EFFECT OF STIMULATION ON IONIC CHANGES IN CANINE GASTRIC POUCHES

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by

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ABSTRACT

The stomach has the unique ability of being able to contain an acid solution as distinct from the property of the parietal cell mass to secrete acid. Using a method of measuring in situ volume and ionic changes within innervated and denervated gastric pouches developed by Wlodek and Leach, this function of the stomach was studied using various stimuli. Feeding in Heidenhain pouches produced an increased competency of the gastric mucosal barrier as measured by the decreased exchange of hydrogen for sodium ions. Antrectomy did not reduce this effect significantly indicating that intestinal or pancreatic factors may be important in addition to gastrin. A comparison of the effect of insulin and gastrin on the mucosal barrier in Pavlov pouches indicated that vagal stimulation probably has no influence on the competency of the mucosal barrier while gastrin significantly increases this competency. Pentagastrin was found to increase markedly the ability of the gastric mucosa to contain hydrogen ions in both Pavlov and Heidenhain pouches.

ACKNOWLEDGEMENTS

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I wish to acknowledge the assistance and co-operation of Mr. Richard Leach, Mr. Roy Ferguson and Mr. Leonard Greenberg in the technical aspects of running these experiments. The IBM programming required for calculating the results and the statistics was done by Mr. Alan Greenberg. Charts were kindly reproduced by Mr. L. Artinian. My thanks to my sister, Doreen A. Adair, and my wife, Joanne E. Adair, for the typing of this thesis.

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1. INTRODUCTION

A. Experimental methods of measuring gastric acid secretion

The stomach has the unique ability to contain an acid solution. This property of the gastric mucosa is not shared by other mucosa-lined organs such as the small intestine. It is this function of the gastric mucosa that permits the stomach to retain the acid it secretes for a sufficient length of time to allow for adequate mixing of acid with food, pepsinogen activation and some digestion of food.

For many years the standard experimental preparation for the measurement of gastric secretion has been the gastric pouch, from which fluid is collected by simple drainage using a cannula. This technique has prevented investigators from adequately assessing the ability of the stomach to retain an acid solution against a concentration gradient. Under certain conditions the parietal cell mass may be secreting hydrochloric acid but, due to an inability of the mucosa to maintain its physiological integrity, this acid may leak back through the gastric mucosa and therefore not manifest itself as recoverable acid. The carbonic anhydrase inhibitor acetazolamide was found to inhibit acid secretion and for

many years this phenomenon was explained as a direct chemical effect on the parietal cell decreasing its output of acid.[1, 2] Recent experiments have demonstrated that the apparent inhibition of acid secretion caused by acetazolamide is due to its damaging effect on the ability of the gastric mucosa to contain an acid solution.[3, 4] Acetic acid, eugenol, acetylsalicylic acid, short-chained fatty acids, sodium fluoride and mersalyl have also been shown to destroy the integrity of the gastric mucosa and thus the ability of the stomach to contain the hydrogen ions secreted.[5, 6, 7, 8]

Pouch secretion experiments using straight drainage also have inherent errors due to the retention of fluid in mucosal folds for long periods of time and trapping of fluid in the pouch and cannula, both of which are not recorded as actual secretion. Furthermore, the classical methods for the straight collection of gastric secretion do not take into account any exchange of ions that may occur across the gastric mucosa. These difficulties have led some investigators in the field of gastric physiology to attempt to develop a more physiological experimental method of accurately measuring the ionic fluxes that occur across the gastric mucosa. The experimental models devised thus far are based on

the introduction of a constant volume of fluid into a gastric pouch and then measuring the volume changes and ionic fluxes of the contained solution per unit time.

Davenport, Warner and Code [5] devised a method for measuring ionic fluxes and confirmed Teorell's postulate [9] that an exchange of hydrogen and sodium ions occurs across the gastric mucosa. This is of fundamental importance to gastric physiologists for it means that in addition to exsorption (secretion from animal into stomach), insorption (occuring from stomach to animal) is an important and variable function of the gastric mucosa. Using a physiological test solution to fill a Heidenhain pouch, Davenport et al [5] recorded ionic fluxes over a thirty minute period after measuring directly the volume changes and making corrections for the dead space in the pouch and cannula. This meticulous technique has to be repeated sequentially and requires numerous emptyings and washings of the pouch preparation during each experiment.

In more recent work, investigators have filled and emptied experimental gastric pouches in an attempt to accurately measure volume and ionic changes. This is a tedious procedure and is subject to the inherent error that distension

of a pouch results in increased gastric secretion and sequential measurements may be incorrect due to this stimulation.[10, 11]

A method for the continuous measurement of net ionic fluxes in gastric pouches was developed in 1966 by Wlodek and Leach.[12] This technique is based upon the use of polyethylene glycol as a marker substance. Swedish investigators have used this substance to measure intestinal transit times and to investigate gastric emptying times.[13] Wlodek and Leach found that polyethylene glycol is an ideal marker substance permitting the measurement of sequential ionic and volume gains or losses within secreting gastric pouches, and avoiding the necessity of repeated emptying or draining of the pouch. A recent refinement using polyethylene glycol labelled with C^{14} has greatly facilitated the measurement of this marker substance. The method of measuring in situ ionic fluxes and volume changes in canine gastric pouches developed by Wlodek and Leach has been used in this series of experiments.

B. The physiology of gastric acid secretion

The mechanism of gastric acid secretion has been classically divided into three phases.(14)

	PHASE	MECHANISM
1.	Cephalic	Vagus
2.	Gastric	Gastrin
3.	Intestinal	Secretin
		Enterogastrone
		Gastrin

Inherent in this division of acid secretion into three separate phases is the concept that each acts independently of the other two. A different mechanism of action was proposed for each phase as depicted above. The cephalic phase was felt to be due to nervous (vagal) stimulation while the gastric and intestinal phases were thought to be controlled by hormones.

The "cephalic phase" of acid secretion is mediated by the parasympathetic nervous system via the vagus nerve.(14) Section of the vagi or administration of anticholinergics such as atropine will abolish this phase.(15) The sight, smell or taste of food may excite the vagus nerve, but the actual passage of food through the oropharynx is the most potent factor initiating acid secretion. This has been demonstrated by Preshaw who compared teasing to sham feeding

in dogs with esophagostomies and Pavlov pouches and found teasing to be a much inferior stimulus of acid secretion.[16] Preshaw also found that sham-feeding produced an acid response comparable to maximum histamine stimulation in these dogs.[16]

Vagal excitation continues long after the initial stimulation associated with eating a meal has come to an end.[15] It has been suggested that this continued stimulation of the vagus is due to reflex afferent pathways originating in mechano- and chemo-receptors in the stomach and duodenum.[17, 18, 19] Thus the cephalic phase of acid secretion is perpetuated through the entire digestive period by nervous factors arising in the stomach and duodenum.

The presence of an antral hormone influencing gastric acid secretion was first proposed by Edkins in 1905.[20, 21] Experiments performed in subsequent years conclusively demonstrated the presence of this antral hormone.[15] However, it was not until 1964 that gastrin was finally isolated from the antral mucosa by Gregory and Tracy.[22] Shortly afterwards numerous synthetic gastrins were developed, the most popular one of which is I.C.I. 50,123.* [23, 24]

*t - butyloxycarbonyl - B - Ala. Try. Net. Asp. Phe. NH_2

The "gastric phase" of acid secretion and the mechanisms involved have been extensively studied by many investigators. Lim, Ivy and McCarthy in 1925, suggested that a hormonal mechanism of gastric origin exists for the stimulation of gastric acid secretion.[25] Using feeding as a secretory stimulus in dogs with either vagotomized pouches of the entire stomach or denervated fundic pouches they concluded that this hormone arises from the antrum, thus confirming Edkins original hypothesis. They also found that distension or chemical stimulation of the antrum of the stomach stimulated acid secretion. Conclusive proof that a gastric hormone is liberated from the antrum was finally obtained in 1948 by Grossman, Robertson and Ivy using the stimulus of distension in transplanted pouches of the gastric antrum.[26] In 1951 Dragstedt et al demonstrated that implantation of a denervated antral pouch into the duodenum or colon, where it was constantly exposed to an alkaline solution, resulted in a marked augmentation of the 24-hour acid secretion from a denervated fundic pouch.[27, 28] If fundic mucosa was included in the antral pouch the hypersecretion was prevented, but reappeared when the cuff of fundic mucosa was excised.[28] The experiments of Dragstedt gave strong support to the

concept that the antrum of the stomach liberates a hormone when locally stimulated by chemical or mechanical means, and that the release of the hormone is inhibited by the presence of free acid in the antrum.

From the above experiments has come the present day textbook description of the gastric phase of acid secretion as being due to the hormone gastrin which is released from the antral mucosa by mechanical distension, chemical stimulation or in the presence of an alkaline pH in the antrum. The inhibitory effect of atropine and cocaine [29] and the potentiating action of urecholine [26] on the release of gastrin were indications that the release of this hormone from the antral mucosa involved some local nervous mechanism in which the vagus might well play a vital role. Uvnas recognized this possibility in 1942 on the basis of acute experiments in cats.[30] He demonstrated that vagal excitation could cause a release of gastrin, and that concurrent vagal excitation was an important factor determining the response of the parietal cell to the action of gastrin. The interaction between the vagus and gastrin was ignored for many years and only in the past five years has it been clearly shown that vagal stimulation causes the release of gastrin.[31, 32] Furthermore, Olbe [31] and Uvnas [32]

separately have clearly shown that gastrin and vagal stimulation act on the parietal cell in a synergistic fashion such that the response of acid secretion to both stimuli administered simultaneously is greater than the simple sum of each acting independently. The dependence of these two forms of acid stimulation on each other has been explained by assuming that each stimulus acts directly on the parietal cell and one has a synergistic effect on the response of the parietal cell to the other. This assumption is based on pouch experiments using the simple drainage method of measuring acid secretion which has several disadvantages as mentioned previously. The possibility that nervous and hormonal stimulation may have different sites of action has been virtually ignored. It may be that vagal stimulation causes release of hydrochloric acid from the parietal cell mass, while gastrin maintains the ability of the stomach to contain the acid by acting on a barrier in the gastric mucosa preventing the reabsorption of hydrogen ions.

At the present time little understanding exists of the mechanisms controlling acid secretion during the "intestinal phase" of acid secretion apart from the fact that it exists and involves the release of hormonal agents. The first recognition that food in the small intestine may stimulate

gastric secretion is generally credited to Leconte (1900),[33] who discovered that in dogs provided with gastric and duodenal fistulae the introduction of various soltuions of foodstuffs into the duodenum resulted in gastric secretion. In 1925, Ivy, Lim and McCarthy gave the first convincing demonstration of the existence of an "intestinal phase" of gastric acid secretion.[25] They used a vagotomized pouch of the entire stomach with anastomosis of the esophagus to the duodenum and demonstrated secretion from the stomach pouch when the dogs were fed. Webster and Armour used dogs with the stomach divided at the pyloric sphincter and cannulas installed into the stomach and duodenum to demonstrate acid secretion from the stomach when food was placed in the duodenum.[34] Day and Webster later showed that acidified food placed in the duodenum inhibited the intestinal phase of acid secretion.[35] Enterogastrone was shown to be a hormone existing in the duodenal and jejunal mucosa, liberated there by the presence of fat, and inhibiting gastric motility [36] and secretion.[37] The exact mechanism of action of this hormone and the method of its release are far from clear. The hormone secretin stimulates pancreatic secretion, but will inhibit gastric secretion if acid is present in the duodenum.[38] Also, it is generally accepted that approximately 10% of gastrin

comes from the duodenum mucosa. Thus there appear to be several hormonal factors involved in the "intestinal phase" of acid secretion and their relative importance is poorly understood. The vagus nerve innervates the duodenum and recent work suggest that vagal stimulation may influence acid secretion during the "intestinal phase" which may be mediated by the release of intestinal hormones.[39, 40] The exact nature of this influence has not yet been determined.

The division of gastric secretion into cephalic, gastric and intestinal phases is clearly artificial and gives a simplified but inaccurate explanation of the mechanisms involved in acid secretion. Gastric acid secretion should really be considered as a single unified process aiding digestion and mediated by a continuous interplay between nervous and hormonal stimuli. This thesis is not concerned with one specific phase of gastric secretion but rather with that unique and fascinating property of the gastric mucosa, namely; its ability to contain an acid solution.

C. Acidity control of the stomach

The stomach has the unique property of being able to contain an acid solution. Much interest has been centered on the mechanisms by which the stomach secretes acid but little attempt has been made to elucidate the means by which the stomach is able to contain the acid once it has been secreted.

It is generally accepted that the secretion of the parietal cell mass contains about 170 milliequivalents of hydrochloric acid per liter and this has been called the "primary acidity" of the stomach. Alterations that occur in this primary acid have been termed the "acidity control" of gastric acid secretion. Pavlov was the first to approach this problem by suggesting that a reduction in primary acidity occurred due to the neutralizing and diluting effects of gastric and salivary mucous.(14) In 1934 Boldyreff proposed that duodenal regurgitation was the mechanism responsible for acidity control in the stomach.(41) The third hypothesis is the "diffusion theory" of Teorell first published in 1933.(9) His theory is that the gastric mucosa behaves as a dialysis membrane for ions and the primary acidity of the gastric juice is reduced by a partial back-diffusion of

hydrogen ions through this membrane. Teorell's findings were confirmed in 1949 by Terner who used isolated preparations of frog gastric mucosa to demonstrate back-diffusion of hydrogen ions through the mucosa when hydrochloric acid was placed in contact with it.(42)

Teorell's theory has gained general acceptance over the former two. Thus, the output of the stomach may be stated as the results of two functions of the stomach, namely:

1. The ability of the parietal cells to secrete hydrogen ions, and
2. The ability of the gastric mucosa to contain hydrogen ions in the lumen of the stomach.

The latter is an obvious but much neglected function of the stomach. It is well known that the gastric mucosa is relatively immune to the presence of the strong, corrosive acid secreted by the parietal cells. This acid is highly injurious to most tissues and if it were introduced into an organ such as the intestine there would by an immediate absorption of the acid with consequent hyperemia and eventual ulceration of the intestinal mucosa. The stomach therefore differs from the intestine and all other mucosa-lined organs in that it is protected from acid-peptic digestion.

D. The mucosal barrier to hydrogen and sodium ions

In 1933 Teorell demonstrated that the acidity of hydrochloric acid introduced into a cat's stomach was reduced by a process which appeared to be ordinary diffusion.(9) This "diffusion theory" was expanded by 1939 to the concept of an exchange-diffusion of hydrogen ions in the lumen of the stomach for sodium ions from the mucosa or blood.(43) Thus Teorell postulated a continuous outward diffusion of HCL from the stomach and a simultaneous inward diffusion of NaCL into the stomach - strictly speaking an ionic exchange between hydrogen and sodium.

In 1941, Elliot, Risholm and O'Brink made similar observations in the human.(44) After introducing 175 N hydrochloric acid into the stomach and measuring volume and ion changes ten minutes later, they found that the acidity of their solution decreased much more than could be explained by diluting and neutralizing secretions such as saliva, gastric mucous or duodenal regurgitation. They suggested that an "exchange diffusion" of hydrogen ions for sodium ions across the gastric mucosa existed and that it accounted for 50 - 80% of the total acidity regulation occurring in the stomach.

The fact that the gastric mucosa offers a barrier to the absorption of sodium, not apparent in the intestine, has been well established. In 1941, Eiseman et al, using rabbits, found that ingested radiosodium (Na^{24}) was insorbed much more quickly into the blood stream when no obstruction was offered to the passage of gastric contents into the small intestine than when the pylorus was ligated.(45) This observation was confirmed by Code et al during a series of experiments performed in dogs and humans from 1955 to 1957.(46, 47, 48) Their method was to introduce radiosodium (Na^{24}) and deutrium (D_2O) into the stomach and then measure their sequential blood levels.

In 1943 Cope, Cohn and Brenizer demonstrated in dogs that radiosodium (Na^{24}) is much more slowly insorbed from secreting than non-secreting canine gastric pouches and that it is more rapidly insorbed from the antral portion of the stomach where acid is not produced.(49) In the same year Cope, Blatt and Ball had similar findings using deutrium (D_2O) instead of radiosodium.(50) Feeding was the stimulus employed in both experiments. Moll and Code in 1962 found that insorption of radiosodium (Na^{24}) from gastric contents to blood in the rat stomach was always faster in non-secreting than in secreting stomachs using feeding as the stimulus.(51) These experiments suggest that the barrier to hydrogen and

sodium ions is a variable function of the gastric mucosa and that the competency of this barrier is increased in the secreting state. Unfortunately feeding was the only stimulus used and therefore it cannot be stated whether this property of the gastric mucosa is due to vagal stimulation and/or the effect of antral, intestinal or pancreatic hormones.

The importance of this exchange of hydrogen for sodium ions and the apparent mucosal barrier regulating their exchange has been emphasized recently by Davenport, Warner and Code.[5] They contend that if no mucosal barrier to hydrogen and sodium ions existed then these ions would equilibrate very rapidly with the interstitial tissue concentrations. The excess intraluminal hydrogen ions would be quickly reabsorbed and replaced by sodium ions. As this does not occur in the stomach, it would seem logical to hypothesize the presence of a gastric mucosal barrier although its exact location has not been defined.

Davenport et al have shown further indirect evidence of this mucosal barrier. They found that eugenol and acetic acid, when applied to the gastric mucosa, destroyed this apparent mucosal barrier and permitted a rapid exchange of intragastric hydrogen ions for interstitial sodium

ions without significantly affecting the ability of the parietal cells to secrete acid.(5) Acetylsalicylic acid, short-chained fatty acids, (6) sodium fluoride and mersalyl(7) have all been shown to have a similar effect. These effects are all reversible. Under the above conditions the stomach is secreting an acid solution normally but is not able to contain the acid. This is indirect proof that a mucosal barrier to sodium and hydrogen ions must exist in the gastric mucosa.

Wlodek and Leach compared the ionic fluxes in denervated and innervated canine pouches under basal conditions and after stimulation with histamine.(52) The total loss of hydrogen ions as reflected by the net gain of sodium ions was similar in both types of pouches. These results suggested that the vagus did not effect the mucosal barrier to hydrogen and sodium ions. In order to clarify this point Wlodek and Leach designed a second experiment to compare the effect of insulin hypoglycemia, feeding and histamine in Pavlov pouches.(53) Insulin hypoglycemia had no effect on the mucosal barrier to sodium and hydrogen ions. Feeding demonstrated a decreased exchange of hydrogen for sodium ions and histamine stimulation resulted in a marked reduction in this exchange. This was felt to indicate that antral stimulation might be

the mechanism controlling the mucosal barrier.

The intention of this work was to shed further light on the nature of the mucosal barrier to hydrogen and sodium ions and to elucidate the possible role of gastrin as the mechanism controlling the barrier.

E. Potassium ionic fluxes across the gastric mucosa

Potassium fluxes across the resting gastric mucosa are very small.(54) When the mucosa is damaged by aspirin, salicylic acid or acetic acid the net movement of potassium from mucosa to lumen increases as much as 10-fold.(54) The potassium in gastric secretion may come from actual secretion, cellular disintegration or from the extracellular fluid.

Davenport studied radiopotassium (K^{42}) movement in Heidenhain pouches in the resting state, after histamine and using salicylic and acetic acids instead of hydrochloric acid.(55) When there was no radiopotassium in the irrigating solution potassium entered the lumen. If the concentration was above 4mN insorption of radiopotassium occurred. Salicylic and acetic acids tended to increase potassium fluxes in both directions. Histamine greatly increased the net output of potassium from the mucosa but did not affect the flux from lumen to mucosa. Gastrin was found to have a variable effect on the movement of potassium. He concludes that in the unstimulated stomach most of the very small amount of potassium comes from the extracellular fluid and the remainder from the intracellular pool. During stimulation, or after temporary damage to the mucosa, potassium comes from both sources.

Using radiopotassium (K^{42}) and radiosodium (Na^{24}), Moll and Code have shown that insorption of potassium is slow, unaffected by the presence of acid and most likely independent of insorption of sodium.(51)

Potassium has not been implicated in the exchange diffusion of ions across the gastric mucosal barrier but it has been measured in this study for completeness.

II. EXPERIMENTAL METHOD

Heidenhain and Pavlov pouches were made in healthy adult mongrel dogs weighing 10-25 kilograms. Pavlov pouches were made by isolating a portion of the fundus of the stomach keeping the branches of the vagus nerve to it intact. Stainless steel cannulas with a fixed inner flange and an adjustable outer flange were used for drainage (see Figure 2). The external flange was tightened during the experiments compressing the inner flange against the gastric mucosa and thus preventing leakage of pouch contents around the cannula. After operation the dogs were permitted a 3-6 week recovery period. They were maintained on a standard kennel diet with supplementary sodium and potassium chloride. Experiments lasting four or six hours were carried out after a 24 hour fast.

The pouch cannula was connected to an empty syringe barrel by a polyethylene tube (see Figure 1). Fifty milliliters in four-hour experiments and sixty milliliters in six-hour experiments of an acid solution were pipetted into the empty syringe barrel. The acid solution contained 0.078 N mannitol, 100 milliequivalents of HCl, 15 milligrams of NaCl, 10 grams of polyethylene glycol* and 50 milligrams of polyethylene glycol -C^{14}** per liter. The syringe barrel was

* Carbowax 4000^{R} - Union Carbide - M.W. 4,000

**New England Nuclear Corp. - Specific activity 0.177 mc/gm.

fixed at a level of 10 centimeters above the cannula and the solution allowed to stabilize for 20 minutes. At thirty minute intervals the contents of the pouch were mixed with the reservoir for 5 minutes by alternately raising and lowering the syringe barrel and then a 5 milliliter sample was removed. Five basal samples were taken in the first 120 minutes of the experiment and the dog was then stimulated. Depending upon the duration of the experiment either three or seven further 5 milliliter aliquots were taken at 30 minute intervals and the pouch emptied completely at 240 or 360 minutes. The pouch was then washed with 50 - 100 milliliters of distilled water to insure the best possible recovery of polyethylene glycol $-C^{14}$.

During each experiment the dog was subjected to some form of stimulation after two hours of basal values had been obtained. One can of proprietary dog food was given to the dog in the feeding experiments and this was generally consumed in entirety. Insulin hypoglycemia was induced by the intravenous administration of 0.5 units of crystalline zinc insulin per kilogram. The gastrin used in these experiments was kindly donated by Dr. R.M. Preshaw who prepared it from hog antral mucosa after a modification of the method of Gregory and Tracy.[22] Doctor Preshaw found that his preparation produced

a maximal acid secretory response when given in a dose of 0.5cc./hour (corresponding to 5 grams of hog antral mucosa) intravenously from dogs prepared with a gastric fistula. Intravenous administration of gastrin requires careful regulation since a single intravenous injection of gastrin will actually inhibit secretion.[55] It was therefore decided that a more standard stimulation would be obtained by administering gastrin as a single subcutaneous injection of 0.5cc. at 120 minutes. The pentagastrin ICI 50,123[23, 24] was given subcutaneously in a dose of 9 micrograms per kilogram.

Each sample has been analyzed for sodium and potassium by flame photometry, chloride by the method of Schales and Schales, [56] hydrogen ions by titration with 0.01 N NaOH to the phenolphthalein end point and polyethylene glycol -C^{14} using a scintillation spectrometer (Packard Model 4322). The analysis of polyethylene glycol -C^{14} was done by adding 0.5 ml. of the sample to 15 ml. of a scintillation medium containing 8 gm. BBOT* and 160 gm. napthalene dissolved in 800 cc. toluene, 600 cc. ethanol 95% and 600 cc. dioxane. Two samples were made from each specimen and both were counted twice. This gave 4 values for each 30 minute sample and the average of the four was used to calculate the volume changes.

* 2,5 - bis - 2 - (5 - tert - butylbenzoxazolyl) - thiopene (Packard).

The measured dilution of polyethylene glycol -C^{14} in each sample was used to calculate the total solution remaining in both pouch and reservoir at each 30 minute interval. The volume secreted was determined by subtracting the expected volume after the previous 5 ml. aliquot had been removed from the calculated volume using polyethylene glycol -C^{14} as the volume marker substance. The total ionic content at each half-hour was calculated and the net fluxes of ions in the solution were obtained by simple subtraction from the preceding half-hour values. The net ionic fluxes per half-hour were designated as positive values for pouch gains and negative values for pouch losses. The validity of each experiment was controlled by measuring the recovery rate of polyethylene glycol -C^{14} expressed as a percentage of polyethylene glycol -C^{14} introduced at the onset of the experiment. Experiments with a recovery of 98% to 102% were acceptable and included in the tabulations.

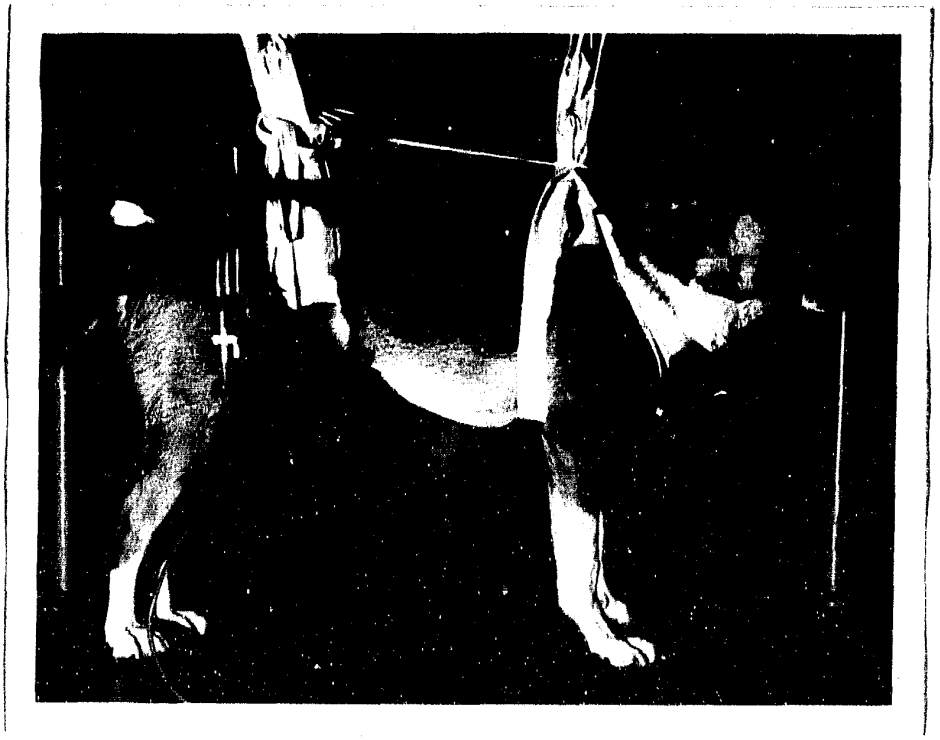

FIGURE 1 During experiments the dogs were kept in Pavlov stands. The 50 milliliter syringe reservoir was placed at 10 centimeters above the pouch and connected to the pouch by a polyethylene tube.

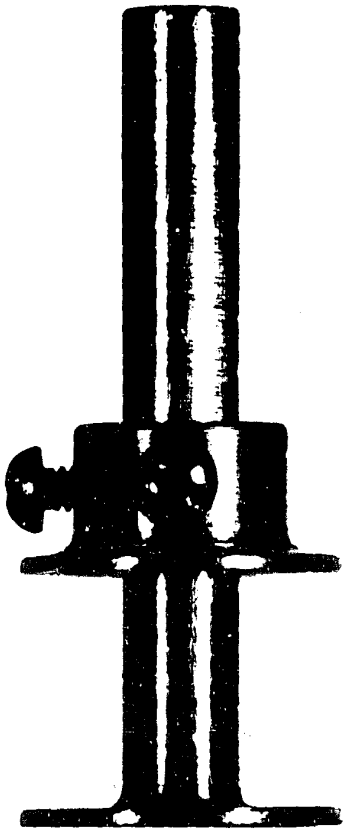

FIGURE 2 The pouch cannula used in these experiments was made of stainless steel. It has an internal fixed flange and an external adjustable flange.

III. RESULTS

A. Method of interpretation

The results of all experiments are recorded in Tables 1 - 29. This represents the averages of 4 - 10 experiments using various stimuli in dogs with Heidenhain or Pavlov pouches or in Heidenhain pouches after antrectomy. Each series consists of experiments using one stimulus on a given pouch preparation and results are reported for individual dogs with a separate table for the averages of all dogs. There were 3 - 5 dogs in each series of experiments. A total of 191 experiments were carried out in 11 dogs but only 141 are reported in this thesis. There were 19 experiments using feeding as a stimulus in 3 dogs with Heidenhain pouches and excluded antrums which were not reported because it was felt that this was a very unphysiological preparation. Of the remaining 31 experiments 23 were pilote projects not carried through to completion and 8 were discarded because of poor recovery of polyethylene glycol-C^{14}.

All measurements have been recorded as changes per 30 minutes. The results in Tables 1 - 29 represent rates of change and not absolute values. All values are reported as the arithmetic mean with the standard deviation. The volume secreted from the pouch was measured in milliliters

per 30 minutes and ionic changes were measured in micro-equivalents per 30 minutes. Negative values indicate a loss of ions from the pouch contents and all other unmarked values are positive indicating a gain of ions to the pouch contents. The change per 30 minute interval is calculated by simply subtracting the expected values of a 5 cc. aliquot removed from the actual values measured.

The basic assumption used in interpreting these results is that every chloride ion secreted is accompanied by an hydrogen ion as hydrochloric acid, that is; chloride ion is secreted solely as hydrochloric acid. The amount of hydrogen gain or loss from the pouch is then calculated by subtracting the measured change in hydrogen ion from the measured change in chloride ion. It was found that there was always a loss of hydrogen ions from the pouch under basal conditions. On the other hand, the pouch contents always showed a gain of sodium ions under both basal and stimulatory conditions. The hydrogen ion loss has been interpreted according to Teorell's hypothesis as an ion for ion exchange with sodium and this exchange process was felt to be indicative of the competency of the gastric mucosal barrier to hydrogen and sodium ions. Previous experiments [12, 52, 53] demonstrated that the calculated hydrogen ion loss was approximately equal

to the sodium ion gain and an attempt has been made to interpret the results recorded here in the light of these findings.

A diagramatic explanation of the above is shown in Figure 3. Here the measured net gain of chloride by a pouch of the stomach has been schematically represented as 100 ueq./30 min. The net change in hydrogen ions during the same 30 minute period is shown as a measured loss of 50 ueq. Assuming the chloride was secreted totally as hydrochloric acid, then 100 ueq. of hydrogen was secreted with 100 ueq. of chloride. However, actual measurements showed a loss of 50 ueq. of hydrogen ions, so that the total loss of hydrogen by the pouch was 150 ueq. During this same 30 minute period the pouch gained 150 ueq. of sodium. Thus 150 ueq. of hydrogen ions were exchanged for 150 ueq. of sodium ions. Even values were used for explanatory purposes but these values approximate those found under basal conditions by Wlodek and Leach in previous experiments.[52, 53]

This interpretation of the ionic changes occurring in the stomach ignores the concept of a "non-parietal" secretion as proposed by Hollander and others.[58, 59, 60, 61, 64] The actual presence of a "non-parietal" component to gastric secretion has not been satisfactorily proven and will be

discussed in more detail later. However, the presence of an alkaline non-parietal secretion would not alter the outcome of the above interpretation of ionic fluxes. This is schematically shown in Figure 4 where one-half of the chloride secretion is attributed to the "non-parietal" component of secretion. Under these conditions 50 ueq. of chloride enters as hydrochloric acid, and 50 ueq. enters accompanied by 50 ueq. of sodium as "neutral chloride". Consequently, only 100 ueq. of sodium per 30 minutes would enter the pouch in the ionic form. As in Figure 3, the measured change of hydrogen ions in the pouch is depicted as 50 ueq. per 30 minutes. Since only 50 ueq. of chloride is entering the pouch per 30 minutes, the total loss of hydrogen is 100 ueq. per 30 minutes. This loss would be replaced by the 100 ueq. of sodium entering the pouch in the ionic form. Thus the presence or absence of a non-parietal chloride secretion, or the proportion of the total chloride secretion it is responsible for, does not alter the validity of this interpretation of ionic fluxes.

Results of individual experiments, average results and all statistical analysis were done on the McGill University Fortran IBM computer. The experimental results were simply obtained by punching the measured data on Fortran cards and feeding these cards with the appropriate program into the

computer. Statistical analysis was performed on all results using the "t-test" and levels of significance have been reported in the standard fashion using "p" values.

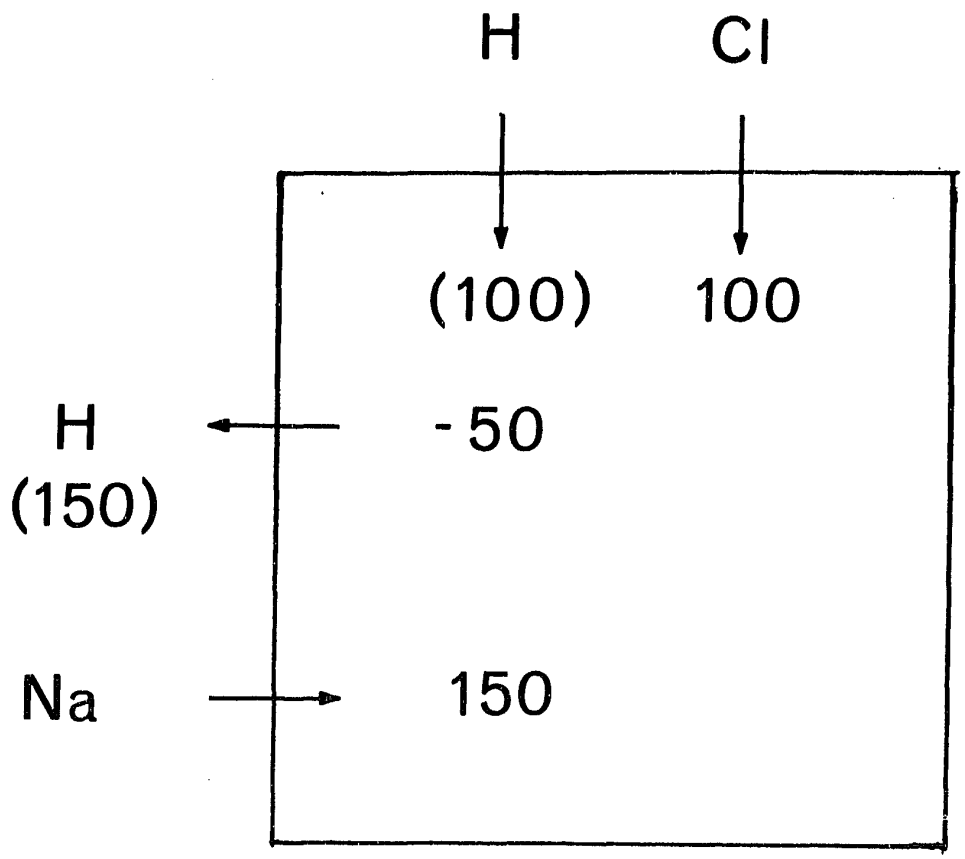

FIGURE 3 Schematic representation of a pouch of the stomach with even values used for explanatory purposes only. Ionic fluxes are interpreted on the basis of Teorell's postulate. All values are in microequivalents per 30 minutes. Figures in brackets represent theoretical or calculated values and those without are actual measurements.

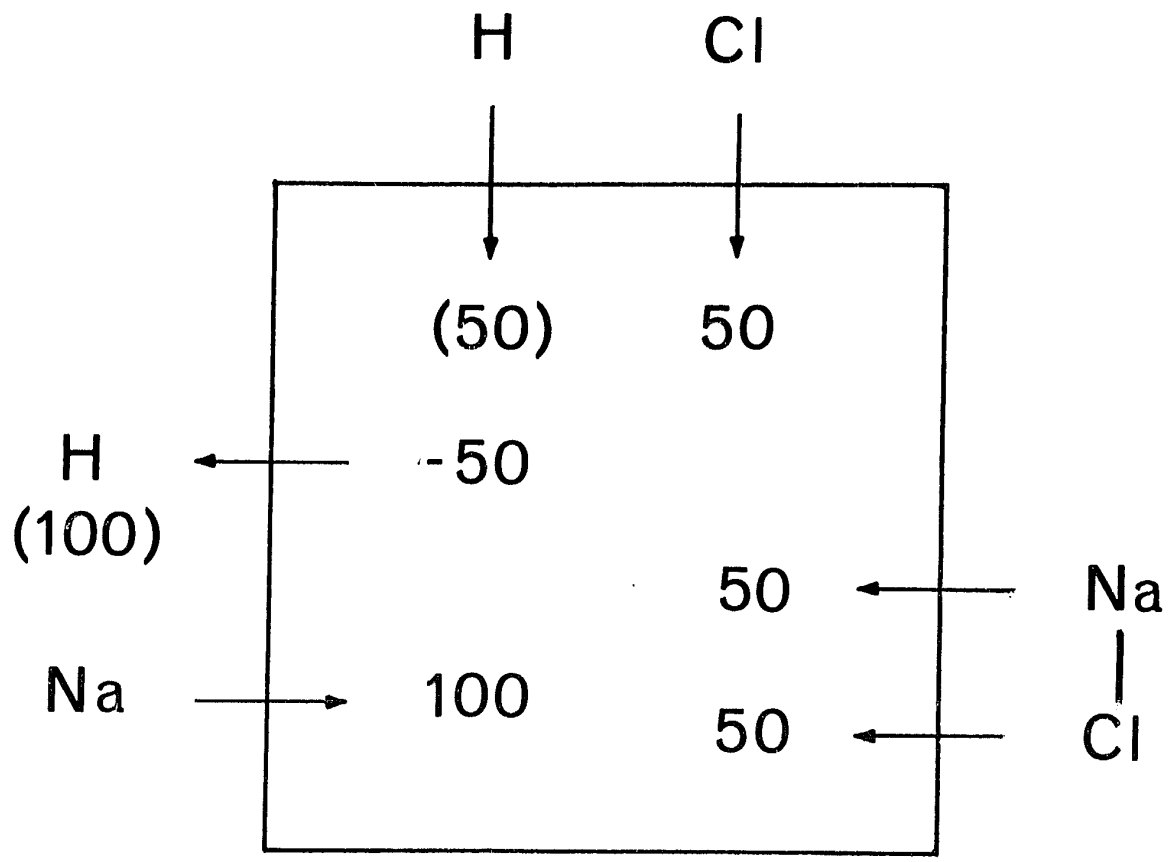

FIGURE 4 Schematic representation of a pouch of the stomach with even values used for explanatory purposes only. Ionic fluxes are interpretated on the basis that one-half of the measured chloride is secreted into the pouch as a non-parietal neutral chloride solution accompanied ion for ion by sodium. All values are in microequivalents per 30 minutes. Figures in brackets represent theorectical or calculated values and those without are actual measurements.

B. The effect of feeding on volume and ionic changes in Heidenhain pouches

The first experiment carried out was feeding in five Heidenhain pouch preparations. The results from experiments in individual dogs are recorded in Tables 1 - 5. Table 6 shows the composite results of a total of 28 experiments done in five dogs. After four basal half-hour measurements, the dogs were fed a standard protein meal and the changes recorded for a further four half-hour periods. The basal average volumes of 0.94 ml./30 min. increased to 1.38 and 1.28 ml./30 min. during the first and second half-hours after feeding and then returned to approximately normal levels in the last two half-hours (see Table 6). The increase in secretion recorded at 150 minutes was significant (p less than 0.01), but the average post-feeding secretion of 1.03 ml./30 min. was not significantly different from the basal secretion. A moderate increase in hydrogen and chloride ionic fluxes in the pouch occurred during the first 30 minutes after feeding and then fell off during the three following half-hour periods toward the basal values. The sodium gain by the pouch decreased after feeding from a basal of 160 ueq./30 min., a decrease of 54 ueq./30 min. from the average basal value (p less than 0.001).

The calculated hydrogen ion loss under basal conditions was determined by taking the assumed secretion of hydrogen ions as hydrochloric acid which was 84 ueq./30 min. During this same two hour period the measured changed in hydrogen ion in the pouch was a loss of 71 ueq./30 min. Thus the calculated hydrogen ion loss was 155 ueq./30 min. The actual gain in sodium ions during this period was 160 ueq./30 min. which is approximately equal to the hydrogen loss. Therefore, under basal conditions 155 - 160 ueq. of hydrogen ions was being exchanged for a similar quantity of sodium ions across the gastric mucosal barrier.

After feeding the calculated hydrogen ion loss was 113 ueq./30 min. while the measured gain of sodium ions was 106 ueq./30 min. Therefore only 106 - 133 ueq./30 min. of hydrogen was being exchanged for sodium after feeding. The decrease in this exchange process was therefore 42 ueq./30 min. as calculated by hydrogen ion loss and 54 ueq./30 min. measured as sodium gain. Both values are highly significant using the t-test giving a "p" value of less than 0.001.

A comparison of the hydrogen and chloride ionic fluxes as well as a comparison of the hydrogen and sodium ionic fluxes has been graphically illustrated in Figures 5 and 6 respectively. Figure 5 shows that the loss of hydrogen

ions by the pouch, as calculated by the area between the two curves, decreased after feeding. The decrease in both the measured sodium gain to the pouch and the calculated hydrogen ion loss after feeding is shown in Figure 6. This is interpreted as a result of an increase in the mucosal barrier to the exchange of hydrogen for sodium ions after feeding.

Similar results for volume and ionic changes and their statistical significance were found in the individual dogs. Dogs 1, 3 and 4 showed a slight but insignificant increase in secretion after feeding, dog 2 did not change and dog 5 showed a slight decrease in secretion. This may be interpreted as variance in the inherent cholinergic activity remaining in the different denervated pouches. The change in chloride ion gain to the pouch could not be correlated with the degree of change in secretion in any dog but particularly in dog 2 where the chloride gain to the pouch increased significantly ($p < 0.01$) from 54 ueq./30 min. to 105 ueq./30 min. inspite of an actual decrease (not significant) in secretion after stimulation.

In this series of experiments it was found that feeding did not significantly affect the volume of secretion in a denervated pouch. However, the secretion of hydrochloric acid, determined by the measured gain of chloride to the pouch per 30 minutes, did increase significantly after

feeding (p less than 0.001). Also a decrease in the exchange of hydrogen for sodium ions and thus an increase in the competency of the mucosal barrier was shown after feeding.

TABLE 1

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.62±0.37	-77±51	89±73	167±47	2±4
60	1.17±0.46	-48±40	126±69	181±53	3±3
90	0.42±0.16	-91±48	37±47	124±37	5±3
120	0.78±0.55	-39±74	79±78	163±22	4±2
Average basal	0.75±0.48	-63±55	83±71	159±44	4±3
150	1.40±0.34	100±68	211±95	74±43	12±7
180	1.72±0.40	135±52	246±91	100±39	10±6
210	1.07±0.63	72±97	160±113	65±28	10±6
240	0.87±0.50	49±65	123±71	51±11	7±4
Average post feeding	1.27±0.56	89±75	185±100	73±35	10±6

Dog #1 Average results of six four-hour experiments in a Heidenhain pouch preparation. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 2

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.75±0.50	-56±57	85±78	117±73	8±8
60	0.90±0.39	-87±19	46±44	145±38	8±5
90	0.69±0.18	-116±66	36±54	135±36	13±10
120	0.66±0.48	-73±31	49±43	150±43	11±7
Average basal	0.75±0.39	-83±50	54±56	137±49	10±8
150	0.95±0.70	54±65	186±99	119±27	10±4
180	0.91±0.35	17±61	82±53	98±15	10±4
210	0.45±0.25	2±35	51±35	80±21	9±3
240	0.65±0.51	30±72	99±71	55±20	7±3
Average post feeding	0.74±0.50	26±60	105±82	88±31	9±4

Dog #2 Average results of seven four-hour experiments in a Heidenhain pouch preparation. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 3

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	1.51±0.29	69±58	187±92	113±19	7±3
60	1.03±0.59	-102±66	68±72	214±90	9±0
90	1.04±0.28	-86±88	108±69	197±117	10±3
120	0.98±0.45	-195±76	130±36	323±119	12±1
Average basal	1.14±0.44	-79±118	123±77	212±115	9±3
150	1.60±0.45	3±61	256±36	203±65	20±4
180	1.27±0.19	-8±52	139±102	153±66	9±2
210	0.89±0.72	-57±61	149±97	174±74	10±5
240	1.07±0.45	-88±13	104±46	176±77	9±5
Average post feeding	1.21±0.52	-38±59	162±90	177±66	12±6

Dog #3 Average results of four four-hour experiments in a Heidenhain pouch preparation. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 4

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	1.11±0.55	-58±46	96±64	216±60	17±7
60	1.82±0.77	-39±59	177±113	250±46	20±9
90	1.13±0.28	-75±45	72±67	207±83	15±7
120	1.31±0.58	-44±36	109±72	207±52	18±10
Average basal	1.34±0.59	-54±46	114±85	220±59	18±8
150	1.96±0.92	140±56	291±128	171±50	25±11
180	1.67±0.47	79±42	215±72	181±35	17±6
210	1.08±0.31	22±29	147±95	121±26	20±7
240	1.26±0.44	30±58	175±71	111±42	14±7
Average Post feeding	1.49±0.64	68±65	207±103	146±47	19±8

Dog #4 Average results of five four-hour experiments in a Heidenhain pouch preparation. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 5

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	1.09±0.54	-52±106	88±72	104±53	4±4
60	0.84±0.91	-81±67	79±75	125±49	8±8
90	0.78±0.21	-63±34	62±8	81±16	6±7
120	0.84±0.48	-95±25	52±41	108±77	7±4
Average basal	0.89±0.57	-73±64	70±54	104±52	6±6
150	1.24±0.40	55±88	171±57	95±52	12±6
180	0.68±0.30	-12±52	84±51	67±38	3±1
210	0.32±0.25	-53±43	41±24	88±34	2±1
240	0.34±0.13	-40±27	31±17	66±22	3±1
Average post feeding	0.64±0.46	-13±68	82±68	79±38	5±5

Dog #5 Average results of six four-hour experiments in a Heidenhain pouch preparation. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 6

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.97±0.53	-42±78	103±78	142±67	7±7
60	1.13±0.69	-71±52	97±84	177±68	9±8
90	0.78±0.32	-88±56	58±54	143±73	10±8
120	0.89±0.51	-83±69	78±61	179±91	10±7
Average basal	0.94±0.54	-71±66	84±71	160±76	9±8
150	1.38±0.66	72±77	217±95	125±63	15±9
180	1.22±0.54	44±76	150±98	115±54	10±6
210	0.73±0.53	0±73	103±90	99±50	10±7
240	0.80±0.51	2±71	104±73	84±55	8±5
Average post feeding	1.03±0.62	30±79	143±100	106±57	10±7

Dogs #1, 2, 3, 4, 5 Average of twenty-eight four-hour experiments in five dogs with Heidenhain pouches. The stimulus was one can of proprietary dog food given at 120 minutes.

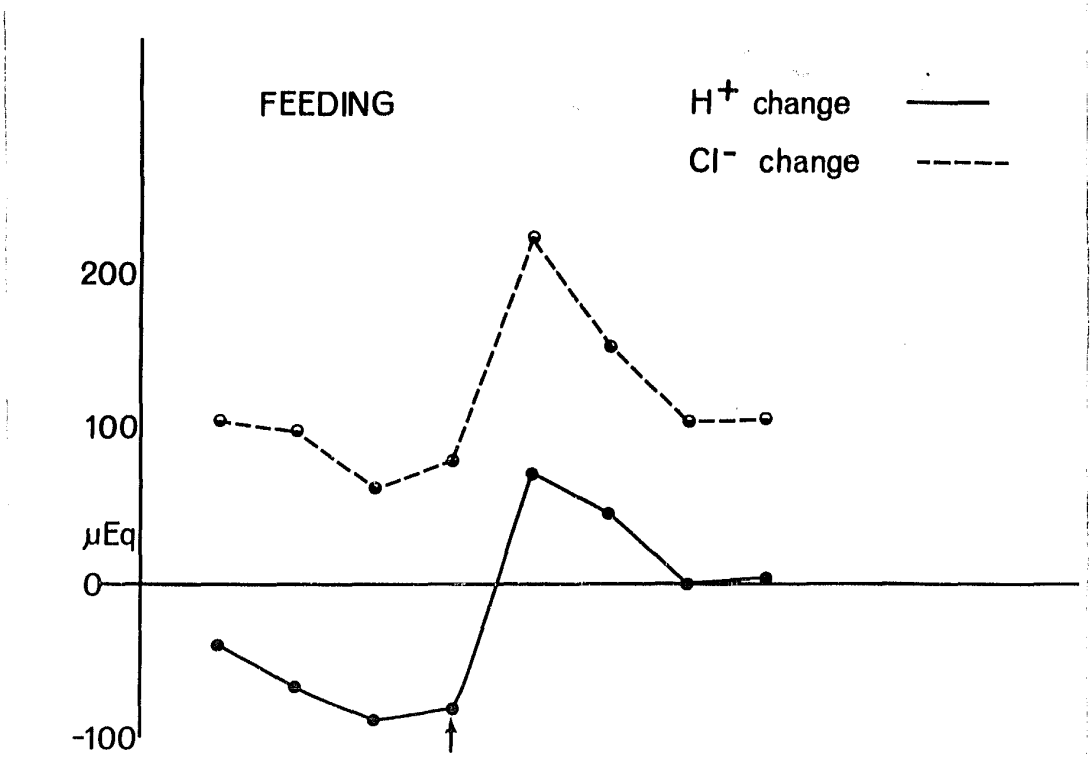

FIGURE 5 Graphic representation of H^+ and Cl^- ionic fluxes per 30 minutes before and after feeding in five dogs with Heidenhain pouches. Points on the graph represent average basal and post-stimulation values taken from Table 6. The stimulus time was 120 minutes as depicted by the arrow.

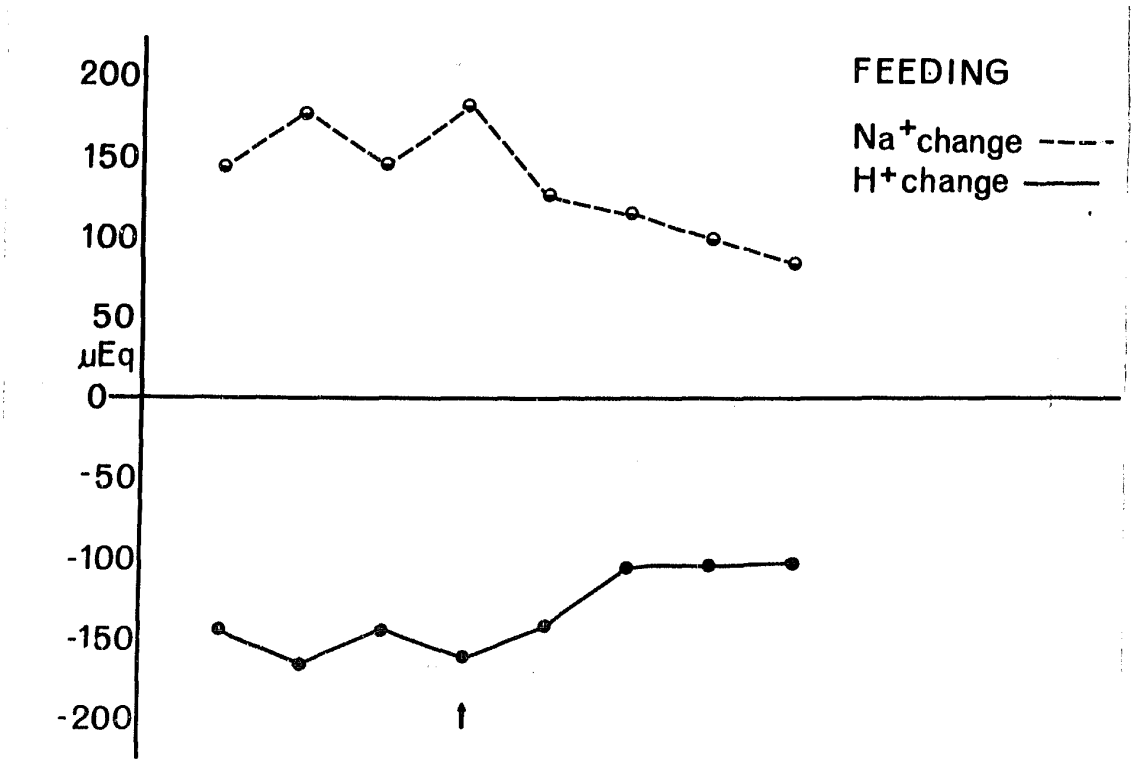

FIGURE 6 Graphic representation of H^+ and Na^+ ionic fluxes per 30 minutes before and after feeding in five dogs with Heidenhain pouches. Points on the graph represent average basal and post-stimulation values taken from Table 6. The stimulus time was 120 minutes as depicted by the arrow.

C. The effect of feeding on volume and ionic changes in Heidenhain pouches after antrectomy

Three dogs with Heidenhain pouches were subjected to antrectomy. Dogs 1 and 3 came from the five dogs used in the previous experiment and dog 6 had both a Heidenhain and an antral pouch in which the antral pouch was removed. Dogs 2, 4 and 5 did not survive antrectomy. After four half-hour basal values were taken the dogs were given one can of proprietary dog food and a further four half-hour periods recorded.

Results for individual dogs are recorded in Tables 7, 8 and 9 and the composite results for the three dogs are found in Table 10. The secretion recorded in these dogs under basal conditions was 0.56 ml./30 min. After feeding no change in secretion rate was noted as the volume secreted remained at 0.56 ml./30 min. However, during the 180 minute interval the secretion increased to 0.71 ml./30 min., although this was not a significant rise. The chloride gain increased during the first two half-hourly measurements but then returned to basal levels by the fourth half-hour. The hydrogen ion went from a net loss of 67 ueq./30 min. to a gain of 11 ueq./30 min. The sodium gain gradually fell from an average basal rate of 95 ueq./30 min. to 62 ueq./30 min. The change in hydrogen

and chloride ionic flux is most marked during the first two half hours returning towards normal by the fourth half-hour while the decrease in sodium ion gain reaches its maximum in the third and fourth half-hours. There is a slight disparity between the calculated hydrogen ion loss (116 ueq./30 min.) and the measured sodium gain (95 ueq./30 min.) which is only slightly significant (p less than 0.05).

A comparison of chloride and hydrogen ion changes is illustrated in Figure 7. The chloride gain to the pouch increased slightly (not significant) after feeding. The change in hydrogen ion flux after feeding was highly significant (p less than 0.001). After feeding the measured sodium gain to the pouch decreased by an average of 33 ueq./30 min. (95-62 ueq./30 min.) and the calculated hydrogen loss decreased by an average of 57 ueq./30 min. (116-57 ueq./30 min.). This is graphically illustrated in Figure 8. Both values are highly significant (p less than 0.001).

Results in individual dogs are comparable to the composite average results. Dogs 1 and 3 showed no increase in chloride content by their pouches while dog 6 had a highly significant increase in the chloride gain after feeding (p less than 0.001). This difference could be due

to a variance in inherent cholinergic activity of these pouches or possibly inadequate antrectomy in dog 6.

Antrectomy in three dogs with Heidenhain pouches abolished the effect of feeding on the chloride gain and had no effect on the volume secreted by the pouch. The decrease in the exchange of hydrogen for sodium ions after feeding was not altered by antrectomy. Thus the competency of the mucosal barrier to this exchange process still appeared to increase after feeding in a denervated pouch after antrectomy.

TABLE 7

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.40±0.21	-96±84	43±35	110±60	3±6
60	0.50±0.15	-51±42	45±31	95±24	3±5
90	0.34±0.50	-93±60	31±44	77±26	3±4
120	0.53±0.23	-25±70	56±17	53±34	4±3
Average basal	0.44±0.29	-66±68	44±32	84±42	3±4
150	0.33±0.12	-52±27	23±15	85±62	5±4
180	0.35±0.20	-25±35	32±28	80±26	1±2
210	0.28±0.14	- 0±29	34±18	32±12	4±3
240	0.64±0.39	48±30	72±34	55±29	5±4
Average post feeding	0.40±0.27	- 7±47	40±30	63±41	4±4

Dog #1. Average results of six four-hour experiments in a Heidenhain pouch preparation after antrectomy. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 8

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.44±0.19	-76±82	28±25	75±38	3±7
60	0.66±0.42	-19±64	58±32	86±39	2±5
90	0.51±0.39	-73±49	50±37	113±20	3±2
120	0.40±0.30	-77±48	25±23	126±53	4±2
Average basal	0.50±0.33	-61±63	40±31	100±42	3±4
150	0.60±0.27	-74±35	41±21	73±36	7±4
180	0.38±0.22	-29±20	26±22	80±36	5±4
210	0.29±0.17	-37±31	39±19	53±32	2±3
240	0.12±0.15	-15±17	15±11	46±32	2±1
Average post feeding	0.35±0.26	-39±20	30±34	63±35	4±4

Dog #3 Average results of six four-hour experiments in a Heidenhain pouch preparation after antrectomy. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 9

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.81±0.61	-96±85	74±65	120±71	4±3
60	0.62±0.41	-85±55	60±41	107±63	7±6
90	0.57±0.38	-53±48	35±28	101±57	6±4
120	0.66±0.33	-53±49	58±30	67±40	5±3
Average basal	0.66±0.44	-71±62	57±44	99±60	6±4
150	0.93±0.64	42±98	126±69	79±49	13±8
180	1.14±0.59	126±99	170±95	67±43	12±6
210	0.73±0.47	41±82	104±66	55±32	7±4
240	0.36±0.25	1±21	52±35	45±30	3±3
Average post feeding	0.79±0.57	52±91	113±80	62±40	9±7

Dog #6 Average results of ten four-hour experiments in a Heidenhain pouch preparation after antrectomy. The dog was fed a proprietary protein meal at 120 minutes.

TABLE 10

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.60±0.47	-90±80	53±52	105±61	4±5
60	0.60±0.35	-58±59	55±35	98±48	5±6
90	0.49±0.41	-69±52	38±34	98±43	4±4
120	0.55±0.30	-52±56	48±28	79±50	5±3
Average basal	0.56±0.38	-67±63	49±38	95±51	4±4
150	0.67±0.51	-16±87	74±67	79±48	9±7
180	0.71±0.57	42±103	93±97	74±36	7±7
210	0.49±0.39	9±67	67±57	48±28	5±4
240	0.37±0.33	10±33	47±36	48±29	3±3
Average post feeding	0.56±0.48	11±79	70±69	62±38	6±6

Dogs #1, 3, 6 Average results of twenty-two four-hour experiments performed on three dogs with Heidenhain pouches and antrectomies. The stimulus was a proprietary protein meal given at 120 minutes.

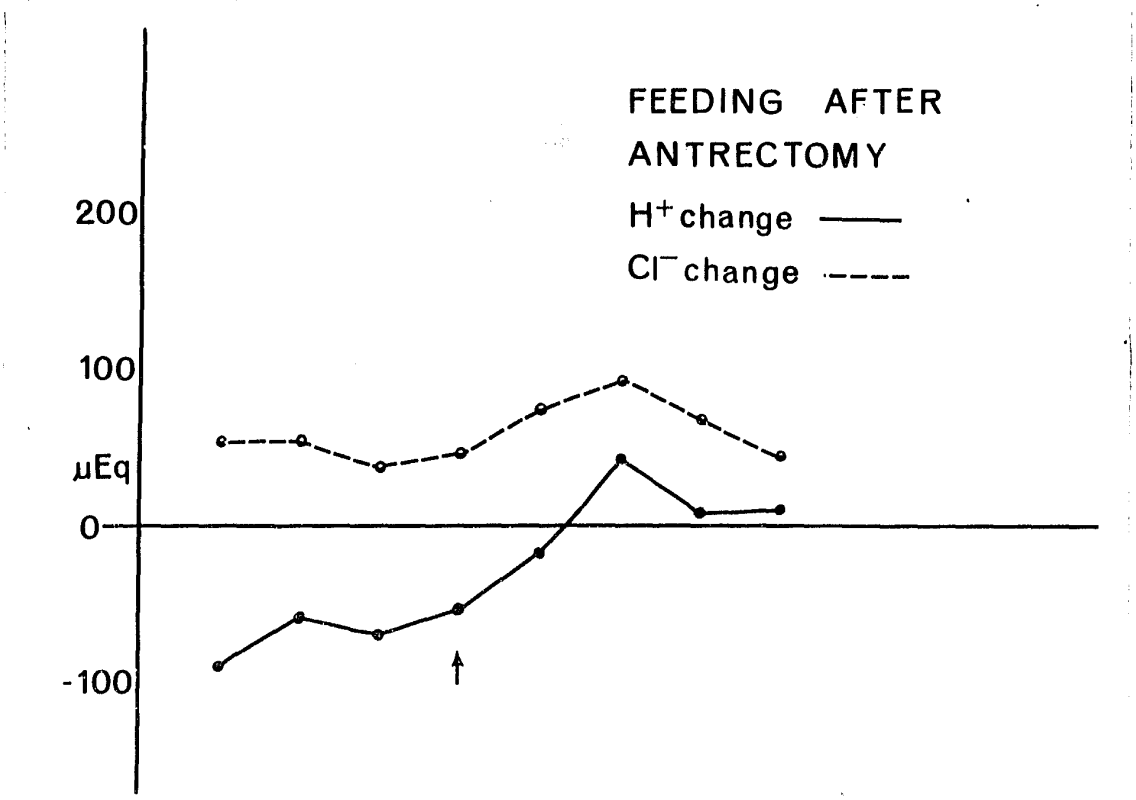

FIGURE 7 Graphic representation of H^+ and Cl^- ionic fluxes per 30 minutes before and after feeding in three dogs with Heidenhain pouches and antrectomies. Points on the graph represent average basal and post-stimulation values taken from Table 10. The stimulus time was 120 minutes as depicted by the arrow.

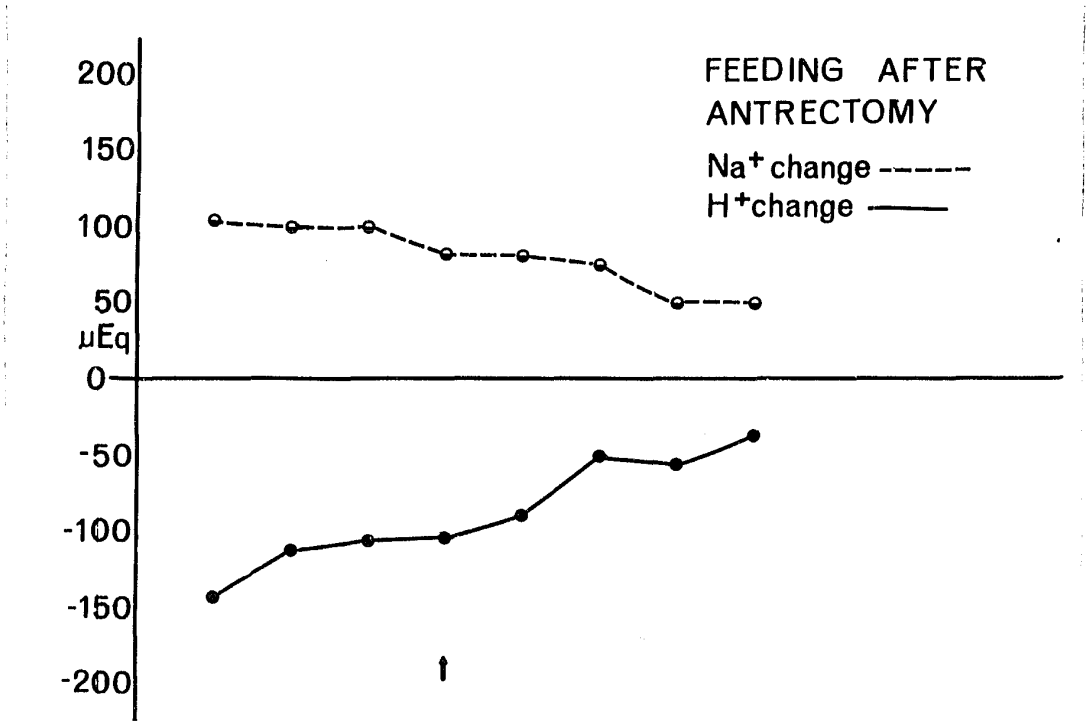

FIGURE 8 Graphic representation of H^+ and Na^+ ionic fluxes per 30 minutes before and after feeding in three dogs with Heidenhain pouches and antrectomies. Points on the graph represent average basal and post-stimulation values taken from Table 10. The stimulus time was 120 minutes as depicted by the arrow.

D. The effect of insulin hypoglycemia on volume and ionic changes in Pavlov pouches

Pavlov pouches were made in five dogs by isolating a portion of the fundus of the stomach keeping the vagal innervation intact. These dogs were given insulin 0.5 units per kilogram intravenously after a two hour basal period and measurements taken every thirty minutes for four hours post-stimulus. These experiments were thus six hours in duration. The results in individual dogs are recorded in Tables 11 - 15 and the average of thirty-three experiments in the five dogs is presented in Table 16. Average post-stimulus valves have been calculated for both the first two hours and the total four hours after stimulation.

The average basal secretion for all five dogs was 0.78 ml./30 min. After insulin it rose to 2.55 ml./30 min. in the second half-hour and gradually fell although never reaching pre-stimulation values during the four hours post-stimulation. The average secretion for the first two hours post-insulin was 2.09 ml./30 min. and for the total four hours post-insulin was 1.65 ml./30 min. The increase in pouch gain of chloride followed a pattern similar to that of measured secretion. All individual post-insulin thirty minute values for secretion and chloride gain were highly significant ($p < 0.001$).

A comparison between chloride and hydrogen ionic fluxes and between sodium and hydrogen ionic fluxes has been graphically illustrated in Figures 9 and 10 respectively. The hydrogen ion loss per thirty minutes is calculated by measuring the distance between points at the same time interval on the two lines in Figure 9. The resulting calculated hydrogen loss has then been plotted separately with the measured sodium gain in Figure 10. The sodium gain per thirty minutes to the pouch did not change significantly after insulin as shown in both the averages for all dogs and also for each individual dog ($p < 0.001$). The calculated hydrogen ion loss (illustrated in Figure 10) was -137 ueq./30 min. under basal conditions and fell to -85 ueq./30 min. during the four hours post-insulin. This is a highly significant change ($p < 0.001$). However, if only post-insulin hydrogen and sodium ion fluxes were compared, during the first 2 hours it was found that the hydrogen loss of -88 ueq./30 min. was only slightly significantly different from the sodium gain of 115 ueq./30 min., and during the total 4 hours the hydrogen loss of -85 ueq./30 min. was not significant different from the sodium gain of 108 ueq./30 min.

The calculated hydrogen loss and measured sodium gain in the individual dogs pre- and post-insulin are

compared in Table 16A. This illustrates that dogs 9, 10 and 11 had no significant change in either calculated hydrogen loss or measured sodium gain between basal and post-insulin values. On the other hand, dogs 7 and 8 showed a significant disparity between calculated hydrogen ion loss and measured sodium ion gain both before and after insulin. Both these dogs (7 and 8) were thin and weak after construction of their Pavlov pouches and failed to gain weight. Dog 8 died of intestinal obstruction shortly after completion of the insulin series of experiments.

If the sodium gain is taken to represent the competency of the mucosal barrier to the exchange of hydrogen for sodium ions, then there is no change in this competency after insulin. The calculated hydrogen ion loss as measured in all five dogs would indicate that the mucosal barrier has become more competent after insulin. However, three of the five dogs showed no significant change in the calculated hydrogen ion loss after insulin while two showed a significant decrease. This series of experiments also casts doubt on the validity of Teorell's hypothesis than an ion for ion exchange of hydrogen for sodium occurs across the gastric mucosa.

TABLE 11

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.60±0.27	-30±50	52±25	53±22	3±6
60	0.34±0.15	-38±47	55±24	61±23	7±6
90	0.46±0.34	-68±41	18±37	65±33	4±2
120	0.95±0.43	-73±80	61±16	93±48	7±6
Average basal	0.59±0.38	-52±57	46±31	68±35	5±5
150	0.46±0.30	-75±69	26±36	61±17	5±4
180	2.00±0.51	187±88	217±73	64±14	13±8
210	2.09±0.50	220±129	240±81	58±24	20±9
240	2.38±1.23	267±193	274±137	66±48	17±8
270	1.75±0.71	190±105	216±82	63±24	16±10
300	1.37±1.18	105±169	144±143	52±22	12±9
330	1.09±1.64	83±211	110±193	48±35	9±14
360	0.82±0.74	37±102	70±70	38±18	6±6
Average post insulin					
150 - 240	1.73±1.02	150±182	189±129	62±27	14±9
150 - 360	1.50±1.09	127±169	162±134	56±27	12±10

Dog #7 Average results of seven six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5 units of insulin per kilogram intravenously at 120 minutes.

TABLE 12

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.67±0.46	-104±132	66±45	91±42	6±5
60	0.70±0.58	-92±110	44±29	79±25	3±3
90	0.59±0.21	-108±28	58±35	85±16	3±2
120	0.91±0.36	-49±82	71±38	78±52	8±4
Average basal	0.72±0.41	-88±91	60±36	83±34	5±4
150	1.10±0.77	91±143	118±95	75±20	5±2
180	3.42±2.71	422±399	388±292	117±58	17±15
210	3.50±2.41	375±361	385±280	106±48	15±12
240	2.24±1.29	239±201	264±151	84±27	19±11
270	1.27±0.94	69±135	160±117	89±21	7±21
300	1.27±0.52	67±134	152±84	88±43	6±4
330	1.49±1.24	103±138	142±122	98±31	7±6
360	1.23±1.02	63±118	111±101	71±44	7±7
Average post insulin					
150 - 240	2.57±2.07	282±302	289±232	95±42	14±12
150 - 360	1.94±1.69	179±250	215±192	91±38	10±11

Dog #8 Average results of five six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5 units of insulin per kilogram intravenously at 120 minutes.

TABLE 13

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.56±0.36	-64±102	66±41	89±37	4±5
60	0.99±0.24	-70±115	81±43	104±68	5±5
90	0.62±0.46	-45±49	65±62	70±36	8±4
120	0.86±0.24	-53±38	72±36	124±75	8±5
Average basal	0.76±0.37	-58±79	71±45	97±58	6±5
150	1.55±1.13	39±100	161±160	116±74	10±12
180	2.27±1.22	258±182	325±194	115±45	18±9
210	1.86±0.77	208±127	277±158	88±40	16±12
240	1.82±1.21	127±95	218±139	98±82	19±10
270	1.01±0.50	30±49	132±108	87±37	5±8
300	0.98±0.55	32±43	119±76	116±53	7±3
330	0.92±0.44	18±39	93±55	101±50	7±4
360	0.71±0.27	4±41	73±30	101±59	6±3
Average post insulin					
150 - 240	1.88±1.08	158±150	245±168	104±61	16±11
150 - 360	1.39±0.95	90±130	175±147	103±55	11±10

Dog #9 Average results of eight six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5 units of insulin per kilogram intravenously at 120 minutes.

TABLE 14

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	1.43±0.45	-75±109	115±73	185±61	2±3
60	1.08±0.25	-118±86	108±56	168±45	4±5
90	0.92±0.30	-150±112	58±16	153±35	2±3
120	1.09±0.19	-122±52	87±46	176±48	4±4
Average basal	1.13±0.35	-116±91	92±54	171±46	3±4
150	1.62±0.48	-112±123	165±49	194±91	6±3
180	3.53±1.53	202±236	362±179	232±121	4±3
210	3.09±1.23	153±155	327±141	175±78	6±3
240	2.58±0.96	142±128	276±94	180±73	5±7
270	2.19±0.85	52±72	228±77	183±75	7±2
300	1.70±0.87	-12±58	172±79	157±71	3±3
330	1.16±0.48	- 1±34	113±44	236±118	5±3
360	0.91±0.52	-36±69	81±53	126±69	5±3
Average post insulin					
150 - 240	2.71±1.27	96±199	283±140	195±89	5±4
150 - 360	2.10±1.23	49±154	216±133	185±89	5±4

Dog #10 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5 units of insulin per kilogram intravenously at 120 minutes.

TABLE 15

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.80±0.59	-33±87	92±57	87±42	3±3
60	0.74±0.41	-43±57	65±59	91±34	5±4
90	0.43±0.36	-73±59	31±51	100±35	6±5
120	0.91±0.62	-61±52	64±74	137±60	8±6
Average basal	0.72±0.51	-53±64	63±61	104±46	5±5
150	1.84±0.93	87±99	215±130	136±85	11±5
180	1.97±0.57	159±67	270±56	131±47	8±4
210	1.76±0.77	155±103	252±142	130±58	9±8
240	1.64±0.97	110±82	221±117	113±48	10±5
270	1.28±0.50	67±94	153±66	104±26	10±4
300	1.04±0.52	40±68	139±70	96±28	7±4
330	1.18±0.35	44±55	124±42	85±19	7±3
360	1.22±0.97	51±88	118±98	81±29	8±6
Average post insulin					
150 - 240	1.80±0.79	128±89	239±112	128±59	10±6
150 - 360	1.49±0.76	89±90	186±106	109±49	9±5

Dog #11 Average results of seven six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5 units of insulin per kilogram intravenously at 120 minutes.

TABLE 16

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.79±0.52	-58±94	78±52	99±59	3±4
60	0.77±0.42	-70±86	72±47	100±55	5±4
90	0.60±0.38	-85±70	45±46	93±44	5±4
120	0.94±0.38	-71±63	70±44	123±64	7±5
Average basal	0.78±0.44	-71±79	66±49	103±57	5±5
150	1.32±0.91	6±129	138±122	117±78	8±7
180	2.55±1.47	237±214	307±171	129±81	12±9
210	2.36±1.31	214±185	289±161	109±63	14±10
240	2.10±1.12	173±148	248±123	107±69	14±10
270	1.48±0.77	82±104	176±94	103±56	9±10
300	1.25±0.77	47±104	143±91	101±56	7±5
330	1.14±0.91	47±115	114±102	111±84	7±7
360	0.96±0.72	23±86	89±71	83±53	6±5
Average post insulin					
150 - 240	2.09±1.30	157±193	245±159	115±73	12±9
150 - 360	1.65±1.17	103±164	188±69	108±69	10±9

Dogs #7, 8, 9, 10, 11 Average results of thirty-three six-hour experiments in five dogs with Pavlov pouches. The stimulus was 0.5 units of insulin per kilogram given intravenously at 120 minutes.

TABLE 16A

DOG	BASAL		POST-INSULIN			
	0 - 120 min.		150 240 min.		150 - 360 min.	
	H	Na	H	Na	H	Na
7	-134	93	-39	62	-35	56
8	-120	78	- 7	95	-36	91
9	-125	124	-87	104	-85	103
10	-219	176	-187	194	-167	185
11	-125	137	-111	128	- 97	109
All dogs	-137	103	- 88	115	- 85	108

Dogs #7, 8, 9, 10, 11 Comparison of pre- and post-insulin hydrogen and sodium ionic fluxes in five dogs with Pavlov pouches. The hydrogen ion loss is a calculated value while the sodium gain is an actual measurement. Post-insulin averages are given for the first two hours and the total four hours. Ionic fluxes are in microequivalents per 30 minutes.

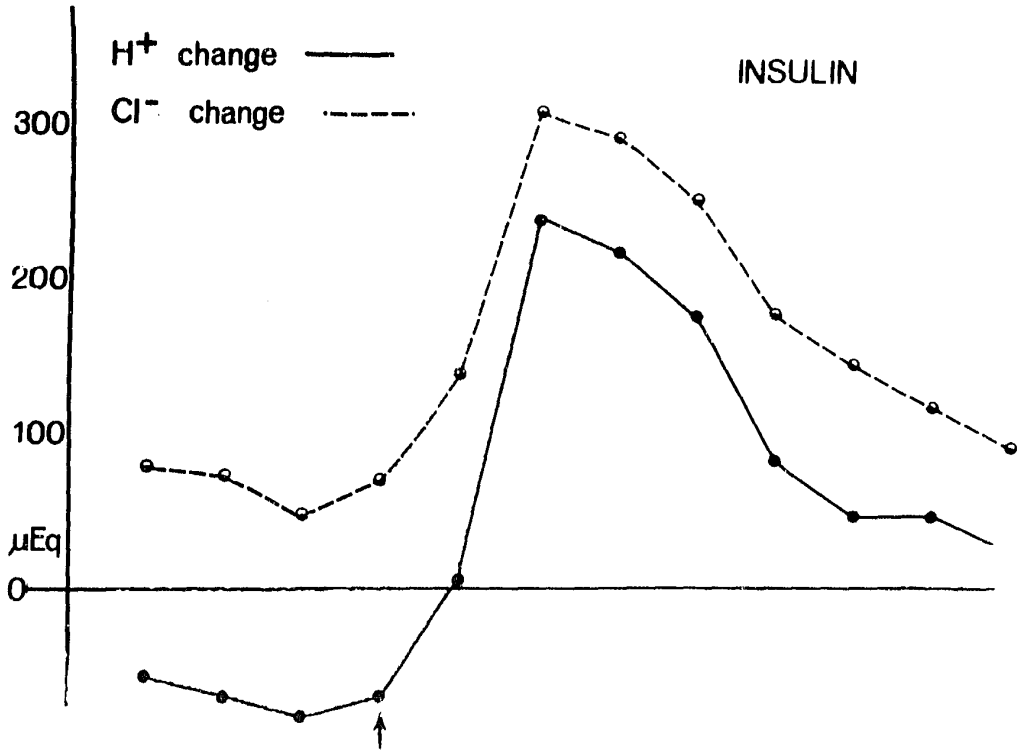

FIGURE 9 Graphic representation of H^+ and Cl^- ionic fluxes per 30 minutes before and after inducing insulin hypoglycemia in five dogs with Pavlov pouches. Points on the graph represent average basal and post-stimulation values taken from Table 16. The stimulus time was 120 minutes as depicted by the arrow.

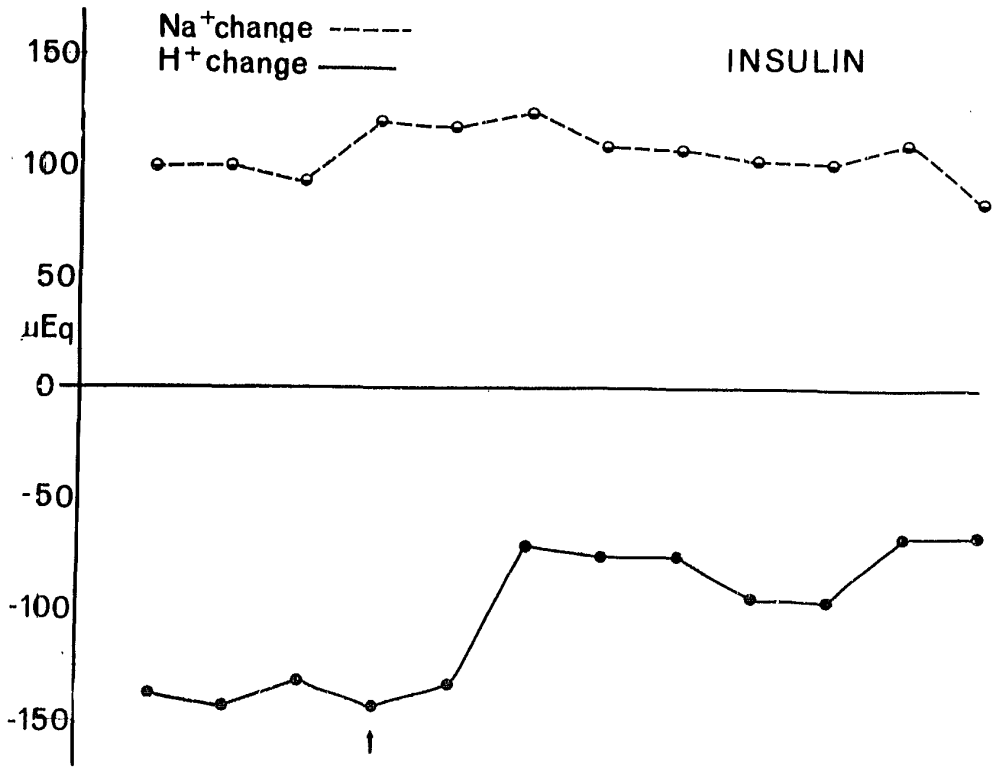

FIGURE 10 Graphic representation of H^+ and Na^+ ionic fluxes per 30 minutes before and after inducing insulin hypoglycemia in five dogs with Pavlov pouches. Points on the graph represent average basal and post-stimulation values taken from Table 16. The stimulus time was 120 minutes as depicted by the arrow.

E. The effect of exogenous gastrin on volume and ionic changes in Pavlov pouches

Four of the five dogs with Pavlov pouches used in the previous experiment were available for this one. Dog #8 died of intestinal obstruction. The dogs were given gastrin 0.5 cc. subcutaneously (containing 5 gm. of hog antral mucosa). The gastrin was supplied by Dr. R.M. Preshaw who prepared it from hog antral mucosa after a modification of the method of Gregory and Tracy.[22] This preparation was found to produce a maximal acid secretory response when given in a dose of 0.5 cc./hr. intravenously in dogs prepared with gastric fistulae. A total of twenty-two experiments were carried out in these four dogs with Pavlov pouches. The results for individual dogs are recorded in Tables 17 - 20 and the total averages for all four dogs are recorded in Table 21.

The stimulus used did not produce a maximal acid response but did give a secretory response comparable to the dose of insulin used in the previous experiment. The basal secretion was 0.82 ml./30 min. which is not significantly different from 0.78 ml./30 min., obtained in the basal periods prior to giving insulin. The average secretory response in four dogs given gastrin was 1.63 ml./30 min. for four hours

after stimulation. The comparable average for the insulin series of experiments was 1.65 ml./30 min. The chloride gain by the pouch followed closely the change in volume secreted with the peak value for both occurring during the third half-hour period (time 210 min.). All increases in secretion and chloride gain post-gastrin were highly significant (p less than 0.001) except for values at 330 and 360 minutes which would indicate that stimulation of acid secretion was sustained for only 3 hours.

A comparison of pre- and post-gastrin hydrogen and chloride ionic fluxes has been graphically illustrated in Figure 11. The hydrogen ion loss per 30 minutes is calculated for any given time by measuring the distance between the chloride and hydrogen curves at that time. This represents the difference between chloride and hydrogen ionic fluxes per 30 minutes. The calculated hydrogen loss under basal conditions was 127 ueq./30 min., for the first two hours post-gastrin it was 30 ueq./30 min. and for the total four hours post-gastrin it was 52 ueq./30 min. Both post-gastrin values show a highly significant difference from the pre-gastrin average (p less than 0.001). The basal calculated hydrogen loss of 127 ueq./30 min. is not significantly different from that found in the insulin series of experiments (137 ueq./30 min.

A comparison of the calculated hydrogen loss and measured sodium gain per 30 minute period is shown graphically in Figure 12. The average sodium gain for the first two hours post-gastrin was 65 ueq./30 min. and for the total four hours was 66 ueq./30 min. Both values are significantly different from the average basal sodium gain of 95 ueq./30 min. (p less than 0.001). However, the calculated hydrogen ion loss under basal conditions of 127 ueq./30 min. is significan different from the measured sodium ion gain of 95 ueq./30 min. (p less than 0.001). In the post-gastrin period, the first two hours showed a significant difference between the calculated hydrogen ion loss of 30 ueq./30 min. and the measured sodium ion gain of 65 ueq./30 min. (p less than 0.01), but there was no significant difference between the two for the total four hours post-gastrin. (52 ueq./30 min. compared to 66 ueq./30 min.).

In this series of experiments there was a disparity between the calculated hydrogen loss and measured sodium gain under basal conditions which was not apparent if the averages for the total four hours post-gastrin were compared. However, the competency of the mucosal barrier to hydrogen and sodium ions did increase after gastrin as reflected by either the calculated hydrogen loss or the measured sodium gain.

TABLE 17

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.62±0.33	-103±81	62±39	55±14	4±3
60	0.59±0.31	-21±23	51±26	82±26	7±7
90	0.88±0.21	-51±88	63±28	97±33	8±2
120	0.93±0.42	-82±74	74±27	85±28	9±3
Average basal	0.76±0.34	-65±74	62±30	80±29	7±5
150	1.66±0.48	142±100	177±70	68±32	22±11
180	2.81±1.59	404±248	388±188	42±15	27±10
210	2.77±1.21	342±192	337±158	69±18	34±25
240	2.00±0.87	248±182	240±96	75±17	19±7
270	0.72±0.35	-2±61	82±29	59±20	8±6
300	0.65±0.29	-17±65	63±33	71±19	7±3
330	0.54±0.28	-55±84	49±25	62±18	6±2
360	0.83±0.12	-3±23	70±17	63±32	6±2
Average post gastrin					
150 - 240	2.31±1.16	284±202	286±152	64±24	25±15
150 - 360	1.50±1.17	132±213	176±155	64±23	16±14

Dog #7 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5cc. of gastrin subcutaneously at 120 minutes.

TABLE 18

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.52±0.19	-50±93	63±34	59±36	4±3
60	0.81±0.54	-20±73	72±51	94±34	8±7
90	0.83±0.29	-55±43	54±33	69±46	5±5
120	0.72±0.35	-47±57	59±40	96±27	10±4
Average basal	0.72±0.36	-43±66	62±38	80±38	7±5
150	0.72±0.44	-27±52	81±53	67±20	10±3
180	1.10±0.38	76±70	124±33	37±26	16±3
210	1.04±0.44	116±71	134±49	34±21	15±3
240	1.26±0.77	126±97	171±80	32±14	19±5
270	1.15±0.62	59±106	135±68	69±44	17±7
300	0.93±0.57	49±85	93±67	62±24	9±8
330	0.38±0.17	-6±6	31±21	33±15	6±4
360	0.25±0.20	-21±51	16±20	20±11	3±2
Average post gastrin					
150 - 240	1.03±0.53	73±93	127±62	43±24	15±5
150 - 360	0.85±0.57	48±86	98±71	44±28	12±7

Dog #9 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5cc. of gastrin subcutaneously at 120 minutes.

TABLE 19

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.89±0.46	-127±119	92±49	170±89	3±3
60	1.35±0.29	-59±95	132±13	163±40	3±3
90	1.05±0.59	-35±116	105±52	176±119	10±4
120	1.08±0.34	-80±157	87±72	167±63	4±2
Average basal	1.09±0.43	-75±116	104±49	169±74	5±4
150	2.70±1.20	209±269	332±178	98±48	7±4
180	3.02±1.51	309±373	375±214	121±71	10±8
210	3.45±1.69	342±276	394±213	121±21	8±6
240	2.10±0.98	85±226	234±137	133±68	10±4
270	1.93±0.83	118±132	208±101	95±40	6±1
300	1.63±0.57	61±124	175±68	90±18	6±2
330	1.91±0.95	73±94	216±113	137±59	5±3
360	1.79±0.39	4±59	180±41	139±71	6±4
Average post gastrin					
150 - 240	2.82±1.33	236±280	334±180	118±51	9±5
150 - 360	2.32±1.15	150±225	264±154	117±51	7±4

Dog #10 Average results of four six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5cc. of gastrin subcutaneously at 120 minutes.

TABLE 20

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	1.23±0.84	-11±120	107±96	69±22	4±3
60	0.74±0.52	-49±64	79±49	86±9	8±7
90	0.58±0.30	-53±59	49±31	82±16	7±4
120	0.65±0.52	-60±64	49±35	74±7	6±3
Average basal	0.80±0.60	-43±78	70±61	78±15	6±4
150	1.28±0.54	83±99	166±89	71±12	20±6
180	3.23±1.38	426±245	388±191	54±32	27±20
210	3.46±1.22	484±179	455±151	43±26	26±15
240	3.34±0.63	465±114	414±80	48±8	24±12
270	2.20±0.67	242±110	271±95	62±30	13±8
300	1.20±0.65	127±95	164±75	57±18	11±2
330	1.05±0.32	36±67	102±28	63±29	9±1
360	0.98±0.34	11±50	87±35	58±15	10±5
Average post gastrin					
150 - 240	2.83±1.31	365±230	356±170	54±23	24±14
150 - 360	2.09±1.28	234±225	256±170	57±23	17±12

Dog #11 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 0.5cc. of gastrin subcutaneously at 120 minutes.

TABLE 21

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.81±0.56	-68±105	80±60	81±59	4±3
60	0.83±0.49	-35±63	79±46	101±40	7±6
90	0.82±0.36	-50±71	63±39	100±65	7±4
120	0.82±0.42	-66±82	65±42	100±45	7±4
Average basal	0.82±0.46	-55±82	72±47	95±53	6±5
150	1.49±0.92	92±152	176±125	74±29	16±9
180	2.50±1.49	303±268	313±195	58±46	21±13
210	2.61±1.49	319±220	324±186	62±38	22±17
240	2.18±1.09	244±208	268±131	67±46	19±9
270	1.46±0.84	103±135	171±103	69±34	11±7
300	1.06±0.60	54±100	119±75	68±22	8±5
330	0.89±0.70	6±79	89±83	68±46	7±3
360	0.88±0.58	-0±37	80±62	64±52	6±4
Average post gastrin					
150 - 240	2.19±1.32	240±231	270±170	65±40	19±13
150 - 360	1.63±1.20	140±204	192±156	66±40	14±11

Dogs #7, 9, 10, 11 Average results of twenty-two experiments in four dogs with Pavlov pouches. The stimulus was 0.5cc. of gastrin given subcutaneously at 120 minutes.

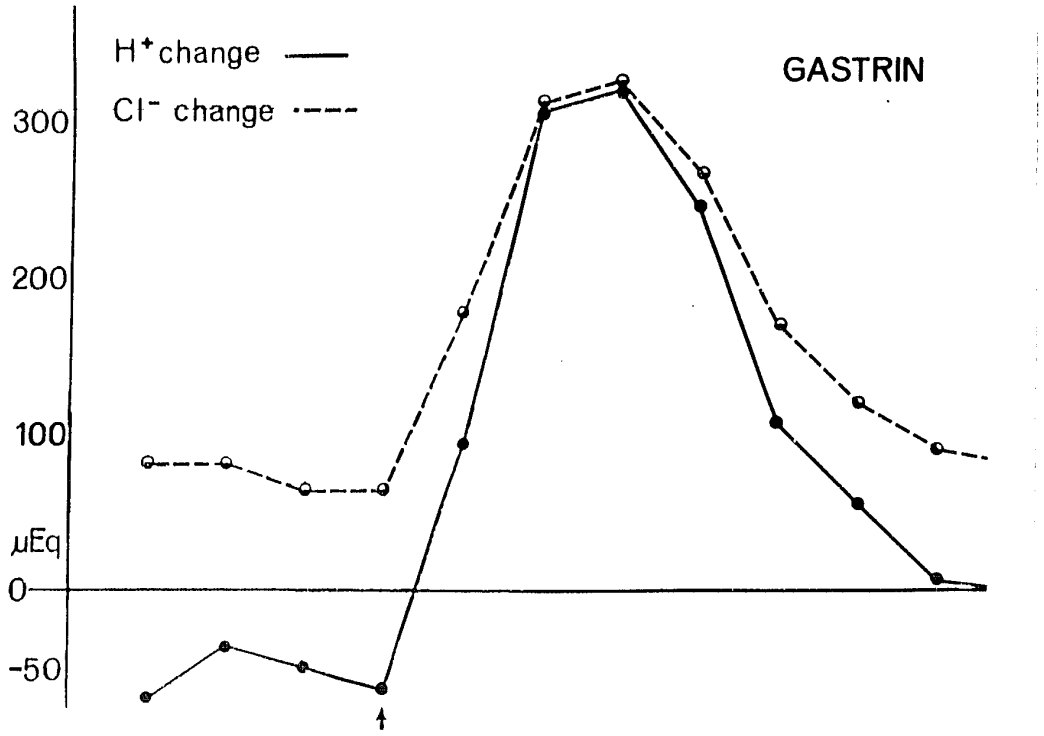

FIGURE 11 Graphic representation of H^+ and Cl^- ionic fluxes per 30 minutes before and after giving gastrin in four dogs with Pavlov pouches. Points on the graph represent average basal and post-stimulation values taken from Table 21. The stimulus time was 120 minutes as depicted by the arrow.

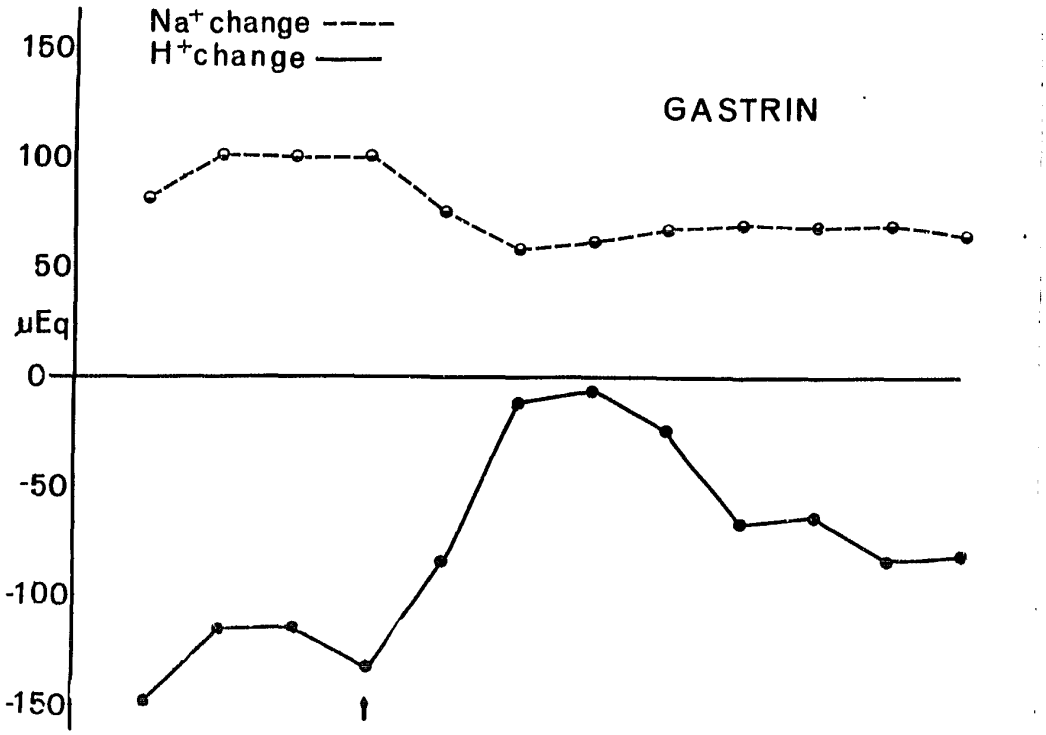

FIGURE 12 Graphic representation of H^+ and Na^+ ionic fluxes per 30 minutes before and after giving gastrin in four dogs with Pavlov pouches. Points on the graph represent average basal and post-stimulation values taken from Table 21. The stimulus time was 120 minutes as depicted by the arrow.

F. The effect of a synthetic gastrin on volume and ionic changes in Pavlov pouches

The synthetic pentapeptide ICI 50,123 has been used as a substitute for gastrin in experimental work.(23, It has a similar amino acid composition to gastrin and has been given to humans in doses ranging from 6 ugm./kgm. to 18 ugm./kgm. Six experiments were carried out in each of three dogs using a dose of 9 ugm./kgm. Dog #10 died of unknown cause after one experiment was carried out and was not included in these results. The results of individual dogs are recorded in Tables 21 - 24 and the average results of eighteen experiments in three dogs is presented in Table 25.

The average basal secretion for all three dogs as shown in Table 25 was 0.82 ml./30 min. which was comparable to that obtained in both the insulin and gastrin series of experiments. The secretory response after administration of the pentagastrin was greater than that obtained with either insulin or gastrin rising to 3.37 ml./30 min. for the first two hours and 3.10 ml./30 min. for the total four hours. Also, there was a considerable difference between the secretory responses of the three dogs (see Tables 21-24). The change in hydrogen ion flux within the pouch was more marked than with the other two stimuli, being 447 ueq./30 min. from average

basal to average 4 hours post-pentagastrin (-35 ueq./30 min. to 412 ueq./30 min.) The change in chloride flux was less than the change in hydrogen flux, being only 326 ueq./30 min. for the 4 hours post-pentagastrin. This difference is graphically illustrated in Figure 13 which shows that the average hydrogen gain to the pouch rises significantly higher than the chloride gain after administration of the pentagastrin. This must mean that either some hydrogen ions are secreted in a form other than hydrochloric acid or that some chloride ions are reabsorbed once they have been secreted.

A comparison of calculated hydrogen loss with measured sodium gain has been made in Figure 14. The calculated hydrogen ion change rises from an average basal loss of 104 ueq./30 min. to an actual average gain to the pouch of 17 ueq./30 min. during the 4 hours post-pentagastrin. This calculated gain of hydrogen ions is not significantly different from zero and may be interpreted as zero. In fact the calculated hydrogen loss in dogs 7 and 9 did approximate zero during the 4 hours post-gastrin (-5 ueq./30 min. and -9 ueq./30 min. respectively). Dog 11 showed a gain of hydrogen ions during the 4 hours post-pentagastrin which was significantly different from zero ($p < 0.001$). The sodium gain to the pouch shows a highly significant decrease

after pentagastrin both in individual dogs and for the average of all three dogs (p less than 0.001).

Thus the competency of the mucosal barrier is increased as determined by either calculated hydrogen ion loss or measured sodium gain. The former shows a more marked change than the latter and the difference between the two is highly significant (p less than 0.001). If there were neither a gain nor a loss of hydrogen ions occurring in a pouch, this would be interpreted as a state of complete competency of the mucosal barrier with no exchange of hydrogen for sodium ions taking place.

TABLE 22

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.82±0.62	-58±63	77±64	101±51	7±11
60	0.64±0.51	-48±62	63±42	97±28	1±9
90	0.64±0.20	-39±51	69±37	99±22	5±3
120	0.72±0.36	-37±52	61±46	97±10	8±6
Average basal	0.70±0.43	-45±54	68±46	98±29	5±8
150	2.55±0.54	281±94	328±82	78±20	33±5
180	4.20±0.77	613±79	543±67	71±24	51±10
210	4.92±0.79	700±114	621±100	88±33	48±8
240	3.31±0.83	472±136	456±117	61±14	34±7
270	2.64±0.53	343±60	338±59	88±32	36±11
300	2.18±0.93	211±88	245±80	70±21	16±4
330	1.75±1.05	129±102	188±110	90±52	16±11
360	1.37±0.59	68±39	137±56	66±32	11±5
Average post pentagastrin					
150 - 240	3.75±1.15	517±191	487±141	74±24	41±11
150 - 360	2.87±1.35	352±231	357±180	76±30	30±16

Dog #7 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 9.0 micrograms of pentagastrin per kilogram subcutaneously at 120 minutes.

TABLE 23

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.95±0.27	-4±61	92±31	93±37	7±7
60	0.96±0.67	-21±61	91±57	88±40	9±7
90	0.93±0.35	-21±48	68±61	76±25	8±3
120	0.90±0.57	-23±46	54±53	112±26	13±4
Average basal	0.93±0.46	-17±51	76±51	92±33	9±6
150	1.13±0.60	52±90	129±48	43±32	15±7
180	1.11±0.68	140±74	167±83	28±16	21±5
210	1.39±0.28	188±53	177±29	38±22	26±14
240	2.97±1.33	358±153	345±126	53±28	30±21
270	2.04±0.43	285±49	272±49	34±18	41±13
300	1.73±0.56	220±70	224±57	36±12	33±7
330	1.87±0.73	211±82	217±81	37±15	25±10
360	2.21±1.01	232±107	229±113	59±25	37±17
Average post pentagastrin					
150 - 240	1.65±1.10	185±147	205±114	41±25	23±14
150 - 360	1.81±0.92	211±120	220±97	41±23	28±14

Dog #9 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 9.0 micrograms of pentagastrin per kilogram subcutaneously at 120 minutes.

TABLE 24

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.84±0.45	-18±55	65±26	76±20	3±3
60	0.84±0.34	-53±98	81±41	69±15	3±5
90	0.43±0.27	-82±38	18±29	62±20	4±2
120	1.13±0.43	-11±82	92±27	99±18	9±9
Average basal	0.81±0.44	-41±73	64±41	77±22	5±6
150	2.65±0.92	315±148	345±121	61±22	32±15
180	4.62±1.43	708±222	609±200	62±15	37±20
210	5.82±1.54	892±244	758±211	49±36	51±17
240	5.77±1.39	889±145	795±138	44±29	54±14
270	6.55±2.27	1034±281	868±234	78±38	53±21
300	4.46±1.63	707±202	659±169	25±37	47±11
330	2.93±2.12	422±347	389±268	27±27	30±12
360	4.16±2.32	428±270	442±278	60±26	37±19
Average post pentagastrin					
150 - 240	4.71±1.81	701±301	627±241	54±26	43±18
150 - 360	4.62±2.09	674±332	608±268	51±32	43±18

Dog #11 Average results of six six-hour experiments in a Pavlov pouch preparation. The dog was given 9.0 micrograms of pentagastrin per kilogram subcutaneously at 120 minutes.

TABLE 25

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.84±0.45	-27±61	75±43	88±38	5±8
60	0.84±0.51	-40±72	81±46	87±30	5±7
90	0.67±0.34	-47±51	52±48	79±26	6±3
120	0.92±0.47	-24±59	69±44	103±19	10±7
Average basal	0.82±0.45	-35±61	69±46	89±30	6±7
150	2.11±0.97	216±161	267±131	61±28	27±13
180	3.31±1.87	487±288	439±235	54±26	36±18
210	4.04±2.18	593±340	519±285	58±36	42±17
240	4.02±1.71	573±271	532±230	53±24	39±18
270	3.74±2.42	554±384	493±305	67±37	43±17
300	2.79±1.63	380±269	376±232	44±31	32±15
330	2.18±1.45	254±238	265±187	51±44	24±12
360	2.58±1.85	243±220	269±211	62±27	28±19
Average post pentagastrin					
150 - 240	3.37±1.88	467±307	439±246	56±28	36±17
150 - 360	3.10±1.91	412±311	395±252	56±32	34±17

Dogs #7, 9, 11 Average results of eighteen six-hour experiments in three dogs with Pavlov pouches. The stimulus was 9.0 micrograms of pentagastrin per kilogram given subcutaneously at 120 minutes.

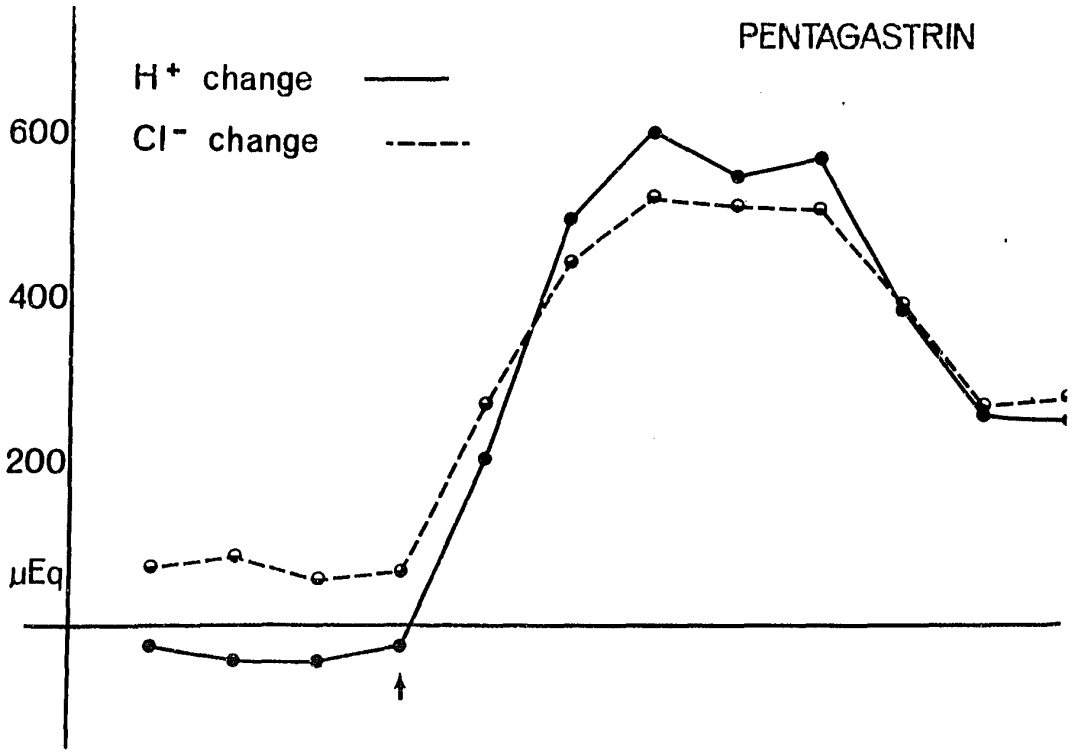

FIGURE 13 Graphic representation of H^+ and Cl^- ionic fluxes per 30 minutes before and after giving pentagastrin in three dogs with Pavlov pouches. Points on the graph represent average basal and post-stimulation values taken from Table 25. The stimulus time was 120 minutes as depicted by the arrow.

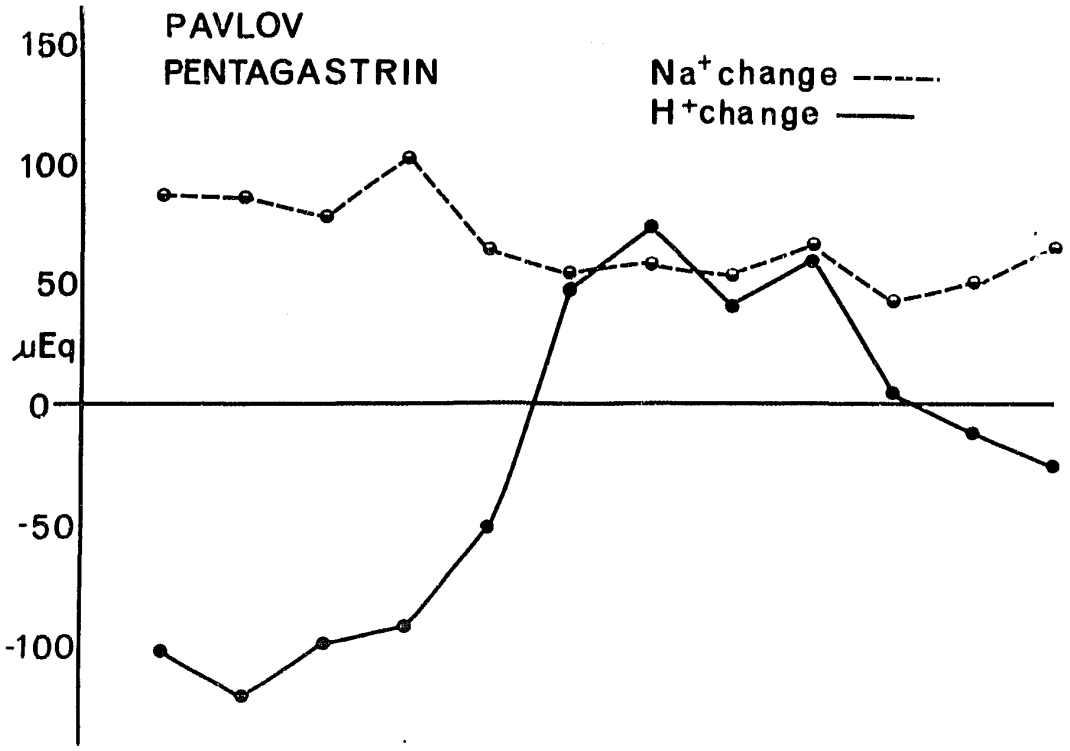

FIGURE 14 Graphic representation of H^+ and Na^+ ionic fluxes per 30 minutes before and after giving pentagastrin in three dogs with Pavlov pouches. Points on the graph represent average basal and post-stimulation values taken from Table 25. The stimulus time was 120 minutes as depicted by the arrow.

G. The effect of a synthetic gastrin on volume and ionic changes in Heidenhain pouches after antrectomy

The synthetic gastrin ICI 50,123 was given to three dogs with Heidenhain pouches and antrectomies in a dose of 9 ugm./kgm. The three dogs used in this series (1, 3 and 6) were the same ones used in the second feeding experiment on dogs with Heidenhain pouches and antrectomies. Six experiments were carried out in each of the three dogs. The results for the individual dogs are recorded in Tables 26 - 28 and the averages for all dogs in Table 29.

The average basal secretion for all dogs was 0.65 ml./30 min. This rose markedly to a peak of 5.28ml./30 min. during the second half-hour post-pentagastrin (180 minutes) with an average of 4.35 ml./30 min. during the first 2 hours after stimulation and 3.43 ml./30 min. for the entire 4 hours. There was considerable variation in the secretor response of the three dogs. It is interesting to note that the secretion rate in these Heidenhain dogs with antrectomies was greater than in the three dogs with Pavlov pouches.

A comparison of hydrogen and chloride ion changes is graphically shown in Figure 15. This graph closely resembles Figure 13 and shows a similar increase in hydrogen gain over the chloride gain at peak levels of secretion.

The ionic changes in hydrogen and sodium are graphically illustrated in Figure 16. Under basal conditions the calculated hydrogen ion loss was 125 ueq./30 min. which was not significantly different from the measured sodium gain of 113 ueq./30 min. The post-pentagastrin hydrogen flux actually showed a gain to the pouch of 26 ueq./30 min. in the first 2 hours after stimulation and a gain of 6 ueq./30 min. for the total 4 hours after stimulation. Both values are not significantly different from zero. The average sodium gain fell from a basal level of 113 ueq./30 min. to 92 ueq./30 min. during the first 2 hours post-pentagastrin ($p < 0.05$) and to 86 ueq./30 min. for the total four hours post-pentagastrin ($p < 0.01$).

In this series of experiments an ion for ion exchange of hydrogen for sodium could be demonstrated under basal conditions but not after stimulation. The competency of the mucosal barrier to sodium and hydrogen ions was increased as demonstrated by either the calculated hydrogen loss or the measured sodium gain, the former indicated a more marked competency than the latter. The ionic responses to pentagastrin in dogs with Heidenhain pouches and antrectomies were closely similar to those found in dogs with Pavlov pouches.

TABLE 26

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	1.55±0.81	-102±108	99±44	155±70	-2±15
60	0.77±0.30	-96±51	85±28	169±43	8±7
90	0.55±0.52	-102±79	59±29	145±99	6±6
120	0.65±0.34	-90±54	41±30	221±75	19±16
Average basal	0.88±0.64	-98±54	41±39	172±76	8±14
150	2.38±0.33	159±104	321±76	76±38	26±5
180	4.30±0.57	531±125	531±116	156±81	40±9
210	4.72±1.30	628±166	624±192	128±37	65±29
240	3.98±1.26	554±99	504±96	120±44	26±29
270	4.13±1.47	547±186	538±192	122±67	42±14
300	4.41±1.47	584±172	542±109	141±88	48±18
330	3.75±1.01	473±143	490±164	95±48	42±15
360	3.35±1.15	396±158	392±138	99±29	25±28
Average post pentagastrin	3.84±1.27 3.88±1.26	468±220 484±196	495±163 493±158	120±57 117±59	39±26 39±23

Dog #1 Average of six six-hour experiments in a Heidenhain pouch preparation after antrectomy. The dog was given 9.0 micrograms of ICI 50,123 per kilogram subcutaneously at 120 minutes.

TABLE 27

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.61±0.33	-55±77	50±52	102±61	2±7
60	0.79±0.54	9±52	95±60	107±22	6±4
90	0.58±0.38	-82±99	62±44	61±14	3±2
120	0.34±0.52	-71±59	21±39	100±54	6±4
Average basal	0.58±0.45	-50±78	57±53	92±44	4±5
150	1.62±0.67	82±147	227±100	115±65	28±15
180	3.49±1.10	470±164	470±136	93±62	49±18
210	3.46±2.07	440±315	479±268	87±45	34±34
240	2.86±1.75	377±188	374±169	111±67	43±18
270	1.77±0.58	203±64	240±87	71±51	22±9
300	1.62±1.01	200±121	212±137	61±45	15±11
330	1.14±0.54	107±85	121±73	44±17	16±10
360	1.72±1.14	176±162	174±127	83±33	25±17
Average post pentagastrin	2.86±1.60 2.21±1.42	342±254 257±213	387±197 287±188	102±58 82±52	38±22 29±20

Dog #3 Average of six six-hour experiments in a Heidenhain pouch preparation after antrectomy. The dog was given 9.0 micrograms of ICI 50,123 per kilogram subcutaneously at 120 minutes.

TABLE 28

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.67±0.72	-73±105	55±40	77±54	1±4
60	0.43±0.29	-27±40	43±26	65±34	5±3
90	0.43±0.50	-67±76	43±46	89±46	8±5
120	0.42±0.39	-60±73	28±53	71±76	2±4
Average basal	0.49±0.48	-57±74	42±41	76±52	4±5
150	3.52±1.93	515±305	495±256	54±18	53±18
180	8.04±1.66	1222±264	987±219	84±36	91±16
210	7.87±1.37	1240±258	1007±112	47±38	86±13
240	5.93±2.06	919±359	806±232	36±30	57±26
270	3.98±2.77	570±439	565±290	37±30	36±29
300	2.17±1.39	287±269	288±180	74±48	24±19
330	1.21±1.22	117±179	153±161	46±27	8±16
360	0.89±0.65	1±108	105±64	76±28	11±9
Average post pentagastrin	6.34±2.49 4.20±3.11	974±410 609±524	824±288 551±386	55±34 57±35	72±24 46±35

Dog #6 Average of six six-hour experiments in a Heidenhain pouch preparation after antrectomy. The dog was given 9.0 micrograms of ICI 50,123 per kilogram subcutaneously at 120 minutes.

TABLE 29

Time (min.)	Volume secreted (ml.)	QH^+ (ueq.)	QCl^- (ueq.)	QNa^+ (ueq.)	QK^+ (ueq.)
30	0.94±0.76	-77±94	68±49	11±67	0±9
60	0.66±0.41	-38±64	74±45	114±54	7±5
90	0.52±0.45	-84±81	55±39	98±70	6±5
120	0.47±0.42	-74±60	30±40	130±93	9±12
Average basal	0.65±0.55	-68±76	57±46	113±72	6±9
150	2.51±1.38	252±273	348±192	82±49	36±18
180	5.28±2.33	741±395	662±283	111±67	60±27
210	5.35±2.44	769±425	703±297	87±51	61±34
240	4.25±2.08	617±324	561±248	89±60	42±27
270	3.29±2.05	440±313	448±246	77±61	34±20
300	2.74±1.75	357±251	348±199	92±70	29±21
330	2.03±1.54	232±220	255±216	62±42	22±20
360	1.99±1.41	191±215	224±166	86±30	20±20
Average post pentagastrin	4.35±2.36 3.43±2.27	595±408 450±373	569±288 444±286	92±57 86±55	50±29 38±27

Dogs #1, 3, 6 Average of eighteen six-hour experiments in a Heidenhain pouch preparation after antrectomy. The dogs were given 9.0 micrograms of ICI 50,123 per kilogram subcutaneously at 120 minutes.

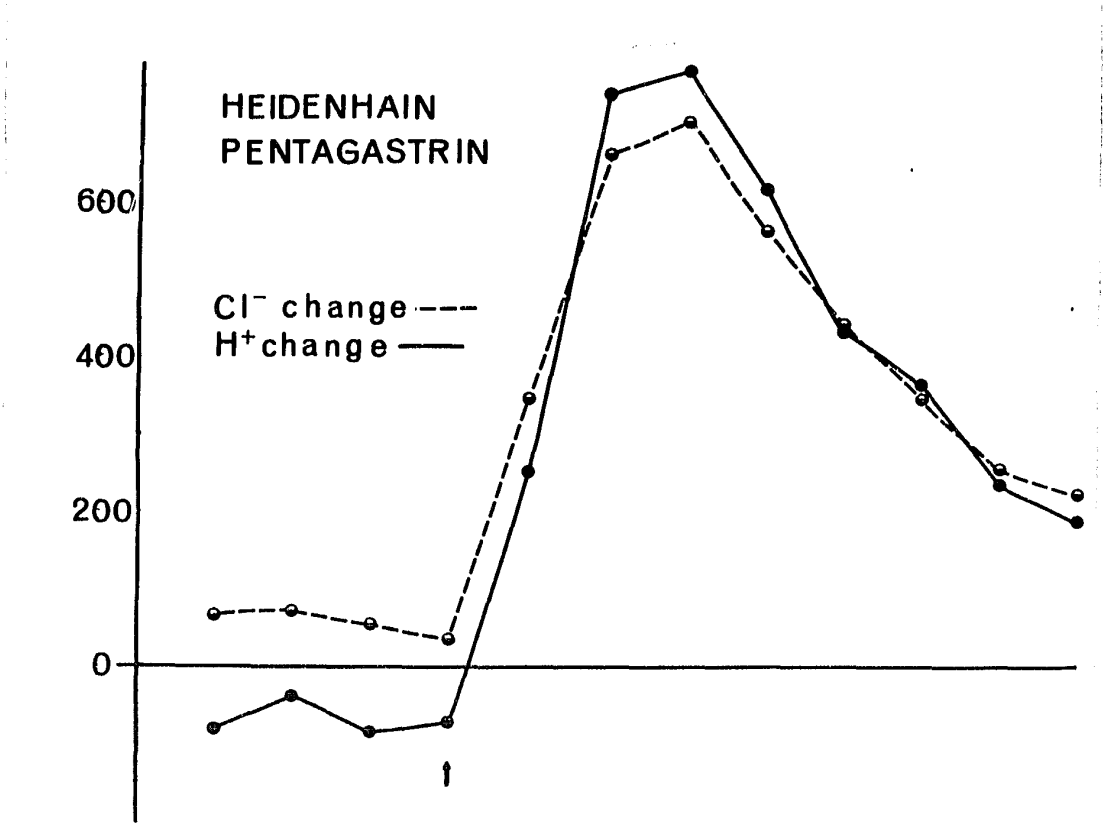

FIGURE 15 Graphic representation of H^+ and Cl^- ionic fluxes per 30 minutes before and after giving pentagastrin in three dogs with Heidenhain pouches and antrectomies. Points on the graph represent average basal and post-stimulation values taken from Table 29. The stimulus time was 120 minutes as depicted by the arrow.

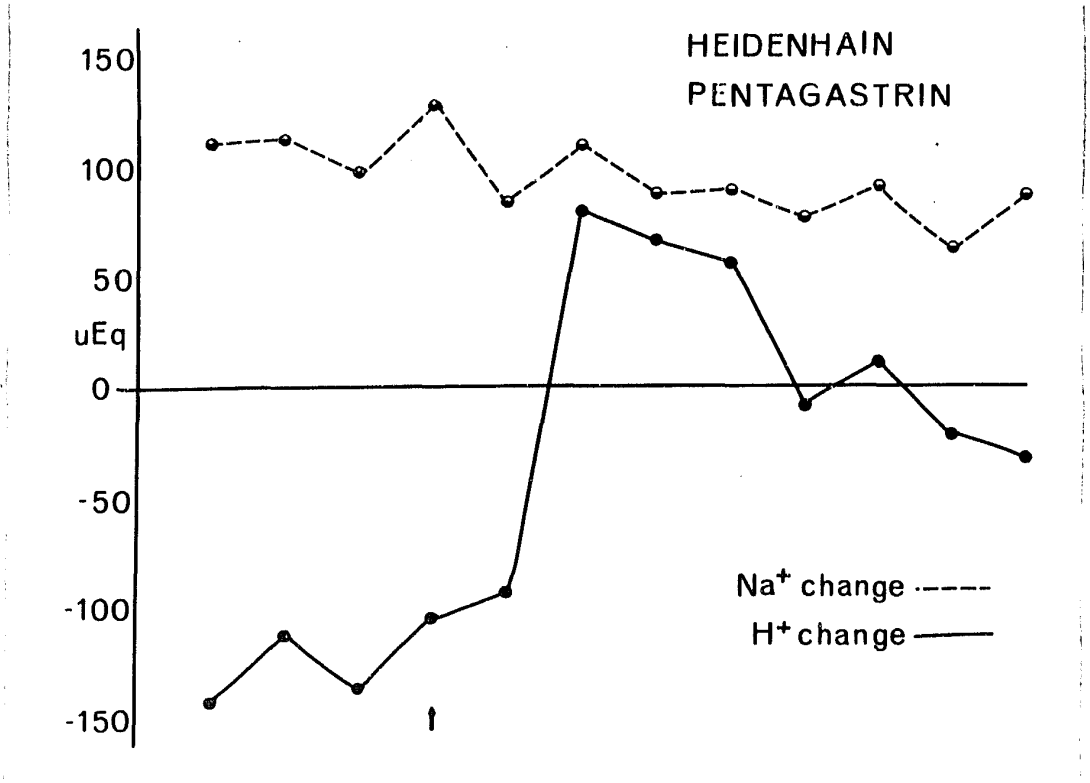

FIGURE 16 Graphic representation of H^+ and Na^+ ionic fluxes per 30 minutes before and after giving pentagastrin in three dogs with Heidenhain pouches and antrectomies. Points on the graph represent average basal and post-stimulation values taken from Table 29. The stimulus time was 120 minutes as depicted by the arrow.

IV. DISCUSSION

A. Validity of the experimental model

As already mentioned, the experimental model used in this thesis was gradually worked out during the past five years by Wlodek and Leach culminating in its report in 1966.[12] The use of polyethylene glycol as a marker substance by Wlodek and Leach in 71 experiments with canine gastric pouches gave a total average recovery of 99.9% with a standard deviation of ±1.8%. This recovery rate was a distinct improvement on those found by investigators using other marker substances, such as phenol red, and it permits a very accurate measurement of volume and ionic changes in gastric pouches.

Polyethylene glycol meets all the physical and physiological criteria of an ideal marker substance. It is a readily soluble, non-irritating, clear, colourless compound that can be used in small quantities so as to reduce any osmotic effects and is easily and accurately measured. Also, it has been shown to be non-absorbable, resist digestion by acid or pepsin, and have no affinity for gastric mucous.[12] The turbimetric method previously used for measuring polyethylene glycol [57] was sufficiently accurate, but it was found to be a tedious and lengthy technical procedure. The addition of

C^{14} to this marker substance has greatly facilitated its measurement while maintaining the highly accurate rate of recovery found with the non-radioactive polyethylene glycol. In this series of experiments recovery of polyethylene glycol $-C^{14}$ between 98% and 102% was considered acceptable and only results in this range were included.

The inherent disadvantages and errors in the external measurement of acid secretion by the straight drainage technique has been alluded to in the introduction to this thesis. The various attempts to overcome these difficulties have also been previously mentioned. The experimental model developed by Wlodek and Leach has the great advantage of combining simplicity with accuracy. The use of an accurate marker substance permits the initial instillation of an acid solution into a gastric pouch with the subsequent removal of a constant aliquot at given time intervals. In this manner, the in situ volume and ionic fluxes are easily and accurately measured without the necessity of repeated emptying of pouch contents and washing out of the pouch that is required by other experimental models such as the one originated by Davenport et al.[5]

A criticism of any experimental model that involves filling a gastric pouch with a solution is that the distension

of the pouch so produced will stimulate acid secretion. This was shown to occur in both innervated and denervated pouches in 1962 by Grossman.[10] The volume secreted under basal conditions in these experiments was 25% to 50% higher in both Heidenhain and Pavlov pouches than results recorded using the method of simple drainage.[15] However, the solution used in this experimental model was always allowed to equilibrate between the pouch and the syringe reservoir at a constant pressure of 10 cm. of water (see Figure 1). The reservoir syringe was maintained at a constant level of 10 cm. above the pouch and mixing of reservoir content with pouch contents was carried out for five minutes prior to the removal of each aliquot by alternately lowering and raising the reservoir syringe to 10 cm. below and then 10 cm. above the pouch. The method of mixing reservoir with pouch contents and the resting level of the reservoir syringe in the interval between removal of aliquots were carefully kept constant. The pouch was only washed once at the end of each experiment and the washing solution used in the determination of the percentage recovery of the marker substance. In this manner it was felt that the effects of pressure on acid secretion, which are otherwise unavoidable in this type of experimental model, were maintained constant from experiment to experiment

and between basal and post-stimulation conditions. Thus the effects of pressure on acid secretion are present in these experiments, but the errors produced are felt to be sufficiently constant not to invalidate the results. The effects of distension on a gastric pouch are much more difficult to control in experimental models where instillation of a new solution and subsequent repeated washings are carried out for each time interval.

B. The non-parietal component of gastric secretion

For decades investigators have sought to characterize quantitatively the secretion of electrolytes in the stomachs of man and animals. As outlined above, the interpretation of the electrolyte contents of gastric secretion used in this thesis has been based on the model proposed by Teorell[9, 43] in which a primary parietal secretion is altered by the back-diffusion of hydrogen ions and their replacement by sodium ions. The two-component hypothesis of gastric secretion is an alternative model formulated by Hollander [58, 59] which maintains that variations in electrolyte content are the outcome of a mixture of a parietal acid secretion and a non-parietal alkaline secretion.

The exact composition of this non-parietal component, both qualitatively and quantitatively, has been variously

postulated. Hollander believes that it is an isotonic solution similar to interstitial fluid the principal constituents of which are neutral chlorides and bicarbonates, the concentration of the former being appreciably greater than that of the latter.[58] By extrapolation he estimated that the alkaline component of gastric secretion is composed of HCO_3^- 25 meq./liter and Cl^- 125 meq./liter. Fisher and Hunt [60] analyzed the work of Ihre [61] on gastric secretion in selected young men in response to histamine or insulin and postulated a HCO_3^- of 40-45 meq./liter and a Cl^- of 100meq./liter. Gray and Bucher [62] have estimated that the non-parietal secretion consists of HCO_3^- 33.0 meq./liter, Cl^- 133.3 meq./liter, Na^+154.5 meq./liter, K^+7.4 meq./liter and Ca^{++}3.7 meq./liter. As can easily be appreciated from the above results, the estimations put forth for the concentrations of bicarbonates and neutral chloride in the hypothetical non-parietal secretion vary considerably depending on the investigator. In addition, these values have all been derived by extrapolation from regression equations and curves. This is an indirect method of measurement and relies upon numerous assumptions which have no quantitative basis since the composition of an alkaline solution has been extrapolated from data obtained during secretion of an acid solution.

Teorell attempted to isolate a neutralizing non-parietal secretion in the rat's stomach but was unable to detect any CO_2 evolution or bicarbonate content from basal gastric secretion.(63) Babkin et al (64) claimed they had directly measured the bicarbonate content of the non-parietal component of gastric secretion. Close reference to their experimental method reveals that secretion was obtained after treating the stomach with acetic acid and alcohol. It is now known that acetic acid damages the gastric mucosal barrier and increases the exchange of intraluminal hydrogen ions for interstitial sodium ions.(65) Thus their results are more reasonably explained on the basis of damage to the gastric mucosa with a decrease in the competency of the mucosal barrier and a loss of interstitial fluid into the lumen of the stomach.

Recent experiments by Altamirano are frequently quoted as demonstrating the presence of bicarbonate in the alkaline component of gastric secretion by direct measurement.(66 His technique depended on acetylcholine given intra-arterially in such massive doses that acid secretion was inhibited and the mucosal secretion became alkaline with a bicarbonate and protein content equal to plasma levels. This is interpreted as a transudate from blood since the alkaline solution could

be completely inhibited by increasing the hydrostatic pressure to the gastric mucosa. It seems unlikely that this represents a physiological alkaline secretion occurring at basal levels, but rather an effect of massive and unphysiological doses of acetylcholine on the gastric mucosa.

The significance of the hypothetical neutral chloride secretion is not at all clear. Many authors continuously refer to "neutral chloride" without giving any indication as to which cation is entering the stomach with chloride. Presumably the predominant cation associated with chloride in a neutral state would be sodium. If this is the case then any interpretation of our results on the basis of Teorell's hypothesis would not be affected by the presence of "neutral chloride" (see Figures 3 and 4).

Berkowitz and Janowitz recently measured volume and ionic changes in vagally denervated canine fundic pouches using phenol red as their dilution indicator.(67) They believe that there must exist within the stomach, mechanisms of a physiologic and protective nature, which reduce the initially high hydrogen ion concentration secreted by the parietal cell. This is in accordance with the basic concept of gastric acid secretion outlined in the introduction to this thesis. After instilling iso-osmotic hydrochloric

acid into the pouches under resting conditions, they observed a progressive decline in hydrogen ion concentration of the retrieved fluid over a four hour period which was accompanied by an equivalent rise in sodium ion concentration. The chloride ion declined slightly over the four hour period. They felt that the hydrogen ion reduction could be accounted for in part by a diffusional exchange of hydrogen for sodium as originally suggested by Teorell.[9, 43, 63] The composition of the non-parietal secretion could not be calculated from their studies since they felt that chloride ions were probably simultaneously leaving and entering the pouch at variable and as yet unknown rates. However, applying 25 meq./liter as the quantitative value for HCO_3^- in the non-parietal secretion to their results and also to those of Hollander,[59] Fisher and Hunt,[60] and Altamirano,[64] they concluded that neutralization by bicarbonate could account for only a fraction of the total hydrogen loss. Their studies indicated that the presence of a non-parietal neutralizing solution, as postulated by Hollander,[58] and back-diffusion of hydrogen ions with exchange for sodium ions, as postulated by Teorell,[9, 43, 63] may both be operative in reducing the primary acidity of the stomach. However, their results

suggested that either process alone was unable to completely account for the reduction in hydrogen ion and they were unable to assign a quantitative significance to their relative importance.

C. The effect of feeding in Heidenhain pouches before and after antrectomy

In previous experiments, Wlodek and Leach showed that the competency of the mucosal barrier to hydrogen and sodium ions was markedly increased in Heidenhain and Pavlov pouches after histamine stimulation and in Pavlov pouches after feeding.[52, 53] This was evident whether the competency was measured as the hydrogen loss or the sodium gain to the pouch. Under basal levels of secretion it was found that the rate at which hydrogen ions were lost from the pouch closely equalled the rate at which sodium ions entered the pouch. This apparent ion for ion exchange of hydrogen for sodium persisted after histamine or feeding although the exchange process diminished after stimulation. The reduction in the ionic exchange of hydrogen for sodium after feeding was approximately 30% and after histamine stimulation approximately 60%. As feeding was only given to dogs with Pavlov pouches it was impossible to assess the relative effects

of vagal excitation and gastrin release on the competency of the mucosal barrier. It was therefore decided to conduct a series of feeding experiments in Heidenhain pouches to determine the effect of antral stimulation on the mucosal barrier.

The construction of Heidenhain pouches used in this series of experiments was accomplished by simply isolating a portion of fundic mucosa which retained its vascular and nervous connection to the splenic pedicle. This type of denervated pouch has not been completely detached from its vagal innervation because of the small residual nervous supply reaching it via the splenic pedicle. A transplanted fundic pouch would eliminate all vagal innervation but the technical difficulties involved prohibited the use of this pouch preparation for the length of time required to carry out these experiments.

Feeding in five Heidenhain pouches produced a small but insignificant increase in the volume of secretion. There was also an increase in chloride gain to the pouches which was significant but not marked. Antral stimulation has been shown to produce only slight acid secretion in a denervated pouch similar to the response obtained in these dogs.[32]

Despite the small amount of secretion there was a pronounced decrease in the exchange of hydrogen for sodium ions across the gastric mucosa. This amounted to a 30% decrease as determined by either calculated hydrogen loss or measured sodium gain which is closely similar to that found by Wlodek and Leach in their feeding experiments in Pavlov pouches.(53) The calculated hydrogen ion loss was not significantly different from the measured sodium ion gain under basal conditions or after feeding. At this point it was felt that antral stimulation, with the subsequent release of gastrin, caused an increased competency of the mucosal barrier thus reducing the exchange of hydrogen for sodium ions on an ion for ion basis. The apparent increase in acid secretion observed after antral stimulation was then due mainly to an increase in the ability of the gastric mucosa to contain hydrogen ions rather than a direct effect on the parietal cell.

To explore this hypothesis further these dogs were subjected to antrectomy. Unfortunately, dogs 2, 4 and 5 did not survive long enough to be included in this series and a dog (#6) with both a Heidenhain and an antral pouch in which the antral pouch had been excised was used along with dogs 1 and 3 for this series of experiments. There was no

significant change in volume secreted or chloride gain after feeding in these dogs. However, the competency of the mucosal barrier did increase by about 30% - comparable to the change observed in the dogs with Heidenhain pouches and intact antrums. In these dogs the ability of the gastric mucosa to contain hydrogen ions improved after feeding inspite of no significant acid secretion.

The hormone gastrin may have a role in the control of the mucosal barrier to hydrogen and sodium ions. However, these experiments demonstrated that intestinal or pancreatic factors probably also play a part in the acidity control of the stomach.

D. The Effect of insulin hypoglycemia and gastrin in Pavlov pouches

Wlodek and Leach demonstrated that the administration of insulin resulted in acid secretion but no increase in the ability of a Pavlov pouch to contain an acid solution.(53) The purpose of these two series of experiments was to confirm these findings and at the same time compare the effect of gastrin and insulin hypoglycemia on the compentency of the gastric mucosal barrier. Insulin hypoglycemia is not the best method of experimentally imitating vagal stimulation, but sham feeding

requires a permanent esophagostomy which is a difficult preparation to keep alive for the length of time involved in completing these experiments.

The observation that insulin hypoglycemia has no effect on the net flux of sodium is not new. Investigators have shown that the amount of sodium in gastric secretion stimulated by cholinergic mechanisms does not decrease per unit time in spite of increased acid secretion. These findings have been minimized and often attributed to a failure to decrease the neutral chloride secretion. Ridley examined the electrolyte content from gastric fistulae in rats under basal conditions and after insulin hypoglycemia and histamine.(68 The acid secretion and sodium content increased significantly after insulin hypoglycemia. Following histamine stimulation the acid secretion increased but the sodium content decreased. Piper et al studied humans undergoing insulin shock therapy.(69) The electrolyte content of the gastric secretion showed no decrease in sodium content after insulin. Parker et al studied a patient with obstruction of the esophagus and was able to obtain gastric juice uncontaminated by saliva via a gastrostomy tube. The sodium content showed a marked fall after histamine but was found to rise after mecholyl and showed no significant change after sham feeding.

In 1950 Fisher and Hunt made an attempt to account quantitatively for variations reported in the composition of gastric juice. These workers used Ihre's (1938) data on the composition of gastric secretion in young men after histamine and insulin hypoglycemia and analysed his reported figures. They used the results in the support of the two-component theory of gastric acid secretion and documented the significant observation that the gastric juice secreted after insulin and histamine stimulation differed in that the neutral chloride content of the secretion after insulin hypoglycemia was significantly higher than that following histamine. Their observations may also be interpreted as signifying that insulin increased acid secretion but failed to increase the competency of the stomach to contain the hydrogen ions and resulted in an increase rather than a decrease in the exchange of hydrogen for sodium ions across the mucosal barrier.

An attempt was made to produce a comparable secretory response with insulin hypoglycemia and exogenous gastrin which was highly successful (compare Tables 16 and 21). Insulin hypoglycemia did not affect the competency of the mucosal barrier as determined by the measured sodium gain. This competency was significantly increased ($p < 0.05$)

as shown by the calculated hydrogen loss during the first two hours post-insulin, but there was no significant change over the total four hour period post-insulin (see Figure 10). The dose of insulin used in these experiments was 0.5 units per kilogram compared to 1.5 units per kilogram used by Wlodek and Leach.[53] The volume of secretion and chloride gain to the pouch were approximately one-third the results reported by Wlodek and Leach. It is now known that vagal stimulation may release gastrin.[30, 31, 32] However, the presence of a high concentration of acid in the antrum will inhibit this vagal release of gastrin. It is possible that the lower acid secretion produced in this series of experiments was not sufficient to inhibit the release of gastrin during the first two hours post-stimulation, but as the amount of hydrogen ions in the antrum increased this release of gastrin was inhibited. If true, this would explain the initial increase in the ability of the stomach to contain hydrogen ions immediately after insulin hypoglycemia and the subsequent decrease in this ability later in the face of persistent acid secretion by the parietal cells.

Exogenous gastrin increased the competency of the

gastric mucosa significantly as determined by both calculated hydrogen loss and measured sodium gain, the former producing a more marked change than the latter (see Figure 12). The insulin experiments showed a slight discrepancy between calculated hydrogen loss and measured sodium gain under both basal and post-stimulation conditions. This disparity was more marked in the gastrin series of experiments.

E. The effect of pentagastrin in Pavlov pouches and Heidenhain pouches after antrectomy

The synthetic pentagastrin I.C.I. 50, 123 was given to three dogs with Pavlov pouches and three dogs with Heidenhain pouches and antrectomies. The main purpose of these experiments was to formulate a base line for the further use of I.C.I. 50, 123 as a substitute for pure gastrin which requires considerable time and expense to prepare.

The results obtained in both series of experiments are very similar (compare Figures 13 - 16). The volume of secretion and chloride gain are increased approximately two-fold over the values recorded in the insulin and gastrin series. An increase in competency of the mucosal barrier is noted in both series, which is particularly marked if one considers the change in hydrogen ion flux after pentagastrin

was administered. The disparity between the calculated hydrogen ion loss and the measured sodium gain was more apparent than in the previous experiments. Thus the concept of an exchange of hydrogen for sodium ions may be only symbolic and not an exact exchange.

V. CONCLUSIONS

Work done using the experimental model designed by Wlodek and Leach has been published recently. Their results tended to confirm Teorell's original hypothesis that there is an ion for ion exchange of hydrogen for sodium across the gastric mucosa.[52, 53] This observation has been made by several other investigators although its validity has not yet been conclusively demonstrated.[5, 44] The method of interpretating our results, as shown in Figure 1, has depended upon a comparison of the actual measured gain of sodium ions by the pouch to the calculated loss of hydrogen ions. The calculated loss of hydrogen ions in turn is based on the assumption that the measured chloride gains represent the actual acid secretion (as explained in results). The first series of experiments performed was feeding in Heidenhain pouch preparations. The results, as shown in Chart 6, followed the pattern of the previous work of Wlodek and Leach insofar as the measured sodium gain to the pouch was approximately equal to the calculated hydrogen loss. Thus at first Teorell's postulate of an ion for ion exchange of sodium and hydrogen was not questioned. However, the remainder of the experiments covered by this thesis showed a

marked, and sometimes highly significant, disparity between measured sodium gain and calculated hydrogen loss. This was in part due to the decrease in basal sodium values recorded and in part to the marked hydrogen ion pouch gain in the post-stimulatory state after gastrin and pentagastrin. The calculated hydrogen loss became an actual gain to the pouch in these experiments.

The perplexing, and at the same time fascinating, observation that a decrease in the measured basal sodium secretion occurred with maturing of a gastric pouch was first noted in two dogs with Heidenhain pouches (dogs #1 and 3). These dogs were started on feeding experiments 3 - 4 weeks after their pouches were made, then their antrums excluded and later the antrums were removed.

A series of feeding experiments was carried out after each procedure and the gradual decrease in basal sodium secretion noted. In Dog 1 the basal sodium gain fell from 159 ueq./30 min. 3 weeks after construction of his Heidenhain pouch to 138 ueq./30 min. after exclusion of the antrum 4 weeks later and to 84 ueq./30 min. 6 weeks later after antrectomy. In Dog 3 the basal sodium fell from 212 ueq./30 min. 4 weeks after construction of his Heidenhain pouch, to 110 ueq./30 min. 4 weeks later after exclusion of the antrum

and to 100 ueq./30 min. 6 weeks later after antrectomy. These changes are all significant ($p<0.01$). The results of feeding experiments in three dogs with excluded antrums and Heidenhain pouches were not reported because this preparation was felt to be too unphysiological.

The initial disparity between measured sodium gain and calculated hydrogen loss was noted in the Pavlov pouches during the first series of experiments using insulin hypoglycemia as the stimulus. The subsequent decrease in basal sodium levels is present but not as pronounced as those recorded in the experiments on Heidenhain pouches. The explanation of the above variance is that the three series of experiments on dogs with Pavlov pouches were run simultaneously in part so that individual experiments in each series overlapped those in the two other series. Thus an attempt was made to conduct experiments using insulin, then gastrin, then pentagastrin, then insulin, etc. in the same dog so that the basal values for sodium would be comparable in each series. Unfortunately much of the insulin series and some of the gastrin series had already been completed before this interesting observation had been made. As a result the basal sodium values were not exactly equalized

and they do show some decrease from the insulin to the gastrin to the pentagastrin series. This decrease in the basal sodium output from a gastric pouch with aging of the pouch is certainly an interesting observation, particularly since it is not accompanied by any change in the other basal ionic fluxes. No reference to this phenomenon could be found in the literature and it is a difficult one to explain. A couple of experiments were carried out in dogs immediately after construction of their pouches and large ionic fluxes were noted. All ionic fluxes were 3 - 4 times those recorded 4 weeks after construction of the pouches. In other words, hydrogen loss, chloride gain, sodium gain and potassium gain under basal conditions were all augmented 3 - 4 times over later values. Unfortunately, an insufficient number of experiments were performed to permit a report on this phenomenon in this thesis. However, similar but less pronounced increases in ionic fluxes were noted by Wlodek and Leach when they induced ulcers by electrocautery in canine fundic pouches.[71] A possible explanation of the phenomenon is that a localized breakdown in the gastric mucosal barrier is present while healing is occurring in the pouch, or after ulceration, and this permits exudation of some extra- or intra-cellular fluid into the pouch. Also an increased

exchange of hydrogen for sodium ions is known to occur with disruption of the mucosal barrier in the presence of various substances.[3, 4, 5, 6, 7, 8]

The above observations do not explain why a chronic gastric pouch shows a decreased flux of sodium ions into it with age. This phenomenon, which became more apparent in the later experiments, tends to negate the concept of an absolute ion for ion exchange between hydrogen and sodium. This concept first proposed by Teorell [9] and later confirmed by several investigators [44, 52] is an appealing one and I am loathe to discard it. However, a considerable amount of investigation must be carried out to clarify this postulate and it is not reasonable to refute Teorell's hypothesis on the basis of the work here presented, although it may have to be modified as suggested by Berkowitz and Janowitz.[67]

Another difficulty arose in our original interpretation of ionic fluxes in this experimental model. When both Heidenhain and Pavlov pouches were given pentagastrin, the gain in hydrogen by the pouch actually exceeded the gain in chloride as illustrated in Figures 9 and 11. If every hydrogen ion enters the pouch accompanied by a chloride

ion as hydrochloric acid, then some chloride ions must have been insorbed through the gastric mucosa during these high levels of secretion and possibly under basal conditions as well. As pointed out by Berkowitz and Janowitz,[67] it seems likely that a continuous flux of all ions in both directions across the gastric mucosal barrier must take place and all we have been able to record are the final products of these ionic fluxes. Work has begun in this laboratory with radioactive chloride in an attempt to determine the degree to which chloride is insorbed across the gastric mucosa. It is well established that sodium ions may travel both ways across the mucosal barrier although the quantitative aspects of this have not been determined.[45, 46, 47, 48, 49, 51] Insorption of hydrogen ions in the stomach have been studied using D_2O.[50] However, hydrogen ions may combine with so many substances (sulphate, phosphate, etc.) that the exact nature of its flux across the mucosal barrier will be more difficult to adequately assess than those of sodium and chloride. Thus the exact nature of the ionic fluxes across the gastric mucosa will have to await further study. Certainly hydrogen ions secreted by the parietal cell are reabsorbed across the gastric mucosa and this phenomenon

must play an important role in the final output of acid by the stomach.

The ability of the stomach to contain the hydrogen ions secreted is an important and variable function of the gastric mucosa. This regulation of hydrogen ion content in the stomach may not be based on an exact ion for ion exchange with sodium but our results tend to support the thesis that this exchange process does play some role in the "acidity control" of the stomach.

VI. SUMMARY

The unique ability of the stomach to contain an acid solution and the mechanisms controlling this important function of the gastric mucosa have been investigated. The exchange process between hydrogen and sodium ions across the mucosal barrier of the stomach appears to exist though it may not be an exact ion for ion exchange.

Feeding in dogs with Heidenhain pouches produced an insignificant increase in the volume of secretion but did significantly decrease the exchange of hydrogen for sodium ions and thus increased the competency of the mucosal barrier. This was interpreted as indicating that gastrin may be the mechanism regulating the mucosal barrier to hydrogen and sodium ions. However, repeating the feeding experiments after antrectomy in these dogs with Heidenhain pouches did not entirely abolish this effect. The interpretation on this finding is that either duodenal gastrin or intestinal or pancreatic hormones may play a part in the regulation of the gastric mucosal barrier.

The competency of this mucosal barrier does not appear to be affected by vagal excitation as demonstrated by producing insulin hypoglycemia in a Pavlov pouch.

Gastrin increased the competency of the mucosal barrier whether determined by the reduction in measured sodium gain by the pouch or by the calculated hydrogen loss. Pentagastrin produced an increased competency of this mucosal barrier in both Heidenhain and Pavlov pouch preparations.

The sodium ion gain by a canine gastric pouch under basal conditions decreases significantly with aging of the pouch. This was demonstrated clearly in those dogs with Heidenhain pouches but not with the Pavlov pouches because the series of experiments were set up in a mixed fashion rather than sequentially. The reason for this occurrance is not obvious and further work will be required for its full explanation.

The basic assumption made that each hydrogen ion secreted is accompanied by a chloride ion as hydrochloric acid appeared to be invalidated by the later experiments using pentagastrin as a stimulus. In these experiments the measured hydrogen gain by the pouch was slightly greater than the chloride gain after stimulation. However, this may be due to insorption of chloride ions through the gastric mucosa. The extent to which this occurs is to be determined in the near future by the use of radioactive chloride.

The property of the stomach that allows it to contain the hydrogen ions secreted into it is an important and variable function of the gastric mucosa. The exact nature of this function and mechanisms controlling it are not clear, but it appears to be due to hormonal influences from the antrum of the stomach, small intestine, pancreas or a combination of these.

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