The augmented histamine test in the differential diagnosis between ulcer and cancer of the stomach

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EDITORIAL SYNOPSIS The maximum gastric acidity has been studied using the augmented histamine test in patients with gastric ulcer, with ulcers in the body of the stomach, with pre-pyloric ulcers, and in patients with gastric carcinoma. The results have not enabled a clear distinction to be made between simple and malignant ulcers.

The differential diagnosis between ulcer and cancer of the stomach is based on the history of the disease, the physical examination of the patient, stomach radiographs, gastroscopy, and exfoliative cytology.

Tests of gastric function have played a minor role in diagnosis. It is generally assumed that patients with gastric cancer have achlorhydria or a very low output of gastric acid but it has also been assumed that many apparently healthy people in the 'cancer age', and even patients with stomach ulcers, may have achlorhydria (Vanzant, Alvarez, Eusterman, Dunn, and Berkson, 1932; Barrett, 1946; State, Varco, and Wangenstein, 1947; Heffernon, Kiefer, and Tracey, 1949; Stewart, 1955; Turner, Dockerty, Priestley, and Comfort, 1957; Comfort, Priestley, Dockerty, Weber, Gage, Solis, and Epperson, 1957) when examined by a test meal or after the injection of 0.5 mg. of histamine. Gastric function tests were much improved when Kay's augmented histamine test was introduced (1953). This test reflects the maximum secretory power of the gastric mucosa, which depends on the number of parietal cells in the stomach (Card and Marks, 1960). When the augmented histamine test is used only few cases of achlorhydria are found, and achlorhydria must then be regarded as a most important sign which makes Addisonian anaemia or gastric cancer the most likely diagnosis.

Hirschowitz, London, and Wiggins (1957) used the augmented histamine test in 31 patients with gastric lesions. In 16 patients with gastric ulcer the maximum acidity of the gastric juice was always more than 80 mEq. H^+ /l., and the chloride concentration more than 135 mEq. Cl^- /l. Fifteen patients with cancer of the stomach had concentrations of H^+ and Cl^- which were constantly lower than 90 and 140 mEq./l. respectively. Using the combined

figures for acid and chloride concentrations (Fig. 1) from several samples from each patient Hirschowitz *et al.* were able to distinguish quite clearly between ulcer and cancer in this series of 31 patients.

Our report describes the results of the augmented histamine test in a larger series of patients with gastric ulcer or gastric cancer.

PATIENTS

From January 1958 to July 1961 348 patients with gastric ulcer and 128 patients with stomach cancer were treated in Surgical Department A, Bispebjerg Hospital, Copenhagen. Thirty-one patients with ulcers and 10 with cancer were not operated upon for a variety of reasons, and are not included in this study. Eighty-one patients with gastric ulcers were operated upon without previous function tests, the majority having emergency operations for bleeding ulcer. Nine with gastric cancer escaped a pre-operative test because of bleeding or stenosis which prevented the passing or placing of gastric tubes. This study is, therefore, based on 236 patients with gastric ulcer and 109 patients with cancer, examined by the augmented histamine test and subsequently operated upon. The diagnosis was histologically confirmed in all cases.

The patients with gastric ulcers were divided into two groups, those with ulcers of the corpus and those with prepyloric ulcers. Prepyloric ulcers are located within the gastric antrum, an arbitrary limit being set at 5 cm. from the pylorus.

The age and sex distribution in the three groups of patients (Table I) shows that the majority of ulcer patients are 10 to 20 years younger than the cancer patients.

FIG. 1. The maximum gastric secretory response in 15 patients with cancer and 16 with gastric ulcer (Hirschowitz, London, and Wiggins, 1957).

TABLE I

AGE AND SEX OF 345 PATIENTS WITH STOMACH ULCER AND CANCER

Age (yr.)	20-29	30-39	40-49	50-59	60-69	70-79	>80	Total
<i>Corpus ulcer</i>								
Male	2	3	8	25	15	14	0	67
Female	1	3	20	19	21	8	3	75
Total	3	6	28	44	36	22	3	142
<i>Prepyloric ulcer</i>								
Male	0	4	14	16	17	7	0	58
Female	0	3	14	14	4	1	0	36
Total	0	7	28	30	21	8	0	94
<i>Gastric cancer</i>								
Male	0	0	4	13	17	25	5	64
Female	0	0	3	3	15	21	3	45
Total	0	0	7	16	32	46	8	109

METHODS

In 232 patients, examined between 1958 and 1960, the augmented histamine test was performed as described by Hirschowitz *et al.* (1957). A continuous infusion of histamine (5.5 mg. histamine diphosphate, corresponding to 2 mg. histamine base, in 1,000 ml. physiological saline, to which had been added 20 mg. mepyramine maleate) was given at the rate of 100 drops per minute. Thus the patient had 10 gamma of histamine per minute. An increase to 14 gamma per minute did not increase the volume nor the hydrochloric acid concentration in the gastric juice (Køster and Thorsøe, 1960). The stomach tube was placed at the greater curvature opposite the angulus, the position of the tube being controlled radiologically. Suction was provided by an electric pump at a negative pressure of 50 mm. Hg, frequently interrupted, and completed by hand suction with a syringe.

The acidity of the gastric juice was measured by electrometric titration to pH 3.3, the same end-point as chosen by Hirschowitz *et al.*, and the chloride concentration by Brun's modification of Schaales and Schaales' method.

One hundred and thirteen patients (1960-61) were examined by Kay's original technique (1953) in which 50 to 100 mg. of mepyramine maleate was injected intramuscularly and 30 minutes later 0.04 mg./kg. of histamine was given subcutaneously. Gastric juice was aspirated and titrated as described above.

Kay's technique and Hirschowitz' modification of it gave essentially the same results when both tests were tried in the same patient, a maximum activation of the secretory capacity. In all patients examined the maximum acidity (mEq. H^+ /l.) and the acid output (mEq. H^+ per hour) were determined. In the 232 patients examined by the Hirschowitz modification the chloride concentration was also determined, and the maximum value (mEq. Cl^- /l.) is reported.

RESULTS

In each of the three groups of patients the maximum acidity (mEq. H^+ /l.) for each patient is plotted against the patient's age. In cases where no free acid was produced, the lowest pH attained is shown in the diagram below the zero line for acidity.

GASTRIC CORPUS ULCER One hundred and forty-two patients were examined and operated upon. At the augmented histamine test 42 patients (30%) attained a maximum gastric acidity of 80 mEq. H^+ /l. or more. Thirty-one patients (22%) produced 20 mEq. H^+ /l. per hour or more (Fig. 2). The chloride concentration reached 135 mEq. Cl^- /l. in 56 of 93 (60%) patients examined (Fig. 3). Three patients did not produce any free hydrochloric acid.

Case 1 A 58-year-old man (No. 1652), had a three months' history. On the augmented histamine test the pH fell from 8.1 to 6.1 and chlorides rose to 80 mEq. Cl^- per litre. An insulin test showed achlorhydria. An ulcer

FIG. 2. Augmented histamine test in 142 patients with gastric (corpus) ulcer. Top: The maximum acidity in each case during the test. Bottom: The hydrochloric acid output per hour.

of the cardia (50 × 50 mm.) was removed by an upper partial gastrectomy. Serial sections showed no sign of malignancy and biopsies from the stomach mucosa showed extensive gastritis and metaplasia with a few parietal cells.

Case 2 A 74-year-old man (No. 4190), had a four months' history. At the augmented histamine test the pH fell from 5.1 to 3.7. An ulcer of the cardia (30 × 25 mm.) was removed by an upper partial gastrectomy. Histologically the picture was that of periarteritis nodosa, also present in other organs, moderate gastritis, metaplasia, and some parietal cells.

Case 3 A 67-year-old man (No. 5619 A), for many years an alcoholic, had a history of one month. On the

FIG. 3. Augmented histamine test in 93 patients with gastric (corpus) ulcer showing combined plot of the maximum concentrations of H^+ and Cl^- in each patient. Limits of H^+ at 80 mEq./l. and of Cl^- at 135 mEq./l. as in Fig. 1.

augmented histamine test the pH fell from 3.8 to 3.6. An ulcer (25 × 40 mm.) low on the lesser curvature was removed by a Billroth I operation. Histologically the ulcer showed no malignancy but atrophic gastritis without parietal cells. Moderate portal hypertension was found and a liver biopsy showed steatosis.

PREPYLORIC ULCERS Prepyloric gastric ulcers were found in 94 patients, of whom 55 (58.5%) attained a maximum acidity of 80 mEq. H^+ per litre. Forty-five patients (48%) produced 20 mEq. H^+ per hour or more (Fig. 4). The chloride concentration reached 135 mEq./l. in 49 of 70 examined patients (70%) (Fig. 5).

One patient produced no free acid. He was a man aged 61 years (No. 5769), with a 10 months' history of illness. On the augmented histamine test the pH fell from 8.3 to 3.7 and chlorides rose from 58 to 78 mEq. per litre. A prepyloric ulcer (30 × 5 mm.) was removed by a Billroth I gastrectomy. Histologically there was no malignancy. Many parietal cells were found in biopsies from the fundus.

CANCER OF THE STOMACH One hundred and nine patients were examined by the augmented histamine

test and later operated upon for this condition. Eight (7.3%) were able to produce gastric juice containing 80 mEq. H^+ or more per litre. Sixty patients (55%) did not secrete any free acid, and of those 20 had an acidity as the pH was above seven. Four patients (3.7%) produced 20 mEq. H^+ or more per hour (Fig. 6). The chloride concentration reached 135 mEq. Cl^- /l. in 17 patients (25%) of 69 examined (Fig. 7). The case histories of the eight patients producing gastric juice of high acidity are summarized in Table II. Characteristically, these eight patients all had radical partial gastrectomies performed.

DIFFERENTIAL DIAGNOSIS BETWEEN ULCER AND CANCER

The highest concentrations of free H^+ and total Cl^- after the maximum histamine test in 232 patients were plotted showing mEq. H^+ per litre on the ordinate and mEq. Cl^- on the abscissa. Samples with achlorhydria are represented below zero by the lowest pH attained during the test. One area of the diagram is defined by the limits of 80 mEq. H^+ and

FIG. 4

FIG. 4. Augmented histamine test in 94 patients with prepyloric ulcer. Top: The maximum acidity in each case during the test. Bottom: The hydrochloric acid output per hour.

FIG. 5

FIG. 5. Augmented histamine test in 70 patients with prepyloric ulcer showing the combined plot of the maximum concentrations of H^+ and Cl^- in each patient. Limits of H^+ at 80 mEq./l. and of Cl^- at 135 mEq./l. as in Fig. 1.

135 mEq. Cl^- per litre, and Hirschowitz *et al.* found that all samples from cancer patients fell in the area situated below these combined limits. For practical reasons the results for patients with corpus ulcers, prepyloric ulcers, and cancer are shown separately (Fig. 3 to 7).

ULCER OF THE CORPUS Ninety-three patients were examined: in 28 (30%) the combined concentrations of free H^+ total Cl^- fell above the combined limits (Fig. 3) in the 'benign' area but in 34 (37%) they fell entirely in the 'cancer' area.

PREPYLORIC ULCER Of 70 patients, in 20 (28.5%) concentrations fell below the combined limits, whereas 38 (54%) produced gastric juice of a higher acidity (Fig. 5).

GASTRIC CANCER Sixty-nine patients were examined: in 65 (94%) concentrations fell below the combined limits in the 'cancer' area, and four patients (6%) produced 80 mEq. H^+ per litre or more (Fig. 7).

DISCUSSION

In this series of investigations we have not been able to distinguish clearly between ulcer and cancer of the stomach by means of the augmented histamine test. Thus we cannot fully confirm the results obtained by Hirschowitz *et al.* (1957). The comparatively low output of acid in many patients with gastric ulcer in the present series constitutes a major divergence between our results and those of Hirschowitz *et al.* One hundred and thirty-five

FIG. 6

FIG. 7

FIG. 6. Augmented histamine test in 109 patients with gastric cancer. Top: The maximum acidity in each case during the test. Bottom: The hydrochloric acid output per hour.

FIG. 7. Augmented histamine test in 69 patients with gastric cancer showing the combined plot of the maximum concentrations of H^+ and Cl^- in each patient. Limits of H^+ at 80 mEq./l. and of Cl^- at 135 mEq./l. as in Fig. 1.

patients, or 57% of all the ulcer patients, produced less than 80 mEq. H^+ /l. after histamine stimulation, and four did not produce any free acid at all. But even those four showed some slight acid secretory activity, as the pH of the aspirated gastric juice dropped by 0.2 to 4.6 in one hour after the injection of histamine (Table III). Thus, there were no patients with ulcer in whom secretion of acid could not be demonstrated to some degree. Our findings are in agreement with those of Card and Sircus (1958).

The resected stomachs and biopsies from the fundus were examined histologically. Gastritis and metaplasia were commonly associated with gastric ulcer, and would account for the low acidity found in many cases. Furthermore, the chronic and atrophic

gastritis, which is seen in the presence of gastric, and to a lesser extent of prepyloric, ulcers (Ball and James, 1961) is indistinguishable from that seen in carcinoma of the stomach, an impression which coincides with the observations of Guiss and Stewart (1948), Morson (1955b), and Joske, Finckh, and Wood (1955).

A less prominent cause of divergence is the high acidity found in certain patients with stomach cancer (Table II). Some of these results are difficult to explain, as the patients had extensive cancers and pronounced gastritis in the examined parts of the gastric mucosa. But others had lesions which by clinical examination, radiographs, gastroscopy, and even at operation were called ulcers. Histology only revealed a small but unmistakable invading cancer in

TABLE II

EIGHT PATIENTS WITH GASTRIC CANCER PRODUCING 80 mEq./l. H⁺ OR MORE

No.	Sex	Age (yr.)	History (yr.)	Augmented Histamine Test			Diagnosis			Size of Tumour or Ulcer (mm.)	Locali- zation	Histology
				H ⁺ /l.	H ⁺ /hr.	Cl ⁻ /l.	Radio- graph	Clinical	At Op- eration			
796	M	78	1/12	96	13	151	Cancer	Cancer	Cancer	20 × 20	1	Chronic ulcer with cancer
1676	F	69	11	104	15	170	Cancer	Cancer	Cancer	40 × 50	1	Chronic ulcer with cancer
1745	M	70	16	80	13	168	Ulcer	Cancer	Ulcer	25 × 30	1	Chronic ulcer with cancer
3607	F	64	1½	102	41	167	Cancer	Ulcer	Cancer	55 × 50	2	Adenocarcinoma
5925	M	66	1	83	19	—	Ulcer	Ulcer	Ulcer	10 × 10	2	Chronic ulcer with cancer
6580	M	44	1½	118	42	—	Cancer	Ulcer	Cancer	40 × 15	2	Adenocarcinoma
6665	M	66	6	85	22	—	Ulcer	Ulcer	Cancer	25 × 25	2	Carcinoma, solid, anaplastic
7484	M	65	16	89	20	—	Ulcer	Ulcer	Cancer	40 × 40	2	Chronic ulcer with cancer

TABLE III

FOUR PATIENTS WITH GASTRIC OR PREPYLORIC ULCER NOT PRODUCING FREE ACID

Stomach Ulcer in 4 Male Patients			Parietal Cells in Biopsy from Fundus	Lowest pH		Drop
No.	Age	Site		Before Histamine	After Histamine	
1652	58	Corpus	Some	8.1	6.1	2.0
4190	74	Corpus	Some	5.1	3.7	1.4
5619A	67	Corpus	None	3.8	3.6	0.2
5769	61	Prepylorus	Many	8.3	3.7	4.6

a typical chronic ulcer. Of the 109 patients with cancer, 49 (45%) produced free hydrochloric acid by the augmented histamine test, while another 23 patients (21%) made certain small amounts of acid, which reduced the pH of the stomach contents to somewhere between 3.3 and 6. The augmented histamine test thus seems to provoke gastric acid secretion in many more patients with stomach cancer than did previous methods of activation.

Swynnerton and Truelove (1951), Björkenheim (1952), and Shahon, Horowitz, and Kelley (1956) found between 22 and 27% of patients with gastric cancer capable of acid secretion. Anthun (1952) found close to 40%, and the figure of 49%, cited by Pack (1953) for a series of operable cases, is the nearest to our findings.

Another factor which contributes to the discrepancies is the selection of patients for study.

The patients of Hirschowitz *et al.* had either small ulcers which healed completely while under observation, and only three required operation, or they had advanced cancers, 10 being inoperable. This would account, at least partly, for the wide difference in gastric acid secretion in their ulcer and cancer patients and made the complete distinction possible. The patients reported here were mostly referred from the medical departments for operation. This implies that ulcer patients have had some kind of medical treatment, which failed to cure them, and that patients with stomach cancers were not obviously inoperable. Thus, the patients examined by Hirschowitz *et al.* and by us are not strictly comparable.

As chronic atrophic or metaplastic gastritis is a common feature of both ulcer and cancer of the stomach, and as the production of hydrochloric acid

TABLE IV

PERCENTAGE OF CANCER FOUND AT VARIOUS LEVELS OF GASTRIC ACID SECRETION AFTER AUGMENTED HISTAMINE TEST

345 Patients with Gastric Lesions	Corpus Ulcer (142 patients)	Prepyloric Ulcer (94 patients)	Gastric Cancer (109 patients)	Total A - B C - D E - F	% Cancer
A pH > 7, anacidity	0	0	20	20	100
B pH 3.3 to 6.9, achlorhydria	3	1	40	44	91
C 1 to 19 mEq. H ⁺ /l.	3	4	15	22	68
D 20 to 79 mEq./l.	94	34	26	154	17
E >80 mEq./l.	42	55	8	105	7.6
F >20 mEq. H ⁺ per hour	31	45	4	80	5

is proportional to the number of parietal cells in the stomach mucosa, it seems unlikely that it should be possible to distinguish sharply between ulcer and cancer by means of augmented histamine tests and hydrochloric acid titration. The weight which might be attached to such investigations is illustrated by the calculations in Table IV.

We find, in accordance with Comfort and Butsch (1937), and with the reservations mentioned by Hirschowitz *et al.*, that if the free acid exceeds 80 mEq. H^+ per litre a lesion of the stomach is almost certainly benign but it must not be ignored that we found 7.6% which were malignant. And we agree with Card and Sircus (1957) that an acid output of 20 mEq. H^+ per hour can almost certainly be taken to exclude carcinoma, as of 80 patients who produced 20 mEq. H^+ or more, only four had cancer. Sixty-four patients of the 345 examined did not produce any free acid, and of those, 60 (94%) had cancer.

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REFERENCES

- Anthun, O. (1952). Carcinoma of stomach. Analysis and follow-up of 525 cases. *Acta chir. scand.*, **104**, 1-13.
- Ball, P. A. J., and James, A. H. (1961). The histological background to gastric ulcer. *Lancet*, **1**, 1365-1367.
- Barrett, M. K. (1946). Avenues of approach to gastric-cancer problem. *J. nat. Cancer Inst.*, **7**, 127-157.
- Björkenheim, G. (1952). Free hydrochloric acid in cancer of stomach. *Finska Läk.-Sällsk. Handl.*, **95**, 154-162.
- Brun, C. (1949). Microdetermination of chlorides in blood. *Nord. Med.*, **42**, 1774-1775.
- Card, W. I., and Marks, I. N. (1960). The relationship between the acid output of the stomach following "maximal" histamine stimulation and the parietal cell mass. *Clin. Sci.*, **19**, 147-163.
- Card, W. I., and Sircus, W. (1957). Gastric acidity. *Lancet*, **2**, 934.
- , — (1958). In *Modern Trends in Gastroenterology (second series)*, ed. F. Avery Jones, p. 186. Butterworth, London.
- Comfort, M. W., and Butsch, W. L. (1937). Differential diagnosis of benign and malignant small lesions of stomach; attempt to evaluate statistically various symptoms and laboratory findings. *Amer. J. Surg.*, **35**, 515-523.
- , Priestley, J. T., Dockerty, M. B., Weber, H. M., Gage, R. P., Solis, J., and Epperson, D. P. (1957). The small benign and malignant gastric lesion. *Surg. Gynec. Obstet.*, **105**, 435-448.
- Guis, L. W., and Stewart, F. W. (1948). Distribution of gastric changes accompanying gastric cancers in various locations. *Arch. Surg.*, **57**, 624-632.
- Heffernon, E. W., Kiefer, E. D., and Tracey, M. L. (1949). Benign gastric ulcers occurring in the presence of achlorhydria. Report of two cases. *New Engl. J. Med.*, **241**, 604-606.
- Hirschowitz, B. I., London, J. A., and Wiggins, H. S. (1957). Differential diagnosis of gastric ulcer and cancer by a study of maximally stimulated gastric secretion. *J. Lab. clin. Med.*, **50**, 447-454.
- Hitchcock, C. R., Sullivan, W. A., and Wangenstein, O. H. (1955). The value of achlorhydria as screening test for gastric cancer; 10-year report. *Gastroenterology*, **29**, 621-632.
- Joske, R. A., Finckh, E. S., and Wood, J. J. (1955). Gastric biopsy; study of 1,000 consecutive successful gastric biopsies. *Quart. J. med.*, new series, **24**, 269-294.
- Kay, A. W. (1953). Effect of large doses of histamine on gastric secretion of hydrochloric acid. An augmented histamine test. *Brit. med. J.*, **2**, 77-80.
- Køster, K. H., and Thorsøe, H. (1960). Ventrikelsekretioner undersøgt med udvidet histaminprøve. *Ugeskr. Laeg.*, **122**, 531-536.
- Morson, B. C. (1955a). Intestinal metaplasia of gastric mucosa. *Brit. J. Cancer*, **9**, 365-376.
- (1955b). Carcinoma arising from areas of intestinal metaplasia in gastric mucosa. *Ibid.*, **9**, 377-385.
- Pack, G. T. (1953). Diagnosis of cancer of the stomach. *New York med. J.*, **53**, 390-392.
- Shahon, D. B., Horowitz, S., and Kelley, W. D. (1956). Cancer of the stomach; an analysis of 1,152 cases. *Surgery*, **39**, 204-221.
- State, D., Varco, R. L., and Wangenstein, O. H. (1947). Attempt to identify likely precursors of gastric cancer. *J. nat. Cancer Inst.*, **7**, 379-384.
- Stewart, M. J. (1955). *Ulcer-cancer of the stomach*, p. 19. (Macewen Memorial Lecture, 1953.) Jackson, Glasgow.
- Swynnerton, B. F., and Truelove, S. C. (1951). Simple gastric ulcer and carcinoma. *Brit. med. J.*, **2**, 1243-1246.
- Turner, J. C. Jr., Dockerty, M. B., Priestley, J. T., and Comfort, M. W. (1957). A clinicopathologic study of large benign gastric ulcers. *Surg. Gynec. Obstet.*, **104**, 746-750.
- Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, J. (1932). The normal range of gastric acidity from youth to old age. An analysis of 3,746 records. *Arch. intern. Med.*, **49**, 345-359.