

Gastric function and histology in chronic renal failure

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SUMMARY Gastric function and histology were investigated in 24 patients with untreated chronic renal failure. At endoscopy nine patients had oesophagitis, 12 patients were considered to have gastritis, and the duodenum appeared inflamed in 20 patients. Endoscopic biopsies were taken at standard sites in the stomach and duodenum; gastritis was found in all patients, and 17 patients had duodenitis.

Stimulated acid secretion was impaired in seven out of 20 patients and acid hypersecretion was found in a further two patients. Pepsin output correlated well with acid output in these patients. Fasting serum gastrin levels were elevated in 12 of the 19 patients tested. Patients with atrophic gastritis had low acid outputs and hypergastrinaemia, and when extensive gastritis was present, the patients tended to have more severe renal failure and hyposecretion of acid.

Three patients were studied again after regular haemodialysis or renal transplantation and were found to show marked endoscopic and histological improvement.

Gastritis and peptic ulceration are frequent complications of uraemia which continue to occur in patients receiving long-term haemodialysis (Goldstein *et al.*, 1967; Shepherd *et al.*, 1973) and after renal transplantation (Hadjiyannakis *et al.*, 1971). Necropsy studies by Jaffé and Laing (1934) and Mason (1952) have documented the presence of gastritis and ulceration in untreated uraemic patients, and Cheli and Dodero (1958) and Murisasco *et al.* (1964) confirmed this using blind gastric biopsy. However, no systematic study of the severity and distribution of gastritis has been made, and the results of gastric function tests have not been correlated with gastric histology.

Studies of acid secretion in undialysed patients have shown conflicting results. Both Cheli and Dodero (1958) and Lieber and Lefèvre (1959) found that stimulated acid output was impaired, but Venkateswaran *et al.* (1972) found a normal response. Overnight acid secretion is often higher than normal (Goldstein *et al.*, 1967; Dekkers *et al.*, 1972; Shepherd *et al.*, 1974).

In contrast, stimulated acid output in patients receiving haemodialysis was shown to be abnormally high by Goldstein *et al.* (1967), Venkateswaran *et al.*

(1972), and McConnell *et al.* (1975). These changes in acid secretion do not correlate with serum gastrin levels, which are frequently elevated (Durkin *et al.*, 1971; Korman *et al.*, 1972).

The purpose of the present investigation was to study the histological changes in the mucosa of the stomach and duodenum in patients with untreated chronic renal failure and to correlate the findings with gastric function.

Patients and methods

Twenty-four patients (18 men, 6 women) with chronic renal failure were studied during the course of their assessment for long-term haemodialysis. The average age was 44 (range 20-61) years and the causes of chronic renal failure are shown in Table 1.

Table 1 Aetiology of chronic renal failure in patients studied

Chronic glomerulonephritis	7
Polycystic renal disease	5
Chronic pyelonephritis	2
Hypertension	1
Diabetic nephropathy	1
Analgesic abuse	1
Treated hypernephroma	1
'End-stage' kidneys	6
Total	24

Creatinine clearances of the patients ranged from 0.7 to 26 (mean 6.8) ml/min and the serum creatinine range was from 3.2 to 31.8 (mean 13.75) mg/100 ml (283-2652 (mean 1146) $\mu\text{mol/l}$).

The gastrointestinal symptoms of each patient were documented together with a drug history and any past history of peptic ulceration. All patients were shown to have a normal thrombotest and platelet count before study.

Endoscopy was performed using an Olympus GIF-D2 or GIF-P panendoscope. Premedication with sodium amytal, 100-200 mg intramuscularly, was given to all patients one hour before the procedure, and diazepam, 5-20 mg intravenously, was administered at the time of endoscopy.

Gastric and duodenal biopsies were taken at five standard sites (Fig. 1) in the duodenum (D), antral (ALC) and mid-lesser curve (MLC), and lower (LGC) and higher greater curve (HGC). The sections were reported without knowledge of the clinical details, and gastritis and duodenitis were graded according to the criteria of Whitehead *et al.* (1972, 1975). In order to assess the severity and extent and any inflammation present, each biopsy was scored as follows: normal mucosa = 0, superficial gastritis = 1, mucosal atrophy = 2. Duodenal biopsies were assessed upon the degree of cellular infiltrate present (mild = 1, moderate = 2, severe = 3). The total histological score for each patient was obtained by summing the scores for each biopsy.

Acid secretion was studied in response to 6 $\mu\text{g/kg}$ pentagastrin intramuscularly after an overnight fast. A flexible gastric tube (16FG) was passed perorally (not transnasally, as this may cause troublesome trauma and epistaxis in uraemic patients) into the fundus of the stomach. The position of the tube was checked radiologically and/or by the water-recovery test (Findlay *et al.*, 1972). Four 15-minute basal samples were collected

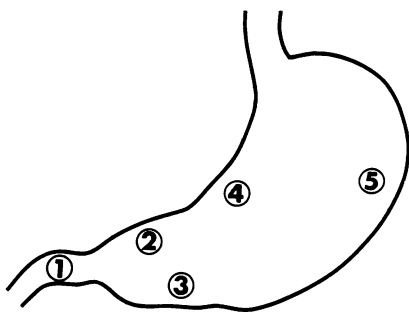


Fig. 1 Standard biopsy sites in the stomach and duodenum.

by intermittent manual suction and, after the administration of pentagastrin, a further 6 \times 15-minute samples were collected. Basal (BAO) and peak (PAO) acid outputs were calculated after titration of samples against 0.1 M sodium hydroxide to pH 7.0.

Pepsin concentration in the gastric aspirates was measured in duplicate by an automated colorimetric method following the action of pepsin on haemoglobin (Vatier *et al.*, 1968).

Blood for fasting serum gastrin levels was taken at the time of acid secretion studies and assayed in duplicate using a radioimmunoassay kit (CIS (GASK) Eurotope Services Ltd), based upon the method of Yalow and Berson (1970), using synthetic gastrin-I as the standard and charcoal for the separation of antibody-free and antibody-bound gastrin. The normal range for this laboratory is 26-75 pg/ml.

Results

GASTROINTESTINAL SYMPTOMS

Anorexia, nausea, and vomiting occurred in each patient, as might be expected in the presence of uraemia. Eight of the 24 patients complained of heartburn in relation to posture, which was relieved by antacids, and two of these had previously been shown to have a hiatus hernia radiologically. One other patient, previously known to have a duodenal ulcer, still complained of epigastric pain related to meals. No patient had a history of alcohol abuse or of recent ingestion of drugs known to be associated with dyspeptic symptoms. Nine of the patients were receiving aluminium hydroxide to control hyperphosphataemia.

ENDOSCOPIC APPEARANCES

Nine of the 24 patients showed endoscopic evidence of oesophagitis, and eight of these patients complained of heartburn.

Six patients appeared to have a normal gastric mucosa. Superficial antral erosions were seen in two patients, and one patient had a prepyloric ulcer. Of the 18 patients with abnormal gastroscopic appearances, six showed mucosal atrophy and the remainder had superficial gastritis. The gastritis was patchy in distribution and most severe in the antrum.

The duodenal mucosa appeared abnormal in 20 patients, 19 of whom showed duodenitis and one patient had a duodenal ulcer.

HISTOLOGY

All patients showed evidence of gastritis in the biopsies. Gastritis was therefore present more frequently than was seen at endoscopy. It was

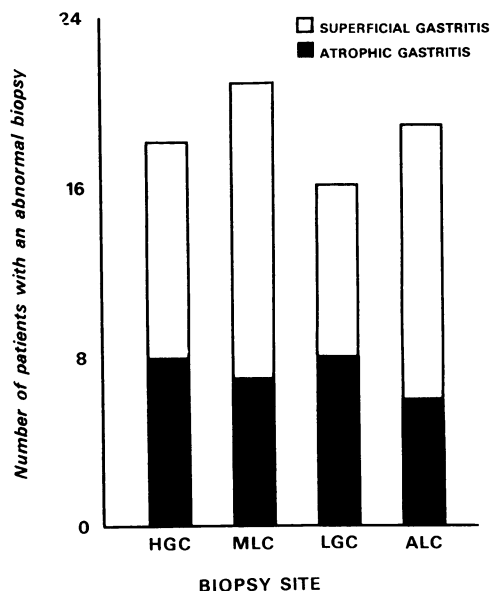


Fig. 2 Distribution of superficial and atrophic gastritis in patients with chronic renal failure (HGC = high greater curve; MLC = mild lesser curve; LGC = lower greater curve; ALC = antral lesser curve).

usually found in more than two biopsy sites, but no site was more frequently affected than another (Fig. 2). In 16 patients superficial gastritis was seen, and in four of these patients there was infiltration of the epithelium by inflammatory cells, indicating active gastritis. A moderate degree of gland atrophy was seen in 11 patients, four of whom also had superficial gastritis. Severe active atrophic gastritis was seen in one patient, and this patient was the only one of the series to show intestinal metaplasia in the gastric biopsies. The histological appearance of superficial and atrophic gastritis in these uraemic patients had no specific features, although multinucleate parietal cells were commonly seen.

Seventeen of the 24 patients showed an inflammatory infiltrate in the lamina propria of the duodenum, which included both chronic and acute inflammatory cells. The infiltrate was considered moderately dense in seven patients and mild in 10.

ACID AND PEPSIN SECRETION

The results for acid (20 patients) and pepsin (18 patients) output after pentagastrin stimulation are given in Figure 3. Basal acid output was markedly raised in two patients. Seven of the 20 patients (35%) showed an impaired response to pentagastrin stimulation (PAO < 10 mmol/h), whereas acid hypersecretion occurred in only two patients. The mean PAO (18.8 mmol/h) for the group as a whole

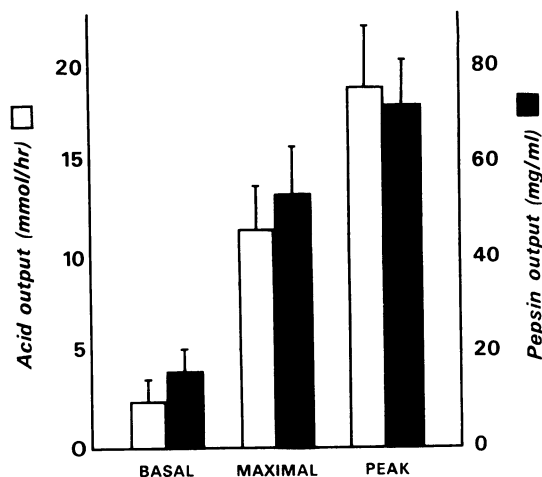


Fig. 3 Mean outputs (± 1 SE) of acid and pepsin during pentagastrin stimulation.

appears to be lower than that found in a normal population. However, in comparison to the normal values described by Baron (1963), if results in this study are separated by sex the mean PAO for males is similar to normal (22.3; normal 21.6 mmol/h) whereas for the five female patients the mean PAO was considerably impaired (8.4; normal 12.2 mmol/h).

Peak acid concentration showed a wide variation (14-286 mmol/h) and in nine patients was below the lower limit of normal (100 mmol/l) but correlated significantly with PAO ($r = 0.61$, $p < 0.01$). Pepsin output also correlated closely with acid output on regression analysis of the data ($r = 0.87$, $p < 0.001$).

GASTRIN LEVELS

Fasting serum gastrin levels were measured in 19 patients (Fig. 4), 12 of whom had elevated levels. There was no relationship between gastrin levels and the age or sex of the patients.

RELATIONS BETWEEN GASTRIC FUNCTION, HISTOLOGY, AND GASTRIN LEVELS

The histological scores showed no statistically significant correlation with age, serum creatinine, or creatinine clearance. This was also true when the scores for gastric body mucosa and antrum were considered separately. However, patients with high scores (that is, extensive gastritis) did tend to have higher serum creatinine levels and a low PAO. Patients with atrophic gastritis in one or more biopsy did have a significantly lower PAO than those with superficial gastritis (Fig. 5), both groups being comparable in terms of age and serum

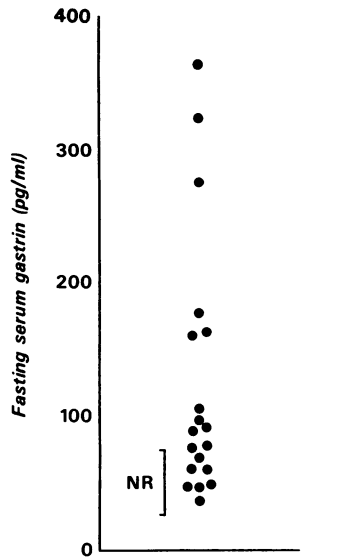


Fig. 4 Distribution of fasting serum gastrin concentrations in patients with chronic renal failure (NR = normal range).

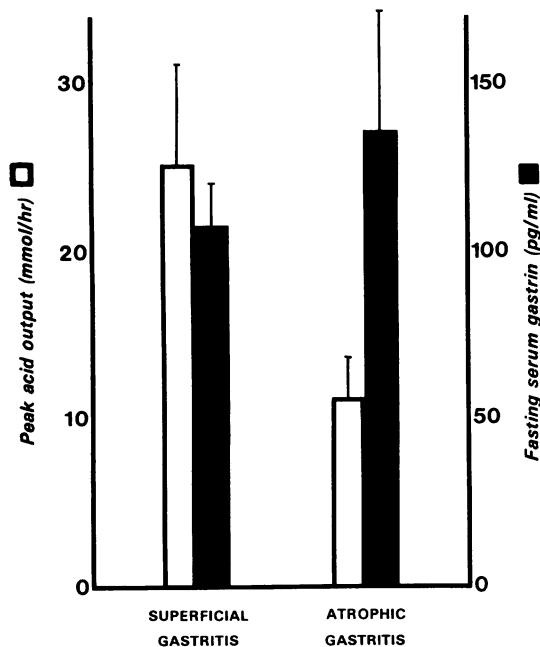


Fig. 5 Peak acid output and fasting serum gastrin concentration (± 1 SE) in patients with superficial and atrophic gastritis.

creatinine levels. The gastrin levels were higher in those patients with atrophic gastritis. The serum gastrin showed no correlation either with the pre-

sence or absence of antritis or with the severity of duodenitis.

The PAO showed no correlation with serum creatinine or creatinine clearance. Neither BAO nor PAO correlated with fasting serum gastrin levels.

POST-TREATMENT STUDIES

Only three patients could be studied again after regular haemodialysis (2) or a successful renal transplant (1). At endoscopy the mucosal appearances had improved in all three cases, and this was confirmed by the histological appearances to the extent that 12 of the 15 biopsies after treatment were normal compared with only two of 15 before treatment (Table 2).

After treatment BAO was unchanged but PAO had increased in all three patients; the increase was most marked in the transplanted patient. Serum gastrin levels were increased in two patients and decreased for the transplanted patient.

Discussion

All patients with severe chronic renal failure had gastritis which is frequently extensive. Unless the patient had oesophagitis or a frank peptic ulcer, the gastritis was asymptomatic but may have contributed to the anorexia, nausea, and vomiting of chronic renal failure.

Approximately one-third of patients studied had an impaired PAO in response to pentagastrin stimulation, and this reduction in acid secretion correlated with histological evidence of atrophic gastritis. The hyposecretors of acid also had low pepsin outputs, a situation which Bardhan *et al.* (1969) found in atrophic gastritis not associated with renal failure. Acid hyposecretion in association with untreated chronic renal failure has been well documented (Cheli and Dodero, 1958; Lieber and Lefèvre, 1959; McConnell *et al.*, 1975). It is interesting that we have also found a proportion of patients with an acid hypersecretion, since there were two patients in this study with high BAO and an additional two patients with an abnormally high PAO, a situation more commonly seen in dialysed patients. None of these four patients showed atrophic changes in the stomach, but they were otherwise similar to the remainder of the patients with respect to renal function.

We have been unable to show a relationship between the severity of renal failure and acid production. However, our patients all have severely reduced creatinine clearances, and it is possible that a relationship between renal function and acid secretion would have emerged if patients with milder degrees of uraemia had been studied.

Table 2 Findings in three patients before and after treatment

Patient	Treatment (duration)	Histology score		BAO (mmol/l) PAO		Serum gastrin (pg/ml)	
		Pre	Post	Pre	Post	Pre	Post
BC	Transplant (8 months)	5	1	0.7 23.7	5.9 39.6	160	75
JF	Haemodialysis (9 months)	11	1	0 3.0	0.1 5.0	325	684
RM	Haemodialysis (10 months)	4	1	0.6 34.6	0.6 37.4	49	112

BAO = basal acid output; PAO = peak acid output

The high incidence of hypergastrinaemia in this study agrees with previous reports from Durkin *et al.* (1971) and Korman *et al.* (1972), who also showed a direct correlation between increasing serum creatinine and gastrin concentrations; this was not observed in the present study, but again patients with mild chronic renal failure were not studied. Gastrin is metabolised in the kidney, and the high levels seen in chronic renal failure may be a direct result of a failure in metabolism (Clendinnen *et al.*, 1973; Davidson *et al.*, 1973).

Becker *et al.* (1973) suggested that gastrin may be partly metabolised in the small intestine, and it is possible that this mechanism is also impaired. The present study did not include an assessment of small intestinal function but it did show that duodenitis was commonly present in chronic renal failure. Serum gastrin levels, however, could not be related to the severity of duodenitis. Nevertheless the difficulties of assessing duodenitis are considerable, since mild changes may occur in about one-third of healthy volunteers and they are frequently patchy in distribution (Kreuning *et al.*, 1978).

Despite the high gastrin levels, patients with chronic renal failure usually have normal or low acid secretion, and, in common with Korman *et al.* (1972), we have found no significant correlation between serum gastrin levels and BAO or PAO.

Patients with atrophic gastritis tended to have higher gastrin levels in association with a low PAO, and it is possible that these patients may have had antral G-cell hyperplasia analogous to that in patients with pernicious anaemia (Polak *et al.*, 1972). Unfortunately, it was not possible for us to make a quantitative assessment of G-cells in the antral biopsies. However, G-cell hyperplasia in response to reduced acid secretion is probably only a minor cause of the hypergastrinaemia observed in uraemic patients because the severity of antritis showed no correlation with serum gastrin levels.

The cause of the gastritis in uraemic patients is likely to be multifactorial. Urea has been shown to

increase the back-diffusion of hydrogen ions across the mucosal barrier although similar data are not available for creatinine, and no specific studies of hydrogen ion diffusion have been made in uraemic patients. If such a mechanism was contributing to the mucosal damage, a relationship between the extent and severity of gastritis and either length of history or degree of renal failure should be apparent, which was not the case in this study. Biliary reflux may also be a contributory factor. However, in this study the gastritis was not limited to the distal stomach. Furthermore, there is no evidence that uraemic patients show reflux of bile more frequently than normal individuals, although we noted the presence of bile in basal acid samples of 12 of the 20 patients studied, and severe biliary reflux was seen at endoscopy in seven examinations. It is still possible that, in the presence of urea and other toxic substances associated with renal failure, small quantities of bile salts may damage the gastric mucosal barrier.

It is unfortunate that we were able to study only three patients after treatment for their chronic renal failure. McConnell *et al.* (1975) demonstrated a marked rise in PAO after dialysis treatment, and they postulated that the amelioration of gastritis by regular haemodialysis allowed the hypergastrinaemia to increase gastric secretory capacity. Our study undoubtedly demonstrated an improvement in gastritis as a result of haemodialysis but the results suggest that the increased PAO is not due to hypergastrinaemia, since gastrin levels actually fell in the patient with the most marked increase in secretory capacity.

From a practical point of view all patients with uraemia will have gastritis. Endoscopy is indicated only for those patients with more specific symptoms than anorexia, nausea, and vomiting.

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