Letters to the Editor

Table I. The activity of N-acetylo-β−hexosoaminidase and cathepsin D in synovial fluid of patients with rheumatoid arthritis (RA), idiopathic juvenile arthritis (JIA) and traumatized knees (p value means that the difference between the experimental and control groups was statistically significant.

Lysosomal enzymes	Enzymatic activity (mean) in the synovial fluid of patients with		
	RA n = 11	JIA n = 14	Traumatized knee (control group) n = 20
Hexosaminidase nM/ml/min	105.96 ± 34.04 p = 0.000003	85.13 ± 26.87 p = 0.0005	12.74 ± 4.25
Cathepsin D Tyr nM/ml/12h	146 ± 31.85 p = 0.000001	107.2 ± 21.19 p=0.00002	51.7 ± 16.42

swollen and painful knees during physical examination and effusion of the joint; duration of the disease was 4-28 years. The second group contained 14 patients with JIA(5 girls, 9 boys; 8-17 years old); six of them had polyarticular and eight oligoarticular onset JIA; duration of the disease was 1-11 years. At the time of sampling eight patients were in very active and six in subacute periods of the disease according to Mallya and Mace (5). Our reference group was composed of 20 patients with injured anterior ligament or meniscus medialis/ lateralis (6 female, 14 male; 15-21 years old).

Arthrocentesis of the knee joint of RA and JIApatients was performed because of prolonged exudation or intra-articular injection of steroids. Samples of the SF of patients with traumatized knees were obtained during routine diagnostic arthroscopy. The activity of HEX in the SF was determined as described by Zwierz *et al*. (6). The activity of cathepsin D in the SF was performed as described by Greczaniuk *et al*. (7).

Statistical analysis was conducted with a Statsoft program by Statistica 6, and the Levine test was applied to the data. This revealed significant differences among the studied groups. We used post hoc analysis calculated by test NIR, which indicated the least significant difference. Results were expressed as mean and SD. Pvalues of less than 0.05 were considered significant. The study design was approved by the Ethical Committee of the Medical University of Bialystok, Poland.

In the SF of patients with RAand JIA, HEX activity was calculated as 105.96± 34.04 nmol/ml/min and 85.13±26.87 nmol/ml/min respectively, and HEX activity in the RA group was significantly elevated (p = 0.000003) in comparison to traumatized patients (Table I). The above results are in agreement with our previously reported data (8).

The activity of cathepsin D in the SF of patient with RAand JIAamounted to 146.5 ± 31.85 Tyr nmol/ ml/ 12h and 107.2± 21.19 Tyr nmol/ml/12h respectively and in RA patients was significantly elevated (p = 0.000001) in comparison to traumatized patients.

Sohar *et al*. (9) recently reported a 1.28 fold increase in HEX, and 1.49 fold increase in cathepsin D activity in the leukocytes of RA patients. It is worthy of note that HEX activity in the SF of our RA and JIA patients was 8.3 and 6.6 but cathepsin D was only 2.8 and 2 times higher than the in the SF of the control group.

Our results suggest that in the knee joint cavities of RAand JIApatients, increased degradation of glycosaminoglycans (hyaluronic acid, chondroitin and keratan sulphates) and of glycoproteins with HEX is greater than degradation of proteins by cathepsin D. Our results are in agreement with data reported by Ortutay *et al*. (2) which suggest that exoglycosidases, which are present in the SF of RA patients, may contribute to the depletion of GAGs from cartilage. The conclusion is that some possible interplay between proteases and glycosidases in the SF of RA patients can take place. Analysis of the above enzyme system may be an important complement to molecular and genetic studies in the effort to fully understand the mechanism of RA. Our data indicate HEX as an important complement of the joint damage diagnostic system and inhibition of HEX as a potential target of RAtherapy.

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Atypical axial osteomalacia: Report of a HLA-B27 negative elderly female patient without features of sacroiliitis

Sirs,

Atypical axial osteomalacia (AAO) is a very rare bone disorder characterized by dense coarseness of the trabecular bone on radiographs located in the axial but not appendicular skeleton, and osteomalacia on bone biopsy of affected areas. Since the first case was described in 1961/62 (1) not more than 18 AAO-patients have been reported (2-9). All of them, except one (report of an affected mother and son) (5) were middle-aged or elderly Caucasian men. The cause of AAO is still unknown and some authors suggest that AAO could be a genetic bone cell abnormality. Sacroiliitis (3/5) and positive HLA-B27 antigen (2/4) is the most described concomitant disease. Axial increased and peripheral decreased bone mineral density (7, 9), moderate phosphate diabetes (8) and associations with polycystic kidney (5) and liver disease (5) have been reported.

A 83-years-old Caucasian female patient was admitted to our unit for dorsal and lumbar back pain. The patient was in normal general health, with no living relatives and no relevant medical or surgical history.

X-rays of the lumbar spine and pelvis showed a marked osteosclerosis without changes in size. There were no signs of sacroiliitis, which was confirmed by CAT, MR and scintigraphic examinations, whereby X-rays and MR are usually sufficient to make diag-

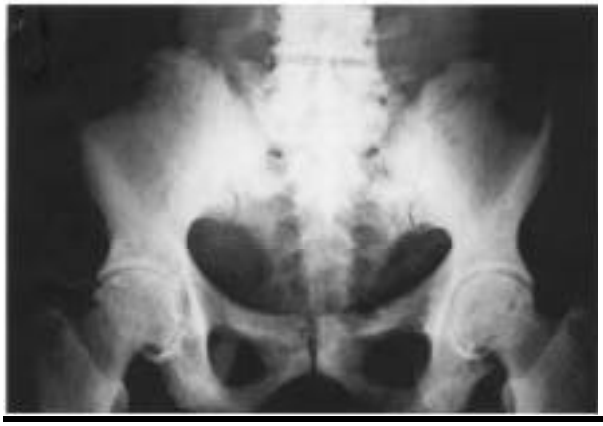

Fig. 1. X-rays of the pelvis: marked osteosclerosis without changes in size.

nosis of a sacroiliitis. The skull, cervical and thoracal spine, upper and lower limbs showed normal bones and moderate osteoarthritic changes. Looser's zones have not been identified. Measurements of bone mineral density (DEXA) revealed a T-score of the lumbar spine (L2-L4) of +3.9 and of the femoral neck of -2.2. Routine laboratory parameters and biochemical markers of bone metabolism, including serum calcium, inorganic phosphate, total alkaline phosphatase, bone specific alkaline phosphatase, 25-hydroxyvitamin D, 1.25-dihydroxyvitamin D, osteocalcin, intact PTH, kreatinin and phosphate clearence were within normal limits. Testing for HLA-B27 was negative. Only one time (due to bone biopsy) there was a slight increase of total alkaline phosphatase. Histological examination of an iliac crest bone biopsy showed thickening of the cortices, increased trabecular bone with broad seams of unmineralized osteoid due to osteomalacia.

The radiologic, densitometric, laboratory and histologic findings in the patient presented herein are compatible with AAO (Fig. 1). The patient was successfully treated with NSAID.

AAO is often asymptomatic and could also be detected in elderly women without any features of sacroiliitis or abnormal bone metabolism. The differential diagnosis of the radiological appearence included bone metastases, systemic mastocytosis, Paget's disease of bone, osteopetrosis, fluorosis, myelofibrosis, fibrogenesis imperfecta ossium, beryllium-, strontium-, cadmium-, plumbum-poisoning, hyperparathyroidism and renal osteodystrophy. For diagnosis other relevant diseases of bone should be excluded by bone biopsy and histologic examination.

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Haemorrhagic gastritis and bleeding following rofecoxib administration

Sirs,

Selective inhibitors of cyclooxygenase-2 (COX-2) have been clinically developed to achieve therapeutic effects comparable to those of conventional non-steroidal anti-inflammatory drugs (NSAIDs), without causing damage to the digestive mucosa (1). Here we describe a case of gastrointestinal bleeding which occurred after treatment with the selective COX-2 inhibitor rofecoxib, reported to us by Pharmasearch, an Italian network of general practitioners for the spontaneous reporting of adverse drug reactions.

A 76-year-old woman referred to her family physician for the onset of severe epigastric pain, associated with the emission of dark stools and one episode of coffee-ground emesis. She was affected by bilateral gonarthrosis, diffuse osteoarthritis, and low back pain. Rofecoxib 25 mg/day had been prescribed by her physician to treat a flare of osteoarthritic pain. The patient assumed rofecoxib for 20 days without complaining of digestive symptoms and then, once the pain was relieved, the treatment was suspended. A few days after rofecoxib withdrawal, the patient developed epigastric pain accompanied by the emission of dark stools and one episode of coffee-ground emesis. After neglecting such disturbances for about one month, the patient referred her symptoms to the physician during a visit scheduled to review the results of routine laboratory examinations (all values being normal). The physician prescribed lansoprazole 60 mg/day, and requested an upper digestive endoscopy. The endoscopic examination revealed haemorrhagic-erosive gastritis, with the body and antrum mucosa being extensively affected by both flat and protruding erosions, and with broad intervening areas of intramucosal bleeding. The patient reported no tobacco or alcohol consumption, but referred previous digestive disturbances in concomitance with NSAID use. The patient's medical history did not indicate documented episodes of peptic ulcer or dyspepsia. The patient had been having treatment with the antiepileptic drug carbamazepine 400 mg/day, for 12 years, following the surgical removal of a meningioma. Lansoprazole treatment for two months fully relieved the patient's digestive symptoms. The application of Naranjo algorithm (2) to the present case allowed to rank as 'probable'the causal link between rofecoxib administration and the occurrence of adverse digestive events. A putative interaction with carbamazepine was taken also into account to explain the above symtoms, but there is no evidence in literature to support such a hypothesis.

Based on pharmacoepidemiological data, this patient can be considered at increased risk for NSAID-induced digestive toxicity, due to sex, age and history of NSAID-induced digestive toxicity (3,4), and therefore she is likely to have experienced an episode of upper digestive bleeding following treatment with a COX-2 inhibitor. Although COX-2-inhibitors appear to be safer than conventional NSAIDs in controlled trials (5), treatments with the former drugs have been associated with upper gastrointestinal complications in post-marketing studies (6). There is also recent evidence of selective prescription of COX-2 inhibitors