

hope and faith to believe that some other Fellow of the College, perhaps some young doctor in this Hall, may be stimulated by what I have said to attempt to solve the problems which still remain.

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## VAGOTOMY FOR PEPTIC ULCER\*

### INDICATIONS AND RESULTS

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It is now over two years since we reported from the Postgraduate Medical School a series of 50 peptic ulcer cases treated by vagus resection and concluded that results were promising enough to secure the operation an important place in ulcer therapy, though we indicated that this might eventually be mainly in support of other procedures (Orr and Johnson, 1947). Increasing experience has confirmed our view that vagus resection is a powerful weapon against ulcer recurrence, and, although it is primarily an attack on the fundamental diathesis and neurogenic hypersecretion, it will certainly bring about healing of many established ulcers.

Continued investigation has shown that vagotomy may be relied upon, when complete, to reduce spontaneous interdigestive gastric acid secretion substantially, and also to

diminish acid response to a meal or to histamine injection. Furthermore, these effects have been shown to endure in cases where repeated insulin tests have established the completeness of the nerve section.

Once an ulcer has penetrated deeply and caused gross scarring in the restricted area of the duodenum, healing of the surface breach alone cannot be relied upon to rid the patient of his symptoms, and removal of the distorted stenosed rigid segment of bowel may become necessary. Vagotomy alone will seldom suffice in such a case. At an earlier stage, however, when the ulcer is still confined to the bowel wall, vagotomy by itself, with its negligible danger to life, may save the patient from years of semi-invalidism and pain with gradually mounting risks should he perforate or bleed.

### Choice of Patients

The results achieved in a series of vagotomy cases will depend to a considerable degree upon the wisdom with which patients are selected for this operation. We have learned much from our failures, and are now able more confidently to say when vagotomy alone is likely to be a success and when it would be better combined with other procedures or not used at all. Selection must always be based upon very thorough investigation as well as upon certain special aspects of the history. Particularly important is the assessment of the relative prominence in the aetiology of hyperacid response to food, neurogenic hyperacidity, and excess of interdigestive and nocturnal secretion, and we employ special routine tests for this purpose.

The patient most suitable for vagotomy is one in whom there is a clear association between worry and relapse. This type of patient usually has a copious and very acid spontaneous night secretion and is often wakened at night, by pain. A not unusual finding in such a case is 500 to 1,000 ml. of night secretion containing 60 to 80 units of free HCl. At the same time it may be remembered that vagotomy produces a lasting fall in acid response to food and to histamine injection.

One source of poor results with vagotomy alone is failure to recognize early pyloric stenosis. After vagus resection a quite moderate degree of narrowing may cause symptoms, as compensatory hyperactivity of gastric muscle has been abolished. We now realize the necessity for some form of by-pass operation whenever there is the least doubt of the absolute patency of the pylorus.

We have also learned that, whereas vagotomy will prevent recurrent duodenal ulcers and will usually completely heal an active ulcer confined to the bowel wall, once an ulcer has become grossly callous or has penetrated into the pancreas it may not heal after vagotomy alone, or, if it does heal, may cause recurrence of symptoms from contraction of scar tissue later. We now consider that such ulcers should be removed and that vagotomy should be added to prevent recurrence.

### Indications for Vagotomy

An ulcer that shows a distinct tendency to recur under conditions of stress which cannot be eliminated or which are no more than the ordinary human lot should come to surgery, provided that the symptoms are not adequately controlled by simple medical measures while at work.

Vagotomy alone may be employed if at operation there is no hint of pyloric stenosis and the ulcer has not penetrated beyond the gut wall. The addition of gastro-enterostomy even in such cases is a wise precaution which may well become a routine measure with more experience. Only the fear that vagotomy might not ultimately prove an

\*The largest group in the series here reported was operated upon at Hammersmith Hospital (Postgraduate Medical School of London) where this investigation was begun and has largely continued.

absolute protection against the late development of jejunal ulcer has deterred us from using this very satisfactory combination more often. This fear is growing less, as we have continued to see completely successful results in following up the patients so treated. In cases where duodenal ulcers have become large and callous or have penetrated into adjacent organs, or where gross haemorrhage has occurred, we recommend vagotomy plus hemigastrectomy.

This operation is very different from the high subtotal gastrectomy now usually employed for duodenal ulcer, being neither so mutilating nor so dangerous; nor is it followed by the unpleasant small-stomach syndrome, the inability to eat a proper meal, and the progressive weight loss now so commonly seen.

It is well known that, if only half the stomach is removed for duodenal ulcer, stomal ulcer subsequently develops in about one in ten patients (Rienhoff, 1945). Such recurrences respond well to vagotomy, and its use for anastomotic ulcer has gained distinguished supporters in recent years (Allen, 1947; Maingot, 1948). In employing a combination of vagotomy and hemigastrectomy in those duodenal ulcer cases unsuitable for vagotomy alone, it is our hope that the vagotomy will reduce the anastomotic ulcer rate to a figure at least as low as that for subtotal gastrectomy, while avoiding the unsatisfactory sequelae and greater mortality of the very high gastric resection. Vagotomy alone is a suitable operation for anastomotic ulcer after earlier gastro-enterostomy or gastrectomy in the majority of cases, and has the advantage of being a much less serious or dangerous undertaking than any alternative procedure available.

The vagi should not be divided in patients in whom at laparotomy no evidence of ulcer is found, unless this is deliberately undertaken for gross antral gastritis confirmed gastroscopically and accompanied by bleeding, or for recurrence of severe symptoms after gastrojejunostomy or gastrectomy when there is evidence of chronic jejunitis.

**Results**

Our series of vagal resections now numbers 215, 191 of them men and 24 women (Table I). Of these, 63 have

TABLE I.—Types of Operation

	Cases	Operations
Duodenal ulcer .. .. .	190	
Vagotomy alone .. .. .		108
Vagotomy plus gastro-enterostomy .. .. .		21
Vagotomy plus gastrectomy .. .. .		61
Combined gastric and duodenal ulcers .. .. .	5	5
Vagotomy alone .. .. .		
Anastomotic ulcers .. .. .	20	18
Vagotomy alone .. .. .		2
Vagotomy plus gastrectomy .. .. .		
All lesions .. .. .	215	
Vagotomy alone .. .. .		131
Vagotomy plus gastro-enterostomy .. .. .		21
Vagotomy plus gastrectomy .. .. .		63
Re-operations after vagotomy:		
Gastro-enterostomy .. .. .		5
Gastrectomy .. .. .		10
For duodenal fistula .. .. .		1
Total operations .. .. .		231

been initially combined with hemigastrectomy and 21 with gastro-enterostomy; 20 have been undertaken for anastomotic ulcer. The earliest was performed five years ago, and 65 of them over two years ago.

**Vagotomy Alone**

Early in our series we used vagotomy alone for all duodenal ulcers and anastomotic ulcers except one or two with well-established pyloric stenosis. We now realize that

several of these subjects were unsuitable. None the less, a number of those in whom we would now consider a combined operation to be indicated still show first-class results with vagotomy alone.

Before we had become well practised at the operation we often failed to achieve complete denervation by the criteria of subsequent insulin tests. Dragstedt, who with his associates has done over 500 vagus resections, still draws attention to the very great difficulty of recognizing and dividing every fibre of both vagi. However, though there were 22 incomplete divisions among our first 100 cases, we have seen only six positive insulin responses among the next 100, and none at all among the last 50.

The results of these partial operations are altogether different and essentially unpredictable, for, though the percentage of failures is high, some of our most remarkable successes have been in this group, and the complications which sometimes follow vagotomy have been rare among them.

Of the 131 cases submitted to vagotomy alone (Table II), nerve section is believed to have been complete in 105.

TABLE II.—Results of Operations Performed Over Six Months and Up to Five Years Ago

Operation	No.	Still Symptom-free	Better but not Symptom-free	Failures
<i>Duodenal ulcers and anastomotic ulcers after earlier operations for duodenal ulcers</i>				
Vagotomy alone: "insulin negative" post-operatively .. .. .	71	54 (76%)	13	4 (6%)
Vagotomy alone: "insulin positive" post-operatively .. .. .	26	9 (35%)	5	12 (46%)
Vagotomy plus gastro-enterostomy, including vagotomy for anastomotic ulcer after gastro-enterostomy .. .. .	29	25 (86%)	3	1 (3%)
Vagotomy plus gastrectomy; including vagotomy for anastomotic ulcer after gastrectomy, and gastrectomy for failure after vagotomy .. .. .	66	58 (88%)	6	2 (3%)
<i>Combined gastric and duodenal ulcers</i>				
Vagotomy alone .. .. .	5	3	0	2

Of these 105 probably complete vagotomies, 82 were for duodenal ulcer, 5 for combined duodenal and gastric ulcers, and 18 for anastomotic ulcers. Eleven cases of duodenal ulcer in which operation was performed less than six months ago, though satisfactory, have been excluded from analysis. In the remaining 71 duodenal ulcer cases in which vagotomy is believed to have been complete and in which the operation was done over six months and up to five years ago, 54 operations (76%) have been entirely successful, 13 have been only partially successful, and 4 have altogether failed to relieve symptoms.

Of the four complete failures, one patient had pyloric stenosis and two others developed stenosis later. These three have been re-operated upon with success, two having had hemigastrectomies and one a gastro-enterostomy. The fourth patient was relieved for only a few months by vagotomy and was then as bad as ever. At re-operation the large duodenal ulcer appeared to be soundly healed, and though a mass of scar tissue was present there was no obvious stenosis. Hemigastrectomy was performed, but the patient is still only partially relieved of his symptoms.

Of the 13 partial successes, one patient who had had a long history of severe pain and several haemorrhages was completely relieved of symptoms. Nevertheless he had a further haematemesis twelve months later. On re-exploration he was found to have a healed duodenal ulcer and several superficial gastric erosions. There was also some stenosis of the pylorus with gastric retention. Five patients have

dyspepsia from time to time, though their symptoms are not so severe as those experienced before operation. There is no x-ray evidence of recurrence, and the symptoms are readily controlled by simple medical measures. Two patients have occasional vomiting but no other symptom. Three have attacks of colic relieved by passage of flatus or belching. Two have intermittent diarrhoea, and, though the earlier one has now been free from trouble for six months, it is too soon to say confidently that this symptom permanently settles sooner or later.

The last of these 13 patients was operated upon two years ago for repeated haematemesis from a large but otherwise symptomless duodenal ulcer. Since operation he has not had another haemorrhage, but has not felt so well as before operation. We would not now submit such a patient to vagotomy alone.

Of the 26 patients in whom vagus resection was inadvertently incomplete, eight have been altogether free from symptoms since operation, up to five years and an average of three years ago. Five have been improved but are not symptomless and 12 have relapsed. Four of these have been submitted since to hemigastrectomy, one of them having a healed duodenal ulcer but a very large active gastric ulcer. Two others whose ulcers healed developed stenosis later and required gastro-enterostomy. Another has since had a massive haemorrhage from which he died.

We do not recommend vagotomy for patients with gastric ulcer, as we hold that there is no sound rationale for vagotomy in this condition, nor have the results of others who use it been convincingly successful.

Of the five cases of combined gastric and duodenal ulcer, three have been altogether cured for up to two years. In the other two cases the duodenal ulcers have healed, but the gastric ulcers continue to relapse. One of these has since been re-operated upon. However, it is possible to select certain patients with combined ulcers as suitable for vagotomy on the basis of the special investigations into secretion which we now make. By our present criteria neither of the two failures recorded in this group should have been vagotomized, for they both had long hypotonic stomachs showing no evidence of hyperacidity or excess of interdigestive secretion.

#### Vagotomy plus Gastro-enterostomy

Twenty-six patients with pyloric stenosis and active ulcers have had gastro-enterostomy with or after vagotomy, seven subsequently proving to have incomplete nerve section. A further 10 have had vagotomies for anastomotic ulcers after earlier gastro-enterostomy, so that there are 36 patients with this ultimate combination in the follow-up, which ranges, in their case, up to 4½ years. The only failure in this group has been due to the persistence of vomiting in one patient in whom nerve section was incomplete. Three others, two of whom also had positive insulin responses after operation, have periods when they are not altogether symptom-free. We have not used vagotomy for patients with pyloric stenosis and healed ulcers.

#### Vagotomy plus Hemigastrectomy

Sixty-three patients with large callous or penetrating ulcers have had vagotomy plus hemigastrectomy, and 10 have had vagotomies for recurrent ulcers after earlier gastrectomy. A further 10 patients have had gastrectomies later for the failures after vagotomy described above—one for a gastric ulcer which did not heal, one for haemorrhage from gastric erosions, four for pyloric stenosis, and four who relapsed after incomplete vagotomy. In all, 83 have

had gastric and vagal resection. The follow-up of this group is relatively short, only the earliest having been operated on more than two years ago. So far the results on the whole have been very satisfactory, though one patient who had had two partial gastrectomies and two other operations for ulcer before he came to us was not much benefited by vagotomy. Six other patients continue to have intermittent symptoms less troublesome than their earlier ulcer distress. No case of anastomotic ulcer has yet been seen.

#### Other Effects of Vagotomy

Vagus section has had the unexpected effect of relieving constipation. Of the patients in the series 50% complained of chronic constipation, and 90% of these have developed regular habits since operation. In two patients constipation has returned after a few months of initial relief. Diarrhoea lasting one week or sometimes two weeks has occurred in several patients, but in only four (under 2%) has it persisted for longer or been really troublesome, and these patients consider themselves better off than before the operation.

Gain in weight over the immediate pre-operative level has averaged 5 lb. (2.27 kg.) in the first six months after vagus resection alone. After vagotomy plus hemigastrectomy it has averaged 4½ lb. (2 kg.) in the same period. This compares very favourably with the weight charts seen after subtotal gastrectomy (Johnson, 1948b).

Two patients who had suffered for several years from pulmonary tuberculosis as well as duodenal ulcer were operated upon at the request of their physicians because their nutrition could not be maintained at a satisfactory level for combating their infection. One has gained 14 lb. (6.35 kg.) in three months and the other 16 lb. (7.25 kg.) in 12 months since operation.

**Complications.**—The complications specific to vagotomy are nearly always mild and transitory, but are of special interest owing to the difficulty of explaining them on physiological grounds. Some patients notice that the stomach and bowel contain an excessive amount of wind, causing frequent eructation and passage of flatus, and occasionally giving rise to bowel colic. This condition, in our experience, has nearly always settled in a few months. If patients are closely questioned many will admit having had several sudden attacks of weakness, sometimes accompanied by sweating and trembling, and lasting twenty minutes, during the first few weeks after operation. In three or four cases these attacks have persisted, occurring about once a week, usually about 3 or 4 p.m., and often after heavy exercise. They were accompanied by low blood-sugar levels in two patients tested during attacks (Johnson, 1948b). Hypoglycaemia is a condition to which duodenal ulcer patients have a tendency without operation.

#### Mortality

There has been no death from vagotomy alone in this series (Table III). One elderly patient died from retention

TABLE III.—Mortality

	No.	Deaths	Mortality (%)
Vagotomy alone .. .. .	131	0	0
Combined operations: Vagotomy plus gastrectomy or gastro-enterostomy ..	84	1	1.2
Re-operations .. .. . (Gastrectomy, 10; gastro-enterostomy, 5; for duodenal fistula, 1)	16	1	6.2
All operations .. .. .	231	2	0.87

of urine and uraemia following a combined hemigastrectomy and vagotomy, and a second died from an operation for closure of a duodenal fistula which developed after a difficult Billroth I gastrectomy with which vagotomy had also been combined. The overall mortality during the surgical treatment of these 215 patients has therefore been under 1%.

### Commentary

The results of the investigations here recorded represent five years of study. During the first year little success was achieved beyond the development of a technique for complete vagus nerve section from below the diaphragm.

The percentage of failures among the early cases was high, but as the technique improved the proportion of incomplete vagotomies decreased, as did the proportion of failures. During the second and third years close follow-ups revealed the limitations of vagus resection as a therapeutic procedure in the treatment of duodenal ulcer, and some of the complications of vagotomy were recognized. Drainage operations were avoided at first, except when gross organic stenosis made it obligatory, until the effects of vagotomy alone had been studied. The observations made in this second period showed beyond question that complete vagotomy resulted in a marked fall in free acid, and that the low acid level was maintained in patients submitted to repeated secretion tests over a period of two years; but it also showed that in spite of a marked fall in free-acid level 25% of patients continued to complain of ulcer symptoms or suffered from recurrence after an initial period of well-being. Furthermore, it was noted that while 75% of vagotomized patients remained free from ulcer symptoms, certain side-effects of an unpleasant nature were apt to appear.

During the third and fourth years of study an analysis of good and bad results suggested that some of those who had been subjected to vagotomy were unsuitable subjects and that others presented too complicated a picture to be dealt with adequately by vagotomy alone, and combined operations were undertaken, such as vagotomy plus gastric resection or gastro-enterostomy.

The remaining period has confirmed that early uncomplicated cases of duodenal ulcer associated with high interdigestive secretion of free acid may be expected to obtain lasting benefit from vagotomy alone. For patients with a history of haemorrhage, perforation, scarring or deep crater formation—in other words, those most often presented to the surgeon—more radical operations are indicated. The results of these combined operations have been most gratifying, and the substitution of partial for high subtotal gastrectomy has done much to lower the post-operative morbidity and mortality of ulcer surgery.

Though resection plus vagotomy is the operation of choice at the moment, a prolonged follow-up of those patients who have had vagotomy plus gastro-enterostomy may prove that this is an adequate procedure with a minimal risk of stomal ulcer. Until this can be established beyond doubt, however, resection plus vagotomy must continue to be favoured. The scope of the resection is limited to removal of the ulcerated portion of the duodenum and enough of the pyloric half of the stomach to eliminate the secretory hormone element.

### Summary

A series of 215 patients submitted to vagotomy over the last five years is reported. The results are satisfactory provided that the cases are skilfully selected and section of the nerves is complete. For large penetrating ulcers hemigastrectomy plus

vagotomy has been tried, with, so far, promising results and avoidance of the "small-stomach syndrome" now becoming so common.

Despite our earlier fears, gastro-enterostomy plus vagotomy has continued to give excellent results in the small group in which it has been used.

The results of inadvertently incomplete vagotomy are variable and unsatisfactory, and only in the later part of our series did our technique become reliable in this respect.

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## THE USE OF PROCAINE PENICILLIN WITH ALUMINIUM MONOSTEARATE IN ADULTS

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Of the many attempts which have been made to prolong the action of penicillin the most successful up to the present time have involved the use of the insoluble salt formed by combining penicillin G and procaine. By the use of this salt in fine suspension in arachis oil it has been claimed that bacteriostatic levels of penicillin in the blood can be maintained for 24 hours. While there is no doubt that in many cases this claim is justified, we have found in common with other observers (Emery, Stewart, and Stone, 1949) that the titre in the blood at 24 hours is very variable and often falls below the usually accepted minimum bacteriostatic level.

The retarding effect of aluminium stearate on the absorption of procaine penicillin has been pointed out by Buckwalter and Dickison (1948). The aluminium ester, which is a water-repellent, seems to produce a unimolecular envelope over the crystals and to delay their absorption. Observations on this preparation have been reported by Thomas, Lyons, Romansky, Rein, and Kitchen (1948), who found that a single injection of procaine penicillin in arachis oil with 2% (w/v) aluminium stearate maintained effective blood concentrations over a longer period than similar preparations without aluminium stearate. Robinson, Hirsh, Milloff, and Dowling (1948), using a similar preparation, found that the majority of cases had assayable blood levels after 24 hours and that one-third had assayable levels after 48 hours.

In this country Young, Andrews, and Montgomery (1949) have estimated the penicillin blood level after injection of procaine penicillin in oil with aluminium stearate. Estimations were made in 65 cases at 24-hour intervals