Differential expression of cyclooxygenase 2 in human colorectal cancer

EDITOR,—We were puzzled by the recent paper by Dimberg and colleagues (Gut 1999;45:730–732) which reported that up-regulation of cyclooxygenase 2 (COX-2) protein expression was prominent in rectal adenocarcinomas compared with that in adenocarcinomas arising from the colon. “Low or undetectable levels of COX-2 protein expression” were demonstrated in 15 of 19 colon adenocarcinomas located proximal to the rectum. Overall, upregulation of COX-2 protein expression was reported in only 56% of colorectal cancers. Previous authors, 1 which include one by the current authors on a not dissimilar case series, 1 and two in the joint authorship of the accompanying commentary writer, 2 have shown consistent upregulation of COX-2 expression in colonic and rectal adenocarcinomas (in 85–90% of cases) compared with matched normal colon mucosa using different techniques, including northern blot analysis, RT-PCR, western blot analysis, and immunohistochemistry. Furthermore, four of these studies refer to the distribution of adenocarcinomas throughout the colon without showing evidence of differential COX-2 expression between rectal and more proximal tumours. 3–5 In the one previous study which analysed COX-2 protein expression in human colorectal cancers by western blot analysis, 6 immunoreactive COX-2 was detected in 76% of cases with a 10-fold increase in median tissue COX-2 concentration compared with normal colon mucosa.

In our view, the authors should attempt to explain the discrepancy between their results and previously published data. It is interesting to note that, in the study of Kargman et al, 7 five of six patients taking NSAIDs had low or undetectable COX-2 protein expression. Moreover, COX-2 expression has recently been shown to suppress induction of COX-2 mRNA and protein in interleukin-1ß and phorbol ester stimulated human endothelial cells and fibroblasts. 8 Do the authors have data on NSAID use in their cohort of patients prior to surgery?

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Reprint

EDITOR,—We agree with Drs Hull and Langman that we found upregulation of COX-2 protein expression in a lower fraction of colorectal cancers (CRC) than previously reported. In part, this may simply be explained by the composition of different tumour types within CRC—that is, the number of colonar versus rectal tumours in our cohort compared with others. In the papers referred to it is difficult to assess the fraction of the different tumour types studied. The differences may also be dependent on the genetic basis for the CRCs studied, which we also have indicated but perhaps not emphasised sufficiently. CRCs with a defective mismatch repair capability, recognised by microsatellite instability (MSI), are accompanied by reduced COX-2 levels. 1 At present, we do not know the fraction of MSI type tumours in our series and therefore cannot assess this possibility. An indirect estimate may be achieved since the Min mouse model and human studies provide direct evidence that COX-2 expression may be related to loss of APC function. 2 APC and ß-catenin mutation analysis of our tumour series shows a good, although not perfect, correlation with COX-2 protein upregulation. Among 18/20 rectal tumours with COX-2 protein upregulation, 12 contained mutations in the APC/ß-catenin genes. In contrast, only one of three APC/ß-catenin mutated colon tumours revealed COX-2 protein induction and among the remaining 15 non-mutated tumours, two displayed COX-2 protein upregulation. Thus the fraction of APC/ß-catenin mutated tumours was also slightly lower (21/38—55%) than previously reported in accordence with the differential COX-2 induction observed. This may indicate that a larger fraction of CRCs in our cohort are of the MSI type.

Other possibilities for the differences in the fraction of COX-2 upregulation in our tumour series may be the definition of “induction”. In our case, a tumour/normal ratio from densitometric scanning of western blots must exceed 2.5 in 2 successive independent experiments of the same sample pair to be considered true induction. The use of different methodologies may also influence relative expression of COX-2, for example RT-PCR is sensitive to the quality of isolated mRNA and PCR, and may yield a quantitatively inaccurate method but needs to be carefully controlled to allow quantitative estimations.

It is also correct, as stated by Drs Hull and Langman, that NSAIDs may suppress COX-2 mRNA induction and Cox-2 protein expression in some of the patients in our series. Normally, all drug treatments are withdrawn at least one week prior to surgery at our hospital, making most patients free at the time of surgery. However, we do not know if patients self-administer these types of drugs during the waiting period. We have reviewed the medical records for all CRCs included in the study and found that 7/39 patients were receiving aspirin for cardiovascular protection. Five of these patients had rectal tumours and displayed 2-fold to 10-fold induction of COX-2 protein. In the two patients with colorectal cancer and aspirin treatment revealed >2- and 10-fold induction, respectively. Thus COX-2 suppression caused by NSAID cannot explain the low level of COX-2 induction in the colonic tumours.

Regulation of COX-2 is not fully understood. Because of the close correlation of upregulated COX-2 with mutations in APC/ß-catenin gene it has been hypothesised that there is a regulatory link and that the chemopreventive effect of NSAIDs can be attributed to inhibition of COX-2. However, in a recent paper by He and colleagues it was demonstrated that PPARα (peroxisome proliferator activated receptor α) is a target of both APC and NSAIDs resulting in suppressed PPARα activity and promotion of apoptosis. In addition, COX-2 null mouse colon cells start fibroblast cells remit as a consequence of antiapoptic and antiproliferative effects of NSAIDs; hence there seems to be other important mechanisms for NSAID mediated tumour suppression.

The samples in our series were obtained consecutively without any selection. At present, we believe that the observed differential expression of COX-2 may be due to underlying differences in genetic alterations and/or that rectal tumours may represent a biologically distinct subtype of bowel cancer. However, we cannot exclude the possibility that the next 39 CRCs collected will display the opposite COX-2 expression pattern, although we believe this is unlikely.

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Proton pump inhibitors for Barrett’s oesophagus

EDITOR,—Recently, the authors of two leading articles, Triadafilopoulos (Gut 2000;46:144–46) and Shepherd (Gut 1998;40:147–49) referred to our paper in Gut. 1 We would like to draw attention to the fact that the legend in tables 4 and 5 in our paper should be read as (cm/month), (squares/month), and (%)/month since the variable is the area under the curve (AUC), which is the product of length and surface and
MCP-3 in inflammatory bowel disease

EDITOR,—We read with interest the article by Wedemeyer and colleagues (Gut 1999; 44:629–35) on chemokines in inflammatory bowel disease.

Monocyte chemotactic protein 3 (MCP-3) expression in inflammatory bowel diseases is a very interesting observation and we agree with the authors that MCP-3 might play an important role in the pathophysiology of these diseases. We have recently published an article on the C-X-C chemokines interleukin (IL)-8 and IP-10, and the C-C chemokines MCP-1 and MCP-3 in the mucosa of active ulcerative colitis. It concerns an immunohistological study in which we showed increased expression of these chemokines in the lamina propria of patients with ulcerative colitis compared with normal controls. Furthermore, we observed a significant difference in expression between inactive and moderate/severe ulcerative colitis based on the histological grading in MCP-1, MCP-3, and IL-8.

Wedemeyer and colleagues state in their discussion that MCP-1 is expressed in the epithelial cells and lamina propria whereas MCP-3 is almost exclusively produced by epithelial cells. However, in the results section and further in the discussion the authors mentioned sporic MCP-3 expression in the lamina propria of inflamed tissue. The photographs show only epithelial cells and it is not possible to see the staining pattern of the lamina propria.

We found MCP-3 expressing cells in the lamina propria which was significantly increased in active ulcerative colitis compared with both inactive ulcerative colitis and normal controls. Furthermore, MCP-3 expression in lamina propria was also enhanced in patients suffering from pouchitis compared with patients with a normal pouch (unpublished data).

In the study of Wedemeyer et al., unfortunately the data on MCP-3 expression in Crohn's disease were not significant which might be because of the small number of patients examined. It would be interesting to further evaluate the role of chemokines in Crohn's disease.

In conclusion, although with some minor differences, both studies have shown that MCP-3 plays an important role in ulcerative colitis.

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One minute unbuffered urease test: should it be read at 10 minutes?

EDITOR,—I read with interest the study by One minute unbuffered urease test performance at one and 10 minutes. Given the overall performance of the test, we are quite happy to plan the treatment of $H$ pylori on the basis of its results.

Histology can be reserved for those cases where urease testing is equivocal or other signs such as mucosal abnormalities, are being sought.

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Table 1 Comparison of the unbuffered rapid urease test performance at one and 10 minutes

<table>
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<th>Min</th>
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<tr>
<td>1</td>
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<td>10</td>
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Sensitivity 49% 83% <0.001
Specificity 96% 92% 0.20
Positive predictive value 91% 90% 0.43
Negative predictive value 69% 87% <0.002
Thalidomide treatment of oesophageal ulceration

EDITOR,—We read with interest the article by Macoń et al (Gut 1998;45:463–464). With others, I reported the first successful use of this drug in oesophageal ulceration in 1992 although the patient we reported on did indeed have AIDS, and the ulceration was diffuse and proliferative rather than discrete, mimicking lymphoma both macroscopically and microscopically.

The precise mechanism of thalidomide’s effectiveness in oesophageal ulceration remains unclear. The case reported raises the intriguing possibility of more widespread application of this drug in idiopathic gastrointestinal ulceration. It has already been used in the lower gastrointestinal tract in Crohn’s disease with some success. Idiopathic aphthous ulceration may be the first step in the pathogenesis of Crohn’s disease—the breach in the mucosal barrier may allow entry of bacterial flora and their products to the internal milieu thus setting in train the inflammatory cascade that becomes clinical inflammatory bowel disease. A portal, orally available, and especially non-teratogenic T cell inhibitor as effective as thalidomide would be a useful addition to the pharmacological weaponry available for use in inflammatory bowel disease and perhaps also in helicobacter negative gastroduodenal and small intestinal ulceration.

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Use of Doppler ultrasound in Crohn’s disease

EDITOR,—We read with interest the article by Macoń et al (Gut 1998;45:463–464). We find it encouraging that other workers are interested in superior mesenteric artery (SMA) flow concerning Crohn’s disease activity. Our group has been working on the subject for several years. However, we found it surprising to read that “according to the literature” SMA flow does not correlate with disease activity. Firstly, disease activity needs to be defined. The Crohn’s disease activity index does not correlate with disease activity in individual patients1 and the reference standard used by Macoń et al is probably not a reliable indicator for disease activity. Secondly, it is not correct in our view to correlate the resistive index in one article with mean velocity in another and flow volume in yet another,2,3 and make the statement “yielding conflicting results” on page 654. In our opinion only flow volume measurements can be used as a reliable indicator.2,4 The fact that Macoń et al did not find a correlation between SMA volume flow and disease activity is probably caused by their choice of reference standard, as pointed out by Kießend and colleagues,5 Hodgson and Bhatti,6 and van Oostayen and colleagues.7


Percutaneous drainage of echinococal cysts (PAIR—puncture, aspiration, injection, reaspiration): results of a worldwide survey for assessment of its safety and efficacy

EDITOR,—In 1996 a letter (Gut 1996;38:936) about the use of PAIR (puncture, aspiration, injection of a sclerotic agent, reaspiration) raised a criticism of Dr Morris, a leading expert on the treatment of echinococcosis.8

At the same time the WHO Informal Working Group on Echinococcosis launched a survey to evaluate the status of this procedure. A number of centres around the world known to be active in this field were requested to complete forms for patients treated with PAIR: 765 abdominal cysts, mostly hepatic, treated with this technique were reported from various countries. We report the results of this survey (table 1).

Either needles (18–22 gauge) or catheters (5–9 French gauge), depending on the size and location of the cysts, were used. Scoliceidal agents were mainly 20% hypertonic saline and 95% ethanol solution. After aspiration and parasitological control of the fluid, a quantity of sclerocidal agent, approximately equivalent to one third of the amount aspirated, was injected into the cyst and left for a time varying from 5 to 30 minutes, and then reaspirated: only in the cases of Giorgio and colleagues9 was the sclerocidal agent not reaspirated. In all cases, except for two failures (0.26%) followed by surgery, various degrees of reduction in size (at least 50%) and involution (healing) of the cysts were observed on ultrasound follow up. Anaphylactic shock occurred in four cases (0.52%) and was promptly treated; in one case (0.13%) death ensued notwithstanding resuscitative manoeuvres. Recurrences were observed in 12 cases (1.57%) but in eight (1.05%) they were related to an insufficient amount of sclerocidal agent (one tenth instead of the average equivalent of one third of the aspirated fluid). Spillage of the fluid in the abdominal cavity was observed in four cases (0.52%) but all patients were receiving prophylaxis with albendazole (seven days to four hours before to 1–4 weeks after) and no peritoneal dissemination occurred. Minor complications (fever, rash, abscess formation, and biliary fistulas) were observed in 105 cases (13.7%); abscess formation was treated with echo guided percutaneous drainage. The follow up is more than five years for 75 cases at the time of presentation of this survey.

These data show that the use of PAIR is widespread and increasing, especially in countries where echinococcosis is endemic. This is also because of its low cost and high efficacy. These data are in accordance with the literature: as of today more than 2400 cysts have been punctured and reported in indexed journals, and success and complication rates are even lower than those of our survey. PAIR is a safe and effective therapeutic tool; the risk of anaphylaxis during PAIR has been greatly overrated. Complication rates, recurrences, and mortality rates are lower than those of surgery.9 Accuracy of follow up may be a problem where the population is nomadic, but so far no case of peritoneal dissemination after PAIR has been reported.

Table 1 Results of the survey on PAIR by the WHO Informal Working Group on Echinococcosis

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<th>Table 1 Results of the survey on PAIR by the WHO Informal Working Group on Echinococcosis</th>
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<td>Total cases (cysts)</td>
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<td>Fever (33), rash (14), pain (30), infection of cavity (11), nausea and vomiting (10), intrastruc-</td>
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<td>tary haemorrhage (3), hypotension (2)</td>
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There is a need for further studies on PAIR. One of the main issues is to standardize the recurrence rate of PAIR. One of the main issues is to standardize the recurrence rate of PAIR is now less than surgical. Surgery is either simplistic or deliberately misleading. Filice et al state that 75 patients (or is it cysts?) have been followed up for five years—the type and frequency of follow up is not stated and this is really critical. Careful ultrasonic follow up can demonstrate recurrence following surgery in up to 22% of patients but one can equally well quote surgical series with poor follow up with low recurrence rates; to claim that recurrence rates are lower following PAIR when the type and completeness of follow up is not even stated in scientifically quite invalid.

That cysts shrink (variably) following PAIR is reported, but what does this mean—is this synchronous with parasite death? I doubt it! Only one PAIR study reported reappearance at three days post-PAIR and 2/14 patients had live proscicles.

The use of albendazole for four hours to seven days prior to and for 1–4 weeks after PAIR is clearly an attempt to reduce the risk of recurrence. In my original laboratory work it took of the order of 30 days to be effective and in humans, two patients who received albendazole for one and three weeks, respectively, prior to operation had viable proscicles. The use of post-spillage therapy to reduce the risk of implantation has been variably effective in animal models of spillage. We have made at least some attempt to define the minimum length of such therapy.

The over representation of a poor presentation of data, which I suspect is of even poorer quality, does not improve my view of PAIR, or of the WHO working group. I am quite prepared to accept that PAIR may be the best available option in some areas of the world where surgery and perioperative care are compromised by economic factors or lack of experience, but its comparison with surgery should await careful long term follow up.
and radiologists. The list of authors includes leading figures in the field of digestive endosonography, namely those who took part in the development of the first pieces of equipment and who described the basic principles of endoscopic ultrasound, and the new generation of practitioners responsible for the most recent developments in this area, particularly the introduction of the endoscopic ultrasound guided puncture. This collective work is complete and exhaustive, it is in large format and divided into seven sections, supplemented by a very detailed and helpful index.

The book is a popular work and the teaching material it contains is very practical, detailed, and useful for beginners. However, the book relies on the experiences of the expert authors, which I find to be of much less interest. Much of their experience is now out of print and the endoscopic images are grouped at the beginning of the book and reproduced in black and white in appropriate chapters.

In summary, this is a book of high quality work with some good illustrations. The division between the technical sections and those on anatomy is well balanced, which is original to this type of work and is very informative. A number of chapters are extremely useful, particularly those on the linear array echoendoscope and portal hypertension. Some areas covered have less impact, particularly those concerned with the authors’ different experiences of gastro-oesophageal and retroperitoneal pathology. Generally, retroperitoneal endosonography is poorly covered; biliary echoendoscopy is not discussed at all. This significant gap is an invitation to other authors to publish a work dedicated to bilopancreatic echoendoscopy, a useful supplement to the work of doctors van Dam and Sivak.

L. PALAZZO


It seems almost unimaginable to me that, somewhere out there, exists a clinical gastroenterologist who would not want to own this book. Maybe I was destined to be the curator of the book review section of Gut just so that a review copy of this majestic atlas might come across my desk. What little effort is it to find words of praise for this tour de force of gastrointestinal radiology.

In one of the most delightfully understated introductions of the century, Reddy Mac-Sween writes that “.this volume brings credit to radiology as a discipline”. Oh yes indeed, and so very much more! Dr Vallance and selected colleagues have produced a book in which every single illustration (and there are many hundreds) is crystal clear. There are many radiological texts that are comprehensive, and there is a lesser number in which the pictures are clear. There are few books indeed in which every picture credibly reveals the pathology in a totally convincing manner. I do not believe there is single illustration in this book that is not of a high order, and this applies equally to plain radiographs, barium studies, ultrasound, CT, MRI, angiography, or EUS.

Despite its visual excellence, there are idiosyncrasies. Quite what CT and MRI scans of parotid tumours are doing in a book of GI radiology quite escapes this reviewer. Less satisfactory still are some of the mini essays introducing each system. I suspect most readers will not be particularly enlightened by the two page essays that introduce each organ—too brief to say any more than most clinicians must surely know already. For example, who would learn much from: ‘Ileostomy enema. The distal small bowel may be examined satisfactorily in patients with an ileostomy by retrograde infusion of barium with or without air, introduced by Foley catheter.’

The essays are weak, but the legends and the figures are of exceptional quality. A well committed legend obviates the need for arrows, or other marks, on the radiograph. In this atlas, arrows do appear from time to time, but they are not intrusive. I suggest that this atlas might very well be added to the extremely short list of books that every gastroenterologist should own.

IAN FORGACS

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2001

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2001 Award. Applications (TWENTY COPIES) should include:

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Entrants must be 40 years old or less on 31 December 2000 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2001. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2000.

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MCP-3 in inflammatory bowel disease

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