Hypergastrinaemia in cirrhosis of liver

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SUMMARY The basal acid output (BAO), post-pentagastrin acid output (MAO), fasting and postprandial gastrin levels in 40 patients with proven cirrhosis of the liver were compared with those in 20 normal controls. The mean BAO and MAO were significantly lower than normal, the mean fasting gastrin level was significantly higher than normal, and the postprandial gastrin response was significantly increased and prolonged. These differences were still significant even when the patients were divided into cryptogenic and alcoholic subgroups. A significant inverse relationship between MAO and the integrated gastrin response to meal was observed both in the normal controls and in the cirrhotic patients. The MAO and integrated gastrin response of the cirrhotic patients did not correlate with the degree of liver function impairment. In five cirrhotic patients fasting and postprandial gastrin levels were unchanged after splenorenal shunt operation. A more consistent abnormality of the gastric mucosa as assessed by endoscopy and biopsies appeared to be mucosal congestion with occasional atrophic gastritis. The severity of mucosal abnormality, however, was unrelated to the degree of hypoacidity. These results indicate, firstly, that the hypergastrinaemia in cirrhotic patients is a reflection of gastric hypoacidity and bears no direct relationship to hepatic dysfunction. Secondly, the gastric hypoacidity does not accrue solely from mucosal abnormality. It is suggested that this hypoacidity may result from the presence of excessive amounts of circulating acid-inhibiting intestinal peptides, which the diseased liver fails to metabolise.

An increased incidence of peptic ulceration in patients with cirrhosis of the liver had been observed by many authors (Schnitker and Hass, 1934; Welbourn, 1952; Palmer and Brick, 1953; Swisher *et al.*, 1955; Fainer and Halsted, 1955; Hällén and Krook, 1963; Patek, 1963; Tabaqchali and Dawson, 1964; Bergman and van der Linden, 1965; Jackson *et al.*, 1965; Orloff *et al.*, 1969; Resnick *et al.*, 1969; Jackson *et al.*, 1971; Phillips *et al.*, 1975), but disputed by some (Ratnoff and Patek, 1942; Lipp and Lipsitz, 1952; Doll, 1952; Sullivan *et al.*, 1954). The pathogenesis for the apparent increase in frequency is unknown. It is unrelated to gastric hyperacidity, since acid secretion in cirrhotic patients has been shown to be abnormally low (Scobie and Summerskill, 1954; Ostrow *et al.*, 1960; Schmidt and Martini, 1969) or to be normal (Tabaqchali and Dawson, 1964).

It is now generally accepted (Grossman, 1974) that the relationship between pentagastrin or histamine stimulated acid output and food stimu-

lated serum gastrin response is such that, in duodenal ulceration, both secretions are on average higher than normal, whereas, in gastric ulceration, the relationship is an inverse one, there being a high fasting serum gastrin reflecting a low acid output.

In this study, the relationship of acid and gastrin release in cirrhotic patients was examined, and an attempt was made to correlate the findings with the severity of disturbance of liver function and the morphology of the gastric mucosa. In addition, the effect of a portosystemic shunting operation on acid and gastrin release was also studied.

Methods

PATIENTS

Forty patients, 35 males and five females, with ages ranging from 24 to 65 years (mean 52.1 years) were studied. The presence of cirrhosis was confirmed by needle biopsies of the liver in 35 patients and at necropsy in the remaining five patients who died between one and seven months after the study. In the latter five patients needle biopsy of the liver was not performed at the time of the study because of

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persistent coagulation abnormalities. In 27 of the cirrhotic patients, no cause of cirrhosis could be determined and, for the purpose of this study, they were designated cryptogenic cirrhotics. The morphological features were those of post-necrotic scarring, as had been previously described (Cook *et al.*, 1963). Among these, 16 were considered by the radiologists to have a small-sized liver and nine to have a normal-sized liver on hepatic scintiscanning. In the remaining 13 patients with cirrhosis a clear history of excessive alcohol consumption was present. Usually more than half a catty double distilled rice wine a day or its equivalent (about 100 g ethanol) was consumed, and these patients were considered to have alcoholic cirrhosis. Ten of the patients in this group had an abnormally large liver and three a normal-sized liver on hepatic scintiscanning. The patients were not allowed to take any alcohol for at least seven days before the study. No peptic ulcer in the stomach or duodenum was demonstrated in any one patient by barium study, endoscopy, at subsequent surgery and/or at necropsy. Blood urea and creatinine were below 7 mmol/l and 125 μ mol/l respectively at the time of the study in all patients. Gastrointestinal bleeding occurred in 12 patients, and for these a period of at least six weeks was allowed before performing the study. When ascites was present, this was ameliorated as far as possible using diuretics until the attending physician was satisfied that no further improvement would be likely.

LIVER FUNCTION SCORE

The liver function of each patient was scored, using a modification of Child's classification (Child, 1964). Five points were given for previous stage I and II encephalopathy, 10 points if the encephalopathy had been stage III or IV (staging by Adams and Foley, 1955). Five points were given when ascites were present, 10 points if this was poorly controlled. Two and a half points were given when serum bilirubin was between 25.7-51.3 mmol/l, 5 points if this was over 51.3 mmol/l. Two and a half points were given when serum albumin was between 25 and 30 g/l, 5 points when this was less than 25 g/l. A patient could thus in theory score a maximum of 30 points. Each patient was then graded as having mild (score 0-10), moderate (score 11-20), and severe (score 21-30) liver function impairment.

CONTROLS

These were carefully selected from among healthy medical and nursing staffs and patients in the general medical wards who had recovered from an unrelated condition and who were otherwise healthy. There were 20 such subjects, 16 males and four females,

aged from 19 to 65 years (mean = 46.2 years). Informed consent was obtained from all.

GASTRIC ACID OUTPUT

The basal acid output (BAO) and the maximum acid output (MAO) after an intramuscular injection of pentagastrin (6 μ g/kg body weight) was measured in the conventional manner in all the 60 study subjects (Baron, 1973). The acid content in the gastric juice was estimated by an automatic titrator (Radiometer, Copenhagen, type TTT II).

SERUM GASTRIN

On a separate day after an overnight fast, a 19 g butterfly needle was inserted into an antecubital vein of the study subject and kept patent by a slow infusion of normal saline. After two fasting blood samples were taken at -15 minutes and zero time, each subject ingested a standard protein meal composed of 50 g protein, 40 g fat, and 40 g carbohydrate. Additional blood samples were taken at 15, 30, 45, 60, 90, and 120 minutes. In 19 cirrhotic patients and 10 normal controls, additional blood samples were collected at 150, 180, 210, and 240 minutes after the meal. Each sample was stored immediately at 4°C. The serum from all samples were extracted by centrifugation immediately at the end of the test and stored at -20°C for subsequent radioimmunoassay of gastrin.

RADIOIMMUNOASSAY OF SERUM GASTRIN

The details of the assay have been previously reported (Byrnes *et al.*, 1976; Lam and Lai, 1976). The antiserum used had been raised in rabbit against gastrin I and II extracted from pig antra using the method of Gregory and Tracy (1964) and conjugated to egg albumin. The association constant of the antiserum was 5.2 and 10¹¹ l/mol. Sensitivity of the assay was down to 2.4 pmol/l (5 pg/ml) of serum using synthetic human gastrin I (Imperial Chemical Industries) as standard. Cross-reaction by cholecystokinin was 2 $\times$ 10⁻⁴ on a molar basis. Within and between assay coefficients of variation were 6.2% and 13% respectively. In each individual the integrated gastrin response from zero time to 120 minutes after the meal (Σ G0-120) was calculated from the area under the gastrin response curve within the two-hour period. Similarly the integrated gastrin response between 120 minutes and 240 minutes after the meal (Σ G120-240) was calculated in those subjects who had blood taken up to four hours after the meal.

GASTRIC MUCOSAL MORPHOLOGY

Twenty-eight of the cirrhotic patients (20 cryptogenic and eight alcoholic) consented to the carrying

Table 1 Acid output and meal stimulated gastrin response in cirrhosis and controls (mean $\pm$ SEM)

	No.	Basal acid output (mmol/h)	Maximum acid output		Σ G0-120 (nmol/min/l)	Σ G120-240 (nmol/min/l)
			(mmol/h)	(mmol/h/kg)		
Normal	20	2.3 $\pm$ 0.3	13.6 $\pm$ 1.1	0.27 $\pm$ 0.02	5.4 $\pm$ 0.4	5.3 $\pm$ 0.8 (10 subjects)
Cirrhosis						
Cryptogenic	27	1.0 $\pm$ 0.4	6.7 $\pm$ 1.5	0.13 $\pm$ 0.03	8.2 $\pm$ 0.8	
Alcoholic	13	0.7 $\pm$ 0.4	6.7 $\pm$ 1.8	0.13 $\pm$ 0.03	8.7 $\pm$ 1.0	
Total	40	0.9 $\pm$ 0.3	6.7 $\pm$ 1.2	0.13 $\pm$ 0.02	8.4 $\pm$ 0.7	8.4 $\pm$ 0.9 (19 subjects)

$P < 0.01$ for all comparisons between normal and cirrhosis.

out of upper gastrointestinal endoscopy, for which an end-viewing endoscope was used (Olympus, GIF-D2). This was performed by the author without prior knowledge of the patient's acid secretion. At least five biopsies were randomly taken from the antrum (one from the lesser curve, one from the greater curve), and corpus of the stomach (two from the lesser curve, high and low, and one from the greater curve) when no abnormality was obvious endoscopically. When abnormalities were detected, further biopsies were taken from these sites.

PATIENTS WITH SPLENORENAL SHUNT

In five of the patients with cryptogenic cirrhosis, a therapeutic splenorenal shunt was subsequently performed. The acid output after pentagastrin stimulation and the serum gastrin response to the standard protein meal was measured approximately one month after surgery. Serum samples for comparison of gastrin content before and after the shunting operation were determined within the one gastrin assay. No attempt was made to establish the patency of the shunt in each case.

STATISTICAL ANALYSIS

Student's *t* test was used to compare unpaired data. For comparison of the postprandial gastrin response between groups of subjects, analysis of variance using a two-way classification was used, and the residual variance obtained was used for the calculation of standard error and for carrying out *t* test when needed.

Results

GASTRIC ACIDITY (Table 1)

The BAO of the cirrhotic patients, whether as a group or subdivided into cryptogenic and alcoholic, was significantly ($P < 0.01$) lower than that of the controls. Likewise, the MAO, whether this was expressed as mmol/hour or in relation to total body weight—namely, mmol/hour/kg TBW—was significantly ($P < 0.01$) lower in the cirrhotic patients than in the controls. It has been established that ex-

pressing MAO in relation to body weight has the advantage of eliminating the difference in acid secretion in the two sexes (Lam and Sircus, 1975) as well as in different ethnic groups (Lam, 1974). There was no difference in BAO or MAO between the cryptogenic and alcoholic cirrhotic patients.

SERUM GASTRIN (Fig. 1 and Table 1)

The mean fasting serum gastrin (at zero time before the meal) of the cirrhotic patients as a group ($41.6 \pm$ SE 3.1 pmol/l) was significantly higher ($P < 0.025$) than that of the controls ($26.3 \pm$ SE 3.4 pmol/l). This holds true even when the patients were divided into cryptogenic ($41.1 \pm$ SE 4.0 pmol/l) and alcoholic ($42.7 \pm$ SE 5.1 pmol/l) groups ($P < 0.025$ and 0.05 respectively).

Fig. 1 Mean serum gastrin levels ($\pm$ standard error) in normal controls (20) and in patients with cryptogenic (27) and alcoholic cirrhosis (13): fasting and in response to a standard protein meal (PM). SEM as computed from residual variance = 3.4 for values after stimulation.

The serum gastrin response in the two hours after the standard protein meal was significantly higher in the cirrhotic patients as a group than in the

Fig. 2 Gastrin response to a standard protein meal (PM) measured for four hours in 10 normal controls and 19 patients with cirrhosis. SEM as computed from residual variance = 5.6 for values after stimulation.

controls ($F = 49.27$, $P < 0.01$). This is still true when the patients were divided into cryptogenic group ($F = 42.25$, $P < 0.01$) and alcoholic group ($F = 40.78$, $P < 0.01$). The mean serum gastrin levels at 15, 30, 45, 90 and 120 minutes after the meal were significantly higher in the cirrhotic patients as a group than in the controls ($P < 0.01$, 0.0125, 0.0025, 0.001, and 0.001 respectively). This also holds true for the patients with cryptogenic cirrhosis ($P < 0.01$, 0.025, 0.01, 0.01, 0.01 respectively) and those with alcoholic cirrhosis ($P < 0.05$, 0.05, 0.005, 0.001, 0.001 respectively). A significantly higher than normal Σ G0-120 was observed in the cirrhotic patients as a group, whether taken as a whole or when broken down into cryptogenic and alcoholic subgroups ($P < 0.01$ in all instances).

Because the initial results showed an increased and sustained release of gastrin in the two hours after the protein meal in the cirrhotic patients this gastrin response was followed for a total of four hours in the subsequent 19 patients and 10 normal controls studied (Fig. 2). The results indicated that the serum gastrin response declined in the third and fourth hour, but this response was still significantly higher than that of the normal controls ($F = 21.84$, $P < 0.01$). The mean serum gastrin levels at 150, 180, 210, and 240 minutes after the meal were significantly higher than the corresponding values in the controls ($P < 0.001$ for all points of time). In addition, the mean Σ G120-240 was significantly higher in the cirrhotic patients than in the controls ($P < 0.01$).

RELATIONSHIP BETWEEN ACID OUTPUT AND GASTRIN RELEASE (Figs. 3 and 4)

In the normal controls, a significant inverse correlation ($r = 0.4929$, $P < 0.05$) was observed between the MAO when this was expressed in mmol/hour/kg TBW and the Σ G0-120. The relationship between MAO as expressed in mmol/hour and Σ G0-120 just failed to reach statistical significance ($r = 0.4423$, $P > 0.1$).

The MAO/kg TBW and Σ G0-120 were correlated in the cirrhotic subjects, both as a group and when divided into cryptogenic and alcoholic subgroups. A significant inverse correlation was observed in each case ($r = 0.5237$, $P < 0.001$; $r = 0.4559$, $P < 0.05$; $r = 0.7286$, $P < 0.01$).

In the 10 normal controls and 19 patients with cirrhosis who had the Σ G120-240 measured, this was correlated with the MAO/kg TBW. No significant correlation was observed in the normal controls ($P > 0.1$), but a significant inverse correlation was present in the cirrhotic patients ($r = 0.5032$, $P < 0.05$).

No significant relationship was demonstrable in the normal controls or patients with cirrhosis between BAO and fasting (zero time) serum gastrin ($r = 0.0998$, $r = 0.2968$ respectively), as well as between BAO and Σ G0-120 ($r = 0.3843$, $r = 0.1885$ respectively). The corresponding coefficients for the cryptogenic cirrhotic group ($r = 0.2882$, $r = 0.2138$ respectively) and alcoholic cirrhotic group ($r = 0.3343$, $r = 0.3258$ respectively) were also insignificant.

Fig. 3 Relationship between maximum acid output in mmol/h/kg total body weight (MAO/kg) and integrated gastrin response in the first two hours (Σ G0-120) and in the third and fourth hours (Σ G120-240) after ingestion of a standard protein meal in normal controls and in patients with cirrhosis (open circles = cryptogenic cirrhosis, closed circles = alcoholic cirrhosis).

Table 2 Relationship of liver function to acid and gastrin secretion (mean $\pm$ SEM)

	Liver function score					
	0-10		11-20		21-30	
	Total cirrhosis	Cryptogenic	Total cirrhosis	Cryptogenic	Total cirrhosis	Cryptogenic
No.	23	13	10	8	7	6
BAO (mmol/h)	0.9 $\pm$ 0.4 ^a	0.5 $\pm$ 0.2 ^d	0.6 $\pm$ 0.2 ^b	0.4 $\pm$ 0.1 ^e	1.3 $\pm$ 0.8 ^c	1.6 $\pm$ 0.9 ^f
MAO (mmol/h)	6.2 $\pm$ 1.5 ^a	5.7 $\pm$ 1.9 ^d	5.9 $\pm$ 1.2 ^b	6.2 $\pm$ 1.4 ^e	9.7 $\pm$ 4.6 ^c	9.6 $\pm$ 5.4 ^f
MAO (mmol/h/kg)	0.12 $\pm$ 0.03 ^a	0.12 $\pm$ 0.04 ^d	0.12 $\pm$ 0.02 ^b	0.12 $\pm$ 0.02 ^e	0.18 $\pm$ 0.08 ^c	0.18 $\pm$ 0.1 ^f
Σ G0-120 (nmol.min/l)	8.3 $\pm$ 1.0 ^a	8.3 $\pm$ 1.6 ^d	8.7 $\pm$ 1.2 ^b	8.2 $\pm$ 0.9 ^e	8.0 $\pm$ 1.2 ^c	8.2 $\pm$ 1.4 ^f
a and b a and c b and c	not significant		d and e d and f e and f	not significant		

RELATIONSHIP BETWEEN LIVER FUNCTION AND ACID AND GASTRIN SECRETIONS (Table 2) No difference in mean BAO, MAO (in mmol/hour and mmol/hour/kg TBW) and Σ G0-120 was observed between groups of cirrhotic patients having different degrees of liver function impairment as assessed by the scoring system. There appeared to be a trend for patients with a score of 21-30 (severe

impairment) to have a higher basal and post-pentagastrin acid output than those with lower score (mild to moderate impairment). This trend became more obvious if the cryptogenic cirrhotic patients alone were considered, but the difference was not statistically significant. No attempt was made to analyse the patients with alcoholic cirrhosis, as the groups with moderate or severe disturbance in liver

Fig. 4 Relationship between basal acid output (BAO) and fasting serum gastrin, and between BAO and integrated gastrin response in the two hours after ingestion of a standard protein meal (Σ G0-120) in normal controls and in patients with cirrhosis.

Fig. 5 Gastrin response to a standard protein meal (PM) in five patients with cryptogenic cirrhosis: before and one month after splenorenal shunt. Mean $\pm$ SEM.

Table 3 Acid secretion before and after splenorenal shunt (mean $\pm$ SEM)

	BAO	MAO	MAO/kg
Before	1.1 $\pm$ 0.3*	6.7 $\pm$ 0.7*	0.15 $\pm$ 0.02*
After	3.0 $\pm$ 1.2†	8.8 $\pm$ 3.0†	0.21 $\pm$ 0.08†

*and † $P > 0.1$

function were too small for statistical evaluation.

EFFECT OF SPLENORENAL SHUNT ON ACID AND GASTRIN OUTPUT (Fig. 5 and Table 3)

The mean BAO and MAO appeared higher after the operation in the five patients studied, but the differences were not statistically significant (Table 3). Figure 5 shows that the mean fasting and post-prandial gastrin levels after surgery were no different from the ones before surgery.

MORPHOLOGY OF GASTRIC MUCOSA (Tables 4 and 5)

In general, the commonest endoscopic finding was diffuse congestion of the whole of the gastric mucosa, as evidenced by the presence of generalised hyperaemia with or without the presence of oedema. This occurred in 15 of the 28 patients. The next most common finding was mucosal atrophy, suggested by the fact that the mucosa appeared thin so that the underlying vessels became clearly visible. This was recorded in eight patients and was always observed in the corporal and fundic regions. Active gastritis was diagnosed when patchy areas of hyperaemia, granularity or nodularity, and/or undue friability were observed. This was found in three patients. In seven patients no abnormality was detected.

Table 4 Upper panel: gastroscopic findings in 28 cirrhotic patients. Lower panel: number of patients with correlating histology

	Normal	Mucosal congestion	Mucosal atrophy	Active atrophic gastritis
Endoscopy	7	15	8	3
Histology	7	7	2	3
	Normal	Superficial gastritis	Atrophic gastritis mild	Atrophic gastritis severe and active
Score	0	1	2	3

Table 5 Relationship of gastric mucosal morphology with acid secretory capacity (MAO), gastrin secretion (Σ G0-120) and liver function impairment

	Mucosal morphology score		
	0	1-3	4-7
No.	7	15	6
MAO (mmol/h)	6.7 $\pm$ 3.7 ^a	6.5 $\pm$ 2.5 ^b	5.4 $\pm$ 0.7 ^c
MAO (mmol/h/kg)	0.12 $\pm$ 0.07 ^a	0.12 $\pm$ 0.04 ^b	0.12 $\pm$ 0.02 ^c
Σ G0-120 (nmol/min/l)	9.9 $\pm$ 2.8 ^a	8.6 $\pm$ 0.6 ^b	7.8 $\pm$ 0.9 ^c
Liver function score	6.8 $\pm$ 1.5 ^a	9.0 $\pm$ 1.7 ^b	10.4 $\pm$ 2.1 ^c

a and b
a and c
b and c } not significant

The histological findings were categorised as normal, superficial gastritis, mild atrophic gastritis, and severe active atrophic gastritis according to Whitehead (1973). In general, the findings correlate fairly well with the endoscopic findings of normal mucosa, mucosal congestion, and active atrophic gastritis, but only poorly so with the endoscopic diagnosis of mucosal atrophy (Table 4). The commonest occurrence in the histological sections was normal histology, there being 14 such reports, for which the endoscopic diagnoses were normal (seven), mucosal congestion (three), and mucosal atrophy (four). Superficial gastritis was reported in nine cases and was observed in both antral and corporal biopsies. Atrophic gastritis was seen in five cases and was found in all cases in the corporal and fundic biopsies, corresponding to the endoscopic diagnosis of mucosal atrophy and active atrophic gastritis in these regions.

The endoscopic findings were scored, giving one point if mucosal congestion was present, two points if mucosal atrophy was seen, and three points if this was associated with features of active gastritis. A maximum of four points could thus be scored. Similarly, the histological findings were scored, giving one point if superficial gastritis (oedema and mild inflammation) was observed, two points if mild atrophic gastritis was present, or three points if the gastritis was severe and active, so that a maximum of three points could be scored.

The total score (endoscopy and histology) was correlated with the MAO, Σ G0-120 and liver function score. No significant relationship, however, was observed in each case. There appeared to be a trend, however, for those with more severe liver function impairment to have more severe mucosal abnormality (Table 5). Comparison of the morphology score between the cryptogenic ($2.5 \pm \text{SE } 0.5$) and alcoholic ($1.8 \pm \text{SE } 0.7$) groups revealed no significant difference ($P > 0.2$).

Discussion

Mazzacca *et al.* (1974) observed higher than normal serum gastrin levels both in the basal state and after an oral dose of glycine in patients with cirrhosis. The post-glycine hypergastrinaemia, however, is difficult to interpret, as the patients were given a parenteral dose of atropine before the oral glycine. The present study confirms the presence of an increased basal serum gastrin and demonstrates that patients with cirrhosis, be this cryptogenic or alcoholic in origin, do indeed have an abnormally high and, in addition, an abnormally prolonged gastrin release in response to a physiological meal (Figs. 1 and 2). The capacity to secrete acid, whether in the basal state or upon stimulation by pentagastrin is appreciably lower than normal (Table 1), a finding that agrees with most previous reports (Scobie and Summerskill, 1954; Ostrow *et al.*, 1960; Schmidt and Martini, 1969) but differs from others (Tabaqchali and Dawson, 1964; Mazzacca *et al.*, 1974). Although there is no relationship between BAO and fasting serum gastrin, a significant reciprocal relationship is present between the acid secretory capacity (as expressed in MAO/kg TBW) and the post-prandial gastrin response (expressed as the integrated gastrin response, Σ G0-120 and Σ G120-240). This inverse relationship (between MAO/kg and Σ G0-120) is also seen in the normal controls, agreeing with previous observations (Byrnes *et al.*, 1976). These findings thus suggest an inverse relationship between the functioning parietal cell mass and the functioning gastrin cell mass in the cirrhotic subjects and also suggest that the increased gastrin release is a result of gastric hypo-acidity and hence decreased feedback inhibition of gastrin secretion. The significance of this in the pathogenesis of the alleged higher incidence of peptic ulcer in cirrhotic patients as reported by many (for references, see introductory section) is unknown. It is of interest to note that an inverse relationship between gastrin release and gastric acidity has been described in atrophic gastritis (Ganguli *et al.*, 1971; Strickland *et al.*, 1971) and in gastric ulceration (Trudeau and McGuigan, 1971; Korman *et al.*,

1972), there being hypergastrinaemia and hypoacidity in both situations.

The hypergastrinaemia and hypoacidity in the cirrhotic patients is unrelated to the degree of liver failure as assessed by the liver function scoring system (Table 2). The same scoring system has been found to be of definite use as an index of the chance of survival in cirrhotic patients undergoing emergency ligation of bleeding oesophageal varices (Ong *et al.*, 1976). As far as the role of the liver in the inactivation of endogenous gastrin is concerned, studies so far (Temperley *et al.*, 1971; Reeder *et al.*, 1972; Dencker *et al.*, 1973; Debas and Grossman, 1974) indicate that this is unlikely to be of any importance. This is further supported by the observation that a splenorenal shunting operation does not affect the serum gastrin level (Fig. 5).

Is the gastric hypoacidity in any way linked with the gastric mucosal morphology? As assessed endoscopically and by multiple biopsies, a more consistent picture of abnormality of the mucosa appears to be mucosal congestion with occasional atrophic gastritis. This picture, however, can at best partly explain the gastric hypoacidity, as there is no relationship between the mucosal morphology and gastric acidity (Table 5). As expected, no relationship exists between the post-prandial gastrin response and mucosal abnormality. It may be argued that the method of histological assessment of the mucosal abnormality is incomplete, as this is based on biopsy specimens, although these were multiple, endoscopically guided, and, as far as possible, representative of both the antrum and the corpus. A more likely explanation may lie in the observation that certain peptides of intestinal origin inhibit acid secretion—namely, secretin (Johnson and Grossman, 1971), gastric inhibitory polypeptide (Pederson and Brown, 1972), and vasoactive intestinal peptide (Barbezat and Grossman, 1971; Rayford *et al.*, 1974). Vasoactive intestinal peptide has been observed to be present in the serum in abnormally high concentration in patients with cirrhosis (Said *et al.*, 1974) and not to inhibit gastrin release except in unphysiologically high doses (Rayford *et al.*, 1974). In addition, oral ingestion of alcohol results in a large release of secretin (Straus *et al.*, 1975). The role of these peptides in the genesis of gastric hypoacidity in cirrhosis is only speculative and remains to be defined.

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