LETTERS TO THE EDITOR

Peripheral arthropathies in inflammatory bowel disease

EDITOR,—We read with interest the paper by Orchard *et al* (*Gut* 1998;42:387-91) describing peripheral arthropathy in inflammatory bowel disease (IBD). However their study concentrated upon those patients with joint swelling or effusion, classifying them as either pauciarticular (type 1) or polyarticular (type 2). We were interested to note the low prevalence of arthralgia in their patients (14.3% for Crohn's disease), and that these patients were disregarded from further study. This report is in the context of a wide variation in the published prevalence of peripheral arthropathy in Crohn's disease (0.4 to 23%).¹

In our own retrospective study of 102 patients with Crohn's disease we found a higher prevalence of joint symptoms (53%). Ankylosing spondylitis was present in 4% of patients, 9% had peripheral arthritis, and 24% had peripheral arthralgia without joint swelling or effusion. The remainder of patients had degenerative joint disease or seropositive arthritis. Figure 1 shows the joint distribution of the peripheral arthropathies. This demonstrates a predilection for arthritis to affect the wrist and joints of the hands when compared with patients with arthralgia, significantly so in the wrists ($p<0.05$). Both the patients with peripheral arthralgia and peripheral arthritis had a significantly greater prevalence of mucocutaneous manifestations of IBD (i.e. oral ulceration, erythema nodosum, pyoderma gangrenosum, and uveitis) when compared with patients without joint symptoms ($p<0.01$ and $p<0.05$, respectively). This pattern is similar in some respects to that of the type 1 peripheral arthropathy described by Orchard *et al*. We also noted that patients with peripheral arthropathy were less likely to have perianal disease than those without peripheral arthropathy ($p<0.05$), although there was no difference in fistulating disease.

In contrast to Orchard *et al*, we found no association between peripheral arthralgia and colonic disease or the requirement for surgery. Non-steroidal anti-inflammatory

drugs (NSAIDs) had been used in 66% of our patients, and had been implicated as triggering an exacerbation of IBD in five patients. Overall 46% of patients with Crohn's disease who used NSAIDs had to cease therapy because of gastrointestinal side effects.

In conclusion, we feel that peripheral arthralgia without joint swelling or effusion, similar to type 1 (pauciarticular) arthropathy, accounts for the majority of locomotor morbidity experienced by patients with Crohn's disease. The prevalence of Crohn's disease arthropathy has probably been underestimated, as these patients have not been included in previous studies.

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1 Gran TG, Husby G. Joint manifestations in gastrointestinal diseases. *Dig Dis* 1992;10:274-94.

Reply

EDITOR,—We were interested to read in more detail the results of the study by Forrest and Russell which had previously been presented in abstract form. It is widely accepted that there is a high prevalence of arthralgia in patients with Crohn's disease and this was highlighted by a previous abstract from the St Mark's group.¹ Although there are little comparative data on arthralgia in patients with Crohn's disease compared with controls, Stein *et al* examined this question in 54 patients and healthy controls.² Of the patients, 44% complained of arthralgia compared with 46% of controls whereas 7.4% of the former had evidence of arthritis on clinical examination. Arthralgia is therefore common in patients with Crohn's disease and also in the general population. Retrospective studies of arthralgia are also extremely difficult to interpret. The nature of the background population (which is not clear from Forrest and Russell) and selection of study patients are of importance. It is not clear from this study how they differentiated arthritis from arthralgia retrospectively and exactly what constituted arthralgia or, indeed, arthritis. Thus 10% of patients with arthralgia in Forrest and Russell's study had "non-specific" joint involvement. Many retrospective studies, and certainly the large one by

Greenstein *et al*,³ have included patients with arthralgia and so are likely to overestimate the prevalence of arthropathy in Crohn's disease rather than underestimate it as asserted by Forrest and Russell.

In assessing this problem for our study we deliberately restricted analysis to those patients with objective evidence of arthritis, recognising that this will give an underestimate of prevalence, in order to explore pathogenic mechanisms. Clearly, precise clinical characterisation is essential for this and our preliminary data on HLA associations⁴ have already justified this approach.

In conclusion, a large number of patients with Crohn's disease do complain of arthralgia, but this may not be any greater than the general population. Studies that include these patients are difficult to interpret and may obscure important clinical and pathogenic associations.

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- 1 Yahia B, Dave U, Keat A, *et al*. Arthropathy in inflammatory bowel disease (IBD): An underestimated problem [abstract]. *Gastroenterology* 1996;110:A1048.
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HFE and alcoholic liver disease

EDITOR,—We read with interest the recent paper by Grove *et al* (*Gut* 1998;43:262-6) which concludes that the two haemochromatosis mutations (C282Y and H63D) influence neither the liver iron content nor risk of fibrosis in alcoholic liver disease. Two factors in this study may have led to an underestimation of the contribution of the haemochromatosis gene (*HFE*) to hepatic iron loading.

Most of the patients in the study had established cirrhosis. Cirrhosis, particularly alcoholic cirrhosis, may itself be a potent cause of hepatic iron loading once it has developed.¹ This rapid iron loading may result in hepatic iron concentrations usually associated with the homozygous haemochromatosis state and might obscure the effect of any iron loading that might occur due to the heterozygous genotype. Also, in haemochromatosis, excess alcohol consumption, although not affecting the hepatic iron concentration, seems to cause iron to redistribute from hepatocytes to reticuloendothelial cells.² The same may be true of hepatic iron stores in heterozygous haemochromatosis when excess alcohol is consumed, thus causing an underestimation of the hepatic iron stores if only hepatocellular iron is scored histologically and hepatic iron concentration (HIC) is not measured biochemically. In their study, Grove *et al* noted the presence of perisinusoidal and portal tract iron but did not estimate the degree of this staining and did not measure HIC.

These two factors may have led to the finding that significant (grade 2 or more) hepatocyte iron staining was not significantly com-

Figure 1 Distribution of peripheral arthropathy in Crohn's disease.

moner in age/sex matched alcoholics with either of the haemochromatosis gene mutations. However, although not quite reaching statistical significance, in this population twice as many alcoholics with one copy of the C282Y mutation did have grade >2 hepatocyte iron compared with those without this mutation (36% v 18%) and twice as many alcoholics with one copy of the C282Y mutation had any degree of histological iron compared with those without the C282Y mutation (46% v 24%).

In order to eliminate the effect of cirrhosis per se on hepatic iron loading it would be interesting to know whether there was any greater association between the *HFE* gene mutations and hepatic iron stores in the 59 patients with precirrhotic alcoholic liver disease. Perhaps more importantly it would be interesting to know in these 59 patients whether there was any relation between hepatic iron stores and the degree of hepatic fibrosis.

The fact that the *HFE* gene mutations were not significantly commoner in patients with fibrotic/cirrhotic alcoholic liver disease than controls does seem to suggest that these mutations do not have a major role in the progression of alcoholic liver disease. However, it is likely that any effect that *HFE* might have on the progression of chronic liver disease is mediated through raising iron stores, as we have shown in non-alcoholic steatohepatitis,³ rather than a direct effect of *HFE* on fibrogenesis. Only a minority of heterozygotes show some phenotypic expression of iron overload,⁴ other causes of iron overload clearly occur^{5,6} and many factors may be involved in the progression of alcoholic liver disease. Therefore a much larger fibrotic alcoholic population may be required to investigate definitively whether or not the *HFE* gene mutations are enriched in this population.

We agree with Grove *et al* that further research is required to investigate the factors that determine liver iron content in alcoholic liver disease and the prognostic significance of this iron. We do not think, however, that the effect of the haemochromatosis gene mutations on liver iron content and disease progression can yet be completely discounted.

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- 3 George DK, Goldworn S, Macdonald GA, *et al*. Increased hepatic iron stores in non alcoholic steatohepatitis are associated with increased liver fibrosis. *Gastroenterology* 1998;114:311–19.
- 4 Bulaj ZL, Griffen LM, Jorde LB, *et al*. Clinical and biochemical abnormalities in people heterozygous for hemochromatosis. *N Engl J Med* 1996;335:1799–805.
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6 The UK Haemochromatosis Consortium. A simple genetic test identifies 90% of UK patients with haemochromatosis. *Gut* 1997;41:841–4.

Reply

EDITOR,—We thank Drs George and Powell for their comments on our paper. We agree that confining our iron studies to the assessment of iron staining in hepatocytes of cirrhotic patients may have led to underestimation of the effect of the *HFE* genotype on iron content in alcoholic liver disease. However, as they point out, our results are fully consistent with the findings in non-alcoholic C282Y heterozygotes—only a minority of whom show evidence of iron overload—and any small effect of C282Y heterozygosity on liver iron content is likely to be swamped by the other causes of iron overload present in heavy drinkers. On the question of whether or not heavy drinkers with the C282Y mutation have more liver iron than drinkers without the mutation, in contrast to George and Powell, we believe our results of *HFE* genotyping do largely exclude a role for this mutation in determining the risk of fibrotic alcoholic liver disease. This is based not only on the similar frequency of the mutation in patients and controls, but also the identical mean age of presentation (and therefore cumulative alcohol intake) in patients with and without the mutation. Moreover, the lack of any increased frequency of the C282Y mutation in patients with alcoholic liver disease compared with controls has been reported by others.¹

With respect to the relation between iron stores and the degree/risk of fibrosis in heavy drinkers, we have no data on iron staining in the patients with fibrosis. However, we have reported recently that the liver iron content of patients with alcoholic fatty liver does not predict the risk of progression to fibrosis or cirrhosis.² If we accept that the C282Y mutation increases liver iron content but not the risk of alcoholic liver disease, taken together, these results would appear largely to exclude a role for excess liver iron in the pathogenesis of alcohol related liver disease.

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- 1 Aldersley MA, Howdle PD, Wyatt JL, *et al*. Haemochromatosis gene mutation in liver disease patients. *Lancet* 1997;349:1025–6.
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Ileal pouch-anal anastomosis for Crohn's disease

EDITOR,—Mr Phillips (*Gut* 1998;43:303–4) enjoys stirring the pot, but we cannot support all of his views on ileo-anal pouch surgery for Crohn's disease. Firstly, we do not think ulcerative colitis and Crohn's disease are necessarily "apples and oranges" (though familial adenomatous polyposis is). We believe that there is often a spectrum of disease and that in some cases only the long term natural history enables clinicians to know whether they are dealing with one or other disorder.

Also, we do not think it is appropriate to compare the outcome of Kock pouch surgery against pelvic pouch surgery for Crohn's disease. If there is a stricture in or above a pouch

which is out of the pelvis, the chances of successful reconstruction without pouch excision is much greater than for pouches in the pelvis (as our own experience confirms).

To confuse matters further, Mr Phillips compares colectomy and ileo-rectal anastomosis with pouch-anal anastomosis for Crohn's disease. This certainly introduces an "apples and oranges" scenario as ileo-rectal anastomosis is selective because of rectal sparing and, furthermore, even quiescent perianal disease or ileal involvement is not generally a contraindication. By contrast, ileo-anal pouches are not advised if there is perianal or small bowel disease.

Much of today's literature highlights a 10% change in diagnosis from ulcerative colitis to Crohn's disease over 10 years.¹ In some cases, as in our earlier experience,² the initial pathological scrutiny was not sufficiently rigorous and the patient had Crohn's disease from the start, whereas in others, small bowel disease develops after pouch construction and the diagnosis has to be revised. To advise pouch construction for known Crohn's proctocolitis when there is no anal or small bowel disease was heretical in the past and, still, is rarely advised. If a patient does not want a stoma a lot of counselling is needed if a surgeon proceeds with the patient's wishes. Admittedly, in our experience, just under half have a reasonable functional result over 10 years. However, for those that fail, morbidity is high with many more hospital admissions, a much greater length of small bowel sacrificed and a far higher risk of perineal sinus than in patients having proctectomy after a failed ileo-rectal anastomosis.

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- 1 Marcello P, Schoetz D, Roberts P, *et al*. Evolutionary changes in pathologic diagnosis after the ileoanal pouch procedure. *Dis Colon Rectum* 1997;40:263–9.
- 2 Grobler S, Hosie K, Affie E, *et al*. Outcome of restorative proctocolectomy when the diagnosis is suggestive of Crohn's disease. *Gut* 1993;34:1384–8.

Reply

EDITOR,—I think the readership will need to decide whether "apples and oranges" have been compared in the past. The leading article simply tried to point out the huge differences between ulcerative colitis and Crohn's disease and queried whether comparisons were fair, or even reasonable. After all, ulcerative colitis is curable by surgery, it has a reasonably low surgical morbidity and good prospects. Conversely, Crohn's disease is not cured by surgery, there is a recognised high surgical morbidity, all anastomoses are prone to recurrent disease, and reoperation is frequent.

As far as disease spectrum is concerned, Keighley *et al* may be right, although another possibility, partly supported by their own final paragraph, is that Crohn's disease may arise in patients with ulcerative colitis just as arthritis, heart disease or asthma may arise in these patients.

The rationale of alluding to Kock pouches was not to indicate that they are exactly equivalent to an ileo-anal pouch, but rather to show that when Kock pouches were made in