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Gastric Cancer—Delay in Diagnosis and its Causes

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Abstract—*Over a period of* 1 *year* 83 *patients, admitted to Nottingham hospitals with gastric neoplasms, were interviewed in order to identify the extent of delay in diagnosis and the possible causes. The mean age was* 71 (*S.D.* ± 10) *and there was a male preponderance of* 1.8 : 1.

The median delay from onset of symptoms to diagnosis was 22 *weeks* (*IQR* 14–35). *Delay by the patient after the onset of symptoms before seeking medical help was* 4 *weeks* (*IQR* 2–12). *Family doctor delay was* 7 *weeks* (*IQR* 3–14) *and this was caused by trial of medication and radiological investigations. The hospital delay of* 3 *weeks* (*IQR* 2–7) *was due to patients waiting for multiple out-patient investigations, inadequate investigation of iron-deficiency anaemia, failure to follow-up gastric ulcers and difficulty in getting histological confirmation of clinically suspicious lesions.*

Seventeen (20%) *patients were treated with a* H_2*-receptor antagonist* (*Cimetidine*). *There was no significant difference in the delay caused by Cimetidine when compared with that due to antacids* (*Mann–Whitney* U = 232, P > 0.5), *and there was no difference in survival between these patients and those not treated with Cimetidine* (χ^2 = 1.9, P > 0.1).

In this study only one of 80 *patients had an early gastric cancer, which supports the view that gastric carcinoma is asymptomatic in its early stages and mass screening of the population would be the only way to detect carcinoma at this stage in its development.*

Family doctor delay can be reduced by immediate referral of patients to hospital for investigation prior to commencing medication. Hospital delay can be improved by avoiding duplication of investigations, fully investigating iron-deficiency anaemia and following up gastric ulcers with endoscopy and biopsy till fully healed.

INTRODUCTION

THE PROGNOSIS for patients with gastric cancer in Europe and North America remains uniformly poor even with the advent of fibreoptic endoscopy [1–5]. The main reason for this is the late stage of the tumour when patients first present with symptoms [5]. Indiscriminate treatment of patients with dyspepsia without prior investigation is a cause of delay and since the introduction of the H_2-receptor antagonists in 1976, there has been continuing discussion as to whether these drugs can mask the symptoms of gastric cancer and therefore delay diagnosis and treatment of this condition [6–8].

The object of this study was to discover whether delay occurs in diagnosing gastric cancer and to ascertain the cause of delay with special regard for the H_2-receptor antagonists.

MATERIALS AND METHODS

Consent was obtained from all consultant surgeons and physicians in Nottingham to interview their patients with gastric cancer. From October 1981 to September 1982, 83 patients with newly diagnosed gastric lesions were interviewed and a careful history of the symptoms, dates of onset of symptoms and drug history were recorded. Results of investigations, management and further progress were also noted over the next two years. The information was stored for further analysis on a 48K TRS-80 microcomputer.

Patients were allocated to one of five social classes using the 1980 *Classification of Occupations* [9].

Cumulative life-tables were constructed using the method described by Peto and Armitage and the log-rank test was used to compare the prognosis in different strata [10]. Independent, unmatched samples were compared using the chi-squared and Mann–Whitney *U* tests.

RESULTS

Altogether, 83 patients with newly diagnosed gastric lesions were interviewed. The final histological diagnosis in three patients showed lymphoma. The patients with lymphoma were included in the

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Table 1. Symptoms of gastric cancer

Symptom	First symptom	Presenting symptoms*	Overall occurrence of symptoms*
Anorexia	12%	7%	71%
Weight loss	15%	5%	70%
Malaise	19%	10%	60%
Nausea	2%	5%	58%
Vomiting	2%	25%	58%
Indigestion	24%	7%	55%
Epigastric pain	19%	24%	55%
Shortness of breath	2%	8%	24%
Dysphagia	2%	17%	19%
Malaena	1%	8%	12%
Haematemesis	1%	6%	8%
Constipation	—	—	4%
Other	1%	7%	13%

*More than one symptom in some patients.

analysis of delay in diagnosis but excluded from the survival analysis.

The mean age was 71 years (S.D. ± 10) and there was a male preponderance of 1.8 : 1.

Ten of the 80 patients with gastric cancer had had previous gastric surgery, four (5%) of these had previously undergone partial gastrectomy, more than 25 years ago. One patient had had a truncal vagotomy and pyloroplasty, one patient a gastroenterostomy, and operative details were not available in four patients. Two of the 80 patients were on monthly vitamin B_{12} supplements for pernicious anaemia.

Forty-one (49%) patients were referred to surgeons for further investigations and management while 36 (43%) were referred to physicians. Four patients were initially seen by the ENT surgeons, one by the haematologists and one patient was admitted by the geriatricians. Twenty-one (25%) patients were admitted as emergencies.

Symptoms

The most common first symptom was indigestion, occurring in 20 (24%) patients. However, all these patients had a history of more than 2 years' indigestion and the reason for their seeking further advice was a change in this symptom. The commonest presenting symptoms were increasing frequency or intensity of epigastric pain, vomiting and dysphagia. Forty-eight (58%) patients presented with one or more of these three symptoms (Table 1). The commonest symptoms overall were anorexia and weight loss. However, in most cases the patient had dismissed these symptoms until admitted to hospital.

When first seen in the clinic 21 (25%) patients had an iron deficiency anaemia, with a haemoglobin concentration of less than 10 g/dl. Increasing shortness of breath was the first symptom in two patients and in seven patients it was the presenting symptom.

Overall delay

The median overall delay from the onset of symptoms until treatment was 22 weeks (IQR 14–35), 25% of patients had a total delay of more than 35 weeks (8 months) prior to treatment.

The distribution of overall delay in weeks and its constituents (patient delay, family doctor delay and hospital delay) are illustrated in Fig. 1

Patient delay

The time from the date of onset of new symptoms to the date of first attendance at the famly doctors surgery is defined as patient delay and in this study there was a median patient delay of 4 weeks (IQR 2–12).

Careful questioning of 76 patients showed that 40 (53%) had no idea why their symptoms occurred, 17 (22%) thought they had an ulcer, four (5%) ascribed their symptoms to indigestion, three (4%) thought they had a cancer and 12 (16%) gave other reasons for their symptoms.

Nineteen patients thought their symptoms serious though 16 had no idea what caused the symptoms.

Twenty-five (33%) patients admitted that they delayed seeing their family doctor. Fifteen thought the symptoms insignificant, two delayed going to their doctor because they had no pain, and a further four were afraid of doctors or what they might be told. Of the other four patients, one was recovering from a cholecystectomy performed for indigestion, one treated the symptoms himself, one patient did not want to trouble his family doctor and the last patient had been investigated at another centre within the last year where a diagnosis of hiatus hernia had been made.

Most patients (81%) discussed their symptoms with family or friends and were usually advised to see the doctor. The main reason for seeking advice was persistence of symptoms.

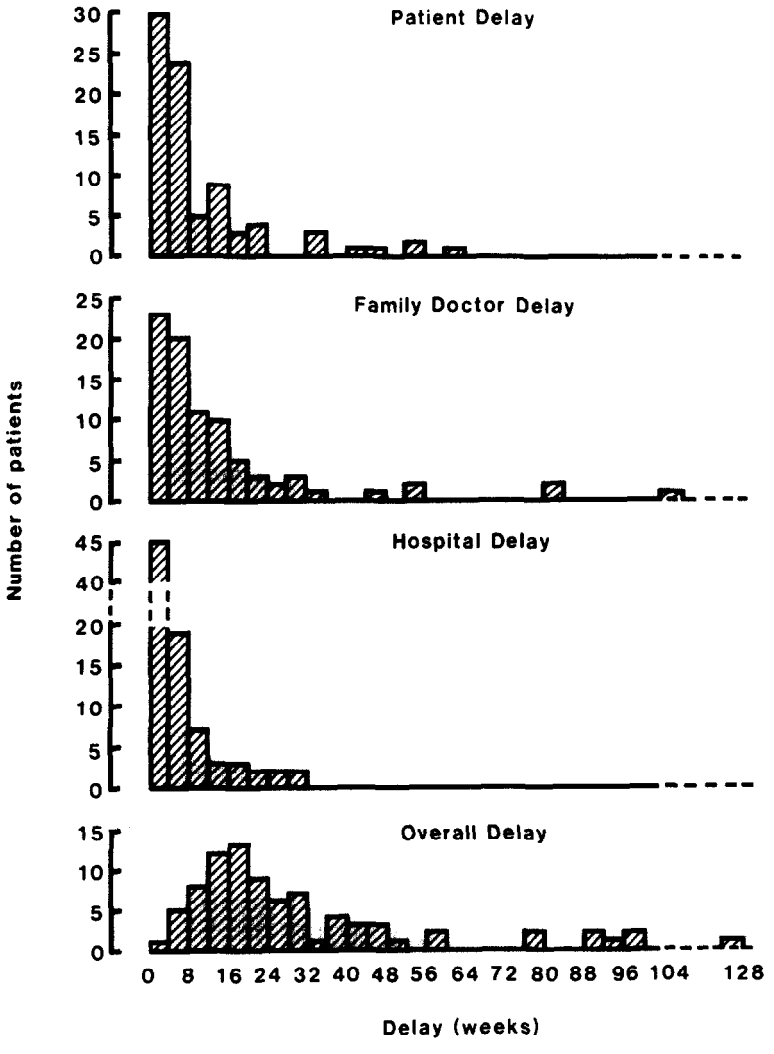

Fig. 1. Histograms showing the distribution of overall delay and its constituents: patient, family doctor and hospital delay, in 83 patients.

Family doctor delay

This is the time from the date of the patients first visit to the family doctor to the date of the referral letter to the hospital. The median delay due to the family doctor was 7 weeks (IQR 3–14). There were two main causes for delay. Forty-seven (57%) patients had a trial of medication which caused a median delay of 6 weeks and 34 patients were referred for radiological investigations.

The family doctor referred 62 (75%) patients to hospital out-patient departments, the other 21 patients were admitted as emergencies. Of the latter patients, 16 were sent in by their own doctors who had previously seen 12 of the patients. Eight of the patients had dysphagia and/or vomiting, five had suffered a haematemesis and/or melaena.

Hospital delay

Hospital delay is the time from the date of the family doctor's referral letter to the date of treatment, whether the latter was surgical or symptomatic only. The median hospital delay was 3 weeks (IQR 2–7). In 45 (54%) patients the delay was less than 4 weeks. Patients whose delay was more than 4 weeks included five (6%) who had to wait more than 3 weeks for their first hospital appointment, in two cases the date of the appointment was altered by the patient and eight (10%) who waited for multiple out-patient investigations. Prolonged delay was the result of failure to adequately investigate iron-deficiency anaemia in three (4%) patients, failure to follow-up gastric ulcers in three (4%) patients and difficulty in making the diagnosis on endoscopy in a further 10 (12.5%) patients. Four of these latter patients had gastric cancers at the cardia extending into the oesophagus and repeated dilatation and biopsy were performed before the diagnosis was established, in the other six patients gastric lesions were repeatedly biopsied before the diagnosis was made. Preparation for surgery, e.g. treatment of anaemia, led to delay in three patients. One patient had difficult concurrent medical problems, one patient had an incorrect initial diagnosis, which caused considerable delay in making the

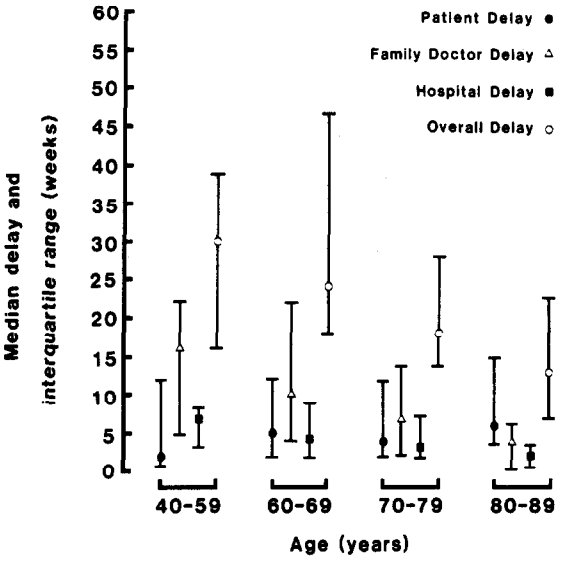

Fig. 2. Influence of age on overall delay and its constituents: patient, family doctor and hospital delay.

diagnosis of the gastric cancer, and an 86-year-old patient was initially managed conservatively and then referred for surgery when vomiting started.

INFLUENCE OF AGE, SEX AND SOCIAL CLASS ON DELAY

Grouping patients' ages by decades shows the influence of age on patient delay, family doctor delay, hospital delay and overall delay (Fig. 2). Two patients in their forties were included with patients in the fifties group.

The shortest patient delay occurred in the youngest group, median delay being 2 weeks (IQR 1–4). Patients in their sixties and seventies delayed 5 and 4 weeks respectively, the interquartile range in both groups being 2–12 weeks. Patients in their eighties waited longest before seeing their family doctor, median delay being 6 weeks (IQR 4–15).

The family doctor delay was longest in the 11 youngest patients with a median delay of 16 weeks (IQR 5–22). This was due to starting treatment without any investigations in seven of eight patients whose delay was more than 4 weeks. The other patient had a 2 month wait for a barium meal organized by the family doctor. This group of patients also suffered the longest hospital delay, median delay being 7 weeks (IQR 3–8). There were seven patients with more than a 4 week hospital delay. Three had to wait for multiple out-patient investigations, one had a prolonged wait for an out-patient appointment and then a further wait for gastroscopy, in two patients there was difficulty in confirming the diagnosis and one patient was treated without investigation.

Family doctor and hospital delay became shorter the older the patient, only two of 12 patients in their eighties were delayed more than 6 weeks by either the family doctor or the hospital.

Patient sex did not affect patterns of delay, both men and women having the same patient, family doctor and hospital delays.

Occupational history was available in 67 patients. The distribution of patients by social class is shown in Table 2. Because the number of patients in each group is small no definite conclusions can be made. However the data suggest that patient delay in social class IV is longest, median delay being 6 weeks (IQR 2–12), while family doctor and hospital delay are shortest being 4 weeks (IQR 1–8) and 2 weeks (IQR 1–7), respectively. This effect appears to be independent of age, only three of the 18 patients being over 80 years and the median age being 69 years.

Thus patients in their eighties and those in social class IV delayed seeing the family doctor longer than any other group but in both these groups the family doctor delay and hospital delay were shortest. The most obvious explanation is that by the time these patients present their symptoms indicate a serious pathology and of these 26 patients, four being in both groups, 15 presented to their family doctor with vomiting, while only six of the remaining 57 patients had this symptom ($\chi^2 = 11.1$, $P < 0.005$). The other presenting symptoms, as listed in Table 1, were similarly distributed between these two groups and the remaining patients.

Influence of previous peptic ulcer surgery on delay

Ten (12.5%) patients in this study had a history of previous gastric surgery. Two of these patients suffered with chronic indigestion and one had symptoms of dumping. All three patients noted a change in their usual symptoms and only one patient delayed presenting to the family doctor by treating himself. There was no difference in patient, family doctor or hospital delay in this subgroup when compared with the other 70 patients.

Medication

Fifty-three (64%) patients received medication prior to the diagnosis being made. Treatment was started by the family doctor in 47 patients and by the hospital in the other six patients. Nineteen patients had a barium meal arranged, one had a barium enema and nine had full blood counts at the first visit or within 1 month of starting therapy. The remaining 24 (45%) patients had no investigations prior to drug therapy.

Thirty-two patients were treated with antacids and seven had more than one type of antacid, the median delay was 5 weeks (IQR 4–9). After failed antacid therapy, eight patients had a course of histamine-2-receptor blocker (Cimetidine), eight patients were started on Cimetidine as a first-line treatment and one patient was started on Cimeti-

Table 2. Delay by social class

		Social class					
		I	II	IIIN	IIIM	IV	V
Number of patients		2	13	7	24	18	3
Median age	(years)	—	68	76	68	69	—
Patient delay	(weeks)	—	4	4	3	6	—
Family doctor delay	(weeks)	—	12	10	12	4	—
Hospital delay	(weeks)	—	3	12	7	2	—

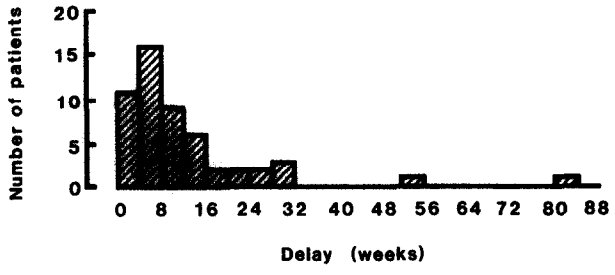

Fig. 3. Histogram showing delay due to starting medication prior to diagnosis.

Table 3. Operations performed in 53 patients

Operation	Number
Distal gastrectomy	22
Total gastrectomy	9
Proximal gastrectomy	8
Oesophagogastrectomy	3
Laparotomy and intubation	3
Laparotomy and gastroenterostomy	1
Laparotomy and no precedure	7
Total	53

dine after a benign gastric ulcer was diagnosed on endoscopy and biopsy, this was later found to be a gastric cancer. The median delay in the 17 patients due to receiving Cimetidine was 6 weeks (IQR 4–9). There was no difference in the distribution of delay caused by Cimetidine compared with delay due to antacids, Mann–Whitney $U = 232$, $P > 0.5$. Five patients received iron replacement therapy for iron deficiency anaemia, two of these had iron injections leading to a 9 week and 24 week delay prior to referral for investigations. Four patients were treated with analgesics for their epigastric pain and in two cases this led to delays of 26 and 80 weeks. While waiting for out-patient appointments two patients had laxatives and one patient was put on an anxiolytic drug. The overall delay in the 53 patients is illustrated in Fig. 3.

Investigations

A barium swallow or meal was performed in 68 (82%) patients. Half of these investigations were organized by the family doctor and the rest at the hospital. The sensitivity of this test was 82% with 52 of the barium studies reported as being diagnostic or suspicious of gastric cancer. Five barium meals were reported as showing a gastric ulcer and benign oesophageal disease in three other studies. On four occasions the barium study was reported as normal.

Upper alimentary endoscopy was performed in 69 (83%) patients and this correctly diagnosed gastric cancer on 63 occasions, i.e. a sensitivity of 91%. Both a barium study and gastroscopy were performed in 49 patients, the correct diagnosis was made on one or other of the investigations in all these patients.

Management

A surgical opinion was obtained in 68 (85%) cases. The surgeon considered 13 patients unfit for surgery. The condition of two patients deteriorated immediately before surgery and they were managed conservatively. Laparotomy was performed in 53 (66%) patients, the different procedures are summarized in Table 3. Forty-two patients underwent gastrectomy giving a resectability rate of 79% in patients having operations and an overall resectability rate of 53%. This is similar to that found by many other investigators in Europe and the U.S.A. [1, 3–5].

The physicians managed a further 12 patients conservatively having confirmed gastric cancer endoscopically and in 11 patients histologically. Seven of these patients were considered unfit for surgery and five had widespread metastases.

Patients having gastrectomy gave a longer history. Fourteen of 42 patients had symptoms for more than 8 months, while only five of the patients managed conservatively had a similar length of history ($\chi^2 = 4.6$, $P < 0.05$).

None of the three patients with lymphoma had a definite diagnosis prior to surgery. In one patient the diagnosis was only made on the operative specimen, while in the other two patients the endoscopic biopsy report suggested the possibility of lymphoma.

Pathology

Histology was available in 73 of the 80 patients with gastric cancer. One patient had a well differen-

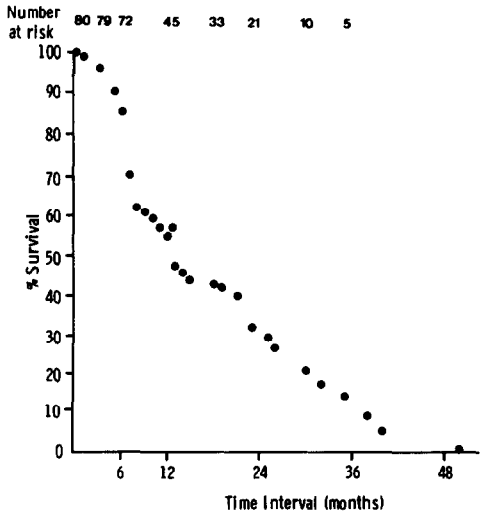

Fig. 4. Cumulative survival from onset of symptoms, of 80 patients with gastric cancer.

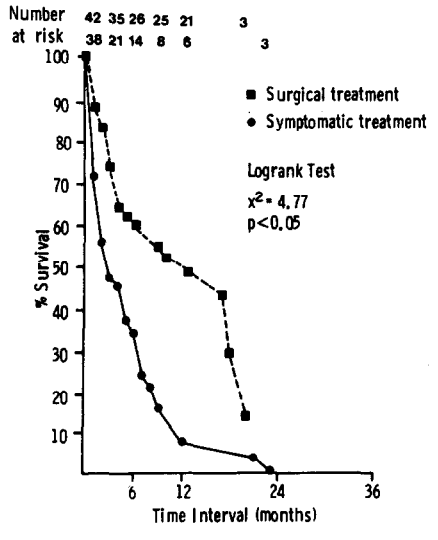

Fig. 5. Cumulative survival of 42 patients treated by gastrectomy compared with 38 patients having symptomatic treatment.

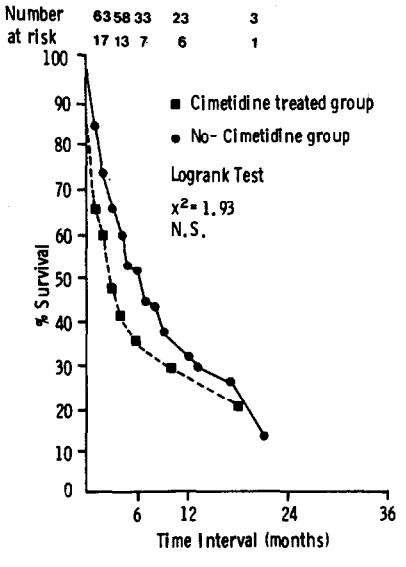

Fig. 6. Cumulative survival of 17 patients treated with Cimetidine compared with the other 63 patients.

tiated gastric cancer, 18 (23%) had moderately-well differentiated tumours, 53 (69%) had poorly differentiated or anaplastic tumours and one patient had linitis plastica. One patient (1.3%) had an early (superficial) gastric cancer.

The other three patients in the survey had diffuse, non-Hodgkin's, large lymphoid cell lymphoma.

Survival

During the follow-up period 61 (76%) of the patients with gastric cancer died. The overall cumulative survival from time of onset of symptoms is shown in Fig. 4. The operative mortality in patients who underwent gastrectomy was 7%. If the patient was able to have a gastrectomy the chances of survival were improved ($\chi^2 = 4.77$, $P < 0.05$) (Fig. 5).

Survival in the patients treated with Cimetidine was no different from that of the other patients ($\chi^2 = 1.93$, $P > 0.1$) (Fig. 6).

The three patients with lymphoma all responded well to surgery followed by chemotherapy and were all alive at 2-year follow-up. These good results underline the importance of histological diagnosis before selecting conservative management.

DISCUSSION

Delay in diagnosing gastric cancer could be avoided either by screening asymptomatic populations or patients who are at risk of development gastric cancer, e.g. those with pernicious anaemia. Otherwise, the clinician has to rely on the patient presenting with symptoms which indicate the presence of gastric pathology.

The commonest first symptoms in this study were indigestion and epigastric pain. They occurred in 43% of the 83 patients interviewed and this prevalence is similar to that reported previously [3]. Almost all the patients in this survey gave a recent history of 'indigestion'. The problem with indigestion, epigastric pain or dyspepsia as early indicators of gastric cancer is that these symptoms are ill-defined and occur commonly in the general population. They can occur in normal people, in patients with benign upper alimentary disorders and occasionally may be referred from other organs, e.g. the heart.

In the present study 24% of patients had suffered with indigestion for over 2 years. A variety of diagnoses had been made and as in other studies it was difficult to obtain medical evidence to support the different diagnoses [2, 11]. These patients presented to their doctor because the symptoms had changed. For example, the epigastric pain had become more persistent or more severe, or they had developed nausea, vomiting or dysphagia. Thus a change in long-standing symptoms is significant.

One of the commonest symptoms to occur was weight loss, and 70% of patients had noticed some weight loss by the time they were admitted to hospital. It was the first symptom in 15% of patients in this study and in 14% of the patients in the Co-operative International Study. However, most patients attached no significance to this symptom, thinking that it was a feature of getting older. Anorexia and malaise were the other common first symptoms.

These non-specific complaints of indigestion, epigastric pain, anorexia, malaise and weight loss occurred as the first symptom of 89% of patients. However, the symptoms that made patients present to their doctor were more sinister and by the time patients were seen in the hospital, 58% had been vomiting, 19% had dysphagia, 12% had malaena and 8% had had a haematemesis.

A symptom previously noted in other studies, but not stressed, was increasing shortness of breath [4]. This was the presenting symptom in 8% of patients, and 24% had shortness of breath due to anaemia at the time of diagnosis. Altogether, there were 21 (25%) patients with iron-deficiency anaemia. This is a smaller proportion than that reported in other studies, in which up to 50% of patients were found to be anaemic [3–5]. This finding underlines the fact that upper alimentary investigations should be mandatory in patients with iron-deficiency anaemia. Significant delay occurred in three (4%) patients, in this survey, due to inadequate investigation of their iron-deficiency anaemias.

Though the symptoms of gastric cancer were very varied, most patients only delayed a short time before seeking advice, the median delay being 4 weeks. However, patients in their eighties and those in social class IV delayed seeing their family doctor longer than other patients with a median delay of 6 weeks.

Delay caused by the family doctor was partly related to trial of medication prior to the diagnosis being established and partly related to delay which occurs when organizing out-patient investigations such as a barium meal. Thirty-four patients referred to the hospital with a barium study, which in 82% of cases showed a gastric cancer, still went on to gastroscopy. Much of this duplication of investigations is unnecessary. An important feature of family doctor delay was that the longest delay occurred in the youngest patients in the 40–59 year age range. This delay could be reduced by early referral for investigation prior to commencing therapy.

Seventeen (20%) patients were treated with a H_2-receptor blocking drug (Cimetidine). The median delay from onset of symptoms or from change of symptoms to referral for further management, was no different in the Cimetidine group (6 weeks), from that for patients treated with antacids (5 weeks). Neither was there a difference in the overall delay, from onset of symptoms to diagnosis between the two groups. This is contrary to the finding of Scotcher *et al.*, who reported a 97 day difference in a group of similar size [12]. The same researchers found a survival difference in favour of the Cimetidine treated group, whereas in the present series there was no difference in survival between the two groups (Fig. 5).

The results presented do not confirm the fears of earlier workers that H_2-receptor blocking drugs may significantly delay the diagnosis of gastric cancer by masking symptoms. However, there is no room for complacency. Three (4%) patients in this study had a benign gastric ulcer diagnosed on endoscopy and biopsy. In two patients Cimetidine was started prior to endoscopy and in one patient after endoscopy. Initially there was improvement in symptoms. However, when these relapsed, repeated gastroscopy and biopsy confirmed the presence of a gastric cancer.

The other 14 patients treated with Cimetidine by their family doctor had no improvement in their symptoms and were referred to out-patients after treatment had failed.

Inadequate follow-up with repeat endoscopy and biopsy of gastric ulcers is one of the preventable causes of hospital delay in detecting malignant change in gastric ulcers. The fact that Cimetidine can alleviate the symptoms should not be used as a diagnostic marker of a benign ulcer.

In the Co-operative International Study, undertaken at the time gastroscopy was being introduced more widely, 28% of patients with gastric cancer had gastroscopy and 18% had a biopsy [3]. In 1981 Weed *et al.* performed gastroscopy in 74% of patients with gastric cancer and 58% had biopsy of the cancer [5]. In this series 83% of patients had gastroscopy and all had the lesion biopsied. Over this time period there has been no change in the proportion of early gastric cancers detected, nor has

there been an improvement in survival.

In this study of 80 patients, who had a median overall delay from onset of symptoms to diagnosis of 22 weeks, only one early gastric cancer was found and if the aim is to diagnose gastric cancer at the mucosal stage, it is inappropriate to wait until the patient is symptomatic.

Once patients present with symptoms their management can be improved and delay prevented by establishing the diagnosis, avoiding multiple investigations and ensuring full follow-up for those patients with suspicious lesions or gastric ulcers.

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