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Cancer of the oesophagus

EDITOR,—In the absence of controlled trials of the treatment of oesophageal cancer several authors have turned to descriptive studies to investigate the survival of patients with this condition.[1–4] The most recent of these was reported by Sagar *et al* (*Gut* 1994; **35:** 941–5). While agreeing with several points made in this paper, we were disappointed that it failed to set their results, based on an audit of patients treated at the General Infirmary at Leeds, in the context of other published studies.

The Table summarises the results of those descriptive studies based in the United Kingdom and published since 1980. Although varying in location and time, each has attempted to avoid the biases of selective case series by reporting the results, after treatment, of all cases diagnosed within a given period from a defined population.

The results of these studies show considerable consistency, and three important points regarding surgery are apparent: surgical resection has poor longterm survival, high early mortality, and is performed in only a few of all patients presenting with oesophageal cancer. Surgery offers the prospect of 'cure' (if taken as five year survival) to less than 3% of all patients presenting and is irrelevant to those 60–80% of patients felt unsuitable for operation. Any argument that surgery should be considered in more patients must face up to postoperative death figures that can amount to a third of patients.

Taken together we feel these studies strongly reinforce the 'nihilistic' view of surgery for oesophageal cancer referred to by Sagar *et al*. If resection is being performed chiefly for symptomatic palliation then it must prove itself on those terms against cheaper and less invasive techniques, such as endoscopic intubation or laser recanalisation.

Surgery can offer cure for oesophageal cancer, but we should recognise that, with the current pattern of disease staging at presentation, this applies to a much smaller proportion of patients than the 20–40% currently being offered surgical resection. We support the call by Sagar *et al* (also voiced in the 1993 NCEPOD report[5]) for oesophagectomy to be carried out by specialist surgeons, however we feel their priority must be the better selection of cases not the treatment of more patients. Equal priority must be given to setting up proper trials of the increasing number of palliative treatments offered to those unsuitable for surgery, who are currently the majority in the United Kingdom.

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Reply

EDITOR,—I read with interest the comments of Drs Oliver and Logan and am grateful for the opportunity to reply.

Their Table shows the similarity in outcome of four United Kingdom studies. We chose not to set our results in the context of United Kingdom studies alone but referred instead to the excellent review of 130 series in the world medical publications by Dr Muller.[1]

We did not advocate a need to simply increase the numbers of patients undergoing oesophagectomy but rather implied a need for more patients with cancer of the oesophagus to be adequately considered for surgical resection and agree that careful selection of cases is essential.

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1 Muller JM, Erasmi H, Stelzner M, Zieran U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; **77:** 845–57.

Current concepts in metastasis

EDITOR,—The progress report (*Gut* 1994; **35:** 996–1000) provides a concise and instructive overview of the role of adhesion molecules in invasion and metastasis. Metastasis is viewed as an evolutionary process entailing the sequential selection of subclones with increasingly aggressive characteristics. This concept has been promulgated mainly on the basis of in vitro and animal models utilising cell lines. Extrapolating these experimental findings to the clinic may lead to conceptual inaccuracies. For example, taking colorectal cancer as the model, is it certain that metastases represent subclones that can be distinguished genetically from the primary tumour? Colorectal cancers show remarkable stability in their morphological and phenotypic characteristics with time. Liver metastases appearing years after removal of the primary may be indistinguishable from the primary. Indeed the same heterogeneity that is seen in the primary may be echoed in the secondary deposits.[1] Are there really multiple cell populations or are we overinterpreting examples of transient epigenetic modulation?

The period in the evolution of colorectal cancer in which there is undoubted subclonal selection is in the stepwise conversion of a normal cell to a cancerous cell through the intermediate stage of an adenoma. The outcome may be a well, moderately or poorly differentiated cancer with a metastatic potential that can be correlated with the grade of differentiation. However, evidence for the further selection of metastatic subclones, at least with respect to colorectal cancer, is lacking.

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1 Jass JR, Mukawa K, Richman PI, Hall PA. Do aggressive subclones within primary colorectal cancer give rise to liver metastases? *Int J Colorect Dis* 1989; **4:** 109–17.

NSAIDs and the chemoprevention of colon and oesophageal cancer

EDITOR,—I read with interest two articles in *Gut*. Drs Choi and Zelig (1994; **35:** 950–4) show that ulcerative colitis and Crohn's disease are pre-neoplastic colorectal lesions with similar clinicopathological features while Manzano *et al* (*Gut* 1994; **35:** 955–60) illustrate that ulcerative colitis is associated with T lymphocyte immunosuppression. Choi and Zelig suggest a potential for non-steroidal anti-inflammatory drugs (NSAIDs) as a chemopreventive measure in patients with inflammatory bowel disease on the basis that chronic inflammation is carcinogenic. I write to expand on this suggestion given the data of Manzano *et al*.

Epidemiological studies have shown that the regular consumption of the NSAID aspirin is associated with a reduced risk of

Descriptive studies of oesophageal cancer treatment (in the UK) published since 1980

Study details			*Surgical resection*				*Radiotherapy*		*Intubation*		*No treatment*	
				Survival rate (%)*		*30 Day mortality*		*Median survival*		*Median survival*		*Median survival*
Time period covered	*Location*	*No*	*No (%)*	*1 Year*	*5 Year*	*(%)*	*No (%)*	*(day)*	*No (%)*	*(day)*	*No (%)*	*(day)*
1956–1976	W Midlands[1]	4680	1104 (24)	36	11	32	725 (16)	NA	1002 (21)	NA	1581 (34)	NA
1975–1988	Leeds[2]	316	134 (42)	40	7	27	29 (9)	175	64 (20)	106	82 (26)	91
1976–1986	N Tees[3]	120	21 (18)	38	10	14	19 (16)	NA	57 (48)	167	16 (13)	NA
1982–1985	Nottingham[4]	268	92 (35)	41	2	9†	35 (13)	190	106 (40)	100	28 (10)	21

*Crude survival rates, †mortality during first hospital admission. NA = not available.

developing fatal colorectal cancer. Aspirin seems to have immunostimulatory and tumoricidal properties in the colon[1 2] thus accounting for the protection. It is these properties that may also make low dose aspirin useful in the chemoprevention of colorectal cancer in high risk patients.[3] This is supported by the data of Manzano *et al.* Pre-neoplastic ulcerative colitis is associated with T lymphocyte immunosuppression and this may permit immunologically unchallenged malignant degeneration in a chronically inflamed mucosa. Aspirin may therefore be useful in the chemoprevention of colorectal cancer by augmenting the immune system thus destroying early tumours.

This principle also applies in the oesophagus as there are several similarities between the carcinogenesis of colorectal and oesophageal cancer. Chronic inflammation may be a pre-neoplastic lesion in both organs[4] while Barrett's oesophagus is also associated with immunosuppression.[5] NSAIDs may thus be useful in the chemoprevention of both colorectal and oesophageal cancer[6] in patients with pre-neoplastic disease. I agree with Choi and Zelig that longterm studies of low dose NSAID prophylaxis are warranted in patients receiving surveillance.

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Reply

EDITOR,—In our study (*Gut* 1994; **35:** 955–60), we have found that T lymphocytes from ulcerative colitis patients exhibit a deficient interleukin 2 conditioned proliferation pathway. This functional T lymphocyte abnormality is not connected to the activity of the disease, as it is also seen in asymptomatic patients. The cause and the pathogenic signification of this T lymphocyte deficiency remain elusive.

It seems that T lymphocytes play an important part in the surveillance function of the immune system against the growth and dissemination of tumours.[1] A potential association between the impaired T lymphocyte function found in ulcerative colitis patients and their enhanced incidence of colorectal tumours might be a certain hypothesis. But, it has not been shown yet.

Aspirin has an antiprostaglandin effect. It has been shown that prostaglandin E_2 may suppress the function of some immune cells including T lymphocytes.[2] However, the effect of the use of aspirin upon T lymphocyte function in patients with ulcerative colitis is unknown.

Despite the encouraging promise of aspirin as an agent for preventing colon cancer, further studies are required for indicating its widespread antitumour prophylactic use in ulcerative colitis.

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Acid and gastric metaplasia in the duodenum

EDITOR,—I am writing with reference to the letter to the editor (Savarino *et al Gut* 1994; **35:** 1151) and the reply concerning the paper by Noach *et al* (*Gut* 1993; **34:** 1510–4). In this paper they support the concept that gastric metaplasia of the duodenum is a response to acid hypersecretion and may be a defence mechanism.[1–3] An alternative concept is that it is a pathological change resulting in a loss of mucosal resistance to acid and pepsin. The small study that we reported comparing light and electron microscopy appearances of the duodenal mucosa in healed duodenal ulcer patients after one year's maintenance treatment with either cimetidine or sucralfate showed little change in the presence of gastric metaplasia and of *Helicobacter pylori* in 64% of the cimetidine group, and an appreciable reduction or absence of both in 73% of the sucralfate group.[4 5] If gastric metaplasia were a response to acid the reverse would be expected, with a reduction in the group receiving cimetidine. Over the next two years the relapse rates were 69% and 18% respectively.

Gastric metaplasia of the duodenal mucosa is almost invariably found accompanying duodenal ulceration. In the absence of gastric metaplasia *H pylori* cannot survive in the duodenum. Opportunistic colonisation of the metaplastic mucosa by *H pylori* may be an additional factor either in the initial formation of an ulcer or in delayed healing or relapse.

It is of interest that Noach *et al* reported no reduction in the extent and prevalence of gastric metaplasia after 12 months of eradication of *H pylori*. This means that these patients could be at risk of recolonisation and possible recurrence of duodenal ulceration. This emphasises the need for a treatment that will restore normal duodenal mucosa. Treatment with longterm sucralfate is one possibility, but alternatively there may be dietary factors that can achieve the same effect and thereby restore normal mucosal resistance.[6]

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1 Patrick WJA, Denham D, Forrest APM. Mucous changes in the human duodenum: a light and electron microscopy study and correlation with disease and gastric acid secretion. *Gut* 1974; **15:** 767–76.
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Reply

EDITOR,—We thank Dr Tovey for his comments on our study. We are aware of his findings and results of other studies that the duodenal mucosa does not return to normal after treatment with cimetidine.[1] In agreement with this, we found no reduction of gastric metaplasia during chronic use of H_2 receptor antagonists. Acid suppression during treatment with these agents is comparatively weak, however, and does not exclude a causal relation between acid production and gastric metaplasia. Our finding that gastric metaplasia is virtually absent in patients receiving omeprazole and after highly selective vagotomy lends further support to the concept that gastric metaplasia is related to acid secretion.

As we did not study the grade of duodenal inflammation after eradication of *H pylori*, we have no data to support the theory that gastric metaplasia primarily is a pathological change of the duodenal mucosa with secondary loss of resistance to acid and pepsin. From other studies, however, it is known that signs of gastritis gradually disappear within a year after eradication of *H pylori*.[2] Theoretically, the persistence of gastric metaplasia may render patients at risk for recolonisation. Overwhelming evidence exists, however, that duodenal ulceration does not recur after eradication of *H pylori* whether or not gastric metaplasia persists.[3] We would therefore prefer the use of anti-*H pylori* regimens rather than longterm maintenance treatments.

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Pathogenesis of bacterial colitis

EDITOR,—The leading article on the pathophysiology of bacterial colitis was timely and informative (*Gut* 1994; **35:** 872–4). Some aspects of this fascinating topic may, however, warrant additional discussion.

As the authors pointed out, the cytotoxic toxins of *Shigella dysenteriae* type 1 and *Escherichia coli* O157:H7 are structurally