MECHANISM OF GASTRIC SECRETION

SOME ASPECTS OF THE MECHANISM OF GASTRIC SECRETION

BY

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Thesis

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INTRODUCTION

The work embodied in this thesis arose as a sequel to an attempted analysis of the conditions necessary for the production of gastric juices by electrical stimulation of the vagus nerves. As shown by previous investigators, secretion produced in this way differed markedly from regular gastric juice. Like the latter it possessed a high digestive power but differed in that it had a comparatively low acidity and contained a large amount of mucus or mucoid-like fluid. In the present investigation, the first procedure followed was to apply electrical currents of different intensity to the vagus nerves. By this method it was observed that two different types of gastric juice were secreted, depending upon the strength of the current employed. In brief, a weak current initiated a secretion, which was mucoid-like in character, whereas a strong current produced a flow of regular gastric juice.

Based upon this fact a new conception of the mechanism regulating gastric secretion was formed, namely, that different stimuli activate the different cytological elements which are present in the gastric mucosa. In attempting to prove our hypothesis, it was approached from another angle. The effects of different chemical stimuli upon the gastric glands of /

of a dog with a Heidenhain pouch were studied. Thus it was definitely established that histamine, one of the most powerful gastric stimulants, activates the parietal cells only, and is responsible for the formation of a highly acid gastric juice with an extremely low digestive power. When the administration of histamine was supplemented by pilocarpine, a "synthetic" regular juice resulted, because pilocarpine is a typical parasympathetic drug which, in the dog, chiefly affects the pepsin- and mucus-producing cells.

A histological study of the gastric mucosa after prolonged vagal or histamine stimulation was undertaken. The peptic cells showed marked changes after strong vagal stimulation and none after prolonged histamine stimulation. These structural changes confirm the physiological results obtained.

The oesophagus was shown to be a rich source of mucous secretion, and it was proved that the vagus nerve is the secretory nerve of the oesophageal glands which produce mucus.

Stimulation of the vagi by previous investigators produced a scanty gastric secretion containing a large amount of mucus. As it was thought that hyperventilation as employed by others in their experiments might have been one of the factors responsible for this, an investigation of the interdependence of gastric secretion and the carbon dioxide content of the blood was made.

This thesis is therefore divided into five parts, each representing a cognate evolution of the same problem. A corresponding review of the literature is prested in each part.

P A R T I

HISTORICAL:

THE VAGUS AS THE SECRETORY NERVE TO THE GASTRIC GLANDS

Physiology, one of the oldest of the biological sciences, reveals its manifold secrets slowly and with reluctance to the ever-probing investigator. The history of the vagus nerve and its functional connection with the gastric mucosa has been no exception to the general rule. As early as 1814 Brodie observed that, when dogs were killed by an intravenous injection of arsenic, there was a copious secretion of mucus and watery fluid in the stomach. He found, however, that, if the vagi were severed previous to the administration of the lethal dose of arsenic, the stomach was always empty at autopsy. Wood (1870) confirmed Brodie's observations. From that time to 1890 various European workers, experimenting along different lines, came to the conclusion that the vagus plays an important part in the regulation of gastric secretion. It remained, however, for Pavlov and Schumov-Simanovski (1890) to discover that the vagus nerve is a secretory nerve to the gastric glands. Numerous investigators have since confirmed this fact, but none have to date added materially to our knowledge concerning the mechanism of vagal action and the effect which it exercises histologically and /

and physiologically upon the gastric glands.

The predecessors of Pavlov were familiar with the effects of a variety of stimulants on receptive surfaces, e.g. eyes, ears, nose and mouth. Pavlov advanced the hypothesis that stimuli thus received were transmitted to the gastric glands by the vagus nerves. The proof of this supposition was based on two simple and yet indisputable experiments. An oesophagotamised dog with a gastric fistula and with the right vagus cut below the recurrent laryngeal nerves, was sham-fed, and the gastric juices thus obtained were analysed. The left vagus nerve was then severed. Sham feeding in the doubly vagotomised animal now initiated not a single drop of secretion. In the second type of experiment, a dog was prepared in exactly the same manner except that the left vagus was cut and allowed to remain in the wound beneath the skin. After two or three days the peripheral end of this nerve was stimulated by an induction current, a few drops of highly acid juice being obtained.

These results were confirmed by Oushakov (1896), who resorted to the acute type of experiment. Gastric juice was obtained after stimulation of the peripheral cut ends of the vagi in the neck by an electrical induction current. The animals were first immobilised by section of the spinal cord below the medulla and the secretion collected through a gastric fistula /

fistula. The acidity of the gastric juice thus obtained was on the average much lower than in normal and oesophagotomised dogs, but the digestive power was high. Approximately one half of the total volume of the secretion was composed of mucus, this accounting for the comparatively low acid values. Oushakov concluded that, in addition to the fibres responsible for the stimulation of acid and pepsin, there were special mucus-stimulating fibres in the vagus. There was a long latent period (from one to one and a half hours) between the beginning of stimulation and the appearance of secretion.

Babkin (1928) draws attention to the difference between the latent periods of the gastric and of the salivary glands following nervous stimulation. He subscribes to the explanation offered by Oushakov that in the vagus there are secretory inhibitory as well as secretory fibres. He suggests that both groups of fibres are stimulated simultaneously but that at the onset of stimulation the inhibitory fibres are more easily excited than the secretory fibres. After a time they become relatively less sensitive, thus permitting the action of the secretory fibres.

A rather ingenious method of stimulating the vagi was reported by Stahnke (1924). He placed specially constructed electrodes in the lower oesophagus near the cardia in dogs. Stimulation /

Stimulation resulted in hypermotility, hypersecretion, pylorospasm, chronic gastritis and ultimate erosion of the gastric mucosa. This technique is certainly much simpler than isolation of the nerves by operative procedures. However, with this method it is impossible to know when the vagi are being stimulated and how far the electrical stimulus spreads and involves other nervous centres.

The only dissenting voice which has been raised since Pavlov first announced his results was that of Farrell (1928), who failed to obtain gastric secretion after vagal stimulation. However, he reported results in agreement with Pavlov after cutting the vagi in an oesophagotomised dog with a gastric fistula.

As has already been stated, cutting of the vagi completely arrested the reflex secretion from sham or psychic feeding (Pavlov).

A great deal of work has been done along these lines, most of which tends to confirm this early finding. All the results are not entirely in accord; for example Ophuls (1906), experimenting upon rabbits, cut the vagi bilaterally below the diaphragm and reports that there was no change in the gastric secretions. In the same year Orbeli(1906), working upon experimental dogs with Pavlov or Heidenhain pouches, found that, when a Pavlov pouch was deprived of its vagal innervation /

innervation, there were changes in the composition of its secretions. He found that the volume of the secretion, as well as the acidity and the peptic output, gradually diminished. There was a response to chemical stimulation resulting from the introduction of food into the main stomach but the type of secretion obtained from the pouch varied with the type of food and never contained such great concentrations of acid and pepsin as before removal of the vagal innervation.

McCrea (1926), reporting the results of vagotomy performed on both men and animals, is definite in stating that "on section of the vagi psychic secretion is lost". He states further that "denervation of the pylorus or resection of the vagal branch to the pylorus gives similar results to vagotomy or complete denervation of the stomach but the early paresis and dilation do not appear". He suggests that the division of the nerves of the pyloric region abolishes the second phase of gastric secretion.

Similar conclusions were arrived at by Hartzell (1929-30) and by Thompson (1930). The latter states that after pyloric resection the psychic phase is the most significant phase of gastric secretion.

The theory that the vagus contains different types of fibres for the gastric mucosa has attracted considerable attention /

attention of recent years. It will be remembered that Oushakov conceived of two sets of fibres in the vagus, one group controlling the acid and peptic glands, the other activating the mucous elements in the mucosa. Working from an entirely different angle, Heinbecker (1930, 1931) and Heinbecker and O'Leary (1933) demonstrated three distinguishable potential complexes in the vagus. The first had physiological properties characteristic of somatic nerve fibres, the other two had properties of a much slower order associated with autonomic motor functions. They have correlated the three potential complexes histologically with three different types of fibres. The first is derived from the larger myelinated fibres, the second from thinly myelinated and the third from non-myelinated fibres. The efferent fibres to the heart have their cells of origin in the central nervous system, whereas the cells of origin for efferent fibres to the lungs and intestine are in the nodose ganglion. There is no evidence of a synaptic junction in their pathway through the ganglion nodosum. Neither are they of sympathetic origin.

Some years ago Savitsch (1922) presented evidence which suggested the presence of mucus secretory fibres in the vagus. He experimented on dogs with a gastric fistula and an oesophagotomy. At the commencement of the experiment the reaction /

reaction in the stomach was acid; sand was then introduced into the animal's mouth, and produced a secretion of alkaline mucus from the stomach which neutralized the acid present. The different effects of vagus stimulation on the gastric mucosa can be explained according to the theory of Kiss (1931, 1933) that the vagus contains sympathetic fibres. He found that the cervical portion of the vagus contains three kinds of fibres, the same thinly and heavily myelinated fibres as in the intracranial portion and in addition a large number of unmyelinated fibres. The unmyelinated fibres are derived from the superior cervical ganglion of the sympathetic and enter the vagus through its own ganglion. He states that the subdiaphragmatic portion of the vagus contains 75% of unmyelinated fibres having their origin not in the vagus but in the sympathetic. The minority of about 25% are thinly myelinated and may be partially sensory (original vagus) and partially preganglionic sympathetic fibres. In conclusion he states that "the so-called parasympathetic influence of the vagus has no anatomical basis in the case of the abdomen. The parasympathetic phenomenon can be only a negative phase of the sympathetic".

McSwiney and Spurrell (1933), however, from their work on cats believe that the cervical vagus receives no contribution from the sympathetic nervous system. They maintain there /

there is no cell station for the gastric fibres in the vagal ganglia. The fibres enter the ganglia as myelinated fibres and lose their myelin sheaths when they leave it.

METHODS /

METHODS

For convenience of description the technical methods used will be classed under two headings:

(1) Acute experiments,
(2) Chronic experiments.

Acute Experiments

Dogs of medium size were used. Care was taken to ensure that each animal received adequate nourishment but yet had an empty stomach on the day of the experiment. Each animal received a bowl of milk twenty-four hours prior to the experiment, and was permitted water at all times.

Standard Preparation

Certain standard technical procedures were employed in the great majority of the experiments: in all other cases the procedures were identical with these except for certain local modifications which will be described under different headings below or elsewhere in the text.

The standard preparation is as follows: A dog is anesthetised by means of ether. Once the induction stage has been achieved the animal is given a mixture of chloralose (0.05 gm. per kg.) and urethane (0.5 gm. per kg.) intravenously. Care must be taken to inject the chloralose-urethane mixture slowly; an injection given too rapidly /

rapidly not infrequently causes paralysis of the respiratory centres, often resulting in death. Through a mid-line incision a tracheotomy is performed and at the same time the oesophagus is carefully isolated from its surrounding structures and tied at the level of the thyroid cartilage. The left external jugular vein is sought and a permanent glass cannula inserted. The carotid sheath is then brought into the wound and cut in a longitudinal direction. At this stage it would be well to point out that the sheath must be cut over the artery and completely separated from it. By so doing the vagus nerve is not traumatised and, on its under surface, maintains its connection with the surrounding sheath. This is important because it has been noticed that a nerve completely separated from its sheath quickly becomes dried up and useless. Nerves prepared as described always appear fresh and moist after many hours of stimulation. The vagus, thus separated from the carotid artery, is now carefully cleaned for a distance of half an inch and severed at the level of the thyroid cartilage. A fine silk ligature is tied around the distal severed end. The nerve is then replaced in its normal position and the remaining operative procedures are carried out. The other vagus is similarly isolated.

A second mid-line incision is now made through the abdominal wall. The stomach is carefully pulled to the left so as to expose the pylorus. The blood vessels and

nerves /

nerves are separated by blunt dissection from the pyloro-duodenal junction and a strong cord tied around the bowel at this level. By this means the stomach is isolated from the duodenum. When the cord is securely tied, there is no possibility of bile regurgitation. This closure has been frequently inspected at autopsy and invariably found to be secure. By means of a purse-string suture a metal fistula is next inserted into the anterior surface of the stomach approximately midway between the incisura and the greater curvature. It is necessary here in acute experimentation to reverse the usual technique employed for inserting a gastric fistula. Ordinarily the mucosa is carefully inverted to avoid leakage and the possibility of peritonitis. In these experiments, rarely of more than 8 hours' duration, the prevention of bleeding is even more important than the avoidance of peritonitis. It will be recalled that the blood vessels of the stomach lie for the most part in the submucosa. Inversion of the mucosa may give rise to bleeding and consequent contamination of the gastric secretion with blood. This is avoided through e-version of the mucosa by means of artery forceps placed on the margin of the incision made through the stomach. The fistula is tied with a strong cord so as to include serosa, submucosa and mucosa. This simple procedure prevents /

prevents any bleeding whatsoever. The stomach is returned to its normal position and the abdominal wall closed about the metal fistula.

At the conclusion of the operative preparation the animal was placed in a prone position on a stand specially designed with a central window through which the gastric fistula projected. The animal was kept warm throughout the experiment.

The vagus nerves were placed on platinum electrodes and rhythmically stimulated (15 interruptions per minute by Metzel's metronome) for a period of 10 minutes each. The induction coil employed was of the type supplied by A. H. Baird, Edinburgh, and was calibrated to give the following currents for the corresponding centimeter readings on the scale:

cm.	milliamperes	cm.	milliamperes
0	9.95	6	4.45
1	9.80	7	2.90
2	9.40	8	1.80
3	8.55	9	1.00
4	7.45	10	0.50
5	5.95	11	0.20

At the beginning the electrodes were always placed close to the severed distal end of the vagus nerves. When there was evidence of diminished local irritability /

irritability of the nerve, the electrodes were moved to a fresh position on the nerve. Criteria of nerve action were based upon changes in the blood pressure and heart rate.

Isolation of the Oesophagus

The isolation of the oesophagus without injury to the secretory nerves of the stomach presented considerable technical difficulty. The most satisfactory method is as follows.

A dog is prepared as described above under Standard Preparation. After the insertion of the gastric fistula the stomach is held as high up as possible on the greater curvature by an assistant who maintains gentle traction downwards with one hand and, with the other, retracts liver and spleen. By this procedure a good exposure of the oesophageal diaphragmatic junction can usually be obtained. The operator then makes a small incision (1/4") through the serosal layer of the oesophagus in a direction parallel to its long axis and just below the diaphragm. A curved blunt dissector is carefully passed around the entire circumference of the oesophagus in the subserosal space. A piece of stout cord is threaded on the dissector and the latter is slowly withdrawn carrying the cord with it. The cord now encircles the oesophagus, and, lying as it does in the subserosal space, it can in no way injure the oesophageal plexus of nerves when tied. In certain experiments the cord is tied; in others, where

a cannula is to be inserted, the primary incision is continued through all the coats of the oesophagus. As soon as the edges of the mucosa present themselves, two artery forceps are applied to the cut surfaces. The opening is then carefully enlarged so as to admit a large curved right-angled glass cannula of 1/2" to 3/4" external diameter. One end of the cannula is inserted through the opening in an upward direction, and is passed through the diaphragmatic portion of the oesophagus to a distance of about one inch above the diaphragm. The other end of the cannula protrudes through the abdominal incision above the gastric fistula. The cord is then tied securely around the oesophagus and cannula. The abdominal wound is sutured about the cannula and fistula. A second glass cannula is inserted into the oesophagus in the region of the neck just below the thyroid cartilage, and securely fixed.

By this method the oesophagus is completely isolated from the saliva of the mouth above and from the gastric juices below. At the same time the stomach is isolated from the oesophageal secretions. When the procedure is carefully carried out, the oesophageal plexus of nerves remains uninjured. Strong stimulation of the vagi in the neck still produces the usual profuse gastric secretions.

Isolation of Stomach (Fundal Portion)

Certain experiments required the complete isolation of the stomach from the oesophagus and from the pyloric mucus-bearing area. The standard preparation was first made, and then the oesophagus was isolated as described above, either with or without oesophageal cannulae. A small longitudinal incision was made on the anterior surface of the pyloric part of the stomach at a distance of 4 to 5 cm. from the pyloric sphincter. The muscular coats alone were sectioned. By careful dissection the submucous mucosa was separated from the muscularis throughout the entire circumference of the pyloric antrum. The isolated submucosa and mucosa were then tied securely. By this method the pyloric part was isolated from the remainder of the stomach with a minimal amount of trauma and without entering into the lumen of the organ.

Hyperventilation, Inspiration of Carbon Dioxide and Intravenous Injections of Acid and Alkali

In these experiments the standard preparation was used. In one group gastric secretion was obtained by electrical stimulation of the vagus nerves; in another group subcutaneous injection of histamine (ergamine acid phosphate) was the means of gastric stimulation employed. Secretion was collected in graduated centrifuge tubes at definite intervals. The volume of /

of each sample was measured, and the chemical composition of the secretion and the blood chemistry were determined by the methods described below. CO_2 was administered by means of Douglas bags filled with 5 or 10% CO_2 and air. These bags were attached to the intake faucet of an air pump. The outlet of the pump was attached to the tracheal cannula. Hyperventilation was employed at the rate of 64 to 80 per minute. The pump used had a stroke volume of 1700 cc. In certain experiments acid (0.5 normal HCl), sodium bicarbonate (10%) and sodium cyanide (1/100 normal) were injected intravenously.

Chemical Methods

The free and total acidities were determined by titration, Töpfer's reagent and phenolphthalein being used as indicators. The total chlorides were determined by the method of Wilson and Bald (1928), and the peptic power by Hawk's modification of Mett's method. The volume of visible mucus was estimated by centrifuging the juice. Blood was withdrawn from one carotid artery, the other being used for recording the blood pressure. All blood samples removed from the carotid were collected and centrifuged under paraffin oil, using the angle centrifuge. The time of centrifuging was usually under two minutes, so that loss of CO_2 was minimized.

The /

The CO_2 content was determined on the true plasma without equilibration, by the method of Van Slyke (1917). Plasma pH was estimated by Cullen's colorimetric procedure (1922), and the chlorides in the blood and plasma by the method mentioned above. Lactic acid in the whole blood was determined by the method of Friedmann, Cotonio and Shaffer (1927), expressed in mg. per 100 cc. of whole blood.

The chemical composition of the oesophageal secretion was determined by the following methods. The specific gravity of the secretion was determined by picnometer and the pH by the indicator method of Clark and Lubs (1928), the samples not having been collected under oil. The acid-combining power was determined by heating 1 cc. of the secretion with 5 cc. of N/50 H_2SO_4 in a boiling-water bath for 5 minutes and by back titration with N/50 NaOH, methyl red being used as an indicator; it is expressed in milli-equivalents per litre. Nitrogen was determined by Pregl's (1930) micro-Kjeldahl procedure. The nitrogen content of the filtrates obtained on precipitation of the mucus secreted with four volumes of absolute alcohol is interpreted as non-protein nitrogen. Amino nitrogen was determined by formol titration according to the method of Van Slyke and Cullen (1914 - see Peters and Van Slyke, 1932, p.547). Potassium was determined by the method of Kramer and Tisdall (1921), calcium by the method /

method of Clark and Collip (1925). Chlorine was determined by the method of Wilson and Bald (1928), phosphorus (total) by the method of Fiske and Subbarow (1925), the wet procedure in which sulphuric and nitric acids are employed being used for digestion. Pepsin was determined by the Mett's tube procedure as modified by Nirenstein and Schiff (1927) with an incubation period of from one to three days.

Chronic Experiments

Heidenhain- and Pavlov-pouch dogs were employed, as well as a dog with oesophagotomy and a gastric fistula. The response of each to standard meals of bread, meat and milk was studied for some months after operation. In all cases care was taken to exclude psychic and conditioned reflexes. Histamine and pilocarpinewere injected subcutaneously, histamine in doses ranging from 0.75 to 1 mg. and pilocarpine in doses of from 4 to 7 mg. It is essential that the stomach should be empty at the beginning of the experiment and the making of a gastric fistula is recommended in the case of every animal with a Heidenhain- or Pavlov-pouch; otherwise it is impossible to be certain that secretions obtained from the pouch are not due to retained stomach contents.

EXPERIMENTAL RESULTS:

THE ACTIVATION OF DIFFERENT ELEMENTS OF THE GASTRIC SECRETION BY VARIATION OF VAGAL STIMULATION

Certain facts have been established in the past fifty years concerning the vagus and its relation to the gastric mucosa. A few of these have been indicated in the preceding section on the literature. Although the vagus nerve had been definitely proven to be a secretory nerve of the gastric glands, many points concerning its action were not clear.

The variations in the composition of the gastric secretion activated during direct stimulation of the vagus (Oushakov, 1896) or in response to reflex stimuli originating in the oral cavity (Savitsch, 1922) have to date remained unexplained. Oushakov observed during his experiments that a large quantity of mucus accompanied the acid juice passing through the gastric fistula. This mucus was alkaline and consequently lowered the acidity of the gastric juice considerably. He concluded that, in addition to the fibres activating the production of regular gastric juice, the vagus nerve contains mucus-secretory fibres for the surface epithelium of the gastric mucosa. Savitsch, on the other hand, using dogs with oesophagotomy and a gastric fistula, produced a flow of mucus from the gastric fistula when the dogs were fed sand. In order to /

to explain these phenomena and the part played by the parasympathetic nervous system in gastric secretion a more detailed investigation was essential.

Another interesting fact disclosed by Oushakov's experiments was the extremely long latent period (from forty-five minutes to one-and- a -half hours) elapsing between the commencement of vagal stimulation and the appearance of gastric secretion. He ascribed this unusual effect to the presence of inhibitory-secretory fibres in the vagus nerve supplying the gastric glands. According to his interpretation the inhibitory fibres were less resistant to the electrical stimulus than the secretory fibres and thus more rapidly lost their excitability. A latent period of such long duration was never observed under normal conditions, the latent time being usually 4 to 10 minutes (dogs with oesophagotomy and gastric fistula and dogs with a Pavlov pouch). It was thus important to know whether the exceedingly long latent period reported by Oushakov was due to inhibitory-secretory fibres or to some peculiarity of his experimental technique.

Numerous workers have obtained different types of gastric secretion when the vagi were stimulated by different means. The gastric juice from sham feeding, for example, was exceedingly high in both peptic power and acid content, whereas the /

the juice obtained by direct stimulation of the peripheral ends of the vagus nerves was high in pepsin and low in acid (Oushakov).

With these facts in mind let us consider the histological structure of the organ in question. In the final analysis the function of an organ of necessity is dependent to a large extent upon its structure. The stomach mucosa, according to recent workers, exhibits at least four different cytological elements: -

1. Surface epithelial cells,
2. The chief neck cells or mucoid cells (Bensley, 1898; Lim, 1922; Aschoff, 1923; Zimmerman, 1928),
3. The chief body cells or peptic cells,
4. The parietal cells or oxyntic cells.

Thus structurally the gastric mucosa is composed of independent units; hence the premise concerning the independent function of these groups has a histological basis. The influence of the vagus nerve on the peptic and parietal cells has already been indicated by Pavlov and other investigators. However, the relation of the vagus fibres to the other cytological elements of the gastric mucous membrane is still somewhat obscure.

In the present investigation an attempt has been made to /

to correlate previously known facts by applying induction currents of different strengths to the vagi in dogs with the object of obtaining gastric secretions of different composition.

Weak Stimulation

In this group of experiments the vagus nerves of dogs were stimulated by a weak induction current, namely, a current of 0.50 milliamp. or less, being barely perceptible to the human tongue. The animals were prepared according to the standard method for acute experimentation (see under"Methods"). Any deviation from standard technique will be mentioned in the text.

The experiment outlined in Table I illustrates the effect of weak stimulation of the vagi upon the stomach secretions. Stimulation was continued over a period of 370 minutes. The current was gradually increased until it approximated to a moderately strong current. The fasting contents were definitely acid (0.05 gm. % free HCl with 0.07 gm. % total HCl). The peptic power was low. (19.2 Mett's units). There was no secretion of free fluid and none of free acid. The volume of secretion increased in the third hour of stimulation and was composed entirely of thick jelly-like mucus. The increase in volume

(samples /

TABLE I.

GASTRIC SECRETION - EFFECT OF WEAK VAGAL STIMULATION

Exp. Oct. 28, 1929.

Dog, weight 7.8 kg. Anaesthetized with Dial, injected intraperitoneally. Artificial respiration used throughout the experiment. Oesophagus tied in the neck; pylorus tied at the junction with the duodenum.

Sample	Time	Volume	Free HCl	Total HCl	pH	Peptic Activity	Remarks
	Mins.	c.c.	Gm. %	Gm. %		Mett's Units	
1	30	1.6	0.05	0.07		19.2	Control period.
2	10	5.2	0.01	0.02		20.8	Continuous stimulation begun: Coil 16 cm.
3	120	0.5	0.00	0.00	7.27	4.0	Stimulation altered, " 13 cm.
4	60	1.7	0.00	0.00	5.85	10.0	" 11 cm.
5	60	2.8	0.00	0.05	3.63	353.4	" "
6	30	2.5	0.00	0.02	4.07	163.8	" "
7	30	3.1	0.00	0.02	4.54	353.4	" "
8	30	1.8	0.00	0.02		338.5	" "
9	30	2.0	0.00	0.02		312.8	" "

(samples 4, 5, 6, 7) corresponded to the gradual increase in the strength of the current. There was an increase in the peptic power which ran parallel to the increased flow of mucus. Samples 3 and 4 were definitely alkaline with an extremely low peptic activity. The increase in peptic power occurred simultaneously with a rise in the total volume of secretion. It cannot, therefore, be considered as being due to concentration but must be regarded rather as a true secretion of pepsin produced by the gradually increasing strength of the electrical stimulus.

A second experiment involving weak stimulation of the vagi is demonstrated in Table II. In this experiment there were certain departures from the standard technique of preparation. The anaesthetic employed was Luminal (0.1 mg. per kg. introduced intravenously). A window was made in the left chest wall by the partial removal of four ribs. The respiratory rate was maintained at normal levels by means of an air pump. The oesophagus was tied, and both vagi were isolated and cut approximately 1½ inches above the diaphragm. Electrodes were applied to the peripheral ends of the severed vagus nerves. Stimulation was continued over a period of eight hours. The total volume of secretion was low throughout (1 c.c. or less per hour). During the first six hours it was composed entirely of a clear gelatinous substance /

TABLE II.

GASTRIC SECRETION - EFFECT OF WEAK VAGAL STIMULATION

Dog, weight 66 kg. Anaesthetized with Luminal, 0.1 mg. per kg., given intravenously. Artificial respiration used. Vagi isolated and cut above diaphragm through window in left chest wall.

Sample	Time	Volume	Mucus	Reaction (Litmus)	Peptic Activity	Remarks
	Mins.	c.c.	c.c.		Mett's Units	
1	30	1.2	0.1	Neutral	1.4	Control period
2	60	0.8	0.3	Alkaline	4.0	Continuous stimulation, coil 12 cm. for 7 hours
3	60	0.35	0.35	"	7.8	
4	60	1.0	1.0	"	51.8	
5	60	0.9	0.9	"	16.0	
6	60	0.6	0.6	"	27.0	
7	60	1.0	0.5	"	16.0	
8	60	0.6	0.3	"	16.0	

substance of high viscosity and definitely on the alkaline side. At the end of this period clear fluid commenced to flow, just as though it were an acid secretion. Such was not the case, however, as it was highly alkaline and still contained approximately 50% mucus by volume.

The experiments just cited were early attempts and the results were not as completely studied as in some of the more recent ones. Nevertheless they show clearly that weak stimulation of the vagi produces a secretion of alkaline or slightly mucoid fluid and not of regular gastric juice. When the stimulation is of sufficient strength, as in the experiment shown in Table II, the mucus possesses considerable digestive power.

In a third experiment conducted along the same lines (see Table III) the vagi were stimulated in the neck as is customary in the standard experiment. The anaesthetic in this case was Dial (0.65 cc. per kg. administered intraperitoneally). Artificial respiration was maintained from the onset. The stomach contents were practically nil, collection over a 75-minute period amounting to 0.2 cc., which was acid to litmus. Weak stimulation was applied over a period of four hours. There was a continuous and steady flow of clear, very viscid secretion. The reaction of the secretion changed from acid to neutral and became definitely /

TABLE III.

GASTRIC SECRETION - EFFECT OF WEAK VAGAL STIMULATION

Exp. Nov. 4, 1930.

Dog, weight 8.6 kg. Anaesthetized with Dial (0.65 c.c.) administered intraperitoneally. Vagi cut in the neck; oesophagus tied in the neck; pylorus tied; fistula in anterior surface of stomach.

Sample	Time		Volume	Reaction (Litmus)	Free HCl	Total HCl	Peptic Activity	Remarks
		Mins.	c.c.		Gm.%	Gm. %	Mett's Units	
	p.m.							
1	12:05-1:20	75	0.2	Acid			125.4	Control period
2	1:20-2:20	60	3.0	Neutral	0	0	36.0	Continuous stimulation begun 1:20. Coil 11 cm.
3	2:20-3:20	60	1.5	Alkaline	0	0	84.6	
4	3:20-4:20	60	3.0	"	0	0	107.1	
5	4:20-5:20	60	0.6	"	0	0	16.0	

definitely alkaline two hours after the commencement of stimulation. There was no change in the concentration of the pepsin in the secretion.

A fourth experiment with weak stimulation is shown in Table IV. The vagi were stimulated for a period of eight hours. The original stomach contents were alkaline with a low peptic activity. After stimulation for one hour the secretion was composed entirely of alkaline mucus and continued thus for four hours. In the fifth hour the secretion became more fluid and its reaction was neutral. The total volume of secretion was somewhat high for weak stimulation.

From the four experiments just quoted it is clear that weak stimulation of the vagus nerves whether in the neck or in the thorax produces mucoid secretion. This secretion is scanty; its reaction is slightly alkaline, neutral or slightly acid, and its digestive power is never very high. In many ways the functional results resemble those obtained by Savitsch after the introduction of sand into a dog's mouth. The source of the mucus will be discussed later in this section. Certainly there are indications that Oushakov may have been right when he suggested that special mucus-secreting fibres might be present in the vagus.

TABLE IV.

GASTRIC SECRETION - EFFECT OF WEAK VAGAL STIMULATION

Exp. Dec. 13, 1929.

Dog, weight 8.6 kg. Under chloralose and urethane anaesthesia. Artificial respiration used; oesophagus tied in the neck; pylorus tied at the junction with the duodenum.

Sample	Time	Volume	Mucus	Free HCl	Total HCl	Reaction (Litmus)	Peptic Activity	Remarks
	Mins.	c.c.	c.c.	Gm.%	Gm.%		Mett's Units	
1		2.3	0.4	0.00	0.00	Alkaline	1.44	Gastric contents
2	60	7.0	7.0	"	"	"	0.64	Continuous stimulation for 8 hours (weak)
3	60	6.4	6.4	"	"	"	16.0	
4	60	3.2	3.2	"	"	"	31.3	
5	60	4.0	4.0	"	"	"	36.0	
6	60	3.3	1.1	"	"	Neutral	23.0	
7	60	3.2	2.0	"	"	"	46.2	
8	60	2.7	1.8	"	"	"	56.2	
9	60	3.0	2.0	"	"	"	16.0	

Strong Stimulation

In the following series of experiments the vagus nerves were stimulated with a strong current, namely, a current of one millivolt or more. In the experiment shown in Table V, strong electrical stimulation was applied to the vagi in the neck and the resultant gastric secretions collected through a gastric fistula. The animal was prepared according to the standard method. The stimulating current was 9 cm. (i.e. 1 milliamp.), being gradually increased to 8 cm. (1.8 milliamp.). There was a latent period of approximately 40 minutes. The rate of secretion gradually increased and reached the peak of its curve within an hour. Over a period of five hours secretion was maintained at a constant level of volume and acidity. At the end of five hours the volume of the secretion diminished, as did the free and total acidity. This decrease was due to diminished excitability of the nerves at the point of contact with the electrodes. The values were returned to their previous levels by moving the electrode to a fresh position on the nerves. This procedure was repeated a little later. At the end of the experiment the nerves were still acting and the dog was in good condition. The total period of stimulation was extended over ten hours. There was a volume output of 80 to 100 cc. per hour of crystal-clear, watery fluid. This fluid however showed /

TABLE V.

GASTRIC SECRETION - EFFECT OF STRONG VAGAL STIMULATION

Exp. Oct. 29, 1931.
Dog, weight 25 kg. Under chloralose and urethane anaesthesia; no artificial respiration; oesophagus tied in the neck; pylorus tied at the junction with the duodenum.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
	p.m.	Mins.	c.c.	Gm.%	Gm. %	c.c.	Mett's Units	
1			17.0	0.00	0.19	1.8	196	Gastric contents
2	4:40-5:10	30	6.0	0.10	0.23	0.5	144	Control period
3	5:10-5:40	30	15.0	0.25	0.39	2.1	144	5.10 p.m. Continuous stimulation begun, Coil 9 cm.
4	5:40-6:10	30	61.0	0.44	0.56	1.9	256	5:40 p.m. Secretion established
5	6:10-7:10	60	54.0	0.38	0.51	1.8	484	6:45 p.m. Stimulation altered, Coil 8 cm.
6	7:10-7:40	30	53.0	0.43	0.55	1.6	900	
7	7:40-8:10	30	62.0	0.44	0.55	1.8	576	
8	8:10-8:40	30	46.5	0.42	0.55	1.9	1296	
9	8:40-9:10	30	41.0	0.42	0.55	1.7	1296	
10	9:10-9:40	30	40.0	0.40	0.55	1.7	1089	
11	9:40-10:10	30	46.0	0.42	0.56	1.0	1024	
12	10:10-10:40	30	40.5	0.39	0.53	1.3	784	
13	10:40-11:10	30	42.0	0.42	0.56	0.6	576	10:40-11:30. Intravenous injection, N/ saline, 235 c.c.
14	11:10-11:40	30	13.5	0.32	0.48	0.5	484	
15	11:40-12:10	30	21.5	0.28	0.39	1.3	1156	11:40, Electrode moved to new place on nerve.
	a.m.							11:50. Stimulation altered,
16	12:10-12:40	30	31.5	0.34	0.47	1.5	1225	coil 7 cm.
17	12:40-1:10	30	42.5	0.37	0.50	0.9	529	
18	1:10-1:40	30	63.0	0.42	0.54	0.5	729	
19	1:40-2:10	30	23.0	0.42	0.52	0.2	400	1:50 a.m. Electrode again moved
20	2:10-2:40	30	39.5	0.31	0.40	0.9	784	to new place on nerve
21	2:40-3:10	30	37.0	0.28	0.38	0.6	784	
22	3:10-3:40	30	45.5	0.22	0.33	0.8	784	
23	3:40-4:10	30	39.0	0.21	0.33	0.7	400	4:10 a.m. Stimulation
24	4:10-4:40	30	34.0	0.34	0.42	0.9	256	altered. Coil 6 cm.

showed a high concentration of both free and total acid (0.44 gm. % free HCl and 0.56 gm. % total HCl). The rise in the acid concentration like that of the pepsin output paralleled the increase in the total volume. All three components diminished when the nerves on account of lowered local excitability failed to act. Likewise all three rose when new points of contact were established between the nerves and the electrodes (see Fig.5, page 150[a]).

There are numerous investigators who hold the view that gastric secretion is a continuous process and that the glands of the stomach are never at rest. Thus, in order to meet this type of criticism, the following control experiments were undertaken (Table VI).

Two dogs were prepared simultaneously according to the standard technique for acute experimentation. The vagus nerves of the animal concerned in Table VI were stimulated with a strong current. No stimulus was applied to the cut nerves of the control animal, but it was placed on a stand and collection of the stomach secretions was proceeded with in exactly the same manner as in the first animal.

Stimulation was commenced with a current of 9 cm. (1 milliamp.). There was a latent period of less than ten minutes before secretion was well under way. The secretory rate rapidly increased as did the free and total acidity. At its /

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* Fig. 1, which was to have been inserted here, has been omitted, as a similar experiment is illustrated in Fig. 5.

TABLE VI.

GASTRIC SECRETION - EFFECT OF STRONG VAGAL STIMULATION

Exp. June 10, 1930.
Dog, weight 21.8 kg. Under chloralose and urethane anaesthesia. No artificial respiration. Oesophagus tied in neck; pylorus tied at the junction with the duodenum.
Latent period of secretion, 10 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
	p.m.	Mins.	c.c.	Gm.%	Gm. %	c.c.	Mett's Units	
1			6.5	0.00	0.17	1.0	484.0	Gastric contents
2	11:30-12:10	40	3.5	0.03	0.13	0.4	256.0	Control period
3	12:10-12:20	10	7.8	0.11	0.18	0.4	676.0	12:10 p.m. Continuous stimulation begun. Coil 9 cm.
4	12:20-12:25	5	8.4	0.25	0.35	0.15	576.0	12:20, Secretion began.
5	12:25-12:30	5	10.5	0.32	0.42	0.1	576.0	
6	12:30-12:40	10	37.5	0.43	0.51	0.4	676.0	
7	12:40-12:50	10	40.5	0.42	0.52	0.9	784.0	
8	12:50- 1:00	10	40.0	0.41	0.51	0.5	973.0	
9	1:0-1:20a.m.	20	50.0	0.34	0.43	0.6	576.0	
	a.m.							
10	1:20-1:40	20	38.0	0.43	0.49	1.4	948.0	1:40, Stimulation discontinued
11	1:40-1:55	15	0.6	0.38	0.52	0.5		
12	1:55-2:40	45	0.9	0.22	0.34	0.3		
13	2:40-3:40	60	0.6	0.07	0.20	0.1		3:40, Stimulation recommenced coil 9 cm.
14	3:40-4:00	20	11.5	0.22	0.32	2.0	2304.0	
15	4:00-4:20	20	40.0	0.37	0.52	2.5	1764.0	4:20. Hyperventilation begun
16	4:20-4:30	10	22.0	0.23	0.43	0.7	1354.0	
17	4:30-4:50	20	31.0	0.26	0.43	3.0	1024.0	
18	4:50-5:10	20	15.0	0.27	0.44	1.4	1024.0	
19	5:10-5:30	20	18.0	0.27	0.44	1.6	1156.0	
20	5:30-5:50	20	16.0	0.23	0.39	1.6	1286.0	5:50. Hyperventilation discontinued
21	5:50-6:10	20	17.0	0.25	0.39	1.6		

N.B. A control animal prepared in the same manner showed no secretion in the absence of vagal stimulation.

its height the volume of output ranged from 150 to 240 cc. per hour. After one-and-a-half hours the stimulation was discontinued for two hours. Immediately after the cessation of stimulation secretion stopped almost completely. There was a fall in both free and total acid (0.43 to 0.07 gm. % and 0.49 to 0.20 gm. % respectively). Stimulation was recommenced and produced a return of secretion which gradually increased in volume and free and total acidity. After 40 minutes the animal was artificially hyperventilated with consequent but gradual fall in all the components of the secretion. This last effect will be discussed in the section on CO_2 and gastric secretion.

The control animal during the same time interval failed to secrete in the absence of vagal stimulation.

Further examples of strong stimulation of the vagi and the resultant production of copious gastric secretion are presented in Tables VII and VIII. Here again the volume of the secretion was large, and its acidity and digestive power high.

From the aforementioned experiments it is evident that two types of gastric secretion are obtained as a result of vagal stimulation, the character of the secretion depending entirely upon whether a weak or strong current is used. Up to this time the combination of weak and strong currents, applied /

TABLE VII.

GASTRIC SECRETION - EFFECT OF STRONG VAGAL STIMULATION.

Exp. Feb. 25, 1929.
Dog, weight 7 kg. Under chloralose and urethane anaesthesia. No artificial respiration. Oesophagus tied in the neck; pylorus tied at the junction with the duodenum. Gastric contents - none. Latent period of secretion, 15 minutes.

Sample	Time	Mins.	Volume	Free HCl	Total HCl	Mucus	Total Chloride	Peptic Activity	Remarks
	p.m.		c.c.	Gm.%	Gm.%	c.c.	Mg.%	Mett's Units	
1	12:05-1:00	55	0.45	0.01	0.02	0.00			Control period.
2	1:0-2:00	60	1.4	0.08	0.14	0.1		144.0	1:15, continuous stimulation begun,
3	2:00- 3:00	60	0.8	0.10	0.14	0.3		196.0	Coil 13 cm.
4	3:0-3:30	30	7.0	0.28	0.33	1.4	573.9	400.0	3:00.. Stimulation altered. Coil 9 cm.
5	3:30-3:40	10	6.5	0.44	0.49	0.6	573.5	324.0	3:15 Secretion commenced
6	3:40-3:50	10	8.0	0.45	0.52	0.6	564.3	400.0	
7	3:50-4:00	10	4.0	0.46	0.52	0.3	560.2	400.0	3:50 Electrode moved to
8	4:00-4:10	10	4.0	0.44	0.50	0.3	565.7	354.4	new place on nerve;
9	4:10-4:20	10	3.8	0.41	0.47	0.5	540.3	368.1	hyperventilation begun.
10	4:20-4:30	10	2.5	0.38	0.48	0.4	538.9	400.0	
11	4:30-4:40	10	2.2	0.34	0.42	0.2	537.5	400.0	
12	4:40-4:50	10	6.5	0.39	0.47	0.7	545.9	400.0	4:40, Hyperventilation
13	4:50-5:00	10	5.1	0.43	0.50	0.2	558.8	324.0	discontinued.
14	5:00-5:10	10	6.0	0.42	0.47	0.3	553.0	324.0	
15	5:10-5:20	10	4.5	0.43	0.50	0.2	547.3	312.9	
16	5:20-5:30	10	5.5	0.43	0.48	0.4	544.5	256.0	

TABLE VIII.

GASTRIC SECRETION - EFFECT OF STRONG VAGAL STIMULATION.

Exp. July 23, 1931.
Dog, under chloralose and urethane anaesthesia; no artificial respiration. Oesophagus tied in the neck; pylorus tied at the junction with the duodenum.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
		Mins.	c.c.	Gm.%	Gm.%	c.c.	Mett's Units	
	a.m.							
1	11:45-12:30	45	0.4	acid	acid	trace		Control period
	p.m.							
2	12:30-12:50	20	1.0	"		0.5		12:30 p.m. Continuous stimulation begun. Coil 9 cm.
3	12:50-1:00	10	4.5	0.05	0.29	0.3	557	
4	1:00- 1:10	10	8.0	0.05	0.29	0.7	369	
5	1:10- 1:20	10	7.2	0.21	0.44	0.5	576	
6	1:20- 1:30	10	6.7	0.26	0.44	0.7	625	
7	1:30- 1:40	10	6.5	0.28	0.49	0.3	676	
8	1:40- 1:50	10	5.5	0.26	0.47	0.4	676	1:50 p.m. Stimulation altered, Coil 8 cm.
9	1:50- 2:00	10	4.6	0.26	0.47	0.3	784	
10	2:00-2:10	10	6.5	0.25	0.43	0.3	676	
11	2:10- 2:20	10	5.2	0.26	0.45	0.2	784	
12	2:20- 2:30	10	4.7	0.26	0.50	0.3	433	
13	2:30- 2:40	10	3.7	0.29	0.44	0.3	557	
14	2:40- 2:50	10	5.0	0.28	0.49	0.3	1024	
15	2:50- 3:00	10	8.4	0.23	0.39	0.4	900	
16	3:00- 3:10	10	11.0	0.27	0.47	0.2	900	
17	3:10- 3:20	10	9.5	0.29	0.50	0.1	784	
18	3:20- 3:30	10	8.5	0.29	0.51	trace	784	
19	3:30- 3:40	10	3.5	0.33	0.50	0.2	784	
20	3:40- 3:50	10	6.5	0.24	0.42	0.2	784	
21	3:50- 4:00	10	8.4	0.22	0.39	0.2	676	
22	4:00- 4:10	10	8.2	0.29	0.48	0.1	484	
23	4:10- 4:20	10	7.5	0.20	0.37	0.1	576	
24	4:20-4:30	10	4.5	0.28	0.47	0.3	400	
25	4:30- 4:40	10	7.5	0.15	0.26	0.4	576	4:40 p.m. Electrode moved to a new place on nerve.
26	4:40- 4:50	10	7.5	0.23	0.42	0.5	729	
27	4:50- 5:00	10	19.0	0.23	0.42	0.2	400	
28	5:00- 5:10	10	9.0	0.27	0.47	0.3	400	
29	5:10- 5:20	10	6.0	0.23	0.42	0.3	196	
30	5:20- 5:30	10	7.0	0.20	0.37	0.3	400	

applied alternately to one vagus nerve or to both nerves at once, in the same animal, had not been attempted. Since it is probable that under normal physiological conditions stimuli of different strengths are sent through the vagi to the gastric mucosa, then in acute experimentation the vagi likewise may be expected to convey different stimuli in one and the same animal. The effect of transition from weak to strong stimulation may be seen in Tables IX and X.

In the experiment shown in Table IX, stimulation was commenced with a weak current (coil 13 cm.). After two hours the reaction of the secretion changed from acid (0.02 gm. % free HCl; 0.11 gm. % total HCl) to alkaline. An alkaline secretion composed almost entirely of mucus was secreted for 270 minutes, at which point a strong current (coil 9 cm.) was introduced, causing a gradual rise in the volume of secretion and a definite secretion of both free and total acid. Hence by variation of the strength of the electrical stimulus applied to the vagus nerves the gastric mucosa was made to swing through three phases of reaction - from acid to alkaline and back again to acid. Two other points are worthy of note in this experiment: firstly, the spectacular rise in peptic units from 64 to 1632 accompanying the appearance of acid secretion; secondly, the curve of the mucus secretion, starting with an absence of mucus in the stomach contents, rising /

TABLE IX.

GASTRIC SECRETION - EFFECT OF TRANSITION FROM WEAK TO STRONG VAGAL STIMULATION

Exp. March 20, 1930.

Dog, weight 13 kg. Under chloralose and urethane anaesthesia. No artificial respiration. Oesophagus tied in the neck; pylorus tied at the junction with the duodenum. Latent period of secretion, 20 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity	Remarks
	a.m.	Mins.	c.c.	Gm.%	Gm. %	c.c.	Mgm. %	Mett's Units	
1			1.7	0.02	0.11	0.00		134.5	Gastric contents
2	10:30-11:30	60	3.0	0.00	0.06	0.00	452.3	369.9	10;30 Continuous
3	11:30-12:00	30	1.0			Trace			stimulation begun,
4	12:00-12:30	30	4.0	0.00	0.01	1.5	429.6	16.0	Coil 13 cm.
5	p.m.								
5	12:30- 1:00	30	5.0	Alkaline		2.0	469.0	16.0	
6	1:00- 1:30	30	3.5	"		2.5	331.8	16.0	Stimulation altered,
7	1:30- 2:00	30	5.0	"		4.9			Coil 11 cm.
8	2:00-2:30	30	2.5	"		2.2	331.8	89.4	" 10 cm.
9	2:30-3:00	30	3.0	"		3.0	334.6	36.0	" 9 cm.
10	3:00-3:30	30	5.5	"		5.0	336.0	64.0	3:10, secretion
11	3:30-3:45	15	3.0	0.00	0.27	3.0	453.7	1632.0	commenced
12	3:45-4:00	15	4.9	0.11	0.43	3.0	472.0	1830.4	
13	4:00-4:10	10	6.5			1.0			
14	4:10-4:20	10	Lost						
15	4:20-4:30	10	2.4	0.29	0.47	0.3	523.2	1324.9	
16	4:30-4:40	10	2.5			0.4			Stimulation altered,
17	4:40-4:50	10	3.0	0.27	0.52	0.5	506.1	1324.9	Coil 7 cm.
18	4:50-5:00	10	1.8			0.3			

TABLE X.

GASTRIC SECRETION - EFFECT OF TRANSITION FROM WEAK TO STRONG VAGAL STIMULATION.

Exp. March 17, 1930.
Dog, weight 10 kg. Under chloralose and urethane anaesthesia. No artificial respiration.
Oesophagus tied in the neck; pylorus tied at the junction with the duodenum.
Latent period of secretion, 25 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity	Remarks
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mgm.%	Mett's Units	
1	10:50-11:20	30	3.1	0.00	0.05	0.4		595.3	Control period
2	11:20-12:20	60	0.35	acid	acid	0.2			11:20. Continuous stimulation begun. Rt. vagus coil 15 cm. Lt. " " 13 "
	p.m.								
3	12:20- 1:20	60	0.75	alkaline		0.75		16.0	11:40. Stimulation altered. Rt. vagus coil 14 cm. Lt. " " 15 cm.
4	1:20- 1:40	20	3.7	"		3.7	479.2	16.0	1:50. Stimulation altered. Rt. vagus coil 13 cm. Lt. " " 12 cm.
5	1:40-2:20	40	0.85	"		0.85		16.0	3:10. Stimulation altered. Rt. vagus coil 11.5 cm. Lt. " " 10.5 cm.
6	2:20- 3:20	60	1.4	"		1.4	486.2	16.0	4:15. Stimulation altered. Rt. & Lt. coil 9 cm.
7	3:20- 4:20	60	1.5	"		1.5		16.0	4:50. Acid secretion began.
8	4:20- 4:55	35	1.9	0.05	0.10	1.9	521.8	576.0	
9	4:55- 5:20	25	3.1	0.23	0.32	3.0	524.6	1024.0	
10	5:20- 5:50	30	3.5	0.15	0.30	2.8	612.2	1632.1	
11	5:50- 6:25	35	11.9	0.24	0.37	3.5	557.2	829.4	
12	6:25- 6:35	10	3.6	0.38	0.51	0.5	576.6	998.5	
13	6:35- 6:45	10	1.6	0.36	0.50	0.2	521.8	924.1	

rising gradually to form 100% of the secretion during weak stimulation and diminishing to a minimum with the advent of secretion produced by strong stimulation.

A similar experiment is presented in Table X.

Strong stimulation of the vagus nerves thus produces a secretion of gastric juices which differs greatly from that obtained by weak stimulation. With the former we obtain a secretion which is high in both free and total acidity and also in peptic power. In composition it resembles closely the secretion of psychic stimulation or of sham feeding. Weak stimulation, on the other hand, is responsible for a secretion composed almost entirely of alkaline mucus with a low peptic activity. The gastric mucosa is capable of responding to either form of stimulation during acute experimentation.

The Source of Mucus in Gastric Juice

It has been shown histologically that there are four possible sources from which mucus in the gastric secretion may be derived:

1. /

1. Oesophagus,
2. Pyloric antrum,
3. The surface epithelium of the fundal part of the stomach,
4. The mucoid cells of the peptic glands.

From a purely histological point of view the presence of mucoid cells in the above regions might be considered sufficient. The physiologist however requires more definite proof. We have in the attempted solution of this question resorted to methods of trial and elimination - an old and time-worn procedure, it is true, and yet not infrequently a most effective one.

First, in order to exclude the oesophagus as a possible source of mucus, its isolation from the secreting stomach was essential. There were many technical difficulties to be surmounted (for details of the procedure finally employed see section on the oesophagus under "Methods"). A dog, prepared according to standard method, was used. A cannula was inserted into the lower end of the oesophagus below the diaphragm without injuring the branches of the vagus nerves. A second cannula was tied into the distal end of the oesophagus in the region of the neck. The vagus nerves were electrically stimulated in the neck and gastric secretions collected from a gastric fistula as in other experiments already mentioned. Under /

Under such conditions weak stimulation of the vagi caused a flow of mucus from the stomach and none from the oesophagus. Strong stimulation, on the other hand, initiated a copious flow of acid juice from the stomach. In addition a considerable amount of thick gelatinous transparent alkaline mucus was obtained separately from the oesophagus. Thus mucus obtained under the influence of weak stimulation comes from the stomach and not from the oesophagus (see Table XI).

In this experiment the current to begin with was weak (14 cm.). It was gradually increased over a period of four hours to 11.5 cm. and finally, 45 minutes later, to 9 cm. (strong). The stomach contents were acid and contained approximately 50% mucus. During the second hour of stimulation the secretion became neutral and in the third hour alkaline. The volume of secretion was small, ranging from 0.2 c.c. to 0.65 c.c. per hour. There was no oesophageal secretion. As the current was increased in strength clear acid fluid appeared. This gradually increased in volume and in free and total acidity, reaching its height in 90 minutes. During this short period the volume rose from 0.65 c.c. to 38.8 c.c. per hour - the reaction changing from alkaline to an acidity of 0.50 gm. % free and 0.54 gm. % total acid. With the advent of strong stimulation the secretion, which previously had contained 100% mucus, became clear with only a faint trace

of /

TABLE XI.

GASTRIC SECRETION - EFFECTS OF VAGAL STIMULATION WHEN OESOPHAGUS IS ISOLATED.

Exp. March 25, 1930.
Dog, weight 5.9 kg. Under chloralose and urethane anaesthesia. No artificial respiration.
Pylorus tied at junction with duodenum; fistulae in oesophagus above and below diaphragm.
Latent period of secretion 10 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity	Remarks
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mgm. %	Mett's Units	
1			3.0	0.00	0.13	1.5	582.7	998.5	Gastric contents
2	11:25-12:25 p.m.	60	0.55	0.00	0.06	0.2			11:25a.m. Continuous stimulation begun, Coil 14 cm.
3	12:25-1:25	60	0.4	neutral		0.4			
4	1:25-2:25	60	0.2	alkaline		0.2			1:45 p.m. Stimulation altered, coil 13 cm.
5	2:25-3:25	60	0.65	"		0.65		640.	2:40 p.m. " 12.5 cm.
6	3:25-4:05	30	1.5	0.09	0.12	trace	481.8	268.9	3:20 p.m. " 11.5 "
7	4:05-4:15	20	5.5	0.36	0.43	"	527.4	484.0	4:05 p.m. " 9 "
8	4:15-4:25	10	6.0	0.44	0.51	"	561.4	256.0	4:15 p.m. Acid secretion started
9	4:25-4:40	15	9.5	0.47	0.54	0,1	589.7	256.0	
10	4:40-4:55	15	9.7	0.50	0.54	faint trace	571.2	268.9	
11	4:55-5:25	30	12.4	0.47	0.53	0.5	592.5	243.3	5:15 p.m. Stimulation altered, coil 6 cm.
12	5:25-5:40	15	3.4	0.40	0.48	clear	571.2	219.0	

of mucus. With strong stimulation, however, a definite secretion of thick alkaline mucus was collected from both the upper and lower oesophageal fistulae.

A similar experiment is reported in Table XII. The current, which at the beginning was somewhat stronger, i.e. 12 cm. (which is still on the weak side), was gradually increased to 9 cm. (strong). The secretion, at first acid, passed through an alkaline phase and then quickly, with the application of a stronger current, reverted to acid. Here much larger quantities of mucus were present during weak stimulation than in the previous experiment. Moreover, mucus continued to be secreted once gastric juices were flowing freely.

A third and more complete example is shown in Table XIII. In this case the total volume of gastric secretion collected was 100.7 c.c. during 280 minutes of strong stimulation, 14.9 c.c. of which was mucus. In addition 20.1 c.c. of mucus were obtained from the upper and lower oesophageal cannulae.

The experiments reported above show that the mucus obtained in gastric juice has at least two sources of origin: (1) Oesophagus, (2) Stomach. Further experimental analysis showed that the great part of the mucus secreted during stimulation of the vagi comes from the fundal part of the stomach. This was proved in the following manner. The oesophagus /

TABLE XII.

GASTRIC SECRETION - EFFECTS OF VAGAL STIMULATION WHEN OESOPHAGUS IS ISOLATED.

Exp. March 21, 1930.
Dog, weight 13.9 kg. Under chloralose and urethane anaesthesia. No artificial respiration. Pylorus tied at the junction with the duodenum; fistulae in oesophagus above and below diaphragm. Latent period of secretion 7 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity	Remarks
	p.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mgm. %	Mett's Units	
1			3.0	0.00	0.08	3.0		324.0	Gastric contents
2	12:05- 1:05	60	1.2	0.00	0.09	1.2		282.0	12:05, continuous stimulation begun, coil 12 cm.
3	1:05- 1:35	30	5.4	alkaline		5.4	472.0	36.0	
4	1:35- 2:35	60	0.9	acid	acid	0.9		529.8	
5	2:35- 3:05	30		0.00	0.04		492.0	243.3	2:43 p.m. stimulation altered, coil 13 cm.
6	3:05- 3:35	30	1.5	0.09	0.17	1.5		484.0	3:25 p.m. stimulation altered, coil 12 cm.
7	3:35- 4:05	30	1.3	0.07	0.14	1.3		576.0	
8	4:05- 4:20	15	5.5	0.18	0.19	3.5	545.9	576.0	4:10 p.m. stimulation altered, coil 9 cm.
9	4:20- 4:45	25	8.0	0.31	0.40	2.5	564.2	576.0	4:17 p.m. secretion started
10	4:45- 4:50	5	10.0	0.41	0.50	1.3	582.7	576.0	
11	4:50- 5:0	10	8.9	0.44	0.53	0.7		416.1	
12	5:0 - 5:10	10	7.5	0.44	0.54	0.6	567.0	416.1	
13	5:10-5:20	10	12.5	0.44	0.54	1.7	566.6	432.0	
14	5:20-5:30	10	15.4	0.44	0.54	0.9	574.3	432.0	

TABLE XIII.

GASTRIC AND OESOPHAGEAL SECRETIONS - EFFECTS OF STRONG VAGAL STIMULATION.

Exp. March 28, 1930.
Dog, under chloralose and urethane anaesthesia. No artificial respiration. Pylorus tied at the junction with the duodenum; fistulae in oesophagus above and below diaphragm.
Latent period of secretion 42 minutes.

Time		Sample	Gastric Secretion						Sample	Oesophageal Secretion		Remarks
			Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity		Volume	Peptic Activity	
	Mins.		c.c.	Gm.%	Gm. %	c.c.	Mgm.%	Mett's Units		c.c.	Mett's Units	
a.m.												
10:50-11:20	30	1	0.5	acid	acid	0.5						10:50. Continuous stimulation begun. Coil 9 cm.
11:20-11:32	12	2	0.7	"	"	0.4		324.0	1	3.5	0	
11:32-12:02	30	3	6.0	0.14	0.37	1.5	480.7	519.8				11:32. Secretion commenced.
p.m.												
12:02-12:12	10	4	3.0	0.30	0.40	1.4	519.0	676.0				
12:12-12:22	10	5	8.4	0.36	0.45	1.8	534.5	501.7	2	4.0	0	
12:22-12:32	10	6	6.5	0.42	0.50	1.2	538.7	416.1				12:32. Stimulation discontinued.
12:32-12:42	10	7	1.7	0.42	0.50	0.15	557.2	400.0				
12:42- 1:30	48	8	1.3	0.33	0.45	0.3		324.0				
1:30- 2:00	30	9	1.4	0.07	0.27	1.4		484.0	3	3.5	0	1:40. Stimulation recommenced.
2:00-2:20	20	10	4.5	0.24	0.36	1.4	528.8	576.0				Coil 8 cm.
2:20- 2:40	20	11	8.7	0.39	0.45	1.4	521.9	484.0				
2:40- 3:00	20	12	8.7	0.42	0.47	1.4	534.5	400.0	4	3.0	0	
3:00- 3:20	20	13	7.3	0.37	0.51	0.7	528.8	353.4	5	1.1	0	
3:20- 3:40	20	14	10.5	0.41	0.48	0.55	626.6	400.0	6	3.0	0	
3:40- 4:40	60	15	31.5	0.42	0.52	0.8	572.6	196.6	7	2.0	0	

oesophagus was tied below the diaphragm and the pyloric antrum isolated from the remainder of the stomach. In order to accomplish the latter operation, a small longitudinal incision was made on the anterior surface of the pyloric part of the stomach at a distance of 4 to 5 cm. from the pyloric sphincter. The muscular coats alone were sectioned. By careful dissection the submucous mucosa was carefully separated from the muscularis throughout the entire circumference of the pyloric antrum. The isolated submucosa and mucosa were then tied securely. By this method the pyloric part was isolated from the remainder of the stomach with a minimal amount of trauma and without entering into the lumen of the organ.

Table XIV represents an experiment in which the above procedure was followed. In spite of the absence of the oesophagus and of the pyloric part of the stomach, i.e. the part secreting alkaline mucoid fluid containing pepsin, there was a flow of mucus after stimulation with a weak current. From a study of this experiment it will be observed that over a period of six hours there was a steady flow of mucus. The reaction of this secretion was faintly alkaline or neutral to litmus paper, but it contained a faint trace of acid when titrated. It is interesting to note that the original contents of the stomach collected during a period of /

TABLE XIV.

GASTRIC SECRETION - EFFECT OF VAGAL STIMULATION WHEN BODY OF STOMACH IS ISOLATED.

Exp. Sept. 19, 1930.
Dog, weight 12.1 kg. Under chloralose and urethane anaesthesia. No artificial respiration. Oesophagus tied in the neck and below the diaphragm; body of stomach isolated from the pylorus. Latent period of secretion 13 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
	p.m.	Mins.	c.c.	Gm.%	Gm. %	c.c.	Mett's Units	
1	3:00-4:30	90	2.0	0.02	0.17	Trace	64.0	Control period
2	4:30-5:30	60	2.5	0.00	0.14	2.4	64.0	4:30 p.m. Continuous stimulation begun: Coil 14 cm.
3	5:30-6:30	60	1.6	0.00	0.05	1.6	36.0	
4	6:30-7:30	60	1.5	0.00	0.03	1.5	16.0	
5	7:30-8:30	60	1.8	0.00	0.001	1.8	36.0	
6	8:30-9:30	60	1.5	0.00	0.001	1.5	36.0	8.40 p.m., Stimulation altered; Coil 13.5 cm.
7	9:30-10:30	60	2.4	0.00	0.001	2.4	100.0	
8	10:30-11:00	30	2.7	0.05	0.18	0.4	324.0	10:30 p.m. Stimulation altered; Coil 9 cm.
9	11:00-11:30	30	1.6	0.09	0.23	1.0	354.0	10:43 p.m. Secretion started
10	11:30-12:00 a.m.	30	4.8	0.14	0.28	4.0	576.0	11:40 p.m. Stimulation altered: Coil 8.5 cm.
11	12:00-12:30	30	5.0	0.18	0.34	4.0	784.0	12:12 a.m. 150 c.c. N/ saline given intravenously
12	12:30-12:50	20	8.5	0.25	0.39	5.0	806.5	
13	12:50- 1:10	20	8.4	0.24	0.40	4.0	900.0	

of 90 minutes contained only a trace of mucus and had a fairly high acidity. This suggests that the traces of acid in samples 2, 3, 4, 5, 6 and 7 represent simply a washing out of the original acid content by freshly secreted mucus. Further, when a strong stimulus was applied there was a flow of free acid within 13 minutes. This occurred after six hours of weak stimulation. The secretion thus obtained gradually increased in volume, acidity and peptic power to values comparable with those obtained in other experiments in which strong stimulation was applied.

A similar experiment is shown in Table XV. The animal was prepared in exactly the same way. Weak stimulation was continued over a period of four hours. A total of 3.0 cc. of mucus was secreted. Strong stimulation was followed by acid secretion which gradually increased in volume, acidity and peptic power.

From the afore-mentioned experiments it is clear that mucus can be obtained from the fundus or body of the stomach by weak stimulation. The most difficult point to establish is the exact source of the mucus secreted during stimulation of the vagi in relation to the histological structure of the stomach. Under the conditions of stimulation employed a certain proportion of the total mucus secreted must, it was thought, be contributed by the surface epithelium, particularly /

TABLE XV.

GASTRIC SECRETION - EFFECT OF VAGAL STIMULATION WHEN BODY OF STOMACH IS ISOLATED.

Exp. June 27, 1930.
Dog, weight 13 kg. Under chloralose and urethane anaesthesia. No artificial respiration.
Oesophagus tied in the neck and below the diaphragm; body of stomach isolated from the pylorus.
Latent period of secretion 14 minutes.

Sample	Time		Volume	Mucus	Remarks
		Mins.	c.c.	c.c.	
	p.m.				
1	1:00- 2:00	60	3.8	1.0	1 p.m., continuous stimulation commenced, Coil 15 cm.
2	2:00- 3:00	60	1.0	1.0	2:15 p.m., stimulation altered, Coil 14.5 cm.
3	3:00- 4:00	60	0.5	0.5	
4	4:00- 5:00	60	0.5	0.5	4 p.m., stimulation altered, Coil 13 cm.
5	5:00- 5:25	25	6.0	5.5	5 p.m., " " " 9 cm. 5:14 p.m., secretion commenced
6	5:25-5:35	10	9.0	1.5	
7	5:35- 5:45	10	6.8	1.0	

particularly if the stimulation of the vagi influences the motility of the gastric mucous membrane. In order to ascertain whether this was true or not the following experiment was performed (see Table XVI).

Direct Observation of Secreting Mucosa

The animal was prepared in the standard manner with certain modifications of technique. A gastric fistula was inserted into the posterior surface of the stomach instead of the anterior surface and brought out through a stab wound in the left flank. A glass window was sewed into the anterior surface of the stomach in such a manner as to permit observation of part of the gastric mucous membrane during the experiment. In the resting state the mucosa was faintly pink and slightly moist. The inter-rugal spaces were dry or just perceptibly moist. After twenty-three minutes' stimulation of the vagi the mucosa became definitely pinker, almost rose-coloured. From the inter-rugal crypts a clear fluid commenced to well up. Shortly after, drops of clear acid fluid appeared in the collecting flask. The secretion followed the course usually observed after strong stimulation of the vagi. Besides the gradual formation of gastric juice, definite movements of the gastric mucous membrane were seen. These movements seemed to be correlated with /

TABLE XVI.

GASTRIC SECRETION - EFFECTS OF STRONG VAGAL STIMULATION, UNDER DIRECT OBSERVATION.

Exp. March 4, 1930.
Dog, weight 6.4 kg. Under chloralose and urethane anaesthesia; metal fistula in posterior surface and glass window in anterior surface of the stomach.
Latent period of secretion 23 minutes.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity	Remarks
	p.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mgm.%	Mett's Units	
1	2:40-3:20	40	4.0	0.23	0.31	0.45	567.2	484.0	2:40 p.m. continuous stimulation begun. Coil 9 cm.
2	3:20-3:40	20	2.3	0.31	0.38	0.1	551.6	484.0	3:03 p.m. secretion seen through window.
3	3:40-3:50	20	4.5	0.33	0.42	0.3	547.3	676.0	
4	3:50-4:00	10	1.8	0.39	0.47	0.1	565.7	676.0	
5	4:00-4:10	10	0.7			Trace		676.0	
6	4:10-4:20	10	1.9	0.34	0.42	0.2	547.3	718.0	4:15 p.m. Stimulation altered. Coil 8 cm.
7	4:20-4:30	10	3.3	0.33	0.43	0.3	554.4	784.0	
8	4:30-4:40	10	4.2	0.36	0.47	0.4	560.2	900.0	4:40 p.m. Hyperventilation begun.
9	4:40-4:50	10	3.1	0.36	0.44	0.3	554.4	784.0	
10	4:50-5:00	10	2.8	0.23	0.36	0.3	558.8	576.0	
11	5:00-5:10	10	2.4	0.25	0.38	0.3	537.5	739.8	5:10 p.m. Stimulation altered. Coil 7.5 cm.
12	5:10-5:20	10	5.1	0.22	0.34	0.3	541.7	636.0	
13	5:20-5:30	10	3.1	0.30	0.44	0.4	548.7	636.0	5:25 p.m. Hyperventilation discontinued.
14	5:30-5:40	10	4.4	0.34	0.45	0.4	562.8	484.0	

with the time of stimulation.

Thus the mucus of the surface epithelium may be washed out by the flow of gastric juice and also pressed out by the movements of the mucous membrane. Further, it is possible that the vagi have a direct action on the secretory elements of the surface epithelium. There are, however, certain facts which indicate that the mucoid secretion may arise from another source. For example: (1) Under vagal stimulation the mucus secreted was obtained in large volumes and had a more liquid character than the mucus of surface epithelial origin. (2) When this mucus was properly diluted with a N/20 solution of HCl, it possessed a marked peptic power. The presence of a high peptic content usually coincided with the increased flow of mucus and the appearance of the first trace of acid secretion. Such was the picture when weak stimulation was applied to the vagus nerves. A strong current produced a secretion of gastric juice which was high is acid and enzyme content but poor in mucus. (3) Webster (1930), working in this laboratory, found a mucin-like substance present in the gastric juice in a soluble state. Its concentration ran parallel to that of the peptic power of the juice.

Hence it might not be unreasonable to suppose that the mucus which possessed digestive enzymes was secreted by special mucoid /

mucoid cells located in the neck of the peptic gland. This hypothesis will be discussed later.

Latent Period of Gastric Secretion

The latent period of secretion was much shorter in our experiments than in those reported by Oushakov. In our experiments there was also a difference between those in which strong stimulation was preceded by the application of a weak current and those in which strong stimulation alone was used. Thus the average latent period for twelve experiments, in which the vagus nerves were stimulated with a weak current prior to the application of a strong one, was 21 minutes. The shortest latent period was 7 minutes and the longest 35 minutes. When a strong current alone was employed, the average latent period for sixteen experiments was 27 minutes, the minimum 15 minutes and the maximum 42 minutes.

DISCUSSION /

DISCUSSION

The experimental data presented above demonstrates that it is possible to obtain two types of gastric secretion by the application of currents of different strength to the vagus nerves in the neck. The gastric mucosa thus responded in a varied manner depending upon the type of stimulus which reached it. When a weak stimulus was applied, a mucoid secretion was provoked, whereas,in response to strong stimulation, gastric juice of normal composition was produced. It will be remembered that previous workers reported a marked difference in composition between the gastric juices obtained by sham feeding and those produced by electrical stimulation.

Pavlov obtained a scanty secretion and Oushakov a secretion containing much mucus when the vagus nerves of a dog were electrically stimulated. A consideration of the composition of the gastric juices thus obtained by the aforementioned authors reveals that it can be compared in every detail with the composition of the gastric secretions obtained in our experiments in response to a weak or moderately weak stimulation of the vagus nerves. Furthermore, the gastric juice of sham feeding as reported by numerous investigators (e.g. Pavlov, Oushakov), except for a lower peptic power, is identical in composition with that obtained when strong /

stimulation is applied to the vagus nerves. In both, the volume and the free and total acidity are high. It may be that previous workers when stimulating the vagi employed only a weak or moderately weak current. Further the large quantity of mucus in the gastric secretion may also be partly attributed to the effect of artificial respiration which was employed in their experiments. From the results presented in Part V it will be seen that hyperventilation of the animal during vagal stimulation greatly diminishes the flow of acid gastric juice without affecting the secretion of mucus. Another source of mucus in gastric secretion of vagal origin lies in the oesophageal glands. These glands are under the control of the vagus nerve (see Part IV) and their mucoid secretion will also be mixed with gastric juice unless its entrance into the stomach is prevented. Evidently these factors were not considered by previous investigators.

Similarly, in the normal physiological functioning of the intact animal, different nervous stimuli are apparently responsible for gastric secretions unlike in composition. It will be recalled that Savitsch (1922) obtained a secretion of mucus from a previously acid stomach by stimulation of the mouth cavity with sand. The stimulus was an unpleasant one and the results were quite different from those produced by /

by psychic stimulation,which is pleasant and provokes a flow of regular gastric juice.

In considering the mechanisms involved in the production of two different types of secretion by stimuli of varied intensity, it seems probable that there are different nerve fibres in the vagus supplying distinct gastric secretory elements and that each fibre or group of fibres is affected by currents of various strengths. This conception has as its foundation certain histo-anatomical physiological facts concerning the vagus nerve which were described by Heinbecker (1930-31) and by Heinbecker and O'Leary (1933).

In considering the effect of strong stimulation of the vagi it is interesting to note that the gastric secretion thus produced possesses a higher peptic content than the gastric juice obtained from dogs with oesophagotomy and gastric fistula or with a Pavlov pouch. Therefore it would seem that the vagus nerve, in addition to its power of activating the parietal cells, bears a definite relation to the pepsin-producing cells of the gastric glands. To use the expression of Heidenhain, the vagus nerve might thus be termed the true "trophic nerve" of the gastric mucosa.

Interpretation of the part played by the gastric mucus in the stomach is by no means easy, nor is it less difficult to comprehend the significance of its production by vagal stimulation /

stimulation. There are two main theories concerning the function of gastric mucus in relation to the stomach. One is that the gastric mucus is a protective agent for the gastric mucosa (Babkin, 1928). The other is the theory subscribed to by Brestkin and Bickoff (1924), who maintain that mucus, when mixed with gastric juice, goes partly into solution and being rich in pepsin thereby raises the digestive power of the juice. The ability of mucus to digest coagulated protein after being acidified is established. However the conception that mucus possesses a weak digestive power, and not a strong one as Brestkin and Bickoff think, is more in accord with the results of this investigation. There is another possibility which cannot be ignored, namely that the pepsin in mucus is the result of contamination with pepsin secreted by the peptic cells during the resting state of the gastric glands.

Again it is possible that mucus may play some part in certain pathological conditions. For example, there might presumably be some correlation between the formation of peptic ulcers and the function or lack of function of the mucoid cells of the gastric mucosa. Kaufman (1908), after analysing many clinical cases, came to the conclusion that free microscopical mucus was decidedly lacking in cases of peptic ulcer. He attributed the relief of pain following gastric /

gastric lavage with a solution of silver nitrate to the excessive amount of mucus thrown out in response to a local irritant. It is possible that mucus protects the gastric mucous membrane against autodigestion. The clinical observations of Kaufman (1908) suggest this probability. More convincing evidence in support of this theory has been advanced by Webster and Kamarov (1932) who found a dissolved mucoprotein in gastric juice, which they designated as "dissolved mucin", and by Babkin and Kamarov (1932) who demonstrated an inhibitory effect of mucus on peptic digestion. Thus it is likely that both "visible mucus" and "dissolved mucin" tend to protect the mucous membrane from autodigestion. In the present investigation it has been demonstrated that the secretion of mucus is under the control of the vagus nerve - which seems to be another of the many important functions of this nerve.

Volkovitch (1898) in Pavlov's laboratory studied a case of spontaneous gastric ulcer which had formed in an isolated Pavlov pouch in a dog. He found that there was no change in the first or nervous secretory phase after feeding but that there was a great prolongation of the second or chemical phase. In addition the acidity of the juice was above normal, while the peptic content was somewhat below normal. Thus it would seem that in the presence of peptic ulcers (in the /

the dog) there is a hypersecretion of gastric juice, but the juice is poor in organic substances and in mucus: that is, it differs in composition from the normal and yet remains highly active. The elements of gastric secretion thus appear to be pathologically separated and may be produced independently in much the same manner as we have succeeded in producing different types of secretion by electrical stimulation of the vagus nerve.

P A R T II

HISTORICAL:

HISTAMINE AND PILOCARPINE IN RELATION TO GASTRIC SECRETION

Thirteen years after the synthetic preparation of histamine (β-iminazolylethylamine) by Barger and Dale (1910) came the discovery of Popielski (1920). He found that subcutaneous injection of this substance was followed by copious gastric secretion. Since that time many investigators have studied the effect of histamine upon gastric secretion. Popielski himself was of the opinion that the effective parts in Edkins' pyloric extract was histamine. Koch, Luckhardt and Keeton (1920) attempted to isolate the active principle contained in extracts of the pyloric mucosa. Although they were unable to obtain histamine in their extracts, they stated that histamine and gastrin "may later be found to be identical or closely related". Indeed in the light of recent work their deductions seem highly justified. Eleven years later Sacks, Ivy, Burgess and Vandolah (1931) isolated histamine as a sulphate from the pyloric mucosa of the hog. One year later the same authors published almost indisputable evidence that the active secretory principle in extracts of the /

the pyloric mucosa is histamine or a very closely related iminazole. They further showed that no iminazoles other than pilocarpine and isopilocarpine and histamine are gastric stimulants. Ivy and McIlvain (1923) have ahown that a continuous application of a 1/1000 histamine solution to the duodenal or jejunal mucosa over a 20-minute period resulted in a gastric secretion which continued for one to two hours. In fact they found that the intestinal application of histamine is even more effective than that of meat extract.

MacKay (1930) points out that histamine can be obtained from both the normal mucous membrane of the alimentary tract and the intestinal contents, and states that "in view of this and the fact that very minute amounts of the amine favour the secretion of gastric juice, it is possible that the substance may play a part in the physiological processes of digestion. Since the intestine serves as a pathway for the stimulation of the glands of the stomach, the presence of histamine there may be one of the important factors in producing the intestinal phase of gastric secretion as well as the continuous gastric secretion."

Additional support for this view is found in the work of Mellanby and Twort (1912). They discovered a colon bacillus capable of converting histidine into histamine.

Some /

Some years later Hanke and Koessler (1922) enlarging upon the work of Mellanby and Twort found that of 29 strains of B. coli communis and B. coli communior investigated, six of these were capable of converting histidine into histamine. This occurred in vitro and under certain conditions, an acid medium being necessary for the process.

It is evident from the above facts that the utilisation of histamine as a gastric stimulant does not introduce a drug which is foreign to the animal or human mechanism. Rather is it to be regarded as one of the naturally occurring and entirely physiological gastric stimulants.

Rate of Gastric Secretion in Response to Histamine

Encouraged by the work of Popielski (1920), investigators both in Europe and American have employed histamine as a secretagogue for the gastric glands. The majority agree that histamine provokes a copious gastric secretion. In volume and total acidity the secretion parallels that obtained with food and other chemical stimuli except that the volume is greater and the total acidity higher. There is some disagreement, however, concerning other constituents of the gastric juice produced by histamine and as to the latent period. In man and in dogs with Pavlov's pouch the latent period following the subcutaneous injection of histamine was found to range from /

from 5 to 15 minutes (Matheson and Ammon, 1923; Gompertz and Vorhaus, 1925; Rachon and Walawski, 1928). There are some workers who report longer latent periods ranging from 30 to 55 minutes for man (Carnot, Koskowski and Libert, 1922). When, however, the gastric mucosa is deprived of its central nervous system connections by isotransplantation into the mammary gland of a gastric pouch taken from the fundus, then the latent period is very much longer, sometimes as long as one hour (Ivy and Farrell, 1925).

The duration of the secretion evoked by histamine varies with the dose of the drug administered. The usual dose of 0.5 to 2 mg. produces a secretion which continues for one to two hours. Popielski (1920) in a dog with a gastric fistula obtained secretion lasting six hours with a dose of 3.2 mg. A smaller dose given to the same animal at a later date evoked a secretion which lasted only one hour and thirty minutes.

The maximum rate of secretion in response to histamine injection, according to the majority of workers, is well established within the first hour. A rapid diminution then occurs, followed by almost complete cessation of secretion after one hour and thirty minutes. This may vary, however, in different individuals.

Gompertz and Vorhaus (1925) in a series of cases found three /

three main groups: The first - comprising 11% of the cases studied - in which the maximum rate of secretion was attained in 15 to 30 minutes; a second group - forming 66% - in which it was reached in from 30 to 60 minutes; and a third - comprising 22% - in which the height of the secretion was reached in from 60 to 90 minutes.

The Acidity of the Histamine Gastric Juice

Among the earliest investigators to use histamine clinically as a gastric stimulant were Carnot, Koskowski and Libert (1922). They reported the results of a study based upon four cases. In three of these the maximum acidity was reached after the volume of the secretion had commenced to decline. In the fourth case, however, the augmentation in the acidity, both total and free, paralleled the increase in volume. About the same time Matheson and Ammon (1923) suggested that there is a definite sequence in the secretion of gastric juice following histamine stimulation. According to their observations the peptic activity increases after injection of histamine and reaches its maximum usually in about 5 to 15 minutes. Shortly afterwards the maximum acidity is attained, and finally a little later the secretory rate reaches its height. Others have failed to confirm any definite sequence in the histamine secretion (Gompertz and /

and Vorhaus, 1926). Bloomfield and Polland (1929), however, found that the curves for the rate of secretion and total acidity reached their maximum at approximately the same time.

The Chlorides of the Histamine Gastric Juice

Following the injection of histamine Berglund, Walquist and Sherwood (1927) found a close correspondence between the curves of titrable HCl and chloride concentration. They concluded that normal stomach juice contains only insignificant amounts of chlorine if in any other forms than HCl. Similar results were obtained by Polland, Roberts and Bloomfield (1928). The increase in the chlorides begins promptly after histamine administration, reaches its maximum within 20 to 30 minutes and is maintained with only a slight decrease during the remaining period of secretion. The fasting level of chloride was 465 mg. per 100 cc. - the maximum reached was 553 mg. per 100 cc. Polland, Roberts and Bloomfield point out that the curve of the total chlorides coincides with the curve of the volume of secretion only in the first part of its course. It reaches its maximum at the same time but does not fall with the diminution of the volume. They conclude, as did Berglund, Walquist and Sherwood, that the curves of titrable acidity and total chlorides were practically parallel. The difference between the two they attribute to /

to the neutralising of some of the juice by mucus and by base secreted by the gastric glands. Thus the total chloride may be considered as an index of the acid-secreting power of the stomach. Recently Gilman and Cowgill (1931) have presented evidence that the total chloride content of histamine gastric juice approximately equals the total ionic content of the blood.

The Peptic Activity of the Histamine Gastric Juice

The question of whether or not histamine stimulates the formation of enzymes in gastric secretion is still a matter of controversy. Rothlin and Gundlach (1921), who were among the earliest experimenters to employ histamine as a gastric stimulant, claimed that there was an increase in proteolytic activity after the injection of this drug into a dog with a Pavlov pouch. Others investigating the secretions of the human stomach came to the same conclusion (Carnot, Koskowski and Libert, 1922; Matheson and Ammon, 1923; Rachon and Walawski, 1928). More recent investigators have been unable to confirm their results. Thus Polland and Bloomfield (1929) report a decrease in the pepsin concentration when the volume of the secretion increases. Since, however, the increase in volume is proportionally greater than the decrease in pepsin concentration, the total amount of pepsin secreted per unit /

unit of time is augmented. In addition they observed a fall in the nitrogen concentration.

Such was the status of the problem in 1930-31 when Gilman and Cowgill (1931) and Vineberg and Babkin (1931) studied it. The results of the latters' investigations will be referred to in the experimental part of this section.

The Mechanism of Histamine Action

The mode of action of histamine upon the gastric glands is not quite clear. Theories concerning this problem seem to fall into two classes. According to the first, enunciated by Popielski (1920), histamine action takes place directly upon the gastric cells themselves. According to the second, advanced by Rothlin and Gundlach (1921), its action is similar to that of a parasympathetico-mimetic drug, i.e. it acts through stimulation of the vagal nerve endings like pilocarpine.

There is much evidence against the latter view, and consequently considerable support for the first. Ordinarily atropine paralyses the parasympathetic nerve endings, and hence inhibits the secretion of the cephalic phase, whether the stimulus be initiated by sham feeding or by stimulation of the vagus nerve with an induction current (Oushakov, 1896). Histamine if a true parasympathetico-mimetic drug should not act /

act when given after atropine. Popielski found that the gastric secretory response to histamine was not affected either by intrathoracic section of the vagi or by atropine. This was confirmed by Lim (1922).

Further evidence in favour of histamine action being independent of the nervous system was presented by Ivy and Farrell (1925). A fundus pouch was transplanted to the mammary region of a dog where it took on a new blood supply. Such a pouch by the nature of its making was deprived of all central nervous system connections, and yet these pouches responded to histamine stimulation. It was observed that during lactation there was a greater histamine response than before. The volume and rate of the secretion were greatly augmented without any change in the quality of the secretion. Ivy and Farrell believed that the increase in the volume of secretion was due to the improved vascularity of the mammary region occurring during lactation.

The vaso-dilatory properties of histamine have been considered by some workers to be the activating force in secretion (Lee, 1929). There is however a great deal of evidence to discredit this view. Some years ago Barcroft (1914), working on the salivary glands, showed that marked vaso-dilation induced with yohimbine failed to produce secretion. MacKay (1930) obtained similar results, using histamine as the /

the vaso-dilator. Perhaps the most convincing evidence is to be found in the work of Ivy and Farrell (1925) already mentioned. Their transplanted gastric pouches responded to vaso-dilation with an increase in the volume of the secretion only; the quality of the secretion did not alter.

Thus it may be concluded that vaso-dilation produced by histamine undoubtedly favours secretion but per se is not responsible for its stimulation.

Pilocarpine as a Gastric Stimulant

Tshurilov (1894) found that pilocarpine is a weak stimulant for the gastric glands. Doses of 0.003 to 0.005 gm. produced profuse secretion of saliva without effect on the gastric secretion. Larger doses, 0.006 to 0.01 gm. and 0.1 to 0.2 mg. per kg. in the dog, did produce gastric secretion but this was scanty in comparison to the salivary secretion stimulated (Zitovitsch, 1902). When a dose of 0.01 gm. pilocarpine was administered subcutaneously, approximately 700 c.c. of saliva were secreted with the production of only 42.5 c.c. of gastric juice. There was a latent period of 8 to 16 minutes, the time varying according to the size of the dose. The acidity generally was low and varied according to the amount of gastric mucus secreted. The most characteristic feature of the gastric secretion obtained in /

in response to pilocarpine is the relatively high organic content and enzyme concentration.

EXPERIMENTAL /

EXPERIMENTAL RESULTS:

THE INDEPENDENT OR SIMULTANEOUS CHEMICAL STIMULATION OF DIFFERENT CYTOLOGICAL ELEMENTS OF THE GASTRIC GLANDS

It was shown in Part I that the qualitative changes in the composition of gastric juice secreted under different conditions are due to unequal quantitative activity of the different groups of secretory elements in the gastric glands. The stimulus used was electrical and reached the gastric glands through the vagus. From the following experiments it may be seen that the same principle holds true for chemical stimulants. Histamine and pilocarpine were chiefly studied.

Heidenhain- and Pavlov-pouch dogs were employed as well as a dog with oesophagotomy and a gastric fistula. For details see "chronic experiments" under "Methods." The necessity of a permanent gastric fistula in all experimental animals has already been indicated. By means of such a fistula it is possible not only to be certain that the stomach is empty but also to follow the reaction of the stomach simultaneously with that of the gastric pouch under observation. In human beings a gastric fistula is an impossibility, which, along with the fact that it has frequently been omitted in the animal experiments of others, explains in part the conflicting reports of gastric function to be found in the literature /

literature. For convenience of comparison we shall first present tables showing the response of a Heidenhain pouch to psychic stimulation and to meals of milk and meat.

The effect of psychic stimulation of a dog with a Heidenhain pouch is shown in Table XVII. After a control period of one hour, during which the dog was isolated from all extraneous influences, he was shown large pieces of raw meat over a period of one hour. Whereas the gastric secretion from the stomach was doubled after the psychic stimulation, there was no increase in the volume of secretion from the pouch, though there was a slight rise in the acidity in the second half-hour of stimulation. While the acidity did not attain the concentration of the control period, yet the slight rise suggested the presence of a few remaining vagal fibres in the pouch.

In the experiments shown in Tables XVIII and XIX the same animal was given milk and meat respectively. Following a control period of one hour the ingestion of food into the main stomach was responsible for an excellent secretion from the isolated pouch. The rise of the secretory rate was closely paralleled by the increase in acid concentration, the maximum rate of secretion corresponding closely to the maximum of acid concentration. There was little or no mucus produced in either experiment, nor was there any increase in /

TABLE XVII.

GASTRIC SECRETION FROM DOG WITH HEIDENHAIN POUCH AND GASTRIC FISTULA - EFFECT OF PSYCHIC STIMULATION.

Feb. 12, 1930.

Sample	Time	Pouch Secretion				Stomach Secretion	Remarks
		Volume	Free HCl	Total HCl	Mucus	Volume	
	Mins.	c.c.	Gm.%	Gm.%	c.c.	c.c.	
1	30	0.6	0.35	0.40	clear	15.0	Control period, one hour
2	30	1.0	0.29	0.35	trace	9.0	
3	30	0.6	0.00	0.04	0.1	18.0	Psychic stimulation, one hour
4	30	0.65	0.12	0.18	clear	11.0	
5	30	0.55	0.11	0.24	trace		

TABLE XVIII.

GASTRIC SECRETION FROM DOG WITH HEIDENHAIN POUCH IN RESPONSE TO MILK.

Jan. 27, 1930.

Sample	Time	Volume	Free HCl	Total HCl	Mucus	Total Chlorine	Peptic Power	Remarks
	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mg.%	Mett's Units	
1	60	0.95	0.33	0.40	0.0	538.8	40.9	Control period Dog fed 600 c.c. whole milk
2	30	2.1	0.31	0.33	0.09	499.1	23.0	
3	30	3.1	0.42	0.44	trace	519.0	10.24	
4	30	4.0	0.44	0.46	"	516.1	0.16	
5	30	10.3	0.47	0.50	clear	524.6	0.0	
6	30	4.6	0.44	0.45	"	513.3	0.0	
7	30	7.4	0.46	0.47	"	517.0	0.0	
8	30	3.0	0.47	0.49	"	545.9	0.0	
9	30	2.0	0.42	0.46	"	504.9	0.0	
10	30	1.6	0.41	0.44	"	489.2	2.5	

TABLE XIX.

GASTRIC SECRETION FROM DOG WITH HEIDENHAIN POUCH IN RESPONSE TO MEAT .

Jan. 28, 1930.

Sample	Time	Pouch Secretion						Stomach Secretion	Remarks
		Volume	Free HCl	Total HCl	Mucus	Total Chlorine	Peptic Power	Volume	
	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mg.%	Mett's Units	c.c.	
1	60	1.3	0.18	0.25	0.05	462.0	92.1	acid empty	Control period
									Dog fed 200 gm. beef heart
2	30	3.6	0.23	0.27	0.2	527.6	92.1		
3	30	6.6	0.44	0.48	clear	527.4	16.0		
4	30	4.3	0.49	0.50	"	537.4	5.76		
5	30	3.5	0.46	0.49	trace	548.6	10.2		
6	30	3.4	0.44	0.50	0.05	530.3	4.0		
7	30	2.5	0.45	0.47	trace	567.2	4.0		
8	30	2.4	0.43	0.49	"	538.8	27.0		

in the proteolytic production. In both experiments the chloride output closely paralleled the total acidity.

An analysis of these experimental results reveals one fact of unusual interest. It is evident that, although the acidity of the gastric juice paralleled the rate of secretion closely with but slight variations, the enzyme concentration on the other hand pursued a peculiar course during the secretory period. Thus in the experiment (Table XVIII) in which 600 cc. of whole milk was the gastric stimulant, samples 5 to 9 failed to show any digestive activity. When 200 gm. of meat were given to the same animal (Table XIX), the decline in the enzyme content of the gastric juice secreted, although reaching low figures, was not so marked (samples 4 to 7). Undoubtedly the milk, which contained a relatively large quantity of fat, inhibited the discharge of enzymes into the gastric juice more than did the meat with its low fat content. At the conclusion of the secretory period the enzyme concentration partially increased in both experiments. Thus in this particular animal with a Heidenhain pouch there was a difference in the production of the fluid and HCl as compared with the pepsin concentration in the gastric juice secreted. One constituent might be formed in abundance, another in small amounts or not at all.

Chemical stimulants are known to activate a secretion of /

of gastric juice possessing a lower enzyme content than is found in gastric secretions of vagal origin (obtained by sham feeding, stimulation of the vagi or pilocarpine). However, the values for pepsin in the experiments just described are lower than those reported by other investigators for a Heidenhain-pouch dog. The peculiarities of the secretion produced by the Heidenhain pouch in the present case may be due to the almost complete absence of vagal fibres, as indicated by the experiments with psychic stimulation, and to the region of the stomach from which the pouch was taken. It was formed partly from the region of the greater curvature and partly from the antrum where the glands contain few peptic cells and many parietal cells or Zwischenzellen. These factors although explaining the low concentration of pepsin obtained did not account for its gradual diminution during the secretory phase. A more adequate explanation was therefore sought. Possibly the impulses to the peptic cells for some reason diminish during the middle of the secretory period, whereas those to the parietal cells retain their full strength. A state would then exist which would be favorable for the secretion of a juice having a high acid concentration and a low enzyme content. In order to test this hypothesis, histamine was used. The experiments which will be described in the following pages were based upon /

upon the correctness of the hypothesis just enunciated.

Gastric Secretion in Response to Histamine

(A) Heidenhain-Pouch Dog

Following histamine stimulation, as shown in Tables XX and XXI, the secretory rate mounted rapidly. The maximum acidity was attained at once in one experiment (Table XXI) and in the other (Table XX) it was not reached for 60 minutes, at which time the secretory rate had commenced to decline. In both there was a gradual decline in the pepsin concentration with an increase towards the termination of secretion. The latent period was approximately 8 minutes in each.

(B) Pavlov-Pouch Dog

Histamine produces in a dog with a Pavlov pouch much the same results as those obtained with a Heidenhain pouch deprived of its vagal innervation (Table XXII). The gastric juices stimulated by histamine in the Pavlov-pouch dog as in the Heidenhain-pouch animal showed a diminution of pepsin concentration which only increased towards the end of secretion as the volume diminished.

(C) /

TABLE XX.

GASTRIC SECRETION FROM DOG WITH HEIDENHAIN POUCH AND GASTRIC FISTULA - EFFECT OF HISTAMINE STIMULATION

June 3, 1930

Sample	Time		Pouch Secretion					Stomach Secretion	Remarks
			Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Volume	
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mett's Units	c.c.	
1	9:55-10:55	60	1.4	0.07	0.14	trace	144.0	20.0	Control period
2	10:55-11:55	60	1.4		0.06	0.7	256.0	15.0	
	noon p.m.								12 noon, histamine (1 mg.) injected subcutaneously.
3	12:00-12:15	15	0.4	alkaline		clear		20.0	
	p.m.								
4	12:15-12:30	15	2.7	0.24	0.30	"	144.0	26.0	12:15 p.m., secretion commenced
5	12:30-12:45	15	2.9	0.36	0.44	"	77.0	30.0	
6	12:45- 1:00	15	1.4	0.40	0.49	"	64.0	18.0	
7	1:00-1:30	30	1.4	0.36	0.48	"	64.0	30.0	

TABLE XXI.

GASTRIC SECRETION FROM DOG WITH HEIDENHAIN POUCH AND GASTRIC FISTULA - EFFECT OF HISTAMINE STIMULATION.

Feb. 9, 1930.

Sample	Time		Pouch Secretion						Stomach Secretion	Remarks
			Volume	Free HCl	Total HCl	Mucus	Chlorine	Peptic Activity	Volume	
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mgm.%	Mett's Units	c.c.	
1	10:00-11:00	60	1.7	0.31	0.33	clear	516.1	19.3	12.0	Control period
2	11:00-11:30	30	0.7	acid	acid	0.4		4.0	11.0	
	noon									11:30 a.m. histamine (0.75 mg.) injected subcutaneously.
3	11:30-12:00	30	7.0	0.42	0.49	0.1	530.3	4.0	35.0	
	noon p.m.									
4	12:00-12:30	30	5.6	0.49	0.51	0.1		4.0	25.0	
	p.m.									
5	12:30- 2:00	90	0.8	acid	acid	0.2		23.0	9.0	

TABLE XXII.

GASTRIC SECRETION FROM PAVLOV POUCH IN A DOG - EFFECT OF HISTAMINE STIMULATION.

April 3, 1930

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Total Chlorine	Peptic Activity	Remarks
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mg.%	Mett's Units	
1	9:40-10:40	60	1.6	0.19	0.26	trace	506.2	256	Control period 10:48 a.m. Histamine (1 mg.) injected subcutaneously.
2	10:48-11.03	15	2.4	0.35	0.41	0.1		144.0	
3	11:03-11:18	15	6.3	0.44	0.52	trace	575.7	46	
4	11:18-11:33 p.m.	15	4.5	0.50	0.54	clear	560.1	46	
5	11:33-12:03	30	1.2	0.49	0.53	"		163.8	

(C) Dog with Oesophagotomy and a Gastric Fistula

Repeated injections of histamine. - One fact which was evident in the experiments on both Heidenhain- and Pavlov-pouch dogs was the apparent inability of histamine to stimulate the peptic glands. In order to be certain of this interesting fact the effect of repeated injections of histamine was studied (see Table XXIII). A dog with oesophagotomy and a gastric fistula was used. The secretion was collected from the stomach. The second dose of histamine was given 30 minutes after the first so as to obtain a superimposition of action. A profuse secretion was produced lasting two hours and twenty-five minutes. Although the rate of secretion and the total acidity were high, there was a gradual decline in the enzyme concentration to a point where readings were impossible on the Mett's tube. This was attained after the second dose of histamine.

Effect of Atropine on Histamine Gastric Secretion

A consideration of the above results suggests that histamine acts entirely upon the acid-secreting cells. The enzymes obtained after histamine stimulation were simply washed out from the peptic glands. The process seems to be a passive one in which the peptic glands play no active part. It is quite different from the active secretion of organic substances /

TABLE XXIII.

GASTRIC SECRETION - EFFECTS OF REPEATED INJECTION OF HISTAMINE.

Dog, weight 20 kg., with oesophagotomy and gastric fistula.

Sample	Time	Volume	Free HCl	Total HCl	Total Chlorine	Peptic Activity	Remarks
	Mins.	c.c.	Gm.%	Gm.%	Mg. %	Mett's Units	
1	60	Mucus					At end of this period reaction in stomach weakly alkaline. Histamine (1 mg.) injected subcutaneously
2	5	0.8					Thick yellow mucus expelled from tube
3	5	8.0			606.0	384.1	Bile admixed
4	5	6.0	0.277	0.321	602.0	153.7	Clear juice
5	5	20.5	0.408	0.452	602.0	64.0	
6	5	24.0	0.459	0.501	615.4	19.3	
7	5	23.0	0.480	0.511	602.0	19.3	
8	5	8.5	0.489	0.525	612.4	16.0	Histamine (1 mg.)injected subcutaneously
9	5	19.0	0.489	0.522	612.4	16.0	
10	5	24.0	0.503	0.532	609.6	10.2	
11	5	21.0	0.511	0.514	609.6	10.2	
12	5	17.0	0.489	0.512	609.6	4.0	
13	5	15.5	0.512	0.535	602.0	Trace	
14	15	43.0	0.489	0.513	601.2	"	
15	15	26.5	0.452	0.489	581.2	"	
16	15	12.4	0.408	0.438	575.6	"	
17	15	4.8	0.350	0.390	564.2	1.2	
18	30	6.0	0.314	0.386	439.4	4.0	

substances and enzymes under the influence of other stimuli. This recalls the controversy started by Popielski (1920) and Rothlin and Gundlach (1921) as to whether histamine acts directly upon the cells, as suggested by Popielski, or indirectly through stimulation of the parasympathetic nervous system.

(A) Heidenhain-Pouch Dog

The following experiments with atropine point to a histamine effect which is entirely independent of the parasympathetic nervous system insofar as the constituents of secretion are concerned (Table XXIV). In this experiment it is evident that, following atropinisation of a dog with a Heidenhain pouch, histamine stimulates the production of free and total acid in concentrations as great as it did without atropinisation. Thus values of 0.48 gm. per cent. free and 0.53 gm. per cent. total acid were obtained. The peptic power fell in the usual manner from 196 to 16 Mett's units. There was only a slight diminution of volume; a total secretion of 7.4 cc. in 85 minutes was obtained as compared with 8.8 cc. in 70 minutes with histamine alone (see Table XX).

(B) /

TABLE XXIV.

GASTRIC SECRETION - EFFECT OF ATROPINE ON HISTAMINE SECRETION

Exp. April 10, 1930.
Dog, weight 18.0 kg., with Heidenhain pouch and gastric fistula. Atropine injection, followed 30 minutes later by histamine.

Sample	Time		Pouch Secretion					Stomach Secretion	Remarks
			Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Volume	
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mett's Units	c.c.	
1	9:00-10:00	60	1.4	0.20	0.32	0.25	196.0	12.5	Control period
2	10:00-10:30	30	0.35	0.28	0.41	Trace		4.5	10:00 a.m. Atropine (2 mg.) injected subcutaneously
3	10:30-10:50	20	2.2	0.31	0.39	0.3	116.6	8.0	10:30 a.m. Histamine (1 mg.) injected subcutaneously
4	10:50-11:05	15	1.8	0.44	0.52	Trace	19.4	9.5	
5	11:05-11:25	20	2.7	0.48	0.53	0.05	19.3	10.5	
6	11:25-11:55	30	0.65	0.29	0.49	clear	16.0	3.5	

(B) Pavlov-Pouch Dog

Atropinisation in these animals greatly curtails the volume of the histamine secretion but as will be seen in Table XXV does not influence the character or quality of the secretion. The total and free acidity rose to normal levels (0.41 gm. per cent. free and 0.52 gm. per cent. total). The enzyme concentration diminished from 400 to 100 Mett's units.

A comparison of the volumes of the histamine secretion obtained respectively from a Heidenhain- and a Pavlov-pouch dog with and without atropinisation is shown in Table XXVI. It is evident that atropine causes only a slight reduction in the volume of secretion of a Heidenhain-pouch animal, whereas in the case of a Pavlov-pouch animal there is a marked reduction. This difference in the volume response to histamine between a pouch with vagal innervation and one without seems to us of considerable significance. It suggests that histamine acts perhaps upon some vaso-dilator mechanism of the vagus without affecting the secretory fibres. Vaso-dilation per se is not sufficient to cause secretion but certainly there is evidence to show that vaso-dilation in the presence of a secretory stimulus augments the volume of the secretion (Ivy and Farrell, 1925; et al.). Consequently atropinisation acting as it does through the parasympathetic curtails /

TABLE XXV.

GASTRIC SECRETION FROM PAVLOV POUCH - EFFECT OF ATROPINE ON HISTAMINE SECRETION.

Exp. June 19, 1930.
Dog, with Pavlov pouch. Atropine injection, followed 15 minutes later by histamine.

Sample	Time		Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
	a.m.	Mins.	c.c.	Gm.%	Gm.%	c.c.	Mett's Units	
1	10:00-11:30	90	0.45	0.06	0.22	0.45		Control period 11:30 a.m., atropine (2 mg.) injected subcutaneously. 11:45 a.m., histamine (1 mg.) injected subcutaneously.
	noon							
2	11:30-12:00	30	1.0	0.00	0.08	1.0	400	
	p.m.							
3	12:00-12:15	15	1.65	0.21	0.38	trace	156	
4	12:15-12:30	15	2.40	0.37	0.42	clear	144	
5	12:30-12:45	15	1.4	0.41	0.52	"	100	
6	12:45- 1:30	45	0.65	0.34	0.60	"		

TABLE XXVI.

VOLUME OF THE SECRETION FROM A PAVLOV AND A HEIDENHAIN POUCH IN RESPONSE TO HISTAMINE WITH AND WITHOUT ATROPINISATION.

	Histamine			Histamine after atropine		
	Experiment	Time	Volume	Experiment	Time	Volume
		Mins.	c.c.		Mins.	c.c.
Pavlov Pouch	Table XXII	75	14.4	Table XXV	120	7.6
Heidenhain Pouch	" XX	90	8.8	" XXIV	85	7.4
	" XXI	150	13.4			

N.B. The above data were taken from experiments shown in Tables XX, XXI, XXII, XXIV and XXV.

curtails the volume of the histamine secretion obtained from a Pavlov pouch to a more marked degree than in the case of a Heidenhain pouch which has been deprived of its vagal dilator fibres. In this connection the work of MacKay (1930) is interesting. She reported that the motor effect of histamine upon the small intestine in situ was almost completely abolished by atropine. Her results suggest that histamine in some way influences the intrinsic nervous system of the gut.

Our observations, explained in this way, would tend to a compromise between the two opposing views of histamine action enunciated earlier in this section. Popielski, neglecting the volume changes but interpreting the quality of the secretion only, concluded that histamine acts directly upon the cells of the gastric glands. Rothlin and Gundlach, considering only the volume changes and overlooking the constant quality of the secretion produced, concluded that histamine acts through the parasympathetic. In a sense perhaps both views were correct in that histamine probably stimulates vaso-dilatation through the parasympathetic and acts directly upon the parietal cells in producing secretion.

Gastric Secretory Response to Pilocarpine

Pilocarpine, closely related in chemical structure to histamine, has a marked secretory effect on the salivary glands /

glands and to a lesser extent on the gastric mucosa. Its mode of action is through parasympathetic stimulation, and is consequently abolished by atropinisation. Table XXVII indicates the type of secretion usually called forth by pilocarpine when administered subcutaneously. A Heidenhain-pouch dog was used. A comparison with the juice secreted in response to histamine reveals three important differences:-

(1) The free and total acidity following pilocarpine stimulation is generally lower than with histamine.

(2) The production of mucus is marked, whereas with histamine it is extremely slight or there is none at all.

(3) Most important of all, however, is the great increase in enzyme content which follows pilocarpine stimulation.

Gastric Secretory Response to Histamine Supplemented by Pilocarpine

As has been seen, the two gastric stimulants histamine and pilocarpine, although chemically closely related, produce different types of gastric secretion. For this reason and because it was believed that, given adequate stimulation, the different cytological units in the gastric mucosa are capable of independent function, a combination of the two drugs was used in certain experiments. In two experiments (see Tables XXVIII and XXIX) a dog with a Heidenhain pouch was /

TABLE XXVII.

GASTRIC SECRETION - EFFECT OF PILOCARPINE STIMULATION.

Exp. May 15, 1930.
Dog, weight 18.4 kg., with Heidenhain pouch and gastric fistula.

Sample	Time		Pouch Secretion					Stomach Secretion	Remarks
			Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Volume	
		Mins.	c.c.	Gm.%	Gm.%	c.c.	Mett's Units	c.c.	
	a.m.								
1	9:25-10:25	60	1.6	0.20	0.28	clear	70.5	44.	Control period 10:27, pilocarpine (7 mg.) injected subcutaneously.
2	10:25-10:40	15	0.5	0.19	0.27	clear		47.0	10:36, salivation began.
3	10:40-10:55	15	3.4	0.33	0.41	0.4	256.0	48.0	
4	10:55-11:10	15	2.5	0.40	0.47	0.15	338.5	96.0	
5	11:10-11:25	15	3.0	0.38	0.50	0.1	400.0	64.0	
6	11:25-11:40	15	0.95	0.36	0.44	0.05	400.0	35.0	11:40, salivation ceased.
7	p.m. 11:40-12:10	30	2.6	0.39	0.47	0.15	484.0	47.0	

TABLE XXVIII.

GASTRIC SECRETION - EFFECT OF HISTAMINE AND PILOCARPINE STIMULATION.

Exp. April 2, 1930.
Dog, with Heidenhain pouch and gastric fistula. Histamine injection, followed 32 minutes later by pilocarpine.

		Pouch Secretion							Stomach Secretion		Remarks
		Sample	Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Chlorine	Sample	Volume	
a.m.	Mins.		c.c.	Gm.%	Gm.%	c.c.	Mett's Units	Mg.%		c.c.	
9:00-10:00	60	1	2.8	0.14	0.26	trace	100.0	496.3	1	34	Control period
											10 a.m. Histamine (1 mg.) injected subcutaneously.
10:00-10:15	15	2	1.7	0.17	0.26	0.25	100.0	500.5			
10:15-10:30	15	3	4.7	0.36	0.45	0.1	36.0	528.8	2	45	
											10:32. Pilocarpine (7 mg.) injected subcutaneously.
10:30-10:45	15	4	4.5	0.39	0.48	trace	16.0	548.7			10:43. Salivation began.
10:45-11:00	15	5	5.6	0.33	0.44	0.3	219.0	521.8	3	100	
11:00-11:15	15	6	1.9	0.30	0.42	0.1	282.2	586.9			
11:15-11:30	15	7	1.7			0.1	282.2	521.8	4	73	
11:30-12:00	30	8	1.25	0.16	0.33	0.35	400.0				11:45. Salivation ceased.
noon p.m.											
12:00-12:30	30	9	1.7	0.11	0.28	0.45	900.0	499.1	5	30	

TABLE XXIX.

GASTRIC SECRETION — EFFECT OF HISTAMINE AND PILOCARPINE STIMULATION.

Exp. May 13, 1930.

Dog with Heidenhain pouch and gastric fistula. Histamine injection followed 43 minutes later by pilocarpine.

Sample	Time		Pouch Secretion					Stomach Secretion	Remarks
			Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Volume	
		min.	c.c.	gm.%	gm.%	c.c.	Mett's units.	c.c.	
1	9:00-10:00 a.m.	60	2.7	0.21	0.28	clear	116.6	30	Control period.
									10:02 a.m. Histamine, 1 mg. injected subcutaneously.
2	10:02-10:32 a.m.	30	4.3	0,26	0.35	0.5	64.0	48	
3	10:32-10:47 a.m.	15	2.5	0.42	0.50	trace	36.0	27	
									10:45 a.m. Pilocarpine, 1 mg. injected subcutaneously.
4	10:48-11:03 a.m.	15	2.1	0.42	0.50	trace	36.0	30	
5	11:03-11:18 a.m.	15	2.5	0.32	0.44	0.7	416.1	73	Salivation only moderate.
6	11:18-11:33 a.m.	15	1.6	0.32	0.44	0.7	775.0	40	
7	11:33 a.m.— 12:03 p.m.	30	1.8	0.22	0.39	0.4	900.0	38	

was used, whereas in a third (Table XXX) a dog with an oesophagotomy and a gastric fistula was the subject of experimentation. Histamine (1 mg.) was administered subcutaneously and followed in half an hour by 6 - 7 mg. pilocarpine. The results are practically the same in all three experiments. In each histamine provoked a good volume of secretion with rapidly rising acidity and equally rapid diminution of the enzyme concentration. At this stage the introduction of pilocarpine caused a rapid rise in enzyme concentration to values many times higher than the fasting levels. A slight diminution in the acid concentration as well as in the rate of secretion was noticed. In addition there was a considerable increase in the production of mucus. Chlorine concentrations, which closely followed the increase in the acidity in the previously reported histamine experiments, did not undergo any marked change after the injection of pilocarpine.

Histamine and Pilocarpine as a Clinical Test of Gastric Function

Recently histamine has been used extensively as a clinical test of gastric function. It has gained favour in the most conservative clinics. Those clinicians who employ it for this purpose agree that more accurate information about the gastric glands is thus obtained than with ordinary food /

TABLE XXX.

GASTRIC SECRETION — EFFECT OF HISTAMINE AND PILOCARPINE STIMULATION.

Dog, weight 20 kg. Oesophagotomy and gastric fistula. Histamine injection followed 30 minutes later by pilocarpine.

Sample	Total Time	Volume	Free HCl	Total HCl	Peptic Activity	Ferment Units	Remarks
	min.	c.c.	gm.%	gm.%	Mett's units.		
1	15	26.0					Control period.
							1 mg. histamine injected subcutaneously.
2	5	22.0	0.39	0.42	36.0	792.0	Trace bile.
3	5	17.5	0.43	0.47	16.0	280.0	Clear.
4	5	15.0	0.44	0.49	4.0	60.0	Clear.
							6 mg. pilocarpine injected subcutaneously.
5	5	11.5	0.46	0.48	16.0	240.0	
6	5	10.5	0.43	0.46	23.0	241.5	Salivation started.
7	5	10.0	0.42	0.45	231.0	2310.0	Much salivation.
8	5	9.8	0.42	0.45	196.0	1920.0	
9	5	10.5	0.42	0.47	196.0	2058.0	
10	5	9.5	0.45	0.47	163.7	1555.1	
11	5	11.0	0.44	0.47	92.1(?)	1013.1	
12	15	9.5	0.20	0.26	163.8	1556.1	Salivation less.
13	15	3.5	0.36	0.40	364.0	1274.0	
14	15	1.1	0.36	0.39	272.0	299.2	Slight salivation.

food stimuli. The advantage claimed for histamine over other tests of gastric function is briefly as follows. It produces a clear gastric juice which is undiluted by food or alcohol. A truer picture of the function of the gastric glands can thus be obtained, as more accurate chemical analysis is possible. The dosage can be standardised and has been shown to give corresponding results following repeated injection in the same patient. In cases of achylia, where the stomach fails to secrete acid with ordinary test meals including alcohol, histamine causes a flow of acid juice in those cases where the achylia has been purely functional. It is thus of aid in differential diagnosis of certain medical conditions.

Notwithstanding the advantages that the histamine test meal possesses over other forms of gastric analysis, it is apparent from the foregoing data that histamine stimulates chiefly the parietal cells which produce HCl and to a much lesser extent (if at all) the peptic and mucoid cells. Hence a test of gastric function, which has as its basis histamine alone, yields information concerning the state of only one group of the cytological elements comprising the gastric mucosa.

In 1930 (Vineberg and Babkin) it was suggested that a combined histamine-pilocarpine test of gastric function be employed /

employed in human subjects for the following reasons: -

(1) The combination of the two drugs activates (in dogs) all the known cytological elements of the gastric mucosa, producing a secretion similar to that obtained by normal stimulation.

(2) There are certain indications that the clinical study of peptic function may be of greater diagnostic value than that of HCl. Polland and Bloomfield (1930), using the histamine test meal, studied the HCl and peptic power of the gastric juice in normal individuals and in patients suffering from various gastric and general diseases. They suggest the possibility "that the low pepsin output is a more delicate index of gastric damage than low acid values".

Following up the suggestion of Vineberg and Babkin the effect of histamine and pilocarpine on gastric secretion was studied by the writer in a few cases (25) in the wards of the Royal Victoria Hospital. The patients selected were those in whom no definite gastro-intestinal lesions were suspected. Most of them were patients on the Surgical Service of Dr. Edward Archibald; others were taken from the Medical Service of Dr. Johnathan Meakins.

Histamine /

Histamine was injected in doses of 0.5 mg. Pilocarpine was then given in doses ranging from 2 mg. to 10 mg. without causing the patient undue discomfort. In one case in which a dose of 14 mg. of pilocarpine was given, marked gastro-intestinal disturbances occurred, followed by severe prostration: this was quickly checked by a large dose of atropine (gr. 1/50) injected intramuscularly. The patient was none the worse for his unpleasant experience.

The usual procedure was as follows. After a 12-hour fast a small Rehfuss tube was passed into the stomach and the stomach contents completely evacuated. It was found by experience that this is best accomplished by posturing the patient. After the administration of the gastric stimulant the stomach was emptied every fifteen minutes and the volume, free and total acidity and enzyme content determined. The patient was kept lying on his left side and was cautioned not to swallow saliva. Unfortunately more than one test on the same patient was not possible because of ward routine.

Repeated Injection of Histamine

The results of two consecutive injections of 0.5 mg. of histamine are shown in Tables XXXI and XXXII. In one patient (Table XXXII) there was hypo-acidity, in the other a normal response. In both cases a good volume of secretion was /

TABLE XXXI.

GASTRIC SECRETION — EFFECT OF REPEATED INJECTION OF HISTAMINE.

July 15, 1931.

Mr. A.T., age 15. Surgical Ward, R.V.H. Twelve-hour fast. Small Rehfuss tube swallowed. Injection of histamine, followed by a second injection 45 minutes later.

Sample	Time	Volume	Free HCl	Total HCl	Peptic Activity	Remarks
	min.	c.c.	gm.%	gm.%	Mett's units.	
1		22.0	0.00	0.04	433	Fasting stomach contents.
						Histamine, 0.5 mg. injected subcutaneously.
2	15	47.0	0.17	0.25	625	
3	15	41.0	0.22	0.30	433	
4	15	26.0	0.25	0.33	484	
						Histamine, 0.5 mg. injected subcutaneously.
5	15	30.0	0.23	0.32	557	
6	15	36.5	0.28	0.38	595	
7	15	37.0	0.33	0.42	484	
8	15	20.0	0.23	0.31	353	
9	15	36.0	0.17	0.24	529	
10	15	17.0	0.17	0.24	529	

TABLE XXXII.

GASTRIC SECRETION - EFFECT OF REPEATED INJECTION OF HISTAMINE.

July 15, 1931.

Mr. C.S. Case No.78081, R.V.H. Twelve-hour fast. Small Rehfuss tube swallowed. Injection of histamine followed by second injection 45 minutes later.

Sample	Time	Volume	Free HCl	Total HCl	Peptic Activity	Remarks
	min.	c.c.	gm.%	gm.%	Mett's units.	
1		55	0.00	0.04	949	Fasting stomach contents.
						Histamine, 0.5 mg. injected subcutaneously.
2	15	40	0.06	0.14	900	
3	15	18	0.08	0.17	502	
4	15	22	0.09	0.17	784	
						Histamine, 0.5 mg. injected subcutaneously.
5	15	8	0.04	0.12	676	
6	15	27	0.17	0.26	538	
7	15	11	0.05	0.13	400	

was obtained. The enzyme concentration in each showed an immediate rise in the first fifteen minutes of secretion, a slight decrease after it had reached its height, and a secondary rise corresponding to the terminal decline in secretion. After the second injection of histamine the level attained by the peptic power was lower than after the first.

Repeated Injections of Histamine Followed by Pilocarpine

From the data shown in Tables XXXIII and XXXIV, it is evident that in man the combination of histamine with pilocarpine does not give the same result as in the dog. In the human experiments here described there is a gradual diminution of the enzyme concentration in response to histamine stimulation; it continues unaffected after the administration of pilocarpine. It is interesting to note in this connection that the volume of secretion increased perceptibly after pilocarpine and at the same time there was a sharp diminution of acidity. The fall in acidity cannot be attributed to bile regurgitation as there was no trace of bile salts in those samples with low acidity. The amount of mucus secreted is difficult to ascertain as the aspirating tube has small apertures; besides, since mucus tends to sink to the bottom /

TABLE XXXIII.

GASTRIC SECRETION - EFFECT OF REPEATED INJECTION OF HISTAMINE FOLLOWED BY PILOCARPINE STIMULATION.

April 29, 1931.
Mr. F. S., No. 77172 R. V. H. Twelve-hour fast. Small Rehfuss tube swallowed.

Sample	Time	min.	Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
			c.c.	gm.%	gm.%	c.c.	Mett's units	
1			17.0	0.00	0.20		1296	Fasting stomach contents.
	a.m.							6:05 a.m. Histamine 0.5 mg. injected subcutaneously.
2	6:05-6:20	15	73.0	0.28	0.32	0.6	784	
3	6:20-6:35	15	28.0	0.24	0.35	0.1	400	
								6:36 a.m. Histamine 0.5 mg. injected subcutaneously.
4	6:35-6:50	15	31.5	0.31	0.36	0.1	576	
5	6:50-7:05	15	26.0	0.27	0.32	trace	400	
								7:06 a.m. Pilocarpine 10 mg. injected subcutaneously.
6	7:05-7:20	15	52.0	0.05	0.11	0.1	256	
7	7:20-7:35	15	92.5	0.00	0.03	0.2	51	
8	7:35-7:50	15	28.0	0.00	0.05	0.2	400	Samples 1 to 9 green in colour owing to bile contamination.
9	7:50-8:05	15	7.8	0.00	0.07	0.1	516	

TABLE XXXIV.

GASTRIC SECRETION - EFFECT OF REPEATED INJECTION OF HISTAMINE FOLLOWED BY PILOCARPINE STIMULATION.

April 29, 1931.
Mr. H. C., No. 77171 R. V. H. Twelve-hour fast. Small Rehfuss tube swallowed.

Sample	Time	min.	Volume	Free HCl	Total HCl	Mucus	Peptic Activity	Remarks
			c.c.	gm.%	gm.%	c.c.	Mett's units	
1			4.4	0.00	0.07	0.7	660	Fasting stomach contents.
								6:10 a.m. Histamine 0.5 mg. injected subcutaneously.
2	a.m. 6:10-6:25	15	15.1	0.18	0.25	0.7	660	
3	6:25-6:40	15	16.3	0.30	0.35	0.2	660	
								6:41 a.m. Histamine 0.5 mg. injected subcutaneously.
4	6:40-6:55	15	37.5	0.29	0.34	0.1	900	
5	6:55-7:10	15	36.0	0.34	0.39	0.2	576	
								7:10 a.m. Pilocarpine 10 mg. injected subcutaneously.
6	7:10-7:25	15	41.0	0.32	0.36	0.1	576	
7	7:25-7:40	15	30.0	0.09	0.14	0.1	400	7:25 a.m. Mild salivation.
8	7:40-7:55	15	39.0	0.00	0.07	0.5	400	7:40 a.m. Sweating marked.
9	7:55-8:10	15	38.8	0.06	0.11	0.2	-	8:10 a.m. Salivation and sweating ceased.
10	8:10-8:25	15	13.0	0.09	0.20	0.1	400	Samples 4 to 6, faint yellow tinge; all others clear.

bottom of a test-tube containing gastric juice, it might conceivably have remained at the lowest level of the stomach in contact with the mucous membrane from which its removal would be difficult. The possibility of neutralisation of the gastric juice by saliva or the mucous secretion of the throat and oesophagus cannot be excluded. It is possible too that in man pilocarpine acts on the gastric glands differently than in dogs.

Both larger and smaller doses of pilocarpine were given in other patients with approximately the same effect, and we were forced to conclude that for some reason the effects produced by pilocarpine injection in dogs could not be obtained in man.

DISCUSSION

The experimental data presented above provide evidence that histamine acts selectively on certain cells of the gastric mucosa. According to our interpretation (Babkin, 1930; Vineberg and Babkin, 1931) it activates those cytological elements of the gastric glands which secrete water and HCl and some other inorganic constituents of the juice. The enzyme content of histamine juice does not represent a true secretion from the peptic cells. The presence of enzymes in the histamine juice is rather the result of a passive action, i.e. simply a "washing-out" process from the lumen of the gland or from the peptic cells brought about by the actively secreting parietal cells.

Quite independently and unknown to us, Gilman and Cowgill (1931), working at Yale University, arrived at the same conclusion with regard to the action of histamine on enzyme concentration in gastric secretions. However, Polland (1932) did not agree with this view. On the contrary he presented evidence which he believed indicates that histamine stimulates the peptic cells. His work was carried out on human subjects and the results show a constant fall in the concentration of pepsin during the period of maximum secretion. Repeated doses of histamine were given; the /

the second and third doses, however, were administered after the effect of the preceding dose had worn off. The total output of enzymes after the initial dose was high - much higher than subsequent responses. Our own observations with repeated doses of histamine in human subjects are similar to those reported by Polland. However, his explanation is hardly justifiable, particularly when, as he has reported, there is a lower output of enzymes with each succeeding histamine stimulation. It would seem rather that in the case of the human gastric mucosa a longer period of secretion is necessary to wash out the enzymes than in the case of a dog.

The action of pilocarpine on the parasympathetic-nervous system has been known for many years, also the fact that it activates chiefly the production of organic substances and enzymes in gastric juice (Tschurilov, 1894; Zitovitsch, 1902). The effects upon gastric secretion of histamine and pilocarpine combined, however, have not been previously determined. The marked increase in enzyme concentration and output, which follows the injection of pilocarpine during histamine secretion in a dog, is most instructive. It shows clearly that the different cytological units in the gastric mucosa are capable of responding to varied chemical stimuli in a somewhat similar manner to that experienced with /

with nerve stimulation.

We are unable to offer an adequate explanation of the failure to obtain similar effects when histamine and pilocarpine were administered to human subjects.

P A R T I I I

THE HISTOLOGICAL CHANGES PRODUCED IN THE GASTRIC GLANDS BY PROLONGED VAGAL AND HISTAMINE STIMULATION.

There is in the literature a scarcity of data concerning the influence of the secretory nerves on the histological structure of the gastric glands. Noll and Sokoloff (1905), using dogs with oesophagotomy and a gastric fistula, investigated the histological changes occurring in the mucous membrane of the stomach after sham feeding. They found that during the period of secretion there was a moderate enlargement of the parietal cells and a diminution of the chief cells.

Di Cristina (1908) fed an animal and one hour later stimulated the vagus nerve for a period of ten minutes. He then found that the granules in the chief cells had diminished in size and that occasionally there was vacuole formation. The parietal cells were observed to be filled with granules.

Anrep, Pavlov and Savitsch (1922) commenced an investigation of the structural changes occurring in the gastric mucosa in response to vagal stimulation. Unfortunately this work was never completed; however, they reported some changes in the chief cells after vagal stimulation.

There appear to be no data available concerning the histology /

histology of the gastric mucosa after histamine stimulation.

In Parts I and II certain physiological data were obtained in dogs which suggested that vagal and chemical stimuli are capable of activating some of the cytological elements of the gastric glands without markedly affecting the other cytological elements. Thus strong vagal stimulation produced a gastric secretion having both a high acid and a high peptic concentration, whereas histamine was shown to produce a secretion with a high acid content but extremely low pepsin concentration.

In order to ascertain whether these differences in function manifested by the peptic cells in response to two different stimuli would be reflected in their histological structure, two types of experiment were undertaken. In one group the histological changes occurring in the gastric glands after prolonged vagal stimulation were studied. In a second group similar studies were made after histamine stimulation. Dogs were used and prepared according to the standard technique described under "Methods". In all the animals, prior to the insertion of the gastric fistula, a control section of mucosa was taken from the anterior surface of the stomach and immediately placed in a fixing solution. Stimulation of gastric secretion was then instituted either by vagal stimulation or by means of histamine administration.

The /

The resulting gastric secretions were collected at definite periods and the volume, free and total HCl, volume of mucus and peptic activity determined. After six to nine hours of stimulation the animals were killed by exsanguination. Sections were immediately taken from the various regions of the stomach and were placed in different fixing solutions. At the commencement of this work much difficulty was experienced in preventing distortion of the peptic cells. However, it was found after some time that this effect was due to shrinking, brought about by the fixatives employed, viz. Zimmerman's fluid, alcohol corrosive sublimate, formol, Zenker's solution, and Rigaud's fluid. Finally, when Zenkers-formol or Bouin's fluid (original) was employed as fixative, there was no shrinkage. After fixation the sections were passed through various strengths of alcohol and stained with Harris's haematoxylin eosin stain.

EXPERIMENTAL /

EXPERIMENTAL RESULTS

In all, fourteen experiments were conducted; gastric secretion was produced by vagal stimulation in nine of these and by histamine in five. A comparison between sections of the mucosa taken before and after long continued electrical stimulation of the vagus nerves showed:

(1) The peptic cells contained fewer granules than before stimulation.

(2) The peptic cells became somewhat shortened, this resulting in a widening of the lumen of the gland.

(3) The cytoplasm in the stimulated peptic cells presented a denser arrangement than that observed in the resting cells.

(4) The nuclei in the stimulated peptic cells shifted towards the centre of the cell. This was in contrast to the more peripheral and basal position occupied in the resting cell.

On the other hand, in those experiments in which histamine was employed as the gastric stimulant, a comparison between the sections of the mucosa taken before and after prolonged secretion showed practically no change in the peptic cells.

DISCUSSION /

DISCUSSION

At the outset it would be well to state that the rather sketchy and incomplete report of the above results represents a preliminary report of work which is still in progress. The evidence presented, however, seems sufficient to permit the deduction of certain conclusions.

The changes which occurred in the peptic cells after prolonged strong vagal stimulation correspond with the physiological observations reported earlier in this work (Part I) and add a new link to the chain of evidence which indicates that the peptic cells are directly under the influence of the vagus nerves.

More important perhaps is the fact that the peptic cells showed very little change after a prolonged stimulation of gastric secretion by histamine. This is not surprising since it can hardly be expected that cells which are not functioning (as indicated by the low pepsin output) will undergo structural rearrangement. The histological picture tends to confirm the view that histamine acts only upon the parietal cells of the gastric glands without markedly affecting the peptic cellular elements. Further, it supports the principle of independent cellular function which was deduced from physiological evidence presented in Part II of this thesis.

P A R T I V

THE INFLUENCE OF THE VAGUS NERVE ON OESOPHAGEAL SECRETION

HISTORICAL

An extensive search of the literature has failed to disclose any facts concerning the vagus nerve and its functional connection with the oesophageal glands. These glands are numerous and in the dog are of two kinds: (1) oesophageal glands and (2) cardiac oesophageal glands. The "oesophageal glands" are numerous in the oesophagus of the dog and are composed of two kinds of cells - mucous and demilune (Klein, 1879; Renant, 1897; Helm, 1907; Goetsch, 1910; Ellenberger, 1911). Goetsch reports an arrangement of the serous complexes which resembles that found in the submaxillary gland. These are provided with intercellular secretory capillaries. Situated in the main and sometimes in the secondary excretory ducts are ampullae filled with mucoid secretion (Schaffer, 1897; Goetsch, 1910). Of the second type of gland found in the oesophagus, viz. the "upper and lower cardiac oesophageal glands" two different kinds have been described. Some have the same structure as the /

the glands of the cardiac portion of the stomach and have practically no parietal cells, while others are glands of a true fundic type and secrete acid gastric juice. Their formation has been called "islands of gastric mucosa" (Schaffer, 1904; Schridde, 1904, 1905, 1908; Helm, 1907; Ellenberger, 1911). The upper cardiac oesophageal glands are absent in the dog, whereas the lower cardiac oesophageal glands are occasionally present. The dog is the only domestic animal which has this type of gland in the oesophagus.

The stomach, pancreas and small intestine are known to receive secretory fibres through the vagus nerves. In the larynx and trachea, which are embryologically derived from the primitive tubular gut, there are also glands innervated by the vagus (Kokin, 1896). Florey, Carleton and Wells (1932) report the activation of the tracheal glands by vagal stimulation. In their experiments dogs and cats were used. During a control period of three hours no obvious mucus was collected in the tracheal cannula. They then stimulated the peripheral end of the vagus with a faradic current, each stimulus lasting one-and-a-fifth seconds with an intervening rest period of one second. After a few minutes mucus secretion began to appear in the cannula being pushed up from the trachea by the cilia. They were able to obtain a similar secretion of mucus with pilocarpine stimulation /

stimulation. Secretions obtained by vagal stimulation and pilocarpine were inhibited by atropine action. By means of histological examinations they showed that prolonged vagal stimulation exhausted the tracheal glands but had no effect upon the globlet cells which failed to discharge their mucoid content. Consideration of the common origin and innervation of trachea and oesophagus and the fact that the tracheal glands can be made to secrete by vagal stimulation suggests that the vagal influence may in a similar manner extend to the oesophageal glands.

EXPERIMENTAL /

EXPERIMENTAL RESULTS

It will be recalled that in order to isolate the stomach during a study of gastric mucus two fistulae were introduced into the oesophagus. One was placed in the organ in the region of the neck, the other was introduced through its diaphragmatic portion and firmly secured (see Part I , Table XIII). During the experiment 20.1 c.c. of mucus were collected from the oesophageal cannulae in response to strong vagal stimulation. This mucus was believed to have been secreted by the oesophageal glands in response to vagal stimulation. This interpretation however had no experimental basis. Objections were raised that the mucus may have been pressed out of the glandular lumina by the motility of the oesophagus and consequently the process was not of a secretory nature. Thus it was necessary to determine whether this were the case or whether the process was truly one of secretion involving a response of the oesophageal glands to vagal stimulation.

Proceeding on the basis that during a secretory process, particularly one of vagal origin, definite chemical changes take place in the products of secretion, chemical analyses were made of fractions of the mucus obtained at different periods throughout the course of stimulation. These were undertaken /

undertaken in collaboration with Dr. S. A. Kamarov.

In all, eight experiments were performed. In two of these the current applied to the vagi was weak at the commencement and was gradually increased in intensity to that of strong stimulation. In five experiments the current applied was strong from the beginning and continued thus throughout the entire duration of the experiment. In two of these chemical analyses were made of the mucus produced.

Oesophageal Secretion: Effect of Transition from Weak to Strong Vagal Stimulation

It was observed, during the study of gastric secretion produced in response to vagal stimulation in those experiments in which the oesophagus was isolated from the stomach, that there was no secretion from the oesophagus during weak stimulation whereas secretion appeared under the influence of strong stimulation. This effect is shown in Tables XXXV and XXXVI. In the experiment shown in Table XXXV, weak stimulation over a period of 245 minutes failed to provoke secretion whereas shortly after strong stimulation secretion of thick mucus began. A total of 11 c.c. of secretion was collected. Similarly, in the experiment shown in Table XXXVI, weak stimulation for 280 minutes caused no secretion /

TABLE XXXV.

OESOPHAGEAL SECRETION — EFFECT OF TRANSITION FROM WEAK TO STRONG VAGAL STIMULATION.

Exp. March 21, 1930.

Dog, weight 13.9 kg. Anaesthesia, chloralose and urethane. No artificial respiration. Cannula inserted in the lower and also in the upper end of the oesophagus; pylorus tied at the junction with the duodenum. Collections of oesophageal secretion from upper and lower cannula respectively.

Sample	Time		Volume			Peptic Activity	Remarks
			Total	Upper Cannula	Lower Cannula		
		min.	c.c.	c.c.	c.c.	Mett's units.	
	12:05-2:44 p.m.	159	0				12:05 p.m. Continuous stimulation begun; coil 13 cm.
	2:44-3:25 p.m.	41	0				2:44 p.m. Stimulation altered; coil 13 cm.
	3:25-4:10 p.m.	45	0				3:25 p.m.: coil 12 cm.
	4:10-4:40 p.m.	30	0				4:10 p.m.: coil 9 cm.
1	4:40-5:30 p.m.	50	11	10	1	0	4:40 p.m.: coil 8 cm.

TABLE XXXVI.

OESOPHAGEAL SECRETION — EFFECT OF TRANSITION FROM WEAK TO STRONG VAGAL STIMULATION.

Exp. March 25, 1930.

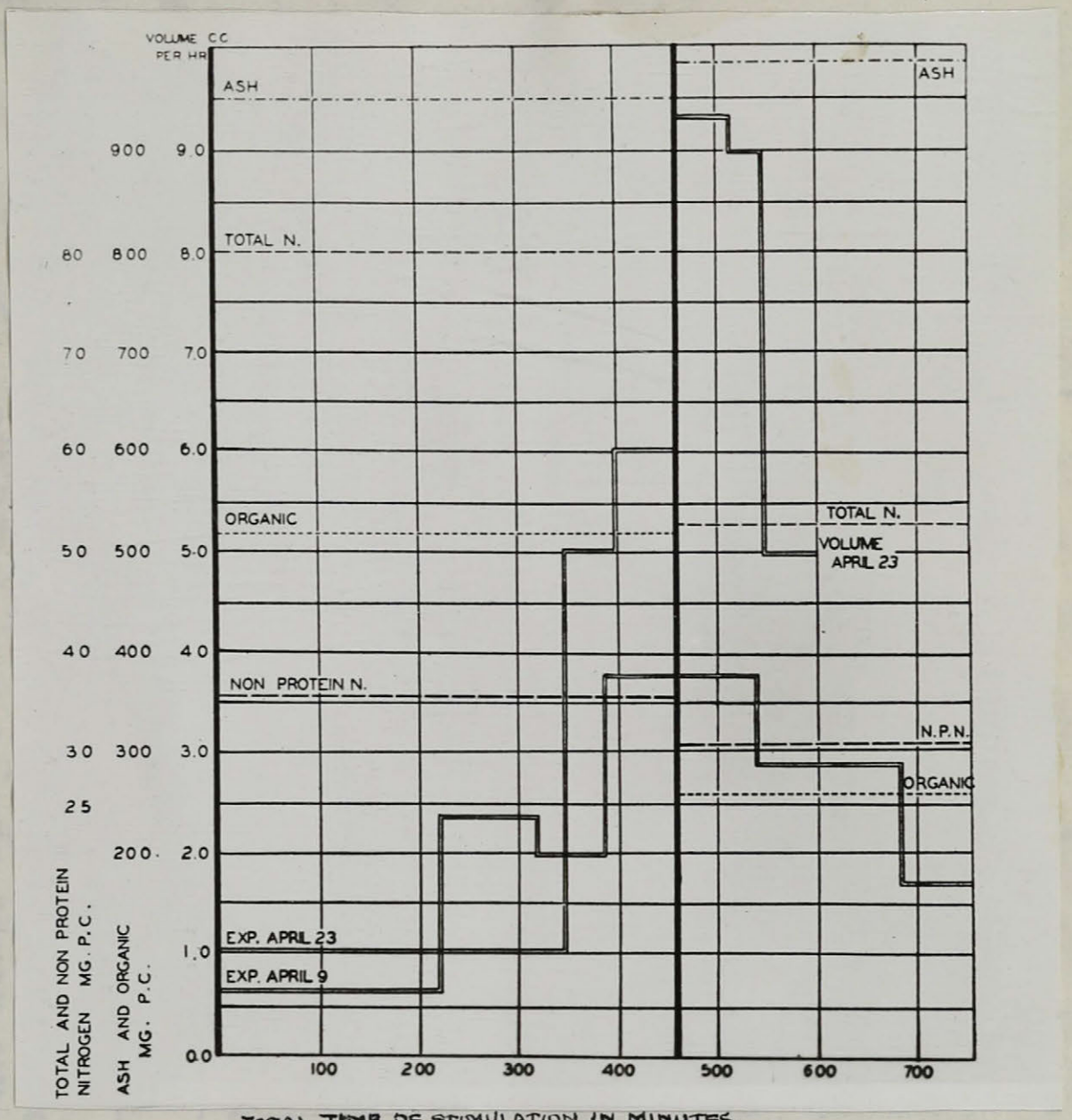
Dog, weight 5.9 kg. Anaesthesia, chloralose and urethane. No artificial respiration. Cannula inserted in the upper and also in the lower end of the oesophagus; pylorus tied at the junction with the duodenum. Collections of oesophageal secretion from upper and lower cannula respectively.

Sample	Time		Volume			Peptic Activity	Remarks
			Total	Upper Cannula	Lower Cannula		
		min.	c.c.	c.c.	c.c.	Mett's units.	
	11:25 a.m.-- 1:45 p.m.	140	0				11:25 a.m. Continuous stimulation begun; coil 14 cm.
	1:45-2:40 p.m.	55	0				1:45 p.m. Stimulation altered; coil 13 cm.
	2:40-3:20 p.m.	30	0				2:40 p.m.; coil 12.5 cm.
	3:20-4:05 p.m.	45	0				3:20 p.m.; coil 11.5 cm.
	4:05-5:00 p.m.	55	0				4:05 p.m.; coil 9 cm.
1	5:00-5:40 p.m.	40	4.5	4	0.5	0	5:00 p.m.; coil 7 cm.

secretion, whereas with strong stimulation 4.5 cc. of mucus were obtained over a period of 95 minutes. When strong stimulation was applied from the start and continued over a considerable period of time there was a definite secretion of thick gelatinous and highly viscid mucus. This substance was crystal clear and extremely tenacious. As stimulation continued there was an increase in the rate of secretion and a change in the character of the secretion from a highly viscid to a semi-fluid substance (Table XXXVII). In all the experiments more secretion was obtained from the upper oesophageal fistula than from the lower one; e.g., in the experiment shown in Table XXXVII, 18.1 cc. were obtained from the upper cannula and only 2 cc. from the lower cannula. In control experiments in which the vagi were not stimulated there was no oesophageal secretion.

Similar results were obtained with strong vagal stimulation in two experiments shown in Table XXXVIII. A more detailed chemical examination of the secretion was made in these experiments. The course of the oesophageal secretion is shown in Fig.2 as well as the concentration of different constituents of the mucus secreted. It is evident in these experiments (see Fig.2) that there was a long initial period of secretion lasting for 200 to 300 minutes. During this period the rate of secretion was 0.55 cc. (Experiment of April 9) and 1.0 cc. (Experiment of April 23) from the upper end /

Figure 2



The course of the oesophageal secretion in experiments of April 9 and April 23 is shown by continuous double lines. The division between the two periods of secretion is indicated by a heavy vertical line. In one experiment (April 23) the concentration of the different constituents of the secretion is charted.

TABLE XXXVII.

OESOPHAGEAL SECRETION — EFFECT OF STRONG VAGAL STIMULATION.

Exp. March 28, 1930.

Dog. Anaesthesia, chloralose and urethane. No artificial respiration. Cannula inserted in the upper and also in the lower end of the oesophagus; pylorus tied at the junction with the duodenum. Collections of oesophageal secretion from upper and lower cannula respectively.

Sample	Time		Volume			Peptic Activity	Remarks
			Total	Upper Cannula	Lower Cannula		
		min.	c.c.	c.c.	c.c.	Mett's units.	
	10:50 a.m.						10:50 a.m. Continuous stimulation begun; coil 9 cm.
1	10:50-11:32 a.m.	42	3.5	3.5	0	0	
2	11:32 a.m.— 12:32 p.m.	60	4.0	4.0	0	0	12:32 p.m. Stimulation discontinued.
	1:40 p.m.						1:40 p.m. Stimulation begun; coil 8 cm.
3	1:40-2:20 p.m.	40	3.5	3.5	0	0	
4	2:20-3:00 p.m.	40	3.0	3.0	0	0	
5	3:00-3:20 p.m.	20	1.1	1.1	0	0	
6	3:20-3:40 p.m.	20	3.0	3.0	0	0	
	4:40 p.m.		2.0		2.0	0	

TABLE XXXVIII.

Detailed chemical analysis of the oesophageal secretion collected from the upper and lower ends of the oesophagus of two dogs, during rhythmic stimulation of the vagi in the neck.

In each experiment, Samples I and II represent the collections made during the first and second periods of secretion, respectively.

Secretion	Experiment, April 9 (Dog 1)			Experiment, April 23 (Dog 2)	
	Sample I (upper end)	Sample II (upper end)	Sample III (lower end)	Sample I (upper end)	Sample II (upper end)
Time of collection (min.)	315	375	690	410	135
Quantity (c.c.)	5.9	18.9	9.3	17.0	18.0
Specific gravity (density)		1007.5			1007.0
pH		8.3		7.5	8.0
Acid-combining power (m.eq./1 litre)		15.0	15.0	11.5	11.6
Solids (gm. %)		1.353		1.477	1.25
Ash (gm. %)		1.05		0.957	0.99
Organic material (gm. %)		0.303		0.52	0.26
Cl (mg. %)		618.0	501.0	504.7	582.8
P — total (mg. %)		1.2		1.2	0.9
K (mg. %)		53.6		51.0	58.2
Ca (mg. %)		6.2		6.9	6.9
Nitrogen — total (mg. %)	142.4	63.3	85.1	80.6	52.5
Nitrogen — non-protein (mg. %)		39.2		36.0	31.6
Nitrogen — amino (formol) (mg. %) ..		2.6		2.5	2.5
Nitrogen — ammonia (mg. %)	4.1	3.64	4.48	4.76	4.72
Nitrogen — urea (mg. %)		6.72	5.88	5.04	4.78
Peptic power	0	0	0	0	0

end of the oesophagus. The secretion during this stage, as in the experiment shown in Table XXXVII, consists of an extremely thick and tenacious mucoid substance which precedes a more copious flow of semi-fluid mucoid substance. This comparatively long period cannot be considered as a true latent period but must rather be attributed to the difficulty with which this viscid material is evacuated. Secretion was well maintained for the next 200 to 300 minutes, gradually declining towards the end of the experiment. This terminal decline was probably due to diminished nerve excitability and also to the dying condition of the animals.

In both these experiments the secretion collected from the upper end of the oesophagus was separated into two parts (Samples I and II). In addition in one experiment (April 9) the secretion from the lower end of the oesophagus was collected as a separate sample. A perusal of Table XXXVIII shows that the reaction of the oesophageal secretion was decidedly alkaline. It was rich in ash with a moderate content of organic substances. The initial secretion was extremely thick but as the flow increased in volume it became somewhat more fluid. The secretion obtained during the first part of the experiment (Sample I, Experiment April 23) contained twice as much organic material as that collected during the second part of the experiment (Sample II). Since /

Since the character of the secretion changed during its course from highly viscous to fluid, it is probable that the sources of the mucus were exhausted during the prolonged stimulation.

The total nitrogen in both experiments was definitely lower in samples of secretion obtained after the secretion was well established. There was however only a slight diminution of the non-protein nitrogen and urea and no change in the values for amino nitrogen and ammonia. There was considerable variation in the inorganic constituents of the secretion collected during the two periods. In Sample II (Exp. April 23) the total ash increased, as did the chlorine and potassium during the second stage of the secretion. The calcium concentration was unaltered whereas the phosphorus concentration fell. The composition of the secretion collected from the lower end of the oesophagus corresponded closely to that of mucus obtained from the upper end (Sample III, Exp. April 9).

Thus from the above data there are indications that stimulation of the vagi activated a true secretion from the oesophageal mucosa. If the process were merely one of squeezing out pre-formed mucus the secretion would not continue for such a long period. What is more important however is that there would be no changes in its chemical composition during /

during the course of the secretion. These changes are similar to those which occur in the composition of saliva during prolonged activity of the mixed glands.

Atropinisation, carried out during the course of the experiment with the object of curtailing the volume of the secretion, yielded indefinite results. Large doses of atropine sulphate (10 to 15 mg.) paralysed the vagus innervation of the heart and other organs and yet a slow flow of mucus continued from the upper cannula. The explanation of this seeming paradox was clear on postmortem examination which revealed a large quantity of viscous material still adhering to the walls of the oesophagus. Thus the flow of mucus continued in spite of atropinisation, its evacuation from the oesophagus being caused by the respiratory movements.

A comparison of the chemical properties of the secretions of the oesophageal, salivary and gastric glands is interesting (see Table XXXIX). Absolute comparative figures are not available since the composition of the secretions from these glands varies with rate of the secretion and the strength of the stimulus: however, a general comparison is of value in that it shows the difference between the chemical composition of the secretion of the oesophageal glands and that of the glands functioning above and below them. The acid-combining power of the oesophageal secretion is /

TABLE XXXIX.

CHEMICAL COMPOSITION OF OESOPHAGEAL SECRETION COMPARED WITH SALIVARY AND GASTRIC SECRETIONS.

	Oesophageal Mucus	Saliva		Gastric Juice
		Submaxillary	Parotid	
Specific gravity (density)	1,007			
pH	7.5 - 8.0			
Acid-combining power (m.eq./l.)	11.5 - 11.6	15.0 - 30.0	25.0 - 65.0	
Solids (gm. %)	1.477- 1.25			0.315- 0.88 (Kersten) 0.387 (Rosemann)
Ash (gm. %)	0.957- 0.99	0.29 -611.0	0.54- 0.89	0.127- 0.136 (Rosemann)
Organic (gm. %)	0.52 - 0.26	1.14	0.45	
Cl (mg. %)	500.0 -618.0	5.8 -246.0	170.0 -328.0	600 (Rosemann) 587-629 (Webster)
P - total (mg. %)	1.2 - 0.9	1.5	1.1	
K - total (mg. %)	51.0 - 58.2	48.0 - 92.5	37.9 - 91.6	30.7-43.3 (Rosemann)
Ca (mg. %)	6.2 - 6.9	5.8 - 13.2	20.0 - 26.0	0.22-0.07
Nitrogen - total (mg. %)	80.6 - 52.5			23.0 -28.0
Nitrogen - non-protein (mg. %)	36.0 - 36.6			9.8 -14.8
Nitrogen - amino(formol)(mg.%)	2.5 - 2.5			0.25- 2.45
Nitrogen - ammonia (mg. %)	4.76 - 4.72			1.8 - 5.6
Nitrogen - urea (mg. %)	6.72 - 4.78			0.16- 0.88
Peptic power	0 - 0			

is lower than that of saliva from the parotid gland (25.0 to 65.0 mil. equiv.) and lower than that of saliva from the mixed glands (about 15.0 to 30.0 mil. equiv.). The oesophageal secretion is much richer in total ash content (about 1.0 gm. per cent.) than the secretion of the mixed glands (0.29 to 0.611 gm. per cent.) or the parotid glands (about 0.54 to 0.89 gm. per cent.). (These data on the inorganic composition of the saliva were obtained by reflex stimulation of the glands, and are taken from unpublished work of Dr. H. Baxter.) It has also a higher ash content than the gastric juice, which according to Rosemann (1907) is 0.127 to 0.136 gm. per cent. Likewise a comparison between the solids of dog's gastric juice and oesophageal secretion shows the figures for the latter (1.25 to 1.477 gm. per cent.) to be nearly three times as high as for the former (0.315 to 0.88 gm. per cent. according to Kersten, [1920] and 0.387 gm. per cent. according to Rosemann [1907]). The chlorine concentration in the oesophageal secretion (500 to 618.0 mg. per cent.) is about equal to or somewhat lower than that of the gastric juice (about 0.6 gm. per cent. [Rosemann, 1907], 0.587 to 629 mg. per cent. [Webster, 1931]) and much higher than in the saliva of the mixed glands (58.0 to 246.0 mg. per cent.) and parotid glands (170.0 to 3280 mg. per cent.). Potassium is lower in the oesophageal secretion (51.0 to 58.2 mg. /

mg. per cent.) than in the saliva of the mixed glands (48.0 to 92.5 mg. per cent.) and parotid glands (37.9 to 91.6 gm. per cent.) but higher than in the gastric juice (30.7 to 43.3 mg. per cent. [Rosemann, 1907]).

The calcium concentration in the oesophageal secretion (6.2 to 6.9 mg. per cent.) is higher than in the gastric juice (0.22 to 0.07 mg. per cent.) but lower than in the saliva of the mixed glands (5.8 to 13.2 mg. per cent.) or of the parotid glands (20.0 to 26.0 mg. per cent.). A large proportion of the total nitrogen present is in the form of non-protein nitrogen. The same seems to be true of the nitrogen in the gastric juice. During the course of secretion there is a marked fall in the total nitrogen with only slight diminution of the non-protein nitrogen. The concentration of ammonia (4.72 to 4.76 mg. per cent.) in the oesophageal secretion is almost the same as in the gastric juice, whereas the concentration of urea is higher in the former (4.78 to 6.72 mg. per cent.) than in the latter (0.16 to 0.88 mg. per cent.) No pepsin was demonstrated in the oesophageal secretion.

Because of the difference in the chemical composition of secretions from the oesophageal, salivary and gastric glands respectively it seems justifiable to conclude that the oesophageal secretion is a special secretion which differs from /

from the secretions of the adjacent upper and lower parts of the alimentary canal.

DISCUSSION /

DISCUSSION

It will be remembered that there are two kinds of oesophageal glands:

1. Oesophageal glands, having two kinds of cells (a) Mucous, (b) Demilune, with an arrangement of the serous complexes resembling that found in the submaxillary gland,

2. Cardiac oesophageal glands:

   (a) Upper oesophageal glands (not present in the dog),

   (b) Lower oesophageal glands, having either the same structure as the cardiac glands of the stomach without parietal cells or the structure of true fundic type of gland containing acid cells.

The glands of Group 1 comprise the majority of the oesophageal glands in the dog and it is probably from these that the oesophageal secretion obtained by vagal stimulation is derived. They are of the mixed type; hence their secretion is of a compound nature. During the first period of stimulation of the vagus the secretion is very viscid and mucoid. The mucus constituents are probably derived partly from the secretion of the mucous cells of the oesophageal glands and partly from the ampullae of the excretory duct where the secretion accumulated during the period of rest. The secretion /

secretion of the demilune cells in this period is overshadowed by the secretion of the mucous cells. After a prolonged period of stimulation of the secretory nerve these sources of mucus were more or less exhausted and the secretion became more fluid in consistency. This also explains the fall in the concentration of the total nitrogen and the rise in the concentration of chloride and potassium in the samples collected during the later hours of stimulation. The absence of demonstrable peptic activity in the secretion obtained from either the upper or lower end of the oesophagus may be explained by the fact that the cardiac glands are rarely found in the oesophagus of a dog. Thus a close relationship exists between the oesophageal secretion and stimulation of the vagi. Stimulation is associated with typical changes in the composition of the secretion which occurs under its influence. It may therefore be concluded that the vagus is a secretory nerve to the oesophageal mucosa.

The glands of the trachea and larynx are under the influence of the vagus (Florey, Carleton and Wells, 1932) which fact lends support to our findings since the respiratory ducts are derived as a ventro-medial outgrowth from the part of the fore-gut which later develops into the oesophagus.

Thus the part played by the vagus in the oesophageal secretion /

secretion is important experimentally because of the possible contamination of gastric secretions of vagal origin by oesophageal mucus.

Further, from the phylogenetic point of view, according to Goetsch (1910) the presence of oesophageal glands in some animals (chiefly mixed feeders) and their absence in others (purely vegetable feeders) make it difficult to understand their rôle. He believes that the glands developed independently in different species in accordance with their special needs. In the dog large pieces of meat or bones require lubrication during their passage through the oesophagus. It seems significant that the same nerve which regulates the motility of the oesophagus can at the same time stimulate the secretion of the oesophageal glands.

P A R T V

HISTORICAL:

THE INTERDEPENDENCE OF GASTRIC SECRETION AND THE CO_2 CONTENT OF THE BLOOD

For some years sporadic indications have appeared in the literature that there is a relation between blood CO_2 content and gastric secretion. Maly's theory, first advanced in 1878, postulated the importance of CO_2 in the formation of HCl, but placed it second however to $NaHPO_4$, which Maly believed to be the compound directly concerned in the formation of HCl.

Alkalis as Gastric Stimulants

Some of the earliest reports on gastric secretion and its relation to the ingestion of alkaline fluids are of great interest when considered in the light of more recent knowledge. In 1843 Blondlot obtained a long continued flow of gastric juice with high acidity after feeding gastrostomised dogs on meat moistened with sodium carbonate. Some forty years later Jaworski (1888) attributed to the alkaline Carlsbad waters the power of causing an atrophy of the secretory tubules /

tubules. He held the opinion that these alkaline waters converted hyperchlorhydria into hypochlorhydria by setting up through irritation a catarrhal condition of the gastric mucosa with consequent diminution of the acid supply. Pavlov (1910) stated that an inhibitory influence must be ascribed to sodium bicarbonate. This conclusion was based on the fact that water always acts as a gastric stimulant whereas in the case of soda "not one of its solutions (varying from 0.05 to 1% strength) when brought in quantities of 150 c.c. into the large stomach were able to evoke even a single drop of juice from the small cavity".

Two French investigators, Linoissier and Lemoine (1894), obtained results which were more in accord with the observations of Blondlot. They were of the opinion that sodium bicarbonate acts as a gastric secretory excitant no matter what the dose, and report having observed a case of anacidity which was transformed into one of hyperacidity after prolonged use of alkaline Vichy waters. Since then numerous authors have observed that feeding large quantities of $NaHCO_3$ over a prolonged period of time raises the level of the acid curve during fractional test meals. Thus Crohn (1918) studied the effects which various alkaline powders, given before or after breakfast (heavy oatmeal gruel) produced upon gastric secretion. He found that magnesium oxide /

oxide (0.8 to 1 gm.) and $NaHCO_3$ (2 gm.) given before or shortly after the test breakfast, although temporarily decreasing the acidity of the gastric contents through direct neutralisation, gave rise to a secondary secretion. The curve of acid concentration steadily rose, reaching hyperacidity levels between one-and-a-half to two-and-a-quarter hours after the giving of the meal. In the case of magnesium oxide the emptying time of the stomach was prolonged by half-an-hour. If, however, the alkali was given one and three-quarters hours after the ingestion of the test meal instead of before or shortly after, there was a rapid and efficient neutralisation of the digestive acidity without a secondary rise. In conclusion he writes: "With too small a dose no beneficent neutralisation is accomplished while the attendant secondary rise in acidity rarely fails to assert itself. When too large a dose is employed, one risks paralyzing the digestion for a considerable period following which there appears a hyperacidity of even greater degree than the one we undertook to combat. The combination of slowly acting with more rapid alkalies is desirable," and finally he states, "It seems questionable whether prolonged use of the alkalies leads to any permanent diminution of the acid secretion of the stomach; in fact it is as likely that the opposite effect is produced."

In /

In an attempt to clarify more thoroughly the relation between alkali and gastric secretion, Boyd (1924) studied the response to food with and without alkali in one Heinhenhain- and three Pavlov-pouch animals. The dogs were studied over a considerable period of time and then were given alkaline powders in divided doses 3 to 9 times daily. The rate of secretion in response to a standard stimulus was found to be higher during the administration of alkali than during the control period, and was maintained for 6 to 7 days after the cessation of alkali administration. Such were the facts when small doses of sodium bicarbonate were given (up to 1 gm. per kg. per day). With large doses (exceeding 3 gm. of alkali per kg. per day), on the other hand, secretion was diminished during the period of alkali administration. When alkalis were no longer given, the secretion gradually augmented and finally attained hypersecretion values. In addition Boyd found that, when large doses of alkali were given, there was a diminution of the blood chloride values and suggested that this accounted for the depressing effect of large doses of alkali upon gastric secretion.

Correlation /

Correlation between Alveolar CO_2 Tension and Gastric Secretion

Higgins (1914) and Erdt (1915) both reported a rise in alveolar carbon dioxide tension in response to digestion. In their interpretations of this fact two workers are markedly at variance. Higgins maintained that the changes in alveolar CO_2 tension observed during digestion were independent of any chemical changes resulting from the secretion of hydrochloric acid into the stomach. He showed that ordinarily a change in posture from the erect to sitting position raises the alveolar CO_2 tension and even more so when the patient assumes the supine position. He believed that this occurred because the respiratory centre was rendered less irritable and that the effect of a meal was due to a similar influence on respiration rather than on the alkaline reserve. Erdt on the other hand suggested that the increase in alveolar CO_2 tension following a meal was due to an increase in the alkali reserve of the blood in consequence of the loss of HCl from the blood to gastric juice.

Similar results are reported by Van Slyke, Stillman and Cullen (1917) who went further in their studies and examined the bicarbonate values for blood plasma before and after a meal. However they found no changes in the bicarbonate values for blood plasma corresponding to the changes observed in the alveolar /

alveolar CO_2 tensions and thus concluded that changes in alveolar CO_2 tension were best explained along the lines suggested by Higgins.

A few years later Dodds (1920-21) in a more extensive investigation on human subjects observed not only changes in alveolar CO_2 tension during digestion but also the fact that there was a definite order in which these changes took place; e.g. it was shown that there was a rise of 2 to 6 mm. Hg in the alveolar CO_2 tension within the first half to three-quarters of an hour after the ingestion of food. Subsequently the rise gave way to a definite decline to 2 to 6 mm. Hg below the original level and then there was a gradual return to the initial level. In one subject, from whom the greater part of the stomach had been removed, there was an initial rise of 0.4 to 0.8 mm. whereas the secondary fall was similar to that observed in normal individuals. There seemed to be a definite correlation between the changes in the alveolar CO_2 tension and the different phases of digestion, the rise corresponding to an outpouring of HCl during gastric secretion and the fall being closely related to pancreatic activation and the consequent outpouring of alkali. In a later paper Dodds and Bennett (1921) presented still more conclusive evidence concerning this subject. By the use of atropine applied locally, first to the gastric mucosa and then /

then to the duodenum prior to the ingestion of food, both the initial rise and secondary decline in alveolar CO_2 tensions were abolished.

The work of these early investigators, however, has not gone unchallenged. Brunton and Israels (1930) report results which are at variance with previously accepted views. In their experiments there was no constant relation between changes in alveolar CO_2 tension and the processes of digestion. For the most part there was no increase in the alveolar CO_2 tension and in some cases only an irregular slow rise reaching a maximum in about 90 minutes after the meal. When drugs alone (histamine and caffeine) were used as gastric stimulants a rise of alveolar CO_2 tension occurred in only one out of seven experiments. Further there was no secondary decline after meals in concurrence with pancreatic secretion. Brunton and Israels reasoned that any excess of blood alkali that normally would result from the secretion of large volumes of hydrochloric acid could be adequately dealt with by the blood and kidneys without causing a measurable rise in the alveolar CO_2 tension.

Gastric Secretion: its Influence on Alveolar CO_2 Tension and Blood CO_2 Changes

The controversy concerning the relation of alveolar CO_2 tension changes to gastric secretion naturally directed the attention of investigators to a study of the blood CO_2 concentrations during digestion. Van Slyke, Stillman and Cullen (1917) were among the first to consider the problem from this angle. They determined the CO_2 combining power of plasma before and after feeding and failed to observe any change during the process of digestion. Dodds and McIntosh (1923) confirmed this finding and showed that, although the plasma exhibited no change during digestion either as regards CO_2 or alkaline reserve, there was a rise in the CO_2 content of the whole blood, which paralleled that of the alveolar CO_2 tension. The rise was associated with gastric secretion and the fall with pancreatic secretion. According to these investigators, "All changes in CO_2 content following meals occur in corpuscles."

There observations were confirmed by Martin and Mogenstern (1931). In order to exclude the effects of extraneous substances in an ordinary test meal, histamine was employed as the gastric stimulant. In the great majority of the patients who secreted an acid juice there was an increase in the CO_2 content of alveolar air and also of plasma and serum. In those cases where there was an anacidity histamine caused either an /

an increase or decrease in the CO_2 content of the alveolar air plasma and serum. There was a parallelism between the changes occurring in the alveolar CO_2 tension and in the serum or plasma.

In a recent article reviewing the literature concerning the acid output of the kidney and the alkaline tide, Brunton (1933) points out that protein meals are universally accepted as best for the production of the alkaline tide and by the same token activate the best gastric secretions. He suggests however that "the effect of food constituents on the acid or acid ammonia output probably depends on other factors besides the gastric secretion: the acid-base balance of the food constituents absorbed, metabolic conditions in the body and the respiratory mechanism".

Alkalis Raise the CO_2 Content of the Blood

In the first part of this section reference was made to some of the evidence suggesting that feeding of alkali to humans or animals tends to augment the gastric secretory response to a given stimulus. No mention was made by the authors referred to of the CO_2 content of the blood in their experiments. During the past ten years the attention of investigators has been drawn to the effect of alkali upon the blood CO_2 content largely through clinicians and mainly as a result /

result of Sippy's alkaline diet, so popular in the treatment of peptic ulcers. Thus Hardt and Rivers (1923) in a study of 32 cases of peptic ulcer treated by Sippy's powders reported that 50% of these showed toxic symptoms during the course of the treatment. These symptoms arose within from 4 to 5 days or not until the third or fourth week of alkaline powder administration. The blood chemistry studied during this treatment showed that the CO_2 combining power of plasma varied from a high normal of 65 to 117 vol. per cent. There were other blood changes due to the complication of renal insufficiency which will not be discussed here.

Jordan (1926) in a study of 41 patients with peptic ulcer treated on a Sippy diet states that the acid base equilibrium is at first somewhat disturbed by the influx of alkali but within a few days the levels of chloride and CO_2 content approach the normal. The majority of cases show no chemical or clinical disturbance due to alkalosis. In those cases (minority) that show clinical signs of alkalemia the CO_2 content rises markedly, and simultaneously there is a decline in the plasma chlorides.

Similar results have been reported by Gatewood, Gaebler, Muntwyler and Myers (1928) from a study of 46 patients with peptic ulcer undergoing treatment with Sippy powders. Two-thirds of these at some time during treatment showed a high blood bicarbonate value /

value or pH, or both. Twenty-one showed an uncompensated alkalosis with electrometric pH values of 7.48 or more. In those cases showing a high blood bicarbonate value the plasma chlorides were comparatively diminished. In conclusion these authors assert that alkalis as commonly administered "always produce characteristic changes in the blood chemistry even though symptoms of alkalosis may not occur".

CO_2 Content of the Blood and Gastric Secretion

In 1928 Bakaltschuk demonstrated an increase in gastric acidity in human subjects after the inhalation of CO_2. An increase was also obtained by Apperly and Semmens (1928) after the rebreathing of the subject's own expired air. In a different type of experiment Szilard (1930) showed an augmented "fasting" secretion following intravenous injection of $NaHCO_3$. The injection of glucose on the other hand caused no such rise.

Apperly and Semmens (1928) showed in human subjects that there was a parallelism between blood bicarbonate content and the response to a standard test meal. They attributed this to a common effect of variation in oxygenation of the blood on both gastric secretion and blood bicarbonate content. It should be noted that the results reported by these investigators have been obtained upon human subjects by means of the /

the gastric test meal. This criterion of gastric secretion is open to serious objection since the values obtained depend not only on the activity of the gastric cells, but also on the emptying time of the stomach, and regurgitation of duodenal contents. Dilution, due to salivation and to the ingested meal and conditioned reflex effects, is also a source of error. Apperly and Crabtree (1931) in a recent article are cognizant of the above sources of error (as indeed were Apperly and Semmens) and believe that they have taken them into account. In this article they report a direct relation between the concentration of gastric hydrochloric acid and the plasma bicarbonate content.

EXPERIMENTAL /

EXPERIMENTAL RESULTS:

THE INTERDEPENDENCE OF GASTRIC SECRETION AND THE CO_2 CONTENT OF THE BLOOD

As has already been mentioned (Part I) active hyperventilation of an animal during the course of gastric secretion obtained by electrical stimulation of the vagi caused a marked diminution in the secretion. This effect suggested the existence of some relationship between the blood CO_2 and gastric secretion. Confirmation of this view was found in the work of other investigators whose results, owing to the lack of experimental proof, were suggestive but certainly not convincing. With the hope of reaching a more definite conclusion regarding this problem the following experiments were conducted. In all the experiments dogs were used; the technique employed followed the "Standard Preparation" described under "Methods". The blood chemistry studies were carried out in collaboration with Dr. J. S. L. Browne.

The experiments were divided into the following groups, and those described are illustrative of other similar experiments.

(1) /

(1) Nerve Stimulation:

Influence of (a) Hyperventilation; (b) Injection of acid (HCl and lactic); (c) Injection of NaCN.

(2) Histamine Stimulation:

Influence of (a) Hyperventilation; (b) Injection of acid (HCl and lactic and of base $NaHCO_3$); (c) Injection of NaCN.

(1) Nerve Stimulation

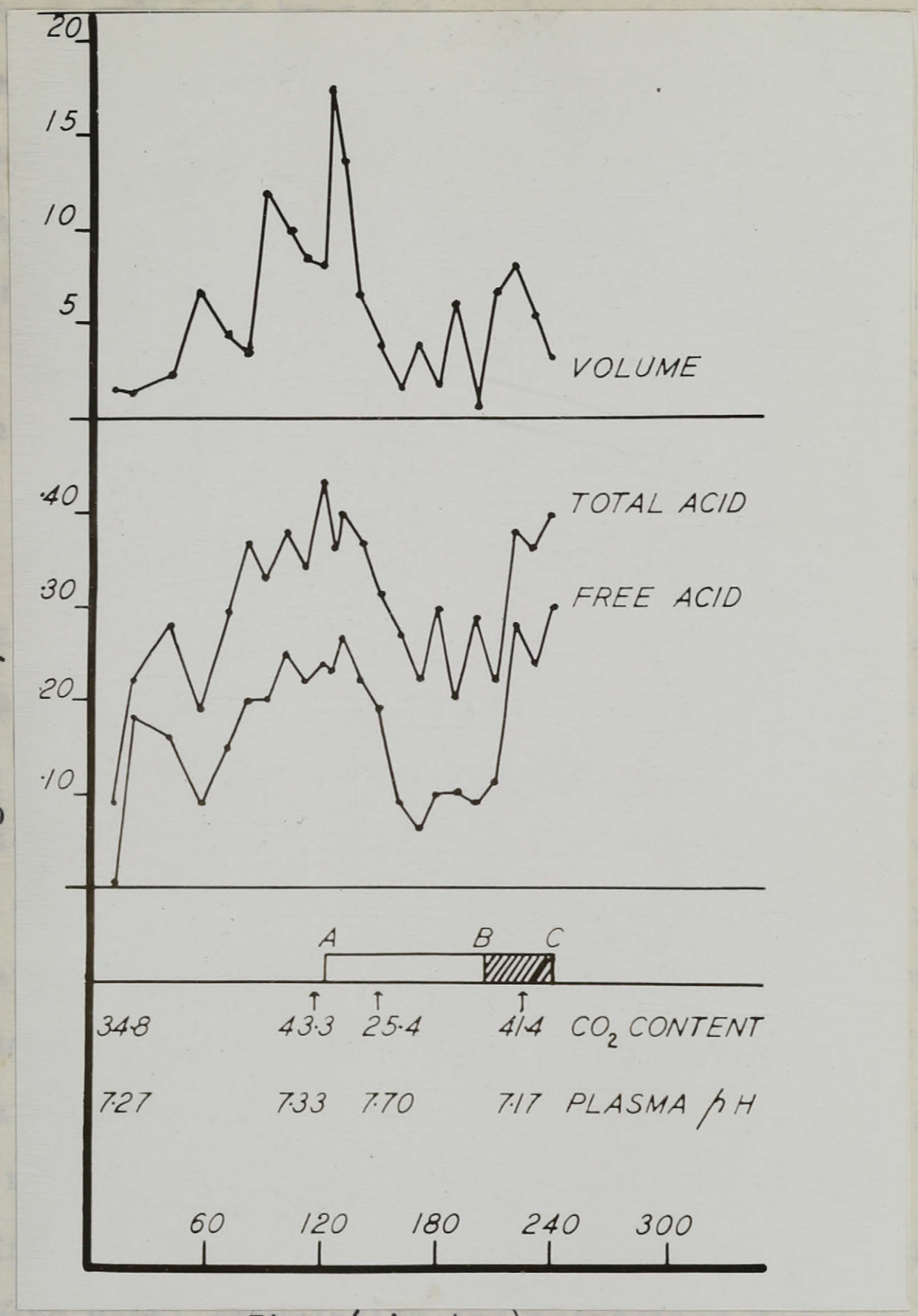
(a) Hyperventilation

Two examples of this type are presented (Figs. 3 and 4).

In the experiment illustrated in Fig.3 the vagus nerves were stimulated with an induction current interrupted 15 times per minute, the left and right vagi being stimulated alternately for periods of ten minutes each. Collections of gastric juice were made in periods of ten minutes; these represent corresponding periods of nerve stimulation. Samples were taken in this way in order to show the variations in nerve response. The difference between the effects of the right and left nerve stimulation is seen in the figures and is especially marked in the volume output. It will be observed that after 120 minutes of stimulation, a satisfactory flow of gastric secretion was obtained and showed the usual values for free and total acidity for this type of stimulation.

During /

Figure 3

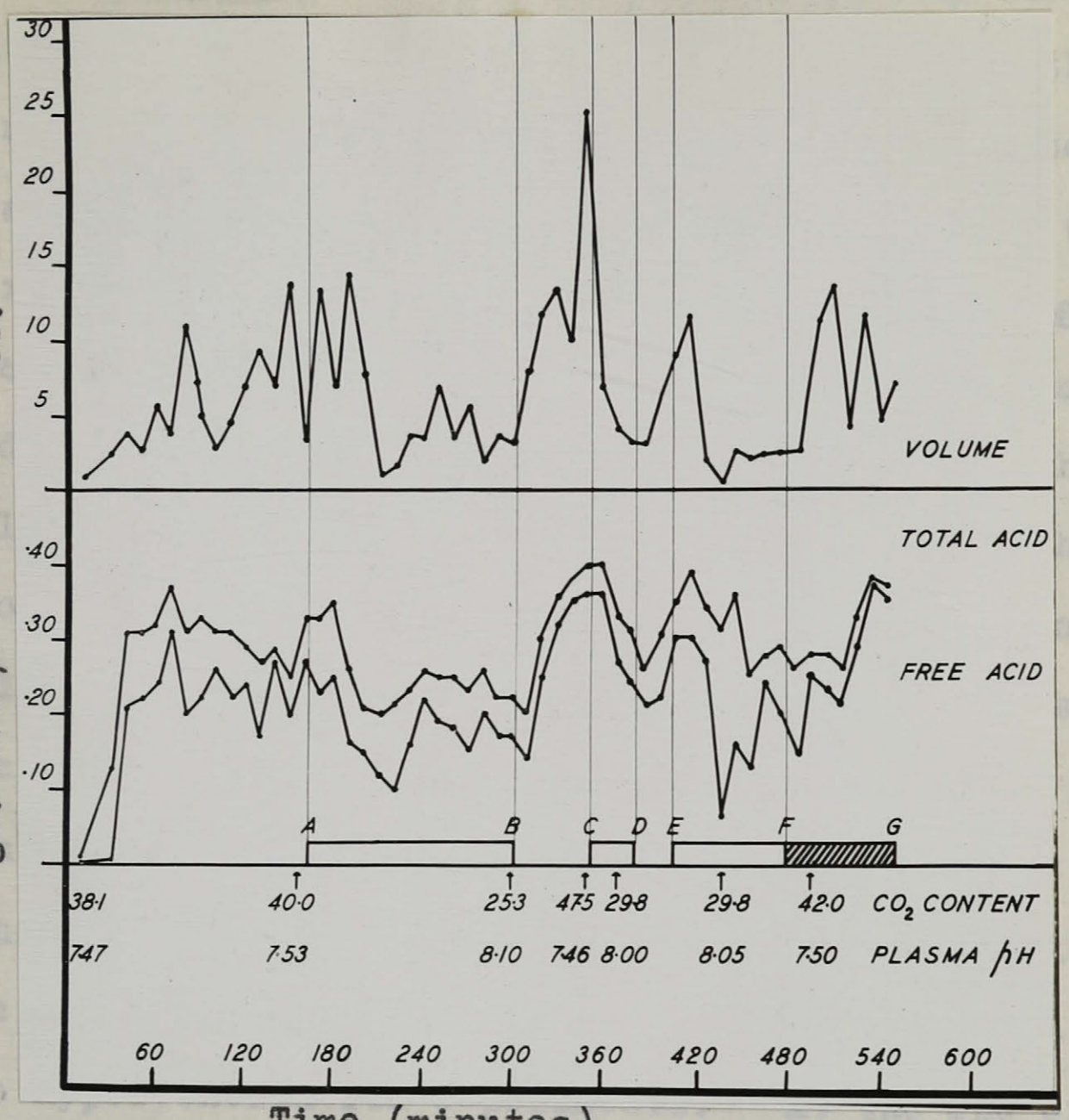


Dog 9. Wt. 13.3 kg. Vagal stimulation. (A-B) artificial ventilation at the rate of 64/min. with air. (B-C) same rate of ventilation. 8% CO_2 in air.

During this period the arterial plasma CO_2 content gradually rose to a value of 43.3 vols. per cent. (this figure is approximately normal for the dog under these conditions). At the point 'A' artificial hyperventilation was applied at the rate of 64 per minute for a period of 80 minutes. The pump used had a stroke volume of 1700 cc. There was a rapid fall in the volume output; twenty minutes later, the free and total acidity also fell. Coincidental with these changes the plasma CO_2 content fell to 25.4 vols. per cent. In other experiments we have found that the CO_2 content usually reaches an approximately constant low level within twenty minutes after the application of hyperventilation. The diminished acidity continued for 60 minutes. At this stage (B) a Douglas bag containing a mixture of 8 per cent. CO_2 and air was connected to the pump inlet. The rate of hyperventilation was kept constant. The acidity rose immediately to control levels; the CO_2 content of the plasma also rose, reaching a level of 41.1 vols. per cent. in 27 minutes; the pH fell below control levels.

In a second experiment (Fig. 4) secretion was obtained following vagal stimulation and maintained for a period of 50 minutes. Hyperventilation applied at 'A' at the rate of 74 per minute reduced the volume of secretion, the free and total acidity and the plasma CO_2 content. Secretion practically /

Figure 4



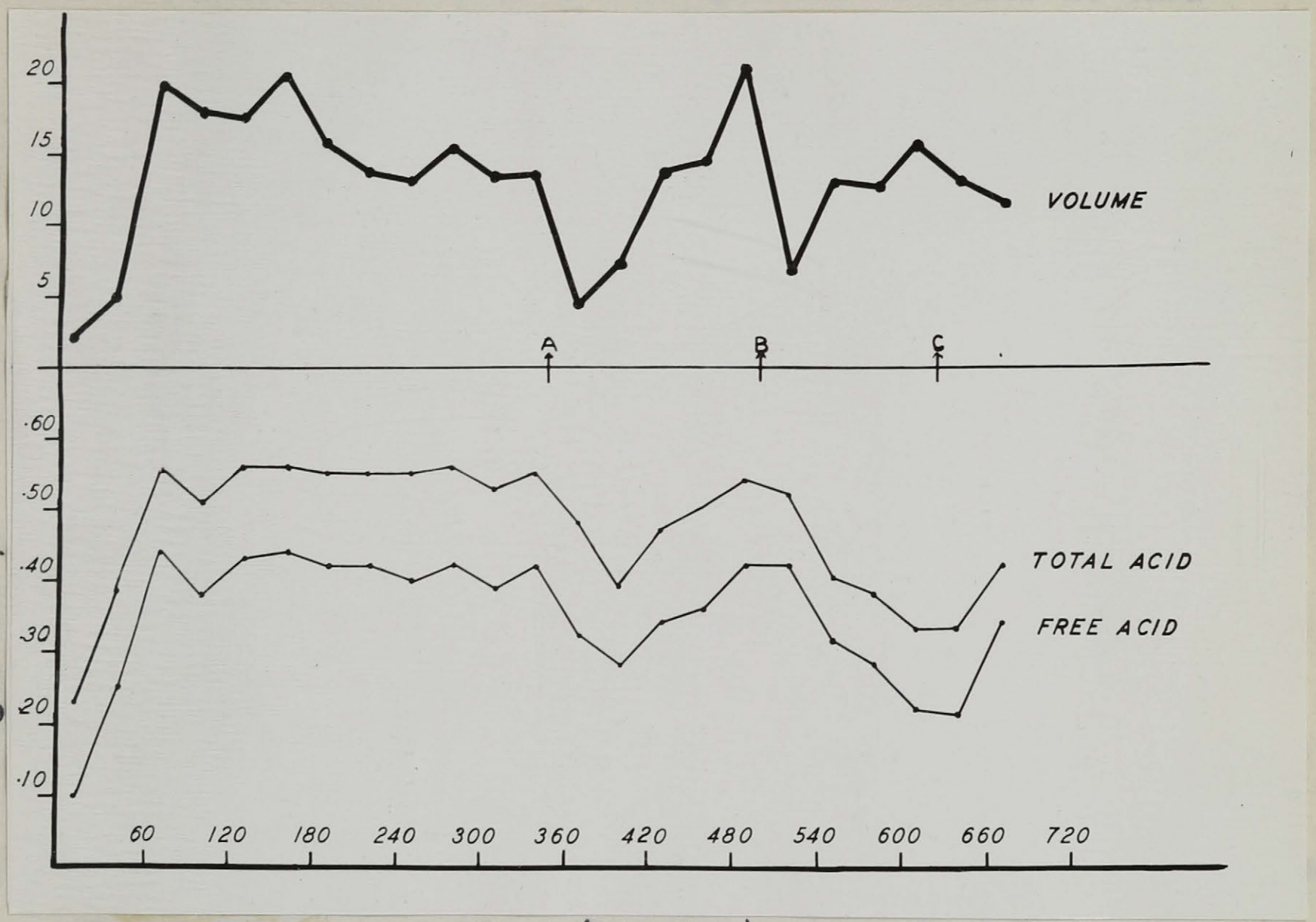
Dog 10. Wt. 16 kg. Vagal stimulation. (A-B) artificial ventilation at the rate of 74/min. with air. (C-D) and (E-F) the same. (F-G) the same rate of ventilation. 5% CO_2 in oxygen.

practically ceased for a period of 100 minutes. Hyperventilation was discontinued at 'B' and the animal resumed a normal respiratory rhythm. The volume and the free and total acidity rose to and above control values, as did the CO_2 content. This procedure was repeated for a shorter period with similar effects as may be seen in the figure (C to D). A third application of hyperventilation (E to F) again reduced all values and these were restored following the introduction of 5 per cent. CO_2 at 'F'. In neither hyperventilation experiment was there any significant change in the total chloride content of the gastric secretion.

In a control experiment, presented in Fig.5, stimulation of the vagus produced gastric secretion which gradually rose and reached its height in one hour. For a period of five hours secretion was maintained at a constant level of volume and acidity. This is longer than the total duration of the hyperventilation experiments. At the end of the five hours ('A' in the figure) the volume of secretion diminished, as did the free and total acidity.

This decrease was due to a diminished excitability of the nerve at the point of contact with the electrodes. The values were returned to previous levels by moving the electrode to a fresh position on the nerves. This procedure was repeated twice. At the end of the experiment the nerves were acting /

Figure 5



Dog 36. Wt. 15 kg. Vagal stimulation.
(A) (B) and (C) - vagus ceased acting on heart; position of electrodes changed.

acting and the dog was in good condition. The total period of stimulation was over ten hours. It has been considered that the vagus nerve is acting satisfactorily when a typical effect on heart rate and blood pressure results at each stimulation. In the experiments shown in Figs. 3 and 4 and in Table XL, the nerves acted satisfactorily throughout according to this criterion.

(b) Injection of acid.

In this experiment (Table XL), an average rate of secretion of 5.6 cc. per ten minutes was maintained over a period of 80 minutes. The average for the free acidity was 0.29 gm. HCl per cent., and for the total acid 0.38 gm. HCl per cent. The CO_2 content was 43.3 vols. per cent. and the pH 7.33. In a period of nine minutes 75 cc. of 0.5 N/HCl were injected intravenously. Immediately after the injection the plasma CO_2 content was still 43.3 but the plasma pH had fallen to 7.00. The respiration of the animal had not yet increased. The secretion continued throughout the injection. The volume gradually fell during the twenty-minute period following the cessation of acid administration. In contrast to this the free and total acidity showed a slight rise. When this length of time had elapsed, the secretion suddenly stopped and did not return during the

remainder /

TABLE XL.

GASTRIC SECRETION — EFFECT OF INTRAVENOUS ACID INJECTION ON VAGAL STIMULATION.

Exp. Sept. 27, 1930.

Dog, weight 17.4 kg. Anaesthetic, chloralose and urethane. No artificial respiration. Oesophagus tied in the neck; pylorus tied at the junction with the duodenum.

Sample	Time		Gastric Secretion					Blood		Remarks
			Vol.	Free HCl	Total HCl	Mucus	Peptic Activity	CO_2 Content	pH	
	p.m.	min.	c.c.	gm.%	gm.%	c.c.	Mett's units.	vol.%		
1	2:30-3:30	60	12.5	0.00	0.10	1.1	576.0			Control period.
2	3:30-3:55	15	1.7	0.00	0.07	0.7	484.0			
3	3:55-4:05	20	1.3	0.00	0.10	0.15	576.0			
4	4:05-4:25	20	1.5	0.06	0.16	0.1	576.0			4:05 p.m. Continuous stimulation begun: coil 9 cm.
5	4:25-4:45	20	4.4	0.09	0.20	0.2	576.0			4:25 p.m. Secretion began.
6	4:45-5:05	20	6.2	0.15	0.23	0.2	576.0			4:50 p.m. Secretion altered: coil 8.5 cm. 4:55 p.m. coil 8.0 cm.
7	5:05-5:25	20	---	0.22	0.31	0.2	423.0			
8	5:25-5:35	10	5.0	0.29	0.37	0.2	484.0			
9	5:35-5:45	10	4.4	0.25	0.36	0.3	380.0			
10	5:45-5:55	10	6.5	0.34	0.40	0.3	519.0			
								43.3	7.3	
11	5:55-6:05	10	6.0	0.25	0.37	0.4	484.0			
12	6:05-6:15	10	6.7	0.32	0.44	0.3	519.0			
13	6:15-6:25	10	5.5	0.26	0.36	0.2	576.0			
14	6:25-6:35	10	5.6	0.28	0.40	0.3	676.0			
15	6:35-6:45	10	5.5	0.30	0.37	0.3	676.0			
										6:48 p.m. Acid injection commenced.
16	6:45-6:55	10	5.4	0.33	0.42	0.3	676.0			
17	6:55-7:05	10	4.6	0.35	0.47	0.1	676.0			6:57 p.m. Total of 75 c.c. 0.5 N/HCl inj.
18	7:05-7:15	10	3.7	0.33	0.45	0.2				
								43.3	7.0	
19	7:15-7:25	10	0.5	0.25	0.43	0.0				
20	7:25-7:45	20	0.3	0.15	0.33	0.0				
								24.2	7.1	
21	7:45-8:15	30	0.2	--	--	0.0				

remainder of the experiment. A blood sample taken ten minutes after the cessation of secretion showed a CO_2 of 24.2 vols. per cent. and a pH of 7.10.

The dependence of secretion upon CO_2 content rather than upon blood pH is indicated in the above experiment.

(c) Injection of NaCN

Since it has been shown that hyperventilation by changing the blood pH has the effect of shifting the dissociation curve of haemoglobin in such a way that it yields oxygen less readily to the tissues, the possibility that the effect of hyperventilation may be due to interference with the oxygen supply of the gastric mucosa must be considered. It was decided to inject sodium cyanide as a means of interfering with tissue oxidation. Repeated injections of 7 cc. of N/100 NaCN were given intravenously. The total amount given was 41 cc. in one hour. Despite this the gastric secretion was not affected. Although the lethal dose for a 14 kg. dog was 30 cc. given in a single injection, the degree of interference with tissue oxidation produced in the above experiment is not known. The changes in the dissociation curve of haemoglobin are dependent upon those in the pH. The significance of the latter will be discussed later.

After the above results were obtained, the possibility of /

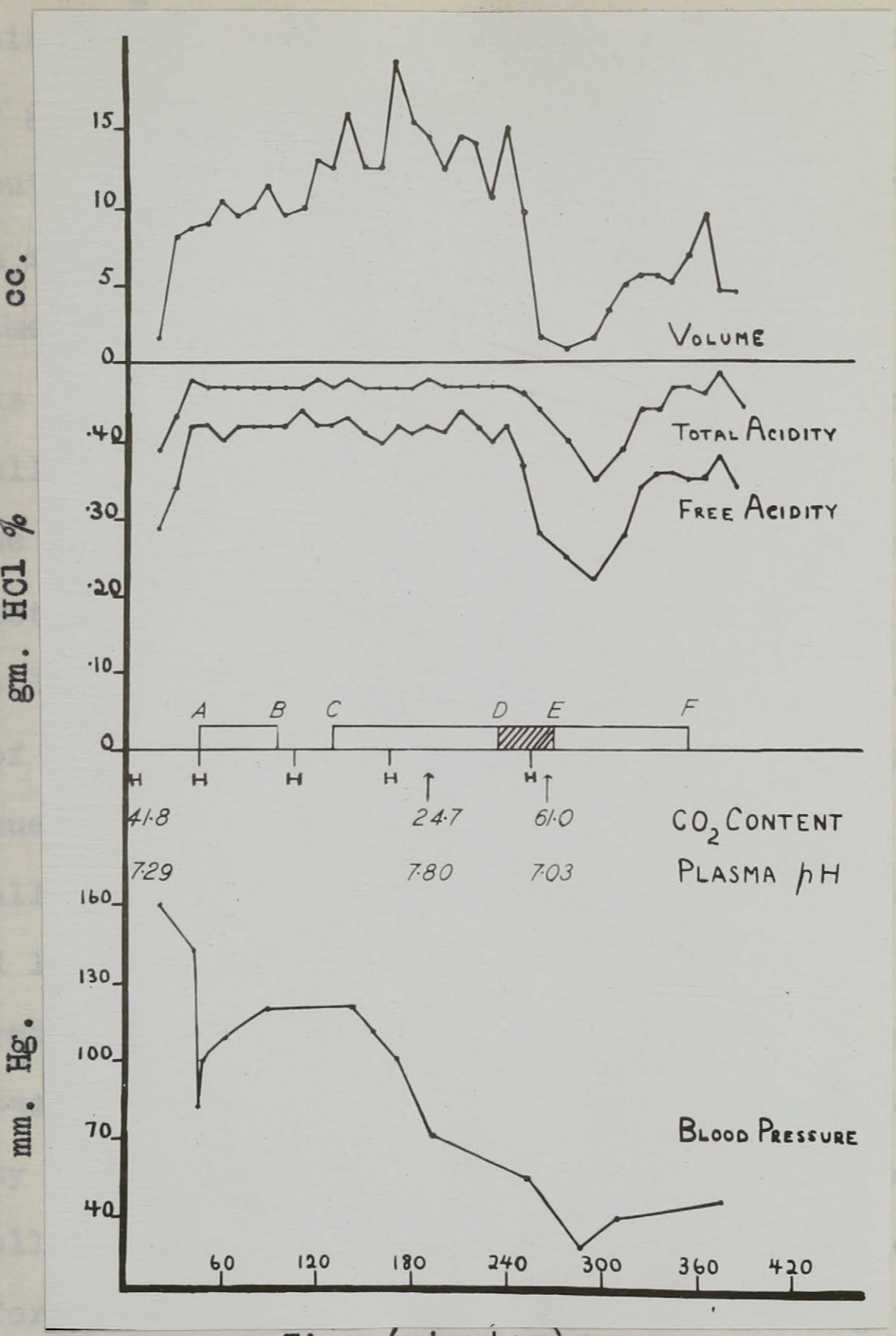
of an altered plasma CO_2 and pH affecting the vagus nerve endings was considered. This was rendered improbable by the continued action of the vagus on the heart during hyperventilation. In an endeavour to exclude this possibility, histamine was used, as it is believed to act directly upon the parietal cells (Popielski, 1920; Vineberg and Babkin, 1931; Cowgill and Gilman, 1931). The operative procedure was identical with that of the nerve experiments. The vagi were severed but not stimulated.

(2) Histamine Stimulation

(a) Hyperventilation

In Fig.6 it may be seen that after a twenty-minute period of secretion, artificial respiration was applied and continued for 60 minutes (A-B) without any effect upon the course of the secretory activity. It was then discontinued for 50 minutes without any effect. The dog was again hyperventilated for 100 minutes (C-D), the volume and acidity remaining practically constant although the plasma CO_2 was lowered to 24.7 vols. per cent. and pH raised to 7.80. 5 per cent. CO_2 was introduced (D-E) with the rate of hyperventilation kept constant for a period of 30 minutes. This raised the CO_2 content of the plasma to 61.0 and lowered the pH to 7.03. The effect of the CO_2 was to diminish the secretion both in volume /

Figure 6

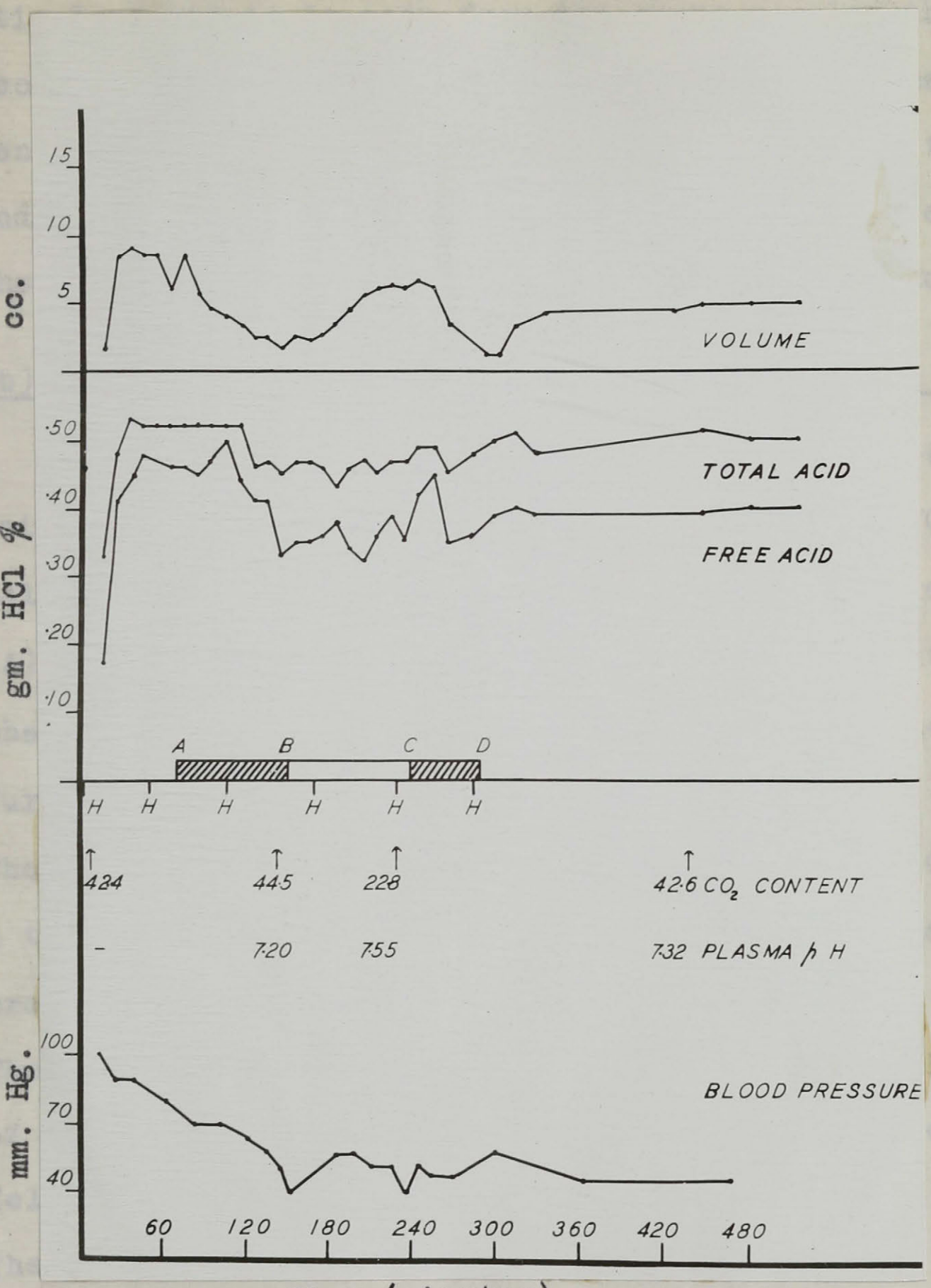


Dog 12. Wt. 14.3 kg. At (H) 4 mg. histamine subcutaneously. (A-B) artificial ventilation at the rate of 76/min. with air. (C-D) the same. (D-E) the same rate of hyperventilation. 5% CO_2 in oxygen. (E-F) same rate with air only.

volume and acidity. This effect persisted for 45 minutes after the CO_2 had been discontinued; hyperventilation was maintained throughout the following 70 minutes (E-F). The volume gradually rose; the free and the total acidity also rose but the former did not reach its previous value.

A second experiment is shown in Figure 7. In this experiment CO_2 and hyperventilation were applied (A-B) as soon as secretion had been established. The volume decreased gradually from the first but the free acidity rose slightly and the total acidity remained constant for 50 minutes and then both fell off abruptly. The CO_2 content of the plasma rose only slightly above control levels. The administration of CO_2 was then discontinued and hyperventilation was continued at the same rate as before (B-C). The volume gradually increased; the free and total acid, however, remained low. Then 5 per cent. CO_2 was again used in the inspired air (C-D). The recommencement of CO_2 was followed by a twenty-minute period in which a definite rise in free acidity took place. There was no change in volume. This was followed by a decrease in both volume and acidity continuing for 30 minutes. At this point (D) the dog was permitted to resume a normal respiratory rhythm, breathing air only. All values immediately rose and were maintained at an approximately constant level for three hours with no further injections of /

Figure 7



Dog. 14. At (H) 4 mg. histamine subcutaneously. (A-B) artificial ventilation at the rate of 74/min. with 5% CO_2 in oxygen. (B-C) same rate of ventilation with air only. (C-D) with 5% CO_2 in oxygen.

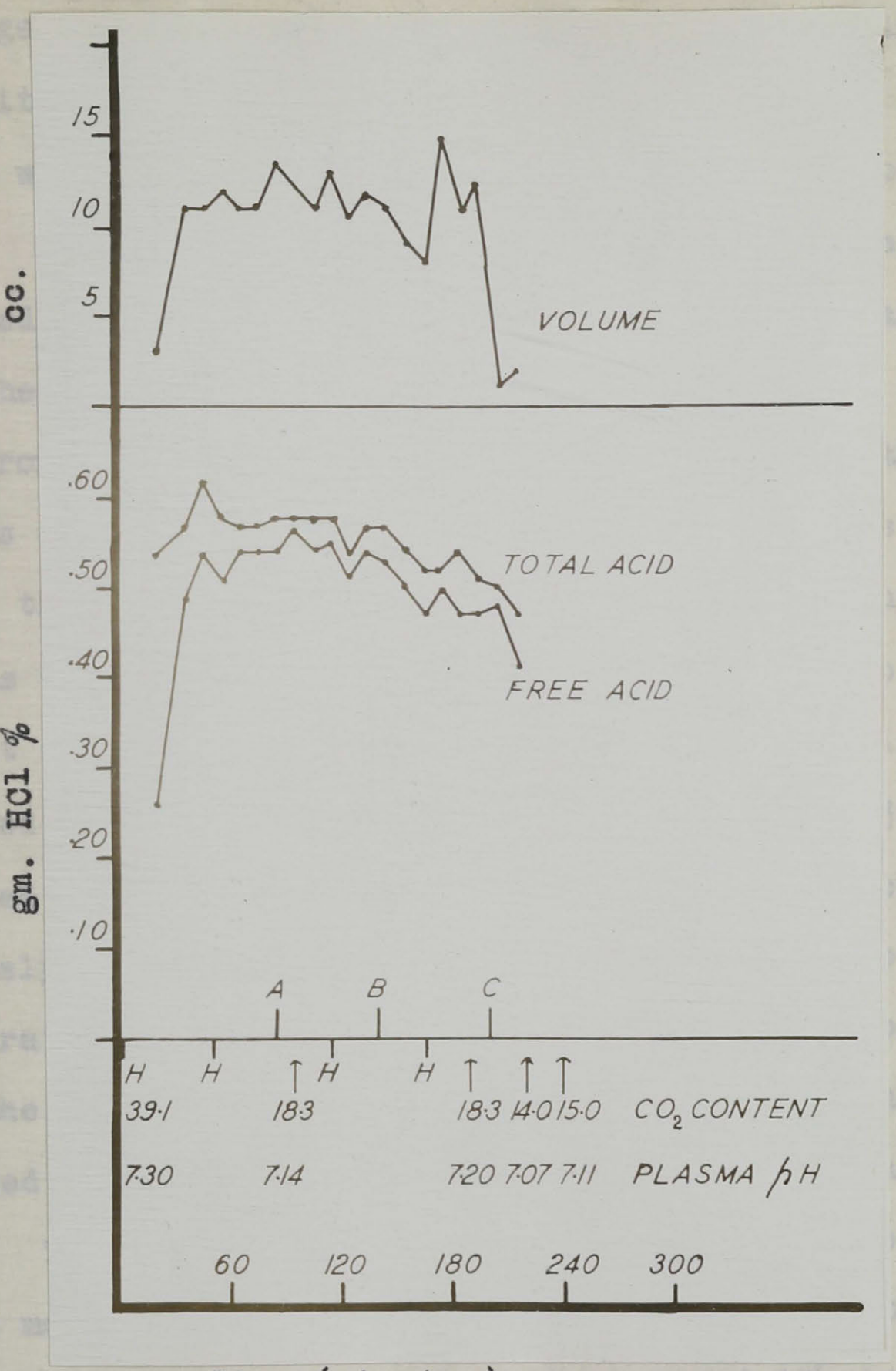
of histamine. Histamine is an extremely powerful gastric stimulant and it is seen from the above results that, once secretion is well established, under its influence hyperventilation has no effect. However, from Fig.7 there are indications that, once histamine secretion has been depressed, the hyperventilation tends to keep the values reduced.

(b) Injection of acid (HCl and lactic) and of base $NaHCO_3$

In the experiment illustrated in Fig.8 secretion was maintained by histamine at a constant level for 70 minutes. Half normal hydrochloric acid was injected intravenously (A) (40 cc. in 5 minutes). For the next 40 minutes no change in the character of the secretion took place. A further 40 cc. of acid was then injected (B) in 3 minutes. The values decreased only slightly for the next 60 minutes. A third injection (C), 23 cc. in 6 minutes, was made. Secretion stopped abruptly and 55 minutes later the dog died. The blood CO_2 content was at the usual level at the beginning of the experiment, but after the first injection of acid fell, and declined with each subsequent injection of acid. The pH also decreased over these periods.

Because HCl is the acid of gastric secretion and because it does not enter the blood in physiological conditions, it was decided /

Figure 8



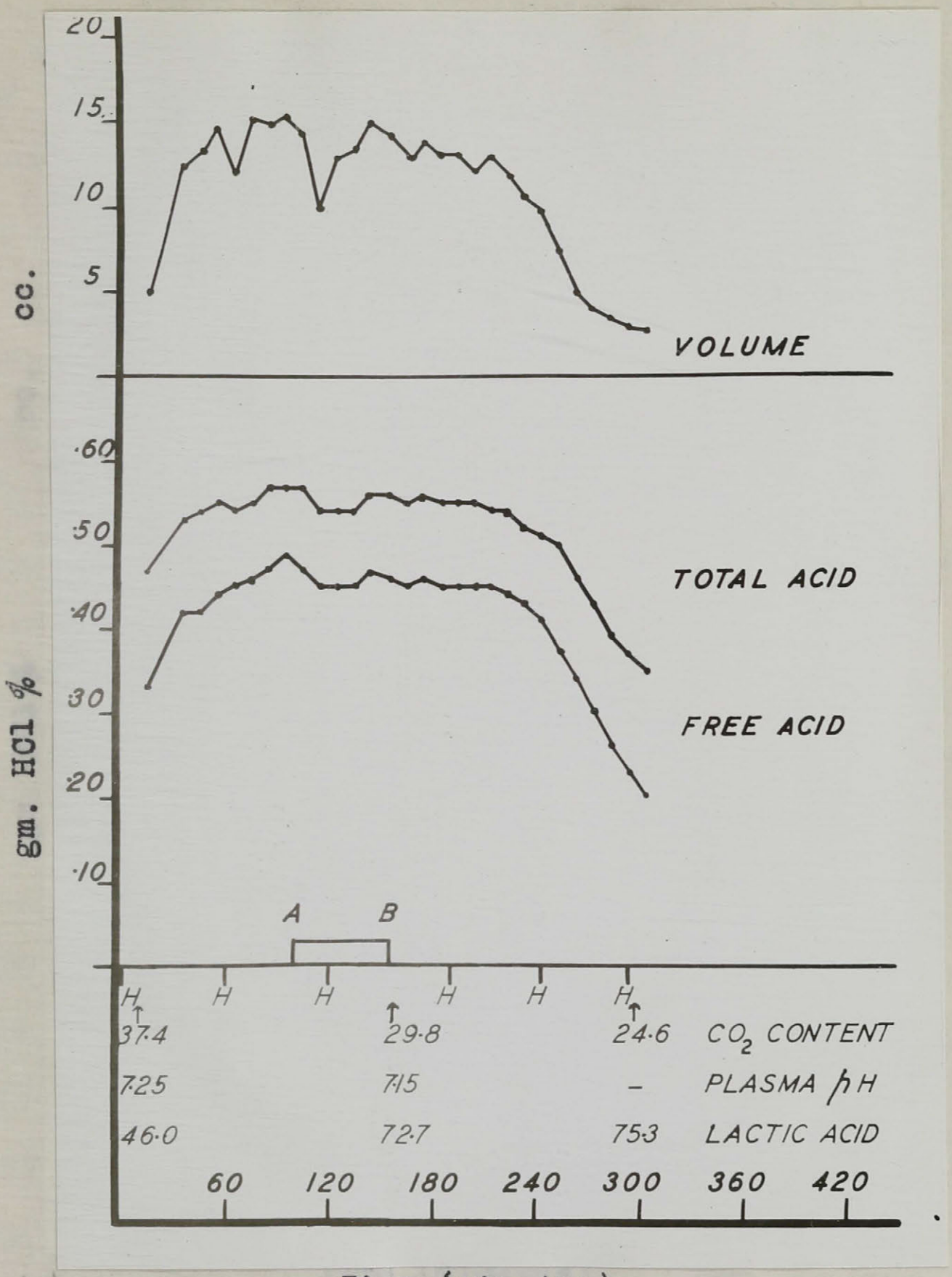
Dog 16. Wt. 10.3 kg. At (H) 4 mg. histamine subcutaneously. At (A) 40 cc. 0.5 N/HCl intravenously in 5 min. At (B) 40 cc. 0.5 N/HCl intravenously in 3 min. At (C) 23 cc. 0.5N/HCl intravenously in 6 min.

decided to use lactic acid, which occurs in normal metabolism. Figure 9 demonstrates the absence of effect which the injection of large quantities of lactic acid has on histamine secretion after it has been established. The CO_2 content and pH of the plasma were lowered and the lactic acid content of the blood rose. Toward the end of the experiment secretion gradually declined. The death of this animal was due to an overdose of anaesthetic.

From the above two figures, it may be seen that under conditions of low plasma CO_2 content and low pH, histamine secretion, unlike that produced by vagal stimulation, continues for long periods unaffected. If, however, these conditions of low CO_2 content and low pH are in existence before the histamine is injected, it fails to produce a flow of gastric juice. This occurred in three experiments. The acidosis occurred spontaneously for unknown reasons. One of these experiments is illustrated in Figure 10. At the commencement of the experiment the plasma CO_2 was 28.4 vols per cent and the pH 7.30. Repeated doses of 4 mg. of histamine were given at hourly intervals. The usual latent period following this dose of histamine is not more than 20 minutes. In this experiment there was no secretion for 145 minutes, but it appeared 15 minutes after the commencement (A) of an intravenous injection of 10 per cent. sodium bicarbonate and was well maintained for a period of 120 minutes. Hydrochloric acid was then injected (C-D) and in this case the secretion gradually diminished and finally ceased.

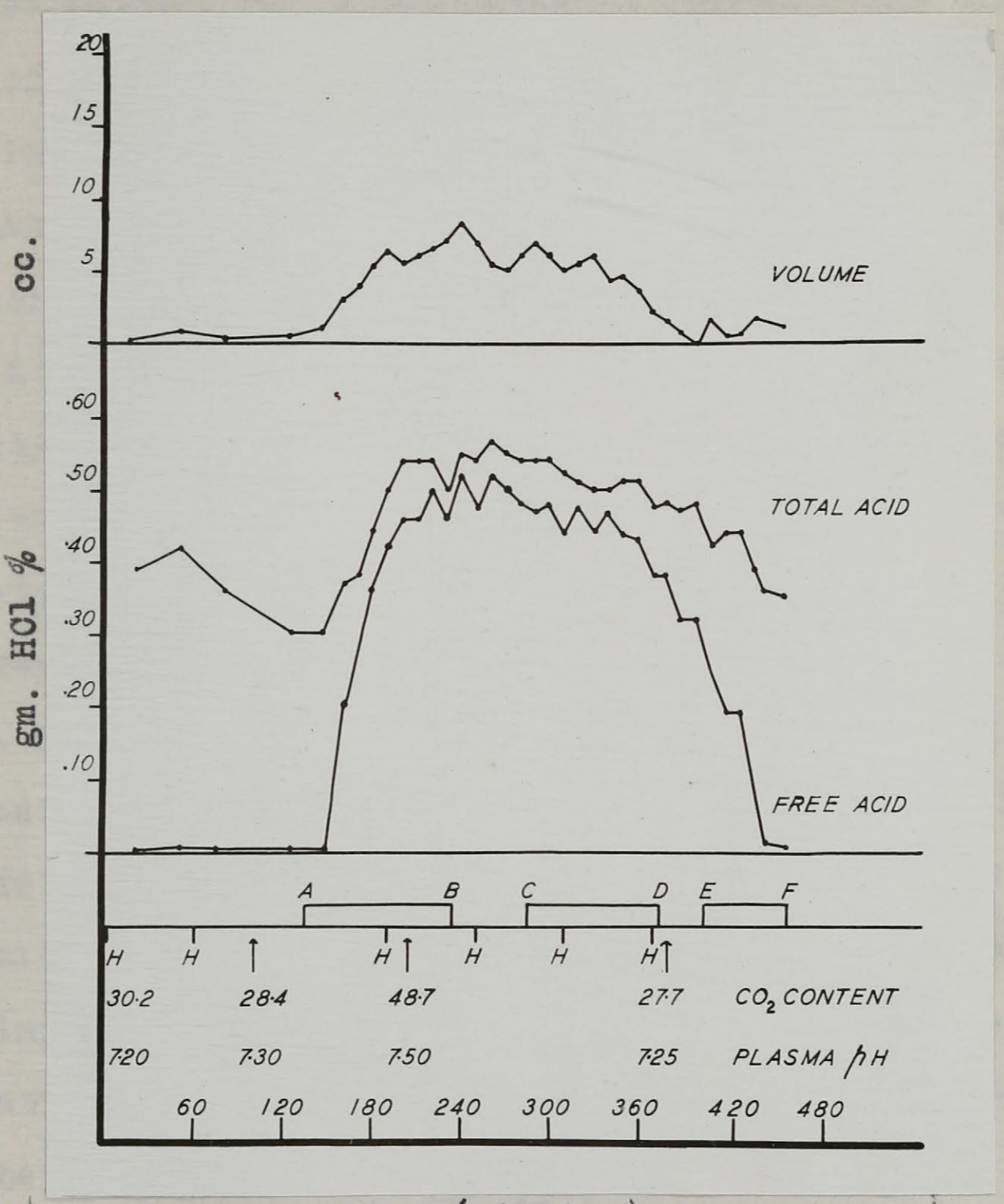
When /

Figure 9



Dog 21. Wt. 23.3 kg. At (H) 4 mg. histamine subcutaneously. (A-B) 120 cc. 0.5 N/lactic acid intravenously at the rate of 3 cc. per min.

Figure 10



Dog 17. Wt. 14.5 kg. At (H) 4 mg. histamine subcutaneously. (A-B) 47 cc. 10% sodium bicarbonate intravenously at the rate of 0.5 cc. per min. (C-D) 120 cc. 0.5 N/HCl intravenously at the rate of 1.3 cc. per min. (E-F) 75 cc. 10% sodium bicarbonate intravenously.

When secretion was well established, the CO_2 content was 48.7 vols. per cent. and the pH 7.5. When secretion ceased after the injection of acid, the CO_2 content was 27.7 and the pH 7.27. It will be observed that a period of 85 minutes elapsed between the last histamine injection and the commencement of secretion after the intravenous injection of $NaHCO_3$. This indicates that the inhibition of gastric secretion under conditions of initial acidosis is not due to a rapid destruction of the histamine injected.

A similar inhibition of secretion under conditions of initial acidosis occurred in vagal stimulation experiments and, as in the case of histamine stimulation, a flow of gastric juice was established after the injection of sodium bicarbonate. In another case of initial acidosis (see Table XLI), where no injection of sodium bicarbonate was given, acidosis progressively increased and repeated hourly injections of histamine failed to stimulate the gastric glands. The animal died five hours after the first histamine injection. The injection of 250 c.c. of normal saline failed to induce secretion. This indicates that dehydration is not the cause of the inhibition of secretion.

C. Injection of Sodium Cyanide.

As in the case of nerve stimulation, repeated doses of 7 c.c. of N/100 sodium cyanide at ten-minute intervals over a long /

TABLE XLI.

INITIAL ACIDOSIS — EFFECT OF HISTAMINE STIMULATION ON GASTRIC SECRETION.

Exp. July 24, 1931.

Dog, wt. 23 kg. Anaesthesia, chloralose and urethane. Oesophagus tied in the neck; pylorus tied at the junction with the duodenum.

Cl P. = chloride in blood plasma; Cl B. = chloride in blood cells; C.V. = cell volume.

Sample	Time		Gastric Secretion				Blood						Remarks
			Vol.	Free HCl	Total HCl	Mucus	Arterial CO_2 Content	pH	Lactic Acid	Cl P.	Cl B.	C.V.	
	p.m.	min.	c.c.	gm.%	gm.%	c.c.	vol.%		mg.%	mg.%	mg.%	mg.%	
1			1.5	0.00	0.24	0.1							
2	4:30-5:10	40	1.7	0.00	0.21	trace	29.8	7.18	38.0	387	269	61	5:10 p.m. Histamine, 4 mg. injected subcutaneously.
													6:10 p.m. do.
													6:35 p.m. Total 250 c.c.N/saline given.
3	5:10-6:50	100	3.2	0.00	0.20	trace							7:10 p.m.Histamine, 4 mg. injected subcutaneously.
4	6:50-7:20	30	4.0	0.00	0.20	trace	16.9	7.23	31.7	393	258	68	
5	7:20-7:50	30	1.5	0.01	0.18	0.2							8:10 p.m. Histamine, 4 mg. injected subcutaneously.
6	7:50-8:40	50	1.6	0.02	0.17	0.2							

long period of time had absolutely no effect on the functioning of the gastric mucosa. The characteristic effect of sodium cyanide on respiration and blood pressure was obtained at each injection.

In all the histamine experiments the standard dose used was 4 mg. injected every hour, and in numerous experiments it was found that once a satisfactory flow of secretion has been established, it is maintained at a constant level of volume and free and total acidity for as long as ten hours.

DISCUSSION /

DISCUSSION

A definite relation between the CO_2 content of the plasma and gastric secretion is seen in the group of nerve stimulation experiments. Hyperventilation causes a cessation of gastric secretion. That this cessation is related in some way to the coincident lowering of the CO_2 content of the plasma is indicated by the restoration of the flow of gastric juice which occurs when the CO_2 content of the inspired air is increased. The mechanism of the above effects is dependent upon numerous factors. While a complete explanation is not possible at the present time, there are certain of these factors which can be excluded. Hyperventilation has been found by previous authors to have a variety of effects upon the vaso-motor system and upon the chemical composition of the blood. Dale and Evans (1922) observed a marked lowering of blood pressure and considerable shock in cats under ether anaesthesia. McDowall (1930) showed that this fall in blood pressure did not always occur under chloralose. Lowering of blood pressure if due to splanchnic vaso-dilation should favour secretion. The blood pressure effect was not marked in our experiments, being at most 30 to 40 mm. of mercury. The initial pressure was high owing to the proportions of the chloralose-urethane mixture used. Also, in several experiments nerve stimulation has maintained satisfactory secretion with blood pressures lower than those produced /

duced by hyperventilation. The changes in systemic blood pressure do not therefore appear to be the causative factor in the gastric effect. This does not, however, exclude the effect of variations in blood flow through the gastric mucosa. Vaso-constriction of blood vessels might be expected to cause a diminution in secretion. It has been indicated by Lim and Necheles (1927) that within limits the rate of gastric secretion is independent of the blood flow through the stomach. Furthermore, hyperventilation has been shown to dilate the splanchnic vessels (Dale and Evans, 1922), and this occurs even under chloralose (McDowall, 1930). Blood flow was not studied in our preparations but its influence may be disregarded in view of the findings quoted above. Mechanical effects of hyperventilation are excluded by the maintenance of a constant rate of ventilation throughout the whole experiment, both during cessation of secretion and during its restoration by CO_2.

The changes in blood electrolytes occurring under hyperventilation have been extensively studied (Henderson and Haggard, 1918; Collip and Backus, 1920; Grant and Goldman, 1920; Davies and others, 1920; Anrep and Cannan, 1923; Haldane and others, 1924). The experiments have been made almost wholly upon human subjects. The main changes which take place are, a lowering in the CO_2 content of the blood, a /

a rise in pH and in lactic acid content, a shift of water and chloride from corpuscles to plasma. Dependent upon the change in pH there is an alteration in the dissociation curve of haemoglobin. Other electrolytes such as phosphates and sulphates also participate in the shift from corpuscles to plasma. The blood picture in our experiments conforms to these findings (see Table XLII). The increased loss of CO_2 through the lungs with the consequent fall in the blood CO_2 content is responsible for the other changes in blood electrolytes, which are of a compensatory nature. That the lowered CO_2 content rather than the raised pH is the factor involved in the gastric effect is indicated by the experiments in which initial acidosis with a lowered CO_2 and a lowered pH prevented the production of secretion. The subsequent injection of sodium bicarbonate raised the CO_2 content of the plasma, raised the pH and caused secretion to commence.

The previously mentioned experiments of Szilard (1930) and others also indicate that a high pH produced by administration of sodium bicarbonate does not inhibit but rather favours the secretion of acid gastric juice. In the case of hyperventilation, no secretion was obtained when there was a low CO_2 content and a high pH, whereas in the case of initial acidosis no secretion was obtained when there was a low CO_2 and a low pH. Raising the CO_2 content and lowering the pH induced secretion in the former instance, and raising the CO_2 and raising the pH induced /

TABLE XLII.

CHANGES IN BLOOD CONSTITUENTS UNDER HYPERVENTILATION WITH A FIVE PER CENT CO_2 OXYGEN MIXTURE.

Dog 13, weight 14 kg. Histamine (4 mg.) injected hourly. Secretion of gastric juice maintained throughout the experiment.

m.eq.. per l. = milliequivalents per litre.

Ventilation	CO_2 Plasma	pH	Lactic Acid Blood	Cl Plasma	Cl Blood	Cl Corpusc.	Plasma Proteins	Inorganic Phosphorus	Total Base Serum	Cell Volume
	m.eq. per l.		m.eq. per l.	m.eq. per l.	m.eq. per l.	m.eq. per l.	gm.%	mg.%	m.eq. per l.	
Before hyperventilation	18.3	7.24	3.67	106.4	86.4	56.3	8.05	6.66	126.2	40
After 50 min. hyperventilation 76 per min.	9.5	7.60	8.22	105.1	84.2	50.7	8.65	3.46	131.4	39
40 min. 5% CO_2 oxygen mixture, ventilation 76 per min.	-	-	-	-	-	-	-	-	-	-
After 30 min. hyperventilation (air only).	9.3	7.57	10.1	105.0	81.7	44.2	9.04	4.70	132.2	39
After 30 min. 5% CO_2 oxygen mixture, ventilation 76 per min.	18.9	7.10	3.81	104.9	85.3	58.3	8.28	7.20	138.6	42
After 30 min. natural respiration (air only).	15.5	7.34	11.9	103.6	83.1	54.1	-	8.33	159.6	41

induced it in the latter. Hence one may conclude that the observed changes in secretion are not directly due to the changes in plasma pH nor to concomitant alterations in the oxygen dissociation curve of haemoglobin. The experiments with cyanide also indicate that the oxygen tension in the secreting cells may be varied to some degree at least without effect on secretion.

Apperly and Crabtree (1931) have attempted to separate the effects of H_2CO_3 and of 'HCO_3'. The former they regard as controlling the amount of gastric acidity and the latter its concentration. Neither their results nor ours, however, justify a definite decision on the relative importance of CO_2 present as H_2CO_3 and as 'HCO_3'. In this connection one may cite the experiment described above (Table XL), where the secretion obtained by vagal stimulation was temporarily increased in free HCl concentration by the injection of hydrochloric acid, while H_2CO_3 concentration increased at the expense of 'HCO_3'. In the experiments with hyperventilation (see Table XLI) the changes in H_2CO_3 are naturally greater than the changes in 'HCO_3'; on the other hand, the induction of secretion and a rapid rise in the concentration and amount of free HCl by injection of sodium bicarbonate into dogs, in which spontaneous acidosis had prevented the response to vagal stimulation or to histamine, is accompanied by great increases in 'HCO_3' with only slight /

slight changes in H_2CO_3 concentration (calculated from the Henderson-Hasselbalch equation).

The lowered plasma CO_2 content may conceivably act either directly upon the nerve or its terminations or alternatively upon the chemical mechanism necessary for the formation of gastric secretion.

Just how changes in plasma CO_2 content affect nerve conduction and nerve endings it would be difficult to state. In the present experiments, when secretion had diminished under hyperventilation, there was no change in the cardio-inhibitory action of the vagus. It is, however, possible that the nerve endings in the stomach might be affected. The possible effect of lowered CO_2 content on the liberation and destruction of a "vagus substance" should also be considered.

On the view that the action of CO_2 is a chemical one rather than an action on nerve sensitivity, its effect may be a direct one in the reaction for the formation of hydrochloric acid in the parietal cells, or else it may act upon the ionic equilibria between blood plasma and tissue fluids or between tissue fluids and parietal cells. The lowered CO_2 content may prevent transfer of chloride to the mucosa or parietal cells. This retention of chloride tends to take place to balance the fixed base liberated when the bicarbonate ion content of the blood or tissue fluid is lowered. In connection /

tion with this it may be noted that recently Babkin and Webster (1932) obtained a gastric secretion by introducing CO_2 gas into the stomach of dogs with different permanent gastric fistulae.

In the group of histamine experiments, it will be observed that the results differ decidedly from those of the nerve stimulation experiments. When histamine secretion was established, hyperventilation had little inhibitory effect, even though blood conditions were similar to those of the nerve experiments. The inhalation of CO_2 is seen to tend to inhibit histamine secretion. While this cannot be explained, it does not invalidate the main argument. In several cases of initial acidosis with low CO_2 and low pH, no secretion was obtained with histamine stimulation, and, as in the nerve experiments, it appeared when the CO_2 and pH were raised as a result of the injection of sodium bicarbonate. On the other hand, when acidosis is produced by the administration of acid during histamine secretion, no inhibitory effect is observed. The absence of effect after histamine secretion has been established does not invalidate a chemical interpretation of the essential part played by CO_2 in the formation of HCl. It is possible that the level of CO_2 required for secretion may be related to the strength of the stimulus producing that secretion. It is impossible to lower the CO_2 content of the blood and of the /

the tissues below a certain level. If the stimulus is an extremely powerful one (such as histamine) the parietal cells may be capable of utilising the remaining CO_2, which they are incapable of doing under a weaker and more physiological one (such as vagal stimulation). The absence of secretion under conditions of acidosis existing prior to the injection of histamine indicates that a lowered CO_2 content is capable of inhibiting the action even of this powerful stimulant.

The clinical application of these results appears to be of some importance. Apperly and Crabtree (1931) have indicated some conditions in which the lowering of gastric secretion may be correlated with lowered sodium bicarbonate in the blood. The following considerations may be of significance in clinical applications. The level of arterial CO_2 content at which inhibition of secretion takes place was found to be about 30 vols. per cent. This is true whether the lowering of the CO_2 is due to hyperventilation or to acidosis. This corresponds to a venous CO_2 content of about 36 vols. per cent. In one experiment where both CO_2 content and the ordinary CO_2 combining power on separated plasma were determined, the initial values were: CO_2 content, 34.8 vols. per cent, and the capacity or combining power, 39.5 per cent; after secretion was well established the values were: content, 43.3, and capacity, 45.1. Under hyperventilation, when secretion had ceased and the /

the CO_2 content had been lowered to 25.4, the capacity was only lowered to 35.8. After the administration of CO_2 the content was 41.4 and the capacity 40.5. These figures are presented to indicate that the CO_2 combining power of the separated plasma is not a suitable index, in the case of hyperventilation, of the relations between CO_2 and gastric secretion. Complete inhibition of secretion in this experiment took place when the arterial CO_2 combining power was 36 vols. per cent. This corresponds to a venous CO_2 combining power of about 42. A definite decrease in secretion might, therefore, be expected even if the CO_2 combining power were only slightly lowered. Such a slight lowering is not uncommon with mild acidosis and with hyperventilation, and might easily influence the character of gastric secretion. It would be difficult to detect these changes in the case of hyperventilation by the use of the ordinary CO_2 combining power determination in venous blood. Changes in CO_2 alveolar air tension, and hence in the CO_2 content of the blood, during sleep and on waking (Leathes, 1919; Endres, 1922) and during digestion (Porges, Leimdorfer and Markovici, 1911; Dodds and Bennett, 1921) do take place under physiological conditions.

It is possible, on the other hand, that a raised CO_2 content sensitises the parietal cells so that they respond more readily to a weak stimulus. This may be of importance in cases of /

of hypersecretion, where apparently a stimulus which in normal individuals would initiate a secretion of average acidity produces an excessive secretion with abnormally high acid content. For some years there has been a controversy as to the usefulness of sodium bicarbonate therapy in the treatment of gastric ulcer with hyperacidity. The results here presented would tend to support the view that its use though producing a temporary neutralisation is followed by a secretion of greatly augmented acidity.

C O N C L U S I O N S

A study of some of the factors involved in the mechanism of gastric secretion shows that similar processes are at work during the production of gastric juice of vagal and of chemical origin. Weak electrical stimulation of the vagus nerves results in a scanty flow of mucoid secretion from the whole stomach as well as from the isolated fundic portion. Strong stimulation, on the other hand, produces a copious flow of highly acid juice with a high digestive activity. These results suggest the possibility that the vagus contains two kinds of secretory fibres for the gastric mucosa, and that each type of fibre when stimulated can independently activate the particular group of gastric cells under its influence. Similarly, certain chemical stimulants are capable of activating special groups of cells present in the gastric mucosa without stimulating the adjacent cells. Histamine, for example, produces gastric secretions having a high acid but an extremely low peptic concentration, which suggests that its action is confined to the parietal cells without affecting, or affecting but slightly, the adjoining peptic cells. Pilocarpine, when administered after histamine, causes an immediate rise in /

in the peptic output, indicating that it acts selectively through the parasympathetic system on the peptic cells. Thus whether by means of vagal or chemical stimulation different elements of the gastric glands may be made to act separately or simultaneously according to the type of stimulation employed.

Histological studies, carried out on the gastric mucosa before and after prolonged vagal or histamine stimulation, tend to support the above physiological findings. For example, the peptic cells, when examined after prolonged vagal stimulation, displayed marked intercellular changes, whereas after long histamine activation no such changes were observed in these cells. On the basis of the above physiological and histological results it is suggested that a similar mechanism is at work in the production of the hypersecretion of juice which occurs in the presence of peptic ulcers and which may be due to a prolongation of the chemical phase (Volkovitch, 1898) or of the nervous phase (Winkelstein, 1929). There may be, for example, an independent action of certain of the cellular elements in the gastric glands resulting in the secretion of a highly acid juice which is extremely poor in organic material and in mucus content. The comparative lack of mucus in this type of secretion may be of pathological significance in the light of the accepted protective function of this substance.

Another /

Another source of the mucus present in the gastric secretion of the dog is the oesophagus. The glands of this organ are under the direct influence of the vagus nerves and can be made to produce a true secretion of a highly alkaline mucous substance in response to electrical stimulation of these nerves. It is probable that this secretion has two functions; as well as acting as a lubricant and protector for the oesophageal mucosa, it possibly assists in the neutralisation of acid stomach secretions.

There is, however, another factor involved in the mechanism of gastric secretion which exerts a more general influence upon it, namely, the CO_2 content of the blood. Gastric secretion produced by vagal stimulation in dogs is definitely inhibited by hyperventilation and is restored by raising the CO_2 content of the inspired air. A similar inhibition occurs when acid is injected intravenously or when a state of acidosis exists prior to nerve stimulation. In this inhibition of gastric secretion, the lowering of the CO_2 content of the plasma is the factor involved, rather than changes in pH. When the CO_2 content of arterial plasma falls below 30 vol. per cent., gastric secretion of vagal origin is inhibited. In the case of histamine stimulation, gastric secretion is inhibited only when there is an existing acidosis prior to its administration. It is possible /

possible that a raised CO_2 content sensitises the parietal cells so that they respond more readily to a weak stimulus. This may be of importance in those clinical cases of hypersecretion where a stimulus, which in the normal individual would initiate a secretion of average acidity, produces an excessive secretion with abnormally high acidity. Further, it lends support to the assertions of a large number of clinical workers that although $NaHCO_3$, when given to patients suffering from peptic ulcer, effects a temporary neutralisation, it is nevertheless responsible for a secondary excessive secretion of acid gastric juices.

S U M M A R Y

1. A satisfactory method of obtaining plentiful gastric secretion in response to vagal stimulation in the dog was developed.

2. Vagal stimulation is responsible for the production of two types of gastric juice depending upon the strength of stimulation applied.

3. Weak stimulation of the vagus nerves results in a scanty secretion of alkaline mucus having a low digestive activity.

4. Strong stimulation produces a flow of normal gastric juice large in volume and high in acidity and peptic power.

5. The results suggest that, by stimulation of the vagus nerves with currents of different strengths, different and possibly independent cytological units in the gastric mucosa are activated.

6. A comparison between the gastric juice obtained by electrical stimulation of the vagus and that obtained by means of normal physiological stimuli of reflex origin shows /

shows a striking similarity.

7. In explanation it is suggested that the vagus possibly contains two sets of fibres, which can be activated independently, and that each group of fibres supplies different gastric secretory elements.

8. One of the sources of the mucus present in gastric secretion obtained by weak stimulation was shown to be the mucus-secreting cells in the mucosa of the body of the stomach, indicating that the vagus nerve is a secretory nerve to these cells.

9. The possible protective function of mucus in preventing digestion of the gastric mucosa is stressed.

10. The gastric secretion obtained in response to histamine stimulation in dogs with a Heidenhain or Pavlov pouch or with oesophagotomy and gastric fistula is comparatively low in pepsin but high in acid concentration.

11. It is suggested that histamine in the dog acts directly upon the parietal cells and fails to stimulate the peptic cells.

12. Atropine curtails only the volume of the secretion obtained from a Pavlov-pouch dog in response to histamine and /

and fails to do so in a Heidenhain-pouch dog deprived of its vagal innervation.

13. Pilocarpine injected after histamine greatly increases the enzyme output in a dog.

14. The ability of the two drugs, histamine and pilocarpine, to activate different cytological elements of the gastric mucosa is shown, and their effect is compared to vagal stimulation.

15. In man only a slight diminution in the enzyme concentration occurs during the course of the secretion produced by histamine stimulation. Likewise pilocarpine when administered to humans does not "selectively" stimulate the peptic cells as it does in dogs.

16. After prolonged gastric secretion of vagal origin the peptic cells show definite histological changes in the dog.

17. No marked changes were observed histologically in the peptic cells following a copious gastric secretion of histamine origin.

18. These histological facts supplement the physiological evidence indicating that histamine activates the parietal cells /

cells only and they also support the principle of independent cellular action.

19. The glands of the oesophagus of the dog are under the influence of the vagus.

20. Strong vagal stimulation provokes in the dog a true secretion of an alkaline mucoid substance from the oesophageal glands.

21. No secretion is obtained with weak vagal stimulation.

22. The chemical compositions of the mucoid secretion from the oesophagus, the salivary glands and the gastric glands, respectively, are compared.

23. It is suggested that the function of the oesophageal secretion in the dog is that of lubrication and protection of the oesophageal mucosa against damage by rough foods, etc.

24. Because of the highly alkaline character of the oesophageal secretion, it probably aids in the neutralisation of the acidity of the stomach.

25. Gastric secretion produced by vagal stimulation in dogs under chloralose and urethane anaesthesia is inhibited /

inhibited by hyperventilation. It is restored by raising the CO_2 content of the inspired air though the hyperventilation is maintained at the same rate as before.

26. Secretion is also inhibited by the intravenous injection of acid and by the occurrence of acidosis prior to the stimulation of the nerves.

27. The factor involved in the effect of hyperventilation and acidosis on gastric secretion is the lowering of the CO_2 content of the plasma rather than the accompanying changes in plasma pH.

28. Gastric secretion in response to vagal stimulation is inhibited when the CO_2 content of the arterial plasma falls below 30 vol. per cent.

29. Gastric secretion in response to injections of histamine is inhibited by the occurrence of acidosis prior to the commencement of secretion but not by acidosis or hyperventilation produced after secretion is established.

30. It is suggested that an increased blood CO_2 content may sensitise the acid cells, thus lending support to the view that sodium bicarbonate therapy in patients with /

with peptic ulcers, although producing a temporary neutralisation, is followed by a secretion of greatly augmented acidity.

B I B L I O G R A P H Y

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