

Differences between males and females in the Hollander insulin test

J. SPENCER, G. P. BURNS, F. C. Y. CHENG, A. G. COX, AND R. B. WELBOURN

From the Royal Postgraduate Medical School and Hammersmith Hospital, London

When treating duodenal ulcer by vagotomy surgeons aim at dividing all the vagal secreto-motor fibres to the stomach. In order to assess whether this aim had been achieved, Hollander (1948) developed the insulin test which has proved a valuable clinical method of judging whether the vagi have been divided completely. The criteria by which the acid secretory response of the stomach to insulin-induced hypoglycaemia is interpreted were established on an empirical basis. Apart from Hollander's criteria, other standards have been suggested for the interpretation of the insulin test by Bachrach (1962), Stempien (1962), and Bank, Marks, and Louw (1967). None of these authors suggested that it might be necessary to employ different criteria for men and women. In this communication we report differences between the secretory response to insulin of male and female patients, and apply them to the interpretation of the Hollander test after vagotomy.

PATIENTS AND METHODS

Insulin tests were carried out on 55 male and 15 female patients with duodenal ulcer before surgery, and on 138 men and 44 women about 10 days after vagotomy and a drainage procedure (pyloroplasty or gastroenterostomy).

All tests were carried out after an overnight fast, a nasogastric tube being positioned under fluoroscopic control in the most dependent part of the stomach. Fasting gastric juice was aspirated and discarded. Basal secretion was collected for two 15-minute periods followed by eight 15-minute collections after the intravenous injection of soluble insulin. Aliquots of the collections were titrated with N/10 NaOH using Töpfer's reagent as indicator for free acid. The volume, pH, acid concentration, and acid output of each sample were measured. The dose of insulin used was 20 units in the earlier tests and 0.25 units/kg body weight in the later tests. Blood samples for glucose estimation were taken at the time of injection of insulin, and 30 and 45 minutes later. The tests were rejected if the blood sugar did not fall below 45 mg per 100 ml after insulin.

The preoperative tests were analysed to establish whether men and women gave different acid secretory responses to insulin.

The postoperative results were analysed in the first instance using Hollander's criteria. A positive response to insulin, indicating incomplete vagotomy, was defined as a rise in acid concentration in any 15-minute period after insulin of 20 or more m-equiv/l above the basal concentration, or of 10 or more m-equiv/l if no free acid was present in the basal secretion. This analysis revealed significantly different incidences of complete vagotomy in men and women. The weights of the patients were studied in order to determine whether heavier patients had a higher incidence of incomplete vagotomy. This did not provide a satisfactory explanation for the difference previously noted and the insulin tests were therefore analysed again using different criteria for men and women.

RESULTS IN PREOPERATIVE TESTS

ACID OUTPUT The mean output of free acid in response to insulin in the males and females is shown in Figure 1. There was an initial slight fall in output after insulin followed by a steep rise to a peak output at 75 minutes. The mean levels were consistently higher in the males, and at the time of peak output the difference between the males (7.3 m-equiv/15 min, SD 4.2) and the females (3.9 m-equiv/15 min, SD 2.3) was highly significant ($P < 0.005$).

ACID CONCENTRATIONS The changes in free acid concentration after insulin are shown in Figure 2. The mean concentrations were consistently higher in the males than in the females though the highest mean concentrations did not differ significantly ($0.2 > P > 0.1$).

PEAK CONCENTRATION Although the peak of the mean concentration curves occurred at 75 minutes, individual patients did not all reach peak concentration at this time. The means of the peak concentrations achieved by individual patients are seen in Table I. The mean of the peak concentrations in the males was 98.7 m-equiv/l (SD 22.8) and in the females was 82.1 m-equiv/l (SD 20.6). This difference was significant ($P < 0.02$).

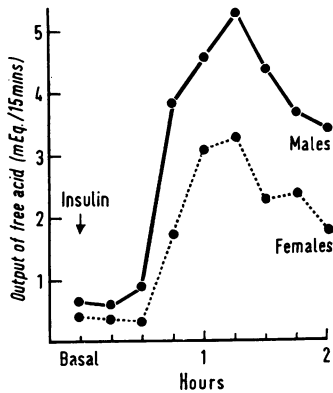


FIG. 1.

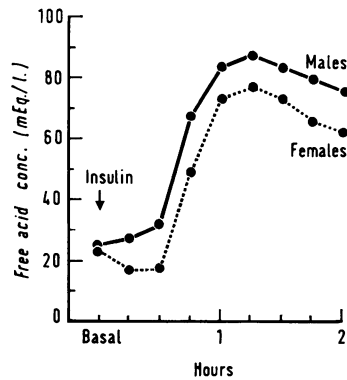


FIG. 2.

FIG. 1. Acid output in response to insulin (duodenal ulcer before surgery). Mean acid outputs in response to insulin of 55 males and 15 females. At peak output the difference between males and females was significant ($t = 2.9$, $P < 0.005$).

FIG. 2. Effect of insulin on acid concentration (Duodenal ulcer before surgery). Mean acid concentrations after insulin in 55 males and 15 females. The difference between the peaks of the mean concentrations was not significant ($t = 1.33$, $0.2 > P > 0.1$).

RISE ABOVE BASAL CONCENTRATION The basal concentration in each patient was subtracted from the peak concentration to obtain the *highest rise* in acid concentration. The means of these values are also seen in Table I. The mean in the males was 71.6 m-equiv/l (SD 22.9) and in the females 59.9 m-equiv/l (SD 22.8). The difference between these means was not quite significant ($0.1 > P > 0.05$).

RESULTS IN POSTOPERATIVE TESTS

ANALYSIS BY HOLLANDER'S CRITERIA The results of these tests using Hollander's criteria are seen in Table II. Of the 182 patients, 61 (34%) had positive responses to insulin. The incidence of positive responses was 38% in the males and 18% in the females, the difference being significant ($P < 0.02$).

WEIGHT ANALYSIS The mean weights of the patients

undergoing vagotomy are shown in Table III. The men were considerably heavier than the women, the difference between the mean weights being highly significant. Neither in the men nor in the women, however, was there any significant difference between the mean weights of those with complete and those with incomplete vagotomy.

TABLE III

WEIGHTS OF PATIENTS UNDERGOING VAGOTOMY				
Patients	Mean Weight (kg)	SD	t	P
All males	64.7	9.8	4.0	< 0.0001
All females	57.6	12.1		
Males with positive response	64.3	9.9	1.28	> 0.1
Males with negative response	66.7	7.6		
Females with positive response	57.1	12.9	0.23	> 0.8
Females with negative response	56.0	10.5		

TABLE II

POSTOPERATIVE INSULIN TESTS

	Total	Positive
All cases	182	61 (34%)
Males	138	53 (38%)
Females	44	8 (18%)

The difference between the incidence of positive responses in males and females is significant. $\chi^2 = 6.552$, $0.02 > P > 0.01$.

TABLE I

DIFFERENCES BETWEEN MALES AND FEMALES IN THE PREOPERATIVE INSULIN RESPONSE

	55 Males		15 Females		t	P
	Mean	SD	Mean	SD		
Peak acid concentrations (m-equiv/l)	98.7	22.8	82.1	20.6	2.47	< 0.02
Highest rise in acid concentration (m-equiv/l)	71.6	22.9	59.9	22.8	1.75	$0.1 > P > 0.05$

ANALYSIS USING DIFFERENT CRITERIA The results of the postoperative tests on the males and females were analysed separately and repeatedly, on each occasion using a different rise in concentration as the criterion for a positive response. In each sex the results obtained in the other sex by the use of each criterion were compared with the results previously

obtained using Hollander's criteria. The results are seen in Tables IV and V.

In males (Table IV) when the criterion used was increased to a rise of 23 m-equiv/l in acid concentration, the incidence of positive responses did not differ significantly from that obtained in the females using Hollander's criteria. When a rise of less than 23 m-equiv/l was used as the criterion, the difference in the incidence in the two sexes was significant.

In females (Table V) it is seen that when the criterion used was a rise of 15 m-equiv/l or more in concentration, the incidence of positive responses differed significantly from that obtained in males using Hollander's criteria. No such difference was seen if 14 m-equiv/l was taken as the standard.

TABLE IV

COMPARISON OF POSITIVE INSULIN TESTS IN MALES AND FEMALES USING VARYING CRITERIA FOR MALES AND THE STANDARD CRITERION FOR FEMALES

Rise in Concentration Used as Criterion for Positive Responses in Males	Positive Responses in Males	Significance of Difference from % Incidence in Females Using Standard Criterion ¹
26	38 (28%)	} Not significant P > 0.1
25	39 (28%)	
24	43 (31%)	
23	43 (31%)	
22	48 (35%)	} Significant P < 0.05
21	48 (35%)	
20	53 (38%)	

¹As defined by Hollander (1948)—see text.

TABLE V

COMPARISON OF POSITIVE INSULIN TESTS IN MALES AND FEMALES USING VARYING CRITERIA FOR FEMALES AND THE STANDARD CRITERION FOR MALES

Rise in Concentration Used as Criterion for Positive Response in Females	Positive Responses in Females	Significance of Difference from % Incidence in Males using Standard Criterion ¹
20	8 (18%)	} Significant P < 0.05
19	8 (18%)	
18	8 (18%)	
17	8 (18%)	
16	9 (20%)	
15	9 (20%)	} Not significant P > 0.1
14	11 (25%)	
13	11 (25%)	

As defined by Hollander (1948)—see text.

DISCUSSION

Analysis of our postoperative insulin tests by conventional criteria revealed a large discrepancy between the incidence of positive responses in men and women after vagotomy. One possible explanation was that the discrepancy represented a true difference in the incidence of complete vagal section in the two sexes. There is no obvious anatomical

reason why this should be the case, but it may be that vagotomy is more difficult in larger patients. The men were considerably heavier than the women, but there was no difference between the weights of the patients with complete and of those with incomplete vagotomy. It seems unlikely therefore that the patients' weights influenced the completeness of nerve section.

Another explanation of the difference is that wrong criteria were being applied to interpret the tests. Hollander's criteria are normally applied indiscriminately to males and females alike. This is a reasonable policy only if the secretory responses to insulin are equal in the two sexes. However, a difference in the response to insulin has been reported by Welbourn and Burns (1964). Our present results on an extended series of patients show a large difference in insulin-stimulated acid output and also indicate that higher acid concentrations are achieved in men than in women.

These findings suggest that different criteria should be applied to the interpretation of the test in the two sexes. In the preoperative tests, the mean highest rise in acid concentration after insulin in men and women was 72 and 60 m-equiv/l respectively. If this difference is taken as an index of relative secretory potential in the two sexes, then a rise in concentration of 20 m-equiv/l in men would correspond to a rise of $\frac{60}{72} \times 20$ or approximately 17 m-equiv/l in women. Conversely, a rise of 20 m-equiv/l in women would correspond to a rise of $\frac{72}{60} \times 20$ or approximately 23 m-equiv/l in men. If Hollander's criteria are accepted for use in one sex, modifying the criteria for the other sex will alter the proportion of positive responses. The results obtained in our patients indicate that if the 20 m-equiv/l standard is used for the men, the standard for women must be lowered to 14 m-equiv/l before the difference in the incidence of positive responses is eliminated. Alternatively, it can be eliminated by using the 20 m-equiv/l standard in women and increasing the standard in the men to 23 m-equiv/l. Whether the criteria should be lowered for the female tests or raised for the male tests remains unanswered. The former course would increase the apparent overall incidence of incomplete vagotomy; the latter course would lower it.

SUMMARY

Hollander insulin tests have been carried out on 70 patients with duodenal ulcer before surgery, and on 182 patients after vagotomy.

The postoperative tests indicated a higher incidence of incomplete vagotomy in the male patients (38%) than in the females (18%), the difference between the two groups being significant. This difference was not related to the difference in weight between the men and the women.

Preoperative tests showed that the secretory output of acid in response to insulin was greater in men than women; the men also achieved significantly higher peak acid concentrations after insulin.

It is suggested that it may be necessary to apply different criteria when interpreting insulin tests in men and women.

We wish to express our appreciation to Miss M. McDermott for help with the analyses, and to staff nurses Alexander, Pope, and Sherman for help with the tests.

REFERENCES

- Bachrach, W. H. (1962). Laboratory criteria for the completeness of vagotomy. *Amer. J. dig. Dis.*, 7, 1071-1085.
- Bank, S., Marks, I. N., and Louw, J. H. (1967). Histamine- and insulin-stimulated gastric acid secretion after selective and truncal vagotomy. *Gut*, 8, 36-41.
- Hollander, F. (1948). Laboratory procedures in the study of vagotomy. *Gastroenterology*, 11, 419-425.
- Stempien, S. J. (1962). Insulin gastric analysis: technic and interpretations. *Amer. J. dig. Dis.*, 7, 138-152.
- Welbourn, R. B., and Burns, G. P. (1964). Choice of operation for duodenal ulcer on the basis of preoperative gastric secretory studies. *Congr. int. Gastroent.*, 1, 163-177.

The March 1969 Issue

THE MARCH 1969 ISSUE CONTAINS THE FOLLOWING PAPERS

Signposts

Selection of the operation for duodenal ulcer NORMAN C. TANNER

The act of vomiting in man K. LUMSDEN and W. S. HOLDEN

Effect of dried beans and silicone on intestinal hydrogen and methane production in man D. H. CALLOWAY and S. E. BURROUGHS

Systemic sclerosis and small bowel involvement RODNEY BLUESTONE, M. MACMAHON, and J. M. DAWSON

Adrenal and clinical responses to corticotrophin and prednisone in inflammatory disease of the colon M. FRIEDMAN, J. M. HINTON, and J. E. LENNARD-JONES

Fate of the rectum and distal colon after subtotal colectomy for ulcerative colitis B. I. KORELITZ, W. P. DYCK, and F. M. KLION

Sodium conservation by the small intestine in a patient with chronic ileostomy diarrhoea N. D. GALLAGHER, D. D. HARRISON, J. V. WYATT, and A. P. SKYRING

Free perforation in regional enteritis K. NASR, D. A. MOROWITZ, J. G. D. ANDERSON, and J. B. KIRSNER

External pancreatic response to food and its relation to the maximal secretory capacity in dogs F. W. HENRIKSEN and H. WORNING

Continuous recording of pH in the duodenal bulb after food and alkali HUGH H. LAWSON and RANDOLPH A. ROVELSTAD

Effect of low dosage of carbenoxolone sodium on gastric ulcer healing and acid secretion J. B. COCKING and J. N. MACCAIG

Role of gastric secretion in iron absorption A. JACOBS and P. M. MILES

Gastric plasmacytoma DAPHNE H. LINE and RONALD H. LEWIS

Unclassified oesophageal motor disorders simulating achalasia WALTER J. HOGAN, CARLTON R. CAFLISCH, and DANIEL H. WINSHIP

Alcohol degradation and bromsulphthalein metabolism in acute alcoholic liver disease PATRICIA WILKINSON, DENIS M. O'DAY, and JAMES G. RANKIN

Techniques

Use of the Heidelberg pH capsule in the routine assessment of gastric acid secretion B. H. R. STACK

Notes and activities

Copies are still available and may be obtained from the PUBLISHING MANAGER,
BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, W.C.1, price 17s. 6d.