

A social worker questioned 1,200 patients with notified respiratory tuberculosis about their present and past smoking habits: 766 were interviewed at the Birmingham Chest Clinic and 434 in the three principal Birmingham sanatoria. The same worker interviewed as controls 588 patients attending the Birmingham Accident Hospital with minor injuries and 391 patients occupying beds in the surgical wards of a large non-teaching hospital in Birmingham.

In both sexes patients of over 30 years of age with respiratory tuberculosis showed a highly significant deficiency of non-smokers and light smokers and an excess of moderate and heavy smokers when compared with the controls. It seems unlikely that this difference is due to a bias in choice of patients and controls or to the method of comparison.

From this and from certain other considerations it is suggested that smoking may be an important cause of the breakdown of healed or quiescent respiratory tuberculosis in adults and may account for a considerable part of the excessive male mortality in middle and late life.

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LATE RESULTS OF VAGOTOMY COMBINED WITH GASTRO-JEJUNOSTOMY OR PYLOROPLASTY IN THE TREATMENT OF DUODENAL ULCERATION

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Sedation, diet, antacids, and antispasmodics have long been accepted in the medical treatment of duodenal ulceration. There is, however, no equivalent unanimous surgical opinion regarding the most satisfactory operative procedure, for the functional result achieved has to be evaluated in conjunction with the incidence of recurrent or stomal ulceration.

Vagal nerve section, reintroduced by Dragstedt *et al.* (1944), soon fell into disrepute for duodenal ulceration because of the high incidence of gastric retention, with all its sequelae, which followed this operation. The addition of gastro-jejunostomy or pyloroplasty as a simultaneous procedure has materially diminished the frequency of this delay in stomach emptying. Nevertheless, both these gastric drainage procedures have complications peculiar to themselves. Particularly is this so with gastro-jejunostomy, in which both the

liability of the stomach region to peptic ulceration and also the production of symptoms by mechanical factors or by the regurgitation of duodenal juice have long been appreciated.

Present Series

In this paper are embodied the results of an analysis of 366 cases of chronic duodenal ulceration treated by vagotomy combined with either gastro-jejunostomy or pyloroplasty. The length of time post-operatively has been five years or longer in most cases. The series consists of consecutive cases drawn from several surgical centres in this country. In this way it is thought to be representative of the overall late results obtained in current surgical practice by these operations.

Out of this complete group, 22 (6%) patients had died from causes unconnected with their duodenal ulceration, and 14 (3.8%) have been lost, leaving 330 (297 males, 33 females) for study. In all cases section of the vagi was performed transabdominally, the nerves being exposed on the lower oesophagus after mobilization of the left lobe of the liver. Pyloroplasty was carried out in most cases by the method of Heineke-Mikulicz, which consists of enlargement of the pyloric opening by an incision parallel to the long axis of the stomach and closure of this by suture at right angles to the original incision. In other patients the method of combined pyloroplasty and pylorotomy advocated by Beattie (1950) was employed. All operations were elective, none being for the emergency treatment of haemorrhage or perforation. In all cases the clinical and radiological diagnosis of duodenal ulceration was confirmed at operation.

Follow-up has been by personal visit to the patient's home in 37 cases (10.2%), out-patient review of 120 cases (36.4%), and by questionnaire in 173 cases (53.4%). The questionnaire covered the following points: (a) the extent of the patient's satisfaction with the operative result; (b) any return of ulcer pain; (c) any further stomach operations; (d) any post-operative haematemesis or melaena; (e) a survey of the possible post-operative symptoms; and (f) weight gain or loss since operation. In any case where there was doubt the patient was seen or the position made clear by further correspondence.

The length of time since operation was four years in 52 (15.8%) cases, five years in 219 (66.4%), six years in 51 (15.4%), and seven years in 8 (2.4%).

The operative procedure in 198 cases (60%) was vagotomy and gastro-jejunostomy, and in 132 cases (40%) it was vagotomy and pyloroplasty.

Clinical Results

The results of the review have been classified in general accordance with the method of Visick (1948). Separation has been made into the following groups:

Grade I: Patients Who are Completely Symptom-free.—There were 167 cases (50.6%) in this grade. With the complete absence of subjective or objective troubles, the excellence of the result obtained leaves nothing to discuss.

Grade II: Patients Who Have Mild Symptoms which Cause No Disability.—There were 113 cases (34.2%) in this grade. It must be emphasized that the symptoms complained of were minor and did not detract from the good operative result, either in the patients' or the reviewer's opinion. They occurred so infrequently in the majority that it was only the rigid adherence to the complete absence of symptoms necessary for classification in grade I that prevented their inclusion in this latter grade. The complaints were of

occasional looseness of stool, attacks of weakness or faintness, flatulence, fullness, and biliary regurgitation or vomiting.

Grade III S: Patients Who Have Moderate Symptoms not Relieved by Care, but Who are Improved Symptomatically and Clinically by the Operation.—There were 19 cases (5.8%) in this grade. Their complaints were analysed as follows:

1. General physical condition poor from congestive heart failure and carcinoma of the prostate respectively, with consequent symptoms overshadowing satisfactory operative result, 2 cases.
2. Moderate dyspeptic symptoms, but no ulcer pain and no evidence of recurrent ulceration, 6 cases.
3. Moderate dyspeptic symptoms, but no ulcer pain and no evidence of recurrent ulceration, but with functional overlay and under psychiatric care, 6 cases.
4. One past attack of ulcer pain after vagotomy but no recurrent ulceration found on investigation then and symptom-free since, 5 cases.

The attack of ulcer type pain suffered by five patients was thought to have been associated with minor stomal ulceration with spontaneous healing, for in each of these patients the stomach drainage operation had been gastro-jejunostomy. The difficulty of achieving complete symptomatic cure in patients who enjoy their disabilities or who have personality disorders is well exemplified in this grade.

Grade III U: Patients Who Have Moderate Symptoms not Relieved by Care and in Whom the Clinical Result is Unsatisfactory.—There were 11 cases (3.3%) in this grade. Their complaints were analysed as follows:

1. Many severe dyspeptic symptoms but no clinical or radiological evidence of recurrent ulceration, 2 cases. These two patients had radiological evidence of gastric retention as shown by a six-hour delay in stomach emptying after a barium meal. This delay in both cases followed vagotomy and pyloroplasty.
2. Symptoms of recurrent ulceration present at all times but radiological or gastroscopic proof unobtainable, 4 cases. These four patients had had vagotomy and gastro-jejunostomy performed. Three presented with ulcer pain and the fourth had had two bouts of haematemesis and melaena. Although proof of recurrent ulceration could not be obtained, it was felt from the extent of the symptoms that sooner or later the presence of such ulceration would be confirmed in these cases.
3. Troublesome diarrhoea, 5 cases. There was barium-meal evidence of delay in stomach emptying in one of these cases.

Grade IV: Patients Not Improved by Operation.—There were 20 cases (6.1%) in this grade. They were subdivided as follows:

1. Recurrent duodenal ulceration, 4 cases. This had been proved in each case at the further operative procedure required. The primary gastric drainage operation in each case was pyloroplasty. The presenting symptom common to all was ulcer pain, and all had radiological evidence of active duodenal ulceration, with marked duodenal stenosis in two. All four cases had had a subsequent partial gastrectomy.
2. Anastomosis ulceration, 5 cases. Ulcer pain was present in all five patients. One had perforated a stomal ulcer in America and had had a simple suture performed, but has since been untraceable. One man had had repeated haematemeses, had not been operated on, and had died four years later from unconnected causes. The remaining three had each had an elective partial gastrectomy performed.
3. Gastric ulceration, 4 cases. In two of these patients, in addition to the presence of lesser-curve ulceration at the angulus, there was coexistent barium-meal evidence of delay in stomach emptying due to duodenal stenosis from pyloroplasty failure. These patients presented with ulcer pain. The third patient was averred to have had a high lesser-curve ulcer found on routine barium-meal examination. He was symptom-free at that time and had been so ever since his primary procedure of vagotomy and gastro-jejunostomy. No further operation had been undertaken in his case and no further investigation was possible. The fourth patient developed a gastric ulcer at the angulus seven years after vagotomy and short-circuit, and presented with ulcer pain.
4. "Gastric cripples," 4 cases. All these had had subsequent partial gastrectomy, but in none of them had any evidence of recurrent ulceration been found, although two had multiple adhesions. One of these patients died from peritonitis following his partial gastrectomy. No improvement in the many symptoms

of the remainder had resulted from partial gastrectomy. One had had a further entero-anastomosis performed and then a further division of adhesions, and still had multiple symptoms.

5. Successful partial gastrectomy for ulcer type of pain but ulcer not confirmed at operation, 3 cases. One patient had pain after food and was tender over the duodenum. At laparotomy he was found to have a stitch abscess associated with unabsorbable suture material used for repairing the duodenum at his original pyloroplasty. The second patient had had ulcer type of pain after food for three years following vagotomy and pyloroplasty, but the absence of active peptic ulceration was confirmed at partial gastrectomy. The third patient with pain after food had developed a stenosis at the pyloroplasty stoma, and was also treated by partial gastrectomy, no active duodenal ulceration being found at this operation. All have subsequently remained well.

Patients in grades I, II, and III S have been regarded as having a satisfactory clinical result, and patients in grades III U and IV as having an unsatisfactory clinical result. The result of this classification, when applied to the whole series, is shown in Table I.

TABLE I.—Grading of Whole Series

Grade		No. of Patients
I	167 (50.6%)
II	113 (34.2%)
III S	19 (5.8%)
Total satisfactory	299 (90.6%)
III U	11 (3.3%)
IV	20 (6.1%)
Total unsatisfactory	31 (9.4%)

Sex in Relation to Clinical Result

There is no difference between the results obtained in males and in females, for, as is shown in Table II, satisfactory results were achieved in 90.2% of males, as compared with 93.9% females, and unsatisfactory results occurred in 9.8% of males, as compared with 6% of females. Allowing for the small size of the female group (33 cases), the small differences in these findings are not significant.

TABLE II.—Sex in Relation to Clinical Result

Grade	Males	Females
I	150 (50.5%)	17 (51.5%)
II	104 (35.0%)	9 (27.3%)
III S	14 (4.7%)	5 (15.1%)
Total satisfactory	268 (90.2%)	31 (93.9%)
III U	11 (3.7%)	0 (0%)
IV	18 (6.1%)	2 (6%)
Total unsatisfactory	29 (9.8%)	2 (6%)

Post-operative Nutrition

All patients were questioned regarding any change in their weight since operation. It was clear that in the majority of patients their weight had returned to normal and had remained steady. Clinical observation confirmed this most strongly, and patients' satisfaction in their ability to eat normal-sized meals was often reflected in their resumption of heavy industrial or mining work, where high calorie intake was essential.

Thus 214 (65%) were keeping to a steady normal weight and 72 (21.8%) had gained weight well, a total of 286 (86.8%) with a satisfactory nutritional result. Minor weight loss had occurred in 27 (8.2%) and considerable loss in 5 (1.5%). This last group of five patients were all graded as unsatisfactory in the general result classification because of their post-operative symptomatology. Thus all patients with weight loss totalled only 32 (9.7%). No information was available concerning the weight of 12 patients.

It is appropriate to compare these figures with weight levels after partial gastrectomy. Ivy, Grossman, and Bachrach (1950) reviewed 864 patients, made up of six series, treated by this operation. They found that the post-

operative weights remained steady or increased in 53% and decreased in 47%. Thus even with any other relevant factors excluded, there appears to be significant evidence that weight maintenance after vagotomy and a gastric drainage operation is more generally satisfactory than after partial gastrectomy.

General Analysis of Post-operative Symptoms

Diarrhoea.—Seventy-four patients in the series complained of loose stools or diarrhoea, an incidence of 22.5%. It was not considered troublesome by 64 (19.4%), and of these 40 stated that they only passed loose stools intermittently, periods of normality of a month or more being usual. On the other hand, 10 (3%) complained of troublesome diarrhoea, but in only three of these was there radiological evidence of delay in stomach emptying.

Flatulence.—Increased flatulence compared with their pre-operative condition was complained of by 67 patients (20.4%). Of the three who found it worrying or severe, two were air swallows. In the third case foul eructations were associated with proved gastric retention. There was radiological evidence of gastric delay in one further mild case. Thirty-three of these patients also complained of occasional diarrhoea.

Biliary Regurgitation or Vomiting.—Occasional biliary regurgitation or vomiting occurred in 44 cases (13.4%). It was generally infrequent or mild, although in nine cases it was accompanied by other post-operative symptoms to an extent sufficient for them to be classified in grade III S. In only one case, following upon a vagotomy and gastro-jejunostomy, was biliary vomiting severe enough to warrant further operation. This man was not improved by subsequent partial gastrectomy and a later entero-anastomosis.

Hypoglycaemic Attacks.—Mild occasional hypoglycaemic attacks were not uncommon following both vagotomy and gastro-jejunostomy (18 patients) and vagotomy and pyloroplasty (27 patients), making a total of 45 cases (13.6%) with this complaint. The attacks occurred typically one to three hours after food; they were characterized by a feeling of weakness or faintness, sometimes accompanied by sweating, and were rapidly relieved by food or a sweet drink. Patients stated that the frequency and severity of these attacks had diminished as time had passed following their operation, and none found them distressing at the time of review.

Other Post-operative Side-effects.—Undue fullness after food was difficult to evaluate as a subjective symptom. It occurred to a significant extent in 10 patients (3%), and only two of these had lost weight post-operatively. There was evidence of coexistent gastric stasis in 3 of these 10 cases. Only one patient complained of symptoms of a typical immediate postprandial "dumping" syndrome, and this followed vagotomy and gastro-jejunostomy.

Post-operative Gastric Retention

Barium-meal examination showed a delay of six hours or longer in stomach emptying in eight patients. They had all had vagotomy and pyloroplasty. Gastric retention did not occur among the group in which vagotomy and gastro-jejunostomy had been carried out. In five patients inadequacy of the pyloroplasty outlet was the cause of the delay in emptying. In two cases recurrent duodenal ulceration with stenosis had occurred. The last case had pylorospasm and obstruction from a gastric ulcer at the angulus with surrounding oedema.

An organic obstruction lesion was present in all these cases of delay in stomach emptying. All presented at periods longer than one year after vagal section. It may be that partial loss of stomach motor function may render almost impassable a degree of pyloro-duodenal stenosis which could be easily overcome by a stomach possessing normal motor power. Thus even if only a minor diminution in stomach tone and peristalsis is likely, the provision of a stomach outlet which remains permanently widely patent is essential.

Recurrent Peptic Ulceration

The site of a recurrent ulceration in the 13 (3.9%) proved cases is shown in Table III, together with a possible explanation for each recurrence. Six (4.5%) followed

TABLE III.—Sites of Recurrent Ulceration

Case	Operation	Site of Recurrence	Vagal Section	Reason for Recurrence
1	V. and P.	D.U.	Incomplete	Incomplete vagotomy
2	"	"	"	"
3	"	"	"	"
4	"	"	"	"
5	"	G.U. at angulus	"	Duodenal stenosis, and inc. vagotomy
6	"	"	"	"
7	V. and G.J.	G.J.U.	"	Incomplete vagotomy
8	"	"	"	"
9	"	"	"	"
10	"	"	"	"
11	"	"	Unknown	Unknown
12	"	G.U.	"	"
13	"	G.U. at angulus	Complete	"

V. and P.=vagotomy and pyloroplasty. V. and G.J.=vagotomy and gastro-jejunostomy. D.U.=duodenal ulcer. G.U.=gastric ulcer. G.J.U.=gastro-jejunal ulcer.

vagotomy and pyloroplasty, four being duodenal ulcers and two being gastric ulcers, and seven (3.5%) followed vagotomy and gastro-jejunostomy, five being gastro-jejunal ulcers and two being gastric ulcers.

In addition to the proved cases there were four other patients (graded III U) whose symptoms of pain or bleeding following vagotomy and gastro-jejunostomy were such as to warrant a presumptive diagnosis of gastro-jejunal ulceration despite negative radiological or gastroscopic findings. If these patients are included, then the proved and presumed recurrence rate totals 5.1% in the whole series and 5.6% following vagotomy and gastro-jejunostomy.

The number of years after operation at which these ulcers occurred is shown in Table IV.

TABLE IV.—Time of Recurrence After Operation

Time in Years of Recurrence after Vagotomy	Site and No. of Ulcers	Total
0-	2 G.J.U.; 1 D.U.	3
1-	3 G.J.U.; 1 D.U.; 1 G.U.	5
2-	1 D.U.	1
3-	1 G.U.	1
4-	1 D.U.	1
5-	1 G.U.	1
6-7	1 G.U.	1

The following points of importance arise: (1) Proved recurrent duodenal ulceration occurred only after vagotomy and pyloroplasty, and its incidence was evenly divided through a five-year follow-up period. (2) Proved gastro-jejunal ulceration, occurring after vagotomy and short-circuit, presented only during the first two post-operative years. (3) There was insulin-test-meal evidence of incomplete vagotomy in eight out of the nine patients with proved anastomotic or recurrent duodenal ulceration. A test-meal examination could not be performed in the remaining case. (4) Gross delay in stomach emptying occurred in two of the four cases in which gastric ulceration had taken place. (5) There is no statistical difference between the total recurrence rate of 5.6% following vagotomy and short-circuit, and that of 4.5% following vagotomy and pyloroplasty (standard error=2.4).

Operative Mortality

Table V is an analysis of the five (1.5%) deaths directly associated with the operative procedure.

One of the deaths from uncontrollable diarrhoea was proved at necropsy to be due to an enteritis severe enough to have caused sloughing of the mucosa of the small bowel. Similar cases, but occurring after partial gastrectomy, have been reported by Williams and Pullan (1953).

TABLE V.—Operative Deaths

	Operation	Survival	Cause of Death
1	V. and P.	3 days	Peritonitis—leak from pyloroplasty
2	"	10 "	"
3	V. and G.J.	4 "	Severe diarrhoea "
4	"	5 "	"
5	"	6 "	Uraemia—renal failure

Comparison between Gastro-jejunostomy and Pyloroplasty as Stomach Drainage Procedures

Table VI shows the respective gradings and the extent of the post-operative complications arising in the 198 patients who had gastro-jejunostomy combined with vagotomy, and in the 132 patients who had pyloroplasty combined with

TABLE VI.—Comparison of Results and Symptoms After Vagotomy and Gastro-jejunostomy With Those After Vagotomy and Pyloroplasty

	Vagotomy and Gastro-jejunostomy	Vagotomy and Pyloroplasty	Standard Error
Total No.	198 (60%)	132 (40%)	—
Satisfactory results	183 (92.4%)	116 (87.9%)	4.5/3.2
Unsatisfactory results	15 (7.6%)	16 (12.1%)	4.5/3.2
Grade I	105 (53%)	62 (47%)	6.0/5.6
" II	65 (32.8%)	48 (36.4%)	3.6/5.6
" III S	13 (6.6%)	6 (4.5%)	2.1/2.6
" III U	7 (3.5%)	4 (3.0%)	0.5/2.0
" V	8 (4.0%)	12 (9.1%)	5.1/2.5
Recurrent ulceration	11 (5.6%)	6 (4.5%)	1.1/2.4
Gastric retention	0	8 (6.0%)	6.0/1.7
Diarrhoea	37 (19%)	37 (28%)	9/4.7
Biliary regurgitation	28 (14%)	16 (12%)	2/3.8
Flatulence	29 (15%)	24 (18%)	3/4.1
Hypoglycaemic attacks	18 (9.1%)	27 (20%)	9/3.8
Operative mortality	3 (1.5%)	2 (1.5%)	—

The standard error is expressed as the ratio of the difference in percentage to the standard error between proportions.

vagotomy. Allowing twice the standard error as a measure of significance, it is clear that the only definite statistically significant differences between the results of these procedures were : (1) There was a higher number of patients not improved by vagotomy and pyloroplasty (9.1%), and thus placed in grade IV, than there were after vagotomy and gastro-jejunostomy (4%). (2) There was a marked incidence of gastric retention following pyloroplasty, 8 cases (6%) occurring, as opposed to the absence of this complication following gastro-jejunostomy. (3) The incidence of hypoglycaemic attacks was higher following pyloroplasty (20%) than after gastro-jejunostomy (11%).

Insulin-test-meal Findings

Adequate records of post-vagotomy insulin test meals were available in only 87 cases. Separation into complete and incomplete vagotomy was made by the criteria of Hollander (1946, 1948). This separation revealed that no fewer than 26 (29.8%) of these 87 cases had insulin test meals showing marked response to hypoglycaemia with very high levels of free acid. These figures do not represent the correct incidence of incomplete vagotomy as a whole, since insulin test meals had sometimes been carried out only when recurrence of ulcer symptoms suggested that vagal section had not reduced free acidity down to a safe level. The seriousness of failing to achieve adequate vagal section is emphasized by anastomotic or recurrent duodenal ulceration developing in 8 (30%) of these 26 cases.

A review of the test meals from one surgical centre, where satisfactory results were available from 62 out of 102 consecutive patients, disclosed that 17 had clear evidence of incomplete vagal section. Thus the incidence of incomplete vagotomy for this hospital lies somewhere between 16.6% and 27.4%.

No case of anastomotic or recurrent duodenal ulceration was found among those patients who had insulin-test-meal evidence of complete vagal section.

Comparison with other Surgical Procedures

Recurrent Ulceration

When simple gastro-jejunostomy headed the surgical field in duodenal ulceration it was clear that pyloroplasty, as a sole procedure, had no place in operative treatment. Even in 1906 Paterson recorded a relapse rate of 54% in 22 cases reviewed. Presumably, therefore, success from vagotomy and pyloroplasty depends on the vagal nerve section. Douglas (1947) found stomal ulceration in 27.1% of 37 cases in which simple gastro-enterostomy was performed for duodenal ulceration without stenosis. Tanner (1952) thought that there was a 30% risk of stomal ulceration in such cases.

Anastomotic ulceration after Polya type partial gastrectomy for duodenal ulceration may be as low as the figure of 0.25% quoted by Pulvertaft (1952), reviewing 458 of Visick's cases, but in his operations the level of gastric section was very high. It is probably true to say that the more radical is the gastrectomy, the more rare is recurrent ulceration, but the higher is the incidence of post-operative symptoms. The figure of 5.1% for recurrent ulceration after this operation quoted by Ivy *et al.* (1950) may well be taken as the expected upper limit.

It has been shown that the proved recurrence rate after vagotomy and gastro-jejunostomy in the present series was 3.5% and that there was an additional presumed recurrence rate of 2.1%, making a total of 5.6%. Crile (1952) reported a recurrence rate of 5% following vagotomy and gastro-jejunostomy in 140 cases, and Hoerr (1953) a recurrence rate of 8% in 146 cases. In more recent papers on the results of vagotomy and short-circuit in duodenal ulceration, Bennett-Jones and O'Domhnaill (1955) reported 7.4% recurrences out of 95 cases followed from four to six years. Holt and Robinson (1955) gave an incidence of 2.7% in 110 of their patients followed for three years. The much higher figure of 12.4% recurrences has been found by Henson and Rob (1955) in 89 of their patients up to 29 months after operation.

With the exception of this last series, there would therefore appear to be only a slightly higher rate of recurrent ulceration following vagotomy and gastro-jejunostomy, when compared with that which would be accepted with equanimity by some surgeons after Polya partial gastrectomy. However, with regard to the series on which this paper is based, it is possible that there may be a further small incidence of recurrence as the years go by. Therefore it may well be that a ten-year follow-up of these patients may disclose further occasional failures. Nevertheless, this figure is not likely to be large, for, as Guy *et al.* (1953) have shown, the great majority of such unsatisfactory results become apparent within the first two years after operation.

The reports of Wilkins (1953) and Weinberg (1954) do not give sufficient long-term data on recurrence after vagotomy and pyloroplasty for their figures to be comparable. In the present series the recurrence after this operation was 4.5%, and this, as previously stated, is not statistically different from that following vagotomy and short-circuit.

Relief of Symptoms

There are no recent long-term evaluations of the results of the Billroth I operation for duodenal ulceration. This procedure is thought by Moloney (1954) to be better than Polya gastrectomy because the loss of weight is not so marked and symptomatic complaints tend to wear off.

Although it might appear from the findings presented earlier in this paper that cases after vagotomy and gastro-jejunostomy or pyloroplasty show a considerable incidence of minor post-operative symptoms, Ivy *et al.* (1950) found that of the 475 cases after Polya type partial gastrectomy where information was available only 46.3% were symptom-free. There is no significant difference between this figure and that of 53% found symptom-free following vagotomy and short-circuit and of the 47% similarly graded after vagotomy and pyloroplasty in the present series.

If those symptoms associated with gastric retention and recurrent ulceration are excluded, a review of the present series shows that complaints after vagotomy and an adequate gastric drainage operation tend to be relatively minor, and do not approach in severity or disablement the syndromes that sometimes follow partial gastrectomy.

Operative Mortality

The mortality rate following partial gastrectomy performed by experts is now low, for Hosford (1949) reported a death rate of 0.5% in 200 consecutive cases, while Goligher and Riley (1952) thought that a figure of 2% to 3% might be regarded as a fair estimate of the operative risk of death. Johnson and Orr (1953) suggested that up to 4% may generally be accepted as the average mortality rate following this operation.

Crile (1952) has reported 2 (0.4%) operative deaths among 445 patients undergoing vagotomy and gastro-jejunostomy, and Hoerr (1953) 0.5% deaths in patients in whom this procedure was performed, while the figure in the series under review is 1.5%.

It thus appears that there is a lower operative risk for vagotomy and gastro-jejunostomy than for partial gastrectomy.

Conclusions

This review indicates that in a gratifyingly large proportion of cases complete vagotomy combined with an adequate gastric drainage operation is followed by a lasting cure of duodenal ulceration.

The finding of statistically similar figures for recurrent ulceration following vagotomy and gastro-jejunostomy (5.6%) and vagotomy and pyloroplasty (4.5%) suggests that recurrence does not depend upon the type of gastric drainage employed but upon the completeness of vagal section. Support for this contention comes from the insulin-test-meal evidence of incomplete vagotomy found in all those cases of anastomotic or recurrent ulceration where the results of this investigation have been available. Nor has recurrent ulceration been found when vagotomy has been complete. Therefore it can only be presumed that the high recurrence rates reported in some series may be closely related to the incompleteness of vagal section. It is therefore of considerable importance that a surgical technique should be employed which is most likely to ensure complete division of the vagal nerves. The anatomical and operative considerations of Chamberlin and Winship (1947), Dragstedt *et al.* (1947), and Jackson (1949) are particularly valuable in this respect.

An additional incidence of 2.1% of presumed though unproved recurrent ulceration after vagotomy and gastro-jejunostomy raises the recurrent rate for this operation to 5.6% and the total rate in the whole series to 5.1%. This figure is not regarded as being at a prohibitive level, although it is higher than that generally achieved by Polya type subtotal partial gastrectomy. It must be remembered, however, that after vagotomy and a gastric drainage procedure there may also be a further incidence of recurrent ulceration as the years after operation pass by. Elucidation of the final figures for recurrence after these operations must therefore be deferred until at least a 10-year follow-up can be made of patients so treated.

The 6% incidence of gastric retention after vagotomy and pyloroplasty, as opposed to the absence of this complication following vagotomy and gastro-jejunostomy, would indicate that pyloroplasty cannot be relied upon as a gastric drainage procedure. It has also been found that post-operative symptoms after vagotomy and pyloroplasty are relatively more common than after vagotomy and gastro-jejunostomy. For

these reasons vagotomy and pyloroplasty cannot be supported as a procedure for general elective use in duodenal ulceration.

When the post-operative symptoms are considered, the absence of severe postprandial "dumping" phenomena must be emphasized. Moreover, while the incidence of biliary regurgitation (14%), diarrhoea (19%), flatulence (15%), and hypoglycaemic attacks (11%) after vagotomy and gastro-jejunostomy is not small, these symptoms were commonly minor and infrequent. Although direct comparison of symptoms with those occurring after partial gastrectomy is not easy, the figure of 92.4% for clinically satisfactory results after vagotomy and gastro-jejunostomy is similar to that generally quoted for Polya type partial gastric resection. Furthermore, the numbers of patients completely symptom-free after either of these two operations correspond closely.

In some important respects, however, the results of vagotomy combined with a proper gastric drainage operation would appear to be better than those of Polya type partial gastrectomy. Particularly is this so from the viewpoint of post-operative nutrition.

Additionally, the data shown in Table II indicate that the clinical results achieved in the series are as satisfactory in women as they are in men. Finally, the evidence shows that vagotomy combined with gastro-jejunostomy or pyloroplasty has a lower operative mortality rate than Polya partial gastrectomy.

Thus for the present the increased risk of recurrence would seem to preclude the general adoption of vagotomy and gastro-jejunostomy as the elective procedure of choice in chronic duodenal ulceration. The incidence of recurrent ulceration found in the present review is not high enough, however, completely to contraindicate this operation, and there is also evidence to suggest that the late recurrent rate is unlikely to be large.

It is felt, therefore, that the clear advantages that have been described merit its employment in certain selected cases. Thus when elective surgery is necessary in the treatment of duodenal ulceration, vagotomy and gastro-jejunostomy seems to be indicated when it is essential that the post-operative calorie intake be high, as in patients who perform heavy physical work or who have pulmonary tuberculosis. Moreover, the satisfactory results obtained in women would favour its adoption in females in preference to subtotal gastric resection, in view of the disappointing clinical results which this latter operation often gives in this sex. Finally, the lower mortality rate also supports the use of vagotomy and gastro-jejunostomy in old or poor-risk patients.

The final decision whether the better clinical results of vagotomy and gastro-jejunostomy in these cases justify its general use in the surgical management of duodenal ulceration must, however, await the determination of the true recurrence rate of this procedure.

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SOME NEW ASPECTS OF THE ACTION OF MORPHINE-LIKE ANALGESICS*

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In 1941 Krueger, Eddy, and Sumwalt published a review on the pharmacology of morphine and summarized the world literature on this subject. It was an admirable achievement. They collected the evidence from more than 9,000 publications and condensed it into a volume of 800 pages. Considering that the analgesic action of morphine is by far the most important of its effects, it is surprising that only 9 of these 800 pages were concerned with analgesia and that only 30 of the 9,000 references dealt with its experimental investigation. More than 99% of the work was devoted to the so-called side-effects.

There is a simple explanation for this strange disproportion. Until 1939 morphine and some of its derivatives, such as heroin, "dilaudid" (dihydromorphinone hydrochloride), and "eukodal," were our only powerful weapons in the struggle against pain. The clinical experience with these drugs was sufficient to evaluate their analgesic potencies. The mechanism of analgesia was explained by the rather vague assumption of an action on the central nervous system. In their review Krueger *et al.* wrote: "Analgesic action is predominantly central, though recent work advocates a peripheral component. Its site and mechanism have not been determined. Nor has the mechanism of narcotic action been ascertained." This statement was made in 1941.

Measuring Analgesic Potency

After the discovery of synthetic substitutes for morphine much more work was devoted to the study of analgesia. Between 1939 and 1942, after the discovery of pethidine (Eisleb and Schaumann, 1939), innumerable substances have been synthesized in the laboratories of the Höchster Farbwerke by varying the chemical structure of active drugs (Kleiderer, Rice, and Conquest,

1945). The pharmacologist was thus faced with the task of looking for analgesic activity in hundreds of compounds and of comparing the potencies of the active derivatives.

This requirement was met by about 50 different methods for measuring analgesia which have been elaborated within the last 10 to 15 years. The purpose of these methods was to provide exact figures for the analgesia produced and to allow a statistical evaluation of the results the accuracy of which could be relied upon.

Nowadays this kind of work is a little overdone, particularly when analgesic potencies are determined up to the second decimal place with well-defined fiducial limits. Often the possibility is overlooked that the values obtained are not the result of analgesia but are due to other factors—for instance, to changes in blood flow. Many workers are not disturbed by the fact that their results are inconsistent with those of other authors, so long as the validity of these results is proved by statistics. In Table I the analgesic potency of pethidine

TABLE I.—Relative Analgesic Potency (Morphine=1)

	Experimental	Clinical
Pethidine		
Author 1	0.135	} 0.15
" 2	0.45	
" 3	0.94	
Methadone		
Author 4	1.2	} 1.5
" 5	6.5	

Clinical doses: morphine, 15 mg.; pethidine, 100 mg.; methadone, 10 mg. Relative potency: morphine, 1; pethidine, 0.15; methadone, 1.5.

and of methadone, as tested by different workers, is compared with that of morphine. There is a wide variation in the ratios, and some of the figures are not in agreement with clinical experience. There is no reason to doubt the experimental results or the statistical evaluation of these different results. However, quantitative comparisons in animal experiments are obviously useful only if the results correspond to the experience obtained in man. Therefore, in many cases inadequate methods must have been used, a possibility not always realized.

Nevertheless, we have a number of reliable methods for measuring analgesia. The most subtle methods, however, are not necessarily always the best. As a historical demonstration I would like to tell you which instrument and which method I used in my discovery of the analgesic property of pethidine and in the determination of the analgesic potencies of methadone and of hundreds of other compounds. It was nothing but a forceps with which I pinched the tails of mice. Nevertheless, with this simple method I determined (Schaumann, 1940) the relative potencies of pethidine, methadone, phenadoxone, and ketobemidone, and the results have been confirmed by the majority of later investigators and by clinical experience. The method was actually described as early as 1929 by Haffner.

Criteria of Specificity

With the synthetic analgesics it became possible to separate the specific from the non-specific effects. An effect is specific if it is common to all analgesics whatever their chemical structure, and if the potency in producing the effect runs parallel to their analgesic potency.

Another criterion for the specificity of an action is its great sensitivity against small changes in the chemical substitution. If we exchange the N-methyl group in morphine or in levorphanol against an allyl group, we obtain two

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