment March 8, 1932.

Cat No. 2. Histamin and Epinephrin .

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose	Mett's Units	
1	20	0.1						Control
2								½ mg. histamin injected subcutaneously.
2	15	2.3	212	358		48.4	100	
3	15	4.0	416	494	590	20.0	16	
4	10	2.5	432	518		17.2	8	0.5 c.c. 1/10,000 epinephrin intravenously.
5	10	2.6	387	511		20.8	16	Pulse accelerated
6	15	2.7	340	523		10.0	8	
7	20	1.2	416	520		10.6	8	
8	15	1.0						

These results are comparable, on the whole, to those obtained after the intravenous injection of epinephrin in the acute experiments, in which the gastric secretion was stimulated by histamin.

(ii) Histamin and Sham Feeding.

Combined experiments with histamin and sham feeding, and pilocarpin and sham feeding, were performed as part of the routine experiments done before section of the splanchnic nerves.

Histamin followed by sham feeding gave in the cat a typical picture resulting from the combination of these stimuli. Histamin given subcutaneously produced a copious secretion of highly acid juice with a low ferment and reducing power. Towards the end of this secretion the animal was sham fed for fifteen minutes. The free and total acidity fell slightly and then rose to their former levels. The ferment and reducing power rose sharply and maintained higher levels. These facts are illustrated in Table XXIV.

TABLE XXIV.

TABLE XXIV.

Experiment Feb. 25, 1932.

Cat No. 2. Splanchnic Nerves Intact. Histamin and Sham Feeding.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose	Mett's Units	
1	20	0.5					400	Control
								½ mg. histamin subcutaneously
2	15	2.8	307	466		12.2	256	
3	15	5.0	400	523	601	6.6	16	
4	15	4.3	389	511	613	10.0	8	
5	15	2.6	394	534	587	1.8	4	
6	15	1.1						
7	15	0.6					16	
								Sham feeding 15 minutes
8	15	4.5	263	435	581	33.2	400	
9	15	6.4	380	540	604	12.8	256	
10	15	3.5	460	609	627	25.6	256	

After section of the splanchnic nerves repetition of the experiment gave exactly the same picture. This would seem to indicate that the centres of the sympathetic system have no essential part in the production of the gastric responses under these conditions (Table XXV).

This result is quite contradictory to the view expressed by Bickel (1925), who claimed that the sympathetic system played the major rôle in the control of the excretion of organic material and enzymes.

If this supposition were correct, then sham feeding after histamin should not produce as great an increase in the peptic power of the gastric secretion after section of splanchnic nerves as it did when these nerves were intact.

TABLE XXV.

Experiment May 12, 1932.

Cat No. 2. Splanchnic nerve sectioned May 6, 1932. Histamin and sham feeding.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose	Mett's Units	
1	30	0.4					400	Control
								½ mg. histamin subcutaneously
2	15	1.7				35.6	256	
3	15	4.0	355	465	590	12.8	8	
4	10	4.1	397	511	598	6.4	2.5	
5	15	4.0	415	512	601	4.0	0.8	
6	15	3.0	421	514	604	6.4	0.0	
7	15	1.3						
								Sham feeding 15 minutes
8	10	4.2	427	531	627	27.8	310	
9	10	5.1	416	540	627	19.2	256	
10	10	513	446	565	635	35.2	210	

(iii) Pilocarpin and Sham Feeding.

Pilocarpin injected subcutaneously in the cat produced somewhat different results from those obtained in dogs. In dogs subcutaneous injection of pilocarpin results in a thick mucoid secretion with a very high enzyme content - Babkin (1930), Vineberg and Babkin (1931). In the cat, however, the result was frequently quite different. The secretion was usually rather scanty and mucoid, but the ferment power often fell progressively and reached low levels. The reducing power of the secretion tended to decline, also the free and total acidity and the total Cl content was lower than that of histamin or sham feeding juice. These facts are demonstrated in Table XXVI. However, when sham feeding was started all values rose to a higher level and remained there.

TABLE XXVI.

Experiment Feb. 11, 1932.

Cat No. 2. Splanchnic Nerves Intact. Pilocarpin.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose	Mett's Units	
1	30	0.4					784	Control
2	30	2.0	162	294		60.0	576	½ pilocarpin subcutaneously Salivation marked
3	30	3.0	202	384	488	12.0	100	" "
4	15	0.5					144	" "
5	10	4.0	361	453	618	28.0	256	Sham feeding 15 minutes
6	10	4.0	351	492	613	25.0	256	
8	10	3.8	358	481	598	32.8	144	

After section of the splanchnic nerves there were no notable changes in the response to pilocarpin and sham feeding, as in shown in Table XXVII.

TABLE XXVII.

Experiment May 16, 1932.

Cat No. 2. Splanchnic nerves sectioned May 6th. Pilocarpin and sham feeding.

No.	Time	Vol.	Free HCl	Total HCl	Total Cl	Reducing Power	Peptic Power	Remarks
	Min.	c.c.	mg.%	mg.%	mg.%	% Glucose	Mett's Units	
1	60	0.6					256	Control
								1 mg. pilocarpin subcutaneously
2	30	1.8				34.4	280	copious salivation
3	30	3.4	372	469	569	20.8	16	" "
4	30	1.3				10.6		" "
5	30	0.6					2.5	Salivation less marked
								Sham feeding 15 minutes animal hungry
6	15	4.5	372	478	658	39.4	256	
7	15	4.0	368	494	647	24.6	310	
8	15	3.0	365	508		20.4	256	

DISCUSSION.

From a consideration of the data presented in this section of the experimental work, it is rather difficult to draw any very definite conclusions regarding the rôle of the sympathetic nervous system in the first or nervous reflex phase of gastric secretion. It would seem that this phase is mediated almost exclusively through the parasympathetic nervous system. Thus Farrell (1928) questions the statement of Volborth and Kudriazeff that the sympathetic nerves are secretory nerves of the gastric glands. Farrell found that after section of the vagi above the diaphragm in dogs sham feeding had no effect. He reasoned that if the splanchnic nerves sent secretory fibres to the gastric glands some effect would result on sham feeding.

However, from our experiments we conclude that removal of the central sympathetic impulses affects the distribution of the total output of enzymes and dissolved mucin, allowing them to reach higher values earlier in the course of the nervous secretion.

The acidity during the nervous phase also shows a slight decline after section of the splanchnic nerves. The Cl content remains unchanged.

SUMMARY

1. Section of the splanchnic nerves in the cat produces certain definite effects on the course of the gastric secretion in response to mucus stimuli under normal conditions.

2. The peptic and reducing power of the juice activated by sham feeding reach their maximum level almost immediately and then decline more or less rapidly to the end of the secretory period.

3. The action of epinephrin on the course of the histamin gastric secretion exhibits in general in chronic experiments the same pictures as in acute experiments (e.g., decrease in acidity, Cl content, and slight rise in peptic power only if the histamin secretion is not too copious).

4. Sham feeding superimposed towards the end of the histamin gastric secretion produces an immediate rise in ferment power after section of the splanchnic nerves equal to that observed in the normal animal.

5. Pilocarpin injected subcutaneously in the cat activates a rather scanty mucoid secretion with diminishing quantity of ferments and reducing power and total chloride content. These constituents are all increased by sham feeding.

6. No change is observed in the response to pilocarpin and sham feeding after bilateral splanchnicotomy.

V. THE EFFECT OF HYPO- AND HYPERGLYCAEMIA ON THE PANCREATIC SECRETION IN THE RABBIT WITH REFERENCE TO THE ROLE PLAYED BY THE SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEMS.

Another approach to the understanding of the influence of the sympathetic nervous system on the digestive glands was the study of the comparative effect of the para- and sympathetic nerves on the pancreatic secretion during hyper- and hypoglycaemia. La Barre and Destrée (1928, 1929), La Barre (1928, 1930) and Destrée (1930) in a series of publications have demonstrated that the hyperglycaemia produced by the intravenous injection of glucose solution increased the pancreatic secretion activated by the continuous injection of secretin. On the other hand, the hypoglycaemic state of the blood induced by insulin or deca-methylin di-guanidine partially or even completely inhibited the flow of pancreatic juice stimulated by secretin. These authors demonstrated that the effect of hyper- and hypoglycaemia in their experiments was due to stimulation of certain centres in the central nervous system which was transmitted to the pancreatic gland via the vagi. In the majority of their experiments the isolated head technique of Heymans was employed. Two or three dogs were used, A, B and C. In some experiments Dog A was connected to the head of Dog B by a carotid to carotid and jugular to jugular anastomosis. The head of B was connected to its body only by the vagi. The pancreatic duct of B was cannulated and it received continuous injection of secretin. Now if Dog A was given insulin and hypoglycaemia developed, the pancreatic secretion of B was inhibited. This did not occur if the vagi were cut or the basal ganglia destroyed.

Removal of the hemispheres had no effect. On the other hand, if the blood of A was made hyperglycaemic the pancreatic secretion of B was stimulated. Section of the vagi or atropin also abolished this stimulating action of glucose. These authors have also shown that hypoglycaemia inhibits the output of insulin, whereas hyperglycaemia stimulates insulin formation (Zunz and La Barre, 1927 a, 1928 a).

The technique employed by these investigators had certain disadvantages. They used continuous injection of secretin, "Bayliss and Starling" and "purified", to activate a continuous pancreatic secretion. It has been repeatedly demonstrated that most preparations of secretin unless highly purified produce a marked lowering of the blood sugar (Penau and Simonet, 1925; Zunz and La Barre, 1928 b; Still, 1930; and La Barre and Still, 1930). Furthermore the concentration of enzymes in the juice activated in this manner gradually diminishes (de Zilwa, 1904; Ishikawa, 1930). In many of their experiments there are no indications that the bile duct and pylorus were ligated, both procedures being necessary for an exact study of the course of the pancreatic secretion. The experiments of La Barre and Destrée do not give any definite information regarding the relative changes in the rate of secretion of the fluid and organic parts of the juice during hypo- and hyperglycaemia. No attempt was made in their experiments to determine the rôle played by the sympathetic nervous system in the reaction of the pancreatic gland to hyper- and hypoglycaemia.

Gayet and Guillaumie (1930) repeated the experiments of La Barre and Destrée with negative results. They claimed that the intravenous injection of secretin preparations (Bayliss and Starling) provoked an irregular secretion and they attributed the increased pancreatic secretion obtained by La Barre and Destrée in response to hyperglycaemia of the higher centres to impurities in their secretin preparation. In addition Gayet and Guillaumie considered that the centres in the isolated head of Dog B in the experiments of La Barre and Destrée sustained too great circulatory interference to permit them to function normally.

The spontaneous pancreatic secretion of the rabbit, regulated by humoral and nervous mechanisms, offers a most suitable medium for an investigation of this type (Baxter, S. G., 1931 a and b), as the use of secretin preparations is rendered unnecessary. Furthermore the relative changes in the rate of secretion of the fluid and organic parts of the juice during hyper- and hypoglycaemia could be studied to advantage in the animal. Accordingly we have investigated this problem in the rabbit in order to determine the effect of changes in the blood sugar level on the pancreatic secretion and the rôles played by the parasympathetic and sympathetic nervous systems in the response of the pancreatic gland to changes in blood sugar.

Experimental Methods.

Rabbits of medium size, fed on a diet of hay and carrots with water ad lib., were used in our experiments. In most cases the animals received nothing but water for 24 hours previous to the experiment. Amytal - iso-amyl- ethyl barbituric acid - (0.5 - 0.8 c.c. intramuscularly) was used as an anaesthetic since it has been shown by several investigators that it is without influence on the blood sugar (Page, 1923; Edwards and Page, 1924; Britton, 1925; and Collins, 1925). However, Weiss (1925) and Underhill and Sprunt (1927) found that amytal might produce hyperglycaemia. We noted in our experiments that amytal usually left the blood sugar level unchanged or occasionally produced a slight hyperglycaemia. Cori (1930) however has demonstrated that amytal greatly intensifies the depressive action of epinephrin on glucose utilization. This fact was confirmed in our experiments and will be referred to later on.

Suppression of epinephrin secretion by destruction of the adrenal medulla or simple section of the splanchnic nerves (Britton,Geeling and Calvery, 1928) or by removal of the sympathetic chains (Dworkin, 1931) resulted in a markedly increased sensitivity to insulin. Accordingly in most of our experiments the adrenals were removed or the adrenal veins ligated. Another reason for excluding the adrenal secretion is the fact that during insulin hypoglycaemia there is an increased output of epinephrin (Cannon, McIver and Bliss, 1924; Houssay, Lewis and Molinelli, 1924; Lewis and Magenta, 1924; and Zunz and La Barre, 1927 b).

In some cases a few whiffs of ether were necessary for the opening of the parietal peritoneum and the slight rise of blood sugar was probably due to this factor. In all experiments the pancreatic duct was cannulated and the common bile duct and pylorus ligated.

Blood sugar determinations were made by the Shaffer-Hartmann micro-method. Insulin prepared by the Connaught Laboratories was used in all the experiments and was injected intramuscularly and intravenously.

Determination of Enzymes. - It has been previously demonstrated by us (Baxter, 1931 a) that the proteolytic, amylolytic and lipolytic enzymes are secreted in parallel concentration in the pancreatic juice of the rabbit. In this work the lipolytic ferment was unactivated. The parallel secretion of enzymes has subsequently been demonstrated for activated lipase as well. (Fig. 3.) Accordingly in this work the proteolytic ferment only was determined by the milk coagulation method of Mellanby (1912).

Experimental Results.

(i) Experiments with Vagi Intact:

The effect of hypoglycaemia on the enzymatic properties of the pancreatic juice in all the experiments (10), independently of the retention or removal of the suprarenals, was identical. In all cases the tryptic action of the juice gradually diminished with the fall of the blood sugar concentration. This phenomenon was in most cases accompanied by a more or less pronounced diminution in the volume of the pancreatic secretion. However, in some of the experiments (3 with intact suprarenals and 1 with suprarenals removed) the inhibition of the secretion was very insignificant or entirely absent. The diminution in the flow of the pancreatic juice does not seem to depend directly on the degree of hypoglycaemia.

Table XXVIII represents one of the experiments in which both the volume of the secretion and the concentration of trypsin fell during hypoglycaemia. One of the causes of the inhibition of the secretion might have been the very low blood pressure which was usually noted during hypoglycaemia. Thus, in a typical experiment (June 8) before the injection of insulin the hourly secretion was 1.1 c.c.; blood sugar, 0.144%; and blood pressure, 70 mm. Hg. When the blood sugar fell from 0.090 to 0.041 %, the hourly secretion averaged 0.25 c.c. and the blood pressure fluctuated between 10 and 20 mm. Hg. Although a moderate lowering of the systemic blood pressure is favourable to the pancreatic secretion (Babkin, 1924), too great a fall might interfere with the secretory function of the gland. It is feasible that in some cases the inhibitory influence of the hypoglycaemia on the pancreatic flow might be neutralised by the moderate lowering of the blood pressure which facilitates it.

TABLE XXVIII.

TABLE XXVIII.

Experiment, November 13.

Rabbit, 2.5 kg. Given water only during previous 24 hours. Suprarenal veins tied, vagi intact. Pylorus and common bile duct ligated. Pancreatic duct cannulated. Operation completed 10:00 a.m.

Time	Procedure	Volume c.c.	Trypsin Units	Trypsin Total output	Blood sugar gm.%
9:35 a.m. 9:40 "	(Before operation) 2 c.c. amytal intramuscularly				0.118
10:00-11:00 "		0.45	600	270	
11:55 11:00-12:00 noon		0.4	520	208	0.162
12:00 " 12:00- 1:00 p.m.	40 units insulin intravenously and 40 units intramuscularly	0.35	150	52.5	
1:00 p.m. 1:00- 2:00 "		0.3	120	36	0.111
2:30 " 2:00- 3:00 "		0.2	100	20	0.068
3:00- 3:30 " 3:30 "	Insulin reaction, 5 c.c. 20% glucose saline intravenously	0.1	80	16*	0.046
3:30- 4:00 " 4:00 "	5 c.c. 20% glucose saline intravenously	0.2	150	60*	
4:30 " 4:00- 5:00	do.	0.55	300	165	
5:15 " 5:00- 6:00 "		0.55	400	220	0.172

Calculated on basis of one hour.

Thus in one experiment (January 9: vagi intact, suprarenals removed) the hourly volumes of the pancreatic secretion were practically equal throughout the experiment (0.2 to 0.25 c.c.). After insulin administration the trypsin units fell from 300 to 120, and the total output of enzymes from 60 ferment units to 30 ferment units. The blood sugar fell from 0.160% to 0.070%, and the lowest blood pressure during hypoglycaemia was 50 mm. Hg.

As a result of the fall of the enzymatic properties of the juice, induced by the lowering of the blood sugar concentration, there was observed in all the experiments a diminished total output of trypsin. Thus in the experiment in Table XXVIII the total output of trypsin during the development of hypoglycaemia fell from 270 to 16 ferment units, i.e. 16.8 times. This fall was markedly less in those cases where the volume of the secretion did not change during hypoglycaemia. Nevertheless here too it could always be seen (e.g. in the above-quoted experiment of January 9).

These facts are the more important since under the action of one single secretory stimulus the digestive power of the pancreatic juice rises in proportion to the diminution of its flow. However, when a new secretory stimulus begins to act, the relative rate of secretion of the fluid parts of the juice and of its enzymes may change (Babkin, 1928). The experiments quoted above leave very little doubt that the hypoglycaemic state of the blood actually diminishes the discharge of enzymes by the pancreatic gland.

Intravenous injection of a hypertonic solution of glucose during hypoglycaemia restored the secretion of the fluid and organic parts of the juice.

(ii) Experiments with Vagi Cut:

In this set of experiments both vagi were cut under the diaphragm, and their section was verified after the death of the animal. The suprarenals were usually excised, or their veins tied. More uniform results were obtained in those experiments in which the secretion of adrenalin was prevented by some means. However, in these cases also a very low blood sugar concentration (0.050 to 0.040 %) and in particular the accompanying convulsions occasionally inhibited the flow of the pancreatic juice. From thirteen experiments in which the vagi were cut, there was inhibition of the pancreatic secretion in three cases (two with suprarenals intact, and one with suprarenal veins tied).

The outstanding feature in all these experiments was the absence of any significant fall in the enzymatic power of the pancreatic juice during hypoglycaemia. A typical experiment of this kind is presented in Table XXIX. Compare the second hour of secretion (11:30-12:30), when the effect of the operation was lessened, with the fifth period (2:30-3:00), when the blood sugar concentration fell to 0.046. If the volume of the secretion was uniform, the total output of trypsin naturally did not change.

TABLE XXIX.

TABLE XXIX.

Experiment, November 2.

Rabbit, 2.7 kg. Given water only during previous 24 hours. Suprarenal veins tied. Vagi sectioned below diaphragm. Pylorus and common bile duct tied. Pancreatic duct cannulated. Operation completed 10:30 a.m.

Time	Procedure	Vol. c.c.	Trypsin		Blood sugar gm.%
			Units	Total output	
9:30 a.m.	(Before operation)				0.101
9:40 "	2 c.c. amytal intramuscularly				
10:30-11:30 "		0.4	240	96	
12:25 p.m.					0.164
11:30-12:30 "		0.3	200	60	
12:30 "	40 units insulin intramuscularly and 40 units intravenously				
12:30- 1:30 "		0.35	240	84	
1:30 "					0.091
1:30- 2:30 "		0.4	200	80	
2:30 "					0.066
2:30- 3:00 "		0.2	190	76[*]	
3:00- 3:30 "	Hypoglycaemia reaction, 5 c.c. 20% glucose saline intravenously	0.2	300	120[*]	0.046
3:30 "	5 c.c. 20% glucose saline intravenously.				
4:10 "	3 c.c. do.				
3:30- 4:30 "		0.35	270	94.5	
4:35 "					0.148
4:30- 5:30 "		0.4	350	145	

[*] Calculated on basis of one hour.

In those experiments where the secretion began to diminish long before the convulsions, the digestive power of the juice rose proportionally, and the total output of the enzymes was practically unchanged. Thus, for example, in the experiment of June 9 (vagi cut, suprarenal veins ligated) two hours after the administration of insulin (30 units intravenously and 40 units intramuscularly) the blood sugar concentration fell from 0.195% to 0.048%. The hourly volumes of the secretion (first figure), and the trypsin units (second figure) before the injection of insulin were:- 0.7 c.c. and 120 units; 0.75 and 133; and after the injection of insulin:- 0.4 and 240; 0.25 and 350. The total output of enzymes was throughout practically the same, i.e. 84; 99.7; 96; 87.5.

In this series of experiments, too, in spite of the disconnection of the vagus centre and the pancreatic gland, intravenous injection of a hypertonic glucose solution restored the flow of the pancreatic juice if it was inhibited. The beneficial effect of glucose, however, did not depend on the integrity of the sympathetic nervous supply to the pancreas. Hence it was of a peripheral nature in these experiments. This observation is demonstrated in Table XXX (experiment of June 10). In this experiment the tryptic power of the juice began to fall after the section of the splanchnic nerves. The repeated injection of small amounts of 20% glucose solution during the last four hours of the experiment raised the blood sugar from 0.114% to 0.287%

and did not affect the volume of the secretion, but restored the tryptic power of the secretion to its previous level.

TABLE XXX.

TABLE XXX.

Experiment, June 10, 1931.

Rabbit, 1.8 kg. Amytal 2.3 c.c. intramuscularly. Pylorus and bile duct tied. Vagi and splanchnics cut below diaphragm. Adrenal veins intact.

Time	Procedure	Vol. c.c.	Trypsin		Blood sugar gm.%
			Units	Total output	
10:00 a.m.	2.3c.c. amytal intramuscularly.				0.114
11:00 "	Operation complete.				
12:00 noon		0.7	400	280	
1:00 p.m.		0.7	300	210	
2:00 "		0.7	160	112	0.162
2:05 "	5 c.c. 20% glucose saline intravenously.				
2:20 "	3 c.c. do.				
2:35 "	3 c.c. do.				
3:00 "		0.6	170	119	0.267
3:00 "	2 c.c. do.				
3:20 "	2 c.c. do.				
3:30 "	2 c.c. do.				
3:45 "	3 c.c. do.				
4:00 "	2 c.c. do.	0.9	350	245	0.359
4:15 "	2 c.c. do.				
4:45 "	2 c.c. do.				
5:00 "		0.6	400	240	
6:00 "		0.6	450	240	0.287

It was noted in this and similar experiments that the fall in enzyme power after section of the splanchnic was much more gradual than noted previously (Baxter, 1931 b) when the vagi were intact. An example of this type of experiment is quoted from a previous publication for comparison.

TABLE XXXI.

Experiment, June 27, 1930.

Rabbit, 2.2 kg. Urethane, 1 g. per kg. intravenously. Bile duct and pylorus ligated. Both splanchnic nerves isolated on threads. Adrenals intact.

Hour	Procedure	Volume c.c.	Trypsin	
			Units	Total output
10-11 a.m.		0.6	300	180
11-12 noon		0.6	300	180
12:00 "	Splanchnic nerves torn in two			
1-2 p.m.		0.9	66	78
2-3 "		0.2	54	10.8
3-4 "		0.6	48	28.8
4-5 "		0.5	70	35.0

In this experiment it will be noted that the tryptic power and total output fell immediately after section of the splanchnic nerves from 300 to 66 units and from 180 to 78 units respectively.

The possibility of "negative trophic" impulses conveyed to the pancreatic gland through the vagi was considered as a feasible explanation of the differences observed in these two sets of experiments. Accordingly the problem was investigated more closely. In several experiments the vagi were sectioned below the diaphragm and the splanchnic nerves isolated on threads. After a control period the splanchnics were torn in two and the course of the secretion followed for several hours. The results of such an experiment are presented in Table XXXII. Here the fall in tryptic power and total output are much more gradual than in Table XXXI. The blood sugar rose somewhat after anaesthetization and operation to 0.152% and then gradually declined.

TABLE XXXII.

TABLE XXXII.

Experiment, Dec. 2, 1931.

Rabbit, 2.7 kg. Pylorus and bile duct tied. Amytal, 2 c.c. intramuscularly. Both splanchnics isolated on threads. Adrenals intact. Vagi cut below diaphragm.

Time	Procedure	Vol. c.c.	Trypsin		Blood sugar gm.%
			Units	Total output	
10:00 a.m.	(Before operation)				0.101
11:00 "	Operation complete. Cannula introduced				
11:55 " 12:00 noon	Splanchnics torn in two	0.55	350	192.5	0.152
1:00 p.m.		0.8	200	160.0	
1:30 " 2:00 "		0.7	141	98.7	0.144
3:00 "		1.0	40	40.0	
3:30 " 4:00 "		0.7	60	42.0	0.138

Thus section of the vagi prevents the abrupt and profound fall in tryptic power which results when the splanchnic nerves are severed and the vagi are intact.

The effect of amytal on the nervous regulation of the pancreatic gland in the rabbit was also studied. Stavraky (1931) demonstrated that in dogs large doses of amytal diminished the effect of chorda tympani stimulation on salivary secretion. Experiments performed on rabbits anaesthetised with a moderate dose of amytal revealed that stimulation of the vagi below the diaphragm with an induction current increased the flow of pancreatic juice as well as the tryptic power of the juice. Strong contraction of the stomach and intestines was also observed. Thus in the experiment of November 12, 1931, the volume of the secretion for two hours before stimulation of the vagi was 0.15 and 0.2 c.c. respectively and the tryptic power was 150 units and 100 units. Stimulation of the vagi alternately (5 minutes' stimulation and 5 minutes' rest) during the next hour increased the volume to 0.5 c.c. and the tryptic power to 250. During the hour following stimulation the volume was 0.2 c.c. and the tryptic power 100 units. Pilocarpin produced similar effects. Therefore amytal apparently does not interfere seriously with the conduction of impulses through the vagi to the pancreatic gland. Clark (1931) has also shown that amytal anaesthesia does not alter the effect of the inhibitory fibres to the islets of Langerhans.

Discussion.

This investigation establishes the fact that in the rabbit the discharge of enzymes by the pancreatic gland is inhibited by hypoglycaemia. The integrity of the vagi is a condition necessary for the development of this phenomenon, since the section of these nerves abolishes it. In certain cases the central inhibition of the enzyme output may occur independently of the formation of the fluid parts of the juice, which in the rabbit is secreted spontaneously. Like Heidenhain designating as "trophic" those nervous impulses which are responsible for the accumulation of the organic constituents in the secretion, we may describe as "trophic-inhibitory" or "negative-trophic" the impulses discharged during hypoglycaemia by the central nervous system along the vagi nerves to the pancreatic gland.

The validity of the theory that hypoglycaemia stimulates "trophic-inhibitory" impulses in the centres of the vagi is supported by the following facts. (1) Since in the rabbit under the conditions of acute experiment the vagus centre does not send continuous "positive-trophic" impulses to the pancreatic gland (Baxter, 1931 b), hypoglycaemia cannot be considered responsible for the weakening of these impulses. (2) The sympathetic nervous system does not participate in the diminution of the enzyme output during hypoglycaemia, although "positive-trophic" impulses are continuously sent along the splanchnics to the gland (Baxter, 1931 b). This is proved by the experiments in which the vagi were cut and the splanchnics left intact, when hypoglycaemia failed to produce any diminution in the tryptic power of the juice.

The inhibition of the pancreatic flow produced through the vagi during hypoglycaemia was a constant phenomenon in the experiments of La Barre and Destrée on dogs. In rabbits, the secretion in them being spontaneous, it was not always observed under the conditions of these experiments. Moreover it was noted sometimes after section of the vagi. In some experiments the pancreatic secretion after insulin administration was influenced not by the absolute concentration of sugar in the blood but by its relative value as compared with the blood sugar concentration before the injection of insulin.

Among the causes which may lead to the diminution or arrest of the pancreatic output in an intact animal during hypoglycaemia, a very low blood pressure and convulsions were already mentioned. To this may be added the contraction of the pancreatic ducts (Anrep, 1915; Korovitsky, 1923) which are under the control of the vagi. It is possible that this factor may have played a part in some of the experiments of La Barre and Destrée (see especially 1928 d). In the experiment quoted by these authors, synthaline hypoglycaemia abruptly stopped the secretion but after the administration of glucose it returned to exactly the same level as before. The total output of enzymes was diminished in proportion to the diminished flow of juice, but there seemed to be no appreciable change in the enzymatic activity of the juice.

According to Yoshioka (1930), the pancreatic ducts in the rabbit are under the control of the vagus and splanchnic nerves, and electrical stimulation of the vagi produces an initial inhibition of the pancreatic flow (Baxter, 1931). There-

:fore the possibility that hypoglycaemia activates the centres of the motor nerves of the pancreatic ducts in this animal is not excluded. However, we cannot yet altogether deny the existence of the true "secretory-inhibitory" fibres which, according to Pavlov (1910), reach the pancreatic gland via the vagi.

The restoration of the pancreatic secretion and discharge of enzymes during hyperglycaemia were not markedly affected by the section of the vagi and splanchnics. It was therefore of peripheral origin. Furthermore the high blood sugar concentration produced chiefly a "trophic" effect on the gland. The latter fact was noted by Babkin and Savitsch (1921) when they compared the effect of acid solution of sugar and of a solution of HCl alone in a dog with a permanent pancreatic fistula. In the experiments of La Barre and Destrée the hyperglycaemic blood circulating through the head of a dog, connected to the trunk only by the vagi, definitely increased the flow of the pancreatic juice. Whether hyperglycaemia exerted a "trophic" effect on the pancreatic gland in their experiments is very doubtful (cf. La Barre and Destrée, 1928 c, and La Barre, 1930).

Summary.

(1) Insulin hypoglycaemia causes a diminished output of enzymes from the pancreatic gland in a rabbit having vagi intact and spontaneously secreting pancreatic juice. This phenomenon is not observed if the vagi are cut.

(2) The inhibition of the flow of pancreatic juice under the above-mentioned conditions is not an absolutely constant phenomenon.

(3) When the spontaneous pancreatic secretion in the rabbit has been arrested by hypoglycaemia, it may be restored by intravenous injection of a hypertonic glucose solution. This effect is observed when the vagi and splanchnics are intact and also after they have been severed.

(4) Section of the vagi lessens the diminution of enzyme content which occurs when the splanchnic nerves are severed.

(5) Moderate doses of amytal in the rabbit do not seriously affect the results of stimulation of the vagi on the pancreatic gland.

VI. HISTO-PHYSIOLOGICAL INVESTIGATION OF THE PANCREATIC SECRETION.

In collaboration with Dr. D. J. Bowie

A more complete understanding of the secretory processes in the digestive glands may be achieved by a combined physiological and histological investigation. Insignificant as they may seem, physiological phenomena may result in great morphological changes of the secretory cells, and vice versa. A striking example is the effect of the stimulation of the cervical sympathetic nerve in a dog on the secretory activity and structural changes in the parotid gland. While the flow of saliva from the gland may be practically nil, the morphological appearance of the secretory cells is that of an active gland.

An opposite case is the moderate or even insignificant changes in the granular content of the pancreatic cells stimulated to a marked secretory activity by the introduction of HCl solution into the duodenum.

Thus the physiological and histological findings act as a control for each other.

The combined histo-physiological investigation of the pancreatic gland was undertaken with a view to clearing up some points related to the activity of the para- and sympathetic secretory nerves. It was limited to the study of the discharge of the secretory granules from the acinous cells of the pancreas under different conditions of its activity.

Literature

The pancreas belongs to the merocrine type of glands. The secretory granules or droplets are formed during the period of rest of the glandular cell, and are discharged from the cell during its activity. This process of synthetic activity of the cell, and a subsequent evacuation from the cell of the products of this activity, form a "secretory cycle", which may be repeated several times. Finally, a cell of the merocrine type is completely evacuated. Therefore the difference between the merocrine and holocrine types of gland is not so great as it seems from the first glance (Lavdovsky, 1877).

According to the modern view (Bowen, 1926; Parat, 1928), the formation of the secretory granules occurs as follows:- The cytoplasm of a gland cell at the beginning is free from granules. First, a watery droplet appears. It is separated from the cell substance by a special membrane, which permits the secretory material to pass into the interior of the vacuole, and at the same time preserves each individual droplet from dissolution. The granules gradually "ripen"; they increase in size, and in some cases the vacuoles which gave origin to them are completely filled with synthetized secretory products. The number of granules increases and they are moved toward the periphery of the secretory cell. In some cases they fill the whole cell.

R. Heidenhain (1883) investigated histologically the pancreatic gland in different periods after feeding of the animal. In the "first period" of digestion (6 to 10 hours) the basal zone of the acinous cells became opaque, gradually diminished in size, and at last almost completely disappeared. The apical zone enlarged, but its increase could not compensate for the losses in the internal zone, so the secretory cells in this period were swollen. In the next 10 to 20 hours after a meal ("second period" of digestion) the reverse process took place: the internal zone was reconstructed and again became visible, whereas the external zone gradually diminished in size.

The discharge of the secretory granules into the lumen of the alveoli during the activity of the pancreatic gland was established firmly by the classical investigation of Kühne and Lea (1882) on the pancreas of the living rabbit. They could see that the secretory granules moved towards the lumen of the gland, becoming somewhat smaller and less sharply outlined, and at last disappeared altogether.

Our investigations were not directed toward the actual formation of the secretory granules in the pancreas, the problem being beyond the scope of this study. Therefore no review of the corresponding literature will be given here. It may be briefly mentioned that the source of the secretory granules has been at various times attributed to the nucleus or some of its constituents and to various structures in the cytoplasm, including the chondriosomes, ergostoplasm and golgi apparatus. No one of the theories can be looked upon as definitely established. Our interest centred around the problem of discharge of secretion-granules into the lumen of the pancreatic gland of the cat under different experimental conditions.

An analogous investigation was performed some time ago on dogs by Babkin, Rubaschkin and Savitsch (1909). However the conditions regulating the pancreatic secretion in cats are somewhat different than those in dogs. This is especially true of the effect of vagus stimulation. In the dog vagus stimulation produces a secretion, although rather scanty if compared with that activated by hydrochloric acid. In cats, if a decerberate preparation is used, it is impossible to obtain a visible secretion of pancreatic juice by rhythmic stimulation of the vagi or by pilocarpine (Korowitsky, 1923). If the secretion is stimulated afterwards by introduction of an HCl solution into the duodenum, the flow of juice was 2 to 2½ times greater than in a control experiment when the action of the acid was not preceded by nerve stimulation. Korowitsky explained this observation by the supposition that the secretion obtained by stimulation of the vagi, or pilocarpine, was retained in the ducts as a result of the coincident contraction of the pancreatic ducts which follows parasympathetic stimulation. This view was supported by special experiments. The juice so accumulated in the duct was added to the secretion activated afterwards by acid. Convincing as they are, Korowitsky's experiments still do not exclude altogether the possibility of an "augmented pancreatic secretion", during which the effect of the previous parasympathetic stimulation could be added to the effect of secretin . Histo-physiological investigation helped to elucidate this important problem. Babkin, Rubaschkin and Savitsch (1909) obtained the following results:

The pancreatic secretion activated by the introduction of HCl into the duodenum is typically large in volume but very poor in organic material - enzymes. Accordingly, the microscope revealed a scanty discharge of secretion granules into the ducts. The granules did not show marked histo-chemical changes during the secretion. They dissolved in the fluid, which passed through the acinous cells. Therefore the secretion from acid is to a certain degree a passive type. The fluid passes through the cells and washes out the granules. Only after a very profuse secretion from acid was the number of granules markedly diminished. There were no visible changes in the cytoplasm, except a formation of channels by fluid passing through the cell. They may be regarded as a visible expression of the passage of fluid through the cell. This latter view was advocated also by earlier investigators - Dogiel (1893), Lagerstein (1894), and E. Muller (1895).

The stimulation of nerves produced a different result. The pancreatic juice secreted as a result of stimulation of the vagi and splanchnics is rich in organic substances and enzymes. The histological changes in the secretory cells were very great. Not only were most of the granules discharged but they showed evidences of certain chemical changes. It is probable that these changes had occurred already inside of the cell. (Several granules fuse together, their reaction to the reagents changes, they form a big droplet which is discharged into the lumen of the gland). As a result of these chemical changes of the granules, the pancreatic juice obtained by nerve stimulation was secreted in an "active" form,and may digest the coagulated protein without the aid of enterokinase. In accordance with the small volume of secretion during nerve stimulation, the intercellular channels were not so well defined as was the case in the secretion resulting from acid stimulation.

Physiological Methods.

The same methods of anaesthetization, and stimulation of the vagi and splanchnics were employed in this part of the investigation as were previously described (See Part II, Methods).

Histological Methods.

For the histological part of the present investigation, pieces of perfectly fresh pancreatic tissue were removed from the animal while it was under the anaesthetic, and these were immediately immersed in various freshly-made fixing solutions. As a normal control, a small portion of pancreas was ligatured off, excised, and placed in the fixing fluids before any attempt was made to stimulate the gland. Most of our sections were made from tissue which was fixed according to ~~the~~ Babkin, Rubaschkin and Savitsch (1909). They employed a Zenker-formol solution composed as follows:

Mercuric chloride		5 gms.
Potassium bichromate,		2.5 gms.
Sodium sulphate,		1 "
Formalin (strong, commercial)		5 c.c.
Water	to	100 c.c.

The formalin is added to the other stock solution just before the tissue is to be fixed and subsequently the mixture is kept in a darkened room during the period of fixation, which is usually about twenty-four hours.

The excess fixative was washed out in several changes of 50% alcohol and then the tissue was transferred to a series of upgraded alcohols to absolute alcohol; passed through three changes of 1% celloidin in methyl benzoate, transferred to

benzol

benzol and then embedded in paraffin according to the method of Romeis.

The paraffin blocks were cut into sections 4 microns thick, and these were fastened to the slide by Mayer's egg-albumen method. The sections were stained by the neutral dye obtained by combining ethyl violet with Biebrich scarlet, according to the method of Bowie (1924). By this method the secretory granules appear as small, dark, purple spheres on a faintly red background, so that the contrast between the granules and the surrounding cytoplasm is very marked.

Experimental Results.

Five experiments were performed for investigation of the histological changes in the pancreatic gland during secretion. During experiments No. 1 and No. 2 the splanchnic nerves were stimulated rhythmically for 3½ hours. In both cases the pancreatic secretion was extremely scanty, being equal in experiment No. 1 to 0.1 c.c., and in experiment No. 2 to 0.015 c.c. As a control in experiment No. 2 the secretion from the stomach was noted. It was scanty and had throughout a mucous character, as usually is observed during splanchnic stimulation. In both experiments the effect of parasympathetic nervous system was excluded by the section of vagi in the neck.

In experiments No. 3 and No. 4 the vagi were stimulated for 3½ and 4½ hours respectively. The difference between the two experiments was that in No. 3 the splanchnic nerves were left intact, and in experiment No. 4 they were cut. In both experiments the pancreatis secretion was extremely scanty, amounting to 0.05 c.c. That the stimulation of vagi was effective is demonstrated by the control observation of acid gastric secretion in experiment No. 3.

Experiment No. 5, with injection of 0.2% HCl solution in the duodenum was selected because it gave a small secretion of pancreatic juice (1.1 c.c. in 3 hrs. 45 min.), and the histological changes could be advantageously compared with those during splanchnic and vagi stimulation.

In every experiment a piece of tissue was removed before the application of any stimulation. It served as a control.

Cat No. 1

CAT No. 1.

Experiment May 19, 1932.

Stimulation of Splanchnics.

Cat 3.1 k. Pylorus and bile duct ligated. Vagi cut in neck. Adrenal veins ligated, both splanchnics cut and placed in shield electrodes. No spontaneous secretion. Stomach empty.

Time	B. P.	Remarks
	mm. Hg	
10.45 - 11.15		No secretion
11.15 - 12.15	80	Stimulation Rt. nerve coil 12 - 11.75, left, 11.5. 5 mins. stimulation and 5 mins. rest each nerve alternately. Both acting well.
11.45	62	Some thick secretion expelled into cannula.
12.15 - 12.45		Stimulation, Rt. 11.75, Lt. 11.5. Both acting well. Scanty secretion.
12.45 - 1.15		No stimulation
1.15 - 2.15		Stimulation Rt. 11.5, Lt. 11.5. Both acting well.
2.15 - 3.15		Stimulation Rt. 11.5-10.0; Lt. 11.25-10.75. Both responding.
3.15	60	Tissue taken during stimulation.
		0.1 c.c. thick brownish juice secreted. Steady secretion during experiment. No sudden gushes.

CAT No. 2.

Experiment May 25, 1932.

Stimulation of Sympathetic.

Cat, 3.8 k. Female	Stomach reaction faintly acid. Oesophagus and vagi tied below diaphragm. Pancreatic and gastric fistulae. Splanchnic nerves tied. Splanchnic nerves cut and placed in shield electrodes. Adrenal veins tied.

Time	B. P. Mg. Hg	Remarks
10.45 - 11.15		No secretion from stomach or pancreas
11.15 - 12.15	110	Stimulation of both nerves. 5 mins. stimulation and 5 minutes rest. Good reaction from both nerves. B.P. 160 - 180. Coil 12. Slight pancreatic sec., no gastric sec.
12.15 - 1.15		Stimulation as above, coil 12. Both nerves acting. Slight pancreatic secretion, thick brownish gastric secretion, 0.1 c.c., thick, faintly acid.
1.15 - 1.45		No stimulation
1.45 - 2.45	70	Stimulation as before, coil 11.75. both nerves responding. 0.5 c.c. neut. mucus from stomach.
2.45 - 3.15	48	Rest
3.15 - 3.30		Stimulation. Coil 11.5. B.P. 38, both nerves responding. Pancreatic secretion 0.15 c.c.
3.30		Tissue taken from pancreas and stomach. Stomach covered with mucus - more in pylorus and body.

CAT No. 4.

Experiment May 30, 1932.

Stimulation of Vagi. Splanchnic Nerves cut.

Cat 4/1 K. Stomach and duodenum empty. Splanchnic nerves cut, pylorus tied with a sub mucous ligature. Vagi cut in neck.

Time	B. P. Mg. Hg	Remarks
10.45 - 11.00		No secretion
11 - 12	90	Stimulation rt. and left vagi, alternately, 5 mins. stimulation and 5 mins. rest. Rt. 10.25, lt. 10. Scanty thick secretion.
12 - 1		No stimulation
1 - 2	80	Stim. rt. nerve only acting, coil 10.0
2 - 3		Stim. rt. 9.75
3 - 3.30	70	stimulation rt. 9.0
3.30		Section taken.
		0.05 c.c. thick brownish secretion.

CAT No. 5.

Experiment May 27, 1932.

Cat, female, 3.9 K. Pylorus and Bd. tied. Cannulae in pancreatic duct and lower jejunum, stomach empty.

Time	Remarks	
10 - 11	No secretion	
11.15	10 c.c. 0.2 HCl in duodenum	Sec. 1.1 c.c. rather thick
11.30	" " "	
11.50	" " "	
12 - 1	No stimulation	
1.00	10 c.c. 0.2 HCl "	
1.20	" "	
1.50	" "	
2.15	" "	
2.40	" "	
3.00	" "	
	Section taken at 3.10, 8 minutes after injection of 10 c.c. acid.	

Histological Data.

Generally speaking, the histological effects of various methods of stimulating the pancreatic secretion in cats corresponds fairly well to that already described by Babkin, Rubaschkin and Savitsch (1909) in dogs. The special method of staining employed by them were not applied to our sections so that a more detailed comparison with their findings cannot be included in this work.

Three methods were used in stimulating the pancreas, namely:

1. Electrical stimulation of the vagus nerves,
2. Electrical stimulation of the splanchnic nerves, and
3. Stimulation by means of HCl introduced into the duodenum.

Fig. 4 shows a typical appearance of the distribution of the secretory granules in a section taken from a normal control piece of pancreas, apparently at a time when the cells were in a "resting" phase of secretion. The nucleus shows only faintly or not at all. The greater part of each cell contains secretory granules and these are accumulated in that part of the cell which is towards the lumen, that is the apical zone. The granules are not uniform in size, some being considerably larger than others. Note the almost complete absence of stainable material in the ductule.

Fig. 5.

Fig. 5 illustrates the effect of vagus stimulation on the size and distribution of the sedretory granules. In this case the greater part of the cytoplasm is free from granules and the majority of them are closely packed in that part of the cell which is adjacent to the lumen. While there are a few large granules, most of them are much smaller than the majority of those present in the normal cells of Fig. 1. In contrast to the normal, the ductules in this case are filled with material which reacts to the dye in the same way as the material of the secretory granules. It therefore seems reasonable to suppose that the material in the ductules is derived from the granule substance within the cells. The intensity of the staining would indicate that the material in the ductules is quite viscid, rather than watery, and therefore it would not pass readily into the large excretory ducts. There is some indication that the ductules are slightly dilated beyond their normal appearance.

Fig. 6 shows the typical microscopic appearance of the cells of a pancreas that has been stimulated through the greater splanchnic nerves. The filling of ductules with material which stains in the same colour as the secretory granules is very similar to the result observed after vagus stimulation. The granules are larger and are not packed so closely together as after vagus stimulation. There is some evidence of dilatation of the ductules due to the contained secretion.

Fig. 7

Fig. 7 represents the results obtained after stimulation of the pancreas following the introduction of HCl into the duodenum. The ductule is practically free from stainable material, so that if it contained some secretion, which is quite probable, the fluid must have been quite watery in consistency. There is no evidence of dilatation of the ductules, nor would such a condition be expected when a watery secretion which escapes readily is being produced. The secretory granules occupy the apical zone of the cell, as usual, but they are not packed so closely together as they are after vagus stimulation. They are somewhat smaller than the granules seen in the normal cells.

Conclusions.

The above reported experiments permit the following conclusions to be made:

The humoral stimulus, i.e., secreti~~o~~n formed in the duodenum under the influence of hydrochloric acid, activates a watery secretion from the pancreas. The microscopic preparations show that there is practically no coagulable or stainable material in the ducts. Although a small amount of such material was undoubtedly evacuated from the acinous cells, it was dissolved in the fluid which passed through the cells and was quickly moved from the small ducts towards the main duct. Another interesting feature of the experiment with acid is that the size of the granules in many instances did not

diminish

diminish. We find in corresponding microscopic preparations a number of large granules, which the resting cells contain in great numbers. Therefore the experiments with acid in general confirmed the findings of Babkin, Rubaschkin and Savitsvh (1909). Pancreatic secretion activated by hydrochloric acid is of a "passive" type; the granules are washed out from the cell by a stream of fluid flowing through the cell.

The above mentioned authors investigated, as we have done too, the microscopic changes in the pancreatic gland after splanchnic stimulation. They quote only one experiment, during which they received from a dog only 2 c.c. of pancreatic juice. According to them the microscopic changes in the cell resembled those obtained when stimulation of a vagus nerve produced a scanty secretion. To these findings we may add some new data. Although the granules in the case of sympathetic stimulation occupy chiefly the apical half of the cells, they are not so closely packed and are not so diminished in size as in case of vagus stimulation. That the actual discharge of the granules took place is clear from the state of the ductules. The latter are filled, may even be somewhat distended, with a material which stains with the same dyes as the granules, but it seems that under the influence of the sympathetic nervous system the granules do not undergo such great changes as under the influence of the vagus.

Turning now to the discussion of the condition in the secretory cells after stimulation of the vagi, we note here the maximal changes in the size, distribution and number of granules. The large granules almost disappeared from the pancreatic cells stimulated to activity through the vagus. This indicates that under the influence of this nerve certain intimate processes occurred in the acinous cells which changed the appearance of the secretory material. The granules were found accumulated in the apical zone of the cell. They were far more densely packed than under any other condition of activity of the gland or during its rest. In many cells their number was greatly reduced, so they occupied only the apex of the cells. The ductules were filled with material which was stained by the same dye as the granules. The organic material evacuated from the cells, in absence of water, was probably so viscid that much of it remained in the ductules where it became coagulated by the fixing reagents. Therefore the vagus possesses the property of changing the granules inside the cell, a fact noted already by Babkin, Rubaschkin and Savitsch (1909). But it has also the power to drive out the granules from the cell in spite of a complete, or almost complete, lack of flow of fluid from the blood vessels through the secretory cell. In this respect the cat as an experimental animal presents even greater advantages than the dog. Whereas in the latter stimulation of vagus gives a rather scanty secretion, the cat's pancreas barely responds to the stimulation of the parasympathetic nerve by a visible flow of juice. Nevertheless, the microscopic changes in the cells of cat's pancreas after vagus stimulation are as great as in a dog. Using the old terminology of Heidenhain, who classified the glandular nerves as "secretory" and "trophic", we may state that the vagus supplies the pancreatic gland of the cat with "trophic" but not with the "secretory" fibres. Heidenhain (1878) claimed such a rôle for the cervical sympathetic nerve in the parotid gland of the dog. Stimulation of the cervical sympathetic produced hardly any secretion from the parotid gland, yet the microscopical investigation of the gland after several hours of stimulation showed changes which, according to Heidenhain, are similar to those occurring after real secretory activity.

Although the presence of true secretory fibres in the cervical sympathetic nerve to the parotid gland in a dog is not denied, yet the view cannot be accepted at the present time chiefly for two reasons: (1) during long-continued, or even rhythmic stimulation of the cervical sympathetic nerve an asphyxiation of the gland must take place, which will be reflected in the fine microscopical structure of the glandular cells; (2) the parotid gland is rich in myoepithelial cells, which are under the control of the sympathetic nerve. We do not know how a long-continued squeezing of the secretory cells by the basket-cells will affect their structure. On the other hand, stimulation of the vagus (1) does not produce vasoconstriction in the pancreas, and (2) the pancreas is practically free from myoepithelial cells (Zimmermann,). Therefore the vagus nerve to the pancreas in the cat must have a direct action on the secretory cells. This action is restricted to the evacuation of organic material, chiefly of the granules, from the cells. It seems that in the cat the vagus is almost completely devoid of the power to produce a flow of fluid through the pancreatic cells. Accordingly, the vagus may be regarded, in accordance with Heidenhain, as a true "trophic nerve" for the pancreatic gland in the cat. This conception accords with the recent investigations in our laboratory. Stavraky (1932) investigated the effect of quinine hydrochloride on the salivary secretion. He observed that in a certain stage of the poisoning with quinine the secretory effect of the chorda tympani was divided into two phases, an initial gush of a few drops of saliva and a more or less prolonged after effect separated from the first by a pause. When the dose of quinine was increased the first phase disappeared altogether, whereas the second still persisted. According to Stavraky, the chorda tympani has a double influence on the submaxillary gland: (1) it possesses the ability to discharge the content of the cells into the ductules and (2) to increase the permeability of the basal membrane of the secretory cells and stimulate the passage of fluid from the blood vessels and lymph spaces into the cells. In normal conditions these two phases follow quickly upon each other; quinine separates them.

This conception regarding the double function of the chorda tympani is confirmed by the experiments of Bunch (1900-01) with a plethysmographic record of the submaxillary gland during the stimulation of its secretory nerves. Thus the action of the vagus on the pancreatic gland in the cat illustrates the first phase of this action of the secretory nerves.

Summary

1. Pancreatic secretion activated by HCl stimulation is of a "passive type", the granules being washed out from the cell by a stream of fluid flowing through.

2. The pancreatic secretion resulting from splanchnic stimulation is scanty, viscid, and has the same staining reaction as the granules.

3. After prolonged splanchnic stimulation the secretory granules occupy chiefly the apical zone of the cells and are somewhat diminished in size, but are not so closely packed as after vagus stimulation.

4. The ductules are well filled with secretion and in some cases are slightly distended.

5. After long continued vagal stimulation, maximal changes in the size and distribution of granules are noted. The granules are much diminished in size and are closely packed towards the free border of the cell.

6. The ductules are filled with secretion which has the same staining reaction as the granules.

7. The splanchnic and, to a greater extent, the vagus nerves have the power to expel the granules from the cell in the complete or almost complete absence of flow of fluid through the cell.

8. The splanchnic and vagus nerves in the cat can be classified as true "trophic" nerves according to the terminology of Heidenhain.

(VII) HISTO-PHYSIOLOGICAL INVESTIGATION OF THE GASTRIC GLANDS.

The histo-physiological investigation was undertaken with the hope of identifying the cytological elements concerned in the production of the mucus secretion activated by splanchnic stimulation. This work, which is being carried out in collaboration with Dr. H. E. Rawlinson, has not yet reached the stage when we may draw very many definite conclusions. However, certain interesting indications will be presented in order to emphasize the importance of this type of investigation in the study of the innervation of the digestive glands and of the stomach in particular.

(i) Histological and Experimental Methods.

Tissue was taken from the stomach of cats that had been subjected to (1) long-continued splanchnic stimulation, (2) vagus stimulation, and (3) the repeated injection of epinephrin. Tissue was taken from the following areas of the stomach:

1. Fundus 2. Body, greater curvature.
3. Body, lesser curvature, 4. Pylorus, greater curvature,
5. Pylorus, lesser curvature.

Blocks of tissue from each of these areas were placed in two fixatives, Zimmermann's sublimat~~ic~~ solution and routine formol-Zenker solution.

A section

A section from each block (10 from each stomach) was stained with a routine haematoxylin and eosin stain. Some difficulty was encountered in staining the surface mucus cells as well as the mucoid cells of the neck - "Nebenzellen", "Zwischenzellen". No definite reaction of either of these cells could be obtained at first to mucicarmin, which is regarded as a specific stain for mucin or mucus-containing cells. It was found that preliminary mordanting of the section in 0.5% HCl enabled the surface mucus cells to take a definite though not perfect coloration with mucicarmin. The susceptibility of the mucin content of the surface cells showed an increasing gradation, from the "intermediate zone" of Aschoff (1923) towards the pylorus, the strongest reaction being obtained in the first part of the duodenum. A slight reaction to mucicarmin was also observed in the mucoid cells of the neck "Zwischenzellen" in the "intermediate zone".

(ii) Histological Results.

Surface cells:

Evidences of activity used were ragged outer cell borders and presence of mucous plugs. There appeared to be some evidence of increased activity of surface cells to splanchnic stimulation and epinephrin, especially in the fundus. The results were not so clear cut in the pylorus.

Parietal cells:

The parietal cells showed evidences of activity after

prolonged

prolonged vagus stimulation as indicated by an abnormal irregularity of shape associated with a loss of sharpness of outline. The cytoplasm showed a more homogeneous appearance than usual with loss of normal sharp granulation.

"Nebenzellen", "Zwischenzellen", "Mucoid cells":

These cells were not distinguished in the fundus, confirming the finding of Aschoff (1923). Differential staining of the cells was not sufficiently sharp to determine evidence of selective activity. Accordingly, as yet no statement can be made regarding the action of the sympathetic or parasympathetic nervous systems on the "Nebenzellen".

Chief Cells:

No definite findings can be reported for these cells on account of indefinite criteria upon which to base an opinion.

Pyloric Cells:

One of the most interesting points of this investigation was the identification of the so-called "chief cell of the base" (Aschoff) found in the base of the pylorus glands. These cells were very numerous, appearing identical with the chief cells of the fundus glands. However, as the pyloric secretion is low in enzyme content these cells must produce some other constituent of the gastric juice. These cells, by reason of their ragged appearance and dilated lumina, appear to respond to sympathetic stimulation and epinephrin more markedly than to vagus stimulation.

CONCLUSION

Thus while only general statements regarding the progress of the investigation can be made at this time, we feel that it shows interesting possibilities and emphasizes the importance of this approach to a more complete understanding of the differential innervation of the cytological elements presented in gastric mucosa.

SUMMARY.

1. The "intermediate zone" of Aschoff was identified in the cat.
2. The surface mucous or goblet cells show evidences of activity under splanchnic and epinephrin stimulation, especially in the fundus.
3. The parietal cells present a definite appearance of activity in response to vagus stimulation.
4. No "Nebenzellen" or "Zwischenzellen" were identified in the fundus glands.
5. The "chief base cells" of the pyloric glands show evidence of activity more markedly after splanchnic stimulation than after vagus stimulation.

PART IV.

DISCUSSION.

In this section an effort will be made to correlate the data reported in the various experimental sections of this thesis, in order to reach some general conclusions regarding the rôle of the sympathetic nervous system in the secretory processes of the digestive glands investigated.

To promote clarity, the same sub-headings will be followed as were used in describing the experimental work:

I. Stimulation of the freshly sectioned splanchnic nerves.
II. Stimulation of the partly degenerated splanchnic nerves.
III. Stimulation of the vagi.
IV. Experiments on cats with gastric fistulae and oesophagotomies.
V. The effect of hypo- and hyper-glycaemia on the pancreatic secretion in the rabbit with reference to the rôle played by the sympathetic and parasympathetic nervous systems.
VI. Histo-physiological investigation of the pancreatic gland.
VII. Histo-physiological investigation of the gastric glands.

I. Stimulation of the Freshly Divided Splanchnic Nerves:

In our experiments long-continued rhythmic stimulation of the splanchnic nerves activated a definite secretion of alkaline mucus, which occurred at a regular rate. The peptic power and chlorine content of this secretion were low. The alkalinity ranged from 8 to 14 milli equivalents. The reducing power was high, indicating a high content of mucoprotein. The quantity of organic material in the secretion was high at first, but gradually declined. The content of ash was practically even throughout. The alkaline mucus secretion was obtained with the use of induction currents of low as well as high frequency (Table IV.).

These results differ markedly from those obtained by Volborth and Kudriazeff (1927) in similar experiments on dogs. However, several points in their technique must be mentioned in this connection. In their experiments these investigations excluded the pyloric part of the stomach by a sub-mucus ligature; we have shown in the experiments with divided stomach technique that the pyloric part of the stomach secretes relatively much more alkaline mucus than the body or fundus. Consequently, in many of their experiments Volborth and Kudriazeff obtained a secretion with an acid reaction.

Furthermore, in our experiments stimulation was carried out for much longer periods (8 to 10 hours) than in the experiments of these investigators (/4 to 4 hours). We have noted that if a strong acid reaction was present at the beginning of the experiment it frequently required 5 to 6 hours of stimulation before the reaction of the secretion became alkaline (Table II).

Further experimental evidence has been presented in support of our observations. The repeated injection of epinephrin produced the same type of secretion as splanchnic stimulation (Table VI). Cocain, which is recognized as a sympathetic sensitizer, increased the response of the gastric

glands

glands to both splanchnic stimulation and the repeated injection of epinephrin (Table VII). Thus we feel justified in maintaining that the splanchnic nerves contain secretory fibres which activate certain elements of the gastric glands, producing an alkaline mucus secretion.

The changes in the composition of the secretion indicate also that we have to deal here with a "true" secretory process, and not with a mere expelling from the stomach of a mucoid fluid formed independently of any nervous influence by the mucus membrane. As in the case of other digestive glands (salivary glands and pancreatic gland) the mucus secretion of the gastric mucosa activated by prolonged stimulation of splanchnic nerves becomes gradually less and less rich in organic material, retaining its ash concentration to the end of the experiment.

The action of splanchnic stimulation and epinephrin on the course of the histamin gastric secretion also gave confirmatory evidence. It was found that if the flow of the histamin secretion was very copious no effect was observed from splanchnic stimulation or epinephrin (Table VIII). However, if the histamin secretion was slower certain definite effects were noted. There was a lowering of the acidity associated with an increase in the amount of dissolved mucin, and a slight increase in the peptic power (Tables IX and X). Thus splanchnic stimulation can only visibly modify the composition of the histamin gastric secretion when the latter is not too copious. Splanchnic stimulation produces modifications expected from the addition of the typical sympathetic secretion, alkaline and having a moderate peptic and high reducing power, to the characteristic histamin secretion - having a high acidity and low reducing and peptic power.

Experiments in which the stomach was divided into three sections - fundus, pylorus and body - gave interesting information regarding the production of the sympathetic mucus secretion from different areas of the stomach. It was found that the greatest quantities of alkaline mucus was obtained from the pylorus. Next came the body, which usually gave an alkaline mucus secretion, but occasionally the reaction was faintly acid, even after many hours of stimulation. Finally, the scantiest secretion was obtained from the fundus, which was usually faintly acid in reaction but occasionally alkaline (Tables XI and XII). These experiments seem to give some information as to the origin of the mucus secretion. Aschoff (1923) has described the distribution of the special mucoid cells "Nebenzellen" or "Zwischenzellen", stating that none are found in the fundus proper, but in the "intermediate zone". The gastric glands are composed exclusively of Zwischenzellen and a few parietal cells. Thus a larger secretion of mucus from the body (containing the intermediate zone) would be expected than from the fundus where the only mucoid cells are the surface goblet cells.

Direct observation of the gastric mucosa during splanchnic stimulation revealed the fact that the secretion of thick clear mucus was accomplished without visible movements of the gastric mucosa or musculature. Moreover, if muscular movements were present stimulation inhibited them. This latter fact is in agreement with observations made by many investigatore - Oser (1892), Doyon (1895), Nolf (1925), Brown, McSwiney & Wadge (1930).

II. Stimulation of the Partly Degenerated Splanchnic Nerve:

Experiments with the partly degenerated splanchnic nerves revealed several interesting facts. The first observation made was the presence of a spontaneous or paralytic secretion of alkaline mucus. This secretion was present 24 to 96 hours after bilateral aseptic section of the splanchnic nerves below the diaphragm. The paralytic secretion presented the same properties as the sympathetic secretion (Table XIII), i.e., alkaline mucus with low Cl content and low peptic power. The spontaneous secretion was increased by splanchnic stimulation and by the repeated injection of epinephrin (Tables XIV, and XV). Cocain markedly increased the effect of stimulation of the partly degenerated nerve (Table XVI). Ergotamin inhibited the spontaneous mucus secretion (Table XVII). These facts lend weight to the supposition that the spontaneous mucus secretion occurring after the degenerative section of the splanchnic nerves is a paralytic secretion similar to that observed after denervation of the salivary and intestinal glands.

Volborth and Kudriazeff also employed the technique of stimulation of the partly degenerated nerve in dogs in acute and "chronic-acute" experiments. In the acute experiments they obtained practically similar results as from stimulation of the freshly cut nerve. The same objections apply to these experiments as were raised in the foregoing discussion, section I. In their chronic-acute experiments a dog with a Heidenhain pouch was used in which the left splanchnic nerve had been aseptically sectioned 6 days previously. On the day of the experiment the wound was opened under ether anaesthesia and the nerves placed in a shield electrode and the animal allowed to recover. Then rhythmic stimulation of the left splanchnic nerve was begun. They obtained small amounts of an acid secretion from the pouch, 0.3 to 0.8 c.c., and larger amounts - 5 to 10 c.c. - from the whole stomach. All specimens were acid, and free HCl was present in some specimens, but no titration figures were given, nor were any other of the gastric constituents determined. Furthermore, the influence of the ether anaesthetic must be considered in this form of experiment.

The whole experiment lasted only three hours, which, as we have shown, is not sufficiently long for a strong acid reaction to subside during splanchnic stimulation.

Therefore it is evident that these experiments with the partly degenerated splanchnic nerves support and amplify the observations made on the freshly sectioned nerves. All data obtained in the experiments with sympathetic stimulation of the gastric mucosa show that it is partly under the control of this division of the autonomic nervous system. It influences predominantly the mucus-forming elements of the gastric mucosa, not only in the pyloric part but also in the body of the stomach. The control of the sympathetic secretory innervation over the fundus is not marked. The influence of the sympathetic innervation on the acid-forming secretory elements cannot be denied altogether, but it is very insignificant.

III. Stimulation of the Vagi:

Weak and strong stimulation of the vagi in the cat gave results similar to those reported by Vineberg (1930). In view of our findings it was necessary to investigate the possibility that sympathetic fibres in the vagus (Kuré et al., 1931 (a); Kiss, 1931) were responsible for the mucus secretion produced by weak vagus stimulation.

In experiments designed for the purpose, we found that atropin inhibited the mucus secretion activated by weak vagal stimulation, whereas ergotamin was without effect (Tables XX and XXI), consequently it must be concluded that weak vagal stimulation activates a mucus secretion by stimulation of a certain type of vagus fibre rather than by excitation of sympathetic fibres contained in the vagus.

IV. Chronic Experiments on Cats with Gastric Fistulae and Oesophagotomies:

In these experiments an attempt was made to determine the rôle played by the sympathetic nervous system in the reflex nervous phase of gastric secretion. The curve of the gastric secretion and its constituents was studied before and after section of the splanchnic nerves below the diaphragm.

As a result of these experiments it must be stated that section of the splanchnic nerves and removal of the central sympathetic impulses has no very pronounced effect on the nervous reflex phase of gastric secretion. It was noted, however, that the curve of the total output of organic substances, pepsin and dissolved mucin, during the course of the secretion activated by sham feeding showed certain changes. Thus the values of these constituents rose to higher levels during the first ten-minute period of the secretion and diminished more rapidly towards the end of the secreto~~us phase~~, after section ry of the splanchnic nerve, than was observed in the normally innervated stomach (Figs. I and II). One of the possible explanations of this phenomenon is as follows: The greater concentration of organic substances during the first ten minutes after sham feeding could be due to the addition of the alkaline paralytic sympathetic secretion to the regular acid gastric juice activated by reflex vagus stimulation. The more rapid diminution of the organic parts of the juice during the course of the secretion could be explained by the lack of reflex influence transmitted through the sympathetic innervation to the gastric mucosa during sham feeding. Even if the sympathetic nervous system has a certain relation to the

production

production of acid gastric juice. as Volborth and Kudriazeff (1927) claim, its effect is insignificant and is completely obscured by the stronger vagal influences. Our results are more in agreement with the conclusion of Farrell (1928) that the sympathetic nervous system could not be regarded as an important factor in the production of gastric secretion during the nervous phase. On the other hand, these data do not support the hypothesis of Bickel (1925), who stated that the sympathetic nervous system played the chief rôle in the production of organic material in the gastric juice while the parasympathetic system controlled chiefly the secretion of water, acid and salts. As was demonstrated in this work, and that of others in our laboratory, reflex or direct stimulation of the vagi activates a flow of gastric juice extremely rich in organic substances. Therefore, the vagi may be looked on as "trophic-nerves" of the gastric glands. But it is true that the sympathetic nervous system has very little, if any, relation to the formation of the hydrochloric acid. However, before any definite conclusions can be made, these experiments must be repeated in animals in which the coeliac ganglia have been removed. This work is now in progress but no results could be reported at this time.

V. The Effect of Hypo- and Hyper-glycaemia on the Pancreatic Secretion in the Rabbit with Reference to the Rôle Played by the Sympathetic and Parasympathetic Nervous System:

Another investigation of the influence of the sympathetic nervous system on the secretory process of the digestive glands was the study of the effect of the para-and sympathetic nervous systems on the pancreatic secretion during hyper- and hypoglycaemia. LaBarre and Destrée (1928, 1929), LaBarre and Destrée (1928 and 1930) and Destrée (1930) have shown that hypoglycaemia inhibited the pancreatic secretion activated by the continuous injection of secretin in a dog. On the other hand, hyperglycaemia increased the secretion and the concentration of enzymes in the juice. If the vagi were sectioned, or the basal ganglia destroyed, these effects of hypo- and hyperglycaemia were not observed.

The experiments of these observers are open to certain criticism, as we have previously pointed out (p. 146). Furthermore, Gayet and Guillaumie (1930) repeated this work with negative results.

The rabbit was considered an advantageous animal for these experiments since we have shown that it has a spontaneous pancreatic secretion, permitting an accurate study of the relative changes of the secretion of the fluid and organic parts of the juice (Baxter, 1931 - a & b).

It was found in these experiments that hypoglycaemia in all cases produced an inhibition of the tryptic power of the pancreatic juice, which was usually accompanied by a more or less pronounced diminution in the volumes of the secretion (Table XXVIII).

However

However, in some experiments the inhibition of the volume of the secretion was slight or nil. The lowering of the B.P. observed during hypoglycaemia is a factor which must be considered as an explanation of this discrepancy. It is known that a moderate lowering of the B.P. is favourable to pancreatic secretion (Babkin, 1924), but too great a fall interferes with the function of the gland. It is probable that in some cases the inhibitory action of hypoglycaemia was neutralized by the moderate lowering of the B.P.

The injection of glucose intravenously restored the volume of the secretion and the enzyme power to their normal level, or even slightly above. After section of the vagi the inhibitory effect of hypoglycaemia on the output of enzymes in the pancreatic secretion was not observed (Table XXIX).

In a few experiments inhibition of the volume of the secretion occurred. This inhibition was probably due to such extraneous factors as insulin convulsions, too great lowering of the B. P., or spasm of the pancreatic ducts. The intravenous injection of glucose in these experiments also restored the volume and enzyme power of the secretion, indicating that glucose has a peripheral action.

The sympathetic nervous system has no participation in these experiments since in experiments in which the vagi were cut and the splanchnics were intact, hypoglycaemia did not produce any effect on the pancreatic secretion. Furthermore, the stimulating action of glucose took place when the splanchnic nerves were sectioned (Table XXX). These results justify the postulation of the "negative trophic" or "trophic inhibitory" impulses which are sent via the vagi to the pancreatic gland during hypoglycaemia. The existence of secreto-inhibitory fibres in the vagus for the pancreatic gland was suggested by Pavlov in 1910. However, spasms of the pancreatic ducts must be considered as a possible explanation of the inhibitory action of hypoglycaemia (Anrep, 1915; Korovitsky, 1923; Yoshioka, 1930; Baxter, 1931 - b).

In controlling these results it was found that amytal anaesthesia did not appreciably affect the results of vagus stimulation on the pancreatic gland. Accordingly, the results of La Barre and Distrée on dogs have been confirmed in some respects on rabbits under simple physiological conditions.

VI. Histo-Physiological Investigation of the Pancreatic Gland:

This part of the work was undertaken with the aim of correlating the physiological data obtained from the pancreatic gland in cats with the accompanying histological changes in the gland cells.

Three different stimuli were employed: (1) HCl introduced into the duodenum. (2) Rhythmic stimulation of the splanchnic nerves. (3) Rhythmic stimulation of the vagi.

The picture produced in the gland cell by HCl stimulation is one which corresponds to the type of secretion obtained, i.e., a watery secretion with a small amount of organic material. Thus the acinous cells did not show any marked depletion of the secretory granules, many of which were similar to the large granules observed in the resting cell (Fig. 7).

The ductules contained practically no coagulable material indicating the rapid evacuation of the watery secretion into the larger ducts. These results confirmed the earlier observations of Babkin, Rubaschkin and Savitsch (1909).

Rhythmic stimulation of the splanchnic nerves gave some new data. Although the secretory granules occupied chiefly the apical zone of the cell, they were not so densely packed as after vagus stimulation, nor were they so markedly diminished in size. The ductules were filled, or even distended, with coagulable material which exhibited the same staining properties as the secretory granules, indicating the production of a thick secretion with a high content of organic material (Fig. 6). Accordingly, the sympathetic nervous system has the power to discharge the secretory granules in the absence of fluid secretion.

Stimulation of the vagi produced maximal change in the size, distribution and number of the secretory granules (Fig. 5). The large granules seen in the resting cell had practically disappeared. The remaining small granules were closely packed towards the free margin of the cell and the ductules were filled with darkly stained secretion. Thus the vagus stimulation produced more pronounced effects than splanchnic stimulation, and also has the ability to cause marked changes in the gland cell, even when the flow of fluid through the cells is absent or extremely scanty.

A certain similarity is observed here to the conditions which obtain in the salivary glands. Heidenhain (1878) stated that the cervical sympathetic supplied the parotid gland ofmthe dog with "trophic" but not with "secretory" fibres, i.e., stimulating of the cervical sympathetic produced practically no secretion, yet the histological changes observed were those of the active gland. While this view has been modified in connection with the parotid gland, yet it offers a possible explanation of the facts observed with sympathetic vagus stimulation of the pancreatic gland in the cat.

It seems that both the vagus and splanchnic nerves are devoid of power to produce a flow of fluid through the pancreatic cells; yet they both - the vagus to a greater degree - have the ability to produce an evacuation of organic material, chiefly of the granules from the cells. Thus using the terminology of Heidenhain, we may ascribe to these nerves a true "trophic" function in the pancreatic gland of the cat.

VII. Histo-physiological Investigation of the Gastric Glands:

A histo-physiological investigation was undertaken in order to ascertain if possible the origin of the mucus secretion obtained by prolonged sympathetic stimulation. Two possible sources of this mucus secretion are possible:

1. The surface mucous or goblet cells.
2. The special mucoid cells of the gastric glands "Nebenzellen", "Zwischenzellen", which have been shown to be of a mucoid character.

While the results of this investigation are far from complete, certain definite observations have been made which indicate the importance of this type of combined histophysiological investigation.

The intermediate zone of Aschoff (1923) has been identified in the stomach of the cat and in some cases after prolonged treatment with mucicarmin, a mucoid precipitate was demonstrated in the "Nebenzellen". However, staining technique must be improved to give sharper differentiation, and as yet no observations have been made as to the effect of splanchnic stimulation or of epinephrin on these mucoid cells.

The surface mucous cells showed signs of activity in the fundus with splanchnic or epinephrin stimulation.

The most interesting observation made was in connection with the so-called "chief cell of the base" (Aschoff), found in the base of the pyloric glands. These cells are very numerous, and resemble the chief cells of the fundus glands. Definite evidences of secretory activity of these cells was observed on splanchnic and epinephrin stimulation. These preliminary results emphasize the importance of the type of observation in the investigation of the relationships of sympathetic and parasympathetic nervous systems to different elements of the gastric mucosa.

SUMMARY.

1. Long-continued rhythmic stimulation of the freshly sectioned splanchnic nerves with an induction current in cats and dogs activates a steady secretion of alkaline mucus. High and low frequency currents produce the same effects.
2. The repeated injection of a small dose of epinephrin has the same effect as splanchnic stimulation.
3. The secretion is scanty, mucoid and alkaline. The alkalinity ranges between 8 and 14 milli equivalents. The concentration of Cl is lower than that of gastric juice. The organic material in the secretion gradually diminishes, the ash remaining constant. The reducing power of the mucus is high, indicating a high content of mucoprotein.
4. High blood pressure is not favourable for the mucoid secretion.
5. Atropin in moderate doses does not inhibit the sympathetic mucus secretion.
6. Previous sensitization with cocain produces an increase in the secretory effect of splanchnic stimulation.
7. Stimulation of the splanchnic nerves, or the injection of epinephrin during the course of histamin gastric secretion modifies the composition of the juice, decreasing the acidity and concentration of Cl slightly and increasing the peptic power, only if the secretion is not too profuse.

8. Separation of the stomach into three parts - fundus, body and pylorus - seems to indicate that the alkaline sympathetic mucus secretion is produced by special mucoid cells, "Nebenzellen" or "Zwischenzellen", found in the gastric glands, and not to a secretion of surface mucus.

9. Direct observation of the gastric mucous membrane through a glass window inserted into the anterior wall of the stomach showed that splanchnic stimulation did not activate any movements of the mucosa or musculature, but inhibited any existing peristaltic movements. The formation of a layer of mucus on the mucous membrane was observed.

10. Aseptic section of the splanchnic nerves in the cat and dog below the diaphragm produces a spontaneous secretion of mucus similar to the "paralytic secretion" observed in the salivary and intestinal glands after denervation.

11. Electrical stimulation of the partly degenerated splanchnic nerves (24-72 hours after section) causes a definite increase in the "paralytic mucus secretion".

12. The repeated injection of epinephrin solution also increases the value of the spontaneous secretion and its peptic power.

13. Cocain sensitizes the partly degenerated splanchnic nerves also, electric stimulation producing a marked increase in the volume of the secretion.

14. Ergotamin inhibits the "paralytic secretion".

15. Rhythmic stimulation of the vagi in the cat with a weak induction current produces a flow of faintly acid mucus having a high digestive power.

16. Strong stimulation activates a secretion of gastric juice with high acidity and digestive and reducing power, and normal Cl content. These results are similar to those obtained in dogs.

17. Atropin inhibits the mucus secretion activated by weak stimulation of the vagi.

18. Ergotamin has no effect on the mucus secretion resulting from weak stimulation of the vagi.

19. It is concluded that weak stimulation of the vagi produces a mucus secretion having characteristic properties by exciting vagus fibres which activate certain elements in the gastric mucosa, and not by stimulation of sympathetic fibres contained in the vagi.

20. Section of the splanchnic nerves in the cat produces certain definite effects on the course of the gastric secretion in response to mucus stimuli under normal conditions.

21. The peptic and reducing power of the juice activated by sham feeding reach their maximum level almost immediately and then decline more or less rapidly to the end of the secretory period.

22. The action of epinephrin on the course of the histamin gastric secretion exhibits in general in chronic experiments the same pictures as in acute experiments (e.g.,

decrease

decrease in acidity, Cl content, and slight rise in peptic power only if the histamin secretion is not too copious.

23. Sham feeding superimposed towards the end of the histamin gastric secretion produces an immediate rise in ferment power after section of the aplanchnic nerves equal to that observed in the normal animal.

24. Pilocarpin injected subcutaneously in the cat activates a rather scanty mucoid secretion with diminishing quantity of ferments and reducing power and total chloride content. These constituents are all increased by sham feeding.

25. No change is observed in the response to pilocarpin and sham feeding after bilateral splanchnicotomy.

26. Insulin hypoglycaemia causes a diminished output of enzymes from the pancreatic gland in a rabbit having vagi intact and spontaneously secreting pancreatic juice. This phenomenon is not observed if the vagi are cut.

27. The inhibition of the flow of pancreatic juice under the above-mentioned conditions is not an absolutely constant phenomenon.

28. When the spontaneous pancreatic secretion in the rabbit has been arrested by hypoglycaemia, it may be restored by intravenous injection of a hypertonic glucose solution. This effect is observed when the vagi and splanchnics are intact, and also after they have been severed.

29. Section of the vagi lessens the diminution of enzyme content which occurs when the splanchnic nerves are severed.

30. Moderate doses of amytal in the rabbit do not seriously affect the results of stimulation of the vagi on the pancreatic gland.

31. Pancreatic secretion activated by HCl stimulation is of a "passive type", the granules being washed out from the cell by a stream of fluid flowing through.

32. The pancreatic secretion resulting from splanchnic stimulation is scanty, viscid, and has the same staining reaction as the granules.

33. After prolonged splanchnic stimulation the secretory granules occupy chiefly the apical zone of the c~~a~~lls and /e are somewhat diminished in size, but are not so closely packed as after vagus stimulation.

34. The ductules are well filled with secretion and in some cases are slightly distended.

35. After long-continued vagal stimulation, maximal changes in the size and distribution of granules are noted. The granules are much diminished in size and are closely packed towards the free border of the cell.

36. The ductules are filled with secretion which has the same staining reaction as the granules.

37. The splanchnic and, to a greater extent, the vagus nerves have the power to expel the granules from the cell in the complete or almost complete absence of flow of fluid through the cell.

38. The splanchnic and vagus nerves in the cat can be classified as true "trophic" nerves according to the terminology of Heidenhain.

39.

39. The "intermediate zone" of Aschoff was identified in the cat.

40. The surface mucous or goblet cells show evidences of activity under splanchnic and epinephrin stimulation, especially in the fundus.

41. The parietal cells present a definite appearance of activity in response to vagus stimulation.

42. No "Nebenzellen" or "Zwischenzellen" were identified in the fundus glands.

43. The "chief base cells" of the pyloric glands show evidence of activity more markedly after splanchnic stimulation than after vagus stimulation.

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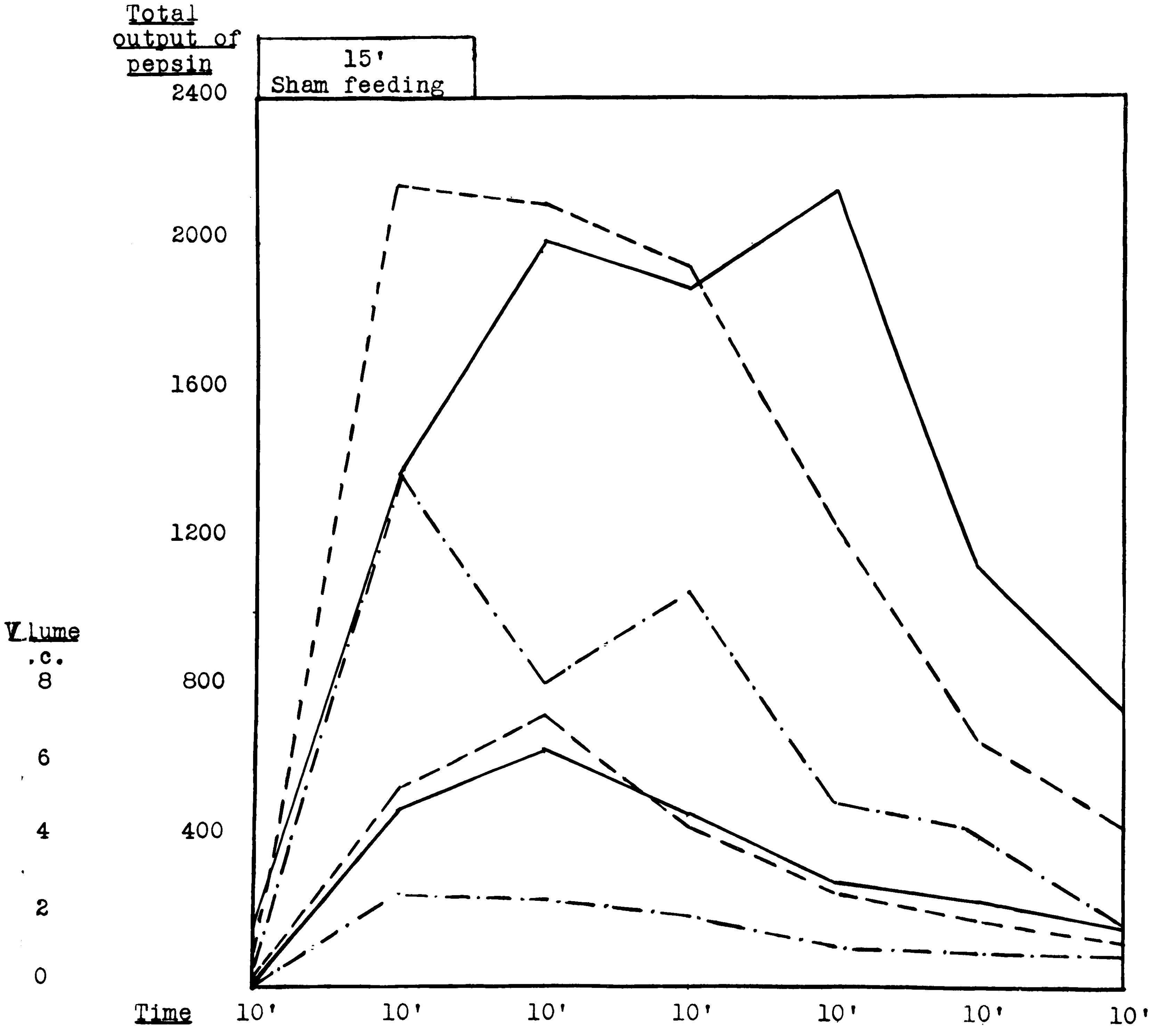
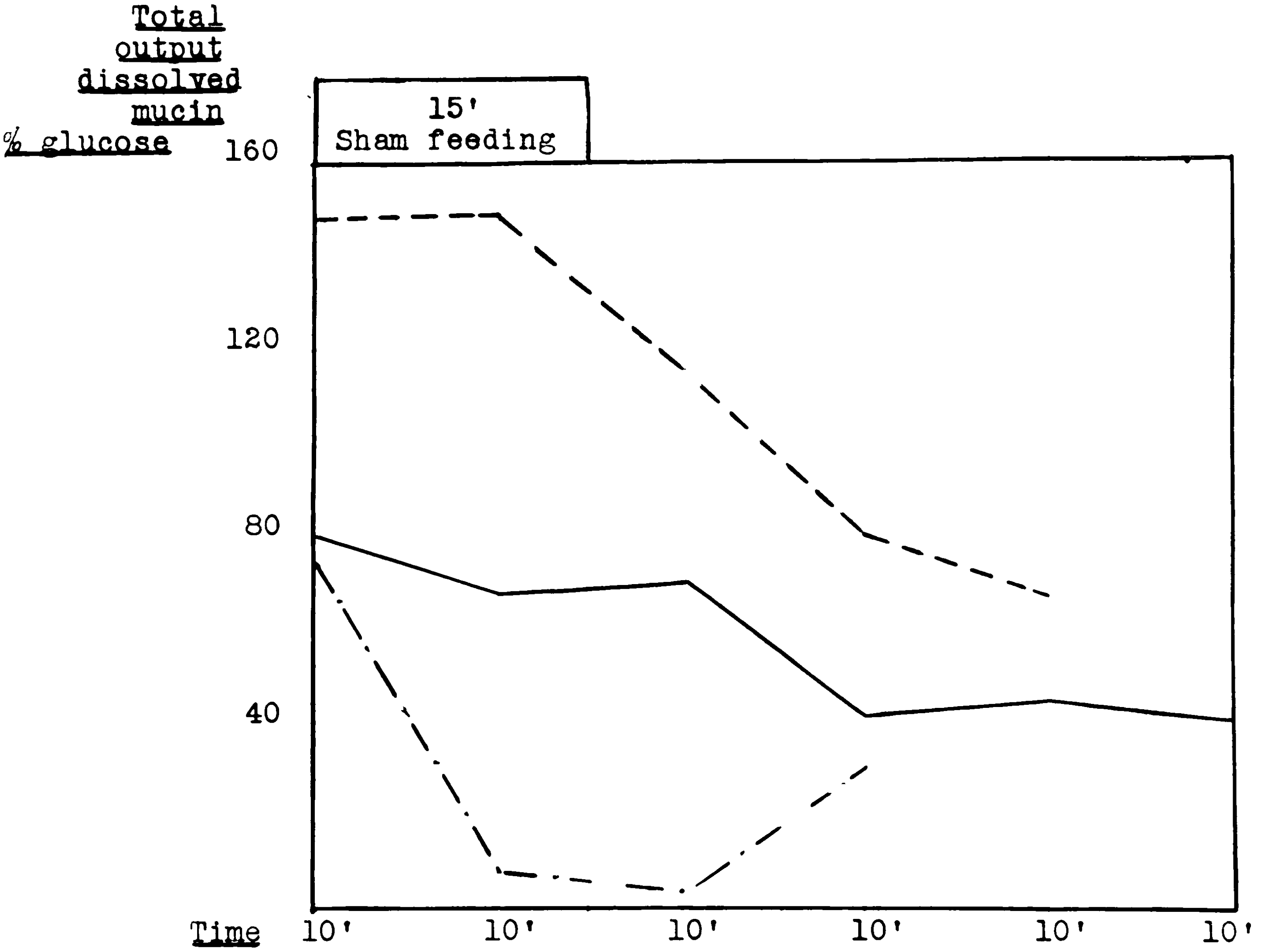
Fig. 1



Total output of pepsin and volume in 10 min. periods.

———— Average before operation.
—·—·— First experiment after section of splanchnic nerves.
— — — Average in all subsequent experiments.

Fig. 2



Total output of dissolved mucin (% glucose) in 10 min. periods.

——————— Average before operation.
—·—·—·— First experiment after operation.
— — — — — Average in all subsequent experiments.

Same volume relations as in Fig.

Fig. 3

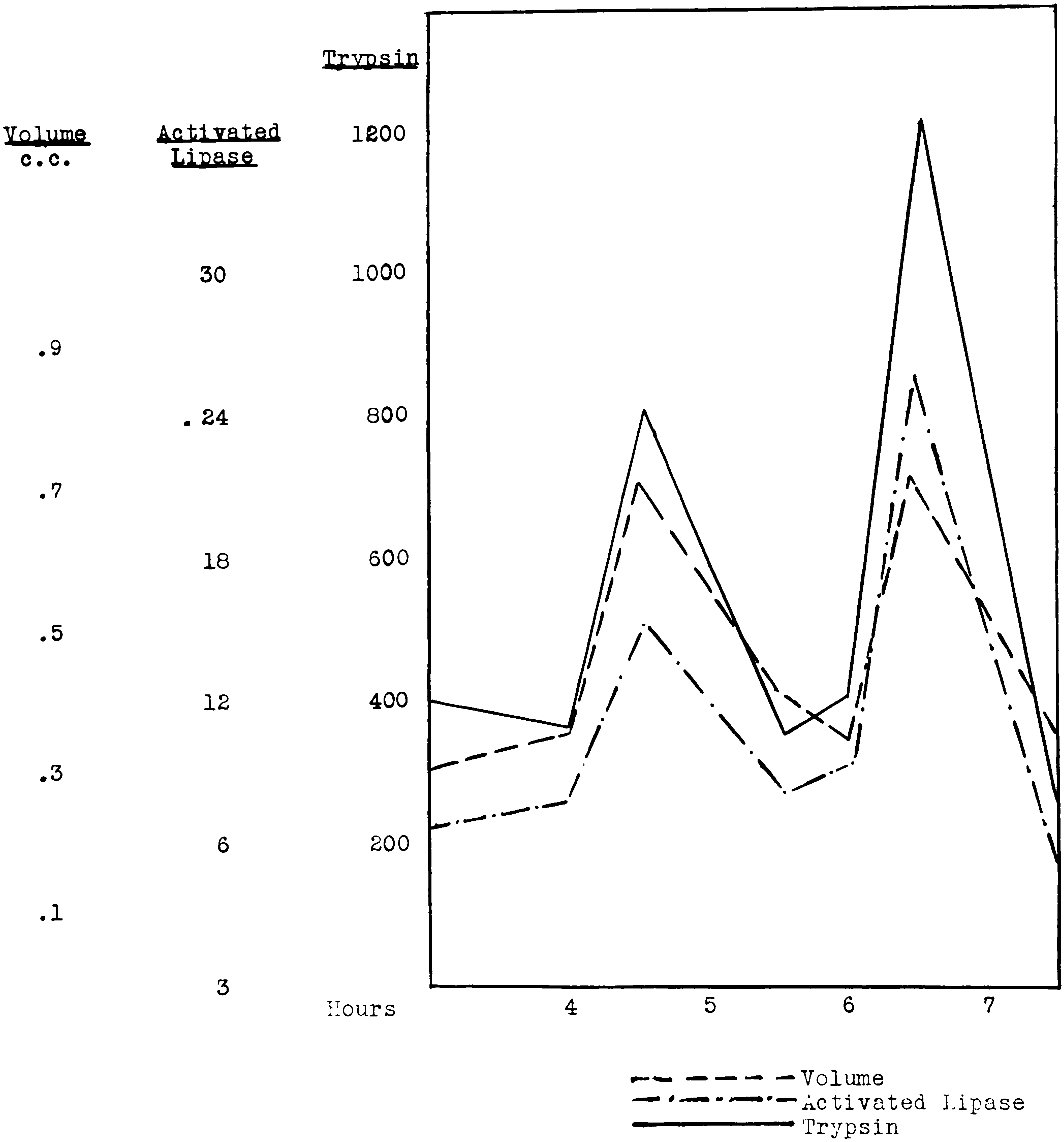

Volume
c.c.
.9
.7
.5
.3
.1
Activated Lipase
30
24
18
12
6
3
Trypsin
1200
1000
800
600
400
200
Hours
4
5
6
7
Volume
Activated Lipase
Trypsin

Fig. 6

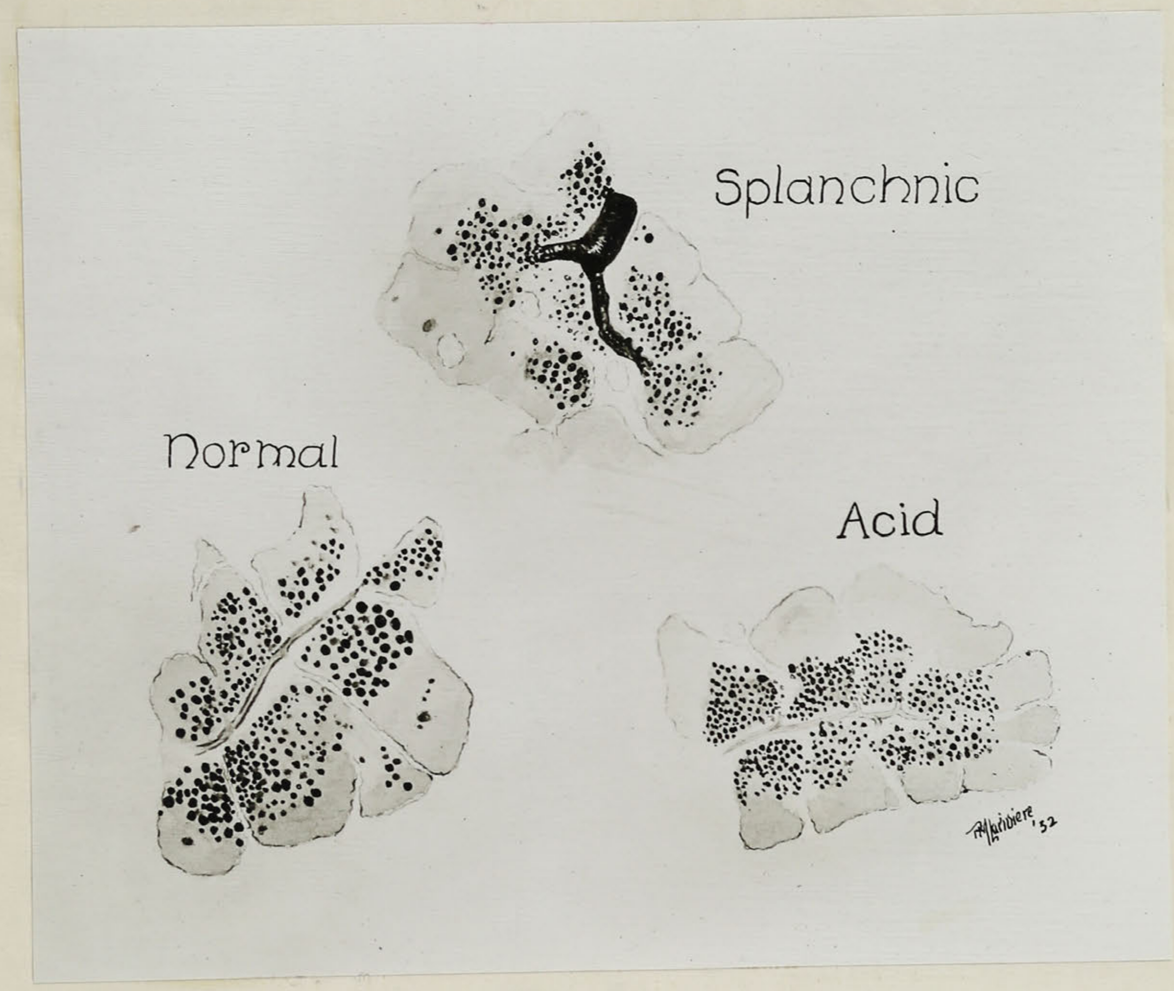


Fig. 4 Fig. 7

(Camera lucida x 950)

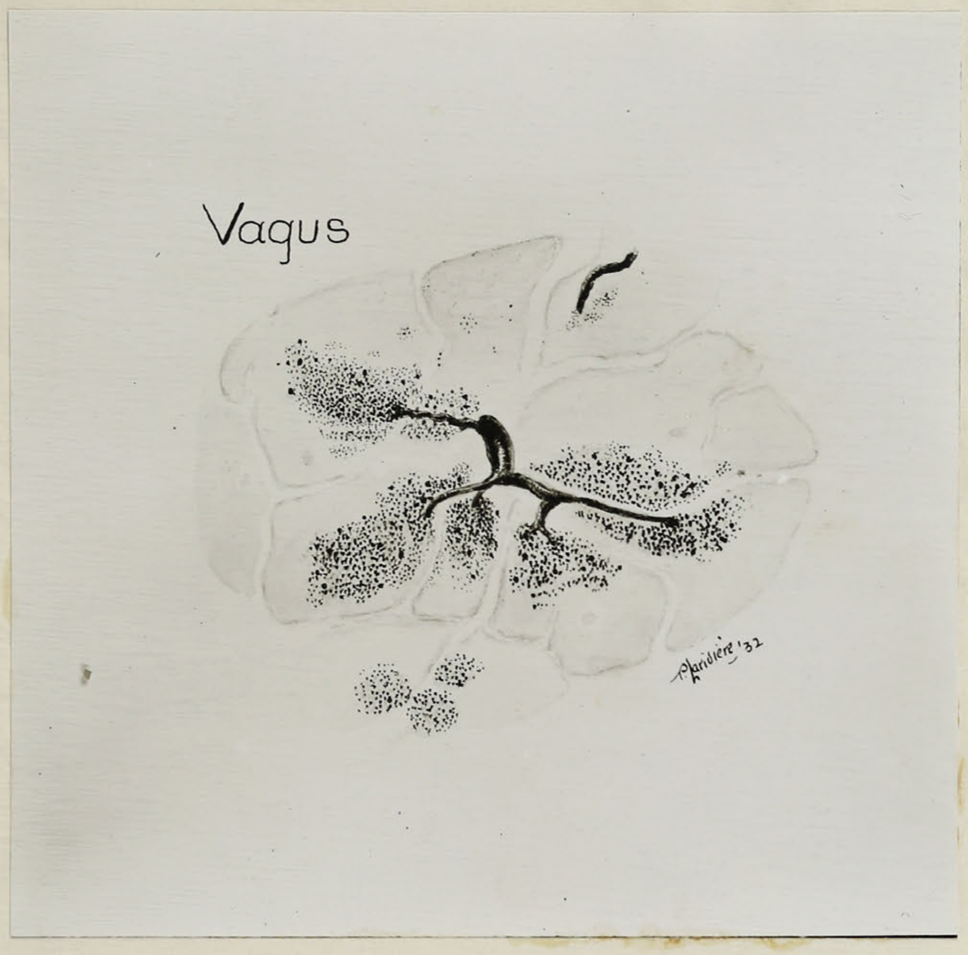


Fig. 5

(Camera lucida x 950)