Much of the material in this thesis is based on wor which was undertaken in collaboration with others.

In the Leeds/York Gastric Follow-up Clinic, I hav worked since 1968 with Professor J. C. Goligher, Dr. C. N. Pulvertaft, Dr. B. E. Walker and Mr. R. Hall. I thank them for permission to quote the data collected in the Clinic.

Our team in Leeds has cooperated with Professor E. Amdrup and Dr. E. Kragelund of Copenhagen in studying the effects of highly selective vagotomy (HSV) on gastric secretion. We have read joint papers at the Surgical Researc Society and the British Society of Gastroenterology on the results of the secretory studies and on the clinical results which were obtained in Leeds and Copenhagen after HSV. Several joint publications are awaiting publication. I have referred in some detail to the results from Copenhagen, with Professor Amdrup's full permission.

In the University Department of Surgery at Leeds, the work has been done by a team, of which I am the researcl director. The idea of highly selective vagotomy without a

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drainage procedure is entirely mine, and I am responsible for the planning of all the studies reported in the thesis. I taught the research assistants how to carry out the tests of gastric secretion, supervised their work closely, and personally carried out many of the tests. Dr. A. R. Wilkins was responsible for most of the tests of gastric emptying of the food-barium meal, and Dr. C. S. Humphrey and Dr. Wilkinson performed nearly all the tests of the emptying of hypertonic glucose. Dr. P. J. Lyndon has continued the studies of fat-induced inhibition which I began in collaboration with Professor Duthie in Sheffield, and after I had supervised the first few tests, Dr. Lyndon has done most of the work without further supervision. In the study of antroneurolysis in dogs, I performed most of the operations and personally carried out about 25 per cent of the secretory tests. Mr. R. Consultant Surgeon, York County Hospital, performed the oth operations, and most of the tests of secretion.

Dr. R. B. Smith performed a large number of pentagastrin, insulin and 'OXO' tests, and also acted as anaesthetist in the animal theatre.

Mr. J. P. Edwards, biochemist to the Department of Surgery, has taken a keen interest in the accuracy and reproducibility of the measurements of pepsin, polyethylene glycol and phenol red.

HIGHLY SELECTIVE VAGOTOMY

WITHOUT A DRAINAGE PROCEDURE

Thesis submitted for the degree of

DOCTOR OF MEDICINE

in

THE UNIVERSITY OF GLASGOW

by

DAVID JOHNSTON

July 1972.

Selective Vagotomy with Innervated Antrum without Drainage Procedure for Duodenal Ulcer

D. Johnston and A. R. Wilkinson, University Department of Surgery, The General Infirmary, Leeds. Br. J. Surg., 56,626.

Stimulated by descriptions of partial gastric vagotomy by Griffith and Harkins (1957) and of segmental gastric resection with innervated antrum by Ferguson et al. (1960), we have selectively denervated the parietal cell mass, dispensing with a drainage procedure, in a consecutive series of 15 patients with uncomplicated chronic duodenal ulcer.

Preservation of vagal nerve-supply for 6cm. proximal to the pylorus was straightforward, even in obese subjects. Precise measurements were made of the innervated antrum. The nerves to the antrum were demonstrated and photographed. Mucosal biopsies taken at the junction of the innervated and denervated areas showed that parietal cells were sometimes left innervated.

Post-operative insulin tests, however, have all been negative. Pentagastrin-stimulated acid output was reduced by 57.0 ± 6 per cent, which is equal to the reduction found in this laboratory after complete conventional vagotomy.

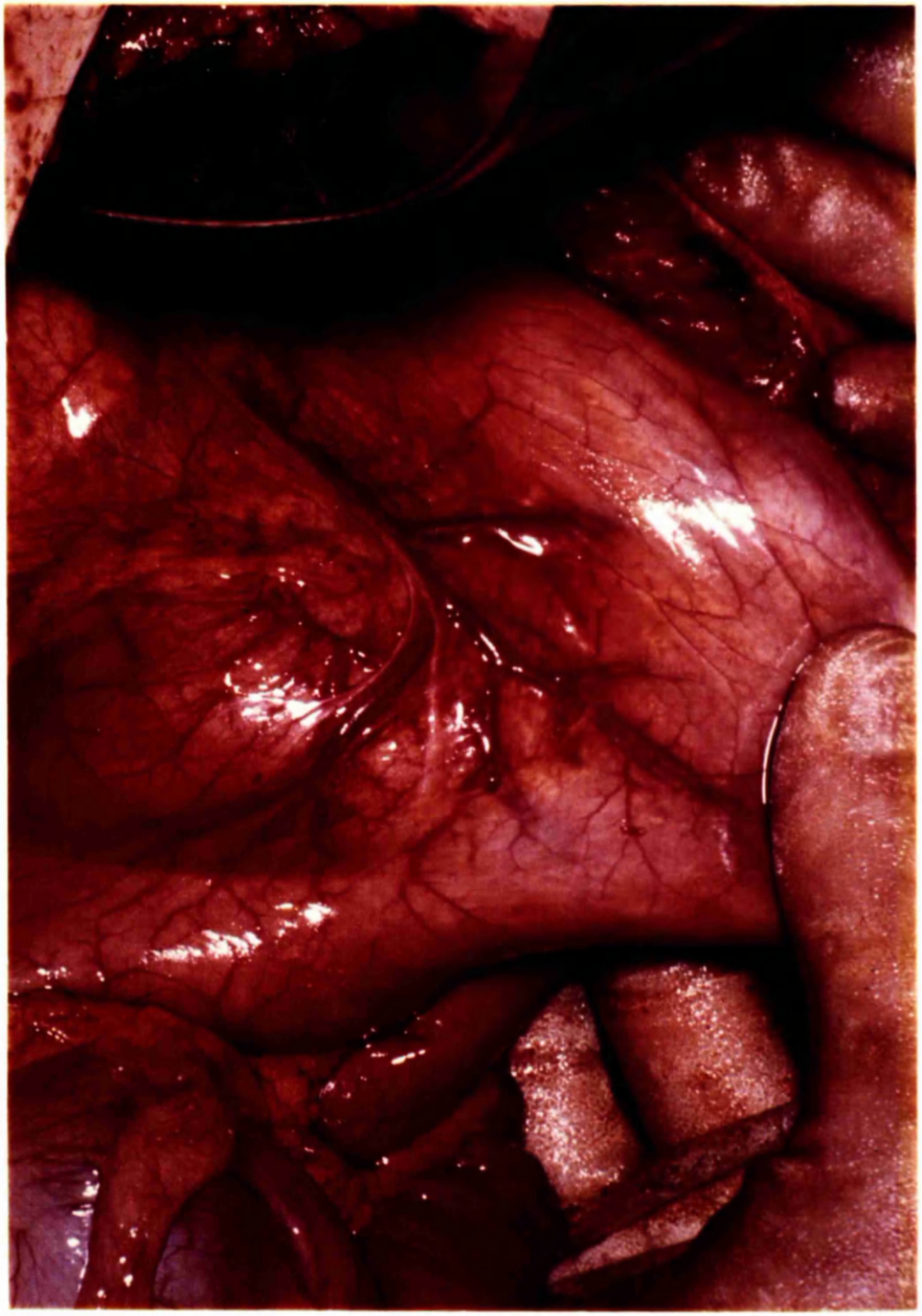
The antrum left innervated is well drained and is exposed to acid inhibition. Normal antropyloroduodenal regulation of gastric emptying is preserved, as is all extra-gastric vagal innervation.

The 15 patients have done well in the short term. These early results are encouraging, but it is the clinical status at 5 and 10 years that really matters.

Ferguson, D. J., Billings, H., Swenson, D., and Hoover, J. (1960) Surgery, St. Louis, 47, 548.

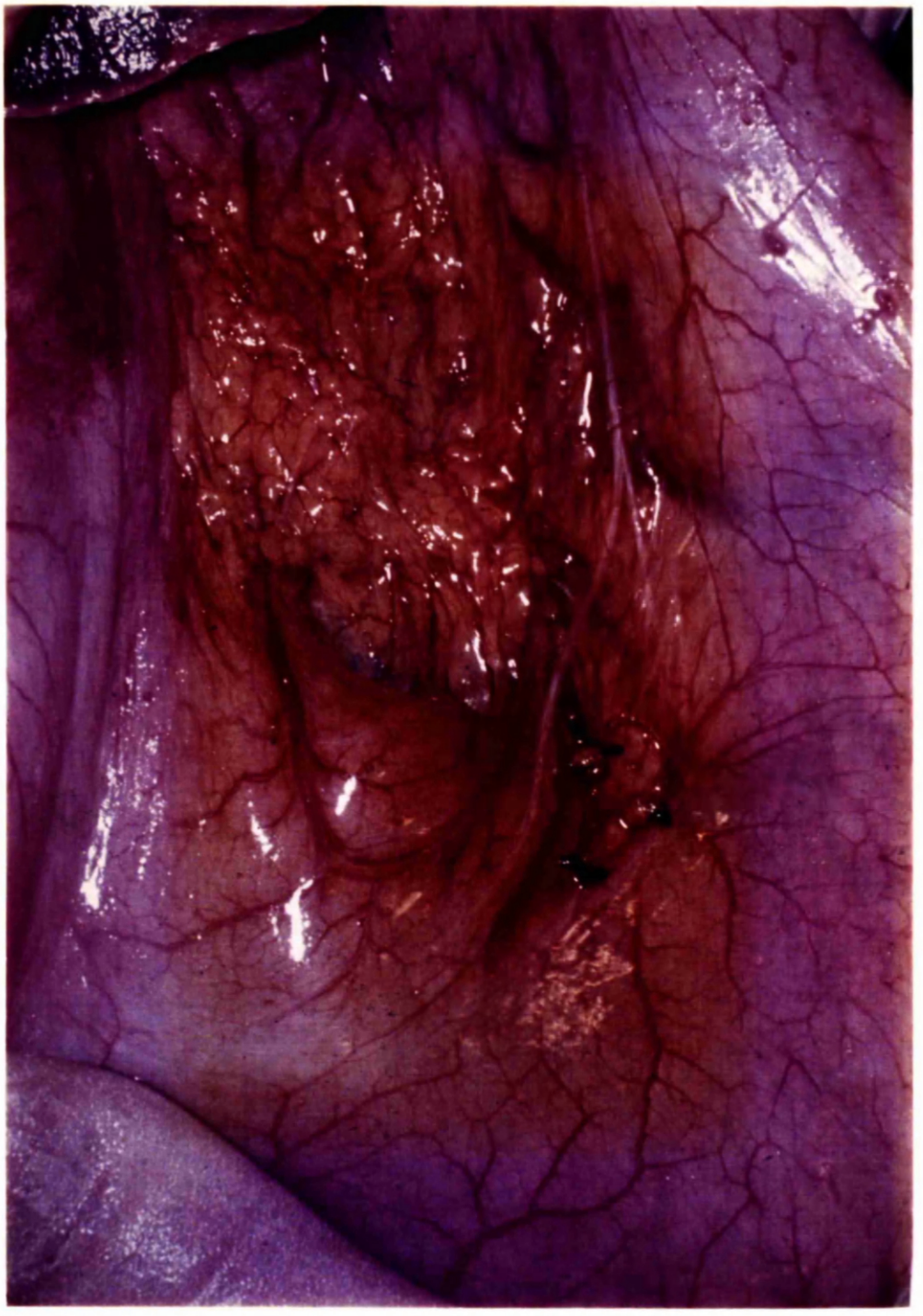
Griffith, C. A., and Harkins, H. N. (1957) Gastroenterology, 32, 96.

This is the first reference to vagotomy confined to the parietal cell mass, without a drainage procedure, in man.



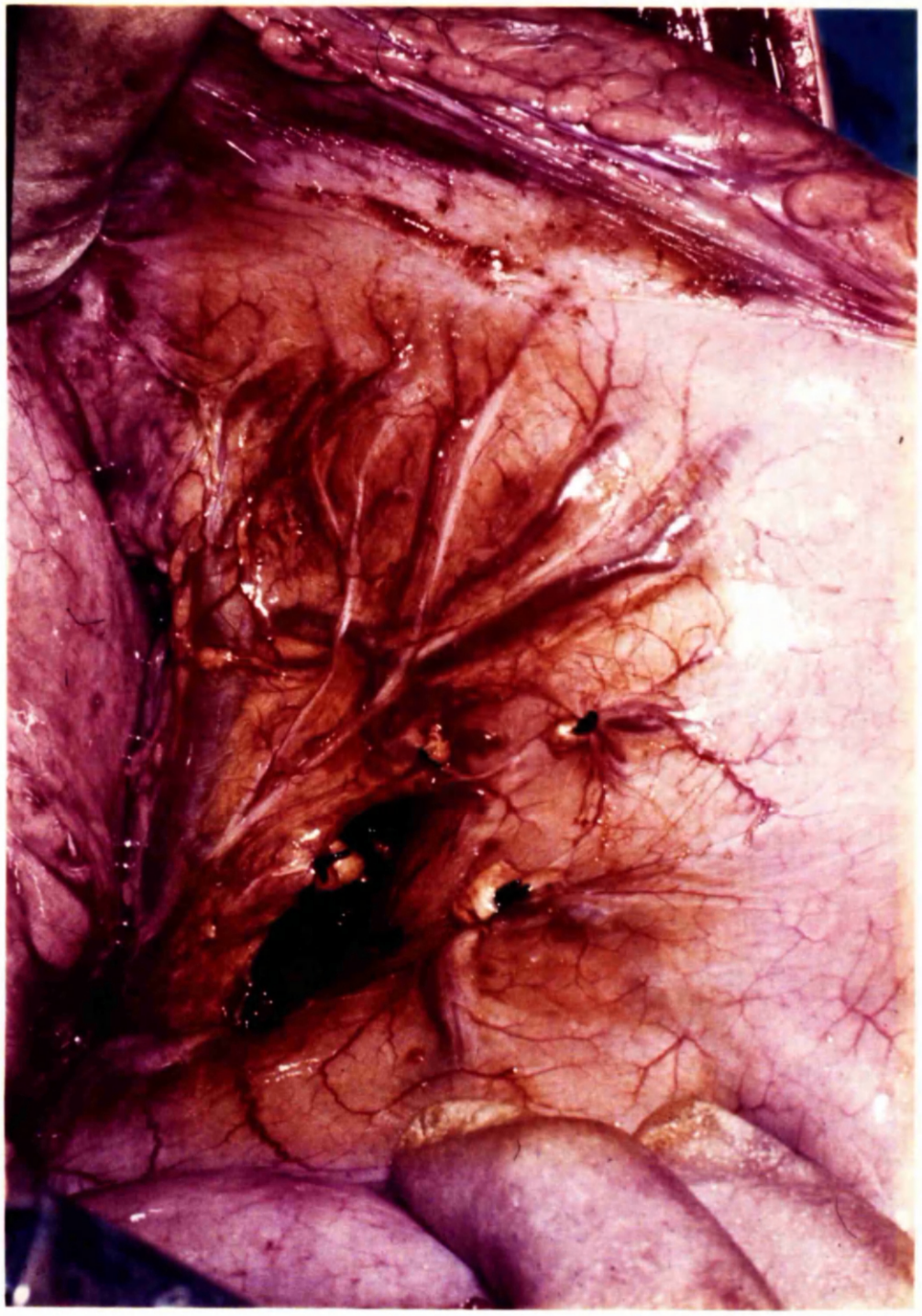
THE ANTERIOR NERVE OF LATARJET

As often happens, it splits into two major terminal branches, which cross onto the "antrum" just beyond the incisura angularis Both these branches are preserved in the performance of highly selective vagotomy.



THE ANTERIOR NERVE OF LATARJET

(in a different patient). HSV has begun, just at the incisura. The main nerve passes onto the "antrum", and is preserved.



THE POSTERIOR NERVE OF LATARJET

You are looking at the posterior wall of the stomach, with the greater curvature, which has been mobilised, at the top and the pylorus off the picture at top left. The terminal branches of the nerve are shown splaying out to supply the antral region. Vagal denervation of the parietal cell mass has commenced at the incisura angularis.

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ABBREVIATIONS USED IN THIS THESIS

OPERATIVE PROCEDURES

HSV:	highly selective vagotomy without a drainage procedure
SV:	selective vagotomy
TV:	truncal vagotomy
P:	pyloroplasty
GJ:	gastrojejunostomy
TV+A:	truncal vagotomy plus antrectomy

STIMULANTS OF GASTRIC SECRETION

PG:	pentagastrin ('Peptavlon': ICI)
OXO:	proprietary meat extract
Ach:	acetylcholine

ACID OUTPUT

BAO:	basal (spontaneous) acid output
PAO:	peak acid output
PAO^{PG}, PAO^{I}, PAO^{OXO}, PAO^{Ach}:	peak acid outputs in response to pentagastrin, insulin, OXO, acetylcholine
MAO:	maximal acid output

T.H.(AO): total-hour acid output

P.H.(AO): peak-hour acid output

E+ : early-positive (first-hour) acid response to insulin

L+ : late-positive (second-hour) acid response to insulin

NS: not significant

ND: not done

Data have been expressed as arithmetic means, plus or minus one standard error ($\pm$ 1 SE) in most of the figures in the thesis.

CHAPTER 1

INTRODUCTION AND REVIEW OF THE LITERATURE

In this Chapter, reference is made only to published work or to unpublished data which were known to me in 1968, when I had the idea of doing highly selective vagotomy for duodenal ulcer. Subsequent publications, for example those detailing the poor results of vagotomy with drainage, the work of Burge and others on bilateral selective vagotomy without drainage, the studies of highly selective vagotomy in dogs, the effects of vagotomy on plasma gastrin concentration, and other relevant literature which appeared between 1969 and 1972, are all discussed in the concluding Chapter. Several additional references appear in the first paper on highly selective vagotomy (Chapter 2), which was published in 1970. Although the pioneering work of Hart and Holle in Munich on selective proximal vagotomy with a drainage procedure or antrectomy had been published in German by 1968, I did not know of it, and discussion of the findings of these workers will therefore also be deferred until later chapters.

" If the pylorus does not relax, it is evident that a wave approaching it pushes the food into a blind elastic pouch, the only exit from which is through the advancing constricted ring. The constrictions are deeper near the end of the antrum, and the rings are small; consequently the food is squirted back through them with considerable violence. As has been noted, the pylorus opens less frequently for a while after a solid piece of food comes to it. In such a case the slow driving waves squeeze the hard morsel and the soft food about it up to the sphincter, only to have the whole mass shoot back, sometimes half way along the antrum. Over and over again the process is repeated till the sphincter at last opens and allows the more fluid parts to pass."

W. B. Cannon

Amer. J. Physiol., 1, 359 - 382, 1898.

There is no previous literature on vagotomy confined to the parietal cell mass without a drainage procedure in man.

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Near the upper end of the alimentary tract there is a large muscular bag whose principal function is to receive the meal, to mix it and grind it and pass it on into the duodenum in small spurts of smooth chyme. The stomach is the "hopper" and the "mill" of the alimentary canal. Its emptying is controlled by nervous reflexes and by hormones which regulate the activities of the antrum, the pylorus and the duodenum[1]. All the standard operations which have been employed since the inception of surgery for duodenal ulcer in the late 19th century - partial gastrectomy, gastrojejunostomy alone, truncal or selective vagotomy with a drainage procedure or antrectomy - have destroyed this precise regulation of gastric emptying which is such a beautiful feature of normal gastric physiology; and they have all destroyed or impaired the "grinding" function of the antral mill. Since they share these basic defects, they all produce side-effects such as dumping and diarrhoea, with the result that fewer than fifty per cent of the patients so treated achieve an absolutely

perfect clinical result[2].

In 1968, being dissatisfied with the results of conventional surgery for duodenal ulcer, I devised a new operation in which vagotomy was confined to the acid- and pepsin-secreting part of the stomach. The vagal nerve supply to the antral region and to all the extra-gastric viscera was preserved, and the pylorus was left intact. This "highly selective" vagotomy was designed to eliminate side-effects such as dumping and diarrhoea by preserving normal regulation of gastric emptying, and to cure a higher percentage of ulcers than did the standard truncal vagotomy, by preserving protective and inhibitory mechanisms which are destroyed or damaged by the standard operations.

THE INDIFFERENT RESULTS OF CURRENT OPERATIONS

The ideal operation for duodenal ulcer would have no mortality, produce no side-effects, and cure every ulcer, permanently. It would also be followed by perfect nutrition in the long term. The achievements of current methods of surgical treatment fall some way short of this ideal. The mortality rate is 1 to 2 per cent, side-effects are the rule rather than the exception, the ulcer recurs in between 1 and 14 per cent of patients,

and in the long term weight loss, iron-deficiency anaemia and even tuberculosis are far from uncommon[2-10]. Five to eight years after operation in the Leeds-York prospective, randomized, controlled trial[2] of truncal vagotomy and gastrojejunostomy, truncal vagotomy and antrectomy and Polya partial gastrectomy, only 44 per cent of the patients who had been treated by vagotomy and gastrojejunostomy were found to have obtained a perfect clinical result, and only 70 per cent had a good-to-excellent result (Visick grades I and II combined). Ten per cent were outright failures and a further 20 per cent had only a "moderate" or "fair" result. The results which were recorded after the other two operations were slightly, but not significantly, better (Table I). All three procedures were followed by a formidable incidence, and variety, of side-effects[2] (Table II), although it should be added that many of these were quite mild in degree. Patients lost ten pounds in weight, on average, after both procedures involving gastric resection, whereas the mean weight loss was four pounds after vagotomy with gastrojejunostomy. In a subsequent study in Leeds[11], the clinical results five to eight years after truncal vagotomy and pyloroplasty were found to be marginally worse than those which were recorded after vagotomy

and gastrojejunostomy. The conclusion that the newer operation of vagotomy with gastrojejunostomy did not yield better results than the time-honoured method of partial gastrectomy was supported by the findings of Cox[12], in his report in 1968 on the results of the prospective random trial of these two operations in Glasgow.

Although laudatory reports on the value of a variety of operations for duodenal ulcer were abundant in the literature, the results of these two well-planned, critical trials seemed to far outweigh the rest. They were also extremely disappointing, for no significant advance in gastric surgery had apparently been made in the preceding eighty years, apart from the decrease in operative mortality, which was due in large measure to factors other than the type of operation which was performed. The superiority of vagotomy with a drainage procedure over partial gastrectomy or vagotomy and antrectomy with respect to (slightly) lower operative mortality and (presumably) better nutrition in the long term was offset by a higher incidence of recurrent ulceration and by overall clinical results which were inferior to those which were found after the resection procedures[13].

TABLE I

Visick grading of functional results five to eight years after operation

CATEGORY	(1) VAG+GJ (% of 119 cases)		(2) VAG+ANTRECTOMY (% of 116 cases)		(3) SUBTOTAL GASTRECTOMY (% of 107 cases)		VAG+PYLOROPLASTY * (% of 164 cases)	
I	44	70	50	78	49	77	45	68
II	26		28		28		23	
III	19		14		17		18	
IV	11		8		6		14	

After Goligher and others (1972)[11]

* Note that patients treated by V-P were not included in the prospective random trial, which compared the operations in columns (1), (2) and (3).

TABLE II

Frequency of Symptoms Due to Disturbance of Alimentary Function

Five to Eight Years after Operation

Symptom	Operation Used			
	Vag. & GJ (% of about* 119 Cases)	Vag. & Antr. (% of about* 116 Cases)	Subtot. Gastrect. (% of about* 107 Cases)	Vag. & P. (% of about* 161 Cases)
Epigastric fullness	40.2	36.3	36.5	37.1
Early dumping	17.9	8.6	21.5	11.9
Late dumping	6.0	4.3	0.9	1.9
Nausea	12.8	17.2	23.4	17.6
Food vomiting	4.3	9.6	5.6	4.4
Bile vomiting	14.5	13.8	13.1	10.1
Heartburn	19.9	15.7	8.4	12.6
Flatulence	17.9	22.8	19.8	20.1
Dysphagia	1.1	0.0	0.0	0.6
Diarrhoea	26.3	23.2	6.5	21.7

* The percentages relate to the total number of cases in which the particular symptom was elicited, which in some instances were a few less than the numbers indicated.

REASONS FOR FAILURE OF STANDARD OPERATIONS

In Leeds, the incidence of complete failure after truncal vagotomy with a drainage procedure was 10 to 12 per cent, 5 to 8 years after operation[2,11]. Half the failures after vagotomy and gastrojejunostomy were due to recurrent ulceration, and half to the occurrence of severe side-effects, particularly dumping, bilious vomiting and diarrhoea. After vagotomy and pyloroplasty, recurrent ulceration accounted for most of the failures. Twenty per cent of patients had a "fair" result (Visick grade III), leaving 70 per cent with a good result (Visick grades I and II). The symptoms which led to patients being placed in category III were predominantly epigastric fullness, early dumping, vomiting and diarrhoea. The challenge, then, was to lower the incidence of recurrent ulceration, and to attempt to eliminate these side-effects.

One possible approach was to change from truncal to bilateral selective vagotomy[14,15]. In selective vagotomy, the stomach is denervated from cardia to pylorus, but the hepatic and coeliac vagal fibres are preserved. It is thus a logical operation, attacking only the target organ, but sparing the para-sympathetic nerve supply to the pancreas, small intestine and

biliary tract. Whereas truncal vagotomy has been shown to cause the gall bladder to dilate in man[16,17], selective vagotomy does not[17]. Selective vagotomy has been claimed to lower the incidence of post-vagotomy diarrhoea[18-23] and also to reduce the incidence of incomplete gastric vagotomy[24]. In addition, it possesses the theoretical advantage of preserving the hepatic and coeliac fibres, which have been shown to mediate inhibition of gastric secretion from Heidenhain pouches in dogs[25-27], and hence might exert an inhibitory influence on acid output from the denervated parietal cell mass in man. Despite its considerable attractions in theory, however, there was no convincing evidence that the overall clinical results after selective vagotomy with a drainage procedure were significantly better than those which were found after truncal vagotomy with a drainage procedure[28-30]. The early, admittedly uncontrolled, experience with selective vagotomy and pyloroplasty in Leeds[30] was not particularly encouraging. There was little reduction in the incidence of diarrhoea, dumping was still a common side-effect, and the incidence of incomplete vagal nerve section as judged by the results of the insulin test was little different from that which was found after truncal vagotomy.

It seemed to me that the incidence of side-effects would be greatly reduced if the pylorus could be kept intact, and not bypassed, and if normal, regulated gastric emptying could be obtained through an intact antro-pyloro-duodenal segment[1]. In 1966, Code and his colleagues[31] had shown how the terminal antral contraction in dogs not merely arrested the progress of solid material near the pylorus but actually retropelled it forcibly into the body of the stomach. The cine film of this work, which Code showed a year later to the British Society of Gastroenterology, gave a clear and exciting picture of the antral mill in action. It was obvious that pyloroplasty would destroy this mechanism, gastrojejunostomy bypass it, while antrectomy or gastrectomy would ablate it altogether. As a result, solid food would pass, un-milled, and sometimes with excessive rapidity, into the small intestine. There, its physical state would make it unsuitable for absorption. These deductions fitted perfectly with the observation of Wastell[32] that pyloroplasty led to a significant increase in the output of faecal fat in dogs. In man, too, malabsorption of fat was well documented after vagotomy with a drainage procedure[8,28,33-37]. Excessively-rapid emptying of solid food after vagotomy and pyloroplasty in man had been

noted by Colmer and his colleagues[38], who found that a normal, albeit radioactive, breakfast emptied much faster after vagotomy and pyloroplasty (at least in the first 20 minutes after the meal) than it had done before operation. This was at variance with the previous findings of Buckler[39], who reported that a test meal of mashed potato left the stomach more slowly after vagotomy and pyloroplasty.

Emptying of fluids from the stomach is also excessively rapid after vagotomy with a drainage procedure[40-42]. This may be due in part to loss of the antrum and pylorus and in part to loss of inhibitory nervous reflexes and to diminished release of hormones which inhibit gastric motility and delay gastric emptying[1]. The role of inhibitory reflexes is illustrated by the findings of Waddell and Wang[43], who noted that a semi-fluid fatty meal slowed gastric emptying in patients with gastro-jejunostomy alone, but that when vagotomy was added to the gastrojejunostomy, the fatty meal left the stomach more rapidly. Again, it has been shown by Hunt[44,97] that the upper small intestine contains osmoreceptors which delay gastric emptying by means of nervous reflexes when solutions of high osmolarity enter the duodenum. After truncal and selective vagotomy with a drainage procedure,

this "braking" mechanism is lost, and fluid test meals of high osmolarity empty in uncontrolled fashion into the small intestine, pass through it rapidly like a saline purgative, and produce urgent diarrhoea[41,42]. The stomach is then truly "incontinent" of liquids. The contribution of the Belfast group[40-42] was thus of great value, by their demonstration that the stomach was "incontinent", that it was illogical to speak of vagotomy with drainage as "preserving the gastric reservoir", and finally that the prime cause of diarrhoea in many (but not all) cases was incontinent gastric emptying. They also showed that posture assumes considerable importance in gastric emptying after vagotomy and pyloroplasty[42]. If the patient lies flat on his back, even liquids empty slowly, but if he assumes the upright posture, gastric emptying is precipitate[42]. The liquid pouring out of the stomach no doubt sweeps solid food with it into the small intestine at an abnormally rapid rate after the terminal antrum and pylorus have been distorted or bypassed.

Disorders of gastric emptying are thus responsible for many of the side-effects and failures of gastric surgery. If emptying is excessively rapid, dumping and diarrhoea may ensue. If it is too slow, because of diminished antral peristalsis after

vagotomy combined with a poorly-functioning pyloroplasty or gastroenterostomy, the patient may experience side-effects such as nausea, vomiting and flatulence. The loss of co-ordination of the contractions of the antrum, pylorus and duodenum after pyloroplasty could lead to copious reflux of alkaline duodenal content, rich in bile salts, onto the antrum. Regurgitation of similar fluid into the stomach after gastroenterostomy is also to be expected. This material in the stomach might cause irritation, nausea and vomiting.

THE NEW OPERATION: VAGOTOMY OF THE PARIETAL CELL MASS WITH PRESERVATION OF ANTRAL INNERVATION WITHOUT A DRAINAGE PROCEDURE

THE FIRST CONCEPT: PREVENTION OF SIDE-EFFECTS BY PRESERVATION OF CONTROLLED GASTRIC EMPTYING THROUGH AN INTACT PYLORUS

It was clear that the results of surgery for duodenal ulcer would improve significantly if the normal control of gastric emptying could be retained; provided, of course, that the operation also cured the ulcer. This was the nub of the problem: how to preserve the entire gastric reservoir and induce it to empty normally through an intact pylorus, while at the same

time ensuring that the ulcer would heal and remain healed. Truncal vagotomy without a drainage procedure was obviously out of the question. Dragstedt had originally performed transthoracic truncal vagotomy without drainage[45], but had to re-operate on many of his patients to add a gastrojejunostomy, because of the occurrence of gross gastric retention[46]. Bilateral selective vagotomy is also a complete gastric vagotomy, because the nerves of Latarjet to the antral region of the stomach are severed. The branches of the hepatic vagi which go to the pylorus and distal antrum have not been shown to have any efferent function, despite careful investigation by several groups of workers[47-49]. For example, Stavney and his colleagues[48], who recorded intra-antral pressure changes in dogs by means of fine polyethylene tubes connected to strain guages, showed that intra-antral pressure increased significantly when the vagal trunks were stimulated electrically. However, after bilateral selective vagotomy, no increase in pressure was detected, nor did direct stimulation of the hepatic fibres of the anterior trunk (which give rise to the pyloric nerve) produce an increase in pressure in the antrum. Similarly, in man, Burge[50] has demonstrated with his electrical stimulation test[51] for completeness of vagotomy that

selective

vagotomy completely eliminates the contractile response of the stomach: electrical stimulation of the hepatic and coeliac vagi does not elicit any gastric contraction. These results provide support for Franksson's observations in 1948[15] that selective vagotomy causes as much gastric stasis as does truncal vagotomy without a drainage procedure. Thus, vagotomy of the whole stomach, whether truncal or bilateral selective in type, diminishes antral peristalsis and leads to gastric stasis. Therefore, if the stomach is to empty through an intact pylorus, vagotomy of the stomach must not be complete, but partial. The portion of stomach remaining innervated should quite clearly be the distal part, the antral "mill", whose powerful contractions, so familiar to the radiologist and gastroscopist, provide the vis-a-tergo which propels the chyme out of the stomach. The vagal nerve supply to the antral region of the stomach[48,52] is provided by the nerves of Latarjet[53], otherwise known as the greater anterior and posterior gastric nerves (of Mitchell)[54]. These nerves run downwards in the lesser omentum parallel to the lesser curvature and end in branches which cross onto the "antrum" near the incisura angularis, about five to seven centimetres proximal to the pylorus. Although the extent

of the "pyloric gland area", or antrum, of the stomach is variable, it usually extends at least five centimetres proximal to the pylorus[55-58]. Thus, preservation of the nerves of Latarjet with their main terminal branches would keep the alkaline antrum innervated, while division of all other vagal fibres to the stomach, along the lesser curvature between incisura angularis and cardia, and on the lower oesophagus, would denervate all, or almost all, of the acid- and pepsin-secreting part of the stomach, the parietal cell mass.

An alternative approach which was considered was to keep the pylorus intact and to perform "supra-pyloric antrectomy", by transecting the stomach two centimetres or so proximal to the pylorus, resecting the major portion of the antrum with a cuff of the parietal cell mass, and anastomosing the (vagotomized) body of the stomach to the pre-pyloric remnant.

Maki and his colleagues had used this operation (without, however, vagotomizing the stomach) in the treatment of gastric ulcer, and claimed that, while gastric stasis was absent, emptying of the stomach was under much better control than was the case after the Billroth or Polya types of gastric resection. This procedure, however, reduced the size of the gastric reservoir, and also

seemed unlikely to lead to as well-regulated gastric emptying as could be expected if the innervated antrum were left in situ. Although it was tempting to excise the source of gastrin, for reasons which are given below I thought that it was unnecessary to do so.

"Partial gastric vagotomy", with preservation of the nerve supply to the antrum, had first been performed in dogs by Griffith and Harkins in Seattle[60]. These authors reported in 1957 that the operation was followed by satisfactory gastric emptying, as judged radiologically by the emptying of barium; and that denervation of the parietal cell mass was also satisfactory, because the insulin test was either negative or only weakly positive. They concluded that "clinical application seems feasible". It was to be many years, however, before the operation was used in man, partly no doubt because the evidence for efficient gastric emptying was not entirely unequivocal, four of the ten dogs exhibiting slightly delayed emptying, partly because the insulin test was weakly positive in seven of the ten dogs, but chiefly, one would imagine, because at that time most surgeons were satisfied with the results of the established operations, so that there was little incentive to try a new procedure which seemed technically difficult and fraught with the danger (as they thought) of recurrent ulceration because the antrum remained innervated.

I decided to use "partial gastric vagotomy" in the treatment of patients with duodenal ulcer, because it seemed to possess all the virtues (real or imaginary!) of selective vagotomy, but had the added advantage that gastric emptying would be well-regulated, because the antro-pyloro-duodenal segment was left undisturbed. Thus it seemed almost certain to reduce the incidence of side-effects such as dumping and diarrhoea. But would the stomach empty satisfactorily, and would the ulcer heal and remain healed?

Gastric emptying was largely dependent upon the vigour of antral peristalsis, and it seemed reasonable to assume that if the antrum was left completely intact, without interference with its blood or nerve supply, emptying would remain unimpaired. Moreover, it had been shown that gastric emptying was almost normal after partial gastric vagotomy in dogs[60]. Finally, one was reassured by the report of Ferguson and his colleagues[61] that gastric emptying was satisfactory after segmental resection of much of the parietal cell mass, with preservation of an innervated antrum and an intact pylorus in men with duodenal ulcer.

The pylorus, then, was to be left intact and the antrum was to be left innervated. The next question to be considered was how dangerous this

innervated antrum would be in terms of recurrent ulceration.

THE SECOND CONCEPT: THAT THE ANTRUM COULD BE LEFT INNERVATED WITH IMPUNITY

During the past decade, most surgeons who did not actually resect the gastric antrum, severed its parasympathetic nerve supply in the course of truncal or selective vagotomy, in the belief that by so doing they were reducing the release of gastrin. This philosophy was based in large measure on the pronouncements of Nyhus, Harkins and their colleagues in 1960 [62], who wrote that if the antrum was to be retained at all in the course of operations for duodenal ulcer, it must be vagally denervated, remain in continuity with the "acid stream", while antral stasis must be prevented by the performance of a drainage procedure. These forthright edicts were based on their findings in another species - the dog; nor were they based on findings in animals with the antrum in situ, but in dogs which were equipped with separated antral pouches shielded from the inhibitory influence of endogenous acid. In such circumstances, vagal release of gastrin is easy to demonstrate[62-64], but when the antrum is left in situ, vagal release of gastrin is extremely difficult to demonstrate, as

Janowitz and Hollander[65], and Burstall and Schofield[66], reported. Acid in contact with the antral mucosa inhibits gastrin release, both in man[67] and in the dog[68,69]. This may represent a direct inhibitory effect on the gastrin cell, which is situated in the mucosa, close to the lumen[70]. In addition, nerve endings sensitive to change in pH have been demonstrated in the antral mucous membrane[71], and it is possible that these give rise to inhibitory nervous reflexes.

The literature on the effect of vagal denervation of the antrum on gastrin release is contradictory, and is discussed in greater detail in a later chapter. Vagal denervation both of the in-situ antrum and of the separated antrum in dogs was reported by many authors[72-76] to lead to a significant reduction in acid output from an indicator pouch of the fundic gland area. On the other hand, Wohlrabe and Kelly[77], and Nyhus and his colleagues[62] found that vagal denervation of the antrum did not reduce gastrin release in response to bathing the mucous membrane of the antrum with beef broth[77] or with alcohol[62], nor did it reduce gastrin release in response to mechanical distension of the antrum[62]. Thus, the literature was conflicting and the findings in dogs equipped with Heidenhain pouches and separated antral pouches were not necessarily applicable to man.

In this connection, it is amusing to consider that the standard laboratory animal which was used for studies of experimental gastric operations was the Heidenhain pouch dog. Any operation which led to an increase in acid output from the Heidenhain pouch was considered "bad"; unsuitable for use in man. Yet it had been shown repeatedly that acid on the antrum inhibited gastrin release[64,66-69]. Hence, any operation which effectively reduced acid output from the parietal cell mass of the main stomach would lead to more alkaline conditions in the antrum, to diminished inhibition of gastrin release, and thus to an increase in acid output from the Heidenhain pouch. Paradoxically, the greater the reduction in acid output in the main stomach, the higher would acid output rise from the Heidenhain pouch (assuming that the antrum was left "in situ").

The disastrous effects of the antral exclusion operation[78-81], which were due to excessive gastrin release as a result of the constant alkaline environment[68,69,81] in the excluded antrum, had left an indelible impression on the surgical world. Generations of surgeons were not allowed to forget the scurvy trick which the antrum had played upon their surgical mentors, The antrum was regarded as a natural foe, to be excised or at least "tamed" by

severance of its vagal nerve supply. Little significance was accorded to the observations of State and his colleagues[82,83], who had shown that when the antrum was kept in continuity with the acid stream, it protected dogs against the development of histamine-induced ulcer. In man, Ferguson and his colleagues[61], who treated over one hundred patients with duodenal ulcer by segmental gastric resection, with preservation of the vagal nerve supply to the antrum, and without a drainage procedure, were able to report a respectable recurrent-ulcer rate of 4 per cent on follow-up ranging from one to four years.

Thus, it appeared that the accepted surgical practice of denervating the antrum was based on evidence which was conflicting and questionable. Certainly, the results of Wohlrabe and Kelly[77] and of Nyhus and his colleagues[62] suggested that the antrum might release just as much gastrin in response to a meal after vagal denervation as it had done before. Besides, vagal denervation of the antrum produced gastric stasis[48,60] and made necessary the performance of a drainage procedure. Even when that had been done, stasis of food was not always prevented. Such stasis might be expected to provoke sustained release of gastrin. In addition, complete gastric vagotomy with pyloroplasty

or gastrojejunostomy permits increased reflux of alkaline duodenal content, containing a high concentration of bile salts, into the stomach. "Bile is seldom found in the stomach, except under peculiar circumstances" wrote Beaumont[84] in his celebrated case report on Alexis St. Martin. Both alkalinity[68,69], and bile salts[85], in the antrum have been shown to promote the release of gastrin. In contrast, if the antro-pyloro-duodenal segment is left intact, duodenal contents are in the main kept in their rightful place, beyond the pylorus[84, 86-88]. "The function (of the pylorus) is to prevent reflux into the stomach during (duodenal) cap systole" (H. D. Johnson)[87]. The co-ordination of the movements of the antrum, pylorus and duodenum in dogs has been described as follows: " .....duodenal contractions were seen immediately after closure of the pyloric sphincter. The junctional zone operated as a unit, displaying a co-ordinated sequence of muscular events: first a gastric peristaltic contraction which, as it moved along the antrum, excited an almost simultaneous contraction of the terminal antral segment, producing closure of the pyloric sphincter with cessation of flow of contents into the duodenum, and then retropulsion of the contents trapped in the antrum into the stomach. Duodenal contractions occurred

SUMMARY OF THESIS:

HIGHLY SELECTIVE VAGOTOMY

WITHOUT A DRAINAGE PROCEDURE

submitted to Glasgow University for the degree of

DOCTOR OF MEDICINE

by

DAVID JOHNSTON

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SUMMARY

This thesis is about a new operation for duodenal ulcer. It is named highly selective vagotomy without a drainage procedure, or HSV. I was the first to desribe its use in man, at the meeting of the British Surgical Research Society on the first of July, 1969.

The unique feature of HSV is that well-controlled gastric emptying is achieved, through an intact pylorus. This has never been done before, in the long history of surgery for duodenal ulcer. In consequence, the well-known side-effects of gastric surgery, such as dumping and diarrhoea, are greatly reduced. Yet, so far as we can tell, these advances have not been secured at the cost of an increased incidence of recurrent ulceration. Indeed, not a single case of recurrent ulceration has been found in 180 patients treated by HSV in Leeds in the past three and a half years.

The publication of the five- to eight-year results of the Leeds-York trial in 1968, and of the early results of truncal vagotomy and pyloroplasty, had shown that the achievements of "modern" surgery (truncal vagotomy with drainage) for duodenal ulcer were no better than those of partial gastrectomy. In ten per cent of patients the operation was a failure, because of recurrent ulceration or severe side-effects, and in a further twenty per cent the outcome was marred by side-effects such as epigastric fullness after meals,

dumping, bilious vomiting or diarrhoea. It was difficult to understand why the results were no better. Vagotomy with drainage seemed to be more "physiological" than partial gastrectomy. It was said to "preserve the gastric reservoir". It should have given better results, but it did not. Nor did selective vagotomy with a drainage procedure seem to yield better overall clinical results, despite reducing the incidence of diarrhoea.

It seemed to me that the results of surgery for duodenal ulcer would improve significantly if the antro-pyloro-duodenal segment, which regulates gastric emptying, could be kept intact. All the standard operations damaged this region. Consequently, all produced unregulated gastric emptying, dumping, and diarrhoea. Carlson, Code and Nelson had shown in 1966 that the terminal antral contraction was essential to the function of the antral "mill". The terminal antrum and pylorus discriminated between solids and fluids. Hence, it was clear that after the standard operations, solids would leave the stomach too rapidly, un-milled, and in an unsuitable state for further digestion and absorption. Two years later, George, Connell, Kennedy and McKelvey showed that liquids left the stomach with undue rapidity after truncal or selective vagotomy with a drainage procedure, and that the abnormality in emptying was greatest in patients with "post-vagotomy" diarrhoea.

For these reasons, I decided to keep the pylorus intact,

in order to keep the stomach "continent". How then was the vagotomized stomach to empty? The answer was to vagotomize, not the whole stomach (as is done in selective or truncal vagotomy), but only the acid- and pepsin-secreting part, the parietal cell mass. In dogs, this "partial gastric vagotomy" (HSV) had been shown to produce effective denervation of the parietal cell mass and to be followed by satisfactory gastric emptying. It had not been used in man, because of fears that the innervated antrum would release excessive amounts of gastrin. I thought, however, that such fears were probably groundless, because if the antrum were left in continuity with the "acid stream" from the body of the stomach, gastrin release would be inhibited by the local action of endogenous acid. In addition the branches of the vagus nerves which were spared in HSV had been shown to mediate inhibition of gastric secretion in the dog. It seemed possible that other protective and inhibitory mechanisms in the antrum and duodenum might function better after HSV than after truncal vagotomy. Such was the physiological rationale of HSV.

The results of the new operation were assessed both at the clinical and at the experimental level. Clinical assessment was made at the Leeds Gastric Follow-up Clinic, where patients treated by HSV attended in company with numerous other patients who had been treated by the standard operations. An experienced panel of gastroenterologists wrote down their findings before being permitted to learn which type

of operation had been performed. In this way, an unbiased verdict was reached. In the laboratory, a variety of tests (of secretion, emptying, etc.) were performed in well-matched groups of patients, who were in good health, more than one year after truncal, selective or highly selective vagotomy.

One hundred and eighty patients have been treated by HSV in the past three and a half years, without operative mortality. Not one has developed a recurrent ulcer. At the clinical level, gastric emptying has been satisfactory. Only one patient has required re-operation on account of gastric stasis. Tests of gastric emptying yielded no evidence of gastric retention after HSV. They also showed that gastric emptying is much closer to normal than in patients after vagotomy with drainage. "Post-vagotomy" diarrhoea has been virtually abolished, bilious vomiting is absent, and the incidence of dumping has been much reduced.

Spontaneous acid output, and the acid outputs in response to pentagastrin, insulin, and meat extract, were found to be diminished as effectively by HSV as by the standard operations. No evidence of excessive release of gastrin was found. While follow-up is too short to allow of firm conclusions, a great deal of evidence already suggests that the incidence of recurrent ulceration after HSV will be less, not more, than after truncal vagotomy with a drainage procedure.

The gall bladder was found to be dilated after truncal vagotomy, but not dilated after HSV.

In the short term, HSV has given satisfactory results in the treatment of patients with benign gastric ulcer, and in a few carefully-chosen patients with duodenal ulceration complicated by haemorrhage, perforation or pyloric stenosis.

The most disappointing findings were that the incidence of epigastric fullness after meals was 25 to 30 per cent after HSV, which is little different from the incidence after the standard operations; and that dumping was not entirely abolished.

Ninety patients were reviewed at the Gastric Follow-up Clinic, one year after HSV; and 48, two years after HSV. 62 per cent had achieved perfect clinical results (Visick grade I), compared with 38 per cent after truncal or selective vagotomy with pyloroplasty. Although this difference is not statistically significant, it is statistically significant ($p < 0.01$) if our results are pooled with those of Professor Amdrup, whose results are virtually identical to our own. The twenty per cent increase in the proportion of patients with perfect results was matched by a significant decrease (in Leeds, $p < 0.01$) in the proportion of patients in Visick grade III (a "fair" result, marred by side-effects).

This is an interim report. The final verdict on HSV will be passed after a longer period of follow-up, and when the results of

prospective random trials become available. However, there are in essence only two main questions to be answered after HSV. Firstly, does the stomach empty, and secondly, does the ulcer recur? The evidence presented in this thesis shows that the stomach does empty, and that the ulcer will almost certainly not recur, while the advantages of HSV over established procedures are clearly demonstrated. This is the first operation in the history of gastric surgery to permit of well-regulated gastric emptying through an intact pylorus.

immediately after closure of the pyloric sphincter, never just before." Thus did Code[91], in 1970, describe the sequence of events which he and his colleagues had recognized in 1966[31]. It follows that if the antro-pyloro-duodenal segment is kept intact, the antrum will continue to be bathed in the stream of endogenous acid from the fundus. Hence, paradoxically, gastrin release might actually be less from the innervated, "undrained" antrum than from the denervated, "well-drained" antrum,

THE THIRD CONCEPT: THAT PRESERVATION OF PROTECTIVE AND INHIBITORY MECHANISMS COULD LEAD TO AN EXTREMELY LOW INCIDENCE OF RECURRENT ULCERATION

My third and final hypothesis concerning the new operation was that ulcer healing would not merely be as good as after truncal vagotomy with a drainage procedure: it might actually be better. Though much of the ensuing discussion in support of this suggestion is freely admitted to be in the realm of speculation, rather than of proven scientific fact, enough facts are available to lend a certain plausibility to the argument. Firstly, there is the fact, already alluded to, that the hepatic and coeliac vagal fibres, which are severed in truncal vagotomy but preserved in highly selective vagotomy, inhibit gastric

secretion in the dog[25-27]. Secondly, Code and Watkinson found that in dogs inhibition of gastric secretion by acid in the duodenum had an important vagal component[89]. Thirdly, Duthie and I observed, to our considerable surprise, that after truncal vagotomy and pyloroplasty in man, inhibition of gastrin- and histamine-stimulated acid output by olive oil in the duodenum was no longer demonstrable[90], although it had been readily shown in subjects with intact vagi before operation, and also in patients who had undergone pyloroplasty without vagotomy. This work was open to the criticism that the tests were performed only seven to ten days after operation. Nonetheless, it suggested that inhibition by fat might have a vagal component. Hence, it was possible that inhibition of gastric secretion would be greater in degree if the small intestine were kept innervated than if it were vagally denervated.

There is "negative feed-back" from the duodenum to the stomach, such that when chyme which is excessively acid[92-94], fatty[95] or hyperosmolar[92,94,96,97] enters the duodenum, gastric emptying is slowed. The "braking" mechanisms probably consists both of inhibitory nervous reflexes[1,98] and of inhibitory hormones such as secretin[99], cholecystokinin[99] and "enterogastrone"[100].

When Waddell and Wang[43] placed barium plus fat in the stomach of patients with gastrojejunostomy without vagotomy, they observed on fluoroscopy that gastric emptying was slow. In contrast, when the same test meal was given to patients who had undergone truncal vagotomy and gastrojejunostomy, gastric emptying was much more rapid. This demonstrated the importance of the vagus nerves in the inhibition of gastric motility by fat in the intestine. Similarly, Hunt[94,97] has shown that the upper small intestine contains osmoreceptors which delay gastric emptying by means of nervous reflexes when solutions of high osmolarity enter the duodenum. One would expect, therefore, that gastric emptying of fluids would be under better control after highly selective vagotomy, in which some reflex arcs from duodenum to antrum are still intact, than after truncal or selective vagotomy, when all such arcs are presumably destroyed. The importance of this better regulation of gastric emptying after highly selective vagotomy (apart from the prevention of dumping) is that potentially-injurious fluids, such as acid of high concentration, can be prevented from entering the duodenal cap, whose mucous membrane is thereby protected against

ulceration more efficiently than is the case after truncal or selective vagotomy with a drainage procedure. In addition, damming the acid back in the antrum will lower the luminal pH in the antrum, diminish gastrin release[67-69], and so decrease acid output from the body of the stomach.

Pursuing this line of argument, it seems possible that truncal or selective vagotomy with pyloroplasty, by destroying the normal co-ordination of motility in the antrum and duodenum[31] and by impairing the propulsive power of the antral musculature[48], might lead to prolonged contact of endogenous acid with the mucous membrane of the proximal duodenum. In contrast, when the antrum, pylorus and duodenum are left intact, systole of the duodenal cap would be expected to expel the bolus of acid rapidly and efficiently[31,87,91]. Impaired motility in the antrum after vagotomy and pyloroplasty would also favour prolonged contact of secretagogues with the mucous membrane of the antrum, particularly in the dog-eared cul-de-sacs which are such a common feature of the Heinecke-Miculicz type of pyloroplasty[101-102]. This, in turn, might lead to prolonged and excessive release of gastrin, with resulting hypersecretion of acid and pepsin. Such a sequence of events would be less likely to take place when the

antrum, pylorus and duodenum are kept intact.

The passage of chyme into the duodenum leads to the release of hormones such as secretin, cholecystokinin and "enterogastrone" which inhibit gastric secretion in man[98,103-106]. Release of these inhibitory hormones might be impaired after vagal denervation of the duodenum, as in truncal vagotomy.

A cephalic phase has been demonstrated of the secretion of bile, in animals[107-109] and man[110]; of pancreatic juice, in animals[111,112] and man[113]; and of succus entericus in animals[114], just as there has long been known to be a cephalic phase of gastric secretion[115]. The effect of this cephalic phase would be to increase the capacity of the duodenal contents to neutralize acid entering from the stomach. One would expect the cephalic phase to be abolished by truncal vagotomy and indeed there is evidence that this is so. For example, in a carefully-performed study, Pfeffer, Stephenson and Hinton[116] showed that ten patients who were in good health, four to five years after transthoracic truncal vagotomy had significant depression of exocrine pancreatic secretion, both in response to secretin and in response to "maximal" stimulation with insulin-plus-secretin in combination, compared with secretion in normal

control subjects. Similarly, Dreiling, Druckerman and Hollander[11] reported that the pancreatic enzyme response to insulin-hypoglycaemia was virtually absent in eight patients who had undergone complete truncal vagotomy in the course of oesophago-gastrectomy for carcinoma, although their response to secretin was normal. In the dog, selective gastric vagotomy was found to reduce the daily volume of pancreatic secretion by 39 per cent (probably by reducing gastric acid output): when the selective gastric vagotomy was converted to a truncal vagotomy, thedaily volume of pancreatic secretion diminished by a further 21 per cent[118]. Extragastric vagotomy in the dog reduced mean daily volume of pancreatic secretion by 32 per cent[118]. In man, gastric distension was found to produce a significant increase in the volume of pancreatic secretion and in the output of amylase[119]. This effect persisted after Billroth I gastric resection[120] (i.e. after removal of the source of gastrin), but in no instance could it be demonstrated after truncal vagotomy[120]. There is no agreement about the effect of truncal vagotomy on the pancreatic response to secretin in the dog, some authors reporting diminution[116,118], others no change[117], and yet others augmentation[121]. The foregoing results strongly suggest that the pancreatic

exocrine response to food will be diminished significantly after truncal vagotomy in man, partly because of loss of the cephalic phase, and partly because of loss of the gastro-pancreatic reflex. In contrast, after highly selective vagotomy, the cephalic phase should be intact and the gastro-pancreatic reflex may still function to some extent, since part of the stomach is still innervated.

Finally, mucus, succus entericus and the secretions of Brunner's glands probably play an important part in the defence against peptic ulceration, although proof of this assertion is hard to come by. It seems reasonable to suggest that these protective secretions will be less altered in composition and less diminished in volume after an operation which leaves their sources intact than after one which vagally denervates these sources.

These, then, were the three fundamental concepts upon which the operation of highly selective vagotomy without a drainage procedure (HSV) was founded. Compared with gastrectomy or antrectomy, it should be a safer operation, since it involves no resection, no anastomosis, no closure of a duodenal stump.

It should also be slightly safer than vagotomy with a drainage procedure, because even pyloroplasties have been known to leak or to bleed, and gastrojejunostomy stomas to become obstructed. In the long term, nutrition may prove to be better than it is after any of the standard operations, because preservation of the antral mill and of well-regulated gastric emptying should ensure that food is presented to the small intestine in a form which is suitable for further digestion and absorption. For the same reasons, loss of fat in the faeces should be less than after vagotomy with a drainage procedure.

It is obviously of crucial importance that the vagotomy of the parietal cell mass should be complete at the time of operation. Incomplete vagotomy is the commonest cause of recurrent ulceration after truncal vagotomy[122,123], and no variety of vagotomy - truncal, selective or highly selective - can be expected to succeed if there is a high incidence of incomplete vagotomy at the time of operation. For this reason, it is desirable that routine insulin testing should be carried out in the post-operative period[122], so that the surgeon may be alerted if positive responses are found.

In summary, the results of conventional surgery for

duodenal ulcer are unimpressive. The operation proves to be a failure in ten per cent of patients who undergo truncal vagotomy with a drainage procedure, and in a further twenty per cent the clinical result is only moderate. Many of the bad results are attributable to disorders of gastric emtpying. The new surgical approach consists of keeping the pylorus, indeed the whole antro-pyloro-duodenal segment, intact, vagotomy being confined to the acid-and pepsin-secreting part of the stomach. Dumping, bile vomiting and diarrhoea should thus be prevented. The innervated antrum is thought not to pose a major threat of recurrent ulceration, because it remains in the acid stream, subject to acid-inhibition of gastrin release. It is far from certain that denervating the antrum diminishes gastrin release. There is reason to believe that protective and inhibitory mechanisms may be more effective after highly selective vagotomy than after truncal vagotomy.

For almost a century, operations for duodenal ulcer had been followed by unregulated gastric emptying. There was ample justification in theory for keeping the antrum, pylorus and duodenum intact. By December of 1968 the time had come to "try the test".

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CHAPTER 2

HIGHLY SELECTIVE VAGOTOMY WITHOUT A DRAINAGE PROCEDURE IN THE TREATMENT OF DUODENAL ULCER

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HIGHLY SELECTIVE VAGOTOMY WITHOUT A DRAINAGE PROCEDURE IN THE TREATMENT OF DUODENAL ULCER

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SUMMARY

A consecutive series of 25 patients with chronic duodenal ulcer has been treated by highly selective vagotomy without a drainage procedure. The vagal fibres passing to the distal 5–7 cm. of the stomach—the nerves of Latarjet—were left intact, as were the hepatic and coeliac branches of the vagus. The object was to denervate only the parietal cell mass, while preserving normal gastric emptying and normal inhibition of gastric secretion from the antrum and duodenum. This operation should cure the ulcer as effectively as vagotomy with drainage does, and at lower cost in terms of side-effects such as dumping and diarrhoea.

The insulin test was negative in each case, suggesting that vagal denervation of the parietal cell mass was complete. Evidence provided by mucosal biopsies taken at operation does not fully support this view, however. Pentagastrin-stimulated acid output was reduced by 70 per cent, and pepsin output by 51 per cent, 3 months after operation. The volume of resting juice was halved and spontaneous acid output was reduced by 97 per cent at this time. Thus, highly selective vagotomy is as effective as truncal or bilateral selective vagotomy with drainage in reducing gastric acid output in the early months after operation.

There have been no deaths. With 2 exceptions, the patients appear to be doing well clinically and few complain of side-effects, but the period of follow-up is only from 3 to 11 months.

These results are encouraging. They suggest that a highly selective vagotomy, denervating the parietal cell mass but leaving the antrum innervated, may be all that is required to cure most patients who have a chronic duodenal ulcer.

A CONSECUTIVE series of 25 patients with chronic duodenal ulcer has been treated by highly selective vagotomy without any form of drainage procedure. The vagotomy was confined to the acid- and pepsin-secreting area, the distal 5–7 cm. of the stomach being left innervated. This operation is thought to possess two specific advantages over truncal or bilateral selective vagotomy with drainage. First, gastric emptying should be almost normal and as a result dumping should be eliminated, because the antro-pyloroduodenal segment remains normal anatomically and its extrinsic vagal nerve-supply is kept intact. Secondly, the neurohumoral inhibitory mechanisms in the antrum and duodenum, which 'apply the brake' to gastric secretion, are preserved. Thus, postoperatively, inhibition is still lively, whereas maximal acid output is only 30 per cent of its former level. This should be enough to ensure that the ulcer heals and remains healed.

METHOD

Patients.—There are 18 men and 7 women (*Table I*) who have been treated during the period February to October, 1969. In each case the diagnosis of duodenal ulceration was made clinically, radiologically, and at operation. The series is consecutive, except that patients with pyloric stenosis and emergency cases were excluded. In an attempt to detect patients with early pyloric stenosis, special attention was paid to symptoms such as vomiting, acid regurgitation, or heartburn, and to the nature and volume of resting juice aspirated from the stomach in preoperative secretory tests, but in fact only 2 patients who did not have clear radiological evidence of pyloric stenosis were rejected, both on account of a history of repeated vomiting. Obese patients and patients with very scarred, but not stenosed, duodenal caps were included.

Operative Technique.—The abdomen is opened by a right upper paramedian incision and the presence of a duodenal ulcer, without other pathological condition, is confirmed. The degree of scarring and stenosis of the duodenum is estimated by inspection and palpation, but if clinical and radiological features of pyloric stenosis are absent, a drainage procedure is not added even when considerable scarring is found.

The greater anterior gastric nerve of Mitchell (Mitchell, 1940) (anterior nerve of Latarjet; Latarjet, 1921) is demonstrated, as it runs in the lesser omentum close to the descending branch of the left gastric artery (*Figs.* 1–3). It lies 0·5–1 in. from the lesser curvature, until it passes on to the anterior wall of the stomach 4–6 cm. from the pylorus. The nerve is usually seen easily and can always be demonstrated, even in obese subjects.

The distal two-thirds of the greater curvature is next mobilized by dividing the greater omentum, so that the posterior nerve of Latarjet may be seen and preserved. Its course (*Fig.* 2 (B)) is similar to that of the anterior nerve, though in a more posterior plane, and its terminal filaments run caudally on the posterior wall of the stomach towards the pylorus. The next step is to free the stomach still further by dividing congenital adhesions between stomach and pancreas.

The lesser curve is now separated from the lesser omentum, within which the nerves of Latarjet run downwards to the antrum. The dissection begins near the incisura (*see arrows, Fig.* 2) and proceeds upwards towards the cardia. The gap between stomach and nerves being a mere 0·5–1 in., it is essential at this stage to use fine instruments and to avoid haemorrhage. Before they are divided, blood-vessels are ligated in continuity with fine thread on the omental side, while Kilner's forceps are applied on the gastric side. The anterior nerve of Latarjet

is kept in view, and liberal use is made of the diathermy to coagulate small vessels, with fine forceps applied close to the stomach, as far from the nerve as possible. The vessels enter the lesser curve in two distinct leashes, one anterior and the other posterior; and since these leashes are best taken separately in the more distal part of the dissection, it is an advantage to have secured good access to the posterior aspect of the stomach. The anterior nerve of Latarjet, which is the direct continuation of the anterior vagal

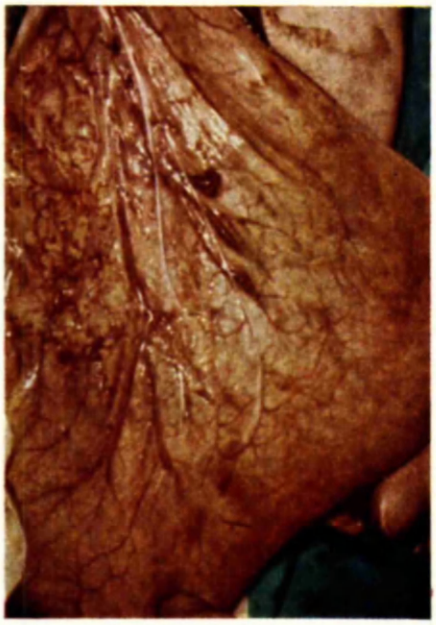

FIG. 1.—Anterior nerve of Latarjet and branches, lesser omentum, and adjacent lesser curvature of stomach, photographed at operation in a slim subject.

trunk, approaches the oesophagus near the cardia and, together with the hepatic branches of the vagus, must be avoided by carrying the dissection obliquely upwards and to the patient's left across the front of the oesophagogastric junction. The anterior aspect of the oesophagus is cleaned of all nerve-fibres, down to bare longitudinal muscle, and finally its posterior aspect is laid bare in like manner. The technique in this region is similar to that employed in the performance of bilateral selective vagotomy, and the hepatic and coeliac branches of the vagi are, of course, also preserved; but it differs from selective vagotomy in that the lesser curve of the stomach is separated completely from the lesser omentum between cardia and 'incisura', that is, to a point about 5–7 cm. from the pylorus (*Fig.* 3). A continuous catgut suture, uniting serosa in front to serosa behind, is sometimes used to invert the raw lesser curvature in an effort to prevent regenerating nerve fibrils passing across from the lesser omentum into gastric muscle. The length of the portion of distal stomach that appears to retain its vagal innervation is measured with a sterile ruler, in the unstretched state. Finally, a number 14 French gauge polythene tube is inserted as a gastrostomy, with its tip directed up into the fundus to permit efficient gastric aspiration when the patient lies supine (Royle and Catchpole, 1967; Hector, 1968), the stomach around it is sutured carefully to parietal peritoneum, any free blood is aspirated, and the abdomen is closed. Operating time varies between 90 and 180 minutes, depending upon the build of the patient, and now averages about 120 minutes.

Three mucosal biopsies were taken from the middle of the anterior wall of the stomach in each of 15 patients, in an attempt to define the position of the antrum–corpus boundary. The first biopsy was obtained 5–7 cm. from the pylorus at the junctional zone between innervated 'antrum' and denervated

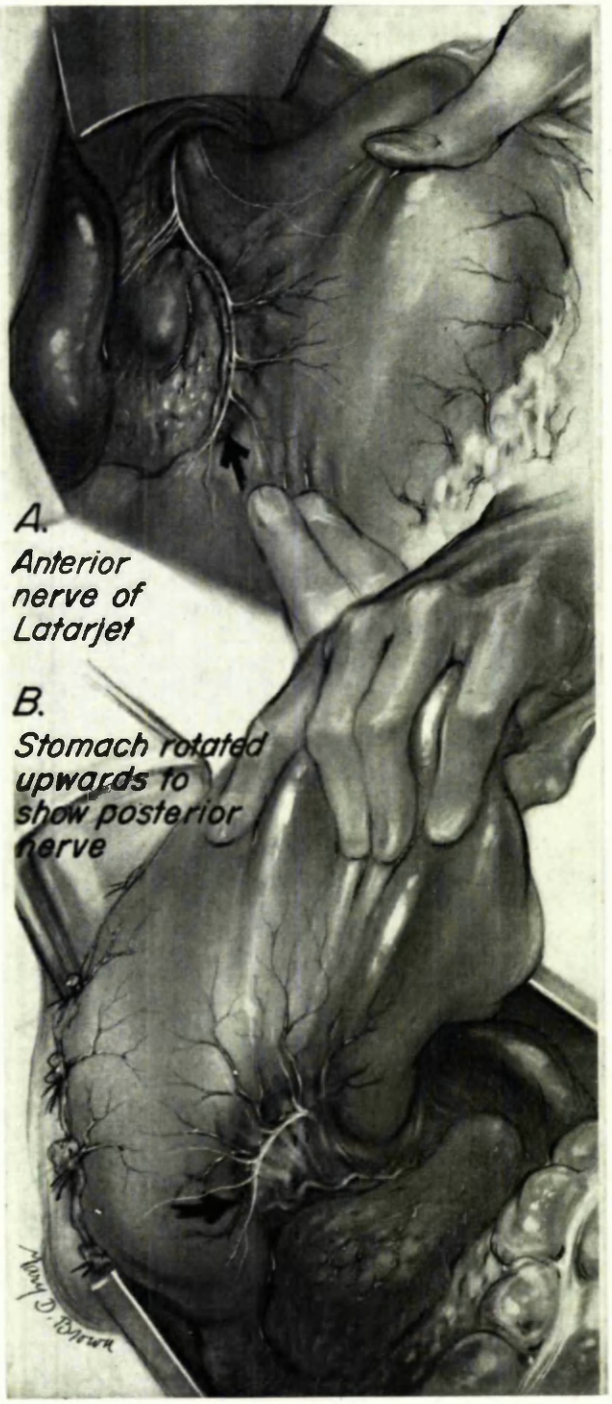

FIG. 2.—The course and distribution of both nerves of Latarjet, as seen at operation. They run parallel to the lesser curve and pass on to the stomach about 4–7 cm. proximal to the pylorus, either as one nerve or as several terminal branches. The dissection begins at the points indicated and proceeds upwards to the cardia, leaving the pyloric gland area innervated

corpus, the second 2 cm. more distally, and the third 2 cm. more proximally. They were submitted to ordinary paraffin-section examination.

Postoperatively, the intravenous drip is discontinued after 24–36 hours. Free oral fluids are given on the third day and a light diet by the fifth or sixth day. Tests of gastric secretion are performed between the fourth and eighth days, after which the gastrostomy tube is withdrawn.

Gastric Secretory Tests.—These were performed before operation, 4–8 days after operation (using the gastrostomy tube), and again 3 months or more later. The methods used have been described (Johnston and Jepson, 1967) and the special precautions necessary to ensure good recovery of gastric juice are well documented (Makhlouf, McManus, and Card, 1965). In 57 tests the efficiency of recovery of gastric juice was checked, using polyethylene glycol; the patient sipped 10 ml. of 1 per cent solution every 5 minutes and the amount present in the gastric aspirate was measured (Hydén, 1955). Acid concentration was measured by titration with *N*/10 sodium hydroxide to *p*H 7·0, using a Radiometer Autotitrator. Spontaneous acid secretion, however, has been expressed in terms of 'free' acid, titrating to *p*H 3·4. Pepsin concentration was measured by Hunt's (1948) method.

The unstimulated gastric secretion aspirated during the first 15 minutes of any test is designated 'resting juice'. Spontaneous, or basal, secretion is then collected for a period of 30 or 40 minutes.

Pentagastrin Test (Johnston and Jepson, 1967).—A dose of 6 μg. per kg. is injected intramuscularly in the preoperative test and 10 μg. per kg. in each test after vagotomy. Twelve collections of gastric secretion are made, each representing a 5-minute period of continuous aspiration. 'Peak acid output' in mEq. per hour is calculated by multiplying the output in the peak 20-minute period by three. 'Total-hour' output comprises all the secretion aspirated in the entire 60-minute period after the injection.

Insulin Test.—Twelve 15-minute collections of gastric secretion are made, 4 before the intravenous injection of 0·15 unit per kg. of soluble insulin and 8 after. Specimens of venous blood are withdrawn 30 and 45 minutes after the injection for blood-glucose estimation on the Autoanalyzer. Since the traditional Hollander (1946) criteria for a positive response are arbitrary, we have judged the response to insulin by multiple criteria, namely those of Hollander (1946) (rise of 20 mEq./l., or 10 mEq./l. if basal specimens anacid), Stempien (1962) (rise of 0·25 mEq. in acid output in any one hour), Bachrach (1962) (basal acid output greater than 2 mEq. per hour or a rise of more than 1 mEq. in any one hour), and Spencer, Burns, Cheng, Cox, and Welbourn (1969) (rise of 20 mEq./l. in men and 15 mEq./l. in women). 'Basal' acid concentration is taken to be the mean of the acid concentrations of the four 'basal' specimens and is compared with the mean of the two highest consecutive concentrations after insulin, or with the single highest acid concentration if a consistent rising trend is apparent.

Antral Stimulation Test.—For exactly 15 minutes 100 ml. of meat broth (Giles and Clark, 1966) or of 0·5 per cent acetylcholine chloride solution are placed in the empty stomach, then aspirated in the course of 5 minutes, after which gastric secretion is collected by continuous suction for 60 minutes.

Tests of Gastric Emptying.—The volume of 'resting juice' in the stomach after an overnight fast provides a rough estimate of whether emptying is satisfactory or not. More elaborate tests involving the use of fluid test meals of saline and of hypertonic glucose are now being done and will be reported in detail later.

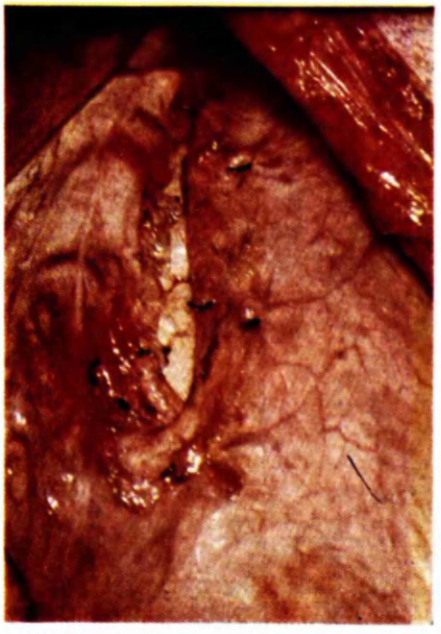

FIG. 3.—Highly selective vagotomy has been completed. The anterior nerve of Latarjet is visible in the lesser omentum. Pancreas is seen in the gap between lesser omentum and the lesser curve of stomach.

RESULTS

Clinical.—There was no mortality and little morbidity. Adequate clinical assessment is not possible because of the short period of follow-up. Two patients have unsatisfactory results at present because of poor appetite, weight-loss, and abdominal discomfort. The others eat normal-sized meals, do not vomit, and most of them have at least regained their preoperative weight. Two have mild dumping. Bowel habit is more constipated in some, slightly looser in others, and in most there has been no change.

There have been no complications from the use of the gastrostomy tube, unless its presence contributed to the incidence of wound infection, which was a lamentable 20 per cent. One patient bled a few hours after operation and was transfused with 3 pints of blood, but was not re-explored. Gastric retention has not been a feature and ileus has not persisted beyond the second day. The patients left hospital on average 11 days after operation (range 8–14 days). One man, who had a 25-year history of dyspepsia and was found to have considerable duodenal scarring at operation, was readmitted a week after his discharge from hospital because of repeated vomiting of food. The vomiting stopped when he was given a liquid diet. Two weeks later he was able to eat normally and he continues to do well. Another patient complained of difficulty in swallowing solid food in the early weeks after discharge, but this trouble also subsided spontaneously; barium swallow was normal.

Table I.—EFFECT OF HIGHLY SELECTIVE VAGOTOMY ON ACID AND PEPSIN SECRETION IN 25 PATIENTS WITH DUODENAL ULCER

Case No.	Age and Sex	Weight (kg.)	Length of History (years)	Time in Hospital after Operation (days)	Spontaneous Acid Output (mEq. per hour)				Maximal Pentagastrin Acid Output (Peak 20-minute period × 3; mEq. per hour)					Pepsin Output (~~Stimulated by~~ 1000 Hunt units ~~pentagastrin~~)		
					Before Operation	At 1 Week	At 3 Months	Reduction at 3 Months (per cent)	Before Operation	After 1 Week	Reduction at 1 Week (per cent)	After 3 Months	Reduction at 3 Months (per cent)	Before Operation	After 3 Months	Reduction at 3 Months (per cent)
1	50 M.	81	10	14	7·1	0·0	0·0	100·0	31·8	14·0	56·0	13·0	59·2	50·1	35·0	31·4
2	45 M.	75	20	11	15·0	0·8	0·0	100·0	51·7	19·4	62·5	17·9	65·4	20·3	14·1	30·5
3	33 M.	74	8	10	0·4	0·1	0·0	100·0	29·9	29·7	0·6	11·1	62·7	43·0	18·3	57·5
4	27 M.	70	5	8	—	0·0	0·0	100·0	71·8	16·8	76·7	17·4	75·8	81·7	16·5	79·8
5	62 M.	72	25	12	—	0·8	0·0	100·0	39·2	17·3	55·7	1·7	96·0	41·0	5·4	76·8
6	35 M.	76	15	9	—	0·0	0·0	100·0	53·9	31·4	41·8	18·2	66·2	19·8	22·6	+14·6
7	29 M.	67	4	10	—	1·5	0·8	80·0*	43·0	24·3	43·5	20·3	52·8	81·4	28·9	64·5
8	34 M.	79	3	9	6·1	0·1	0·4	93·7	35·4	12·5	64·6	5·1	85·5	—	—	—
9	18 M.	59	4	9	—	0·7	—	—	64·9	37·3	42·6	—	—	—	—	—
10	22 M.	52	4	10	5·0	0·5	—	—	37·4	22·8	39·0	—	—	—	—	—
11	47 M.	62	3	10	6·7	0·0	0·2	96·4	43·7	16·3	62·6	8·4	80·7	50·7	23·0	54·6
12	43 M.	61	10	13	3·9	0·5	0·0	100·0	35·7	18·7	47·6	15·7	91·6	62·5	25·8	58·7
13	33 M.	56	3	11	10·3	0·7	—	—	37·0	13·3	64·0	—	—	—	—	—
14	33 M.	66	6	8	—	1·2	—	—	48·6	22·0	56·6	—	—	—	—	—
15	40 M.	80	2	9	9·1	0·6	—	—	36·6	15·6	57·5	—	—	—	—	—
16	34 M.	66	15	9	1·6	0·0	—	—	38·2	32·3	15·5	—	—	—	—	—
17	28 M.	75	2	10	20·1	0·5	—	—	56·0	28·9	48·5	—	—	—	—	—
18	54 M.	77	3	10	7·0	0·0	—	—	34·5	5·2	85·0	—	—	—	—	—
19	48 F.	41	20	9	1·6	0·2	—	—	18·3	13·6	25·8	—	—	—	—	—
20	40 F.	48	5	12	6·5	0·0	0·0	100·0	28·5	7·2	74·7	—	—	—	—	—
21	34 F.	57	2	10	2·5	0·0	—	—	36·4	11·2	69·2	—	—	—	—	—
22	40 F.	50	7	11	9·6	1·2	—	—	30·0	20·9	30·5	23·4	21·9	27·0	8·5	68·4
23	34 F.	74	10	13	6·0	0·7	—	—	38·0	20·6	45·7	—	—	—	—	—
24	21 F.	59	5	14	4·7	1·3	—	—	26·9	13·3	51·6	—	—	—	—	—
25	48 F.	63	7	11	3·4	0·0	—	—	25·6	19·2	25·1	—	—	—	—	—
Mean of 25 ±1 S.E.	37·28	65·60	7·92	10·48	6·65 ±1·10	0·45 ±1·10	0·13 ±0·08	97·3	39·71 ±2·48	19·35 ±1·59	49·71 ±3·95	—	—	—	—	—
Mean of 11 re-tested 3 months postoperatively	—	—	—	—	—	—	—	—	42·36	20·11	—	12·68	68·89	48·75	19·81	50·76 ±8·94

* Estimated reduction.

The insulin test was negative in each of the 25 patients.

Gastric Emptying.—Most of the patients are eating well, none complains of foul eructations, and only 1 is troubled by vomiting if she eats a large meal. The resting juice present in the stomach after an overnight fast was 94±S.E. 10 ml. before operation, 61±11 ml. 1 week after, and 48±6 ml. more than 3 months after operation. The results of more sophisticated tests of gastric emptying (to be published) suggest that a fluid test meal empties slightly faster after this operation than it did before operation, whereas in subjects who have undergone truncal or selective vagotomy with pyloroplasty the same test meal empties a great deal faster postoperatively.

Completeness of Vagotomy.—This has been judged by insulin testing and by the evidence afforded by the mucosal biopsies.

1. *Insulin Tests.*—Each of the 25 tests, which were performed within 10 days of the operation, was negative by all criteria, suggesting that vagal denervation of the parietal cell mass is complete. Blood-glucose concentration decreased to less than 50 mg. per cent in each test.

2. *Gastric Mucosal Biopsies.*—Eight of 15 biopsies taken at the presumed junction of innervated with denervated stomach consisted of antral tissue, but 4 were from the corpus and in 3 both types of mucosa were represented. All the biopsies taken 4–5 cm. from the pylorus consisted of antral tissue, whereas at 9 cm. from the pylorus all biopsies were from the parietal cell mass.

Gastric Secretion.—

1. *Spontaneous Secretion.*—Mean output of free acid per hour was 6·6±S.E. 1·1 mEq. before operation (19 patients), 0·45±0·10 mEq. 6 days after (25 patients), and 0·13±0·08 mEq. 3 months after operation (11 patients). At 3 months, 8 of the 11 patients tested did not secrete free acid and the mean reduction was 97·3 per cent (*Table I*).

2. *Pentagastrin-stimulated Secretion.*—

a. Acid output (*A.O.*): Compared with preoperative A.O., peak A.O. was reduced by a mean of 50±S.E. 4 per cent at 6 days and 69±6 per cent at 3 months after operation (*Table I*). 'Total-hour' A.O. was reduced by 55±4 per cent at 6 days and 72±6 per cent at 3 months. The decrease in acid secretion between 6 days and 3 months postoperatively is statistically significant ($n=11$, $t=3{\cdot}33$, $P<0{\cdot}01$). Recovery of polyethylene glycol averaged 89 per cent before operation, 90 per cent in the early postoperative tests, and 81 per cent in tests performed more than 3 months after operation.

b. Pepsin output: Three months after operation 'total-hour' output had decreased by 50·8±8·9 per cent in 11 patients.

3. *Response to Antral Stimulants* (*Meat Broth and Acetylcholine*).—These tests have not yet been repeated 3 months or more after operation. The mean acid response to meat broth was 55 per cent of the maximal pentagastrin acid output (M.A.O.) in 11 tests before operation, and 20 per cent of the postoperative M.A.O. in 11 tests after operation. The response to acetylcholine was 27 per cent of M.A.O. in 12 preoperative tests, but only 3 per cent of the M.A.O. in 6 tests after operation. For comparison, the acid response to meat extract 7 days after truncal or selective vagotomy and pyloroplasty was 11 per cent of the maximum in 4 patients.

DISCUSSION

Final judgement on this operation for duodenal ulcer must be reserved until the incidence of recurrent ulceration is known, but these early results are most encouraging. The insulin tests were all negative by all criteria in the early postoperative period, and reduction in the maximal acid response to pentagastrin of 70 per cent is the same as is found after truncal or selective vagotomy with drainage (Multicentre Study, 1967; Jepson, Lari, and Johnston, 1968; Mason, Giles, Graham, Clark, and Goligher, 1968). The follow-up period is too short to permit any useful assessment to be made of the clinical results, but the patients' progress overall has been satisfactory. One patient complains of weight-loss and another is troubled by inability to eat full meals and by occasional vomiting. The others are eating well, not vomiting, and most have regained their preoperative weight. Dumping and diarrhoea are either absent altogether or are of very mild degree.

The evidence for good gastric emptying after highly selective vagotomy is largely clinical at present, and thus perhaps unreliable, but it is known that resting juice in the stomach is reduced by 50 per cent. Also, tests of gastric emptying now in progress have so far confirmed the clinical impressions. Finally, it is noteworthy that studies of gastric emptying in dogs, none of which had had a drainage operation, revealed no gastric retention after highly selective vagotomy, whereas after truncal or bilateral selective vagotomy, severe and moderate degrees of stasis respectively were found (Amdrup and Griffith, 1969a; Shiina and Griffith, 1969).

The evidence for completeness of the vagotomy in all cases, as provided by the insulin test, is gratifying, but there can be little doubt that some positive responses will be discovered on retesting at a later date. Certainly the histological reports on the mucosal biopsy specimens suggest that a narrow cuff of distal parietal cells has been left innervated in some cases. This has prompted us to define the antrum–corpus boundary routinely at operation, by means of the indicator dye Congo Red, which turns black when it is in contact with acid-secreting mucosa (Moe, Klopper, and Nyhus, 1965). The insulin test was positive, though weakly so, in many of the dogs after highly selective vagotomy (Griffith and Harkins, 1957; Amdrup and Griffith, 1969a, b). In man, a negative response to insulin in the early postoperative test is no guarantee that reversion to positive will not occur later (Mason and Giles, 1968; Gillespie, Elder, Gillespie, Kay, and Crean, 1969). In our own series the insulin test has been repeated in only 2 patients. It was negative in 1, but early positive in the other, though the acid response to insulin was small. None the less, the large and significant decrease in acid output that takes place between 6 days and 3 months postoperatively indicates that widespread reinnervation of the parietal cell mass has not taken place in our patients.

That the achievements of current methods of surgical treatment for duodenal ulcer leave considerable room for improvement was suggested by the report of Goligher, Pulvertaft, de Dombal, Clark, Conyers, Duthie, Feather, Latchmore, Matheson, Shoesmith, Smiddy, and Willson-Pepper (1968a), which showed that the results of truncal vagotomy and

pyloroplasty, when assessed 2 years postoperatively, were significantly worse than those of either Polya partial gastrectomy or vagotomy and antrectomy at the same period after operation. Although this particular comparison was made in 'non-randomized' series of patients, the results of a prospective controlled trial (Goligher and others, 1968b) also revealed that, 5–8 years after operation, patients were faring worse after vagotomy and gastro-enterostomy than after either Polya gastrectomy or vagotomy and antrectomy. Other recent reports (Dellipiani, MacLeod, Thomson, and Shivas, 1969; Kennedy and Connell, 1969) stress the high incidence of side-effects, such as epigastric fullness, dumping, and diarrhoea, which is found in patients after vagotomy with a drainage procedure.

If change is needed, it is by no means clear what direction it should take. A return to the routine use of Polya gastrectomy would be unthinkable, because of the increased operative mortality and the greater incidence of weight-loss, anaemia, and bone disease in the long term. Vagotomy with antrectomy yields excellent results in some hands (Scott, Sawyers, Gobbel, Herrington, Edwards, and Edwards, 1966) but combines many of the disadvantages of vagotomy and of gastrectomy. One is thus driven to try to discover why vagotomy with drainage fails, and to attempt to remedy the defects while retaining the good features.

Much recent evidence points to the drainage procedure, rather than the vagotomy, as being the cause of many of the poor clinical results. Pyloroplasty, for example, destroys the co-ordination of motility in the antrum and the proximal duodenum and weakens the propulsive power of the antral musculature (Ludwick, Wiley, and Bass, 1969). In the dog it is responsible for increased losses of fat in the faeces, whereas vagotomy alone produces no such change (Wastell, 1966). In man, gastric emptying of a test meal of mashed potato was delayed after pyloroplasty alone and after vagotomy and pyloroplasty (Buckler, 1967). In direct contrast, George, Connell, and Kennedy (1968) and McKelvey, Connell, and Kennedy (1969), using the multiple-sampling technique of George (1968), have shown that gastric emptying of a fluid meal is much faster after vagotomy and pyloroplasty than before operation, that intestinal transit time is diminished, and that these changes are particularly marked in patients who are troubled by 'post-vagotomy' diarrhoea. Differences in the consistencies of the test meals used cannot explain these conflicting results, since Colmer, Davies, Owen, and Shields (1969) found that a normal, albeit radioactive, breakfast emptied much faster after vagotomy and pyloroplasty (at least in the first 20 minutes after the meal) than it had done before operation. The work of Colmer and others (1969) and McKelvey and others (1969) suggests that the reservoir function of the stomach is severely impaired after vagotomy and drainage operations, or, as the latter authors pithily put it: 'the stomach is incontinent'. This provides an explanation for many of the patients' complaints—the inability to eat large meals and hence weight-loss, nausea, epigastric fullness or discomfort after meals, early dumping, and post-cibal diarrhoea. Normal gastric emptying depends upon the existence of an anatomically—and physiologically—normal antro-pyloroduodenal segment (Thomas, 1957), and it seems obvious that avoidance of interference with that segment would be a highly desirable feature of any new operation for peptic ulcer.

Preservation of a normal antrum, pylorus, and duodenum should carry other advantages. For example, this region is the site of the physiological 'brake' on gastric motility (Thomas, 1957) and secretion in man (Griffiths, 1936; Shay, Gershon-Cohen, and Fels, 1942; Gillespie, 1959; Køster and Rune, 1963; Johnston and Duthie, 1964, 1965, 1966, 1969). The secretory inhibition probably has both a nervous component (Code and Watkinson, 1955; Iggo, 1957; Sircus, 1958; Johnston and Duthie, 1966, 1969) and a humoral component (Woodward, Lyon, Landor, and Dragstedt, 1954; Greenlee, Longhi, Guerrero, Nelsen, El-Bedri, and Dragstedt, 1957; Andersson, 1960, 1963, 1969; Kamionkowski, Grossman, and Fleschler, 1964; Wormsley and Grossman, 1964; Johnston and Duthie, 1966). Inhibition of motility is also neurohumoral in nature (Thomas, 1957). The passage of acid on to the antrum and of acid chyme into the duodenum activates the braking mechanism. By contrast, gastric acid secretion increases greatly if the antro-pyloroduodenal segment is by-passed (Uvnäs, Andersson, Elwin, and Malm, 1956). The protective effect of a retained antrum in the acid stream is illustrated by the fact that dogs subjected to a 50 per cent resection of the parietal cell mass are significantly less likely to develop histamine-induced ulcer if the antrum is left in the acid stream than if the antrum is excised (State, Katz, Kaplan, Herman, Morgenstern, and Knight, 1955; State, 1960). This protective effect of the antrum may be due to the fact that 'the antrum in an acid environment will inhibit gastric secretion, whether it be of vagal, antral or intestinal origin' (Shimizu, Morrison, and Harrison, 1958). Such a beneficent role contrasts with the dire effects of a retained antrum that is excluded from the acid stream (von Eiselsberg, 1920; Devine, 1925; Finsterer and Cunha, 1931). The profuse secretion of mucus in the antral region of the stomach (Jennings and Florey, 1940; Menguy and Thompson, 1967) is no doubt also a protective feature. In an important recent paper, Hart (1968) has reported that the vagal antral nerves (of Latarjet) mediate inhibition of gastric acid secretion. In summary, when vagotomy is confined to the parietal cell area, the natural defences against ulceration, which are weakened by the more conventional types of operation, are kept intact.

The basic problems, then, are that total gastric vagotomy, whether truncal or bilateral selective, produces gastric stasis (Dragstedt, Harper, Tovee, and Woodward, 1947; Shiina and Griffith, 1969) and that drainage procedures designed to relieve the stasis produce side-effects of their own. The logical deduction from these data led Griffith and Harkins (1957) to experiment with a 'partial gastric vagotomy' (selective vagotomy of the parietal cell area) in dogs. They concluded that the operation was effective in denervating the parietal cell mass, did not produce gastric stasis, and could be applied clinically. Later experiments (Amdrup and Griffith, 1969a, b) confirmed both the absence of gastric stasis and also the fact that the insulin response was either very small or

entirely absent. By contrast, both truncal and bilateral selective vagotomy without drainage produced marked delay in gastric emptying (Shiina and Griffith, 1969). In man, preservation of an innervated antrum in the acid stream was pioneered successfully by Ferguson, Billings, Swensen, and Hoover (1960). Some widening of the pyloric region was judged necessary in only 28 per cent of their 185 patients with duodenal ulcer: in the remainder no drainage procedure was used. At follow-up, dumping was noted to be absent or very mild and the recurrent ulcer rate was 4 per cent. The physiological studies of Hart (1968), showing the inhibitory role of the nerves of Latarjet, have been pursued in conjunction with clinical studies (Holle and Hart, 1967; Holle, 1967) in which the antrum has been left innervated in several hundred patients; but it appears that a concomitant drainage procedure or resection is invariably added. Bilateral selective vagotomy without a drainage procedure has been used by Burge, MacLean, Stedeford, Pinn, and Hollanders (1969) in treating more than 100 selected cases of duodenal ulceration. Studies of gastric emptying (Shiina and Griffith, 1969) and motility (Wohlrabe and Kelly, 1959; Stavney, Kato, Griffith, Nyhus, and Harkins, 1963) in dogs subjected to bilateral selective vagotomy without drainage suggest, however, that antral motility is much reduced and that gastric stasis is severe in some cases. A trend towards gastric stasis is discernible in the radiological studies performed on the patients of Burge and others (1969), but their clinical progress has on the whole been satisfactory.

The most controversial feature of highly selective vagotomy is undoubtedly the retention of an innervated antrum, because accepted teaching has been that if the antrum is to be retained at all, it should be well drained, should lie in the acid stream, and should be vagally denervated (Nyhus, Chapman, De Vito, and Harkins, 1960). The first two conditions are satisfied. As to the necessity for vagal denervation, it would appear that, in man, the antrum has been left vagally innervated with impunity in many hundreds of operations for duodenal ulcer (Ferguson and others, 1960; Holle and Hart, 1967). In our own cases the acid response to meat extract was only 20 per cent of the maximum acid output after operation, compared with 55 per cent before operation; and the response to acetylcholine solution was reduced from 27 per cent of the maximum acid output preoperatively to a mere 3 per cent after operation. Thus, we think that antral stasis is unlikely to occur, that gastrin release will be inhibited in part by contact of acid with the antral mucosa, and that such gastrin as is released must act upon vagally denervated, and hence less sensitive (Uvnäs, 1942), parietal cells.

In conclusion, it seems fair to say that traditional surgical operations for duodenal ulcer have involved an aggressive attack on the nervous and humoral mechanisms responsible for stimulating gastric secretion. The importance of preserving the natural defence mechanisms in the antrum and duodenum has received scant attention, while the pyloric sphincter and the related antrum and duodenum, so important for maintaining the 'reservoir' function of the stomach and for controlling gastric emptying, have been sacrificed with little thought for the consequences. The results presented here appear to justify a new surgical approach, which is strictly confined to interruption of the vagal nerve supply to the acid- and pepsin-secreting area, while the vagal innervation of the antrum, pylorus, and duodenum is carefully preserved. There is no interference with the integrity of the stomach and no drainage procedure is deemed necessary. Acid and pepsin outputs are reduced as effectively as in the conventional operations, but there is less interference with mechanisms that normally protect against peptic ulceration. Gastric emptying should be almost normal.

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COMMENT

This is the first paper in the world literature on vagotomy confined to the parietal cell mass (HSV) without a drainage procedure in man. The findings of satisfactory gastric emptying and of large reductions in acid output (as large as after truncal vagotomy) have been amply confirmed by all our subsequent work. The reduction in maximal acid output in patient number12 (Table I) three months after HSV was 56 per cent, not 92 per cent as stated, and the mean reduction at three months was therefore 66 per cent.

The first attempt at HSV in December 1968 had failed because, instead of dissecting in the plane just outside the muscular layer of the lesser curvature, I dissected upwards from the incisura in the plane between the muscle and the mucosa, attempting to perform a myotomy, in order to be quite sure of preserving the nerves of Latarjet. The plan was to stay in this plane as far as the cardia, but to dissect around the oesophagus outside the muscle layer in the usual way. However, this procedure proved to be difficult and haemorrhagic, and while the anterior wall of the stomach was probably denervated successfully as far as the antrum, I got into difficulties, perforated the gastric mucosa in two places, and eventually performed a posterior truncal vagotomy. The patient had a late-positive (second-

hour) response to insulin soon after operation, but has done very well clinically. After this débacle, I decided to dissect outside the muscular layer of the gastric wall, but to stay very close to it, and to the muscle of the lower oesophagus, hoping in this way to avoid damaging the nerves of Latarjet and the hepatic and coeliac branches. I have not made a practice of identifying the vagal trunks, or the coeliac branch, preferring to keep well away from them. In the absence of a test for the integrity of the hepatic and coeliac vagal fibres, I am at present unable to prove that they have been spared. While I would admit the possibility that the coeliac branch may occasionally have been damaged inadvertently at the time of HSV, I feel sure that in the great majority of patients damage to the extra-gastric vagi has been avoided. All the same, proof would be preferable. In January of 1969 I performed three highly selective vagotomies, but in two of these patients a small wedge resection of the parietal cell mass was added, the triangle of tissue being based on the greater curve. These patients have also done well clinically.

Examination of the mucosal biopsies suggested that a small distal cuff of parietal cell mass was being left innervated in many patients, although this was impossible to prove because one could not define the exact distribution of the antral nerve fibres which

were preserved. For reasons which are explained in the concluding Chapter, we have yet to be convinced that "antral mapping" by means of the Congo Red test or the pH probe is necessary. After a brief flirtation with the Congo Red test at ten HSV operations, we found it to be a fickle jade, at least in our hands, because it did not invariably outline the antrum clearly, and we abandoned its use.

The sceptical reader might well jib at the phrase in the introduction "inhibition is still lively" (i.e. inhibition from the antrum and duodenum, after HSV). As will be shown later, inhibition of antral release of gastrin does appear to be "lively" after HSV, because spontaneous acid output is low, vagal stimulation by insulin-hypoglycaemia elicits only small acid outputs, and the response to a test meal of meat extract is no greater than the response which is found after truncal vagotomy with a drainage procedure. Whether inhibition of gastri[illegible]retion from the duodenum after HSV is "livelier" than after truncal vagotomy is not clear, and this theme receives [illegible]tention later in the thesis.

CHAPTER 3

SPONTANEOUS ACID OUTPUT

PART I: Serial tests of BAO before, and for up to two years after, HSV.

PART II: A comparison of the effects of truncal, selective and highly selective vagotomy on BAO.

CHAPTER 3

SPONTANEOUS ACID OUTPUT

PART I: Serial tests of BAO before and for up to two years after HSV

The term "spontaneous" is preferred to "basal", acid output, because unstimulated secretion from the stomach was measured after the patient had fasted for only 8 to 10 hours overnight. Thus, he could not be claimed to be in a basal state. The contraction, "BAO", however, will be used, because it has acquired respectability through use and wont.

Inappropriate, excessive secretion of "spontaneous" acid is a well-known characteristic of patients with duodenal ulcer[1]. Such hypersecretion may continue throughout the night, when the stomach is empty. While normal people secrete 0 to 9 mEq per hour of BAO, with a mean in healthy adults of about 2.5 [2], patients with duodenal ulcer secrete 0 to 20 or more mEq per hour, with a mean of 6 mEq per hour. Both of Dragstedt and Owen's original patients had spontaneous hypersecretion[3], as shown by continuous aspiration of the stomach for 12 hours overnight, but after transthoracic truncal vagotomy the hypersecretion was abolished. Subsequently, it has been shown on many occasions that vagotomy, whether truncal or bilateral selective in type, with a drainage

procedure, reduces BAO by between 60 and 85 per cent[4-7]. Some of the previous studies were flawed, however, by the fact that measurement of BAO was performed too soon (within 10 days) after operation. Ideally, such tests should be deferred until at least one year has elapsed from the time of operation. In other studies, it is impossible to tell whether vagotomy was complete or incomplete, because results of insulin tests are lacking. Measurement of BAO after HSV was of great interest for a variety of reasons. Firstly, one wished to know whether HSV reduced BAO as effectively as did truncal or selective vagotomy with a drainage procedure. Secondly, if low levels of BAO were found after HSV it would suggest that gastrin release from the innervated antrum was not excessive, whereas the finding of high levels of BAO would suggest that circulating levels of gastrin were high. High gastrin levels could result from vagal stimulation of the antrum via the intact nerves of Latarjet, from antral stasis, or perhaps from both of these factors. If antral stasis did exist, its presence would be revealed in the course of the tests by the finding of large volumes of resting juice and of food residues in the stomach.

For these reasons, the simple measurement of spontaneous secretion might be expected to give a good guide to the eventual success

or failure of HSV. Indeed, in the past, failure of inadequate operations for duodenal ulcer could probably have been predicted on the basis of measurements of BAO. For example, after the antral-exclusion operation of von Eiselsberg[8] and Devine[9], gastrin release from the antrum was excessive, and hence BAO was high. Again, gastroenterostomy alone did not reduce BAO significantly.[10] Finally, in patients who develop recurrent ulceration after incomplete truncal or selective vagotomy with a drainage procedure, BAO is usually found to be high (see Table IV, p 201).

In our preliminary paper[11], a mean reduction of 97 per cent in "free" BAO (to pH 3.5) 3 months after HSV was reported, in 11 patients. No fewer than 8 of the 11 failed to secrete spontaneous free acid. It remained for us to carry out serial tests of BAO for up to 2 years after highly selective vagotomy.

METHOD

Patients BAO was measured before, and for up to 2 years after, HSV, in 57 patients. 50 patients were studied both before operation and 4 to 8 days after operation. Thereafter, 41 patients returned for further tests of BAO, between 3 and 24 months after HSV. 17 patients were tested both at 3 months and at 12 - 24 months after HSV. 8 were tested

both 6 - 12 months and 12 - 24 months after HSV. BAO was measured 67 times in 39 patients more than one year after HSV. The patients who returned for testing were representative of the entire group of patients treated by HSV, with respect to age, weight, sex, pre- and post-operative maximal acid output and clinical (Visick) status (Table I)

Technique Tests were performed in the morning after the patients had fasted overnight. The methods used were standard (Chapter 4 Part II). The first 15 minutes were spent in the aspiration of "resting juice", after which spontaneous secretion was collected. In most tests, BAO was collected for 60 minutes, but in about 10 per cent of tests it was collected for 30 - 40 minutes only. Titration of acid was to the twin end-points of pH 3.5 and pH 7.0. BAO was expressed as mEq of "free" acid and as mEq of "acid" respectively.

RESULTS

Except where specifically stated, figures quoted refer to spontaneous acid output to pH 7.

BAO was reduced by a mean of 89 per cent at 1 week, 92 per cent at 3 months, 83 per cent at 9 months and 76 per cent at 12 to 24 months after HSV (Fig.1 , Table I). The increase in BAO between 3 months and 12 - 24 months after HSV was statistically highly significant

SERIAL TESTS OF SPONTANEOUS ACID OUTPUT AFTER HIGHLY SELECTIVE VAGOTOMY.

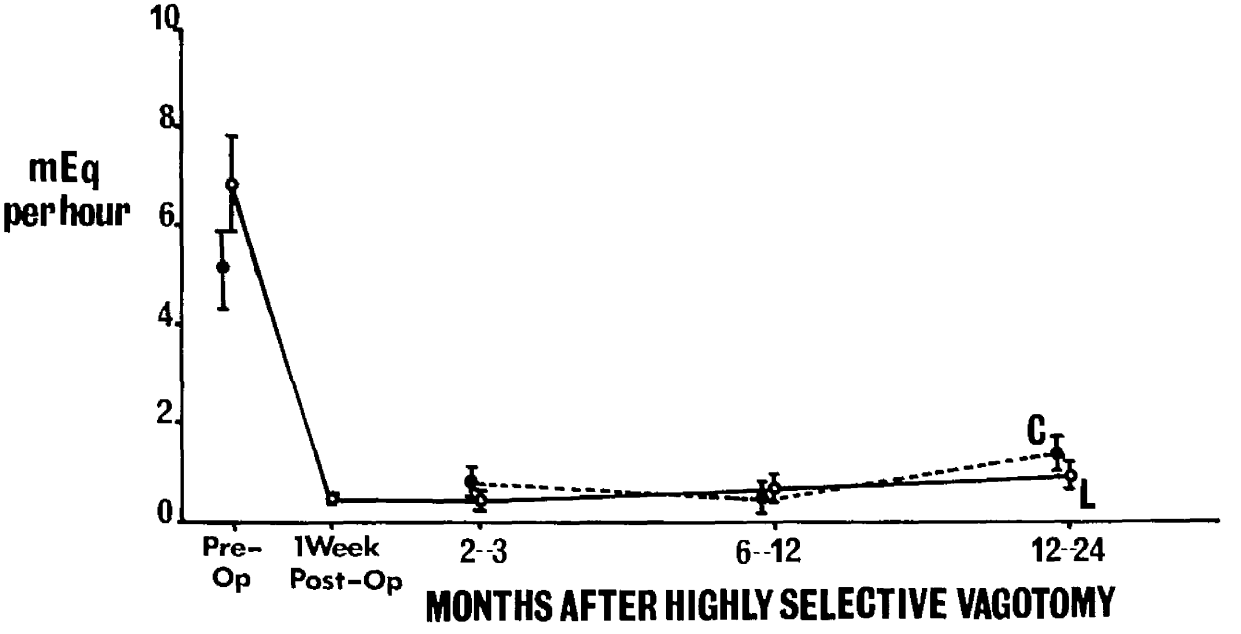

Fig. 1 Mean outputs (± 1 SE) of "free" acid after HSV in patients in Leeds (L) and Copenhagen (C) - data from the latter patients by courtesy of Professor E. Amdrup. The mean reduction more than one year after HSV is about 80 per cent. There is little difference between the results from the two centres.

(17 paired tests: mean increase 0.74 mEq $\pm$ 1 S.E. 0.177, $t = 4.169$, $p < 0.001$). In 50 tests before operation, mean BAO was 7.01 (free) and 8.27 mEq per hour. More than one year after HSV, in 67 tests on 39 patients, mean BAO was 0.99 (free) and 1.54 mEq per hour. No free acid was present in the spontaneous gastric secretion in 27 of these 67 tests. Very small reductions in BAO were recorded in a few patients whose BAO was low before operation (Table I). If 7 patients with a pre-operative BAO of less than 3.1 mEq per hour are excluded, the mean reduction in BAO in the remaining 30 patients was 83.75 per cent. The mean reduction in 'free' BAO more than one year after HSV was 82 per cent.

DISCUSSION

Spontaneous (free) acid output was reduced by a mean of 82 per cent, in 39 patients who were tested more than one year after HSV. 11 of the 39 patients had no free acid in their spontaneous secretion at that time, and 20 of the 39 had no free acid in at least one test more than one year after HSV. Free acid was absent in 27 of 67 tests of BAO, more than one year after HSV. When titration was taken to pH 7, the mean reduction in BAO was 76 per cent, or 84 per cent if patients with low pre-operative BAO were excluded. These reductions

are at least as great as those reported previously in patients after truncal or bilateral selective vagotomy with a drainage procedure[1,4-7] (see Part II). It is not known at present whether BAO continues to increase beyond 2 years after HSV, but since pentagastrin-stimulated MAO does not increase after 1 year, it seems unlikely that BAO will go on rising.

In Copenhagen, 18 patients of Amdrup's[12] had a mean 'free' BAO of 1.37 mEq per hour, and a mean BAO [illegible].14 mEq per hour, mor than one year after "parietal-cell" vagotomy without a drainage procedure This operation differs from HSV only in the respect that the antrum is accurately "mapped" at the time of operation. The mean reduction in 'free' BAO was 73 per cent. The reduction in 'total' BAO (to pH 7) could not be calculated because 'total' BAO had not been estimated pre-operatively.

In view of these large reductions in BAO after HSV, it would appear that gastrin release is probably not excessive in the fasting patient after HSV, and gastric stasis is unlikely to be present. The latter suggestion is supported by the studies of gastric emptying after HSV (vide infra), and also by the fact that food residues were not found in the resting juice after the patients had fasted overnight. Volumes of resting juice were small.

The possible reasons for the significant increase in BAO between 3 - 12 months and 12 - 24 months after HSV will be discussed in a later Chapter. Here, one would merely state that pentagastrin- and insulin-stimulated acid outputs also increased significantly, and that partial vagal re-innervation of the parietal cell mass seems to be the likeliest explanation.

(REFERENCES AT THE END OF PART II)

Table I

LONG-TERM EFFECT OF HIGHLY SELECTIVE VAGOTOMY ON SPONTANEOUS ACID OUTPUT (mEq per hour)

CASE NO.	AGE AND SEX	WEIGHT KG.	INSULIN TEST AT 1 WEEK	INSULIN TEST AT > 1 yr.	VISICK GRADE > 1yr.	BEFORE HSV (F)		ONE WEEK AFTER (F)	% ↓		% ↓	3 MONTHS	% ↓	6 - 12 MONTHS	% ↓	1 - 2 YEARS AFTER HSV (F)	% ↓		% ↓
1 R.R.	50 M	81	-ve	E +ve	I	7.14	8.46	0.00	100.00	0.28	96.69	0.27	96.81			1.08	84.87	1.36	83.92
2 R.P.	45 M	75	-ve	-ve	II	14.96	16.78	0.81	94.59	1.69	89.93	0.20	98.81			1.63	89.10	2.04	87.84
3 G.W.	33 M	74	-ve	E +ve	II	0.38	1.32	0.14	63.13	0.38	71.21	0.00	100.00	0.00	100.00	0.00	100.00	0.15	88.64[1]
4 G.M.	27 M	70	-ve	E +ve	II	6.98	8.24	0.00	100.00	0.00	100.00	0.00	100.00	2.46	70.15	0.00	100.00	1.04	87.38
5 F.D.	62 M	72	-ve	-ve	I	-	-	(0.79)	-	(1.05)	-	0.04	98.00*			0.00	100.00	0.00	100.00
6 A.W.	35 M	76	-ve	-ve	I	-	-	(0.00)	100.00	(0.17)	-	0.00	100.00			0.00	100.00	0.43	92.00*
7 D.A.	29 M	67	-ve	-ve	IV	-	-	(1.49)	-	(1.88)	-	1.68	75.00*	0.97	85.57*	0.52	-	1.43	-
8 F.A.	34 M	79	-ve		II	6.06	7.32	0.00	100.00	0.08	98.91	0.78	89.34			0.90	85.15	1.92	73.77
9 J.C.	22 M	52	-ve	E +ve	I	5.00	6.00	0.45	91.00	0.95	84.17					1.33	73.40	1.92	68.00
10 J.I.	47 M	62	-ve	-ve	I	6.68	7.10	0.00	100.00	0.00	100.00	1.12	84.23	0.12	98.31	0.10	98.50	0.56	92.11
11 E.L.	43 M	61	-ve	-ve	I	3.24	3.86	0.15	95.38	0.47	87.82	0.14	96.37			0.00	100.00	0.13	96.63
12 B.S.	33 M	56	-ve	-ve	IV	9.02	10.26	0.40	95.57	0.48	95.32			1.20	88.30	4.23	53.10	4.61	55.07
13 R.C.	40 M	80	-ve	L +ve	II	8.20	9.06	0.34	95.85	0.42	95.36					0.94	88.54	1.61	82.23
14 P.S.	34 M	66	-ve	-ve	II	1.62	2.80	0.00	100.00	0.54	80.71	1.57	43.93			2.21	(-36.42)	2.36	(-2.14)[1]
15 S.G.	28 M	75	-ve	L +ve	I	20.12	28.30	0.74	96.32	1.81	93.60					5.36	73.36	5.97	78.90
16 T.B.	54 M	77	-ve		II	7.02	8.68	0.00	100.00	0.00	100.00								
17 H.H.	40 F	48	-ve	L +ve	III	5.20	6.48	0.00	100.00	0.00	100.00	0.00	100.00			0.00	100.00	0.31	95.22
18 M.W.	34 F	57	-ve			2.49	3.00	0.00	100.00	0.00	100.00								
19 A.D.	40 F	50	-ve	E +ve	II	9.60	12.10	1.15	88.02	1.23	89.83					0.36	96.25	0.86	92.89
20 S.B.	34 F	74	-ve		I	5.97	6.20	0.68	88.61	0.10	98.39								
21 P.A.	21 F	59	-ve	-ve	III	4.04	4.70	1.01	75.00	1.26	73.20					1.01	75.00	1.27	72.98

TABLE
I

22 M.C.	48	F	63	-ve		I	3.36	4.04	0.04	98.81	0.38	90.60							
23 M.F.	48	F	41	-ve	E +ve	II	1.60	2.04	0.17	89.37	0.57	72.06					0.66	58.75	1.29	36.76[1]
24 F.W.	47	M	70	-ve	E +ve	I	5.40	6.58	0.13	97.59	0.52	92.10	0.19	97.11			1.55	71.30	2.11	67.93
25 A.T.	16	M	51	-ve	L +ve	I	10.64	11.28	0.46	95.68	0.93	91.76	1.98	82.45			2.88	72.93	3.47	69.24
26 H.N.	51	M	83	-ve	L +ve	II	2.96	5.00	1.07	63.85	1.26	74.80			0.84	83.20	0.20	93.24	1.23	75.40
27 C.C.	53	M	75	-ve	L +ve	I	4.08	4.86	0.00	100.00	0.00	100.00	0.00	100.00	1.09	77.57	0.44	89.22	1.15	76.34
28 F.C.	34	M	84	-ve	-ve	I	8.10	9.22	1.13	86.05	1.95	78.85					1.41	82.59	2.20	76.14
29 F.P.	45	M	59	-ve		II	14.50	16.02	0.00	100.00	0.00	100.00								
30 W.B.	49	M	58	-ve	L +ve	I	11.60	12.89	0.00	100.00	0.25	98.06					0.00	100.00	0.10	99.22
31 K.B.	37	M	67	-ve	-ve	II	4.55	5.32	0,00	100.00	0.14	97.37					0.00	100.00	0.00	100.00
32.W.M.	47	M	60	-ve	L +ve	I	2.42	3.08	0.00	100.00	0.24	92.21					1.55	35.95	2.53	17.86[1]
33 J.T.	58	M	82	-ve	-ve	I	4.92	5.82	0.27	94.51	1.37	76.46					0.00	100.00	0.00	100.00
34 E.S.	49	M	83	-ve	L +ve	III	(1.50)	(1.92)	-	-	-	-					0.86	42.67	1.46	23.96[1]
35 N.H.	66	M	54	-ve	E +ve	I	24.60	25.30	0.00	100.00	0.42	98.34					0.69	97.20	1.32	94.78
36 A.G.	65	M	57	-ve		II	9.06	10.80	0.00	100.00	0.05	99.54								
37 A.B.	27	M	59	-ve	L +ve	I	2.17	3.79	2.68	25.30	3.26	13.98					0.18	91.71	0.60	84.17
38 J.W.	49	M	72	-ve		I	17.46	18.60	0.00	100.00	0.36	98.06								
39 E.A.	44	M	94	-ve	L +ve	I	7.22	7.80	0.19	97.37	0.57	92.69					1.71	76.32	2.04	73.85
40 H.W.	46	M	57	-ve	L +ve	I	2.33	2.86	0.00	100.00	0.00	100.00					0.23	90.13	0.98	65.73[1]
41 J.P.	50	M	76	-ve		III	10.26	10.98	0.00	100.00	0.05	99.55								
42 H.W.	48	M	64	-ve		I	4.20	4.62	0.07	98.33	0.70	84.85								
43 M.B.	41	F	51	-ve	L +ve	II	5.54	7.16	0.00	100.00	0.45	93.72	0.00	100.00			0.00	100.00	1.00	86.03
44 E.H.	35	F	83	N.D.		I	(4.83)	(6.15)	-	-	-	-	0.00	100.00						
45 J.K.	20	F	44	-ve		II	4.20	5.52	0.95	77.38	1.22	77.90								
46 B.O.	28	F	53	-ve		I	0.00	0.36	0.00	100.00	0.13	63.89								
47 I.S.	51	F	65	N.D.		I	1.80	2.22	0.00	100.00	0.00	100.00								
48 J.B.	53	M	71	-ve		I	2.50	2.88	0.00	100.00	0.83	71.18								

TABLE I
Contd.

49 J.J.	39 M	74	-ve		I	10.81	11.60	0.00	100.00	0.79	93.19								
50 D.E.	55 F	53	-ve		I	8.08	8.89	0.00	100.00	0.18	97.98								
51 J.D.	51 M	66	-ve	L +ve	I	2.70	5.64	0.27	90.00	0.65	88.48			0.10	98.23	0.00	100.00	0.53	90.60
52 W.C.	42 M	67	-ve	E +ve	I	9.54	11.32	0.55	94.23	1.01	91.08					1.94	79.66	3.06	72.97
53 N.K.	49 M	63	-ve	-ve	I	20.46	24.40	1.37	93.30	2.29	90.61	2.76	88.69			2.26	88.95	3.26	86.74
54 S.C.	51 M	82	-ve	L +ve	III	-	-	(1.15)	-	(1.42)	-					2.02	-	2.64	-
55 H.K.	61 M	67	-ve		II	-	-	(0.00)	100.00	(0.87)	-			3.36	50.00*				
56 S.M.	59 F	66	-ve		I	7.56	9.54	0.26	96.56	0.48	94.97								
57 E.H.	56 F	52	-ve	E +ve	I	1.92	2.18	0.00	100.00	0.50	77.06					0.16	91.67	0.55	74.77[1]
MEAN	43.04	66.26	-ve	13 -ve		7.01	8.27	0.34	92.91%	0.63	88.93%	0.60	91.71%	1.13	83.48%	0.99	82.25%	1.54	76.16%
± 1SEM	1.54	1.55		15 L+ve		0.76	0.86	0.07	2.60	0.10	2.07	0.20	3.32	0.38	5.36	0.19	4.28	0.21	3.85
n =	(57)	(57)	(55)	10 E+ve (38)		(50)	(50)	(55)	(52)	(50)	(50)	(18)	(18)	(9)	(9)	(39)	(37)	(39)	(37)

Acid outputs refer to acid titrated to pH 7, except where 'F' indicates 'free' acid, to the pH 3.5 end-point. E +ve insulin test; positive in first hour after insulin; L +ve - positive in the second hour, by Hollander's (1948) criteria.

* estimated reduction. [1] signifies patients whose BAO before operation was less than 3.1 mEq per hour. Such patients with low BAOs tended to have relatively small reductions after HSV. If these 7 patients are excluded, the mean reduction in BAO more than 1 year after HSV was 83.75%.

The increase in BAO between 3 months and 1 to 2 years after HSV is statistically highly significant (17 pairs, mean difference = 0.738 mEq/hr ± 1SE 0.177; $t = 4.169$, $p < 0.001$).

TABLE I
Contd.

SPONTANEOUS ACID OUTPUT

PART II: A comparison of the effects of truncal, selective and highly selective vagotomy on BAO

To make a statistically-valid comparison between the effects of the three types of vagotomy on BAO is at present virtually impossible. The variables are too numerous. Thus, some authors collect BAO for 12 hours overnight, some for 2 hours, for one hour, or for half an hour. Acid is titrated variously to pH 3.5, to the "Töpfer" end-point, to pH 7, or to the rather shifty end-points provided by the indicators phenol red or phenolphthalein. The secretory tests may have been done weeks, months or years after operation, and precise details of the time-interval are often lacking. Again, results may be expressed as arithmetic means, plus or minus one standard error or deviation, without details of the results for individual patients being supplied. No doubt the patients differ from city to city and from one country to another, and assuredly the surgeons also differ in their degree of technical expertise. The results of insulin tests give some guide to the latter factor, but often insulin tests were not done.

Nonetheless, even although any conclusions reached must necessarily be tentative, the comparison of BAOs after the three types

of vagotomy is an interesting one to make. In the main, comparison of BAO after HSV is made with BAOs after TV or SV as reported by authors who gave results for individual patients. In addition, BAO more than one year after HSV has been compared with BAO more than one year after truncal or selective vagotomy with drainage, in patients at Leeds who were in good health.

METHOD

Review of the literature Most authors had collected BAO for a period of one hour. The varying titration end-points are shown in Table II. In many papers, details of age, sex and weight for individual patients were not given.

Patients in Leeds BAO was collected as described elsewhere (p 101) more than one year after HSV in 39 patients, more than one year after TV+P in 28 patients, and more than one year after SV+P in 15 patients. In addition, the BAOs of a further 18 patients who had undergone SV without drainage more than one year previously (see Chapter 6) were available for analysis. All patients tested more than one year after vagotomy were in good health (except for one HSV patient), and free from symptoms of gastric stasis.

RESULTS AND DISCUSSION

Effect of truncal vagotomy on BAO (review of the literature) The results are summarized in Table II, at the foot of which the results in HSV patients are given for comparison. The findings of Dragstedt, Woodward and their colleagues in 1949 - 50 [1,13], in studies of 12-hour overnight secretion in patients who had undergone TV without a drainage procedure, were little different from those of subsequent workers who measured BAO for one hour in patients who had undergone TV with a drainage procedure. Before TV, mean BAO ranged from about 4.4 to 6.4 mEq per hour. It should be noted, however, that in the mid-1960s, most authors began to quote results in terms of "total" BAO (to pH 7 - 8), instead of "free" BAO to pH 3.5, and hence the earlier data are "falsely" low. In the early weeks after TV, with or without drainage, most authors recorded a mean BAO in the range of 0.7 to 1.3 mEq per hour, and the (arithmetic) mean percentage reduction in BAO ranged from 54 to 83 per cent, with a median of about 77 per cent (Table II).

BAO one week after TV Comparing 'free' BAO soon after HSV (0.3 $\pm$ 0.1 mEq per hour) with 'free' BAO after TV+GJ [4,5] (0.8 $\pm$ 0.1 mEq per hour), the difference is statistically significant ($p < 0.01$, Table VI), if one makes the assumption that the two groups of patients

are comparable. However, when BAO soon after HSV was compared with BAO soon after TV+P / GJ [16-18] in 54 patients, 49 of whom had negative insulin tests, the difference was not statistically significant (Table VI). In another thorough study, Bank, Marks and Louw[6] found that TV+P / GJ reduced mean BAO from 4.7 ± S.D. 3.7 mEq per hour to 1.8 ± S.D. 1.9 mEq per hour, a mean reduction of only 62 per cent. However, insulin tests which were performed in 13 representative patients suggested that the incidence of incomplete vagotomy in this large series of truncal vagotomies may have been as high as 32 per cent. Since BAO for each individual patient was not given, statistical analysis of the difference between BAO after HSV and BAO after TV+P / GJ in the series of Bank et al. was not possible.

BAO 3 months after TV That the higher mean BAO after TV than after HSV may not be attributable entirely to incomplete TV is suggested by the findings of Bank et al. (1966)[19], Konturek et al.[20] and Dignan[7], who measured BAO about 3 months after operation, and also gave the results of the insulin tests. For example, mean BAO in 12 of Bank's patients who had proven complete vagotomy was 2.5 mEq per hour 3 months after TV+P / GJ, a mean reduction of only 60 per cent. Similar findings were recorded by Konturek et al. (mean BAO 3.0 ± 0.9 mEq

per hour 3 months after complete TV+P in 12 patients: mean reduction not quoted, but probably about 50 per cent since mean BAO before operation was 5.7 mEq per hour in 20 different patients), and by Dignan (mean BAO 1.3 mEq per hour in 16 patients with negative insulin tests more than 6 weeks after TV+P: mean reduction 66 per cent). A discordant finding was that Jordan and Condon[21], who found that mean BAO 6 months after TV+P was only 0.6 mEq per hour, compared with 4.6 mEq per hour before operation and this despite the fact that 50 per cent of the patients developed positive responses to insulin. However, these authors did not give the results for individual patients, the numbers of patients from which the mean data were derived were not given, and the unusually large mean reduction found in histalog-stimulated MAO (from 32 to 8 mEq per hour: contrast the 50 to 60 per cent reduction in MAO found in our own and other laboratories - Chapter 4) suggests that the large reduction in BAO may also be suspect. Thus, review of the literature suggests that the mean percentage reduction in BAO, three months after TV with drainage, is between 60 and 70 per cent in patients with negative insulin tests, and the actual mean BAO ranges from 1.3 to 3.0 mEq per hour.

In contrast, mean BAO 3 months after HSV was 0.6 mEq per hour, in 18 patients, and the mean reduction was 92 per cent.

Mean BAO after HSV was significantly lower ($p < 0.05$) than after TV+P and SV+P combined, in 30 patients from Dignan's series who had negative insulin tests (Table VI). Again, it must be pointed out that this comparison may not be a valid one: the series of patients may not be comparable (Dignan's patients were on average 6 years younger and 4 kg. heavier than ours): Dignan's use of phenol red as indicator may have produced a slightly higher reading for acid concentration than titration to pH 7 in our series, and finally, comparison of acid outputs 1 week to 3 months after HSV with acid outputs more than 6 weeks after TV+P in Dignan's series might be challenged. The comparison seems justifiable, however, because mean BAO after HSV did not change between 1 week and 3 months, whether one considers the mean data for 50 patients at 1 week and for 18 patients at 3 months (Table I), or the data for the latter 18 patients at both 1 week and 3 months (mean BAO 0.6 $\pm$ 0.2 mEq per hour at each time - interval after HSV).

BAO more than one year after TV Detailed results were given by Gillespie et al.[11], who compared BAO soon after TV+P / GJ with BAO 1 to 4 years later. To avoid bias against TV by the inclusion of excessive numbers of patients with positive insulin tests, we selected the data for 30 patients who had negative insulin tests soon after TV,

plus those of 4 representative patients with late-positive insulin tests soon after TV (nos. 2 and 3, their Table 3; and nos. 9 and 19, their Table 4) and of 1 patient with an early-positive insulin test soon after TV (no. 8, their Table 5). Mean BAO in these 35 patients was 1.65 ± 0.31 mEq per hour, 1 - 4 years after TV. This is little different from the mean BAO more than one year after HSV of 1.54 ± 0.21 mEq per hour.

A somewhat different picture was found in 28 patients in Leeds whose BAO was measured on average 25 months after TV+P (Table III). These patients were in good health. Their mean BAO was found to be 3.39 ± 1.07 mEq per hour. Two patients who were in perfect health had BAO of 27 and 16 mEq per hour respectively. If results for these two patients are excluded, mean BAO was 2.0 ± 0.4 mEqper hour, which is not significantly greater than the mean BAO of patients after HSV (Table VI).

Effect of bilateral selective vagotomy on BAO

1 - 3 months after SV: The most detailed papers on BAO in the early months after SV+P / GJ are those of Bank etal., and of Dignan[7] (Table IV). Bank et al., however, did not give results for individual patients, and performed insulin tests in only 17 of the 52 patients after SV (20 per cent of the insulin tests were Hollander-positive).

Mean BAO 4 - 8 weeks after SV+P / GJ was 1.9 mEq per hour, both in South African and in English patients, whereas after HSV in Leeds and Copenhagen, mean BAO was 0.6 to 0.8 mEq per hour. Mean reductions in BAO compared with pre-operative values were 62 - 66 per cent after SV, and 84 [illegible] 92 per cent after HSV respectively. Although 20 to 40 per cent of patients after SV had Hollander-positive insulin tests, the mean reduction in BAO in 14 patients with negative insulin tests[7] was only 66 per cent. At this relatively early period after operation, BAO seems to be significantly less after HSV than after SV. Such a conclusion can only be tentative, however, for the reasons already given.

In an extensive study of BAO three months after SV+P in patients in South India, Tovey et al.[22] found that mean BAO was reduced by 67 per cent compared with before operation. The washout technique which these authors used to collect BAO probably acted as a weak stimulus to gastric secretion, as they themselves point out.

More than one year after SV: 15 patients after SV+P in Leeds had a mean BAO of 2.6 mEq per hour, but one of them had a BAO of 15 mEq per hour, and if his BAO was "reduced" by an arbitrary 10 mEq per hour, the mean BAO of the group was 2.0 ± 0.6 mEq per hour (Table V). In 18 patients who had undergone SV without drainage

(mostly at the West London Hospital), mean BAO was 2.7 mEq per hour, and again the mean was greatly elevated by the results of a few patients who had very high BAO (Table V). Nonetheless, all these patients were in good health, and exclusion of their results does not seem justifiable. The subjects selected for testing were, so far as we could tell, a representative sample of the entire population of patients who had undergone SV with or without drainage. Indeed, exclusion of the clinical failures in Leeds (most of whom had high acid outputs and recurrent ulceration) rendered the group of patients tested somewhat better than the average, in terms of the clinical outcome. In Table V, it can be seen that the contrasted groups of patients after HSV or SV were well-matched for age and weight, but that HSV patients were tested on average 16 months after operation, compared with 23 months for the patients after SV. BAO after HSV (1.5 mEq per hour) was not significantly different from BAO after SV (2.7 mEq per hour). Comparison of BAO more than one year after HSV (1.5 mEq per hour), with BAO more than one year after TV and SV combined (3.0 mEq per hour) shows that the difference was not statistically significant (Table VI).

This comparison of BAO after HSV with BAO after TV or SV thus suggests (but does not prove) that BAO is lowered more effectively by HSV than by TV or SV. The difference is particularly

marked when one considers BAO measured either in the immediate post-operative period or two to three months after operation (Tables I, II and VI). More than one year after operation the difference is less marked, and is not statistically significant. Indeed, none of the differences in BAO which have been demonstrated can be claimed to be statistically significant, because of possible disparities between the groups of patients with respect to age, weight, sex and completeness of vagotomy. Differences in the end-points to which titration was taken also weaken the validity of the attempted comparison. Thus, we have produced some evidence that HSV lowers BAO to a greater extent than do TV or SV, but the evidence is inconclusive and further studies are needed in larger numbers of patients, and, ideally, in consecutive series of patients who have been allocated in a random manner to one or other of the three types of vagotomy.

If the difference is a real one, and not artefactual, what could it be due to? It could be due to greater stimulation of the parietal cell mass after TV/SV than after HSV; or weaker inhibition of the PCM, or both. A possible explanation is provided by the recent observation[23] that serum gastrin concentration increased from a mean of 16 $\pm$ 1.5 pg per ml before vagotomy, to 84 $\pm$ 7.9 pg per ml three months to seven years after TV with anterior pylorectomy. This increase

was greater than could be obtained by the removal (with bicarbonate) of acid-inhibition of gastrin release in patients with duodenal ulcer before operation. The authors attributed the increase to diminished inhibition of gastrin release by endogenous acid, to reflux of alkaline duodenal content onto the antrum and to the possible release of gastrin from an extragastric source. If BAO is indeed significantly less after HSV than after TV or SV, the reason might be that serum gastrin levels are lower in the fasting patient after HSV than after TV or SV. This, in turn, could be due merely to the occurrence of less reflux of alkaline duodenal content after the pylorus-preserving operation than after vagotomy with drainage. In addition, however, inhibition of gastrin release by endogenous acid might be livelier in the innervated antrum[24-26] after HSV than in the denervated antrum after TV or SV.

Preliminary data on plasma gastrin concentrations after either HSV or SV with gastrojejunostomy in man[27] indicate that plasma gastrin levels are twice as high after SV+GJ as after HSV. These results provide support for our suggestion that BAO is lower after HSV than after TV or SV. Thus, our findings could be of considerable clinical significance, because the level of spontaneous acid output determines the nature of the pH environment of the mucosa of the duodenal bulb for a large proportion of the twenty-four hours.

Table II

EFFECT OF TRUNCAL VAGOTOMY

(REVIEW OF

figures are arith-

REFERENCE	DRAINAGE PROCEDURE	TITRATION END-POINT: INDICATOR	NO. OF PATIENTS	BEFORE OP. mEq/hr MEAN ± 1 S.E.
Titration to pH 3.5				
Woodward[1] et al. 1949*	NONE	pH 3.5 " Topfer	70	4.6
Dragstedt[13] et al. 1950*	NONE	pH 3.5 " Topfer	19	5.2 ± 0.6
McArthur et al.[5] 1960	gastro-jejunostomy	pH 3.5 " Topfer	20	5.7
I.E. Gillespie et al.[4] 1960 (C)	gastro-jejunostomy	pH 3.5 " Topfer	23	5.4 ± 0.7
I.E. Gillespie and Bowen[14] 1962 (C)	gastro-jejunostomy	?pH 3.5 " Topfer	20	4.4 ± 0.6
Titration to pH 7 - 8				
Adams et al.[15] 1967	7 pyloro-plasty 8 gastro-jejunostomy	pH 6.8 - 8.4 phenol red	15	5.7 ± 1.0
Bank et al.[6] 1967	half pyloroplasty half gastro-jejunostomy	pH 8 phenolphthalein	84	4.7 (±SD 3.7)
Jepson and Johnston[16] 1968	pyloroplasty	pH 8 phenolphthalein	9	6.4

ON SPONTANEOUS ACID OUTPUT

LITERATURE)

metic means ± 1 SEM

1 - 6 WEEKS AFTER TV mEq/hr MEAN ± 1 S.E.	% REDUCTION MEAN ± 1SE.	2-6 MONTHS AFTER TV mEq/hr MEAN ± 1SE.	% REDUCTION MEAN ± 1SE.	> 1 YEAR AFTER TV mEq/hr MEAN ± 1SE.	% REDUCTION MEAN ± 1SE.
0.9	76.0				
1.3 ± 0.4	76.1 ± 5.6			1.0 ± 0.2	83.0 ± 4.1
0.8	83.1				
0.7 ± 0.2	78.9 ± 5.9				
2.0 ± 0.4	34.3 ± 18.6 54.3 ± 9.2				
1.1 ± 0.4	not given				
1.8 (±SD 1.9)	62.0				
0.8	76.3 ± 9.0				

REFERENCE	DRAINAGE PROCEDURE	END-POINT INDICATOR	PATIENTS	MEAN + 1 S.E.
G. Gillespie et al.[17] 1970 a (C)	half pyloroplasty half gastro-jejunostomy	pH 6.8 - 8.4 phenol red	30 (IT -ve)	-
G. Gillespie et al.[18] 1970 b	8 pyloro-plasty 10 gastro-jejunostomy	pH 6.8 - 8.4 phenol red	17	5.5 - (23 different patients)
Bank et al.[19] 1966 (C)	"drainage procedure"	pH 8 phenolphthalein	12	-
Konturek et al.[20] 1968	pyloroplasty	pH 6.8 - 8.4 phenol red	12	5.7 ± 0.3 (20 different patients)
Dignan[7] 1970	pyloroplasty	pH 6.8 - 8.4 phenol red	22 16	5.1 4.4
Jordan and Condon[21] 1970	pyloroplasty	pH 7.3 autotitrator	not clear, ?about 50 - 90	4.6 ± 3.8 SD
G. Gillespie[1] et al. 1970 a (C)	half pyl-oroplasty half gastro-jejunostomy	pH 6.8 - 8.4 phenol red	35	-
Johnston 1972 (Leeds patients)	pyloroplasty	pH 7 autotitrator	26	-
HSV FOR COMPARISON	NONE	pH 7.0 autotitrator		8.3 ± 0.9 (n = 50)

AFTER IV mEq/hr MEAN ± 1S.E.	REDUCTION MEAN ± 1S.E.	AFTER IV mEq/hr MEAN ± 1SE.	REDUCTION MEAN ± 1S.E.	AFTER IV mEq/hr MEAN ± 1S.E.	REDUCTION MEAN ± 1S.E
1.1 ± 0.4 **	- -			1.6 ± 0.3	- -
0.8 xx -	- -				
		2.5	60.2 (complete vagotomies)		
		3.0 ± 0.9	(all had complete vagotomy)		
		1.7 — 65.7 (all cases) 1.3 — 66.2 (vagotomy complete)			
		0.6 ± 1.2 SD	(50% of vagotomies incomplete)		
1.2 ± 0.3 **				1.7 ± 0.3	-
-		-		2.0 ± 0.4	-
0.6 ± 0.1 (n = 50)	88.9 ± 2.1	0.6 ± 0.2 (n = 18)	91.7 ± 3.3	1.5 ± 0.2 (n 39)	76.2 ± 3.9

LEGEND TO TABLE II

* Converted from 12-hour overnight BAO, in patients with TV without drainage.

(C) Calculated from authors' data.

• Counting an increase in BAO as 0 per cent decrease.

** omitting results of 2 patients with BAO $>$ 16 mEq per hour soon after operation.

IT -ve : patients with negative insulin tests in the early post-operative period.

xx : omitting BAO of 11 mEq per hour in 1 patient.

SD : Standard deviation.

$\frac{1}{2}$: Mostly patients with -ve insulin tests (see text).

Table III

SPONTANEOUS ACID OUTPUT MORE THAN ONE YEAR AFTER TRUNCAL VAGOTOMY AND PYLOROPLASTY

(Leeds patients, in good health. Titre. to pH 7)

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS POST-OP.	INSULIN RESPONSE > 1 yr.	VISICK GRADE	BAO mEq/hr.
1	A.P.	72	M	67	21	E+	II	2.23
2	W.B.	57	M	56	31	L+	II	0.80
3	J.G.	37	M	64	(7yrs)	-ve	I	1.34
4	C.R.	48	M	63	42	L+	II	5.01
5	J.D.	58	M	63	24	E+	I	2.03
6	G.B.	30	M	74	35	-ve	I	0.10
7	J.W.	48	M	83	36	E+	I	3.12
8	S.R.	47	M	74	16	-ve	II	1.14
9	F.H.	56	M	66	17	-ve	II	1.70
10	T.R.	63	M	67	12	L+	I	0.20
11	T.Y.	51	M	69	17	-ve	II	1.50
12	B.M.	46	M	80	24	E+	I	(27.36)
13	K.T.	35	M	74	12	-ve	II	3.06
14	B.W.	24	M	64	12	E+	II	2.95
15	P.D.	57	M	85	16	L+	II	0.36
16	F.B.	46	M	78	29	-ve	I	2.90
17	E.R.	75	M	57	14	L+	III	0.71
18	W.J.	35	M	62	16	-ve	I	2.35
19	H.T.	73	M	73	19	-ve	II	3.58
20	J.G.	55	M	85	35	-ve	II	0.00
21	J.L.	37	M	70	22	L+	I	1.84
22	T.M.	52	M	59	30	L+	I	9.14
23	G.T.	43	M	63	50	L+	II	1.90
24	S.W.	58	M	83	30	L+	II	2.32
25	G.R.	62	M	60	(6yrs)	-ve	III	1.18
26	J.G.	45	M	68	36	ND	I	(15.61)
27	R.H.	41	M	59	24	E+	III	0.48
28	R.K.	55	F	48	(7yrs)	-ve	III	0.00
MEAN		50.21		68.36	24.80[1]	12 -ve		3.39
± 1 SEM		2.39		1.80	2.05	9 L+ 6 E+		1.07 (28)
								2.00* ± 0.38 (26)

* excluding patients 12 and 26

[1] excluding nos. 3, 25 and 28.

Table IV

COMPARISON OF THE EFFECTS OF HSV AND OF SELECTIVE VAGOTOMY (SV) WITH DRAINAGE ON SPONTANEOUS ACID OUTPUT WITHIN 3 MONTHS OF OPERATION

OPERATION	AUTHORS	NO. OF WEEKS AFTER OPERATION	NO. OF PATIENTS	BAO BEFORE OP. mEq/hr. MEAN ± 1 SE	BAO AFTER OP. mEq/hr. MEAN ± 1 SE	REDUCTION PER CENT MEAN ± 1 SE
	DJ	1	50	8.27 ± 0.86	0.63 ± 0.10	88.9 ± 2.1
HSV	DJ	12	18	8.19 ± 1.49	0.60 ± 0.20	91.7 ± 3.3
(PCV)	Amdrup*	8 - 12	30	5.10 ± 0.78	0.75 ± 0.32	83.6 ± 7.2
SV+P / GJ	Bank et al. 1967	<8	52	5.60 ± 5.4 (SD)	1.90 ± 2.1 (SD)	66.0 -
SV+P	Dignan 1970	>6	24	5.30 ± 1.15	1.93‡ ± 0.75	62.0 ± 7.5

* "free" acid output. Titration was to pH 7 - 8 in the other series.

‡ one patient had a BAO of 17.7 mEq per hour. If, instead, a figure of 4.1 mEq per hour is substituted, mean BAO in Dignan's series becomes 1.37 ± 0.33 mEq per hour.

Note that 20% of the patients in Bank et al's series, and 39 per cent of Dignan's patients, had positive responses to insulin by Hollander's criteria.

Comparing BAO in 55 patients 1 week after HSV (0.66 ± 0.09), with BAO in Dignan's 24 patients more than 6 weeks after SV+P, degrees of freedom = 77, $t = 2.470$, $p < 0.02$ (BAO one week after HSV = BAO three months after HSV).

Table V

SPONTANEOUS ACID OUTPUT MORE THAN ONE YEAR AFTER HSV AND SELECTIVE VAGOTOMY WITH, AND WITHOUT, A DRAINAGE PROCEDURE

PATIENTS AFTER HSV										PATIENTS AFTER SV							
NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS POST-OP.	INSULIN RESPONSE 1 YR.	VISICK GRADE	HSV: BAO	SV BAO	VISICK GRADE	INSULIN RESPONSE 1 YR.	MONTHS POST-OP.	WEIGHT KG.	SEX	AGE YR.	NAME	NO.
1	R.R.	50	M	81	20	E+	I	1.36	0.81	II	L+	48	67	M	47	M.S.	1
2	R.P.	45	M	75	12	-ve	II	2.04	0.52	I	-ve	14	60	M	69	A.G.	2
3	G.W.	33	M	74	21	-ve	II	0.15	0.59	II	E+	14	70	M	61	J.H.	3
4	G.M.	27	M	70	15	E+	II	1.04	0.93	II	E+	15	64	M	45	D.M.	4
5	F.D.	62	M	72	24	-ve	I	0.00	0.15	III	-ve	8	73	M	44	I.M.	5
6	A.W.	35	M	76	21	-ve	I	0.43	0.00	III	-ve	21	61	M	40	G.M.	6
7	D.A.	29	M	67	15	-ve	IV	1.43	*14.58	III	-ve	36	69	M	43	J.B.	7
8	F.A.	34	M	79	12	ND	II	1.92	4.64	III	L+	24	74	M	31	T.M.	8
9	J.C.	22	M	52	24	E+	I	1.92	0.00	II	-ve	48	70	M	46	C.H.	9
10	J.I.	47	M	62	18	-ve	I	0.56	8.60	II	E+	44	64	M	16	A.S.	10
11	E.L.	43	M	61	18	-ve	I	0.13	0.18	I	E+	27	69	M	44	K.C.	11
12	B.S.	33	M	56	13	-ve	IV	4.61	3.09	II	ND	18	68	M	24	F.S.	12
13	R.C.	40	M	80	16	L+	II	1.61	2.98	I	ND	26	60	M	56	A.W.	13
14	P.S.	34	M	66	14	-ve	II	2.86	2.38	II	ND	22	65	F	34	S.C.	14
15	S.G.	28	M	75	12	L+	I	5.97	0.00	II	ND	18	70	F	47	M.W.	15
16	M.H.	40	F	48	22	L+	III	0.31	*2.63			25.53	66.93	43.13		Mean	
17	A.D.	40	F	50	18	E+	I	0.86	±1.05			3.31	1.15	3.48		± 1 SEM (15)	

18	P.A.	21	F	59	18	-ve	III	1.27	6.29	I	L+	21	85	M	34	J.B.	16
19	M.F.	48	F	41	14	E+	II	1.29	2.38	I	E+	20	80	M	46	R.D.	17
20	F.W.	47	M	70	15	E+	I	2.11	0.76	I	L+	18	80	M	68	A.H.	18
21	A.T.	16	M	51	15	L+	I	3.47	5.03	I	L+	21	55	M	67	F.L.	19
22	H.N.	51	M	83	14	L+	II	1.23	1.11	I	E+	42	51	F	41	D.C.	20
23	C.C.	53	M	75	15	L+	I	1.15	0.94	II	E+	14	77	M	54	J.S.	21
24	F.C.	34	M	84	14	-ve	I	2.20	2.37	II	L+	12	60	M	49	N.B.	22
25	W.B.	49	M	58	15	L+	I	0.10	0.69	III	E+	20	54	F	39	A.C.	23
26	K.B.	37	M	67	15	-ve	II	0.00	3.59	I	E+	16	60	M	17	G.G.	24
27	W.M.	47	M	60	15	L+	I	2.53	1.79	II	E+	17	76	M	39	F.H.	25
28	J.T.	58	M	82	15	-ve	I	0.00	3.12	III	L+	16	70	M	39	D.F.	26
29	E.S.	49	M	83	13	L+	III	1.46	6.81	I	L+	16	67	M	29	D.M.	27
30	N.H.	66	M	54	12	E+	I	1.32	9.56	II	ND	40	71	M	59	F.T.	28
31	A.B.	27	M	59	14	L+	I	0.60	1.87	I	ND	21	72	M	33	R.B.	29
32	E.A.	44	M	94	15	L+	I	2.04	0.26	I	ND	17	61	M	62	E.H.	30
33	H.W.	46	M	57	13	L+	I	0.98	0.13	I	ND	21	76	M	27	J.M.	31
34	M.B.	41	F	51	14	L+	II	1.00	1.87	II	ND	24	50	F	53	K.F.	32
35	J.D.	51	M	66	14	L+	I	0.53	0.00	I	ND	21	51	F	54	S.H.	33
36	W.C.	42	M	67	16	E+	I	3.06	2.70			20.94	66.44	45.00		Mean (16 - 33	
37	N.K.	49	M	63	18	-ve	I	3.26	±								
38	S.C.	51	M	82	12	L+	III	2.64	0.62			1.89	2.69	3.38 ± 1		SEM	
39	E.H.	56	F	52	16	E+	I	0.55									

CONTINUED OVERLEAF

Mean ± 1 SEM	41.67	66.72	15.82	13 -ve 15 L+ 10 E+ 1 NOT DONE	1.54 0.21 (39)	2.67 0.58 (33)	5 -ve 8 L+ 10 E+ 10 NOT DONE	23.03	66.67	44.15	Mean ± 1 SEM
	1.82	1.99	0.52					1.83	1.54	2.40	

The insulin test was negative in each HSV patient one week after operation.

SV patients 1 - 15 had SV+P performed in Leeds.

SV patients 16 - 33 underwent SV without a drainage procedure, most of them at the West London Hospital (Mr. H. Burge)

* If BAO in SV patient No. 7 (14.58 mEq per hour) were reduced to 4.58 mEq per hour), mean BAO in 15 Leeds patients after SV+P = 1.97 ± 0.64 mEq per hour.

Comparing BAO after HSV with BAO after SV

degrees of freedom = 70, t = 1.83, $0.1 > p > 0.05$.

TABLE V CONTINUED

Table VI

STATISTICAL ANALYSIS OF DIFFERENCES BETWEEN BAO AFTER HSV
AND BAO AFTER TRUNCAL OR SELECTIVE VAGOTOMY WITH A DRAINAGE PROCEDURE

TIME AFTER OPERATION	REFERENCE	VAGOTOMY WITH DRAINAGE			HSV		DEGREES OF FREEDOM	t	p
		TYPE OF OPERATION	n	MEAN ± 1 SEM	n	MEAN ± 1SEM			
1 week	McArthur et al., 1960 Gillespie et al., 1960	Truncal V. + gastro-jejunostomy	43	0.78• ± 0.13	55	0.34• ± 0.07	96	3.000	< 0.01
1 week	Gillespie et al., 1970a* Gillespie et al., 1970b‡ Jepson and Johnston, 1968	Truncal V. + ½ pyloroplasty ½ gastro-jejunostomy	54	0.95 ± 0.22	55	0.67 ± 0.09	107	1.190	$0.3 > p > 0.2$
1 week to 3 months	Dignan, 1970x	16 truncal 14 selective + pyloroplasty	30	1.30 ± 0.29	73	0.65 ± 0.08	101	2.286	< 0.05
more than 1 year	Leeds data, 1972 see tables III and V	28 truncal 33 selective + pyloroplasty	61	3.00 ± 0.58	39	1.54 ± 0.21	98	1.965	$0.1 > p > 0.05$

• 'free' acid, (titre. to pH 3.5) * All patients with negative insulin tests, omitting 2 with BAO > 16 mEq per hour. ‡ omitting JS with BAO of 11 mEq per hour. x patients with negative insulin tests.

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CHAPTER 4

MAXIMAL ACID OUTPUT

PART I: Determination of the dose of pentagastrin which elicits maximal acid output.

PART II: The effect of highly selective vagotomy on maximal acid output in response to pentagastrin.

PART III: A comparison of the effects of truncal, selective and highly selective vagotomy on maximal acid output.

CHAPTER 4

THE EFFECT OF HIGHLY SELECTIVE VAGOTOMY WITHOUT DRAINAGE ON PENTAGASTRIN-STIMULATED MAXIMAL ACID OUTPUT

PART I Determination of the dose of pentagastrin which elicits maximal acid output

Jepson and I [1] had shown previously that a dose of 6 ug per kg of intramuscular pentagastrin was sufficient to elicit maximal acid output (MAO) in subjects with intact vagi. After truncal vagotomy with a drainage procedure, however, we subsequently found that 10 ug per kg was needed[2]. Similarly, in the Multi-Centre Study published in 1967[3], it was found that 6 ug per kg per hour of intravenous pentagastrin elicited MAO in patients with intact vagi, whereas after truncal vagotomy with drainage, 12 ug per kg per hour were required on average to elicit MAO. The work of Konturek, Wysocki and Oleksy[4] and of Aubrey and Forrest[5] confirmed that significantly higher doses of histamine and pentagastrin were required to elicit MAO after truncal vagotomy than were needed before operation.

In order to define the dose of pentagastrin which is

required to elicit MAO after HSV, we carried out a combined study in collaboration with Professor Amdrup and Dr. Kragelund of Copenhagen. In Leeds, we performed dose-response studies in patients one week after HSV, while the Danes carried out similar studies in patients 8 to 20 (mean 12) months after HSV.

METHOD

Dose-response to pentagastrin one week after HSV

We described the details of the intramuscular pentagastrin test in 1967[1]. The tests were performed in 10 patients in Leeds who had undergone HSV 5 to 10 days previously. In patients 1 - 7, the operation was done for duodenal ulcer and in patients 8, 9 and 10 for pyloric or pre-pyloric ulcer (Table). Completeness of the parietal-cell vagotomy, by Hollander's criteria[6], was demonstrated in each case by the finding of a negative response to insulin hypoglycaemia. The dose of insulin used was 0.2 units per kg. Blood glucose concentration decreased to less than 35 mg per 100 ml in each patient. A 14F polyethylene gastrostomy tube whose tip was placed in the body of the stomach at operation was used to collect gastric secretion. Each patient underwent two pentagastrin tests on separate days, a dose of

6 ug per kg body weight being given intramuscularly in one test, and 10 ug per kg in the other. The tests were done in random order. All the usual measures were taken to secure maximal recovery of gastric secretion (see Part II). The collecting flask was changed at 5-minute intervals. Each test lasted for 40 minutes after the injection of pentagastrin. Titration was to pH 7.0 with 0.1N NaOH, on a 'Radiometer' autotitrator. Acid output was expressed as peak acid output (PAO = acid output in the 4 consecutive 5 minute periods which gave the highest reading, x 3, in mEq per hour) and as the total amount of acid secreted in the 40 minutes of the test.

RESULTS

There was no significant difference between the acid outputs in response to 6 and 10 ug per kg of pentagastrin (Table).

TABLE

Acid outputs in response to 6 and 10 ug per kg doses of intramuscular pentagastrin in patients 5 to 10 days after highly selective vagotomy

Patient No.	Insulin Test	Peak acid output*		Total output in 40 mins.	
		6 ug/kg	10ug/kg	6 ug/kg	10ug/kg
		mEq per hour		mEq	mEq
1	-ve	19.9	23.0	9.9	10.9
2	-ve	34.7	31.2	17.1	17.1
3	-ve	30.6	24.0	16.0	13.3
4	-ve	9.0	8.4	4.3	4.7
5	-ve	20.4	20.5	10.6	9.5
6	-ve	14.8	15.4	9.8	7.8
7	-ve	28.2	23.2	14.8	11.3
8	-ve	9.1	5.1	4.0	2.1
9	-ve	8.3	13.6	3.7	6.5
10	-ve	18.2	13.4	9.2	7.0
Mean		19.33	17.77	9.94	9.04
± 1 SE.		± 2.98	± 2.52	± 1.56	± 1.38

* Acid output in peak 20-minute period, x 3.

DISCUSSION

It is important when "maximal" gastric acid output is being measured after vagotomy operations that the dose of stimulant used should be capable of eliciting a maximal secretory response in the vagotomized patient. After truncal vagotomy, for example, it is now known that a significantly larger dose of histamine or pentagastrin is needed to elicit MAO than is needed before operation[2-5]. In contrast, this study has shown that the dose of pentagastrin (6 ug per kg) which elicits MAO before highly selective vagotomy is also adequate to elicit MAO after operation.

The results obtained by Amdrup and Kragelund in Copenhagen were similar to our own (Kragelund, Amdrup, Johnston et al., in press). One year after HSV, no significant difference was found between the acid outputs in response to 6, 10 and 15 ug per kg of subcutaneous pentagastrin. In 17 patients, the dose of 6 ug per kg elicited 20.18 $\pm$ 1 SE 2.00 mEq per hour, while 10 ug per kg elicited 21.51 $\pm$ 2.22 mEq per hour. In 11 patients, each of whom underwent 3 tests on separate days, 6 ug per kg elicited 22.56 $\pm$ 2.26 mEq per hour, 10 ug per kg elicited 23.64 $\pm$ 2.36 mEq per hour and 15 ug per kg elicited 22.87 $\pm$ 2.36 mEq

per hour. Figures quoted are peak-30-minute outputs multiplied by 2. In these patients, 8 to 20 months after HSV ("parietal cell vagotomy") the insulin test was negative, by Hollander's criteria, in 9, early-positive[7] in the first hour in 2 and late-positive in 5.

The reason for the differing dose requirements for pentagastrin after truncal and highly selective vagotomy is not clear. It may be that parietal cell sensitivity to pentagastrin is diminished after truncal vagotomy, but not after HSV. Alternatively, a smaller proportion of the injected dose of pentagastrin may reach the parietal cells after truncal vagotomy than after HSV, reflecting, perhaps, diminished mucosal blood flow[8] after truncal but not after highly selective vagotomy. A third possibility is that release of endogenous gastrin might be less from the vagally-denervated antrum of a patient after truncal vagotomy than from the normally-innervated antrum of a patient who had undergone HSV. Whatever the explanation, it seems possible that the gastric acid response to any particular submaximal blood level of endogenous gastrin may be greater in patients who have undergone HSV than in patients who have undergone truncal vagotomy.

By the time that these dose-response studies had been completed, a large number of intramuscular pentagastrin tests had already been performed in patients who had undergone truncal, selective and highly selective vagotomy. The dose of 10 ug per kg had been used in all these tests, because of our previous demonstration[2] that this was the correct dose for eliciting MAO in patients after truncal vagotomy. Although the results of the dose-response study showed that a dose of 6 ug per kg was sufficient to elicit MAO in patients after HSV, there seemed no reason to stop using the dose of 10 ug per kg in all vagotomized patients, because the acid outputs elicited by that dose were maximal, and side-effects were negligible. Accordingly, in all subsequent tests of MAO after vagotomy, a standard dose of 10 ug per kg of intramuscular pentagastrin was used.

SUMMARY

Comparison of gastric acid outputs in response to 6 and 10 ug per kg doses of intramuscular pentagastrin one week after highly selective vagotomy showed that a dose of 6 ug per kg is sufficient to elicit maximal acid output after HSV. Our co-workers in Copenhagen showed that this dose also elicited MAO one year after "parietal cell" vagotomy. Whereas a higher dose of histamine or pentagastrin has been shown to be necessary to elicit MAO after truncal vagotomy than before operation, the dose required after HSV is the same as that required before operation.

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THE EFFECT OF HIGHLY SELECTIVE VAGOTOMY ON MAXIMAL ACID OUTPUT IN RESPONSE TO PENTAGASTRIN

PART II

In the first paper[1], mean reductions in MAO after HSV of 50% at 1 week and 69% at 3 months were described. This suggested that HSV reduced MAO as effectively as do TV or SV. The next step was to find out whether the 70% reduction in MAO found 3 months after HSV was maintained on longer follow-up. Accordingly, serial tests of MAO were carried out for up to 20 months after HSV.

METHOD

Patients 27 patients participated in the serial testing. About 80% of the patients who were asked to help agreed to undergo repeated testing. These volunteers were representative of the entire group of patients treated by HSV, with respect to age, weight, sex, pre- and early-post-operative acid output and clinical (Visick) status.

Measurement of maximal acid output (MAO) The tip of a 14 or 16F polyethylene naso-gastric tube was placed in the body of

the stomach in the morning, after the patient had fasted overnight. Tests in the early post-operative period, however, were performed via a gastrostomy tube. Continuous suction was exerted on the tube throughout the test, except when air was injected at 60 second intervals to ensure that the lumen remained patent. The patient lay supine or on his left side, and expectorated saliva. He was encouraged to take deep breaths after clearing of the tube with air, to help "pump" out any unaspirated secretion. If flow diminished unaccountably, the position of the tube, or of the patient, or of both, was altered. Each test was supervised closely by an experienced, medically-qualified, gastric tester.

The first 15 minutes were spent in aspirating "resting juice". Spontaneous secretion was then collected into 4 x 15-minute or 6 x 10-minute samples for 1 hour. Pentagastrin (PG, Peptavlon, ICI) was then given by intramuscular injection[2] to stimulate MAO. Before operation, a dose of 6 ug per kg was used[2]. After HSV, a dose of 10 ug per kg was used because of previous evidence[3,4,5] that after truncal vagotomy in man larger doses of PG are required to elicit MAO than are needed before operation. In fact, as we have now shown, either of these doses of PG suffices to elicit MAO after HSV. Gastric acid output in response to PG was collected

into 12 x 5-minute batches. The samples of gastric juice were filtered through gauze and 1 ml. aliquots titrated electrometrically to pH 7 on a 'Radiometer' TTTI Autotitrator, using 0.1N NaOH. MAO in mEq per hour is expressed both as peak acid output[6] (PAO), which is peak-20-minute acid output[2] multiplied by 3, and as the total acid output in the hour after the PG injection (T.H. AO). Figures quoted are arithmetic means plus or minus one standard error of the mean.

Timing of tests These were carried out (1) before operation in 100 patients (2) one week after HSV, in 100 patients (3) 3 months after HSV, in 19 patients (4) 6 to 12 (mean 10.3) months after HSV, in 15 patients (5) 12 to 24 (mean 15.0) months after HSV in 20 patients.

The results of serial insulin tests on the same patients are given in a later section.

Efficiency of aspiration system In 86 tests, 10ml. of an 0.1 per cent solution of polyethylene glycol (PEG) were imbibed by the patient each 5 minutes throughout the pentagastrin test. The PEG content of the gastric aspirate was measured[7], and hence the degree of recovery of PEG calculated.

Statistical analysis The significance of differences between acid outputs in paired tests on the same patients was calculated using

Student's 't' test for paired data[8].

RESULTS

Taking pre-operative PAO as 100 per cent, PAO was reduced by a mean of 48 per cent, one week after HSV, and by 69 per cent, 3 months after HSV (Table I, Fig. 1). In 100 patients, mean PAO was 44.6 $\pm$ 1.30 mEq per hour before HSV, and 22.6 $\pm$ 1.0 mEq per hour one week after HSV. The mean reduction in PAO was 47.9 $\pm$ 1.9 per cent. Corresponding figures for 'total-hour' acid output were 35.0 $\pm$ 1.1 mEq per hour before HSV and 15.6 $\pm$ 0.7 mEq after HSV, a mean reduction of 54.8 $\pm$ 1.7 per cent. The decrease in PAO between 1 week and 3 months was statistically highly significant ($p < 0.001$, $n = 19$). PAO then increased, and the mean reduction in PAO 6 to 12 months post-operatively was only 54 per cent. The increase in PAO between 3 and 6-to-12 months was statistically significant ($p < 0.02$, $n = 13$). Thereafter, no significant change in PAO took place (Table I, subjects 1 - 7, and No. 20). Mean PAOs in mEq per hour were 40.3 before HSV, 20.2 at one week, 13.4 at three months, 18.6 at nine months and 19.3 at one to two years.

Mean reductions in 'total-hour' MAO were 56 per cent at one week, 70 per cent at 2 to 3 months, 54 per cent at 6 to 12 months and

56 per cent at 12 to 24 months after HSV (Table II). Again, the decrease in MAO between one week and three months, and the increase between three and nine months after HSV, were both statistically significant ($p < 0.01$).

Recovery of Gastric Content Mean recovery of PEG was 94.0 ± 2.5 per cent in 24 tests before operation; 86.4 ± 2.9 per cent one week after HSV (18 tests); 83.9 ± 3.1 per cent at 3 months (11 tests); 84.5 ± 2.6 per cent at 6 to 12 months (15 tests) and 89.4 ± 2.1 per cent in 18 tests more than one year after HSV.

DISCUSSION

Mean recovery of 84 to 94 per cent of the marker substance is similar to what has been reported previously[9-11], suggesting that recovery of gastric secretion was satisfactory. Variation in the degree of recovery of gastric content at the different time intervals after HSV was too small to detract from the significance of differences between acid outputs at these times.

The 52 per cent mean reduction in pentagastrin-stimulated MAO more than one year after HSV seems likely to be permanent, since mean MAO remained unchanged between 10 and 15 months after HSV (in unpaired tests), and was still unchanged at 18 to 22 months in 7

SERIAL TESTS OF MAXIMAL ACID OUTPUT AFTER HIGHLY SELECTIVE VAGOTOMY.

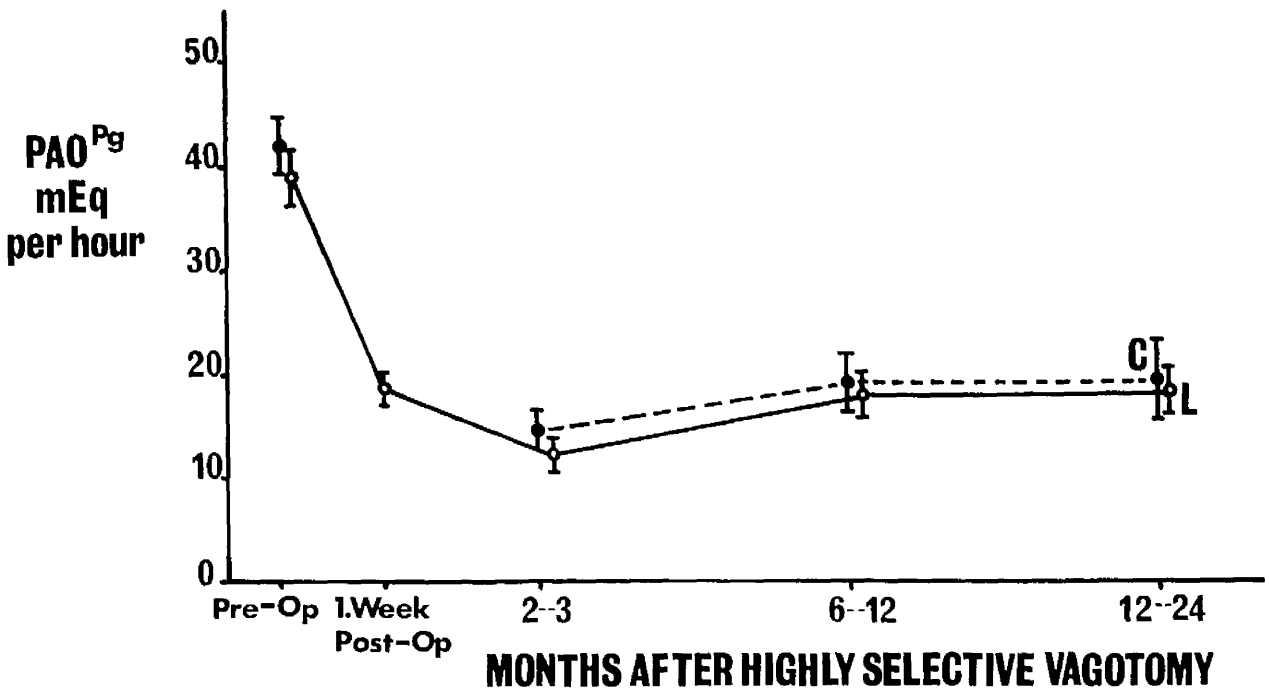

Fig. 1 This shows the mean changes (± 1 SE) in peak acid output in response to pentagastrin (PAO^{PG}) in patients in Leeds (L) and Copenhagen (C) after HSV. Data on Copenhagen patients are included by kind permission of Professor E. Amdrup. PAO here represents peak-30-minute acid output x 2 (unlike in the text) to permit comparison between the results in the two centres. Note that routine antral "mapping" at operation in Copenhagen does not produce different acid outputs from those obtained in Leeds. PAO increased significantly between 3 and 10 months after HSV, but thereafter does not seem to increase. Numbers of patients are given in the text.

subjects who were tested both at 6 to 12 months and at 18 to 22 months (Tables I and II, patients 1 - 7). Whether this reduction in MAO is as great as that produced by truncal or bilateral selective vagotomy with drainage (TV, SV) is not entirely clear. Until recently, it was accepted that TV reduced MAO by about 70 per cent[12,13] but the true figure may be less than 60 per cent[3-5,10,14-18], if the 20 - 50 per cent of patients who are insulin-positive after TV[19-22] are included, if acid output is expressed in the form of peak-30-minute output as suggested by Baron[6] and if the dose of histamine or pentagastrin used to elicit MAO is doubled compared with that used in pre-operative tests[3-5,16]. In our own laboratory (see below) HSV, SV and TV are each found to have reduced MAO by 45 to 55 per cent both in the early post-operative period and more than one year after operation. After TV, histamine-stimulated MAO has been shown not to change significantly in the course of the first three post-operative years[23], despite the fact that the incidence of positive responses to insulin increases from 20[19] to 50 per cent[20-22] in the same period. This suggests that the final mean reduction in MAO after TV may be no more than 50 to 60 per cent. After SV, the final reduction in MAO is unlikely to be greater than that found after TV, because the acid responses to insulin were found to be greater after SV than after TV, in patients who were tested 5 years after either type of vagotomy[20]. Thus, any differences between the mean MAOs in the long term after TV, SV and HSV will probably prove to be small.

SUMMARY

Serial tests of maximal acid output (MAO) were performed in patients with chronic duodenal ulceration, before operation, and 1 week, 2 to 3 months, 6 to 12 months and 12 to 24 months after HSV. HSV reduced MAO by a mean of 48 per cent at 1 week, 69 per cent at 2 to 3 months, 54 per cent at 6 to 12 months and 52 per cent at 12 to 24 months. The decrease in MAO between 1 week and 3 months after HSV ($p < 0.001$) and the subsequent increase between 3 and 9 months ($p < 0.02$), were both statistically significant. Thereafter, MAO did not change significantly. Thus, HSV probably brings about a permanent reduction in MAO of about 50 per cent.

TABLE I

RESULTS OF SERIAL PENTAGASTRIN TESTS IN PATIENTS AFTER HSV (PEAK ACID OUTPUT - mEq/hr.)

NO.	NAME	AGE YRS.	SEX	WEIGHT KG.	VISICK GRADE AT > 1YR.	BEFORE	(1) 1 WEEK	% ↓ 1 WEEK	3 (3) MONTHS	% ↓ 3 MONTHS	6 - 12 MONTHS	% ↓ 6 - 12 MONTHS	1 - 2 YEARS	% ↓ 1 - YEAR
1	R.R.	50	M	81	I	31.80	14.00	56.00	(6 12.99	59.15	(11 19.71	38.02	(20 15.18	52.2
2	R.P.	45	M	75	II	51.72	19.40	62.50	17.91	65.38	(11 14.64	71.70	(18 14.88	71.2
3	F.D.	62	M	72	I	39.18	17.30	55.70	1.65	96.03	(11 3.42	91.27	(18 3.96	89.8
4	A.W.	35	M	76	I	53.85	31.40	41.80	18.18	66.24	(11 29.73	44.79	(18 32.13	40.3
5	D.A.	29	M	67	IV	43.00	24.30	43.50	20.31	52.78	(10 26.61	38.12	(22 26.01	39.5
6	F.A.	34	M	79	II	35.40	12.50	64.60	5.13	85.51	(9 15.36	56.61	(18 8.52	75.9
7	A.D.	40	F	50	II	30.00	20.85	30.50	(5 23.37	22.10	(11 18.00	40.00	(18 21.96	26.8
8	J.I.	47	M	60	I	43.65	16.30	62.60	8.40	80.70			(15 10.02	77.(
9	E.L.	43	M	61	I	35.70	18.72	47.57	3.00	91.60			(15 6.15	82.7
10	P.S.	34	M	66	II	38.16	32.25	15.49	21.66	43.24			(12 17.08	55.3
11	S.G.	27	M	75	I	56.04	28.86	48.51	(4½ 24.00	57.17			(12 46.86	16.3
12	F.W.	46	M	70	I	46.08	15.00	67.45	8.25	82.10			(12 24.54	46.7

13	A.T.	16	M	51	I	42.60	29.97	29.45	21.75	48.94			(12 26.22	38.
14	B.S.	33	M	56	IV	37.02	13.32	64.00					(13 16.77	54.
15	R.C.	40	M	80	II	36.60	15.57	57.50					(13 10.35	71.
16	W.C.	42	M	67	I	51.60	28.74	44.30					(12 29.88	42.
17	N.K.	49	M	63	I	69.42	36.48	47.45					(12 28.62	58.
18	E.H.	56	F	52	II	27.69	14.79	46.60					(13 18.00	35.
19	M.F.	48	F	41	II	18.27	13.56	25.78					(15 13.50	26.
20	P.A.	21	F	57	III	26.88	13.29	51.60			(7 17.25	35.83	(12 15.63	41.
21	H.H.	40	F	48		28.53	7.23	74.66	(3 9.66	67.14	(11 19.50	31.65		
22	C.C.	53	M	75		38.10	22.50	40.94	5.58	87.97	(10 12.93	6 .04		
23	J.D.	51	M	6		30.00	12.69	57.70	2.49	91.70	(11 3.84	87.20		
24	F.N.	51	M	83		35.97	20.1	43.95	11.34	68.47	(11 14.94	58.47		
25	G.W.	33	M	74		29.85	29.70	0.00	11.13	2.70	(11 13.05	54.27		
26	G.M.	27	M	70		71.79	16.80	76.70	17.37	75.81	(11 37.38	47.93		
27	H.K.	60	M	67		55.95	ND	-	-	-	(8 31.92	43.00		
	MEAN	41.19	22M 5F	66.00		40.34	20.22	48.38%	13.38	68.67%	18.59	53.66%	19.31	52.1
	±1SEM	±2.22		± 2.15		±2.49	±1.50	±3.46	±1.73	±4.38%	±2.46	±4.76	±2.32	±4.5
		(27)				(26)	(26)	(26)	(19)	(19)	(15)	(15)	(20)	(20

TABLE I - LEGEND

Statistical analyses:

(1) Paired tests at 1 week and 3 months. Mean decrease in PAO = 7.67 ± 1.49 mEq per hr.

$n = 19$, $t = 5.148$, $p < 0.001$

(2) Paired tests at 3 and 6 - 12 months. Mean increase in PAO = 5.586 ± 1.847 mEq per hr.

$n = 13$, $t = 3.024$, $p < 0.02$

The insulin test was negative in each patient in the early post-operative period.

Figures in parenthesis indicate number of months after HSV.

TABLE II

EFFECT OF HSV ON PENTAGASTRIN-STIMULATED MAO (TOTAL-HOUR)

(mEq per hour)

NO.	NAME	BEFORE	1 WEEK (1)	% ↓ 1 WEEK	3 MONTHS (2)	% ↓ 3 MONTHS	6 - 12 MONTHS (3)	% ↓ 6 - 12 MONTHS	1 - 2 YEARS (4)	% ↓ 1 - 2 YEARS
1	R.R.	28.51	9.22	67.66	9.96	65.06	16.31	42.79	12.22	57.14
2	R.P.	41.17	13.70	66.72	14.33	65.19	11.15	72.92	13.19	67.96
3	F.D.	32.05	10.06	68.61	1.07	96.75	2.19	93.17	2.72	91.51
4	A.W.	41.42	21.84	47.27	12.28	70.35	23.55	43.14	19.60	52.68
5	D.A.	41.50	18.16	56.24	15.35	61.62	21.35	48.55	20.42	50.80
6	F.A.	30.89	8.65	72.00	4.16	86.54	11.91	61.44	6.17	80.03
7	A.D.	28.00	12.30	56.07	17.84	36.29	15.03	46.32	15.21	45.68
8	J.I.	40.06	8.20	79.53	6.97	82.60			7.07	82.35
9	E.L.	32.25	15.15	53.03	2.03	93.71			3.84	88.10
10	P.S.	29.69	22.22	25.16	18.17	38.80			16.10	45.78
11	S.G.	38.01	21.71	42.89	17.01	55.25			31.87	16.15
12	F.W.	39.93	9.97	75.03	7.12	82.17			or 23.34 18.90	52.07
13	A.T.	34.25	21.51	37.20	19.58	42.83			20.99	38.72
14	B.S.	32.15	9.90	69.21					14.46	55.02
15	R.C.	32.54	10.18	68.72					8.00	75.41

16	W.C.	38.72	17.15	55.71					24.34	37.14
17	N.K.	53.88	21.03	60.97					19.25	64.27
18	E.H.	24.62	9.21	62.59					14.52	41.02
19	M.F.	14.46	7.83	45.85					10.76	25.59
20	P.A.	20.19	9.89	51.02			5 14.38	28.78	10.62	46.53
21	H.H.	19.78	4.03	79.63	5.33	73.05	11 14.35	27.45		
22	C.C.	28.32	13.15	53.57	3.67	86.33	10.24	63.84		
23	J.D.	24.75	8.77	64.57	1.63	92.91	2.70	88.85		
24	F.N.	25.79	15.01	41.80	8.58	67.73	11.98	53.55		
25	G.W.	18.98	21.83	(15.02)	8.28	56.40	11.02	41.94		
26	G.M.	62.99	12.20	80.63	12.25	80.55	29.13	53.75		
27	H.K.	39.71					25.17	36.62		
	MEAN	32.881	13.572	56.410%	9.79°	70.20%	14.70[1]	53.54[1]%	14.513	55.73%
	± 1 SEM	2.096	1.037	3.954	1.36[1]	4.235	1.956	5.060	1.024	4.558
		(26)	(26)	(26)	(19)	(19)	(15)	(15)	(20)	(20)

Statistical Analyses: (1) 19 paired tests at 1 week and 3 months. Mean decrease was 4.246 ± 1.155 mEq per

$t = 3.676$ $p < 0.01$

(2) 13 paired tests at 3 and 6 - 12 months after HSV. Mean increase was 5.065 ± 1.553 mEq per hour.

$t = 3.261$ $p < 0.01$

APPENDIX

Measurement of acid concentration The instrument used was a 'Radiometer' autotitrator. 1 ml. aliquots of filtered samples of gastric juice were titrated with 0.1 N sodium hydroxide, to an end-point of pH 7. In some tests, twin end-points at pH 3.5 and pH 7 were used. The needle setting was checked each morning by the use of buffer solutions, and the accuracy was estimated at regular intervals by the titration of standard solutions of hydrochloric acid. In duplicate measurements of the acid concentration of samples of gastric juice, which were performed each day, the second measurement was invariably within 2 per cent of the first.

Estimation of the concentration of polyethylene glycol 4000 in gastric juice The method used was that of Hydén (1955). Each day, standard solutions of PEG ranging in concentration from 0.1 to 1.0 mg per ml were prepared, and a standard curve drawn. A linear relationship existed between optical density and PEG concentration between 0.1 and 1.0 mg per ml. The concentration of PEG in gastric aspirate was read from this

standard curve. Reproducibility of the method was checked each day by the performance of duplicate estimations on the same samples. The coefficient of variation, calculated from twenty pairs of duplicate determinations in gastric juice with varying concentrations of PEG, varied between 2 and 12 per cent. This compares poorly with Hydén's figure of 0.7 per cent.

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PART III A COMPARISON OF THE EFFECTS OF TRUNCAL, SELECTIVE AND HIGHLY SELECTIVE VAGOTOMY ON MAXIMAL ACID OUTPUT

The operations which were compared were truncal vagotomy and pyloroplasty (TV+P), bilateral selective vagotomy and pyloroplasty (SV+P), and highly selective vagotomy without a drainage procedure (HSV). The pyloroplasties were mostly of the Heinecke-Mikulicz variety, though a few were of the Finney type. Patients had not been allotted to one or other of these operations in a random manner. As a result, it was difficult to eliminate bias. MAO was compared at two different time-intervals after operation; firstly, in the early post-operative period, 5 to 10 days after operation; and secondly, more than one year after operation.

An attempt was made to compare the effects of complete vagotomy on MAO, by selecting patients whose insulin tests were negative in the early post-operative period. Since, over the past eight years, the incidence of incomplete TV in Leeds and Sheffield has been 16 per cent and of incomplete SV, 14 per cent[1], whereas the incidence of incomplete vagotomy after HSV was 3 per cent, the exclusion of insulin-positive cases may have biased the results against HSV. Again, patients judged to be clinical failures (Visick grade IV)

after TV or SV

were excluded when the late tests, more than one year after operation, were performed. Although at this time the clinical results after HSV in Leeds are somewhat better than those observed after TV+P or SV+P, only patients who were in good health after TV or SV were selected for testing, which may also have introduced some element of bias against HSV. Patients tested after HSV were a representative sample, and both the patients who were clinical failures at one year were included.

METHOD

Stimulus As before, intramuscular pentagastrin provided the stimulus to gastric secretion. The dose used before operation was 6 ug per kg, and in all tests after vagotomy, 10 ug per kg. The methods used have been described above.

Patients Most of the patients were treated in the University Department of Surgery, the General Infirmary at Leeds, but some were at Sheffield Royal Infirmary. Full data are available for patients at Leeds, but details about the weights and pre-operative MAOs of the patients at Sheffield were sometimes lacking.

RESULTS

The results in individual patients are given in Tables I to

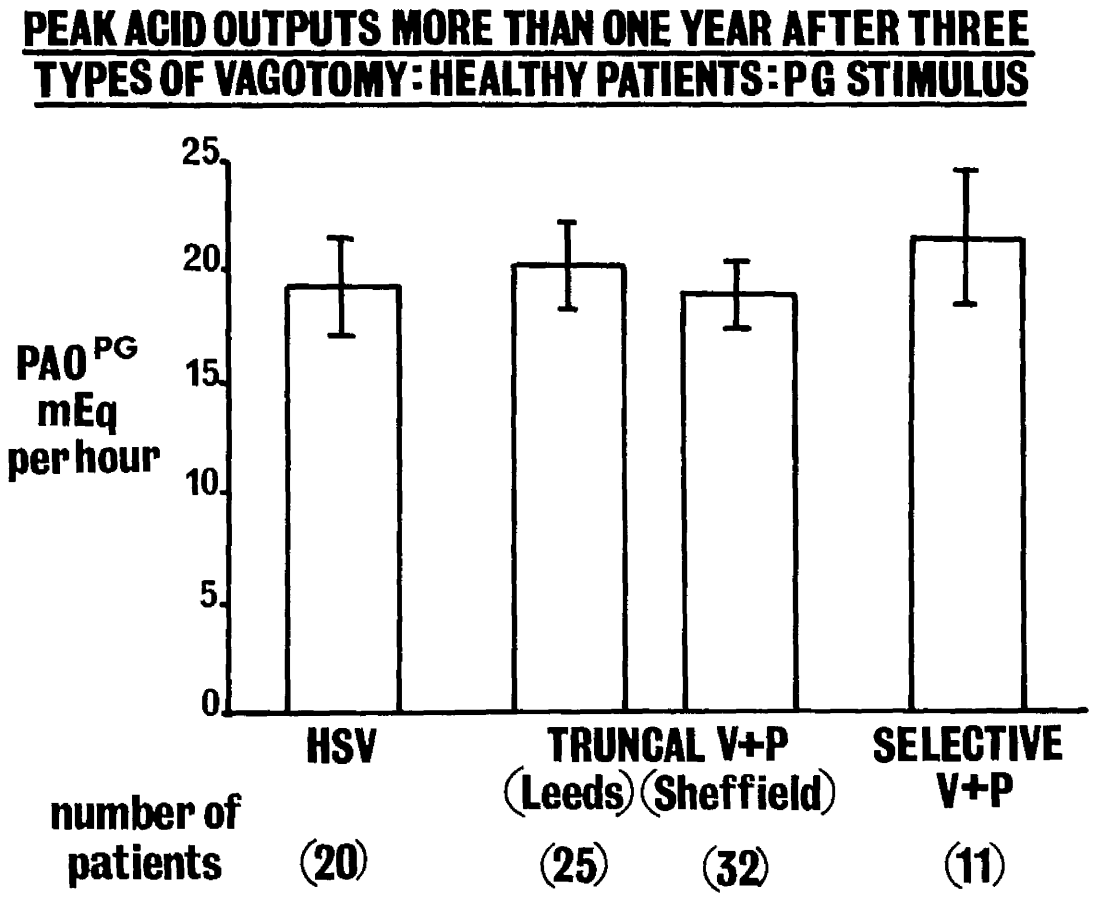

Fig. 1 There was no significant difference between the mean peak acid outputs (± 1 SE), more than one year after truncal, selective or highly selective vagotomy. All these patients had "Hollander-negative" insulin tests in the early post-operative period.

VII, and should be compared with the results of serial pentagastrin tests in patients after HSV (see Tables I and II in the preceding section).

PAO in the early post-operative period The effects of the three types of vagotomy on PAO^{PG} were found to be virtually identical (Tables I, II and VI). Each reduced PAO by about 50 per cent.

PAO more than one year after vagotomy (Fig. 1; Tables III, IV, V and VII) Again, there was little difference between the mean PAOs after the three types of vagotomy. Mean PAO was still in the region of 20 mEq per hour, and the mean reduction in PAO compared with pre-operative PAO was about 50 per cent.

DISCUSSION

Taking the results of the tests performed in the early post-operative period first, it can be seen (Table VI) that the patients were well-matched with respect to sex ratio and pre-operative MAO. Patients subjected to TV+P were on average 7 to 8 years older than those who underwent SV+P or HSV. Patients treated by SV+P may have been 4 to 5 kg lighter on average than those in the other two groups, but such a suggestion can only be tentative, because details of the weights of patients treated by SV+P in Sheffield were not available. It is considered unlikely that these relatively small mean differences

between the three main groups of patients could have exerted an important influence upon the observed reductions in MAO. Again, it should be reiterated that some bias against HSV was deliberately introduced, by the exclusion of patients who had evidence of incomplete vagotomy on insulin-testing after TV+P or SV+P. These results indicate that each of the three types of vagotomy reduces MAO by about 50 per cent, as judged by testing in the early post-operative period.

More than one year after the three vagotomies, the picture is essentially unchanged (Fig. 1, Table VII). Despite the deliberate exclusion of patients who were faring badly after TV or SV, and the inclusion of both the clinical failures after HSV, the latter procedure seems to be as effective as the other two operations in reducing MAO, at least for up to two years after operation. What is remarkable is the similarity of the mean PAOs in each of the three groups of patients (around 20 mEq per hour), and the similarity of the percentage reductions in PAO, which average about 50 per cent, just as in the early post-operative period. It should be noted that matching of the three groups was again imperfect. Patients treated by SV+P or HSV were on average 7 years younger than patients treated by TV+P, and about 5 kg lighter in weight. Patients after HSV were tested, on

average, 15 months after operation, whereas in the other two groups the mean interval between operation and performance of the pentagastrin test was 24 months. It is conceivable that if the patients after HSV had been tested 24 months after operation, their acid outputs might have been higher. This possibility is thought to be unlikely, however, because of the evidence from the serial tests after HSV that MAO increases significantly between 3 and 10 months after operation, but that it then remains constant in the ensuing 12 months.

SUMMARY

Intramuscular pentagastrin was used to elicit PAO in patients before, one week after, and more than one year after, truncal vagotomy and pyloroplasty, selective vagotomy and pyloroplasty, and highly selective vagotomy without a drainage procedure. Patients chosen for testing more than one year after operation were in good health, and their insulin tests had been negative in the early post-operative period. One week after operation, it was found that each of the three types of vagotomy had reduced PAO by 50 per cent, to about 20 mEq per hour. More than one year after operation, mean PAO was again found to be about 20 mEq per

hour, and the mean reduction compared with pre-operative PAO was in the region of 50 per cent.

Differences existed between the three groups of patients, in respect of age, weight and the interval between operation and secretory testing. Nonetheless, it seems justifiable to conclude that each of the three types of vagotomy, properly performed, leads to a permanent mean reduction in maximal acid output of about 50 per cent. Thus, HSV is as effective as truncal or selective vagotomy with pyloroplasty in reducing maximal acid output.

REFERENCE

1. Johnston, D. and Goligher, J. C. (1971) Gut, 12, 963.

TABLE I

EFFECT OF TRUNCAL VAGOTOMY AND PYLOROPLASTY ON PENTAGASTRIN-STIMULATED PEAK ACID OUTPUT (EARLY POST-OP.)

NO.	NAME	AGE YRS.	SEX	WEIGHT KG.	PAO^{PG} mEq/hr.		% REDUCTION
					BEFORE	AFTER	
1	R.C.	43	M	76	41.31	25.71	37.76
2	E.W.	68	M	64	19.71	21.63	- 9.74
3	J.S.	41	M	83	74.94	14.76	80.30
4	H.F.	47	F	53	26.97	26.67	1.11
5	E.R.	73	M	63	28.95	12.69	56.17
6	J.L.	36	M	64	48.47	7.95	83.58
7	M.L.	51	M	46	46.86	24.06	48.66
8	A.S.	67	M	65	41.07	11.73	71.44
9	A.H.	72	M	52	21.66	15.36	29.09
10	S.R.	46	M	74	38.88	22.59	41.90
11	M.W.	25	M	80	61.83	33.93	45.12
12	H.T.	71	M	63	63.45	22.08	65.20
13	B.G.	72	M	56	41.79	3.81	90.88
14	D.A.	49	F	63	30.54	13.20	56.78
15	M.M.	33	F	75	22.10	23.10	- 4.52
16	T.R.	63	M	60	44.13	22.74	48.47
17	T.M.	52	M	53	53.19	26.64	49.99
18	J.P.	32	M	63	54.09	28.65	47.04
19	K.F.	65	M	70	30.09	12.50	58.46
20	T.C.	67	M	61	14.16	9.21	36.97
21	B.M.	44	M	79	39.15	12.03	69.28
22	J.D.	56	M	64	44.79	24.78	44.68
23	J.B.	55	M	54	53.28	34.29	35.64
24	F.M.	43	M	76	42.78	24.51	42.71
25	G.B.	27	M	70	52.14	19.41	62.77

TABLE I CONTINUED

26	F.T.	62	F		35.70	26.04	27.06
27	J.P.	35	M		50.46	21.60	57.19
28	G.J.	36	F		44.55	20.55	53.87
29	J.J.	52	M		52.62	17.37	66.99
30	J.P.	45	M		18.90	8.79	53.49
31	E.S.	60	M		59.40	31.47	47.02
32	J.D.	26	M		39.96	24.84	32.79
33	B.Q.	34	M		65.13	47.61	26.10
34	G.B.	43	M		36.00	9.18	74.50
35	L.M.	37	M		28.08	10.02	64.32
36	J.K.	64	M		38.13	17.31	54.60
37	G.G.	47	M		47.28	17.34	63.32
38	T.B.	38	M		58.77	17.43	70.34
	MEAN	49.39 YEARS		65.08 KG.	42.32	20.09	49.51
	± 1 SEM	± 2.32			± 2.30	± 1.43	± 3.61

PAO^{PG} is peak-20-minute acid output, x 3, in mEq per hour.

All the insulin tests were negative by Hollander's (1948) criteria, 5 - 10 days after operation. Patients 1 - 25 were in Leeds and patients 26 - 38 in Sheffield. Weights of Sheffield patients were not available at the time of writing.

TABLE II

EFFECT OF BILATERAL SELECTIVE VAGOTOMY + PYLOROPLASTY ON PENTAGASTRIN-STIMULATED PEAK ACID OUTPUT (EARLY POST-OP., AT 5 - 10 DAYS)

NO.	NAME	AGE YRS.	SEX	WEIGHT KG.	PAO^{PG} mEq/hr.		% REDUCTION
					BEFORE	AFTER	
1.	R.K.	45	M	67	53.49	33.18	37.97
2.	B.M.	32	F	56	20.07	12.48	37.82
3.	T.M.	31	M	74	35.06	25.56	27.12
4.	F.B.	54	F	54	32.10	16.89	48.40
5.	E.W.	49	F	54	44.70	22.23	50.27
6.	H.H.	44	M	67	23.82	21.75	8.73
7.	L.B.	56	M	57	45.30	19.83	56.23
8.	L.P.	40	F	48	29.80	4.83	83.90
9.	M.W.	47	F	70	23.76	9.00	62.13
10.	G.S.	50	M	62	40.00	13.77	65.60
11.	G.H.	35	M	61	64.71	43.83	32.30
12.	R.G.	31	M		39.69	30.15	24.04
13.	D.J.	30	M		43.60	17.91	58.92
14.	M.C.	42	F		28.44	10.38	63.50
15.	O.L.	63	M		39.00	10.89	72.08
16.	B.A.	36	F		17.77	8.43	52.56
17.	N.H.	48	M		46.08	19.02	58.72
18.	J.C.	26	M		38.19	13.11	65.67
19.	A.C.	63	M		90.99	32.58	64.19
20.	G.H.	16	M		59.34	34.68	41.56

TABLE II CONTINUED

21.	H.S.	49	M		34.26	14.82	56.74
22.	J.E.	53	M		54.09	11.82	78.15
23.	H.T.	54	M		45.00	35.43	21.27
24.	G.G.	60	M		30.15	20.34	32.54
25.	H.O.	39	M		61.95	36.63	40.87
26.	L.W.	33	M		50.37	13.74	72.72
27.	A.K.	18	M		58.26	33.36	42.74
28.	J.W.	44	M		49.53	48.75	1.57
29.	F.G.	46	M		66.90	29.28	56.23
	MEAN	42.55 YEARS		60.91 KG.	43.67	22.23	48.78%
	± 1 SEM	2.28 (29)		2.39 (11)	3.00 (29)	2.13 (29)	3.75 (29)

PAO^{PG} is peak-20-minute acid output, x 3, in mEq per hour. Dose of PG was 6 ug/kg before, and 10 ug/kg after, HSV.

All insulin tests were negative by Hollander's (1948) criteria 5 - 10 days after HSV.

Cases comprise two short consecutive series of patients, 11 in Leeds and 18 in Sheffield, who had negative insulin tests after SV+P, and satisfactory pre- and post-operative pentagastrin tests.

Weights of Sheffield patients were not available at the time of writing.

TABLE III

EFFECT OF TRUNCAL VAGOTOMY AND PYLOROPLASTY ON PENTAGASTRIN-STIMULATED PEAK ACID OUTPUT, MORE THAN ONE YEAR AFTER OPERATION (LEEDS PATIENTS)

mEq per hour

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS POST-OP.	VISICK GRADE	PAO^{PG} BEFORE	PAO^{PG} AFTER	% ↓
1	J.G.	37	M	64	84	I	42.00*	22.74	45.86
2	C.R.	48	M	63	33	II	52.65	23.58	55.21
3	G.B.	30	M	74	35	I	52.14	14.28	72.61
4	J.W.	48	M	83	31	I	49.98	30.87	38.24
5	S.R.	47	M	74	16	II	38.88	7.14	81.64
6	B.M.	46	M	80	24	I	39.15	39.87	(-1.02)
7	K.T.	35	M	74	12	II	52.95	33.30	37.11
8	W.B.	57	M	56	31	I	26.91	11.94	55.63
9	P.D.	57	M	85	16	II	47.22	16.65	64.74
10	F.B.	46	M	78	29	II	32.58	29.91	8.20
11	M.W.	29	M	80	17	III	61.83	36.54	40.90
12	W.J.	35	M	62	16	I	30.54	14.13	53.73
13	H.T.	73	M	73	19	I	63.43	15.72	75.22
14	J.G.	55	M	85	35	II	32.60	4.50	86.20
15	D.L.	37	M	70	22	I	48.42	15.36	68.28
16	T.M.	45	M	59	29	I	53.19	29.16	45.18
17	G.P.	55	M	81	12	I	48.80	21.42	56.11
18	J.C.	46	M	66	16	I	36.00	19.26	46.50
19	J.M.	54	M	62	12	I	29.50	13.62	53.83
	MEAN	46.32	M	72.05	22.50+	12 I 6 II	44.15	21.05	51.80
	± 1 SEM	2.51		2.11	1.98	1 III	2.51	2.28	5.09
	No.	(19)		(19)	(18)		(19)	(19)	(19)

TABLE III CONTINUED

20	T.Y.	51	M	69	17	II	-	27.03	-
21	B.W.	24	M	64	12	I	-	6.18	-
22	G.T.	43	M	63	50	II	-	19.44	-
23	R.H.	41	M	59	24	III	-	17.28	-
24	S.W.	58	M	83	30	II	-	19.65	-
25	G.R.	62	M	60	72	III	-	18.45	-
	MEAN	46.36	M	70.68		13 I 9 II		20.32	
	± 1 SEM	2.27 (25)		1.86 (25)		3 III		1.85 (25)	

+ excluding patient No. 1. * response to I.V. histamine infusion.

Dose of pentagastrin was 6 ug per kg before operation, and 10 ug per kg after operation.

The early post-operative insulin test was not performed in patients 11, 24 and 25; late-positive in No. 2, and negative by Hollander's (1948) criteria in the remainder.

TABLE IV

PEAK ACID OUTPUT IN RESPONSE TO PENTAGASTRIN, MORE THAN ONE YEAR AFTER TRUNCAL VAGOTOMY AND PYLOROPLASTY (SHEFFIELD PATIENTS)

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS POST-OP.	PAO mEq/hr.
1	P.R.	50	M	63	32	19.38
2	L.S.	32	M	80	20	13.83
3	E.P.	59	M	64	18	6.81
4	J.B.	40	M	83	23	24.45
5	A.R.	33	M	73	23	28.41
6	G.T.	65	M	69	24	12.66
7	S.R.	58	M	73	17	6.03
8	W.C.	64	M	63	21	32.46
9	P.C.	48	M	60	21	31.02
10	G.F.	47	M	79	21	16.20
11	R.R.	41	M	60	21	10.62
12	M.G.	59	M	61	22	15.48
13	R.B.	42	M	73	33	13.86
14	D.H.	27	M	57	22	17.10
15	R.H.	59	M	85	31	38.25
16	R.F.	23	M	82	18	18.72
17	W.G.	52	M	80	35	26.67
18	J.M.	55	M	85	34	15.06
19	G.A.	48	M	79	28	17.46
20	G.C.	56	M	60	33	16.38
21	P.H.	51	M	78	32	25.05
22	R.H.	38	M	59	33	28.11
23	T.W.	53	M	66	34	21.78
24	R.P.	39	M	82	21	26.16

TABLE IV CONTINUED

25	J.B.	46	M	68	32	23.04
26	G.P.	33	M	79	29	23.97
27	J.W.	55	M	63	33	0.00
28	W.B.	59	M	67	16	16.77
29	J.W.	50	M	45	24	17.37
30	G.H.	58	M	65	38	24.27
31	H.P.	59	M	70	36	12.03
32	F.R.	46	M	64	38	6.78
(32)	MEAN	48.28	ALL M	69.88	26.97	18.94
	± 1 SEM	1.93		1.74	1.20	1.49

The insulin test was negative by Hollander's criteria in each patient in the early post-operative period, and all were in good-to-excellent health (Visick grades I to III), 1 to 4 years after TV+P.

The dose of pentagastrin was 10 ug per kg I.M. in each test.

TABLE V

EFFECT OF BILATERAL SELECTIVE VAGOTOMY AND PYLOROPLASTY ON PENTAGASTRIN-STIMULATED PEAK ACID OUTPUT MORE THAN ONE YEAR AFTER OPERATION

(mEq per hour)

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS POST-OP.	VISICK GRADE	PAO^{PG} BEFORE	PAO^{PG} AFTER	% ↓
1	I.M.	44	M	73	12	III	44.76	29.46	34.18
2	G.McD.	40	M	61	21	II	+40.00	8.91	77.72
3	T.McG.	31	M	74	24	III	35.07	27.15	22.58
4	C.H.	46	M	70	48	II	+30.00	30.12	(-1.00)
5	A.S.	16	M	64	44	II	+49.00	38.88	20.65
6	K.C.	44	M	69	27	I	25.77	8.67	66.36
7	F.S.	24	M	68	18	II	+56.00	27.00	51.79
8	A.W.	56	M	60	26	I	+47.50	12.66	73.35
9	S.C.	34	F	65	22	II	34.47	23.46	31.94
10	M.W.	47	F	70	18	II	23.76	12.87	45.83
11	S.M.	58	M	58	12	I	+58.00	18.60	67.93
	MEAN	40.00	9M 2F	66.55	24.73	3 I 6 II	40.39	21.62	44.67
	± 1 SEM	3.87		1.61	3.51	2 III	± 3.52	±3.00	± 7.63

The insulin test was negative in each patient in the early post-operative period, except in patient No. 9, whose test was late-positive.

\+ Pre-operative tests carried out with intravenous pentagastrin as the stimulus, in a dose of 1.2 or 6.0 ug per kg per hour. Intramuscular pentagastrin, 10 ug per kg, was used in all post-operative tests.

TABLE VI

COMPARISON OF THE EFFECTS OF TRUNCAL, SELECTIVE AND HIGHLY SELECTIVE VAGOTOMY ON PENTAGASTRIN-STIMULATED PEAK ACID OUTPUT

5 TO 10 DAYS AFTER OPERATION

	NUMBER TESTED	AGE YRS.	SEX	WEIGHT KG.	PAO mEq/hr.		% REDUCTION
					PRE-OP.	AT 1 WEEK	
TRUNCAL VAG. + PYLOROPLASTY	38	49.4	33M 5F	65.1*	42.3	20.1	49.5
SELECTIVE VAG. + PYLOROPLASTY	29	42.6	22M 7F	60.9*	43.7	22.2	48.8
HIGHLY SEL. VAGOTOMY	26	41.2	22M 5F	66.0	40.3	20.2	48.4

* data incomplete. The insulin test was negative by Hollander's criteria in each patient.

PAO is peak-20-minute output multiplied by three.

TABLE VII

COMPARISON OF THE EFFECTS OF TRUNCAL, SELECTIVE AND HIGHLY SELECTIVE VAGOTOMY ON PENTAGASTRIN-STIMULATED PEAK ACID OUTPUT

MORE THAN ONE YEAR AFTER OPERATION

	NUMBER TESTED	AGE YRS.	SEX	WEIGHT KG.	MONTHS AFTER OP.	VISICK GRADES	PAO mEq/hr. PRE-OP.	PAO mEq/hr. > 1 YR. AFTER OP.	% REDUCTION
TRUNCAL VAGOTOMY + PYLOROPLASTY	32*	48.3	ALL M	69.9	27.0	I to III	-	18.9	-
	19	46.3	ALL M	72.1	22.5	12 I 6 II 1 III	44.2	21.1	51.8
SELECTIVE VAGOTOMY + PYLOROPLASTY	11	40.0	9 M 2 F	66.6	24.7	3 I 6 II 2 III	40.4	21.6	44.7

HIGHLY SELECTIVE VAGOTOMY	20	39.9	16M 4F	65.0	15.0	10 I 7 II 1 III 2 IV	40.7	19.3	52.1

* The 32 patients after TV+P were in Sheffield. Data on their pre-operative PAO, and exact Visick status, is lacking. All the remaining patients were treated in the University Department of Surgery, The General Infirmary, Leeds. Almost all patients had negative insulin tests in the early post-operative period, and were in good health (Visick grades I to III) at the time of testing.

CHAPTER 5

THE INSULIN TEST AFTER HIGHLY SELECTIVE VAGOTOMY

PART I: Serial insulin tests after HSV.

PART II: On the significant increase in spontaneous, maximal and insulin-stimulated acid outputs during the first 1 - 2 years after HSV.

PART III: Comparison of gastric acid outputs in response to insulin in healthy patients more than one year after truncal, selective or highly selective vagotomy.

PART IV: Comparison of spontaneous, maximal and insulin-stimulated acid outputs in two groups of patients with Hollander-positive insulin tests:

group I, more than one year after HSV.

group II, with recurrent ulceration after truncal or selective vagotomy with pyloroplasty.

CHAPTER 5

THE INSULIN TEST AFTER HIGHLY SELECTIVE VAGOTOMY

PART I: SERIAL INSULIN TESTS AFTER HSV

Although the patients' clinical progress after HSV has been excellent for up to 3 years, one major imponderable remains: the incidence of recurrent ulceration in the long term. After any type of vagotomy, vagal nerve regeneration or sprouting may lead to recurrence, but patients after HSV could, in theory, be at especial risk, firstly because at the time of operation the vagotomy of the parietal cell mass (PCM) might be incomplete distally in addition to proximally, and also because in the months after operation the PCM might become reinnervated from its distal as well as from its proximal margin. Even in the absence of vagal nerve regeneration, gastrin release from the innervated antrum in response to food or vagal stimulation might be excessive.

Serial insulin tests were performed in patients before HSV and for up to 2 years after HSV, in an attempt to answer two main questions :- firstly, was the parietal-cell vagotomy complete initially, and secondly did it remain complete as time passed? It was hoped that in this way some idea might be gained about the probable incidence of

recurrent ulceration in the long term.

METHOD

Patients The diagnosis of duodenal ulceration was confirmed in each patient at operation, and each was treated by HSV. Insulin tests[1] were performed :- before operation in 10 patients, one week after HSV in 100 patients, 3 to 6 months after HSV in 7 patients, 6 to 12 months after HSV in 4 patients, and 1 to 2 years after HSV in 35 patients. The patients who underwent serial testing are considered to be representative of the whole group of HSV patients, and include patients who were clinical failures.

Insulin Test The techniquedf gastric testing was similar to that used in the pentagastrin tests. Gastric secretion was aspirated by continuous suction for 3 hours. After four 15-minute collections of spontaneous (basal) secretion had been made, soluble insulin was injected intravenously in a dose of 0.2 unit per kg. body weight. This dose of insulin has been shown to elicit a secretory response that is maximum for insulin, both in subjects with intact vagi[2,3], and in patients with incomplete vagotomy[4]. Eight further 15-minute samples of gastric secretion were then collected. Venous blood was withdrawn, 30 and 45 minutes after the injection of insulin, for blood glucose

estimation by the glucose oxidase method[5] on an autoanalyzer. Blood glucose concentration decreased to less than 35 mg per 100 ml in each of the tests reported. The samples of gastric juice were filtered through gauze and 1 ml aliquots titrated with 0.1N sodium hydroxide to pH 7 on a TTTI 'Radiometer' autotitrator. Acid output was expressed as peak acid output in mEq per hour (PAO^1 = acid output in the 2 consecutive 15-minute periods which gave the highest reading, multiplied by 2)[6]. PAO^1 has been shown to be reproducible in the same subject[6,7].

Interpretation of results In view of the empirical nature of the time-honoured Hollander[1] criteria, which depend solely on changes in acid concentration, the actual acid outputs both in the basal hour and in response to insulin were analyzed, by the seven criteria[1,8-12] shown in TableIII. A slight modification of Ross and Kay's criteria was used, whereby an "early-positive" response denoted a positive response in the first hour after insulin, rather than a response in the first 45 minutes. For assessment by Hollander's criteria, the mean acid concentration in mEq per litre in the 2 consecutive collection periods which gave the highest reading before the insulin injection was subtracted from the mean acid concentration in the 2 consecutive collection periods which gave the highest reading after insulin. An increase of 20 mEq per litre or more denoted a positive response. An increase of 10 mEq per litre was regarded as positive if the basal specimens were anacid.

Anacid was defined as a pH greater than 3.5.

Statistical analysis The significance of differences between paired observations in the same patients was calculated using Student's t test for paired data[13].

RESULTS

Results for each patient tested more than one year after HSV are to be found in Table V. The changes in PAO^{I} with time are depicted in Fig. 1.

Response to insulin before operation (10 tests) Mean PAO^{I} was 36 mEq per hour, 75 per cent of the pentagastrin peak acid output (PAO^{PG}, Fig. 1, Table I). In this particular context, PAO^{PG} was taken as peak-30-minute output multiplied by two. All 10 tests were positive within the first hour ("early-positive"[8]) by Hollander's criteria[1]. They were also positive by all other criteria (Tables III and IV).

One week after HSV (100 tests) Mean PAO^{I} was 0.5 mEq per hour, 1 per cent of the pre-operative PAO^{PG}. If the spontaneous acid output is subtracted, mean PAO^{I} was nil. 97 tests were Hollander-negative and 3 were late-positive. If the mean acid concentration of all 4 basal samples, instead of the 2 consecutive samples with the highest reading, was used as the baseline measurement, 5 tests were late-positive.

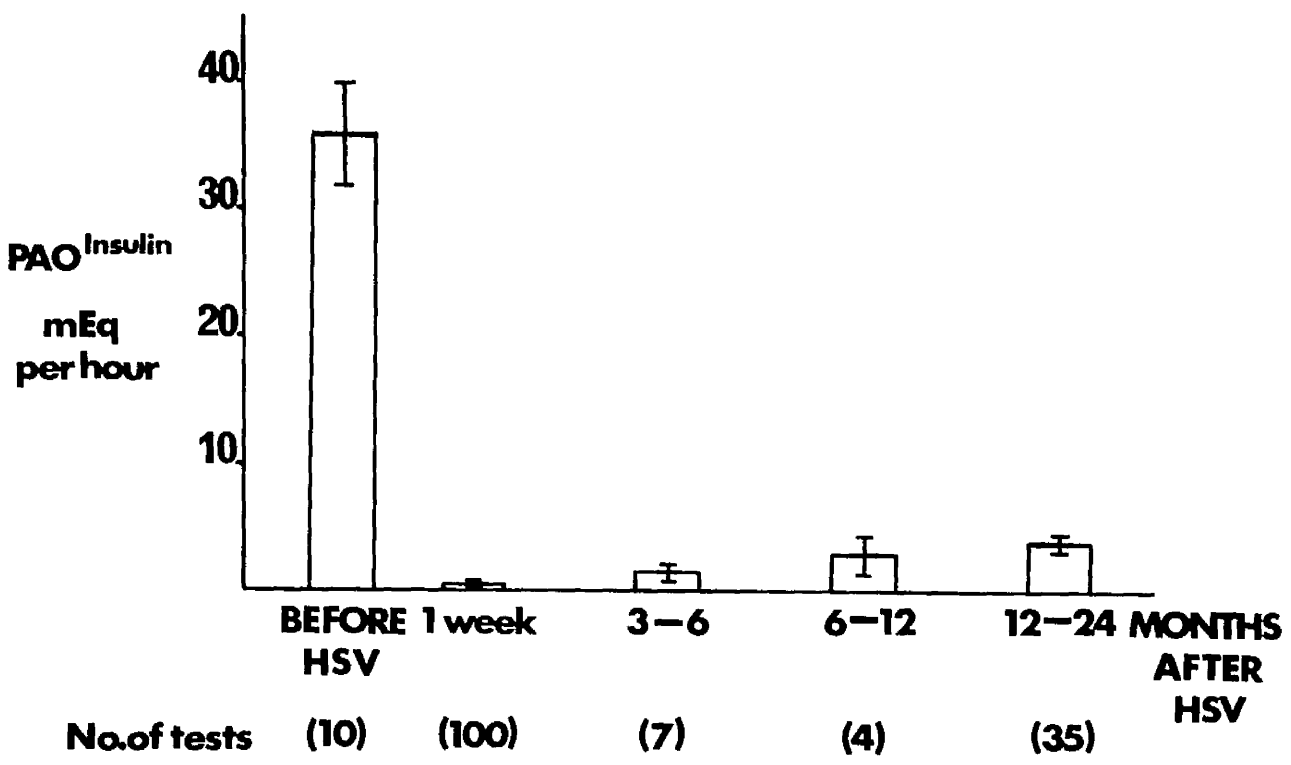

Fig. 1 Before HSV, mean peak acid output (± 1 SE) in response to insulin (PAO^I) is a high percentage of the maximal acid output. One week after HSV, PAO^I is no greater than basal secretion, in 100 patients. Thereafter, a small but statistically significant increase takes place in the acid response to insulin. More than half of the patients tested more than one year after HSV had Hollander-positive responses, but the mean acid response is still very small.

TABLE I

PEAK ACID OUTPUTS IN RESPONSE TO INSULIN BEFORE AND AFTER HIGHLY SELECTIVE VAGOTOMY

mEq per hour

	BEFORE HSV	AFTER HSV			
		1 WEEK	3 - 6 MONTHS	6-12 MONTHS	1 - 2 YEARS
NUMBER OF TESTS	10	100	7	4	35
HOLLANDER RESPONSE -ve, L+ or E+	10 E+	97-, 3L+	4-, 1L+, 2E+	2-, 1L+, 1E+	15-, 12L+, 8E+
PAO^{I} mEq per hour ± 1 SEM	35.82 ± 4.09	0.54 ± 0.10	1.48 ± 0.73	2.85 ± 1.65	3.74 ± 0.62
PAO^{I} as % of pre-op. PAO^{PG} ± 1 SEM	74.98% ± 4.87	1.08% ± 0.27	3.57% ± 1.72	5.03% ± 2.17	9.72% ± 1.57

E+, early-positive in the first hour after insulin, by Hollander's criteria.

L+, late-positive, in the second hour.

PAO^{I} - peak acid output in response to insulin (peak-30-minute output x 2).

PAO^{PG} - peak acid output in response to pentagastrin (peak-30-minute output x 2).

For results in individual patients at 1 - 2 years see Table V

Three to six months after HSV (7 tests) Mean PAO^{I} was 1.5 mEq per hour, 3 per cent of pre-operative PAO^{PP}. Three tests were Hollander-positive (2 early-positive and 1 late-positive), and 4 were negative.

Six to twelve months after HSV (4 tests) Mean PAO^{I} was 2.9 mEq per hour, 5 per cent of pre-operative PAO^{PP}. Two tests were positive by Hollander's criteria, one "early" and one "late".

Twelve to twenty-four months after HSV (35 tests) Mean PAO^{I} was 3.7 mEq per hour, 10 per cent of pre-operative PAO^{PP}. 57 per cent of the tests were positive by Hollander's criteria. Eight (23 per cent) were early-positive and 12 (34 per cent) were late-positive.

Results of paired tests in the same patients In paired insulin tests performed 3 to 6 and 12 to 24 months after HSV in 9 patients, mean PAO^{I} increased from 3.2 ± 1.1 mEq per hour to 7.0 ± 1.7 mEq per hour, a statistically significant increase ($p < 0.01$). PAO^{I} increased in all 9 patients (Table II). It should be noted that these 9 patients include 2 who had HSV performed for "duodenitis", and 1 patient who had a small resection of the PCM in addition to HSV.

Assessment of results by multiple criteria (Tables III and IV) Before HSV, all the tests were positive by all seven criteria. One week after HSV, they were negative by nearly all criteria, except in the

3 patients whose tests were (late) positive by Hollander's criteria. Thereafter, as the months passed, the insulin tests became increasingly positive, as judged by all 7 criteria. Even 1 - 2 years after HSV, however, the responses to insulin were much less "positive" than those recorded before operation. For example, whereas before HSV all 10 tests were positive by all criteria, more than one year after HSV, none of the 35 tests was positive by all criteria and 17 tests were positive by fewer than 3 criteria (Table IV).

Spontaneous and pentagastrin-stimulated acid outputs in patients with negative, late-positive and early-positive insulin tests Full details of the results obtained in patients who were tested more than 1 year after HSV are presented in Table V. Acid outputs in patients with "late-positive" responses to insulin were almost as high as those in patients with "early-positive" responses. For example, mean BAO in 12 patients with late-positive insulin tests was 1.72 mEq per hour, compared with 1.73 mEq per hour in 8 patients who had early-positive insulin tests. Mean PAO^{PG} was 20.09 mEq per hour in the 'late-positive' patients, and 21.67 mEq per hour in the 'early-positive' group. Although inevitably, PAO^{I} was much higher in patients who had positive insulin tests than in those who had negative tests, the differences between the insulin-positive and insulin-negative groups were much less marked when

spontaneous and pentagastrin-stimulated acid outputs (BAO, PAO^{PG}) were considered. Within each group, a wide scatter was found in the percentage reductions in BAO and PAO^{PG} compared with the pre-operative values.

DISCUSSION

The objects of this study were to find out whether HSV denervated the parietal cell mass (PCM) effectively and whether the denervation persisted with the passage of time. The answers to these questions were expected to give some clue as to the likelihood of recurrent ulceration. The magnitude of the acid outputs in response to insulin were also expected to give some guide to the amounts of gastrin released from the innervated antrum in response to direct vagal stimulation. If acid outputs were found to be high, the cause might be excessive gastrin release, vagal nerve regeneration, or both these factors; but if acid outputs were found to be low, it would suggest that vagal release of gastrin was not excessive.

The results of the 100 nearly-consecutive insulin tests which were performed one week after HSV indicate that this operation provides effective denervation of the PCM. No fewer than 97 of the tests were negative by Hollander's criteria[1], and none was early-positive[8].

As far as we are aware, these results are better than any previously reported[11,14-18] for a large series of insulin tests performed after vagotomy with drainage for duodenal ulcer. They contrast with a reported mean incidence of 20 per cent positive insulin tests by Hollander's criteria in several thousand patients after truncal vagotomy (TV)[16] and between 5 and 20 per cent after bilateral selective vagotomy (SV)[11,14,15,17,18]. In Leeds and Sheffield, where the method of insulin testing was identical with that used in this study, positive responses to insulin were found in 16 per cent of 515 patients one week after TV and in 13 per cent of 150 patients one week after SV[18] (Fig. 2). It would be premature to claim, however, that the results obtained in the early post-operative period after HSV are significantly better than those obtained after TV or SV, since all the HSV operations were performed by two surgeons, whereas TV and SV in Leeds and Sheffield[18] were performed by a large number of surgeons. In addition, the patients who were treated by HSV may differ in some unrecognized way from those treated by TV or SV. Such a possibility seems unlikely, however, since they comprise a consecutive series of patients coming to elective surgery.

The 97 per cent incidence of negative responses to insulin soon after HSV in Leeds would be difficult to improve upon by the use

RESULTS OF INSULIN TESTS ONE WEEK AFTER 3 TYPES OF VAGOTOMY.

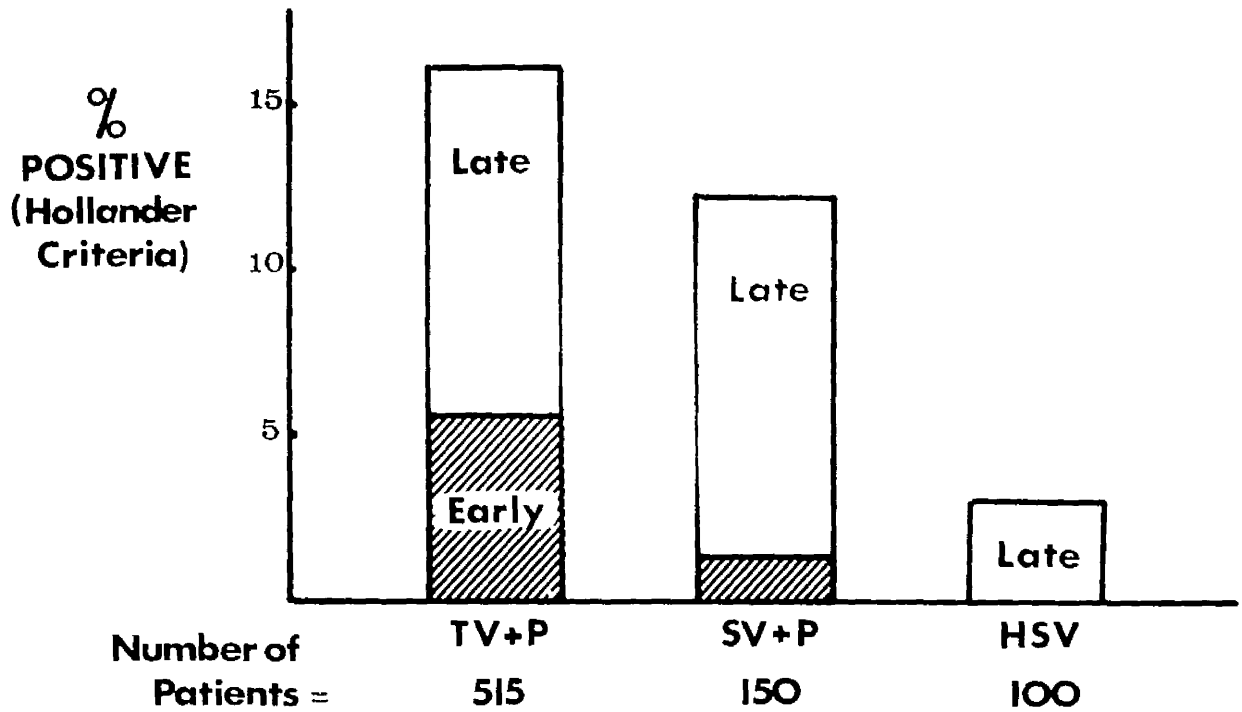

Fig. 2 Only 3 per cent of patients were shown to have incomplete vagotomy after HSV, compared with 13 per cent after selective vagotomy (SV) and 16 per cent after truncal vagotomy (TV). This large difference could be due to (a) HSV itself, (b) the surgeon, (c) the type of patient, or to combinations of all three factors. Early-positive:- in the first hour after insulin. Late-positive:- in the second hour.

of any of the intra-operative tests for completeness of vagotomy[19-21]. The operative technique which we used, without antral mapping, seems to be adequate to ensure complete vagotomy of the PCM at the time of operation in nearly every case. Whatever may be the anatomical variations of the vagi at the oesophageal hiatus, the vagal branches supplying the PCM must congregate around the cardia and along the lesser curvature of the stomach[22], where they can all be severed in the performance of HSV. It should be noted, however, that a high incidence of positive responses to insulin (and 2 recurrent ulcers) after HSV has been reported recently from another centre[23]. This serves to emphasize that the achievement of a complete vagotomy of the PCM is never easy, no matter whether the vagotomy be truncal, selective, or highly selective in type. Surgeons who use any variety of vagotomy without antrectomy in the treatment of duodenal ulcer should keep a check on the efficiency of their vagotomies[18,24], and if a high incidence (say, more than 15 per cent) of positive responses to insulin is persistently found soon after operation, they might consider adding an antrectomy in all except their "poor-risk" patients. The case for such a policy would be particularly strong if more than 5 per cent of the responses to insulin were found to be "early-positive", because such a response is probably indicative of inadequate vagotomy[8,24].

Although the results of the insulin tests performed soon after HSV are good, those of the tests performed in the ensuing 2 years are much less impressive. In the course of the first year after HSV, acid outputs in response to insulin, and the incidence of Hollander-positive tests, both increased significantly. More than one year after HSV, 57 per cent of 36 insulin tests were Hollander-positive. 23 per cent were early-positive and 34 per cent late-positive. These figures, although disappointing after the excellent results obtained soon after operation, are no worse than the results recorded more than one year after TV or SV with a drainage procedure[25-28]. It is not clear why so many of the insulin responses should change from negative to positive after HSV. One might postulate that the denervated PCM became supersensitive to humoral stimuli[29], or that more gastrin was released in the later tests than in the earlier ones in response to direct vagal stimulation. However, as is explained in more detail in the next Chapter, we think that the PCM probably acquires some measure of vagal reinnervation with the passage of time. If this explanation is correct, it seems unlikely that much further reinnervation takes place beyond one year from the time of operation. Although mean PAO^{I} appeared to increase between 6 - 12 and 12 - 24 months in patients at Leeds, it should be noted that only 4 patients were tested between 6 and

12 months after HSV. In Copenhagen, Amdrup found that mean PAO^{I} ('free' acid titrated to pH 3.5) in 18 patients one to two years after HSV (3.4 mEq per hour) was no greater than mean PAO^{I} in 14 patients six to twelve months after HSV (3.5 mEq per hour: Amdrup, Kragelund, Johnston et al.: in press).

Reinnervation, if that is the correct explanation for our findings, seems to involve only a small proportion of the entire PCM. Before operation, mean PAO^{I} was 36 mEq per hour, 75 per cent of PAO^{PG}. In contrast, more than one year after HSV, there was no response to insulin in 43 per cent of the 35 tests and the mean PAO^{I} was only 3.7 mEq per hour (Table I, Fig. 1), which is 20per cent of PAO^{PG} more than 1 year after HSV, and 10 per cent of the pre-operative PAO^{PG}. Patients with positive responses to insulin more than 1 year after HSV had higher acid outputs (BAO, PAO^{PG} and PAO^{I}) than had patients with negative insulin tests, but the differences between the mean acid outputs of the insulin-positive and the insulin-negative groups were not large (Table V). In particular, 70 - 75% mean reductions in BAO were found in patients with positive insulin tests. The intact hepatic and coeliac vagal fibres were perhaps exerting their inhibitory influence on gastric secretion in these patients[30-33]. Acid outputs in the "early-positive" group were little different from those in the "late-positive" group, which suggests that the risk of recurrent

ulceration may be much the same in these two groups of patients.

Since precise "mapping" of the pyloric gland area, or antrum, of the stomach by pH probe[34] or the Congo Red test[35] is an invariable feature of parietal cell vagotomy (HSV) as performed by Amdrup in Copenhagen, but was scarcely used at all in Leeds, it is interesting to note that acid outputs more than 6 months after HSV were very similar in the two centres (Table VI). Of 32 insulin tests which were performed more than 6 months after HSV in Copenhagen, 47 per cent were positive by Hollander's criteria (22 per cent early-positive) and the mean PAO^{I} (to pH 7) was 4.3 ± 1.1 mEq per hour. Although 57 per cent of the 35 insulin tests performed more than 1 year after HSV in Leeds were Hollander-positive, the BAO and PAO^{I} of the Leeds patients were slightly lower than the corresponding values for patients in Copenhagen. These results provide little support for the routine use of antral "mapping" in the performance of HSV. Omission of this time-consuming manoeuvre would render the operation more acceptable to surgeons, who are already deterred by the rather lengthy nature of the procedure as compared with truncal vagotomy.

Finally, what of recurrent ulceration? This topic is discussed more fully in the next Chapter but here it may be said that despite the finding of a high incidence of positive responses to insulin more than one year after HSV, we think that the results presented here

and in other Chapters provide considerable support for the view that the eventual incidence of recurrent ulceration after HSV will be low; firstly, because of the large reductions observed in spontaneous secretion; secondly, because there was no acid response to insulin in 43 per cent of the patients who were tested more than one year after HSV and the response to insulin in most of the remainder was small; thirdly, because the low spontaneous acid outputs and small acid responses to insulin suggest that gastrin release is not excessive from the innervated antrum; fourthly, because no evidence of gastric stasis was found, the resting juice being small in amount and free from food residues, and fifthly, because the reductions in maximal acid output after HSV are little different from those found after TV or SV. It should be borne in mind, too, that protective and inhibitory mechanisms in the antrum and duodenum may be preserved better after HSV than after TV. In a 3 year experience with 200 patients treated by HSV in Leeds and Copenhagen, not a single case of recurrent duodenal ulcer has been diagnosed. Yet recurrence, if it were to occur, would probably be early - within two or three years of operation - as it is after TV[16] or SV (our unpublished observations). HSV has been found to protect dogs against histamine-induced ulcer significantly better than does vagotomy with antrectomy[36]. Thus, there is reason to believe that recurrent ulceration will not prove to be a major problem after HSV. We must now await the results of the 5 and 10-year clinical follow-up.

SUMMARY

97 of 100 insulin tests performed one week after HSV were negative by Hollander's criteria. Three were late-positive. In the course of the first year after HSV, acid outputs in response to insulin increased significantly ($p < 0.01$). More than one year after HSV, 20 of 35 insulin tests were positive (57 per cent), 23 per cent being early-positive in the first hour after insulin and 34 per cent being late-positive. However, the mean peak acid output in response to insulin (PAO^{I}) was still only 3.7 mEq per hour, compared with 36 mEq per hour in 10 insulin tests which were performed before operation. Before HSV, PAO^{I} was 75 per cent of the pentagastrin-stimulated PAO. More than one year after HSV, PAO^{I} was 10 per cent of the pre-operative PAO^{PG}.

Thus, vagal release of gastrin does not appear to be excessive after HSV. It is suggested that HSV denervates the parietal cell mass effectively, as shown by the results of the insulin tests which were performed soon after operation. A small proportion of the parietal cell mass probably becomes re-innervated in the course of the first year after HSV, in 50 to 60 per cent of patients. These findings provide grounds for believing that recurrent ulceration will not prove to be a major problem after HSV.

TABLE II

RESULTS OF PAIRED INSULIN TESTS IN THE SAME PATIENTS

(a) 3 to 6 MONTHS and (b) MORE THAN ONE YEAR, AFTER HSV

NO.	NAME	MONTHS AFTER HSV		RESULT OF INSULIN TEST		PAO^{I} mEq/hr.		(b) minus (a)
		(a)	(b)	(a)	(b)	3 - 6 MONTHS (a)	> 1 YEAR (b)	
1	R.R.	3	22	E+	E+	1.44	2.52	1.08
2	F.W.	4	15	E+	E+	2.08	4.32	2.24
3	A.T.	5	15	L+	L+	5.54	10.50	4.96
4	M.B.	3	14	-ve	L+	0.12	2.08	1.96
5	N.K.	5	18	-ve	-ve	0.00	2.14	2.14
6	H.H.	3	22	-ve	L+	0.38	4.60	4.22
7	H.S.*	6	12	E+	E+	3.08	9.30	6.22
8	E.W.*	3	21	E+	L+	8.68	17.18	8.50
9	S.M.+	3	13	E+	E+	7.50	10.36	2.86
MEAN		3.89	16.89			3.20	7.00	3.80
± 1SEM		0.39	1.32			1.09	1.72	0.80

The increase in acid output between 3 - 6 months, and more than 1 year, after HSV is statistically significant, $t = 4.75$, $p < 0.01$.

* Patients 7 and 8 had HSV performed for "duodenitis" associated with gross hypersecretion.

\+ Patient No. 9 had a small (70g) resection of parietal cell mass, in addition to HSV. He was one of the first patients treated by HSV, in January 1969, and is not included in the first 100 cases, because of the added gastric resection.

TABLE III

ANALYSIS OF INSULIN TESTS BEFORE AND AFTER HSV BY MULTIPLE CRITERIA

CRITERIA FOR POSITIVE RESPONSE	BEFORE HSV	1 WEEK	3 - 6 MONTHS	6 - 12 MONTHS	1 - 2 YEARS
n =	10	100	7	4	35
1) Hollander[1], acid concentration increase 20 mEq/l	10	3	3	2	20
% +ve	100.0%	3.0%	42.9%	50.0%	57.1%
2 a) Early-positive[8], in 1st hour after insulin	10	0	2	1	8
% +ve	100.0%	0.0%	28.6%	25.0%	22.9%
2 b) Late-positive[8], in 2nd hour after insulin	0	3	1	1	12
3) Stempien[9] 1962 acid output increase of 0.25 mEq/hr.	10	4	4	4	24
4) Bachrach[10] 1962 acid output increase of 1 mEq/hr.	10	2	3	1	17
5) Bank et al.[11] 1967 acid output increase of 2 mEq/hr.	10	1	1	1	14
6) Gillespie et al.[12] 1970 acid output increase 3 x BAO	10	3	3	2	17
7) Bachrach[10] 1962 spontaneous acid output > 2 mEq/hr.	10	6	1	1	6

TABLE IV

ANALYSIS OF INSULIN TESTS BEFORE AND AFTER HSV

BY MULTIPLE CRITERIA

NUMBER OF POSITIVE CRITERIA	BEFORE HSV		AFTER HSV				
			1 WEEK	3 - 6 MONTHS	6 - 12 MONTHS	1 - 2 YEARS	
	(10)	%	(100)	(7)	(4)	(35)	% of 35
7 (+)	10	100%	0	0	1	0	0
6 (+)	0	0	0	0	0	9	25.7
5 (+)	0	0	1	2	0	5	14.3
4 (+)	0	0	1	0	0	2	5.7
3 (+)	0	0	1	2	1	2	5.7
2 (+)	0	0	0	0	0	4	11.4
1 (+)	0	0	[illegible]	1	1	4	11.4
0 (+)	0	0	91	2	1	9	25.7

Table V

INSULIN-STIMULATED, PENTAGASTRIN-STIMULATED AND SPONTANEOUS ACID OUTPUTS IN 35 PATIENTS MORE THAN ONE YEAR AFTER HSV

).	NAME	AGE YR.	SEX	WEIGHT KG.	TIMING OF POST-OP. INSULIN TEST (MONTHS)	CLINICAL (VISICK) GRADE - > 1yr.	INSULIN TEST	PAO^{I} mEq/hr A	% of PRE-OP. PAO^{PG}	PENTAGASTRIN TEST (PAO^{PG}) mEq/hr B	mEq/hr A	% REDUC-TION	SPONT. ACID OUTPU mEq/hr B	mEq/hr A	% REDU TION
1	R.R.	50	M	81	20	I	early +ve (4)	2.52	7.96	31.80	15.18	52.27	8.46	2.76	67.3
2	J.C.	22	M	52	24	I	early +ve (3)	16.34	44.23	37.44	23.61	36.94	6.00	1.92	68.0
3	A.D.	40	F	50	18	I	early +ve (3)	5.00	14.99	30.00	21.96	26.80	12.10	0.86	92.8
4	M.F.	48	F	41	14	II	early +ve (4)	3.82	21.20	18.27	13.50	26.11	2.04	1.28	37.2
5	F.W.	46	M	70	15	I	early +ve (3)	4.32	9.75	46.08	24.54	46.74	6.58	1.85	72.1
6	N.H.	66	M	54	12	I	early +ve (4)	7.68	11.38	70.77	26.70	62.27	25.30	1.32	94.1
7	W.C.	42	M	67	16	I	early +ve (4)	7.20	14.77	51.60	29.88	42.09	11.32	3.06	72.9
8	E.H.	56	F	52	16	II	early +ve (4)	1.14	4.33	27.69	18.00	35.00	2.18	0.77	64.6
8	EARLY POSITIVES	46.38		58.38	16.88		early positive	6.00 = 16.08%		39.21	21.67	41.03	9.25	1.75	71.2
	EAN ±1SE	4.53		4.62	1.33			mEq/hr ± 1.67	± 4.41	5.84	2.01	4.41	2.64	0.30	6.3

1	R.C.	40	M	80	16	II	late +ve (5)	9.30	25.85	36.60	10.35	71.72	9.06	1.55	82.[illegible]
2	S.G.	27	M	75	12	I	late +ve (6)	8.10	16.23	56.04	46.86	16.38	28.30	5.97	78.[illegible]
3	H.H.	40	F	48	22	III	late +ve (6)	4.60	17.02	28.53	19.50[1]	31.65	6.48	0.31	95.[illegible]
4	A.T.	16	M	51	15	I	late +ve (5)	10.50	26.54	42.60	26.22	38.45	11.28	3.82	66.[illegible]
5	F.N.	51	M	83	14	II	late +ve (7)	3.06	9.16	35.97	14.94[1]	58.47	5.00	1.26	74.[illegible]
6	C.C.	53	M	75	15	I	late +ve (5)	3.94	11.27	38.10	12.93[1]	66.04	4.86	1.15	76.[illegible]
7	W.B.	49	M	58	15	I	late +ve (8)	1.10	3.31	37.80	7.02	81.43	12.89	0.10	99.[illegible]
8	W.M.	47	M	60	15	I	late +ve (6)	1.98	4.56	45.63	27.36	40.04	3.08	1.24	59.[illegible]
9	J.S.	49	M	83	13	III	late +ve (5)	3.28	10.55	31.89	13.11	58.89	1.92	1.46	23.[illegible]
10	M.B.	41	F	51	14	II	late +ve (6)	2.08	5.56	39.09	28.40*	27.35	7.16	1.00	86.[illegible]
11	J.D.	51	M	66	14	I	late +ve (5)	1.82	6.22	30.00	14.25	52.50	5.64	0.18	96.[illegible]
12	S.C.	51	M	82	12	III	late +ve (7)	9.94	18.84	(59.04)	-	-	10.00	2.64	73.[illegible]
12 LATE POSITIVES MEAN ±1SE		42.92 3.24		67.67 3.92	14.75 0.75		late positive	4.98 = 12.93% mEq/hr ± ± 1.01 2.30		38.39 (11) 2.34	20.09 (11) 3.44	49.36 (11) 6.09	8.89 2.02	1.72 0.49	76.1 5.8
1	R.P.	45	M	75	12	II	negative	1.48	3.02	51.72	14.88	71.23	16.78	2.88	82.8
2	G.W.	33	M	74	21	II	negative	1.50	6.18	29.85	13.65	54.27	1.32	0.15	88.6
3	F.D.	62	M	72	24	I	negative	0.38	0.96	39.18	3.96	89.89	-	0.00	100.0
4	A.W.	35	M	76	21	I	negative	0.34	0.60	53.85	32.13	40.33	-	0.43	-
5	D.A.	29	M	67	15	IV	negative	0.96	2.09	43.00	26.01*	39.51	-	1.48	-
6	J.I.	47	M	60	18	I	negative	0.48	1.13	43.65	10.02	77.04	7.10	0.40	94.3

CONTINUED OVERLEAF

TABLE V CONTINUED

								INSULIN TEST		PENTAGASTRIN TEST			SPONTANEOUS		
7	E.L.	43	M	61	18	I	negative	0.24	0.70	35.70	6.15	82.77	3.86	0.00	100.
8	B.S.	33	M	56	13	IV	negative	3.68	10.22	37.02	16.77	54.70	10.26	4.61	55.
9	P.S.	34	M	66	14	II	negative	2.52	6.73	38.16	17.08	55.30	2.80	2.59	7.
0	P.A.	21	F	57	18	III	negative	2.04	8.31	26.88	15.63	41.74	4.70	1.27	72.
1	F.C.	34	M	84	14	I	negative	5.90	9.59	64.14	41.76*	34.89	9.22	2.20	76.
2	K.B.	37	M	67	15	II	negative	1.22	3.35	38.10	6.24	83.62	5.32	0.00	100.
3	J.T.	58	M	82	15	I	negative	0.00	0.00	59.25	14.40	75.70	5.82	0.00	100.
4	N.K.	49	M	63	12	I	negative	2.14	2.95	69.42	28.62	58.77	24.40	1.50	93.
5	L.B.	63	F	51	12	II	negative	0.28	0.74	(37.78)	-	-	-	0.69	-
5 NEGATIVE MEAN ±1SE		41.53		67.40	16.13		negative	1.55 = 3.59% mEq/hr ±	±	44.99 (14)	17.66 (14)	61.41 (14)	8.33 (11)	1.22 (15)	80.9 (12)
		3.20		2.50	0.96			0.41	0.85	3.42	2.90	4.95	2.05	0.35	7.7
TOTAL:										(33)	(33)	(33)	(31)	(31)	(31)
5 TESTS 1 YEAR MEAN ± 1SE		43.20 ±		65.43 ±	15.83 ±			3.74 = 9.72% mEq/hr ±	±	41.39 ±	19.44 ±	52.45 ±	8.75 ±	1.62 ±	75.9 ±
		2.00		2.06	0.57			0.62	1.57	2.17	1.73	3.36	1.22	0.25	3.9

PAO^{PG}: peak-20-minute acid output x 3 (but peak-30-min. output x 2 was used to calculate PAO^{PG}, when PAO^{I} was expressed as a percentage of PAO^{PG}).

* signifies that the pentagastrin test was done immediately after the insulin test.

‡ test performed 11 months after HSV.

( ) figure in brackets is the 15-minute period after insulin in which the test became positive by Hollander's criteria.

B, before HSV. A, after HSV.

TABLE VI

COMPARISON OF RESULTS OF INSULIN TESTS AFTER HSV IN LEEDS (WITHOUT ANTRAL MAPPING) WITH THOSE AFTER "PARIETAL CELL" VAGOTOMY (PCV) IN COPENHAGEN (WITH ANTRAL MAPPING)

	COPENHAGEN PATIENTS > 6 MONTHS AFTER PCV	LEEDS PATIENTS > 1 YEAR AFTER HSV
NUMBER =	32	35
INSULIN-POSITIVE (Hollander's criteria)	15 = 47%	20 = 57%
EARLY-POSITIVE (in first hour)	7 = 22%	8 = 23%
MEAN PAO^{I} (mEq per hour)	4.27 ± 1.06	3.74 ± 0.62
MEAN PH^{I} (mEq per hour)	3.51 ± 0.89	3.07 ± 0.55

Titration was to pH 7 in both cities

PAO^{I} = peak-30-minute acid output x 2

PH^{I} = peak-hour acid output after insulin

(unpublished data, courtesy of Professor Erik Amdrup, University of Aarhus, Denmark - formerly at Surg. Dept. I, Kommunehospitalet, Copenhagen)

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CHAPTER 5

THE INSULIN TEST AFTER HIGHLY SELECTIVE VAGOTOMY

PART II: ON THE SIGNIFICANT INCREASE IN SPONTANEOUS, MAXIMAL, AND INSULIN-STIMULATED ACID OUTPUTS DURING THE FIRST 1 - 2 YEARS AFTER HSV

In this section, we attempt to answer three main questions. Firstly, does gastric acid output increase significantly in the course of the first one to two years after HSV? Secondly, if it does increase, why does it increase? And thirdly, what is the significance of the increase with respect to recurrent ulceration? These questions have received passing attention in the preceding pages, but it is felt that the question of vagal re-innervation of the stomach after HSV is so important that a separate section should be devoted to it.

METHODS

These have been described in preceding Chapters.

RESULTS

Spontaneous acid output (BAO) In paired tests on the same 17 patients, 3 months and 12 - 24 months after HSV, BAO increased significantly

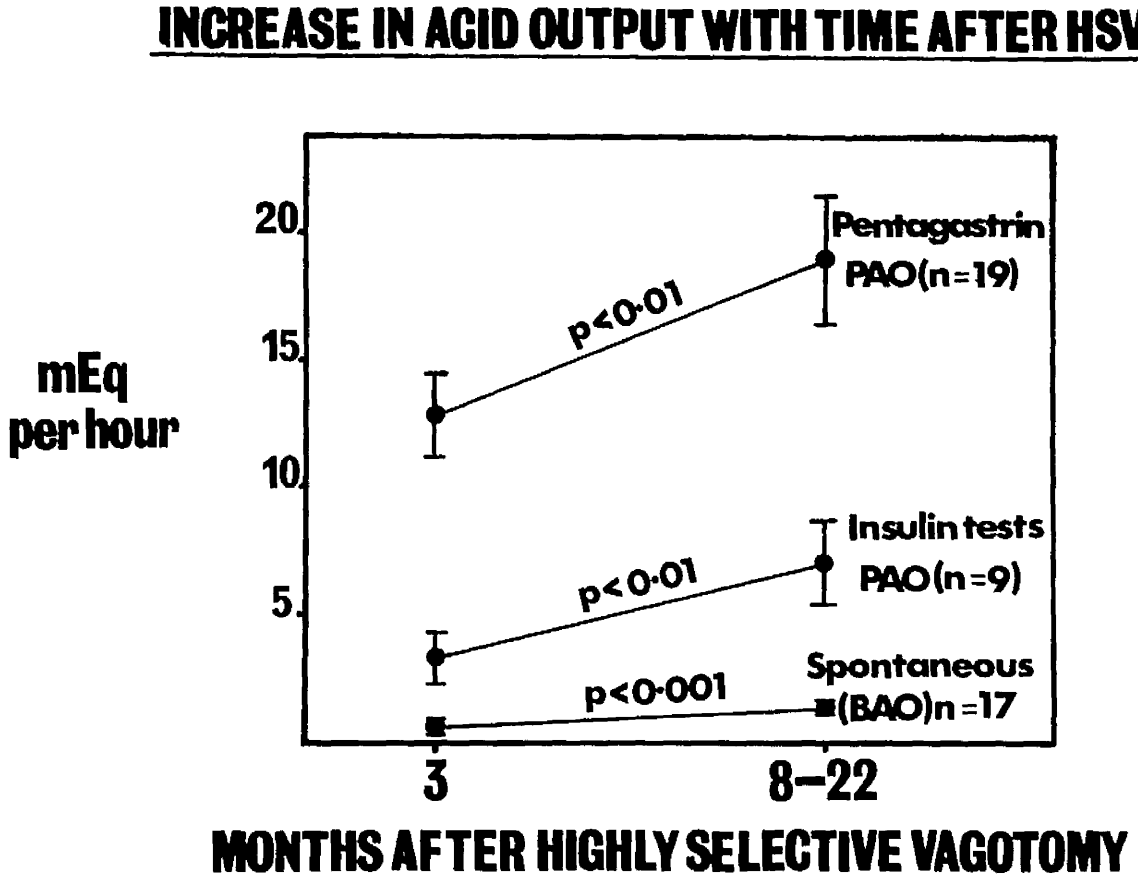

Fig. 1 These are mean acid outputs (± 1 SE) in paired tests on the same patients, 3 months and 8 to 22 months after HSV. Significant increases were found in spontaneous acid output and in the acid responses to insulin and to pentagastrin.

($p < 0.001$), from a mean of 0.6 mEq per hour to 1.4 mEq per hour (Table I, Fig. 1). However, even at the time of the second test, free acid was absent in 7 of the 17 tests.

Pentagastrin-stimulated maximal acid output (PAO^{PG}) In 19 paired tests, mean PAO^{PG} increased from 12.9 to 19.0 mEq per hour, a statistically significant increase ($p < 0.01$, Table II, Fig. 1).

Acid output in response to insulin (PAO^{I}) In 9 paired tests, PAO^{I} increased from a mean of 3.2 mEq per hour, 3 to 6 months after HSV, to 7.0 mEq per hour 12 to 24 months after HSV ($p < 0.01$, Table III, Fig. 1).

DISCUSSION

The significant increase in acid output Clearly, the answer to the first question is that acid output does increase significantly in the course of the first one to two years after HSV. The serial tests of MAO suggest that most of the increase is over by about 10 months after HSV, because MAO increased significantly between 3 and 10 months, and beyond one year no further increase was found. However, only 7 patients were tested first at 6 to 12 months, and again at 12 to 24 months, and further serial testing of MAO is desirable. The data on BAO and PAO^{I} (Tables I and III) certainly do not permit a conclusion that spontaneous and

insulin-stimulated acid outputs have stopped increasing 2 years after HSV, and further studies at 3 and 4 years will be required. However, as was mentioned earlier, Amdrup performed insulin tests on 14 patients 6 to 12 months after HSV in Copenhagen, and on 18 (different) patients 12 to 24 months after HSV, and found that mean acid output in the latter group was no higher than in the former group. Thus, it seems likely that the major increase in gastric secretion takes place during the first year after HSV, and that any subsequent increase will be small.

Reason for the increase One must next ask why secretion increased. Hypersensitivity of denervated parietal cells to circulating humoral stimuli is one possibility[1], but it seems an unlikely one, for two reasons. Firstly, it was shown by Murray and Thompson[2] that hypersensitivity was at a peak two to three weeks after denervation and declined with subsequent reinnervation. Similarly, Muren[3] showed that hypersensitivity in the stomach after vagotomy was maximal within the first month and subsequently declined. Thus, the fact that the significant increase in gastric secretion took place between 3 and 15 months after HSV casts doubt on the hypothesis that hypersensitivity is the cause of the increase. The second objection to the "hypersensitivity" hypothesis is provided by the observation that more pentagastrin, not less, is

needed to elicit MAO after truncal vagotomy[4], which denervates the parietal cell mass (PCM) as effectively as HSV does.

Another possible explanation for the increase is that more gastrin may have been released in response to the stimulus of insulin hypoglycaemia[5] in the later tests than in those which were performed 3 to 6 months after HSV. Yet significant increases in acid output were found not merely in the insulin tests, but also in the pentagastrin tests and in the measurements of BAO. If there was a common cause for the increase, it is unlikely to have been increased levels of endogenous gastrin in the later series of tests, because in such circumstances acid output in response to the "maximal" doses of exogenous pentagastrin would not have increased. Another point against the idea that increased gastrin release was the cause of the rise in acid output is that gastric emptying was not defective three months after HSV, as judged clinically and by gastric intubation studies carried out at that time. This suggests that the vagal nerve supply to the antral region was functioning well at three months, and hence that vagally-mediated release of gastrin was probably as effective then as one year later. Unfortunately, we have been unable to obtain measurements of plasma gastrin concentrations after HSV, which would have been of great interest in this context.

It seems to us that the most obvious explanation for the increasing acid outputs during the first year after HSV is also the most convincing; namely, that some degree of vagal re-innervation of the PCM takes place. The fact that only 3 of 100 insulin tests were positive by Hollander's criteria in the early post-operative period, compared with 20 of 35 fifteen months later, lends weight to this suggestion. Moreover, in the paired tests at 3 and 15 months after HSV, the greatest percentage increases in acid output were found in the responses to the insulin test, which is the recognized test for integrity of the gastric vagal fibres. Where and how vagal re-innervation of the stomach might have taken place is not clear. Regenerating vagal fibres could have re-grown down the oesophagus or entered the lesser curvature, while "sprouting" of intact vagal fibres[2,6] in the antral region might have produced re-innervation of the distal part of the PCM. It has been shown by Murray and Thompson[6] that if 90 per cent of the preganglionic sympathetic supply to an organ is cut, the remaining intact nerve fibres sprout new fibres which grow out to connect up with the denervated effector organ. Recovery of function in these circumstances may be complete within one to two months. The vagus nerve was also shown to be capable of sprouting. If only 1 per cent of an organ's nerve supply was left intact, the process of reinnervation was prolonged for many

months and recovery offunction was far from complete for up to one year after operation.

"Sprouting" from intact nerve fibres might thus provide a plausible explanation for the increase in acid output which took place between 3 and 15 months after HSV, because the distal quarter or so of the stomach is deliberately left innervated at the time of operation. By contrast, since the entire stomach is vagally denervated by truncal or selective vagotomy (TV, SV), sprouting is a much less likely explanation for any increase in acid output which might take place after these types of vagotomy. Yet, we have found (Part III) that both mean PAO^{I} and the incidence of Hollander-positive responses were similar in patients who were tested more than one year after TV+P or SV+P, to those which were found after HSV. This suggests that there may be a cause for the change in the insulin response that is common to patients after all three types of vagotomy. If there is a common cause, it is less likely to be nerve sprouting, and could well be nerve regeneration of the classical type, with new nerve fibres growing from the central stump to reach effector organs in the stomach. These considerations are of course in the realm of hypothesis, and it must be admitted that although there is a good deal of evidence that the PCM acquires some measure of vagal reinnervation after HSV, we do

not know precisely how the reinnervation is brought about.

Our finding of increasing acid outputs during the first year after HSV in man is at variance with the findings of Griffith and his colleagues[7-9], who performed deliberately-incomplete vagotomy in rats and dogs, and looked for evidence of vagal reinnervation as time passed, by two separate methods. The first was to map the area of innervated gastric mucosa by the intravenous injection of the dye, neutral red, which was secreted from innervated, but not from denervated, gastric mucosa. The second method was to measure gastric acid output, and to record the severity of the ulceration produced by ligation of the duodenum, at varying intervals after vagotomy. Neither method yielded evidence of significant vagal re-innervation of the stomach, in observations extending for 12 to 15 months after partial gastric vagotomy. Similar conclusions were reached by Spencer and Stening[10], who performed incomplete vagotomy in dogs equipped with fistulas of the whole stomach. They found that acid outputs in response to histamine and insulin did not increase significantly during the 6 months after operation. We are unable to explain the difference between our findings in man, and those of other workers in animals. Perhaps the difference in the species studied was the crucial factor. It should be noted that our findings are not in

disagreement with those of Bell[11]. Although he found no significant increase in the augmented histamine response in the course of the first three years after TV in man, whereas we observed a significant increase in the response to pentagastrin after HSV, Bell used as his "baseline" the measurement of MAO obtained one week after operation, whereas our "baseline" measurement was that made 3 months after operation. If MAO one week after HSV is compared with MAO in the same patients 15 months later, no significant difference is found (Table I , Chapter 4, PART II).

Clinical significance of the increase in acid output At present, it is not clear what these increases in acid output mean in terms of recurrent ulceration. Although they are statistically significant, they might be unimportant clinically. On the other hand, they might be the harbingers of recurrent ulceration. It is impossible to tell at the moment. Certainly, the large increases in MAO which were recorded in patients No. 13 and 17, for example, (Table II) are disquieting, and must surely be associated with an increased risk of recurrent ulceration. However, it seems likely that, in most patients, reinnervation (if that is the correct explanation) affects only a small proportion of the PCM, because even more than one year after HSV, the mean reductions in BAO (76 per cent) and MAO (52 per cent) are little different from those

recorded in patients after TV or SV with drainage. In addition, the mean peak acid response to insulin (PAO^{I}) increased to a level that was only 10 per cent of the pre-operative PAO^{PG}, whereas before operation the mean PAO^{I} elicited from the vagally-innervated PCM was 75 per cent of PAO^{PG}.

The similarity of the mean acid outputs (PAO^{PG} and PAO^{I}) after TV, SV and HSV described in Part III, could be explained on the basis that vagal reinnervation also takes place after TV and SV, particularly since we now know that 50 per cent or more of the insulin responses eventually become positive after TV or SV. If this line of reasoning is correct, it would suggest that the risk of recurrent ulceration might not be greater after HSV than after TV or SV. The risk of recurrence would be low, if the surgeon was a good vagotomist, as proved by the results of the insulin test in the early post-operative period, whereas the risk would be great if a high incidence of positive responses to insulin, particularly of early-positive responses, were to be found at that time. So far, no patient has developed a recurrent ulcer after HSV, and no correlation has been found between the results of tests of gastric secretion and the clinical status of the patients. Both the patients who came to re-operation on account of suspected recurrent ulceration had negative insulin tests on repeated testing. The lack of

recurrent ulceration after HSV may already be of clinical significance, despite the short period of follow-up (maximum, 39 months, mean, 19 months), because recurrent ulceration after TV or SV plus drainage is characteristically early, presumably because the ulcer is left in situ, and if a suitable change in its environment has not been achieved, it either does not heal at all, or else it recurs within a year or two. That said, there can be no substitute for a careful 5-to 10-year clinical follow-up, and the optimism engendered by the good clinical results achieved so far must still be tempered with caution about the outlook in the long term.

Table I

SPONTANEOUS ACID OUTPUT (BAO) - mEq per hour

No.	PATIENT	titration FREE BAO (to pH 3.5) (1) at 3 MONTHS	(2) at 12-24 MONTHS	(2) - (1) +	(2) - (1) -	BAO (to pH 7) (1) at 3 MONTHS	(2) at 12-24 MONTHS	(2) - (1) +	(2) - (1) -
1	R.R.	0	1.08	1.08		0.27	1.36	1.09	
2	R.P.	0	1.63	1.63		0.20	2.04	1.84	
3	G.W.	0	0	=		0	0.15	0.15	
4	G.M.	0	0	=		0	1.04	1.04	
5	F.D.	0	0	=		0.04	0	=	
6	A.W.	0	0	=		0	0.43	0.43	
7	D.A.	0.42	0.52	0.10		1.68	1.43		0.25
8	F.A.	0.38	0.90	0.52		0.78	1.92	1.14	
9	J.I.	0.42	0.10		0.32	1.12	0.56		0.56
10	E.L.	0	0	=		0.14	0.13	=	
11	P.S.	2.54	2.21		0.33	1.57	2.86	1.29	
12	H.H.	0	0	=		0	0.31	0.31	
13	F.W.	0	1.55	1.55		0.19	2.11	1.92	
14	A.T.	1.60	2.88	1.28		1.93	3.47	1.49	
15	C.C.	0	0.44	0.44		0	1.15	1.15	
16	M.B.	0	0	=		0	1.00	1.00	
17	N.K.	1.96	2.26	0.30		2.76	3.26	0.50	
MEAN		0.43	0.80	0.365		0.63	1.37	0.738	
± 1 S.E.M.		±0.18	±0.22	±0.150		±0.21	±0.27	± SE 0.177	
				t = 2.433				t = 4.169	
				p < 0.05 > 0.02				n = 17	
								p < 0.001	

Table II

PENTAGASTRIN-STIMULATED MAXIMAL ACID OUTPUT

No.	PATIENT	PEAK ACID OUTPUT (peaks-20-min. x 3) mEq/hr				TOTAL-HOUR ACID OUTPUT mEq/hr			
		(1) at 3 MONTHS	(2) at 6 - 12 MONTHS	(2) - (1) +	(2) - (1) -	(1) at 3 MONTHS	(2) at 6 - 12 MONTHS	(2) - (1) +	(2) - (1) -
1	R.R.	12.99	19.71	6.72		9.96	16.31	6.35	
2	R.P.	17.91	14.64		3.27	14.33	11.15		3.18
3	F.D.	1.65	3.42	1.77		1.07	2.19	1.12	
4	A.W.	18.18	29.73	11.55		12.28	23.55	11.27	
5	D.A.	20.31	26.61	6.30		15.35	21.35	6.00	
6	F.A.	5.13	15.36	10.23		4.16	11.91	7.75	
7	A.D.	23.37	18.00		5.37	17.84	15.03		2.81
8	H.H.	9.66	19.50	9.84		5.33	14.35	9.02	
9	C.C.	5.58	12.93	7.35		3.87	10.24	6.37	
10	J.D.	2.49	3.84	1.35		1.83	2.76	0.93	
11	F.N.	11.34	14.94	3.60		8.58	11.98	3.40	
12	G.W.	11.13	13.65	2.52		8.28	11.02	2.74	
13	G.M.	17.37	37.38	20.01		12.25	29.13	16.88	
Mean of 13		12.09	17.67	5.585		8.86	13.92	5.065	
± 1 S.E.M.		± 1.92	± 2.03	± 1.848		± 1.49	± 2.10	± 1.553	
				t = 3.022				t = 3.261	
				p < 0.02				p < 0.01	
		at 3 MONTHS	at 12-24 MONTHS			at 3 MONTHS	at 12-24 MONTHS		
14	J.I.	8.40	10.02	1.62		6.97	7.07	0.10	
15	E.L.	3.00	6.15	3.15		2.03	3.84	1.81	
16	P.S.	21.66	17.08		4.58	18.17	16.10		2.07
17	S.G.	24.00	46.86	22.86		17.01	31.87	14.86	
18	F.W.	8.25	24.54	16.29		7.12	18.90	11.78	
19	A.T.	21.75	26.22	4.47		19.58	20.99	1.41	
MEAN of 19		12.85	18.98	6.127		9.79	14.72	4.933	
± 1 S.E.M.		± 1.73	± 2.54	± 1.766		± 1.38	± 1.89	± 1.342	
				t = 3.469				t = 3.676	
				p < 0.01				p < 0.01	

Table III

PAIRED INSULIN TESTS IN THE SAME PATIENTS

(1) 3 - 6, (2) 12 - 24 months after HSV

NO.	PATIENT	PAO^I = peak-30-minute acid output x 2 = mEq/hr (1) 3 - 6 MONTHS MONTH	RESULT	PAO^I mEq/hr	(2) 12 - 24 MONTHS MONTH	RESULT	PAO^I mEq/hr	(2) - (1) mEq/hr.
1	R.R.	3	E+	1.44	22	E+	2.52	1.08
2	F.W.	4	E+	2.08	15	E+	4.32	2.24
3	A.T.	5	L+	5.54	15	L+	10.50	4.96
4	M.B.	3	-ve	0.12	14	L+	2.08	1.96
5	N.K.	5	-ve	0.00	18	-ve	2.14	2.14
6	H.H.	3	-ve	0.38	22	L+	4.60	4.22
7	S.M.*	3	E+	7.50	13	E+	10.36	2.86
8	H.S.‡	6	E+	3.08	12	E+	9.30	6.22
9	E.W.‡	3	E+	8.68	21	L+	17.18	8.50
MEAN (9)		3.89		3.20	16.89		7.00	3.80
± 1 SE		±0.39		±1.09	± 1.32		± 1.72	±0.80
								t = 4.75
								p < 0.01

SM* had HSV + a small (70g) segmental gastric resection. He was one of the first patients to be treated by HSV.

‡ HS and EW were hypersecretors, with dyspepsia and giant mucosal folds in the duodenum, but no definite duodenal ulcer at operation. Both were treated by HSV. E+, early-positive, L+, late-positive.

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CHAPTER 5

THE INSULIN TEST AFTER HIGHLY SELECTIVE VAGOTOMY

PART III: COMPARISON OF GASTRIC ACID OUTPUTS IN RESPONSE TO INSULIN IN HEALTHY PATIENTS MORE THAN ONE YEAR AFTER TRUNCAL, SELECTIVE OR HIGHLY SELECTIVE VAGOTOMY

A review of the literature (see Part I) and our own data, indicate that the incidence of (Hollander+) positive responses to insulin is no less than 50 to 60 per cent, more than one year after each of the three types of vagotomy. It would be of great interest however to know whether the actual acid outputs were also equal after the three types of vagotomy. Accordingly, acid outputs in response to insulin were compared in patients who were in good health, more than one year after TV, SV, or HSV. The operations had all been performed in the University Department of Surgery in Leeds, and completeness of the vagotomy had been demonstrated by the finding of a negative response to insulin in the early post-operative period.

METHOD

The method of insulin testing has been described. Acid outputs are expressed as PAO^{I}, the output in the peak-30-minute period after insulin, multiplied by two: and as PH^{I}, the output in the peak hour after insulin.

RESULTS

HSV patients (Table V, p 160) Mean PAO^I in 35 patients was 3.74 ± 0.62 mEq per hour.

Patients after truncal vagotomy and pyloroplasty Mean PAO^I in 23 patients was 3.14 ± 0.79 mEq per hour. Results in one patient whose PAO^I was 42.5 mEq per hour were excluded when the mean figure was calculated (Table I).

Patients after selective vagotomy and pyloroplasty Mean PAO^I in 16 patients was 3.50 ± 1.10 mEq per hour (Table II).

The comparison of PAO^I in the three groups of patients is summarized in Table III.

DISCUSSION

In making these comparisons of insulin-stimulated acid outputs more than one year after vagotomy, we tried to avoid any suggestion of bias in favour of HSV, by excluding patients who were known to be in Visick grade IV after TV+P or SV+P (though two such patients after HSV were included), and also by excluding patients who had evidence of incomplete vagotomy on the early post-operative insulin test. Thus, the Visick status of the HSV patients was representative of the group as a whole, whereas the Visick status of

patients after TV+P and SV+P was rather better than that of the group from which they were selected. The ages, weights and pre-operative MAOs of the patients in the three groups were fairly similar, patients after TV+P tending to be slightly older and heavier. Patients after TV+P also had a higher proportion of negative insulin tests than had patients in the other two groups. A prominent difference between the groups, however, is that HSV patients had their insulin tests performed on average 16 months after operation, whereas after TV+P and SV+P the tests were done, on average, 35 months after operation. This could have biased the results in favour of HSV, if acid outputs are still increasing between 16 and 24 months after HSV. However, as stated previously, there is reason to believe that the major increase in secretion has ceased by one year after HSV.

No significant difference was found between the acid outputs in response to insulin more than one year after HSV, TV+P or SV+P (Table III). It could be argued that with perfect matching of the three groups, significant differences might have emerged, but it seems very unlikely. HSV seems to vagally-denervate the parietal cell mass as effectively as TV+P or SV+P, at least for up to two years after operation.

SUMMARY

Insulin-stimulated acid outputs were compared in patients who were in good health, more than one year after HSV, TV+P or SV+P. No significant differences between the acid outputs in the three groups of patients were found.

Table I

ACID OUTPUTS IN RESPONSE TO INSULIN IN HEALTHY PATIENTS
MORE THAN ONE YEAR AFTER TRUNCAL VAGOTOMY AND PYLOROPLASTY

NO.	NAME	AGE YRS.	SEX	WEIGHT KG.	MONTHS POST-OP.	PRE-OP. PAO^{PG} mEq/hr	VISICK GRADE	INSULIN TEST RESULT at > 1 yr.	PAO^{I} mEq/hr	PH^{I} mEq/hr
1*	B.M.	46	M	80	24	39.15	I	E+	42.48	38.24
2	J.W.	48	M	83	35	49.98	I	E+	2.78	2.68
3	B.W.	24	M	64	13		I	E+	13.62	12.95
4	J.D.	58	M	63	24	44.79	I	E+	12.30	11.27
Mean of 4 Early +ve		44.0		72.5	24.0	44.64		EARLY POSITIVE	17.79	16.29
Mean of 3, excluding patient No. 1									(9.57)	(8.97)
5	J.B.	54	M	54	24	53.28	III	L+	2.54	2.36
6	S.W.	58	M	83	29		II	L+	8.24	7.80
7	C.R.	46	M	63	33	52.65	I	L+	4.48	3.27
8	T.R.	64	M	67	12	44.13	I	L+	0.98	0.81
9	W.B.	57	M	66	32	26.91	I	L+	1.88	1.18
10	P.D.	57	M	85	16	47.22	II	L+	2.90	2.30
11	D.L.	37	M	70	22		II	L+	1.98	1.52
12	T.M.	54	M	59	30	53.19	I	L+	7.82	6.31

13	G.T.	43	M	63	48		II	L+	2.60	2.51
Mean of 9 Late +ve		52.22		67.78	27.33	46.23 (m. of 6)		LATE POSITIVE	3.71	3.12
± 1 SE		2.84		3.44	3.52	4.16			0.87	0.79
14	J.G.	42	M	64	72[1]	42.00	I	-ve	3.32	2.88
15	G.M.	42	M	64	36		III	-ve	0.18	0.12
16	G.B.	30	M	74	35	52.14	I	-ve	0.10	0.07
17	S.R.	47	M	74	16	45.12	II	-ve	1.04	0.56
18	T.Y.	51	M	69	17		I	-ve	0.12	0.09
19	H.T.	73	M	73	18	63.43	II	-ve	0.82	0.62
20	J.G.	55	M	85	36	30.16	II	-ve	0.0	0.0
21	K.T.	35	M	70	13	52.95	II	-ve	0.37	0.36
22	F.H.	56	M	68	17		III	-ve	0.90	0.64
23	F.B.	46	M	78	30	32.58	II	-ve	2.28	1.99
24	W.J.	36	M	62	16	30.54	I	-ve	1.06	0.84
Mean of 11 negative		46.64		71.00	23.40	43.62 (8)		NEGATIVE	0.93	0.74
± 1 SE		3.62		2.04	3.02	4.29			0.31	0.27
MEAN OF 23		48.29		70.04	25.04	44.72 (m. of 17)	12 I 9 II 3 III	3 E+ 9 L+ 11 -ve	* 3.14 0.79	* 2.75 0.74
± 1 SE		2.28		1.76	2.01	2.45				

* Acid outputs of patient No. 1 were omitted from the calculation of the mean, because his results were so divergent from all the rest.

1 Excluded from calculation of the mean.

Table II

ACID OUTPUTS IN RESPONSE TO INSULIN IN HEALTHY PATIENTS
MORE THAN ONE YEAR AFTER BILATERAL SELECTIVE VAGOTOMY AND PYLOROPLASTY

NO.	NAME	AGE YRS.	SEX	WEIGHT KG.	MONTHS POST-OP.	PAO^{PG} PRE-OP.	VISICK GRADE	INSULIN TEST RESULT at > 1 yr.	PAO^{I} mEq/hr	PH^{I} mEq/hr
1	K.C.	44	M	69	30	25.77	I	E+	3.57	3.38
2	J.H.	61	M	70	14	42.50	II	E+	4.20	3.80
3	A.B.	39	F	58	18	34.50	II	E+	6.06	5.22
Mean of 3 Early +ve		48.00		65.67	20.67	34.26		Early-positive	4.61	4.13
4	A.S.	16	M	64	19	48.80	I	L+	9.00	6.35
5	M.S.	47	M	67	47	48.08	II	L+	1.76	1.37
6	A.G.	69	M	60	14	40.20	I	L+	0.52	0.48
7	G.M.	40	M	61	21	44.00	III	L+	0.50	0.25
8	T.M.	31	M	74	24	35.07	III	L+	5.14	3.44
9	R.K.	46	M	62	17	53.49	III	L+	15.36	13.68
10	H.D.	48	M	63	12	29.00	II	L+	0.82	0.76
Mean of 7 Late +ve		42.43 ± 6.18		64.43 ± 1.81	22.00 ± 4.44	42.66 ± 3.22		Late-positive	4.73 ± 2.13	3.76 ± 1.85

11	J.B.	43	M	69	36	71.00	III	-ve	8.30	7.15
12	C.H.	46	M	70	48	N.D.	II	-ve	0.00	0.00
13	H.Y.	53	M	57	48	N.D.	I	-ve	0.00	0.00
14	C.E.	47	F	57	12	19.80	III	-ve	0.10	0.09
15	T.C.	46	M	54	12	36.50	I	-ve	0.16	0.10
16	M.C.	33	M	68	20	48.04	I	-ve	0.44	0.40
Mean of 6 Negative		44.67 ± 2.69		62.50 ± 2.95	29.33 ± 6.90	43.84 ±10.75		Negative	1.50 ± 1.36	1.29 ± 1.17
MEAN of 16		44.31	14M 2F	63.94	24.50	41.20	7 I 4 II 5 III	3 E+ 7 L+ 6 -ve	3.50	2.91
± 1 SE		3.00		1.46	3.31	3.44			1.10	0.94

Table III

COMPARISON OF PEAK ACID OUTPUTS IN RESPONSE TO INSULIN (PAO^{I}) MORE THAN ONE YEAR AFTER TRUNCAL, SELECTIVE OR HIGHLY SELECTIVE VAGOTOMY, IN HEALTHY PATIENTS

(figures are arithmetic means)

OPERATION	NO. OF PATIENTS	AGE YRS.	WEIGHT KG.	MONTHS POST-OP.	PRE-OP. PAO^{PG} mEq/hr.	VISICK GRADE	RESULT OF INSULIN TEST at 1 week	RESULT OF INSULIN TEST at > 1 year	PAO^{I} > 1 yr mEq/hr.
HSV	35	43.2	65.4	15.8	41.4	19 I 10 II 4 III 2 IV	-ve	8 Early +ve 12 Late +ve 15 negative	3.74 ± 0.62
TRUNCAL V + P	23	48.3	70.0	25.0	44.7*	11 I 9 II 3 III	-ve	3 Early +ve 9 Late +ve 11 negative	3.14 ± 0.79
SELECTIVE V + P	16	44.3	63.9	24.5	41.2	7 I 5 II 4 III	-ve	3 Early +ve 7 Late +ve 6 negative	3.50 ± 1.10

* data incomplete

Details for individual patients and the standard errors of the means are to be found in Tables I and II (this section), and in Table V, p

CHAPTER 5

THE INSULIN TEST AFTER HIGHLY SELECTIVE VAGOTOMY

PART IV: COMPARISON OF SPONTANEOUS, MAXIMAL AND INSULIN-STIMULATED ACID OUTPUTS, IN TWO GROUPS OF PATIENTS WITH HOLLANDER -POSITIVE INSULIN TESTS: GROUP I, MORE THAN ONE YEAR AFTER HSV, GROUP II, WITH RECURRENT ULCERATION AFTER TRUNCAL OR SELECTIVE VAGOTOMY WITH PYLOROPLASTY

Most patients with recurrent duodenal ulcer after TV+P or SV+P have (Hollander-) positive insulin tests[1,2], but most patients with positive insulin tests do not develop recurrent ulcer. More than 50 per cent of patients after TV, SV or HSV eventually develop positive responses to insulin[3-6], but only 5 to 10 per cent develop recurrent ulceration[7]. Thus, the concept of incomplete, but adequate, vagotomy and of inadequate, incomplete vagotomy[8], appears to be valid.

For reasons stated previously, we think that a positive response to insulin after HSV probably means that part of the parietal cell mass has become re-innervated. That is, the vagotomy is incomplete. To try to assess whether the incomplete vagotomies which were demonstrated in over 50 per cent of patients after HSV are "adequate" to achieve permanent healing of the ulcer, or "inadequate",

we compared the positive responses to insulin which were recorded more than one year after operation in 20 HSV patients (Table I), with the positive responses to insulin which were recorded in patients with recurrent ulceration after TV+P or SV+P. It is recognized that a diagnosis of recurrent ulceration can be an extremely difficult one to make, even when the abdomen has been opened. However, a confident diagnosis of recurrent ulcer was indeed made at laparotomy in many of these patients (Tables II and III), and in the remainder the diagnosis was strongly suspected because of the occurrence of haematemesis, melaena, or because the patient complained of pain similar to that of his original ulcer. All these patients had been placed in Visick grade IV at the Gastric Follow-Up Clinic.

METHOD

Each patient underwent an insulin test, which in most cases was performed more than one year after operation. An intramuscular pentagastrin test was also carried out in most of the patients, usually on a separate day, but sometimes immediately after the insulin test. The pentagastrin response is expressed as PAO^{PG} (peak-20-minute output x 3) and the insulin response as PAO^{I} (peak-30-minute output x 2), in mEq per hour. 20 patients had positive insulin tests more

than one year after HSV. 25 patients were studied who had positive insulin tests and recurrent ulcer after TV+P, and 8 patients who had positive insulin tests and recurrent ulcer after SV+P.

RESULTS

Patients after HSV Eight had early-positive responses to insulin, and 12 had late-positive responses. Mean BAO was 1.7 ± 0.3 mEq per hour; mean PAO^{PG}, 20.8 ± 2.1 mEq per hour, and mean PAO^{I} 5.4 ± 0.9 mEq per hour (Table I).

Patients with recurrent ulcer after TV+P The insulin response was early-positive in 14 and late positive in 11. Mean BAO was 5.6 ± 0.6 mEq per hour; mean PAO^{PG}, 37.6 ± 2.4 mEq per hour, and mean PAO^{I} 15.7 ± 1.9 mEq per hour (Table II).

Patients with recurrent ulcer after SV+P The insulin response was early-positive in 6 and late-positive in 2. Mean BAO was 4.0 ± 0.3 mEq per hour, mean PAO^{PG}, 38.7 ± 4.1 mEq per hour and mean PAO^{I}, 17.9 ± 3.2 mEq per hour (Table III).

A summary of the data from Tables I - III is presented in Table IV. In Fig. 1, BAO and PAO^{I} for each patient are depicted.

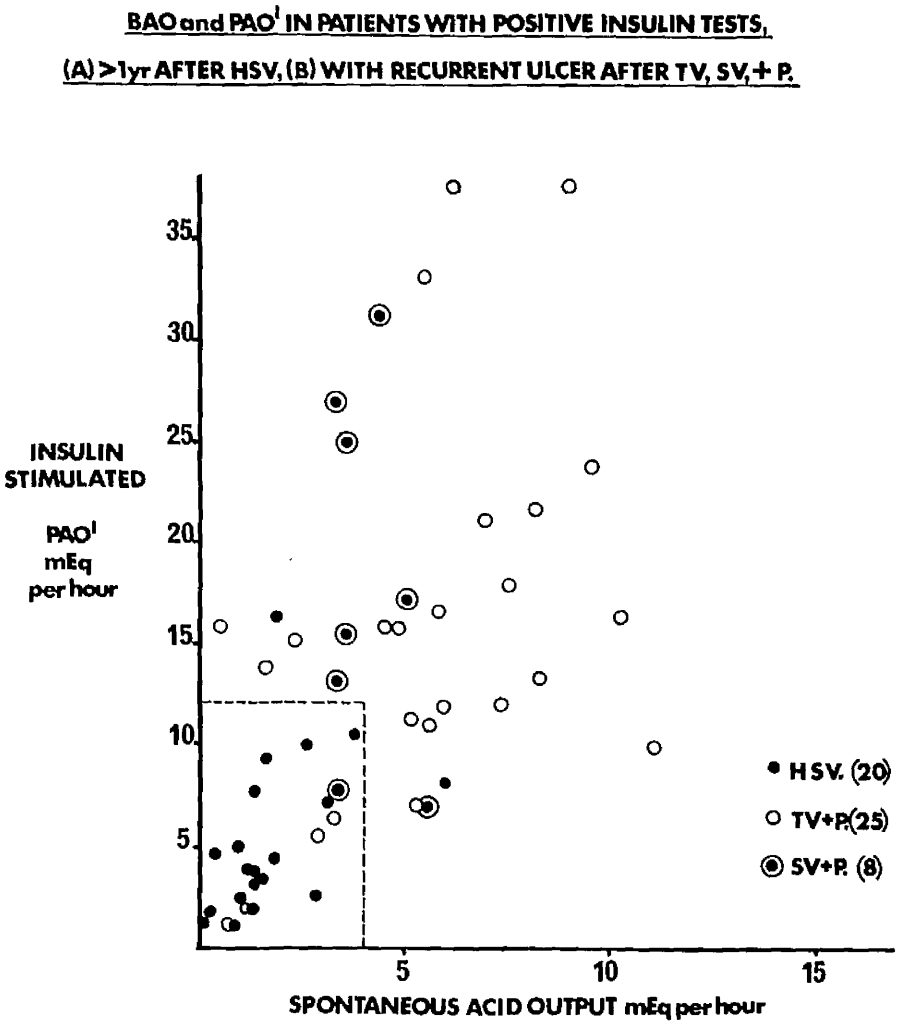

Fig. 1 Patients with positive insulin tests by Hollander's criteria after HSV (small black dots) have significantly lower acid outputs than patients with both positive insulin tests and recurrent ulceration after truncal or selective vagotomy with pyloroplasty.

Patients after HSV differed significantly from the patients with recurrent ulcer (Table V), in that their acid outputs were significantly lower ($p < 0.001$). As the dotted rectangle in Fig. 1 shows, an area can be defined which includes 18 of 20 HSV patients, but only 4 of 25 patients after TV+P and 1 of 8 patients after SV+P. Calculation of the product of BAO x PAO^{PG} x PAO^{I} did not improve further the discrimination between HSV patients and the patients with recurrent ulcer. PAO^{I} was greater than 10.5 mEq per hour in only 1 of 20 patients after HSV, but in 19 of 25 patients after TV+P ( )(^{2} = 6.82, $p < 0.01$), and in 6 of 8 patients after SV+P ( )(^{2} = 6.89, $p < 0.01$, comparing HSV with TV+SV combined). BAO was greater than 3.1 mEq per hour in 2 of 20 patients after HSV, in 19 of 25 patients after TV+P ( )(^{2} = 5.36, $p < 0.05$) and in all 8 patients after SV+P ( )(^{2} = 5.87, $p < 0.02$, HSV vs TV+SV). PAO^{PG} was greater than 30 mEq per hour in only 1 of 20 patients after HSV, but in 16 of 22 patients after TV+P ( )(^{2} = 6.55, $p < 0.02$) and in 6 of 8 patients after SV+P ( )(^{2} = 6.69, $p < 0.01$, HSV vs SV+TV).

DISCUSSION

In the preceding section, it was shown that PAO^{I} more than one year after HSV was very similar to the PAO^{I} of patients who were

in good health more than one year after TV+P or SV+P. In striking contrast, PAO^{I}, PAO^{PG} and BAO were all highly significantly lower in patients with positive insulin tests after HSV than in patients with positive insulin tests and recurrent ulcer after TV+P or SV+P. A few HSV patients, such as numbers 2, 7, 10 and 12 (Table I), certainly have alarmingly high acid outputs; but, as a group, the HSV patients have quite different characteristics of gastric secretion from those of patients with recurrent ulcer. Patients who have a BAO of less than 3 mEq per hour and a PAO^{I} of less than 10 mEq per hour more than one year after vagotomy would appear to run relatively little risk of recurrent ulceration, although they are not entirely immune from the threat of recurrence. It seems reasonable to conclude that all 15 patients who remained insulin-negative more than one year after HSV have had an adequate vagotomy, and that most of the 20 patients who were insulin-positive at that time have also had an adequate vagotomy.

Table I

SPONTANEOUS, MAXIMAL AND INSULIN-STIMULATED ACID OUTPUTS IN 20 PATIENTS WITH POSITIVE INSULIN TESTS MORE THAN ONE YEAR AFTER HSV

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS AFTER OP.	PAO^{PG} PRE-OP. mEq/hr	BAO mEq/hr	PAO^{PG} mEq/hr	PAO^{I} mEq/hr	RESPONSE TO INSULIN 1 yr. POST-OP. (HOLLANDER)	$\frac{PAO^{I}}{PAO^{PG}}$ POST-OP. %	PRODUCT OF BAO x PAO^{PG} x PAO^{I} (UNITS)
1	R.R.	50	M	81	20	31.80	2.76	15.18	2.52	early +ve	16.60	106
2	J.C.	22	M	52	24	37.44	1.92	23.61	16.34	"	69.21	741
3	A.D.	40	F	50	18	30.00	0.86	21.96	5.00	"	22.77	94
4	M.F.	48	F	41	14	18.27	1.28	13.50	3.82	"	28.30	66
5	F.W.	46	M	70	15	46.08	1.85	24.54	4.32	"	17.60	194
6	N.H.	66	M	54	12	70.77	1.32	26.70	7.68	"	28.76	271
7	W.C.	42	M	67	16	51.60	3.06	29.88	7.20	"	24.10	658
8	E.H.	56	F	52	16	27.69	0.77	18.00	1.14	"	6.33	16
8 EARLY POSITIVE	$M \pm 1$ SE	46.38		58.38	16.88	39.21	1.73	21.67	6.00		26.71%	268
		4.53		4.62	1.33	5.84	0.30	2.01	1.67		6.60	98
9	R.C.	40	M	80	16	36.60	1.55	10.35	9.30	late +ve	89.86	149
10	S.G.	27	M	75	12	56.04	5.97	46.86	8.10	"	17.29	2266
11	H.H.	40	F	48	22	28.53	0.31	19.50	4.60	"	23.59	28
12	A.T.	16	M	51	15	42.60	3.82	26.22	10.50	"	40.05	1052

13	F.N.	51	M	83	14	35.97	1.26	14.94	3.06	"	20.48	58
14	C.C.	53	M	75	15	38.10	1.15	12.93	3.94	"	30.47	59
15	W.B.	49	M	58	15	37.80	0.10	7.02	1.10	"	15.67	1
16	W.M.	47	M	60	15	45.63	1.24	27.36	1.98	"	7.24	67
17	J.S.	49	M	83	13	31.89	1.46	13.11	3.28	"	25.02	63
18	M.B.	41	F	51	14	39.09	1.00	28.40	2.08	"	7.32	59
19	J.D.	51	M	66	14	30.00	0.18	14.25	1.82	"	12.77	5
20	S.C.	51	M	82	12	(59.04)	2.64	-	9.94	"	-	-
12 LATE POSITIVE	M	42.92		67.67	14.75	38.39	1.72	20.09	4.98		26.34	346
	± 1 SE	3.24		3.92	0.75	2.34	0.49	3.44	1.01		7.00	212
MEAN OF 20		44.25		63.95	15.60	38.73	1.72	20.75	5.39		26.50%	313
± 1 SE		2.61		3.10	0.72	2.71	0.31	2.12	0.88		4.78	127

( ) No. 20 was excluded from the mean

The response to insulin was negative in each patient in the early post-operative period.

Table II

SPONTANEOUS, MAXIMAL, AND INSULIN-STIMULATED ACID OUTPUTS IN PATIENTS WITH POSITIVE INSULIN TESTS AND RECURRENT ULCERATION AFTER TRUNCAL VAGOTOMY AND DRAINAGE

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS AFTER OP.	RECURRENCE PROVED (P) OR SUSPECTED (S)	BAO mEq/hr	PAO^{PG} mEq/hr	PAO^{I} mEq/hr	RESPONSE TO INSULIN (HOLLANDER)	$\frac{PAO^{I}}{PAO^{PG}}$ % POST-OP.	PRODUCT OF BAO x PA x PAO^{I} (UNITS)
1	E.M.	41	M	81	5	P	7.59	41.28	17.78	early +ve	43.07	5571
2	J.R.	37	M	56	36	P	11.06	32.58	9.86	early +ve	30.26	3553
3	A.E.	63	M	65	20	P	6.23	43.48*	37.50	early +ve	86.25	10158
4	C.H.	29	M	66	14	S	4.87	34.47*	15.80	early +ve	45.84	2636
5	I.T.	44	F	67	7	S	4.57	47.07*	15.80	early +ve	33.57	3399
6	A.H.	31	M	74	20	S	2.85	28.11*	5.52	early +ve	19.64	442
7	S.H.	62	M	48	24	P	5.48	-	32.98	early +ve	-	-
8	B.L.	not recorded	F	54	8	P	8.24	55.59*	21.64	early +ve	38.93	9912
9	H.C.	34	M	70	24	S	9.04	58.92	37.48	early +ve	63.61	19963
10	D.C.	24	M	63	48	S	5.16	38.91	11.26	early +ve	28.94	2261
11	M.W.	27	M	80	17	S	1.60	36.54	13.94	early +ve	38.15	815
12	A.R.	73	M	51	3 yrs.	S	9.63	-	23.66	early +ve	-	-

13	N.W.	28	M	66	6	S	0.53	50.00	15.84	early +ve	31.68	420
14	J.M.	36	M	not recorded	17	P	6.99	ND	21.08	early +ve	-	-
14 EARLY-POSITIVE MEAN ± 1SEM		40.69 ± 4.34		64.69 ± 2.87	20.14 ± 3.41		5.99 ±0.81	42.45 ± 2.92	20.01 ± 2.65		41.81% ± 5.60(11)	5375 ±1785
15	A.P.	[illegible]	M	72	37	P	2.28	30.36	15.24	late +ve	50.20	1055
16	A.R.	28	M	53	36	S	5.40	31.26*	6.98	late +ve	22.33	1178
17	H.J.	66	M	38	(16yrs)	S	10.28	-	16.28	late +ve	-	-
18	J.R.	44	M	62	49	P	0.72	20.43*	1.14	late +ve	5.58	17
19	E.H.	51	M	73	64	P	8.26	39.30*	13.28	late +ve	33.79	4311
20	P.S.	24	M	71	8	S	5.94	42.87*	16.48	late +ve	38.44	4197
21	D.D.	35	M	72	23	P	3.34	28.20*	6.38	late +ve	22.62	601
22	J.J.	42	M	64	36	P	7.37	46.26	12.00	late +ve	25.94	4091
23	W.B.	33	M	70	38	S	1.09	21.16*	1.94	late +ve	9.17	45
24	A.M.	38	M	78	24	S	5.64	44.80*	10.88	late +ve	24.29	2749
25	G.R.	not recorded	M	74	45	S	6.00	18.72*	11.90	late +ve	63.57	1337
11 LATE-POSITIVE MEAN ± 1SEM		41.10 ± 3.92		66.09 ± 3.49	36.00 ± 4.87		5.12 ±0.91	32.34 ± 3.30	10.23 ± 1.63		29.59% ± 5.59(10)	1958 ± 546 (1

	yrs.	kg.	months		BAO	PAO^{PG}	PAO^{I}			
MEAN OF 25	40.87	65.33	26.75		5.61	37.63	15.71		35.99%	3748
± 1 SEM	2.92	2.19	3.22		0.60	2.42	1.90		4.10	1022
	(23)	(24)	(24)		(25)	(21)	(25)		(21)	(21)

* PAO^{PG} measured immediately after the insulin test.

The drainage procedure was a pyloroplasty, in all except nos. 12, 14, 15, 17 and 25, in whom gastro-jejunostomy had been performed.

Records of pre-operative PAO^{PG} in these patients were inadequate.

TABLE II CONTINUED

Table III

SPONTANEOUS, MAXIMAL AND INSULIN-STIMULATED ACID OUTPUTS IN PATIENTS WITH POSITIVE INSULIN TESTS AND RECURRENT ULCERATION AFTER BILATERAL SELECTIVE VAGOTOMY AND PYLOROPLASTY

NO.	NAME	AGE YR.	SEX	WEIGHT KG.	MONTHS AFTER OP.	PAO^{PG} PRE-OP. mEq/hr	BAO mEq/hr	PAO^{PG} mEq/hr	PAO^{I} mEq/hr	RESPONSE TO INSULIN (HOLLANDER)	$\frac{PAO^{I}}{PAO^{PG}}$ POST-OP. %	PRODUCT OF BAO x PAO^{PG} x PAO^{I} (UNITS)
1	J.G.	43	M	75	21	30.80	3.60	42.00*	15.52	early +ve	36.95	2347
2	P.R.	25	M	80	20	46.40	3.39	20.50	13.14	"	64.10	913
3	L.T.	30	M	64	10	94.40	3.27	55.89	26.80	"	47.95	4898
4	B.M.	31	M	64	13	48.50	4.38	43.20*	31.20	"	72.22	5904
5	D.R.	33	M	66	60	52.00	3.61	40.65	24.94	"	61.35	3660
6	J.R.	45	M	70	46	59.00	3.36	37.05	7.74	"	20.89	964
7	I.C.	23	M	69	10	55.80	5.07	ND	17.16	late +ve	-	-
8	W.H.	51	M	65	54	53.00	5.61	31.83	6.94	"	21.80	1239
MEAN of 8		35.13		69.13	29.25	54.99	4.04	38.73	17.93		46.47%	2846
± 1 SEM		3.56		2.04	7.32	6.39	0.31	4.12	3.16		7.79	761

The diagnosis of recurrent ulcer was established at re-laparotomy in patients 1 - 6, and was strongly suspected in patients 7 and 8.

stimulus to secretion was intravenous histamine or pentagastrin and PAO^{PG} refers to peak-30-minute output, x 2.

The post-operative PAO^{PG} was elicited by intramuscular pentagastrin, and refers to peak-20-minute output, x 3

* PAO^{PG} measured immediately after the insulin test.

Table IV

COMPARISON OF MEAN ACID OUTPUTS IN PATIENTS WITH POSITIVE INSULIN TESTS MORE THAN 1 YEAR AFTER HSV, WITH OUTPUT IN PATIENTS AFTER TV+P OR SV+P WHO HAD BOTH POSITIVE INSULIN TESTS AND RECURRENT ULCER

(figures are arithmetic means)

					(1)	(2)	(3)		
OPERATION	NO. OF PATIENTS	AGE YR.	WEIGHT KG.	MONTHS AFTER OP.	BAO mEq/hr	PAO^{PG} mEq/hr	PAO^{I} mEq/hr	$\frac{PAO^{I}}{PAO^{PG}}$ %	PRODUCT columns (1) x (2) x (3) (units)
HSV	20	44.3	64.0	16	1.7	20.8	5.4	26.50	346
TRUNCAL V + P	25	40.9	65.3	27	5.6	37.6	15.7	35.99	3748
SELECTIVE V + P	8	35.1	69.1	29	4.0	38.7	17.9	46.47	2846

For standard errors of the means, see Tables I - III

Table V

STATISTICAL ANALYSES

('t' test for unpaired data)

	HSV	TV+P	HSV compared with TV+P DEGREES OF FREEDOM	t	P	TV+P and SV+P together	HSV compared with (TV+P) (SV+P) DEGREES OF FREEDOM	t	P
1) BAO mEq/hr	1.72 ± 0.31	5.61 ± 0.60	43	5.35	<0.001	5.23 ± 0.47	51	5.35	<0.001
2) PAO^{PG} mEq/hr	20.75 ± 2.12	37.63 ± 2.42	38	5.20	<0.001	37.91 ± 2.05	45	5.64	<0.001
3) PAO^{I} mEq/hr	5.39 ± 0.88	15.75 ± 1.90	43	4.55	<0.001	16.24 ± 1.61	51	4.96	<0.001
4) PRODUCT $BAO \times PAO^{PG} \times PAO^{I}$	313 ± 127	1958 ± 546	38	3.174	<0.01	3523 ± 786	45	3.33	<0.01

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CHAPTER 6

THE RESPONSE TO A TEST MEAL AFTER HSV

PART I: The choice of stimulant of antral release of gastrin: comparison of meat extract, acetylcholine and alcohol.

PART II: The effect of highly selective vagotomy on the response to a test meal: comparison with the effects of truncal and selective vagotomy.

Chapter 6

THE RESPONSE TO A TEST MEAL AFTER HSV

PART I: THE CHOICE OF STIMULANT OF ANTRAL RELEASE OF GASTRIN: COMPARISON OF MEAT EXTRACT, ACETYLCHOLINE AND ALCOHOL

In view of the key position which the antrum holds in surgery for peptic ulcer, it seemed desirable that a standard test of antral function should be developed for use in man. We wished in particular to study the effect of the three types of vagotomy on the response to a test meal. Such a test would depend upon the release of gastrin from the antral mucosa in response to chemical and mechanical stimulation. In the dog, acetylcholine has been shown to provide the best stimulus to gastrin release[1]. In man, no formal comparison of different antral stimulants appears to have been made, though several groups of workers found that a solution of meat extract evoked the secretion of large amounts of acid[2-4].

In an attempt to develop a satisfactory test of antral function, we compared the response to meat extract, acetylcholine or alcohol with the maximal acid output in response to pentagastrin in the same subjects. The reproducibility of the response to meat extract was also assessed.

PATIENTS AND METHODS

PATIENTS 47 patients with duodenal ulcer (DU), 2 patients with gastric ulcer (GU), 2 patients with "X-ray-negative" dyspepsia and 7 normal subjects (N) participated. The diagnosis of DU or GU was made radiologically and was confirmed at operation. The patients with ulcer were tested shortly before operation and their ulcers were either active at the time of testing, or had recently been active. Details of the subjects' ages, weights and sex are given in the Tables.

METHOD Each subject underwent at least two tests on separate days, the gastric secretory response to one of the three test meals being compared with that elicited by a 'maximal' dose of intramuscular pentagastrin (PG)[5]. The tests were done in random order. In 6 DU patients, acid responses to meat extract, acetylcholine and PG were measured on separate days. The volume of each test meal was 100 ml, and it was given at room temperature.

Test meals (1) Meat extract (OXO) Three cubes of OXO were dissolved in water to make a 100 ml solution and the pH was adjusted to 7 with molar sodium bicarbonate. 26 tests were performed.

(2) acetylcholine chloride 0.2 per cent solution was used in 13 tests,

0.5 per cent in 8 tests and 1 per cent in 4 tests. The pH of these solutions was 5.9 to 6.0.

(3) alcohol a 10 per cent solution of ethyl alcohol in water was used in 6 tests, and a 1 : 1 solution of Scotch whisky (70 per cent proof) and water in 4 tests. The pH of the 10 per cent alcohol was 5.9 and of the whisky 4.0.

Antral stimulation test The methods used in collecting gastric secretion were described in a previous section. Spontaneous (basal) secretion was collected for 30 to 60 minutes, in 15-minute samples. The suction was then disconnected. The patient sat in a chair, and the 100 ml test meal, at room temperature, was syringed gently down the tube, which was then spigoted. Care was taken to prevent the patient smelling the OXO solution. (In the four tests with Scotch whisky, the alcohol was taken orally). The test meal was left in the stomach for exactly 15 minutes, to stimulate release of gastrin. No suction was applied during this period. At the end of the 15 minutes, the patient lay down again, the suction was reconnected, and the gastric content aspirated for 5 minutes. With the suction still connected, the patient drank 200 ml of tap-water rapidly to wash out any of the test meal that still remained. Recovery of this water was usually very rapid (within 2 minutes) and the collecting flask was emptied again at the end of 5 minutes. For the ensuing hour the gastric juice secreted in response to the test meal was aspirated by means of continuous suction, the collecting flask being

changed every 10 minutes. After the volume of each sample of gastric juice had been measured, the juice was filtered through gauze, its pH was measured, and a 1 ml aliquot titrated to pH 7 with 0.1 N NaOH on a Radiometer TTTI autotitrator. Acid output in mEq per hour was expressed both as 'total-hour' output (T.H.) and as 'peak' output (PAO), which is the acid output in the two highest consecutive 10-minute periods multiplied by three.

Pentagastrin test The methods used have been described[5]. The dose of Peptavlon (ICI) was 6 ug per kg, given intramuscularly. The gastric secretory response was followed for 1 hour, the collecting flask being changed every 5 minutes. Acid output was expressed as PAO^{PG} and TH^{PG}.

Reproducibility of the OXO response In 9 subjects, the OXO test was repeated, after an interval of 1 to 6 days (52 days in one subject).

RESULTS

Response to OXO In 26 tests in patients with DU, mean PAO^{OXO} was 21.7 mEq per hour, 47 per cent of the PAO^{PG}, which averaged 47.3 mEq per hour (Table I, Fig. 1). The response to OXO ranged from 11 per cent to 86 per cent of PAO^{PG}, but was less than 33 per cent of PAO^{PG} in only 3 of the 26 subjects (Table I, Fig. 2). The profile of

the mean acid response to OXO (Fig. 3) shows that the peak acid output occurred on average between 0 and 30 minutes.

Response to acetylcholine (Ach) The 4 tests with 1 per cent Ach were unsuccessful, because the Ach produced vomiting in each test. Both the 0.5 per cent solution, in 8 tests, and the 0.2 per cent solution, in 13 tests, elicited mean peak acid outputs that were only 19 per cent of PAO^{PG} (Table II, Figs. 1 and 2).

Response to OXO and acetylcholine in the same subjects PAO^{OXO} was greater than PAO^{Ach} in 5 of the 6 patients (Table III). Mean PAO^{OXO} was 12.8 ± 1.5 mEq per hour, compared with the mean PAO^{Ach} of 7.4 ± 2.3 mEq per hour.

Response to alcohol In 6 tests with 10 per cent alcohol, the mean PAO was 23 per cent of PAO^{PG} (Table IV, Figs. 1 and 2). Half-strength whisky (given orally) to 3 normal subjects and to 1 patient, elicited a mean PAO that was 37 per cent of PAO^{PG} (range 24 to 45 per cent, Table IV, Figs. 1 and 2).

Reproducibility of the OXO response Although mean acid outputs in the second test were almost identical to those in the first test (Table V), individual PAOs in the second test differed from those in the first test by a mean of 36 per cent. 'Total-hour' acid output in the second test differed from that in the first by 40 per cent. However, these mean

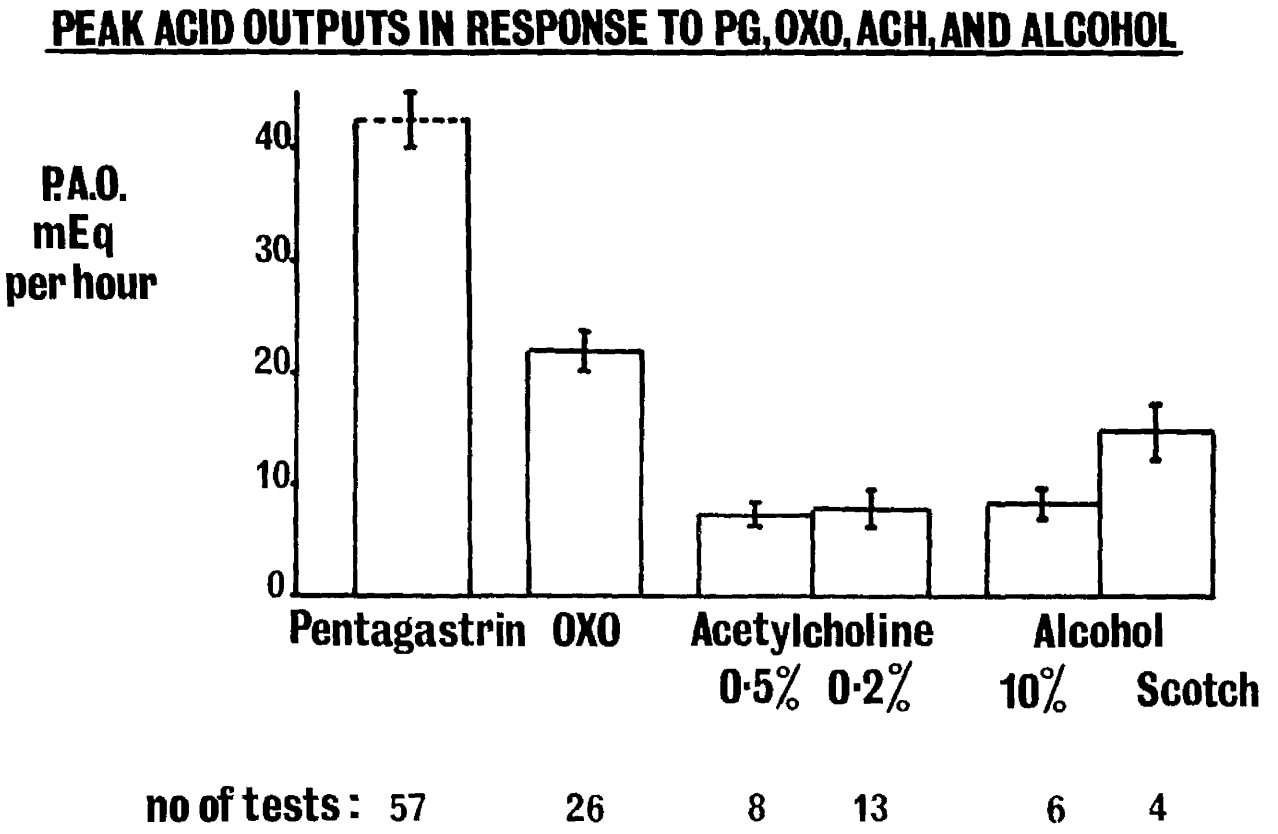

Fig. 1 The OXO test meal elicited larger mean acid outputs (± 1 SE) than did acetylcholine or alcohol.

COMPARISON OF OXO, ACH, AND ALCOHOL AS ANTRAL STIMULANTS

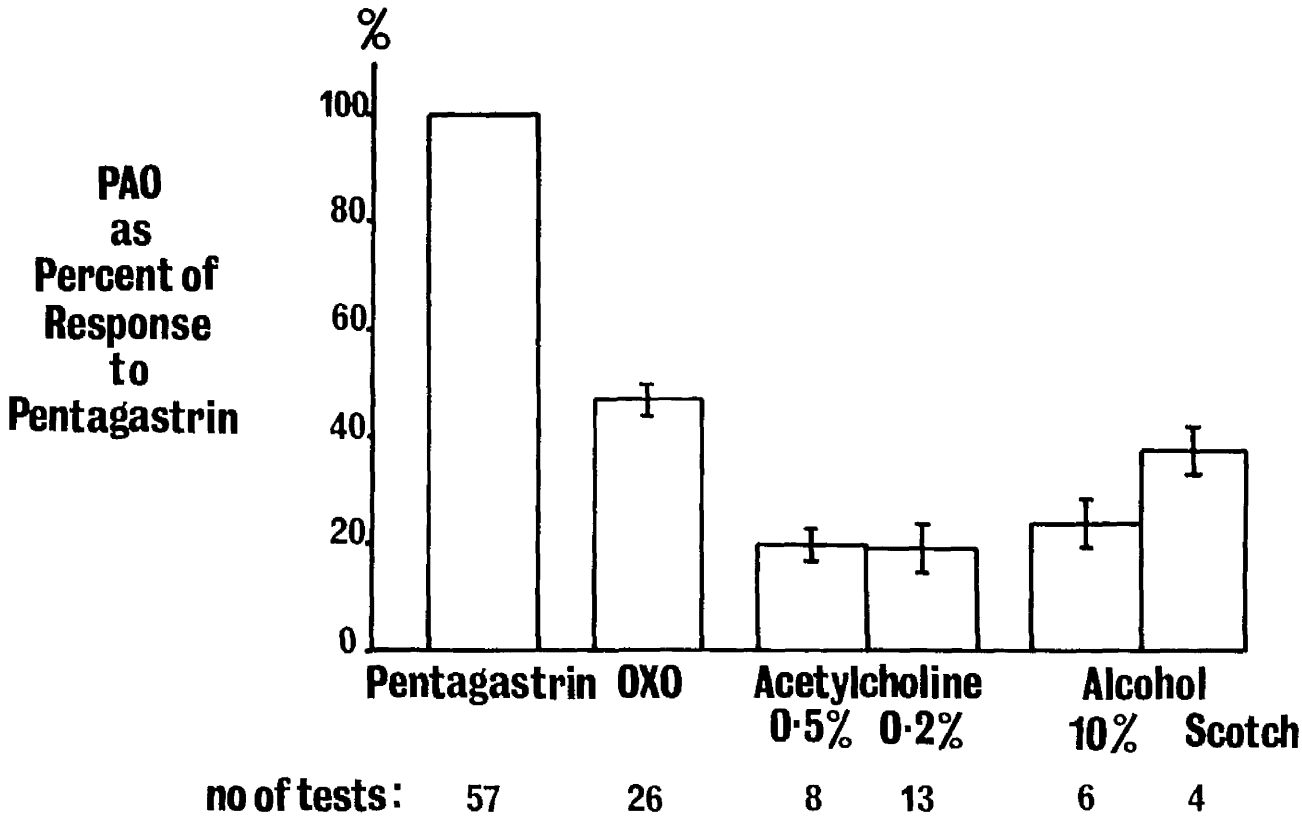

Fig. 2 The test meal of meat extract (OXO) elicited a peak acid output (PAO) which was about 50 per cent of the peak acid response to pentagastrin. Acetylcholine and alcohol were weaker stimulants.

RESPONSE TO OXO IN PATIENTS WITH DUODENAL ULCER BEFORE HSV.

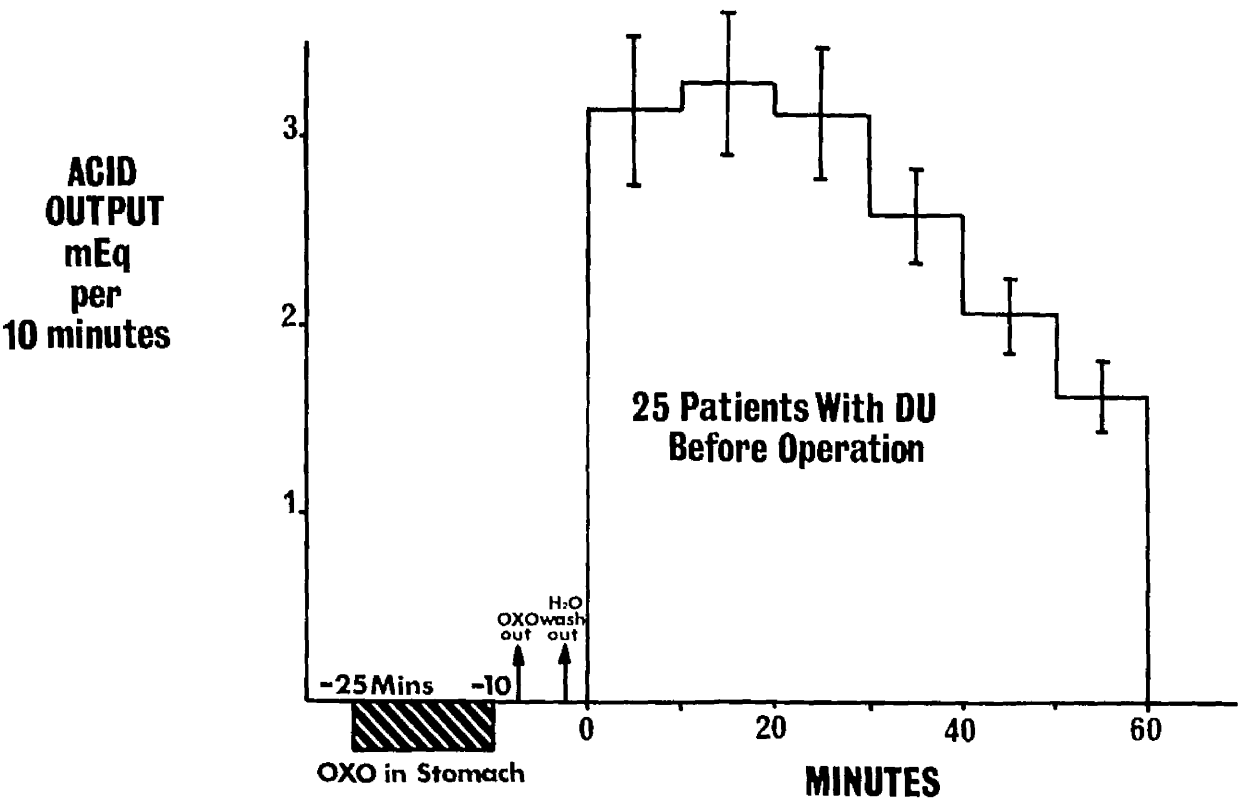

Fig. 3 This shows the time-relationship of the mean acid response (± 1 SE) to the test meal of meat extract, which are in accord with what is known of the time-relationships of gastrin release in response to a meal in man.

differences are "weighted" by the results in one subject whose two tests differed greatly (No. 9, Table V). PAO in the second test was within 20 per cent of that in the first test in 5 subjects, and differed by 40, 41, 61 and 119 per cent respectively in the remaining 4 subjects.

DISCUSSION

A solution of meat extract (OXO) was found to be a much more potent antral stimulant than either acetylcholine or alcohol, in patients with duodenal ulcer. A more concentrated solution of acetylcholine produced vomiting. It seems unlikely that the small difference in pH between OXO solution, at pH 7, and acetylcholine or 10 per cent alcohol, at pH 6, could have been responsible for the large difference between the acid responses to OXO and to the other test meals. Some evidence was obtained that half-strength Scotch whisky is a more powerful antral stimulant than 10 per cent ethyl alcohol, but since the whisky was given orally, vagal stimulation probably resulted, as well as gastrin release, and no firm conclusions can be drawn. Our findings differ from those obtained previously in dogs[1], in which 0.2 per cent solution of acetylcholine was found to elicit a mean acid output that was 95 per cent of the maximal response to

intravenous histamine, whereas liver extract and peptone elicited only 16 to 20 per cent of the maximum. They confirm previous observations[2-4] that meat extract is a powerful stimulant of gastric acid secretion in man. Although, in the absence of measurements of plasma gastrin concentration in this study, conclusive proof is lacking that the acid outputs obtained were in response to gastrin released by the test meals, such would seem to be the likeliest explanation, because the cephalic phase was eliminated by the use of a tube to place the meal in the stomach, the volume of the meal was kept small to avoid gastric distension (and hence secretion in response to vago-vagal reflexes[6]), and the time-relationships of the secretory response to OXO are consistent with a response to endogenous gastrin[7,8]. The degree of reproducibility of the OXO test is relatively poor compared with that of the augmented histamine test[9], the pentagastrin test[5] or the insulin test[10]. Both Welbourn and Burns[2] and Giles and Clark[3] had noted previously that reproducibility of the OXO test was relatively poor. Nonetheless, meat extract has been shown to be a powerful stimulant of gastric acid output, eliciting acid outputs averaging 48 per cent of MAO. The OXO test seems to be the best available method for the measurement of antral secretory function in man.

SUMMARY

A comparison was made of certain well-known stimulants of antral gastrin release, in patients with duodenal ulcer. Gastric acid output in response to a test meal of meat extract (OXO solution) averaged 48 per cent of the maximal acid output (MAO) in response to intramuscular pentagastrin. Acetylcholine chloride solution (0.2 and 0.5 per cent) elicited an output averaging 19 per cent of MAO. Ethyl alcohol, in 10 per cent solution, elicited acid outputs averaging 23 per cent of MAO. Thus, of the substances tested, meat extract provided the best stimulus to gastrin release.

The reproducibility of the OXO test, however, was relatively poor.

APPENDIX

COMPOSITION OF OXO

Ingredients These are stated on the packet to be hydrolysed protein, beef stock, flour, yeast extract, caramel, salt, beef extract, beef fat, spices and onion powder.

Enquiry to the manufacturers (Brooke Bond OXO Ltd.), elicited the following information. The total amino acid content is approximately 20 per cent, made up from the 16 per cent derived from acid-hydrolysed protein and 4 per cent from autolysed yeast extract. Small quantities of amino acids are contributed from meat extract, desiccated beef and the gluten contained in wheat flour. Qualitatively, the whole range of naturally-occurring amino acids is found in the OXO cube.

The general analysis of the cube is as follows :-

	per cent
water	10.0
ash	28.5
salt	26.9
T.N. (total nitrogen)	6.0
protein	37.5
fat	4.0
phosphate	0.9
calcium	0.17
magnesium	0.07
sodium	10.80
potassium	0.70
iron	250 ppm
copper	6 ppm
carbohydrate	15.0% (determined as glucose)
nicotinic acid	180 ug/g

(Courtesy of P. O. Dennis, Chief Chemist, OXO and Fray Bentos Division)

Table I

GASTRIC ACID RESPONSES TO MEAT EXTRACT (OXO) AND PENTAGASTRIN IN 26 PATIENTS WITH DUODENAL ULCER BEFORE OPERATIO

NO	AGE (YRS.)	SEX	WEIGHT (KG.)	RESTING JUICE (ml.)	VOLUME* RECOVERED AFTER 15 MINUTES	RESPONSE TO OXO (mEq per hour) PAO	TH	RESPONSE TO PENTAGASTRIN (mEq per hour) PAO	TH	OXO / PG PAO	PER CENT TH
A [1]	41	M	85	89	201	60.15	40.77	81.90	68.47	73.44	59.54
1	34	M	84	105	208	22.89	17.34	64.14	49.43	35.69	35.08
2	21	F	57	85	110	13.47	10.66	26.88	19.86	50.11	53.68
3	36	M	66	115	145	14.19	12.04	38.16	29.69	37.19	40.55
4	44	M	61	77	131	14.88	14.18	35.70	32.25	41.68	43.97
5	47	M	60	122	117	21.42	17.51	43.65	40.06	49.07	43.71
6	48	F	41	63	94	13.59	7.59	18.27	14.46	74.38	52.49
7	47	M	70	86	145	16.47	14.58	46.08	39.93	35.74	36.51
8	27	M	75	127	211	30.42	27.59	56.04	38.01	54.28	72.59
9	16	M	51	110	103	36.66	16.43	42.60	34.25	86.06	47.97
$\bar{M}$ (10)	36.10		65.00	97.90	146.50	24.41	17.87	45.34	36.64	53.76	48.61
± 1 SE	3.63		4.43	6.63	14.15	4.70	3.05	5.81	4.78	5.74	3.62

10	44	M	94	70	100	29.70	19.40	57.03	50.61	52.08	38.34
11	50	M	60	172	163	18.66	11.56	29.49	23.62	63.28	48.94
12	50	M	76	121	145	14.43	9.11	71.58	59.01	20.16	15.44
13	48	M	64	46	106	20.37	14.78	45.66	34.18	44.61	43.24
14	46	M	57	93	121	7.92	4.71	69.18	51.40	11.45	9.16
15	53	M	71	89	157	18.00	12.85	39.27	32.48	45.84	39.56
16	39	M	83	98	150	19.29	13.98	50.13	41.21	38.48	33.92
17	36	M	76	88	104	22.80	17.79	68.04	53.57	33.51	33.21
18	48	F	63	44	87	5.61	4.20	25.62	22.70	21.90	18.50
19	53	M	77	78	148	25.95	22.57	34.47	30.32	75.28	74.44
20	34	F	76	70	80	22.92	20.09	38.01	33.64	60.29	59.72
21	39	M	72	25	75	25.32	16.60	62.13	43.57	40.75	38.10
22	72	M	56	101	141	14.31	12.45	35.25	29.03	40.60	42.89
23	32	M	67	45	192	22.32	16.60	41.04	33.80	54.39	49.11
24	31	M	74	41	92	15.30	9.98	35.07	28.18	43.63	35.42
25	39	M	74	108	175	36.78	22.49	61.80	44.75	59.51	50.26
MEAN (26)	41.35		68.85	87.23	134.65	21.69	15.69	46.82	37.63	47.82	42.94
± 1 SEM	2.23		2.31	6.35	7.84	2.15	1.46	3.17	2.46	3.48	2.96

* This consists of OXO solution which has not yet left the stomach plus added gastric secretion.

‡ All patients had duodenal ulcer except patient A, who had dyspepsia and giant mucosal folds in the duodenum. Results in patients A and 1 - 9 are analysed separately because they also underwent OXO tests more than one year after HSV (see PART II)

Table II

RESPONSE TO ACETYLCHOLINE COMPARED WITH RESPONSE TO PENTAGASTRIN IN THE SAME SUBJECTS

PATIENT NO.	AGE YR.	SEX	WEIGHT KG.	$^{1}PAO^{Ach}$ mEq/hr	$^{2}PAO^{PG}$ mEq/hr	1 ÷ 2 PER CENT	$^{3}TH^{Ach}$ mEq/hr	$^{4}TH^{PG}$ mEq/hr	3 ÷ 4 PER CENT
1	48	F	63	5.46	25.62	21.31	5.15	22.70	22.69
2	49	M	68	3.36	31.05	10.82	2.46	27.82	8.84
3	51	M	83	12.24	35.97	34.03	8.06	25.79	31.25
4	24	M	70	9.00	41.19	21.85	7.43	30.55	24.32
5	45	M	66	10.14	55.08	18.41	7.27	44.41	16.37
6	35	F	83	2.91	48.81	5.96	1.96	36.08	5.43
7	41	F	51	7.20	39.09	18.42	3.29	30.86	10.66
8	36	M	66	9.24	38.16	24.21	6.77	29.69	22.80
Mean of 8	41.13		68.75	7.44	39.37	19.38	5.30	30.99	17.80
± 1 SE	3.22		3.71	1.17	3.30	3.00	0.86	2.37	3.16
9	40	F	48	3.42	29.79*	11.48	2.59	23.34	11.10
10	43	M	67	0.90	23.82	3.78	0.54	19.23	2.81
11	21	M	52	4.95	37.44*	13.22	4.12	34.15	12.06
12	49	F	54	13.05	44.70*	29.19	7.59	31.10	24.41
13	52	M	53	10.86	53.19*	20.42	3.29	48.31	6.81
14	42	M	67	16.59	51.60	32.15	10.94	38.72	28.25
15	57	F	48	0.21	23.19	0.91	0.16	15.82	1.01
16	49	M	63	17.01	69.42	24.50	11.75	53.88	21.81
17	33	M	56	2.88	37.02	7.78	2.01	32.15	6.25
18	31	M	74	4.08	35.07	11.63	3.23	28.18	11.46
19	21	F	57	17.04	26.88	63.39	9.42	19.86	47.43
20	48	F	41	0.66	18.27	3.61	0.44	14.46	3.04
21	72	M	56	7.71	35.25	21.87	5.82	29.03	20.05
Mean of 13	42.92		56.62	7.64	37.36	18.76	4.76	29.86	15.11
± 1 SE	3.95		2.52	1.80	3.97	4.64	1.11	3.32	3.63

* pentagastrin test done immediately after the acetylcholine test.

All 21 patients had duodenal ulcer.

0.5 per cent solution of acetylcholine was used in patients 1 - 8, and 0.2 per cent solution in patients 9 - 21.

Table III

COMPARISON OF THE GASTRIC ACID RESPONSES TO TEST MEALS OF OXO AND ACETYLCHOLINE SOLUTION IN 6 PATIENTS WITH DUODENAL ULCER

NO.	AGE AND SEX	WEIGHT (KG.)	RESPONSE TO OXO (mEq per hour)		RESPONSE TO ACETYLCHOLINE (mEq per hour)		ACH / OXO PER CENT	
			PAO	TH	PAO	TH	PAO	TH
1	21 F	57	13.47	10.66	17.04	9.42	126.50	88.37
2	48 F	41	13.59	7.59	0.66	0.44	4.86	5.80
3	31 M	74	15.30	9.98	4.08	3.23	26.67	32.36
4	72 M	56	14.31	12.45	7.71	5.82	53.88	46.75
5	36 M	66	14.19	12.04	9.24	6.77	65.12	56.23
6	48 F	63	5.61	4.20	5.46	5.15	97.33	122.62
MEAN	42.67	59.50	12.75	9.49	7.37	5.14	62.39	58.69
± 1 SEM	7.23	4.57	1.45	1.27	2.28	1.25	18.25	16.94

0.2 per cent solution of acetylcholine was used in patients 1 - 4 and 0.5 per cent solution in patients 5 and 6.

Table IV

RESPONSE TO ALCOHOL COMPARED WITH RESPONSE TO PENTAGASTRIN IN THE SAME SUBJECTS

ALCOHOL TEST MEAL	PATIENT NO.	AGE YR.	SEX	WEIGHT KG.	DIAGNOSIS	$^{1}PAO^{ALC}$ mEq/hr	$^{2}PAO^{PG}$ mEq/hr	1 ÷ 2 PER CENT	$^{3}TH^{ALC}$ mEq/hr	$^{4}TH^{PG}$ mEq/hr	3 ÷ 4 PER CENT
	1	63	M	60	DU	6.78	44.13	15.36	5.60	30.67	18.26
100 ml	2	53	M	75	DU	3.42	38.10	8.98	3.12	28.32	11.02
	3	20	F	52	DU	8.13	26.13	31.14	5.35	24.21	22.10
10%	4	44	F	52	DU	9.93	41.58	23.88	8.69	30.55	28.44
	5	38	M	59	DU	11.10	31.38	35.37	5.07	25.18	20.13
$C_2 H_5OH$	6	52	M	80	N	9.60	39.60	24.24	8.19	31.64	25.88
Mean of 6		45.00		63.00		8.16	36.82	23.16	6.00	28.43	20.97
± 1 SEM		6.09		4.83		1.13	2.76	3.98	0.85	1.27	2.50
50ml 70% proof	7	47	M	86	DU	18.63	44.97	41.43	17.18	38.60	44.51
Scotch Whisky	8	24	M	68	N	12.66	32.73	38.68	11.54	30.27	38.12
+ 50ml Water	9	22	M	65	N	7.23	30.54	23.67	5.91	25.63	23.05
	10	22	M	73	N	18.87	41.76	45.19	16.66	36.61	45.51
Mean of 4		28.75		73.00		14.35	37.50	37.24	12.82	32.78	37.80
± 1 SEM		6.10		4.64		2.77	3.48	4.72	2.63	2.97	5.18

DU - duodenal ulcer. N - normal volunteer. ALC - alcohol. PG - pentagastrin. The 10 per cent alcohol was given by stomach tube to patients 1 - 6. The Scotch Whisky was given orally.

Table V

RESULTS OF PAIRED OXO TESTS IN THE SAME SUBJECTS

NO.	NAME	AGE AND SEX	WEIGHT KG.	DIAGNOSIS	INTERVAL BETWEEN TESTS (days)	RESPONSE TO OXO (1st test) mEq per hour		RESPONSE TO OXO (2nd test) mEq per hour		2 ÷ 1 PER CENT		DIFFERENCE larger - smaller		DIFFERENCE AS PERCENTA OF OUTPUT I 1ST TEST	
						PAO	TH	PAO	TH	PAO	TH	PAO	TH	PAO	T
1	E.M.	33 M	61	GU	3	6.45	4.35	5.55	4.68	86.05	107.59	0.90	0.33	13.95	7
2	R.T.	31 M	65	'dyspepsia'	52	55.02	36.14	47.40	32.86	86.15	90.92	7.62	3.28	13.85	9
3	J.K.	54 M	62	DU	2	26.25	22.97	29.01	17.82	110.51	77.58	2.76	5.15	10.51	22
4	M.U.	68 F	45	DU	2	25.53	21.48	25.95	21.63	101.65	100.70	0.42	0.15	1.65	0
5	G.D.	26 M	71	'dyspepsia'	1	13.20	11.86	21.27	14.71	161.14	124.03	8.07	2.85	61.14	24.
6	V.W.	41 M	65	GU	1	7.59	6.33	9.03	5.95	118.97	94.00	1.44	0.38	18.97	6.
7	J.P.	28 M	97	N	2	22.59	12.59	13.53	5.85	59.89	46.47	9.06	6.74	40.11	53.
8	J.R.	21 M	70	N	2	13.26	9.52	7.86	6.54	59.28	68.70	5.40	2.98	40.72	31.
9	S.B.	21 M	64	N	6	8.88	5.37	19.44	16.26	218.92	302.79	10.56	10.89	118.92	202.
MEAN		35.89	66.67			19.86	14.51	19.89	14.03	111.40	112.53	5.14	3.64	35.54	39.
± 1 SEM		5.30	4.54			5.08	3.49	4.39	3.14	17.01	24.95	1.29	1.18	12.16	21.

GU - gastric ulcer. DU - duodenal ulcer. N - normal. Patients 2 and 5 had symptoms suggestive of duodenal ulceration, but barium meal examination was negative. The difference between the two tests has been expressed as a percentage, PAO and TH in the first test being taken as 100 per cent.

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THE RESPONSE TO A TEST MEAL AFTER HSV

PART II THE EFFECT OF HIGHLY SELECTIVE VAGOTOMY ON THE RESPONSE TO A TEST MEAL: COMPARISON WITH THE EFFECTS OF TRUNCAL AND SELECTIVE VAGOTOMY

The antrum of the stomach is the principal source of gastrin[1-4]. Stimulation of its vagal nerve-supply leads to the release of gastrin in man[5], as in the dog[6-9]. Division of its vagal nerve-supply (in dogs) has been shown to diminish the output of acid from Heidenhain pouches[6-12]. For these reasons, during the 1960s surgeons were happy to accept the advice of Nyhus, Harkins and their colleagues[9] that if the antrum was to be retained, rather than being resected, in operations for duodenal ulcer, it must be vagally-denervated and remain in continuity with the 'acid stream', while antral stasis must be prevented by the addition of a drainage procedure. This philosophy continues to dominate surgical thinking at the present day, and nearly all surgeons in Britain, if they do not resect the antrum, at least deprive it of its vagal nerve-supply by performing truncal or bilateral selective vagotomy.

Implicit in such a policy is the belief that failure to vagally-denervate the antrum would lead to excessive release of gastrin, to excessive outputs of acid and pepsin, and hence to an unacceptably high incidence of recurrent ulceration. We had already found that spontaneous

acid output was not excessive in patients after HSV. The next step was to try to find out whether they produced excessive amounts of acid after a meal. If they did not, the case for routine antral denervation would be weakened considerably. Accordingly, we used a test meal of meat extract (Oxo solution) to stimulate the release of gastrin in patients after HSV, who still had a vagally innervated antrum, and in patients after truncal or selective vagotomy (TV, SV), in whom the antrum had been vagally denervated. All patients were studied more than one year after operation and were in good health and free from symptoms of gastric stasis.

METHOD

PATIENTS

Group I Highly selective vagotomy without drainage (HSV): vagally-innervated antrum

Twenty-eight patients were tested. In twenty-six, the operation had been performed for duodenal ulcer, and in two on account of epigastric pain associated with hypersecretion of acid and the presence of giant mucosal folds in the duodenum. Details of their sex, age, weight, length of history before operation, number of months elapsed since operation, and Visick status are given in Table I. Oxo tests had been performed in 10 of the 28 patients before operation.

Group II Truncal vagotomy and pyloroplasty (TV+P): vagally-denervated antrum

Details of the 11 patients who were tested are given in Table IV.

Group III Bilateral selective vagotomy and pyloroplasty (SV+P): vagally-denervated antrum

Details of the 10 patients are given in Table V.

Group IV Bilateral selective vagotomy without a drainage procedure (SV): vagally-denervated antrum

Details of the 18 patients tested are given in Table VI.

All the patients in groups I to IV were in good health, except for one patient in group I (HSV). No sign of gastric retention, such as the presence of food residues in the stomach, was found in the course of these tests. Patients in groups I - III had been treated in the University Department of Surgery at Leeds General Infirmary. In each, evidence of completeness of the parietal cell vagotomy had been obtained by the finding of a negative response to insulin, by Hollander's criteria[13], in the early post-operative period. Of the 18 patients in group IV, 15 were in the care of Mr. H. Burge at the West London Hospital, 2 in the care of Mr. R. M. Kirk at the Hampstead General Hospital and 1 was the patient of Mr. J. S. F. Hutchison at Glasgow Royal Infirmary. In all except one of the patients at the West London Hospital, the vagotomy had

been shown to be complete at the time of operation by the use of the Burge electrical stimulation test[14]. An insulin test was performed in the early post-operative period in 6 of the patients at the West London Hospital and was negative[13] in each case.

All patients were volunteers, who had given informed consent to the tests, which they knew were for research purposes. In consequence they do not comprise a consecutive series, but they are considered to be representative of the larger groups of patients who were treated by HSV, TV+P, SV+P or SV alone.

TESTS OF GASTRIC SECRETION These tests measured BAO, the response to a test meal of meat extract (Oxo), the response to insulin (0.2 units per kg) and MAO in response to intramuscular pentagastrin (10 ug per kg). The methods used in each of these tests were described in preceding sections.

The tests were performed on separate days, in patients at Leeds (Groups I - III). Details of the rare exceptions to this rule are given in Tables I, IV and V. In 21 of the HSV patients the pentagastrin test was also performed immediately after the end of the insulin test. The pentagastrin test was repeated at the end of the insulin test in 10 of the 11 patients after TV+P. In patients who had undergone SV+P (group III, Table V) Oxo tests only were performed. "Late", or "delayed"

insulin tests were not done. MAO had been measured in 8 of the 10 patients more than one year after SV+P, but the stimulus had been intravenous pentagastrin, in a dose of 6 ug per kg per hour, rather than intramuscular pentagastrin. Each patient with SV alone underwent one test in which BAO and the response to Oxo were measured. In 12 patients with SV alone, a second test was carried out at which were measured BAO, the response to insulin, and MAO in response to pentagastrin.

Analysis of results The titration end-point was pH 7. BAO was expressed as mEq per hour. The responses to Oxo and to pentagastrin were expressed as PAO (peak-20-minute response, x 3) and as total-hour acid output (TH), in mEq per hour. The response to insulin was expressed as PAO and PH (peak-30-minute response, x 2, and peak-60-minute response, respectively). Acid outputs for each group were expressed as the arithmetic mean plus or minus one standard error (S.E.M.).

RESULTS

Effect of HSV on response to OXO (Tables I - III, fig. 1).

In 25 patients after HSV, PAO^{OXO} was 10.1 $\pm$ 1.5 mEq per hour, 50 per cent of PAO^{PG} (Table I). In the 10 patients who underwent OXO tests both pre- and post-operatively (Table II), mean PAO^{OXO} diminished from 24.4 to 14.9 mEq per hour. The mean decrease was

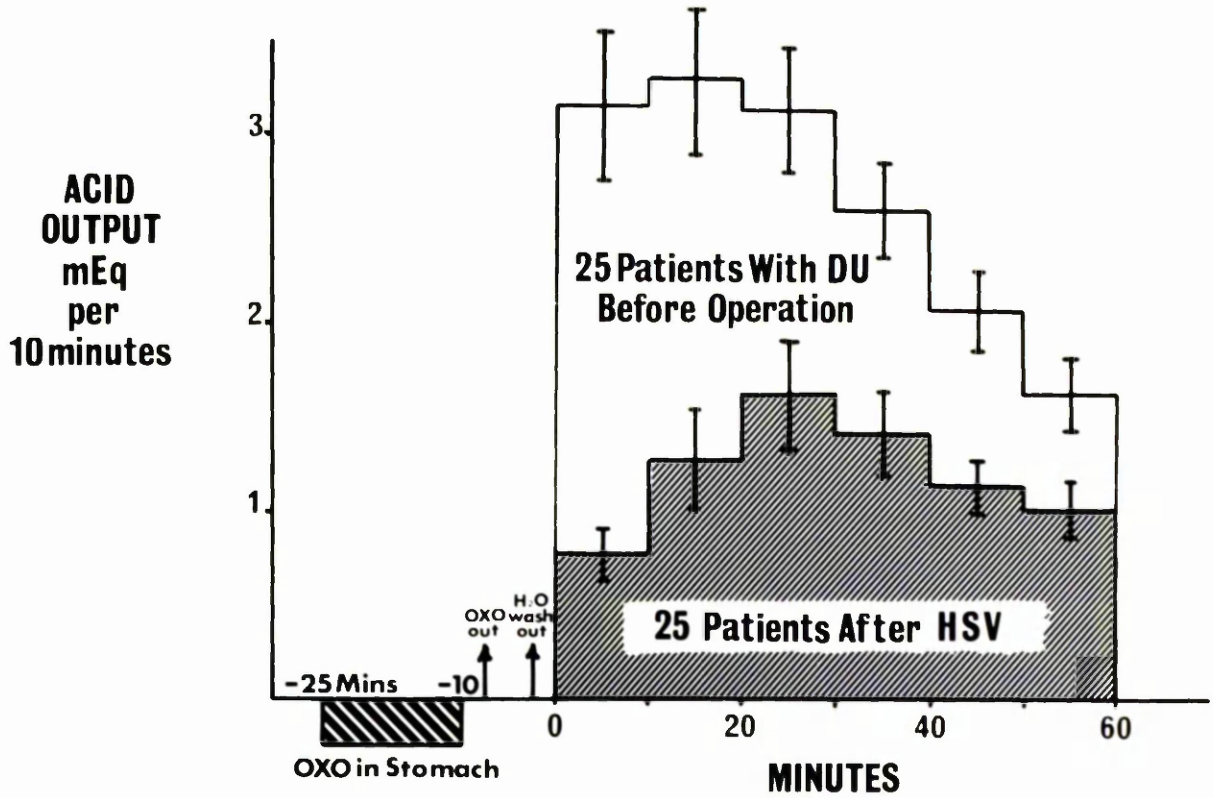

Fig. 1 HSV reduced the acid response to meat extract by about 50 per cent. Note that the 25 patients who were tested after HSV are not the same 25 who were tested before operation (ten were common to both groups). Note also the slightly slower response after HSV.

40 per cent. Before operation, in these 10 patients, PAO^{OXO} averaged 54 per cent of PAO^{PG}: after HSV, it averaged 53 per cent of the post-operative PAO^{PG}. In the larger, unmatched, groups of patients who were tested before, or after, HSV (Table III), mean PAO^{OXO} before operation was 21.7 mEq per hour, 48 per cent of PAO^{PG}; and after HSV was 10.1 mEq per hour, 50 per cent of post-operative PAO^{PG}, The 25 patients with duodenal ulcer who underwent OXO tests after HSV were similar to the 26 patients who were tested before operation with respect to sex, age and weight, but their mean pre-operative MAO was somewhat lower (Table III).

In the 10 patients who had paired pre- and post-operative OXO tests, the mean reductions in BAO (71 per cent) and in PAO^{PG} (46 per cent) were less than those which were found in patients after HSV as a whole (mean reduction in BAO, 77 per cent, and in PAO^{PG}, 52 per cent). Thus, HSV reduces the peak acid response to OXO by about 45 to 50 per cent. After HSV, as before operation, the acid response to OXO is about half of the maximal response to pentagastrin.

Comparison of the effects of truncal, selective and highly selective vagotomy on the response to OXO Mean PAO^{OXO} in mEq per hour was 10.1 $\pm$ 1.5 after HSV, 19.6 $\pm$ 3.9 after TV+P, 11.0 $\pm$ 2.9 after SV+P and 14.2 $\pm$ 1.9 after SV alone (Tables I, IV - VII; Figs. 2 - 5).

RESPONSE TO OXO AFTER HSV COMPARED WITH RESPONSE AFTER TRUNCAL V+P.

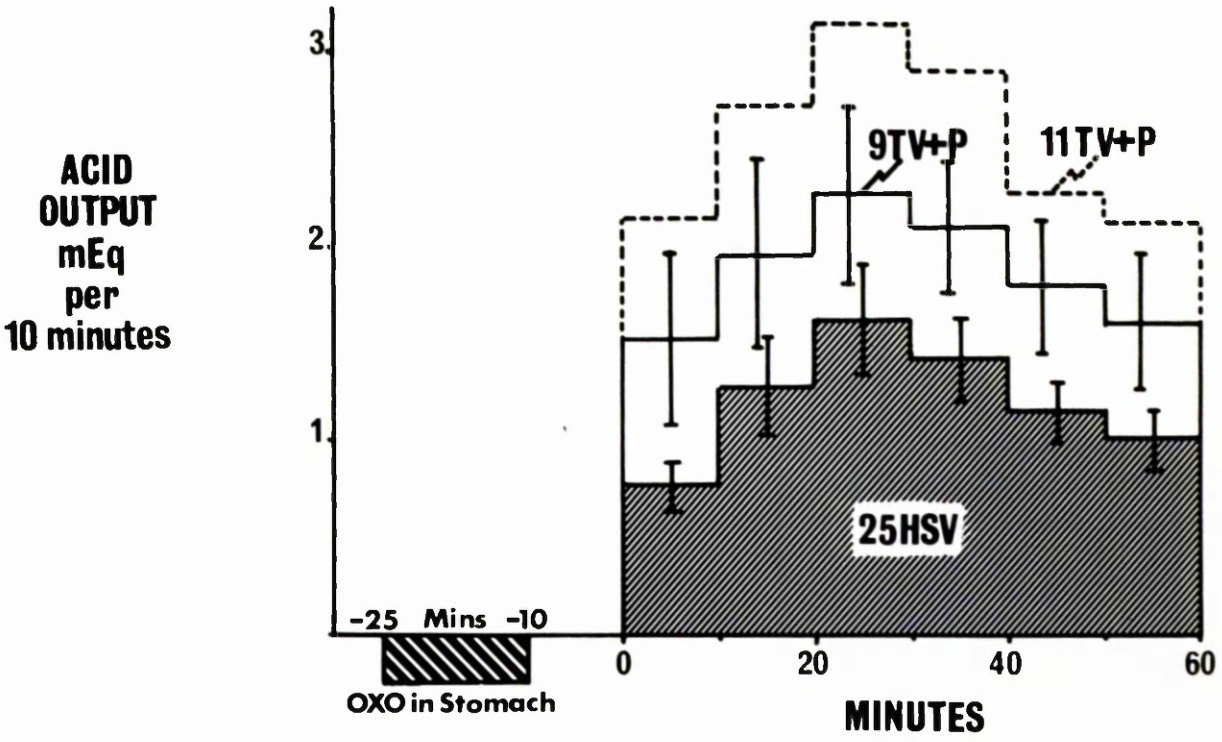

Fig. 2 The mean acid response (± 1 SE) to meat extract in patients after truncal vagotomy and pyloroplasty was higher than the mean acid response in patients after HSV, but the difference was not statistically significant. Mean acid outputs after TV+P are shown both for 11 patients, and for 9 of the 11 after the results in two patients with exceptionally high acid outputs had been deleted.

RESPONSE TO OXO AFTER HSV COMPARED WITH RESPONSE AFTER SELECTIVE V+P.

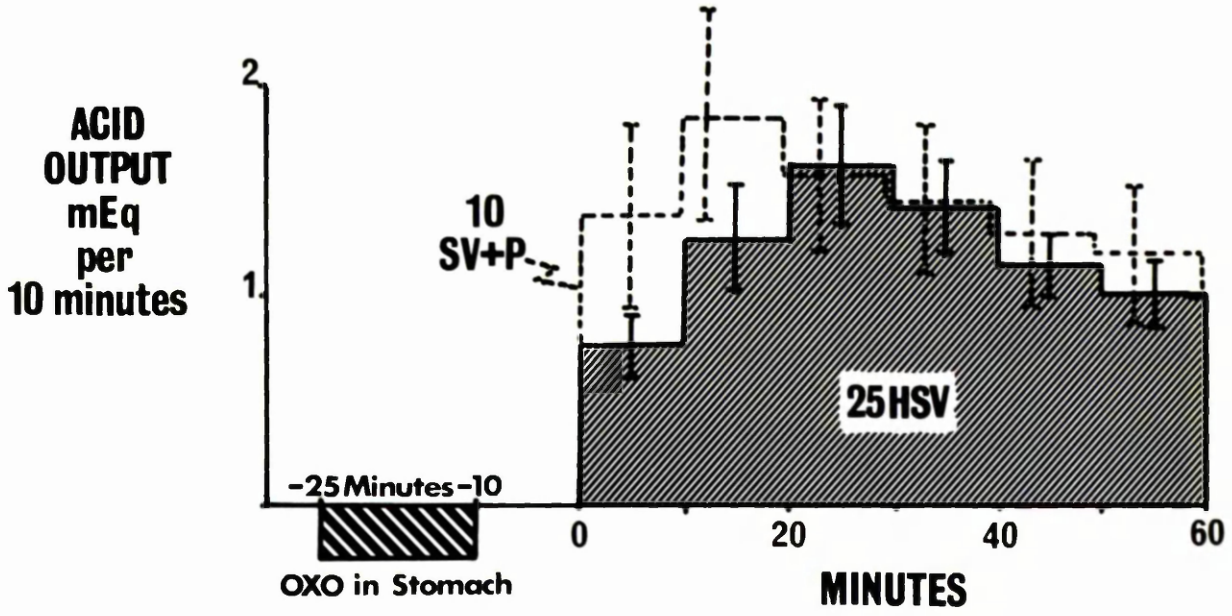

Fig. 3 There was little difference between the mean acid response to meat extract in patients after HSV compared with the mean response in patients after selective vagotomy and pyloroplasty.

RESPONSE TO OXO AFTER HSV COMPARED WITH RESPONSE AFTER SELECTIVE VAGOTOMY ALONE.

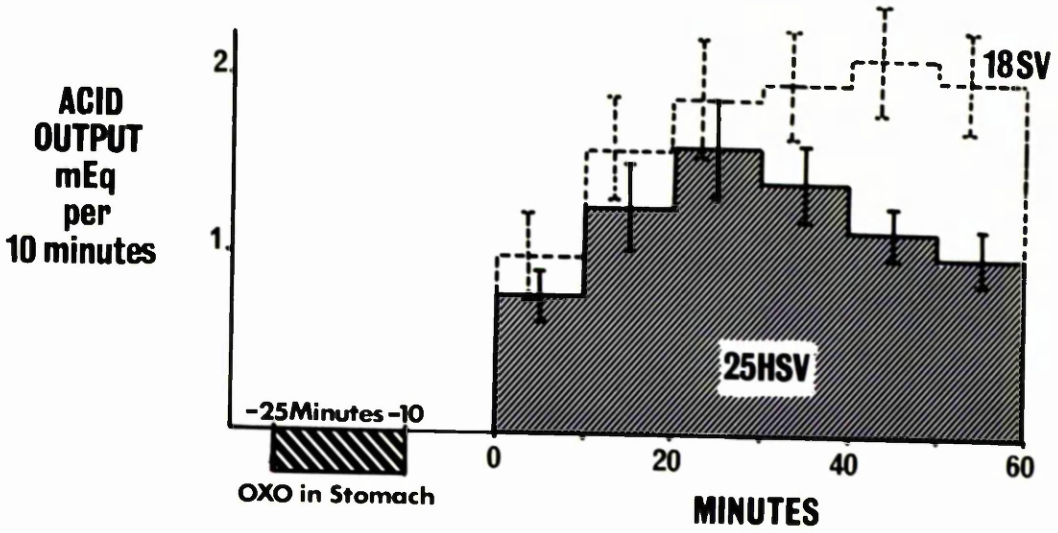

Fig. 4 After selective vagotomy without drainage, the mean acid response to meat extract was higher than after HSV, particularly in the latter half of the test.

RESPONSES TO OXO IN HEALTHY PATIENTS>1 YEAR AFTER DIFFERENT TYPES OF VAGOTOMY.

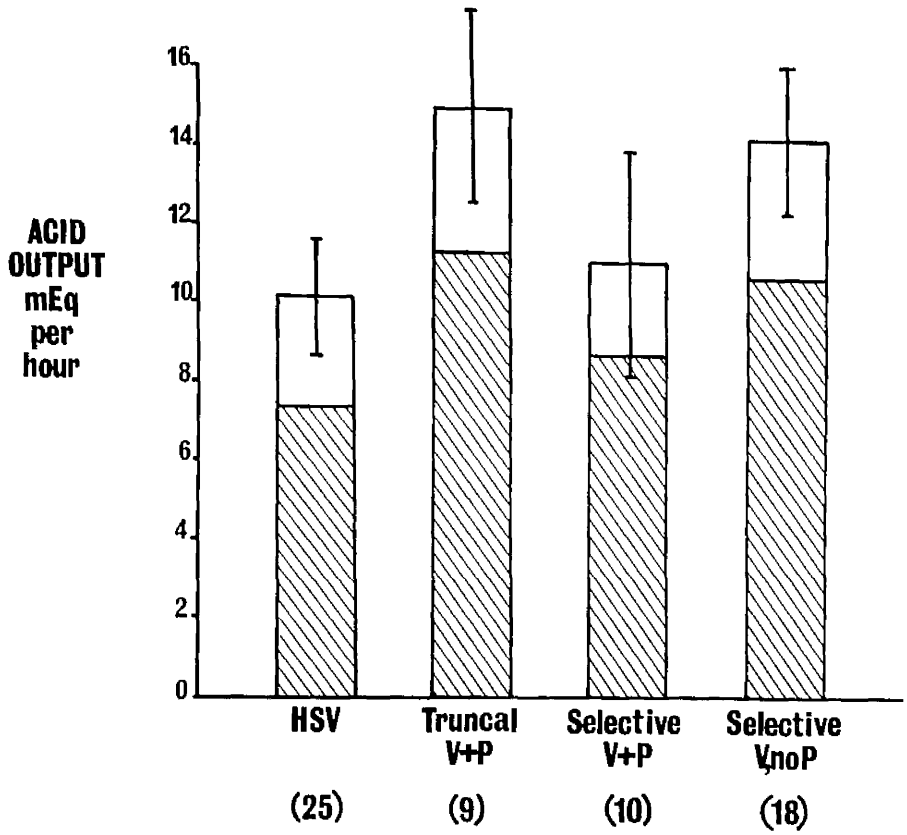

Fig. 5 This is a summary of the results. Columns represent mean peak acid outputs ± 1 SE, and shaded areas 'total-hour' acid outputs. There is no evidence that acid outputs in response to meat extract are greater in patients with vagally-innervated gastric antra (HSV) than in patients with vagally-denervated antra (TV+P, SV+P, SV alone).

No evidence was found that patients who had a perfect clinical result (Visick grade I) had lower acid responses to OXO than patients who were in Visick grades II and III. Two patients after TV+P had very high BAO and OXO responses, although they were in perfect health (Table IV). If their results are excluded, the mean PAO^{OXO} in the remaining 9 patients in the TV+P group was 14.9 $\pm$ 2.4 mEq per hour. Similarly, patients 2 and 9 after SV+P had unusually high BAO. They too had a perfect clinical result, and there seems to be no valid reason for excluding their results.

OXO response as a percentage of pentagastrin response (Tables I - VI) After HSV, the response to OXO, expressed for each patient as a percentage of his response to pentagastrin, averaged 50 per cent, compared with 64 per cent in patients after TV+P and 55 per cent in patients after SV+P (Table VII). When the results of the pentagastrin test which had been performed immediately after the insulin test were used, PAO^{OXO} averaged 55 per cent of PAO^{PG} in patients after HSV, and 65 per cent in patients who had undergone SV without drainage (Table VII).

Matching (Table VII) Patients after HSV, TV+P and SV+P were well-matched in the following respects:- (1) the insulin test performed in the early post-operative period (in Leeds) was negative (2) more than one year had elapsed from the time of operation (3) patients were in good-to-excellent health, without evidence of recurrent ulceration.

(4) the mean length of ulcer history before operation was about 10 years (5) mean age was 40 - 50 years (6) mean weight was 65 - 70 kg (7) most of the patients were men. In addition, the tests yielded no evidence of gastric stasis in any of the groups of patients.

(a) Comparison of patients after HSV and TV+P (Tables I, IV and VII; Figs. 2 and 5). The mean interval between operation and the OXO test was 16 months in patients after HSV, and 29 months in patients after TV+P. Patients after TV+P were, on average, 8 years older, and their PAO^{PG} before operation was 56 mEq per hour, compared with 40 mEq per hour in the HSV patients. If 2 patients with very high BAO and high responses to OXO are excluded from the TV+P group, matching is improved to the extent that mean acid outputs in response to insulin and pentagastrin become fairly similar (Table VII), but mean BAO in the TV+P patients is still more than double that of patients after HSV. Four patients whose insulin tests were negative more than one year after TV+P (Table IV) secreted a mean PAO of 12.6 mEq per hour in response to OXO. Four patients with late-positive responses to insulin more than one year after TV+P (Table IV) secreted a mean PAO of 14 mEq per hour in response to OXO. Thus, no evidence was obtained that patients after TV+P secreted less acid in response to OXO than did patients after HSV.

(b) Comparison of patients after HSV and SV+P (Tables I, V and VII; Figs. 3 and 5). On average, the OXO test was performed 4 years after SV+P, compared with 16 months after HSV. "Late" insulin tests were not done in patients after SV+P. A further defect was that PAO^{PG} had been elicited by intravenous pentagastrin and that these pentagastrin tests had been performed 1 to 2 years after SV+P, and thus 2 to 3 years before OXO tests were done. No significant difference was found between the responses to OXO in the two groups of patients.

(c) Comparison of patients after HSV and SV without drainage (Tables I, VI and VII, Figs. 4 and 5). Matching of the two groups was satisfactory for age, weight, and interval between operation and secretory testing. Mean BAO in SV patients was also closer to the BAO of HSV patients than was the BAO of patients after TV+P or SV+P. However, the mean responses to pentagastrin and insulin were both appreciably higher in patients after SV than in patients after HSV (Table VII). The mean peak response to OXO was 14.2 mEq per hour compared with 10.1 mEq per hour after HSV. Even after matching of comparable groups of patients (Tables I and VI, Figs. 6 and 7), the OXO response in patients after SV was not found to be less than in patients after HSV.

Time-relationships of response to OXO (Figs. 1 - 4)

Compared with the response to OXO before operation (Fig. 1), when

OXO Response in 6 Matching Pairs of Patients

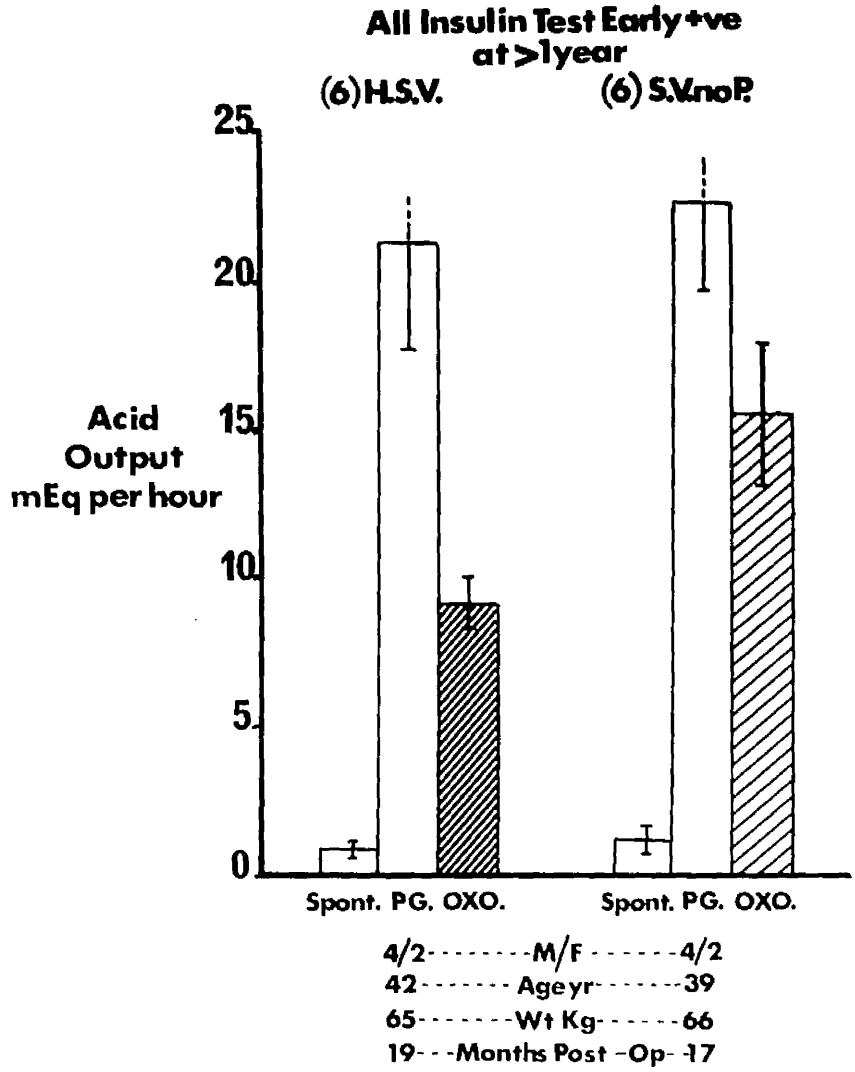

Fig. 6 This is a comparison of mean acid outputs (± 1SE) in two well-matched groups of patients (selective vagotomy without drainage on the right, HSV without drainage on the left). The main variable between the groups was the presence (HSV), or absence (SV), of the vagal nerve supply to the antrum. All patients had early-positive (first-hour) acid responses to insulin more than one year after operation. The two groups were well-matched for spontaneous acid output, pentagastrin (PG) -stimulated acid output, sex, age, weight, and time-interval after operation. The mean acid response to meat extract (OXO) in the 6 patients with innervated antrum (HSV) was certainly no greater than in the 6 patients whose antra had been vagally denervated (SV, no P).

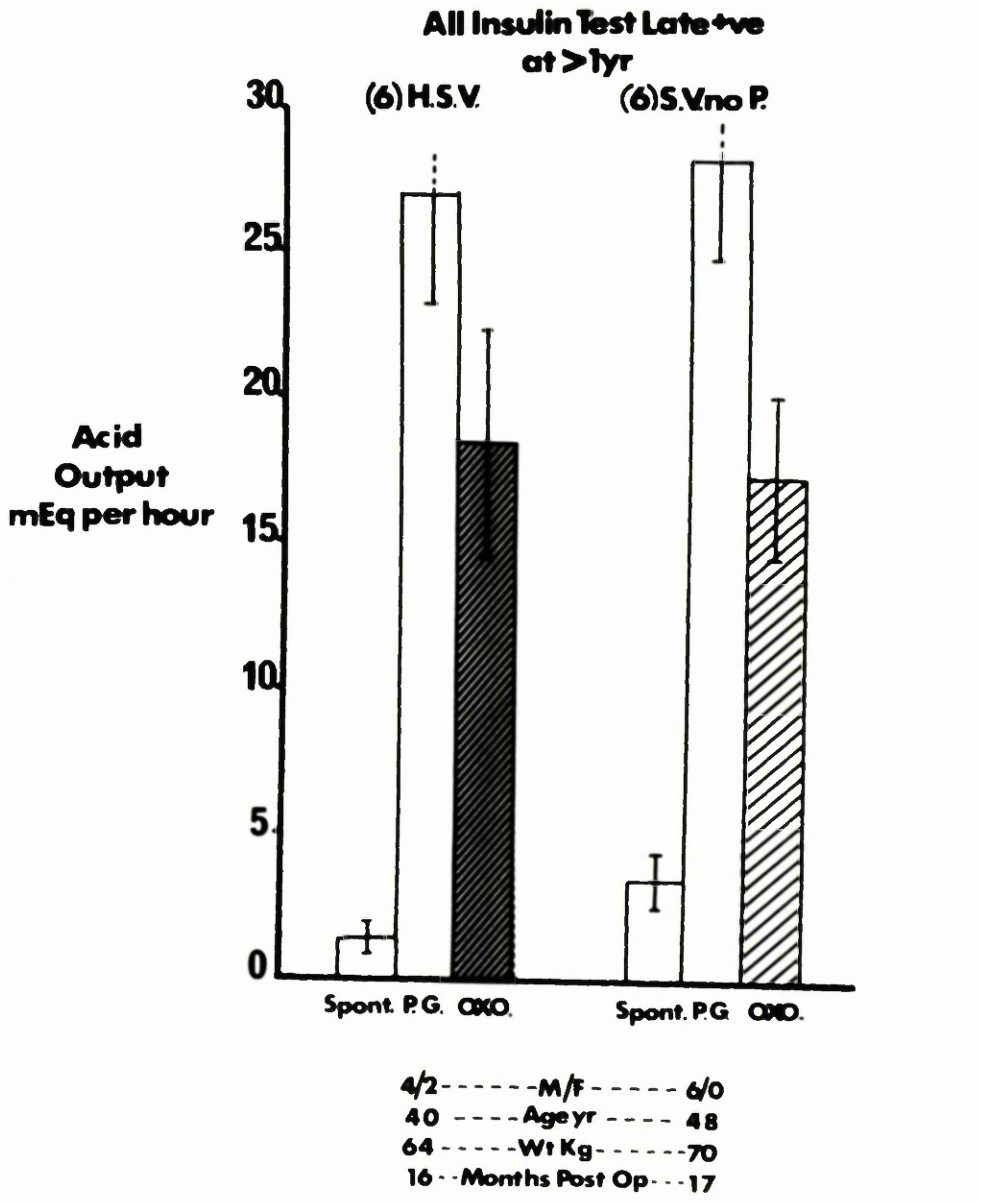

Fig. 7 This is a comparison of mean acid responses to meat extract (OXO) in two matching groups of patients. The group of 6 patients represented by the histogram on the left had undergone HSV without drainage, while the 6 patients represented by the histogram on the right had undergone selective vagotomy without drainage. Matching of the two groups was fairly close with respect to spontaneous and maximal (PG) acid outputs, sex, age, weight, and time-interval after operation. The acid response to OXO was no greater in patients with innervated antra (HSV) than in patients with vagally-denervated antra (SV, no P).

mean peak acid output occurred between 0 and 20 minutes from the start of the test (that is, 25 - 45 minutes from the time when OXO was placed in the stomach), the response after any type of vagotomy was delayed (Figs. 1 - 4). Mean-peak-10-minute output was obtained between 20 and 30 minutes (HSV), between 20 and 30 minutes (TV+P), between 10 and 20 minutes (SV+P) and between 40 and 50 minutes (SV). In patients after SV without drainage, the response to OXO was as rapid in onset as in patients after HSV, TV+P or SV+P, but peak secretion was sustained for a longer period (Fig. 4).

BAO, and acid outputs in response to pentagastrin and to insulin

Details are given in Tables I, and IV - VI, and a summary of the mean data is presented in Table VII. A high incidence of positive responses to insulin was found in patients after HSV, TV+P and SV alone. Of the positive responses, nearly half were early-positive, in the first hour after insulin. The mean acid responses to insulin were approximately equal in patients after HSV and after TV+P, but were less than those found in patients after SV alone. Mean BAO was lowest in patients after HSV, but the high mean values after TV+P and SV+P are to some extent explained by the finding of very high levels of BAO in a few patients (Tables IV and V). Mean acid responses to pentagastrin were 19.7 mEq per hour after HSV, 23.1 after TV+P, 19.2 after SV+P and 25.5 after SV alone. It should be noted that pentagastrin tests in patients after SV were performed immediately after the end of the insulin test.

DISCUSSION

The main finding was that gastric acid output in response to a test meal of meat extract was no greater in patients with a vagally innervated gastric antrum (HSV) than in patients with a vagally denervated antrum (TV+P, SV+P, SV). The test meal of OXO solution was designed to act principally as a chemical stimulus to gastrin release. Since it was administered via a stomach tube, the cephalic phase was bypassed. A tasty normal meal eaten in the normal way might elicit prompt release of gastrin by direct vagal stimulation[5] in patients after HSV, but would not be expected to do so in patients who have undergone complete truncal or selective vagotomy. Again, a meal provokes gastrin release not only by chemical[15], but also by mechanical,[16] stimulation. The latter type of stimulation was reduced to a minimum in the OXO tests, partly because the volume of the test meal was small and partly because its fluid consistency probably provided less mechanical stimulation than a meal consisting of solid food would have done. For these reasons, our findings do not preclude the possibility that a large, tasty, normal meal, eaten in the normal way, might evoke higher acid outputs in patients with vagally innervated antra than in patients whose gastric antra have been vagally denervated.

The question of whether intact vagal innervation of the antrum is necessary for the full efficiency of gastrin release by local chemical stimulation has received much attention in the past. Most of the work has been done in dogs, and the results have been conflicting. For example, Dragstedt and his colleagues[17] found that transplantation of the innervated antrum into the duodenum in dogs increased acid output from the vagotomized "complete" stomach pouch eight- to thirty-fold, and that this stimulation persisted after vagal denervation of the antral pouch. Likewise, vagal denervation of an isolated antral pouch was found not to alter significantly the response of the antrum to chemical stimulation by beef broth, as judged by the output of acid from a Heidenhain pouch (Wohlrabe and Kelly, 1959[18]). However, Wohlrabe and Kelly also found that acid output from the Heidenhain pouch over a 24-hour period decreased significantly (by 60 per cent) after the antral pouch had been vagally denervated. Nyhus and his colleagues[9] reported that the operation of antroneurolysis, which vagally-denervates the antral mucosa, did not diminish gastrin release in response to chemical stimulation with 10 per cent ethyl alcohol or to mechanical stimulation with a balloon, as judged by the acid output from a Heidenhain pouch. We ourselves[19] found no significant change in the acid responses from the innervated corpus of the stomach in dogs, in response to test meals of meat extract or acetylcholine, after the mucous membrane of the

antrum had been vagally denervated by antroneurolysis (see next section). In the latter experiments, the antrum was left "in situ", and was not excluded from contact with the "acid stream" from the body of the stomach. Similarly, in a recent report, Hunt and Cox[20] noted that vagal denervation of the "in situ" antrum in dogs did not diminish acid outputs either from vagally innervated or from vagally denervated pouches of the fundus, in response to a meal of meat. The results of Hunt and Cox could be criticized on the grounds that vagal denervation of the antrum without the addition of a drainage procedure might have produced stasis of food in the antrum, with sustained release of gastrin in consequence. A similar objection could be made to our own work[19] with antroneurolysis in dogs, although after that operation the muscular wall of the antrum retains its vagal nerve supply, and no signs of gastric stasis were noted in our dogs.

In contrast to the findings of the above authors, Forrest[10] found that the response of a denervated fundic pouch to irrigation of an isolated, vagally-innervated antral pouch with liver extract was reduced after vagal denervation of the antral pouch. He concluded that vagal innervation of the antrum "potentiates its excitatory action on gastric secretion". A similar conclusion was reached by Thal, Perry and Wangensteen[21], who found that tubular resection of the body of the stomach, without vagal denervation of the antrum, led to a

significant increase in 24-hour acid output from a denervated fundic pouch, whereas a similar resection when accompanied by vagal denervation of the antrum did not lead to hypersecretion of the denervated fundic pouch. Vagal denervation of the "in situ" antrum was found by De Castella and Irvine[22] to lead to a significant decrease in the response to a meal of meat from Heidenhain pouches in dogs. Although peak acid outputs from Pavlov pouches were unaltered, the acid outputs in the later stages of the response did diminish significantly. In man, Welbourn and Burns[23] found that the acid response to OXO solution was reduced by a mean of 67 per cent (from 10.6 to 3.6 mEq per hour) in 35 patients 10 days after complete truncal vagotomy. Similarly, Giles and Clark[24] found that the response to OXO was absent in 23 of 36 patients, 7 to 10 days after complete (insulin-negative) vagotomy and pyloroplasty, while in the remaining patients the response was much reduced. The papers of Welbourn and Burns[23] and of Giles and Clark[24], however, record the effects of vagal denervation both of the antrum and of the parietal cell mass, rather than the specific effect of antral denervation alone. We also found that acid responses to OXO are very small in the early post-operative period. Thus it would appear that in man, the response to OXO is temporarily grossly impaired in the early weeks after either HSV or TV+P, but that it subsequently increases in the course of the first year after operation.

The available evidence on the effect of vagotomy on gastrin release in response to a distension stimulus is also conflicting. Nyhus and his colleagues[9] reported that vagal denervation of the antral mucosa by the operation of antroneurolysis had no effect on gastrin release in response to distension of a separated antral pouch in dogs. On the other hand, Sugawara and his colleagues[25] found that in dogs equipped with isolated innervated antral pouches and Heidenhain pouches, truncal vagotomy led to a significant decrease in acid output from the Heidenhain pouches in response to antral distension.

It seems justifiable to speak of a "vagally innervated" antrum in relation to patients after HSV and of a "vagally denervated" antrum in patients after TV or SV, because careful motility[26,27] and secretory[28] studies carried out in the dog have shown that the nerves of Latarjet, which are preserved in HSV but cut in TV or SV, are the sole extramural pathway whereby vagal fibres reach the antrumof the stomach. Stimulation of the hepatic and coeliac branches of the vagus does not lead to an increase in the gastric antral pressure[26,27] or to the release of gastrin[28]. Intramural vagal fibres passing to the antrum in Meissner's submucosal plexus[28] probably have their central connections severed in the performance of the vagotomy of the parietal cell mass which is common to all three types of vagotomy. However, the high incidence of positive responses to insulin which we found more than one year after

HSV, TV+P and SV (and which would no doubt have been found also in patients after SV+P had they been tested), suggests that partial vagal reinnervation of the parietal cell mass took place in many patients, and it is possible that the antral region of the stomach may also have acquired partial reinnervation in many patients after TV or SV. This observation does not weaken the general conclusion that the response to the test meal is not greater after HSV than after TV or SV, because there is no reason to believe that the patients who were tested after TV or SV were in any way atypical. Indeed, they were rather superior, on average, to the generality of patients after TV or SV, in the sense that clinical failures were excluded, and also because the patients at Leeds (TV+P, SV+P groups) had all been shown to have negative insulin tests in the early post-operative period. A high insulin-positive incidence on late testing after vagotomy is certainly not peculiar to this series of patients. It is a characteristic finding several months or more after both truncal[29-31] and bilateral selective[32] vagotomy.

No claim is made that the acid response to meat extract was significantly greater in patients after TV+P or SV than in patients after HSV; merely that it was not significantly less. The responses to OXO in the HSV and SV+P groups of patients were very similar. Although the mean response to OXO was considerably greater after TV+P than after HSV (19.6 mEq per hour compared with 10.1), the numbers of

patients tested are too small, and "matching" of the groups too imperfect, for any significance to be attached at present to this difference. Nevertheless, the possibility that gastrin release may be greater after TV+P than after HSV in response to chemical stimulation merits further study. An alternative explanation for the higher responses to OXO after TV+P than after HSV is that onward passage of part of the test meal into the intestine during the 15-minute "incubation' period may have released from the mucosa of the small bowel more of some humoral stimulator, or less of some humoral inhibitor, of gastric secretion after TV than after HSV. It is well recognized that in dogs, performance of truncal vagotomy is followed by a significantly greater increase in acid output from Heidenhain pouches than is found after the performance of bilateral selective vagotomy[33-35]. This has been attributed[36] to the inhibitory influence of the hepatic and coeliac branches of the vagus, acting, presumably, by means of a humoral mechanism, since they are able to inhibit acid output from vagally-denervated pouches of the body of the stomach. In short, the much greater acid response to OXO in patients after TV+P than in patients after HSV may have arisen by chance, but the intriguing possibility exists that the difference is a real one, and of clinical importance. Further study of well-matched groups of patients after TV+P and HSV is certainly

indicated.

The mean acid response to OXO in 18 patients after SV without drainage (14.2 mEq per hour) was considerably greater than the mean response in 25 patients after HSV (10.1 mEq per hour). However, the mean acid output in response to insulin (8.1 mEq per hour) after SV was also much greater than that which was found in patients after HSV(3.7 mEq per hour), and all 12 patients who underwent insulin testing after SV had positive responses. In addition, their mean response to pentagastrin (25.5 mEq per hour) was greater than that of patients after HSV, whose mean PAO^{PG} (after insulin) was 19.4 mEq per hour. Hence, the most reasonable explanation for the greater response to OXO in patients after SV alone appears to be that a greater proportion of their parietal cell mass had become reinnervated, or, at any rate, <u>was</u> innervated at the time of testing. The observation of a late, and long-sustained, peak of secretion in response to OXO in the SV patients (Fig. 4), but in no other group, suggests that subclinical antral stasis, leading to prolonged release of gastrin, may have been a factor contributing to their relatively high acid response. Although the mean volume of resting juice in the stomach after SV alone was little different from that found after HSV, TV+P or SV+P, the mean volume of (OXO + added gastric secretion) recovered at the end of the

15-minute "incubation" period (114ml.) was considerably greater than the mean volume recovered after HSV (82ml.), TV+P (75ml.) or SV+P (65ml.). Perhaps the subsequent gastric wash-out failed to remove the last traces of OXO solution in patients after SV. This would provide an explanation for their long-sustained secretory response to OXO.

The finding that gastric acid output in response to a test meal of meat extract is no greater in patients with a vagally innervated antrum (HSV) than in patients with a vagally denervated antrum (TV, SV) provides further evidence in support of the idea that the gastric antrum need not be vagally denervated in the course of operations for duodenal ulcer, provided that it is well drained and that it remains in continuity with the "acid stream" flowing from the body of the stomach. By "well drained" is meant that stasis of food in the stomach is absent. It does not imply that routine performance of a drainage procedure is essential. The suggestion that preservation of the vagal nerve supply to the antrum is permissible derives support also from our studies of BAO and of the responses to insulin-induced hypoglycaemia, which are no greater in patients after HSV than in patients after TV+P. Thus we have shown that acid output after HSV is not excessive, whether in the fasting patient, in response to direct vagal stimulation, or in

response to a test meal. Although it is still conceivable that gastrin release might be excessive when the various "phases" of gastric secretion are combined; as, for example, when a large tasty meal is eaten, such a possibility is, in our opinion, unlikely. In the dog, vagal release of gastrin is much less when the antrum is left "in continuity", exposed to acid-inhibition[2,6,37] than when the antrum is "separated", and thus shielded from the inhibitory action of endogenous acid[7-10]. Low intra-antral pH is a potent inhibitor of gastrin release in man[38], as in the dog[8,9,17,39]. When the antrum is left in continuity with the acid stream in dogs, far from being an ulcerogenic influence, it actually protects against ulcer[40,41]. Furthermore, the protection which it affords is better if its vagal nerve-supply is left intact than if it is cut[42]. The few surgeons who have preserved the vagal nerve-supply to the antrum in operating for duodenal ulcer have found low ulcer recurrence rates on medium-term follow-up of their patients[43,44]. For example, Holle[44], reports a recurrence rate of less than 1 per cent in 171 patients who were followed up for 1 to 7 years after "SPV" (HSV) with drainage or antrectomy. Most of his patients had a drainage procedure, which took the form of a pyloroplasty in 90 per cent of cases: follow-up was about 80 per cent complete (Holle, personal communication) The loss to follow-up of 20 per cent of his patients should not be

regarded as a major indictment of Holle's figures, because he finds it difficult to trace migrant workers from other parts of Europe, who spend only a few years in Bavaria before returning home.

In dogs which have been equipped with Heidenhain pouches, HSV without a drainage procedure has been shown to be followed by an increase in pouch secretion in response to feeding[35,45] or over a 24-hour period[46]. The mean increase in 24-hour acid output in Amdrup and Griffith's dogs[46] was 47 per cent. Klempa, Holle and their colleagues recorded a much larger increase in acid output in response to a meal of meat[45]. It is important to note, however, as Takita's results show clearly[35], that the increase in pouch secretion after HSV is much less than that which follows TV, and that the increase after SV is intermediate between that produced by HSV and that produced by TV. Takita[35] repeated his experiments in dogs with pyloroplasty added to the HSV, SV or TV, and obtained the same results: HSV led to the smallest increase in pouch secretion, and TV to the greatest. While Holle and his colleagues[46] attribute the increase in pouch secretion after SPV (HSV) to antral stasis, leading to excessive release of gastrin, an alternative explanation is that gastrin release is increased merely because of diminished flow of HCl from the body of the stomach after HSV, leading to diminished inhibition of gastrin release. In keeping with their conclusions, Klempa and Holle's[45] dogs

were shown to have delayed gastric emptying after SPV (HSV) without a drainage procedure. However, Amdrup and Griffith[46] and Interone et al.[42] did not observe delay in gastric emptying in their dogs after HSV without drainage. We have found little evidence of gastric stasis in 150 patients with gastric or duodenal ulcer who underwent HSV in the past three and a half years (vide infra).

As the results of radioimmunoassay of serum gastrin concentration become available, it has been fascinating to learn that truncal vagotomy and pyloroplasty in man is followed by a five-fold increase in plasma gastrin concentration[47], and that gastrin levels, both in fasting patients and after a protein meal, are significantly higher after truncal vagotomy than after selective vagotomy[47,48]. Ardill, Buchanan and Kennedy have found that fasting plasma gastrin concentration after selective vagotomy with a drainage procedure is greater than that which is found after HSV, although not significantly so (T. Kennedy, personal communication). These results are in accord with our findings with respect to spontaneous acid output and the response to meat extract in patients after TV, SV and HSV.

SUMMARY

In 26 patients with duodenal ulcer before operation, the mean peak acid output in response to a test meal of meat extract (OXO solution) was 21.7 mEq per hour. In 25 patients more than one year after HSV, it was 10.1 mEq per hour. HSV was found to reduce the response to OXO by 45 to 50 per cent, and the mean acid response to OXO was 50 per cent of the 'maximal' response to pentagastrin, both before operation and more than one year after HSV. No evidence was found to suggest that release of gastrin was excessive after HSV.

The response to OXO after HSV was compared with the responses to OXO after truncal V+P, bilateral selective V+P and bilateral selective vagotomy without drainage (SV). The patients studied were in good health, more than one year after operation, and completeness of the vagotomy had been proved by the finding of a negative insulin test in the early post-operative period. The mean peak acid response to OXO in 11 patients after TV+P was 19.6 mEq per hour; in 10 patients after SV+P was 11.0 mEq per hour and in 18 patients after SV alone was 14.2 mEq per hour. Thus the mean acid output in response to the test meal was no greater in patients with a vagally innervated gastric antrum (HSV) than in patients with a vagally denervated gastric antrum (TV, SV). Within the limits of the experiment, in which the cephalic phase was bypassed and mechanical

stimulation reduced to a minimum, no evidence was found to suggest that vagal denervation of the "in situ" antrum in man reduces the acid response to a test meal. This suggests that vagal denervation of the antrum as in truncal or bilateral selective vagotomy may not accomplish its purpose of diminishing the release of gastrin. Hence, vagal denervation of the antrum in man may not provide protection against recurrent ulceration. Conversely, patients with a vagally innervated antrum may not be at greater risk of recurrent ulceration than are patients whose gastric antrum has been vagally denervated.

Table I

PATIENTS WITH HIGHLY SELECTIVE

NO.	NAME	AGE AND SEX	WEIGHT (kg.)	LENGTH OF ULCER HISTORY (years)	LENGTH OF FOLLOW-UP (months)	VISICK GRADE	PRE-OP PAO / PG mEq/hr	RESTING JUICE (ml.)	VOLUME OF OXO + GASTRIC JUICE RECOVERED AFTER 15 MINS. (ml.)	SPON-TANEOUS BAO (mEq/hr)	RESPONSE TO OXO (mEq per hour)	
											PAO	TH
A	S.M.	45 M	62	8	24	I	69.75	50	140	4.71	25.02	20.04
B	E.W.	45 M	66	12	14	II	55.08	33	56	3.22	28.23	24.04
C	H.S.	41 M	85	10	15	III	81.90	35	145	2.80	30.15	16.75
1	F.C.	34 M	84	8	12	I	64.14	132	140	2.20	26.55	18.78
2	P.A.	21 F	57	5	18	III	26.88	51	135	1.27	10.89	5.75
3	P.S.	36 M	66	15	14	II	38.16	75	144	2.86	7.92	6.26
4	E.L.	44 M	61	10	18	I	35.70	38	55	0.13	0.93	0.67
5	J.I.	47 M	65	3	18	I	43.65	12	37	0.56	1.78	1.32
6	G.W.	35 M	75	8	21	II	29.85	60	160	0.15	0.30	0.18
7	B.S.	35 M	60	3	13	IV	37.02	30	76	4.61	14.28	10.26
8	F.D.	64 M	72	25	20	I	39.18	75	86	0.00	1.98	1.33
9	A.W.	36 M	78	15	12	I	53.85	45	98	0.43	9.09	7.63
10	R.P.	47 M	67	20	12	II	51.72	19	79	2.04	6.63	5.65
11	H.H.	42 F	53	5	22	III	28.53	35	48	0.31	8.82	5.06
12	S.G.	30 M	75	2	14	I	56.04	50	not recorded	5.97	28.80	21.38
13	A.T.	19 M	56	4	14	I	42.60	101	78	3.47	24.36	14.36
14	M.B.	42 F	50	2	14	II	39.09	57	53	1.00	10.56	7.37
15	R.C.	41 M	80	2	15	II	36.60	23	47	1.61	12.63	11.54
16	J.D.	52 M	70	20	14	I	30.00	45	55	0.53	1.68	1.14
17	H.N.	52 M	83	10	14	II	35.97	65	53	1.23	9.99	8.46
18	C.C.	54 M	75	20	15	I	38.10	45	64	1.15	14.16	10.40
19	M.F.	50 F	43	20	13	II	18.27	38	75	1.29	10.47	8.68
20	F.W.	47 M	74	16	14	I	46.08	83	97	2.11	7.23	4.25
21	W.C.	43 M	69	13	16	I	51.60	98	83	3.06	7.77	6.35
22	E.H.	57 F	54	6	16	II	27.69	37	62	0.58	7.08	4.16
23	A.D.	42 F	57	7	20	I	30.00	52	112	0.86	11.40	9.35
24	G.M.	29 M	68	5	21	II	71.79	50	55	1.04	6.72	5.04
25	R.R.	51 M	80	10	22	I	31.80	56	72	1.36	11.13	8.43
MEAN OF 25		42.00	66.88	10.16	16.08		40.17	54.88	81.83	1.59	10.13	7.35
± 1 SEM		2.16	2.21	1.39	0.66		2.49	5.49	6.96	0.29	1.48	1.05

Patient A (SA) had undergone HSV plus a small (70G) resection of parietal cell mass.
Patients B and C had undergone HSV in the treatment of "duodenitis" associated with hypersecretion.

VAGOTOMY (INNERVATED ANTRUM)

RESPONSE TO PENTAGASTRIN (mEq/hr)				RESPONSE TO INSULIN (mEq per hour)			OXO / PG PER CENT			
PG ALONE		PG AFTER INSULIN					(PG ALONE)		(PG AFTER INSULIN)	
PAO	TH	PAO	TH	PAO	PH	POSITIVE OR NEGATIVE	PAO	TH	PAO	TH
34.98	27.34	-	-	10.36	8.43	early +ve	71.53	73.30	-	-
-	-	34.50	32.16	17.18	11.84	late +ve	-	-	81.83	74.75
52.44	42.55	-	-	9.30		early +ve	57.49	39.36	-	-
-	-	41.76	32.44	5.90	4.71	-ve	-	-	63.58	57.89
15.63	10.62	20.16	13.33	2.04	1.47	-ve	69.67	54.14	54.02	43.14
17.08	16.10	17.34	14.32	2.52	2.43	-ve	46.37	38.88	45.67	43.72
6.15	3.84	-	-	0.24	0.15	-ve	15.12	17.45	-	-
10.02	7.07	12.48	8.05	0.48	0.30	-ve	17.76	18.67	14.26	16.40
13.65	11.02	-	-	0.00	0.00	-ve	2.20	1.63	-	-
16.77	14.46	-	-	3.68	3.48	-ve	85.15	70.95	-	-
3.96	2.72	8.16	5.45	0.38	0.23	-ve	50.00	48.90	24.26	24.40
32.13	19.60	20.76	12.59	0.34	0.17	-ve	28.29	38.93	43.79	60.60
14.88	13.19	10.65	8.58	1.48	1.07	-ve	44.56	42.84	62.25	65.85
19.50	14.35	17.88	14.87	4.60	3.01	Late +ve	45.23	35.26	49.33	34.03
46.86	31.87	29.43	25.27	8.10	6.49	Late +ve	61.46	67.09	97.86	84.61
26.22	20.99	29.61	23.33	10.50	7.81	Late +ve	92.91	68.41	82.27	61.55
-	-	28.40	23.80	2.08	1.59	Late +ve	-	-	37.18	30.88
10.35	8.00	12.39	10.64	9.30	8.27	Late +ve	122.03	144.25	101.94	108.49
-	-	14.25	7.82	1.82	1.58	Late +ve	-	-	11.79	14.58
-	-	22.20	18.61	3.06	1.83	Late +ve	-	-	45.00	45.46
-	-	20.01	17.47	3.94	3.43	Late +ve	-	-	70.76	59.43
13.56	10.76	10.68	9.14	3.82	3.32	Early +ve	77.21	80.67	98.03	94.97
24.54	23.34	22.14	18.76	4.32	4.26	Early +ve	29.46	18.21	32.66	22.65
29.88	24.34	23.52	20.12	7.20	6.47	Early +ve	26.00	26.09	33.04	31.56
18.00	16.80	11.25	8.54	1.14	1.08	Early +ve	39.33	24.76	62.93	48.71
21.96	15.21	16.68	12.05	5.00	4.76	Early +ve	51.91	61.47	68.35	77.59
37.38	29.13	-	-	7.64	7.18	Early +ve	17.98	17.30	-	-
15.18	12.22	17.73	15.28	2.52	2.38	Early +ve	73.32	68.99	62.77	55.17
19.69	15.28	19.40	15.26	3.68	3.10		49.80	47.24	55.32	51.51
(20)	(20)	(21)	(21)				(20)	(20)	(21)	(21)
2.38	1.74	1.76	1.51	0.60	0.51		6.74	7.15	5.65	5.54

Table II

EFFECT OF HSV ON BAO AND ON RESPONS

(Patients tested before, and m

	PRE-OP. AGE yr.	SEX	PRE-OP. WEIGHT kg.	MONTHS POST-OP.	VISICK GRADE >1yr.	RESTING JUICE ml. in 15 mins. Before	After	PER CENT REDUCTION	SPONTANEOUS ACID OUTPUT mEq/hr Before	After	PER CENT REDUCTION
A[1]	41	M	85	15	II	89	35	60.67	35.34	2.80	92.08
1	34	M	84	12	I	105	132	(25.71)	9.22	2.20	76.14
2	21	F	57	18	III	85	51	40.00	4.70	1.27	72.98
3	36	M	66	14	II	115	75	34.78	2.80	2.59	7.50
4	44	M	61	18	I	77	38	50.65	3.86	0.00	100.00
5	47	M	60	18	I	122	12	90.16	7.10	0.40	94.37
6	48	F	41	13	II	63	38	39.68	2.04	1.28	37.25
7	47	M	70	14	I	86	83	3.49	6.58	1.83	72.19
8	27	M	75	14	I	127	50	60.63	28.30	3.67	87.03
9	16	M	51	14	I	110	101	8.18	11.28	3.47	69.24
MEAN	36.10		65.00	15.00		97.90	61.50	36.25	11.22	1.95	70.88
± 1SEM	3.63		4.43	0.70		6.63	11.39	10.56	3.60	0.39	9.00

1 All patients had duodenal ulcer except A, who had dyspepsia and giant duodenal mucosal folds.

ES TO OXO, PENTAGASTRIN AND INSULIN

ore than one year after, HSV)

RESPONSE TO OXO PAO^{OXO} (mEq/hr)			RESPONSE TO OXO T.H.^{OXO} (mEq/hr)			RESPONSE TO PENTAGASTRIN PAO^{PG} (mEq/hr)			RESPONSE TO INSULIN Hollander- +ve / -ve After HSV	PAO^{I} mEq/hr	$\frac{PAO^{OXO}}{PAO^{PG}} \cdot$ PER CENT	
Before	After	PER CENT REDUCTION	Before	After	PER CENT REDUCTION	Before	After	PER CENT REDUCTION			Before	After
60.15	30.15	49.88	40.77	16.75	58.92	81.90	52.44	35.97	early +	9.30	73.44	57.49
22.89	26.55	-15.99	17.34	18.78	-8.30	64.14	41.76*	34.89	-ve	5.90	35.69	63.58
13.47	10.89	19.15	10.66	5.75	46.06	26.88	15.63	41.85	-ve	2.04	50.11	69.67
14.19	7.92	44.19	12.04	6.26	48.01	38.16	17.08	55.24	-ve	2.52	37.19	46.37
14.88	0.93	93.75	14.18	0.67	95.28	35.70	6.15	82.77	-ve	0.24	41.68	15.12
21.42	1.78	91.69	17.51	1.32	92.46	43.65	10.02	77.04	-ve	0.48	49.07	17.76
13.59	10.47	22.96	7.59	8.68	14.36	18.27	13.56	25.78	early +	3.82	74.38	77.21
16.47	7.23	56.10	14.58	4.25	70.85	46.08	24.54	46.74	early +	4.32	35.74	29.46
30.42	28.80	5.33	27.59	21.38	22.48	56.04	46.86	16.38	late +	8.10	54.28	61.46
36.66	24.36	33.55	16.43	14.36	12.60	42.60	26.22	38.45	late +	10.50	86.06	92.91
24.41	14.91	40.06	17.87	9.82	42.40	45.34	25.43	45.51		4.72	53.76	53.10
4.70	3.60	11.08	3.05	2.37	12.25	5.81	4.44	6.65		1.15	5.74	8.14

* Pentagastrin test performed immediately after insulin test.

Table III

RESPONSE TO OXO IN PATIENTS WITH DUODENAL ULCER BEFORE AND AFTER HSV

	SEX	AGE yr.	WEIGHT kg.	PRE-OP. PAO^{PG} mEq/hr	RESPONSE TO OXO (mEq per hour)			
					PAO^{OXO}	PER CENT OF PAO^{PG}	TH^{OXO}	PER CENT OF TH^{PG}
26 PATIENTS BEFORE HSV	22 M	41.35	68.85	46.82	21.69	47.82	15.69	42.94
	4 F	±2.23	± 2.31	± 3.17	± 2.15	± 3.48	± 1.46	± 2.96
25 PATIENTS* ONE YEAR AFTER HSV	19 M	42.00	66.88	40.17	10.13	49.80	7.35	51.51
	6 F	±2.16	± 2.21	± 2.49	± 1.48	± 6.74	± 1.05	± 5.54

* Patients tested after HSV include 10 of those tested before HSV, plus 15 others.

Table IV

PATIENTS WITH TRUNCAL VAGOTOMY AND PY

O.	NAME	AGE AND SEX	WEIGHT (kg.)	LENGTH OF ULCER HISTORY (years)	LENGTH OF FOLLOW-UP (months)	VISICK GRADE	PRE-OP. RESPONSE TO PG PAO mEq/hr	RESTING JUICE (ml.)	VOLUME OF OXO + GASTRIC JUICE RECOVERED AFTER 15 MIN. (ml.)	SPONT-ANEOUS ACID OUTPUT mEq/hr
1	J.W.	48 M	83	3	36	I	48.98	80	57	3.12
2	B.M.*	46 M	80	8	24	I	39.15	106	192	27.36
3	J.M.	52 M	59	10	30	I	53.19	78	100	9.14
4	G.T.	43 M	63	20	50	II	-	21	57	1.90
5	C.R.	48 M	63	16	42	II	52.65	80	135	5.01
6	S.W.	58 M	83	2	30	II	-	14	55	2.32
7	F.H.	56 M	66	10	18	II	-	40	117	2.48
8	K.T.	35 M	74	8	17	II	52.95	110	40	3.06
9	H.T.	73 M	73	22	19	II	63.45	51	75	3.58
0	W.J.	35 M	62	15	16	I	62.85	52	42	2.35
1	J.G.	45 M	68	?	36	I	-	98	73	15.61
EAN OF 11)		49.00	70.36	11.40	28.90		53.32	66.36	85.73	6.90
1 SEM		3.26	2.64	2.12	3.40		3.14	9.96	14.07	2.39
EAN OF 9 excluding os. 2 and 11)		49.78	69.56	11.78	28.67		55.68	58.44	75.10	3.66
1 SEM		3.98	3.03	2.34	4.07		2.45	10.40	10.20	0.75

* The drainage procedure in patient No. 2 was a gastrojejunostomy. "Mean of 9" was calculated, excluding patients 2 and 11, because of their exceptionally high levels of spontaneous secretion. Both, however, were in Visick grade I.

LOROPLASTY (VAGALLY-DENERVATED ANTRUM)

RESPONSE TO OXO (mEq per hour)		RESPONSE TO PENTAGASTRIN (mEq per hour)		RESPONSE TO INSULIN (mEq per hour)			OXO / PG ALONE PER CENT		RESPONSE TO PG AFTER INSULIN (mEq per hour		OXO / PG-AFTER-INSULIN PER CENT	
PAO	TH	PAO	TH	PAO	PH	POSITIVE OR NEGATIVE	PAO	TH	PAO	TH	PAO	TH
27.09	22.84	30.87	23.55	2.78	2.68	Early +	87.76	96.99	37.44	32.00	72.36	71.38
48.96	47.46	39.87	34.22	42.48	38.24	Early +	122.80	138.69	57.54	50.60	85.09	93.79
21.45	14.05	29.16	21.01	7.82	6.31	Late +	73.56	66.87	26.49	19.97	80.97	70.36
2.85	1.60	19.44	14.78	2.60	2.51	Late +	14.66	10.83	18.21	14.49	15.65	11.04
20.13	16.78	23.58	21.51	4.48	3.27	Late +	85.37	78.01	31.86	27.11	63.18	61.90
11.46	9.35	19.65	15.46	8.24	7.80	Late +	58.32	60.48	21.99	19.53	52.11	47.88
15.06	11.54	22.00	16.72	0.90	0.64	-ve	68.45	69.02	15.96	9.59	94.36	120.33
14.10	8.03	33.30	23.24	0.42	0.37	-ve	42.34	34.55	18.60	13.13	75.81	61.16
13.38	10.99	15.72	11.99	0.82	0.62	-ve	85.11	91.66	16.53	12.89	80.94	85.26
8.88	6.23	14.13	10.38	1.06	0.84	-ve	62.85	60.02	11.01	9.12	80.65	68.31
32.61	19.44	-	-	-	-	-	-		-	-	-	-
19.63	15.30	24.77 (10)	19.29 (10)	7.16 (10)	6.33 (10)		70.12 (10)	70.71 (10)	25.56 (10)	20.84 (10)	70.11 (10)	69.14 (10)
3.86	3.70	2.62	2.21	4.03	3.63		9.19	11.02	4.35	4.05	7.10	9.09
14.93	11.27	23.09	17.63	3.24	2.78		64.27	63.16	22.01	17.54	68.45	66.40
2.40	2.06	2.24	1.63	1.00	0.89		7.92	8.97	2.81	2.62	7.71	9.69

PG - pentagastrin.

Note that patients with a perfect clinical result (Visick grade I) had a greater response to OXO (on average) than had patients with a less-than-perfect result.

TABLE V

Table V

PATIENTS WITH BILATERAL SELECTIVE VAGOTOMY

NO.	NAME	AGE AND SEX	WEIGHT (kg.)	LENGTH OF ULCER HISTORY (years)	LENGTH OF FOLLOW-UP (months)	VISICK GRADE	RESPONSE TO PG* PRE-OP. PAO mEq/hr
1	C.K.	40 M	77	12	55	I	60.00
2	S.M.	61 M	60	12	47	I	58.00
3	F.S.	28 M	57	4	36	II	56.00
4	M.W.	50 F	56	5	31	II	23.76
5	D.W.	50 M	65	18	56	III	39.60
6	G.M.	46 M	64	10	52	III	40.40
7	H.G.	67 M	62	9	56	I	24.00
8	H.C.	65 M	82	30	52	III	50.00
9	G.H.	39 M	65	6	38	I	71.34
10	C.H.	50 M	64	8	52	III	30.50
MEAN		49.60	65.20	11.40	47.50		45.36
± 1SEM		3.88	2.61	2.44	2.90		5.15

PG*, pentagastrin, which in pre-operative tests was given intravenously, in a 'maximal' dose of 1.5 or 6.0 ug per kg per hour.

AND PYLOROPLASTY (VAGALLY-DENERVATED ANTRUM)

RESTING JUICE (ml.)	VOLUME OXO + GASTRIC JUICE RECOVERED AFTER 15 MIN. (ml.)	SPONTANEOUS ACID OUTPUT (PAO) mEq/hr	RESPONSE TO OXO (mEq per hour)		RESPONSE TO PENTAGASTRIN‡ (mEq per hour)	OXO / PG PER CENT ALONE
			PAO	TH	PAO	PAO
17	25	1.78	7.80	6.82	17.20	45.35
72	111	14.29	16.98	15.33	-	-
75	23	5.40	11.55	8.01	26.93	42.89
130	110	0.00	0.00	0.00	-	0.00
21	32	2.35	5.37	4.38	13.44	39.96
40	32	0.49	10.02	8.33	8.91	112.46
75	72	2.01	11.76	9.79	10.60	110.94
25	105	0.00	0.54	0.18	8.40	6.43
91	85	13.53	31.11	24.87	43.83	70.98
50	55	0.36	15.06	9.02	24.30	61.98
59.60	65.00	4.02	11.02	8.67	19.20	54.56
11.33	11.47	1.72	2.85	2.30	4.28 (8)	13.22 (9)

‡ Note also that in patients after SV+P only, the "response to pentagastrin" is PAO in response to intravenous infusion of 6 or 12 ug per kg per hour of pentagastrin, and the measurement was made 1 - 2 years post-operatively.

Insulin and intramuscular-pentagastrin tests were not performed in these patients.

Response to OXO was greater (on average) in patients in Visick grade I that in patients with a less good clinical result.

TABLE VI

Table VI

PATIENTS WITH BILATERAL SELECTIVE VAGOTOMY WITH

NO.	AGE AND SEX	WEIGHT (kg.)	LENGTH OF ULCER HISTORY (years)	LENGTH OF FOLLOW-UP (months)	VISICK GRADE	RESTING JUICE	VOLUME OXO + GASTRIC JUICE RECOVERED AFTER 15 MIN. (ml.)	SPONTANEOUS ACID OUTPUT B.A.O. (mEq/hr)
1	34 M	85	3	21	I	135	not recorded	6.29
2	68 M	80	15	18	I	60	76	0.76
3	67 M	55	30	21	I	49	63	5.03
4	49 M	60	7	12	II	38	63	2.37
5	39 M	70	20	16	III	60	67	3.12
6	29 M	67	9	16	I	125	not recorded	6.81
7	46 M	80	6	20	I	39	106	2.38
8	41 F	51	6	42	I	83	163	1.11
9	54 M	77	20	14	II	89	150	0.94
10	39 F	54	5	20	III	85	148	0.69
11	17 M	60	1	16	I	57	170	3.59
12	39 M	76	9	17	II	46	143	1.79
13	59 M	71	20	40	II	76	145	9.56
14	33 M	72	1	21	I	98	87	1.87
15	62 M	61	25	17	I	40	117	0.26
16	27 M	76	5	21	I	189	145	0.13
17	53 F	50	10	24	II	22	129	1.87
18	54 F	51	20	21	I	31	49	0.00
Mean ± 1SEM	45.00 3.38	66.44 2.69	11.78 2.06	20.94 1.89		73.44 10.04	113.81 10.18	2.70 0.62

OUT DRAINAGE (VAGALLY-DENERVATED ANTRUM)

RESPONSE TO OXO		RESPONSE TO PENTAGASTRIN AFTER INSULIN (mEq per hour)		RESPONSE TO INSULIN (mEq per hour)			OXO PER CENT PG AFTER INSULIN	
PAO	TH	PAO	TH	PAO	PH	POSITIVE OR NEGATIVE	PAO	TH
24.63	21.63	32.28	26.76	8.82	8.71	Late +	76.30	80.83
22.02	19.35	31.23	24.68	6.02	5.24	Late +	70.51	78.40
11.22	9.69	24.30	20.80	5.90	5.53	Late +	46.17	46.59
11.10	8.94	25.08	22.30	4.92	4.63	Late +	44.26	40.09
10.65	6.82	15.93	12.19	2.50	2.47	Late +	66.85	55.95
24.09	16.81	40.71	36.03	22.86	19.32	Late +	59.17	53.62
12.84	7.81	24.00	20.41	9.22	9.02	Early +	53.50	38.27
9.51	6.86	12.96	10.94	2.86	2.78	Early +	73.40	62.71
12.99	9.99	24.84	20.66	2.94	2.86	Early +	52.29	48.35
14.01	6.46	19.50	14.85	5.50	5.15	Early +	71.85	43.50
27.00	23.00	34.74	32.40	18.98	18.25	Early +	77.72	70.99
16.86	12.35	19.95	16.97	6.86	6.25	Early +	84.51	72.78
24.75	22.88	-	-	-	-	-	-	-
5.22	3.41	-	-	-	-	-	-	-
1.80	1.39	-	-	-	-	-	-	-
16.20	7.48	43.47*	33.45	-	-	-	37.27	22.36
9.96	5.96	24.75*	18.26	-	-	-	40.24	32.64
0.0	0.0	3.90*	2.15	-	-	-	0.0	0.0
14.16	10.60	25.46[1]	21.58[1]	8.12	7.52	6 late+	64.71[1]	57.67[1]
1.87	1.70	2.33	2.01	1.85	1.78	6 early+	3.96	3.84

* Pentagastrin test done immediately after OXO test

1 Mean of results in patients 1 - 12.

Table VII

SUMMARY OF RESULTS: MEAN RESPONSES

IN PATIENTS WITH VAGALLY-INNERVATED (HSV) O

	AGE (years)	WEIGHT (kg.)	LENGTH OF ULCER HISTORY (years)	LENGTH OF FOLLOW-UP (months)	PRE-OP. PAO^{PG} mEq/hr	RESTING JUICE (ml.)	VOLUME OXO + GASTRIC JUICE RECOVERED AFTER 15 MINS. (ml.)	SPONT-ANEOUS BAO mEq/hr
HSV (25)	42	67	10	16	40.2	55	82	1.6
TV+P** (9)	50	70	12	29	55.7	75	75	3.7
SV+P (10)	50	65	11	48	45.4*	60	65	4.0
SV (18)	45	66	12	21	-	73	114	2.7

* response to intravenous pentagastrin. ± mean results in 12 patients.

** excluding results of 2 patients after TV+P who had exceptionally-high spontaneous acid output and very high responses to OXO also.

TO OXO, PENTAGASTRIN AND INSULIN

R VAGALLY-DENERVATED (TV, SV) GASTRIC ANTRA

RESPONSE TO OXO (mEq per hour)		RESPONSE TO PENTAGASTRIN (mEq per hour)				RESPONSE TO INSULIN (mEq per hour)			OXO/PG PER CENT			
		PG ALONE		PG AFTER INSULIN				POSITIVE OR NEGATIVE	PG ALONE		PG AFTER INSULIN	
PAO	TH	PAO	TH	PAO	TH	PAO	PH		PAO	TH	PAO	TH
10.1	7.4	19.7	15.3	19.4	15.3	3.7	3.1	8 L+ 10 -ve 7 E+	50	47	55	52
14.9	11.3	23.1	17.6	22.0	17.5	3.2	2.8	3 -ve 4 L+ 1 E+	64	63	68	66
11.0	8.7	19.2*	-	-	-	-	-	-	55	-	-	-
14.2	10.6	-	-	25.5	21.6	8.1	7.5	6 L+ 6 E+ 6 not tested	-	-	65[1]	58[1]

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CHAPTER 7

INHIBITION OF GASTRIC SECRETION BY FAT IN THE INTESTINE

PART I: EFFECT OF FAT IN THE DUODENUM ON GASTRIC ACID SECRETION BEFORE AND AFTER TRUNCAL VAGOTOMY IN MAN

PART II: EFFECT OF HIGHLY SELECTIVE VAGOTOMY AND OF TRUNCAL VAGOTOMY AND PYLOROPLASTY ON INHIBITION OF GASTRIC ACID SECRETION BY FAT IN THE DUODENUM

INHIBITION OF GASTRIC SECRETION BY FAT IN THE INTESTINE

PART I EFFECT OF FAT IN THE DUODENUM ON GASTRIC ACID SECRETION BEFORE AND AFTER TRUNCAL VAGOTOMY IN MAN

The inhibitory effect of fat on gastric secretion and motility was described by Ewald and Boas[1] in 1886, but uncertainty persists as to the precise mechanism of the inhibition. A considerable weight of evidence[2-8] suggests that fat in the intestine liberates a hormone which inhibits gastric secretion. Inhibition by fat of the motility of a transplanted gastric pouch in the dog[9] indicated the release of an inhibitory hormone. That the vagus nerves play a part in the inhibition has, however, also been emphasized[10,11]. In this study fat in the duodenum has been found to inhibit gastric acid secretion in men with intact vagus nerves, but not in men who had undergone truncal vagotomy.

METHOD

Gastric acid secretion was stimulated by a constant submaximal infusion of histamine or gastrin in men with intact vagi and in men after truncal vagotomy. When a 'plateau' of secretion was reached, olive oil emulsion was syringed slowly into the duodenum in the course of 15minutes and the effect on gastric acid output followed for one hour. Control infusions

were performed without fat in the duodenum.

Stimulants of gastric secretion Histamine acid phosphate or pure gastrin II were given at constant rate intravenously for 135 to 150 minutes using a slow-infusion pump. The dose rate was chosen to elicit an acid output about 50 per cent of the maximum. In men with intact vagi gastrin II 2.5 ug per hour and histamine 3.0 ug per kg per hour were given; after vagotomy the dose rates were: gastrin II, 4 ug per hour, and histamine, 6.0 ug per kg per hour.

Fat in duodenum Sixty ml. of pure olive oil were used in 5 of 23 tests. In the remaining 18 tests an emulsion was used. Equal volumes of olive oil and of the subject's own duodenal aspirate were blended in a homogenizer for 10 minutes at the start of the test. The resulting stable emulsion had a pH between 6.1 and 7.2, with a mean of 6.8. Fifty to sixty ml. were used in the normal subjects and 30 to 150 ml. in those with duodenal ulceration. None of the subjects became nauseated when fat was placed in the duodenum.

Subjects All were males, to whom the purpose of the test was explained and who agreed to participate. Group 1 (intact vagi: gastrin stimulus) consisted of 5 healthy medical students, aged from 18 to 27 years and weighing from 62 to 81 kg. Group 2 (intact vagi: histamine stimulus) consisted of 6 men, aged 16 to 30 years and weighing from 59 to 71 kg.

Five of the 6 had undergone a laparotomy 6 to 10 days previously. In 3 a perforated chronic duodenal ulcer had been treated by simple suture, and two others had a negative exploration and pyloroplasty alone for suspected duodenal ulceration. At operation a triple-lumen gastrostomy tube (Fig. 1) was placed in position. One wide lumen was used to drain the stomach, while the two other fine polyethylene tubes were manipulated into the second part of the duodenum and were used for feeding in the post-operative period. The sixth subject was a man of 54 with a chronic duodenal ulcer who had not undergone surgery.

Group 3 (vagi severed, gastrin stimulus) Five tests were done on 4 men, aged 35 to 69, and weighing 62 to 76 kg. who had undergone truncal vagotomy with Heinecke-Miculicz pyloroplasty 6 to 11 days previously, in the treatment of chronic duodenal ulceration. Group 4 (vagi severed, histamine stimulus) Seven tests were performed on 6 men who had undergone truncal vagotomy and Heinecke-Miculicz pyloroplasty for duodenal ulceration 7 to 10 days previously. All the patients studied after vagotomy had negative insulin tests of gastric secretion according to the criteria of Hollander[12].

Procedure Subjects who had not had an operation fasted overnight before the test, which commenced about 9 a.m. Patients convalescing

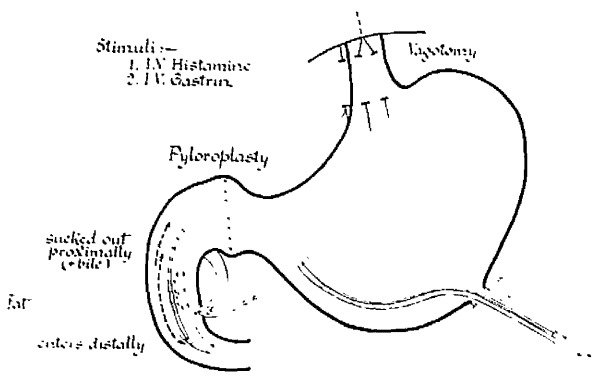

Fig. 1 The aspiration system used in the patients after operation. Continuous suction was applied to the gastric and to one of the duodenal tubes. The tip of the gastric tube and the whole of one duodenal tube were radio-opaque. Tubes were passed transnasally in subjects who did not have an operation.

after vagotomy ingested liquids only from lunch time on the preceding day.

Tubes Two radio-opaque tubes were passed transnasally under radiological control in subjects who had not had an operation. The tip of one was positioned low in the stomach and that of the other, which was biluminal, in the distal second part of the duodenum. The position of the tubes was checked during and at the end of each test. The duodenal suction holes lay between the tip of the duodenal tube, where the fat emerged, and the pylorus or pyloroplasty and were designed to prevent regurgitation of duodenal content into the stomach. Continuous suction from 2 electric pumps was exerted on both gastric and duodenal tubes throughout the test. The subject lay supine or on his left side, expectorated saliva and took deep breaths from time to time to help 'pump' out gastric content. The suction was interrupted at intervals of 30 seconds and air blown down the gastric tube to maintain patency. The gastric aspirate was collected into specimens representing 15-minute periods. One ml. aliquots were titrated to the phenolphthalein end-point using 0.01 N NaOH. Acid output was expressed as mEq per 15 minutes. The pH of the fat emulsion and of the duodenal aspirate was measured using a Cambridge pH meter.

Regurgitation of duodenal content into the stomach was assumed to have occurred if bile appeared in the gastric aspirate and simultaneously the acid concentration decreased. In the tests reported, such regurgitation was either absent or very slight. Twelve other tests were abandoned

on this account: one in group 1, 2 in group 2, and 9 in groups 3 and 4.

Control gastrin and histamine infusions Control infusions were performed on 16 men with intact vagi: 6 were normal, 7 had duodenal ulcer, and 3 had x-ray-negative dyspepsia. Thirteen men with a negative insulin test after truncal vagotomy and pyloroplasty for duodenal ulcer were also studied, 7 to 10 days after operation.

Statistics The control infusions confirmed that gastric acid output did not change significantly after the first hour. The significance of changes in gastric secretion when fat was introduced into the duodenum was therefore calculated using the null hypothesis and Student's t-test for paired observations. For each test, acid output in the 30-minute period immediately preceding the infusion of fat was compared with the acid output in the last 30 minutes of the test.

RESULTS

Group 1 Intact vagi - gastrin stimulus Significant inhibition ($p < 0.02$) of the output of gastric acid in response to gastrin II was produced by fat in the duodenum (Fig. 2). The mean decrease in acid output was 36 per cent. Acid concentration increased by 6 per cent.

Group 2 Intact vagi - histamine stimulus Fat in the duodenum caused highly significant inhibition ($p < 0.001$) of the output of gastric acid in response to histamine (Fig. 2). Complete inhibition occurred

in one man without ulcer. Fifty ml. of olive oil had been placed in his duodenum. In the other 'normal' man, who received 55 ml. of fat emulsion, acid output decreased by 88 per cent (Fig. 3). Mean inhibition was only 26 per cent in the four men with duodenal ulcer. Acid concentration decreased by 76 per cent in the 2 'normal' men but did not change in the 4 with duodenal ulcer.

Group 3 After vagotomy - gastrin stimulus Acid output increased after fat by 14, 19, 76, 116 and 164 per cent respectively in the 5 tests, the mean increase of 78 per cent being probably significant ($p < 0.05$) (Fig. 4). Acid concentration increased by a mean of 23 per cent (Fig. 5).

Group 4 After vagotomy - histamine stimulus Acid output increased in 6 of the 7 tests when fat was placed in the duodenum, the mean increase for the 7 being 75 per cent. This was not statistically significant ($p < 0.3$) because variance was high. Mean acid concentration increased by 40 per cent (Figs. 4 and 5).

Taking Groups 3 and 4 together, the increase in acid output in the 12 cases was significant ($t = 2.50$, $p < 0.05$).

DISCUSSION

Fat in the duodenum inhibited gastric acid secretion in all 11 tests in subjects with intact vagi, but in only 1 of 12 tests in men after truncal vagotomy and pyloroplasty. Pure olive oil and the olive oil emuls - ion were

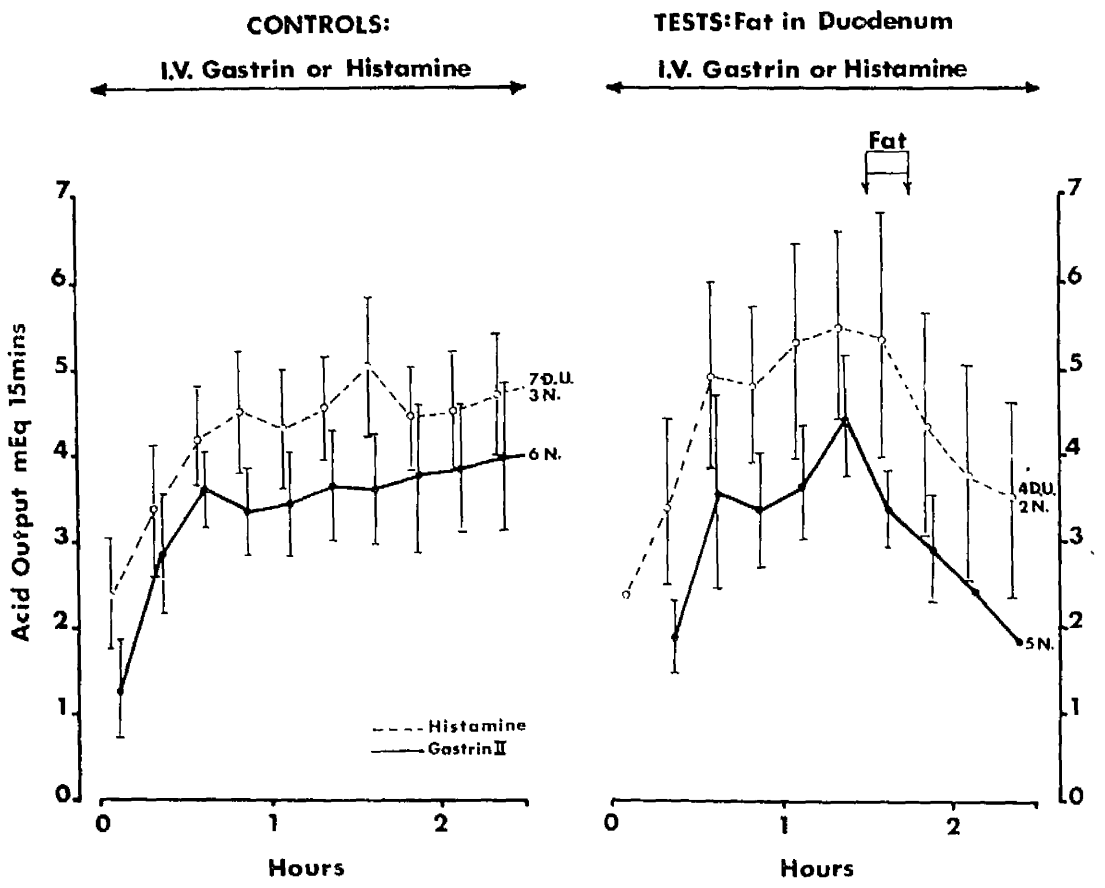

Fig. 2 The inhibitory effect of fat in the duodenum on gastric acid output in men with intact vagus nerves. N = normal, DU = duodenal ulcer. Each line represents the mean ± 1 S.E.m. Inhibition had probably not reached its maximal degree by the end of each test. Standard errors have been omitted in the last half hour of the tests on 5 normals because one test ended 15 minutes early, and there was slight contamination of the gastric aspirate with bile in another.

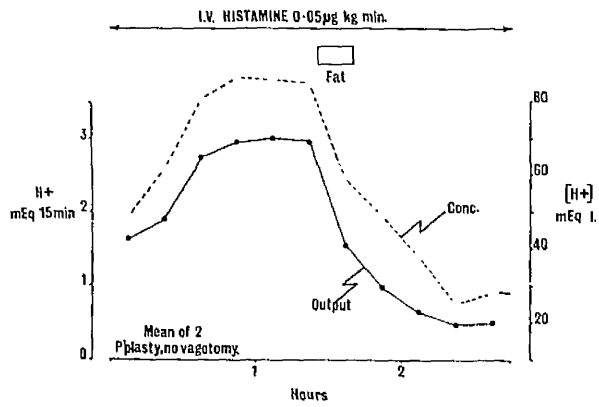

Fig. 3 Marked inhibition produced by fat in the duodenum in 2 men who had undergone laparotomy and pyloroplasty, without vagotomy.

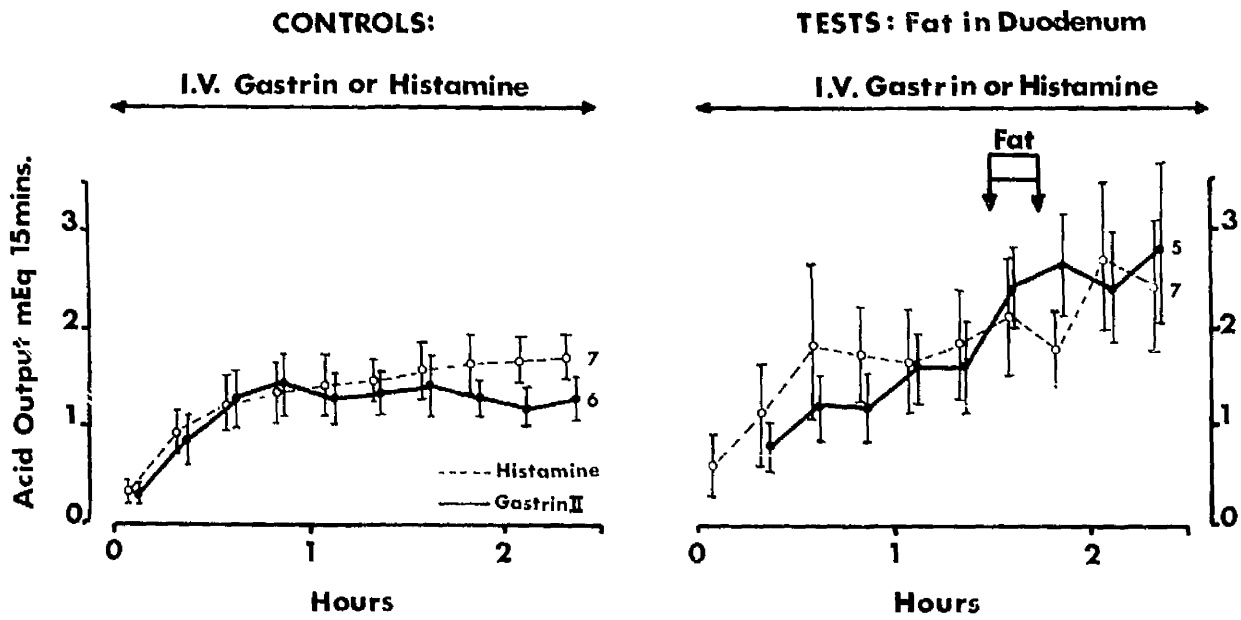

Fig. 4 Fat in the duodenum led to an increase in acid output in vagotomized men. Each subject had a duodenal ulcer treated by truncal vagotomy and pyloroplasty about 8 days previously. Numbers indicate number of tests. Lines are mean ± 1 S.E.m. Inhibition occurred in only one out of twelve tests.

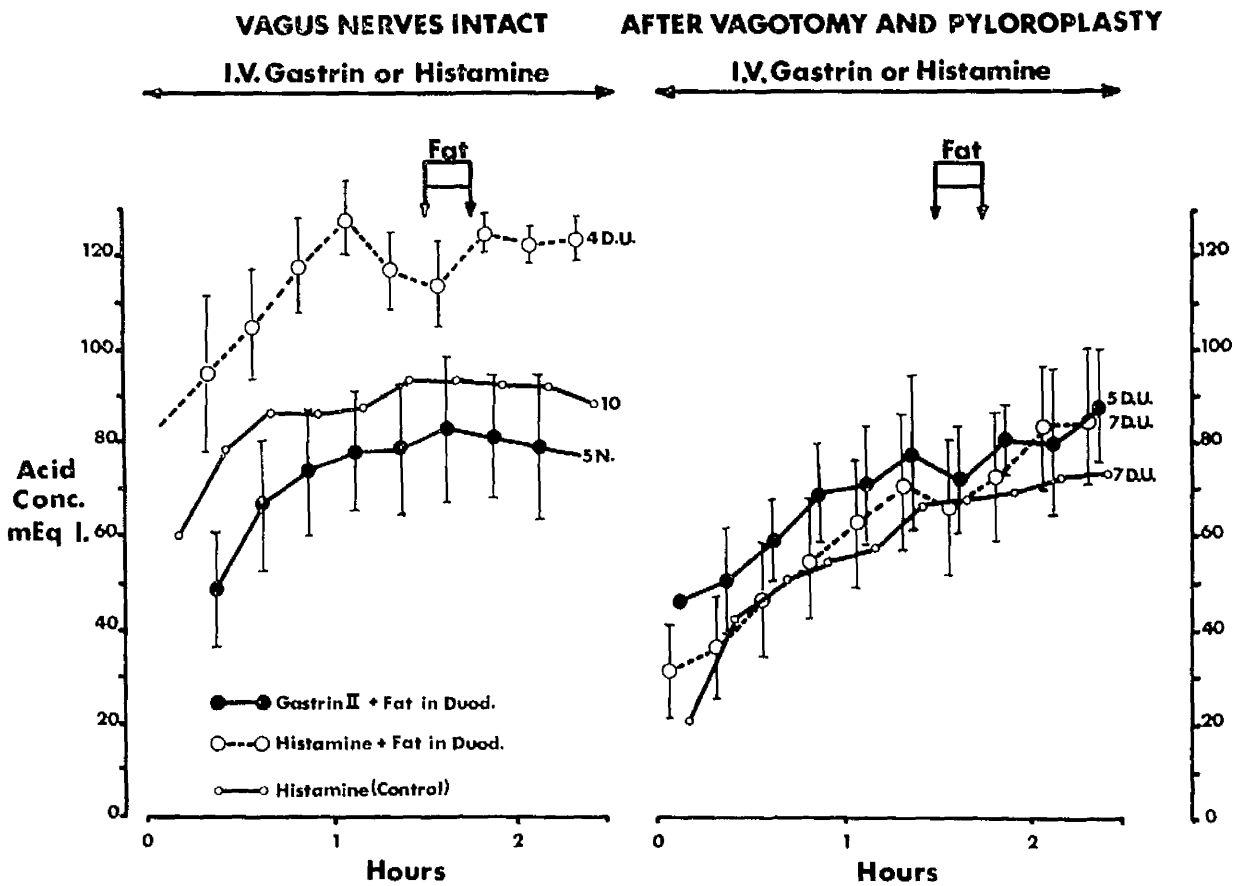

Fig. 5 Mean acid concentration, in men with intact vagi on left, and in men after vagotomy on the right. N = normal, D.U. = duodenal ulcer. For the sake of simplicity, data for control gastrin infusions have been omitted: they were similar to those for the control histamine infusions. Fat led to a decrease in acid concentration in only 3 tests (see text). These data suggest that there was little contamination of gastric acid by alkaline duodenal content.

equally effective, perhaps because the pure oil was quickly split by lipase and bile on entering the duodenum. Inhibition was seen in each of the 4 men with duodenal ulcer who still had intact vagi, but the degree of inhibition was less than in men without ulcer. By contrast, a mean increase in acid output of 76 per cent occurred in the 12 tests in men who had undergone truncal vagotomy and pyloroplasty for duodenal ulceration, when fat was placed in the duodenum. That the vagotomy was the important factor in the changed response to fat, rather than the pyloroplasty or the preceding surgical trauma, is shown by the fact that inhibition by fat could still be demonstrated in 5 subjects in Group 2, all of whom had undergone laparotomy with, in two cases, a pyloroplasty as well (Fig. 3). Pyloroplasty alone does not interfere with the inhibitory effect of fat on gastric emptying[13].

Nausea was not a factor in causing inhibition, perhaps because the amount of olive oil used was relatively small. The subjects were all asked if they had felt nauseated, but none had done so.

The inhibition observed in men with intact vagi is the expected result. It was not due to unsuspected regurgitation of duodenal content, since the concentration of gastric acid did not diminish (Fig. 5). The failure to demonstrate inhibition by fat of gastric acid secretion in vagotomized men is more surprising, since most previous workers[2-8]

found that fat in the intestine inhibited acid secretion from pouches in dogs. On the other hand, Gregory and Tracy[14] showed that fat in the duodenum had little or no action against a histamine stimulus if the factor of nausea was excluded. In the present study, the acid output of the vagotomized men increased in 11 of 12 tests after fat was placed in the duodenum, whereas little or no increase was observed in the control infusions.

These results imply that, in man, the vagus nerves play an important part in fat-induced inhibition of gastric secretion. They also suggest an explanation for the enhanced intestinal phase of gastric secretion that has been noted after vagotomy in dogs[15]. Whatever inhibitory hormone(s) is released by fat in the intestine, it does not seem to have been effective in the absence of a cholinergic background in our patients in the early days after truncal vagotomy. Hence, it would appear that the nervous component of the inhibition may be greater in man than in the dog. Apart from a possible species difference, the discrepancy between our own and previous data might be due to the smaller amount of fat administered in this study. For example, Halvorson et al.[7] gave 100 ml. of oil in 2 minutes to dogs weighing 16 kg. In the present study 30 to 75 g of olive oil were given in the course of 15 minutes to men weighing 70 kg. These quite small amounts of fat, equivalent to about

the mean daily intake in the human diet, were sufficient to elicit inhibition, without nausea, in the subjects with intact vagi. Despite the administration of up to twice that amount of fat to the vagotomized men, no inhibition was seen.

Another inhibitory action of fat in the intestine, namely inhibition of gastric motility, has been reported to have an important vagal component, both in dogs[10] and in man[11]. This would parallel the results of our study.

What part secretin and cholecystokinin-pancreozymin play in the inhibition of gastric secretion has not been defined with precision. Secretin has been shown to inhibit gastric acid secretion stimulated by gastrin but not that stimulated by histamine[16-19]. Cholecystokinin-pancreozymin has been shown to inhibit histamine- and gastrin-stimulated gastric secretion in the dog[18], but is a competitive inhibitor of gastrin and may also stimulate gastric secretion in man[20,21]. It seems likely that in the present series of experiments both hormones were liberated by the presence of olive oil in the duodenum, not only before but also after vagotomy: yet if secretin was the inhibitory agent in the men without vagotomy, its action seems to have been abolished by the operation of truncal vagotomy.

SUMMARY

In normal men and patients with duodenal ulcer whose vagus nerves were intact, fat in the duodenum produced significant inhibition of gastric secretion stimulated by gastrin II or by histamine. Inhibition could not be demonstrated in patients 6 to 11 days after truncal vagotomy and pyloroplasty for duodenal ulceration. It is suggested that inhibition of gastric secretion in man by fat in the duodenum has an important vagal component.

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Comment

The results of this study, which was published in 1969[1], were extremely surprising, not least to its authors. It was therefore encouraging to read the report by Isaza and his colleagues[2] in 1971 that denervation of the small intestine virtually abolished the inhibition by fat in the intestine of pentagastrin-stimulated acid output from the whole innervated stomach in the dog.

In view of the fact that truncal vagotomy led to a large increase in 24-hour acid output from Heidenhain pouches in dogs, whereas bilateral selective vagotomy produced a much smaller increase in secretion, it seemed to us that, in man, fat-induced inhibition of gastric acid secretion might prove to be more effective if the vagal nerve supply to the small intestine were spared (as in selective or highly selective vagotomy) than if it were cut, as in truncal vagotomy. We decided, therefore, to compare fat-inhibition in patients who had undergone either TV+P or HSV, and to eliminate some of the weaknesses of the above study by carrying out the experiments, not in the early post-operative period, but more than one year after operation, and also by using the same dose of stimulus (pentagastrin) and "inhibitor" (olive oil) in all subjects.

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INHIBITION OF GASTRIC SECRETION BY FAT IN THE INTESTINE

PART II EFFECT OF HIGHLY SELECTIVE VAGOTOMY AND OF TRUNCAL VAGOTOMY AND PYLOROPLASTY ON INHIBITION OF GASTRIC ACID SECRETION BY FAT IN THE DUODENUM

The results of the preceding study suggested that inhibition of gastric secretion by fat in the duodenum had an important vagal component. We thought, therefore, that inhibition by fat would prove to be greater after HSV than after an operation such as truncal vagotomy which vagally-denervates the small intestine.

METHOD

Patients (1) Five patients with active duodenal ulceration were studied before operation. (2) Six patients were studied more than one year after HSV. In all six, the insulin test (which was performed as described previously) had been negative by Hollander's criteria[1] soon after operation. The insulin test was repeated in these six patients more than one year after HSV, and was found to be still negative in four and late-positive[2] in two. (3) Six patients were studied more than one year after TV+P. In each, the insulin test was negative both in the early post-operative period and more than one year later. All seventeen patients were men. The patients after TV+P or HSV were

in good health. For details of patients and of each test, see Table. Six other tests in men after vagotomy were abandoned because of difficulties with intubation or because of regurgitation of bile into the stomach. As in the previous section such regurgitation in the tests reported here was either absent or very slight.

Stimulus to gastric secretion Pentagastrin was given by constant infusion from a Palmer pump, in a dose of 0.2 ug per kg per hour, for $2\frac{1}{2}$ to 3 hours.

Procedure The methods used were almost identical to those described in the preceding paper. Gastric secretion was collected into samples representing 10-minute, rather than 15-minute, periods. Two tubes were passed transnasally and the tip of one positioned in the stomach to the left of the vertebral column, while the tip of the other was placed in the distal second, or third, part of the duodenum. Continuous suction was exerted on both tubes throughout the test. When a steady plateau of gastric acid output had become established in response to the pentagastrin infusion (usually between 70 and 100 minutes from the start), 60ml. of pure olive oil at room temperature and pH 6.7 were syringed gently into the duodenum in the course of 5 to 8 minutes and the effect on gastric acid output followed for 60 to 70 minutes. The olive oil did not cause nausea in any patient.

Statistics We have shown previously that the plateau of acid output in response to intravenous pentagastrin in a dose of 0.10 to 0.15 ug per kg per hour is maintained for 150 minutes in normal volunteers and in patients with duodenal ulcer before operation[3]. We have not performed control pentagastrin infusions for 3 hours in patients after vagotomy, but have assumed that the plateau remains constant after 90 minutes, just as it did in the control gastrin and histamine infusions in vagotomized patients. Good plateaux had been established for 30 to 40 minutes in most of the tests in the present study before fat was placed in the duodenum. The significance of changes in gastric secretion was calculated by means of Student's t-test for paired observations. For each test, the acid output in the two 10-minute collection periods immediately preceding fat-infusion was compared with the acid output in the two consecutive 10-minute periods after fat-infusion which gave the lowest reading. Changes in acid concentration were calculated from the same four ten-minute periods.

RESULTS

Patients with duodenal ulcer before operation Fat in the duodenum produced significant inhibition ($p < 0.01$) of gastric acid output (Table, Fig. 1). Mean acid output decreased from 7.9 to 2.0 mEq

per 10 minutes, a mean decrease of 74 per cent. Mean acid concentration decreased from 123 to 103 mEq per litre, a statistically significant decrease ($p < 0.01$). The time-course of inhibition varied considerably. On average, the nadir of acid output occurred 44 minutes after the start of fat infusion.

Patients tested two years after HSV Since no difference in response was seen in the two patients with late-positive insulin tests, compared with that in the four patients whose insulin tests were negative, all six patients will be considered together (Table, Fig. 2). Fat produced inhibition of acid output in four tests, but did not produce inhibition in two tests. Mean acid output diminished from 3.6 to 2.6 mEq per 10 minutes, a decrease which was not quite significant ($0.1 > p > 0.05$). The mean decrease was 33 per cent. Acid concentration did not change significantly. The mean nadir of acid output occurred 52 minutes after the start of fat infusion.

Patients tested two years after truncal vagotomy and pyloroplasty Acid output decreased significantly ($p < 0.02$) after fat, from a mean of 2.5, to 1.6, mEq per hour (Table, Fig. 3). Acid output diminished in each of the six tests. Acid concentration did not change significantly. The mean nadir of acid output was reached 43 minutes after the start of fat infusion.

EFFECT OF FAT IN DUODENUM IN 5 PATIENTS WITH DUODENAL ULCER BEFORE OPERATION.

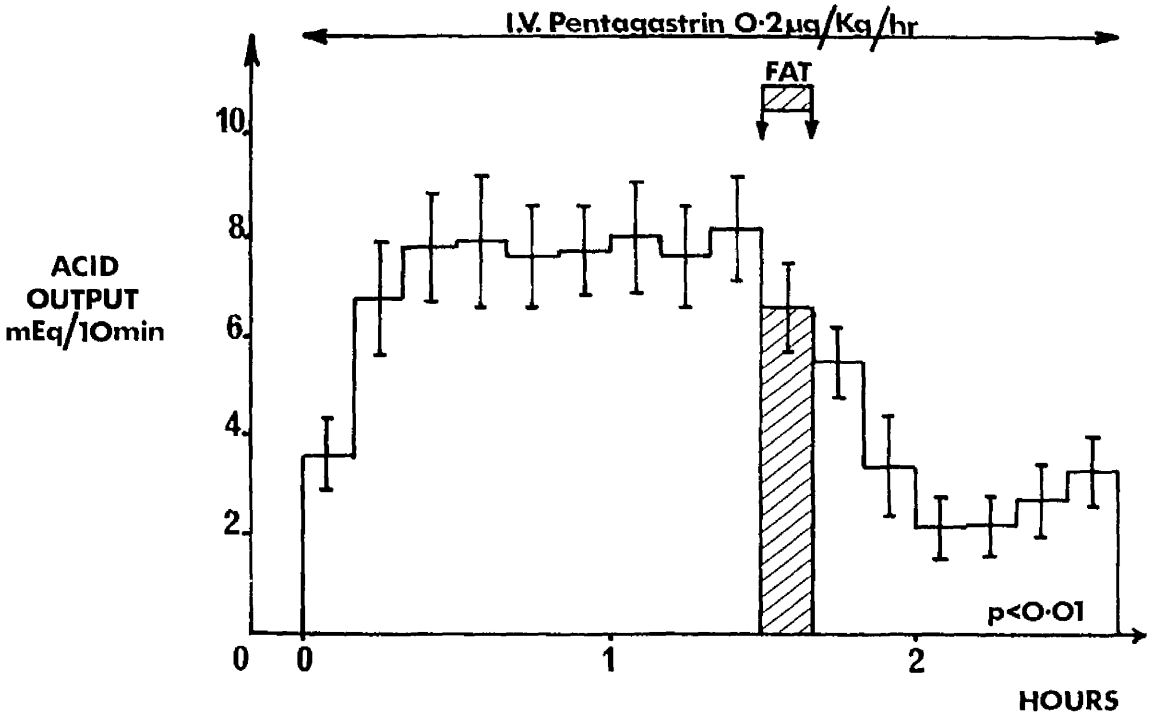

Fig. 1 Olive oil in the duodenum produced a significant mean decrease in acid output of 74 per cent. Figures are means ± 1 SE.

EFFECT OF FAT IN DUODENUM IN 4 PATIENTS WITH NEGATIVE INSULIN TESTS GREATER THAN 1 YEAR AFTER HSV

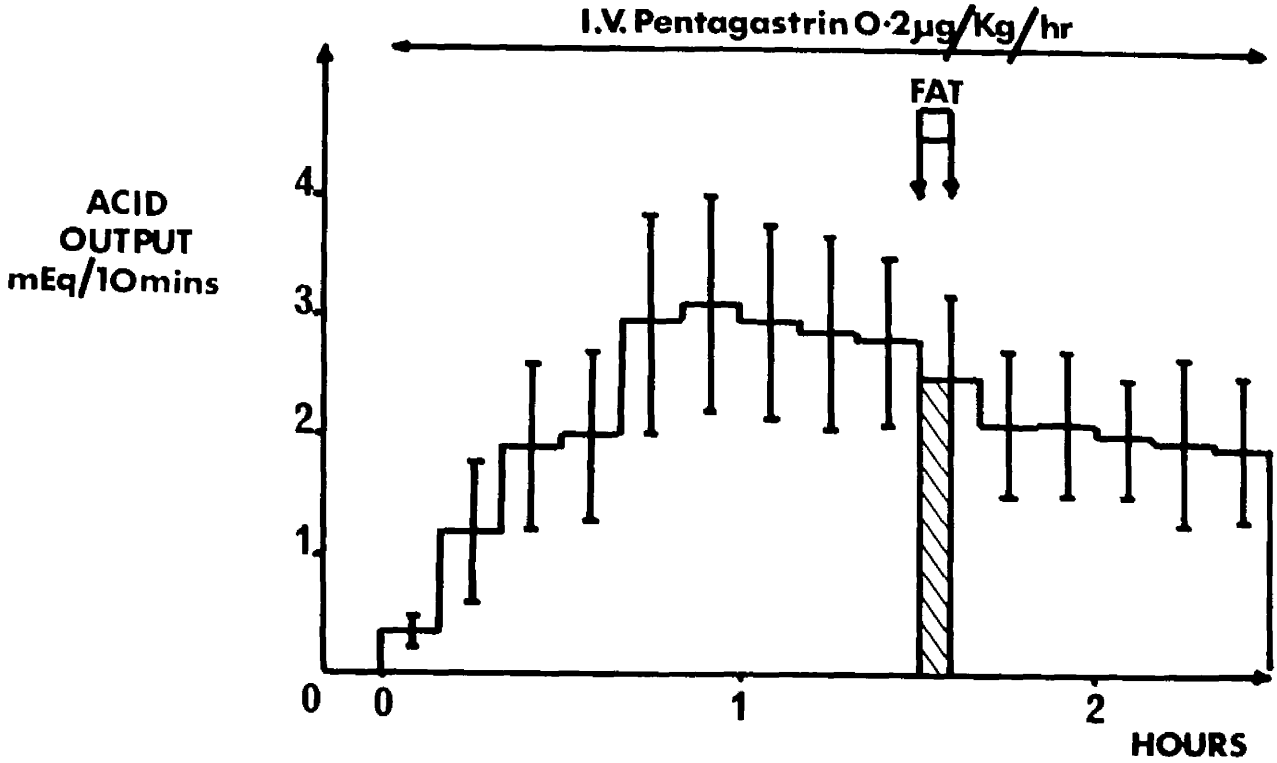

Fig. 2 In four patients with complete (insulin-negative) HSV, olive oil in the duodenum inhibited pentagastrin-stimulated acid output by a mean of 39 per cent.

EFFECT OF FAT IN DUODENUM IN 6 PATIENTS WITH NEGATIVE INSULIN TESTS GREATER THAN 1 YEAR AFTER TV+P

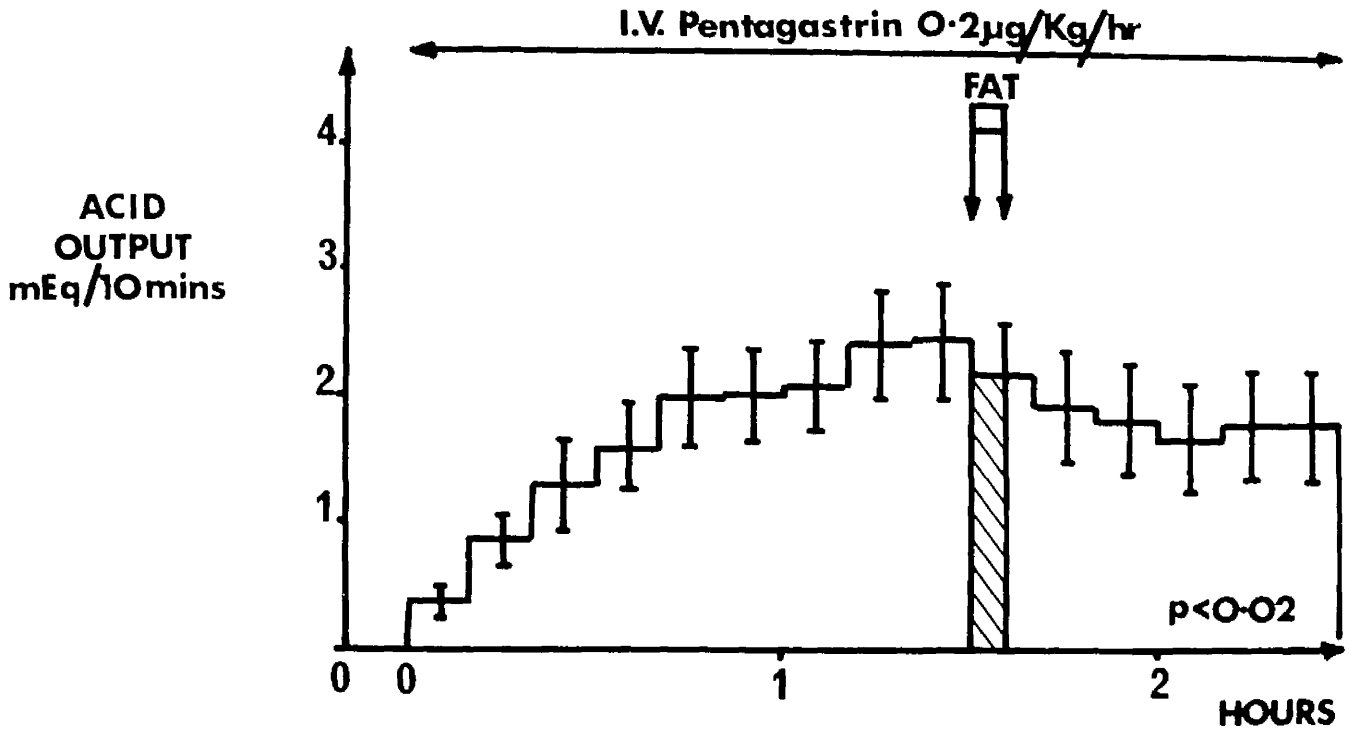

Fig. 3 In six patients whose insulin tests were negative more than one year after truncal vagotomy and pyloroplasty, olive oil in the duodenum produced significant inhibition of acid output (mean decrease, 39 per cent).

TABLE

Effect of olive oil in duodenum on pentagastrin-stim

No.	OPERATION	AGE (years)	WEIGHT (kg.)	MONTHS POST-OP.	VISICK GRADE	INSULIN RESPONSE at > 1yr.
PRE-OPERATIVE PATIENTS						
1	PRE-OP.	21	64	-	-	-
2	PRE-OP.	51	70	-	-	-
3	PRE-OP.	22	74	-	-	-
4	PRE-OP.	42	86	-	-	-
5	PRE-OP.	55	73	-	-	-
MEAN		38.20	73.40	-	-	-
± 1SEM		7.14	3.60	-	-	-
PATIENTS AFTER HSV						
1	HSV	36	67	27	III	-ve
2	HSV	47	65	34	II	-ve
3	HSV	60	91	24	I	-ve
4	HSV	39	67	24	II	-ve
MEAN (4)						
5	HSV	46	102	18	I	Late +ve
6	HSV	47	57	18	I	Late +ve
MEAN		45.83	74.83	24.17		
± 1SEM		3.40	7.16	2.46		
PATIENTS AFTER TRUNCAL V + P						
1	TV+P	56	68	21	III	-ve
2	TV+P	49	73	20	I	-ve
3	TV+P	48	80	33	II	-ve
4	TV+P	30	76	41	I	-ve
5	TV+P	55	87	36	II	-ve
6	TV+P	36	67	19	I	-ve
MEAN		45.67	75.17	28.33		
± 1SEM		4.28	3.09	3.88		

ulated gastric acid output in three groups of patients

(1)	(2)		ACID OUTPUT mEq per 10 mins.			ACID CONCENTRATION mEq per litre		TIMING OF NADIR OF ACID OUTPUT AFTER FAT (mins.)
PAO^{PG} mEq/hr	PLATEAU mEq/hr	(2) ÷ (1) PER CENT	PLATEAU	NADIR AFTER FAT	PER CENT REDUCTION	PLATEAU	NADIR AFTER FAT	
68.82	59.10	85.88	9.85	1.44	85.38	126	115	20 - 40
60.42	30.30	50.15	5.05	0.56	88.91	120	100	20 - 40
52.38	40.38	77.09	6.73	3.89	42.20	103	88	60 - 80
47.43	43.26	91.21	7.21	2.35	67.41	121	103	30 - 50
76.08	63.06	82.89	10.51	1.51	85.63	145	109	40 - 60
61.03	47.22	77.44	7.87	1.95	73.91	123.0	103.0	44.00
5.23	6.09	7.20	1.01	0.56	8.78	6.73	4.55	7.48
17.08	24.54	143.68	4.09	2.57	37.16	100	90	40 - 60
14.88	20.22	135.89	3.37	1.67	50.45	107	99	40 - 60
14.40	19.44	135.00	3.24	3.20	1.23	108	104	50 - 70
6.24	3.12	50.00	0.52	0.17	67.31	17	7	30 - 50
16.83	13.15	116.14	2.81	1.90	39.09	83.00	75.00	
-		-	4.93	5.21	(-5.68)	130	132	40 - 60
-		-	5.32	2.87	46.05	111	120	50 - 70
			3.58	2.62	32.75	95.50	92.00	51.67
			0.70	0.68	11.80	16.23	18.08	3.07
22.00	24.96	113.45	4.16	3.50	15.87	81	90	30 - 50
7.14	9.54	133.61	1.59	1.24	22.01	80	76	50 - 70
29.91	16.80	56.17	2.80	2.04	27.14	99	97	50 - 70
14.28	15.78	110.50	2.63	1.10	58.17	90	76	40 - 60
4.50	4.14	92.00	0.69	0.33	52.17	63	67	10 - 30
33.30	17.22	51.71	2.87	1.15	59.93	97	70	20 - 40
18.52	14.74	92.91	2.46	1.56	39.22	85.00	79.33	43.33
4.85	2.92	13.46	0.49	0.49	8.05	5.45	4.79	6.67

The dose of pentagastrin was 0.2 ug per kg per hour intravenously. Note that this elicited near-maximal levels of acid output. PAO^{PG} (column (1)) was elicited by intramuscular pentagastrin in a dose of 6 ug per kg in pre operative patients and 10ug per kg after vagotomy. "Plateau" refers to the 20-minute period before fat was placed in the duodenum (see text).

"Plateau" of gastric secretion This proved to be little different from the maximal acid output in response to intramuscular pentagastrin (Table).

DISCUSSION

In contrast to our findings in patients one week after truncal vagotomy, we found in this study that fat in the duodenum produced significant inhibition of gastric acid output more than one year after truncal vagotomy in man. The other main findings were that inhibition was no greater after HSV than after TV+P, and that the degree of inhibition after either type of vagotomy was much less than that which was found in patients whose vagus nerves were intact.

Thus, it would appear that our failure to demonstrate inhibition by fat in patients one week after TV+P was due in some way to the short period of time which had elapsed after operation. Inhibition in the present study could not be attributed to regeneration of the vagus nerves, because the insulin test had been repeated in each of the six patients, eighteen months, on average, after operation, and was still negative in each. The use in this study of pentagastrin instead of gastrin II, and of pure olive oil instead of an emulsion is unlikely to have been responsible for the different response to fat in the intestine

at two years, compared with at one week, after TV+P.

Inhibition of pentagastrin-stimulated acid output by fat in the intestine was demonstrated by Windsor, Cockel and Lee[4], in a single patient, three months after TV+P. An insulin test had not been performed in that patient, but his MAO had been reduced by about 50 per cent by the vagotomy. The degree of inhibition was 37 per cent, compared with a mean of 70 per cent in six patients with duodenal ulcer who were tested before operation. More recently, Ward[5] has reported that inhibition of pentagastrin-stimulated gastric acid secretion by fat in six men one year after complete (insulin-negative) TV+P was "marked" in each case, and that the degree of inhibition was as great after vagotomy as before operation. Hence, he suggested that inhibition of gastric secretion by intraduodenal fat was mediated by a non-vagal mechanism, and that from this point of view there was little to be gained by preserving the vagal nerve supply to the duodenum, as is done in HSV or SV.

Certainly, we were disappointed to find in the present study that inhibition by fat after HSV (mean inhibition, 33 per cent in 6 men) was no greater than that which was found in 6 men after TV+P (mean inhibition, 39 per cent). Inhibition was significant ($p < 0.02$) in patients after TV+P, but not quite significant ($p < 0.1$) in patients after

HSV. The time-relationships of the inhibition were similar in the two groups of patients (Figs. 2 and 3). These findings suggest that fat in the intestine released as much "enterogastrone" (humoral inhibitor substance(s)) from the vagally-denervated intestine as from the normally-innervated intestine. We must therefore agree with Ward[5] that, from this point of view, there appears to be little advantage in preserving the vagal nerve supply to the biliary tract, pancreas and small intestine.

Comparison of the degree of inhibition in patients with intact vagi (Fig. 1) with that which was found in patients after HSV (Fig. 2) or TV+P (Fig. 3) reveals a striking difference. Inhibition was much greater (74 per cent) before vagotomy than after either type of vagotomy (36 per cent). Since the numbers of patients in each group were small, it cannot be claimed that this difference is statistically significant. However, a mean 70 per cent inhibition of pentagastrin-stimulated gastric acid output by fat in the duodenum was also found by Windsor et al.[4] in six patients with duodenal ulcer before operation, whereas after TV+P, in one patient, the degree of inhibition was only 37 per cent. The time-relationships of the inhibition were similar to those which were found in our patients. In dogs, Isaza and his colleagues[6] found that 15ml. of a 50 per cent emulsion of olive oil when introduced

into the proximal jejunum inhibited pentagastrin-stimulated acid output from the vagally-innervated stomach by 69.7 per cent (mean of 25 experiments in five dogs). As in our patients, the onset of inhibition in the dogs was rapid, and inhibition was maximal about 45 minutes after the start of fat infusion. Since the amounts of fat used by Windsor et al.[4] (40ml. of ground nut oil) were fairly similar to those used by ourselves, and since the dose of pentagastrin used by Windsor et al. elicits near-maximal levels of acid output, while that used in our study elicited acid outputs averaging 77 per cent of maximal, it seems reasonable to conclude that 40 to 60ml. of fat, when placed in the upper intestine of patients who have duodenal ulceration and intact vagus nerves, inhibit maximal, or near-maximal, pentagastrin-stimulated acid output by about 70 per cent. After vagotomy, whether highly selective or truncal in type, the degree of inhibition is approximately halved (39 per cent inhibition in 6 patients after TV+P and 33 per cent inhibition in 6 patients after HSV). The similar degrees of inhibition after TV+P and HSV suggest that equal amounts of humoral inhibitor are released by fat in the intestine after either type of vagotomy. The lesser degree of inhibition found after vagotomy compared with before operation suggests that integrity of the vagal nerve supply to the parietal cell mass is necessary for the

full efficiency of action of that humoral inhibitor. Thus, just as there is synergism between the vagus nerves and gastrin in the stimulation of gastric secretion[7,8], so there would seem to be synergism between the vagus nerves and "enterogastrone" in the inhibition of gastric secretion. And just as we have shown that in man vagotomy (TV, SV or HSV) diminishes the peak acid response to pentagastrin by about 50 per cent (vide supra), so now we have obtained preliminary evidence that vagotomy (TV, HSV) of the parietal cell mass diminishes the inhibitory effect of fat in the intestine on near-maximal acid output by about 50 per cent. This suggests that vagotomy of the parietal cell mass diminishes the inhibitory effect of "enterogastrone" on pentagastrin-stimulated gastric acid secretion by 50 per cent. In our previous study, which was performed in patients soon after operation, we suggested that truncal vagotomy abolished inhibition of gastric acid output by fat in the duodenum. On the basis of this study of patients two years after truncal or highly selective vagotomy, we would now suggest that vagotomy reduces fat-induced inhibition of gastric acid output by about half, and that this reduction in the degree of inhibition is attributable to vagal denervation of the parietal cell mass, rather than to vagal denervation of the intestine.

SUMMARY

The effect of placing 60ml. of olive oil in the duodenum in the course of 5 to 8 minutes on maximal, or near-maximal, gastric acid output in response to pentagastrin infusion was studied in three groups of patients. In five patients with duodenal ulcer before vagotomy, fat produced marked (74 per cent), statistically significant ($p < 0.01$) inhibition of gastric acid output. In six healthy patients two years after complete (insulin-negative) truncal vagotomy and pyloroplasty, inhibition was again significant ($p < 0.02$), but lesser in degree (mean, 39 per cent). In six patients who were in good health two years after HSV (4 had negative insulin tests and two, 'late-positive' tests more than one year after HSV), mean inhibition after fat was 33 per cent, which was not quite significant ($p < 0.1$). Since numbers are small, conclusions can only be tentative. These conclusions are :- (1) fat in the duodenum releases as much humoral inhibitor ("enterogastrone") from vagally-denervated intestine (TV+P patients) as from vagally-innervated intestine (HSV patients). (2) in consequence, no evidence has been found that preservation of the vagal nerve supply to the small intestine leads to greater inhibition of gastric secretion by fat than occurs if the intestine is vagally-denervated, and (3) vagal denervation of the parietal

cell mass reduces by about 50 per cent the effectiveness of the humoral inhibitor released by fat. As with stimulation of gastric secretion, so with inhibition, a vagal "permissive" [9] background seems to be essential for the full efficiency of action of humoral substances acting upon the parietal cell mass. As we suggested previously, inhibition of gastric secretion in man by fat in the duodenum has an important vagal component. That component is not, however, the vagal nerve supply of the small intestine, but the vagal nerve supply of the parietal cell mass.

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CHAPTER 8

ON THE POSSIBLE INHIBITORY ROLE OF THE NERVES OF LATARJET AND OF THE EXTRA-GASTRIC VAGI ON GASTRIC ACID SECRETION

(effect of insulin on the response to pentagastrin)

THE EFFECT OF INSULIN ON THE ACID RESPONSE TO PENTAGASTRIN IN SUBJECTS WITH INTACT VAGI AND IN PATIENTS AFTER TRUNCAL, SELECTIVE AND HIGHLY SELECTIVE VAGOTOMY

The hepatic and coeliac branches of the vagi mediate inhibition of gastric secretion in the dog[1,2]. They are sacrificed in truncal vagotomy (TV), but preserved by HSV. Stimulation of the nerves of Latarjet to the antrum of the stomach in the dog has also been reported to produce inhibition of gastric acid output[3]. The nerves of Latarjet are sacrificed in TV (and in selective vagotomy, SV), but preserved by HSV. In human subjects with intact vagus nerves, vagal stimulation by means of insulin-hypoglycaemia has been shown to significantly increase the "maximal" acid output in response to the augmented histamine test[4]. The latter effect is thought to be due to the "cholinergic background" [5,6] which is produced at the vagal nerve endings in the parietal cell mass. Thus, it would appear that the vagal nerve trunks contain some fibres which stimulate gastric acid secretion and others which inhibit it. When the vagus nerves are stimulated in intact human

subjects, the net effect on gastric secretion is stimulation, because the stimulatory effect is stronger than the inhibitory one.

Since HSV preserves all the vagal fibres which have been shown (in the dog) to inhibit gastric secretion but severs all the fibres to the parietal cell mass, we thought that if the vagus nerves were stimulated in patients after HSV, an inhibitory effect on gastric secretion might be found, whereas if the same stimulus were applied in patients after TV, there would be no effect. Insulin-induced hypoglycaemia was chosen as the means of stimulating the vagi. In the following experiments, its effects were noted on gastric acid output elicited by pentagastrin, in subjects with intact vagi and in patients who had undergone truncal, selective or highly selective vagotomy.

METHOD

Subjects Five groups of subjects were studied: 7 normal, healthy students (N); 6 patients with duodenal ulcer before operation (DU); and patients who were in good health, more than one year after truncal vagotomy and Heinecke-Miculicz pyloroplasty (TV+P, 24 patients); bilateral selective vagotomy

and H-M pyloroplasty (SV+P, 9 patients), and HSV (22 patients). Most of the vagotomized patients were in Visick grades I or II. Patients judged to be clinical failures were excluded. Each patient after vagotomy had been found to have a negative[7] insulin test in the early post-operative period. One normal volunteer and four patients after HSV were female. The remainder were male. Details of the patients' ages, weights and insulin-test status at the time of testing are presented in the Tables.

Tests of acid secretion Each subject underwent two tests on separate days. The tests were performed in random order. One test was a standard, intramuscular pentagastrin (PG) test[8], which has been described previously. It lasted for 90 to 120 minutes. After collection of "basal" secretion for 30 to 60 minutes, PG was injected and the subsequent gastric aspirate collected into twelve samples, each representing a 5-minute period. The dose of PG was 6 ug per kg in subjects with intact vagi[8], and 10 ug per kg[9] in patients after vagotomy. In the other test, the PG injection was preceded by a standard 3-hour insulin test (one hour "basal", and two hours after insulin). This test too has been described earlier in the Thesis. The dose of insulin was 0.2 units per kg[10],

and was given intravenously two hours before the intramuscular injection of pentagastrin. Gastric acid was collected and titrated as described previously. The acid response to insulin was judged early-positive (in the first hour), late-positive, or negative, according to the criteria of Hollander[7] and the modified Ross and Kay criteria[11]. The acid response to PG was expressed in mEq per hour, (a) as "PAO^{PG}", which is the acid output in the four consecutive five-minute collection periods which gave the highest reading, multiplied by three, and (b) as total-hour acid output ("MAO"), which is the total acid output in all twelve 5-minute collection periods.

Statistical analysis The differences between acid outputs in response to PG alone, and in response to PG given after insulin, were analysed by Student's t test for paired data[12].

For purposes of illustration (Fig. 1), the mean acid response to PG alone for each group of subjects was taken as 100 per cent, and the mean acid response to PG-after-insulin was expressed as a percentage of that response.

RESULTS

Normal subjects (N) Prior vagal stimulation led to a highly significant increase ($p < 0.001$) in MAO from 22.7 ± 1.4 to

35.4 ± 2.6 mEq per hour (Tables I and II, Fig. 1). The mean increase was 56 per cent. MAO in response to PG-after-insulin was greater than "MAO" in response to PG alone in all 7 subjects.

Patients with duodenal ulcer before operation (DU) The total-hour acid response (MAO) to PG-after-insulin was 40.8 ± 2.3 mEq per hour, compared with 34.8 ± 1.6 mEq per hour in response to PG alone (Tables I and III, Fig. 1). The mean increase was 17 per cent, and was statistically significant ($p < 0.05$). The acid response to PG-after-insulin was greater than the response to PG alone in 5 patients, and lower in one.

Patients after truncal vagotomy and pyloroplasty (TV+P) Prior insulin stimulation produced no significant change in MAO in response to pentagastrin (Tables I and IV, Fig. 1). PG-stimulated MAO after insulin averaged 93.3 per cent of MAO in response to PG alone. In the PG test with insulin, PG-MAO was greater in 10 patients and less in 14 patients, than MAO after PG alone. The mean difference in MAO in the 24 paired tests was 1.1 ± 1.0 mEq per hour ($0.3 > p > 0.2$).

Patients after selective vagotomy and pyloroplasty (SV+P No significant change in the response to PG was observed in

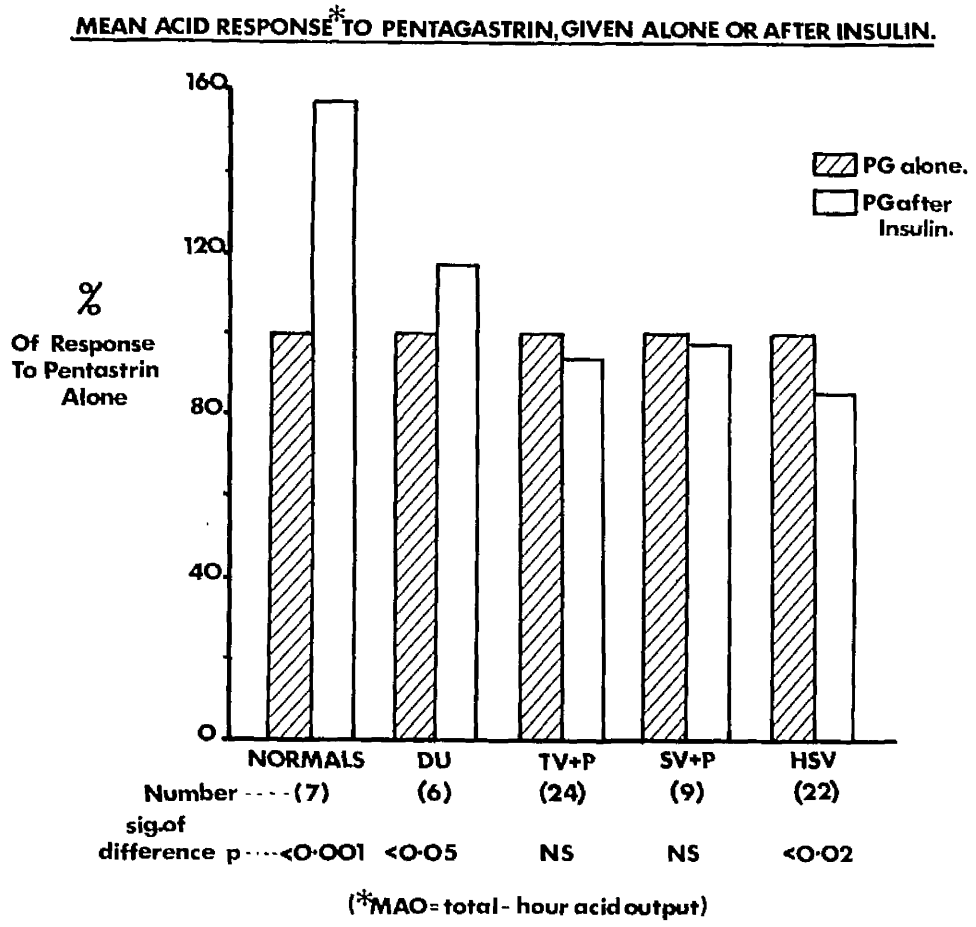

Fig. 1 'Total-hour' acid output (MAO) in the 60-minute period after the injection of pentagastrin alone, compared with MAO in response to pentagastrin given two hours after insulin. When the vagi were intact (N, DU) insulin produced significant stimulation of the pentagastrin response; after truncal or selective vagotomy (TV, SV) it produced no significant change; after HSV, insulin produced significant inhibition.

COMPARISON OF MEAN RESPONSES TO PG ALONE AND TO PG AFTER INSULIN.

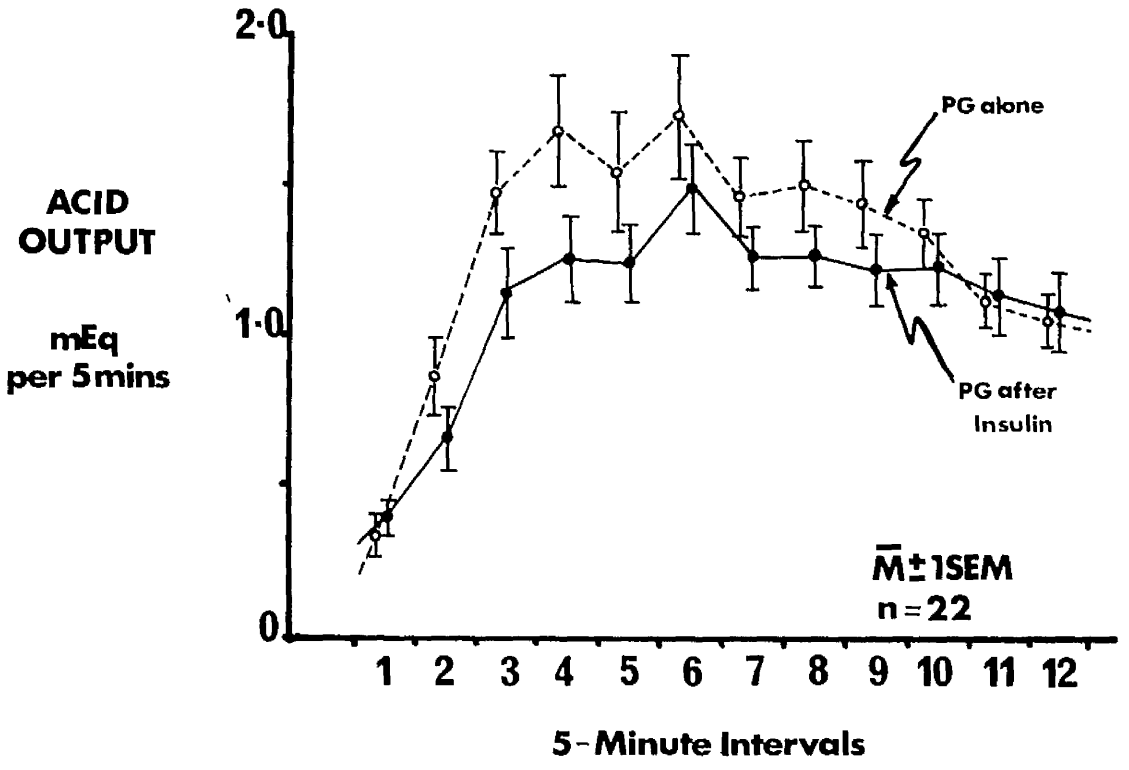

Fig. 2 The mean acid response to pentagastrin alone was significantly greater ($p < 0.02$) than the mean acid response to pentagastrin given after insulin, in 22 patients more than one year after HSV.

the PG tests with insulin (Tables I and V, Fig. 1). PG-stimulated MAO after insulin was 97.7 per cent of the MAO in response to PG alone. Acid output increased in 5 patients and decreased in four. The mean difference in MAO in paired tests in 9 subjects was 0.6 ± 1.7 mEq per hour ($0.8 > p > 0.7$).

Patients after HSV Prior injection of insulin produced a significant ($p < 0.02$) decrease in pentagastrin-stimulated MAO from a mean of 15.4 ± 1.5 mEq per hour to 13.2 ± 1.3 mEq per hour (Tables I and VI, Figs. 1 and 2). The mean decrease was 15 per cent. Pentagastrin-stimulated MAO after insulin was less than MAO in response to PG alone in 16 patients, and greater in 6 patients.

DISCUSSION

The statistical analysis was based on the assumption that the pentagastrin (PG) response is reproducible after any of the three types of vagotomy. It is certainly reproducible before operation[8]. Although reproducibility of the PG response after vagotomy has not to our knowledge been proved, it seems likely to be reproducible because the pentagastrin test[8], like

the augmented histamine test[13], is based on the principle that each parietal cell is stimulated to produce the maximum amount of acid of which it is capable in response to the pentagastrin, or histamine, stimulus. Dose-response studies performed in Copenhagen (vide-supra) of the response to PG after HSV, in which the doses of 6, 10 and 15 ug per kg of PG were used, showed that each of these large doses of PG elicited virtually the same acid output.

In subjects with intact vagi, the increase in so-called "maximal" acid output after vagal stimulation was striking, 12 of the 13 subjects showing an increase in "MAO", and only one a decrease. The increase in the 13 subjects was statistically highly significant ($p < 0.001$). In normal subjects, the increase ranged from 5.4 to 19.0 mEq per hour, the mean increase being 12.71 mEq per hour, while in DU patients, the increase ranged from 2.5 to 13.4 mEq per hour, the mean increase being 5.9 mEq per hour (Tables I to III). Whether these large increases in acid output represent "potentiation" by insulin of the response to pentagastrin is a matter for debate. In the words of Checketts et al.[4] :- "There would seem to be

no satisfactory means of clearly defining true potentiation in such a series of clinical measurements, with the attendant variations for experimental error, and other sources of imprecision. It therefore seems impossible to establish an absolute level of difference between a histamine test and an insulin plus histamine one, above which potentiation can be confidently assumed, and below which it can be excluded." One criterion which was used by Gillespie and Grossman[14] was that potentiation may be considered to have occurred if the response to a combination of two agents exceeds the maximal response attainable by either agent given alone. Unfortunately, we cannot claim to know what the maximal acid outputs were in response to insulin alone and to PG alone in our subjects with intact vagi, because dose-response studies to insulin were not performed, and because PG was not given by intravenous infusion. Therefore no claim is made that the significant increase which was found in the response to PG after insulin represents potentiation. The design of our experiment, in which PG was given two hours after insulin in order that the acid response to insulin could be defined and that

the phase of direct insulin-inhibition would be over before the PG injection, is different from the methods which were used by other workers who have studied the effect of combinations of pentagastrin and insulin on human gastric secretion. When Halter et al.[15] gave to 10 normal subjects either subcutaneous pentagastrin (6 ug per kg), or intravenous insulin (12 units), or both (insulin + pentagastrin) together, the mean peak acid outputs obtained in the three tests were similar. This could have been because the phase of direct insulin-inhibition coincided with the time of peak acid response to PG in some patients. When PG was administered 30 minutes after insulin[15], a slightly-elevated peak acid response to PG was found, which was not statistically significant. Halter et al. concluded that insulin did not potentiate the maximal acid response to PG in man. A similar conclusion was reached by Limbosch et al.[16], who stimulated gastric secretion with intravenous PG infusion (6 ug per kg per hour), and injected 20 units of insulin rapidly intravenously when a plateau of secretion had been attained. In 16 patients with intact vagi, insulin did not alter the acid response to PG, whereas it strongly stimulated pepsin secretion. In contrast, in 14 patients who had undergone truncal vagotomy,

which was complete by the Ross and Kay[11] criteria, injection of insulin produced significant inhibition of PG-stimulated acid output, and was also said to inhibit pepsin output, though the degree of inhibition did not appear convincing. Our findings were thus at variance with those of Halter et al. and Limbosch et al., probably because of differences in the design of the experiments. They were in agreement, however, with those of Checketts et al.[4] who had shown previously in patients with duodenal ulcer that acid output in response to the augmented histamine test was increased significantly ($p < 0.001$) when insulin was given prior to the injection of histamine. What was surprising in the present study was the almost invariable increase in MAO which was observed after vagal stimulation, in contrast to Checketts et al's. more variable results. In their study, although a statistically-significant mean increase in MAO was found, histamine-stimulated MAO decreased after insulin in no fewer than 18 of their 67 patients.

In contrast to our findings in patients with intact vagi, insulin was not found to influence the pentagastrin response significantly in patients who had undergone TV+P or

SV+P. The findings in the patients after TV+P were not unexpected, because after section of all intra-abdominal vagal fibres at operation, impulses in the vagus nerves were presumably unable to reach their effector organs below the diaphragm. In patients who were found to have positive responses to insulin in these tests more than one year after TV+P, patches of the parietal cell mass were probably vagally-innervated[17], and this may have contributed to the large increases in PG-MAO which were observed after insulin in a few patients (Table IV). However, increases in acid output were also observed in some patients whose insulin tests were still negative. Insulin has been shown to produce inhibition of gastric acid output in dogs[18-23], probably as a result of the hypokalaemia[20-22] which it produces. Both in dogs[22] and in man[16] truncal vagotomy was found not to abolish inhibition of histamine- or pentagastrin-stimulated acid secretion by insulin. However, this inhibitory effect was demonstrated against the plateau response to a constant intravenous infusion of the stimulant. In the tests which we report, such direct insulin-inhibition took place during the first 30 to 45 minutes of the insulin test, and had passed off or had been overridden by vagal stimulation of acid output by

the time the injection of PG was given. Thus, in patients after TV+P, non-specific insulin-induced inhibition of the acid response to pentagastrin was not observed, probably because the pentagastrin was given such a long time after insulin.

The failure of insulin-induced vagal stimulation to inhibit the pentagastrin response in patients who had undergone SV+P was more surprising, because in these patients the hepatic and coeliac vagal fibres were presumably still intact. These fibres have been shown to mediate inhibition of gastric secretion in the dog[1,2]. A variety of explanations for the lack of inhibition could be offered. A weak inhibitory effect might have been masked by "potentiation" of secretion from patches[17] of vagally-innervated parietal cells, particularly because, as can be seen in Table V, acid outputs in response both to insulin and to pentagastrin were very high - much higher than in patients after TV+P or HSV. While the proportion of patients with positive insulin tests (two-thirds) in this group was little different from the proportion in the groups of patients after TV+P or HSV, it seems likely that a larger

proportion of the parietal cell mass was innervated in the SV+P patients than in patients after TV+P or HSV. When the results in two patients after SV+P who had very high acid outputs (patients 6 and 7, Table V) were excluded, there was still no evidence of inhibition of the PG response after insulin in the remaining seven patients. As in the TV+P group, non-specific insulin-induced inhibition was not observed. Other possible explanations for the lack of inhibition are that the extra-gastric vagi may not inhibit gastric acid secretion in man, in contrast to their role in the dog; that the methods which we employed were unsuitable for demonstrating inhibition (too high a dose of PG, given too late after insulin); or that the extra-gastric vagi had been damaged inadvertently at the time of operation. The last explanation is felt to be most improbable.

Thus, the only subjects in which statistically-significant "inhibition" ($p < 0.02$) was found were the patients who had undergone HSV. The decrease in acid output was small, amounting to a mere 15 per cent. As stated previously, its significance is dependent upon the assumption, which is as yet

unproven, that the response to PG is reproducible after HSV. In addition, some part of the decrease in acid output could be due to the sheer length of the test, which lasted for two hours longer than the test with PG alone: acid output may have declined spontaneously. Again, it could be argued that background vagal stimulation might have caused more acid to be lost via the pylorus, by stimulating antral peristalsis. In the absence of measurements of the recovery of a marker, such as PEG or phenol red, such a suggestion cannot be refuted. However, vagal stimulation would not stimulate peristalsis in the body of the stomach, where the acid was being produced and whence it was being aspirated by continuous suction. Besides, the significant increase in the acid response to PG after insulin in subjects with intact vagi argues against the possibility of excessive loss of acid via the pylorus. Finally, it is noteworthy that a small, 7 per cent, decrease in the PG response after insulin was found in patients after TV+P, which detracts from the significance of the 15 per cent decrease in the HSV patients.

Assuming for the moment that the above objections

are invalid, and that the decrease in acid output in the HSV patients was truly significant, it is by no means clear why inhibition took place. A direct inhibitory effect of insulin on gastric secretion (not mediated by the vagi) such as has been shown previously in dogs[22] and in man[16] after truncal vagotomy, does not seem to provide a convincing explanation, because such inhibition should have been evident also in patients after TV+P or SV+P. At the end of the two-hour period after the injection of insulin, most of the HSV patients were secreting acid at more than basal rates: 14 had Hollander-positive responses to insulin and only 8 were Hollander-negative. The results in the three groups of vagotomized subjects could be explained on the basis of varying degrees of removal of the stimulatory action of the vagus, with no change in the inhibitory action of insulin. In other words, inhibition in the HSV group could be explained by the HSV patients having a more complete vagotomy of the parietal cell mass than had patients after TV+P or SV+P. However, the results of the insulin tests after TV+P and HSV provide no evidence in support of this idea. The proportion of patients with a Hollander-positive response to insulin was much the same

in all three groups, and acid outputs in response to insulin and PG were very similar in the TV+P and HSV groups of patients (Table I). Although mean PG-MAO in patients after SV+P was unusually high, no evidence of inhibition after insulin could be discerned when the results in two hypersecretors (which skewed the mean value) were excluded. There are thus good grounds for believing that the inhibition which was observed in patients after HSV was specific, and not merely due to the non-specific inhibitory action of insulin. If it was specific, it may have been mediated by the extra-gastric vagi and by the nerves of Latarjet (Fig. 3) - particularly the nerves of Latarjet , because inhibition was not found in patients after SV+Pwhose extra-gastric vagal fibres were (presumably) still intact. Support for the idea that the nerves of Latarjet may mediate inhibition of gastric secretion is available from other quarters. For example, Iggo[24] has demonstrated the presence of pH - sensitive nerve endings in the mucosa of the antrum of the stomach, which give rise to impulses in vagal afferents when the intra-luminal pH decreases. Again, stimulation of the nerves of Latarjet, either by insulin-induced hypoglycaemia or electrically, has been reported to produce

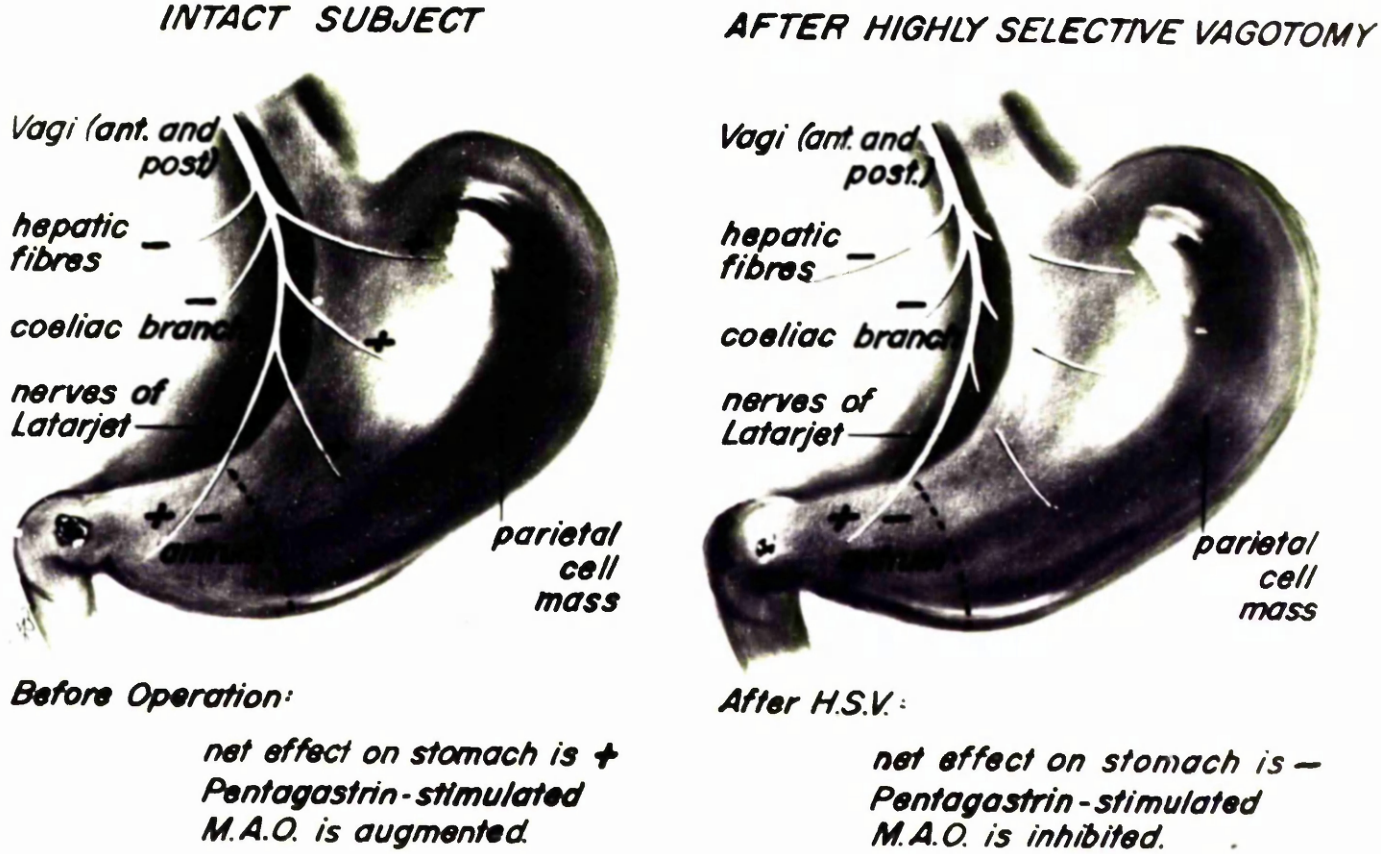

Fig. 3 These twin diagrams illustrate our concept of how the secretory results may be explained. In subjects with intact vagus nerves, insulin-induced vagal stimulation produces a cholinergic background which potentiates the action of pentagastrin on the parietal cell mass, and overrides the relatively weak inhibitory influence of the hepatic, coeliac and antral vagal fibres. Selective vagal denervation of the parietal cell mass in the operation of HSV removes the stimulatory action of the vagus on acid output, while preserving the inhibitory influence of the nerves of Latarjet and of the extra-gastric vagi.

significant inhibition of gastric secretion from vagally-denervated fundic pouches in dogs[25]. In another study, Takita[26] found that HSV in dogs was followed by a significant increase in acid output from "indicator" Heidenhain pouches (presumably because of the resulting rise in pH in the antrum, leading to diminished inhibition of the release of gastrin): when the nerves of Latarjet were subsequently cut, acid output from the Heidenhain pouches increased still further. This could have been due (a) to antral stasis, leading to increased release of gastrin, or (b) to removal of an inhibitory action exerted by the nerves of Latarjet. For this reason, Takita[26] repeated his experiments in another series of dogs, with the difference that a Finney pyloroplasty was constructed at the first operation (HSV+P). The results were the same: HSV+P led to an increase in acid output from the Heidenhain pouches, and subsequent section of the nerves of Latarjet produced a further significant increase in pouch secretion. As Takita concluded "In our experiment, pouch secretion was significantly less after SPV (= HSV) than after SV, regardless of the drainage procedure. This fact seems to implicate the secretory role of the antral branch of the vagus!" He obviously meant

"the inhibitory role" of the nerves of Latarjet with respect to gastric secretion. This brilliant series of experiments was completed by the performance of truncal vagotomy in the same dogs, which led to a further significant increase in pouch secretion. Professor Takita's work[26] provides the best evidence which has yet been adduced that the nerves of Latarjet are capable of inhibiting gastric secretion. However, Bombeck and his colleagues[27] have also reported, without giving details, that perfusion of the isolated antrum in dogs produced greater inhibition of gastric acid output from a Heidenhain pouch if the antral pouch was innervated than if it was vagally denervated.

The protection which a vagotomy that is confined to the parietal cell mass affords against peptic ulceration may be greater than the protection which is afforded by TV+P or SV+P. For example, Interone et al.[28] reported that HSV protected dogs against histamine-induced ulcer significantly better than did SV+P or SV plus antrectomy. In man, SPV plus pyloroplasty (= HSV+P) in the hands of Professor Holle[29] has been followed by a less-than-one-per-cent incidence of

recurrent duodenal ulceration, in 171 patients who have been followed for up to seven years. In the past three and a half years, Amdrup and I have treated 250 patients with duodenal ulcer by HSV without a drainage procedure, and we have yet to encounter a single case of recurrent duodenal ulcer. Though some have attributed these results to the enthusiastic, or meticulous, way in which the operations were performed, (and others to the euphoric way in which they imagine the patients were assessed!), it is difficult to avoid the conclusion that the superior results (with respect to recurrent ulceration), compared with those which are recorded after TV+P, may be related to the operative procedure itself. Clearly, the suggestion that a well-performed HSV provides better protection against recurrent duodenal ulceration than a well-performed [illegible]ical vagotomy with a drainage procedure remains to be proved. If proof is forthcoming, the superiority of HSV over TV+P will, we suggest, be due in part to preservation of an inhibitory influence on gastric acid output. The preliminary and somewhat inconclusive studies which are reported here suggest that the nerves of Latarjet exert such an inhibitory influence.

SUMMARY

Five groups of subjects were studied:- normal students, patients with duodenal ulcer before operation (DU), and patients who were in good health, more than one year after truncal vagotomy and pyloroplasty (TV+P), selective vagotomy and pyloroplasty (SV+P) or HSV. Each subject underwent two pentagastrin tests on separate days. In one test, insulin was given intravenously two hours before the pentagastrin, to stimulate the vagus nerves. The two tests were performed in random order. In each of the three groups of vagotomized patients, the acid response to insulin was found to be positive by Hollander's criteria in approximately 65 per cent of the patients, despite the fact that in each patient the insulin test had been negative in the early post-operative period. The groups of patients after TV+P and HSV were well-matched for age, sex, weight, and acid output in response to insulin and pentagastrin. Patients after SV+P had higher acid outputs than had patients after TV+P or HSV.

The assumption was made that the acid response to the pentagastrin test is reproducible in vagotomized subjects.

The preceding injection of insulin produced a significant increase ($p < 0.001$) in the so-called "maximal" response to pentagastrin in subjects with intact vagi, a significant decrease ($p < 0.02$) in the response to pentagastrin in patients after HSV, and had no significant effect on the response to pentagastri in patients after TV+P or SV+P.

The interpretation of these results is to some extent speculative, for reasons which are discussed. However, in our opinion, the significant decrease in acid output which was observed in patients after HSV was probably specific - otherwise it would have been found also in patients after TV+P, whose acid responses to insulin were comparable to those of the patients after HSV. These results suggest that the vagal fibres which are preserved in HSV, the nerves of Latarjet in particular, inhibit gastric secretion in man.

TABLE I

Subjects	Number	Months Post-op.	Age (years)	Weight (kg.)	Response to insulin (by Hollander's criteria)		Response to insulin (Acid Output)	
					early post-op.	>1 year post-op.	PAO^{I} (mEq/hr)	Peak-hour (mEq/hr)
Normal Controls N	7	-	21.38 ± 0.32	63.75 ± 2.97	(all early +ve)		31.29 ± 2.79	29.22 ± 2.62
Pre-op. DU patients	6	-	46.67 ± 2.20	65.67 ± 3.36	(all early +ve)		32.81 ± 2.53	30.40 ± 2.20
TV+P	24	28.21 ± 2.85	46.79 ± 2.42	69.83 ± 1.81	all -ve	4 early +ve 9 late +ve 11 -ve	3.10 ± 0.74	2.65 ± 0.66
SV+P	9	39.22 ± 4.33	42.33 ± 3.14	67.00 ± 1.63	all -ve	3 early +ve 3 late +ve 3 -ve	6.37 ± 1.64	5.57 ± 7.48
HSV	22	17.36 ± 0.68	43.72 ± 2.50	66.82 ± 2.62	all -ve	7 early +ve 7 late +ve 8 -ve	3.55 ± 0.67	2.96 ± 0.56

Numbers are means ± 1 SE.

Dose of pentagastrin : 6 ug/kg I.M. pre-operatively and 10 ug/kg after operation.

Dose of insulin : 0.2 units per kg intravenously.

TABLE I
Contd.

Response to Pentagastrin (PAO = peak 20 min acid output x 3)						Response to Pentagastrin (MAO = total-hour output)					
(1) PG alone (mEq/hr)	(2) PG after insulin (mEq/hr)	(2) ÷ (1) %	(2) minus (1) (mEq/hr)	t	p	(1) PG alone (mEq/hr)	(2) PG after insulin (mEq/hr)	(2) ÷ (1) %	(2) minus (1) (mEq/hr)	t	p
31.78 ± 1.79	41.10 ± 2.65	129.33	9.32 ± 2.04	4.57	<0.01 ‡	22.73 ± 1.39	35.44 ± 2.57	155.92	12.71 ± 1.92	6.62	<0.001 ‡
41.61 ± 1.86	47.46 ± 2.89	114.06	5.85 ± 2.27	2.58	<0.05 ‡	34.83 ± 1.58	40.77 ± 2.25	117.05	5.94 ± 2.15	2.76	<0.05 ‡
20.90 ± 1.91	19.53 ± 1.83	93.27	-1.37 ± 1.13	1.21	$0.3 > p > 0.2$	16.46 ± 1.66	15.36 ± 1.64	93.32	-1.10 ± 0.98	1.13	$0.3 > p > 0.2$
31.76 ± 6.97	33.17 ± 7.26	104.44	1.41 ± 1.98	0.71	$0.5 > p > 0.4$	25.40 ± 5.32	24.81 ± 4.79	97.68	-0.59 ± 1.66	0.35	$0.8 > p > 0.7$
19.66 ± 2.05	16.83 ± 1.60	85.61	-2.83 ± 1.22	2.31	<0.05 *	15.42 ± 1.48	13.16 ± 1.29	85.34	-2.26 ± 0.86	2.62	<0.02 *

‡ insulin given before pentagastrin produced a significant increase in the acid response to pentagastrin in subjects with intact vagi.

* after HSV, insulin given before pentagastrin significantly inhibited the acid response to pentagastrin.

TABLE II

EFFECT OF INSULIN ON THE RESPONSE TO PENTAGASTRIN IN 7 NORMAL SUBJECTS

NO.	AGE (yr.)	WEIGHT (kg.)	RESPONSE TO INSULIN			RESPONSE TO PENTAGASTRIN (PG)			
			by Hollander's criteria	PAO^{I} (pk 30^{1} x 2) mEq/hr	PH^{I} (peak hour) mEq/hr	PG ALONE (PAO) mEq/hr	PG AFTER INSULIN (PAO) mEq/hr	PG ALONE (MAO) mEq/hr	PG AFTER INSULIN (MAO) mEq/hr
1	22	65	early +ve	27.8	23.8	30.4	39.9	20.6	32.1
2	22	70	"	41.0	38.9	39.6	47.6	29.4	43.5
3	23	57	"	18.6	17.9	27.2	33.0	17.1	29.7
4	21	62	"	37.2	34.5	28.9	49.2	23.2	**41.7**
5	20	47	"	29.2	28.2	29.6	32.8	22.8	28.2
6	21	69	"	35.4	31.8	29.5	37.8	22.6	30.4
7	22	67	"	29.8	29.4	37.4	47.4	23.5	42.6
MEAN	21.43	62.43	all early +ve	31.29	29.22	31.78	41.10	22.73	35.44
$\pm$ 1 SEM	0.37	3.07		2.79	2.62	1.79	2.65	1.39	2.57
						Mean difference = 9.32 ± 2.04		Mean difference = 12.71 ± 1.92	
						$t = 4.57$		$t = 6.62$	
						$p < 0.01$		$p < 0.001$	

DOSE OF PG: 6 ug/kg i.m.

DOSE OF INSULIN: 0.2 u/kg i.v.

MAO = total-hour acid output

PAO^{PG} output in peak 20 min., x 3.

Prior injection of insulin produced a significant increase in the acid response to pentagastrin. Note that the mean peak response to insulin (PAO^{I}) is not greater than the mean PAO^{PG}.

TABLE III

EFFECT OF INSULIN ON THE RESPONSE TO PENTAGASTRIN IN 6 PATIENTS WITH DUODENAL ULCER BEFORE OPERATION

NO.	AGE (yr.)	WEIGHT (kg.)	RESPONSE TO INSULIN			RESPONSE TO PENTAGASTRIN (PG)			
			by Hollander's criteria	PAO^{I} (pk 30^{1} x 2) mEq/hr	PH^{I} (peak hour) mEq/hr	PG ALONE (PAO) mEq/hr	PG AFTER INSULIN (PAO) mEq/hr	PG ALONE (MAO) mEq/hr	PG AFTER INSULIN (MAO) mEq/hr
1	42	79	early +ve	31.6	30.7	38.2	43.2	31.4	36.2
2	51	63	"	31.4	29.8	45.6	53.1	39.6	47.4
3	47	57	"	33.7	32.8	35.7	49.1	29.5	43.8
4	55	63	"	33.8	30.4	46.8	56.1	38.2	45.7
5	42	72	"	42.9	37.7	44.4	46.9	35.1	37.0
6	43	60	"	23.5	21.1	39.0	36.4	35.3	34.5
MEAN	46.67	65.67	all	32.81	30.40	41.61	47.46	34.83	40.77
$\pm$ 1 SEM	2.20	3.36	early -ve	2.53	2.20	1.86	2.89	1.58	2.25
						mean difference = 5.85 $\pm$ 2.27		mean difference = 5.94 $\pm$ 2.15	
						t = 2.58		t 2.76	
						p < 0.05		p < 0.05	

DOSE OF PG: 6 ug/kg i.m.

DOSE OF INSULIN: 0.2 u/kg i.v.

Prior injection of insulin produced a significant increase in the acid response to pentagastrin. Note that the peak response to insulin (PAO^{I}) is less than the peak response to pentagastrin (PAO^{PG}).

TABLE IV

EFFECT OF INSULIN ON THE RESPONSE TO PENTAGASTRIN IN 24 PATIENTS AFTER TRUNCAL VAGOTOMY AND PYLOROPLASTY

NO.	AGE (yr.)	WEIGHT (kg.)	RESPONSE TO INSULIN			RESPONSE TO PENTAGASTRIN (PG)			
			by Hollander's criteria	PAO^{I} (pk 30^{1} x 2) mEq/hr	PH^{I} (peak hour) mEq/hr	PG ALONE (PAO) mEq/hr	PG AFTER INSULIN (PAO) mEq/hr	PG ALONE (MAO) mEq/hr	PG AFTER INSULIN (MAO) mEq/hr
1	41	59	early +ve	2.8	2.6	17.3	21.1	14.7	16.2
2	48	85	"	2.8	2.7	30.9	37.4	23.6	32.0
3	27	80	"	13.9	11.4	36.5	29.8	28.8	24.4
4	24	65	"	11.3	10.7	38.9	36.9	35.7	31.3
5	54	54	late +ve	2.5	2.4	29.8	30.8	24.6	26.6
6	58	83	"	8.2	7.8	19.7	22.0	15.5	19.5
7	46	63	"	4.5	3.3	23.6	31.9	21.5	27.1
8	64	67	"	1.0	0.8	8.9	7.6	7.5	6.1
9	57	66	"	1.9	1.1	11.9	15.9	7.9	11.9
10	57	85	"	2.9	2.3	16.7	16.4	13.9	12.4
11	37	70	"	2.0	1.5	15.4	8.8	8.8	6.5
12	54	59	"	7.8	6.3	29.2	26.5	21.0	20.0
13	43	63	"	2.6	2.5	19.4	18.2	14.8	14.5
14	42	64	negative	3.3	2.9	22.7	19.1	19.4	15.3
15	42	64	"	0.2	0.1	13.6	17.4	10.2	13.3

16	30	74	"	0.1	0.1	14.3	14.7	11.0	10.5
17	47	74	"	1.0	0.6	7.1	11.7	5.1	7.1
18	51	69	"	0.1	0.1	27.0	18.0	20.2	12.1
19	73	73	"	0.8	0.6	15.7	16.5	12.0	12.9
20	55	85	"	0.0	0.0	4.5	1.6	2.5	1.2
21	35	70	"	0.4	0.4	33.3	18.6	23.2	13.1
22	56	68	"	0.9	0.6	22.0	16.0	16.7	9.6
23	46	78	"	2.3	2.0	29.9	20.8	26.3	15.8
24	36	62	"	1.1	0.8	14.1	11.0	10.4	9.1
MEAN ± 1 SEM	46.79 ± 2.42	69.83 ± 1.81	4 E+ve 9 L+ve 11 -ve	3.10 ± 0.74	2.65 ± 0.66	20.94 ± 1.91	19.53 ± 1.83	16.46 ± 1.66	15.36 ± 1.64
						mean difference = 1.41 ± 1.13 t = 1.209 0.3 > p > 0.2		mean difference = 1.10 ± 0.98 t = 1.127 0.3 > p > 0.2	

DOSE OF PG: 10 ug/kg i.m.

DOSE OF INSULIN: 0.2 ug/kg i.v.

Prior injection of insulin had no significant effect on the response to pentagastrin in patients after TV+P. Note that acid outputs in response to insulin and to pentagastrin are very similar to the acid outputs in patients after HSV (Table VI). Thus there is no evidence that the parietal cell mass was less-well-denervated in patients after TV+P than in patients after HSV.

TABLE V

EFFECT OF INSULIN ON THE RESPONSE TO PENTAGASTRIN IN 9 PATIENTS AFTER SELECTIVE VAGOTOMY AND PYLOROPLASTY

NO.	AGE (yr.)	WEIGHT (kg.)	RESPONSE TO INSULIN			RESPONSE TO PENTAGASTRIN (PG)			
			by Hollander's criteria	PAO^{I} (pk 30^{1} x 2) mEq/hr	PH^{I} (peak hour) mEq/hr	PG ALONE (PAO) mEq/hr	PG AFTER INSULIN (PAO) mEq/hr	PG ALONE (MAO) mEq/hr	PG AFTER INSULIN (MAO) mEq/hr
1	45	70	early +ve	7.7	6.2	37.1	36.4	27.3	31.3
2	21	73	"	10.3	9.5	38.9	37.3	34.2	30.7
3	40	69	"	3.5	3.4	8.7	10.7	7.3	9.4
4	35	68	late +ve	5.1	3.4	27.3	30.1	24.6	25.6
5	51	65	"	6.9	6.9	31.8	24.2	25.1	19.0
6	46	62	"	15.4	13.7	45.6	59.4	35.3	41.2
7	48	69	negative	8.3	7.2	72.1	70.3	54.8	45.1
8	50	70	"	0.0	0.0	24.3	30.1	20.1	21.1
9	45	57	"	0.0	0.0	0.1	0.0	0.1	0.0
MEAN	42.33	67.00	3 E+ve 3 L+ve	6.37	5.57	31.76	33.17	25.40	24.81
$\pm$ 1 SEM	3.14	1.63	3 -ve	1.64	1.48	6.97	7.26	5.32	4.79
						mean difference = 1.41 ± 1.98 $t = 0.71$ $0.5 > p > 0.4$		mean difference = 0.59 ± 1.66 $t = 0.35$ $0.8 > p > 0.7$	

DOSE OF PG: 10 ug/kg i.m.

DOSE OF INSULIN: 0.2 u/kg i.v.

Prior injection of insulin had no significant effect on the acid response to pentagastrin. Acid outputs are very high, but if the results in patients 6 and 7 are excluded, there is still no evidence of inhibition. The acid responses to insulin are much higher than in patients after TV+P or HSV, suggesting that a higher proportion of the parietal cell mass was innervated in the group of patients who had undergone SV+P.

TABLE VI

EFFECT OF INSULIN ON THE RESPONSE TO PENTAGASTRIN IN 22 PATIENTS AFTER HIGHLY SELECTIVE VAGOTOMY

NO.	AGE (yr.)	WEIGHT (kg.)	RESPONSE TO INSULIN			RESPONSE TO PENTAGASTRIN (PG)			
			by Hollander's criteria	PAO^{I} (pk 30^{1} x 2) mEq/hr	PH^{I} (peak hour) mEq/hr	PG ALONE (PAO) mEq/hr	PG AFTER INSULIN (PAO) mEq/hr	PG ALONE (MAO) mEq/hr	PG AFTER INSULIN (MAO) mEq/hr
1	48	39	early +ve	3.8	3.3	13.6	10.7	10.8	9.1
2	47	70	"	4.3	4.3	24.5	22.1	23.3	18.8
3	43	74	"	7.2	6.5	29.9	23.5	24.3	20.1
4	43	54	"	5.0	4.8	22.0	16.7	15.2	12.1
5	51	80	"	2.5	2.4	15.2	17.7	12.2	15.3
6	56	53	"	1.1	1.1	18.0	11.3	16.8	8.5
7	66	65	"	7.7	6.2	26.7	24.6	22.5	16.4
8	30	71	late +ve	8.1	6.5	46.9	29.4	31.9	25.3
9	18	55	"	10.5	7.8	26.2	29.6	21.0	23.3
10	41	82	"	9.3	8.3	10.4	12.4	8.0	10.6
11	51	82	"	3.1	1.8	14.9	22.2	12.0	18.6
12	54	78	"	3.9	3.4	12.9	9.4	10.2	7.6
13	48	56	"	2.0	1.7	27.4	15.5	21.0	12.7
14	51	62	"	1.1	0.6	7.0	4.1	5.6	3.4

15	22	56	negative	2.0	1.5	15.6	20.2	10.6	13.3
16	35	66	"	2.5	2.4	17.1	17.3	16.1	14.3
17	48	65	"	0.5	0.3	10.0	12.5	7.1	8.1
18	37	78	"	0.3	0.2	32.1	20.8	19.6	12.6
19	47	65	"	1.5	1.1	14.9	10.7	13.2	8.6
20	31	60	"	0.2	0.1	26.6	26.0	21.4	20.4
21	59	92	"	0.4	0.4	14.4	9.9	10.7	5.7
22	37	67	"	0.9	0.6	6.2	3.7	3.8	4.8
MEAN ± 1 SEM	43.77 ± 2.50	66.82 ± 2.62	7 E+ve 7 L+ve 8 -ve	3.55 ± 0.67	2.96 ± 0.56	19.66 ± 2.05	16.83 ± 1.60	15.42 ± 1.48	13.16 ± 1.29
						mean difference = 2.83 ± 1.22 t = 2.31 p < 0.05		mean difference = 2.26 ± 0.86 t = 2.62 p < 0.02	

DOSE OF PG: 10 ug /kg i.m.

DOSE OF INSULIN: 0.2 u/kg i.v.

Prior injection of insulin led to a significant decrease in the total-hour response to PG ($p < 0.02$) and in the peak response to PG ($p < 0.05$). The decrease in the 7 patients with early-positive insulin tests was significant ($p < 0.05$). Note that acid outputs in response to insulin and PG are very similar to those in patients after TV+P.

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CONTENTS

VOLUME 2

CHAPTER 9

VARIATIONS ON THE THEME OF ANTRECTOMY

MUCOSAL ANTRECTOMY

SUPRA-PYLORIC MUCOSAL ANTRECTOMY

ANTRONEUROLYSIS

MUCOSAL ANTRECTOMY AND ANTRONEUROLYSIS

It quickly became clear that there was no clinical problem with gastric emptying after HSV in man. If the operation was to fail, it would do so because of recurrent ulceration, caused by excessive release of gastrin from the innervated antrum. So impressed was C. A. Griffith by the potential danger of the innervated antrum in this respect, that, in spite of his interest in "partial gastric vagotomy" (HSV) since 1957[1], and his generally favourable findings with respect to gastric emptying and secretion in dogs subjected to this operation[1,2], he hesitated to apply HSV clinically, and instead sought to find an additional procedure, such as supra-pyloric mucosal antrectomy or supra-pyloric antral resection[3], that would eliminate the threat posed by the intact, innervated antrum.

We also thought it prudent to insure against the possible failure of HSV alone, by experimenting with mucosal antrectomy and antroneurolysis in dogs. Both these procedures were designed to reduce or eliminate gastrin release, while preserving intact all of the innervated antral muscle, and the pylorus.

MUCOSAL ANTRECTOMY

This operation had been used by Kirk[4] in the treatment of

duodenal ulcer, in combination with vagotomy. Kirk resected all the antral mucosa, sutured fundic mucosa to duodenal mucosa, and closed the gastro-duodenal incision transversely as a wide pyloroplasty. In order to keep the pylorus intact, Amdrup and Griffith[3] employed supra-pyloric mucosal antrectomy in combination with HSV. 1, 2 or 3cm. respectively of distal antral mucosa were left intact in the three dogs which underwent this procedure. Fundic mucosa was sutured to the pre-pyloric cuff of antral mucosa. In theory, this seemed an attractive operation to combine with HSV, because it appeared to offer the possibility of ablating all of the vagal, and most of the gastrin-induced, drive on the parietal cells, while retaining a propulsive antrum and an intact pylorus. Thus, recurrent ulceration might be as rare as after conventional vagotomy with antrectomy (less than one per cent[5]), but side-effects would be minimised. Amdrup and Griffith[3] found that gastric emptying of barium was not delayed after selective vagotomyof the parietal cell mass (HSV) plus supra-pyloric mucosal antrectomy. Acid outputs from the "indicator" Heidenhain pouch over a 24-hour period decreased significantly in the dogs in which 1, or 2cm., of antral mucosa remained, but increased significantly in the dog in which a 3cm. cuff of antral mucosa had been left.

SUPRA-PYLORIC MUCOSAL ANTRECTOMY IN TWO DOGS

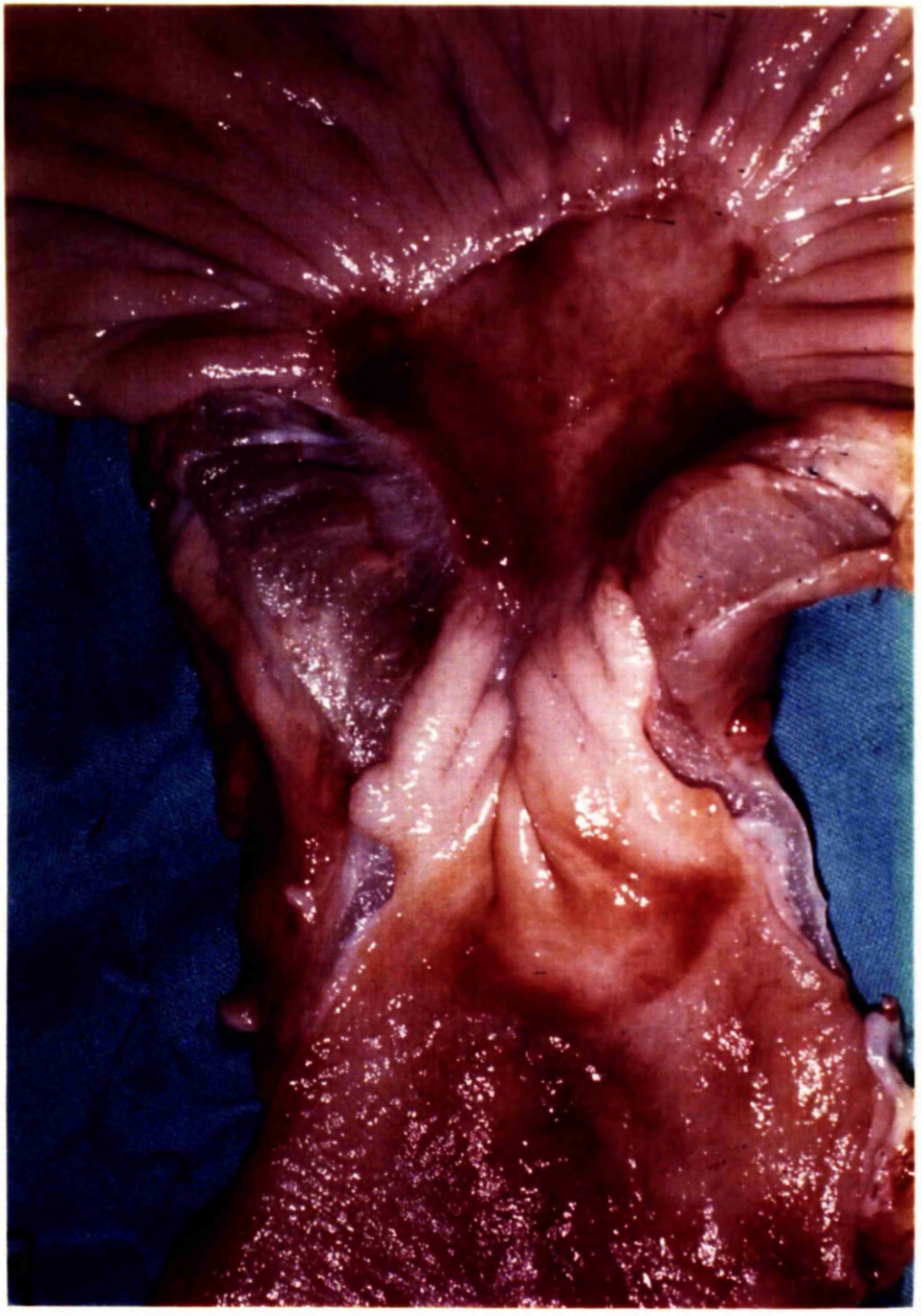
In view of the remarkable capacity of gastric mucosa to regenerate rapidly[6], we decided to modify the technique which had been used by Amdrup and Griffith[3], by simply performing supra-pyloric mucosal antrectomy, without suturing fundic mucosa to the small cuff of antral mucosa. We wished to avoid the distorsion of the antral musculature which is produced by suture of the mucosal defect, and hoped that the mucosal defect would be rapidly covered by undifferentiated epithelium which would not secrete gastrin.

METHOD Each dog was anaesthetized by an endotracheal technique. The technique of antral mapping[7] is described in the section on antroneurolysis. The mucosa of most of the antrum was excised, the distal 1 cm. of antral mucosa being left intact in one dog, and 2 cm. in the other. The gastrotomy was closed without any attempt being made to approximate the cut edges of mucosa. 20g of mucosa were excised in one dog and 28g in the other. Histological sections confirmed that a 1 cm. cuff of fundic mucosa was present at the proximal margin of the specimen. Blocks taken more distally revealed the presence of pyloric glands only. Muscularis mucosae and submucosa were present in each block.

SUBSEQUENT PROGRESS Both dogs fared badly. They ate little, vomited, lost weight steadily, and eventually had to be sacrificed, approximately three weeks after operation. At autopsy, the antral region in each dog was greatly thickened by oedema and fibrosis, and examination of the mucosal aspect revealed the presence of a large gastric ulcer. The pyloric canal was narrowed by the gross antral thickening. (Fig.)

COMMENT Our hopes that the gap in the gastric mucosa after supra-pyloric mucosal antrectomy would be rapidly covered by regenerating epithelium were not fulfilled. There is no place for resection of antral mucosa, without suture of the mucosal defect, in surgery for duodenal ulcer in man.

(For REFERENCES, see end of next section)



Legend to Figure

Photograph at autopsy of pyloro-duodenal region in a dog after mucosal antrectomy, without suture of the mucosal defect. Duodenal mucosa is at the bottom and gastric fundic mucosa at the top. A large gastric ulcer is present. The white area in the centre is the small cuff of antral mucous membrane which was left intact. Note the oedematous thickening of the gastric wall proximal to the pylorus.

HIGHLY SELECTIVE VAGOTOMY WITH SUPRA-PYLORIC MUCOSAL ANTRECTOMY IN MAN : A CASE REPORT

Gastric emptying of barium was found not to be delayed in three dogs which underwent HSV with supra-pyloric mucosal antrectomy[3] It was unchanged in the two dogs with 1cm. and 2cm. respectively of residual antral mucosa, and was faster than it had been pre-operatively in the dog with 3cm., of residual antral mucosa. We decided to use this operation in a man with very high acid secretion, after acquiring familiarity with the technique in dogs.

Case report Mr. O. H., a 36 year old driller, had suffered from intermittent epigastric pain for 13 years. For one year the pain had been much worse, radiating into the back, and was poorly relieved by antacid medicines. He was losing time from work. He vomited food at times during exacerbations of pain. His appetite was good and his weight increasing. He was five feet eight inches tall and weighed 78 kg. He suffered from flatulence, with belching of wind, and experienced heartburn on occasions. His bowels acted regularly, once per day, without episodes of diarrhoea. There was no history of haemorrhage or of perforation.

On examination, he was a pleasant, stoical, healthy-looking

man, stocky in build, not anaemic, and he was very tender in the epigastrium.

Barium meal examination showed that the stomach contained an increased amount of resting fluid. The duodenal cap was deformed and contained an ulcer crater.

His BAO was 4.8 mEq per hour, peak acid response to pentagastrin (PAO^{PG}) 68.0 mEq per hour and total-hour response 53.6 mEq per hour. PAO^{OXO} was 22.8 mEq per hour, 33.5 per cent of PAO^{PG}.

At operation, on 6.10.70, the first part of the duodenum was found to be scarred by chronic ulceration, but the pylorus and proximal duodenum did not seem to be narrowed. Both the anterior and the posterior nerves of Latarjet could be seen clearly, despite the patient's obesity. Pentagastrin was infused intravenously in a dose of 6 ug per kg per hour (atropine was omitted from the premedication), and Congo Red dye[7] sprayed onto the gastric mucosa after the stomach had been opened by a gastrotomy incision near the greater curvature. The antrum-corpus boundary was defined, about 7cm. proximal to the pylorus, just proximal to where the nerves of Latarjet crossed onto the stomach. Mucosal antrectomy was performed as described by Kirk[4], the dissection being facilitated by infiltration of 1 : 250,000 adrenaline-in-saline

solution into the submucosal layer. About 1cm. of parietal cell mucosa was resected, with most of the antral mucosa, but 2.5cm. of antral mucosa were left intact proximal to the pylorus, because it was feared that a more distal dissection might produce scarring, pyloric stenosis and gastric stasis. The mucosal antrectomy proved tedious, particularly on the lesser curve aspect where the entry of numerous small arteries posed a problem with haemostasis. The edge of the mucosa of the parietal cell mass was sutured to the distal cuff of antral mucosa with continuous catgut. This produced distorsion of the sero-muscular layer of the antrum. The gastrotomy incision was closed as it had been made, longditudinally, and the operation was completed by performance of HSV in the usual way. Total operating time was three and a half hours.

The pathological report was that the specimen weighed 14 grams and consisted principally of inflamed mucosa from the pyloric-gland area. Mucosa of the body of the stomach was also present at the proximal margin.

Post-operative progress O. H. made an uneventful recovery. Five days after operation, PAO^{PG} was 14.9 mEq per hour. The insulin test at seven days was negative by all criteria. No acid was secreted throughout the test.

At follow-up, six and nine months later, he was fairly well, at work, without ulcer pain; but he complained of foul flatulence, epigastric fullness after meals, and of occasional episodes of diarrhoea which lasted for one or two days. He had a good appetite and could eat quite large meals. At nine months, his weight was still 10 kg. less than it had been before operation. Thirteen months after operation, he was assessed "blindly" by the panel of doctors at the Gastric Follow-Up Clinic. He was graded Visick III[8], a "fair" result only, on account of symptoms which he could not control with care; namely, occasional nausea, epigastric fullness after meals, flatulence and occasional vomiting of food. He restricted the size of his meals to two-thirds of what he ate formerly. His bowels acted regularly, once per day, and the episodes of diarrhoea had ceased. His weight was 72kg., compared with 78kg. before operation.

Follow-up secretory test: 14 months after operation, the resting juice aspirated from the stomach in 15 minutes measured 110ml., with a pH of 2.6. BAO was 1.1 mEq per hour (77 per cent reduction), although free acid was present in only the first of the four specimens. An OXO test was performed as described previously: PAO^{OXO} was 2.6 mEq per hour (88 per cent reduction). At the end of the OXO test, pentagastrin was injected intramuscularly in a dose of 10 ug per kg,

and elicited a PAO^{PG} of 27.7 mEq per hour (59 per cent reduction) and a total-hour output of 19.1 mEq per hour (64 per cent reduction).

Comment This is the only case in which we have combined supra-pyloric mucosal antrectomy with HSV. The main reason is that patients are doing well after HSV alone. In addition our experience with Mr. O. H. was not such as to encourage us to make more extensive use of mucosal antrectomy. The operation was tedious technically, taking three and a half hours to complete. Closure of the gap in the mucosa produced distorsion of the antral musculature and it did not seem likely that antral motor activity would prove to be normal. The weight loss, post-cibal fullness, foul flatulence and episodic diarrhoea which O.H. experienced in the first year after operation were probably attributable in part to some degree of gastric stasis, and the overall clinical result leaves much to be desired. Admittedly, a few patients do experience similar symptoms after HSV alone, but in general the result which they achieve is better than that of O.H. The large reduction in antral release of gastrin, as shown by the small response to the OXO test meal, appears to have been bought at a heavy price. We could perhaps be criticized for choosing this particular patient for mucosal antrectomy, because the pre-operative history of food vomiting and flatulence, in conjunction with

the barium meal report of an excessive volume of resting juice, might have suggested that gastric emptying was impaired before operation. On the other hand, the patient had been eating well, was actually gaining weight on his "ulcer" diet, and the volumes of resting juice (96ml. and 80ml.) in the two pre-operative tests of secretion were not excessive.

SUMMARY

A patient with chronic duodenal ulceration and high acid secretion was treated by HSV combined with supra-pyloric mucosal antrectomy. The operation was difficult, slow, and bloody. Acid secretion in response to meat extract was reduced from 22.8 to 2.6 mEq per hour (an 88 per cent reduction). The peak response to pentagastrin was reduced from 68 to 28 mEq per hour (59 per cent reduction). The patient has experienced complete relief from ulcer pain, but he has lost 6kg in weight, and was troubled by foul flatulence and episodic diarrhoea in the first year after operation. The overall clinical result is only moderate (Visick grade III). This single case may give a falsely bad impression of supra-pyloric mucosal antrectomy, but it would be surprising if this procedure did not impair gastric motility and hence gastric emptying to some extent. Further use of

supra-pyloric mucosal antrectomy in man is not recommended, particularly since patients do well, in general, after HSV alone.

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EFFECT OF ANTRONEUROLYSIS ON GASTRIC SECRETION IN DOGS WITH TOTAL GASTRIC FISTULA

Mucosal antrectomy did not seem an attractive procedure to combine with HSV, while the use of antrectomy of the usual type would render the performance of HSV pointless. We decided to try a third method, by which gastrin release from the antrum might be reduced, yet without sacrifice of the pylorus or of the kneading and propulsive activity of the distal five to seven centimetres of the stomach. This was the operation of antroneurolysis, in which vagal denervation of the antrum is confined to the mucosal layer, the seromuscular layer being left innervated. Antroneurolysis had been shown previously to reduce acid output in response to food by about 50 per cent in dogs with Heidenhain pouches[1,2]. Accordingly, we assessed this procedure in dogs, and measured secretion from the entire stomach rather than from a pouch, both because such a preparation was closer to the situation in patients, and because pouch secretion does not always mirror that of the main stomach[3,4].

MATERIAL AND METHOD

Five mongrel dogs, weighing 14 to 18kg., were equipped under general anaesthesia with either a gastric cannula (3 dogs) or a gastric fistula (2 dogs), the latter consisting of a short length of jejunum connecting the skin with the body of the stomach[5]. Gastric secretion was collected by opening the cannula or by passing a tube along the fistula and exerting continuous suction on it. Three to 5 weeks were allowed to elapse after operation before testing began. Each test was preceded by a fast of at least 16 hours and no dog was tested more often than three times per week. The dogs remained in good health throughout the series of experiments. They were trained to stand calmly in a Pavlov frame in a quiet room.

Pentagastrin Tests Maximal acid output was stimulated by intramuscular injection of pentagastrin in a dose of 10, 20, 30, or 40 ug. per kg. The resulting secretion was collected into seven to nine batches, each batch representing a 10-minute collection period.

Insulin Tests The vagal phase of gastric secretion was stimulated by intravenous injection of soluble insulin, in a dose of 0.25 unit per kg. body weight. Samples of venous blood were withdrawn 30 and 45 minutes later for blood-glucose estimation on the Autoanalyser.

Gastric secretion was collected continuously for 2 hours after insulin injection, in eight 15-minute batches.

Antral Stimulants Release of gastrin was stimulated by instillation via the cannula or the fistula of either meat-extract solution (three cubes of OXO dissolved in water to 100ml.[6,7]) or of acetylcholine chloride solution (100ml. of 0.5 per cent solution[8]). The test meal was at room temperature. The pH of the OXO solution was adjusted to 7 with sodium bicarbonate. The acetylcholine was left at its natural pH of 6. Care was taken to prevent the dog smelling the meat extract. The stimulant solution was left in the stomach for exactly 15 minutes. The gastric content recovered in the ensuing 5 minutes was discarded. Secretion was then collected continuously in 10-minute batches until the secretory response was waning; that is, for between 40 and 120 minutes.

Recovery of Gastric Content In 25 tests the efficiency of recovery of gastric content was estimated by instillation of 10ml. of 0.5 per cent polyethylene glycol (PEG) solution (M.W., 4000) into the stomach every 10 minutes throughout the test and measurement of the amount recovered[9]. The PEG was instilled slowly through a second tube.

Acid was titrated to pH 7 with 0.1 N sodium hydroxide, by means of an autotitrator (Radiometer, Copenhagen). Peak acid output

in mEq per hour was calculated by multiplying peak 20-minute output by 3, or in the case of the insulin tests, peak 30-minute output by 2.

The results reported are the results of the technically 'best' tests. Despite all precautions, about two-thirds of all tests performed were imperfect for some reason. In some, food residues contaminated the specimens; in others, the dog vomited or seemed unwell, or else the injection was thought not to have entirely reached its target because the dog jumped away as soon as it felt the prick of the needle. However, the most important cause of error was the inexplicable variation in some dogs' responses to the same stimulus at different times. For example, four dogs had 5 tests each with the dose of 20 ug. per kg. of pentagastrin and because of the variation that was found in the acid outputs, only the results of the two tests giving the highest outputs are quoted. The 10 and 20 ug. per kg. doses of pentagastrin elicited maximal levels of acid secretion. The results of tests in which higher doses were used are not reported, since acid outputs were less than maximal. If the results of all tests are considered, perfect or otherwise, the results and conclusions remain unaltered.

Antroneurolysis was performed under general anaesthesia in each dog by the method of Jones and others[1]. The stomach was

opened by a longitudinal incision placed close to the greater curvature to avoid damage to the vagal nerve-supply of the muscle layers. The extent of the pyloric gland area was defined by spraying Congo-red dye on to the gastric mucosa[10,11], while acid secretion was stimulated by intravenous infusion of histamine acid phosphate (H.A.P.). 2 to 3 mg. of H.A.P. were administered intravenously in 200 - 300 ml. of 0.9 per cent saline solution over a 30-minute period. The red dye turns black when it comes in contact with acid-secreting mucosa. A sharp line of demarcation between black parietal cell area and red "antrum" was seen in each dog. The mucosa of the antrum was then dissected off the muscular layer of the gastric wall by a technique similar to that used by Kirk[12] in the performance of mucosal antrectomy in man. Injection of a solution of adrenaline in saline (I in 200,000) into the submucosa made the plane of dissection more obvious and greatly reduced haemorrhage. The dissection extended from 2cm. proximal to the corpus-antrum border to 1cm. proximal to the pylorus, but was not carried more distally lest pyloric obstruction should result. The mucosal flap was then reconstituted as a tube with a running suture of catgut, and the sero-muscular layer was closed separately.

Each dog made a satisfactory recovery from this procedure

and was able to eat well without vomiting. At subsequent operation the antral region of the stomach appeared almost normal and peristalsis was seen to be active. After an interval of 3 - 5 weeks the secretory tests were repeated.

RESULTS

Antroneurolysis did not produce a significant decrease in the outputs of acid in response to any of the secretory stimulants (Fig. 1, Tables I and II). Indeed, small increases were noted in the output of acid in response to pentagastrin, insulin, and acetylcholine after antroneurolysis. The acid response to meat extract decreased slightly.

Recovery of polyethylene glycol (PEG) averaged 89 per cent in 25 tests, ranging from 86 to 95 per cent in the 5 dogs. In 2 dogs with Mann-Bollman fistula, PEG recovery was 88 $\pm$ S.E. 2.5 per cent in 11 tests, while in 14 tests on the 3 dogs with metal cannulae, recovery was 90 $\pm$ 2.5 per cent.

DISCUSSION

Antroneurolysis, which severs the vagal nerve supply to the antral mucosa, failed to reduce the secretion of acid from the innervated whole stomach in the dog. This was a little surprising,

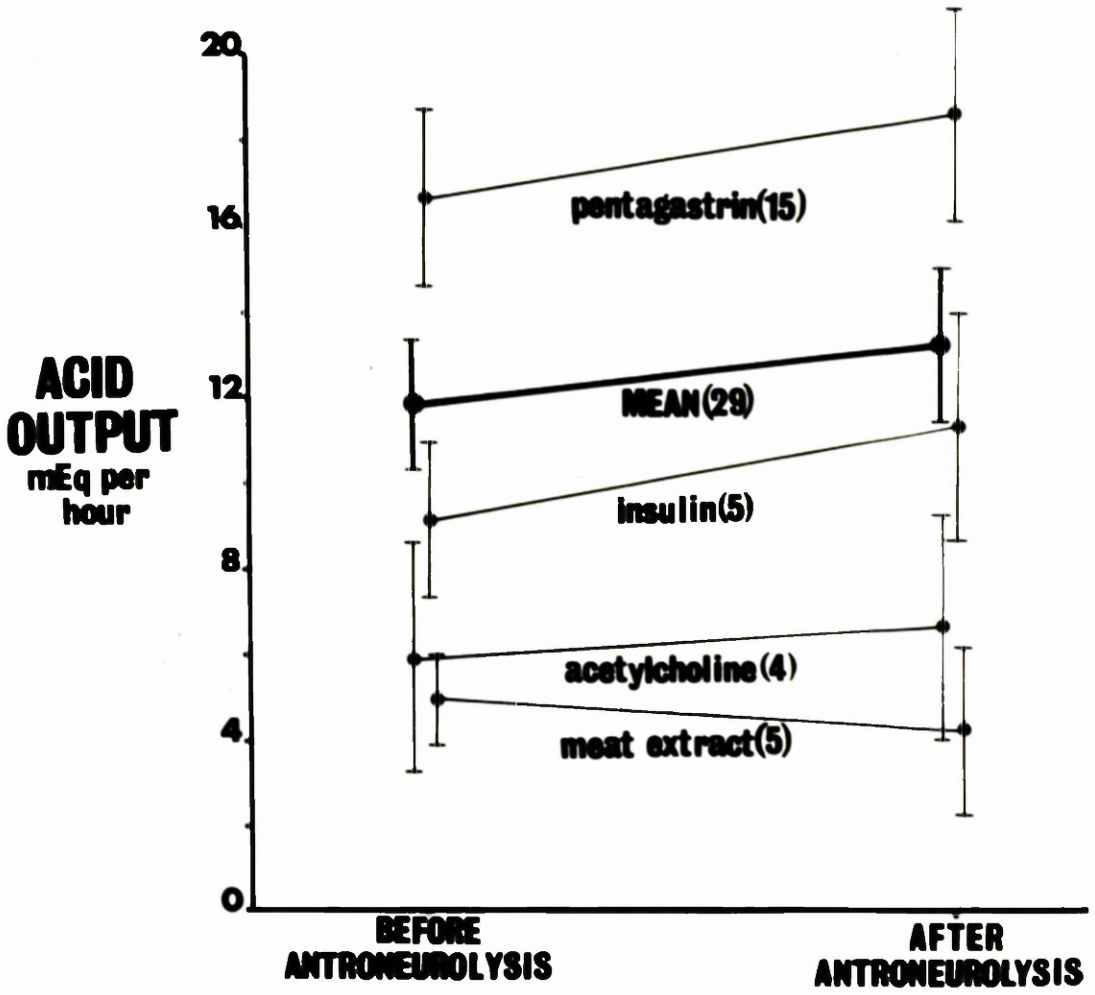

Fig. 1 Mean gastric acid outputs (± 1 standard error) from the entire stomach in response to various stimuli before and after antroneurolysis. The heavy line joins the means of all tests before and after antroneurolysis. The small mean increase is not significant ($p > 0.1$). Numbers of paired tests are shown in brackets.

Table I

Results of paired tests of acid secretion before and after antroneurolysis

TEST NO.	STIMULUS	DOG	BEFORE ANTRONEUROLYSIS mEq/hr.	AFTER ANTRONEUROLYSIS mEq/hr.	DIFFERENCE
1	PENTAGASTRIN 20 ug per kg.	I	17.64	10.65	- 6.99
2		I	17.67	11.23	- 6.44
3	*	I	24.00	22.94	- 1.06
4		II	4.49	6.81	+ 2.32
5	"	II	3.90	6.30	+ 2.40
6		II	3.72	4.26	+ 0.54
7		III	30.54	34.77	+ 4.23
8	"	III	29.58	21.69	- 7.89
9		IV	18.54	30.96	+12.46
10	"	IV	17.55	28.92	+11.37
11		IV	17.10	28.56	+11.46
12	*	V	17.73	16.20	- 1.53
13	"	V	17.43	21.18	+ 3.75
14		V	16.80	21.15	+ 4.35
15		V	13.95	13.86	- 0.09
1		I	8.72	14.66	+ 5.94
2	INSULIN	II	2.50	4.92	+ 2.42
3		III	11.02	18.88	+ 7.86
4	0.25 u per kg.	IV	11.12	12.28	+ 1.16
5		V	12.56	5.94	- 6.62
1	ACETYLCHOLINE	I	6.32	12.09	+ 5.77
2	0.5 per cent	II	0.30	1.17	+ 0.87
3	solution	IV	3.65	7.59	+ 3.94
4		V	13.11	5.67	- 6.44
1	MEAT EXTRACT	I	6.54	9.75	+ 3.21
2		I	5.34	7.77	+ 2.43
3	OXO SOLUTION	II	1.35	0.02	- 1.33
4		II	3.84	0.06	- 3.78
5		III	7.53	3.60	- 3.93

* dose of pentagastrin was 10 ug per kg. in these two tests.

Table II

Effect of antroneurolysis on acid secretion from the whole stomach*

STIMULUS	NO. OF PAIRED TESTS	BEFORE ANTRONEUROLYSIS	AFTER ANTRONEUROLYSIS	t	P
		Acid output (mEq per hour)			
Pentagastrin	15	16.71 ± 2.08	18.63 ± 2.49	1.21	0.2 < P < 0.3
Insulin	5	9.18 ± 1.78	11.34 ± 2.64	0.86	0.4 < P < 0.5
Acetylcholine	4	5.85 ± 2.72	6.63 ± 2.63	0.39	0.7 < P < 0.8
Meat extract	5	4.92 ± 1.08	4.42 ± 1.98	0.45	0.6 < P < 0.7
Mean of all tests	29	11.88 ± 1.51	13.24 ± 1.79	1.40	0.1 < P < 0.2

* Figures are means ± 1 standard error of the mean. Significance of difference in secretion after antroneurolysis was calculated using Student's t-test for paired data.

in view of evidence that the vagus nerves play an important part in the release of antral gastrin[13-16], that antroneurolysis protects dogs against the development of experimental peptic ulcer[19], and that antroneurolysis produces a significant decrease in acid output from Heidenhain pouches in dogs[1,2,20].

The slight increase in gastric acid output which we found after antroneurolysis is in agreement, however, with the results of those workers who used vagally innervated (Pavlov) pouches in dogs to monitor levels of circulating gastrin before and after vagal denervation of the antrum[1,2]. De Castella and Irvine[17] found no significant change in acid output in response to a meal from Pavlov pouches after vagal denervation of the "in situ" antrum. Our experimenta preparation, in which the body of the stomach retains its vagal innervatior is more akin to a Pavlov than to a Heidenhain pouch. Vagal release of gastrin was probably minimal in our dogs, because the response counteracted the stimulus: that is, secretion of HCl from the oxyntic cells would quickly produce an acid pH in the antrum, which in turn would lead to inhibition of gastrin release[21]. Vagal release of gastrin is notoriously difficult to demonstrate when the antrum remains in continuity with the body of the stomach[14, 22-24] and can be demonstrated convincingly only in animals with separated or excluded antral pouches,

shielded from the inhibitory effect of acid[20,25-27]. Gastrin release in response to mechanical (balloon distension) and chemical (alcohol) stimulation of the antrum was found by Nyhus and others[20] to be undiminished after vagal denervation of the antrum, which is in keeping with our results. On the other hand, Sugawara and others[18] found that release of gastrin in response to balloon distensiondf the separated antrum in dogs decreased significantly when the antrum was vagally denervated.

Why secretion tended actually to increase after antroneurolysis is not clear. The increase was not statistically significant, but this may merely be due to the relatively small number of tests which were performed. If the increase was a real one, one might postulate that some inhibitory mechanism had been disturbed. Certainly the gastric antrum is the seat of powerful inhibitory as well as of stimulatory mechanisms[27,28]. The presence of pH-sensitive nerve-endings in the antral mucosa, which might be the source of inhibitory nervous reflexes, has been demonstrated by Iggo[29], while stimulation of the vagal antral nerves (the nerves of Latarjet) in dogs has been shown to lead to inhibition of gastric acid output[30,31].

In conclusion, this study, which was designed to evaluate the effect of antroneurolysis on secretion from the whole, innervated

stomach, has yielded no evidence to suggest that the procedure reduces gastric acid secretion. Although it is in the nature of a pilot study, further observations in the same animals would have been unlikely to have altered the main conclusion. It is a pity that larger numbers of insulin tests were not performed, because the increase in acid output (Table I)(Fig. 1) might have been found to be statistically significant, which would have provided more evidence for an inhibitory role by the nerves of Latarjet. Further investigation to measure the effect of antroneurolysis on secretion from the vagally denervated parietal cell mass in the dog seems indicated, in view of the disparity between the results previously obtained in dogs with Pavlov pouches as compared with those obtained in dogs with Heidenhain pouches.

SUMMARY

The operation of antroneurolysis is performed by circumferential sharp dissection in the submucosal plane of the gastric antrum. Thus it severs the vagal nerve-supply to the antral mucosa. It might be regarded as a conservative variant of antrectomy, and its purpose is to diminish gastrin release without disturbing antral peristalsis or the mechanism of the pylorus. Its possible value as an adjunct

to highly selective vagotomy in man is evaluated in this study in the dog.

The antroneurolysed antrum was left in continuity with the remainder of the stomach, whose vagal nerve-supply remained intact. Gastric secretion was collected via a cannula or fistula draining the whole stomach. Outputs of acid in response to insulin, pentagastrin, meat extract, and acetylcholine were found to be undiminished after antroneurolysis. It is concluded that antroneurolysis has no place at present in clinical gastric surgery.

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CONCLUSION

In this section, we have attempted to evaluate several methods by which the possible danger of recurrent ulceration, caused by the presence of the innervated antrum after HSV, might be averted.

ANTRECTOMY itself renders the performance of HSV pointless. Supra-pyloric antrectomy, as described by Amdrup and Griffith[1], has the advantage that the pylorus is preserved, but since it involves transection of the nerves of Latarjet or of their terminal branches, it also is an inappropriate operation for use in combination with HSV. It might prove to be useful in combination with selective vagotomy. However, it involves an anastomosis very close to the pylorus, and might well be followed by pre-pyloric fibrosis, stenosis, and gastric stasis. This sequence of events in fact took place in one of the two dogs in which Amdrup and Griffith performed supra-pyloric antrectomy[1]. Thus, it seems an unattractive procedure for use in man.

MUCOSAL ANTRECTOMY For these reasons, we concentrated our effort towards reducing or eliminating the release of gastrin, without damaging the muscle layers of the antrum, or the pylorus. Gastrin is produced in the mucosal layer only of the antrum,

and Kirk[2] had shown previously that mucosal antrectomy was practicable in man. Remembering Milton, Maxwell and Finckh's[3] demonstration that the gastric cavity rapidly becomes re-epithelialised after most of the mucosal lining has been excised, we excised most of the antral mucosa in two dogs, in the hope that the raw surface would quickly be covered by epithelium of a less specialized variety, which would produce less, or no gastrin. Unfortunately, the experiment failed, because the dogs ate poorly, became thin and weak, and at autopsy were shown to have unhealed ulceration of the gastric antrum, accompanied by gross thickening of the wall of the antrum. Clearly this procedure could not be used in man.

SUPRAPYLORIC MUCOSAL ANTRECTOMY Following the example of Kirk[2], who performed complete mucosal antrectomy in man, sacrificing the pylorus; and of Amdrup and Griffith[1], who performed supra-pyloric mucosal antrectomy in the dog, preserving the pylorus, we performed HSV with supra-pyloric mucosal antrectomy in one patient who had a duodenal ulcer in association with a very high maximal acid output. The pylorus was left intact. However, the operation was time-consuming and technically difficult, and apposition of the cut edges of gastric mucosa produced distortion of the antral musculature. Post-operatively, the patient experienced symptoms

suggestive of gastric stasis, and has achieved only a "fair", Visick-grade-III, result. Since the evidence from work in dogs suggests that even when the antrum is left in continuity with the acid stream, most of the antral mucosa has to be excised before Heidenhain-pouch acid output will diminish significantly[1]; and since it would appear that the defect in the mucosa must be closed by direct suture, it follows that distortion of the antrum is almost certain to be produced by supra-pyloric mucosal antrectomy. Such distortion may well lead to impaired gastric emptying. Thus, supra-pyloric mucosal antrectomy, without pyloroplasty, cannot, in our opinion, be recommended for use in man.

ANTRONEUROLYSIS seemed to be the most promising procedure for use in combination with HSV, because in the dog it had been found not to lead to gastric stasis, yet produce a significant decrease in acid output from Heidenhain pouches[4-6]. After antro-neurolysis of the "in situ" antrum in the dog, we were able to confirm that gastric emptying was satisfactory, because the dogs ate heartily without vomiting, and maintained their weight. In addition, at laparotomy the antroneurolysed antra looked little different from normal, were not obviously thickened, and could be seen to contract vigorously. Unfortunately, we were unable to demonstrate that antroneurolysis

produced significant inhibition of gastric acid output. The remainder of the stomach remained vagally-innervated in these dogs, and it is conceivable that had the body of the stomach been vagally denervated, a different result might have been obtained after antroneurolysis.

Finally, it should be noted that all the experiments which are reported in this section were in the nature of pilot studies. We would regard the two experiments in dogs with mucosal antrectomy without suture as "crucial", and feel justified in concluding that use of such a procedure would be quite unjustifiable in man. On the other hand, the impaired gastric emptying, which we suggest - but did not prove - took place after HSV mucosal plus supra-pyloric/antrectomy in one patient, was not seen in Amdrup and Griffith's[1] three dogs which were subjected to the same procedure. Thus the possibility of future use of supra-pyloric mucosal antrectomy in man cannot be entirely dismissed. The experiments with antroneurolysis were few, but yielded no evidence of a decrease in acid output. Indeed, the increase in insulin-stimulated acid output after antroneurolysis in four out of five dogs suggested that an inhibitory influence had been removed. The work should be repeated in dogs with a vagally-denervated body of stomach.

None of the procedures tested - mucosal antrectomy,

supra-pyloric mucosal antrectomy, or antroneurolysis - seems in the least promising as a possible adjunct to highly selective vagotomy in man. The need for any such complementary operation is in any case not established, because there is no evidence that gastrin release is excessive after HSV, and to date recurrent ulceration has not been a problem in our patients. Others[7] have reported recurrent ulceration after HSV, but the incidence of incomplete vagotomy on insulin-testing soon after operation in their patients was 28 per cent, compared with 3 per cent in our first 100 patients. Thus, recurrent ulceration in their patients was probably due to inadequate vagotomy of the parietal cell mass at the time of operation.

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CHAPTER 10

EFFECT OF THE THREE VAGOTOMIES ON GASTRIC EMPTYING AND INTESTINAL TRANSIT OF A FOOD-BARIUM MEAL

GASTRIC EMPTYING OF A FOOD-BARIUM MEAL

A radiological method such as this is a relatively crude way of investigating gastric emptying. It is capable only of demonstrating the existence of large differences between groups of subjects. One cannot, for example, state that the stomach is 35 per cent empty or 80 per cent empty. However, certain definite statements can be made. One can say that gastric emptying has started or that it has not, that the stomach is completely empty or that it is not, and that the head of the meal has reached the colon or that it has not.

METHOD

Patients 13 patients with duodenal ulceration, without clinical or radiological signs of pyloric stenosis, were studied before operation. Patients who were studied after vagotomy were in good health (nearly all in Visick grades I and II), one to three years after operation, and in each of them the vagotomy had been shown to be complete on insulin testing[1] in the early post-operative period. All the patients were men, with the exception of two women after selective vagotomy and one woman in the

HSV group. Twelve patients had undergone truncal (T) V+P; 10, bilateral selective (S) V+P, and 14, highly selective vagotomy (HSV). The pyloroplasty was of the Heinecke-Miculicz type in each case. The mean (± 1 SE) ages of the patients were 45.1 ± 3.7 (DU), 49.8 ± 3.5 (TV+P), 44.8 ± 2.4 (SV+P), and 44.5 ± 2.5 years (HSV). Mean weights were, respectively, 67.3 ± 2.3 kg. (DU), 68.2 ± 1.8 (TV+P), 62.9 ± 2.7 (SV+P) and 68.3 ± 1.9 kg. (HSV).

Meal This consisted of two slices of toast, one ounce (28g.) of butter, two scrambled eggs, 170 ml. of tea with milk and one teaspoonful of sugar, 30 ml. of 'Raybar' and 30 ml. of water. These ingredients were homogenized in a blender for 10 minutes. The resulting meal was semi-fluid in consistency and tasted surprisingly pleasant, like a rather chalky cake-mix. It was served warm, and eaten with a spoon because it was too thick to drink.

Procedure The test began at 6 p.m., the patient having fasted from lunchtime, about 1 p.m. First of all a plain x-ray film of the abdomen was taken. Then the patient sat upright in a chair, and ate the meal in the course of five to ten minutes. Further abdominal radiographs were taken, 15, 30, 45, 60, 90, 120 and

150 minutes from the start of the meal, with the patient lying prone on the x-ray table. In the intervals between exposures, he sat in a chair, or strolled about the x-ray Department.

Assessment The films were assessed by an experienced radiologist, who was unaware of the group to which the patient belonged. He was asked to answer three questions :-

(1) Which was the first film which showed that gastric emptying had begun? (ie the presence of barium in the duodenum or beyond).

(2) When was the stomach completely empty? (apart perhaps from the merest traces of barium clinging to the gastric mucosa).

(3) When did the head of the meal reach the colon?

Statistics Differences between groups were analyzed by means of simple probability theory (see Appendix). Numbers were too small for application of the χ^2 test.

RESULTS

Time taken for gastric emptying to start Gastric emptying had begun by the time the 15-minute film was exposed in all the patients who had undergone TV+P or SV+P, but in only 10 of

the 13 pre-operative DU patients and 12 of the 14 patients after HSV (Fig. 1). These differences are not statistically significant. By 30 minutes, gastric emptying had begun in all patients.

Time taken for stomach to empty completely Gastric emptying was significantly faster in patients who had undergone TV+P or SV+P than in pre-operative DU patients or in patients after HSV (Fig. 2). There was no significant difference between DU patients and patients after HSV. For example sixty minutes after the meal, there was evidence of significantly faster gastric emptying in the TV+P group (DU cf TV+P, $p = 0.03$; HSV cf TV+P, $p < 0.01$). Ninety minutes after the meal, the stomach was completely empty in none of the 13 DU patients, 9 of 12 patients after TV+P, 5 of 10 patients after SV+P, and 2 of 14 patients after HSV. The differences between the DU group and the TV+P group, and between the DU group and the SV+P group, were both statistically significant. At 120 minutes, the stomach was completely empty in significantly more of the (TV+P, SV+P) groups combined than in the DU group ($p < 0.01$) or the HSV group ($p < 0.01$).

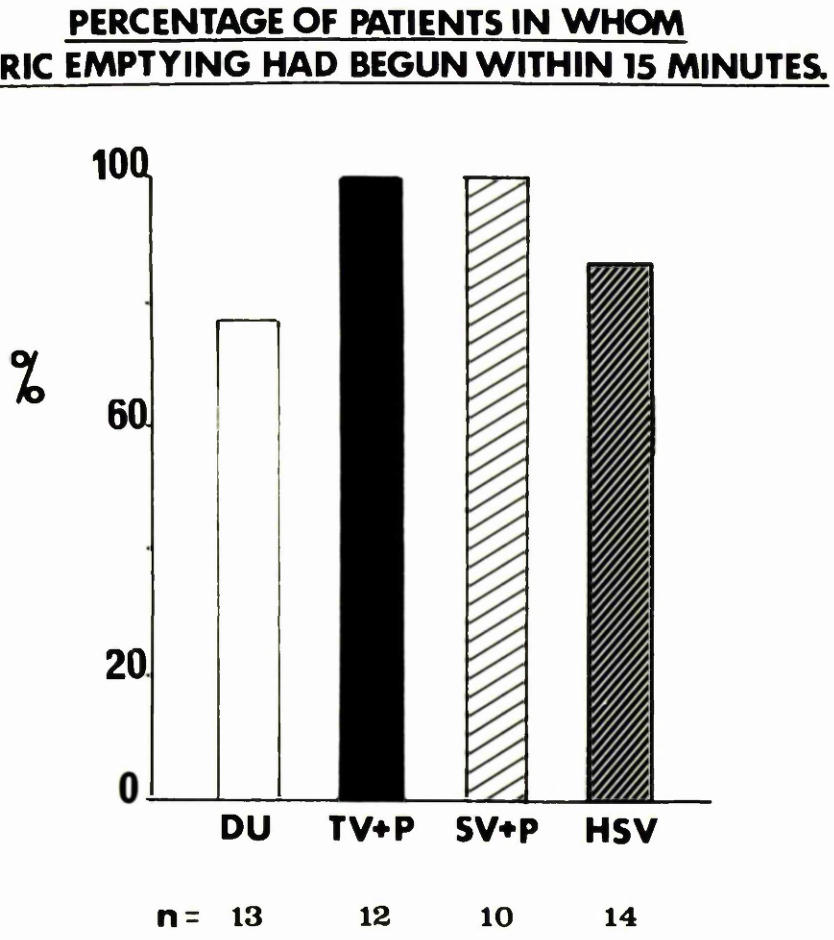

Fig. 1 In most patients, barium was visible in the duodenum or beyond at 15 minutes. The start of gastric emptying is slightly faster in patients after TV+P and SV+P than in pre-operative DU patients or patients after HSV. By 30 minutes, gastric emptying had begun in all patients.

PERCENT OF PATIENTS WITH AN EMPTY STOMACH AT VARYING INTERVALS AFTER THE MEAL.

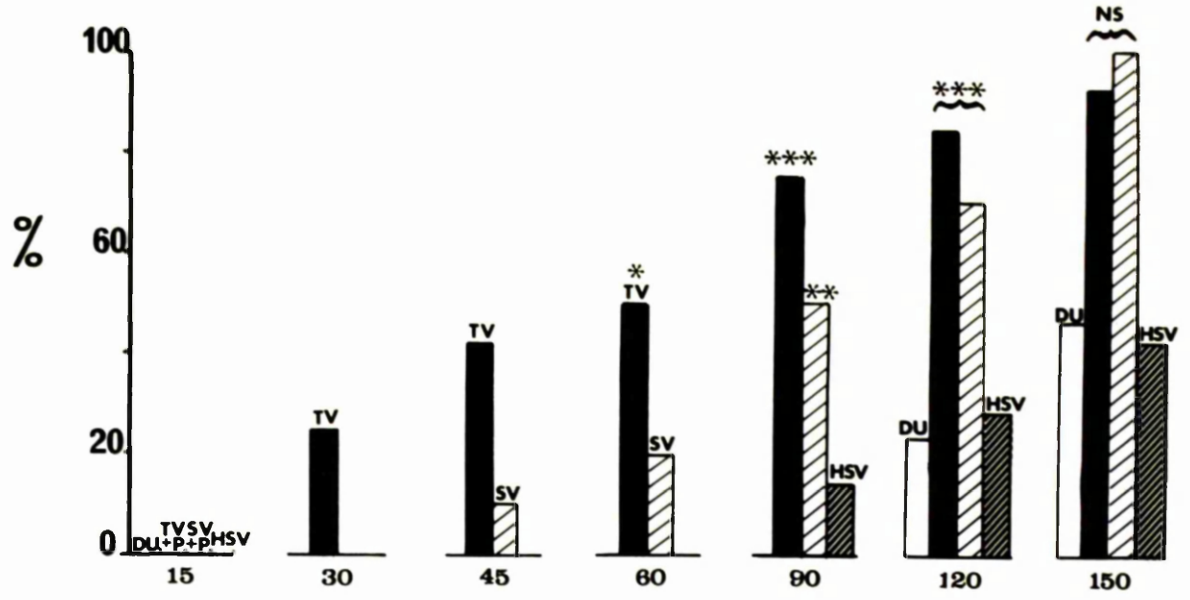

Fig. 2 Asterisks indicate significant difference from DU patients. *, $p < 0.05$; **, $p < 0.02$; ***, $p < 0.01$. Note that at 120 minutes, patients after (TV+P + SV+P) have been considered together. At 60, 90 and 120 minutes, there were significantly more patients in the TV+P group than in the DU group who had a completely empty stomach. The HSV group of patients differed little from the pre-operative-DU group of patients.

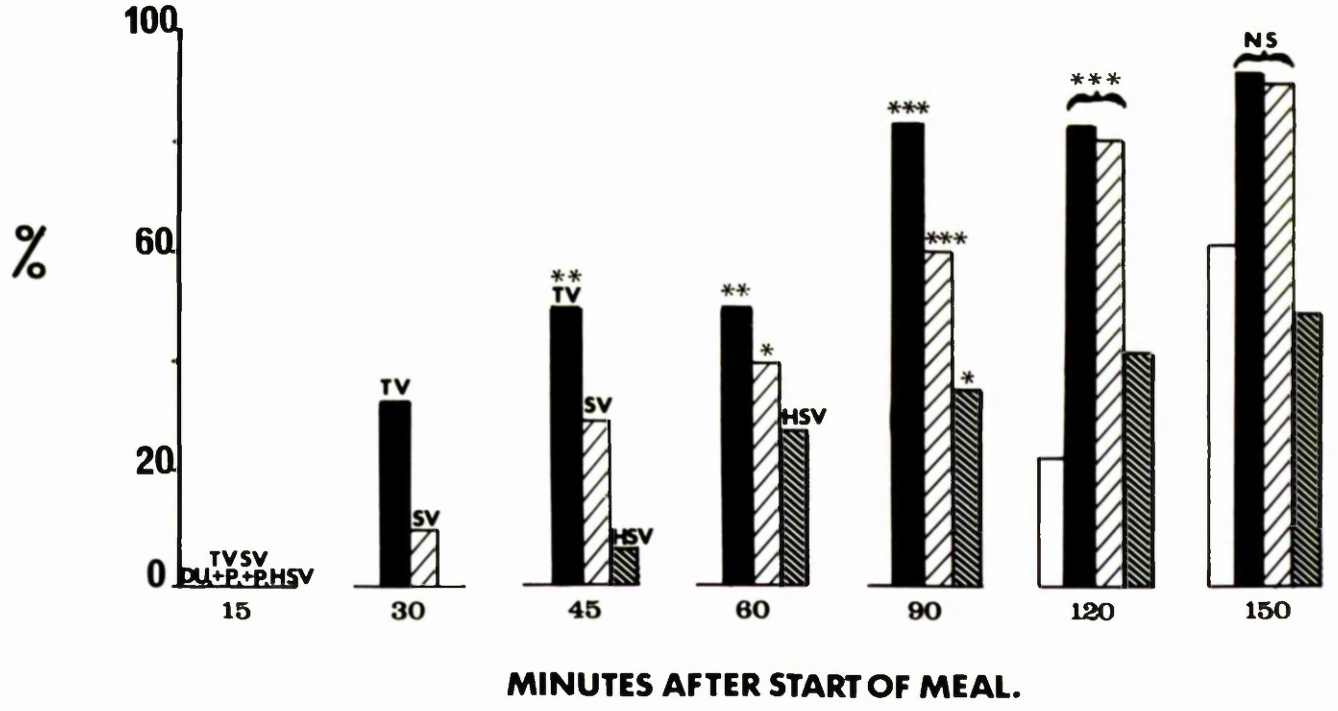

Fig. 3 Asterisks indicate significant difference from the group of pre-operative DU patients. *, $p < 0.05$; **, $p < 0.02$; ***, $p < 0.01$. At the 120-minute time interval, patients after (TV+P + SV+P) were considered together. The head of the meal reached the caecum significantly faster in patients after TV+P and SV+P than in pre-operative DU patients. Intestinal transit in the HSV patients was faster than in DU patients (significantly so at 90 minutes), but much slower than in patients after TV+P or SV+P.

Time taken for the head of the meal to reach the caecum

Small-bowel transit, as judged by the time taken for the head of the meal to reach the colon, was significantly faster in patients after TV+P and SV+P than in pre-operative DU patients (Fig. 3). Small-bowel transit was also faster in HSV patients than in pre-operative DU patients, but the difference was much less marked than in patients after TV+P or SV+P. For example, 45 minutes after the meal, the head of the meal had reached the colon in none of the pre-operative DU patients, 6 of 12 TV+P patients ($p < 0.02$), 3 of 10 SV+P patients (N.S.) and 1 of 14 HSV patients (N.S.). Ninety minutes after the meal, barium had reached the colon in none of the DU patients, 10 of 12 TV+P patients ($p < 0.001$), 6 of 10 SV+P patients ($p < 0.01$) and 5 of 14 HSV patients ($p = 0.03$). At 120 minutes, the difference between the DU patients and the (TV+P and SV+P) groups combined was statistically significant ($p < 0.01$). At 150 minutes, differences between groups were not statistically significant (Fig. 3).

DISCUSSION

It is assumed, on the basis of previous work by others[2], that gastric emptying is normal, or at least not slower than normal

in patients with duodenal ulcer who do not have clinically-manifest pyloric stenosis.

The results which we have obtained are in accord with those of previous workers[3-5] who found that gastric emptying of fluids was significantly faster after truncal or selective vagotomy with a drainage procedure than in patients with duodenal ulcer before operation. They are not in agreement with the report by Buckler[6] that gastric emptying is delayed after truncal vagotomy and pyloroplasty, nor with that of Cowley et al.[7] who found that gastric emptying was within normal limits after truncal vagotomy and pyloroplasty. Buckler[6] and Cowley et al.[7] used a test meal of solid food, which may explain why gastric emptying in their patients was slower than in our patients after TV+P or SV+P, whose test meal was semi-fluid. The posture adopted by the patients during the test may also provide an explanation for the differing results, because Cowley et al's. patients were kept in a recumbent position throughout the test, whereas our patients sat in a chair or walked about except when radiographs were being taken. According to the work of McKelvey et al.[3,4], posture does not exert an important influence on gastric emptying in the intact individual, but after

vagotomy with a drainage procedure it assumes great importance, gastric emptying being slow if the patient lies supine and rotated towards the left, whereas emptying is precipitate if the patient assumes the upright posture. These findings of McKelvey et al. apply only to fluids, but they are probably relevant to the emptying of normal meals. For example, dinner consists of fluids (aperitif, soup) followed by solids and semi-solids (meat, gravy and potatoes), followed by solids with hypertonic liquid (fruit salad with syrup and ice-cream), followed by more fluids (coffee). The conclusions of Cowley et al.[7] that gastric emptying is within the normal range after TV+P are also difficult to accept because it is known that 10 to 30 per cent of patients experience early dumping in the first year after TV+P or SV+P (see later chapters), which suggests strongly that their gastric emptying is abnormally rapid. Finally, after the demonstration by Code and his colleagues[8] that the pylorus and terminal antrum discriminate between solids and liquids, holding back solids and retropelling them into the body of the stomach while liquids are allowed to pass, it seems

inconceivable that gastric emptying of solids should be normal when the pylorus has been destroyed by pyloroplasty or bypassed by gastrojejunostomy. Indeed, it was subsequently shown by Dozois, Kelly and Code[9] that when the terminal antrum is excised, solid spheres empty more rapidly from the stomach of dogs.

SUMMARY

Gastric emptying of a food-barium meal was measured radiographically in patients with duodenal ulcer without pyloric stenosis before operation, and in well-matched groups of patients who were in good health more than one year after HSV, truncal V+P and selective V+P. In each patient, the vagotomy was complete on insulin testing in the early post-operative period. The meal was palatable, and semi-solid in consistency. The patients were allowed to sit in a chair or to walk about when they were not being x-rayed.

The meal began to leave the stomach slightly, but not significantly, earlier in patients after TV+P and SV+P than in DU or HSV patients.

The stomach was completely empty significantly sooner in patients who had undergone TV+P and SV+P than in DU or HSV patients.

The head of the meal reached the colon significantly sooner in patients after TV+P and SV+P than in pre-operative DU patients. In other words, gastro-intestinal transit was significantly faster in patients who had undergone TV+P or SV+P than in patients with DU before operation. In patients after HSV, small-bowel transit was slightly faster than in DU patients, but was much less rapid than in patients after TV+P or SV+P.

These findings indicate that gastric emptying and small bowel transit times are closer to normal in patients who have undergone HSV than in patients who have undergone TV+P or SV+P. On the other hand, there was no evidence of delayed gastric emptying after HSV.

APPENDIX

(Probability theory)

Statistics

Example

Suppose we compare two groups, "DU" and "TV+P", each containing 10 patients. In the DU group, suppose the stomach is empty in none by 90 minutes, whereas in the TV+P group, the stomach is empty in 6 patients.

Thus, we have $\frac{\text{DU}}{0}$ cf $\frac{\text{TV+P}}{6}$ / 10 / 10

The chances that the stomach will by chance be completely empty in one patient in the TV+P group, but in none of the DU group, are $\frac{10}{20}$ or $\frac{1}{2} = 0.5$,

that it will be empty in 2 of the TV+P group, but in none of the DU group, are $\frac{10}{20} \times \frac{10}{20} = 0.25$,

and that the distribution should by chance be $\frac{0}{10}$ versus $\frac{6}{10}$ are

$$\left(\frac{10}{20}\right)^6 = \frac{1}{2x2x2x2x2x2} = \frac{1}{64} \quad \text{i.e. } p < 0.02.$$

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CHAPTER 11

GASTRIC EMPTYING OF A HYPERTONIC FLUID MEAL AFTER HIGHLY SELECTIVE, SELECTIVE AND TRUNCAL VAGOTOMY

GASTRIC EMPTYING OF A HYPERTONIC FLUID MEAL AFTER HIGHLY SELECTIVE, SELECTIVE AND TRUNCAL VAGOTOMY

Truncal or selective vagotomy with a drainage procedure has been found to produce "incontinent" emptying of a hypertonic fluid meal from the stomach[1-3]. We have compared gastric emptying of a fluid test meal of hypertonic glucose in patients with duodenal ulcer before operation and in patients more than one year after truncal vagotomy and Heinecke-Miculicz pyloroplasty (TV+P), bilateral selective vagotomy and Heinecke-Miculicz pyloroplasty (SV+P), and highly selective vagotomy without a drainage procedure (HSV).

METHOD

There were ten patients in each group. All the patients were male. Patients after vagotomy were in good health (Visick grades I, II or III), clinical failures being excluded. The clinical status of the HSV patients was slightly better than that of patients after TV+P or SV+P, in accordance with the overall clinical results (see later chapter). Thus, each of these small groups of ten patients was so chosen as to be typical of the larger groups of patients from which they were selected. The pre-operative patients were free

from symptoms or signs of pyloric stenosis. The four groups were well-matched for age (see Table) and fairly well-matched for weight, with the exception of the HSV patients who were considerably heavier than patients in the other three groups.

TECHNIQUE OF TEST The patient fasted overnight before the test, which began at 9 a.m. A nasogastric tube was passed into the stomach, which was emptied by continuous suction for 15 minutes. The patient then drank 100ml. of tap water rapidly, to wash out the stomach. This fluid could usually be aspirated immediately.

When the stomach was completely empty, and the patient had become accustomed to the presence of the tube, suction was discontinued, the tube spigotted, and the patient was asked to sit upright in a chair. He then drank 350ml. of 25 per cent glucose solution, containing 250 parts per million of phenol red, in the course of one to two minutes. He remained sitting upright in the chair for exactly 19 minutes from the time at which he began to drink the test meal. He then lay down flat on his back on a bed, and exactly 20 minutes from the start of the meal, suction was re-applied, and the gastric contents aspirated in the course of 5 minutes. The stomach was then washed out with a further 100ml. of water which were drunk by the patient.

Calculations The weight of phenol red put into the stomach (W1) is known, and the weight recovered (W2) is measured. Hence, the amount which is lost through the pylorus is (W1 - W2). Phenol red has been shown not to be absorbed by the stomach[4,5]. This value (W1 - W2) gives the volume of the test meal leaving the stomach. For example, if half the phenol red placed in the stomach is recovered, half of the test meal is assumed to have left the stomach in 20 minutes. If only one quarter of the phenol red is recovered, three-quarters of the test meal is assumed to have left the stomach.

Estimation of phenol red concentration The method used was a modification of that described by George[6]. 0.1 ml. of gastric aspirate, which had been centrifuged to remove mucus, was added to 5 ml. of 0.029 M trisodium orthophosphate buffer, whose pH was 11.8, and the purple colour which developed was measured on an SP 600 spectrophotometer at 560 mu. A linear relationship was shown in our laboratory to exist between the concentration of phenol red and the optical density (O.D.) between 25 and 250 ppm. The coefficient of variation in 20 duplicate tests was 2.1 per cent.

The exact method was as follows:-

	(1) STANDARD	(2) STANDARD BLANK	(3) TEST	(4) TEST BLANK
distilled water	-	5.0 ml.	-	5.0 ml.
gastric juice	-	-	0.1 ml.	0.1 ml.
standard phenol red solution, 250 ppm	0.1 ml.	0.1 ml.	-	-
buffer	5.0 ml.	-	5.0 ml.	-

All tubes were read against a water blank in the spectrophotometer SP 600 at 560 mu using 1 cm. cells.

Concentration of phenol red in the gastric juice

$$= \frac{\text{O.D.(3)} - \text{O.D.(4)}}{\text{O.D.(1)} - \text{O.D.(2)}} \times 250 \text{ ppm.}$$

RESULTS

The mean volumes of the test meal leaving the stomach in twenty minutes were 155 $\pm$ 13 ml. (DU patients), 213 $\pm$ 24 ml. (HSV patients), 278 $\pm$ 19 ml. (TV+P patients) and 259 $\pm$ 28 ml. (SV+P patients) (see Table). Gastric emptying was significantly

TABLE

GROUP OF PATIENTS	NUMBER IN GROUP	AGE (yr.)	WEIGHT (kg.)	VOLUME OF GLUCOSE MEAL LEAVING STOMACH IN 20 MINUTES (ml.)	COMPARISON WITH GROUP I		
					DEGREES OF FREEDOM	t	p
I PRE-OP. DU	10	48.80 ± 4.18	64.50 ± 2.35	155.43 ± 12.79	-	-	-
II HSV	10	49.40 ± 2.98	75.90 ± 3.96	212.68 ± 23.62	18	2.13	<0.05
III TV+P	10	49.40 ± 4.42	67.80 ± 2.44	278.25 ± 18.90	18	5.38	<0.001
IV SV+P	10	49.50 ± 1.89	64.70 ± 1.03	259.32 ± 28.23	18	3.92	<0.01

Gastric emptying was also significantly faster after TV+P than after HSV ($p < 0.05$), but the difference between the HSV and SV+P groups was not statistically significant ($0.2 > p > 0.1$).

faster in each of the three groups of vagotomized patients than in the group of patients before operation. The smallest difference from the pre-operative DU patients was found in patients after HSV ($p < 0.05$), and the greatest difference in patients after TV+P ($p < 0.001$). Gastric emptying was significantly faster after TV+P than after HSV ($p < 0.05$), but the difference between the HSV and SV+P groups was not statistically significant.

DISCUSSION

These results confirm previous reports[1-3] that gastric emptying of fluids is significantly faster in patients after truncal or selective vagotomy with a drainage procedure than in patients with duodenal ulcer before operation. This provides an explanation for the symptoms of dumping which many of these patients experience. In addition, the meal may pass with abnormal rapidity through the small intestine and produce diarrhoea[1,2]. Presumably the "braking" mechanism which is responsible for slowing the emptying of hyperton ic fluids[7] from the stomach is destroyed by both TV+P and SV+P. The osmoreceptors in the duodenum are probably denervated by the performance of truncal vagotomy, while after selective vagotomy they may be able to send afferent impulses, but the efferent

side of the reflex arc, to the stomach, is lost.

Gastric emptying of fluid after HSV, far from being delayed, was found to be more rapid than in pre-operative patients. Why this should be so is not entirely clear. The efferent side of the reflex arc, whose afferent impulses originate from the duodenal osmoreceptors, is to a large extent interrupted by HSV. The intestine may still be able to inhibit antral motility, but may lose much of its ability to modify pressure in the body of the stomach. Moreover, as several workers have now shown, vagotomy of the entire stomach leads to an increase in intra-gastric pressure[8-10], and to impairment of the receptive relaxation which normally takes place in response to a distension stimulus[11-14]. This abnormal increase in intra-gastric pressure after, for example, the ingestion of a fluid meal, is likely to cause the fluid to leave the stomach more rapidly. Our findings provide an explanation for the small but definite incidence of mild early dumping after HSV, and for the increased incidence of early dumping in HSV patients after the ingestion of hypertonic glucose, compared with the incidence in pre-operative patients (see later section on dumping). However, if gastric emptying of fluids was abnormally rapid after HSV, it was at

least found to be significantly slower ($p < 0.05$) than in patients who had undergone truncal vagotomy and pyloroplasty. This may explain why the latter group of patients have a higher incidence both of dumping and of diarrhoea than do patients after HSV (see later section).

The time-honoured[4,5] use of phenol red as a dilution indicator in the stomach was subjected to renewed scrutiny after the report by Bloom and his colleagues[15] of a 5 to 8 per cent loss of phenol red from Heidenhain pouches in dogs. Subsequently, however, Clarke and Williams[16] found that phenol red was a more satisfactory non-absorbable marker in the stomach than was chromic chloride, and Ivey and Schedl[17], who compared radioactive chromium, polyethylene glycol and phenol red as gastric non-absorbable indicators in man, concluded that there was minimal absorption from the stomach of all three indicators and that all three were equally valid.

SUMMARY

The proportion of a test meal of hypertonic glucose solution which had left the stomach within twenty minutes was measured in patients with duodenal ulcer without pyloric stenosis, and in patients more than one year after truncal vagotomy and pyloroplasty, selective vagotomy and pyloroplasty or highly selective vagotomy without a drainage procedure. There were ten patients in each group. Gastric emptying was found to be significantly faster in each of the groups of vagotomized patients than in patients before operation. Truncal vagotomy with pyloroplasty produced the greatest difference, and HSV the least.

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CHAPTER 12

VAGOTOMY WITHOUT DIARRHOEA

VAGOTOMY WITHOUT DIARRHOEA

About 25 per cent of patients experience episodic diarrhoea after truncal vagotomy with a drainage procedure for duodenal ulcer[1,2] (Table I). The diarrhoea is usually quite mild in degree, but in 2 or 3 per cent it is so severe that in spite of relief from ulcer pain, the patient considers that the operation has been a failure. The cause of the diarrhoea is not known, and it can be very difficult to treat. The incidence of diarrhoea is significantly less after bilateral selective vagotomy[3], (Table I) in which the vagal nerve supply to the pancreas, biliary tract and small intestine is preserved, but the incidence of around 12 per cent is appreciable and a few patients still suffer severely. A different explanation for the diarrhoea is suggested by the finding that the stomach is incontinent of fluids after truncal or selective vagotomy with a drainage procedure[4,5]. Rapid gastric emptying is followed by the swift passage of the liquid through the intestines, resulting in diarrhoea. Thus "post-vagotomy" diarrhoea may be produced in some patients by vagal denervation of extragastric viscera, while in others destruction or bypass of the pylorus in combination with gastric vagotomy may be the principal factor.

Table I

A comparison of the effects of truncal and selective vagotomy* on the incidence of post-vagotomy diarrhoea

Source	Truncal vagotomy		Selective vagotomy	
	No. patients	Per cent diarrhoea	No patients	Per cent diarrhoea
Burge, et al., (1961)	100	26	100	12
Elliot-Smith, et al. (1961)	131	2	44	2
Harkins, et al., (1963)	60	68	52	29
Hedenstedt and Lundquist, (1966)	30	50	44	6
Williams and Irvine, (1966)	43	9	22	0
Kraft, et al., (1967)	50	37	50	27
Mason, et al., (1968)	42	33	40	20
Sawyers, et al., (1968)	90	21	53	12
Hendry and Abdulla, (1969)	300	23	100	9
Inberg, (1969)	81	36	101	12
Tovey, (1969)	118	7	100	9
Kronborg, et al., (1970)	35	46	36	11
Kennedy and Connell, (1970)	50	30	48	8
	1130	24.6	790	12.3

* with pyloroplasty, gastrojejunostomy or antrectomy. In each series the same drainage procedure or resection was employed.

If this hypothesis is correct, the incidence of diarrhoea should be very low indeed after highly selective vagotomy, in which the vagal nerve supply to the extragastric viscera is preserved and the antro-pyloro-duodenal segment is left completely intact. We report here the results of an investigation into the bowel habits of 3 groups of patients one year after truncal vagotomy and pyloroplasty, selective vagotomy and pyloroplasty, and highly selective vagotomy without a drainage procedure.

PATIENTS AND METHODS

The 150 patients studied had undergone elective surgery for duodenal ulcer at least one year previously in the University Department of Surgery at the General Infirmary at Leeds. The operative procedures used were truncal vagotomy and pyloroplasty, bilateral selective vagotomy and pyloroplasty, and highly selective vagotomy without a drainage procedure. Details of bowel habit were recorded when the patients attended the Gastric Follow-Up Clinic for review one year after operation. The patients were interviewed by a panel consisting of a physician, a radiologist and two surgeons who were unaware of the type of gastric operation which had been performed. The last 50 consecutive patients treated by each type of vagotomy and seen one year after operation were chosen for review. Although the choice of

operation had not been made in random manner, the three consecutive series of patients are nonetheless well-matched with respect to sex, age, weight and pre-operative maximal acid output (Table II).

The patient's bowel function one year after operation was recorded in detail, and compared with the pre-operative state. Three main categories of result were recognized :-

(1) "no change", when bowel habit had not altered or was slightly more constipated.

(2) "improved", when there had been little change from constipation before operation to an easier or more frequent bowel action after operation. The motions in these patients were usually normally-formed, but on occasion were porridgy or soft.

(3) "diarrhoea", when the motions were liquid or very loose in consistency, and were passed with some degree of urgency. Diarrhoea was classified as severe if the degree of urgency was so great that the patient was in danger of being incontinent, or if the attacks of diarrhoea were so frequent or troublesome that they were considered by the patient to interfere greatly with his way of life. Diarrhoea was usually episodic rather than continuous in nature. Transient diarrhoea which cleared up after the first three or four post-operative months has been ignored.

Table II

Details of Patients

	TRUNCAL VAGOTOMY and PYLOROPLASTY	SELECTIVE VAGOTOMY and PYLOROPLASTY	HIGHLY SELECTIVE VAGOTOMY
Number of patients	50	50	50
Sex M : F	42 : 8	40 : 10	37 : 13
Age years*	44.2 ± 1.6	42.8 ± 1.6	40.3 ± 1.7
Pre-operative weight Kg*	65.3 ± 1.9	62.5 ± 1.2	65.8 ± 1.6
Pre-operative maximal acid output mEq* / hr‡	42.6 ± 1.8	41.3 ± 1.8	42.4 ± 1.9

* Mean ± 1 SEM

‡ Peak 20 minute acid output x 3 in response to IM pentagastrin, 6 ug/kg

Control studies A post-operative assessment of bowel habit of this type is to some extent subjective and depends upon a comparison of bowel habit at the time of interview with that pertaining before operation. To obtain a better baseline for this study, two control groups were also examined. The first consisted of 50 patients who had undergone appendicectomy, herniorrhaphy, or operation for varicose veins one year previously and who were asked to attend at the Gastric Follow-Up Clinic without the prior knowledge of the interviewing panel. These patients were questioned closely on all aspects of gastrointestinal funtion, including bowel habit. As a second form of control, detailed records of bowel habit were recorded in 75 patients who were admitted to the wards for surgical treatment of chronic duodenal ulcer.

Response to a test meal of hypertonic glucose Fifteen representative patients from each group took part in an experimental study in which an attempt was made to provoke the onset of diarrhoea artificially by means of a test meal of hypertonic glucose solution. Particular care was taken to make the three groups representative of the larger groups with respect to clinical symptoms such as dumping and diarrhoea and to the overall Visick grading. An additional 15

patients with duodenal ulcer before operation took part in this study. After fasting overnight the patients drank 350 ml. of a 25 per cent solution of glucose rapidly while standing upright. They remained standing for 10 minutes, then sat in a chair for the remainder of the two-hour test. "Diarrhoea" in the context of this test signifies the passage of a fluid motion, with urgency, in the course of the test. "Severe" diarrhoea denotes the occurrence of two or more such episodes.

RESULTS

The patterns of bowel habit found one year after each of the three operations are shown in Table III and Fig. 1. The overall incidence of diarrhoea after truncal vagotomy and pyloroplasty was 24 per cent, compared with 10 per cent after selective vagotomy and pyloroplasty. 6 per cent had severe diarrhoea after truncal vagotomy compared with 2 per cent after selective vagotomy. These differences are not statistically significant ( )(^{2} = 0.29, $p > 0.6$). After highly selective vagotomy, only one case of mild diarrhoea was found. The incidence of 2 per cent is significantly less than that which was recorded after truncal vagotomy ( )(^{2} = 10.7, $p < 0.001$) or selective vagotomy ()(^{2} = 7.1, $p < 0.01$).

Table III

Bowel habit one year after truncal or selective vagotomy and pyloroplasty (TV+P, SV+P) or highly selective vagotomy without a drainage procedure (HSV)

	TV+P % of 50 cases	SV+P % of 50 cases	HSV % of 50 cases
No change	40	50	58
Improved	36	32	40
Diarrhoea: Mild or Moderate	18	16	2
Severe	6	2	0
All cases of diarrhoea	24	18	2

The incidence of diarrhoea after HSV is significantly less that after TV+P ($p < 0.001$) or SV+P ($p < 0.01$)

INCIDENCE OF DIARRHOEA ONE YEAR AFTER VAGOTOMY.

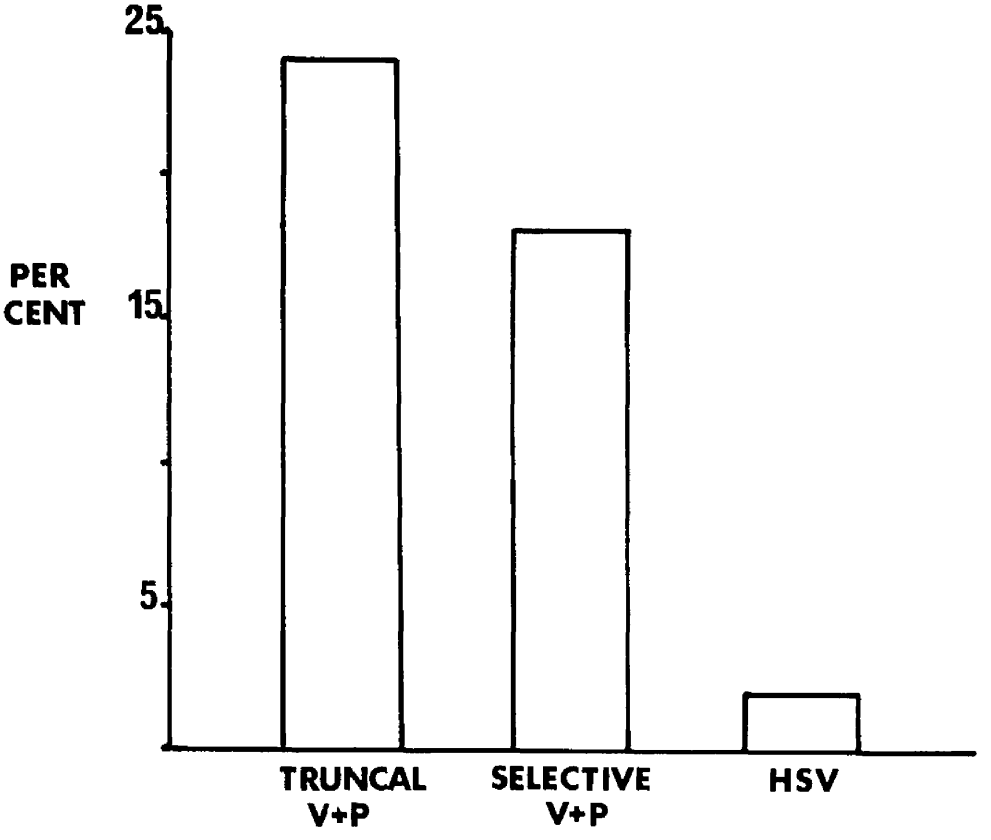

Fig. 1 Diarrhoea was significantly ($p < 0.01$) less common after HSV than after either truncal or selective vagotomy with pyloroplasty.

The hypertonic glucose meal produced diarrhoea in 67 per cent of patients after truncal vagotomy, 60 per cent after selective vagotomy, but only 13 per cent after highly selective vagotomy (Table IV). The difference between the highly selective vagotomy group and the truncal vagotomy group is statistically significant ( )(^{2} = 6.81, $p < 0.01$). The difference between the highly selective vagotomy group and the selective vagotomy group is also statistically probably significant ( )(^{2} = 4.93, $p < 0.05$). In none of the pre-operative patients with duodenal ulcer could the onset of diarrhoea be provoked by this test meal (Fig. 2).

The patterns of bowel habit which were recorded one year after surgery in the control group are shown in Table V. Although 4 per cent of these patients had experienced occasional mild diarrhoea since operation, 92 per cent were adamant that there had been no change in their bowel habit.

Of the 75 patients with duodenal ulcer who were questioned in detail before operation about their bowel habits, three (4 per cent) said that they had episodic attacks of diarrhoea and fourteen (19 per cent) reported that they were usually constipated with either infrequent or hard and painful motions.

Table IV

The incidence of diarrhoea produced by a test meal of hypertonic (25 per cent) glucose

	DU 15 cases	TV+P 15 cases	SV+P 15 cases	HSV 15 cases
Mild or Moderate	0	4	3	1
Severe	0	6	6	1
Total	0	10	9	2

The incidence of diarrhoea after HSV is significantly less than after TV+P ($p < 0.01$) or SV+P ($p < 0.05$)

INCIDENCE OF DIARRHOEA AFTER ORAL 25%GLUCOSE.

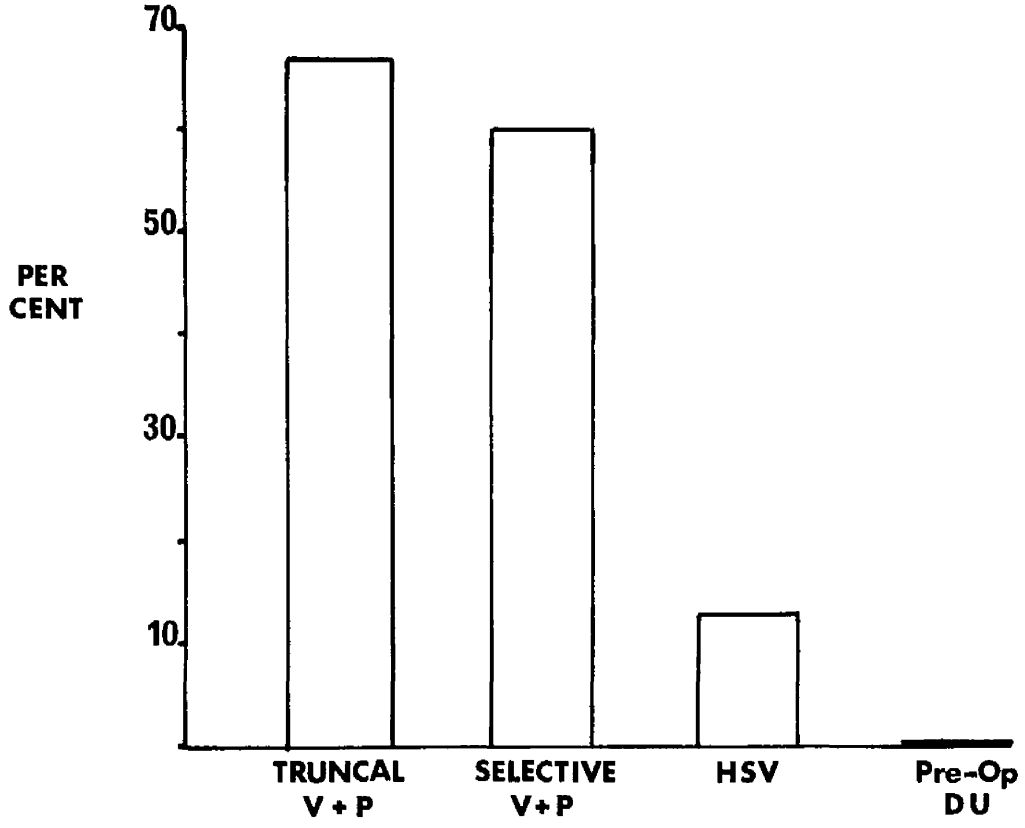

Fig. 2 Hypertonic glucose did not elicit diarrhoea in any of the pre-operative patients. The incidence of diarrhoea in patients after HSV is significantly less than the incidence in patients who had undergone TV+P or SV+P.

Table V

Bowel habit one year after "non-abdominal" surgery *

	% of 50 cases
No change	92
Improved	4
Diarrhoea :	
Mild or Moderate	4
Severe	0
All cases of diarrhoea	4

* Control series of patients who had undergone herniorrhaphy, appendicectomy or varicose vein operations

DISCUSSION

Two major criticisms could be levelled at this study. Firstly, it might be argued that the results are invalid because the type of vagotomy which was used in any particular patient had not been chosen in a random manner. The patients, however, were all treated in the same surgical unit, in which the indications for operation did not change, and the assessments of bowel habit were made "blindly" by the same panel of observers at the Gastric Follow-Up Clinic. The three groups of patients were well-matched (Table II). For these reasons we think that the observed differences in bowel habit are directly attributable to the type of operation employed, rather than to dissimilarities among the groups of patients coming to operation.

Secondly, it might be objected that an assessment which was made only one year after operation was much too early, and that different results might have been obtained if the review had been carried out several years later. However at the same Gastric Follow-Up Clinic, the incidence of diarrhoea in 161 patients five to eight years after truncal vagotomy and pyloroplasty was found to be 22 per cent [2] and in 214 patients five to eight years after truncal

vagotomy and gastroenterostomy it was 27 per cent [1].

Two to five years after selective vagotomy and pyloroplasty the incidence was 17 per cent in 85 patients[6] (Table VI). There is little difference between these incidences and those which we have found at one year after operation. Thus we think that the comparisons which we have made here are valid. 150 patients have now been treated by highly selective vagotomy, the maximum period of follow-up is three and a half years, and the incidence of diarrhoea is 3 per cent. "Post-vagotomy" diarrhoea appears to be due to changes in gastrointestinal physiology which are produced at the time of operation. The findings one year after surgery are unlikely to change appreciably.

These results suggest that troublesome post-vagotomy diarrhoea will not occur after highly selective vagotomy. There are probably two reasons for this. Firstly, highly selective vagotomy preserves the vagal innervation of the extragastric viscera, and secondly, by virtue of the retained antral innervation and the absence of a drainage procedure it also preserves a more normal pattern of gastric emptying. This is not to say that gastric emptying is entirely normal after highly selective vagotomy, because it is not. Although post-operative changes in the direction of more rapid gastric emptying

Table VI

Bowel habit 5 to 8 years after truncal vagotomy and pyloroplasty and 2 to 5 years after selective vagotomy and pyloroplasty

	TV+P per cent of 161 cases	SV+P per cent of 85 cases
No change	50.4	44.7
Improved	27.9	38.8
Diarrhoea :		
Mild or Moderate	17.4	15.3
Severe	4.3	1.2
All cases of diarrhoea	21.7	16.5

and small bowel transit are much less pronounced after highly selective vagotomy than after truncal or selective vagotomy with a drainage procedure, such changes do still occur, particularly when the meal is of fluid or semifluid consistency (see chapterson gastric emptying). This may explain why no fewer than 42 per cent of the 50 patients after highly selective vagotomy experienced a change in bowel habit - although the change was for the better in 40 per cent and for the worse in only one patient (2 per cent).

Those patients who reported an "improvement" in their bowel function form an interesting group, Although by no stretch of the imagination could they be classified as having diarrhoea, there can be no doubt that their bowel habit has been altered by operation. That the alteration represents a definite response to altered gastrointestinal physiology rather than a subjective response to "an operation" is suggested by the results obtained in the 'control' patients who had undergone non-gastric operations, of whom 92 per cent were unable to detect any change in their bowel habit (Table V).

The problem of post-vagotomy diarrhoea is thus largely avoidable. It is necessary to sound a note of caution however, for if the hepatic or coeliac nerves were to be damaged at operation, the incidence of diarrhoea would undoubtedly increase. As Burge[7] and

Griffith[8] have pointed out, preservation of both these groups of vagal fibres is important in the prevention of post-vagotomy diarrhoea. The nerves of Latarjet are of equal importance. If they should be damaged inadvertently in the course of highly selective vagotomy, the patient would have, in effect, an ordinary selective vagotomy without drainage, and gastric retention would probably ensue in a proportion of patients[9]. The resulting stasis and fermentation of gastric content might then give rise to diarrhoea, as happened when truncal vagotomy was performed without an added drainage procedure[10].

In conclusion, we have shown that after highly selective vagotomy without a drainage procedure the incidence of diarrhoea is no higher than that which is found in a control population, and the severe diarrhoea which afflicts a few patients after truncal or selective vagotomy with drainage is entirely absent.

SUMMARY

The incidence of diarrhoea after three types of vagotomy was assessed in "blind" fashion at a Gastric Follow-Up Clinic, one year after operation. Diarrhoea was recorded in 24 per cent of patients after truncal vagotomy and pyloroplasty, in 18 per cent

after selective vagotomy and pyloroplasty, but in only 2 per cent of patients after highly selective vagotomy without a drainage procedure. The three groups of patients were well-matched. The incidence of diarrhoea was significantly less ($p < 0.01$) after highly selective vagotomy than after either truncal or selective vagotomy with a drainage procedure.

Hypertonic glucose solution given orally to 15 representative patients from each group and to 15 patients before operation provoked the onset of diarrhoea in 67 per cent of the patients who had undergone truncal vagotomy and pyloroplasty, 60 per cent of those who had undergone selective vagotomy and pyloroplasty, 13 per cent of those who had undergone highly selective vagotomy without a drainage procedure, and 0 per cent of the pre-operative patients. Again the difference between the "highly selective" group and the other two groups of vagotomized patients was statistically significant.

It is suggested that post-vagotomy diarrhoea is attributable both to unregulated gastric emptying after truncal or selective vagotomy with a drainage procedure and to the extragastric denervation that is produced by truncal vagotomy.

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CHAPTER 13

DUMPING

THE INCIDENCE OF DUMPING AFTER TRUNCAL AND SELECTIVE VAGOTOMY WITH PYLOROPLASTY AND HIGHLY SELECTIVE VAGOTOMY WITHOUT A DRAINAGE PROCEDURE IN MAN

The precise cause of post-cibal symptoms such as somnolence, faintness, sweating and palpitations, which afflict so many patients after gastric surgery, and which are collectively termed "early dumping", has been the subject of debate for many years. There is little doubt, however, that the basic defect is loss of "pyloric" control of gastric emptying, leading to the precipitate entry of unsuitable material into the upper small intestine. The operation of highly selective vagotomy with preservation of an innervated antrum and without a drainage procedure was introduced in the hope that it would minimize side-effects such as dumping and diarrhoea, yet preserve protective and inhibitory mechanisms in the antrum and duodenum. In this section we compare the incidence of dumping in patients treated by highly selective vagotomy with that in patients who were treated by conventional truncal or bilateral selective vagotomy with pyloroplasty on the same surgical unit.

PATIENTS AND METHODS

The 150 patients, 50 after each of the 3 types of vagotomy, were described in the preceding section.

Clinical Symptoms of dumping were assessed one year after operation in a "blind" manner at the Gastric Follow-Up Clinic. Dumping was considered to be present when the patient volunteered, or admitted to, such symptoms as faintness, sweating, palpitations or excessive somnolence shortly after a meal. Epigastric fullness alone was not considered to constitute dumping. Dumping was regarded as mild or moderate if the symptoms were so slight as to require little change in eating habits, or could be avoided by such simple expedients as the omission of fluids and sugar with a meal. Symptoms of such severity as to necessitate a major reduction in the size of meals together with an alteration in their composition, which forced the patient to lie down after a meal, or which continued to cause marked inconvenience despite the exercise of care, have been classified as severe.

Response to oral hypertonic glucose Inevitably, any assessment of the severity of dumping at a Gastric Follow-Up Clinic is to some extent subjective. For this reason, a test meal of hypertonic glucose, which

is known to provoke dumping in susceptible individuals, was used to highlight and exaggerate any clinical differences in the liability to dumping which might exist among the different groups of subjects. Three groups of 15 patients who were representative of the three larger groups of post-vagotomy patients, and 15 patients with uncomplicated duodenal ulcer before operation were chosen for this study. Details of the provocative meal were given in the previous section. In addition to the recording of any symptoms experienced by the patients and of such objective signs as pallor, sweating, and changes in conscious level varying from mild sleepiness to actual collapse, serial measurements of pulse rate and blood-pressure were made throughout the test. By these means a much more objective assessment of the severity of dumping was achieved than was possible from simply listening to the patients at the Gastric Follow-Up Clinic.

Control study To avert the possible criticism that the searching interrogation of the Gastric Follow-Up Clinic might lead to a falsely high impression of post-vagotomy problems, 50 patients who had undergone relatively minor surgical procedures one year previously were included in the Clinic without the prior knowledge of the interviewing panel, (see previous chapter).

RESULTS

Clinical Assessment The incidence of early dumping which was found one year after the three operations is shown in Table I. Selective vagotomy and pyloroplasty led to the highest incidence of dumping, 34 per cent of the patients being affected. It was only in this group of patients that symptoms of severe dumping were recorded. After truncal vagotomy and pyloroplasty the incidence of dumping was less (20 per cent), and no severe cases were encountered. However the difference between truncal and selective vagotomy with pyloroplasty was not significant ( )(^{2} = 2.43, $p > 0.1$). After highly selective vagotomy without a drainage procedure, the incidence of dumping was 6 per cent, significantly less than after truncal ( )(^{2} = 4.33, $p < 0.05$) or selective vagotomy ( )(^{2} = 12.25, $p < 0.001$). 4 per cent of the control group who had undergone herniorrhaphy, appendicectomy or operation for varicose veins admitted to symptoms of mild dumping.

The hypertonic test meal produced dumping in 20 per cent of patients before operation, in 73 per cent of patients after truncal vagotomy and pyloroplasty, 80 per cent after selective vagotomy and pyloroplasty and 47 per cent after highly selective vagotomy (Table II). The difference between the "highly selective" group and the two other

Table I

The clinical incidence of early dumping one year after truncal or selective vagotomy and pyloroplasty (TV+P, SV+P) or highly selective vagotomy without a drainage procedure (HSV)

	TV+P % of 50 cases	SV+P % of 50 cases	HSV % of 50 cases	CONTROLS % of 50 cases
Mild or Moderate	20	32	6	4
Severe	0	2	0	0
All cases of dumping	20	34	6	4

For statistical analysis, see text.

Table II

The incidence of dumping produced by a test meal of hypertonic glucose

	D.U. 15 patients	TV+P 15 patients	SV+P 15 patients	HSV 15 patients
Mild or Moderate	3	7	7	5
Severe	0	4	5	2
Total	3	11	12	7

For statistical analysis, see text.

Table III

Cardiovascular changes following ingestion of hypertonic (25 per cent) glucose solution

	D.U. 15 patients	TV+P 15 patients	SV+P 15 patients	HSV 15 patients
Increase in* pulse rate beats/min.	15.5 ± 2.10	29.3 ± 3.9	23.9 ± 3.3	17.9 ± 3.4
Decrease in* blood pressure mm. Hg. (systolic)	5.3 ± 1.3	15.5 ± 2.3	12.8 ± 2.3	8.1 ± 2.1

* Mean ± 1 S.E.M. of greatest change from steady pre-test value

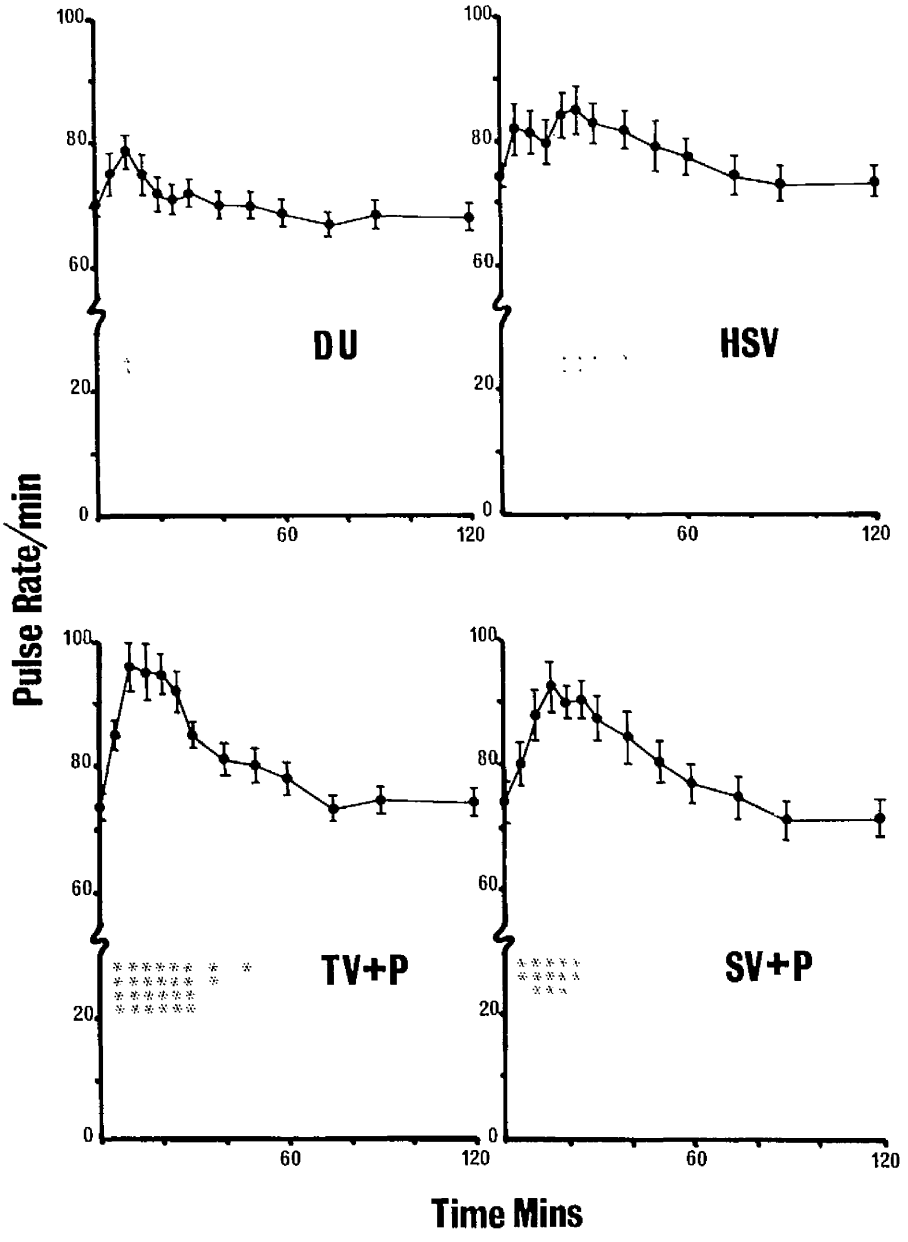

Fig. 1 Changes in pulse rate following ingestion of hypertonic glucose solution. Mean values ± 1 S.E.M. Significance of difference from steady pre-test values:

* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$; **** $p < 0.001$

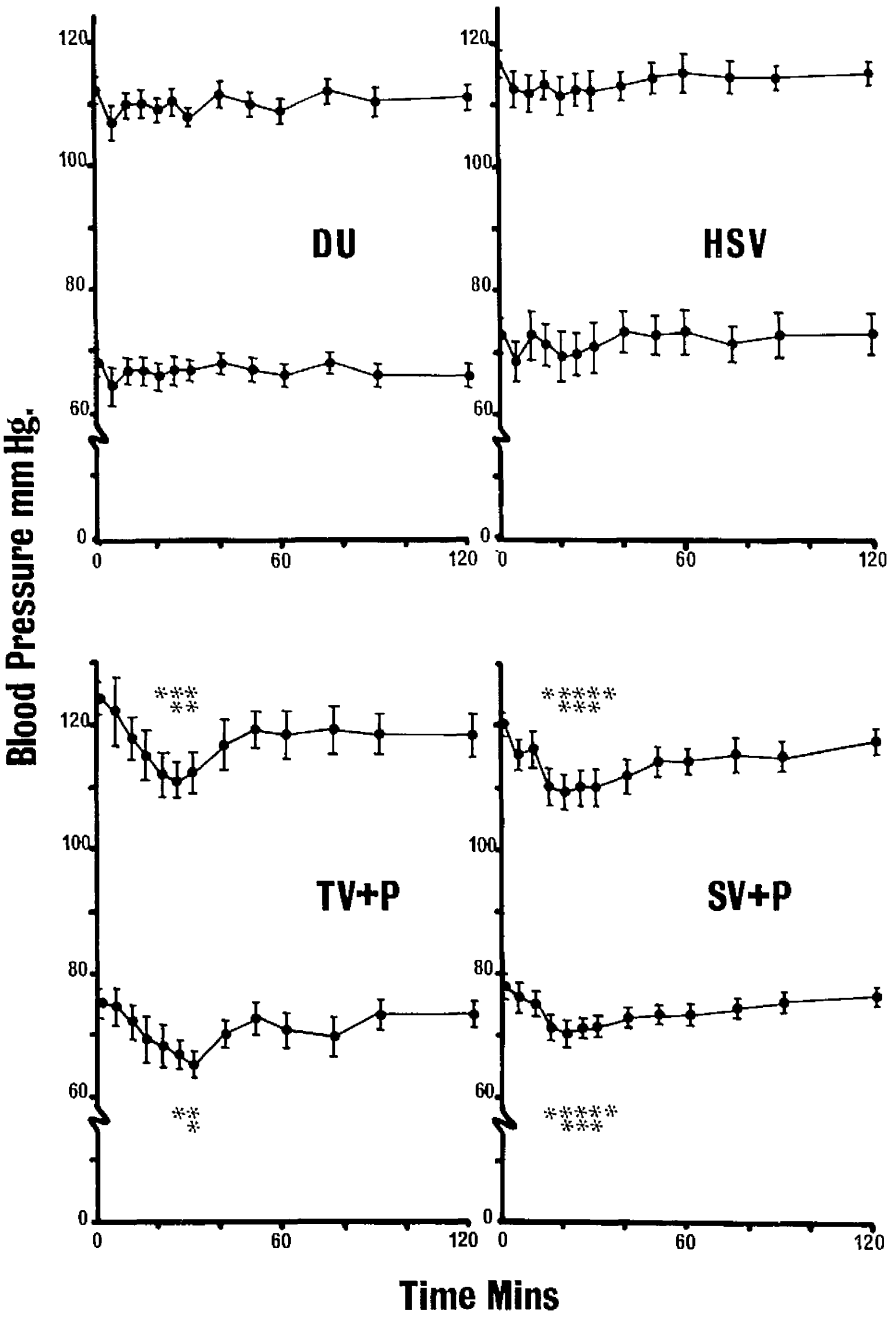

Fig. 2 Changes in blood pressure following ingestion of hypertonic glucose solution. Mean values ± 1 S.E.M. Significance of difference from steady pre-test values :

* $p < 0.05$; ** $p < 0.02$.

vagotomized groups taken together is statistically not quite significant ( )(^{2} = 2.81, $p < 0.1$). However, the incidence of dumping in patients after both truncal vagotomy and pyloroplasty ($p < 0.02$) and selective vagotomy and pyloroplasty ($p < 0.01$) was significantly greater than in patients with duodenal ulcer before operation. The incidence of dumping in patients after highly selective vagotomy was not significantly greater ($p > 0.1$) than in pre-operative patients.

The changes in pulse rate and blood pressure in the course of the test are shown in Figs. 1 and 2 and Table III. Ingestion of hypertonic glucose produced significantly greater hypotension ($p < 0.05$) and significantly greater tachycardia ($p < 0.05$) in patients after truncal and selective vagotomy with pyloroplasty combined than in patients who had undergone highly selective vagotomy.

DISCUSSION

A clinical study which compares the results of different forms of treatment is undoubtedly open to criticism when the patients had not been allocated randomly to one or other of the treatment groups. As stated in the previous section however, we think that

the comparisons made here are probably valid, since the operations were all performed on the same surgical unit, and the results have been assessed in an unbiased manner by a panel who used the same criteria for assessment throughout.

It is also necessary to consider whether the results reported here, consisting of information obtained only one year after operation, are likely to be maintained on longer follow-up. This is particularly relevant since the incidence of dumping which we have found one year after vagotomy and pyloroplasty is very high. To a certain extent this question can be answered by comparing the one year results reported here with the latest information we have in our possession on patients after truncal and selective vagotomy. 158 patients were followed for 2 years after truncal vagotomy and pyloroplasty in Leeds and York, and of these 9.7 per cent reported symptoms of dumping[1]. The 5- to 8-year results of this group show an incidence of early dumping of 11.9 per cent[2]. The incidence of dumping in 85 patients followed for 2- to 5-years after selective vagotomy and pyloroplasty in Leeds was 22.4 per cent[3]. Thus after both these operations, the well-known tendency for dumping to decrease with the passage of time can be discerned. This may be due to the fact that many of the patients learn in time to avoid food

which is particularly liable to provoke dumping. There seems to be no reason why the same process should not apply to the incidence of dumping, small as it is, after highly selective vagotomy.

The incidence of dumping of all grades of severity which we have found after truncal and selective vagotomy with pyloroplasty is high, but is in agreement with the figures quoted by some other authors[4-8]. Although this incidence may be expected to decrease with longer follow-up, it is still likely to remain significantly greater than that which is found after highly selective vagotomy. Why dumping should occur more frequently after selective than after truncal vagotomy is difficult to explain, although this observation is not new[5-8]. It may be related in some way to the fact that the vagal innervation of the small intestine is intact after selective vagotomy, but absent after truncal vagotomy[8]. This would perhaps be in keeping with the observation that dumping is more common in patients who have an incomplete vagotomy than in those whose vagotomy is complete on insulin testing[5]. Although the exact pathogenesis of an attack of dumping has not been established conclusively, there is considerable evidence to implicate the release of certain vasoactive peptides and hormones from the small bowel[9-11]. It is tempting to speculate that denervation of the small bowel impairs the release of

these substances. Certainly the histamine content of the upper small intestine seems to be reduced after truncal vagotomy[12], and our own measurements of the plasma concentrations of immunoreactive insulin after oral and intravenous glucose test meals also suggest that some gut hormones are released less readily from a vagally-denervated intestine[13].

We have shown that the incidence of dumping is significantly lower after highly selective vagotomy without a drainage procedure than after vagotomy and pyloroplasty. Likewise Amdrup in Copenhagen finds significantly less dumping after highly selective vagotomy than after Polya partial gastrectomy for duodenal ulcer[14]. This is scarcely surprising when one considers the importance of the antrum, pylorus and duodenum for the regulation of gastric emptying[15-17], and thus for the prevention of dumping[18-21]. It is perhaps more surprising that this operation should be followed by dumping at all! The explanation is that gastric emptying is not quite normal after highly selective vagotomy. Although the stomach is by no means "incontinent" of fluids after highly selective vagotomy, as it is after vagotomy and pyloroplasty[22], nonetheless both fluid and semi-fluid meals leave the stomach more rapidly after highly selective vagotomy without drainage than before operation. These changes, however, are much less

pronounced than those which are found when antro-pyloro-duodenal regulation of gastric emptying is destroyed by total gastric vagotomy combined with pyloroplasty or gastrojejunostomy. It should be noted that symptoms of dumping are not entirely confined to patients who have undergone gastric surgery, for in the group of 50 patients who had undergone herniorrhaphy, appendicectomy or operation for varicose veins at least one year previously, 4 per cent admitted to symptoms of mild dumping, when they were reviewed in "blind" fashion at the Gastric Follow-Up Clinic.

SUMMARY

The incidence of dumping after truncal or selective vagotomy with pyloroplasty, and highly selective vagotomy without a drainage procedure was assessed at the clinical and experimental level. At a Gastric Follow-Up Clinic, dumping was found to be significantly less frequent in patients who had undergone highly selective vagotomy without a drainage procedure than in patients who had undergone truncal or selective vagotomy with pyloroplasty. Hypertonic glucose given orally provoked the onset of dumping in 20 per cent of patients with duodenal ulcer before operation, in 72 per cent after truncal vagotomy and pyloroplasty, 80 per cent after selective vagotomy and

pyloroplasty and 47 per cent after highly selective vagotomy. The test meal produced significantly greater decreases in blood pressure and increases in pulse rate in patients who had undergone vagotomy with pyloroplasty than in patients who had undergone highly selective vagotomy.

Preservation of an intact, innervated antrum, pylorus and duodenum, without bypass, as in the operation of highly selective vagotomy, leads to a large reduction in the incidence of dumping compared with that which is found after truncal or selective vagotomy with a drainage procedure.

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CHAPTER 14

THE CLINICAL RESULTS

CLINICAL RESULTS OF HIGHLY SELECTIVE VAGOTOMY WITHOUT DRAINAGE FOR DUODENAL ULCER

One hundred and forty patients have been treated by highly selective vagotomy without a drainage procedure for duodenal ulcer in the University Department of Surgery, Leeds General Infirmary, since January 1969. The total number of patients treated by HSV is 180. There has been no operative mortality, no re-operation for the relief of gastric stasis and no recurrent ulceration. In this chapter we describe the clinical results which were recorded in the first 100 patients to be treated by HSV.

PATIENTS

Eighty were men and 20 were women. Their ages ranged from 16 to 66 years and their weights from 38 to 100 kg. Further details are given in Table I. All patients were operated upon electively or at most semi-urgently (several days after the cessation of bleeding), emergency cases and those with the clinical features of pyloric stenosis being excluded. Eighty-six were operated on by the author and 14 by Professor Goligher. The author's cases form an almost-consecutive series. Three elderly,

TABLE I

Details of 100 elective cases of duodenal ulcer treated by HSV

SEX: 80 men 20 women

AGE:

< 20	2
20 - 29	10
30 - 39	24
40 - 49	31
50 - 59	26
60 - 69	7

WEIGHT: 38 - 100 kg.

mean, 65 kg.

LENGTH OF ULCER HISTORY: 1 - 30 years : mean, 9 years.

INDICATIONS FOR OPERATION:

(1)	pain, failure of medical treatment:	98
(2)	previous perforation:	13
(3)	previous haemorrhage:	16

FOLLOW-UP: 97 per cent complete.

1 died in accident

2 changed addresses

length of follow-up: 8 - 42 months,

mean, 21 months

90 patients reviewed at Gastric Follow-up Clinic at 1 year.

48 patients reviewed at Gastric Follow-up Clinic at 2 years.

15 patients reviewed at Gastric Follow-up Clinic at 3 years.

unfit patients were treated by the quicker method of truncal vagotomy and pyloroplasty. The series thus includes many obese patients and also many who had a long history of ulcer, and gross duodenal scarring, often with some degree of stenosis.

The question, "to drain or not to drain?" A drainage procedure was thought to be necessary if one or several of the following features were present:- (1) a history of repeated copious vomiting, (2) succussion splash (3) radiological evidence of gastric stasis and (4) a large volume of 'resting juice' (greater than 200 ml.) containing food residues in the stomach after an overnight fast. On the other hand, many patients who vomited frequently during exacerbations (of whom a few also had a succussion splash) were free of symptoms or signs of gastric retention when their ulcer symptoms went into remission. Thus, the decision "to drain or not to drain" was based on function rather than form, and even if at operation a severe degree of scarring and some stenosis were found, a drainage procedure was not added if the following conditions had been met:- (1) no history of vomiting, or vomiting that ceased when symptoms remitted, (2) patient able to eat heartily when in remission, (3) absence of succussion splash in the pre-operative period, (4) no hold-up of barium on x-ray, and (5) 'resting' juice

in the stomach after an overnight fast less than 200 ml. in volume and free from food residues (test performed in the pre-operative period).

This policy was based on the concept that the stomach compensated for narrowing of its outlet by means of hypertrophy and by increased force of contraction by the antrum. Moreover, obstruction was often due in part to the oedema of an active ulcer, so that when oedema subsided as a result either of spontaneous remission or of surgical cure of the ulcer, the gastric outlet would become wider. Provided that the vigour of antral peristalsis could be preserved, by preservation of the nerves of Latarjet, it seemed likely that gastric drainage would be required only in cases with gross, long-standing, unremitting pyloric stenosis. In consequence, only about one patient in twenty has had a drainage procedure added.

Indications for operation Pain, unrelieved by medical treatment, was the prime indication (Table I), but in a minority operative intervention was indicated principally on account of previous haemorrhage, perforation, or both.

Follow-up was 97 per cent complete (Table I). 90 patients were

reviewed one year after HSV in "blind" manner by the panel of doctors at the Gastric Follow-up Clinic: 48 were reviewed at 2 years and 15 at 3 years. At this Clinic, patients who had undergone HSV were intermingled with patients who had undergone truncal or selective vagotomy with pyloroplasty or gastro-jejunostomy, vagotomy-antrectomy, or Polya partial gastrectomy in the treatment of duodenal ulcer, simple closure of perforated duodenal ulcer, gastrectomy for gastric ulcer, and subtotal or total gastrectomy for gastric carcinoma. The panel usually consisted of three doctors: Dr. C. N. Pulvertaft (radiologist) or Dr. B. E. Walker (physician), Professor J. C. Goligher and the author. Members of the panel were not allowed to know which operation had been performed until they had recorded their findings and their verdict regarding the patient's grading. In this way bias arising from preconceived ideas of the relative merits of the different operations was largely avoided, although it must be admitted that on occasion a member of the panel might be able to remember which type of operation had been performed.

Since the findings in female patients were little different from those in males, (Table X) the results for both sexes will be considered together.

WEIGHT : HAEMOGLOBIN Before operation, and at each yearly visit to the Gastric Follow-up Clinic, the patient was weighed, and a sample of blood taken for estimation of haemoglobin concentration. Some of the data is missing, however, either because the measurements were not made, or because the results were not recorded in the patients' notes.

FINDINGS

OPERATION The duration of the operation decreased as the surgeons acquired familiarity with the technique. Mean operating time fell from 120 minutes to 90 minutes, the range being from 45 minutes in a thin patient to about 150 minutes in a fat patient with a narrow subcostal angle. The author has not had to abandon the procedure in any patient on account of technical difficulty, but HSV is certainly a tedious and difficult operation in about 10 per cent of patients. Splenectomy has been necessary in two patients on account of iatrogenic trauma at operation. Ischaemia of the stomach has not been observed, nor was it expected, since only the branches of the left gastric artery are sacrificed, all other arteries to the stomach being left intact.

OPERATIVE MORTALITY There was none.

POST-OPERATIVE RECOVERY Only one patient was dangerously ill soon after operation. This was an obese 35 year old woman who developed deep venous thrombosis, and recurrent pulmonary embolism despite adequate anticoagulation with heparin infusion. She was treated by ligation of the inferior vena cava. She now has a perfect result with respect to her stomach, but complains of bursting pain in her legs on exercise.

There were five wound infections in the first twenty-five cases, due perhaps to slow operating, to the use of gastrotomy to permit the Congo Red test to be performed, and perhaps also to the insertion of a gastrostomy tube at the end of the operation. There has been only one further wound infection in the next 75 cases, perhaps because of speedier operating, abandonment of the Congo Red test, and the routine application of 1 gram of Ampicillin powder to the wound after closure of the peritoneum.

There have been no other major complications, though minor degrees of atelectasis and chest infection were quite common in the first few days after operation. A striking feature has been the absence of gastric stasis. Prolonged gastric retention, such as is seen in perhaps two per cent of patients after truncal vagotomy with a drainage procedure, has not occurred in any of

the 180 patients treated by HSV. Aspirates via the gastrostomy tube (which was employed in the first 100 patients but whose use has now been abandoned) were small in volume, and patients drink free fluids within 48 hours of operation. Persisting ileus of the small bowel has likewise not been seen. The mean length of stay in hospital after operation was 10 days.

FINDINGS ON FOLLOW-UP

The findings at one year and at two years were almost identical, with respect both to individual symptoms and to the overall clinical assessment. The two-year results were slightly superior to those at one year (Table II). The results after HSV at one to two years have therefore been compared with the results which were recorded in the same clinic two years after truncal vagotomy and pyloroplasty (TV+P) or gastrojejunostomy (TV+GJ), selective vagotomy and pyloroplasty (SV+P), truncal vagotomy and antrectomy (TV+A) and Polya partial gastrectomy (PG) (Ref. 1 and unpublished observations on the results of SV+P). Such a comparison, not being based on a random allocation of patients, is open to the criticism that the patients who were treated by HSV may differ from those treated by the

TABLE II

Incidence of symptoms due to disturbance of alimentary function two years after HSV and other operations for duodenal ulcer *

SYMPTOM	1 HSV (% of 90 patients at 1 year)	1 HSV (% of 48 patients at 2 years)	2 TV+P (% of 158 patients)	3 TV+GJ• (% of 110 patients)	4 TV+A• (% of 106 patients)	5 Polya PG• (% of 93 patients)
Nausea	13	10	26	16	13	20
Bile vomiting	0	0	11	16	14	12
Food vomiting	6	4	8	6	5	10
Epigastric fullness	30	25	47	28	35	40
Early dumping	4	6	10	11	11	17
Late dumping	0	2	3	6	6	1
Flatulence	20	13	31	12	18	16
Heartburn	12	10	18	15	10	2
Dysphagia	2	2	1	0	0	0

* data from Leeds-York Gastric Follow-up Clinic. • The operations listed in columns 3, 4, 5, were those which were compared in the Leeds-York trial. TV, truncal vagotomy; P, pyloroplasty; GJ, gastrojejunostomy; A, antrectomy; PG, partial gastrectomy.

Statistical analysis

The incidence of bile vomiting after HSV is significantly less than after any other operation ($p < 0.01$, except HSV cf TV+P,)(^{2} = 5.86, $p < 0.02$). Early dumping after HSV is significantly less than after partial gastrectomy ($p < 0.05$), but not significantly less than after the other operations.

other operations. In addition, many surgeons took part in the Leeds-York trial of TV+GJ, TV+A and Polya PG, whereas the author has performed most of the HSV operations himself. However, all the patients came from the same region of Britain, and so far as we are aware the indications for operation did not change. Certainly we consciously resisted the temptation to use this ultra-conservative operation at an earlier stage in the disease process: the mean length of ulcer history in the 100 patients was nine years. Moreover, the method of assessment of the patients' condition on follow-up was identical, because exactly the same criteria (and almost the same panel of assessors) were used both in the Leeds-York trial[2] and in the assessment of the patients after highly selective vagotomy.

FREQUENCY OF SYMPTOMS DUE TO ALIMENTARY DYSFUNCTIO

The relative frequency of the commoner symptoms of which the patients complained is shown in Table II. Two years after HSV, most symptoms were slightly less frequent than they had been at one year. Nausea and early dumping[4] occurred less

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4 early dumping is defined as a sensation of epigastric fullness, accompanied by a feeling of faintness, sweating, somnolence or palpitation occurring soon after a meal, and late dumping as a feeling of faintness and weakness coming on an hour or more after food, probably due to hypoglycaemia.

frequently after HSV than after any of the other operations. The incidence of early dumping after HSV (5 per cent) was approximately one half of the incidence after vagotomy with drainage and one third of the incidence after partial gastrectomy (Table II). Bile vomiting was not recorded after HSV and the difference from the incidence after the other operations was significant ($p < 0.01$). If gastric emptying had been delayed after HSV, the incidence of symptoms such as flatulence and vomiting would have been higher after HSV than after the other operations, but in fact these symptoms were not more frequent after HSV, which suggests that gastric emptying was, in the main, satisfactory. A disappointing finding after HSV was the 25-to-30 per cent incidence of epigastric fullness after the main meal of the day, which was little different from the incidence after other operations. Persisting dysphagia was a rare symptom after any of the operations, and late dumping was also encountered rarely. Heartburn was very unusual after partial gastrectomy, but was noted in 10 to 18 per cent of patients who had undergone any type of vagotomy. Thus, it is obvious that all the operations studied gave rise to an impressive incidence and variety of side-effects, but it must be emphasized that most of these symptoms were both mild and intermittent.
In general, HSV produced fewer side-effects than did the other operations, the greatest advantage

TABLE III

Bowel habit one to two years after HSV compared with bowel habit after other operations for duodenal ulcer*

BOWEL HABIT	HSV AT 1 - 2 YEARS (% of 90+ - 48+ patients)	SV+P at 1 YEAR (% of 50 patients)	SV+P AT 2 - 5 YEARS (% of 85 patients)	TV+P AT 1 YEAR (% of 50 patients)	TV+P AT 2 YEARS (% of 158 patients)	TV+P AT 5 - 8 YEARS (% of 161 patients)	TV+GJ AT 5 - 8 YEARS (% of 118 patients)	TV+A AT 5 - 8 YEARS (% of 112 patients)	Polya P AT 5 - 8 YEARS (% of 1 patients
No change	71	5	46	40	44	50	42	39	57
Improved	27	3	39	36	34	28	32	38	36
Diarrhoea (total)	2	18	16	24	22	22	26	23	7
Mild or moderate	2	16	15	18	20	18	21	20	6
Severe	0	2	1	6	2	4	5	3	1

+ 90 HSV patients at 1 year and 48 at 2 years. * data from Leeds-York Gastric Follow-up Clinic.

Note that after TV+P, the incidence of diarrhoea at one year was the same as at 2 years and at 5 - 8 years; and after SV+P, the incidence at 1 year was the same as at 2 - 5 years. After HSV, the incidence of diarrhoea was 2 per cent both at one year and at two years. This was significantly less ($p < 0.01$) than after any other operation except partial gastrectomy.

being in respect of bile vomiting and of early dumping.

ALTERATION OF BOWEL HABIT The changes which took place in bowel habit after HSV and the other gastric operations are shown in Table III. Three types of result have been recognized: No change, when bowel function has either not changed at all since operation or has become slightly more constipated. Improved, which means that the motions have become slightly looser than before operation andsometimes a little more frequent. For example a patient may find that instead of having one constipated motion every second day he now passes one or two motions without difficulty each day. The motion is formed in character and this state of affairs could not be described as diarrhoea. In fact the patient usually thinks that it is one of the most agreeable effects of the operation.

Diarrhoea of varying degrees of severity The use of the term "diarrhoea" implies that the motions were very loose or liquid in consistency, that they were passed with some degree of urgency and that the attacks of diarrhoea were usually episodic and not continuous. If the patient had one attack of diarrhoea every three months or so, the attack lasting for less than a day and not interfering with his way of life, the diarrhoea was graded

as mild in severity. On the other hand if the attacks occurred every week or fortnight, if the degree of urgency was great, if the patient was incontinent, passing the motion into his clothes, and if he or she was unable to pursue a normal way of life, the diarrhoea was classified as severe. In a few patients the degree of urgency was such that if they were unable to reach the lavatory very quickly they might be unable to control the motion. In these circumstances the diarrhoea was classified as severe even if the attacks did not occur with great frequency. Diarrhoea of moderate severity was intermediate between the mild and the severe types.

It will be seen from Table III that severe diarrhoea was not recorded after highly selective vagotomy. Only two patients experienced diarrhoea and in both of them it was mild in character. In contrast, after all other types of operation involving vagotomy the overall incidence of diarrhoea lay between 16 and 26 per cent. The incidence after truncal vagotomy was between 22 and 26 per cent, of which 2 to 6 per cent was severe. It will also be seen that the incidence of diarrhoea which was recorded one year after truncal or selective vagotomy persisted virtually unchanged at two to five years in the case of selective vagotomy and at five to

eight years in the case of truncal vagotomy. The incidence of diarrhoea after highly selective vagotomy was significantly less ($p < 0.01$) than after any of the other operations involving vagotomy, irrespective of whether the vagotomy was selective or truncal in type. The incidence of diarrhoea after highly selective vagotomy was not significantly less than after Polya partial gastrectomy. Thus in respect of bowel function HSV enjoys an advantage over both truncal and selective vagotomy with a drainage procedure, the results of which are undoubtedly marred to some extent by the occurrence of post-vagotomy diarrhoea.

PATIENTS' WEIGHT AFTER HSV

It has not been possible to compare the effect of HSV with that of other operations, on patients' weight, because the data from the Leeds-York Gastric Follow-up Clinic relate to weights recorded five to eight years after the other operations. The changes which were recorded in patients' weight after highly selective vagotomy are shown in Table IV. One difficulty in interpreting these data is that some patients had lost weight before operation. Thus the figure of 65kg. for the mean weight before operation is an underestimate of the patients' true, or ideal, weight. However, none of these patients had

TABLE IV

Patients' weight before and after highly selective vagotomy

	BEFORE HSV	ONE YEAR AFTER HSV	TWO YEARS AFTER HSV
NUMBER OF PATIENTS	100	74	33
WEIGHT (kg.) MEAN ± 1 SEM	65.3 ± 1.1	67.8 ± 1.4	70.7 ± 2.1
MEAN WEIGHT GAIN (kg.)		2.20 ± 0.48	3.54 ± 0.84 ‡
t-test		$t = 4.708$, $p < 0.001$	$t = 4.21$, $p < 0.001$
> 5 kg. GAIN		21 = 28%	15 = 46%
0 - 5 kg. GAIN		35 = 47%	14 = 42.3
0 - 5 kg. LOSS		16 = 22%	3 = 9%
> 5 kg. LOSS*		2 = 3%	1 = 3%

* 3 patients complained of weight loss, which amounted to 11kg., 8kg. and 3kg. respectively.

‡ Weight gain at two years refers to the increase in weight compared with pre-operative weight.

clinical pyloric stenosis and some were overweight before operation because they had been eating frequent small meals rich in dairy products. Before operation, most patients were fairly close to their normal weight. The mean weight of 100 patients before highly selective vagotomy was 65.3kg.; one year after HSV in 74 patients it was 67.8kg. and two years after HSV in 33 patients it was 70.7kg. The gain in weight in the 74 patients one year after HSV compared with the pre-operative weight was statistically highly significant and the gain in weight in 33 patients 2 years after HSV was also statistically highly significant compared with the pre-operative weight. One year after HSV, 75 per cent of patients had gained weight and 25 per cent had lost weight. Two years after HSV 88 per cent of patients had gained weight and only 12 per cent had lost weight. Weight loss was a matter of concern to only 3 of the 100 patients. One fifty-year-old man weighed 75kg. before operation, which was his ideal weight. After operation he found he had to restrict the size of the main meal of the day to one half to two-thirds of what he had eaten formerly, on account of a sensation of epigastric fullness. One year after operation his weight had decreased to 64kg. and three years after HSV his weight was still only 64kg., though in other respects he

felt perfectly well and was graded as a Visick II result. Another young man of twenty-eight weighed 74kg. before operation and said that his best weight was around 78kg. After HSV, he too experienced epigastric fullness after meals and one year after operation he weighed only 70kg. His weight has now risen to 77kg. however, and he is satisfied. He has been graded Visick II on account of the epigastric fullness after meals. The third patient was a very thin lady of forty-eight whose best weight many years previously had been 48kg. and who weighed only 43kg. at the time of operation. Post-operatively she found that she had to restrict the size of her meals to about two-thirds of what she had eaten formerly. She lost a further 3kg. in weight, which distressed her somewhat because she was already much too thin. Two years after HSV her weight is still only 40kg.

In the Leeds-York trial[2] it was found that five to eight years after vagotomy and gastroenterostomy the mean weight loss of four pounds was not significant compared with the optimal pre-operative weight. In contrast, after either truncal vagotomy and antrectomy or subtotal gastrectomy the mean weight loss was ten pounds, a statistically highly significant difference. While we have not calculated the optimal

weight of the HSV patients from Life Assurance Tables as was done in the Leeds-York trial, it is of interest to note that the calculated optimal weight for 321 male patients in the Leeds-York trial was 154 pounds (70kg.) before operation. Before HSV, the 100 patients, including 20 women, weighed on average 65kg. but there was evidence of progressive weight gain after HSV and the mean weight of 33 patients two years after HSV was 70.7kg. Furthermore these 33 patients included 10 women and if the latter's weights are excluded the mean weight in the 23 male patients two years after HSV was 72kg.

OCCURRENCE OF ANAEMIA AFTER HSV

The mean haemoglobin concentration before HSV was 15.1g per 100ml. (excluding the results of patients who had bled in the pre-operative period). One year after HSV mean haemoglobin concentration was 14.6g per 100ml. and two years after HSV it was 14.5g per 100ml. (Table V). The decrease in haemoglobin concentration at one year compared with before operation was statistically significant ($p < 0.01$) but the decrease which was recorded at two years was not statistically significant. In Table VI the changes in haemoglobin concentration after highly selective vagotomy are compared with those which were found at

TABLE V

Changes in haemoglobin concentration after HSV

	BEFORE HSV	ONE YEAR AFTER HSV	TWO YEARS AFTER HSV
Number of patients	69 *	50	20
Mean Hb concentration (g per 100 ml.) ± 1 SEM	15.13 ± 0.13	14.58‡ ± 0.18	14.48‡ ± 0.29
	Mean decrease 0.56 ± 0.18 in 41 patients t = 3.11, p < 0.01 (before, compared with one year after HSV)		
	Mean decrease 0.31 ± 0.22 in 17 patients t = 1.41, 0.2 > p > 0.1 (before, compared with two years after HSV)		

* excluding 7 patients who were anaemic pre-operatively due to haemorrhage from their ulcer.

‡ If anaemia is defined as a haemoglobin of less than 13 grams in a man and less than 12 grams in a woman, only two patients (4 per cent) were anaemic at one year (Hb, 10.0 and 10.9 g/100ml. respectively) and one patient was anaemic at two years (Hb 10.5 g/100ml.).

• estimated on a Coulter automatic counter. (normal range, for the haematology laboratory, Leeds General Infirmary, 13.0 to 18.0 g/100 ml. in men, and 11.5 to 16.5 g / 100ml. in women).

TABLE VI

Effect of different types of vagotomy operation on Haemoglobin (Leeds-York* Data)

Operation	Number of patients	Haemoglobin (g/100ml.: mean ± 1 SE)		p
		Before operation	1 year after	
HSV	41	15.1 ± 0.1	14.6 ± 0.2	< 0.01
TV+P	67	15.1 ± 0.2	14.1 ± 0.1	< 0.01
TV+GJ	55	14.9 ± 0.2	14.3 ± 0.2	> 0.05
TV + Antrect.	40	15.3 ± 0.2	13.8 ± 0.3	< 0.01

* Data on all operations except HSV are taken from 'After Vagotomy', London, Butterworths, by kind permission of the publishers.

the Leeds-York Gastric Follow-up Clinic after truncal vagotomy and pyloroplasty, truncal vagotomy and gastrojejunostomy and truncal vagotomy and antrectomy[3]. It will be seen that one year after any type of vagotomy mean haemoglobin concentration was 0.5 to 1.5g per 100ml. less than it had been before operation. This decrease was statistically significant, except in patients after truncal vagotomy and gastrojejunostomy. The smallest decrease was found in patients after HSV, but the difference between the decrease in the HSV patients and in the other patients is not statistically significant.

INCIDENCE OF RECURRENT ULCERATION

Pain of ulcer type was recorded in 3 out of 90 patients who were interviewed at the Gastric Follow-up Clinic one year after HSV and in 1 out of 48 patients who were seen at the clinic two years after HSV. In addition, abdominal pain which was not localised to the epigastrium and quite different from the pain of the ulcer was experienced by a further 3 patients who were interviewed one year after HSV and by 3 of the 48 patients who were interviewed two years after HSV. Only two patients were seriously suspected of harbouring recurrent ulceration. Both were young men in their late twenties who complained of numerous

other symptoms in addition to pain. The pain itself was similar to that of their ulcer. One patient was a shiftless and unreliable individual (D.A.) who before his operation had been involved in numerous fights, with resulting admissions to hospital for the treatment of head injuries. After operation (at which he was found to have convincing evidence of duodenal ulceration) his abdominal symptoms continued much as before. The other man (B.S) appeared to be of normal personality. Both patients were investigated in the usual way with barium meal examinations which merely showed some deformity of the duodenal cap, which was to be expected, but no definite sign of recurrent ulceration. Fibre-gastroscopy yielded negative results in both. An insulin test was carried out in each approximately one year after HSV and in each it was negative by Hollander's criteria[4], though the spontaneous acid output in B.S. was 4.6 mEq/hr, which made the test positive by the criterion of Bachrach[5]. Both patients eventually came to further laparotomy, about one year after their original operation. It was then found that a pyloroplasty had been performed in patient D.A., during one of his numerous admissions to other hospitals subsequent to the highly selective vagotomy operation. The region of the pyloroplasty was supple, and careful

inspection of the stomach and duodenum did not reveal any abnormality. The non-absorbable sutures which had been used for the pyloroplasty were removed and the pyloroplasty incision opened. Thorough inspection of the terminal antrum and proximal duodenum from the luminal aspect did not reveal any breach of the mucosa. The pyloroplasty was re-fashioned and nothing further was done. During the subsequent two years this patient's symptoms have improved spontaneously and he is now in Visick grade III, although, because he has been subjected to a second operation, he also remains permanently in Visick grade IV. In the second patient, B.S., the antrum, pylorus and duodenum were also carefully mobilised at the second operation and were found to be soft and supple with no sign of ulceration on external inspection. The duodenum was again inspected from the inside and no ulcer was found. Antrectomy was carried out, with gastro-jejunal anastomosis. This patient continues to complain of all manner of symptoms including abdominal pain, nausea, vomiting, dumping and heartburn and is still graded Visick IV.

The incidence of recurrent ulceration two years after various gastric operations including HSV is recorded in Table VII. Recurrent ulceration was more common after truncal vagotomy and

pyloroplasty and

TABLE VII

Recurrent ulceration at two years after various operations*

Degree of Certainty	HSV (90+ patients)	TV+P (158 patients)	TV+GJ (110 patients)	TV+A (106 patients)	Polya PG (93 patients)
Proved	0	4	1	0	0
Suspected	2	6	3	0	0
Total	2	10	4	0	0

* Data from Leeds-York Gastric Follow-up Clinic.

\+ 90 patients were interviewed one year after HSV, and 48 patients, two years after HSV.

truncal vagotomy and gastrojejunostomy than after highly selective vagotomy, truncal vagotomy and antrectomy or Polya partial gastrectomy, but the differences are not statistically significant.

OVERALL ASSESSMENT OF PATIENTS' FITNESS

For this purpose as in the previous studies from Leeds-York[1,2], we have used a slight modification of the Visick classification, which recognizes essentially four categories of result (Table VIII).

Overall Grading of Results (Modified Visick Classification)

Category		Definition
I	Excellent	Absolutely no symptoms. Perfect result.
II	Very good	Patient considers result perfect, but interrogation elicits mild occasional symptoms easily controlled by minor adjustment to diet.
III	Satisfactory	Mild or moderate symptoms not controlled by care, causing some discomfort, but patient and surgeon satisfied with with result, which does not interfere seriously with life or work.
IV	Unsatisfactory	Moderate or severe symptoms or complication which interferes considerably with work or enjoyment of life; patient or doctor dissatisfied with result. Includes all cases with proved recurrent ulcer and those submitted to further operation, even though the latter may have been followed by considerable symptomatic improvement.

Categories I and II can be regarded as highly satisfactory and they have been grouped together in the analysis. Category IV comprises the failures, which include patients with proved recurrent ulcer, patients who have undergone further laparotomy because of suspected recurrent ulceration and patients who have required re-operation for bilious vomiting, dumping etc. even though they may have secured a reasonably good result after the second operation. Category III comprises patients who usually have obtained a cure of their ulcer but who are troubled by side-effects such as dumping, diarrhoea, bile vomiting etc. which cannot be controlled by the exercise of care.

When this classification was applied two years after the various gastric operations (Table IX), a higher proportion of cases were found to be in categories I and II after HSV than after any of the other operations. There was not much difference between the results of HSV and those of either truncal vagotomy and antrectomy or Polya partial gastrectomy. On the other hand, the difference compared with truncal or selective vagotomy and pyloroplasty was striking. Whereas 90 per cent of patients were in Visick grades I and II, two years after highly selective vagotomy only 64 per cent of patients after selective vagotomy and pyloro-

plasty, and 73 per cent of patients after truncal vagotomy and gastrojejunostomy, were in Visick grades I and II. There was little difference in the failure rates (Visick grade IV) at two years, but a large difference was noted in the proportion of patients who were in Visick grade III when the highly selective vagotomy group was compared with the groups of patients who were treated by vagotomy with a drainage procedure. 4 to 7 per cent of HSV patients were in Visick grade III compared with 22 to 26 per cent after vagotomy with a drainage procedure. When comparison is made with TV+P or TV+GJ this difference is statistically significant ($p < 0.01$, Table IX). The three patients who have been classified as failures after HSV include the two men with suspected recurrent ulceration who have been described, and a third man aged 35 years who complains of churning discomfort in his epigastrium, epigastric fullness after meals and difficulty in swallowing. Although he is able to continue with his work he regards the outcome of his operation as unsatisfactory. Radiological examination by barium swallow and meal did not reveal any abnormality. His weight before operation was 66kg. which was close to his ideal weight and his weight three years after HSV is 67kg. His haemoglobin both before and two years after HSV was

TABLE IX

Visick grading of patients two years after HSV and other operations for duodenal ulcer*

VISICK GRADING	Proportion of patients in each category after :-						
	HSV		SV+P	TV+P	TV+GJ	TV+A	Polya PG
	AT 1 YEAR (% of 90 patients)	AT 2 YEARS (% of 48 patients)	(% of 67 patients)	(% of 158 patients)	(% of 110 patients)	(% of 100 patients)	(% of 93 patients)
I	61 } 90	63 } 90	39 } 64	37 } 64	54 } 73	58 } 84	60 } 83
II	29 }	27 }	25 }	27 }	19 }	26 }	23 }
III	7	4	26	24	22	12	15
IV	3	6	10	12	5	4	2

* Data from Leeds-York Gastric Follow-up Clinic.

Statistical analysis

Assuming that results in the 90 patients after HSV will be the same at two years as at one year, the numbers of patients in Visick grade III after HSV are significantly less ($p < 0.01$) than the numbers in Visick grade II after either TV+P or TV+GJ. The numbers of patients in Visick grade I after HSV are not-quite-significantly greater ($p < 0.1$) than the numbers in grade I after TV+P, or after (TV+P and SV+P) combined - ($p < 0.1$).

TABLE X

Comparison of clinical results of HSV in male and female patients

VISICK GRADING	AT ONE YEAR				AT TWO YEARS			
	MALES (% of 72 patients)		FEMALES (% of 18 patients)		MALES (% of 37 patients)		FEMALES (% of 11 patients)	
I	62	90	56	89	65	92	55	82
II	28		33		27		27	
III	6		11				18	
IV	4		0		8		0	

The results in women were only slightly (not significantly) inferior to those in men.

15.1g per 100ml.

Comparison of the clinical results of HSV in male and female patients (Table X) shows that the results in women were little different from those in men.

DISCUSSION

Firstly it should be emphasized that the patients who were treated by HSV form a nearly-consecutive series. Thus, the comparison which we have made of their results with those which were recorded in patients after other types of gastric operation may not be entirely valid. Although we believe that the respective series of cases are very similar, such a contention could be challenged. However, it seemed to us that the comparison was worth making, because the series of patients seemed to be similar, the indications for operation had not changed, and the method of assessment was standard.

It has been shown that HSV is an extremely safe operation. The total number of patients treated by this operation for a variety of conditions in Leeds is 189 and there has been no operative mortality. This is similar to the experience of Amdrup, (personal communication), who has treated more than 150 patients

by HSV without an operative death. It is perhaps not surprising that HSV should be safe, because the alimentary tract is not opened and there is no anastomosis or suture-line. Three of the four major arteries to the stomach are left intact, only the branches of the left gastric artery being ligated. Thus there is little danger of gastric ischaemia. For these reasons it is felt that in the long run HSV will prove to be a significantly safer operation than partial gastrectomy and marginally safer even than vagotomy with a drainage procedure.

In the early post-operative period, gastric emptying seems to be better after HSV than after truncal or selective vagotomy with a drainage procedure, because the patients are able to drink fluids freely, and later to eat a normal diet, sooner than patients who have undergone the conventional types of vagotomy with drainage. Paralytic ileus, too, seems to occur less frequently. Like so many clinical impressions, this one could well be erroneous. Nonetheless these clinical observations are in accord with what would be expected from the fact that the motor innervation to the antrum and small intestine is preserved in HSV whereas it is cut in the performance of truncal vagotomy.

While the clinical result after highly selective vagotomy are still far from perfect, it can be claimed with confidence that side-effects are no more frequent than those which are recorded after any of the other gastric operations and in some respects they are much reduced. The most impressive gains have been in relation to so-called "post-vagotomy" diarrhoea, which has been entirely eliminated, and to bile vomiting, which has also been eliminated. Early dumping has not been abolished entirely, but at least its incidence has been reduced considerably. Moreover, follow-up is still relatively brief, and the incidence of dumping after HSV may well diminish further with the passage of time just as it does after other gastric operations. No patient has been afflicted by severe dumping after HSV. We attribute dumping after HSV to more rapid gastric emptying, particularly of fluids (vide supra). This, in turn, is probably due to loss of receptive relaxation[6-9] in the body of the stomach after vagotomy of the parietal cell mass, with the result that intra-gastric pressure rises[10-12] to a greater extent after a meal is eaten than is the case before operation. Perhaps the most disappointing finding after HSV was that the incidence of epigastric fullness after meals is still in the region of 25 to 30 per cent. A high

incidence of epigastric fullness after meals had been consistently recorded in the Gastric Follow-up Clinic in patients who had undergone truncal vagotomy with antrectomy or with a drainage procedure. We had postulated earlier that this was a form of early dumping, attributable to rapid emptying of the meal into the upper small intestine where it produced distention and discomfort, and we had hoped that it would not be found after HSV. However, we have found that epigastric fullness is little if any less frequent after HSV than after the other operations (Table II) and are forced to conclude that the symptom is attributable to the gastric vagotomy, to failure of receptive relaxation[6-9] and to the consequent increase in intra-gastric pressure[10-12]. The symptom is not particularly troublesome, however, and most patients find that they can avoid it altogether if they reduce the size of their main meal of the day by about one-third.

It is obviously much too early to make any firm pronouncements about the effect of HSV on nutrition, but the gain in weight which has been observed in most patients is encouraging and the decrease in haemoglobin level at one year, while statistically significant, is very small. Weight loss has been a clinical problem in only three patients, one of whom has now

re-gained most of the lost weight. Only two patients out of 50 were found to be anaemic one year after HSV and only one of 20 was anaemic two years after HSV. It will be of great interest to observe the changes in weight, haemoglobin, serum iron and vitamin B12 with the passage of time, particularly after the recent disturbing report by Wheldon and her colleagues[13] of a high incidence of iron-deficiency anaemia and of weight loss fifteen to twenty years after truncal vagotomy and gastrojejunostomy.

So far there has been no indication that the improvement in the clinical results after HSV with respect to bile vomiting, dumping and diarrhoea has been bought at the expense of a higher incidence of recurrent ulceration. Indeed we have not found a single case of proven recurrent ulceration after HSV. Thus, in a follow-up which ranges from one to three and a half years the incidence of recurrence is less than that which is found after truncal vagotomy and pyloroplasty or gastrojejunostomy. Likewise, Amdrup in Copenhagen has not found a single case of recurrent duodenal ulceration after 150 HSV operations, though one of his patients has developed a gastric ulcer in association with gastric retention. These results are encouraging, particularly because recurrence, if it is going to occur after vagotomy with

pyloroplasty, characteristically does so early, frequently in the first two years after operation[14]. One would expect that this would happen also after HSV. The ulcer, after all, is left completely undisturbed and if the operative procedure were inadequate it would either not heal or else it would recur within a short space of time. 171 HSV operations with pyloroplasty have been performed by Holle[15] in the past seven years, with a recurrent-ulcer rate of less than one per cent. Since gastric emptying is satisfactory after HSV without pyloroplasty[16,17], one would doubt whether the added pyloroplasty in Holle's patients confers any additional benefit in terms of diminished gastric stasis or diminished release of gastrin. Hence, if the incidence of recurrence is low after HSV with a drainage procedure, it should also be low after HSV without a drainage procedure. Finally, HSV in dogs has been found to confer significantly better protection against histamine-induced ulcer than does selective vagotomy with antrectomy[18], which is an extremely effective anti-ulcer operation in man. For these reasons, although our follow-up is brief, we think that there is already a great deal of evidence to suggest that in the long run the incidence of recurrent ulceration after HSV will be low, and certainly not greater than is found after

truncal or selective vagotomy with pyloroplasty. However, it is obviously of crucial importance that the denervation of the parietal cell mass should be complete. As has been stated previously, it is quite clear that no variety of vagotomy - truncal, selective or highly selective - can be expected to succeed if the vagotomy of the parietal cell mass is frequently incomplete. The only group[19] to report recurrent duodenal ulceration after HSV also reported that their insulin-positive rate in the early post-operative period was 28 per cent.

While we are not in a position to claim that the overall clinical results after HSV are significantly better than those of truncal or selective vagotomy with pyloroplasty or gastrojejunostomy, they certainly appear to be much better at this stage. Approximately 90 per cent of patients achieve a Visick grade I or II result after HSV as compared with approximately 70 per cent after vagotomy with a drainage procedure. As can be seen from Table IX this 20 per cent improvement is attributable to the transfer of 20 per cent of patients from Visick grade III to Visick grade I, and analysis of the individual symptoms suggests that this improvement is due to the elimination of post-vagotomy diarrhoea and bile vomiting and to a considerable reduction in the

incidence of early dumping. HSV has not been followed by any noticeable diminution in the numbers of cases in Visick grade IV. This failure is probably attributable to the selection for surgery of some patients who for psychological or other reasons were unsuitable. However, after all types of gastric operation the numbers of failures are relatively small and it would be surprising to find significant differences at this stage. No doubt when the results of several thousand HSV operations become available it will be possible to make a more valid assessment of whether this operation reduces the incidence of failure.

The results of HSV at two years appear to be considerably better than those of vagotomy with a drainage procedure, but they do not seem to be much better than those of truncal vagotomy with antrectomy or of partial gastrectomy (Table IX). However, HSV is almost certainly a significantly safer operation than either of these resection procedures. Moreover, in the Leeds-York trial[2] it was found that patients had lost an average of ten pounds in weight after the operations which involved gastric resection. It is most unlikely that this degree of weight loss will be recorded after HSV. Likewise in the long term it seems reasonable to expect that the incidence of iron-deficiency anaemia, bone disease and tuberculosis will be less after HSV than after partial gastrectomy.

SUMMARY

Since January 1969, 180 patients have been treated in the University Department of Surgery at Leeds General Infirmary by highly selective vagotomy without a drainage procedure. Of these, 140 were treated for duodenal ulceration. There has been no operative mortality, no need to re-operate for the relief of gastric stasis, and no proven recurrent ulcer.

The author has found it possible to treat 100 almost-consecutive cases of duodenal ulcer by HSV. Emergency cases and those with established pyloric stenosis were excluded. The clinical results which were achieved in the first 100 patients treated by HSV for duodenal ulcer are reviewed. Assessment was carried out in the Gastric Follow-up Clinic by a panel of doctors who were unaware of which type of operation had been performed until they had written down their findings and their collective verdict. The results after HSV are compared with those which were recorded after other gastric operations, although it is conceded that the comparison may not be entirely valid one because of possible differences in selection of patients and because the HSV series is largely the work of one surgeon.

The post-operative period after HSV was notable for the absence of gastric stasis and of ileus. Patients were discharged on average ten days after operation. Serious complications were few in number and not specifically related to the type of vagotomy which had been performed.

Ninety patients were reviewed one year after HSV and 48 patients two years after HSV. Only 3 had lost a significant amount of weight and only 2 were anaemic. The incidence of so-called "post-vagotomy" diarrhoea was 2 per cent after HSV, but more than 20 per cent after either type of vagotomy with a drainage procedure. This difference is statistically significant ($p < 0.01$). Bile vomiting did not occur after HSV whereas it was recorded in more than 10 per cent of patients after all the other gastric operations ($p < 0.01$). Mild early dumping was recorded in 5 per cent of patients after HSV compared with 10 per cent after vagotomy with a drainage procedure and 17 per cent after partial gastrectomy.

Vomiting and flatulence, which would have been prominent symptoms after HSV if gastric emptying has been unsatisfactory, were found to be no more frequent than after the other operations. Epigastric fullness after meals was recorded

in 30 per cent of patients after HSV which was little different from the incidence after the other gastric operations.

Overall assessment of the outcome two years after the various operations showed that better results were achieved after HSV than after any other operation. The differences as compared with truncal and selective vagotomy with pyloroplasty or gastrojejunostomy were large, but compared with vagotomy and antrectomy or partial gastrectomy they were small. From these data one would deduce that a prospective random trial of HSV against vagotomy with pyloroplasty would probably show a significant superiority in favour of HSV, but that a similar trial comparing HSV with either vagotomy with antrectomy or partial gastrectomy would have little chance of showing a significant superiority for any one operation, at least in the first five to ten years after operation. HSV is nevertheless considered to be a better operation for duodenal ulcer than vagotomy with antrectomy or partial gastrectomy, for several reasons. Firstly, the patient is less likely to die of the operation. This point is particularly relevant if each type of operation were to be used in a consecutive series of patients, without recourse to non-resectional surgery in unfit patients or in those with large,

"difficult" ulcers. In the Leeds-York trial about 25 per cent of patients were considered to be unsuitable for the randomisation procedure. That is, gastrectomy or antrectomy was thought to be excessively hazardous. Again, certain side-effects such as early dumping and bilious vomiting are more severe after partial gastrectomy or antrectomy than after HSV. There is reason to believe that in the long term the incidence of weight loss, anaemia, bone disease and possibly tuberculosis will be less after HSV than after procedures involving gastric resection. The incidence of recurrent ulceration after HSV should be no higher than after truncal vagotomy or selective vagotomy with a drainage procedure, and failures due to recurrence or gastric stasis after HSV should be amenable to cure by the performance of antrectomy. In contrast, failures after gastric resection are much more difficult to treat, especially if failure is due, not to recurrent ulceration, but to metabolic disturbances or to dumping.

This clinical evaluation of HSV suffers from the disadvantages that follow-up of the patients is relatively short and that comparison of the results with those of the other gastric operations may not be entirely valid. A clearer picture of the value of HSV will emerge when the results of a five to eight year follow-up are available and when the results are published of the various prospective random trials which are now in progress.

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CHAPTER 15

THE GALL BLADDER

EFFECT OF TRUNCAL, SELECTIVE AND HIGHLY SELECTIVE VAGOTOMY ON THE RESTING VOLUME AND CONTRACTILITY OF THE GALL BLADDER IN MAN

It has been shown previously that truncal vagotomy is followed by dilatation of the gall bladder in man.[1-6] Anterior selective vagotomy, in contrast, does not produce significant dilatation of the gall bladder[2,3,5]. Presumably the gall bladder dilates after truncal vagotomy because in that operation the hepatic vagal fibres, which supply the gall bladder, are transected, whereas in selective vagotomy they are preserved. Since the hepatic fibres of the vagus are also preserved in HSV, one would expect that HSV would not produce dilatation of the gall bladder.

To test this hypothesis, and to learn more about the function of the biliary tract after the three types of vagotomy, we measured the resting volume of the gall bladder, and its contraction in response to a normal meal, in four groups of subjects :- in patients with duodenal ulcer before operation (DU), and in patients who were in good health, more than one year after HSV, truncal vagotomy and pyloroplasty (TV+P) or bilateral selective vagotomy and pyloroplasty (SV+P). Completeness of vagotomy (of the parietal cell mass) had been established in each

patient by the finding of a negative response[7] to insulin in the early post-operative period.

METHOD

Patients The resting volume of the gall bladder was measured in 16 DU patients, 16 patients after HSV, 16 patients after TV+P and 12 patients after SV+P. Details of their ages, weights, sex, results of insulin-tests more than one year after operation (if available), clinical (Visick) status, and of the interval between the time of operation and the testing of gall bladder function, are to be found in Table I. In the DU patients, the diagnosis had been made on the basis of a typical history and on barium meal examination. Twelve of the 16 patients later came to operation, at which the diagnosis was confirmed in each case. The SV was "bilateral" in each patient, with preservation both of the hepatic and of the coeliac vagal fibres. The pyloroplasty was of the Heinecke-Miculicz variety in all except 2 patients, in whom it was of the Finney type. The contraction of the gall bladder in response to a meal was followed for 90 minutes in all 16 DU patients, in 10 of 16 patients after HSV, 15 of 16 patients after TV+P and 4 of 12 patients after SV+P.

Measurement of volume of resting gall bladder, and contraction after a meal The gall bladder was demonstrated by means of oral

TABLE I

TABLE I

COMPARISON OF THE FOU-

GROUP	I PRE-OP. DU		II HIGHLY SELECTIVE VAGOTOMY HSV					III
NO.	AGE AND SEX	WEIGHT (kg.)	AGE AND SEX	WEIGHT (kg.)	MONTHS POST-OP.	VISICK GRADE	INSULIN TEST > 1 yr. POST-OP.	AGE AND SEX
1	49 M	44	57 F	54	24	II	E+	51 M
2	55 M	63	30 M	75	22	I	L+	30 M
3	48 M	60	47 M	67	23	II	-ve	46 M
4	53 M	64	41 M	80	23	II	L+	62 M
5	47 M	60	47 M	74	21	I	E+	57 M
6	26 M	67	52 M	70	20	I	L+	48 M
7	50 M	77	54 M	63	11	I	not done	58 M
8	58 M	54	51 M	70	24	I	-ve	58 M
9	47 M	61	44 M	61	29	I	-ve	35 M
10	29 M	76	36 M	78	32	I	-ve	35 M
11	65 M	64	66 M	65	19	II	not done	62 M
12	59 M	64	50 M	76	21	III	L+	70 M
13	65 M	56	49 M	64	17	I	L+	58 M
14	47 M	72	38 M	57	20	II	L+	44 M
15	60 M	68	59 M	67	15	I	not done	27 M
16	39 M	71	47 M	55	17	I	L+	48 M
MEAN ± 1 SEM	49.81 ± 2.81	63.81 ± 2.10	48.00 ± 2.26	67.25 ± 2.02	21.13 ± 1.27			49.31 ± 3.14

R GROUPS OF PATIENTS

TRUNCAL VAGOTOMY TV+P				IV BILATERAL SELECTIVE VAGOTOMY SV+P			
WEIGHT (kg.)	MONTHS POST-OP.	VISICK GRADE	INSULIN TEST > 1 yr. POST-OP.	AGE AND SEX	WEIGHT (kg.)	MONTHS POST-OP.	VISICK GRADE
69	16	I	-ve	36 M	71	19	II
74	45	I	-ve	69 M	54	24	I
78	27	II	-ve	27 M	57	48	II
67	18	I	L+	46 F	60	48	I
85	13	II	L+	39 M	63	36	I
83	38	I	E+	45 M	78	31	I
56	30	III	L+	60 M	63	32	II
63	24	I	-ve	60 M	60	46	I
72	15	II	not done	66 M	56	54	I
74	20	II	-ve	49 M	70	43	II
90	13	I	not done	29 M	66	63	II
68	12	I	not done	56 F	44	33	II
62	48	I	not done				
72	10	III	not done				
75	42	III	not done				
75	60	I	not done				
72.69	26.94			48.50	61.83	39.75	
2.19	3.83			4.04	2.58	3.70	

Late-post-operative insulin tests were not performed in patients after selective vagotomy and pyloroplasty.

L+ , late positive, in second hour: E+, early positive in first hour after insulin.

cholecystography. Ten hours before the examination, the patient ingested three grams of 'Solubiloptin' powder in water after a meal. Thereafter, he fasted, but took a further three grams of 'Solubiloptin' in water 5 hours later. Radiographs were taken in the same x-ray room, in a standard way, by one highly experienced radiographer. The patient lay prone on the x-ray table, and was placed carefully in the same position before each exposure was made. The distance from the x-ray tube to the film was known, and the antero-posterior thickness of the patient's body at the level of gall bladder was measured in centimetres. These measurements permitted calculation of a correction factor[8] which was later applied to the computed volume of the gall bladder.

Meal After the first film had been taken, to demonstrate the volume of the "resting" gall bladder ("resting volume"), the patient was asked to sit in a chair. He then ate a small meal consisting of one slice of a standard white loaf of bread, ("Sunblest") with 28 grams of butter and one standard cup (180ml.) of tea, to which were added milk and sugar to taste. Two teaspoonfuls (8ml.) of thin barium emulsion were eaten with the meal, so that contraction of the gall bladder could be timed, not from the time of eating, but from the time at which the head of the meal first entered the duodenum. The first teaspoonful of barium

was taken with the first mouthful of bread and butter. Immediate screening of the first 10 patients showed that barium entered the duodenum quickly, within 2 - 5 minutes in each case. This rapid initial emptying was seen to occur both in DU patients and in patients after TV+P and HSV. Thereafter, the assumption was made that gastric emptying would be rapid, and in all subsequent tests serial radiographs were taken at 15-minute intervals after the end of the meal for 90 minutes. In the intervals between the exposure of radiographs, the patient sat upright in a chair.

Reproducibility studies The resting volume of the gall bladder was measured on a second occasion in 12 patients :- in 3 patients with DU before operation, 3 patients after HSV, 4 patients after TV+P and 2 patients after SV+P. The interval between the first and second measurements varied from 3 to 29 weeks, with a mean of 11 weeks.

Calculation of the volume of the gall bladder The two-dimensional picture of the gall bladder, giving the area, was converted to a figure representing the volume of the gall bladder in millilitres, by means of the standard tables provided by Siffert de Paula e Silva[8]. This computed volume was then converted to the "corrected" volume by application of the correction factor, to compensate for the magnification of the image on the film. The "thicker" the patient - that is, the

greater his antero-posterior "diameter" as he lies prone on the table - the greater is the distance between his gall bladder and the x-ray film, and hence the greater is the magnification produced. Thus, in a fat man, the "true" volume might be obtained from the computed volume by multiplication by 0.68, whereas in a thin man a smaller correction is needed.

The outline of the gall bladder was traced onto unexposed x-ray film with a fine-pointed ball-point pen. Contrary to expectation, little difficulty was experienced in deciding where Hartmann's pouch ended and cystic duct began, and the two observers - radiologist and surgeon - were able to reach complete agreement on this score.

Measurement of diameters of the gall bladder The method of Siffert de Paula e Silva[8] consists essentially of "slicing" the traced outline of the gall bladder into strips, each strip being 3, 5 or 8mm. wide. The width of each strip is measured with a ruler in millimetres. This measurement gives the diameter of a cylinder, 3, 5 or 8mm. in height, and the volume of that cylinder is read off from the standard tables provided. (The assumption is made that the gall bladder is circular on cross-section). Two observers each calculated the volumes of the same 20 gall bladders, and the volumes which they obtained were compared.

Volumes of the gall bladder in each of the 4 groups of patients were expressed as arithmetic means plus or minus one standard error of the mean. The significance of differences between groups was calculated using Student's t-test for unpaired data. Student's t-test for paired data was used for calculation of the significance of changes in the volume of the gall bladder after the meal.

RESULTS

DU Patients - The mean resting volume of the gall bladder was 27 $\pm$ 1 ml., in 16 patients (Figs. 1 and 2, Table II). The range was from 15 to 36 ml. After food, the mean volume decreased to 12 $\pm$ 2 ml., in the same 16 patients (Figs. 2 and 3, Table II). The mean smallest single volume was 10.9 $\pm$ 1.4 ml. If the resting volume of the gall bladder is taken as 100 per cent, themean smallest volume recorded after the meal was 39 $\pm$ 4 per cent. The smallest mean volume (12.5 ml.) was reached at 45 minutes, but was little smaller than the mean volume recorded at 30 minutes (13 ml.). The difference between the volumes at 30 and 45 minutes p.c. was not statistically significant ($0.4 > p > 0.3$). The mean volume of the gall bladder increased from 12 to 14 ml. between 45 and 90 minutes. This increase was not statistically significant ($0.1 > p > 0.05$).

TABLE II

VOLUME OF THE GALL BLADDER IN SIXTEEN PATIENTS WITH DUODENAL ULCER BEFORE OPERATION, SHOWING RESPONSE TO A MEAL

(ml.)

PATIENT NO.	NAME	AGE AND SEX	WEIGHT (kg.)	RESTING VOLUME	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.
1	E.S.	49 M	44	29.4	21.7	8.2	6.6	8.4	13.9	8.8
2	R.M.	55 M	63	25.0	11.9	7.4	6.2	7.5	9.9	8.4
3	K.B.	48 M	60	23.4	16.5	10.8	10.7	10.5	14.3	15.5
4	N.S.	53 M	64	28.6	15.4	12.4	15.2	10.9	15.7	13.7
5	S.S.	47 M	60	14.5	13.8	9.8	8.0	12.7	15.0	13.9
6	T.W.	26 M	67	33.9	30.9	28.8	27.4	27.9	29.0	23.8
7	A.W.	50 M	77	27.2	17.5	11.9	11.5	12.2	15.8	15.2
8	A.F.	58 M	54	24.7	19.7	13.4	9.6	12.6	17.6	19.5
9	K.R.	47 M	61	32.9	21.0	21.0	28.5	20.2	24.1	32.1
10	P.C.	29 M	76	32.0	18.4	15.0	15.7	19.1	13.5	12.4
11	H.T.	65 M	64	36.3	23.7	18.9	20.2	20.6	24.1	20.3
12	H.T.	59 M	64	23.8	14.1	11.0	8.6	8.5	8.2	9.0
13	J.W.	65 M	56	27.9	14.5	10.3	6.6	6.3	15.2	12.8
14	C.M.	47 M	72	23.5	9.9	6.8	5.4	8.7	9.0	8.4
15	T.L.	6 M	68	32.5	19.3	11.6	8.5	11.9	9.7	9.5
16	G.P.	39 M	71	22.2	12.7	10.3	10.7	11.5	7.5	7.5
MEAN		49.81	63.81	27.35	17.61	12.98	12.47	13.08	15.14	14.42
± 1 SEM		2.81	2.10	1.38	1.31	1.42	1.80	1.47	1.53	1.68

Note that the mean volume diminished very little after 30 minutes. The increase in volume between 45 and 90 minutes is not statistically significant ($t = 2.059$, $0.1 > p > 0.05$).

GALL BLADDER VOLUMES AFTER 3 TYPES OF VAGOTOMY.

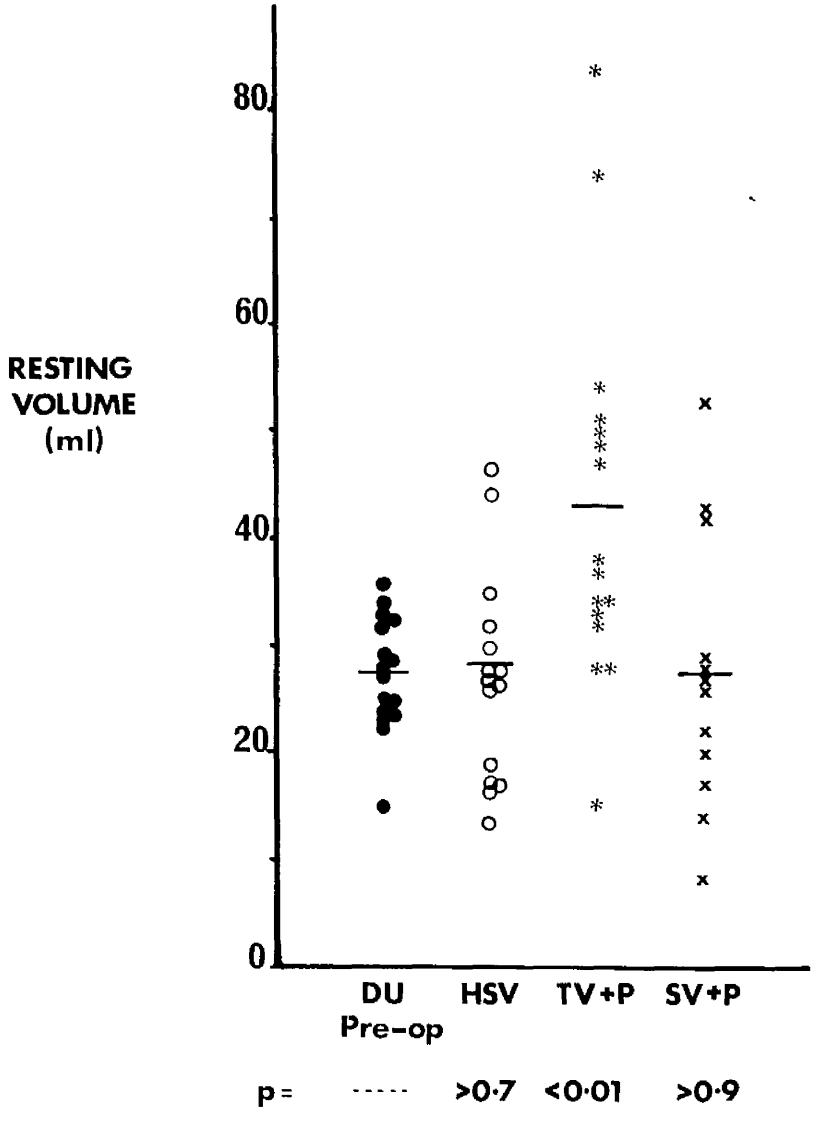

Fig. 1 Resting volume of the gall bladder is shown, for each patient. Horizontal lines indicate arithmetic mean. Truncal V+P is followed by significant dilatation of the gall bladder: SV+P and HSV are not, though the gall bladder is dilated in a few individuals after these procedures.

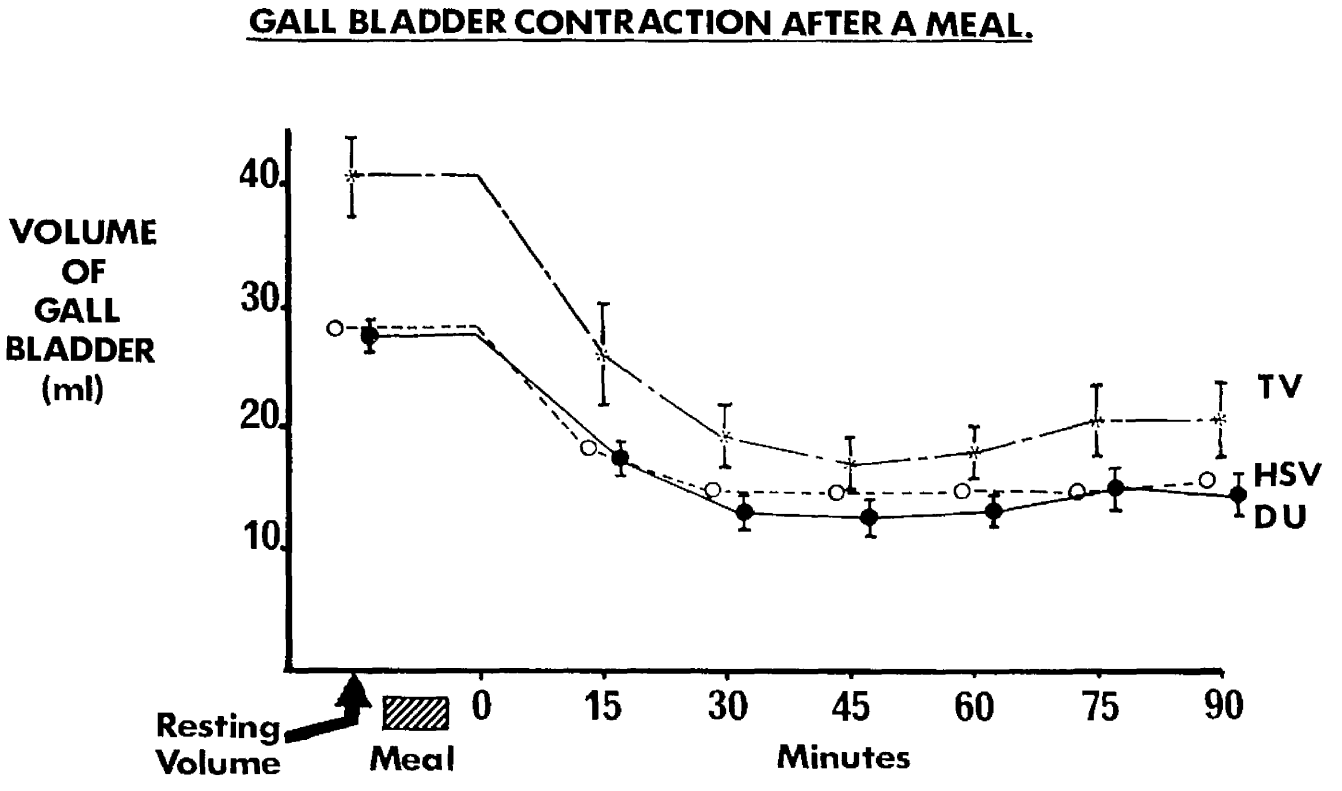

Fig. 2 There is no impairment of gall bladder contraction after TV+P or HSV. Even after maximal contraction, the volume of the gall bladder in patients after TV+P is greater than in patients after HSV or in pre-operative DU patients.

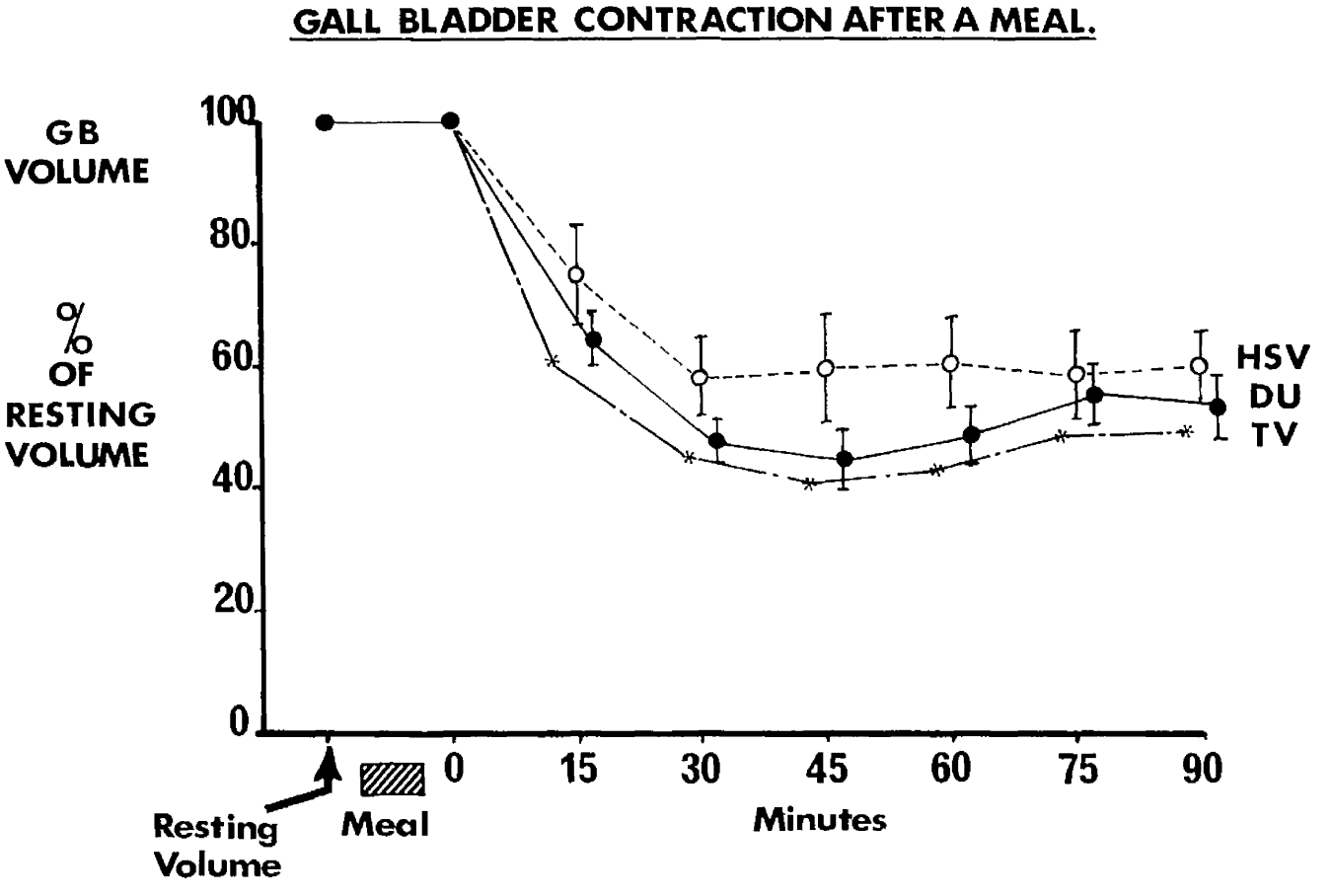

Fig. 3 Contractility of the gall bladder in response to a meal is not impaired after truncal vagotomy, and also not significantly impaired after HSV.

TABLE III

VOLUME OF THE GALL BLADDER IN SIXTEEN PATIENTS AFTER HSV, SHOWING THE RESPONSE TO A MEAL

(ml.)

PATIENT NO.	NAME	AGE AND SEX	WEIGHT (Kg.)	MONTHS POST-OP.	VISICK GRADE	INSULIN TEST > 1 yr. POST-OP.	RESTING VOLUME	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.
1	E.H.	57 F	54	24	II	E+	16.9	18.6	10.0	8.0	9.7	11.4	16.4
2	S.G.	30 M	75	22	I	L+	17.3	11.7	13.4	21.0	18.1	13.8	12.5
3	R.P.	47 M	67	23	II	-ve	32.3	23.4	20.0	14.4	13.8	15.2	16.5
4	R.C.	41 M	80	23	II	L+	28.5	18.0	13.5	10.8	14.1	11.0	15.0
5	F.W.	47 M	74	21	I	E+	35.4	14.4	11.0	9.4	13.8	13.3	18.8
6	J.D.	52 M	70	20	I	L+	26.2	20.8	14.7	13.0	10.4	6.7	7.1
7	H.K.	54 M	63	11	I	not done	29.8	18.2	17.1	18.5	20.9	17.8	19.3
8	N.K.	51 M	70	24	I	-ve	27.1	36.4	26.3	25.5	20.4	27.8	22.8
9	E.L.	44 M	61	29	I	-ve	18.9	9.9	8.3	12.0	15.8	15.4	14.7
10	A.W.	36 M	78	32	I	-ve	28.5	19.10	13.3	12.7	11.3	12.2	11.3
11	J.G.	66 M	65	19	II	not done	35.5						
12	E.S.	50 M	76	21	III	L+	46.5						
13	H.W.	49 M	64	17	I	L+	26.6						
14	F.P.	38 M	57	20	II	L+	44.2						
15	B.H.	59 M	67	15	I	not done	16.6						
16	H.W.	47 M	55	17	I	L+	13.3						
MEAN of 16		48.00	67.25	21.13			28.30	18.12	14.76	14.51	14.82	14.46	15.42
± 1 SEM		2.26	2.02	1.27			2.48	1.63	1.67	1.74	1.25	1.76	1.41

The mean volume diminished very little after 30 minutes. The decrease in volume between 30 and 45 minutes, and the increase between 45 and 90 minutes, were not statistically significant ($p > 0.8$ and $p > 0.5$ respectively). Mean resting volume in patients 1 to 10 was 26.09 ± 2.01 ml.

TABLE IV

OLUME OF THE GALL BLADDER IN SIXTEEN PATIENTS AFTER TRUNCAL VAGOTOMY AND PYLOROPLASTY, SHOWING THE RESPONSE TO A ME

(ml.)

PATIENT NO.	AGE AND SEX	WEIGHT (Kg.)	MONTHS POST-OP.	VISICK GRADE	INSULIN TEST > 1 yr. POST-OP.	RESTING VOLUME	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.
1	51 M	59	16	I	-ve	53.5	14.1	25.7	18.4	18.4	21.3	15.3
2	30 M	74	45	I	-ve	49.2	28.8	20.6	18.4	23.3	31.1	23.1
3	46 M	78	27	II	-ve	51.1	43.9	38.5	27.6	36.5	40.8	31.5
4	62 M	67	18	I	L+	28.5	18.2	9.4	8.5	7.3	3.6	3.2
5	57 M	85	13	II	L+	50.4	45.8	25.9	20.6	24.5	28.0	22.0
6	48 M	83	38	I	E+	47.4	28.2	30.4	30.5	26.3	31.4	34.5
7	38 M	56	30	III	L+	14.9	3.2	3.7	6.9	6.5	6.2	6.9
8	58 M	63	24	I	not done	32.8	20.2	14.1	13.0	13.5	14.4	19.5
9	35 M	72	15	II	not done	34.2	22.6	10.5	9.2	8.1	9.2	12.1
10	35 M	74	20	II	-ve	28.3	15.7	12.1	10.9	10.7	7.0	3.5
11	62 M	90	13	I	not done	37.1	24.0	15.8	15.2	14.0	17.5	18.9
12	70 M	68	12	I	not done	74.1	71.0	36.1	32.3	28.1	33.4	46.8
13	58 M	62	48	I	not done	38.3	20.3	15.6	11.5	14.3	18.3	19.1
14	44 M	72	10	III	not done	84.0*	-	-	-	-	-	-
15	27 M	75	42	III	not done	34.4	13.7	14.0	19.1	23.5	28.1	32.5
16	48 M	75	60	I	not done	31.8	19.2	15.3	11.3	10.8	16.5	17.9
MEAN	49.31	72.69				43.12*	25.91	19.18	16.88	17.72	20.45	20.45
± 1 SEM	3.14	2.19				4.37	4.29	2.61	2.08	2.30	2.92	3.12

* Mean of 15, excluding patient No. 14, is 40.4 ± 3.66.

The insulin test was negative in each patient in the early post-operative period. L+, Late positive; E+, Early positive in first hour after insulin.

The decrease in volume between 30 and 45 minutes, and the increase between 45 and 90 minutes, are both statistically significant ($t = 2.28$, $p < 0.05$; $t = 2.30$, $p < 0.05$, respectively).

TABLE V

VOLUMES OF THE GALL BLADDER IN TWELVE PATIENTS AFTER BILATERAL SELECTIVE VAGOTOMY AND PYLOROPLASTY, SHOWING THE RESPONSE TO A MEAL

(ml.)

PATIENT NO.	AGE AND SEX	WEIGHT (Kg.)	MONTHS POST-OP.	VISICK GRADE	RESTING VOLUME	15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.
1	36 M	71	19	II	42.9	13.3	11.4	11.6	8.7	9.9	14.5
2	69 M	54	24	I	53.1	25.4	20.3	20.8	14.3	18.1	22.3
3	27 M	57	48	II	26.9	14.2	9.7	6.0	3.5	3.4	4.0
4	46 F	60	48	I	42.0	20.2	17.2	8.6	5.7	4.7	4.6
5	39 M	63	36	I	17.0						
6	45 M	78	31	I	28.1						
7	60 M	63	32	II	22.1						
8	60 M	60	46	I	20.1						
9	66 M	56	54	I	14.1						
10	49 M	70	43	II	25.9						
11	29 M	66	63	II	28.8						
12	56 F	44	33	II	8.4						
MEAN	48.50	61.83	39.75		27.45[1]	18.27	14.64	11.75	8.05	9.01	11.34
± 1 SEM	4.04	2.58	3.70		3.74	2.84	2.46	3.23	2.32	3.32	4.37

1 Mean resting volume in patients 1 - 4 was 41.2 ± 5.4 ml.

Insulin tests were not performed in these patients more than one year after operation. In each patient the insulin test had been negative in the early post-operative period.

Patients after HSV - The mean resting volume of the gall bladder was 28 ± 2 ml., in 16 patients. The range was from 13 to 46 ml., or from 13 to 60 ml. if the result of the second test in a reproducibility study is included (Figs. 1 and 2, Table III). Two of the 16 patients had gall bladder volumes greater than 40 ml. (44 and 46 ml.). After the meal, the mean volume decreased from 27 ± 2 ml. to 14 ± 2 ml., in 10 patients. The mean smallest volume (regardless of when it occurred) was 11.7 ± 1.4 ml., 46 ± 5 per cent of the initial volume. The smallest mean volume was recorded at 45 and at 75 minutes, but as in the pre-operative DU patients, the smallest mean volume had almost been reached by 30 minutes (Table III). Between 45 and 90 minutes, mean gall bladder volume increased by only 0.9 ml., from 14.5 to 15.4 ml. The resting volume of the gall bladder, and its contractility in response to food, were not significantly different in patients after HSV from those which were found in DU patients before operation (Table VI).

Patients after TV+P The mean resting volume of the gall bladder was 43 ± 4 ml., in 16 patients. Volumes ranged from 15 to 84 ml., and 7 of the 16 patients had gall bladder volumes greater than 40 ml. After the meal, the mean volume decreased from 40 ± 4 to 17 ± 2 ml., in 15 patients (Figs. 1 and 2, Table IV). The mean smallest volume, regardless of when it occurred, was 14.4 ± 2.2 ml., 33 ± 3 per cent

of the resting volume. The smallest mean volume was recorded at 45 minutes (Fig. 2). The mean volume decreased from 19.2 ml. at 30 minutes to 16.9 ml. at 45 minutes, then increased again to a mean of 20.5 ml. at 90 minutes. The decrease in volume between 30 and 45 minutes, and the subsequent increase in volume between 45 and 90 minutes, were both statistically significant ($p < 0.05$).

The resting volume of the gall bladder was significantly ($p < 0.01$) greater after TV+P than in DU patients before operation. It was also greater than in patients after HSV ($p < 0.01$) or SV+P ($p < 0.02$) (Table VI). Also, the two consecutive lowest volumes attained after the meal, in patients after TV+P, were probably significantly greater than the two consecutive lowest volumes in DU patients or in HSV and SV+P patients combined ($p < 0.05$, Table VII).

Patients after SV+P The mean resting volume was 27 $\pm$ 4 ml., in 12 patients. The volumes ranged from 8 to 53 ml. (Fig. 1). 3 of the 12 patients had gall bladder volumes greater than 40 ml. Contractility in response to food was measured in only 4 patients, in whom the mean volume decreased from 41 $\pm$ 5 to 8 $\pm$ 2 ml. (Fig. 2, Table V). The mean smallest volume was 18 $\pm$ 4 per cent of the resting volume. The smallest mean volume was recorded at 60 minutes. The resting volume of the gall bladder after SV+P was not significantly greater than

TABLE VI

COMPARISON OF RESTING VOLUMES OF THE GALL BLADDER IN THE FOUR GROUPS OF PATIENTS:

(by means of Student's t test for unpaired data)

GROUPS COMPARED	RESTING VOLUME (ml.) (MEAN ± 1 SEM)		DEGREES OF FREEDOM	t	p
group 1 cf group 2	group 1	group 2			
TV cf DU	43.1 ± 4.4	27.4 ± 1.4	30	3.439	< 0.01
TV cf HSV	43.1 ± 4.4	28.3 ± 2.5	30	2.946	< 0.01
TV cf SV	43.1 ± 4.4	27.5 ± 3.7	26	2.608	< 0.02
TV cf (DU+ HSV+ SV)	43.1 ± 4.4	27.7 ± 1.4	58	4.388	< 0.001
DU cf HSV	27.4 ± 1.4	28.3 ± 2.5	30	0.335	$0.8 > p > 0.7$
DU cf SV	27.4 ± 1.4	27.5 ± 3.7	26	0.029	> 0.9
HSV cf SV	28.3 ± 2.5	27.5 ± 3.7	26	0.196	> 0.8

The gall bladder is significantly dilated after truncal vagotomy (TV) and pyloroplasty, compared with the volumes recorded in pre-operative patients with duodenal ulcer (DU). Resting volumes of the gall bladder in patients after selective (SV) and highly selective vagotomy (HSV) are not significantly different from those recorded in pre-operative DU patients.

that of pre-operative DU patients ($p > 0.9$, Table VI) and contractility was unimpaired in the 4 patients in whom it was measured.

Reproducibility of measurement of resting volume Good agreement, within 20 per cent, was obtained in 7 of the 12 patients. Reproducibility was poor in 5 patients (Table VIII). The difference between the paired measurements averaged 21 per cent of the first measurement. The mean difference in volume between first and second tests was 7.5 ± 1.9 ml.

Correlation between measurements made by two observers The mean (uncorrected) resting volume recorded by the first observer was 49.0 ± 4.8 ml., in 20 patients, and that recorded by the second observer in the same patients was 48.7 ± 4.7 ml. (Table IX). The mean difference was 0.77 ± 0.13 ml., 1.5 ± 0.2 per cent of the value recorded by the first observer.

DISCUSSION

Effect of the three vagotomies on gall bladder size and emptying The "resting volume" of the gall bladder was found to be significantly larger ($p < 0.01$) in patients who had undergone TV+P than in patients with duodenal ulcer before operation. After HSV or SV+P, the gall bladder was not dilated, on average, although a few individual patients

were found to have dilatation of the gall bladder. This may have been due to inadvertent damage to the hepatic fibres at the time of operation and has been noted previously in an occasional patient after SV[5,9]. Our findings confirm those of previous workers who reported that the gall bladder was dilated after TV in man[1-6], and that it is not dilated after SV[2,3,5]. We have added the new information that the gall bladder is not dilated after HSV, which was the expected finding, since HSV preserves all the structures which are preserved by SV. The gall bladder has been shown to dilate progressively in the course of the first year after TV[1], which may explain why a few authors[10,11], who measured the volume of the gall bladder less than a year after TV, did not find significant dilatation.

As is evident from the data presented in Table I, matching of the four groups of patients was not perfect. In particular, patients after TV+P were heavier on average than pre-operative patients, and the interval between operation and measurement of gall bladder size was longer in patients after SV+P than in patients after HSV or TV+P. Further defects of the study are that patients were not tested both before and after operation, and that reproducibility of the measurement of gall bladder volume left much to be desired (Table VIII), the volume recorded on the second occasion differing from that recorded on the

first occasion by an average of 21 per cent. In addition, although the method of de Paula e Silva which we used is the standard method, it too must involve some degree of error, particularly with regard to the correction factor, whose magnitude depends upon an estimate of the distance between the gall bladder and the radiographic plate. Despite these drawbacks, the difference which we have found between gall bladder volumes after TV+P and those in the other three groups of patients is indeed striking. It would seem reasonable to ascribe it to the operative procedure itself, rather than to imperfections of the method.

While it has been stated that the volume of the gall bladder approximately doubles after TV in man[2,3], our own findings are more in keeping with those of Krause and his colleagues, who reported that the mean volume of the gall bladder in 13 patients was 33 ml. before operation and 49 ml. after TV with a drainage procedure[6]. As in our own study, the increase in size of the gall bladder varied widely from patient to patient, and was less than 10 per cent in 3 of the 13 patients and less than 2 ml. in 4 of the 13. If an arbitrary figure of 37 ml. is taken as the upper limit of normal for gall bladder volume (Fig. 1), 9 of our 16 patients had dilated gall bladders after TV+P.

Although on average the resting volume of the gall bladder seemed to be significantly greater after TV+P, contractility after a meal was unimpaired (Figs. 2 and 3). That the vagally-denervated gall bladder contracts vigorously in response to the presence of fat in the intestine has been known for many years[1,10,12,13]. This is explicable on the grounds that contraction is due mainly to the release of cholecystokinin[14]. However, the smallest mean volume which the gall bladder attained after contraction (14.4 ml.) in patients after TV+P was still larger than the volumes which were recorded in patients before operation (10.9 ml.) or in patients after HSV (11.7ml.). The difference (DU cf TV) was not quite significant ($0.2 > p > 0.1$), but if the two consecutive lowest volumes attained in each test are compared, the difference is just statistically significant (DU cf TV; $p < 0.05$: DU cf [HSV + SV], $p < 0.05$, Table VII). That the volume of the gall bladder is much increased after TV, even after contraction, has been noted previously[2,5]. Thus, the residual volume of bile in the gall bladder after contraction is probably increased significantly after TV. This may predispose to the subsequent formation of gallstones.

Other differences were found between patients who had undergone TV+P and the other groups of patients when the characteristics

of gall bladder contraction in response to the meal were analysed. Maximal or near-maximal contraction of the gall bladder had taken place by 30 minutes in pre-operative patients and in patients after HSV, whereas further significant contraction ($p < 0.05$) took place between 30 and 45 minutes in patients after TV+P (Fig. 2). Later, between 49 and 90 minutes after the meal, the volume of the gall bladder increased significantly ($p < 0.05$) in the TV+P group of patients, but in no other group. These results are in agreement with those of Snape[15], who found that in dogs with duodenal and gastric fistulae, the latent period between the introduction of casein or oleic acid directly into the duodenum and contraction of the gall bladder increased from 2 to 3 minutes before vagotomy to 6 to 10 minutes after TV. Glanville and Duthie[10] showed that there was no significant increase in the volume of the gall bladder between 45 and 90 minutes after a fatty meal in normal subjects or in patients with duodenal ulcer before operation, whereas in patients after TV+P the volume of the gall bladder increased significantly. The latter study was also of interest for its demonstration that gall bladder size and contractility were the same in pre-operative patients with duodenal ulcer as in normal subjects. Glanville and Duthie found no change in the rate of gall bladder emptying after TV when contraction was timed from the

passage of the meal through the pylorus[10]. Since we do not know exactly when, in the first 15 minutes after the meal, the head of the meal entered the duodenum in our subjects, we are unable to tell whether the longer time taken to reach a nadir of volume in patients after TV+P represents a significant difference or not. The difference, compared with the time taken in pre-operative patients and in patients after HSV, could have been due to slower gastric emptying after TV+P, though it must be added that we think such a possibility to be remote, because elsewhere in the thesis we show that gastric emptying both of fluids and of food-and-barium is faster after TV+P than after HSV or than before operation.

At this point, discussion of our results is complete, but before finishing it seems relevant to summarize briefly the literature on the effect of vagotomy on bile flow, on the composition of bile, on the absorption of fat, and on the chances that vagotomized patients will subsequently develop gallstones.

Effect of vagotomy on bile flow and composition

Stimulation of the vagi leads to an increase in bile flow[16-18] and to an increase in the solid content of the bile[17], in dog[16,17] and man[18]. It has been shown in the dog that much of the choleretic effect of vagal

stimulation is attributable to vagal release of gastrin[19-21], rather than to a direct effect of the vagi on the liver. Truncal vagotomy in the dog leads to a diminution in bile flow[17,22,23] and to a change in the composition of the bile, such that it is more lithogenic[22-24].

After truncal or selective vagotomy with a drainage procedure, the mean output of faecal fat increases significantly[11,25-31]. The increase is as great after selective vagotomy as after truncal vagotomy[11,30]. According to some[29,31-33], vagotomy alone does not lead to a significant increase in the output of faecal fat, whereas others find that it does[25,27]. Pyloroplasty alone in dogs gives rise to a significant increase in faecal fat output[31]. If vagotomy is added to pyloroplasty[31] or gastroenterostomy[33], the output of faecal fat increases still further. Hence it would be untrue to say that the increase in output of faecal fat after vagotomy with a drainage procedure is entirely attributable to the drainage procedure: both the drainage procedure and the vagotomy contribute to the increase. Micellar fat formation in the small intestine was found to be severely altered after truncal vagotomy with a drainage procedure and this was no doubt due to the diminution in the concentration of bile acids and decreased pancreatic lipase activity which were also observed[34].

As a result, increased concentrations of intraluminal fat were found in the distal small intestine[34].

The results obtained by previous workers are more confusing and conflicting than is suggested by the above outline, which indicates merely the trend of the evidence. For example, although the careful work of Baldwin and his colleagues strongly suggests that insulin-hypoglycaemia stimulates bile flow in man[18], Liedberg[35] did not find that bile flow was stimulated by insulin hypoglycaemia in two patients with total biliary fistula. The fact that they both had pancreatic carcinoma, whereas Baldwin et al's. patients[18] had been operated on for gallstones, may explain why the findings were different. There seems to be no doubt,however, that both truncal and selective vagotomy with pyloroplasty are followed by steatorrhoea. As already stated, the loss of fat seems to be no less after selective vagotomy than after truncal vagotomy. While it has been suggested that the amount of fat lost in the stool is insufficient to produce nutritional deficiencies[36], it is noteworthy that in 21 of 84 patients after truncal vagotomy and gastrojejunostomy, faecal fat losses were found to be greater than 10 grams per day[26]. Such steatorrhoea may well be accompanied by excessive loss of fat-soluble vitamins and of iron, calcium and magnesium, which could lead to

weight loss, anaemia and skeletal problems in the long term. This risk is more than theoretical, because Wheldon, Venables and Johnston[37] have recently reported the finding of a high incidence of weight loss, iron-deficiency anaemia and tuberculosis in patients 15 to 20 years after truncal vagotomy and gastrojejunostomy.

There are thus at least three reasons why biliary function, and the digestion and absorption of fat, should be better after HSV than after TV+P. Firstly, HSV preserves the vagal nerve supply to the antrum. Gastrin release in response to vagal stimulation will produce a choleresis[17-21]. After TV+P, such a mechanism is lost. Secondly, a drainage procedure is unnecessary with HSV, and in consequence of the better-regulated gastric emptying, it can be expected that smaller amounts of fat and of other nutrients will be lost in the faeces[29,31-33]. Finally, preservation of the vagal nerve supply to the biliary tract should prevent the dilatation of the gall bladder, diminished bile flow and altered composition of bile which have been shown to follow truncal vagotomy. Admittedly, the changes in bile flow and composition have been demonstrated only in the dog, and not in man, and further study of these factors in man is indicated.

Effect of vagotomy on gallstone formation The formation of gallstones is favoured by stasis of bile, infection, and alteration in composition

of bile such that the ratio of cholesterol to bile acids is increased[38]. Since truncal vagotomy leads to an increase in the volume of the gall bladder (both "resting" and after a meal), and to a diminution in bile flow, it is probable that it produces some degree of biliary stasis compared with the state of affairs which exists before operation. Our findings suggest that HSV is followed by little change in the size or contractility of the gall bladder. Thus, on the evidence available to date, HSV would seem less likely to produce stasis than is TV.

It has been shown by Cowie and Clark[23] that truncal vagotomy and pyloroplasty almost abolishes bile flow in response to a fatty meal in cholecystectomized dogs, and also leads to a large increase in cholesterol concentration in the bile, with a concomitant large decrease in the concentration of phospholipid. There was also a slight decrease in the concentration of cholate[23]. These changes make the bile potentially more lithogenic. Increase in the viscosity and particulate content of gall bladder bile had been noted previously after truncal vagotomy in the dog[24], and in the same study the wall of the gall bladder was found to be thickened and infiltrated by chronic inflammatory cells. Such studies will have to be repeated in dogs after HSV. However, since HSV keeps intact both the hepatic vagal

fibres, and the antro-pyloro-duodenal segment which is the source of hormones such as gastrin, secretin and cholecystokinin - all of which have been shown to stimulate bile flow[30,39,40] - there seems good reason to believe that HSV will be followed by less change in the flow and composition of bile than is TV.

The observations of Krause[41] indicated that the incidence of gallstones in patients with peptic ulceration who do not undergo surgery is much the same as the incidence in the normal population. Several recent reports[4,42-44] have suggested that an increased incidence of gallstones follows TV in man. Though all are inconclusive, the paper by Cave and Gasper[4] is particularly impressive. These authors performed cholecystography in 92 patients after TV+P, and found that no fewer than 21 patients (23 per cent) had evidence of gall bladder disease. Fourteen of the 21 had gallstones and 7 had a non-functioning gall bladder. Fourteen of the 21 positive x-ray studies were obtained in the first 4 years after operation. Of 55 patients who had both a normal cholecystogram before operation and a gall bladder that was normal to palpation at the time of operation, 24 per cent were later found to have evidence of gall bladder disease. This developed within the first few years after operation, affected younger patients on average than those who usually develop gallstones, and the customary

female-to-male predominance was reduced almost to a 1 : 1 ratio. Obviously, this study is open to criticism: no control group was analyzed: assessment of the gall bladder by palpation at operation may give misleading results. As Fletcher and Clark[45] conclude in their careful review of the topic, proof is lacking that truncal vagotomy leads to gallstone formation. Nonetheless, there is good evidence that truncal vagotomy causes the gall bladder to dilate, bile flow to diminish and the bile to become more lithogenic in composition. When this information is considered in conjunction with clinical reports suggesting that truncal vagotomy predisposes to gallstone formation, the case against truncal vagotomy becomes more convincing. On the basis of the circumstantial evidence at present available some surgeons might now feel that until truncal vagotomy is proved not to predispose to gallstone formation, it might be preferable to preserve the vagal fibres to the biliary system, by performing selective or highly selective vagotomy. To do so cannot do harm and might do some good. Obviously such a decision would also be influenced by whether the surgeon thinks that selective or highly selective vagotomy is as effective as truncal vagotomy in curing the duodenal ulcer.

TABLE VII

COMPARISON OF THE SMALLEST VOLUMES REACHED AFTER A MEAL IN THE FOUR GROUPS OF PATIENTS

(by Student's t test for unpaired data)

	GROUPS COMPARED group 1 cf group 2	RESTING VOLUME (ml.) (MEAN ± 1 SEM) group 1 (TV)	 group 2	DEGREES OF FREEDOM	t	p
LOWEST	TV cf DU	14.4 ± 2.2	10.9 ± 1.4	29	1.380	0.2 > p > 0.1
SINGLE	TV cf (HSV+ SV)	14.4 ± 2.2	10.6 ± 1.3	27	1.489	0.2 > p > 0.1
VOLUME	TV cf (DU+ HSV+ SV)	14.4 ± 2.2	10.8 ± 0.9	43	1.803	0.1 > p > 0.05
TWO CONSECUTIVE LOWEST VOLUMES	TV cf DU	15.8 ± 1.7	11.7 ± 1.0	60	2.086	<0.05
	TV cf HSV	15.8 ± 1.7	12.6 ± 1.1	48	1.423	0.2 > p > 0.1
	TV cf (HSV+ SV)	15.8 ± 1.7	11.4 ± 1.0	56	2.208	<0.05

TABLE VIII

RESTING VOLUME OF THE GALL BLADDER:
RESULTS OF PAIRED TESTS IN THE SAME PATIENTS

NO.	NAME	GROUP	TIME INTERVAL BETWEEN TESTS (weeks)	1. vol. at 1st test ml.	2. vol. at 2nd test ml.	DIFFERENCE ml.	DIFFERENCE : PER CENT OF VOLUME AT FIRST TEST
1	C.M.	DU	3	23.48	24.76	1.28	5.45
2	T.L.	DU	3	32.48	30.57	1.91	5.88
3	H.F.	DU	8	24.67	26.75	2.08	8.43
4	E.L.	HSV	11	18.91	26.50	7.59	40.14
5	N.K.	HSV	29	36.41	60.31	23.90	65.64
6	A.W.	HSV	10	28.45	32.79	4.34	15.25
7	T.C.	SV	29	53.00	41.87	11.19	21.09
8	F.H.	SV	8	41.96	29.82	12.14	28.93
9	J.Y.	TV	8	37.07	42.16	5.09	13.73
10	G.W.	TV	9	74.00	67.05	7.01	9.47
11	R.H.	TV	8	38.25	48.92	10.67	27.90
12	L.B.	TV	10	34.15	31.18	2.97	8.70
MEAN			11.33 wks.	36.91	38.56	7.51	20.88
± 1 SEM			2.49	4.28	4.01	1.85	5.13

TABLE IX

CORRELATION BETWEEN RESULTS OBTAINED BY 2 OBSERVERS WHO MEASURED THE SAME 20 GALL BLADDERS

(uncorrected volumes - before application of correction factor)

NO.	(1) (ml.)	(2) (ml.)	DIFFERENCE (ml.)	DIFFERENCE / VOLUME (1) PER CENT
1	41.02	39.67	1.35	3.29
2	59.98	59.67	0.31	0.52
3	96.06	93.80	2.26	2.35
4	87.91	87.25	0.66	0.75
5	37.97	37.02	0.95	2.50
6	48.79	47.77	1.02	2.09
7	42.72	43.43	0.71	1.66
8	65.88	64.50	1.38	2.09
9	37.68	38.42	0.74	1.96
10	36.09	36.39	0.30	0.83
11	19.51	19.51	0.50	0.0
12	11.42	11.46	0.04	0.35
13	51.71	51.99	0.28	0.54
14	60.09	61.64	1.55	2.58
15	37.69	36.98	0.71	1.88
16	23.03	22.45	0.58	2.52
17	38.56	38.69	0.13	0.34
18	67.77	66.43	1.34	1.98
19	68.90	69.42	0.52	0.75
20	46.40	47.03	0.63	1.36
MEAN ± 1 SE	48.96 ± 4.79	48.68 ± 4.73	0.77 ± 0.13	1.52% ± 0.21

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CHAPTER 16

TREATMENT OF GASTRIC ULCER BY HIGHLY SELECTIVE VAGOTOMY WITHOUT A DRAINAGE PROCEDURE

TREATMENT OF GASTRIC ULCER BY HIGHLY SELECTIVE VAGOTOMY WITHOUT A DRAINAGE PROCEDURE

Provided that his ulcer could be induced to heal and his stomach to empty satisfactorily, the patient with a gastric ulcer would probably be better off with his pylorus than without it; better with his whole stomach than bereft of half of it. Encouraged by our results with highly selective vagotomy for duodenal ulcer we treated 19 patients who had benign gastric ulcer without evidence of gastric stasis by highly selective vagotomy without a drainage procedure (HSV). Compared with Billroth I gastrectomy, HSV should have a lower operative mortality, produce fewer side-effects such as dumping, and be followed by less weight loss and anaemia in the long term.

PATIENTS AND METHODS

Patients Full details are given in the Table. Of the 19 patients, 16 were male and 3 were female. Many were underweight. Fourteen patients had gastric ulcer alone, and five had gastric ulceration plus scarring of the duodenum. The duodenal ulcer appeared to be active in only two patients. Most of the patients with gastric ulcer alone had received full medical treatment, including carbenoxolone sodium, and

were referred for surgery either because the ulcer had failed to heal or because it had recurred. One patient was operated on as an emergency for haematemesis. Thirteen of the ulcers were situated near the incisura angularis or more distally, two were in the middle of the lesser curvature and four were in the upper third of the stomach. At the time of operation, 15 of the 19 ulcers were found to be active, and 4 had healed. Initially, for technical reasons, only a few selected patients with gastric ulcer were treated by HSV, but with increasing experience it was found possible to treat all patients in this way, and the last 14 patients form a consecutive series.

The possibility of ulcer-cancer was excluded in each patient by the use of a combination of tests:- barium meal examination, fiberoscopy, studies of acid output and finally by excision of the ulcer with frozen section examination by an experienced pathologist at the time of operation. Cancer was not found unexpectedly at frozen section examination in any other patient with gastric ulcer.

The possibility that the gastric ulcer had arisen as a result of gastric stasis was excluded by clinical methods, supplemented by the information obtained from barium meal examination and by measurement of the volume of resting juice in the stomach at the start of pre-operative tests of gastric secretion. At operation, the absence of pyloro-duodenal

narrowing was confirmed in each patient by the passage of a finger or Hegar's dilators through the pylorus and proximal duodenum.

Tests of Gastric Secretion

(1) Spontaneous acid output (BAO) and maximal acid output (PAO^{PG})

Before operation, spontaneous acid output (in one hour) and the response to intramuscular pentagastrin[1], in a dose of 6 ug per kg body weight, were measured in 17 patients. The pentagastrin response was expressed as peak acid output (PAO^{PG} = output in the peak 20-minute period x 3, in mEq per hour). Measurement of BAO and PAO^{PG} was repeated 4 to 8 days after operation in each patient. The dose of pentagastrin used then was 10 ug per kg body weight[2].

(2) Response to meat extract (OXO)[3,4,5] This test was used as a measure of the activity of the gastric antrum. Gastrin release was stimulated by placing 100ml of OXO solution at pH 7 and room temperature into the stomach via a naso-gastric tube. Nine patients, all of whom had gastric ulcer alone, underwent this test before operation. Acid output was expressed as PAO^{OXO} (peak 20-minute acid output x 3 = mEq per hour).

(3) A Hollander insulin test[6] was performed 4 to 8 days after operation in 17 patients, and omitted in two on account of age and cardiovascular disease. The dose of insulin used was 0.2 units per kg. Venous blood

samples withdrawn 30 and 45 minutes after the insulin injection established that blood glucose concentration had decreased to less than 35 mg per 100ml in each test. Acid output was expressed as PAO^{I} (peak 30-minute output x 2).

The methods used in these tests have been described in previous chapters. Titration was to the pH 7 end-point, but BAO was also expressed as "free" acid, with titration to pH 3.5.

Clinical Result This was judged at the Gastric Follow-Up Clinic by a panel of observers who were kept in ignorance of the pre-operative diagnosis or of the type of operation which had been performed, until they had written down their collective assessment in accordance with a modified Visick classification[7,8]. Visick grade I signifies a perfect result; II, near perfection with only trivial side-effects easily controlled by care; IV means failure due to recurrent ulceration or severe side-effects, while III signifies a satisfactory result with freedom from ulcer pain, but somewhat marred by side-effects which cannot be entirely avoided. No formal assessment was attempted in eight patients who were followed up for less than nine months. Their clinical progress has been satisfactory to date.

Barium meal examination was carried out in each of eleven patients who had been followed-up for at least nine months after operation.

Operative Technique The technique of highly selective vagotomy without drainage for duodenal ulcer has been described previously in detail. The presence of a gastric ulcer poses special problems, firstly because the ulcer is usually close to the antral nerves (nerves of Latarjet), which must be preserved, and also because it must be excised and submitted to frozen section examination to exclude the possibility of malignancy. At first, these factors deterred us from using HSV in any but the occasional case of gastric ulcer, but with increasing experience we have found it possible to treat all cases of gastric ulcer in this way. A trans-gastric approach to the ulcer via an appropriately-sited gastrotomy incision is preferred (Fig. 1), because it is difficult to excise the ulcer from outside the stomach without damaging the nerves of Latarjet. The entire ulcer, together with a disc of surrounding mucosa, is excised with the diathermy blade or scalpel. The fibrous base of the ulcer was usually so thick that the stomach wall was perforated during this manoeuvre in only 6 of the 19 cases. Bleeding was controlled by deeply-placed interrupted catgut sutures. The gastrotomy incision is made longditudinally and is placed, whenever possible, in the proximal three-quarters of the stomach, which is to be vagally-denervated. The incision is closed longditudinally. In the case of an ulcer that is distal to the incisura, the gastrotomy has

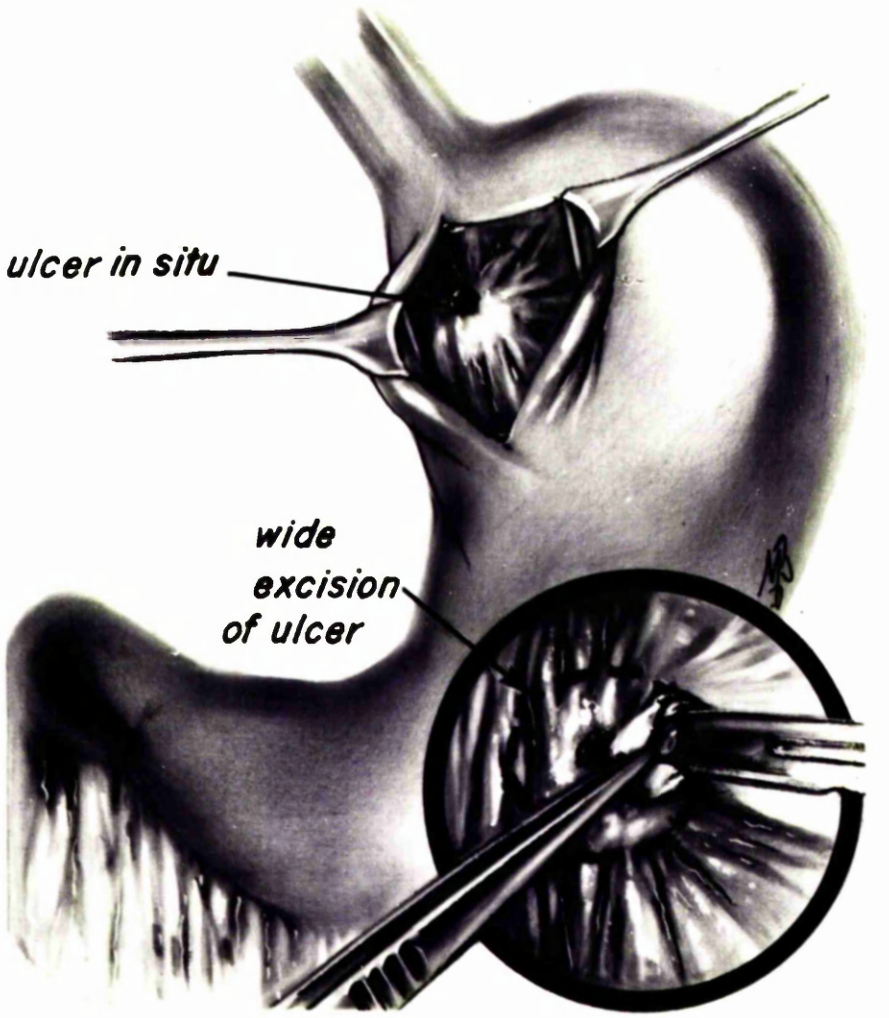

Fig. 1 Malignancy is excluded by complete excision of the ulcer via a longditudinal gastrotomy, followed by immediate frozen section examination of the specimen.

to be made in the antral region, on whose motility gastric emptying will depend. The incision should then be placed, not in the middle of the anterior gastric wall, but along the greater curvature, so that denervation of the inferior half of the anterior wall of the antrum may be avoided. Again the incision is closed as it is made, longditudinally. Edge-to-edge apposition is the aim, without inversion. Oedema and fibrosis around the ulcer often obliterate the normal plane of dissection between the lesser curvature of the stomach and the lesser omentum which contains the nerves to the antrum. This problem can be overcome by the use of a combined approach, from the front and from the lesser sac after mobilisation of the greater curvature, and by the ligation of tissues in continuity with transfixion sutures, placed close to the wall of the stomach. A finger, or a Hegar's dilator, is passed through the pylorus into the second part of the duodenum, and if the "pyloric channel" does not admit the distal finger-joint or a 14mm. dilator[9], some degree of obstruction to the gastric outlet must be suspected. In these circumstances it might be advisable toresort to gastric resection or to vagotomy with a drainage procedure instead of HSV. Stenosis was found in only one of our patients and was treated by simple digital dilatation.

The length of pre-pyloric stomach left innervated ranged from

5 to 8 cm. Operating time varied from 60 to 150 minutes, with a mean of 110 minutes.

RESULTS

Clinical

(a) In hospital The patients' convalescence was without incident and none developed gastric retention. The mean length of stay in hospital after operation was 12 days.

(b) Follow-up The patients have fared well since their discharge from hospital, Of the 11 who have been followed for more than nine months, 3 are in Visick grade I, 6 are in grade II and 2 are in grade III. The commonest side-effect is epigastric fullness after meals, which causes almost half the patients to restrict the size of their main meal to about two-thirds of what they ate formerly. Of the two patients in Visick grade III, one has episodic diarrhoea of moderate severity, and the other experiences epigastric discomfort which is unlike the pain of his ulcer. None of the patients has experienced pain of ulcer type and none has symptoms suggestive of gastric stasis.

Barium meal examination in the 11 patients who have been followed for at least 9 months revealed no sign of recurrent ulceration. The volume of resting juice in the stomach was not excessive and gastric

emptying was satisfactory.

Gastric secretion (see Table for details)

(a) Response to Meat Extract Before Operation Mean peak acid output in response to 'OXO' solution (PAO^{OXO}) was 5.6 mEq per hour in the 9 patients who were tested. This was, on average, only 20 per cent of their PAO^{PG}. There was no secretory response to the meat extract in 3 of the 9 patients. (These figures should be compared with the mean PAO^{OXO} in 26 patients with duodenal ulcer before operation of 21.7 mEq per hour, 47.8% of their PAO^{PG}).

(b) Spontaneous acid output (BAO) Only two patients were found to be still secreting 'free' acid after operation. BAO (to pH 7) decreased from a mean of 2.2 mEq per hour before HSV to 0.3 mEq per hour after HSV, in 12 patients with gastric ulcer alone. The mean reduction was only 76 per cent, largely because there was little reduction in BAO in two patients who were hyposecretors before operation.

(c) Response to pentagastrin (PAO^{PG}) Mean PAO^{PG} in 12 patients with gastric ulcer alone was 25.1 mEq per hour before HSV and 8.0 after HSV, a mean reduction of 66 per cent. The mean reduction in 4 patients with combined gastric and duodenal ulcers was 57 per cent.

TABLE

Patient No.	Age (Years) and Sex	Weight (kg.)	Length of Ulcer History (Years)	EFFECT ON GASTRIC ACID OUTPUT (Stimuli) SPONTANEOUS Titre to pH7 B mEq/hr	SPONTANEOUS Titre to pH7 A mEq/hr	PENTAGASTERIN (PAO^{PG}) B mEq/hr	PENTAGASTERIN (PAO^{PG}) A mEq/hr	PENTAGASTERIN (PAO^{PG}) Reduction %	MEAT EXTRACT (PAO^{OXO}) B mEq/hr	MEAT EXTRACT (PAO^{OXO}) % of PAO^{PG}	INSULIN (PAO^{I}) A +ve/-ve	INSULIN (PAO^{I}) A mEq/hr	CLINICAL RESULT Length of Follow-up (months)	CLINICAL RESULT Visick Grade
*1	39 M	70	20	4.06	0.79	18.75	9.75	48.00	-	-	negative	0.38	36	II
2	37 M	59	15	2.08	0.30	25.53	8.43	66.99	15.12	59.23	negative	0.62	30	I
3	47 M	70	3	1.26	0.00	27.90	5.13	81.61	-	-	negative	0.00	17	II
4	33 M	61	2	2.88	0.00	28.38	2.16	92.39	6.00	21.14	negative	0.00	14	III
5	26 M	43	3	0.24	0.15	18.06	7.86	56.48	0.57	3.16	negative	0.00	13	II
6	41 M	65	5	2.87	0.61	28.71	11.34	60.50	8.32	28.98	negative	0.00	12	II
7	60 M	58	3	0.03	0.32	18.60	10.80	41.94	-	-	negative	0.00	9	II
8	54 F	76	2	6.58	0.00	44.61	14.91	66.58	12.48	27.98	negative	0.00	12	III
9	48 M	65	4	3.21	0.12	13.83	3.81	72.45	-	-	negative	0.00	9	I
10	55 M	57	2	4.50	0.34	33.84	9.09	73.14	0.30	0.89	negative	1.24	6	-
11	71 M	63	0	-	1.05	-	17.85	-	-	-	NOT PERFORMED		5	-
12	50 M	64	10	0.00	0.00	26.19	8.46	67.70	0.00	0.00	negative	0.00	1	-

13	60 F	54	12	2.10	1.55	15.75	9.42	40.19	3.27	20.76	negative	0.00	1	-
14	48 M	54	5	0.46	0.00	19.83	5.04	74.58	4.41	22.24	negative	0.00	1	-
Mean of 13 ± 1SE (Nos. 2 - 14)	48.46 ± 3.38	60.69 ± 2.27	5.08 ± 1.24	2.19 ± 0.58 (12) Mean reduction = 76.4 ± 10%	0.29 ± 0.13 (12)	25.10 ± 2.50 (12)	8.04 ± 1.03 (12)	66.21 ± 4.33 (12)	5.61 ± 1.81 (9)	20.49 ± 6.16 (9)	all negative		7.69 ± 2.22	
15‡	45 M	61	18	4.57	0.80	50.31	17.01	66.19	-	-	negative	0.30	22	I
16‡	48 M	76	29	7.32	0.00	59.67	25.44	57.37	-	-	negative	0.00	26	II
17‡	71 M	57	10	3.43	0.35	48.00	26.25	45.31	-	-	negative	0.38	7	short follow-up
18‡	54 F	58	25	0.82	0.62	23.64	9.24	60.91	-	-	negative	0.56	3	-
19‡	63 M	58	30	-	0.00	-	17.40	-	-	-	NOT PERFORMED		2	-
	50.00 ± 2.75 (19)	61.53 ± 1.82 (19)	22.40 ± 3.75 (5)	4.04 ± 1.35 (4) 74.2 ± 17% reduction	0.45 ± 0.17	45.41 ± 7.68 (4)	19.49 ± 4.00 (4)	57.45 ± 4.43 (4)	-	-	all negative		11.89 ± 2.35 (19)	3 I 6 II 2 III (11 patient 9 month after operation

Patients 1 - 14 had gastric ulcer alone; (‡ 15 - 19 had both gastric and duodenal ulcers).
Nos. 2 - 19 were treated by HSV alone.

* No. 1 had a 70 gram segmental gastric resection in addition to HSV.

B - before operation. A - 5 - 9 days after operation. PAO - peak acid output.

(d) Insulin Test All 17 tests were negative[6], signifying that the vagotomies were complete. They were negative by Hollander's criteria, and also by nearly all other criteria, since a secretory response was noted in only 2 of the 17 tests. The test in patient no. 10 was positive by Stempien's criterion[10] (increase of 0.25 mEq in any one hour), but that of patient no. 2 was negative by all criteria, since the peak-hour acid response to insulin was less than 0.25 mEq greater than BAO, although PAO[1] was 0.32 mEq per hour greater than BAO (Table).

DISCUSSION

Firstly, it should be pointed out that the follow-up is very brief, only nine patients having been followed for more than one year, and none for longer than three years. Hence no claims can be made for the effectiveness of HSV in curing gastric ulcer in the long term. On the other hand, there is good evidence, both clinical and radiological, that gastric emptying is satisfactory, despite the absence of a drainage procedure. If gastric stasis has not become manifest within a year of operation, it is unlikely to develop at a later date. Thus, one potential cause of recurrent gastric ulceration appears to be absent.

Although the incidence of recurrent ulceration is higher after vagotomy than after gastrectomy for gastric ulcer, truncal or selective vagotomy with a drainage procedure provides a cure for most cases of gastric ulcer[11-18]. This achievement is all the more impressive when one considers that 20 per cent of the vagotomies are likely to have been incomplete[19]. Highly selective vagotomy (selective proximal vagotomy) with a drainage procedure has been claimed previously to yield good long-term results in the surgical treatment of gastric ulcer[20]. The results of the present study indicate that highly selective vagotomy without a drainage procedure (HSV) gives good clinical results in the treatment of patients with benign gastric ulcer, at least in the short-term. Particularly encouraging features were the complete relief from ulcer pain experienced by each patient, and the absence of vomiting and of other symptoms of gastric stasis. The results of post-operative barium meal examinations were satisfactory, although it is recognized that the emptying of barium does not necessarily reflect the emptying of solid food. The results of the secretory tests were also satisfactory, with evidence of completeness of the parietal-cell vagotomy in each case, virtual abolition of spontaneous secretion of 'free' acid and reduction of the peak response to pentagastrin (PAO^{PG}) by 66 per cent.

Certain important objections to the surgical approach which we have adopted will now be considered. It has been suggested, for exam e, that it is illogical, if the Dragstedt theory of the aetiology of gastric ulceration is assumed to be correct; that it is dangerous, because of the risk that an ulcer-cancer will be missed, and finally that the results of Billroth I gastrectomy for gastric ulcer are so eminently satisfactory, and so clearly better than those of vagotomy with a drainage procedure, that any change in surgical management is quite unjustifiable. Let us examine each of these objections in turn.

According to Dragstedt[21,22], gastric ulceration develops as a result of gastric stasis, excessive release of gastrin, and the resulting gastric hypersecretion. Certainly, it is true that anything which causes delayed gastric emptying, such as pyloric stenosis[13] or complete gastric vagotomy[23], is liable to lead to gastric ulceration. But though stasis causes gastric ulceration, it does not follow that the gastric ulcers which we see in clinical practice are caused by stasis. Studies of gastric emptying which were performed in patients with gastric ulcer by Buckler[24] and by Griffith, Owen, Campbell and Shields[25] suggest that gastric emptying of solid food is within normal limits in most patients with gastric ulcer, although a few individuals do have delayed emptying. In our own patients, the following features led us

to believe that gastric stasis was not the cause of their ulcer. They did not vomit copiously. They did not have a succussion splash. There was no delay in the emptying of barium before operation. When a naso-gastric tube was passed, the volume of the resting juice in the stomach was not excessive (less than 150ml), and food residues were not found. Spontaneous acid output was low-normal, suggesting that circulating gastrin levels were not unduly high, because the finding of maximal acid outputs within the normal range implied that the parietal cell mass was normal in size. The acid responses to a test meal of meat extract, far from being excessive, as might have been expected if the Dragstedt theory were correct, were in fact small - only 20 per cent of the maximal acid output and about one quarter of the acid response to meat extract of patients with duodenal ulcer. At operation, a finger was passed from the stomach into the second part of the duodenum in each patient. No sign of pyloric obstruction, or of duodenal obstruction, was found in any of the patients with gastric ulcer alone; and only one of the five patients with combined gastric and duodenal ulcers was found to have pyloro-duodenal stenosis (defined as a pyloro-duodenal channel which will not admit the distal inter-phalangeal joint of the index finger, or a number 14mm Hegar dilator[9]).

It has been argued that vagotomy of any kind is an illogical

operation to use in the treatment of patients with gastric ulcer, because their spontaneous and maximal acid outputs are already within the normal range. Such an argument presupposes that methods of treatment in medicine must have a logical basis: in other words, that we must first understand the disease, and then take the appropriate steps to cure it. In fact, we must admit that the cause of gastric ulceration is not known, and neither the Dragstedt theory[21,22], nor the Du Plessis[26]-Lawson[27]-Capper[28] theory of bile reflux, seems adequate to explain all cases of gastric ulceration. Hence, treatment must be empirical, and if HSV provides a permanent cure in most cases of gastric ulcer, we will not be too concerned that we do not understand precisely why the operation works. It should also be pointed out that half of the patients with duodenal ulcer coming to surgery have maximal acid outputs within the normal range[29,30], yet few object to the use of vagotomy in their treatment on the grounds that it is "illogical". One final point. The old adage "no acid, no ulcer" still holds true, and at least we can take comfort from the knowledge that HSV reduces acid output considerably in patients with gastric ulcer.

As to the problem of ulcer-cancer, clearly the treatment of a potentially-curable lesion by a conservative operation would be a tragic error. As many as 5 to 10 per cent of patients whose gastric ulcer

appears to be benign on gross inspection have, in fact, an occult ulcer-cancer[16]. If such cancers are treated by radical resection, the prognosis is much better than that of gastric cancer in general[31,32]. While all this is beyond dispute, we think that the chances of an ulcer-cancer being missed can be reduced to a minimum by the use of clinical methods supplemented by fibrescopic examination of the ulcer, with biopsy and cytological examination. An accuracy rate of 99.3 per cent in differentiating between benign and malignant ulcers of the stomach can be achieved by such means[33]. Finally, at operation, the surgeon has a further opportunity to inspect the ulcer directly, and if he still harbours the slightest suspicion that the ulcer is malignant, he should perform a gastrectomy. Even if the ulcer appears benign, however, it should always be excised in toto, or at the least its epithelial margin should be excised, and the specimen submitted to immediate frozen-section examination by an experienced pathologist. In our opinion, the routine use of these measures will virtually eliminate the possibility that an early carcinoma will be treated in an inappropriate fashion.

It might well be asked what possible advantages HSV could possess compared with the time-honoured Billroth I gastrectomy for gastric ulcer, which yields good results in 80 to 90 per cent of patients

and has a recurrent ulcer rate of 0 - 2 per cent[17,34]. We would answer that an operation which involves neither resection of one half to two-thirds of the stomach, nor an anastomosis, is likely to be safer than one which does; statistically significantly safer, not within any individual surgeon's experience, but in the global context of the treatment of many thosands of patients. We have now treated 180 patients by HSV without operative mortality and indeed without any major post-operative complication related to the operative procedure. Secondly, in the case of gastrectomy, what is done cannot be undone. Many patients will develop iron-deficiency anaemia and a few will become thin, anaemic, osteoporotic "gastric cripples"[35]. Their lost stomach cannot be restored to them. Such sequelae should be rare after HSV, which preserves the entire gastric reservoir, with its emptying still regulated by a normally-innervated antro-pyloro-duodenal segment. Dumping has been found to be much less frequent after HSV than after vagotomy with a drainage procedure, and significantly less frequent than after partial gastrectomy of the Polya variety (see Chapter 14). If the ulcer should recur after HSV, effective treatment is available in the form of gastrectomy. Admittedly, Duthie and his colleagues[17] have shown that Billroth I gastrectomy yields better results than truncal vagotomy and pyloroplasty

in the treatment of benign gastric ulcer. HSV, however, is followed by significantly fewer side-effects such as dumping and diarrhoea than is vagotomy with drainage when used in the treatment of duodenal ulcer (vide supra) and hence it may well prove superior to vagotomy and drainage in the treatment of gastric ulcer also.

In conclusion, it has been shown that patients with gastric ulcer can be treated successfully in the short term by an operation which entails neither gastric resection nor destruction or bypass of the pylorus. The potential advantages of such a procedure are obvious, but its use should probably be confined at present to centres in which complete physiological evaluation and prolonged clinical follow-up of the patients are assured. Longer follow-up of larger numbers of patients and controlled trials are needed to show whether the early promise of highly selective vagotomy in the treatment of gastric ulcer will be fulfilled.

SUMMARY

Fourteen patients with gastric ulcer alone, and five with combined gastric and duodenal ulceration, were treated by highly selective vagotomy without a drainage procedure, in the past three years. Before operation, no evidence of gastric stasis was found, clinically,

radiologically or during tests of gastric secretion. Spontaneous acid output was low. Acid outputs in response to a test meal of meat extract were also found to be low. There was no evidence that in the patients with gastric ulcer alone, the ulcer was due to pyloric channel disease with excessive release of gastrin by the antrum.

Each gastric ulcer was proved to be benign at the time of operation, by frozen section examination. No problems with gastric stasis were encountered in the early post-operative period. The vagotomy was shown to be complete on insulin testing in each of the 17 patients who were tested.

Follow-up ranges from one month to three years. The clinical progress of the patients has been good, and none has symptoms suggestive of recurrent ulceration or of gastric retention. Barium meal examination in each of the eleven patients who were followed for more than nine months showed satisfactory gastric emptying, without recurrent ulceration. While the need for much longer follow-up is obvious, these preliminary results are encouraging. Further trial of highly selective vagotomy for gastric ulcer, preferably in the form of a prospective, randomized comparison with Billroth I gastrectomy, now seems desirable.

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CHAPTER 17

THE SUMMING UP

TABLE I

SUMMARY OF RESULTS

NO OPERATIVE MORTALITY IN 180 HSV OPERATIONS

INSULIN TEST: 3% POSITIVE
IN EARLY POST-OPERATIVE PERIOD

NO RECURRENT ULCER

NO GASTRIC STASIS REQUIRING RE-OPERATION

TABLE II

TABLE II

SUMMARY (continued)

MEASUREMENT	PRE-OPERATIVE DU	MORE THAN ONE YEAR AFTER TV+P
GASTRIC ACID OUTPUT (mEq per hour)		
SPONTANEOUS	8.0	2.0[4]
PG-MAXIMAL (PAO^{PG})	41.0	19.6
∠ INSULIN STIMULUS (PAO^{I})	35.8	3.1
∠ OXO STIMULUS (PAO)	21.7	19.6
EFFECT OF FAT IN DUODENUM (Pentagastrin stimulus)	74% reduction	39% reduction
EFFECT OF INSULIN-HYPOGLYCAEMIA ON PENTAGASTRIN STIMULATED MAO	SIGNIFICANT INCREASE ($p < 0.05$)	NO SIGNIFICANT CHANGE

TABLE II

MORE THAN ONE YEAR AFTER SV+P	MORE THAN ONE YEAR AFTER HSV	HSV compared with TV+P and SV+P
2.0 [1]	1.5	same or lower 1 a few high values were excluded
21.0	19.3	same
3.5	3.7	same
11.0	10.1	same, ? significantly lower than TV+P when larger numbers are available
-	33% reduction	same degree of inhibition as after TV+P : less inhibition than before operation
NO SIGNIFICANT CHANGE	SIGNIFICANT DECREASE ($p < 0.02$)	nerves of Latarjet may inhibit acid output in man: but study was inconclusive

CONTINUED OVER/

TABLE II

CONTD

GASTRIC EMPTYING			
RESTING JUICE		92 ml.	-
CLINICAL		-	NO STASIS
FOOD + BARIUM		"NORMAL"	SIGNIFICANTLY FASTER ($p < 0.01$)
FLUID (GLUCOSE)		TAKEN AS "NORMAL"	SIGNIFICANTLY FASTER ($p < 0.001$)
GALL BLADDER:	RESTING VOL. (ml.)	27.4	43.1 ($p < 0.01$)
	CONTRACTILITY	unimpaired	unimpaired
DIARRHOEA	a) clinical	-	24%
	b) after glucose	0%	67%
EARLY DUMPING	a) clinical at 1 year	4% (in "control" subjects)	20%
	clinical at 2 years	-	10%
	b) after glucose	20%	73%
OVERALL CLINICAL RESULTS AT 2 YEARS (Visick grades per cent)	I	-	37
	II	-	27
	III	-	24
	IV	-	12

- NO STASIS SIGNIFICANTLY FASTER ($p < 0.02$) SIGNIFICANTLY FASTER ($p < 0.01$)	60 ml. NO STASIS ALMOST NORMAL: NO STASIS SIGNIFICANTLY FASTER ($p < 0.05$)	less than before operation and free from food residues emptying after HSV not normal, but much nearer normal than after TV+P or SV+P
27.3 unimpaired	28.3 unimpaired	gall bladder dilated after TV+P, but not dilated after SV+P or HSV.
18% 60%	2% 13%	HSV virtually abolishes "post-vagotomy" diarrhoea Under maximal provocation, more diarrhoea than in pre-operative patients but significantly less than after TV+P or SV+P.
34% - 80%	6% 6% 47%	HSV reduces the incidence of early dumping, but some mild early dumping still occurs.
39 25 25 10	62* 28 4‡ 6	*Large increase in the proportion of patients with a perfect result: ‡ Significant decrease in Visick III, "fair" results. Fewer recurrent ulcers so far.

SUMMING UP*

Highly selective vagotomy without a drainage procedure has been used in the treatment of 180 patients in the University Department of Surgery, Leeds General Infirmary, in the past three-and-a-half years. The clinical results were assessed in an unbiased way at the Gastric Follow-up Clinic. These results have been compared with those which were recorded after other types of operation for duodenal ulcer. Such a comparison may not be entirely valid, because the respective groups of patients were not allocated in random manner to one or other of the operative procedures, but it nevertheless seemed worth making. In addition to this clinical assessment, a physiological assessment of the new operation was made by comparing such functions as gastric secretion and gastric emptying in well-matched groups of patients, who were in good health, more than one year after truncal vagotomy and pyloroplasty (TV+P), bilateral selective vagotomy and pyloroplasty (SV+P) or highly selective vagotomy without a drainage procedure (HSV). A definitive appraisal of HSV will be

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* Many references which have been quoted in relevant parts of the thesis are not cited again here.

possible only when the present series of patients has been followed-up for at least a further five years, and when the results of prospective random clinical trials become available.

Our main findings are shown in Tables I and II.

The relatively poor clinical results after vagotomy with drainage for duodenal ulcer have been highlighted in several publications since 1969[1-5]. In a well-planned prospective clinical trial, Jordan and Condon[1] found the results of truncal vagotomy with antrectomy to be superior to those of truncal vagotomy and pyloroplasty. In Leeds[2], also, the results after truncal vagotomy and pyloroplasty were found to be poorer than those of any of the other standard operations for duodenal ulcer, although it must be added that the value of the comparison was diminished by the fact that patients had not been randomly allocated to the different operative procedures. Very indifferent clinical results were found 5 to 10 years after truncal vagotomy and gastrojejunostomy in Edinburgh[3]. Severe dumping occurred in 11 per cent of patients, severe diarrhoea in 5 per cent, and only 39 per cent of patients achieved a perfect, Visick I, result. Wheldon and her colleagues[4], who reviewed 255 patients fifteen to twenty years after truncal

vagotomy and gastrojejunostomy, found weight loss of more than 6kg. in 33 per cent of men and 60 per cent of women, and iron-deficiency anaemia in 44 per cent of men and 84 per cent of women. 7 per cent of patients had pulmonary tuberculosis. The results of the prospective random trial of truncal vagotomy and pyloroplasty versus truncal vagotomy and gastrojejunostomy in Glasgow[5] show no superiority for one procedure over the other. Thus in the long term weight loss and anaemia may be as common after truncal vagotomy and pyloroplasty as after truncal vagotomy and gastro-jejunostomy. Our own continuing experience (unpublished) of the results of selective vagotomy with a drainage procedure in over 100 patients in Leeds does not suggest that the clinical results are any better than those of truncal vagotomy with a drainage procedure. Although Kennedy and Connell[6,7] found that selective vagotomy produced a significant reduction in the incidence both of incomplete vagotomy and of diarrhoea, compared with those which were recorded after truncal vagotomy, there is little evidence that the overall clinical results are significantly better after selective vagotomy than after truncal vagotomy. These dismal results of the currently-popular operations for duodenal ulcer serve to emphasize that there is ample room for improvement,

as the results of the Leeds-York trial[8] had shown.

The disturbances in physiology which follow pyloroplasty, distal antrectomy or vagotomy with a drainage procedure, have been defined in the past four years. Pyloroplasty in dogs was shown to destroy the normal co-ordination of motility in the antrum, pylorus and duodenum, and to impair the propulsive properties of the antral musculature[9]. Distal antrectomy, by ablating the terminal antral contraction and the ability of the pylorus to discriminate between solids and fluids, was found to lead to excessively-rapid emptying of solid spheres from the stomach in dogs[10]. In man, vagotomy with a drainage procedure was shown to produce excessively-rapid emptying of solids[11] and of liquids[12,13], (though not all workers would agree[14]). When hypertonic liquid left the stomach rapidly, it frequently produced diarrhoea[12,13]. Hence it is incorrect to state that vagotomy with a drainage procedure "preserves the gastric reservoir". On the contrary, the dam of the reservoir is "bust". The stomach is "incontinent".

These findings provide ample justification for our efforts to preserve the pylorus in surgery for duodenal ulcer. By

so doing, we hoped to achieve better regulation of gastric emptying, with a consequent reduction in the incidence of dumping and of diarrhoea. The idea that preservation of the nerves of Latarjet was essential to ensure efficient emptying of the stomach through the intact pylorus has found considerable support in the past four years. Burge, who for the same reasons as ourselves had been anxious to preserve the pylorus, published a favourable report[15] in 1969 on the results of bilateral selective vagotomy without a drainage procedure (SV) which he had performed in more than 100 patients with duodenal ulcer. However, at the 4th World Congress of Gastroenterology in Copenhagen, Burge stated that fewer than fifty per cent of his patients coming to surgery for duodenal ulcer were suitable for SV alone, and that if the slightest trace of pyloro-duodenal stenosis were found at operation, a pyloroplasty was added. From the results of studies of gastric emptying in his paper, it is clear that SV without drainage was followed by a considerable degree of gastric retention in many patients, and that re-operation for addition of pyloroplasty was necessary in a few. Since 1970, Burge has abandoned SV and is now an enthusiastic advocate of HSV, which

he uses in all cases of duodenal ulcer, except for those with clinically-manifest pyloric stenosis (personal communication). Kirk, too, tried SV without drainage in twenty-five patients with duodenal ulcer[16], but reported that he had been compelled to re-operate on three of them to relieve gastric retention. At the second operation, organic pyloro-duodenal stenosis was absent: the defect was functional rather than anatomical. Others who tried SV alone, such as J. S. F. Hutchison in Glasgow (personal communication) soon gave it up because of the problems which they encountered with gastric retention. Recently, it has been reported that SV alone in a small series of fifteen patients was followed not only by gastric stasis, but in three cases by gastric ulceration[17]: in contrast, patients who were treated by HSV by the same group of surgeons (personal communication) were not troubled by stasis or by recurrent ulceration. Bente M. Amdrup and her colleagues[18] reported that truncal vagotomy (TV) without drainage in rabbits was almost invariably followed by gastric ulceration, SV without drainage by gastric ulceration in fifty per cent of rabbits, whereas HSV was not followed by gastric ulceration. These differences were thought to reflect differences in gastric emptying after the three types of vagotomy without drainage. In dogs, SV without drainage

was found to lead to gastric retention[19]. In contrast, two independent groups of workers in America reported that HSV did not produce gastric retention in dogs[20,21]. Klempa et al., however, reported that dogs developed gastric retention after HSV[22]. In man, reports of unimpaired gastric emptying after HSV have come from Pedersen and Amdrup[23], Amdrup and Jensen[24], Clarke[25], and from ourselves. Clarke[25] also confirmed our findings that HSV is followed by more rapid emptying of a fluid test meal. E. Amdrup has had to re-operate on only one of his first hundred cases of HSV, who had developed a gastric ulcer in association with gastric retention (personal communication). Two patients in Leeds complained of vomiting food, soon after their discharge from hospital. Both were given a liquid diet, improved spontaneously, and are now able to eat normally. To date, we have not had to re-operate on any patient on account of gastric retention, and, as a group, the patients after HSV are no more liable to complain of excessive flatulence or of vomiting than are patients after truncal or selective vagotomy with a drainage procedure. However, in the past week we have admitted to hospital a man who has developed persistent vomiting of food, without loss of weight, several months after HSV.

He can retain milk and beer, but not solid food. The food-barium meal shows slight delay in gastric emptying (though hypertonic glucose empties rapidly), and we intend to re-operate on him in the near future. In summary, selective vagotomy without drainage cannot be used as a routine procedure in the treatment of duodenal ulceration, because of its tendency to produce gastric retention. In contrast, highly selective vagotomy without a drainage procedure has been used in the treatment of a consecutive series of 100 patients with duodenal ulcer in Leeds (only emergency cases and those with clinically-manifest pyloric stenosis being excluded). Gastric emptying has been shown to be satisfactory, by the use of a food-barium meal and of a test meal of glucose solution. No evidence of gastric stasis was found in these studies, and emptying was much closer to the "normal" (i.e. to what was found in pre-operative patients) than was the case after truncal or selective vagotomy with pyloroplasty, when gastric emptying was found to be abnormally rapid. The mean volume of 'resting juice' in the stomach measured 92ml. in 100 patients before operation, and 60ml. in 100 tests on 50 patients more than six months after HSV. This juice was "clean" and free from food residues in all except one test after HSV, and in all tests its

volume was less than 200ml. Clinical evidence of gastric retention was found in 2 of 180 patients within one month of HSV, but the difficulty was transient. One patient has now developed persisting gastric retention after HSV. Thus, clinical problems with gastric retention seem to be rather less frequent after HSV than after vagotomy with a drainage procedure. Early fears that the pyloro-duodenal channel would become stenosed as the ulcer healed have proved to be unfounded. If gastric emptying is satisfactory in the first year or two after HSV, it is most unlikely to become impeded later. Thus, the evidence which is now available from studies in dogs and in man suggests that the answer to one of the most important questions is favourable. Gastric emptying after HSV is satisfactory.

HSV has been shown by our own group to diminish spontaneous acid output, pentagastrin-stimulated "maximal" acid output, the acid response to insulin and the acid response to a test meal of meat extract as effectively as do truncal or selective vagotomy with a drainage procedure. The findings of Amdrup and his colleagues in Copenhagen were similar[24,26], with the exception that they have not used meat-extract stimulation. The mean

spontaneous acid output and mean acid output in response to 'OXO' solution were considerably less after HSV than after truncal vagotomy and pyloroplasty, and it is possible that these differences will prove to be statistically significant when larger numbers of patients have been tested. The results of these secretory tests, which were performed more than one year after operation, provide good evidence that gastrin release is not excessive after HSV. This deduction is of crucial importance, because if correct it means that vagal denervation of the gastric antrum, as in truncal or selective vagotomy, is not necessary. The theoretical justification for vagal denervation of the antrum is that gastrin release is thereby reduced, and that the patient is thus protected against recurrent ulceration. Recent reports[27-30] of serum gastrin concentration as measured by radioimmunoassay (Tables III and IV) have shown, however, that truncal or selective vagotomy with a drainage procedure produce large increases in serum gastrin concentration: fasting gastrin levels and the gastrin response to a meal are both increased. The increase after truncal vagotomy is significantly greater than after bilateral selective vagotomy[28]. It has also been shown[31] that truncal vagotomy in man does not prevent the increase in serum gastrin concentration

TABLE III

EFFECT OF VAGOTOMY ON SERUM GASTRIN:

(A) CONCENTRATION OF GASTRIN IN SERUM OF FASTING PATIENTS WITH DUODENAL ULCER

(pg per ml.)

REFERENCE	BEFORE OPERATION	AFTER TRUNCAL VAGOTOMY + PYLOROPLASTY		AFTER SELECTIVE VAGOTOMY + PYLOROPLASTY
Korman et al.[27,28]	16 ± 2 (72)	84 ± 8 (50)	significant difference $p < 0.005$	52 ± 6 (30)
Stern and Walsh[29]	65 ± 7 (9)	128 ± 27 (9)		
Trudeau and McGuigan[30]	76 ± 7 (22)	95 ± ? (?)		

Figures in brackets refer to numbers of patients tested.

TABLE IV

EFFECT OF VAGOTOMY ON SERUM GASTRIN:

(B) PEAK GASTRIN CONCENTRATION IN SERUM OF DUODENAL ULCER PATIENTS AFTER A MEAL

(pg per ml.)

REFERENCE	MEAL	BEFORE OPERATION	AFTER TRUNCAL VAGOTOMY + PYLOROPLASTY	AFTER SELECTIV. VAGOTOMY + PYLOROPLASTY
Korman et al.[27,28]	protein meal of steak, cheese and milk	94 ± 16 (5)	259 ± 38 (5)	136 ± 8 (30)
Stern and Walsh[29]	eggs, toast, orange juice	160 ± 15 (9)	363 ± 75 (9)	
Trudeau and McGuigan[30]	180g. beef	129 ± ? (71% increase over fasting levels) (22)	72% increase compared with fasting level of 95 ± ? pg/ml.	

Note also that serum gastrin concentration in response to insulin rose from a mean of 104 to a mean of 148 pg per ml. in 23 D.U. patients before operation, and from a mean of 103 to a mean of 140 pg per ml. in 19 patients after complete truncal vagotomy and pyloroplasty (Stadil, 1972)[31].

Figures in brackets refer to numbers of patients tested.

in response to insulin-hypoglycaemia. Some increase in plasma gastrin concentration is to be expected after any type of vagotomy which involves denervation of the parietal cell mass, because the pH in the antrum may be expected to rise and acid-inhibition of gastrin release will be reduced. This does not explain, however, why gastrin levels should be higher after truncal than after selective vagotomy. Since stasis of food in the antrum does not seem to occur after HSV, one would predict that plasma gastrin levels will not be higher after HSV than after truncal vagotomy with a drainage procedure. Indeed, they might be significantly lower, because HSV should share the advantage which selective vagotomy possesses over truncal vagotomy[28] in this respect, and also because reflux of alkaline duodenal contents containing bile salts[32] onto the antrum should be less after HSV than after vagotomy with a drainage procedure. In support of the latter contention, one would cite evidence from the recent paper by Miller et al.[33] that spontaneous acid output (BAO) was reduced by only 38 per cent in patients who underwent HSV with pyloroplasty, whereas we have found that BAO is reduced by over 90 per cent at a comparable period (six weeks) after HSV without pyloroplasty. Yet "maximal" acid output was reduced by 50 per cent in Miller

et al's. patients, as in ours. From these data, we deduce that HSV may be superior to HSV+P in keeping bile out of the stomach, in maintaining a low intra-antral pH and thus in preserving inhibition of gastrin release by endogenous acid in the antrum.

We found that more than 50 per cent of patients had Hollander-positive responses to insulin, more than one year after HSV, but this is no different from what has been found by others after truncal or selective vagotomy (see Chapter on insulin test). Analysis of the secretory response to insulin reveals no significant difference between the acid outputs after HSV and the acid outputs after truncal or selective vagotomy. Furthermore, it was shown that spontaneous acid outputs and the peak acid responses to insulin were significantly less in patients with positive insulin tests after HSV than in patients with recurrent ulceration and positive insulin tests after truncal or selective vagotomy. Small, but statistically-significant increases in BAO, MAO, and insulin-stimulated acid output took place in the first year after HSV, and though this rise probably comes to an end in the second year (at least so far as MAO is concerned), further serial studies of acid output, three, four and

five years after HSV should be done. The reason for these increases in acid output is not clear. We suggest that they probably represent vagal re-innervation of a small proportion of the parietal cell mass.

In the early stages of our work with HSV, we experimented with the use of antroneurolysis and mucosal antrectomy in dogs, with the aim of reducing gastrin release without diminishing the size of the gastric reservoir or the propulsive power of the antral musculature. However, antroneurolysis was found not to reduce acid output from the main, innervated stomach in the dog, and mucosal antrectomy without suture of the mucosal defect led to chronic gastric ulceration and inanition in two dogs. One patient was treated by HSV combined with mucosal antrectomy, but the operation was technically difficult, and the clinical result achieved was far from perfect. Thus, none of the "conservative" methods of surgical attack on the gastrin mechanism - antroneurolysis, mucosal antrectomy or supra-pyloric antrectomy - seems attractive for use in man. All are likely to impair the function of the antrum as a "mill", and it remains to be proved that they have any additional benefit to offer in recompense, compared with HSV alone. This opinion is supported by the

remarkable paper of Interone et al.[21], who found that HSV alone in dogs gave significantly better protection against histamine-induced ulcer than did SV with antrectomy. Thus, it appeared that State was right[34], and that if the antrum is left undisturbed, in continuity with the acid stream, it gives protection against ulceration, despite the fact that it is the principal source of gastrin.

When we introduced HSV, we suggested that protective and inhibitory mechanisms in the antrum and duodenum would be preserved, whereas after conventional types of surgery for duodenal ulcer they might be impaired. Little evidence has been found in support of such a view. In contrast to our previous observation that fat-induced inhibition of gastric secretion could not be demonstrated in the early weeks after truncal vagotomy and pyloroplasty, we found that, more than one year after truncal vagotomy and pyloroplasty, fat in the duodenum produced significant inhibition of pentagastrin-stimulated gastric acid secretion. The degree of inhibition after truncal vagotomy and pyloroplasty was just as great (39 per cent) as that which was found in patients after HSV (33 per cent). In both groups of vagotomized patients, inhibition was much less than that which was observed in patients with duodenal ulcer before operation (74 per cent). Insulin given

two hours before injection of pentagastrin produced a significant decrease in the acid response to pentagastrin in patients after HSV, but did not produce a significant decrease in patients with intact vagi or in patients after truncal or selective vagotomy with pyloroplasty. Though it is tempting to ascribe the decrease in acid output in patients after HSV to an inhibitory effect of the nerves of Latarjet and of the extra-gastric vagi, such a conclusion would be unjustifiable at present for a variety of reasons. It could be the correct explanation for our findings, however, and further study of the interactions of the vagi and of gastrin or its analogues in these patients seems desirable. Our failure to establish that protective mechanisms are spared by HSV but damaged by other operations does not imply that the original hypothesis was incorrect. Such failure may merely reflect the crudity of our investigative efforts; of our inability, thus far, to measure antral mucus, the secretions of Brunner's glands, bile, and pancreatic secretion after the three types of vagotomy in man. Many years ago, Florey and his colleagues[35] showed that stimulation of the vagus nerves in the cat led to significant stimulation of secretion from the Brunner's gland area, and more recently Wise and Ballinger[36] have reported that vagal stimulation leads to a significant increase

in the output of mucus from the stomach in man. Such mechanisms seem likely to be protective, and are probably destroyed by truncal vagotomy.

The results of the studies on the gall bladder were unexceptional. Truncal vagotomy was found to produce dilatation of the gall bladder, which had been shown many times before. Selective vagotomy did not, as had been reported previously, and HSV likewise was not followed by dilatation of the gall bladder. Contractility of the gall bladder was found to be unimpaired in all three groups of patients. Other workers have provided strong circumstantial evidence that truncal vagotomy may predispose to the formation of gall stones, but firm proof is lacking.

The studies of gastric emptying, dumping and diarrhoea may conveniently be considered together. The operation of HSV was founded on the concept that emptying of fluids from the stomach was excessively rapid after truncal or selective vagotomy with a drainage procedure, and that it would be much better-regulated if the antro-pyloro-duodenal segment were left intact. Hence, the incidence of dumping and diarrhoea would decrease. That is exactly what was found. Gastric emptying was slightly faster after HSV than in pre-operative patients, whereas after truncal

or selective vagotomy with pyloroplasty gastric emptying was very much faster. These findings have been confirmed by others[23,25,37]. HSV was found to provide almost complete protection against diarrhoea, both at the clinical and at the experimental level (when it was provoked by the ingestion of hypertonic glucose solution). Thus, so-called "post-vagotomy" diarrhoea is virtually absent after HSV, whereas it is found in more than 20 per cent of patients after truncal vagotomy with a drainage procedure. HSV also provided significantly better protection against diarrhoea than did selective vagotomy with a drainage procedure. Mild early dumping still occurs on occasion after HSV, probably because of rapid emptying of liquids from the stomach, but its incidence, both clinically and after a provocative glucose drink, was half that which was found in patients who had undergone truncal or selective vagotomy with pyloroplasty.

Dumping after HSV, and also the epigastric fullness after meals which afflicts 25 to 30 per cent of patients after HSV, are both probably due to failure of receptive relaxation by the body of the stomach, with a resulting abnormal increase in intra-gastric pressure after a meal. Obviously, the less of the stomach which is vagally-denervated, the less troublesome will these

symptoms become, but the greater will be the risk of recurrent ulceration. However, if the results of Interone et al's. experiments in dogs[21] are applicable to man; that is, if HSV provides men with better protection against duodenal ulcer than does vagotomy with antrectomy, the vagal denervation involved in HSV represents "overkill", and a lesser degree of vagal denervation of the stomach would suffice. Such a suggestion may appear far-fetched, at a time when HSV is still widely regarded as an experimental procedure which is likely to fail on account of a high incidence of recurrent ulceration. But it should be remembered that Holle has reported a recurrent-ulcer rate of less than one per cent after HSV plus pyloroplasty in 171 patients who were followed for up to seven years, and that Amdrup and I have treated 300 patients with duodenal ulcer by HSV without drainage in the past three-and-a-half years, without encountering a single case of recurrent ulceration. Such figures would be difficult to match after truncal or selective vagotomy with a drainage procedure. Already, de Miguel, Burge and Kennedy have commented that HSV may be an excessively-radical operation (personal communications to the author). If such be the case, how much denervation of the stomach is enough? Should one

tailor the extent of the vagal denervation in proportion to the pre-operative maximal acid output, which gives a measure of the size of the parietal cell mass? It would be interesting to define what degree of vagal denervation of the parietal cell mass in dogs gives a protection against histamine-induced ulcer that is equal to that which is afforded by selective vagotomy plus antrectomy.

The clinical results which have been recorded after HSV in Leeds are much better than those which were found after truncal or selective vagotomy with a drainage procedure. Amdrup's results after HSV are equally satisfactory. We have little doubt that were we willing to subject our patients to a prospective random trial of HSV versus truncal vagotomy and pyloroplasty, HSV would prove to be the better operation. Having shown that HSV possesses significant advantages over truncal vagotomy with pyloroplasty, and having found no advantage for truncal vagotomy and pyloroplasty over HSV, we did not feel justified in carrying out such a trial, but hope that surgeons who at present employ truncal or selective vagotomy with a drainage procedure as their standard method will be prepared to put HSV

to the test of a prospective random trial. If they do so, they must of course be sure that they have acquired an equal facility in the performance of HSV as that which they already possess in respect of the other operation. Whether HSV could be shown to have a significant advantage over partial gastrectomy or vagotomy with antrectomy on a five-to-eight-year follow-up seems doubtful, but if the functional results at that time were approximately equal, HSV would almost certainly be the better operation, because it would be safer, and would produce fewer "gastric cripples" in the long term.

The indications for HSV have been extended cautiously in the past three years. For example, I have treated four patients with perforated duodenal ulcer by HSV. These patients were carefully chosen. They were relatively young, slim and fit, with a long ulcer history, and a short interval between the time of perforation and admission to hospital. In the short term (from four to ten months after HSV) their progress has been excellent. Similarly, I have used HSV in the treatment of seven patients with "X-ray-negative dyspepsia" and very high acid outputs[38,39] (more than 50mEq per hour). Some of them also had giant mucosal folds in the duodenum. The clinical progress of this group has been indistinguishable from that of the patients with duodenal ulcer who were treated by HSV.

In each of these patients I opened the duodenal cap longditudinally, without transecting the pylorus, inspected the interior of the duodenum to make sure that a small ulcer on the posterior wall was not being overlooked, and then closed the duodenotomy longditudinally with fine sutures to achieve edge-to-edge apposition, without inversion. When this is done, there is no need to perform a pyloroplasty. I have opened and closed the duodenal cap in this way in 25 patients, in each of whom convalescence has been uneventful, without evidence of leakage from the duodenum or of gastric retention. This approach has been used to gain access to a bleeding duodenal ulcer in three patients. The ulcer was underrun in the usual way, the duodenotomy closed, and HSV carried out. These patients made a good post-operative recovery and did not re-bleed.

In view of the low incidence of positive responses to insulin soon after HSV, which suggested that the dissection technique used in HSV might be the best method of ensuring that gastric vagotomy was complete, I employed HSV in the treatment of three patients who had recurrent duodenal ulceration and strongly-positive insulin tests after truncal vagotomy and pyloroplasty. If a complete vagotomy of the stomach,including the antrum, resulted, that would not matter, since the presence of the pyloroplasty would protect

against gastric stasis. Technically, these cases proved a little difficult because the under surface of the liver was adherent to the lesser omentum, the lesser curvature of the stomach and the cardia, but when the plane of dissection between lesser omentum and stomach was found, the remainder of the operation was straightforward. In each of these patients, the early-positive response to insulin was converted to negative in the early post-operative period, and the patients themselves are doing well in the short term.

The most interesting application of HSV, however, has been in the treatment of patients with pyloric stenosis. This diagnosis encompasses patients who have a vast, atonic, dilated stomach hanging down into the pelvis, associated with copious vomiting and dehydration. Obviously, to treat such patients by HSV would be folly. On the other hand, in many patients the obstruction to the gastric outlet is partly attributable to oedema and spasm associated with an active ulcer. When such patients are treated by rest in bed and other medical measures, they usually stop vomiting, the succussion splash can no longer be elicited, and they are again able to eat heartily. On barium meal examination, they are found to have gross deformity of the pyloro-duodenal region, with a stomach that is not greatly dilated and a hyper-motile antrum.

The stomach has "compensated" for partial obstruction of its outlet by undergoing hypertrophy, and by "pushing harder". In the past year, I have treated six such patients by HSV without a drainage procedure. At the time of operation, a finger was introduced via a small gastrotomy into the pyloro-duodenal canal, which was always found to be narrowed, and would not admit the finger-tip, nor a Hegar's dilator greater than no. 6 in size, whereas in 24 patients with duodenal ulcer without symptoms of pyloric stenosis, it has always been possible to pass the index finger beyond the distal inter-phalangeal joint or a number 14 Hegar dilator through the pylorus and first part of the duodenum. These findings are in accord with the previous observations of Kirk[16]. The stenotic segment was then forcibly but gently dilated until the index finger beyond the proximal inter-phalangeal joint could be passed through the narrowed area. The site of the stenosis was usually half to one inch distal to the pyloric ring. In two patients this manoeuvre caused splitting and anterior perforation of the first part of the duodenum. The perforation was sutured transversely with interrupted catgut sutures. After this HSV plus "sphincter stretch", all six patients convalesced normally. Follow-up ranges from three to ten months, and the patients' progress continues to be satisfactory.

The obvious objection to such a method of treatment is that re-stenosis might take place as the ulcer heals, but so far this has not happened. Barium meal examinations performed more than four months after operation in three of these patients revealed no evidence of gastric retention or of recurrent ulceration.

At the technical level, HSV is a straight forward, if somewhat tedious, operation, which takes us about twenty minutes longer to perform than does a truncal vagotomy and pyloroplasty. Having taken careful note of the position of the anterior nerve of Latarjet at laparotomy in 200 patients, and of the position of the posterior nerve of Latarjet in the course of 150 HSV operations, we can state with confidence that the course of these nerves is constant, although there are minor variations in the way in which the terminal branches are distributed to the antral region of the stomach. The anterior nerve of Latarjet is plainly visible in over 90 per cent of cases, and usually two or more major terminal branches cross onto the gastric wall just beyond the incisura angularis, 5 to 7 centimetres proximal to the pylorus (see Frontispiece). The posterior nerve of Latarjet is more difficult to see, even after the greater curvature of the stomach has been mobilised by division of the gastro-colic omentum, but its

major terminal branches are usually clearly visible.

Whether the extent of the antrum should be "mapped" routinely at the time of operation is debatable. My own opinion is that it should not, because to do so makes an already lengthy operation even longer, the Congo-Red test does not invariably give a clear-cut demarcation between corpus and antrum (at least within my limited experience of ten tests in man), and, most important, the clinical value of the test has not been established. In Copenhagen, where antral mapping is the rule, Amdrup records clinical results, and decreases in gastric acid output, which are little different from those which we find in Leeds. If the test shows the parietal cell mass to extend close to the pylorus, should the nerves of Latarjet then be cut? I think not, because by so doing one would expose the patient to the risk of developing gastric retention and gastric ulceration. If, on the other hand, "mapping" shows that the antrum is unusually extensive, does it matter if its proximal margin is denervated? Again, I would doubt it. Of far greater importance, in my opinion, is the idea that the gastric vagal denervation of HSV may be more than is required to heal the ulcer. We must attempt to find out how little of the stomach has to be denervated.

The stomach, duodenum, biliary tract and pancreas normally work together in harmony, their activities being co-ordinated by nerves and hormones. We have learned a great deal about the actions and interactions of these nerves and hormones in the course of the past ten years, and have marvelled at their intricacy. We have also been shown the depths of our former ignorance about the physiology of this region which we operate upon in the course of our daily work. And it is quite certain than when ten more years have passed, we will have to admit how ignorant we were in 1972, in that field of human endeavour in which we now consider ourselves to be expert. For this reason it is incumbent upon us to follow unswervingly that old maxim "primum non nocere". No structure, no function, should be sacrificed unnecessarily.

In line with this philosophy, we think that in surgery for duodenal ulcer the surgical attack should be confined to the stomach. Those who continue to advocate the use of truncal vagotomy should be asked to <u>prove</u> that vagal denervation of the biliary tract, pancreas and small intestine in some way benefits the patient. Surgeons should reconsider the advisability of denervating the antrum of the stomach, which does produce gastric stasis, but which

does not appear to diminish the release of gastrin. Both truncal and selective vagotomy impair gastric emptying and make necessary the performance of a drainage procedure, which in turn leads to unduly-rapid gastric emptying; to dumping, diarrhoea and steatorrhoea. For the first time in the history of surgery for peptic ulcer, it has been shown that the pylorus can be left intact and that the stomach can be induced to empty in a well-regulated manner. Side-effects have thus been reduced. When vagotomy is confined to the parietal cell mass, acid output is reduced as effectively as by conventional types of vagotomy. There is no evidence of excessive release of gastrin from the innervated antrum. Longer follow-up of the patients who have already been treated, and prospective random trials of HSV, are certainly required. Meanwhile, there is reason to believe that highly selective vagotomy without a drainage procedure is the best operation yet devised for the treatment of duodenal ulcer in man.

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