Multiple recurring gastric erosions (aphthous ulcers)

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SUMMARY Five patients are described who had repeated endoscopy because of continuing dyspeptic symptoms associated with a negative barium meal. They were found to have multiple recurring gastric erosions (aphthous ulcers). No common aetiological factor could be found, although four of these patients did have a mild or moderately active superficial chronic gastritis. Conventional peptic ulcer therapy failed to control either symptoms or ulceration. Two patients finally came to gastric surgery (highly selective vagotomy), which resulted in the relief of symptoms and healing of the gastric aphthous ulceration.

Barium replaced bismuth in gastrointestinal radiology during the first world war, and the barium meal examination still remains the sheet anchor for the diagnosis of disorders of the upper gastrointestinal tract (*Lancet*, 1974). It has been refined by many workers, particularly those in Japan who pioneered the double contrast technique (Ichikawa, 1972) in order to delineate the surface pattern of the stomach and show the *areae gastricae*. Some centres in Britain can claim to reproduce this degree of refinement (Kreel *et al.*, 1973), but others, for various reasons, cannot achieve such satisfactory results. In many centres, therefore, endoscopy is used as a complementary examination to the barium meal (Cumberland, 1975). In radiologically negative dyspepsia endoscopy may give a positive diagnosis in up to 32% of cases (16% by Cumberland, 1975; 20% by Salmon *et al.*, 1972; 22% by Cotton and Rosenberg, 1971, and 32% by Cotton, 1973). Usually this reveals an unsuspected duodenal or gastric ulcer, but occasionally it may turn up completely new appearances or diseases. This report describes five patients who were investigated for barium negative dyspepsia.

Methods

Endoscopy was performed using an end-viewing gastroduodenoscope (Olympus GIFD) with the patient in the left lateral position. Premedication was with pethidine 50 mg, atropine 0.6 mg, ap-

proximately an hour beforehand, followed by an amethocaine gargle and diazepam 10-45 mg intravenously.

The histological criteria for the diagnosis and classification of gastritis used in this report is that proposed by Whitehead, Truelove and Gear in 1972. Endoscopic biopsy material and stools were inoculated into monkey kidney, human amnion, vero cell lines, and suckling mice for virus culture. Electron microscopy was performed on sections of fixed gastric biopsy material as well as on emulsion of the tissue. Screening for HBAg was by immunoelectro-osmophoresis and turkey erythrocyte haemagglutinations and HBAb by immunoelectro-osmophoresis. The rate of gastric mucus synthesis was measured by the rate of incorporation of N-acetyl ³H glucosamine into gastric mucosal glycoproteins, using endoscopic gastric biopsy material (Lukie and Forstner, 1972; Parke *et al.*, 1975). Haematological and biochemical estimations and tests for autoimmune antibodies were performed using standard techniques. In the two patients who came to surgery, a highly selective vagotomy was done according to the technique of Johnston and Wilkinson (1970). The completeness of the vagotomy was checked by an insulin test meal within 10 days of the operation (Hollander, 1948).

PATIENTS STUDIED

Patient 1

A 29 year old lorry driver was admitted in March 1972 with a haematemesis. He had been complaining

of vague epigastric pain for some two to three weeks before this. A barium meal was normal and a presumptive diagnosis of acute gastric erosions was made. Over the following two months he developed increasingly severe dyspeptic symptoms. In June he was readmitted with a further haematemesis. Barium studies were normal. Endoscopy showed a few small erosions (aphthous ulcers) lying on the lesser curve. These ulcers were mainly round or oval in shape, some 2-4 mm in diameter, with a depressed centre containing slough and a ring of reddened mucosa surrounding the ulcer for a distance of about 2 mm.

Although the gastric mucosa looked otherwise normal, histology showed that these aphthous ulcers were superimposed upon a moderately active chronic superficial gastritis.

Over the next eight months he was given conventional antacid therapy combined with metoclopramide and then in turn with carbenoxolone, Caved S, and De Nol. He continued to complain of severe dyspeptic symptoms and recurrent episodes of gastrointestinal bleeding (eight in all). As a pentagastrin test meal showed a moderately elevated maximal acid output (Table 1) a highly selective

Table 1 *Haematological and biochemical data*

	Patient identification					
	Normal range	1	2	3	4	5
Haemoglobin (g/dl)		16.2	14.0	11.4	12.8	14.6
ESR (West) (mm/h)		1	5	10	—	25
Serum folate (ug/l)	4.5-11.0	—	9.0	13.7	5.2	11.1
Red cell folate (ug/l)	85-160	—	85	301	163	158
Serum B ₁₂	130-700	—	200	640	920	560
Serum iron (umol/l)	11-31	—	—	—	9.7	14
Blood urea (mmol/l)	2.6-7.1	4.0	4.0	4.0	8.0	4
Serum calcium (mmol/l)	2.12-2.54	2.35	2.4	2.35	2.44	2.35
GPT (units)	9-36	—	13	—	9	9
GOT (units)	10-40	—	—	30	30	—
Serum albumin (g/l)	33-44	—	38	42	36	38
Serum globulin (g/l)	24-41	—	28	28	29	31
IgG (iu/ml)	80-220	—	89	129	95	147
IgA (iu/ml)	50-285	—	110	177	105	203
IgM (iu/ml)	57-230	—	57	188	232	117
Rate of gastric mucus synthesis						
Antrum (dpm/mg/h)	2090 ± 140	—	784	—	—	—
Lesser curvature (dpm/mg/h)	1400 ± 140	—	1145	—	—	—
Greater curvature (dpm/mg/h)	1440 ± 170	—	1115	—	—	—
Serum gastrin (pg/ml)	50-155	—	135	—	—	—
Pentagastrin test meal (mEq/(H+))						
Basal acid output		2.08	0.7	—	—	—
Total acid output		34.9	15.0	—	—	—
Maximum acid output		41.1	27.9	—	—	—

Table 2 *Histological data, screening tests for autoimmune disease and virus studies*

Histological data	Patient identification				
	1	2	3	4	5
Biopsies of gastric mucosa adjacent to aphthous ulceration showed:					
Mucosa					
Body type	+	+	+	+	+
Pyloric	+	+	+	+	+
Normal gastric		+			
Superficial gastritis					
Active (mild) chronic	+		+		+
Active (moderate)				+	
Operative full thickness gastric biopsy		Nor.			
Full thickness jejunal biopsy		Nor.			
Antibody data					
Gastric parietal cell antibodies		Neg.	Neg.	Pos.	Neg.
ANF thyroid microsomal antibodies					
Thyroglobulin TCAT Rh factor		Neg.	Neg.	Neg.	Neg.
Latex fixation test					
Viral data					
HBsAg and HbAb		Neg.	Neg.	Neg.	Neg.
CFT for herpes simplex and other viruses		Neg.	Neg.	Neg.	Neg.
Virus culture of endoscopic biopsy and stool		Neg.	Neg.		
Electron microscopy of endoscopic biopsy for virus particles		Neg.	Neg.

Fig. 1 Endoscopic findings (+ aphthous ulcers present; - endoscopy normal).

Figs. 2 Photographs (a), (b) of the aphthous ulceration, taken at endoscopy.

Fig. 3 Gastric mucosa showing superficial necrosis: the slough contains fibrin and polymorphs. $\times 12$.

vagotomy was performed in October 1973. A post-operative insulin test meal confirmed the completeness of vagotomy. Since then he has continued to have occasional mild dyspeptic symptoms but repeat endoscopies performed at four, 12, and 16 months postoperatively have shown no recurrence of the aphthous ulceration.

A summary of investigations and endoscopic details are listed in Tables 1 and 2 and Fig. 1.

Patient 2

A 29 year old nursing sister was seen in August 1974 with upper abdominal pain after cholecystectomy. A barium meal was normal but endoscopy showed multiple aphthous ulcers lying in the pyloric antrum associated with marked bile reflux (Figs 2 and 3). The surrounding gastric mucosa looked normal and this was confirmed by multiple biopsies.

Treatment with carbonoxolone followed by De Nol, Caved S, metoclopramide, Gaviscon, secholex, and antacids in turn all failed either to control the symptoms or to heal the aphthous ulcers. In view of the continuing severe dyspeptic symptoms medical treatment was abandoned. In September 1975 a highly selective vagotomy was performed; a post-operative insulin test meal confirmed the completeness of the vagotomy. This was rapidly followed by relief of symptoms, and endoscopy at two and five months later was normal.

A summary of investigations and endoscopic details are listed in Tables 1 and 2 and Fig. 1.

Patient 3

A 41 year old plumber was admitted in April 1974 with severe substernal and epigastric pain radiating through to the back. Screening for ischaemic heart disease was negative. A barium meal suggested a small gastric ulcer on the lesser curve.

De Nol therapy was started but on endoscopy two weeks later he was found to have three or four aphthous ulcers lying in the antral region. Five months later because of continuing dyspeptic symptoms unrelieved by either De Nol, Caved S, or antacids endoscopy was performed and he was found still to have multiple aphthous ulcers in the antrum. Histology showed that these were superimposed upon a mildly active chronic superficial gastritis. Treatment was changed to carbonoxolone and this resulted in the relief of symptoms. Endoscopy two months after starting therapy was normal and he was able to return to work for the first time for a year.

A summary of investigations and endoscopic details are listed in Tables 1 and 2 and Fig. 1.

Patient 4

A 53 year old housewife was admitted in May 1975 for an emergency splenectomy for delayed rupture of the spleen two months after a road traffic accident. In July she developed a severe dyspepsia and endoscopy confirmed the presence of a large gastric ulcer.

She was treated with carbonoxolone, but still had

Fig. 4 Gastric body-type mucosa showing chronic superficial gastritis. $\times 48$.

severe dyspepsia. Endoscopy 2½ months later showed that, although the ulcer had healed, there were now multiple aphthous ulcers lying mainly on the lesser curve. Biopsies of the surrounding normal looking mucosa showed the presence of moderately active chronic superficial gastritis (Fig. 4). Carbenoxolone therapy was continued for a further three months by which time she was free of symptoms and endoscopy was normal.

A summary of investigations and endoscopic details are listed in Tables 1 and 2 and Fig. 1.

Patient 5

A 56 year old housewife was admitted for a right medial menisectomy in June 1975. She was complaining bitterly of dyspeptic symptoms which had occurred in attacks over the past five years. A barium meal and cholecystogram were normal. In November endoscopy was performed and she was found to have multiple small aphthous ulcers lying mainly on the lesser curve and incisura. Biopsies showed that these were superimposed upon a mild active superficial chronic gastritis.

She was treated with De Nol for three months without relief of symptoms or ulcer healing.

A summary of investigations and endoscopic details are listed in Tables 1 and 2 and Fig. 1.

Discussion

Persisting dyspepsia with normal barium studies is

now generally accepted as one of the indications for upper gastrointestinal tract endoscopy (*Lancet*, 1974). This report deals with five such patients. They all gave a fairly long history of dyspepsia. The discomfort was felt mainly in the upper abdomen but was often diffuse and difficult to localize accurately, and in three patients was occasionally severe enough to require strong analgesics. Food usually exacerbated the symptoms and conventional medical therapy (antacids, carbenoxolone, Caved S, and De Nol) failed to control them, or produce healing. In one, recurrent gastrointestinal haemorrhage was an additional problem.

At endoscopy all had multiple aphthous ulcers of the stomach, varying in number from four to 20 or more. In some patients these were confined to the antrum and in others to the body of the stomach. They were round or oval punched out lesions, 2-4 mm in diameter, containing slough. The edges were raised and sharply demarcated from the surrounding normal looking mucosa. Biopsies of the aphthous ulcers demonstrated sloughing of the superficial mucosa. In one patient the normal looking surrounding mucosa was also histologically normal, and this was confirmed by multiple full thickness gastric biopsies taken at surgery (patient 2). In the other four patients the ulceration was superimposed upon a mild or moderately active chronic superficial gastritis.

Moutier in 1933, in a gastroscopic study of 73 cases of chronic gastritis, produced a classification

which included five patients with gastritis aphthosa. Schindler and Ortmyer in 1936 also described aphthous-like gastric erosions, but it was not until the advent of the fiberoptic endoscopy with its biopsy facilities that reliable correlation between the endoscopic appearance of the gastric mucosa and the underlying histological abnormality became possible. (Whitehead *et al.*, 1972). Taor and his colleagues (1975) have shown that, if the gastric mucosa is thought to have gastritis endoscopically, this will be confirmed in 97% of cases on histological examination. Conversely, if the mucosa looks normal on endoscopy, there is a one in three chance of it being abnormal on histological review. The recent report of Turner *et al.* (1974) of aphthous ulceration in patients with antral gastritis is thus difficult to assess, as this study did not include histology. Others have described persisting erosions (Kawai *et al.*, 1970). Roesch and Ottenjaun (1970) have attempted to classify gastric erosions, using endoscopic appearance and histology of gastric biopsies. They recognize four categories: haemorrhagic erosive gastritis, incomplete erosions, complete mature, and immature erosions. One patient in their study does not appear to fit into their classification. The lesions seen in our patients were complete but never haemorrhagic. They persisted for more than a few days so that they cannot be classified as immature, and there was no fibrosis of the lamina propria so they cannot be classified as mature. They resemble more closely the lesions described by Moutier (1933) and Schindler and Ortmyer (1936). We have therefore called them aphthous ulcers. In four of our five patients the aphthous ulceration was associated with an underlying mild or moderately active superficial chronic gastritis. It is unlikely that the gastritis is the cause of the ulceration, since, in the modern literature, erosions are usually confined to cases with severe superficial gastritis or atrophic gastritis (Taylor, 1969; Whitehead *et al.*, 1972). Moreover, in one patient, there was no evidence of gastritis at all; nor did she have coeliac disease, which is occasionally associated with oral aphthous ulcers and small bowel ulcers (Bayless *et al.*, 1967; Ferguson *et al.* 1975). Assay of the rate of gastric mucus synthesis in this patient showed very low values for the antral mucosa, which was the site of the aphthous ulceration; these low values are usually associated with gastric ulcer, or the ingestion of drugs irritant to the gastric mucosa. It is interesting to speculate as to whether these changes are the cause of, or secondary to, the aphthous ulceration, and further gastric mucus studies are required.

In spite of careful and thorough investigations no precipitating cause could be found for the aphthous ulcers in any of our patients. None was taking any

known gastric irritant. Their alcohol intake was small (social only) but three smoked fairly heavily (10-20 per day). Since cigarette smoking will produce pyloric incompetence and allow bile to reflux into the stomach (Read and Greel, 1973) and as this reflux can produce mucosal damage (Davenport, 1964; Cole, 1969) an attempt was made to reduce their smoking, but this failed. In the one patient who had obvious bile reflux, Secholex, a bile salt chelating agent, was tried but with no effect. Haematological and biochemical screenings were normal. A pentagastrin test meal was performed in the two patients submitted to surgery, and in one the maximum acid output was high, within the duodenal ulcer range. Complement fixation tests for Herpes simplex and other viruses were negative, and in two patients culture of endoscopic biopsy material and stools showed no growth of any virus. Electron microscopy of the endoscopic biopsies was also performed and showed no sign of any virus particles. Screening for an autoimmune process produced negative results apart from one patient with positive parietal cell antibodies.

The five patients in this report were remarkably similar. They all presented with a longstanding barium negative dyspepsia and on endoscopy were found to have aphthous ulcers of the stomach, which on prolonged endoscopic follow-up were shown to be persistent. No aetiological cause could be found and conventional medical therapy failed to control both symptoms and ulceration. In two patients a highly selective vagotomy was performed after a year of unsuccessful medical therapy. In both patients the relief of symptoms was dramatic and repeated endoscopies have shown no further aphthous ulceration. In one of these patients the ulceration was accompanied by chronic gastritis, but in the other patient the surrounding mucosa was normal. In view of this response to highly selective vagotomy, it would be interesting to treat future patients with this syndrome with a H_2 -receptor antagonist. These have been shown to reduce basal and maximal acid output and pepsin to the same extent as a vagotomy (*Lancet*, 1975).

This report is being published as we believe that other endoscopic units may have seen similar patients and we hope that this study will stimulate further investigation of this small but obviously important group of patients.

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