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 (NSAIDs) & 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 (NSAIDs) & 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' 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