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Increased intestinal permeability in ankylosing spondylitis

SIR,—We read with great interest the excellent paper by Morris *et al* (*Gut* 1991; **32**: 1470–2) on intestinal permeability in ankylosing spondylitis but we do not agree, however, with their conclusions.

Using the ^{51}Cr-EDTA resorption test[1 2] we recently studied gut permeability in inflammatory rheumatic disorders. Intake of non-steroidal anti-inflammatory drugs (NSAIDs) significantly increases gut permeability irrespective of the underlying disease. Patients with ankylosing spondylitis and with other spondylarthropathies not taking NSAIDs also presented a significant increase of gut permeability compared with controls. This indicates that the disturbance is disease related. Gut permeability was not significantly increased in patients with histological gut lesions on ileocolonoscopy, or in patients with a normal ileum, although patients with ankylosing spondylitis and chronic gut lesions (resembling Crohn's disease) showed a significant increase in gut permeability compared with patients with ankylosing spondylitis and acute gut lesions.

There are several explanations for the absence of a relationship between increased gut permeability and ileocolonoscopic evidence of gut inflammation. On ileocolonoscopy only the terminal aspect of the ileum, which is only a very small part of the small bowel, can be examined. Moreover, the distribution of the observed lesions was patchy. Intake of NSAIDs causes such major disturbances in gut permeability that minor and local inflammation of the ileum would not influence the results of the ^{51}Cr–EDTA resorption test.

Inflammatory gut lesions were not found in patients with rheumatoid arthritis[3] taking high doses of NSAIDs for prolonged periods, while such lesions were present in more than 50 patients with spondyloarthropathies[4] who had not taken antiinflammatory drugs. This suggests that primary lesion in the ileocaecal region is associated with the spondyloarthropathies, while intake of NSAIDs probably induces more extensive and diffuse functional disturbances of the entire small bowel.

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Reply

SIR,—We do not feel that the evidence presented by Mielants *et al* in this letter convincingly shows that there is a primary pathology of the terminal ileum in patients with spondylarthropathies. Although patients with spondylarthropathies not taking non-steroidal antiinflammatory drugs (NSAIDs) did have significantly increased permeability compared with the controls, this was, by the authors' own admission, a very small group in whom no details of gut histology are given. Chronic lesions, resembling subclinical Crohns' disease, as described by the authors, may have been present and thus affected the results by increasing permeability in some of those patients.[1 2]

The argument that local or patchy inflammation of the ileum may not affect results of ^{51}Cr–EDTA absorption does not seem valid when previous studies have shown that ^{51}Cr–EDTA excretion increases towards the end of a nought to six hours collection consistent with increased absorption more distally in the small bowel.[3] Local inflammation in the ileum would be expected to have a relatively greater effect on ^{51}Cr–EDTA results and the lack of correlation between ileocolonoscopic findings and permeability (by Mielants *et al*) requires further explanation.

The fact that no inflammation was observed in rheumatoid arthritis patients at ileocolonoscopy should be considered in the context of more proximal inflammation and ulceration observed by our group using small bowel enteroscopy.[4] It may be that NSAID treatment is affecting different areas of the gut preferentially in ankylosing spondylitis and rheumatoid arthritis, thus explaining the increased permeability in rheumatoid arthritis patients on NSAIDs without ileocolonoscopic evidence of inflammation observed by Mielants and colleagues. Overall we find that the evidence for NSAID small bowel damage is more compelling than for a primary abnormality in spondylarthropathy.

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Crohn's disease after ileocolic resection

SIR,—Olaison, Smedh and Sjödahl (*Gut* 1992; **33**: 331–5) have provided endoscopic evidence that in many cases of Crohn's disease renewed ileal ulceration occurs soon after surgical resection; 22 of 30 examined at three months and proportionately more at 12 months. The authors consider that their data support views held by many that the bowel is permanently affected in Crohn's disease and is therefore liable to frequent clinical relapse even after apparent radical resection. Yet some follow up studies have also shown that as many as 25% of patients remain free of clinical symptoms for many years or even indefinitely. Nevertheless, with a relapse or recurrence rate as high as it is, it is clearly the responsibility of every physician and surgeon to do all that is possible to stave off renewed activity of the disease. Olaison *et al*'s report suggests that this needs to be done if possible before the onset of clinical symptoms when the disease process will have progressed to extensive ulceration and/or strictures.

Most clinicians at present monitor progress of these patients by regular checks for symptoms and signs of recurrence and test for anaemia, a rise in sedimentation rate and muramidases. Others, influenced by reports such as this one, may be inclined to prescribe maintenance doses of drugs such as aminosalicylates, immunosuppressives or corticosteroids. There is, however, evidence that such measures alone are not always enough. That evidence concerns the adverse affect of definitive emotional stress in this disorder which has either been forgotten or overlooked, or disbelieved and therefore ignored. The case both for and against it has been reviewed in the section on Crohn's disease in a recent book.[1] Appropriate psychological management of such cases is well within the competence of a non-psychiatrically trained physician once he or she has become aware of what is needed to help these sensitive and vulnerable people to change their previously damaging coping mechanisms in dealing with abrasive interpersonal strife in their immediate environment. How to do this is described with case histories and transcripts.[1] What so often happens now, however, is that patients, many of them very young, are returned without psychological help to the same abrasive domestic or social environment which immediately preceded the onset or relapse of their disease. Case histories and the few outcome studies available illustrate the value of such intervention in cutting short relapses when domestic strife escalates and patients find themselves caught in the middle. Before treatment they lack the ability to cope or escape. Many such patients managed in this way remain free of disease for many years or suffer only minor relapses. The authors of the article from a Department of Surgery may be unaware that the first reports on psychosomatic

aspects in the pathogenesis of Crohn's disease came from surgeons, who before 1955 treated most patients over many years. Physicians at that time lacking effective drugs had little to offer.

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1 Paulley JW, Pelser HE. *Psychological managements for psychosomatic disorders.* Heidelberg: Springer, 1989.

Reply

SIR,—We read with interest the comments by J W Paulley on our paper. We agree that patients with Crohn's disease in addition to medical and surgical care should also have appropriate psychological management, which is within the competence of each physician. In our experience, this is best achieved if the patient has regular contact with a medical team specialising in inflammatory bowel disease treatment. Professional care will relieve much anxiety about the future with this chronic disease, and also enable the patient to cope with the symptoms that most inevitably develop. The disease, however, can no longer be regarded as a psychosomatic disorder. Our studies and others clearly show that Crohn's disease is a chronic gastrointestinal process with a permanently present intestinal inflammation. There should be no antagonism between medical, surgical, and psychological therapy. The best support a patient with Crohn's disease can be given, is for the disease to be recognised as a chronic gastrointestinal disease. Present available medical and surgical treatment, although palliative, may offer a substantial reduction of symptoms. To abstain from such treatment today, using only psychotherapy for recurrent symptoms after surgery, is not adequate.The care of patients with Crohn's disease is a multidisciplinary task. At the University Hospital, Linköping, Sweden, all patients are regularly reviewed by a team including a gastroenterologist, gastrointestinal surgeon, endoscopist, dietetian, stoma therapist, and specially assigned nurse. The team has a joint treatment strategy; the aim of which is to minimise the symptoms during their lifetime, and all decisions on treatment are taken regarding the chronicity of the disease. Medical and surgical treatment are regarded as complementary. The treatment is governed by the patients disease activity, intensity – that is, activity for a longer period – and aggressiveness. Psychological management is a part of the regular care.

We studied 238 patients in 1991 with Crohn's disease. The treatment outlined above resulted in clinical remission of 83% at the end of 1991 (Crohn's disease activity index <150). The patients own experience of their disease was also, in our view, satisfying. Sixty nine per cent considered themselves healthy or almost healthy (>80% healthy, self estimation on a visual analogue scale). We believe that the best help a patient with Crohn's disease can have is the psychological, medical, and surgical support from a knowledgeable team.

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Osteomalacia after gastrectomy

SIR,—I congratulate Bisballe *et al* (*Gut* 1991; **32**: 1303–7) for evaluating their postgastrectomy patients for metabolic bone disease. All too often, we, as physicians caring for patients with gastrointestinal problems that lead to abnormal bone nutrition and metabolism – that is, postgastrectomy, inflammatory bowel disease, small bowel malabsorption, and states of diminished oral intake, ignore the patients' developing bone disease because the process is insidious and the patients are often asymptomatic until the disease is so profound that much of it may be irreversible.

I must take issue, however, with the authors' conclusion advocating supplemental vitamin D for all postgastrectomy patients. The authors have found evidence of bone abnormalities by histomorphometry in up to 62% of 51 patients, but only eight patients were considered to have osteomalacia. It is not clear that vitamin D supplementation is beneficial in non-osteomalacia bone disorders.

The authors suggest that the low mean levels of 25-hydroxyvitamin D are relevant and thus warrant supplementation. Yet, five of eight patients with a diagnosis of osteomalacia had normal levels, highlighting the lack of value serum measurements may have in predicting bone disorder diagnoses. The authors do not state how many of their non-osteomalacia patients had levels that were abnormal (they state only that the mean overall was abnormal). That 1,25-dihydroxyvitamin D levels, the active circulating vitamin D metabolite, were normal in these patients, underscores how complex vitamin D metabolism is and how serum values may not be predictive of an abnormality.

Although the authors agree in their final paragraph that serum biochemical results are of limited value, they use these results as the premise for a therapeutic intervention. They showed that patients who took vitamin D supplementation had higher levels of serum 25-hydroxyvitamin D. It is not sufficient to recommend vitamin D therapy simply because patients have metabolic bone disease. Vitamin D supplements in excess doses can be toxic and may not necessarily be helpful. There is no indication that those patients on supplements had less bony abnormalities on histomorphometry. In fact, half of the patients with osteomalacia were using supplementation.

To determine whether vitamin D is of therapeutic benefit, a study is needed whereby vitamin D therapy is compared with placebo in a randomised blinded group of postgastrectomy patients and not where the use of vitamin D in a group of patients is compared with a non-diseased control group. Oral ingestion of dietary vitamin D needs to be controlled. Investigators of such a study would need to show that bone histomorphometry improved or did not worsen over time while on therapy.

Vogelsang *et al*[1] showed that overall, a group of Crohn's disease patients randomised to vitamin D 1000 IU/day therapy did not have a statistically significant improvement in bone mineral density. Although maintenance doses of vitamin D 400 IU/day with calcium supplementation maintained bone mineral density in a group of corticosteroid using rheumatology patients, higher doses of more potent 1,25-dihydroxyvitamin D were of no benefit and led to raised serum and urine calcium concentrations.[2]

Although low dose vitamin D therapy (400–600 IU/day) in postgastrectomy patients is likely nontoxic – that is, in terms of effects on calcium, this remains to be proved in a systematic fashion. The benefit of this therapy in postgastrectomy patients certainly needs to be proved and has not been in Bisballe *et al*'s paper.

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Reply

SIR,—We thank Dr Bernstein for his constructive comments on our paper on osteomalacia in postgastrectomy patients and his emphasis on the importance of the problem. We also consider bone disease after gastrectomy a problem very often ignored in daily clinical practice.

The diagnosis of osteomalacia in our study was based on very stringent histological criteria, which delineate severe mineralisation defects affecting virtually all bone surfaces. The remaining patients with abnormal bone histology revealed varying degrees of secondary hyperparathyroidism with focal areas of mineralisation defects – that is, earlier stages in the osteomalacic process. Further analysis of serum biochemistry in these patients was hampered by the lack of good parathyroid hormone assays (the study was performed before the advent of assays for intact parathyroid hormone (1–84)). Theoretically, such patients would also benefit from vitamin D supplementation, because the high turnover state associated with secondary hyperparathyroidism leads to osteopenia. We do not think, however, that the study on Crohn's disease by Vogelsang *et al* is of great relevance in this respect. The bone in patients with Crohn's disease is characterised by osteopenia and only very discrete osteomalacia is demonstrable.[1]

We do not advocate the use of more potent analogues (1-alpha-vitamin D_3 or $1,25(OH)_2D_3$) for postgastrectomy patients. We agree with Dr Bernstein that these compounds demand close monitoring because of the risk for severe intoxication. We have, however, administered daily doses of 18 000 IU calciferol (D_2) over a five year period to more than 200 osteoporotic women (mean age 65 years) without any cases of vitamin D-intoxication.[2] Thus, we do not think that vitamin D supplements are dangerous as long as they are given in the form of D_2 analogues in a dose range of 400–800 IU. We agree, however, that a controlled clinical study is necessary in order to test for optimal dose, efficacy and side effects.

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