New NSAIDs—Inhibitors of Cyclooxygenase 2—and Renal Damage

Sir—We have read with interest the excellent articles on meloxicam, a new non-steroidal anti-inflammatory drug (NSAID), included in Supplement 1 (April 1996) of the British Journal of Rheumatology. Data reported in these articles, together with new findings based on genetic investigations, help our understanding of important problems.

In addition to their acute anti-inflammatory and analgesic actions, NSAIDs have been demonstrated to be effective against chronic diseases, such as heart attacks and strokes [1] and colon carcinoma [2]. Nevertheless, the deleterious side-effects of NSAIDs can be significant, including damage to renal function [3]. Both the therapeutic and toxic effects of NSAIDs can be attributed to a decrease in the production of prostaglandins [4]. Prostaglandin synthase (PS), also called cyclooxygenase (COX), is the primary enzymatic target for NSAIDs [5]. This enzyme has two isoforms, COX-1 and COX-2, and their respective genes are PS1 and PS2. It is now believed that the beneficial effects of NSAIDs are due to inhibition of COX-2, whereas the side-effects are due to inhibition of COX-1 [6]. However, experimental procedures based on gene disruption in animal models have shown that COX-2 deficiency is associated with significant side-effects. Recently, Morham et al. [7] have reported the consequences after disruption of the gene encoding COX-2. The more severe effects related to the inactivation of PS2 are kidney abnormalities: inflammation and fibrosis, and papillary mineralization. These findings demonstrate that the absence of COX-2 impairs renal differentiation, resulting in a reduced number of nephrons. Those nephrons that are present must increase their workload, which leads first to compensatory hypertrophy and subsequently to glomerular sclerosis [8].

In conclusion, the identification of selective inhibitors of COX isoforms leads to important benefits in the therapy of rheumatological disorders. However, despite the development of new NSAIDs, side-effects may also be important and must not be forgotten.

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Subarachnoid Haemorrhage Secondary to Ruptured Cerebral Aneurysm in a Patient with Osteogenesis Imperfecta

Sir—Osteogenesis imperfecta (OI) is an inherited disorder of connective tissue which, besides exhibiting the classical clinical signs, may present diverse neurological complications. We report a patient with OI type I who developed subarachnoid haemorrhage secondary to ruptured intracranial saccular aneurysm. This complication, which has not previously been reported in the literature, may be the result of a deficiency of collagen in and around the blood vessels, with an increased vascular weakness.

The patient was a 22-yr-old woman suffering from OI type I: blue sclerae, short stature (height 1.45 m), osteopenia and a history of two fractures prior to puberty without major skeletal deformities. There was no family history of OI.

She was referred to our hospital for severe headache of sudden onset, with transient loss of consciousness and vomiting. Neurological examination revealed signs of meningeal irritation, without focal deficits. Cranial computed tomography (CT) showed cortical atrophy and the presence of subarachnoid haemorrhage. Subsequent cerebral arteriography disclosed a saccular aneurysm involving the right anterior communicating artery; venous phase demonstrates marked tortuosity, dilatation and corkscrewing of the cortical veins with patency of dural sinuses.

Complete coagulation studies were normal. Rumpel-Leede test was positive. Surgical clipping of the neck of the aneurysm was performed, and the patient remained asymptomatic.

Diverse neurological complications have been reported in OI, including brain stem compression and plathybasia, hydrocephalus, severe scoliosis with spinal cord compression, intracranial haemorrhage resulting from trauma at birth, subdural and epidural haematomas (non-traumatic or caused by mirror trauma), and carotid-cavernous fistula [1–7]. Factors influencing the development of these complications are peculiar to this disorder and include the propensity to bony fractures, an increased weakness of the vessel walls caused by inherent disturbances of the vascular connective component with blood vessels which are unable to constrict adequately [4–7] and, occasionally, coagulation abnormalities [8, 9]; the combination of these factors explains the certain bleeding tendency found in patients with OI [10].

In our patient, the increased vascular weakness was proven by a positive Rumpel–Leede test; for this reason, we think that vascular fragility stands out as an important factor in the pathogenesis of the cerebral aneurysm rupture, making a coincidental association improbable. In summary, although this letter deals with an unusual complication, our case advises that OI
may potentially produce a variety of neurological complications, some of them secondary to vascular abnormalities and haemorrhagic diathesis. These complications are not commonly recognized and should be kept in mind when evaluating a patient with OI.

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Polyarteritis Nodosa Presenting as Ischaemic Colitis

SIR—A 37-yr-old woman was admitted because of fever and weight loss. She had no remarkable medical history. The 6 months previous to admission, she presented with fever, severe myalgia and loss of 10 kg. On admission, she began with bloody diarrhoea. The physical examination only disclosed mild abdominal tenderness and a temperature of 39°C. Investigations were: haemoglobin 10.6 g/dl; leucocytes 11.5 x 10⁹/l; platelets 475 x 10⁹/l; ESR 103 mm; CRP 56 mg/dl (normal <0.8). ANA, RF, ANCA, hepatitis B virus and hepatitis C virus serology and cryoglobulins were negative. The barium enema and colonoscopy showed signs of colitis around the splenic flexure of the colon (Fig. 1). The distal descending and sigmoid colon and the rectum were spared. The radiologist's and endoscopist's diagnosis was inflammatory bowel disease (IBD). The microscopic examination of a colonic biopsy disclosed signs of ischaemic colitis, with signs of polyarteritis nodosa (PAN) in the medium-sized arteries.

Treatment included broad-spectrum antibiotics, i.v. methylprednisolone, 60 mg/day, and three weekly i.v. pulses of cyclophosphamide of 750, 500 and 500 mg, respectively. After discharge, a progressive withdrawal of prednisone was accomplished and, after 3 x monthly pulses of cyclophosphamide, she was changed to azathioprine. One year after discharge, PAN has not relapsed.

Although gastrointestinal involvement is frequent in PAN, the isolated abdominal presentation is very uncommon and the large bowel is seldom involved [1]. Since 1975, only five cases of colitis due to PAN have been published in the English-language literature (Table I). All patients were symptomatic for a period ranging from 2 weeks to 1 yr, and four had extra-intestinal symptoms. Although colonic involvement was demonstrated in every case by barium enema or endoscopy, all underwent surgery.

The presentation of colonic PAN may mimic IBD in young patients and atherosclerotic ischaemic colitis in older ones. Thus, any gastrointestinal symptoms which are preceded by fever, weight loss, myalgia or arthralgias, should raise the possibility of vasculitis. In those patients who do not require an urgent intervention, a deep endoscopic biopsy must be taken. This can give the diagnosis without the need for surgery.