Reduced gastric acid output in cirrhosis : Quantitation and relationships¹

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EDITORIAL SYNOPSIS Basal and maximal (post-histamine) acid outputs were significantly reduced in patients with cirrhosis. A subnormal secretory response to stimulation with peptone was also found. Gastric hyposecretion was not related to the aetiology or severity of the hepatic disease nor to the extent or presence of a portal-collateral circulation. Increased gastric production of ammonia in cirrhosis did not affect acid output significantly, and the reduced response to histamine was not due to increased serum histaminase activity. Since a significant relationship was demonstrated between hypokalaemia and hyposecretion, and since the output of gastric juice appeared more greatly reduced in volume than acid concentrations, the possibility of a relationship between gastric hyposecretion and disorders of water and electrolyte metabolism is considered.

Few clinical studies of gastric secretory function in the presence of hepatic disease have been reported, and the results often appear inconsistent with experimental data. In animals, increased production of acid results from cholestasis (Silen, Skillman, Hein, and Harper, 1962), hepatocellular injury (Hein, Silen, Skillman, and Harper, 1963), or the creation of a portal-systemic collateral circulation (Gregory, 1958). Although these circumstances are pertinent, together or separately, in humans with cirrhosis, qualitative (Wang, 1936; Bockus, 1963) and quantitative studies (Ostrow, Timmerman, and Gray, 1960) indicate a diminution in gastric secretion with this disease. Nevertheless, increased acid production might be anticipated if there is a greater incidence of peptic ulcer with cirrhosis (Swisher, Baker, and Bennett, 1955), especially after portacaval anastomosis (Bendett, Fritz, and Donaldson, 1963) and if haemorrhage from oesophageal varices is attributable to acid-peptic reflux (Chiles, Baggenstoss, Butt, and Olsen, 1953; Liebowitz, 1961).

The primary purpose of the present investigation was therefore a comparison of gastric secretion in control individuals and in patients with cirrhosis, both under basal circumstances and following stimulation, the latter by an augmented dose of histamine or peptone broth. Simultaneously, factors which might influence gastric secretion in the

presence of cirrhosis were studied also, including hepatic function, the presence of a portal-systemic collateral circulation, the content of electrolytes and ammonia in gastric juice, the histology of the stomach, and the relationship of secretory responses after histamine injection to serum histaminase activity.

MATERIAL

Twenty-three men, aged 18 to 79 years (mean 56), and three women, aged 44 to 63 years (mean 54), with hepatic cirrhosis were studied. Sixteen patients, all male, gave a history of excessive consumption of alcohol; cirrhosis was of uncertain aetiology in the remainder. Patients with other types of cirrhosis were excluded. Ascites was present in 13 patients and four were jaundiced. Fifteen gave a history of massive gastrointestinal bleeding presumed to have originated from varices, and a portacaval anastomosis had been performed in four. Oesophageal varices were demonstrated by x-ray examination or by oesophagoscopy in eight patients; two had duodenal ulcers. The latter two patients are considered separately in the text.

The diagnosis of cirrhosis was made on clinical grounds, being supported by tests of hepatic function and, in 15 patients, confirmed by histological examination of hepatic tissue. At the time of study, all patients were afebrile and ambulant; none was markedly anaemic, blood haemoglobin concentrations being 10.0 g./100 ml. or higher. None had experienced gastrointestinal bleeding within the previous four weeks, nor was any azotaemic. Diuretic medication had been prescribed for eight

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patients but was discontinued for at least 24 hours before studies of gastric secretion. Sixteen patients had received diets restricted in sodium. None had undergone previous gastric surgery.

The control individuals comprised two groups. The first group (Scobie, 1964) was a consecutive series of patients in their sixth decade or older who were classified as having irritable bowel syndromes by criteria which included negative clinical and radiological investigation of the gastrointestinal tract. This group contained 15 males, aged 50 to 80 years (mean 59), and 13 females, aged 50 to 62 years (mean 53). The second group comprised healthy adults (members of the hospital staff or hospital employees) and four patients with duodenal ulcer for comparative studies involving the administration of peptone, determinations of serum histaminase activity, and observations on gastric juice electrolyte concentrations.

METHODS

Quantitation of the basal gastric secretion and the subsequent augmented histamine response was performed by a modification of Kay's method (Card and Circus, 1958). A size 16 F. tube was passed by mouth, and the tip was positioned in the dependent part of the stomach under radiological control. After withdrawal of the resting juice the stomach was continuously aspirated by pump at a pressure of 50 cm. of water, with frequent checking by syringe; specimens were pooled at 15-minute intervals. At the end of a one-hour basal collection period, pyrilamine (Neoantergan, 1.5 mg./kg.) was injected intramuscularly. Thirty minutes later, histamine acid phosphate (0.04 mg./kg.) was given subcutaneously, and the gastric contents were collected for the subsequent hour in four 15-minute aliquots. Saliva was expectorated throughout the test. Using phenosulphonphthalein as a marker, this procedure allows a mean recovery of 84% of the gastric contents in our laboratory (Scobie and Rowelstad, 1964). In five patients with cirrhosis, the test was extended to exclude a delayed response to histamine. The volume and total acid concentration (using electro-metric titration with N/10 NaOH to pH 7.0) were measured in the basal hour, in the four post-histamine 15-minute collections, and in the 30-minute post-Neoantergan specimen. Basal and maximal acid outputs were recorded as milliequivalents per hour.

A fresh 10% aqueous solution of beef peptone (Armour) was given on an arbitrary basis (2.9 ml./kg. of body weight) to six patients with cirrhosis and to five control subjects as an alternative gastric secretagogue. Basal gastric secretion was collected as described earlier; peptone solution was introduced into the stomach by gastric tube; the stomach was aspirated completely 30 minutes later, and four 15-minute collections of gastric juice were then obtained and measured by the method described.

Serum histaminase activity was determined by a microchemical method (Kapeller-Adler, 1956) from venous blood of fasting subjects, being expressed as permanganate units per 0.5 ml. of serum per 24 hours. Ammonia concentrations in arterial blood and gastric

juice were measured by the method of Seligson and Hirahara (1957); electrolyte concentrations in serum and gastric juice were determined by standard methods. Mucosa from the gastric fundus was obtained by aspiration biopsy in two patients and at operation in a third; portal hypertension and prolonged prothrombin times contraindicated gastric biopsy in the majority of patients with cirrhosis.

RESULTS

GASTRIC SECRETORY VOLUME AND ACID OUTPUT (TABLE 1) Mean values for volume of gastric secretion and acid output under both basal and histamine-stimulated circumstances were much lower in patients with cirrhosis than in control subjects (Fig. 1). Data were analyzed for each sex separately because of possible differences in gastric secretory function (Pollard, 1933; Baron, 1963), a likelihood supported by our results (Table I), and because of the small number of females with cirrhosis. A reduction in basal acid output in men with cirrhosis in relation to control subjects was present ($p < 0.05$). This reflected the significantly reduced volume secreted by those with cirrhosis ($p < 0.01$) since no significant difference in acid concentration ($p = 0.84$) was present. Significant differences in secretion were also present after the administration of histamine with regard to reductions in both volume response ($p < 0.01$) and acid output ($p < 0.01$) in patients with cirrhosis compared with control individuals; again, acid concentrations were not significantly different ($p = 0.32$). A reduction in the conjunctival injection and facial flush in response to histamine administration was also observed in patients with cirrhosis. Thus, the mean response (graded 0 to 4) was 1.8 in the latter as opposed to 2.7 in a consecutive series of 25 control individuals.

In the five patients with cirrhosis and the lowest basal volumes (< 10 ml./hr.), the specimen was inadequate for measurement of acid concentration in three, but the others had values of 44 and 48 mEq./l., which were above the mean control readings. A similar disproportion between volume and acid concentration was also evident after histamine stimulation; excluding one with achlorhydria, the five patients with cirrhosis whose volume output was below the lower range of normal (Fig. 1) had a mean acid concentration of 72 mEq./l., which approximates to the mean normal value. Patterns of basal and histamine-stimulated secretion were similar in females with cirrhosis (Fig. 1), but were too few to allow statistical comparison. Peak acid outputs (related to 15-minute periods) in patients with cirrhosis occurred during the second period in two patients, during the third period in 14, and during the fourth period in nine. A highly significant

TABLE I
GASTRIC SECRETION IN CIRRHOSIS AND IN CONTROL INDIVIDUALS
(MEAN AND STANDARD ERROR OF MEAN)

Patients	Basal Secretion (60 minutes)			Secretion after Histamine (60 minutes)		
	Volume (ml.)	Acid		Volume (ml.)	Acid	
		Concentration (mEq./l.)	Output (mEq.)		Concentration (mEq./l.)	Output (mEq./l.)
Control individuals						
Female (13)	71	23	1.5	153	76	13
Male (15) ¹	65.4 ± 6.5	25.5 ± 4.0	1.7 ± 0.4	197.3 ± 18.3	87.1 ± 7.8	18.1 ± 2.2
Cirrhosis						
Males with cirrhosis (22) ¹	26.6 ± 4.2	26.9 ± 5.4	0.7 ± 0.2	84.0 ± 11.4	76.6 ± 6.9	7.1 ± 1.2
Cirrhosis—gastric biopsy (3)	3	48	0.1	40	105	4.1
Cirrhosis of alcoholic (15)	27	27	0.7	97	76	8.1
Cirrhosis and duodenal ulcer (2)	44	31	1.4	240	104	24.8
Ascites (13)	29	29	0.8	90	83	7.8
Serum bilirubin						
>3.0 mg./100 ml. (8) ¹	—	—	0.8 ± 0.1	—	—	8.2 ± 8.0
<3.0 mg./100 ml. (15) ¹	—	—	0.8 ± 0.1	—	—	4.5 ± 6.5
No shunt operation (18) ¹	—	—	0.5 ± 0.1	—	—	6.6 ± 1.3
Shunt operation (4) ¹	—	—	1.8 ± 0.9	—	—	9.4 ± 3.2
Oesophageal varices (7)	23	20	0.4	84	77	6.7
Haemorrhage from varices (18)	24	28	0.7	87	79	7.1
Serum potassium						
>4.0 mEq./l. (8) ¹	36.2 ± 7.9	—	0.9 ± 0.2	123.1 ± 15.7	—	10.6 ± 1.6
<4.0 mEq./l. (10) ¹	17.2 ± 3.6	—	0.4 ± 0.3	56.1 ± 13.5	—	4.6 ± 1.6
Serum histaminase activity						
Present (5)	9	28	1.6	50	84	4.2
Absent (8)	20	12	0.3	60	70	4.2

¹Statistical significance of differences given in text.

FIG. 1. Basal and maximal gastric secretion in control subjects and in patients with cirrhosis.

FIG. 2. Relationship between peak (P.A.O.) and maximal (M.A.O.) acid outputs in cirrhosis.

relationship to maximal acid output ($r = 0.993$) prevailed (Fig. 2).

The reduced secretory volume and acid output in three male patients with cirrhosis and striking gastric hyposecretion (Table I) could not be attributed to parietal cell damage, since gastric biopsies showed no evidence of atrophic gastritis. In the latter regard, there was no difference in the gastric secretory pattern in alcoholics with cirrhosis, the findings being remarkably similar to those in the group as a whole (Table I).

Two patients with duodenal ulcer associated with cirrhosis had volume and acid outputs comparable with those found in control subjects under basal circumstances and above the mean control value following histamine stimulation (Table I). In both instances, volume and acid concentration after histamine were higher than in all but one of the patients with cirrhosis uncomplicated by ulcer.

EFFECTS OF HEPATIC FUNCTION AND PRESENCE OF A PORTAL COLLATERAL CIRCULATION ON GASTRIC SECRETION There were no significant differences in

volume or acid output either under basal circumstances or after the administration of histamine in relation to individual tests of hepatic function (concentrations of serum albumin, serum glutamic oxalacetic transaminase activity, or bromsulphalein retention), or to the presence of ascites or jaundice. Gastric secretory findings in patients with ascites were comparable to those of the group as a whole (Table I); basal acid outputs were identical in patients with serum bilirubin concentrations above and below 3.0 mg./100 ml., while secretion after histamine was not significantly different ($p = 0.72$) (Table I). The presence of a portacaval anastomosis had no significant effect on basal ($p = 0.13$) or maximal ($p = 0.42$) acid output; similarly, findings in patients with demonstrable varices or a history of haemorrhage from varices were comparable with those in the whole group (Table I).

ELECTROLYTE CONCENTRATIONS IN SERUM AND GASTRIC JUICE Ten patients were hypokalaemic (serum potassium < 4.0 mEq./l.), and of these, four also had hyponatraemia (serum sodium < 135 mEq./l.). Basal gastric secretion was significantly reduced in volume ($p < 0.05$) and acid output ($p < 0.05$) in comparison with the eight normokalaemic patients with cirrhosis; significant reductions in volume ($p < 0.01$) and maximal acid output ($p < 0.05$) were present after histamine stimulation (Table I).

Observations on electrolyte concentrations in gastric juice showed no relevant differences between patients with cirrhosis and those with duodenal ulcer or healthy control subjects (Table II). During basal studies and after histamine stimulation, concentrations of chlorides and hydrogen ion tended to parallel each other, being predictably higher in patients with duodenal ulcer than in healthy volunteers and in patients with cirrhosis, while those of sodium tended to vary reciprocally (Table II). Ammonia concentrations in gastric juice were also measured and are to be reported elsewhere. Basal concentrations, like those in arterial blood, were

TABLE II
CONCENTRATIONS OF ELECTROLYTES
(MEAN AND STANDARD DEVIATION) IN GASTRIC JUICE

Patients	Basal Secretion (mEq./l.)				Secretion after Histamine (mEq./l.)			
	Hydrogen Ion	Sodium	Potassium	Chlorides	Hydrogen Ion	Sodium	Potassium	Chlorides
Cirrhosis (7) ¹	22.1 ± 12.2	63.4 ± 12.2	15.6 ± 3.2	95.8 ± 16.3	85.6 ± 17.7	34.8 ± 9.1	17.9 ± 2.8	132.6 ± 8.0
Others								
Duodenal ulcer (4)	53.0	61.0	11.9	123.0	124.0	18.5	16.4	152.0
Controls (4)	48.6	54.3	14.0	118.0	122.8	15.5	18.5	141.3
Mean ¹	50.8 ± 24.6	57.9 ± 14.7	12.7 ± 2.4	121.0 ± 4.8	123.0 ± 9.9	16.9 ± 5.2	17.4 ± 2.0	146.0 ± 17.5

¹Statistical significance of difference reported in text.

with histamine was also reported by this group, and by applying our control data to the work of Bendett and others (1963), it may be inferred that the response to augmented histamine stimulation was subnormal in their patients with cirrhosis. Gastric secretion following stimulation with peptone also appeared reduced in patients with cirrhosis, thus indicating that the depressed response to injected histamine is not strictly selective. However, the parietal cells may under certain circumstances retain a greater secretory potential in cirrhosis, since patients with coexistent duodenal ulcer had higher acid outputs, a finding also recorded by Ostrow *et al.* (1960). The concept of a maximal response to histamine (Kay, 1953), therefore, may not be applicable to cirrhosis, and one patient of Bendett *et al.* (1963) had a greater acid output after histamine by mouth than the calculated maximal response by injection.

Gastric hyposecretion has been attributed to parietal cell damage (Minot, Strauss, and Cobb, 1933; Faber, 1935), but no relevant histological abnormality was present in gastric tissue from three of our patients with cirrhosis and strikingly low acid outputs. So-called alcoholic gastritis is unlikely to be a causal factor in hyposecretion, since acid outputs were comparably low in alcoholics and in non-alcoholics; moreover, the incidence of fundal atrophic gastritis in alcoholics with cirrhosis is similar to that found in matched control individuals (Cox, 1948; Stadel, Heinkel, and Berg, 1963). Fitzgerald (1946) postulated that ammonia might partially neutralize acid in the stomach, and gastric ammonia production is greater in patients with cirrhosis than in control individuals (Rappaport and Kern, 1963). However, the amount present was insufficient to influence either basal or maximal acid outputs significantly in the present study.

The presence of jaundice, ascites, or greater abnormalities of tests of hepatic function was unrelated to gastric secretory function, and others (Ostrow *et al.*, 1960; Bendett *et al.*, 1963) have been unable to equate diminished gastric secretion with the severity of the hepatic disease. Although the creation of a portal-collateral circulation in animals enhances the gastric response to histamine or meat (Gregory, 1958), others (Bendett *et al.*, 1963) like ourselves found no increase in gastric secretion in patients with portacaval anastomosis; nor was secretion higher in patients with portal-collateral circulations or a history of bleeding varices under basal circumstances or following the administration of either histamine or peptone. Our results are also hard to equate with the gastric hypersecretion of experimental liver damage (Hein *et al.*, 1963), which may be due to failure of hepatic inactivation of

histamine (Eiseman, Moore, and Normell, 1964) absorbed from the intestine under basal circumstances (Irvine, Duthie, Ritchie, and Waton, 1959). Surprisingly, maximal doses of histamine produced subnormal gastric secretory responses in patients with cirrhosis and less conjunctival injection and facial flushing than in control individuals. These findings are compatible with an accelerated systemic degradation of histamine. It was therefore of interest that pregnancy is associated with increased serum histaminase activity (Anrep, Barsoum, and Ibrahim, 1947) and a reduced gastric secretory response to histamine (Murray, Erskine, and Fielding, 1957). However, no significant relationship existed between measurements of serum histaminase activity and gastric acid output after histamine in cirrhosis.

The lower acid output associated with cirrhosis may reflect primarily impaired volume secretion, since acid concentrations appeared relatively high at low rates of secretion in comparison both with control individuals and with the extensive data summarized by Ihre (1938). The degree, if any, to which contents of water, acid, and electrolytes in gastric juice are independent of each other is unknown. Anticholinergic drugs reduce volume more than acid concentration in animals (Gray, 1937) and mineralo-corticoids appear to reduce the volume of intestinal contents disproportionately in relation to electrolyte concentration (Goulston, Harrison, and Skyring, 1963).

Although concentrations of acid and electrolytes in gastric juice in patients with cirrhosis were not significantly different from those in control subjects, a significant relationship was demonstrated between gastric hyposecretion and hypokalaemia. Potassium depletion depresses acid secretion in animals (Carone and Cooke, 1953; De Muro, Rowinski, Calaresu, and Fraghi, 1961) and is common in hepatic disease (Birkenfeld, Leibman, O'Meara, and Edelman, 1958). Secondary hyperaldosteronism in cirrhosis (Wolff, Koczorek, Jesch, and Buchborn, 1956) may contribute to potassium depletion, and there is experimental evidence that aldosterone influences transport mechanisms of electrolytes across the mucosa of the gastrointestinal tract (Spät, Saliga, Sturcz, and Sólyom, 1963). Other disorders of water and electrolyte metabolism and of endocrine function develop with cirrhosis. Gastric hyposecretion without histological change in the gastric mucosa has been reported with adrenal, pituitary, and thyroid gland disorders (Smith, Delamore, and Williams, 1961; Bock and Witts, 1963), as well as in undernutrition (Webster and Armour, 1934). Adrenal insufficiency and undernutrition appear irrelevant to gastric secretion in cirrhosis (Ostrow *et al.*, 1960; Bendett *et al.*, 1963),

and primary nutritional or endocrine disease was not identified in our patients; thus, possible metabolic relationships with gastric secretion in cirrhosis remain obscure.

In conclusion, the practical implications of basal gastric hyposecretion and a subnormal maximal acid output in cirrhosis are consistent with the views of those who question the increased incidence of ulcer (MacDonald and Mallory, 1958) and the contribution of acid-pepsin reflux to haemorrhage from varices (Orloff and Thomas, 1963) in this disease.

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