CERTAIN ASPECTS OF NERVOUS AND HORMONAL MECHANISMS
INVOLVED IN GASTRIC ACID SECRETION.

AMBROSE ERIC ONYANGO WASUNNA

A THESIS SUBMITTED IN PART FULFILMENT FOR THE DEGREE

OF M.D. IN THE UNIVERSITY OF NAIROBI.

1972

i.

P R E F A C E

This is a Thesis of research work undertaken by me in the Department of Surgery, Glasgow University, between January, 1970 and February 1971, on a Commonwealth Medical Fellowship. The work was carried out under the supervision of Andrew W. Kay, Regius Professor of Surgery, University of Glasgow, and Iain E. Gillespie, Professor of Surgery, University of Glasgow. The laboratory facilities used were those of the Wellcome Surgical Research Institute.

This Thesis has not been submitted for a degree in any other University.

13th February, 1972

A.E.O. WASUNNA

ii.

A C K N O W L E D G E M E N T S

TABLE OF CONTENTS

GENERAL INTRODUCTION:

Although the first scientific methods of studying gastric physiology were started towards the end of the last century, principally by the Pavlov School of Physiologists, it is only recently that major advances have been made. Of the many diseases that affect the stomach and the duodenum, there is considerable evidence associating peptic ulceration with variations in gastric juice secretion, in particular, the volume and concentration of the hydrochloric acid and pepsin components. The wide variety and the rapidly changing forms of treatment of peptic ulceration signifies our inadequate knowledge not only of the aetiology of the condition, but also that of the normal control of gastric juice secretion. The many recent excellent general reviews on the subject of gastric secretion include: Farrar and Bower[1], Gillespie[2], and Myren and Semb[3].

This thesis deals with a series of experiments carried out on dogs, to assess the normal control of gastric acid secretion. There are three main sections, viz:

1. Acid Responses of Denervated Fundic
    (Heidenhain) Pouches to meals compared
    with those to Histamine and Pentagastrin.

2. Vagal influence on antral gastrin release.

3. The contribution of the vagus nerves and
    the stomach to acid response to a meal.

Each section of the thesis is complete with introduction, experimental details, results, discussion and conclusions.

1.   ## ACID RESPONSES OF DENERVATED FUNDIC (HEIDENHAIN) POUCHES TO MEALS COMPARED WITH THOSE TO HISTAMINE AND PENTAGASTRIN

In previous experiments on dogs with denervated (Heidenhain) pouches, Master et al[7] and Thomas and Forrest[8] suggested that acid outputs equivalent to maximal response to histamine (exogenous stimulant) could be obtained by repeated small feeds (endogenous stimulation) throughout the test. The more usual physiological endogenous acid stimulation by a single feed has not been systematically compared with acid output evoked by exogenous agents like histamine or pentagastrin. This study was undertaken in order to:-

i.   Compare the acid responses to single large meals with those to different doses of histamine and of pentagastrin.

ii.   Provide a base-line for subsequent experiments described in this thesis.

Three dogs were used. The results suggested that:-

i.   Large single feeds resulted in acid outputs approximately equal to the maximal response to histamine.

ii.   The maximal acid response to pentagastrin was less than 50% of that to the meal or to the maximal dose of histamine.

COMMENT:

It is suggested that combinations of endogenously released stimuli (in response to a meal) can produce a potentiated gastric acid response which exceeds that produced by pentagastrin (exogenous gastrin) alone.

Some material from this part of the thesis was included in an article recently published in the Scandinavian Journal of Gastroenterology[4].

2.   VAGAL INFLUENCE ON ANTRAL GASTRIN RELEASE

Although the observation that an antral mechanism contributes to acid response produced by vagal activity was first made by Straaten[19] in 1933, controversy about vagal release of antral gastrin raged for years after this. Today, vagal release of gastrin is well-established, however, there remains conflicting evidence on the part which vagal activity may play in regulating the effectiveness of gastrin release in response to stimulants in the lumen of the stomach.

This study was designed to determine whether intact vagal innervation of the pyloric antrum is essential for efficient release of gastrin by:-

   i.   Local irrigation of the antral mucosa
          using acetylcholine;

   ii.   Meal, prevented from coming into direct
          contact with antral mucosa; and

   iii.   Simultaneous feeding, and irrigation of
          the antral pouch.

These gastric acid responses were also compared with those obtained by administering histamine and pentagastrin.

Three dogs were used in this study. The following conclusions were drawn from the observations:-

   i.   Vagal denervation of an isolated antral
          pouch produced no significant alteration
          in acid response to either submaximal or
          maximal doses of injected histamine or
          pentagastrin.

ii.   Intact vagal innervation of the isolated
antrum is essential for both the maximal
and overall acid response to food.

iii.   Denervation of the isolated gastric antrum
reduces the maximal acid response from the
Heidenhain pouch to food by 60-70%.   This
observation gives some   estimate   of   the
extent of the role of vagal innervation of
the   antrum in the release and interaction
of endogenously released stimulants of gas-
tric acid secretion.

iv.   Vagal   innervation   of the   antrum   is   not
essential for full gastrin release   in   res-
ponse   to   bathing   antral   mucosa   with
acetylcholine.   This probably does not imply
that vagal background in the antrum   con-
tributes little to local chemical release of
gastrin but rather reflects on the   special
mode of action of acetylcholine.   Further
work is required to settle this point   by
substituting food for acetylcholine in   the
antral pouch.

v.   The observation that antrectomy did not further
reduce   acid   response   to   meal   suggests   that
beneficial   effect   of   antrectomy   as   used
clinically in the management of duodenal   or
gastric ulcers owes more to the total exclusion
and denervation of this part of the stomach
than to its actual removal.

Some of the material in this section of the thesis was in-
cluded in a paper read at the 12th Annual Conference of   the
Association   of Surgeons of West Africa,   meeting   in Accra   in
January, 1972.

3. THE CONTRIBUTION OF THE VAGUS NERVES TOGETHER WITH THE

STOMACH TO ACID RESPONSE TO FEEDING

Recent work by Nyhus and his associates[36] indicates that the mechanism of gastric secretion in response to food is more intricate than was previously thought; and that the sharp division of the various phases into 'Cephalic', 'Gastric' and 'Intestinal' is inaccurate.

This study was therefore designed to assess the contribution of the vagus together with the stomach in the gastric acid response to food. Further, the findings were intended to give an indirect estimate of the contribution from the small intestine.

Three dogs were prepared each with an innervated (Pavlov) pouch, an antral cannula and an arrangement in the first part of the duodenum to allow for exclusion of the whole of the distal gut from the food stream, as required.

The results suggest that:-

i.   The vagus and the stomach are together responsible for the peak acid response to food.

ii.   When consideration is taken of the entire physiological acid response to a meal, and in particular, the time relations of this, there is a very sizeable contribution from the small intestine.

iii. The contribution of the vagus and the stomach to the overall acid response to food is thus considerably smaller than was once thought, amounting to only about 54%.

iv.   Further work with this animal preparation
may be necessary to assess the contri-
bution of the central vagal stimulation
('Cephalic' phase) by introducing food
directly into the stomach via the antral
cannula.

Some of these observations were included in a paper read
at the Association of Surgeons of East Africa, Annual Conference
in Kampala, December, 1971.

CHAPTER 1

ACID RESPONSES OF
DENERVATED FUNDIC (HEIDENHAIN) POUCHES TO MEALS
COMPARED WITH THOSE TO HISTAMINE AND PENTAGASTRIN

There have been several studies comapring the gastric acid responses of vagally innervated pouches in dogs to both endogenous and exogenous stimuli[5], [6]. However, it appears that the only systematic comparable experiments in dogs with denervated (Heidenhain) pouches have been those of Master et al[7] and Thomas & Forrest[8]. In all these experiments it was suggested that acid outputs equivalent to the maximal response to histamine could be obtained by repeated feeds throughout the test.

In this study, the acid responses to single large meals and to different doses of histamine and of pentagastrin, have been compared.

MATERIALS AND METHODS

Three mongrel dogs, (W_1, W_2 and W_4) each weighing between 15 and 20 kg., were prepared with separated fundic (Heidenhain) pouches of the stomach, drained by titanium cannulas of the Gregory pattern[9] Fig.1.

Acid secretion tests were started four weeks after surgery. In all experiments gastric juice from the Heidenhain pouches was collected continuously by free drainage into graduated test tubes. Every 15-minute volume was recorded and the concentration of acid was determined by titration with 0.01N sodium hydroxide to the end-point of 0.02 per cent phenol red (pH 6.8 to 8.4). Acid outputs were calculated by multiplying volume and concentration values.

Following an 18-hour fast, basal secretion was collected for at least 45 minutes.

Insulin hypoglycaemia was used to confirm the denervation of the Heidenhain pouches[10] 0.5 units/kg. of soluble insulin was given as a single intravenous injection and gastric secretion
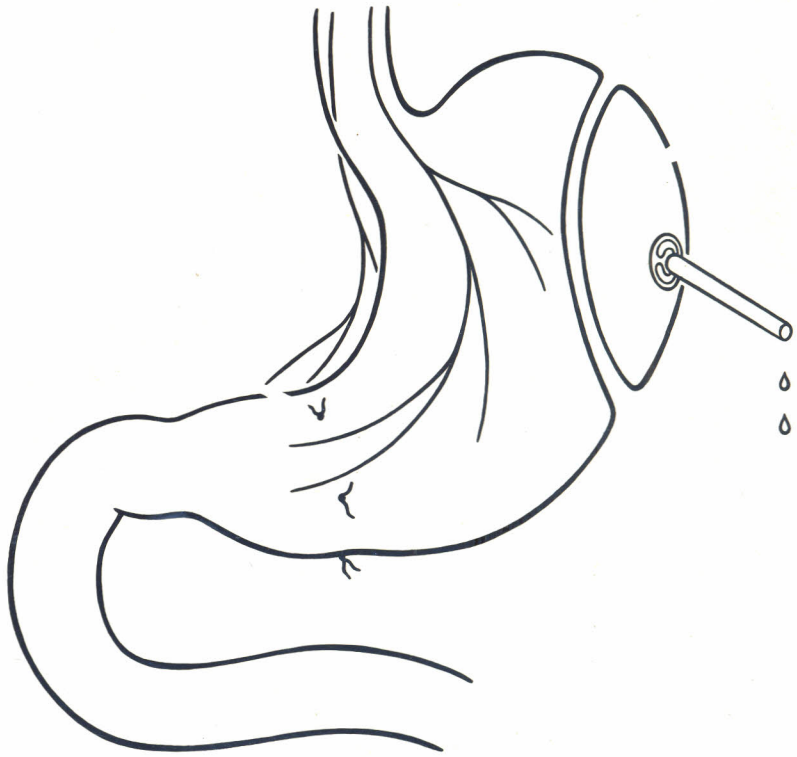
FIG. 1. The denervated fundic (Heidenhain) pouch
of the stomach with the cannula draining
it are shown.

was collected from the Heidenhain pouch for at least two hours.

Dose-response curves of Heidenhain pouch acid secretion were determined using the following stimuli: histamine acid phosphate, pentagastrin, and meals consisting of a mixture of 66 per cent commercial dog food ('Luda Banquet', 1.6 per cent carbohydrate, 11.5 per cent protein, and 7.5 per cent fat by weight), with 33 per cent ox liver made into a puree.

Histamine acid phosphate and pentagastrin, in 0.9 per cent sodium chloride solution, were administered by continuous intra-venous slow infusion Palmer pump connected to an intravenous catheter (size TW 24, Polypeco Limited), via a 50 ml Brunswick disposable sterile syringe and a No.23G $1\frac{1}{4}$ needle. The appara-tus delivered 21 ml/hour.

After the basal collections of gastric juice, histamine, pentagastrin, or a meal was given. For acid response to hista-mine or pentagastrin, each experiment was started with a small dose of the agent, and acid output from the Heidenhain pouch was determined every 15 minutes until the rate of secretion varied by less than 15 per cent in at least three consecutive collections. The dose of the stimulant was then doubled and the procedure repeated. The acid output at each dose level was ex-pressed in milliequivalents per 45 minutes (taking the sum of the last three steady outputs).

In meal experiments, 15-minute collections of acid were made following feeding until there was no further increase in output. The sum of the 3 highest consecutive acid outputs was taken to represent the response to that amount of food.

Histamine acid phosphate was given in doses of 0.025, 0.05, 0.1, 0.2, 0.4 and 0.8 mg/kg/hour; doses of pentagastrin admin-istered were: 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 ug/kg/hour. The meal mixture was given in amounts of either 30 or 60 g/kg. The smaller meal was usually quickly and completely eaten, but the larger meal was consumed over a period of 30 minutes or more.

RESULTS

There was no acid response from the Heidenhain pouch to insulin hypoglycaemia in any of the 3 dogs, confirming denervation of the pouches. Tables I-III.

Acid outputs from the Heidenhain pouches increased with larger doses of histamine, pentagastrin, or the size of the meal. Increasing the dose of histamine and pentagastrin above that required for maximal output produced similar or reduced response. These results are illustrated in Figure 2.

Taking the maximal acid response from the Heidenhain pouch to histamine as 100 per cent, the responses to the larger meal, and the maximal response to pentagastrin were 93 and 43 per cent respectively. Thus, maximal response to histamine and to the meal were about the same, while pentagastrin gave a lower response. The details of these results are shown in Tables IV-VI.

DISCUSSION

The general assumption that the acid response from a Heidenhain pouch to feeding is lower than that which follows maximal stimulation with histamine is no longer tenable[7, 8]. Previous workers who failed to obtain large responses to single and repeated feeds used relatively small meals[6]. Thomas & Forrest[8], however, showed that by giving large single or repeated feeds, high rates of acid secretion equal to maximal stimulation by histamine could be obtained. In the present study, single feeds were increased to 60 g/kg body weight in all dogs to obtain acid secretion equivalent to maximal response to histamine. This amount given as a single feed is comparable to the 900 g meal fed to Heidenhain pouch dogs by Ivy et al.[11] to obtain high rates of acid secretion.
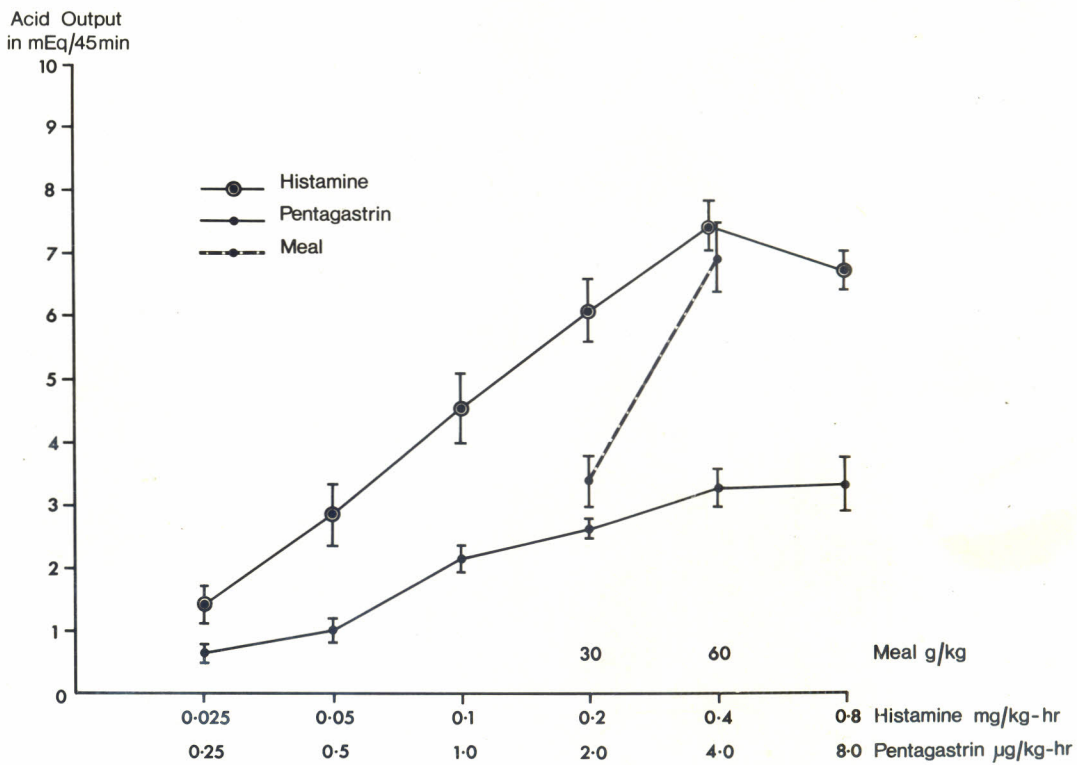
FIG. 2. Heidenhain pouch acid response to histamine, pentagastrin and meal. Each point represents three experiments on each of the three dogs. Vertical bars indicate standard error of the mean.

The maximal acid response to pentagastrin was less than half that to histamine. This observation is in agreement with that of Thomas & Forrest[8]. However, there is so far no explanation why in denervated (Heidenhain) pouches, meal response (accepted to be due to endogenously released gastrin) should be greater than the response to pentagastrin (exogenous gastrin). It has been shown that the maximal response of a Heidenhain pouch to exogenous gastrin can be enhanced by cholinergic activity, induced by intravenous infusion of subthreshold doses of cholinergic drugs or by local distension of the pouch [12, 13, 14]. Both these factors are probably initiated by food, but would not be expected to operate in the freely draining separated pouch. Another possible explanation is that combinations of humoral and/or neural stimuli, endogenously initiated by food, can produce a potentiated gastric acid response which exceeds that produced by a single exogenous stimulant, e.g. histamine [5] or pentagastrin alone, in dogs. Previous work from our laboratory[15] suggest that the contribution of the intestinal phase to the overall acid response to a meal is greater than was once thought[16]. The present findings further suggest that potentiation may exist between the gastric and intestinal phases of acid secretion.

The difference between the response to meals and that to exogenous gastrin preparations might be explained by a difference in inhibition from duodenal acidification. With the meal, in addition to gastrin being released endogenously from the pyloric antrum, there is likely to be some buffering or neutralization of the luminal contents and therefore less exposure of the first part of the duodenum to acid. By contrast, following the injection of exogenous gastrin or pentagastrin, there would be a considerable release of unopposed acid into the lumen of the gastric remnant, and subsequent exposure of the proximal duodenum to this acid, with inhibition possibly resulting. This hypothesis, however, would require that histamine was relatively more resistant to the inhibitory effects of duodenal acidification, which is in keeping with earlier findings[17]. However the observations of

Cooke [18] suggest that maximal acid output from denervated fundic pouches in response to exogenous gastrin and to histamine is not significantly altered by duodenal acidification. Finally, a difference in the action of the full gastrin molecule, as compared to pentagastrin, might account for the difference in the level of maximal response.

SUMMARY AND CONCLUSION

Gastric acid responses to meals were compared with those to histamine and pentagastrin in 3 dogs with Heidenhain pouches. Large single feeds resulted in acid outputs that were approximately equal to the maximal response to histamine. The maximal acid response to pentagastrin was less than 50% of that to the meal or to the maximal dose of histamine. It is suggested that combinations of endogenously released stimuli (in response to a meal) can produce a potentiated gastric response which exceeds that produced by pentagastrin (exogenous gastrin) alone.

CHAPTER 2

VAGAL INFLUENCE ON ANTRAL GASTRIN RELEASE IN DOGS

The observation that an antral mechanism contributes to acid response produced by vagal activity was first made by Straaten in 1933[19]. He demonstrated that sham feeding in dogs resulted in a reduced acid output after partial gastrectomy including resection of the antrum. Following this, Uvnas[20] carrying out acute experiments in cats, produced the hypothesis that vagal stimulation releases gastrin from the antrum and also that the cephalic phase of gastric acid secretion is controlled by a neuro-humoral mechanism in which antral gastrin plays a major role. Controversy about vagal release of gastrin raged for years after this, evidence being produced for[21-24] and against[25-27] the existence of such a mechanism. However, the matter was settled by Pe Thein and Schofield in 1959[66]. These workers produced convincing evidence of the release of gastrin from the antrum during the vagal stimulation. They obtained acid response to sham feeding from denervated and transplanted gastric pouches in dogs with isolated innervated antrum. They further showed that the acid response could be abolished or markedly reduced by antrectomy or acidification of the antrum. Indeed Pe Thein and Schofield were the first to recognise the importance of acidification of the antrum and duodenum in ex-periments designed to evaluate the contribution of the vagal release of gastrin. Further, they were the very first to take measures deliberately to avoid antral and duodenal acidification, and thus became the first group to succeed in demonstrating any response at all to vagal stimulation of the antrum. Olbe's ex-periments[28-30] confirmed the findings of Pe Thein and Schofield. He concluded that vagal release of gastrin, although a weak stimulus of acid secretion by itself, could exert an important control over the cephalic phase of gastric secretion.

Although vagal release of gastrin is now established, there is conflicting evidence[31-35] on the part which vagal activity may play in regulating the effectiveness of gastrin release in

response to stimulants in the lumen of the stomach. This study was designed to determine whether intact vagal innervation of the pyloric antrum is essential for efficient release of gastrin by:

1.   antral pouch irrigation with acetylcholine;

2.   meal, prevented from coming into contact with antral mucosa; and

3.   simultaneous feeding and irrigation of the antral pouch.

The gastric acid responses were also compared with thos obtained by administering histamine and pentagastrin.

MATERIALS AND METHODS

Surgical Technique:

Three mongrel dogs (W_2, W_3 and W_4) weighing between 15 and 20 kg. were used. Each dog was prepared with a vagally denervated (Heidenhain) pouch of the body of the stomach, and an innervated antral pouch. The antral pouch was constructed in the following manner:-

> Through the opening in the stomach after Heidenhain pouch construction, the zone between the antrum and the acid-producing area of the stomach was determined using litmus paper after histamine stimulation[28]. A double mucosal wall was fashioned between the antrum and main stomach at this zone. The pyloric end of the antrum was brought through the abdominal wall as a mucosal fistula. Continuity of the alimentary tract was restored by gastrojejunostomy and the duodenum closed. (Figure 3).
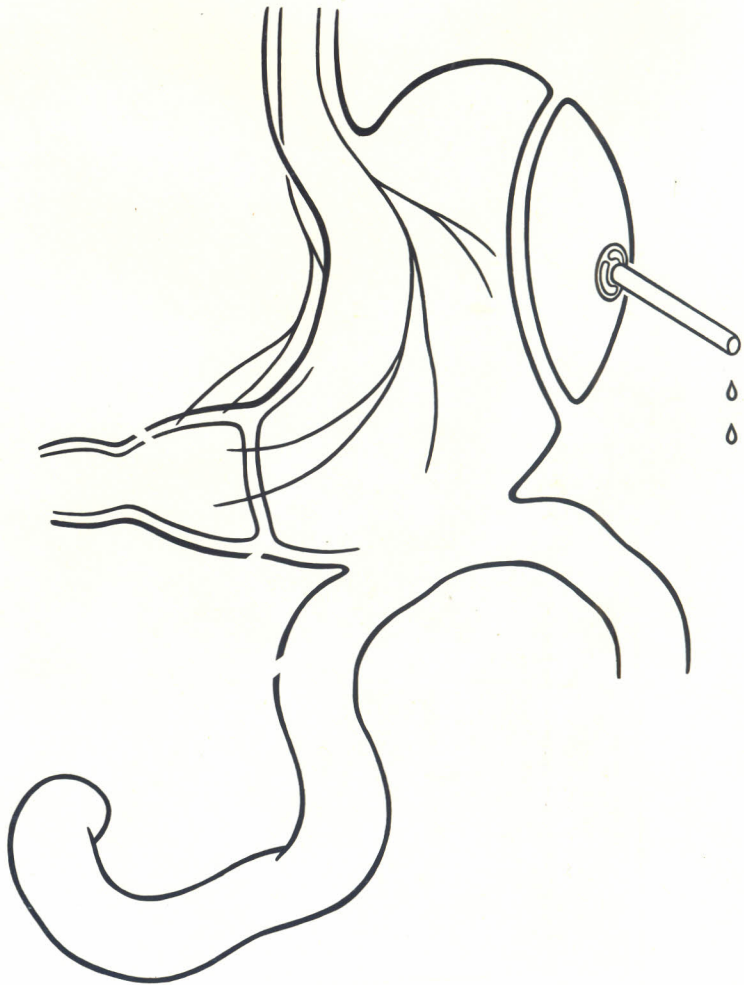
FIG. 3. Denervated fundic (Heidenhain) pouch of
the stomach, innervated antral pouch and
gastrojejunostomy are depicted. The
antral pouch is separated from the rest
of the stomach by a double mucosal septum.

After completing the initial series of experiments the
antral pouch was denervated by cutting between the two mucosal
walls and dividing the lesser and greater omenta and all struc-
tures in them. The pouch thus became attached only to the
abdominal wall from which it derived its blood supply. (Fig.4)

Experimental Techniques:

Acid secretion tests were started 6 weeks following opera-
tion. In all experiments, gastric juice from the Heidenhain
pouch was collected continuously by free drainage into graduated
test tubes. Every 15 minutes the volume was recorded and the
concentration of acid determined by titration with 0.01N sodium
hydroxide to the end point of 0.02% phenol red (pH 6.8 to 8.4)[37].
Following at least 18 hours fast, basal secretion was collected
for a minimum period of 30 minutes.

Insulin hypoglycaemia was used to confirm the denervation
of the Heidenhain pouch[10]. A dose of 0.5 units/kg. of soluble
insulin was given as single intravenous injection and gastric
secretion collected from the Heidenhain pouch for at least two
hours.

Dose response curves of Heidenhain pouch acid secretion
were determined for the following agents:

histamine, pentagastrin, meal and bathing the
antral mucosa with solutions of acetylcholine.

Further observations were made of the acid response to simul-
taneous feeding and irrigating antral pouch mucosa with acetyl-
choline. Solutions of histamine acid phosphate and pentagastrin
were made in 0.9% saline and administered by continous intra-
venous slow infusion Palmer pump. The pump was set to deliver
21 ml. per hour. The meal consisted of a mixture of a com-
mercial dog food (Luda Banquet, Luda Meaties Lt., Louth, England)
66%, with pureed ox liver, 33% in weight. The commercial food
itself was made up of 1.6% carbohydrate, 11.5% protein and 7.5%
fat by weight.
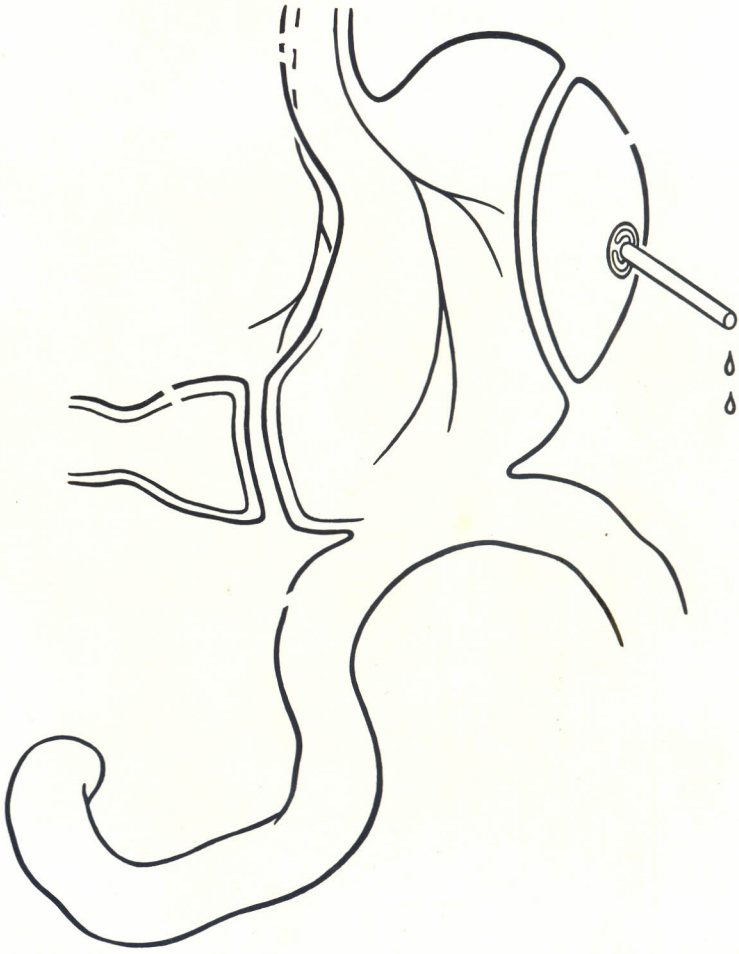
FIG. 4.   The double mucosal septum (and lesser
          and greater omenta) already divided to
          denervate the antral pouch.

In histamine, pentagastrin and antral pouch irrigation
experiments, each test was started after basal collections,
using a small dose of the agent. Acid output from the Heiden-
hain pouch was collected continuously and the volume and con-
centration of acid determined every 15 minutes, until the acid
output varied by less than 15% in at least three consecutive
collections. The dose of the stimulant was then doubled and
the procedure repeated. The acid output at each dose level was
expressed in milliequivalents (mEq.) per 45 minutes (taking the
three steady outputs).

Meals were used to induce endogenous vagal stimulation
which it was hoped, would travel to the empty antrum, and thus
release gastrin without actual contact between the food and
antral mucosa. In meal experiments 15 minute determinations of
gastric juice from the Heidenhain pouch were made following feed-
ing until there was no further increase in the output. The
highest acid response in any three consecutive collections was
taken to represent the response to that amount of food. In
simultaneous feeding and antral pouch irrigation experiment,
antral pouch perfusion with acetylcholine was started at the
time the meal was offered, and continued throughout the test.

For antral pouch irrigation experiments, a two-way Foley
catheter was inserted into the pouch and the balloon distended
to 5 ml. Graduated concentrations of acetylcholine dissolved
in 0.9% saline were used for perfusion, from a Palmer infusion
pump, set to deliver 84 ml. per hour. The pH of the fluid
draining from the antral pouch was checked at least once for
each strength of acetylcholine solution.

Vagal gastrin released was tested before and after antral
denervation using 200 mg./kg. of 2-deoxy-D-glucose (2-D-G)
(Sigma Chemical Company, St. Louis, Mo.) given as a single
intravenous injection against a background of stimulated with
hestamine[21]. 2-D-G was injected after a steady rate of acid
secretion had been obtained with histamine. The dose of intra-

venous histamine acid phosphate selected was that which evoked 30 to 45% of the maximal acid response to histamine.

RESULTS

Effect of Intravenous Injection of Insulin:

There was no acid response from the Heidenhain pouch to intravenous injection of 0.5 units/kg. of soluble insulin in any of the 3 dogs. In each case blood sugar level was reduced to less than 45mg./100 ml. Denervation of the fundic pouches was thus confirmed. Tables II, III and VII.

Effect of Intravenous Injection of 2-D-G:

Before denervation of the antral pounch the intravenous injection of 2-D-G against the background acid stimultion with histamine evoked a marked increase in acid output from the fundic pouch in each dog. The peak acid output was reached in the 3rd to 5th 15 minute period and amounted to 197, 160 and 194% of the pre-injection level respectively in the 3 dogs. Following the division of the double mucosal septum and isolation of the antral pouch from the gastric remnant, the corresponding highest acid responses after 2-D-G in the 3 dogs were 149,110 and 91% of the pre-injection levels (Figs. 5-7). Throughout the tests, the pH of the effluent from the antral pouch ranged between 6.0 and 7.2.

The background of intravenous histamine was given partly to potentiate or otherwise to magnify the response to 2-D-g, and also to give a certain "priming" of the acid secreting cells. It is interesting to note that in comparable preliminary studies using intravenous insulin instead of 2-D-G, insulin did not alter the rate of acid secretion stimulated by the background histamine, from the Heidenhain pouches.

Effect of Antral Pouch Denervation on Pentagastrin Stimulated Acid Secretion

Denervation of the antral pouch did not alter the sub-maximal or the maximal acid response from the fundic pouches to
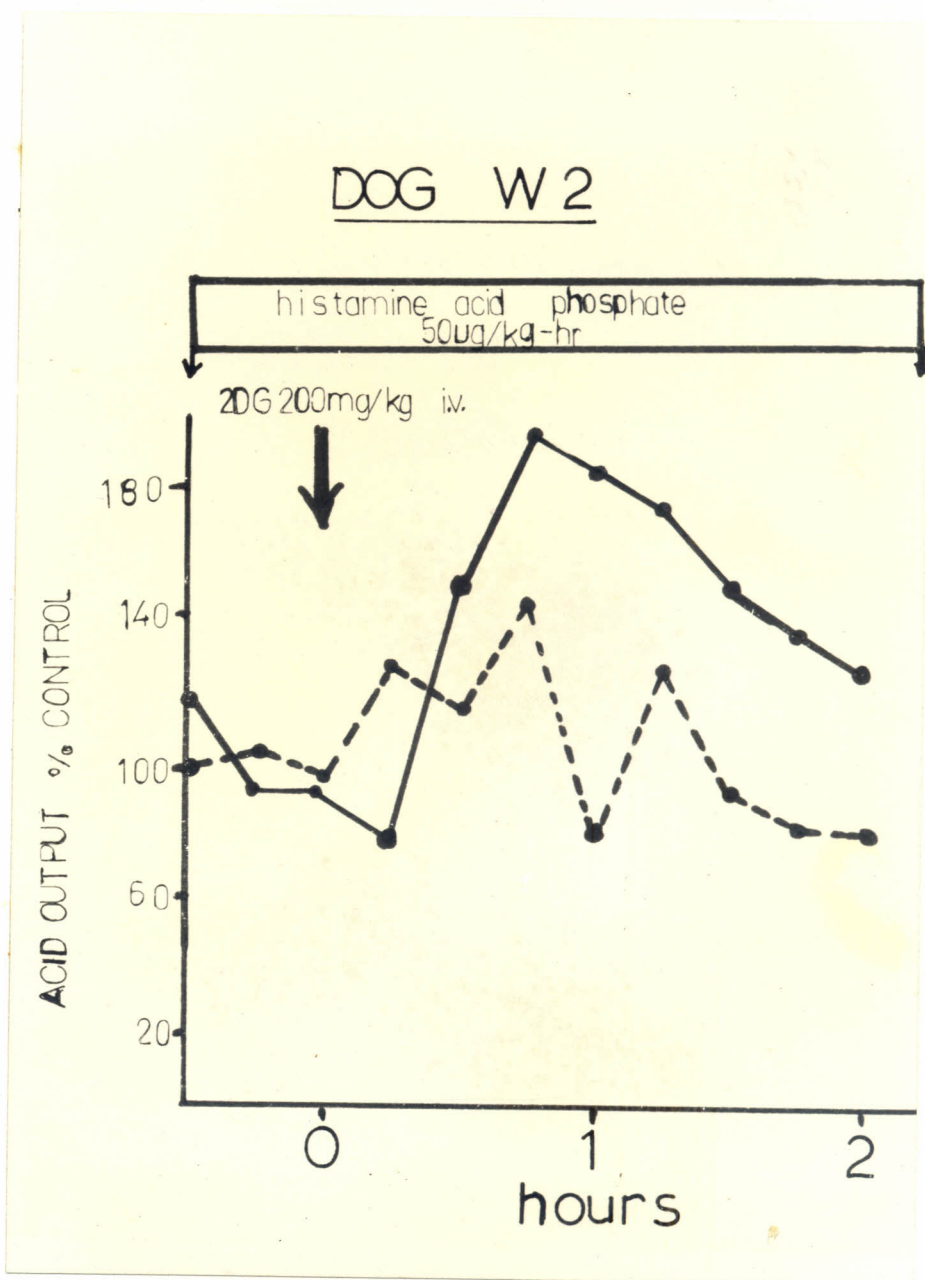
FIG. 5. Effect of an intravenous injection of 2-deoxy-D-glucose on histamine stimulated acid secretion from the Heidenhain pouch before (solid line) and after (dotted line) denervation of the antral pouch. Each point represents one experiment in the animal. The 100% (pre-injection) level before and after denervation of the antral pouch were not significantly different (P>0.05).
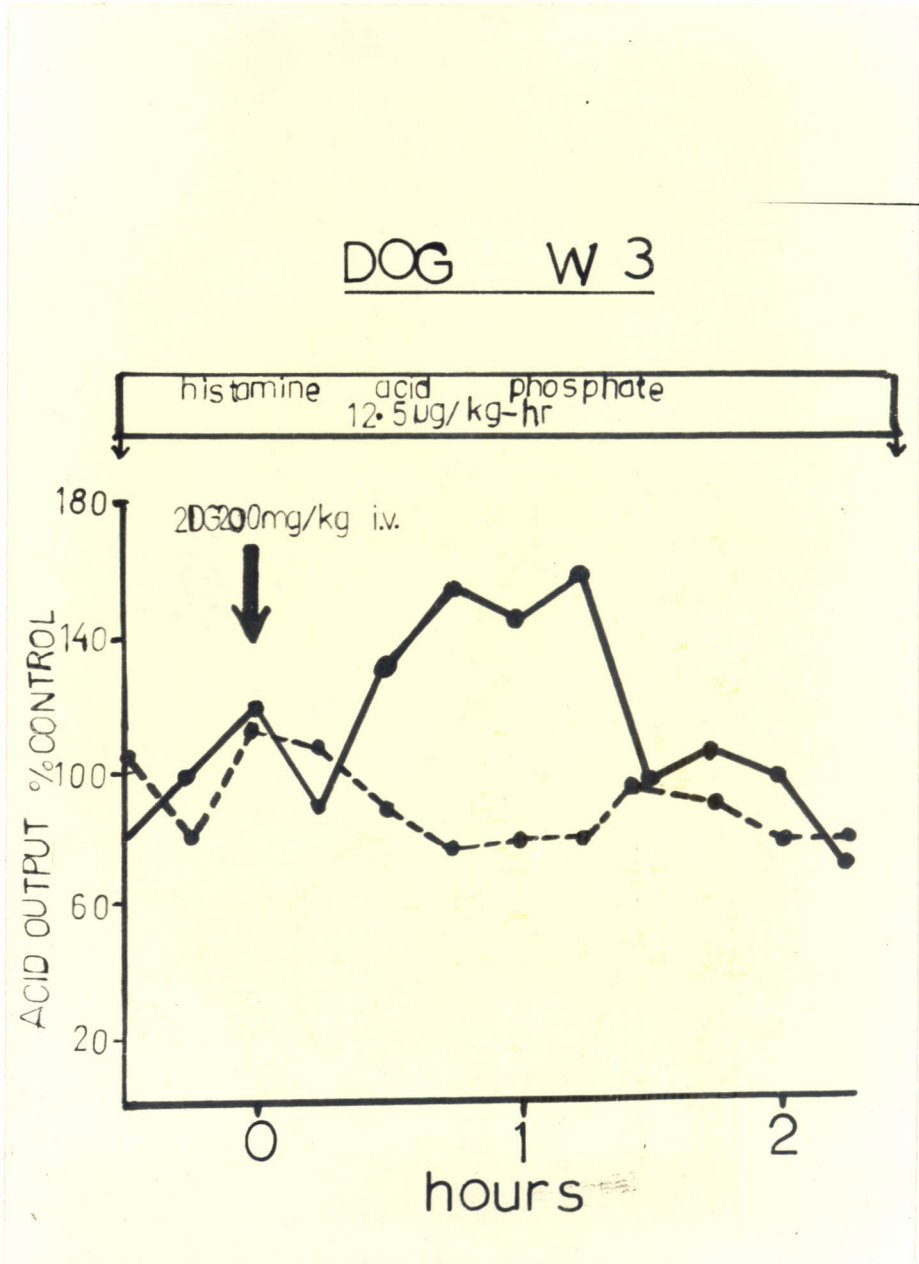
FIG. 6.   Effect of an intravenous injection of 2-deoxy-D-glucose
           on histamine stimulated acid secretion from the Heiden-
           hain pouch before (solid line) and after (dotted line)
           denervation of the antral pouch. Each point represents
           one experiment in the animal. The 100% (pre-injection)
           level before and after denervation of the antral pouch
           were not significantly different (P>0.05).
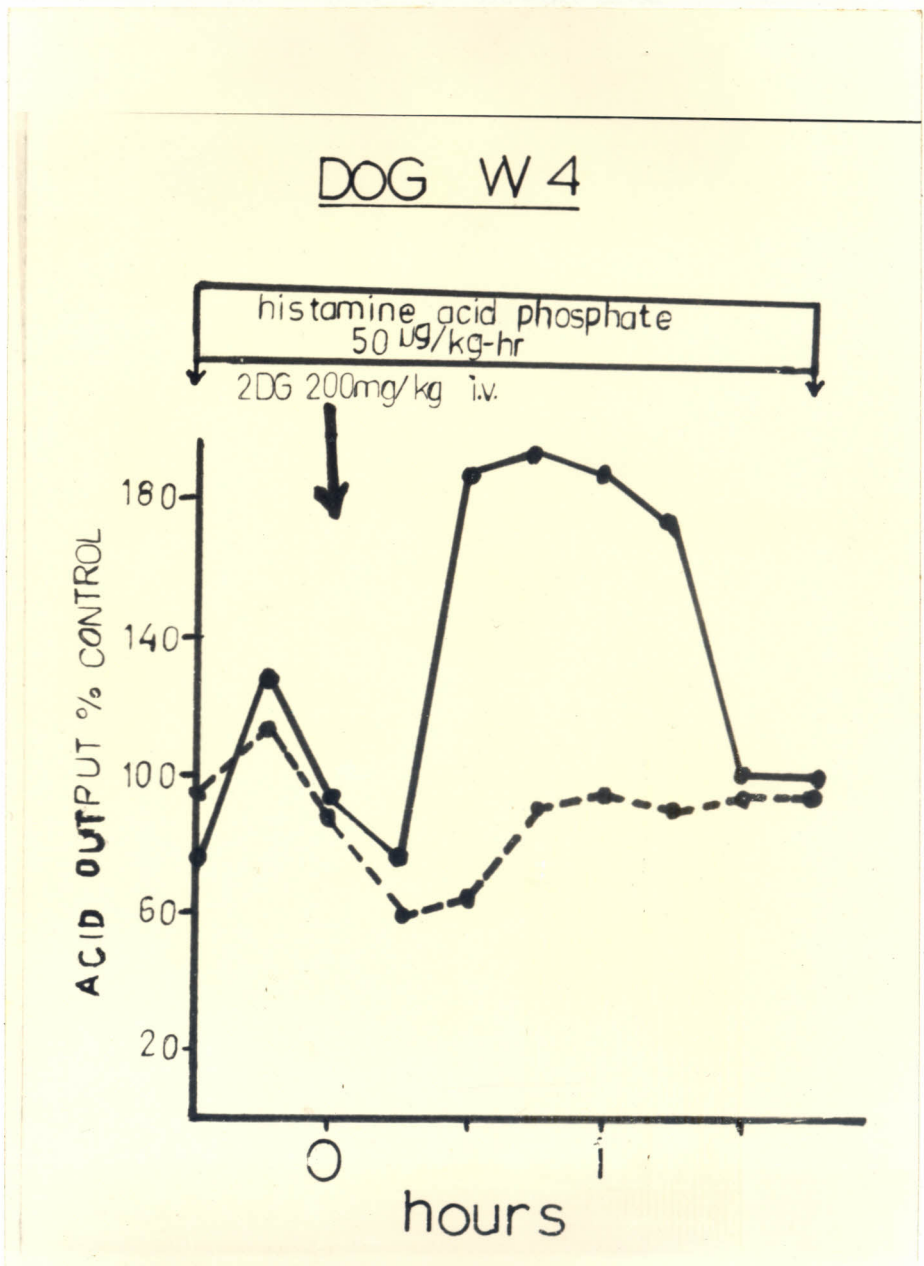
FIG. 7.   Effect of an intravenous injection of 2-deoxy-D-glucose
          on histamine stimulated acid secretion from the Heiden-
          hain pouch before (solid line) and after (dotted line)
          denervation of the antral pouch. Each point represents
          one experiment in the animal. The 100% (pre-injection)
          level before and after denervation of the antral pouch
          were not significantly different (P>0.05).

continuous intravenous infusion of varying doses of pentagastrin ($p > 0.05$). Mean peak acid response was obtained by giving 8.0 ug./kg-hour (Fig. 8).

Effect of Antral Pouch Denervation on Histamine Stimulated Acid Secretion

The intravenous infusion graded doses of histamine acid phosphate produced gradually increasing amounts of acid response from the fundic pouches. The mean peak acid output was obtained when histamine acid phosphate was administered at 400 ug./kg-hour. Denervation of the antral pouch did not sig-nificantly alter the submaximal or the maximal acid response to this stimulant ($p > 0.05$). Further, antral denervation did not alter the amount of histamine acid phosphate required to elicit maximal responses. These results are summarised in Figure 9.

Effect of Antral Pouch Denervation on Acid Response to Meal

Denervation of the antral pouch markedly reduced the peak acid responses to 30 and 60 g./kg. meal ($p = 0.05-0.01$ and $p < 0.01$, respectively). The proportion of the reduction of the acid out-puts were about 40% for the smaller meal and 67% for the larger meal, (Fig. 10). This suggests a diminution in the vagally re-leased antral gastrin following antral pouch denervation.

Effect of Antral Pouch Denervation on Acid Response to Bathing the Antral Pouch with Acetylcholine Solution

Irrigation of the antral pouches with varying concentra-tions of acetylcholine chloride solution produced graded acid response, the mean peak response being obtained by perfusing 0.4% solution. Denervation of the antral pouch produced no significant change in either submaximal or maximal levels of acid secretion ($p > 0.05$). The pH of the effluent from the antral pouches varied between 5.7 and 7.4. Fig.11 illustrates these findings.

ACID RESPONSE TO I.V. PENTAGASTRIN
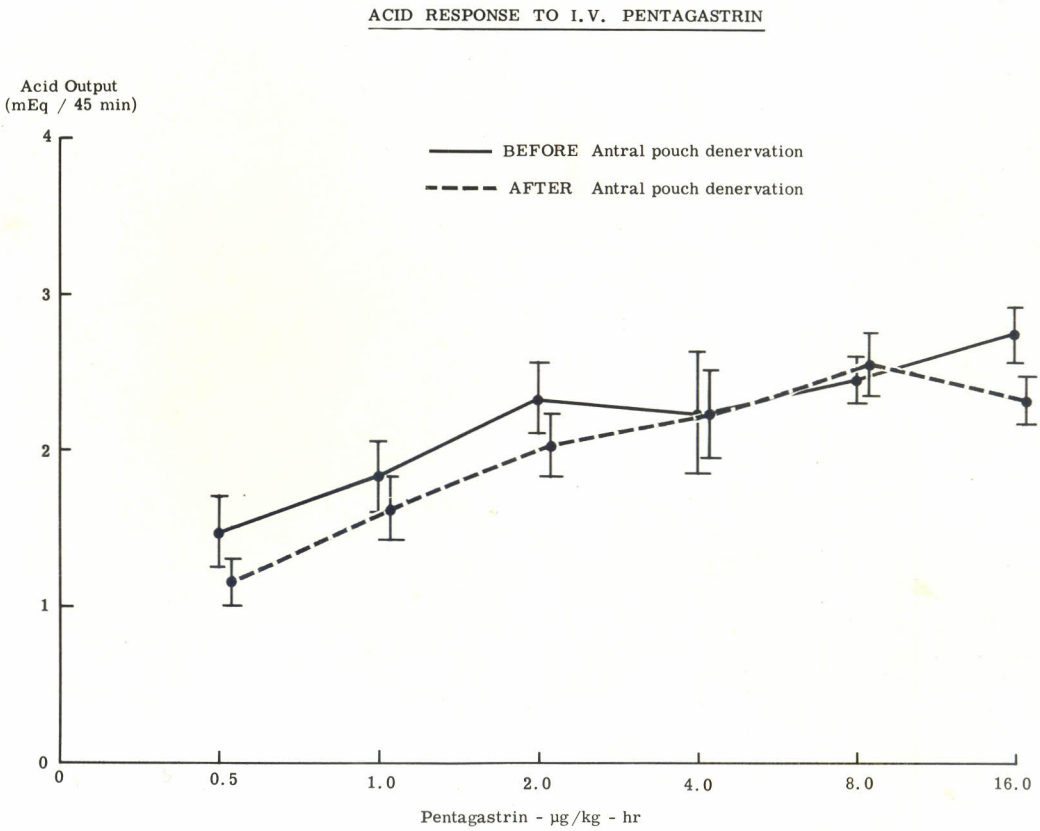
FIG. 8. Heidenhain pouch acid response to intravenous
pentagastrin before and after antral pouch
denervation. Each point represents three
observations on each of the three dogs.
Vertical bars indicate standard error of the
mean.

FIG. 9. Effect of antral pouch denervation on acid
response from Heidenhain pouch to varying
doses of intravenous histamine. Each point
represents three experiments on each of the
three dogs. Vertical bars indicate standard
error of the mean.

ACID RESPONSE TO MEAL
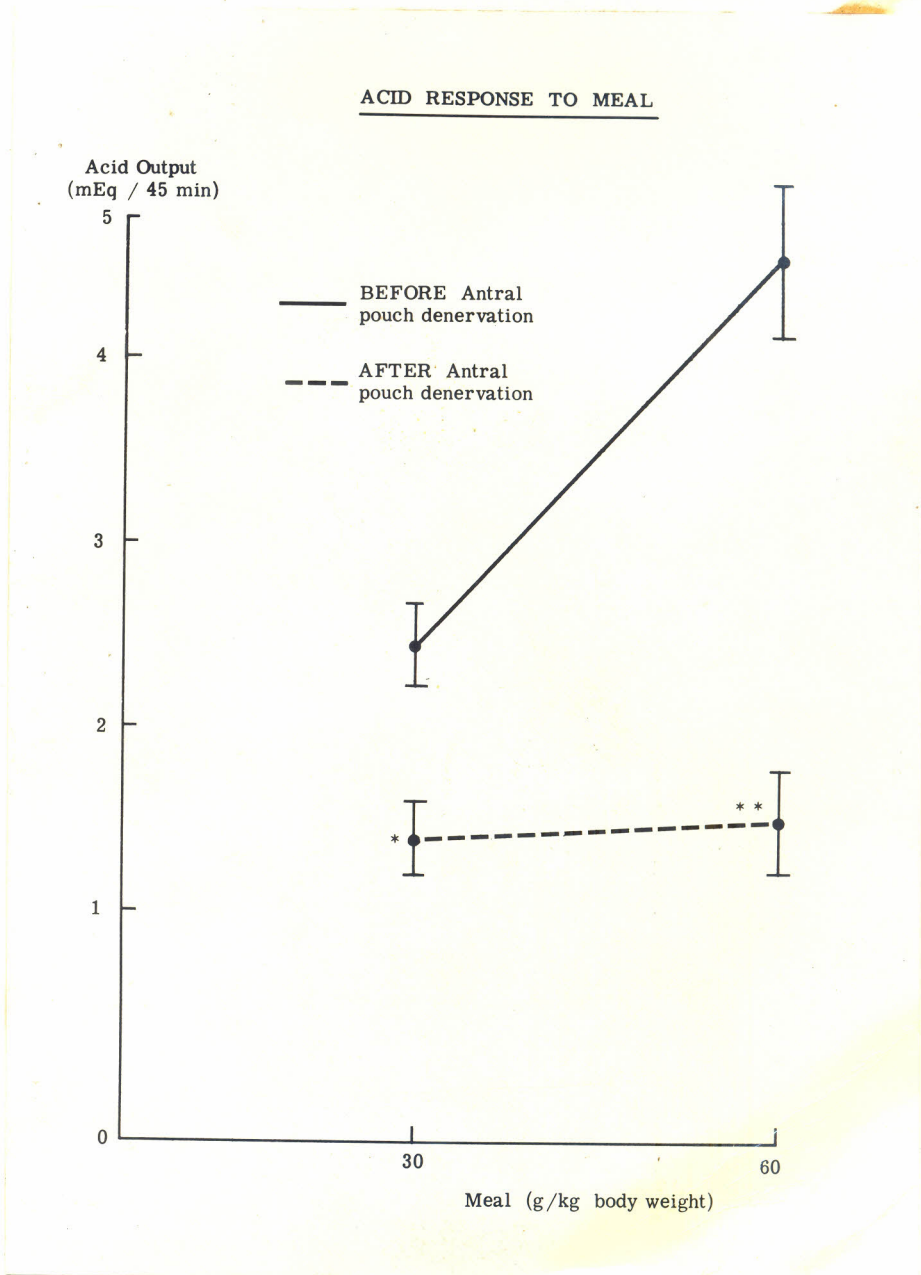
FIG. 10. Peak acid response from Heidenhain pouch to different amounts of standard meal before and after denervation of the antral pouch. Each point represents three experiments in each of the three dogs. Vertical lines indicate standard error of the mean; asterisks the degree of significance of difference between responses before and after denervation of the antral pouch; * 0.01<p<0.05; ** p<0.01. (0.01<p<0.05; ** 0.001<p<0.01; *** p<0.001)

ACID RESPONSE TO ANTRAL POUCH IRRIGATION WITH ACETYLCHOLINE

Acid Output
(mEq / 45 min)

——— BEFORE Antral pouch denervation

- - - - AFTER Antral pouch denervation

Acetylcholine Chloride - % Solution
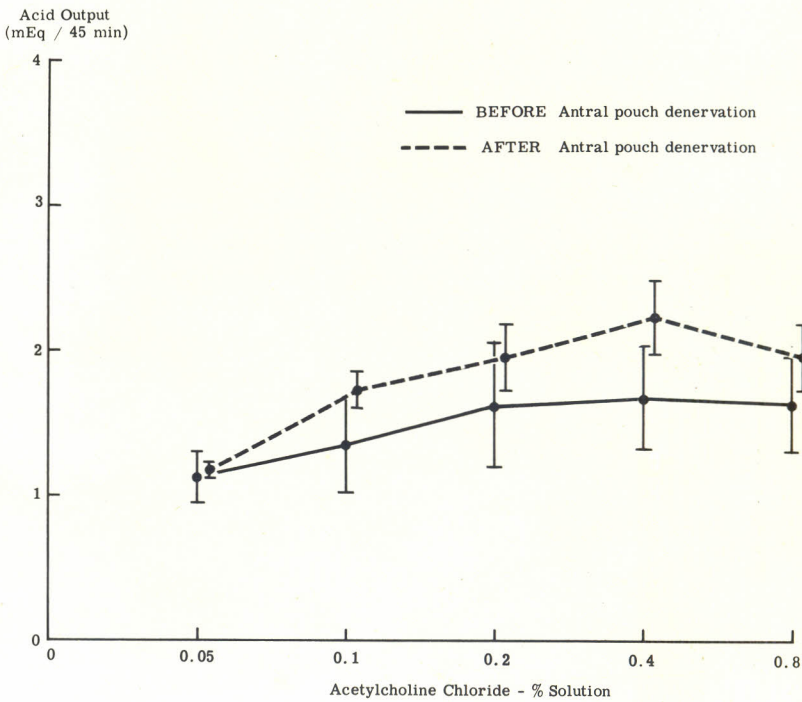
FIG. 11. Acid response from Heidenhain pouch to
antral pouch irrigation with varying
concentrations of acetylcholine
chloride solution, before and after
denervation of the antral pouch. Each
point represents three experiments in
each of the three dogs. Vertical bars
indicate standard error of the mean.

Effect on Antral Pouch Denervation on Acid
Response to Combined Feeding and Antral Pouch
Irrigation with Acetylcholine Chloride Solution

The peak acid response to 30 g./kg. meal combined with
continuous antral pouch irrigation with 0.4% acetylcholine
chloride solution, was identical with the response obtained when
the meal was increased to 60 g./kg. Denervation of the antral
pouch made no significant difference to this relationship ($p > 0.05$).
However, following denervation, the acid responses were markedly
reduced as compared with pre-denervation levels ($p < 0.01$ in either
case), and represented about 60% of the original (Fig.12).

The above findings on the effect of antral denervation are
summarised in Fig. 13. Details of the results are shown in Tables
VIII to XVIII.

DISCUSSION

The effectiveness of the antral denervation in greatly de-
creasing the efficiency of the vagal release of gastrin was shown
by the marked reduction in the acid response to 2-D-G in all 3
dogs. This finding is in agreement with that of Eisenberg,
et. al.[38]; Emase and Grossman[39]; and Emas, et. al.[36].

In contrast, there is no general agreement on the effect of
vagal denervation of the isolated gastric antrum on the Heiden-
hain pouch response to histamine. Anderson and Grossman[40], found
that denervation of antral pouches resulted in a reduction of the
Heidenhain Pouch acid response to submaximal but not to maximal
doses of histamine. In 1969 Emas, et. al.[33] reported no change
in the response of the Heidenhain pouch to submaximal doses of
histamine, following antral pouch denervation. The present
observations, suggest that the acid output from the denervated
fundic pouches in response to both submaximal and maximal doses
remain unaltered after antral pouch denervation. This casts some
doubt on the hypothesis that intact vagal innervation of the antrum
potentiates acid response to injected histamine[40].

ACID RESPONSE TO MEAL AND ANTRAL POUCH IRRIGATION

WITH 0.4% ACETYLCHOLINE
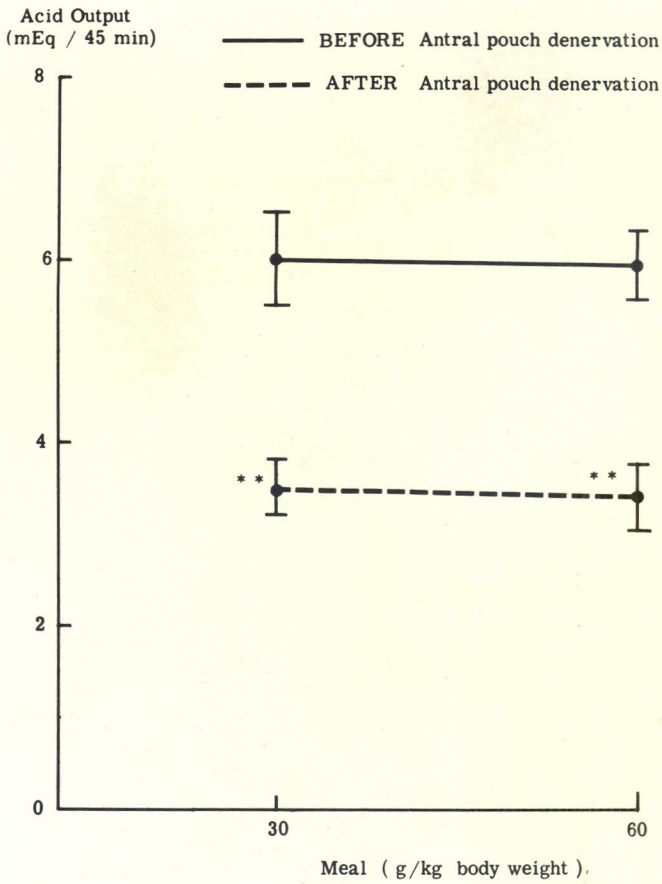
FIG. 12. Effect of antral pouch denervation on
Heidenhain pouch acid response to
simultaneous feeding and irrigation of
the antral mucosa with acetylcholine
solution. Each point represents three
experiments in each of the three dogs.
Vertical bars indicate standard error
of the man; asterisks the degree of
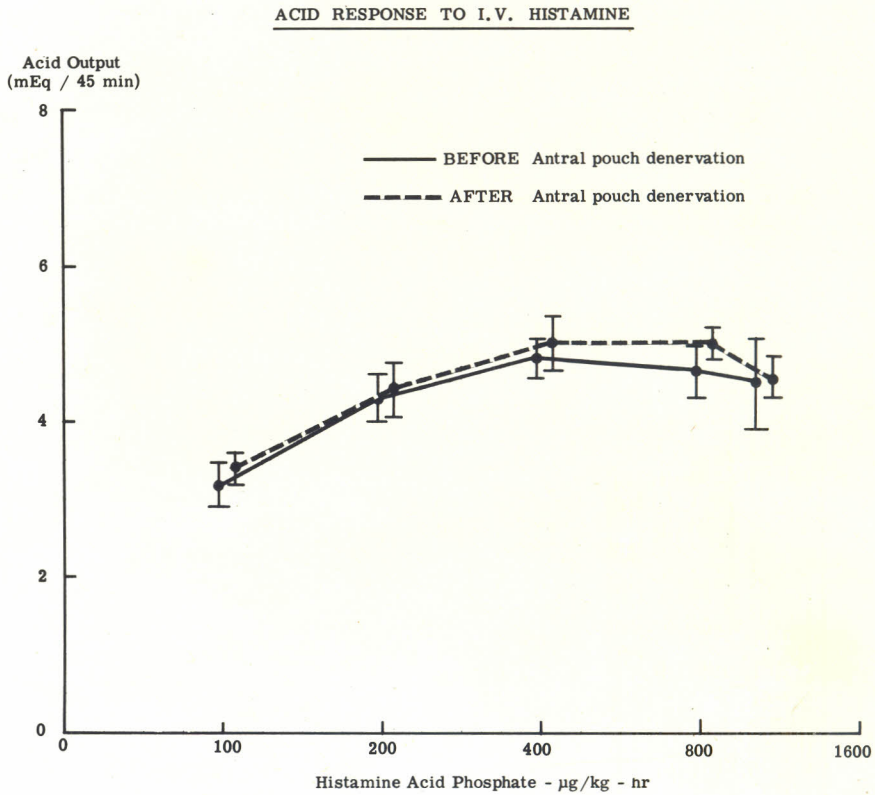significance of difference between
responses before and after antral pouch
denervation, ** p<0.01.

MAXIMAL ACID RESPONSES FROM HEIDENHAIN POUCHES
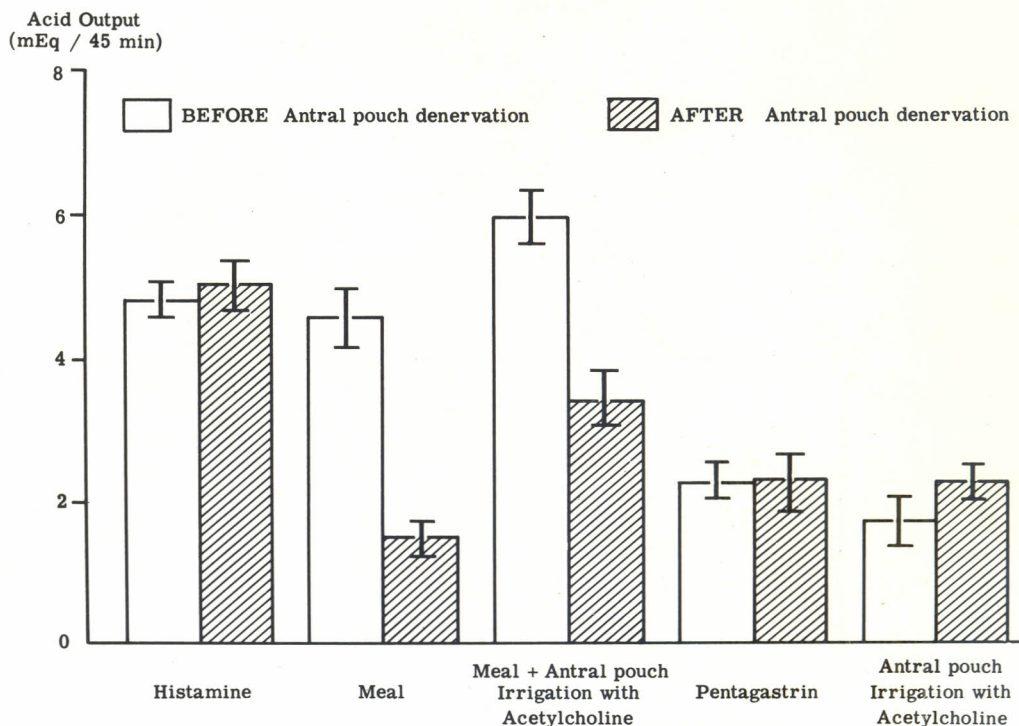
FIG. 13. A summary of the effect of denervating the antral pouch on peak acid response from Heidenhain pouch to histamine, meal, simultaneous feeding and antral pouch irrigation with acetylcholine solution, intravenous pentagastrin and to bathing antral mucosa with acetylcholine solution. Each result represents three experiments in each of the three dogs; standard error of the mean is shown by the sort vertical bar.

The present findings with regard to acid response curves to varying doses of pentagastrin resemble those obtained with histamine acid phosphate, namely, that antral pouch denervation produced no significant change in the response. This conficts with the observations of Andersson and Grossman[40] who found no alteration in the submaximal but a significant reduction in the maximal acid response to gastrin following antral denervation. However, Emas, et. al.[33] found no change in acid response to *gastrin after antral pouch denervation; indeed it appeared as* though the acid output continued to increase above the pre-vagotomy levels with the last largest dose of gastrin(3.2g/kg-hr) given. From the present results, there is nothing to suggest that a vagal background in the isolated antrum is essential for the full efficiency of exogenous gastrin to evoke acid response from a denervated fundic pouch.

Forrest[31] making studies on dogs surgically prepared in the same fashion as in this experiment, found that denervation of the antral pouch by division of its sero-muscular connection with the main stomach resulted in a reduction of the 24 hour hypersecretion of acid which had been provoked by the construction of the antral pouch. Thal, et. al.[32] studying the physiological effects of the various types of gastrectomy on acid secretion, found that 8 hour acid response to a standard meal was increased by the operation of tubular gastrectomy in which vagal fibres to the antrum were pre-served. Conversely, section of the antral vagal fibres during the operation of segmental gastrectomy did not result in this acid hypersecretion state. Further, they observed that division of the vagal fibres to the antrum after tubular gastrectomy was followed by a temporary reduction in gastric acid secretion. Wohlrabe and Kelly[35] found similar results on monitoring 24 hour acid response from denervated fundic pouches before and after antral pouch denervation. In all these experiments it was concluded that the vagus potentiated gastrin release. In the experiments of Thal, et. al.[32] there was of course additional factor of food coming into actual contact with the antral mucosa thus exerting both its chemical and mechanical properties apart from vagal stimulation,

in releasing gastrin. In all these experiments, no attempt was made to quantitate the magnitude of the reduction in acid response consequent upon denervation of the antrum. Further, they failed to assess whether the fundic pouches themselves had in fact changed in their responsiveness to stimulants following antral denervation.

In the present study denervation of the isolated antral pouch resulted in a marked reduction of both submaximal and maximal acid response to a standard meal by 40% and 67% respectively. The fact that the fundic pouch responses to both histamine and pentagastrin remained unchanged throughout the two stage experiment suggest that the observed reduction in acid response to food was due to the denervation of the antral pouch. From the observations of the previous workers and the results of the present experiments it appears that intact vagal innervation of the gastric antrum is essential for both the maximal and overall acid response to food in a situation where other modifying factors such as direct contact of food with the antral mucosa, distension and acidification of the antrum are excluded.

There appears to be a major controversy and confusion regarding the effect of vagal denervation of the gastric antrum on its efficiency to release gastrin in response to local stimulants introduced into its lumen. Forrest[31] found that Heidenhain pouch acid response to antral pouch irrigation with liver extract was reduced following antral denervation. Wohlrable and Kelly[35] found no significant difference between the acid responses to perfusion of the antral pouch with acetylcholine both before and after antral denervation. Similarly, Myhus, et. al.[36] after their experiments concluded that vagal denervation of the isolated antrum did not significantly alter the response of the antrum to mechanical (distension) or chemical (alcohol) stimulation. However, Dragstedt, et. al.[41] found that vagal denervation of the antral pouch markedly reduced the release of gastrin in response to perfusions of the antral pouch with food (liver), but had little or no effect if the perfusated was acetylcholine solution. More recently, Emas, et. al.[33]

found a greatly decreased acid output from denervated fundic pouches in response to antral pouch irrigation with solutions of acetylcholine, after antral denervation. It is interesting that no changes were observed in acid response to exogenous gastrin and to submaximal doses (used) of histamine, yet in a previous paper from the same laboratory[40] it was reported that antral pouch denervation resulted in reduction of Heidenhain pouch acid response to submaximal doses of histamine and also to maximal response to exogenous gastrin, while no significant difference was noted in the maximal response of histamine or with submaximal doses of gastrin. In the present study, antral pouch denervation produced no significant change in the acid response to antral irrigation with acetylcholine solutions. This finding confirms that of Dragstedt, et. al.[41] and is indirectly supported by the constant observation that while local anaesthetics such as cocaine applied to the antral mucosa significantly reduce local gastrin release by antral perfusion with food or food extracts, they have little or no effect when the antral mucosa is bathed with acetylcholine solution[35, 42-45]. Further atropine inhibits the response to food and food extracts, acetylcholine and urecholine[35, 45]. These observations strongly suggest that food and food extracts act through a mucosal receptor and a nervous pathway in order to stimulate the gastrin releasing cell. It is likely that vagal tone plays an important part in the activity of this local nervous pathway. On the other hand, acetylcholine would appear to act directly on the gastrin releasing cell, hence its effect is not blocked by local anaesthetics or vagotomy, while atropine reduces its efficiency. Further work is certainly required to settle this matter in the same dogs and antral pouch perfusion done using food extract and acetylcholine solution with and without local anaesthetics, before and after antral denervation.

The results of acid response to combined antral pouch perfusion with 0.4% acetylcholine and feeding are interesting. Denervation of the antrum brought about marked reduction in acid output whether the amount of food given was 30 or 60 g/kg. However, comparing these responses and those obtained with 0.40%

acetylcholine solution or food alone, it is clearly seen that the acid response to the combined agents (giving the smaller meal) before antral denervation, was greater than the sum of the response to the same doses of the agents given separately, namely 6.0 mEq./45 minutes as opposed to 3.8 mEq./45 minutes. Nevertheless, this did not fulfil the criteria for potentiation proposed by Gillespie and Grossman[46]. This effect was not seen with the larger meal before denervation of the antrum, and not at all after antral denervation. This finding suggests, at any rate partially, that vagal supply to the antrum facilitates acid response to endogenously released stimulants.

Conclusions from Observations on the
Effect of Antral Pouch Denervation

1. Vagal denervation of an isolated antral pouch
    produced no significant alteration in acid re-
    sponse from a Heidenhain pouch in response to
    either submaximal or maximal doses of injected
    histamine or pentagastrin.

2. This observation casts some doubt on the hypo-
    thesis that intact vagal innervation of the
    gastric antrum potentiates acid response to
    injected histamine or exogenous gastrin.

3. Intact vagal innervation of the isolated antrum
    is essential for both the maximal and the over-
    all acid response of food. This confirms the
    suggestion of vagal release of gastrin. Denerva-
    tion of the isolated gastric antrum reduces the
    maximal acid response from the Heidenhain pouch
    to food by 60-70%. This gives some estimate of
    the extent of the role of vagal innervation of
    the antrum in the release and interaction of
    endogenously released stimulants of gastric acid
    secretion. Further support for this vital role
    of the vagus given by the results of combined
    feeding and antral pouch perfusion.

4. Vagal innervation of the antrum is
    not essential for full gastrin release
    in response to bathing the antral
    mucosa with acetylcholine chloride
    solution. Although at first sight
    this may appear to imply that vagal
    background in the antrum contributes
    little to local chemical release of
    gastrin, it probably reflects the
    special mode of action of acetyl-
    choline. Further work is required
    to settle this point by substituting
    food for acetylcholine in the antral
    pouch.

Effect of Antrectomy on Histamine Stimulated Acid Response

Acid dose response curves to intravenous histamine acid phosphate before and after antrectomy were not significantly different ($p > 0.05$ at all dose levels) Tables XI and XIX.

Effect of Antrectomy on the Maximal Acid Response to Meal

The peak acid response to meal (by feeding 60 g./kg. of the standard meal) was unaltered following antrectomy, as compared with the response obtained with the denervated antral pouch preparation ($p > 0.05$). However, antrectomy markedly reduced the peak acid response to the meal, relative to the output with innervated antral pouch ($p < 0.01$) Fig. 14. See also Table XX.

Comments on the Effect of Antrectomy on Heidenhain Pouch Response to Histamine and to Food

The observation that antrectomy did not significantly alter the acid output from denervated fundic pouches to histamine stimulation compared with the response obtained with denervated antral pouch, confirms the finding of Anderson and Grossman[40]. This suggests that the presence of an isolated, denervated and transplanted gastric antrum whose mucosa is free from both mechanical and chemical stimulation, has insignificant contribution to hestamine stimulated gastric acid secretion. Similarly, antrectomy produced no further change in acid response to meal. Thus, a denervated antrum, free from both mechanical and chemical stimulation is of little or no significance in the generation and action of endogenously released stimulants in response to food. Woodward, et al.[47] reported that antrectomy produced 86% reduction in 24 hours gastric acid output in both denervated and innervated fundic pouches of the stomach. In the previous section it was noted that antral pouch denervation caused a 60-70% reduction in the maximal acid response to meal from the Heidenhain pouch. It is therefore reasonable to suggest that the beneficial effect of antrectomy as used clinically in the management of duodenal[48] or gastric ulcers[49, 50] owes more to total exclusion

MAXIMAL ACID RESPONSES TO MEAL
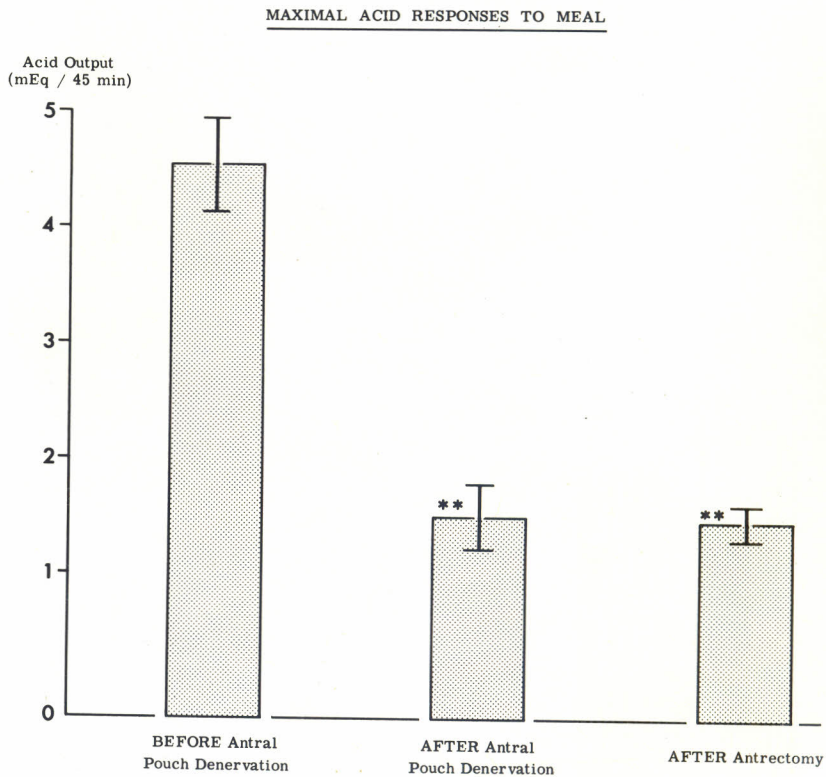
FIG. 14. Peak acid responses from Heidenhain pouch to maximally feeding the standard meal (60 gm/kg) before and after denervating the antral pouch, and after antrectomy. Each result represents three experiments in each of the three dogs. The short vertical bars indicate standard error of the mean; asterisks the degree of significance of difference between responses before and after antral pouch denervation, and before antral pouch denervation and after antrectomy; ** p<0.01.

and denervation of this part of the stomach than to its actual removal, in reducing endogenously released gastrin. The findings of Thal, et. al.[14] that tubular gastrectomy resulted in marked acid hypersecretion whereas segmented gastrectomy (which included the section of antral vagal fibres) did not produce this picture, but subsequent division of the vagal fibres to the antrum brought about a temporary reduction in gastric acid secretion, lend indirect support to this view.

CHAPTER 3

THE CONTRIBUTION OF THE VAGUS NERVES AND
THE STOMACH TO ACID RESPONSE TO FEEDING

Pavlov and his pupils[51] at the end of the last century performed experiments on dogs which led them to conclude that there existed several phases in the stimulation of gastric juice with food. In particular, this school recognised two phases of gastric secretion: the "cephalic phase" which was demonstrated experimentally by sham feeding, and the "gastric phase" in which the presence of food substances in the stomach itself evoked gastric secretion[52]. However, the suggestion of the existence of antral hormone was first made by Edkins[53] in 1906. Although the evidence to confirm Edkin's suggestion took a long time to arrive, the occurrence of gastrin, an antral hormone, is now undisputed. A few of the many recent reviews on the development of this significant discovery are those written by Gregory[54, 55] and Grossman[56]. Professor Gregory has the full credit for isolating this hormone. It is now known that food in contact with antral mucosa evokes antral gastrin release through mechanical[57] and chemical stimulation[45].

Although Pavlov[51] might have recognised that food in the small intestine may stimulated gastric secretion, the credit for the discovery of this fact is generally given to Leconte[58]. However, Ivy and his colleagues[59] were the first to produce convincing demonstration of the existence of an "intestinal phase" of gastric secretion in response to meal. In their experiments dogs were prepared with the entire stomach pouches, i.e. "total pouch" dogs. This inevitably created nutritional problems. Further, as the stomach pouches were totally denervated, the secretory responses must have represented only part of the true "intestinal phase" of gastric secretion. These animal preparations, as those of later workers[60,61] suffered from a common drawback in that both the stomach and duodenum were denervated. However, they served to incriminate a humoral agent analogous to gastrin released by the small intestine in response to food. Thus Dragstedt, et. al.[16] found that separately the vagus and the

antral gastrin phase appeared to contribute each approximately 45% of the 24 hour acid outputs, and therefore by substraction suggested that the "intestinal phase" of stimulation by meal was relatively unimportant, probably accounting for less than 10% of the total secretory response, and further, that this mechanism is normally inactive[62].

Recent work by Nyhus and his associates[36] indicates that the mechanism of gastric secretion in response to food is more intricate than was previously thought; and that the sharp divi- sion of the phases into 'cephalic', 'gastric' and 'intestinal' is inaccurate. Instead the phases of gastric secretion ought to be considered as direct vagal, vagal-antral, local antral and intestinal. We have recently reported[15] that partly digested food (chyme) introduced into the upper jejunum thus by-passing the upper gastrointestinal tract, accounts for between 18 and 38% of the total acid response to meal.   Realising the complex inter-relationship between nervous and humoral mechanisms evoked by meal, this study was designed to assess the contribution of the vagus together with the stomach in the gastric acid secretion in response to food.

METHODS

Surgical Techniques:

Three mongrel dogs, $(W_5, W_6$ and $W_7)$ each weighing 15-20kg. were used. Each dog was prepared with an innervated fundic pouch of the stomach constructed along the lines of Gregory's modification of the Pavlov. pouch[63]. The pouch was drained by a titanium Gregory type gastric cannula[64]. The first part of the duodenum was gently dissected free and a dacron tape about 2 cm. wide wrapped around it; the ends of the tape were sewn together with 3/0 silk, care being taken not to reduce the lumen of the gut. A titanium Gregory type duodenal cannula was inserted into the lower part of the antrum and the other end brought out to the surface through the abdonimal wall. Before closing the abdomen, the length between the duodenal band and the outer end of the

antral cannula, and the volume necessary to occlude the duo-
denum were assessed using a Foley type catheter passed along
the cannula to just beyond the duodenal band, and the bulb
gradually disended with air while gentle retrograde traction
was applied to the catheter until the catheter bulb failed to
move any further. Figure 15 shows the salient features of the
preparation.

Experimental Technique:

    Secretory tests were started four weeks after surgery.
In all experiments gastric juice from the innervated fundic
pouch was collected continuously by free drainage into
graduated test tubes. Every fifteen minutes the volume of
the juice was recorded and the concentration of acid deter-
mined.by titration with 0.01N sodium hydroxide solution to
the end point of 0.02% phenol red pH 6.8 to 8.4.

    After at least eighteen hours fast, basal secretion
was collected for at least thirty minutes.

    Insulin hypoglycaemia was used to confirm innervation
of the fundic pouches[10]. A dose of 0.5 units/kg. of soluble
insulin was given as a single intravenous injection and gas-
tric secretion collected from the pouch for at least two hrs.

    A dose-response curve of acid secretion from the fundic
pouches was determined using histamine acid phosphate. Solu-
tions of histamine acid phosphate were made in 0.9% saline and
administered by continuous intravenous slow infusion Palmer
pump (C.F. Palmer Limited, London) connected to an intravenous
catheter (size TW24, Polypeco Limited, Garden City, England)
via a 50 ml. Brunswick disposable sterile syringe and a number
23G $1\frac{1}{4}$ needle. The infusion rate was 21 ml./hour. Histamine
acid phosphate was given in doses on 0.05, 0.1, 0.2, 0.4 and
0.8 mg./kg.-hour.

    The meal consisted of a mixture of a commercial dog food
(made up of 1.8% carbohydrate, 11.5% protein and 7.5% fat and

dacron tape
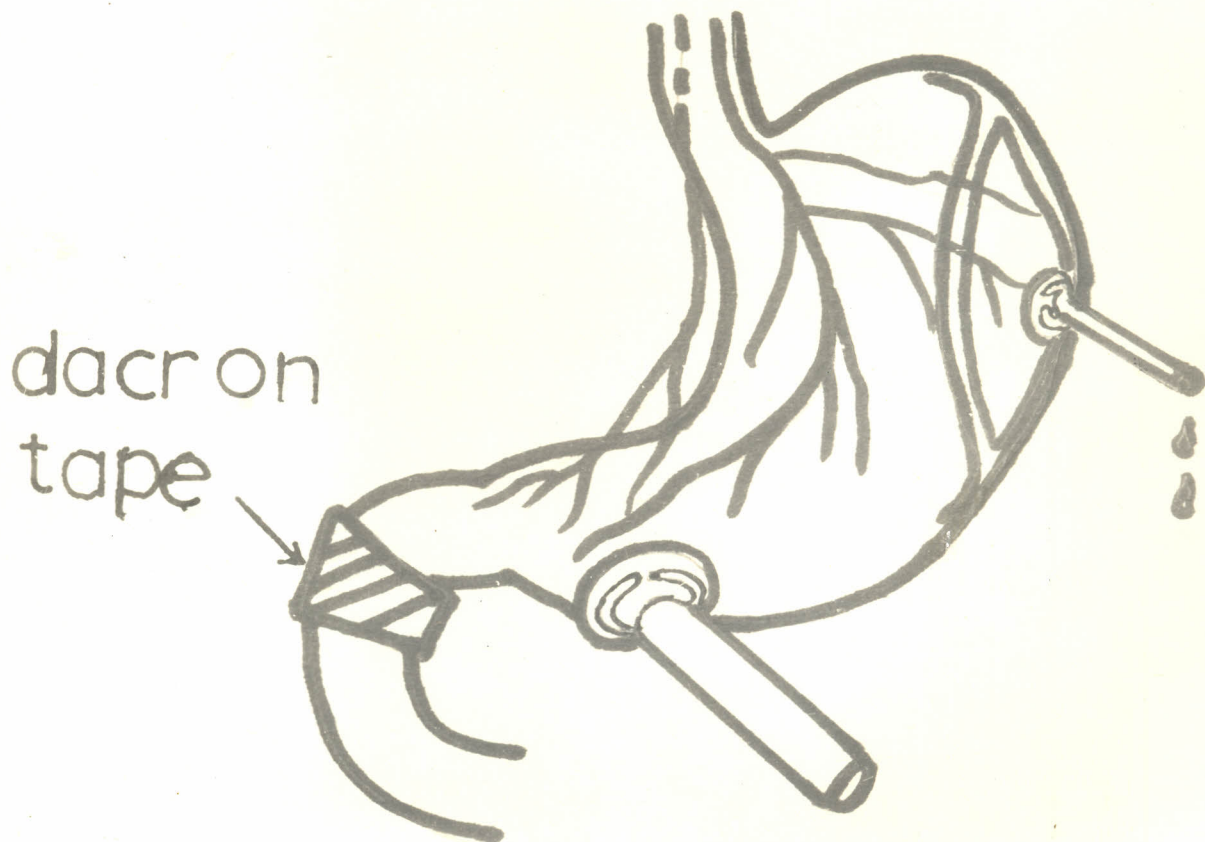
FIG. 15. Innervated fundic (Pavlov) pouch of
the stomach, a cannula inserted in
the antrum and a tape around the
duodenum are shown.

marketed under the trade name 'Luda Bangquet', Luda Meaties Ltd., Louch, England) 66%, with pureed ox liver, 33% in weight. Dogs were given the food mixture in amounts of 20 g./kg. and 40 g./kg. body weight (this larger amount of food being the maximum amount of food that could be eated completely within 30 minutes.) These meal experiments were carried out with the antral cannula closed, and again with the cannula open and the duodenum occluded by a Foley catheter, as described in the section of operative techniques, food and gastric secretions were thus diverted to the exterior through the cannula. The gastric contents were co-collected continuously and the volume determined at the end of three hours, in diversion experiments.

Barium meal studies were done to assess the time taken for the stomach to empty, using a total mixture of barium with the standard food of 40 g./kg. body weight. These tests were performed with the antral cannula closed.

In histamine experiments, each test was started using a small dose of this agent and acid output determined every 15 minutes until there was no change greater than 15% in three consecutive 15 minute acid outputs. The dose was then doubled and the procedure repeated. The acid output at each dose level was expressed in mEq. per 45 minutes (taking the sum of the last three steady outputs).

In meal experiments, 15 minute acid outputs were recorded following feeding until there was no further increase in acid response. The highest acid output in any three consecutive readings was taken to represent the response to that amount of food. Further observations were made with the 20 g./kg. meal in that acid collections were done until the secretion returned to basal levels, the acid response was then expressed in mEq./hour for each hour of the test.

For statistical analysis of the maximal acid responses, the mean maximal response to histamine acid phosphate was taken as 100% for each dog and all other responses to meal expressed as

a percentage of this. For the analysis of overall acid response to a meal, the mean total response to undiverted meal was taken as 100% and all responses expressed as a percentage of this.

RESULTS

Barium meal studies suggested that the stomach was empty within about three hours of feeding. (Figures 16 and 17).

The Effect of Insulin Induced Hypoglycaemia on Acid Secretion

Following an intravenous insulin at a dose of 0.5 units/kg. there was an increase in both the volume and concentration of acid secreted by the pouches. This secretory response started about 30 minutes after the injection of insulin, and lasted 2-3 hours. Blood sugar levels decreased in all experiments to 39 mg./100 ml. or lower (Tables XXI-XXIII).

Acid Output in Response to Histamine

Varying doses of intravenous infusion of histamine acid phosphate evoked a graded response of acid from the pouches, reaching a maximum with a dose of 400 ug./kg-hour, in all dogs. Administering a larger dose of histamine did not alter the acid response (Table XXIV).

Peak Acid Response to feeding with the Gastric Cannula Closed

Feeding the dogs with the standard meal in amounts of 20 g./kg. and 40 g./kg. resulted in similar peak acid outputs from the pouches ($p > 0.05$). Further, the peak acid response to either amount of meal was not statistically different to the maximal acid response to histamine ($p > 0.05$) (Figure 18).
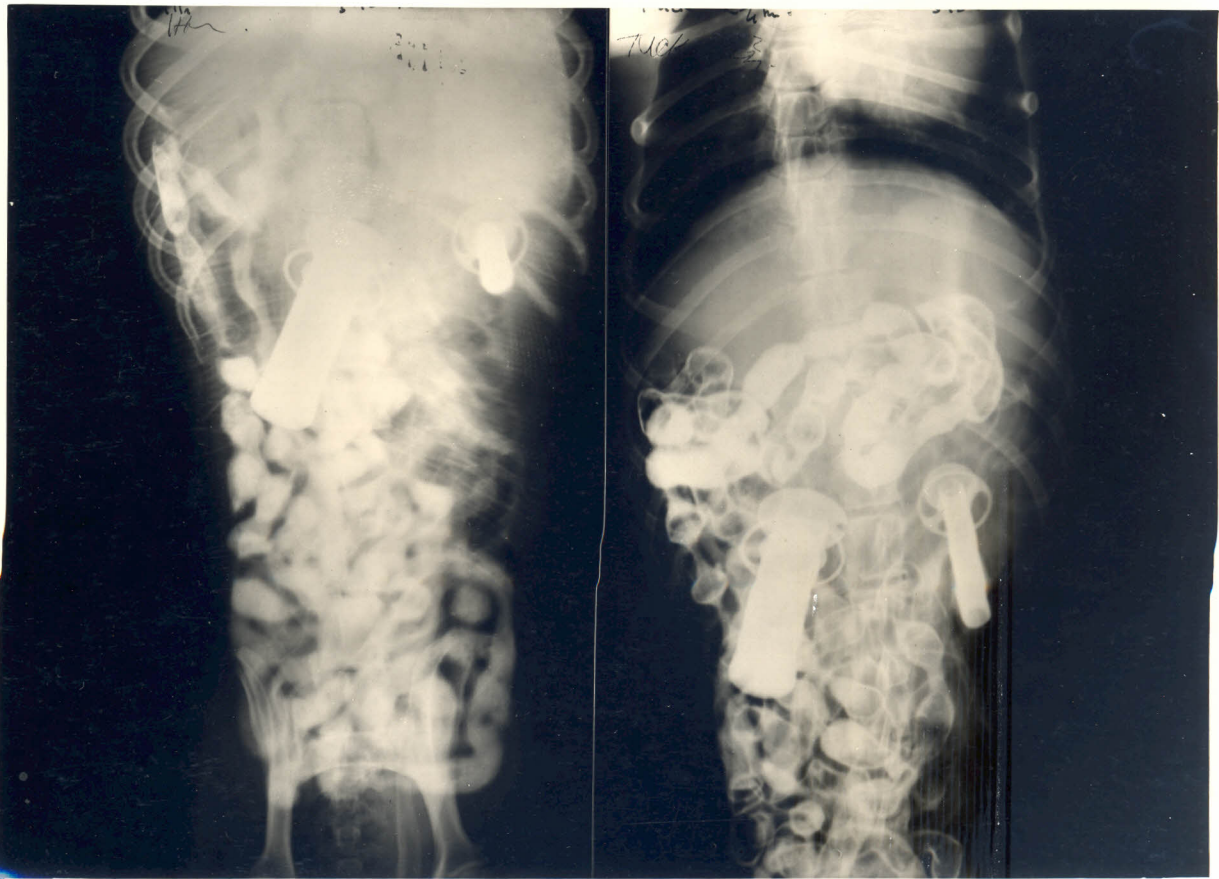
FIG. 16. Barium meal taken with the antral cannula
closed to assess gastric emptying time. The
picture on the left was taken 1 hour, and
the one on the right 3 hours after a barium
meal. There is hardly any barium in the
stomach at the end of three hours.

Dog W$_S$.
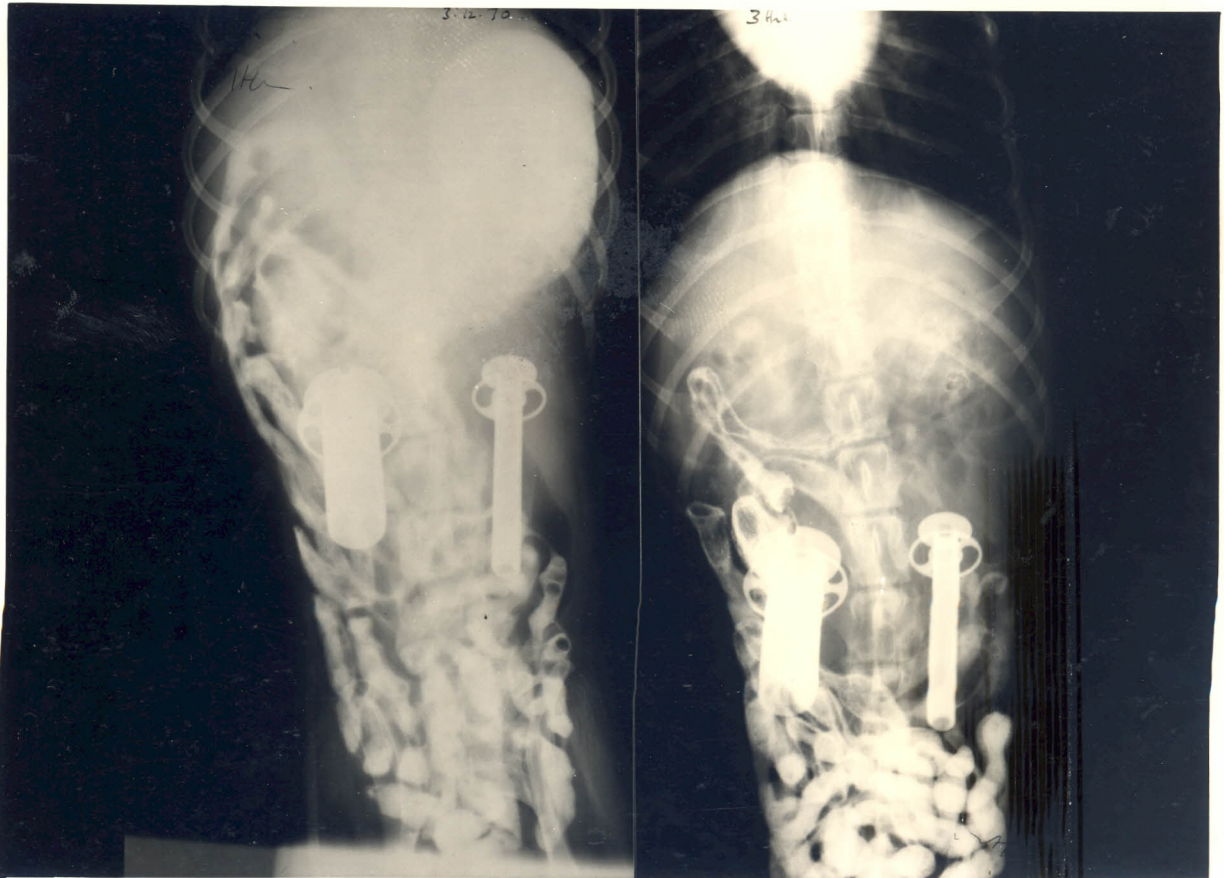
FIG. 17. Barium meal taken with the antral cannula
closed to assess gastric emptying time. The
picture on the left was taken 1 hour, and
the one on the right 3 hours after a barium
meal. There is hardly any barium in the
stomach at the end of three hours.

Dog W$_6$.
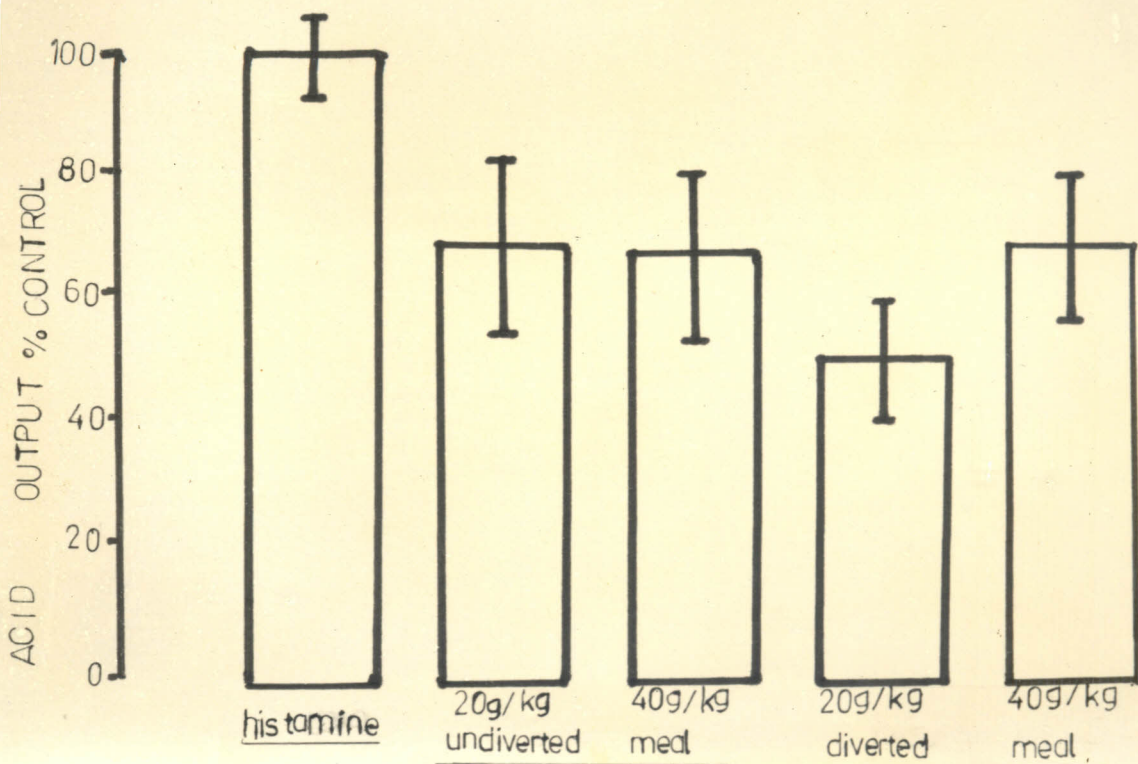
FIG. 18. Peak Pavlov (innervated) pouch acid response
to histamine, undiverted and diverted standard
meals. Peak acid response to histamine is
taken as 100%. Each result represents three
experiments in each of the three dogs. The
short vertical bars indicate standard error
of the mean.

Peak Acid Response To Feeding with the
Gastric Cannula Open and the Duodenum Occluded

With the food allowed to come out through the gastric
cannula, and the duodenum blocked with a Foley-type chatheter,
peak acid responses to 20 g./kg. and 40 g./kg. meals were not
statistically different ($p > 0.05$) and were the same as with the
gastric cannula closed ($p > 0.05$) Figure 18. In these diversion
experiments, the volume of the effluent from the gastric cannula
at the end of three hours was about 150-200% of that of the meal
administered.

Overall Acid Response to a Meal

When the dogs were fed a 20 g./kg. meal and acid response
monitored continuously until the secretion returned to basal
levels, it was found that the response in the first hour was the
same whether the gastric cannula was closed or open with duodenal
occlusion. However, from the second to the fifth hour the acid
response to the diverted food was significantly less than the
response to undiverted food ($p < 0.01$). The overall acid response
to the diverted meal was 54% of the total meal response, Fig.19.
Tables XXV-XXVIII give details of the meal results.

DISCUSSION

In our recent studies on the intestinal phase of acid
secretion in dogs [15] referred to above, we found that if chyme was
allowed to escape through a cannula in the upper jejunum, the
stomach was empty, as judged by barium meal examination, within
three to four hours after meal. The present observations suggest
that this time sequence was not unduly altered by the use of the
duodenal band. Further, the degree of the efficiency of the
diversion procedure, though not directly tested, was consistent
with our previous findings [15].

As in the study on acid responses from Heidenhain pouches
reported in the first part of this thesis, the maximal acid re-
sponses to histamine and food were approximately the same. In
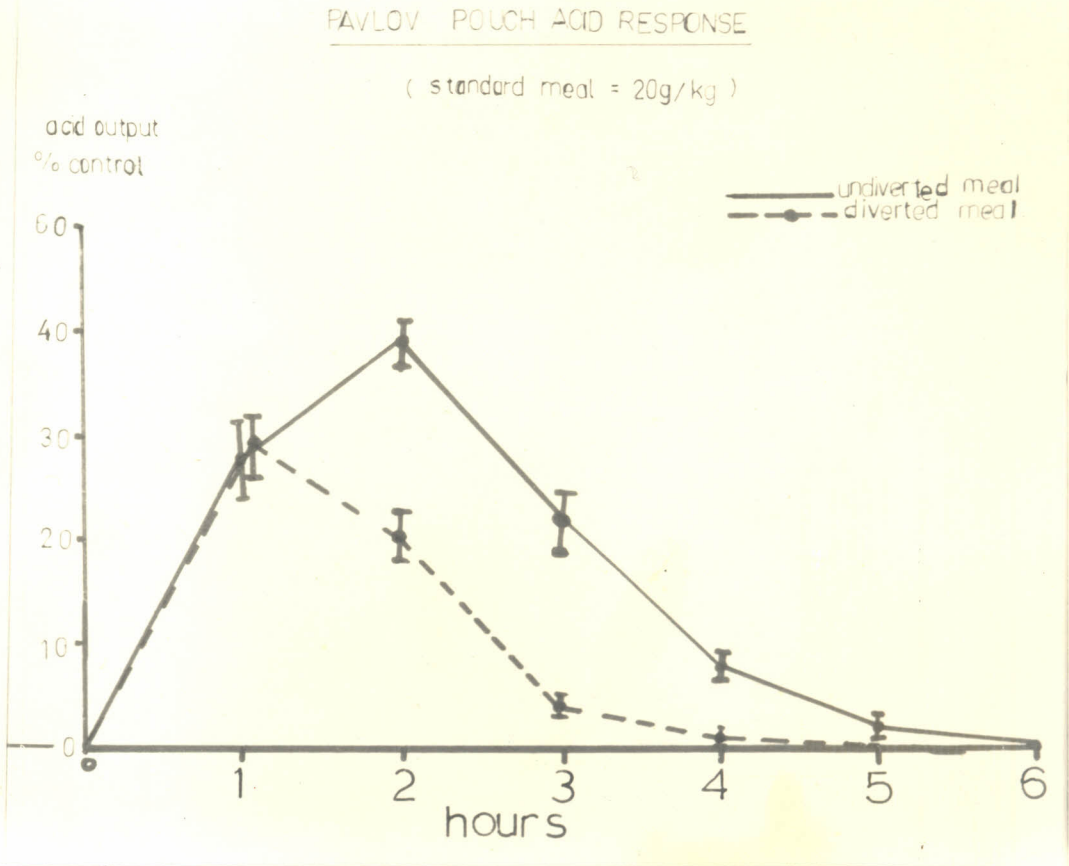
FIG. 19. Overall acid response from Pavlov pouch to
undiverted and diverted standard meal. Total
acid response in 6 hours is taken as 100%.
Each point represents three experiments in
each of the three dogs. Vertical bars
indicate standard error of the mean.

contrast with the Heidenhain pouch dogs, even 50% of the maximal amount of food that the dogs were able to tolerate, evoked the same degree of acid secretion from the innervated fundic pouches as histamine. This pattern of peak acid response was unaltered by diverting food through the gastric cannula. These results do suggest that the vagus and the stomach are responsible for the neuro-humoral mechanisms which stimulate peak acid response to the ingested food.

The further observation that the vagus and the stomach account for just over half the overall acid response to meal is important for several reasons. Firstly, it is a considerably smaller proportion than was thought by previous workers. Secondly, it indirectly reflects on the magnitude of the true intestinal component of acid secretion and possibly the potentiated effect of the various humoral agents released in response to meal.

Conclusions Drawn from these Studies:

1.   The vagus and the stomach are together responsible for the peak acid response to the ingested food.

2.   When consideration is taken of the entire physiological acid response to a meal, and in particular the time relations of this, there is a very sizeable contribution from the small intestinal phase. Thus the contribution of the vagus and the stomach to the overall acid response to food is considerably smaller than was once thought, amounting to about 54%.

3.   Further work with this animal preparation may be necessary to assess the contribution of the central vagal stimulation ('Cephalic' phase) indirectly, by introducing food into the stomach via the antral cannula.

TABLE I   INSULIN TEST

DOG W_1:

VOLUME (mls)	CONCENTRATION (uEq/Litre)	OUTPUT (uEq)
0.8	0	0
0.9	2	2
0.5	10	5
Insulin 10 I.U. I.V.,	Blood Sugar	105.5 mg.%
0.3	11	3
0.7	13	9
1.2	10	12 Blood Sugar 35mg.%
1.8	9	16
2.1	12	25
2.3	8	18
1.5	6	9
1.0	11	11
0.6	5	3

TABLE II   INSULIN TEST

DOG W_2:

VOLUME (mls)	CONCENTRATION (uEq/Litre)	OUTPUT (uEq)
0.7	20	14
0.3	36	12
1.0	13	13
2.1	9	18
12 I.U. Insulin I.V.,	Blood Sugar	104.9 mg.%
0.7	30	15
1.0	6	6
0.3	9	3
1.0	10	10 Blood Sugar 30.8 mg.%
0.8	4	3
1.0	8	8
0.7	13	9

TABLE III   INSULIN TEST

DOG W$_4$:

VOLUME (mls.)	CONCENTRATION (uEq/Litre)	OUTPUT (uEq)
1.0	60	60
1.0	80	80
1.0	70	70
Insulin 10 I.U. I.V.	Blood Sugar	111.5 mg.%
0.9	80	72
1.0	90	90
1.0	28	28 Blood Sugar 32.2 mg.%
0.5	22	11
0.4	25	10
0.7	20	13
1.0	13	13
0.8	14	11
0.7	12	8
0.3	33	10
1.0	11	11

TABLE IV

ACID RESPONSES OF HEIDENHAIN POUCH TO FEEDING

Acid Outputs in uEq./45 Minutes

DOG NO.	AMOUNT OF FOOD (g./kg.)	
	30	60
W_1	2481	4398
	1951	6731
	1817	7237
W_2	3825	9038
	4305	8499
	4417	8625
W_4	2809	6747
	4746	5202
	3502	5351
MEANS	3398	6870
S.E.M.	415	550

TABLE V

ACID RESPONSES OF HEIDENHAIN POUCH TO HISTAMINE

Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. HISTAMINE ACID PHOSPHATE DOSE (ug./Kg.-hour)					
	25	50	100	200	400	800
W_1	1500	2434	5179	6540	7735	6302
	1004	2580	4683	5985	7985	6509
	660	1335	3842	9301	9301	8045
W_2	1094	2326	3825	6794	4794	6364
	1054	2352	3028	6138	6138	5988
	651	1700	1829	6170	6170	6964
W_4	3718	4150	6707	8340	8170	7014
	1495	5337	7098	8062	8500	6521
	1462	2355	4013	5292	5715	6825
MEANS	1404	2864	4467	6032	7839	6764
S.E.M.	308	487	559	516	411	300

58.

TABLE VI

ACID RESPONSES OF HEIDENHAIN POUCH TO PENTAGASTRIN

Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. PENTAGASTRIN DOSE (ug./Kg.-hour)					
	0.25	0.5	1.0	2.0	4.0	8.0
W_1	859	921	1579	2814	2799	3313
	914	1452	2421	1927	1990	1881
	435	1023	1069	2136	2875	2601
W_2	506	962	1900	2971	4580	4875
	3	220	2499	3004	3471	4432
	2	219	2385	3009	4500	4650
W_4	1461	1379	3038	2806	3696	3493
	508	1842	2270	2164	3236	3129
	1163	1130	1990	2217	2097	1924
MEANS	650	1016	2128	2560	3249	3292
S.E.M.	164	178	191	146	308	429

TABLE VII   INSULIN TEST

DOG W$_3$:

VOLUME (mls)	CONCENTRATION (uEq/Litre)	OUTPUT (uEq)
0.4	88	35
0.2	75	15
1.1	11	11
Insulin 10 I.U. I.V.	Blood Sugar	110.8 mg.%
3.0	3	10
2.0	3	6
0.8	10	15 Blood Sugar 32.5 mg.%
0.7	20	14
0.3	45	15
0.5	32	16
0.6	40,	20
0.4	38	15
0.5	26	13
0.3	21	7
0.6	11	5
0.7	14	10

TABLE VIII

ACID RESPONSES OF HEIDENHAIN POUCH TO
PENTAGASTRIN BEFORE ANTRAL POUCH DENERVATION
Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. PENTAGASTRIN DOSE (ug./kg.-hour)					
	0.5	1.0	2.0	4.0	8.0	16.0
W_2	1265	1075	2020	2689	2476	2588
	814	1902	2300	2832	3105	3141
	777	1129	1827	2459	2120	2757
W_3	1447	2765	2874	930		
	1648	2268	2321	776		
	707	681	1107	825		
W_4	2531	1945	2238	3437	1990	2391
	2296	2355	3198	3022	2410	3396
	1767	2319	3031	2948	2695	2320
MEANS	1472	1827	2324	2213	2466	2766
S.E.M.	219	235	217	354	164	174

TABLE IX

ACID RESPONSES OF HEIDENHAIN POUCH TO

PENTAGASTRIN AFTER ANTRAL POUCH DENERVATION

Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. PENTAGASTRIN DOSE (ug./kg.-hour)					
	0.5	1.0	2.0	4.0	8.0	16.0
W_2	1495	1879	2444	2677	2240	2236
	1232	1581	2213	2713	3101	2161
	950	1502	2137	2609	3150	2537
W_3	480	1317	1346	910		
	235	495	857	722		
	1520	2685	3024	2773		
W_4	295	1715	2012	2590	2241	1849
	2697	2263	1808	2001	2045	2927
	1551	2033	2316	3140	2755	2295
MEANS	1162	1718	2017	2237	2589	2334
S.E.M.	260	206	210	286	195	149

TABLE X

ACID RESPONSES OF HEIDENHAIN POUCH TO HISTAMINE

BEFORE ANTRAL POUCH DENERVATION

Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. HISTAMINE ACID PHOSPHATE DOSE (ug./kg.-hour)				
	100	200	400	800	1100
W$_2$	2852	3588	3495	4732	3333
	1513	3080	4497	4593	3950
	2902	3710	5126	5508	5163
W$_3$	3386	4830	5898	5977	5403
	3904	5365	4049	2380	7650
	3958	5752	5632	3641	1504
W$_4$	2728	3728	4960	4630	4176
	4150	4524	4671	5422	4713
	3460	4189	4944	5218	4467
MEANS	3206	4307	4808	4678	4484
S.E.M.	272	295	248	365	552

TABLE XI

ACID RESPONSES OF HEIDENHAIN POUCH TO

HISTAMINE AFTER ANTRAL POUCH DENERVATION

Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. HISTAMINE ACID PHOSPHATE DOSE (ug./kg.-hour)				
	100	200	400	800	1100
W_2	2818	4011	4417	4170	3583
	3060	4645	4580	4685	3998
	2086	2671	3106	4093	4026
W_3	3677	4895	6140	5456	5607
	4148	6698	6464	5567	5437
	3974	4550	5277	5803	5791
W_4	4062	4630	5419	5153	4338
	3519	3594	4150	4402	3887
	2933	3820	4495	5269	4246
MEANS	3364	4390	4894	4958	4545
S.E.M.	230	368	347	212	277

TABLE XII

ACID RESPONSES OF HEIDENHAIN POUCH TO FEEDING

BEFORE ANTRAL POUCH DENERVATION

Acid Outputs in uEq./45 Minutes

DOG NO.	AMOUNT OF FOOD (g./kg.)	
	30	60
W_2	1199	3696
	1774	3482
	2602	3201
W_3	3392	4933
	3206	7055
	2713	5983
W_4	1905	3389
	2865	5098
	2402	4082
MEANS	2451	4547
S.E.M.	237	441

TABLE XIII

ACID RESPONSES OF HEIDENHAIN POUCH TO FEEDING

AFTER ANTRAL POUCH DENERVATION

Acid Outputs in uEq./45 Minutes

DOG NO.	AMOUNT OF FOOD (g./kg.)	
	30	60
W_2	1907	700
	908	620
	775	1019
W_3	2099	2392
	1432	2497
	2477	2660
W_4	1363	1248
	740	782
	980	1550
MEANS	1409	1496
S.E.M.	209	273

TABLE XIV

ACID RESPONSES OF HEIDENHAIN POUCH TO IRRIGATION OF

INNERVATED ANTRAL POUCH WITH ACETYLCHOLINE CHLORIDE SOLUTION

Acid Outputs in uEq./45 Minutes

DOG NO.	ACH CHLORIDE SOLUTION (%)				
	0.05	0.1	0.2	0.4	0.8
W_2	1726	1100	3852	3661	3255
	1062	2566	3540	2169	1756
	2685	3021	848	2470	1846
W_3	620	480	700	353	355
	3	260	354	658	150
	35	92	210	255	990
W_4	1389	1414	1732	1830	1767
	1555	1690	1785	1593	1703
	954	1520	1586	2117	2763
MEANS	1114	1349	1623	1678	1620
S.E.M.	283	334	437	370	338

TABLE XV

ACID RESPONSES OF HEIDENHAIN POUCH TO IRRIGATION OF

DENERVATED ANTRAL POUCH WITH ACETYLCHOLINE CHLORIDE SOLUTION

Acid Outputs in uEq./45 Minutes

DOG NO.	ACH CHLORIDE SOLUTION (%)				
	0.05	0.1	0.2	0.4	0.8
W_2	1264	1877	2498	2665	2454
	1074	2081	2895	2906	2865
	1172	1801	2167	2826	2673
W_3	954	1512	985	1301	1192
	1122	1412	1370	1670	1898
	904	1182	1242	1445	1106
W_4	1484	2058	2405	2535	1908
	1188	1551	1801	1409	1202
	1368	2146	2312	3246	2126
MEANS	1170	1735	1964	2222	1936
S.E.M.	61	112	216	252	220

TABLE XVII

ACID RESPONSES OF HEIDENHAIN POUCH TO COMBINED FEEDING
WITH IRRIGATION OF THE DENERVATED ANTRAL POUCH
WITH 0.4% ACETYLCHOLINE CHLORIDE SOLUTION
Acid Outputs in uEq./45 Minutes

DOG. NO.	AMOUNT OF FOOD (g./kg.)	
	30	60
W_2	3698	4208
	4550	4876
	4856	4377
W_3	4155	3717
	3586	3332
	2827	3259
W_4	2732	1691
	2108	2977
	2558	2418
MEANS	3452	3428
S.E.M.	318	333

TABLE XIX

ACID RESPONSES OF HEIDENHAIN POUCH TO HISTAMINE AFTER ANTRECTOMY

Acid Outputs in uEq./45 Minutes

DOG NO.	I.V. HISTAMINE ACID PHOSPHATE DOSE (ug./kg.-hour)			
	100	200	400	800
W_2	1905	3616	4460	4275
	2780	4270	4451	4327
	2712	3039	4407	4419
W_3	3293	6380	6960	7356
	4054	6425	8370	8614
	4488	7280	9078	8260
W_4	2321	3158	4276	2975
	2527	4157	5860	5969
	2844	3848	4252	3605
MEANS	2992	4686	5790	5533
S.E.M.	275	521	634	697

TABLE XX

MAXIMAL ACID RESPONSES OF HEIDENHAIN PO
TO FEEDING AFTER ANTRECTOMY
Acid Outputs in uEq./45 Minutes

DOG NO.	AMOUNT OF FOOD 60 g./kg.
W_2	1174 860 940
W_3	1813 1407 2364
W_4	1518 1467 1491
MEANS	1448
S.E.M.	152

TABLE XXI   INSULIN TEST

DOG W$_5$:

VOLUME (mls)	CONCENTRATION (uEq/Litre)	OUTPUT (uEq)
1.5	110	165
1.5	120	180
1.6	100	160
Insulin 8 I.U. I.V. Blood Sugar		105 mg.%
1.5	100	150
1.5	80	120
3.5	130	455 Blood Sugar 37.2 mg.%
3.0	145	435
2.0	100	200
1.8	95	170
1.5	100	150
1.5	83	125

TABLE XXII   INSULIN TEST

DOG W$_6$:

VOLUME (mls)	CONCENTRATION (uEq/Litre)	OUTPUT (uEq.)
0.0	0	0
0.1	0	0
0.1	50	0
Insulin 8 I.U. I.V. Blood Sugar		102 mg.%
0.2	0	0
0.2	30	6
0.5	50	25 Blood Sugar 29 mg.%
0.4	120	48
0.6	83	50
0.5	80	40
0.6	66	40
0.9	80	70

TABLE XXIII   INSULIN TEST

DOG W$_7$:

VOLUME (mls)	CONCENTRATION (uEq./Litre)	OUTPUT (uEq.)
0.0	0	0
0.0	0	0
0.6	0	0
0.4	(2)	1
Insulin 8 I.U. I.V. Blood Sugar		106 mg.%
0.1	10	1
1.0	60	60
1.3	92	120 Blood Sugar 39 mg.%
0.4	75	30
0.6	70	42
0.6	60	35
0.5	70	35
0.5	80	40

TABLE XXIV

ACID RESPONSE OF PAVLOV POUCH TO HISTAMINE
Acid Outputs in uEq./45 Minute and % Control

DOG NO.	Control uEq./45 Min.	I.V. HISTAMINE ACID PHOSPHATE (ug./Kg.-hour)									
		50		100		200		400		800	
		uEq./ 45 Min.	% Control	uEq./ 45 Min.	% Control	uEq./ 45 Min.	% Control	uEq./ 45 Min.	% Control	uEq./ 45 Min.	% Control
W_5	3063	520	17	1072	35	2081	68	2808	92	2385	78
		1379	45	2211	72	3186	104	3750	122	3250	106
		747	24	1285	42	1872	61	2630	86	3010	98
W_6	699	30	4	220	31	355	51	510	73	425	61
		240	34	399	57	836	119	848	121	620	89
		50	7	141	20	320	46	739	106	550	79
W_7	2494	921	37	1755	70	2254	90	2622	105	2264	91
		1322	53	1653	66	1944	78	2116	85	2090	84
		996	40	1732	69	2288	92	2745	110	2230	89
MEANS			29		51		79		100		86
S.E.M.			6		7		8		6		4

Control = Mean maximal acid response to histamine acid phosphate in each dog.

TABLE XXV

MAXIMAL ACID RESPONSES OF PAVLOV POUCH TO FEEDING

Acid Outputs in uEq./45 Minutes and % Control

DOG NO.	Control uEq./45 Min.	AMOUNT OF FOOD (g./kg.)			
		20		40	
		uEq./45 Min.	% Control	uEq.45/min.	% Control
W5	3063	3682	120	3053	100
		3075	100	3212	105
		4386	143	4516	147
W6	699	415	59	319	46
		336	48	245	35
		392	56	275	39
W7	2494	870	35	1347	54
		1034	41	1129	45
		667	27	941	38
MEANS			70		68
S.E.M.			14		13

Control = Mean maximal acid response to histamine acid phosphate in each dog.

TABLE XXVI

MAXIMAL ACID RESPONSES OF PAVLOV POUCH TO FOOD
DIVERTED THROUGH GASTRIC CANNULA
Acid Outputs in uEq./45 Minutes and % Control

DOG NO.	Control uEq./45 Min.	AMOUNT OF FOOD (g./kg.)			
		20		40	
		uEq./45 Min.	% Control	uEq./45 Min.	% Control
W_5	3063	2109	69	4202	137
		2637	86	3297	108
		2775	91	2665	87
W_6	699	386	55	340	49
		316	45	390	56
		195	28	398	57
W_7	2494	633	25	1102	44
		786	32	1440	58
		760	30	940	38
MEANS			51		70
S.E.M.			9		11

Control = Mean maximal acid response to histamine acid
phospahte in each dog.

TABLE XXVII

ACID RESPONSES OF PAVLOV POUCH TO A STANDARD 20 g./kg. MEAL

Acid Outputs in uEq./hour and % Control

DOG NO.	Control uEq./6 hrs.	HOURS AFTER FEEDING											
		1		2		3		4		5		6	
		uEq./hour	% Control	uEq./hour	% Control	uEq./hour	% Control	uEq./hour	% Control	uEq./hour	% Control	uEq./hour	% Control
W_5	10826	4863	45	4552	42	2138	20	680	6	183	2	0	0
		3292	30	3528	33	1962	18	807	7	381	4	0	0
		3402	31	4191	39	1524	14	700	6	220	2	0	0
W_6	1112	263	24	507	46	325	29	98	9	3	0	0	0
		50	4	411	37	336	30	85	8	0	0	0	0
		131	11	537	48	405	36	166	15	20	2	0	0
W_7	2576	820	32	742	29	391	15	145	6	35	1	0	0
		1093	42	1157	45	462	18	264	10	131	5	0	0
		900	35	783	30	517	20	233	9	55	2	0	0
MEANS			28		39		22		8		2		0
S.E.M.			4		2		3		1		0.5		0

Control = Mean overall acid response to the standard meal in 6 hours.

TABLE XXVIII

ACID RESPONSES OF PAVLOV POUCH TO A STANDARD 20 g./kg.
MEAL WITH DIVERSION THROUGH GASTRIC CANNULA
Acid Outputs in uEq./hour and % Control

DOG NO.	Control uEq./6 hrs.	HOURS AFTER FEEDING											
		1 uEq./hour	% Control	2 uEq./hour	% Control	3 uEq./hour	% Control	4 uEq./hour	% Control	5 uEq./hour	% Control	6 uEq./hour	% Control
W_5	10826	3250	30	2422	22	528	5	0	0	0	0	0	0
		3155	29	903	8	167	2	15	0	0	0	0	0
		1299	12	2689	25	295	3	660	6	10	0	0	0
W_6	1112	235	21	128	11	0	0	0	0	0	0	0	0
		351	31	269	24	50	4	0	0	0	0	0	0
		325	29	336	30	30	3	0	0	0	0	0	0
W_7	2576	935	36	561	22	95	4	0	0	0	0	0	0
		966	38	660	26	244	9	27	1	0	0	0	0
		798	31	431	17	177	7	6	0	0	0	0	0
MEANS			29		21		4		0.8		0		0
S.E.M.			3		2		0.9		0.6		0		0

Control = Mean overall acid response to the undiverted standard meal in 6 hours.

1.   Basic Animal Preparations and General Care:

In all experiments mongrel dogs weighing 15 to 20 kg. wer
used. All surgical operations were performed under endotrachea
general anaesthetic with 1% fluorothane and oxygen, after
induction with 10 ml. of 5% intravenous pentothal.   Aseptic pre
cautions and routine theatre rituals were observed throughout
operative procedures.

Middle incision was used for opening the abdomen. One or
more of the following procedures was carried out in each dog, to
gether with any special preparations, as pointed out in the rele
vant sections.

2.   Denervated Fundic (Heidenhain) Pouch:

This was prepared from the middle third of the greater
curve region of the stomach. The opening in the main stomach
and the pouch flap were both closed in two layers of continuous
suture, the inner one being catgut and outer 3/0 silk. Through
an approximately 1 cm. incision in the pouch the bevel of the
base of a Gregory type titanium cannula (C104-T Gregory type (A)
gastric tube, Down Brothers and Mayer and Phelps Limits, Mitcham,
England)[65] was introduced, and the cannula rotated into position
in the pouch. "Purse-string" 3/0 silk sutures were used to make
an air-tight closure of the pouch around the neck of the cannula.
After wrapping a layer of omentum around the pouch, the cannula
was brought out to the surface through a small stab wound to the
left of the main wound. The cannula was then anchored to the
abdominal wall using 2/0 silk stitches passed around the flange
at the neck of the cannula and deeply into abdominal wall muscu-
lature.

3.   Innervated Fundic Pouch:

Although innervated gastric pouch was invented by Pavlov,
and therefore bears his name, in this work where vagally inner-
vated fundic pouch was required it was constructed using the

method of Gregory's modification[63] of the original Pavlov pouch. After making a curved incision, about 5 cm. long in the middle third of the greater curvature of the stomach, a double mucosal septum was constructed to divide the rest of the stomach from the pouch. Three layers of continuous suture were used in constructing the septum: 4/0 silk for the two mucosal layers stitched separately, and fine catgut for the muscularis forming an intermediate layer. The insertion and anchorage of the Gregory cannula was the same as for the denervated fundic pouch above.

4.   Gastric Fistula:

A Gregory type titanium duodenal cannula (104-07-T duodenal tube, Down Brothers and Mayer and Phelps Limited, Mitcham, England) was introduced through the anterior wall of the stomach about 4 cm. proximal to the junctional zone between the fundus and the pyloric gland area. It was then passed through the abdominal would via a stab wound to the right of the main wound, fashioned to make the cannula site into the stomach the most dependent part of the stomach when the animal assumed the normal standing posture.

5.   Post-Operative Care:

The dogs were allowed only water and 200 ml. of milk to drink each day in the first two post-operative days. Normal kennel diet "Spillers" (Spillers Limited, Cambridge) was commenced on the third day. Antibiotics was administered postoperatively only if there had been soling of the peritoneal cavity at operation.

Throughout the period of experiments, the dogs were regularly weighed and also serum electrolytes estimations done.

Composition of the Commercial Dog Food Banquet
(Luda Meaties Limited, Louth, England) by weight:

Water	78.3%
*Protein	11.5%
Fat	7.5%

Carbohydrate	1.55%
Ash	1.15%

*Protein consisted of liver, lung and lean meat.

REFERENCES:

1.   FARRAR, G.E., & BOWER, R.J. (1967). Gastric juice and
              Secretion: Physiology and Variations in
              disease. Ann. Rev. Physiol. 29: 141 - 168.

2.   GILLESPIE, I.E. (1969)in After Vagotomy
              Eds: Williams J.A. and Cox, A.G. Butterworths,
              PP 15-37.

3.   MYREN, J. & SEMB, L.S. (Eds): (1968). The Physiology of
              Gastric Secretion. Universitetsforlaget, Oslo.

4.   WASUNNA, A.E.O., Buxton, B.F., Bedi, B.S., and Gillespie,
              I.E., (1971) Acid Resposes of Denervated
              Fundic (Heidenhain) Pouches to meals compared
              with those to Histamine and Pentagastrin
              Scand. J. Gastroent. 6: 407-410.

5.   BROOKS, A.M. & GROSSMAN, M.I. 1970. Maximal acid response
              of Pavlov pouches to food and histamine. Gut
              11, 153, 157.

6.   CODE, C.F. & WATKINSON, G. 1955. Importance of vagal
              innervation in the regulatory effect of acid
              in the duodenum on gastric secretion of acid.
              J. Physiol. (Lond.) 130, 233-252.

7.   MASTER, S.P., GOVAERTS, J.P. & GILLESPIE, I.E. 1965.
              Physiological stimulation of gastric acid
              secretion to 'maximal' histamine levels. Brit.
              J. Surg. 52, 626.

8.   THOMAS, W.R.G. & FORREST, A.P.M. 1967. Acid secretion
              from canine separated fundic pouches. Gas-
              troenterology 52, 192-197.

9.   GREGORY, R.A. 1958. Gastric secretory responses after
              portal ligation. J. Physiol. (Lond.) 144,
              123-137.

10. JEMERIN, E.E., HOLLANDER, F. & WEINSTEIN, V.A. 1943.
              Comparison of insulin and food as stimuli
              for the differentiation of vagal and non-
              vagal gastric pouches. Gastroenterology
              1, 500-512.

11. IVY, A.C., LIM, T.M. & LANGBERG, G. 1957. Gastric
              secretory response to various amounts of
              food. Amer. J. Physiol. 188, 71-75.

12. GREGORY, R.A. & TRACY, H.J. 1960. Secretory responses
              of denervated gastric pouches. Amer. J.
              dig. Dis. 5, 308-323.

13.   GROSSMAN, M.I. 1961. Cholinergic potentiation of the
              response to gastrin, J. Physiol. (Lond.)
              157, 14p-15p.

14.   GROSSMAN, M.I. 1961. Stimulation of secretion of acid
              by distension of denervated fundic pouches
              in dogs. Gastroenterology 41, 385-390.

15.   BUXTON, B.F., WASUNNA, A.E.O., BEDI, B.S. & GILLESPIE,
              I.E. 1970. The magnitude of the intestinal
              phase of gastric acid secretion. Brit. J.
              Surg. 57, 857-858.

16.   DRAGSTEDT, L.R., OBERHELMAN, H.A., ZUBIRAN, J.M. &
              WOODWARD, E.R. 1953. Antrum motility as a
              stimulus for gastric secretion. Gastroen-
              terology 24, 71-78.

17.   ANDERSON, S. 1960. Inhibitory effects of HCI in antrum
              and duodenum on histamine-stimulated gastric
              secretion in Pavlov and Heidenhain pouch
              dogs. Acta physiol. scand. 50, 1-11.

18.   COOKE, A.R. 1968. Observations on the effect of diver-
              sion of acid from the duodenum in response
              to gastrin and histamine. Gastroenterology
              55, 268-271.

19.   STRAATEN, T. 1933. Die Bedeutung der Pylorusdrusenzone
              fur die magensaftsekretion. Ein experiment-
              eller Beitrag zur Resektionsbehandlung des
              Geschwursleidens. Arch. Klin Chir., 176:
              236-251.

20.   Uvnas, B. 1942. Thepart played by the pyloric region in
              the cephalic phase of gastric secretion. Acta
              Physiol. Scand., 4: suppl. 13: 1-86.

21.   LINDE, S. 1950. Studies on the stimulation mechanism of
              gastric secretion. Acta Physiol. Scand., 21,
              suppl. 74: 1-92.

22.   LIM, R.K.S. and MOZER, P. 1951. Does vagus excitation
              liberate pyloric gastrin.   Fed. Proc. 10: 84.

23.   Noring, O. 1951. The cephalic phase of gastric secretion
              following partial gastrectomy. Gastroen-
              terology, 19: 118-125.

24.   BURSTALL, P.A. and SCHOFIELD, B. 1954. The effects of
              pyloric antrectomy on the secretory responses
              of Heidenhain pouches in dogs to central vagal
              stimulation. J. Physiol., 123: 168-186.

25.   BABKIN, B.P. and SCHACHTER, M. 1944. The chemical phase
              of gastric secretion and the surgery of the
              stomach. McGill Med. J., 13: 127-138.

26.   JANOWITZ, H.D. and HOLLANDER, F. 1951. Critical evidence
              that vagal stimulation does not release gastrin.
              Proc. Soc. Exp. Biol. Med., 76: 49-52.

27.   PEVSNER, L. and GROSSMAN, M.I. 1955. The mechanism of
              vagal stimulation of gastric acid secretion.
              Gastroenterology, 28: 493-499.

28.   OLBE, L. 1963. Significance of vagal release of gastrin
              during the nervous phase of gastric secretion
              in dogs. Gastroenterology, 44: 463-468.

29.   OLBE, L. 1964. The effect of resection of gastrin releas-
              ing regions on acid response to sham feeding
              and insulin hypoglycaemia in Pavlov pouch dogs.
              Acta Physiol. Scand., 62: 169-175.

30.   OLBE, L. 1966. Vagal release of gastrin in Gastrin, edited
              by M.I. Grossman 1966. Butterworths (London),
              pp. 83-107.

31.   FORREST, A.P.M. 1956. The importance of innervation of
              the pyloric antrum in the control of gastric
              secretion in dogs. 20th International Congress
              of Physiology: Abstract of Communications
              pp. 299-300.

32.   THAL, A.P., PERRY, J.F. Jr., and WANGENSTEEN, O.H. 1957.
              The physiological effects of various types of
              gastrectomy on gastric acid production with
              special reference to the function of the dener-
              vated gastric antrum. Surgery, 41: 576-588.

33.   EMAS, S., VAGNE, M. and GROSSMAN, M.I. 1969. Heidenhain
              pouch response to antral stimulation before and
              after antral denervation in dogs. Proc. Soc.
              Exp. Biol., 132: 1162-1166.

34.   DRAGSTEDT, L.R., OBERHELMAN, H.A. Jr., STORER, E.H. and
              SMITH, C.A. 1951. Effect of transplantation
              of the antrum of stomach on gastric secretion
              in experimental animals. Amer. J. Physiol.,
              165: 386-397.

35.   WOHLRABLE, D.E. and KELLY, W.D. 1958. Studies on the role
              of the nervous mechanisms in antral function.
              Surg. Forum, 9: 430-433.

36.   NYHUS, L.M., CHAPMAN, N.D., de VINTRO, R.V. and HARKINS,
          H.N. 1960. The control of gastrin release :
          An experimental study illustrating a new
          concept. Gastroenterology, 39: 582-589.

37.   BARON, J.H., 1970. The clinical use of gastric function
          tests. Scand. J. Gastroent., suppl. 6: 9-46.

38.   EISENBERG, M.M., EMAS, S. and GROSSMAN, M.I. 1966.
          Comparison of the effect of 2-deoxy-D-glucose
          and insulin on gastric secretion in dogs.
          Surgery, 60: 111-117.

39.   EMAS, S. and GROSSMAN, M.I. 1969. Response to Heidenhain
          pouch to histamine, gastrin and feeding before
          and after truncal vagotomy in dogs. Scand. J.
          Gastroent., 4: 497-503.

40.   ANDERSON, S. and GROSSMAN, M.I. 1966. Effect of denerva-
          tion and subsequent resection of antral pouches
          on secretion from Heidenhain pouches in respons
          to gastrin and histamine. Gastroenterology,
          51: 4-9.

41.   DRAGSTEDT, L.R., dela ROSA, C., WOODWARD, E.R., HERRERA-
          FERNANDEX, F. and TSUKAMOTO, M. 1968. The
          mechanism of gastrin release. Arch. Surg.,
          97: 816-825.

42.   WOODWARD, E.R. and SCHAPIRO, H. 1958. Effect of local
          anaesthetics on the isolated antrum of the
          stomach in dogs. Amer. J. Physiol., 92:
          479-481.

43.   GREGORY, R.A. 1962. In Secretory Mechanisms of the
          Gastrointestinal Tract. Edward Arnold (Lond.)
          p. 51.

44.   SCHOFIELD, B., REDFORD, M., GRABHAM, A.H. and NUAIMI, K.
          1967. In Gastric Secretions, Mechanisms and
          Control, edicted by T.K. SHNITKA, et. al.,
          Pergamon Press, Oxford pp. 91-104.

45.   ELWIN, C.E. and UVNAS, B. 1966. in Gastrin, edited by
          M.I. Grossman, Butterworths (Lond.) pp.69-82.

46.   GILLESPIE, I.E. and GROSSMAN, M.I. 1964. Potentiation
          between Urecholine and gastrin extract and
          between Urecholine and histamine in the stimu-
          lation of Heidenhain pouches. Gut, 5: 71-76.

47.   WOODWARD, E.R., BIGELOW, R.R. and DRAGSTED, L.R. 1950.
          Effect of resection of antrum of the stomach
          on gastric secretion in Pavlov pouch dogs.
          Amer. J. Physiol., 162: 99-109.

48.   PALUMBO, L.T., SHARPE, W.S., LULU, D.J., BLOOM, M.H. and
            DRAGSTEDT, L.R. II 1970. Distal antrectomy
            with vagectomy for duodenal ulcer. Arch.
            Surg., 100: 182-190.

49.   NYHUS, L.M. 1970. Gastric ulcer. Scand. J. Gastroent.
            suppl. 6: 123-138.

50.   DRAGSTEDT, L.R. and WOODWARD, E.R. 1970. Gastric stasis
            as a cause of gastric ulcer. Scand. J.
            Gastroent., suppl. 6: 243-252.

51.   PAVLOV, I.I. 1910. The work of digestive glands. 2nd
            edition. Translated by W.H. Thompson. Griffin
            (London).

52.   BABKIN, B.P. 1928. Die Aussere Sekretion der Verdanungs-
            drusen. 2nd edition. J. Springer (Berlin).

53.   EDKINS, J.S. 1906. The chemical mechanism of gastric
            secretion. J. Physiol., 34: 133-144.

54.   GREGORY R.A. 1962. Secretory mechanisms of the gastro-
            intestinal tract. Edward Arnold (London) pp.
            23-65.

55.   GREGORY, R.A. 1966. The isolation and chemistry of gastrin
            Gastroenterology, 51: 953-959.

56.   GROSSMAN, M.I. 1966. Notes on the history of gastrin. In
            Gastrin, edited by M.I. Grossman (1966) Butter-
            worths (London), pp. 1-7.

57.   GROSSMAN, M.I., ROBERTSON, C.R. and IVY, A.C. 1948. Proof
            of a hormonal mechanism for gastric secretion
            - The humoral transmission of the distension
            stimulus. Amer. J. Physiol., 153: 1-9.

58.   LECONTE, P. 1900. Cellule 17: 307. Quoted in reference
            53 above, p.66.

59.   IVY, A.C., LIM, R.K.S. and McCARTHY, J.E. 1925. Contribu-
            tions to physiology of gastric secretion II
            the intestinal phase of gastric secretion.
            Quart J. Exp. Physiol., 15: 55-68.

60.   GREGORY, R.A. and IVY, A.C. 1941. The humoral stimulation
            of gastric secretion. Quart. J. Exp. Physiol.,
            31: 111-128.

61.   SIRCUS, W. 1953. The intestinal phase of gastric section.
            Quart. J. Exp. Physiol., 38: 91-99.

62.   DRAGSTEDT, L.R. 1957. The physiology of the gastric ar
            Arch. Surg., 75: 552-557.

63.   GREGORY, R.A., HALLENBECK, G.A., and CODE, C.F. 1942. A
               modification of the method of Hollander and
               Jeremin for making Pavlov pouches. Proc. Soc.
               Exp. Biol. NY Ag: 400-403.

64.   GREGORY, R.A. 1950. Some factors influencing the passage
               of fluid through intestinal loops in dogs. J.
               Physiol. 111: 119-137.

65.   GREGORY, R.A. 1950. Some factors influencing the passage
               of fluid through intestinal loops in dogs. J.
               Physiol., 111: 119-137.

66.   PE THEIN & SCHOFIELD, B. 1959.
            Release of gastrin from the pyloric antrum
            following vagal stimulation by sham feeding
            in dogs.

            J. Physiol., 148: 291.