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EFFECT OF MEDICAL AND SURGICAL VAGOTOMY ON THE AUGMENTED HISTAMINE TEST IN MAN

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When the evolution of surgery in the treatment of duodenal ulcer is traced it is evident that during the last half-century surgeons have directed their efforts along two main channels. Firstly, search has been made for an operation which would cure the existing ulcer and guarantee prevention of recurrent ulceration; new procedures have been numerous and varied, but, after a brief vogue, most have been shown deficient in some respect. Secondly, and more recently, there have been well-planned clinical trials with accurate follow-up results on some of these procedures, in the hope that a particular single operation would be found to be so superior to others as to be suitable for *all* patients with duodenal ulcer. Partial gastrectomy, vagotomy with drainage, and antrectomy with vagotomy are well-tried and useful operations, but each carries a risk of recurrent ulceration and of other unpleasant side-effects. The quest for an ideal operation is now being relinquished in favour of a new objective—the selection of an operation or combination of operations which will most accurately meet the requirements of the individual case. The current studies are directed towards the identification of these requirements.

Surgical vagotomy, which regularly reduces the basal secretion of gastric juice, the nocturnal secretion, insulin-stimulated secretion, and histamine-induced secretion (0.5 mg. of histamine acid phosphate), has also been shown to cause a significant reduction in the maximal histamine secretion as judged by the augmented histamine test (Gillespie, Clark, Kay and Tankel, 1960). This test, preferred to the others on account of its ability to give reproducible results, is routinely used by us to measure the effect of surgical vagotomy on acid gastric secretion.

More recently it has been shown that hexamethonium and atropine in combination ("medical vagotomy") is also capable of reducing the augmented histamine response and that a significant correlation exists between this reduction and the reduction due to subsequent surgical vagotomy (McArthur, Tankel, and Kay, 1960). The possible application of these findings to the selection of duodenal ulcer cases suited to vagotomy as surgical treatment was envisaged. In this paper we report the results of such a study.

Methods

All patients included in this study were males with proved duodenal ulcer who had been accepted for surgical treatment. They were selected only in so far

that elderly and poor-risk patients were excluded; treatment by gastro-jejunostomy was preferred in these circumstances. A total of 40 patients have been studied. Regardless of the results of the pre-operative acid tests, each was treated by vagotomy with gastro-jejunostomy. The vagal trunks were divided subdiaphragmatically after mobilization of the lower oesophagus, and a posterior gastrojejunostomy was made at the most dependent part of the stomach.

Before operation each patient had two tests: the first was an augmented histamine test; in the second, the effect of medical vagotomy on the augmented histamine test was studied. After operation the augmented histamine test was repeated in all 40 patients.

Medical Vagotomy Modification of the Augmented Histamine Test.—The test is preceded by a 12-hour fast.

mEq HCl

An augmented histamine response is represented by the solid line. The effect of medical vagotomy (hexamethonium 50 mg. + atropine 0.325 mg.) is depicted by the interrupted line. The shaded area represents the reduction in "maximal" acid output produced by medical vagotomy.

A No. 16 French gauge "neoplex" gastric tube is introduced through the nose and the fasting contents of the stomach are aspirated by means of an electric suction apparatus. Throughout all subsequent collections, complete aspiration of the gastric juice is ensured by frequently interrupting the suction and injecting a little

air to maintain patency of the tube. A single intramuscular injection of hexamethonium bromide, 50 mg., with atropine sulphate, 0.325 mg., is followed by the collection of four 15-minute total aspirates. The fourth specimen usually reveals absence of free hydrochloric acid. An antihistamine (100 mg. of mepyramine maleate) is now given intramuscularly and followed in 30 minutes by a subcutaneous injection of histamine acid phosphate, 0.04 mg./kg. body weight. A further three 15-minute aspirates are then collected as in the standard augmented histamine test (Kay, 1953). All 15-minute aspirates are measured for volume, pH, and free hydrochloric acid output by titration with N/10 sodium hydroxide, using Topfer's indicator. Comparison of the acid output in the last two 15-minute aspirates in the standard augmented histamine test and in the test after medical vagotomy represents the effect of medical vagotomy on the augmented histamine response (see Chart on previous page).

Mild postural hypotension, the only side-effect observed commonly during the medical vagotomy test, was controlled by keeping the patients recumbent for about two hours after the test.

Results

Effect of Surgical Vagotomy.—The effect of surgical vagotomy on the augmented histamine response in the series of 40 patients is shown in Table I. The average reduction obtained was 58.5%.

TABLE I.—Effect of Medical and Surgical Vagotomy on the Augmented Histamine Response. Acid Outputs in mEq in 30 Minutes

Case No.	Before Vagotomy	After Medical Vagotomy	% Reduction	After Surgical Vagotomy	% Reduction
1	23.6	13.6	43	6.3	73
2	17.7	10.5	41	6.5	64
3	18.1	11.0	40	6.4	65
4	21.6	14.4	33	4.5	79
5	16.1	8.5	47	5.0	69
6	10.6	7.5	29	5.3	50
7	17.3	14.5	16	11.8	32
8	16.1	8.9	45	9.1	44
9	28.6	15.7	45	17.7	38
10	30.7	13.5	56	6.8	78
11	14.0	7.6	46	2.0	85
12	21.9	13.4	39	8.1	63
13	23.0	13.5	41	7.7	67
14	16.6	11.3	32	0	100
15	21.9	16.5	25	9.9	55
16	13.1	9.1	31	7.2	45
17	18.7	13.1	30	7.6	60
18	12.2	5.5	55	1.3	89
19	17.6	11.6	34	12.1	32
20	26.5	13.6	49	11.8	56
21	16.6	9.0	46	9.8	41
22	12.8	10.0	21	9.0	29
23	21.7	9.1	58	4.1	81
24	23.0	6.4	72	8.3	64
25	20.0	6.7	67	10.4	48
26	17.8	10.3	42	7.5	58
27	7.2	0.4	95	4.2	41
28	12.9	10.6	18	6.7	49
29	17.3	14.6	16	13.8	20
30	21.4	8.2	62	6.4	70
31	22.7	19.5	14	9.6	58
32	12.7	10.5	17	7.8	38
33	39.2	17.7	55	31.1	21
34	17.3	5.7	67	5.1	71
35	15.2	14.1	8	9.4	39
36	9.9	0.1	99	2.0	79
37	19.8	11.1	44	3.4	83
38	23.6	10.1	57	5.7	76
39	10.2	6.1	40	3.8	63
40	16.0	9.4	41	5.1	68

Average % reduction 58.5

Comparison of Pre-operative Medical Vagotomy and Surgical Vagotomy

The acid outputs obtained after the medical vagotomy modification of the augmented histamine test, and the percentage reductions of these on the standard augmented histamine tests, are also shown in Table I.

Prior to detailed consideration of these results, attention is directed to technical defects in the performance of the investigation in four patients. In Case 27 blood was present in the pre-operative medical vagotomy tests, and collection difficulties were encountered in the pre-operative medical vagotomy tests in Cases 35 and 36. Case 33 would appear to have had an incomplete surgical vagotomy, as a much greater reduction in the augmented histamine response occurred after medical vagotomy (55%) than after operation (21%); a discrepancy of this order was not encountered in any other case. Incomplete vagotomy has since been confirmed by the results of secretion studies after transthoracic vagotomy.

For the reasons given, these four cases have been excluded from the subsequent analysis. There is good correlation between the effect of medical and surgical vagotomy on the augmented histamine response in the remaining 36 cases ($r=0.4783$, $t=3.176$, $P<0.01$). The reduction after surgical vagotomy was generally greater than that following hexamethonium and atropine; this is due largely to the effect of the gastro-jejunostomy stoma (McArthur *et al.*, 1960).

Table I shows that, although in most cases reductions in the augmented histamine response of more than 50% occur after surgical vagotomy, there are five in which the reductions are less than 35% (Cases 7, 19, 22, 29, and 33). In one of these five (Case 33) vagal section was incomplete. The other four show reasonable agreement between the two reductions, indicating that surgical vagotomy was complete. The mean percentage reduction of the augmented histamine response after surgical vagotomy in this group of four is 28.3%, with a standard deviation of 4.9%, whereas that of the remaining 35 patients is 63.1%, with a standard deviation of 15.8%. Although there is no valid mathematical support for a separation, these figures must suggest that duodenal ulcer patients may be divided into two groups as regards the effect of surgical vagotomy on acid production. This is discussed later.

The period of clinical follow-up ranges from six months to four years. To date, two patients in the present series have developed recurrent ulceration. In the first (Case 33) acid secretion tests had indicated incomplete vagotomy, and the recurrence was treated by transthoracic vagotomy to ensure division of all vagal fibres. The other recurrence appeared within four months of vagotomy in Case 29, one of the four with a small reduction of the augmented histamine response (20%); evidence of complete nerve section is provided by the failure of the post-operative medical vagotomy test to effect a further significant reduction (Table II).

TABLE II.—Summary of Secretion Studies in Case 29

	Augmented Histamine Response. Acid Output in mEq in 30 Minutes	% Reduction of Pre-operative Augmented Histamine Response
Before vagotomy	17.3	—
After medical vagotomy	14.6	16
.. surgical vagotomy	13.8	20
Post-operative medical vagotomy	12.1	30
A.H.R. at 4 months (stomal ulcer)	15.5	10
After antrectomy	2.1	88

At the operation for the recurrent ulcer it was decided to ablate the chemical phase of secretion rather than carry out subtotal resection. Antrectomy was performed, histological confirmation being obtained that the antrum alone had been excised. Thus, in tests after

this second operation, the original population of parietal cells was still available for stimulation. These tests showed that the reduction of the augmented histamine response had now increased to 88%. The acid responses in this patient before and after his two operations are summarized in Table II.

Discussion

The results of acid-secretion studies in this series of 40 duodenal ulcer patients confirm that vagotomy reduces the acid output of the stomach in response to the augmented histamine test. Inspection of the reductions effected by surgical vagotomy shows that the majority were greater than 50%, that there was a wide variation in individual results, and that small reductions occurred in a few patients. A figure of 35% reduction in the augmented histamine response has been chosen arbitrarily to divide the series into two groups: 35 patients had a reduction of more than 35% (group A) and 5 had a reduction of less than 35% (group B). Extension of the series will be required if a critical level is to be established by statistical means. However, scrutiny of data relating to the effect of vagotomy on the augmented histamine test by other workers (Janowitz, 1961; Kyle, 1961, personal communication) shows that they too found a few patients with a remarkably small reduction after operation.

As in the present investigation, Janowitz and Kyle had been careful to perform special studies on their patients which provided good evidence that the surgical vagotomy had been complete. Consequently, the possibility has to be envisaged that the vagus nerves, while dominating the control of acid secretion in most cases of duodenal ulcer, may exert only a minor influence in some cases. In this minority, the antral (hormonal) influence may dominate, and these patients would seem to be unsuited for surgical vagotomy as the treatment of duodenal ulceration. If this finding is confirmed, it will become important in practice to identify such patients before selecting the appropriate surgical operation for the treatment of their duodenal ulceration. This hypothesis should be the subject of further study.

Statistical analysis of the overall series of 40 patients shows that the results of the medical vagotomy described in this paper correlate satisfactorily with the results of subsequent surgical vagotomy. In particular, a small reduction in the augmented histamine acid response was predicted in all four patients in group B in whom subsequent complete surgical vagotomy effected the same small reduction. It is of particular interest that one of these four (Case 29) has already reported with symptoms of recurrent ulceration; the only other recurrence in the series so far has been in the patient shown to have an incomplete vagotomy (Case 33). At reoperation on Case 29 it was decided to perform antrectomy alone rather than subtotal gastrectomy (the usual operation in cases of stomal ulceration), thus ablating the chemical production of acid secretion without reducing the number of acid-secreting cells. Subsequent tests in this patient showed that the augmented histamine response had now been reduced by almost 90% from the original level. In this patient the antral phase, and not the vagal phase, would seem to have been the predominant cause of his acid hypersecretion—as had been predicted by the results of the medical vagotomy tests.

Although these tests predicted that surgical vagotomy would effect a small reduction in the augmented

histamine response in four patients, a similar small reduction from medical vagotomy was associated with a much larger reduction after surgical vagotomy in six others (Cases 6, 15, 17, 28, 31, and 32). The results of the pre-operative tests in these patients would have led to their classification as unsuited to surgical vagotomy; antrectomy with vagotomy or partial gastrectomy would have been preferred. It should be noted, however, that the error of the test was in this direction only, and the net result would mean that a few patients in group A would be subjected to antrectomy with vagotomy as opposed to vagotomy with a simple drainage procedure. The results in these patients, which merit careful consideration, raise the question of whether there are defects in the test which can be overcome. Two of the six patients having anomalous results (Cases 28 and 32) were obese, and it is possible that the dose of hexamethonium and atropine was inadequate to produce complete medical blockade. The possibility that a body-weight dose-curve exists for hexamethonium-atropine combination is at present under consideration. Again, the timing of the hexamethonium plus atropine injection described in this paper may permit the effect of medical vagotomy to wane during the period of maximal histamine stimulation; studies are in progress concerning this point.

The major considerations in selecting an operation which will most accurately meet the requirements of the individual case include the immediate mortality and the risk of recurrent peptic ulceration. The following figures have been taken from a recent review of the surgical treatment of peptic ulcer by Welbourn and Johnston (1961). Subtotal gastrectomy has an immediate mortality of 3.7%, with a recurrent ulcer rate of 1.4%; this mortality can be attributed largely to the necessary dissection in the neighbourhood of the duodenal ulcer and the technical difficulties of closing the duodenal stump. Vagotomy with a drainage procedure has an immediate mortality of 0.6% and a recurrent ulcer rate of 1.8%; it should be noted that the average follow-up period of this operation is about 10 years, and a more accurate recurrent ulcer rate cannot be determined until the results of a full 20-year follow-up period are available for study.

Vagotomy with antrectomy is theoretically the most physiological procedure, as it removes both the nervous and the hormonal phases of acid gastric secretion. The immediate mortality from this procedure is 2.6%, with a recurrent ulcer rate at five-year follow-up of 0.4%. This combination of operations probably offers the best protection against recurrent ulceration, but by reintroducing the hazards of closure of the duodenal stump the immediate mortality is greater than that associated with simple vagotomy. Again, while the actual reduction in gastric capacity produced by removal of the antrum is not great, the rate of gastric emptying may be increased (particularly when a gastro-jejunal anastomosis is made), thus reducing the effective capacity of the stomach; accordingly, the "small stomach" syndrome may again be a sequel to this operation just as it has been the main cause of poor results from subtotal gastrectomy. It can be concluded that vagotomy without gastric resection is the safest of these three acceptable operations.

On the basis of the present study a surgical policy for the surgical treatment of duodenal ulcer can be formulated. Before operation an augmented histamine test is done (A = the acid output in mEq) and the effect of medical vagotomy on the augmented histamine test

is also estimated (B =the acid output in mEq). The percentage reduction of the augmented histamine response obtained from medical vagotomy (C) is readily obtained thus:

$$C = \frac{A - B}{A} \times 100$$

Where C is greater than 35%, vagotomy with a drainage procedure is selected as the surgical procedure; where C is less than 35% vagotomy with antrectomy is preferred.

This policy ensures that the majority of patients will be treated by the simplest and safest operation and also ensures that patients in whom vagotomy can be expected to give but a poor reduction in acid secretion will be given the greater guarantee from recurrent ulceration which is afforded by the combined procedure of antrectomy with vagotomy.

The main endeavour of the gastric surgeon to-day is to reduce the proportion of patients in whom the result is unsatisfactory. This will not be achieved by the adoption of any one standard operation, but by the clear definition of the situations in which each procedure is likely to be most effective. The hypothesis proposed in this paper provides a physiological basis for recurrent ulcer in a proportion of cases. It is important that the hypothesis, and the pre-vagotomy test which has stemmed from it, be subjected to further study.

Summary

The effect of hexamethonium and atropine (medical vagotomy) on the augmented histamine response has been studied in 40 duodenal ulcer patients with a view to predicting the effect of surgical vagotomy on this response. Good correlation exists between the reductions from medical and surgical vagotomy.

The medical vagotomy test picked out four patients who had a small reduction, and a similar reduction was found in these cases after surgical vagotomy. On this basis, a hypothesis has been formulated that duodenal ulcer patients may be divided into two groups: in the majority the nervous control of acid secretion appears to be dominant; a minority group with antral dominance would seem unsuited for surgical vagotomy and the medical vagotomy modification of the augmented histamine test described in this paper may be of value in selecting patients belonging to this group.

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The Atomic Energy Authority and the National Institute for Research in Nuclear Science have agreed that the development of particle accelerators hitherto carried out by the Accelerator Division, A.E.R.E., Harwell, should be the responsibility of the Rutherford Laboratory of the National Institute for Research in Nuclear Science.

SOME PSYCHIATRIC CONSEQUENCES OF GASTRECTOMY

BY

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Mental disturbances after surgical operation are fairly frequent and in most cases short-lived. Their clinical characteristics have been described in a number of papers under the heading of post-operative psychoses which are well recognized by surgeon and psychiatrist alike. Whereas the acute post-operative psychosis is fairly well documented less is known about the long-term effects upon the psyche of surgery. As Navratil (1959) points out, follow-up studies of surgical cases are usually carried out by surgeons, who are less likely to ask specifically about neurotic and personality disorders than are their psychiatric colleagues. An acute psychosis in the ward immediately after an operation cannot be ignored. Neurotic symptoms of fairly severe degree can be missed at a follow-up clinic unless specific questions are asked to elicit them.

Compared with most of his colleagues the psychiatrist sees a not inconsiderable number of patients who date their symptoms from the time of an operation. The woman who develops an intractable neurotic illness after a hysterectomy is a fairly familiar figure in the psychiatric out-patient department. Surprisingly little has been written on the psychiatric sequelae of partial gastrectomy and other surgical procedures for the relief of peptic ulcer, although European workers seem more familiar with the problem—particularly when alcoholism is concerned—than do their American and British colleagues. It was a chance observation of patients who had become chronic alcoholics after a partial gastrectomy that led to a further examination of a number who had been admitted to the psychiatric wards at some time after this operation.

Results

In all, 25 patients were examined (17 men and 8 women). At the time of their first admission to a psychiatric ward the men's ages ranged from 28 to 60 years, with a mean of 46, while the ages of the women varied from 37 to 55, with a mean of 47. Of the 17 men, nine were admitted directly or indirectly because of alcoholism, two for treatment of drug addiction, and the remaining six for mixed neurotic and depressive states. Three of the women were drug addicts, and the remainder had mixed depressive and anxiety symptoms. All except one of the women had been operated on for duodenal ulceration, and all except two of the men who had gastric ulcers were similarly affected. Only two of the women appeared to be in a good nutritional state, and all except four of the men were thin and underweight. Almost all the patients complained bitterly of severe dumping symptoms. The alcoholics and four of the drug addicts all said that their drug relieved these symptoms.

It was difficult to obtain a clear picture of the pre-morbid personalities of these patients, and only the most general features emerged. Judging by work record, by absence of overt psychiatric illness, and by the general level of social adaptation, three of the male alcoholics had been normal up to the time of operation, five had