Changes in the postoperative insulin test in relation to recurrent duodenal ulceration

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SUMMARY The gastric secretory response to insulin changes in many patients between 'immediate' tests, within two weeks of vagotomy, and 'delayed' tests, done at least six months later. Patients who develop recurrent duodenal ulceration after vagotomy and pyloroplasty show highly significant increases in peak and rise in concentration and output of acid. Those who do not have recurrent dyspepsia show varied individual changes in the test results, but for the group as a whole there is no increase in the peak response and only a slight increase in the rise in acid concentration and output.

These findings are interpreted as evidence for vagal recovery, either from neuropraxia or by collateral nerve sprouting, as a major factor in the production of recurrent ulceration. Indeed, it appears to be as important as the functional state of the vagi at the end of the operation. Consequently, only the delayed insulin tests can be of any value in the prediction or diagnosis of recurrence.

The insulin test of gastric secretion may be used in two ways in studying patients after surgical vagotomy, either as a routine test for the completeness of vagal denervation of the stomach or as a diagnostic aid when patients return with further dyspepsia. The latter use depends on the assumption that incomplete vagotomy is the main cause of recurrent ulceration (Bachrach and Bachrach, 1967). This dual role accounts for some of the controversy surrounding the interpretation of the test (Kay, 1967).

Recently, the task of establishing standards for this interpretation has been further complicated by reports of changes in the acid response to insulin with the passage of time after vagotomy (Mason and Giles, 1968 and 1969; Gillespie, Elder, Gillespie, Kay, and Campbell, 1970). Using Hollander's (1948) criteria, as modified by Ross and Kay (1964), the proportions of positive and early positive results in these studies were found to increase with time. The significance of these changes has not been established. We have, therefore, compared the acid response to insulin immediately after vagotomy and several months later, in patients with or without recurrent duodenal ulceration. Significant increases in the acid response have been observed in the later tests in patients with recurrence.

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Method

An unselected series of 210 men had had a vagotomy and pyloroplasty performed for duodenal ulcer at least two years previously, followed by an insulin test within two weeks of the operation. Men only were studied, in view of the sex difference in the results of insulin tests (Spencer, Burns, Cheng, Cox, and Welbourn, 1969). One hundred and fifty-five (74.8%) of these patients attended a follow-up clinic; seven had died of causes unrelated to duodenal ulcer, 36 declined to attend, and 12 were untraced owing to extensive rehousing in the Sheffield area.

The patients attending for interview were designated as 'recurrence' or 'non-recurrence' solely on the basis of their histories because, in contrast to a recent report (Williams and Toye, 1970), we have found radiological appearances difficult to interpret after pyloroplasty. To avoid bias, the assessment was made independently of the insulin test results. Each patient was graded according to Visick's (1948) classification; a decision was then made as to whether severe symptoms (grades 3u and 4) were due to recurrent duodenal ulceration or to the side effects of the operation. Re-operation did not automatically place a patient in the recurrence

group. If symptoms were suggestive of gastric ulceration a barium meal examination and a gastroscopy were performed. On this basis, 132 men had no recurrence and 15 had a recurrence; one had a gastric ulcer and seven defied classification.

INSULIN TESTS

All tests were performed in the Department of Surgery by experienced staff. After an overnight fast, a 5 mm diameter tube was passed into the stomach and adjusted to give a free return of fasting juice, with the patient recumbent and slightly tilted to his left. Continuous aspiration at a negative pressure of 5 cm Hg was applied, with either frequent air insufflation or the use of a second, air-vent, tube. After three 15-minute basal collections 0.2 units/kg of soluble insulin were given intravenously and a further eight 15-minute samples collected.

The volume of each sample was measured and its acid content titrated to pH 8.4 (the phenolphthalein end point) or to pH 7.0 using an Autotitrator (Radiometer). The actual acid values are reported, rather than rating each test as positive or negative with regard to some fixed criterion. 'Basal' figures are the mean of three 15-minute basal readings. 'Peak' acid concentration is the maximum in any 15-minute period after insulin. 'Peak' acid output is taken as the mean of the two highest consecutive 15-minute outputs. The 'rise' in concentration or output is the peak minus the basal value.

TIMING OF INSULIN TESTS

Tests are described as 'immediate' if done within two weeks of vagotomy and 'delayed' when performed at six months or later. These terms are introduced to avoid confusion with 'early' and 'late' positive responses to insulin (Ross and Kay, 1964).

Sixty of the 132 non-recurrence patients agreed to delayed tests, all of which were done at least two years postoperatively. The median values for the immediate tests in these 60 are not different from those for the other 72 patients (Table I) so that they appear representative of the whole series. Fifty of this group with two tests had had a truncal vagotomy and 10 selective vagotomy.

All 15 patients with recurrence had delayed tests. In seven, these had been carried out at between six months and two years from the primary operation: the remainder were tested at least two years postoperatively. In one immediate test in this group recovery of gastric content after giving insulin was unsatisfactory, so that his concentration and basal output data only could be used. Ten of this group had truncal and five had selective vagotomy.

The paired immediate and delayed tests in 60 non-recurrence and 15 recurrence patients are the subject of comparison in this paper.

STATISTICAL METHODS

Non-parametric methods have been used because the data were not normal in distribution (eg, Figs. 1 and 3). The Mann-Whitney U test (Mann and Whitney, 1967) has been used for the significance of differences between groups and Wilcoxon's matched pairs signed ranks test (Wilcoxon, 1945) for changes between pairs of tests. Correlations between the immediate and delayed tests were sought by means of Spearman's rank correlation coefficient (Hotelling and Pabst, 1936).

Results

ACID CONCENTRATION

Comparison of paired immediate and delayed tests in the non-recurrence group showed a small decrease in the basal concentration with a corresponding increase in the rise after insulin; peak concentration did not change significantly. In the recurrence group a significant increase was found in median peak acid concentration, from 70 to 105 m-equiv/litre ($P < 0.01$) and in the rise in acid concentration from 7 to 72 m-equiv/litre ($P < 0.01$) (Fig. 1). For clarity, these changes in the median values are presented without supporting data in Figure 2.

Comparison of the immediate tests in the non-recurrence and recurrence groups showed no statistically significant differences, but in the delayed tests the peak and rise in concentration were significantly greater in the recurrence group ($P < 0.001$).

Patient	Acid Concentration ¹ (m-equiv/litre)			Acid Output ¹ (m-equiv/15 min)		
	Basal	Peak	Rise	Basal	Peak	Rise
60 with paired tests	35	49.5	+9	0.48	0.37	+0.01
72 with immediate test only	26.5	36	+3.5	0.40	0.33	-0.04

Table I Median values for acid secretion in immediate insulin tests in non-recurrence patients

¹For each comparison $P > 0.05$.

Fig. 1 Acid concentration data in immediate and delayed insulin tests (bars indicate median values).

Fig. 2 Median acid concentration values in immediate and delayed insulin tests.

ACID OUTPUT

A pattern similar to the changes in concentration was observed (Fig. 3), there being large and statistically significant increases in peak and rise in output in the recurrence group ($P < 0.01$ and $P < 0.02$ respectively). There were corresponding highly significant differences between the groups in the delayed tests ($P < 0.001$).

INDIVIDUAL CHANGES

When changes between the immediate and delayed tests were studied in the individual patients (Figs. 4 and 5) it was found that in the non-recurrence group the changes had an approximately normal distribution centred on zero. The recurrence group showed a predominance of increases in the 'peak' and 'rise' results. The wide scatter of changes indicated that some results moved from one end of the range to the other and that this might occur in

Fig. 3 Acid output data in immediate and delayed insulin tests (bars indicate median values).

either direction. The small number of patients with selective vagotomy showed no separate trend.

When a correlation was sought between the results of the immediate and delayed tests, low values were obtained for the correlation coefficient even though it reached statistically significant levels in some instances (for values for Spearman's rank correlation coefficient and associated probabilities see Table II).

RESPONSE ACCORDING TO THE ESTABLISHED CRITERIA

The effect of these changes on the incidence of positive responses according to various established criteria for interpretation of the insulin test is set out in Table III. The criteria based on acid output have been modified to conform to our 30-minute peak output measurement. By these criteria, between

	Non-recurrence Group	Recurrence Group
Basal acid concentration	0.247 ($P > 0.05$)	0
Peak acid concentration	0.342 ($P < 0.01$)	0.313 ($P > 0.05$)
Rise in acid concentration	0.410 ($P < 0.01$)	0.567 ($P < 0.05$)
Basal acid output	0.222 ($P > 0.1$)	0.300 ($P > 0.05$)
Peak acid output	0.412 ($P < 0.01$)	0.612 ($P < 0.05$)
Rise in acid output	0.254 ($P > 0.05$)	0.503 ($P < 0.05$)

Table II Spearman's rank correlation coefficient for immediate and delayed insulin tests

Fig. 4 Frequency distribution of changes in acid concentration between immediate and delayed insulin tests. The crosshatched areas represent selective vagotomies.

Fig. 5 Frequency distribution of changes in acid output between immediate and delayed insulin tests. The crosshatched areas represent selective vagotomies.

Criteria for a Positive Result	No. of Patients	No. Positive by Immediate Test	No. Positive by Delayed Test	Change	
				Negative to Positive	Positive to Negative
Rise in concentration 20 m-equiv/litre (Hollander, 1948)	60 NR ¹ 15 R	15 5	32 13	20 8	3 0
Early positive (within first 60 min) (Ross and Kay, 1964; Bell et al 1965)	60 NR 15 R	6 1	15 9	11 8	2 0
Basal output 2.0 m-equiv/hour (Bachrach, 1962)	60 NR 15 R	29 8	19 8	9 2	19 2
Peak output 2.5 m-equiv/30 min (after Bachrach and Bachrach, 1967) ^a	60 NR 14 R	20 7	16 9	9 2	13 0
Peak output 0.5 m-equiv/30 min (after Bachrach and Bachrach, 1967) ^a	60 NR 14 R	43 12	40 14	9 2	12 0
Rise in output 0.125 m-equiv/30 min (After Stempien, 1962) ^a	60 NR 14 R	25 5	36 13	18 8	7 0
Rise in output 1.0 m-equiv/30 min (After Bank et al, 1967) ¹	60 NR 14 R	13 5	21 11	13 7	5 1
Multiple criteria, four or five positives (After Bank et al, 1967) ^a	60 NR 14 R	8 2	15 8	9 6	2 0
Mean for the eight criteria	60 NR			12.3 (20.5%)	7.9 (13%)
Mean for the eight criteria	14 or 15 R			5.4 (37.4%)	0.4 (2.6%)

Table III Results of insulin tests according to various established criteria

¹NR = non recurrence, R = Recurrence^aThe output criteria quoted have been reduced from the one or two hour periods specified by their authors to a proportionate value for the peak 30 min period used in this study.

a fifth and a half of the patients changed status between immediate and delayed tests.

In the non-recurrence group the average change for these eight criteria was from negative to positive in 20.5% of patients and from positive to negative in 13%. The change in the recurrence group was nearly always from negative to positive, there being only three exceptions. Overall, there was a net change from negative to positive in 7.6% of instances in the non-recurrence group and in 35% of the recurrent ulcer group.

Discussion

These changes in the gastric secretory response to insulin over the first six months to two years after vagotomy are in general agreement with those previously reported. We have employed the actual acid values in making this comparison, while others have compared the proportions of patients positive on Hollander's (1948) criteria. Mason and Giles (1968 and 1969) found that of 36 patients who had given negative results within 10 days of vagotomy, 17 gave positive results at six months or later, while of 26 patients with positive tests initially, all but two remained so. Similarly, Gillespie *et al* (1970) had 17 of 31 patients change from negative to positive, but only four of 43 positive patients became negative on retesting three months to four years postoperatively. In the present combined series of 75 non-recurrence and recurrence patients,

28 changed from negative to positive, while three went in the reverse direction. None of these series is made up of consecutive vagotomies, so they are not directly comparable, nor do they indicate the true incidence of changes in the insulin response; this must await a prospective study. Nevertheless, they all show a net increase in the proportion of positive responses (Hollander, 1948) in the months following vagotomy. A similar effect is seen when other criteria for interpretation of the test are applied to the data from the present series (Table III).

The new feature demonstrated is the marked increase in acid concentration and output in the delayed tests in the recurrent ulcer group, while the non-recurrence patients, as a group, show little change over the immediate test. This finding has implications for the pathogenesis of recurrent ulceration and for the timing and significance of insulin tests.

MECHANISM OF THE CHANGES

These changes in the acid response to insulin in the recurrent ulcer group might, theoretically, be due to increased responsiveness of the parietal cells, recovery from a transient nerve lesion (neuropraxia), or re-innervation. The latter might occur by regeneration at the site of vagal section or by collateral nerve sprouting from a small number of intact fibres (Murray, 1962). The stability of the response to histamine from 10 days to three years postoperatively (Bell, 1964) and the tendency for pentagastrin-

stimulated secretion to diminish over a like period (Johnston, Lari, and Jepson, 1970) appear to rule out any increase in end organ sensitivity. Regeneration of nerve fibres to bridge the gap is unlikely to be the mechanism in view of the usual finding, at re-operation, of a virgin vagal strand (Fawcett, Johnston, and Duthie, 1969).

Direct evidence is lacking regarding the other possibilities. In particular, that concerning collateral sprouting is far removed from human gastric secretion. The evidence in its favour was obtained from gastric motility studies in cats (Clark, 1964) while that against was based on measurement of the area of mucosa capable of secreting phenol red in the dog (Legros and Griffith, 1970) and the rat (Jones and Griffith, 1970a), supported by secretory measurements (using the pyloric ligation technique) in a separate group of rats (Jones and Griffith, 1970b). We, therefore, cannot at present exclude the possibility of collateral sprouting in man.

We have no anatomical information concerning the state of the vagi in our patients and can only speculate about the mechanism of the changes. Any theory must accord with their observed characteristics of unpredictability, delayed onset, and gradual progression over several months. The time course is unduly prolonged for simple neuropraxia to be the sole explanation. Collateral sprouting appears more likely to have the above characteristics, but its extent is put in doubt by the animal evidence.

THE TIMING AND SIGNIFICANCE OF INSULIN TESTS

The practical value of the insulin test after vagotomy for duodenal ulcer lies in the correlation between the results and recurrence. This is the basis for its use, whether as a routine check on operative technique or as part of the investigation of recurrent symptoms.

The present study confirms the expectation that a correlation exists between delayed insulin tests and recurrence. Immediate tests, done within two weeks of operation, give no indication as to which patients are at risk. The delayed tests described here were carried out at least six months and, generally, two years after vagotomy. The minimum interval after which the 'final' state of vagal innervation of the stomach has been attained remains to be established by serial tests at intervals of a few months. The longer this interval proves to be, the less feasible will routine testing become. Meanwhile, pending a definite figure for this minimum interval, decisions concerning the diagnosis or surgical treatment of recurrence should take account only of tests done after the onset of symptoms.

Previous favourable reports of discrimination

between recurrence and non-recurrence (Johnston, Thomas, Checketts, and Duthie, 1967) exploited the increases in the response to insulin which occur in the postoperative months. They were generally comparing immediate tests in the non-recurrence patients with delayed tests in patients with recurrent ulceration. The wide scatter of individual results in Figs. 1 and 3 shows that when the delayed test is used for both groups, there is considerable overlap between them. Thus, even the delayed insulin test does not differentiate fully between those liable or not liable to recurrent duodenal ulceration after vagotomy. The degree of discrimination obtainable is assessed, using larger groups of patients, in a subsequent paper (Watkin and Duthie, 1970).

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