

# Comparison of 'early gastric cancer' in Britain and Japan

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**SUMMARY** Before the introduction of endoscopy, four out of 720 cases of gastric cancer were diagnosed before the cancer had breached the muscularis propria, an incidence of 0.5%. Using endoscopy and endoscopic biopsy, 10 out of 101 cases of gastric cancer were diagnosed at this 'early' stage, an incidence of 10%. Their clinical, morphological, and histological characteristics are compared with those of Japanese 'early gastric cancers' and reveal a remarkable similarity. The results of this study suggest that a higher proportion of British gastric cancers could be diagnosed at an 'early' stage by more intensive investigation of dyspeptic patients using up to date radiological techniques, fiberoptic endoscopy, and endoscopic biopsy.

The Japanese experience of gastric cancer is a singular one. Their incidence of the disease is among the highest in the world; their age standardised death rate is more than three times that of England and Wales and more than eight times that of the USA (Segi and Kurihara, 1966); their age at diagnosis is approximately 10 years younger than that of the European or North American patient (Kubo, 1974). Five year survival rates of more than 90% have been reported in those surgically treated patients in whom the cancer is limited to the mucosa or submucosa—that is, 'early gastric cancer' (Kidokoro, 1972). There are several reports of the rapid increase in the rate of diagnosis of 'early gastric cancer' in recent years from Japan. Muto *et al.* (1968) showed that the proportion of 'early gastric cancers' rose from 1.3% in the period 1941-45 (a rate that is comparable with most European and North American clinics today) to 36% in 1965. In parallel with this, a correspondingly dramatic increase in the overall five year survival from operated cases from 10% to 26% was noted over the same period (Hirayama, 1975).

This difference in prognosis has led to the view that Japanese gastric cancer may be different from the European or American variant of the disease in that it may be more readily diagnosable and slowly growing. This view appeared to have some support from the work of Laurén (1965) who observed that gastric carcinomas could be divided into two main

types, 'intestinal' and 'diffuse', and suggested that these two types could have a different aetiology. His finding of a high incidence of the 'intestinal' type in countries of high risk was confirmed by Muñoz *et al.* (1968) who also suggested that these two types of cancer might be of different aetiology.

Epidemiological data, however, suggest that the gastric cancers in high and low risk areas may be similar. Studies of migrant Japanese (Haenszel, 1961) and Polish families (Staszewski and Haenszel, 1965) indicate that migration from a high to a low risk country is followed by a decreased mortality from gastric cancer. Moreover, Kubo (1974) has questioned the findings of Laurén (1965) and Muñoz *et al.* (1968). He has made an age-specific comparison on the same data and showed no essential differences in the nature of the gastric cancers between the high and low risk countries. In his own study, he also found no major difference in the type, site, or morphology of gastric cancers in different countries. It is important to establish whether or not the disease is the same in different countries and, for that reason, we report our series of 'early gastric cancers' and attempt to compare their morphology, histology, and behaviour with those of Japanese series.

## Methods

A review of all patients with a histological diagnosis of gastric cancer from 1960-77 at Llandough Hospital was undertaken. Those cases in which the cancer had not infiltrated beyond the submucosa were designated 'early gastric cancer' and comprise the present series of 14 cases.

Fiberoptic endoscopy with biopsy was introduced

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in this hospital in 1972. The resected stomachs of patients 1-7 were examined by routine histological techniques but the remainder were subjected to a more exhaustive pathological analysis adapted from the Japanese methods (Mochizuki, 1972). The fresh specimen was opened along the greater curvature, pinned out flat, photographed fresh, fixed in formalin, and an outline tracing of the fixed material made. The stomach was then cut in longitudinal slices from which numbered blocks were prepared for histological examination. This enabled a reconstruction to be made of the cancer and any other lesions present. All sections were stained with haematoxylin and eosin, periodic acid Schiff (PAS), and alcian blue (pH 2.5).

Comparison with Japanese 'early gastric cancers' were based partly on examination of histological material in major Japanese centres, partly on published material reported by Sano (1972), Nakamura *et al.*, (1967), Nagayo (1971), and Mochizuki (1972) and partly on discussions with these and other Japanese pathologists.

## Results

Between January 1960 and March 1977, 14 cases of 'early gastric cancer' were diagnosed: 10 were male and four female with ages ranging from 43 to 83 years. During the 12 years before 1972, four cases were diagnosed out of a total of 720 cases of gastric cancer diagnosed in this hospital, an incidence of 0.5%. During the subsequent five years—that is, after endoscopy had been introduced—10 cases of 'early gastric cancer' were diagnosed out of a total of 101 cases of gastric cancer, an incidence of 10%.

### SYMPTOMS

Eleven patients presented with dyspepsia. Five of the six patients treated with antacids or carbenoxolone obtained relief of symptoms (and usually a delay in

diagnosis). It is of interest that the mean length of symptoms before diagnosis in the four 'pre-endoscopy' patients was seven years nine months (SD 3.2 years) compared with one year 10 months in the 'post-endoscopy' group (SD 3.0 years). Males (10) had a longer history than females (four), with a mean duration of 4½ years compared with one year. The ulcerated forms of early gastric cancer had a very much longer symptomatic history before diagnosis than did the protuberant lesions, the mean durations being 4½ years (SD 4.0 years) and three months (SD 0.4 years) respectively.

### DIAGNOSIS

Of the four 'early gastric cancers' in the 'pre-endoscopy' period, two were unsuspected until routine sections from an apparently benign gastric ulcer revealed evidence of malignancy. Barium meals provided only one definite diagnosis of malignancy and this after a hospital delay of over four years. In only one other case was malignancy suspected preoperatively (Table 1).

Of the 10 patients diagnosed in the 'post-endoscopy' period, eight out of nine who were subjected to operation were diagnosed as malignant preoperatively. In case 14 the lesion was so small that it could be diagnosed only after histological examination of the resected specimen. The contribution of endoscopy and gastric biopsy to diagnosis in this group of patients is clear from Table 2, where it can be seen that, in patients 5, 6, 8, and 10, a false benign diagnosis made radiologically was modified preoperatively after endoscopic biopsy. In three patients (9, 11, and 13) a radiological indication of malignancy was confirmed by endoscopy and biopsy. In case 12, the 'early gastric cancer' was an incidental necropsy finding after coronary occlusion.

### PATHOLOGICAL FEATURES

On the basis of histological structure, the 'early

Table 1 *Diagnosis in 'pre-endoscopy' period*

Patient no.	Length of symptoms (yr)	Ba. meals (no.)	X-ray diagnosis	Pre-operative diagnosis	Method of diagnosis
1	5	4 (over 4 yr 9 m)	1. Pre-pyloric ulcer 2. Normal 3. Coarse mucosal folds 4. Ca. gastric antrum	Malignant	4th ba. meal
2	10	2 (over 6 m)	1. Gastric dilatation? DU 2. Gastric dilatation	Benign	Resected specimen
3	11	2 (over 9 yr)	1. Benign GU 2. Antral stricture ? malignant	Benign	? Ba. meal Resected specimen
4	5	1	1. Benign prepyloric ulcer	Benign	Resected specimen

Table 2 Diagnosis in 'post-endoscopy' period

Patient no.	Length of symptoms	Ba. meals (no.)	Ba. meal diagnosis	Endoscopic finding	Biopsy	Preop. diagnosis	Diagnosis
5	9 m	1	1. Benign GU	Benign GU	Malignant	Malignant	Endoscopic biopsy
6	9 m	1	1. Antral polyp	Malignant	Benign	Malignant	Endoscopy
7	2 yr 6m	3	1. GU 2. GU 3. ? Malignant ulcer	Benign Benign Benign	Benign Benign Benign	Malignant	Ba. meal/ resected specimen
8	10 yr	2	1. GU 2. ? GU	Benign GU ? GU	Malignant	Malignant	Endoscopic biopsy
9	7 m	1	1. Malignant	Malignant	Malignant	Malignant	Ba. meal/ endoscopy/ endoscopic biopsy
10	2 yr	1	1. Benign GU	Benign	Malignant	Malignant	Endoscopic biopsy
11	1 m	1	1. Malignant polyp	? Malignant polyp	Malignant	Malignant	Ba. meal/ endoscopic biopsy
12			Incidental post-mortem findings of malignant polyp at pylorus				
13	18 m	1	1. Malignant ulcer	Malignant U	Malignant	Malignant	Ba. meal/ endoscopy/ endoscopic biopsy
14	1 m	1	1. Benign GU	Benign GU	Benign	Benign GU	Resected specimen

gastric cancers' were divided into two groups, differentiated and undifferentiated. The differentiated group comprised 10 out of the 14 cases and were characterised by a structure which was mainly tubular (Fig. 1) and, to a lesser extent, tubulopapillary.

Seven of the 10 stomachs in the differentiated group showed extensive intestinal metaplasia characterised

by goblet cell formation (Fig. 2). Unlike normal gastric mucin the goblet cell mucin gives a strongly positive reaction with alcian blue at pH 2.5.

The four cancers in the undifferentiated group were all of predominantly mucocellular (signet ring cell) type (Fig. 3). These cells give a positive reaction with PAS which is often helpful in their recognition. Numbers of non-mucus-secreting cancer cells were

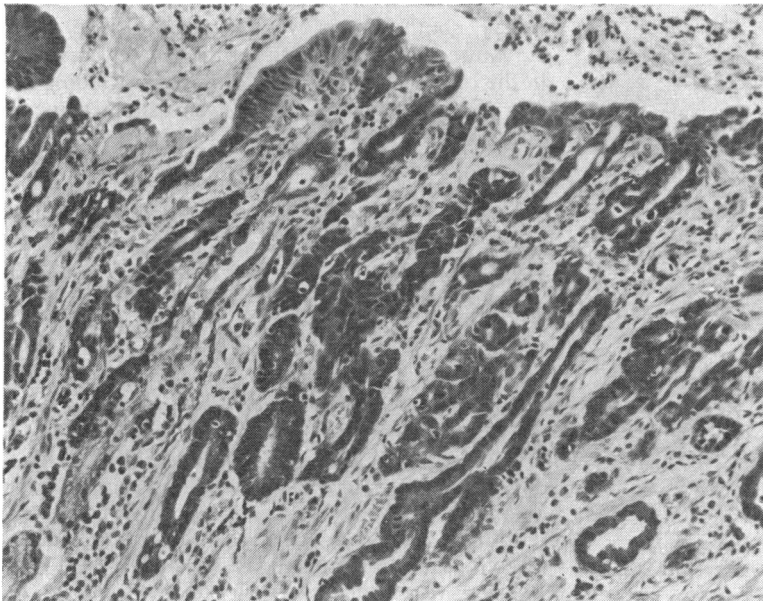


Fig. 1 Differentiated carcinoma of tubular type. H and E, original magnification  $\times 500$ .

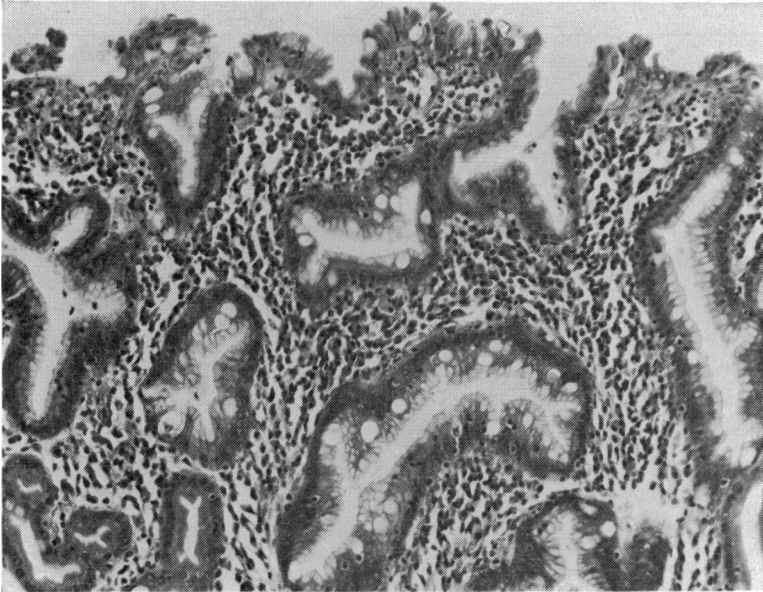


Fig. 2 *Intestinal metaplasia of gastric mucosa, showing goblet cell formation. H and E, original magnification  $\times 500$ .*

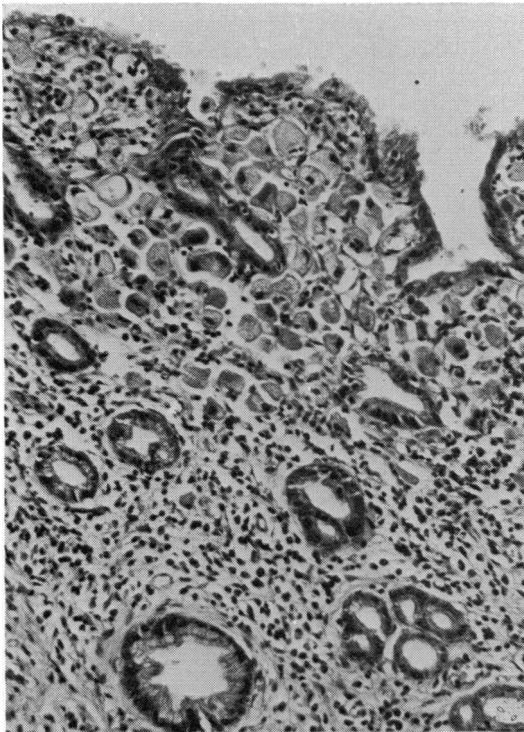


Fig. 3 *Undifferentiated carcinoma of mucocellular ('signet ring cell') type. H and E, original magnification  $\times 500$ .*

also present. In only one of the four cases was there a significant amount of intestinal metaplasia.

These 'early gastric cancers' showed a marked predilection for the lesser curvature where, in 12 out of the 14 cases, the main lesions were situated, the other two being located on the greater curvature. In one of the 12 lesser curvature cancers there was a second 'early gastric cancer' situated on the greater curvature. In two other cases with double 'early gastric cancer', both lesions were situated on the lesser curvature in one and both on the greater curvature in the other. Twelve of the 17 lesions, including the four on the greater curvature, were situated in the distal half of the stomach.

#### MORPHOLOGICAL TYPES

The various morphological types recognised by the Japan Society of Gastroenterological Endoscopy in 1962 (Murakami, 1971) were found to occur in the following proportions (Fig. 4).

The three cases of protuberant (type I) cancer were all in the differentiated group, with a tubular structure. In case 6, two morphologically and histologically separate tumours were present. In case 11, there was extensive surrounding intramucosal spread of slightly raised cancer giving an alternative designation of type I + IIa. In case 12 (Fig. 5) the primary lesion was still intramucosal but intravenous extension had already occurred, although no evidence of extragastric metastasis was detected.

There were four cases of superficial (type II)

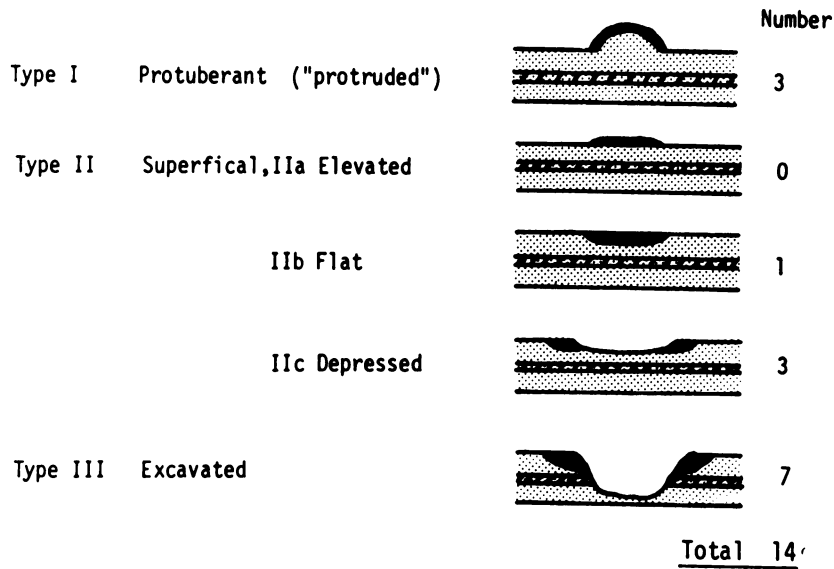


Fig. 4 Frequency of the different morphological types of 'early gastric cancer'.

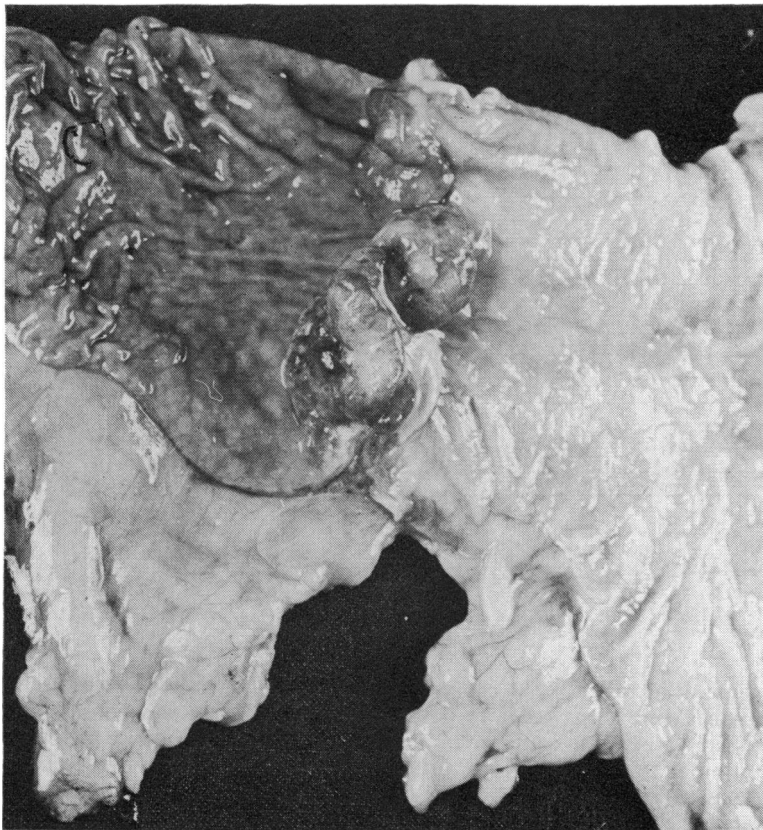


Fig. 5 Protuberant (type I) carcinoma, situated at pylorus.

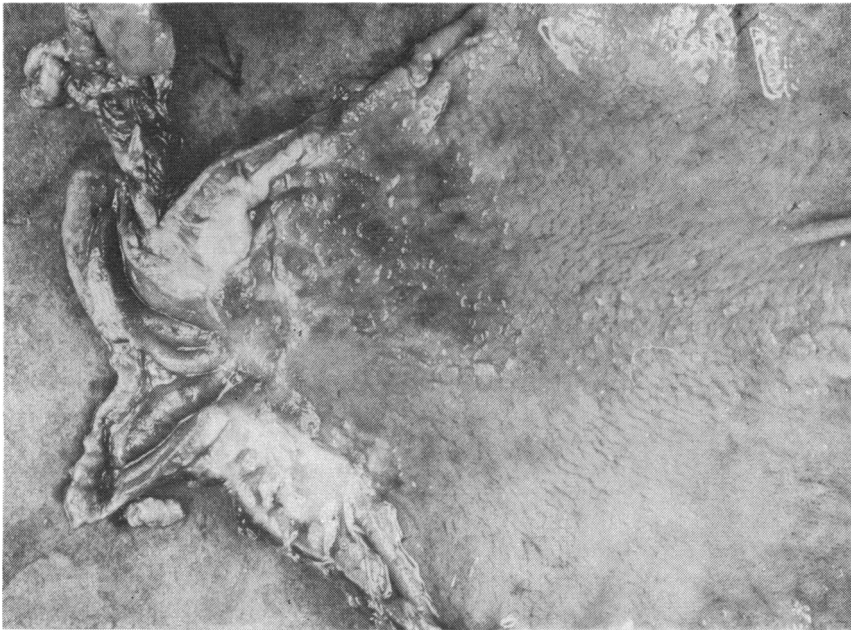


Fig. 6 (Top) *Slightly depressed (type IIc) carcinoma in case 5. Compare with Fig. 7.*

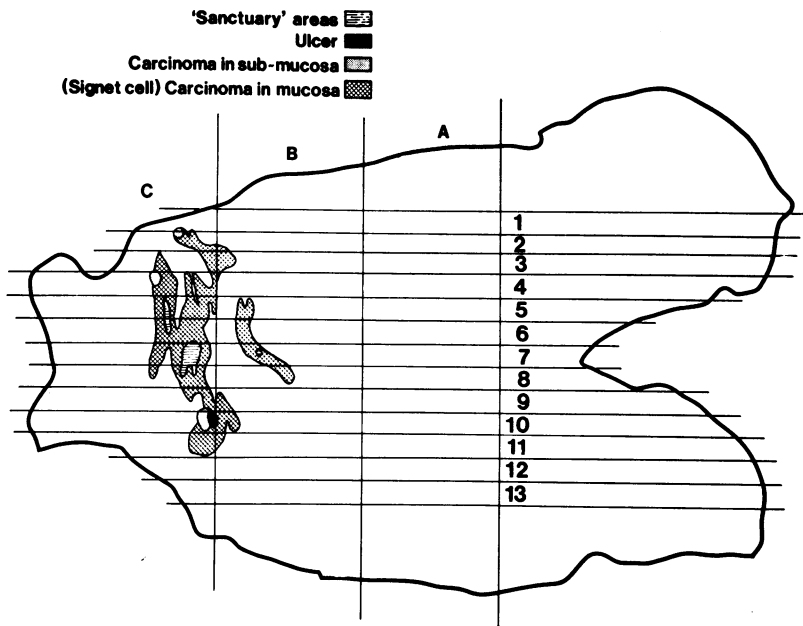


Fig. 7 (Bottom) *Map of histological findings in case 5. Compare with Fig. 6.*

cancer. None was designated as superficial raised (type IIa), although slightly raised zones were seen adjoining a predominantly depressed (type IIc) lesion, giving an alternative designation as type IIc + IIa. Similarly, although only one cancer was designated as flat (type IIb), there were large zones of

flat cancer adjoining two depressed (type IIc) cancers. In both cases the flat cancer was considerably greater in area than the visible depressed lesion, as in Figs. 6 and 7, so that they could have been designated as type IIb + IIc. Another feature shown in Fig. 7 is the presence of a 'sanctuary area', a zone

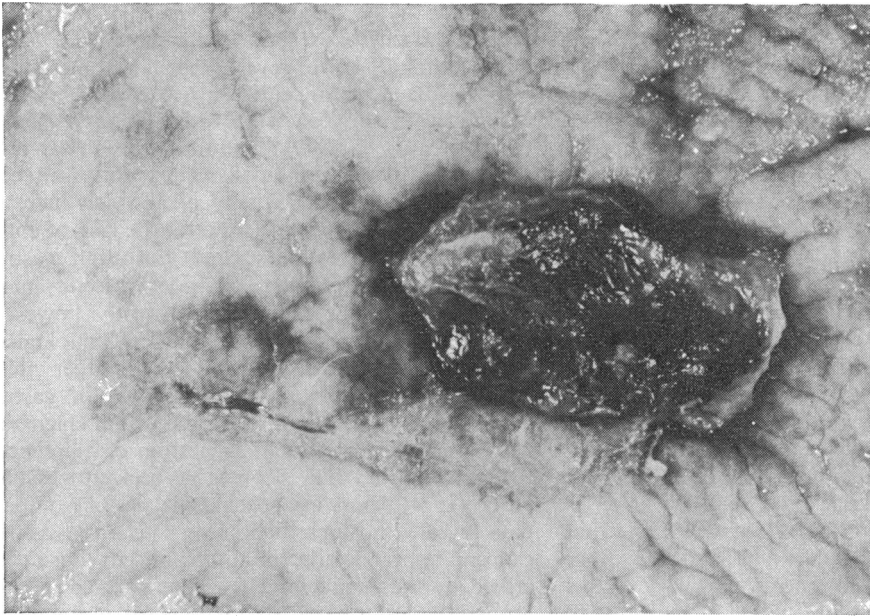


Fig. 8 Excavated (type III) carcinoma showing resemblance to simple peptic ulcer.

of non-cancerous tissue completely surrounded by cancer tissue. These zones were present in two of our four cases of type II cancer. Both occurred in the flat (type IIb) zones of the lesions.

A characteristic feature of the depressed (type IIc) lesion is their macroscopic (and radiological) resemblance to peptic ulcers. A differential feature is the rounding off, sometimes with slight hump formation, of the fused mucosal folds at the margin of the depression, due to the filling in of the mucosa—and, in some lesions, the submucosa — by neoplastic infiltration. The presence of ulceration in these depressed lesions explains their clinical presentation with ulcer symptoms. Two of the three cancers designated as slightly depressed, showed a marked tendency to spread horizontally in the mucosa rather than to invade vertically. One of these (case 5) was of undifferentiated mucocellular type (Figs. 6 and 7) and the other (case 8) was of differentiated tubular type. Much of the intramucosal spread did not involve the full depth of the mucosa, a feature of significance for endoscopic biopsy diagnosis.

Excavated (type III) lesions show a greater depth of ulceration and macroscopically may resemble simple peptic ulcers to a striking degree, as in case 14 (Fig. 8). Seven cases had lesions of this type. One of them also showed extensive horizontal spread in the mucosa so that it could have been designated type IIb + III. Because of their similar clinical presentation, type III (excavated) and type IIc (depressed) lesions may be grouped together. This group of

ulcerated cancers, comprising 71% of our series, includes all four undifferentiated mucocellular cancers as well as six differentiated tubular cancers.

### Discussion

Comparison of the 'early gastric cancers' in this series with those seen in Japan and described in Japanese reports (Sano, 1972; Nakamura *et al.*, 1967; Mochizuki, 1972; Nagayo, 1971) reveals very similar features in both groups. In both countries the histological types which mostly occur are the differentiated lesions of tubular and tubulopapillary structure, generally associated with extensive intestinal metaplasia and corresponding to Laurén's (1965) 'intestinal' cancers. In both, the protuberant tumours are all of differentiated type. Some of these differentiated cancers give rise to venous spread while still at an 'early' stage as seen in case 12. Japanese studies (Hayashida, 1969) have shown that this characteristic can result in early hepatic metastases, which is not a feature of 'early' cancers of the undifferentiated or diffuse type. The result of this is that, unlike advanced cancers, the 'early' diffuse cancer actually has a better prognosis than the 'early' intestinal cancer. Hayashida quotes a five year survival of 100% for the 'early' mucocellular carcinoma, compared with 84% for the 'early' tubulopapillary cancer.

Another feature common to cancers of both countries is the occasional occurrence of 'sanctuary areas',

islands of non-malignant mucosa completely surrounded by cancer tissue (Mochizuki, 1974). These are of diagnostic importance in that if an endoscopic biopsy is taken from this site, a false benign diagnosis may be made. Sanctuary areas may represent a small isolated portion of the original gastric mucosa which has escaped the spread of the surrounding neoplastic change, or may be the result of ulceration and subsequent healing of the relatively unstable carcinoma tissue. The tendency of carcinoma to ulcerate is fortunate in that it gives rise to ulcer symptoms with the possibility of a morphologically 'early' diagnosis. The occurrence of ulceration in 70% of our 'early' cancers is exactly comparable with the proportion observed in Japanese series.

The fact that some cases of 'early gastric cancer' of each morphological type can spread horizontally in the mucosa rather than invade more deeply is well recognised in Japan (Okabe, 1972) and in our series is exemplified by cases 5, 8, 11, and 13, the first being of diffuse mucocellular type and the other three of intestinal tubular type. A corollary of this feature is that a cancer may enlarge in size and yet remain 'early', as far as depth of invasion is concerned for several years. Okabe gives examples of cases which remained as superficial 'early' cancer for three or four years.

The higher proportion of gastric cancers diagnosed at a morphologically early stage of development by the Japanese is more likely to be due to their extensive use of fiberoptic endoscopy and improved radiological techniques in upper gastrointestinal diagnosis than to their lesions being a more biologically favourable form of cancer. Fiberoptic endoscopy has become widely accepted in European countries only within the past seven years and the use of double contrast radiology is not widespread outside Japan. Nonetheless, there are encouraging signs that 'early' gastric cancer is becoming more frequently recognised in centres outside Japan which are using improved diagnostic methods (Miller and Kauffmann, 1974; Elster *et al.*, 1975; Fevre *et al.*, 1976; Machado *et al.*, 1976). Our own findings also suggest this possibility. During the 12-year period before the introduction of endoscopy, four cases were diagnosed out of a total of 720 cases (0.5%), whereas in the five years after endoscopy was used, a further 10 cases were diagnosed out of a total of 101 cases (10%). Short follow-up data are available on the majority of these recent cases but only one patient in the whole series died of probable recurrent disease. So there is a strong suggestion that in both Britain and Japan this superficial stage of gastric cancer represents a stage of the disease which is usually curable.

It may be said by the therapeutic nihilist that 'early gastric cancers' are those that 'select' them-

selves for 'early' diagnosis by virtue of their slow growth and lengthy symptomatic course (MacDonald and Kotin, 1954). However, the fact that increasing rates of diagnosis of 'early gastric cancer' parallel an improved surgical rate of the resected gastric cancers (Muto *et al.*, 1968) and have been related to the recently decreased Japanese mortality from the disease (Hirayama, 1975) renders this view increasingly difficult to support. Hitherto, the lack of comparison between Japanese and European gastric cancer has given strength to the widely voiced opinion that they cannot be compared. Indirectly, however, the evidence suggests the reverse: epidemiological studies indicate that environmental rather than genetic factors are largely responsible for gastric cancer (Haenszel, 1961; Staszewski and Haenszel, 1965) and Muñoz's (1968) suggestion of differences between high and low risk areas has been criticised by Kubo (1974) whose age specific analysis of Muñoz's data revealed no such differences. Our 'early gastric cancers' appear similar in all respects to those described by the Japanese. They were situated largely around the lesser curve and particularly in the distal half of the stomach; they had similar morphological and histological characteristics occurring in similar proportions with a similar growth pattern and a similar mode of clinical presentation, usually with dyspeptic symptoms due to ulceration. Additionally, the differentiated carcinomas in our series, as in the Japanese reports, tended to be associated with extensive intestinal metaplasia of the gastric mucosa, whereas undifferentiated carcinomas usually arise from stomachs showing little intestinal metaplasia. The demonstration of 'sanctuary' zones of normal epithelium within a neoplastic lesion (Fig. 7) as occurred in two of our patients, is well recognised by Japanese pathologists.

This apparent similarity between the Japanese and a small series of British 'early gastric cancers' needs, of course, to be further examined in a large study but there appears to be no support for the view that the British stomach cancer, with its appalling prognosis, is different in nature from that of the Japanese. We may thus hope for earlier diagnosis more frequently once the dyspeptic patient is intensively investigated by up to date radiological and endoscopic techniques.

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