The predictive accuracy of the postvagotomy insulin test¹: A new interpretation

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SUMMARY Insulin-stimulated gastric secretion alone, without reference to basal secretion, has been examined in 45 male patients with duodenal ulcer in whom no gastric operation had been performed and in 124 patients following vagotomy for duodenal ulcer. Gastric juice was examined in terms not only of conventional indices, observed volume, titratable acidity and acid output, but also V_G , the volume corrected for pyloric loss and duodenal reflux.

The range of secretion of the unoperated subjects was established in terms of peak and half-to-two-hour values for all indices. By reference to these ranges, secretion of postvagotomy subjects could be divided into two groups: (a) those with secretion within the preoperative range, and (b) those with secretion less than the lower limit of the preoperative range.

The best discrimination was given by V_G ; those within the preoperative range (peak V_G in excess of 140 ml/hour and V_G half to two hours in excess of 105 ml/hour) had a 50% liability to recurrent ulcer, while those below the preoperative range had a zero liability to recurrent ulcer.

Of the conventional indices acid output gave the best discrimination, which was almost as good as V_G . Peak acid output of 8 mmol/hour or acid output one half to two hours of 5.25 mmol/hour discriminated into two groups, with a 50% or zero liability to recurrent ulcer. Titratable acidity (Hollander's index of secretion), being highly susceptible to reflux, was not an adequate discriminant.

Surgical division of the vagus nerves as a treatment for duodenal ulceration was reintroduced by Dragstedt and Owens in 1943. After reporting preliminary results on canine stomach pouches (Hollander, Jemerin, and Weinstein, 1942) Hollander (1946) described the use of the insulin test for detecting the presence of intact vagal fibres in patients following vagotomy. Two years later (Hollander, 1948) he modified his criteria and defined a positive test as one in which the free acidity in response to insulin-induced hypoglycaemia was more than 20 mmol/litre in excess of basal acidity. However he remained cautious with regard to these criteria saying, 'At no time have we stated that the test can predict the chances that the patient will be relieved of his ulcer or its symptoms, or that they will not recur at some future date'. After another two years' experience he

clearly stated, 'The insulin test cannot be used to prognosticate clinical results of vagotomy' (Weinstein, Hollander, Lauber, and Colp, 1950).

Many authors have suggested other criteria for defining a positive test, culminating in the multiple approach of Bank, Marks, and Louw (1967). They used five criteria, those of Hollander (1948), Waddell (1957), Bachrach (1962), Ross and Kay (1964), and one of their own, and scored one plus for each positive criterion. However, the value of any of the newer criteria in predicting the likelihood of recurrent ulceration in the individual patient rather than in groups of patients was dismissed by Kronberg (1971) who said: 'All these criteria have a higher discriminative ability than those of Hollander, but their value in the diagnosis of recurrence is small.'

All criteria previously used have defined the result of the insulin test in terms of a rise in secretion during the insulin-stimulated period compared with the basal period. Yet basal secretion is well known to be very variable (Baron and Alexander-Williams, 1973). It seemed to us, therefore, that insulin-stimulated

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secretion alone, without reference to basal secretion, might with greater accuracy predict the liability to recurrent peptic ulceration after vagotomy.

We have examined insulin-stimulated secretion not only in terms of conventional indices, ie, observed volume, titratable acidity, and acid output, but also as V_G , the observed volume of gastric juice after correction for pyloric losses (Hobsley and Silen, 1969) and duodenal reflux (Hobsley, 1974).

Experimental Design and Patients

Each subject fasted and abstained from tobacco and all medication known to affect gastric secretion from midnight. From 9 am the subject lay semirecumbent on a couch, a specially prepared two-lumen nasogastric tube (Thomson, Russell, and Hobsley, 1973) was passed, and its correct position in the stomach checked by the water recovery test of Hassan and Hobsley (1970). In 123 subjects phenol red was, throughout each study, instilled into the stomach via the small lumen (Hobsley and Silen, 1969). After at least a half-hour basal collection, soluble insulin (0.2 units/kg) was injected intravenously, and gastric juice was collected in 10-minute samples for a further two hours. Venous blood samples, for the measurement of blood glucose, were taken at intervals during the study, and only tests where adequate hypoglycaemia (<40 mg/100 ml) (Sun and Shay, 1960) was obtained were included in this study.

Studies were performed on (1) 45 male patients with duodenal ulceration, in whom no gastric operation had been performed (unoperated subjects), and in 37 of these patients phenol red was used; (2) 124 male patients following treatment for duodenal ulcer by vagotomy (81 truncal, 35 selective, and eight proximal gastric) with or without a drainage procedure, and phenol red was used in 86 of these subjects. The length of follow up was between six months and 10 years.

Methods and Calculations

On each sample volume was determined, and, then after filtration through Whatman's no 1 filter paper, the following measurements were made: titratable acidity (Radiometer automatic titrator, titrations to pH 7), sodium, potassium, and chloride ion concentrations (EEL flame photometer and chloride meter), and phenol red concentration (Uicam SP spectrophotometer at 550 and 410 nm). The reason for making readings at two wavelengths was to correct the phenol red readings for the presence of blood and bile. The correction for blood was first described by Crawford and Hobsley (1968), and since then we have found that the same method

corrects for the presence of bile also. The correction formula is:

Corrected reading = reading at 550 nm - 0.13511 (reading at 410 nm) + 0.0039.

The electrolyte estimations were checked by comparing the sum of the cations with the chloride concentration (Hirschowitz, 1961). The phenol red standard was handled as described by Hobsley and Silen (1969).

The volume (V_{obs}) of each sample of gastric juice was, in those cases where phenol red was used, divided by the recovery fraction of phenol red to determine the pyloric loss-corrected volume (V_{cor}). The volume of duodenal reflux (V_R) present in each sample was calculated from the sodium output and volume by the formula:

$$V_R = 7.34 Q_{Na} - 0.0712 V_{cor} - 1.281$$

validated during insulin-stimulated secretion by Faber, Russell, Royston, Whitfield, and Hobsley (1974). This formula is an updated version of that originally propounded by Hobsley (1974).

Results

UNOPERATED SUBJECTS

Gastric secretion corrected for pyloric loss and duodenal reflux— V_G

Gastric secretion was first examined in the 37 unoperated subjects in whom phenol red had been used. The volume of secretion, expressed as V_G ml/hr, was determined for each of the four half-hour periods following the injection of insulin (fig 1). As the groups were not normally distributed, means and standard errors were calculated after logarithmic transformation.

In the first half hour, secretion was always less than in any of the subsequent half hours. The greatest output was obtained sometimes in the second, sometimes in the fourth, but most often in the third half hour, and the mean secretion during the third half hour was significantly greater than in the second ($t = 3.78$, $P < 0.001$) or fourth ($t = 2.98$, $P < 0.01$). In view of these findings, stimulated secretion was therefore expressed in two ways: (1) peak secretion, defined as the sum of the V_G of the three highest consecutive 10-minute samples, multiplied by 2 (ml/hr); (2) half- to two-hour secretion, which was the sum of the V_G of the nine samples during this period, divided by 1.5, thus again expressed as ml/hr. The ranges of secretion of the preoperative group, in terms both of peak and half- to two-hour secretion, were defined as being within two standard deviations of the mean (95% tolerance limits) and are shown in figure 1.

Fig 1 Secretory response, V_G ml/hour, to insulin 0.2 units/kg iv in 37 unoperated subjects: (a) in each half hour after the injection of insulin; (b) peak value calculated as the sum of the three highest consecutive 10-minute samples multiplied by 2 (ml/hour); (c) half- to two-hour value as sum of secretion in second, third, and fourth half hours, divided by 1.5 (ml/hour). Means, standard errors of means, and 95% tolerance limits have been calculated after logarithmic transformation. At the top is shown the numbers of patients whose secretion was greatest in the half hour indicated. In some patients, peak secretion was greater than the value of the maximal half hour, the three highest consecutive samples not being within one half-hour period.

CONVENTIONAL INDICES OF MEASUREMENT
Insulin-stimulated secretion was considered, in all 45 unoperated subjects, in terms of observed volume, titratable acidity, and acid output. As with V_G , secretion during the first half hour was less than in the subsequent three half-hour periods by all indices of measurement. Therefore peak secretion and half- to two-hour secretion were also calculated for these indices and the preoperative ranges established. Like V_G , secretion expressed as observed volume or acid output was distributed on a logarithmic scale, and statistical analysis was performed after logarithmic transformation. Unlike all the other indices of measurement, it was found that the best way to transform to a normal distribution the values of secretion expressed as titratable acidity was to take

the square of each value. The 95% (ie, 2 standard deviations from the mean) and 99% (ie, 3 standard deviations from the mean) tolerance limits for each group were calculated. In table I, the mean values and lower 95% and 99% limits of the range of each group are shown; observed volume, titratable acidity, acid output, and V_G are all expressed as peak and half- to two-hour secretion.

POSTVAGOTOMY SUBJECTS

Secretion corrected for pyloric losses and duodenal reflux— V_G
Stimulated secretion, expressed as V_G ml/hr, in the 86 postvagotomy subjects in whom phenol red was

	Observed Volume (ml/hour)		Titratable Acidity (mmol/litre)		Acid Output (mmol/hour)		V_G (ml/hour)	
	Peak	1/2-2 Hour	Peak	1/2-2 Hour	Peak	1/2-2 Hour	Peak	1/2-2 Hour
Mean	270	213	115	105	29.40	22.09	283	226
Lower 95% tolerance limit of range	125	88	83	75	12.42	8.51	142	105
Lower 99% tolerance limit of range	85	57	61	53	8.07	5.28	100	71

Table 1 Insulin-stimulated secretion in male patients with duodenal ulcer

Fig 2 Comparison of secretion, expressed as V_G , in the unoperated and postvagotomy groups. Mean, standard error of mean, and 95% tolerance limits of range of the unoperated group calculated after logarithmic transformation. In the postvagotomy group closed circles represent patients with recurrent ulcer, triangles patients with recurrent symptoms, and open circles patients with no symptoms.

used compared with the preoperative range of secretion (95% tolerance limits) is shown in fig 2 and summarized in table II. The V_G of all nine patients who developed recurrent ulcers (eight seen at re-operation, one on gastroduodenoscopy) was

within the preoperative range. Likewise the secretion in all four subjects with symptoms suggestive of recurrent ulceration was within the preoperative range. However, of the 73 subjects with no symptoms suggestive of recurrent ulceration, only six in terms of peak secretion and seven in terms of half-to two-hour secretion were within the preoperative range; all other subjects secreted less than the preoperative group.

Conventional indices of measurement

Insulin-stimulated secretion in all 124 postvagotomy patients was compared with the preoperative range of secretion, both peak and half-to two-hour values, in terms of observed volume (V_{obs}), titratable acidity, and acid output.

In table II the distribution of patients relative to the lower 95% tolerance limit of the unoperated group is summarized. Only observed volume gave a discrimination of subjects into two groups to an extent comparable to that achieved in terms of V_G . In terms of peak V_{obs} all patients with recurrent ulcer or recurrent symptoms secreted within the preoperative range, and as V_{obs} half-to two-hours only one patient with a recurrent ulcer secreted less than the lower limit of this range. However, 16 and 20 asymptomatic subjects were within the preoperative ranges of the peak and half-to two-hour periods respectively. Both titratable acidity and acid output failed adequately to discriminate, because the number of patients with recurrent ulcer below the lower limits of the respective preoperative ranges was unacceptably high.

In table III the distributions of patients in terms of titratable acidity and acid output relative to the lower 99% tolerance limits of the unoperated group are summarized, and for comparison the Hollander status is added. Titratable acidity one half to two-hours still failed adequately to discriminate into two groups, and, whereas peak titratable acidity did do so, 26 asymptomatic patients secreted within the preoperative range. Of the conventional indices, acid output (fig 3) gave the best discrimination; when

	Observed Volume		Titratable Acidity		Acid Output		V_G	
	Peak	1/2 Hour	Peak	1/2 Hour	Peak	1/2 Hour	Peak	1/2 Hour
<i>Above Unoperated Lower 95% Tolerance Limits</i>								
Recurrent ulcer	15	14	8	7	11	11	9	9
Recurrent symptoms	7	7	4	2	6	6	4	4
No symptoms	16	20	9	7	6	5	6	7
<i>Below Unoperated Lower 95% Tolerance Limits</i>								
Recurrent ulcer	0	1	7	8	4	4	0	0
Recurrent symptoms	0	0	3	5	1	1	0	0
No symptoms	86	83	93	95	96	97	67	66

Table II Distribution of postvagotomy patients by reference to the unoperated lower 95% tolerance limits

Distribution by Our Criteria				Distribution by Hollander Status		
Criterion	Clinical Status	Number in Terms of Titratable Acidity		Number in Terms of Acid Output		Number
		Peak	½-2 Hour	Peak	½-2 Hour	
Above unoperated lower 99% tolerance limits	Recurrent ulcer	15	13	15	15	13
	Recurrent symptoms	7	6	7	7	6
	No symptoms	26	26	13	15	44
Below unoperated lower 99% tolerance limits	Recurrent ulcer	0	2	0	0	2
	Recurrent symptoms	0	1	0	0	1
	No symptoms	76	76	89	87	58

Table III Distribution of postvagotomy patients by reference to two sets of criteria

Fig 3 Comparison of secretion, expressed as acid output, in unoperated and postvagotomy groups. Mean and standard error of mean in the unoperated group calculated after logarithmic transformation. The dotted line represents the 95% tolerance limits, and the lowest closed line the lower 99% tolerance limit of the unoperated group. In the postvagotomy group closed circles represent patients with recurrent ulcer, triangles patients with recurrent symptoms, and open circles patients with no symptoms.

compared with the lower 99% tolerance limit of the unoperated group all 15 patients with recurrent ulcer and seven patients with recurrent symptoms were above this value, together with only 13 and 15 asymptomatic subjects for the peak and half-to two-hour periods respectively. As the numbers are not identical, comparison between the discrimination in terms of peak V_G and peak acid output is difficult. However, five of the 13 asymptomatic subjects within the preoperative peak acid output range were below the peak V_G range.

By contrast, when examined by Hollander's criteria two patients with recurrent ulcer and one with recurrent symptoms were negative and 44 asymptomatic subjects were positive.

Discussion

Hollander's contribution (Hollander, 1946) was to direct attention to insulin-induced hypoglycaemia as a vagal stimulus to gastric secretion. However, his fundamental approach to measurement of the response to this stimulus was to compare gastric secretion during insulin-induced hypoglycaemia with the same subject's basal secretion immediately before the insulin was given (Hollander, 1948). This was merely an example of the technique of using the subject as his own control, a technique of recognized validity and proven worth in countless fields. Unfortunately, this approach depended on the assumption that basal gastric secretion is reproducible and constant in any individual, and this assumption has since been disproved (Baron, 1963; Gillespie, Elder, Smith, Kennedy, Gillespie, Kay, and Campbell, 1972).

The present study has therefore ignored basal secretion. As a standard for comparison, we have replaced basal secretion after vagotomy with insulin-stimulated secretion in male patients with duodenal ulcer before vagotomy. We emphasize that our findings, therefore, necessarily related only to male

patients after vagotomy for duodenal ulcer. The principle of our test is that the gastric secretion of such patients during insulin-induced hypoglycaemia is compared with the range of values obtained in a group of patients with duodenal ulcer who had not undergone vagotomy.

In making the comparison, we have studied not only the conventional indices of gastric secretion—volume, titratable acidity, acid output—but also V_G , the volume of gastric juice after correction for pyloric losses and duodenal reflux. In making the comparison between data for unoperated patients and data after operation we have used the 95% tolerance limits of the former for volume and V_G but the 99% tolerance limits for titratable acidity and acid output. These two indices are particularly liable to negative errors occasioned by the reflux of alkaline liquid from the duodenum into the stomach. Because of this tendency we have found it necessary to reduce the lower limit defining the unoperated range in respect of these indices.

Our findings have been that volume, acid output, and V_G all give a much better prediction of recurrent ulceration, proven or suspected, than the Hollander criteria. The best prediction, as one might expect, is given by the most accurate index of gastric secretion, ie, V_G : all patients with recurrence had an insulin-stimulated secretion in the preoperative range, while only six out of 73 patients with no evidence of recurrence had a secretion level within that range. Acid output and volume gave a reasonable, but definitely less good, prediction; titratable acidity, the basis of Hollander's criteria, gave a very poor prediction. Since V_G is the most accurate index and its estimation requires the measurement of pyloric losses, it was fortunate that the errors introduced by bile into the spectrophotometric determination of phenol red could be circumvented (see Methods).

The reason for the poor index given by titratable acidity is presumably its great susceptibility to the error produced by reflux of alkaline material from the duodenum into the stomach; such reflux greatly reduces titratable acidity both by dilution and by neutralization. The mathematical relationships have been fully explored by Fiddian-Green, Faber, Russell, Whitfield, and Hobsley (1974). On the other hand, reflux reduces acid output only by neutralization, and the acid output therefore falls proportionately less than does the titratable acidity. In retrospect, it was unfortunate that Hollander chose not only basal secretion as his standard for comparison, but titratable acidity as his index of gastric secretion—the one index that is most susceptible to error.

The application of the criteria suggested in this paper to past or future data on insulin-stimulated secretion after vagotomy should, if there is any merit

in our approach, cast light on some other puzzling features that have been reported: for example, the apparent variability of the response to hypoglycaemia at various times after the operation (Smith, Gillespie, Elder, Gillespie, and Kay, 1972), and the disparity in incidence of 'complete' and 'incomplete' vagotomy from different centres.

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