LETTERS TO THE EDITOR

Survival for colorectal cancer

EDITOR,—The EUROCAR study of Gatta et al (Gut 2000;47:533–8) provides important information on survival for colorectal cancer in different parts of Europe. In particular, it relates survival to stage, a feature which was absent from earlier studies. 1 The study also looks at procedures used in determining stage which may be important factors in accurate staging—for example, higher numbers of lymph nodes sampled will be more likely to detect small metastases and consequent upstaging of tumours. 1

However, the usefulness of this study is reduced by inaccuracies in the descriptions of staging and choice of staging system. The authors have chosen to use Dukes’ staging system which has been in use for at least 50 years and has been well characterised by many studies with long term follow-up. 2 Unfortunately, they have given incorrect labels to some of the stages in this system. In tables 2 and 3, Dukes’ stages A and B are described as being “confined to the bowel wall” which is incorrect. Dukes’ stage A is invasion into, but not through, the bowel wall whereas Dukes’ stage B is invasion through the bowel wall but without lymph node metastases. 3 Dukes’ stages A and B combined could have been correctly labelled as no lymph node metastases. In the methods section the authors state that where only the TNM stage was available, TNM categories were converted to Dukes’ stages and where stage was not explicitly stated this was reconstructed from information records (in 45% of cases in the study). It is hoped that the correct descriptions of Dukes’ stages were used for this encoding process.

While it is understandable that the authors have chosen to use a well established staging system, the Dukes’ system does have a major flaw which is improved by the TNM system. 4 The Dukes’ B stage contains tumours which may be in the pT3 stage (tumour invades through the muscularis propria into the subserosa or into non-peritonealised pericolic or perirectal tissues) or pT4 stage (tumour directly invades other organs or structures and/or perforates visceral peritoneum) both with a pN0 nodal stage. The prognosis for pT3 pN0 tumours is relatively good whereas the prognosis for pT4 pN0 tumours is poor with a high risk of local recurrence. 5

A final histopathology observation on this study is that there is a threshold set for the number of lymph nodes examined. The authors state that “it is generally considered that at least 12 lymph nodes should be examined for accurate staging” but this is not a universally accepted threshold. The recommendation from the Royal College of Pathologists in the UK is that all lymph nodes identified in the resection specimen should be examined histologically but does not specify an arbitrary minimum number 6 as recognised by the number of lymph nodes identifiable in a specimen varies with a number of factors which include the type of specimen, extent of resection, operative chemoradiotherapy and/or radiotherapy, and the patient’s immune response, in addition to the diligence with which the histopathologist discloses the specimen. In a recent study in a teaching hospital with optimal dissection and sampling of the entirety of each lymph node the median number of lymph nodes identified was 12 so a blanket statement that “at least 12 lymph nodes” should be examined is an unhelpful pressure on hard pressed diagnostic histopathologists.

These criticisms should not obscure the valuable information that is reported in this study but they do suggest that a greater histopathology input at its inception would have been helpful.

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Reply

EDITOR,—We thank Dr Cross for his interest in our paper (Gut 2000;47:533–8). The issue he raised concerning the definition of stage at diagnosis is important for meaningful comparison of cancer statistics between populations. We are pleased to offer the following clarifications.

INACCURACIES IN STAGE DESCRIPTIONS

We confirm that we incorrectly referred to Dukes’ A and B colorectal cases as “confined to the bowel wall.” As pointed out by Dr Cross, Dukes’ B includes tumours perforating the visceral peritoneum and directly invading other organs (T4), and our category “Dukes’ A and B” will encompass pT1–T4 with pN0–M0. A better definition of this category would have been “absence of lymph node and distant metastasis.” The stage definitions of Hermanek and Sobin’ were in fact used for the encoding process, as stated in the article. Furthermore, they were specified a priori in the study protocol as the reference standard, so as to avoid problems of comparison between registries.

CHOICE OF STAGING SYSTEM

We used Dukes’ instead of TNM because in 1990 Dukes’ was the most widely used staging procedure in all countries. The other reason we decided to use Dukes’ was that from the information available to us (patients’ clinical and pathological notes), it was not possible to clearly separate pT3pN0 from pT4pN0 cases (all Dukes’ B) which, as Dr Cross pointed out, differ markedly in prognosis. Furthermore, it was often impossible to distinguish pT2 from pT3 cases, and for this reason we considered Dukes’ A and B together. The population based nature of our study implied the use of information from numerous hospitals and pathology laboratories, which had various ways of recording information. Greater standardisation of stage reporting in pathology notes would be highly desirable.

We are currently engaged in a new high resolution EUROCAR study on colorectal cancers diagnosed in 1997 when the TNM system was more widely used than in 1990. However, the distinction between pT categories is still not adequately made in a considerable number of cases.

NUMBER OF LYMPH NODES EXAMINED

Our statement that “at least 12 lymph nodes should be examined for accurate staging” derives from the International Documentation System, referenced by Fielding and colleagues in their article in 1991. This is the recommendation that, “Before deeming a radical resection to be without lymph node metastasis, it is recommended that at least 12 lymph nodes be examined ...”. Furthermore, the 1993 TNM supplement 7 states: “histological examination of a regional lymphadenectomy specimen ... will ordinarily include 12 regional lymph nodes,” and this number is considered “adequate for staging”.

Our analysis used four categories for the number of nodes examined: 0, 1–5, 6–11, and ≥12; choosing other division points did not change the rank of the registries. However, it is interesting to note that in the hospital study taken as an example by Dr Cross’, 12 or more lymph nodes were examined in 50% of cases—well above the percentages reported by our study (range 2–31%). This suggests that in 1990 the extent of resection or the thoroughness of the pathological examination (or both) would not be considered adequate by today’s standards.

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4 Van Wyk Q, Hosie KB, Balasiti M. Histopathological detection of lymph node metastasiser
**Helicobacter pylori, Lewis antigens, and inflammation**

**Editor—**In a recent issue of Gut, Zheng et al reported that fucosylated blood group O Lewis antigens were associated with increased expression of Lewis (Le) antigens but not cagA, iceA, or vacA in Chinese patients infected with Helicobacter pylori (Gut 2000;47:18–22). These data raise as many questions as they answer as to the role of Lewis antigens in the pathogenesis of this important infection. We present these data in the context of recent work from our laboratory and the literature.

Le- and Le- blood group determinant expression is commonly found on the lipopolysaccharide (LPS) of H. pylori isolates. These determinants have been identified on approximately 80–90% of isolates from all patient series examined to date. In our own series, 74/84 (88%) isolates expressed either Le- or Le- antigen, 47/84 (56%) expressed both, and 11/84 (13%) isolates were classified as Le-negative. Differences in the prevalence of Le- or Le- expression on H. pylori strains isolated from ulcer patients and those strains isolated from patients with uncomplicated gastritis, nor was there an association demonstrated between host and bacterial Lewis phenotype. The report of Zheng et al we have reviewed our raw data regarding the prevalence of strains expressing two or more Le- antigens. We found that two or more Le determinants were present in 9/12 (75%) isolates from duodenal ulcer patients and in 4/10 (40%) isolates from gastritis ulcer patients. This gives an overall prevalence of 17/22 (77%) (13/22 isolates) for isolates from patients with ulcer disease. Thirty four of 62 (55%) patients with histological evidence of chronic gastritis also had isolates expressing two or more Le- antigens. A significant difference between H. pylori strains isolated from Chinese patients and those from our population is the finding of 48/104 (46%) isolates expressing three or more Le- determinants. This compared with 9/12 (75%) isolates from a homogenous Irish population. In our series, only one strain expressed all class 1 and class 2 Le- antigens—that is, Le-, Le- and their isomers Le- and Le-. The high prevalence of the Le determinants in our population is similar to that reported by Zheng et al in their recent study. In this work, they found that the prevalence of cagA genotype was high among H. pylori isolates, with 47/84 (56%) of isolates coexpressing cagA and Le- phenotype. The prevalence of cagA genotype in our population was 35/47 (74%) and was significantly higher than that reported by Zheng et al. These findings are similar to those previously reported by us using histochemical staining for gastric mucins (dual staining with MUC5AC and the human gastric mucous cell line) and immunostaining for H. pylori. GOTS recognises galactose or N-acetyl galactosamine residues of gastric surface mucous cell cell membrane in conjunction with MUC5AC in the human stomach by Van den Brink et al (Gut 2000;46:601–7). The authors used antibodies against gastric mucin core proteins (anti-MUC6 and MUC5AC) in conjunction with antibody against H. pylori and demonstrated staining of H. pylori to gastric surface mucous cells and the presence of H. pylori in extracellular mucins derived from gastric surface mucous cells.

These findings are similar to those previously reported by us using histochemical staining specific for gastric mucins (dual staining consisting of galactose-oxidase cold thioglycolic acid Schiff reaction and di- oxalidocanavanilin A staining (PCS)) and immunostaining for H. pylori. GOTS recognises galactose or N-acetyl galactosamine residues of gastric surface mucous cell cell membrane in conjunction with MUC5AC in the human stomach. In the study of Van den Brink et al (Gut 2000;46:601–7), the authors used antibodies against gastric mucin core proteins (anti-MUC6 and MUC5AC) in conjunction with antibody against H. pylori and demonstrated staining of H. pylori to gastric surface mucous cells and the presence of H. pylori in extracellular mucins derived from gastric surface mucous cells.

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Figure 1 (A, B) Formalin fixed normal fundic mucosa. (A) Galactose-oxidase cold thionine Schiff reaction (GOTS) stains gastric surface mucous cell mucins blue and parabacillary carcinocanavulin A staining (PCS) stains mucous neck cell mucins brown (dual staining of GOTS-PCS). (B) Immunostaining with anti-MUC5AC (45M1) labels gastric surface mucous cells. The reactivity of anti-MUC5AC (45M1) is identical to that of GOTS (see (A)) (immunoperoxidase method with anti-MUC5AC (45M1)). (C) Carnoy fixed gastric mucosa without Helicobacter pylori infection. Immunostaining with anti-MUC5AC (45M1) is identical to that of GOTS (see (A)) (immunoperoxidase method with anti-MUC5AC (45M1)). (D, E) Carnoy fixed gastric mucosa with H pylori infection. (D) H pylori is stained red by an immuno-alkaline phosphatase method with anti-H pylori antibody. Numerous H pylori exist on the surface mucous cells but not on pyloric gland cells (dual staining of GOTS-PCS). (E) H pylori is stained red by an immuno-alkaline phosphatase method with anti-H pylori antibody. Numerous H pylori preferentially colonise in the layer of surface mucous cell type mucins (dual staining of GOTS-PCS followed by immunostaining for H pylori). (F) Carnoy fixed gastric mucosa with H pylori infection. H pylori is stained red by an immuno-alkaline phosphatase method with anti-H pylori antibody. Numerous H pylori preferentially colonise in the layer of surface mucous cell type mucins (dual staining of GOTS-PCS followed by immunostaining for H pylori).
molecules. Glycosylation is a complex process that may easily become disturbed in *H pylori* infection, for example. Thus as glycosylation may change under pathological conditions, I would urge the authors and other workers in the field to concentrate on the invariant part of the mucins: the non-O-glycosylated parts of the protein, as discussed by us previously.¹

One of the issues addressed by Ota et al is the correlation of *H pylori* infection with disturbance of the laminated gastric mucus layer, as demonstrated in fig 1C versus fig 1D. In common with the authors, it is tempting to speculate that *H pylori* has a direct role in this disturbance. Similar to most bacteria, *H pylori* produces enzymes that in principle can degrade mucins, such as proteases and “mucinas”, as referred to by the authors. I personally doubt whether *H pylori* is directly responsible for disturbance of the mucus layer for two reasons. Firstly, as the bacterium resides in the mucus layer, what would be the benefit of destroying its own milieu? Secondly, there are data by many authors to indicate that the tissue dynamics of the gastric mucosa is altered by *H pylori* infection. Accompanying the inflammatory response, epithelial turnover is enhanced, and there are profound shifts in cell populations within the epithelium. As a result, which was also mentioned in our previous article, there are data by many authors to concentrate on the development of one group of patients (group C) increased with a simultaneous decrease in serum gastrin. Therefore, we divided DU patients into three groups according to changes in MAO by *H pylori* eradication (group A: MAO decreased more than 1 mEq/h; group B: no change; group C: MAO increased more than 1 mEq/h) and found that group C patients had the lowest serum pepsinogen (PG) I levels and PG I/II ratios among the three groups (PG I: group C 44.7 (1.6), group A 64.5 (2.5), group B 57.8 (2.6); PG I/II: group C 2.52 (0.18), group A 3.98 (0.24), group B 3.60 (0.19); p<0.05). These data indicate that patients in group C had suffered atrophy of the fundic mucosa.

Data on changes in gastric stimulated acid secretion after eradication in patients with DU are controversial;² although most reports show a decrease in acid secretion.³ As Iijima et al indicated, the most likely reason for the controversy may be that a considerable number of patients with DU had corpus gastritis, which may somehow cause hypochlorhydria. We previously reported that gastric acid secretion in Japanese subjects is lower than that in Europeans or North Americans, irrespective of *H pylori* infection.⁴ As *H pylori* is reported to induce corpus gastritis more easily in subjects with decreased acid secretion,⁵ we suggested that innate low gastric acid secretion of the Japanese may be responsible for the higher incidence of corpus gastritis and atrophy in Japanese subjects with *H pylori* infection. This appears to be the case even for patients with DU in Japan, and it may be the reason why acid secretion was not significantly reduced after *H pylori* eradication in our DU patients.

**Helicobacter pylori** infection and acid secretion in patients with duodenal ulcer in Japan

**Editor.**—*Helicobacter pylori* infection affects gastric acid secretion of the host in various ways, including corpus gastritis and subsequent development of mucosal atrophy induced by *H pylori* infection result in decreased acid secretion.² In contrast, several investigators have reported elevated acid secretion in patients with duodenal ulcer.

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> **Figure 1** Effects of Helicobacter pylori eradication on maximum acid output (MAO) in Japanese patients with duodenal (DU) and gastric (GU) ulcers. MAO in response to pentagastrin (6 µg) was measured before and after 6 months after *H pylori* eradication. *p<0.05* vs before eradication.

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**Figure 2** Correlation between decrease in serum gastrin concentration (ΔGastrin) and increase in maximum acid output (ΔMAO) in response to pentagastrin (6 µg) by *Helicobacter pylori* eradication in Japanese patients with duodenal (DU) and gastric (GU) ulcers. Groups A, B, and C show DU patients in whom MAO decreased (more than 1 mEq/h), did not change, and increased (more than 1 mEq/h) after eradication, respectively.

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**Notes**


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**References**


3. Vandenbroucke JJ, HIR Z. Glycosylation is a complex process that may easily become disturbed in *H pylori* infection, for example. Thus as glycosylation may change under pathological conditions, I would urge the authors and other workers in the field to concentrate on the invariant part of the mucins: the non-O-glycosylated parts of the protein, as discussed by us previously.¹

4. One of the issues addressed by Ota et al is the correlation of *H pylori* infection with disturbance of the laminated gastric mucus layer, as demonstrated in fig 1C versus fig 1D. In common with the authors, it is tempting to speculate that *H pylori* has a direct role in this disturbance. Similar to most bacteria, *H pylori* produces enzymes that in principle can degrade mucins, such as proteases and “mucinas”, as referred to by the authors. I personally doubt whether *H pylori* is directly responsible for disturbance of the mucus layer for two reasons. Firstly, as the bacterium resides in the mucus layer, what would be the benefit of destroying its own milieu? Secondly, there are data by many authors to indicate that the tissue dynamics of the gastric mucosa is altered by *H pylori* infection. Accompanying the inflammatory response, epithelial turnover is enhanced, and there are profound shifts in cell populations within the epithelium. As a result, which was also mentioned in our previous article, there are data by many authors to concentrate on the development of one group of patients (group C) increased with a simultaneous decrease in serum gastrin. Therefore, we divided DU patients into three groups according to changes in MAO by *H pylori* eradication (group A: MAO decreased more than 1 mEq/h; group B: no change; group C: MAO increased more than 1 mEq/h) and found that group C patients had the lowest serum pepsinogen (PG) I levels and PG I/II ratios among the three groups (PG I: group C 44.7 (1.6), group A 64.5 (2.5), group B 57.8 (2.6); PG I/II: group C 2.52 (0.18), group A 3.98 (0.24), group B 3.60 (0.19); p<0.05). These data indicate that patients in group C had suffered atrophy of the fundic mucosa.

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**Correction**

In contrast, several investigators have reported elevated acid secretion in patients with duodenal ulcer in Japan, for example. Thus as glycosylation may change under pathological conditions, I would urge the authors and other workers in the field to concentrate on the invariant part of the mucins: the non-O-glycosylated parts of the protein, as discussed by us previously.¹


I was taught as a medical student that the major function of the colon was that of a storage reservoir, hence premises about the colon have evolved and the complexities of colon function is much better understood, as described by Gibson and Roberfroid’s (editors) multiauthored book Colon Microbiota, Nutrition and Health.

Although the editors state that the purpose of the book is to overview current knowledge of the activities and functions of the gut microbiota, it goes beyond these boundaries and takes us on an ecological journey into the exciting life of gut microflora and their impact on colon function in health and disease, and the intimate critical relationship between diet, gut flora and the machinery of life.

Gastroenterologists are still recovering from the impact that a bacterium, Helicobacter pylori, has had on upper gastrointestinal tract pathology. In this context it is interesting to note that the large bowel is the most heavily colonised part of the gastrointestinal tract yielding up to 10^11 bacteria per gram of intestinal contents in healthy human subjects. It is a complex ecosystem in which the numerous and different species of bacteria degrade and ferment substrates that have escaped digestion in the small bowel. Major genera include bacteroides, bifidobacteria, lactobacilli, clostridia, and enterobacteria, and the main products of bacterial fermentation of the substrate that reaches the colon are short chain fatty acids (SCFA) and gases, including hydrogen, carbon dioxide, and in some individuals, methane. The difference in SCFA is that they act as a source of energy for intestinal mucosal cells and reduce the pH of colonic contents. One particular SCFA, butyrate, may be important in protecting against colorectal cancer. The relevance of fermentation to human metabolism can be gauged from the fact that the energy equivalent of 15–40 g of carbohydrate is metabolised by the large bowel. The book outlines the technological revolution that has occurred in understanding the natural microbial world. Molecular biology has invaded gut microbiology with the limitations of enrichment cultural techniques being integrated into techniques based on the detection of genomic DNA or analysis of rRNA.

A fascinating aspect of the book that concerns and affects all of us is the chapters on food. With the craze of low carbohydrate diets to counter obesity sweeping the USA, it is refreshing to realise the importance of carbohydrates and the relevance of fermentation to human metabolism. A rather unusual aspect of SCFA is the importance of fibre-rich foods in the body in a positive way due to the presence of health enhancing ingrediants. Colonic foods are an example of such functional foods that are used to target the large intestine. These are foods that contain an ingredient that does not undergo significant modification during transit through the small intestine but reach the colon where they are utilised by the resident bacteria producing metabolites that influence the physiological and biochemical processes in a beneficial manner. Dietary fibre is the best known of the “colonic foods” and is divided into soluble and insoluble fibre. Soluble fibres include pectin, guar gum, B glucan, and psyllium, and result in modest reductions in blood lipids affecting total and LDL cholesterol fractions. Insoluble fibres (cellulose and lignin) are mainly responsible for faecal bulking. Dietary fibre may play a protective role in diverticular disease and colorectal cancer. Other functional foods are the fructans and resistant starch which, in animal models, affect triglyceride rich fractions. A novel and potentially important approach to prevention and therapy of colonic diseases is the concept of prebiotics and probiotics. The probiotic approach involves adding live microorganisms to the gastrointestinal tract while prebiotics enhance certain components of the existing flora. Probiotics have potential in the prevention and treatment of rotavirus infections, lactose malabsorption, and food allergy. Tnentative claims for benefits of prebiotics include reduction in obesity, improved control of non-insulin dependent diabetes, reduction in the risk of atherosclerotic cardiovascular disease, and prophylaxis of acute gastroentritis.

How does the above affect individuals? It seems that we should include the following foods in our diet: garlic, onions, asparagus, chicory, dandelion, artichokes, soy beans, leeks, Jerusalem artichokes, wheat, bananas, and rye. Quite a tall order!

The authors have made an important contribution to the concept of local and systemic effects of prebiotics. Such an approach to the prevention and therapy of a healthy colon is the evolution of the idea that functional foods have prophylactic and therapeutic properties. A minor criticism is that there is repetition of ideas in certain chapters. I would highly recommend this excellent work for gastroenterologists as a seminaral study. This book should be used as a guide not only for gastroenterologists, primary care physicians, and nutritionists but also for all health workers.
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AN INVESTIGATION INTO THE IMPACT OF ALGINATES AND EPIDERMAL GROWTH FACTOR ON ENDOCYTOSIS-A STUDY IN FOUR OESOPHAGEAL CELL LINES

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Introduction: Endocytosis is a process whereby eukaryotic cells take up extracellular material by a variety of different mechanisms. These endocytic functions are of great importance and are involved in the regulation of cell surface receptor expression, maintenance of cell polarity, cholesterol homeostasis and a host of other physiological processes. In this investigation we looked specifically at fluid phase endocytosis and the impact alginates and epidermal growth factor (EGF) have on this activity.

Background: Alginates are extracted from seaweed with their use restricted to medical applications. These carbohydrate polymers made up of D-mannuronic (M block) and L-guluronic (G block) acid residues, and may also be made up of sequences of mixed residues (MG blocks). These carbohydrate polymers appear to promote migration and restitution in gastro-intestinal epithelial cells in vitro and in vivo by modulating the expression and functional activity of cell junctional proteins such as the E-cadherin-catenin complex. EGF is a 6kd polypeptide that has a role in tissue repair, cell proliferation, ulcer healing and cell migration. EGF also inhibits acid production and imparts a cytotoxic mechanism protecting the oesophageal mucosa from gastric reflux.

Similar biological effects have been recognised with alginates that are used extensively in medications to alleviate symptoms associated with gastric reflux.

Methods: In this study we have used four oesophageal carcinoma cell lines, 2 squamous cell carcinomas and two adenocarcinomas. Cells were incubated with combinations of fluorescent microspheres (0.02μm), alginate and EGF for 1 hour, and then analysed by FACScan®. Alginates were used at a concentration of 2mg/ml and EGF at 10ng/ml.

Results:
- All alginates used in this study up-regulate fluid phase endocytosis.
- EGF up-regulates endocytosis.
- Incubation with EGF and alginate up regulates fluid phase endocytosis.
- Levels of up-regulation varied depending on alginate used.
- Alginates up-regulate fluid phase endocytosis more than physiological levels of EGF.

Conclusions: We have shown that both alginates and EGF up-regulate fluid phase endocytosis in all cell lines used in this study. However alginates up-regulate this process significantly whereas EGF does not. The mechanism for this alginate action is not yet identified, but it is possible that alginates interact with the receptor for EGF.

References

[1] Alginates are extracted from seaweed with their use restricted to medical applications.
[2] These carbohydrate polymers made up of D-mannuronic (M block) and L-guluronic (G block) acid residues, and may also be made up of sequences of mixed residues (MG blocks). These carbohydrate polymers appear to promote migration and restitution in gastro-intestinal epithelial cells in vitro and in vivo by modulating the expression and functional activity of cell junctional proteins such as the E-cadherin-catenin complex.

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