LETTERS TO THE EDITOR

Cereal fibre and rectal epithelial cell proliferation: a possible link with duodenal ulceration

EDITOR,—It is interesting that Macrae *et al* (*Gut* 1997;41:239-45) found that unprocessed wheat bran had a greater effect than processed bran or oat bran on the reduction of labelled cells in the top two fifths of rectal epithelial crypts. There is evidence that wheat bran may have effects on other mucosal surfaces, particularly that of the duodenum. The prevalence of duodenal ulceration is lower in India in the unrefined wheat eating areas of the Punjab than in the polished rice eating areas of the South.¹⁻³ Our experimental work on several animal models has shown that wheat bran is protective against peptic ulceration and that this protection is linked with its lipid content.^{4,5} The evidence so far suggests that this effect may be related to a unique combination of lipids in certain cereal fibres and not to a particular type of fibre.

F I TOVEY
M HOBBSLEY

Department of Surgery,
University College London Medical School,
67-73 Riding House Street,
London W1P 7LD, UK

- 1 Tovey FI. Peptic ulcer in India and Bangladesh [progress report]. *Gut* 1979;20:329-47.
- 2 Tovey FI, Jayaraj AP, Lewin MR, *et al*. Diet: Its role in the genesis of peptic ulceration. *Dig Dis* 1989;7:309-23.
- 3 Tovey FI. Diet and duodenal ulcer. *J Gastroenterol Hepatol* 1994;9:177-85.
- 4 Jayaraj AP, Tovey FI, Clark CG. Possible dietary protective factors in relation to the distribution of duodenal ulcer in India and Bangladesh. *Gut* 1980;21:1068-76.
- 5 Tovey FI. Fibre and duodenal ulcers. *Lancet* 1982;ii:878.

"Golf ball liver": a cause of chronic hepatitis?

EDITOR,—A 23 year old man was referred to the outpatient clinic in view of persistently abnormal liver function tests for five years. In 1992, he had a gastrointestinal illness manifest by abdominal pain, diarrhoea and vomiting which lasted intermittently for one month. At that time, investigations by his general practitioner revealed that his liver function tests were abnormal: alkaline phosphatase (ALP) 408 U/l, aspartate aminotransferase (AST) 383 IU/l, alanine aminotransferase (ALT) 922 U/l, γ -glutamyl transferase (GGT) 147 IU/l. Viral serology for hepatitis A and B and a Paul-Bunnell test were negative. His symptoms resolved, but his liver function tests did not return to normal.

He was referred to the medical outpatient clinic in 1997 because of the development of further symptoms: episodic abdominal pain, diarrhoea, itch, and fatigue. His urine was noted to be dark and his faeces was pale. Alcohol consumption was moderate and confined to social occasions. He had no history of recent foreign travel, substance or drug misuse. He had no contacts with jaundice and no previous blood transfusions.

Liver function tests were persistently abnormal at that time: ALP 622 U/l, AST 86 IU/l, ALT 193 U/l, GGT 555 IU/l. Other investigations including full blood analysis, erythrocyte sedimentation rate, coagulation screen, urea and electrolytes, serum ferritin, serum copper, and alpha-1-antitrypsin were normal. Analysis of plasma proteins revealed albumin 45 g/l, globulin 37 g/l, total protein 82 g/l. IgG (30.3 g/l) and IgM (4.65 g/l) were raised. Titres of antinuclear antibody (IgG 1:20) and anti-smooth muscle antibody (IgG 1:40) were low. Viral serology for hepatitis A, B and C and Epstein-Barr and cytomegalovirus were negative. Abdominal ultrasound revealed an enlarged spleen, which was not palpable, and normal liver architecture.

Percutaneous liver biopsy revealed nodules separated by fibrous bands and a moderately dense mononuclear cell infiltrate within the portal tracts and fibrous bands, composed mainly of lymphocytes. The bile ducts were well preserved. There was moderately active lymphocytic piecemeal necrosis. Stains for Wilson's disease and alpha-1-antitrypsin deficiency were carried out and were negative. The appearances suggested chronic hepatitis progressing to cirrhosis.

This young man has been a very keen amateur golfer for many years and licks his golf balls during every round. All investigations as indicated above have failed to reveal a specific cause for his chronic hepatitis and cirrhosis. In view of the recent case report (*Gut* 1997;40:687-8) relating acute hepatitis to inadvertent ingestion of 2,4-D, it is proposed that ingestion of this substance by golfers may also lead to chronic hepatitis and even cirrhosis as in the case of this young man with no other apparent cause for his liver disease. The results of abstinence from licking his golf balls are eagerly anticipated.

S JOHNSTON
G MCCUSKER
T J TOBINSON

Craigavon Area Hospital Group HSS Trust,
68 Lurgan Road,
Portadown,
Craigavon BT63 5QQ, UK

Reply

EDITOR,—We were interested to read the letter by Johnston *et al*, further to our report in the July issue, which appears to document a case of chronic active hepatitis possibly caused by the patient's habit of licking his golf balls. It appears that the habit of golf ball licking is certainly not confined to Ireland and appears, at least anecdotally, to be a relatively common practice. Given this widespread practice and the now documented ability of 2,4-D to cause an acute hepatitis, it is certainly within the realms of possibility that a chronic hepatitis may also result from chronic exposure to 2,4-D.

However, the case reported by Johnston *et al* requires some clarification. It would be helpful to know whether any eosinophils were seen on the liver biopsy sample, and if not readily seen on straightforward stains then possibly monoclonal markers such as EG1 or EG2 could be used. This is of importance as if chronic golf ball liver exists then it raises the question of whether it is a toxic phenomenon or a chronic allergic/hypersensitivity process.

It would also be of interest to know whether the authors documented that 2,4-D was actually being spread on the patient's golf course. How long had the patient been licking his golf balls prior to the initial illness in 1992,

and had the chemicals used on the patient's golf course changed in or around this time. Was there any temporal relation between the patient's symptoms and the times of heaviest concentration of 2,4-D on the golf course or the frequency of this patient's golfing excursions? We await with interest any further developments.

C LEONARD

Division of Pulmonary & Critical Care Medicine,
Stanford University Medical Center,
Stanford, CA 94305, USA

C M BURKE

Department of Respiratory Medicine,
James Connolly Memorial Hospital,
Dublin 15, Ireland

C O'KEANE

Department of Histopathology,
Mater Misericordiae Hospital,
Eccles Street, Dublin, Ireland

J S DOYLE

Professor of Medicine - Emeritus,
Beaumont Hospital,
Dublin, Ireland

Mesalazine as a maintenance treatment in Crohn's disease

EDITOR,—We read with interest the occasional viewpoint by Sahmoud and Mary (*Gut* 1997;40:284-5). As is too often the case in such reviews, the authors have failed to identify all of the relevant literature pertinent to the topic: the maintenance of remission or prevention of recurrence of Crohn's disease. For example, with regard to azathioprine, rather than two trials of treatment, actually six trials (including the NCCDS Parts I and II) have been published. The results were summarised recently in a meta-analysis.¹ This systematic review concluded that the common odds ratio for maintaining remission for azathioprine treated patients was 2.3 (95 confidence interval (CI) 1.8 to 2.9) and that there was a relation between the cumulative dose of azathioprine prescribed and the response. Azathioprine should be considered an option for maintenance treatment.

The authors have also selectively reviewed the literature with regard to mesalazine. Turning to the postoperative population, a large North American trial² which identified a benefit for mesalazine for prevention of recurrence has been ignored, as well as trials which used endoscopic recurrence as a surrogate end point.³ A second systematic review, published in the same year as that of Messori *et al* reached similar conclusions and has been updated recently.⁴ Patients who received mesalazine were more likely to remain in remission compared with those on placebo. The relative risk of relapse was 0.63 (95% CI 0.50 to 0.79) for patients receiving mesalazine as compared with placebo.

We agree with the authors that additional studies are required and that differences in patient selection provides a likely explanation for differences in response. Identification of patients at higher risk of relapse could result in more cost effective treatment. Results have been conflicting with regard to clinical attributes of disease activity. While recognising that an analysis based on individual patient data might provide additional insight, the lack of consistent biological markers for high risk of recurrence (for example, permeability studies) in previous studies might make the approach irrelevant.

The issue as to whether or not to initiate maintenance treatment with either mesala-

zine or azathioprine remains a matter for discussion between patient and physician.

L R SUTHERLAND
A H STEINHART
Department of Medicine,
University of Calgary,
3330 Hospital Drive NW,
Calgary, AB, T2N 4N1,
Canada

- 1 Pearson DC, May GR, Fick GH, *et al.* Azathioprine and 6-mercaptopurine in Crohn's disease. A meta-analysis. *Ann Intern Med* 1995;123:132-42.
- 2 McLeod RS, Wolff BG, Steinhart AH, *et al.* Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology* 1995;109:404-13.
- 3 Brignola C, Cottone M, Pera A, *et al.* Mesalamine in the prevention of endoscopic recurrence after intestinal resection in Crohn's disease. *Gastroenterology* 1995;108:345-9.
- 4 Steinhart AH, Hemphili DJ, Greenberg GR. Sulfasalazine and mesalazine for the maintenance therapy of Crohn's disease: A meta-analysis. *Am J Gastroenterol* 1994;89:2116-24.

Emergency admission to hospital for colitis due to inflammatory bowel disease

EDITOR,—We were interested to read the study by Evans *et al* (*Gut* 1997;40:619-22) as we have recently reported a prospective study of colitis drawing similar conclusions.¹ Our study, however, showed a much stronger association. Forty five of 62 (72.4%) new cases of colitis were taking non-steroidal anti-inflammatory drugs (NSAIDs) or salicylates compared with 38 (7%) of 513 of a control population sample (odds ratio 33.1, 95% confidence interval 17.31 to 63). This difference between the two papers is almost certainly owing to the fact that our group of colitics comprised a much broader spectrum of disease than those reported by Evans *et al*, who were clearly only studying patients with colitis in relapse.

In addition, we enquired about the usage of over-the-counter NSAIDs and salicylates which was not possible in the study design of Evans *et al*. We would maintain that exposure misclassification could easily have occurred if over-the-counter usage of these compounds was not considered.

The incident cases of Evans *et al* were de novo cases of colitis but it is not apparent why they do not regard NSAIDs as causal in these cases, as they acknowledge that these drugs have been reported as causing de novo colitis in the introductory paragraph of their paper. In our study, which was exclusively of de novo colitis, many cases have recovered completely following withdrawal of NSAIDs and salicylates suggesting a cause/effect relationship. In these patients histological differentiation from ulcerative colitis "due to inflammatory bowel disease" was not possible in the majority of cases. However, in a minority (30%) subsequent independent histological assessment has revealed some of the criteria of NSAID colitis.² These criteria of NSAID colitis had not been established at the time of the study (1989-93) by Evans *et al*. Thus the interpretation of their cases as Crohn's or ulcerative colitis according to the criteria of Lennard-Jones³ may not be entirely valid.

In our opinion future epidemiological studies of the possible association of colitis and drugs need standardised histopathological review, preferably by a pathologist blinded

to the drug history of the patient, which must be stringently determined by the referring clinician. It is probable that many patients classified as having "colitis due to inflammatory bowel disease" will in fact be suffering from colitis induced by NSAIDs. These drugs may be some of the most important environmental factors in the pathogenesis of colitis.

M H GLEESON
Department of Gastroenterology,
The General Hospital,
Jersey JE2 3QS, UK

B F WARREN
Department of Cellular Pathology,
John Radcliffe Hospital,
Oxford OX3 9DU, UK

- 1 Gleeson MH, Hardman JV, Clinton C. Colitis, non-steroidal anti-inflammatory drugs (NSAID's) & salicylates — a strong association [abstract]. *Gut* 1996;39(suppl 3):A243.
- 2 Lee FD. Importance of apoptosis in the histopathology of drug related lesions in the large intestine. *J Clin Pathol* 1993;46:118-22.
- 3 Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol* 1989;24:2-6.

Reply

EDITOR,—Gleeson and Warren agree with the conclusions of our recent paper, that exposure to NSAIDs is associated with colitis. Where they disagree is on the strength of the association between exposure and colitis. Unfortunately, the abstract of the study they cite contains insufficient data to make a meaningful comparison between the two studies.¹ However, one possible reason for the difference is that their control group (513 attendees at a minor injuries clinic), recalled less prior NSAID exposure than their cases. Cases (who are ill) often recall past exposure more than controls (who are not ill). Recall bias is a common and difficult problem in epidemiology. The population based dispensed prescribing data we used as our measure of exposure did not suffer from this bias.

We agree that the NSAIDs aspirin and ibuprofen which are available in low dose over-the-counter formulas, might have resulted in some exposure misclassification, but we judge this to be a small effect when compared with recall bias.

Gleeson and Warren suggest that the difference between the two studies can be explained by differences in the spectrum of disease studied. In terms of severity, this might be true. Our cases were all severe enough to warrant hospitalisation. It is possible that milder colitis might be more strongly associated with exposure to NSAIDs. Gleeson and Warren go on to suggest that NSAID colitis might be a more specific condition. Nearly all of our cases had firm diagnoses of ulcerative colitis or Crohn's colitis. It is possible that a specific NSAID induced, less severe form of colitis exists. We did not study this.

In our study incident colitis was quite strongly associated with current NSAID exposure (odds ratio (OR) 2.96) whereas non-incident colitis was not (OR 1.16). Causality is one possible explanation of an association. Our study was carried out to clarify the "signal" of possible NSAID associated colitis suggested by case reports. It seems illogical to suggest that we should then use case report evidence to strengthen our causality inference. Case reports provide a low standard of

evidence of causality. They are anecdotes and the plural of anecdote is not data.

Arguments for a causal association depend upon the strength of the association, presence of biological gradient (dose response), consistency of the findings (lots of studies showing the same), and biological plausibility (a mechanism). We are further towards a causal association than before these studies were performed. However, we still have a lot of work to do before causality can be accepted.

The important point of our paper is that exposure to NSAIDs is associated with a severe adverse event, namely hospitalisation for incident (Crohn's and ulcerative) colitis. A milder, specific, NSAID colitis may exist. This is an attractive hypothesis which should be tested using epidemiological studies. We would be happy to collaborate with such a venture.

T M MacDONALD
Medicines Monitoring Unit,
Department of Clinical Pharmacology,
Ninewells Hospital & Medical School of Dundee,
Dundee DD1 9SY, UK

- 1 Gleeson MH, Hardman JV, Clinton C. Colitis, non-steroidal anti-inflammatory drugs (NSAID's) & salicylates — a strong association [abstract]. *Gut* 1996;39(suppl 3):A243.

Surveillance of the duodenum in patients with familial adenomatous polyposis

EDITOR,—We compliment Vasen *et al* (*Gut* 1997;40:716-19) on their attempt to quantify the benefit of surveillance of the duodenum in patients with familial adenomatous polyposis (FAP). We should like to make the following points:

The St Marks's study¹ is not strictly comparable to the Scandinavian study in that in the former results are based on the use of a side-viewing endoscope to focus particularly on the high risk periampullary area, whereas the Scandinavian study used forward viewing endoscopes only.

Vasen *et al* state that pancreaticoduodenectomy has substantial morbidity and mortality; this statement contradicts another within the body of the text referring to the decline in mortality from this operation over the past decade. It would be fair to say that the operation has the potential for substantial morbidity and mortality. However, this potential has not been fulfilled, especially in the context of a performance of a pylorus-sparing pancreaticoduodenectomy (E Tirtet and C Penna, Hôpital St Antoine, Paris, France, personal communication), together with encouraging results with regard to the lack of recurrence of duodenal adenomas.

We would suggest that a baseline screening examination be done before the age of 30. This might be done at the time of colectomy. This may be particularly worthwhile in those patients with a family history of duodenal cancer where such an examination would hopefully also reassure them.

There is additional evidence to that cited in favour of the existence of the adenoma-carcinoma sequence in the duodenum.² For example, adenomas were found in or adjacent to duodenal cancer in 84% (38/45) of patients with FAP.

We agree that the results of surveillance should be collected in a uniform manner at a central registry. In this way the quoted criteria for population screening, namely the natural history of duodenal adenomas, the