LETTERS TO THE EDITOR

Anti-Tumour Necrosis Factor Therapy Ameliorates Joint Disease in a Chronic Model of Inflammatory Arthritis

Str—There is clear evidence to indicate that tumour necrosis factor α (TNF-α) plays an important role in the pathogenesis of inflammatory joint diseases. TNF-α has been identified in the synovial membrane of RA patients, and induces cartilage and bone resorption [1–3], suggesting a key role in the pathogenesis of RA. Antibodies to TNF-α have been shown to diminish the production of proinflammatory cytokines by rheumatoid synovium-derived mononuclear cells. Therefore, this cytokine not only promotes connective tissue degradation, but also participates in the induction of the chronic inflammatory state [4].

Recent years have seen much interest in the use of anti-TNF-α in modulating disease in both clinical and experimental inflammatory arthritis. In particular, injection of anti-TNF has been shown to ameliorate joint damage in collagen-induced arthritis (CIA) in DBA/1 mice [5]. CIA is an antigen-induced, acute model of joint disease where symptoms peak around day 35, with complete resolution by day 70 post-induction. We have studied another murine model of inflammatory arthritis, over a number of years, namely pristane-induced arthritis (PIA). The i.p. injection of the mineral oil pristane (2,6,10,14-tetramethylpentadecane) results in the development of a remitting and relapsing, chronic CD4+ T-cell-mediated arthritis (scored by ankle swelling) 100–200 days later in ~30% of the animals [6–8]. However, inflammatory cell infiltrate and synovial hyperplasia can be observed histologically as early as day 60 post-pristane injection. This disease mimics RA in many respects, both histologically and serologically, including cartilage degradation, pannus formation and the presence of rheumatoid factor as well as abnormalities in IgG glycosylation [9–11]. Because of its chronicity, we are able to treat the mice at various time points during the development of the disease. Here we report experiments where anti-TNF treatment was begun at around the time of disease onset [6], this being more relevant to the clinical situation.

Mice were injected i.p. with four 250 μg doses of a ‘murinized’ hamster IgG1 monoclonal antibody specific for murine TNF-α/β (TN3γ1, kindly supplied by Celltech, Slough) in saline, at weekly intervals, commencing at day 80 post-pristane injection. Animals were monitored at various time points, thereafter, for the development of disease. Observable symptoms (ankle swelling) were apparent in the control group of animals by day 90. By day 120, the incidence of PIA in the control group was 16% (4/25), which was significantly different from the treated group (P < 0.05, χ² test) where such symptoms were not seen until day 160. Final incidence and severity were assessed histologically on termination of the experiment at day 200. Longitudinal sections of knee joints from the groups were graded on a 0–3 basis [12], depending on the extent of joint damage. The control group of mice exhibited a disease incidence of 32% (8/25) with a mean severity score of 1.63 ± 2.55. By contrast, the anti-TNF-treated group showed a lower incidence of 15% (3/20), together with a lower mean severity score of 0.75 ± 0.87. The difference in the mean severity scores was significant between the two groups (P < 0.05, t-test).

In short, anti-TNF therapy delayed the onset and lowered the incidence and severity of PIA. These results add to the published literature and support the view that targeting TNF is a realistic therapeutic approach in chronic disease such as RA.

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Longitudinal Stress Fractures of the Tibia: Report of Three Cases

Sir—The majority of tibial stress fractures are transverse or oblique [1]. There are only isolated reported cases of the longitudinal type, usually related to twisting [2, 3] or repetitive impact activities [2–7]. The age at menopause in women was not mentioned and bone mass was not measured in any of them [3–5, 8–9]. We present three cases in postmenopausal women with no activity-related fracture. Laboratory tests including serum calcium, phosphate and alkaline phosphatase and urinary calcium excretion were normal in all three. In two of them, osteoporosis was diagnosed by dual X-ray absorption (DEXA). The findings found on different imaging modalities are also analysed.

Case 1 was a 65-yr-old woman with osteoarthritis of both knees who presented with a history of 4 weeks of pain in the right lower leg. She had her menopause at age 48. A simple radiograph was normal. ⁹⁹ᵐTc bone scan demonstrated increased uptake in the distal tibia, and CT a linear fracture line with endosteal and periosteal bone formation. Measurement of bone mass showed normal results.

Case 2 was a 64-yr-old woman who underwent the menopause at age 50. She had osteoarthritis of both knees and attended because of pain in her left lower leg of 6 weeks duration. Plain radiographs showed thin periosteal reaction along the lateral aspect of the tibia, bone scan increased uptake in this area, MRI low signal on T1- and high signal on T2-weighted spin-echo scans in the tibial diaphysis, and CT a fracture line with periosteal and endosteal reaction. Measurement of bone mass showed a T-score = −4.02 S.D. in the lumbar region and −3.86 S.D. in the femoral neck.

Case 3 was a 64-yr-old woman who complained of having had pain in her right lower leg for 6 weeks. Her age at menopause was 47. Simple radiographs were normal. Bone scan revealed increased uptake throughout the distal tibial diaphysis (Fig. 1), and MRI and CT the same findings found in case number 2 (Figs 2 and 3). Measurement of bone mass showed a T-score = −3.58 S.D. in the lumbar region and −2.86 S.D. in the femoral neck.

Longitudinal stress fractures of the tibia are usually related to physical activity [2–7]. In other cases, a twisting injury suggests that they may be incomplete spiral fractures [2–3]. In patients in whom previous trauma, twisting mechanism or increase in exercise are not present prior to the onset of symptoms, searching for a condition associated with insufficiency fractures is necessary [10]. However, in the revised reports, the age of menopause was not mentioned and bone mass was not measured in any patient [3–5, 8–9]. It was abnormal in two of ours. Osteoarthritis of the knee (present in two of our cases) has been reported by Goupille et al. [8]. They suggest that biomechanical changes in individuals with osteoarthritis of the knees can be a risk factor for the development of this type of fracture.

Diagnosis is difficult and imaging modalities are usually necessary. Simple radiographs are normal or show periosteal changes, although a lucent longitudinal line can be seen [2]. Bone scintigrams are important because of the longitudinal pattern of uptake [2–3, 5–9]; they can be sufficient if clinical suspicion is present. Although the fracture line can be seen with MRI [4], CT is the best imaging modality because of its high sensitivity in the assessment of cortical bone detail [2–3, 5, 7–9].

Longitudinal stress fractures of the tibia must be suspected in patients with leg pain; anamnensis and clinical assessment must include risk factors: twisting, osteoarthritis of the knee, physical activity, and all causes of insufficiency fractures [10]. Measurement of
bone mass is necessary in postmenopausal women and when risk factors for stress fractures are absent.

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Gout due to Xanthine Derivatives
Sir—A 54-yr-old woman’s family history revealed that her mother had mild hyperuricaemia and her brother suffered from gout. She had suffered from right hemiplegia due to subarachnoid haemorrhage in 1987. She is now free of hemiplegia. She had been under treatment for bronchial asthma with theophylline 600 mg/day and procaterol hydrochloride 100 µg/day, aminophylline 200 mg/day, prednisolone 1 mg/day, and beclometasone dipropionate. Her serum level of uric acid (Sua) was 6.0 mg/dl, as determined by an enzymatic method using uricase-peroxidase, in 1988, before medication. The Sua was between 6.8 and 9.5 mg/dl from 1989 to July 1995.

She felt severe pain at the metatarsophalangeal joint of the left hallux on 28 September 1995. She was admitted on September 30. The Sua was 8.2 mg/dl. We diagnosed the case as a gout attack, because it was compatible with the diagnostic criteria of the American Rheumatism Association [1]. Theophylline and aminophylline were reduced gradually from October 6. The patient received the last dose of xanthine derivatives on October 10 and had an attack of bronchial asthma on October 13. The Sua was 6.3 mg/dl on October 14. Theophylline and aminophylline were administered again. The Sua increased to 8.4 mg/dl on November 6. Benzbromarone and allopurinol caused side-effects. At present, the Sua has been maintained at <6.1 mg/dl with probenecid without a gout attack.

Recently, it was reported that xanthine derivatives induce hyperuricaemia [2–9]. Most cases were males. There has been no report that xanthine derivatives caused gout, to our knowledge. In this case, the patient’s Sua without xanthine derivatives was a little high for a female. She has a family history of gout and hyperuricaemia. We may assume that she has a gene that can induce hyperuricaemia, but it cannot be confirmed at present. We can only determine the Sua and evaluate family history. Based on our experience, we think that when a female patient with bronchial asthma is treated with xanthine derivatives, she should be carefully monitored for Sua, especially in the case of hyperuricaemic patients with a family history of gout or hyperuricaemia.

Benzbromarone and probenecid do not increase the serum level of theophylline, but allopurinol increases it [5, 10]. The serum level of theophylline must be carefully monitored if a hyperuricaemic patient who is under treatment for bronchial asthma with xanthine derivatives is administered allopurinol.

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More on Enterococcal Osteoarticular Infections: Vertebal Osteomyelitis

Str—We read with interest the paper by Markov et al. [1] regarding the case of a patient with systemic lupus erythematosus who presented septic arthritis of the knee due to Enterococcus faecalis. Since this microorganism is extremely rare as a cause of osteoarticular infections, we consider it of interest to report a patient who developed vertebral osteomyelitis due to E. faecalis.

A 73-yr-old male was admitted because of back pain, polachyuria and intermittent fever and chills, that had started 1 month before. Past history indicated non-insulin-dependent diabetes diagnosed when he was 70 yr old.

Physical examination indicated a severely ill patient. The axillary temperature was 37.5°C, the pulse rate was 98, and the arterial blood pressure 110/70 mmHg. The patient was alert, but confused. There was a marked pain and rigidity in the lower thoracic spine, and the rest of the examination was normal or negative.

Main haematological data indicated: Hb 10.3 gr/dl, haematocrit 30.7%, mean corpuscular volume 90 fl, mean corpuscular haemoglobin 30.1 pg. The white blood cell count was 7000/mm³ (72% neutrophils). The ESR was 123 mm. Main biochemical tests were normal. Urinalysis indicated >150 leucocytes per high-power field. Culture of the urine, as well as two sets of blood cultures, indicated growth of E. faecalis sensitive to ampicillin and aminoglycosides.

The chest X-ray and abdominal X-ray were normal. A CT scan of the spine indicated narrowing of the D11–D12 intervertebral space, partial destruction of both vertebral bodies and the presence of gas in the retroperitoneum (Figs 1 and 2), these findings being highly suggestive of vertebral osteomyelitis and perivertebral abscess. A ⁹⁹mTc-bone scan indicated radionuclide accumulation in the D11 and D12 vertebral bodies. A two-dimensional transthoracic echocardiogram was reported to be normal.

The diagnosis of bacteraemia and metastatic vertebral osteomyelitis due to E. faecalis from the urinary tract as a source was established. Treatment with ampicillin 2 g/4 h and gentamicin 80 mg/8 h, i.v., was started. An attempt at percutaneous drainage was unsuccessful. The condition of the patient deteriorated quickly and he experienced a massive upper digestive haemorrhage, with shock and multiorgan failure, and subsequently died. Necropsy was refused.

Infectious discitis due to enterococci is an uncommon disease. In a retrospective review of 19 patients with infectious discitis and/or vertebral osteomyelitis seen in our hospital during the last few years, only one case (the present report) was due to Enterococcus and through a MEDLINE search, covering from January 1969 to June 1996, we could find only five additional cases. Two have been reported in a large series of infectious discitis [2], whereas the other three

Figs 1 and 2.—CT scan of the thoracic spine. Partial destruction of the body of the 11th and 12th thoracic vertebrae, and gas in the right paravertebral area.
were described in detail as case reports [3, 4]. As in our patient, all the cases reported in the literature were of advanced age (from 65 to 77 yr) and their chief complaint was back pain, usually lasting for more than 1 month. This long lapse of time between the beginning of the symptoms and the diagnosis emphasizes that vertebral osteomyelitis continues to be diagnosed with delay.

Infectious discitis or vertebral osteomyelitis is diagnosed in the setting of an elderly patient with a drug regimen that is ineffective against enterococci. If infectious discsit or vertebral osteomyelitis is diagnosed in the setting of an elderly patient with a concomitant urinary tract infection, *Enterococcus* should be suspected and adequately covered.

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**Tattooing-Induced Psoriasis and Psoriatic Arthritis**

Str—Tattooing, a very old procedure which is widespread throughout the world, especially in young people, may carry several risks, including the transmission of infectious diseases [1], local granulomatous dermatitis [2] and, in some cases, systemic reactions such as sarcoid granulomas [3], antiphospholipid antibody syndrome [4] and uveitis [5]. In this context, we would like to describe the case of a patient who developed psoriasis and psoriatic arthritis following tattooing.

In May 1995, a 26-yr-old Caucasian man underwent tattooing of the left shoulder skin area. The procedure was performed by a non-professionally trained friend, and was followed by moderate local pain and light discomfort that lasted 3 days. One week later, however, a well-delineated, raised erythematous skin reaction with small plaques appeared on the tattoo area, followed, 3 days later, by similar lesions on the ears, elbows and umbilicus. After a week, arthritis consisting of swelling, pain and tenderness occurred in the left elbow and wrist. The patient was then referred to our division of rheumatology. Microbiological investigations, including anti-streptococcal antibodies, and viral tests for hepatitits A, B and C, Epstein–Barr, parvovirus and HIV, were all negative. Additional laboratory tests showed a normal total blood count; erythrocyte sedimentation rate 40 mm/h; C-reactive protein 1.3 mg/dl (normal < 0.6); rheumatoid factor 16 IU/ml (normal < 40) and absence of antinuclear, antineutrophil cytoplasmic and antiphospholipid antibodies. HLA typing revealed A1, A4; B18, B39; Cw6; DR7, DR11. In synovial fluid, the white blood cell count was 13 100/mm³, 75% neutrophils and without eosinophils; crystals were not found and culture was negative. A skin biopsy was performed showing histological features of psoriasis. The diagnosis of psoriatic arthritis was then made.

To our knowledge, until now no other case of psoriasis and/or psoriatic arthritis induced by tattooing has been reported. Pathogenic mechanisms explaining skin and articular reactions may include trauma with resulting Koebner-like response, local hypersensitivity reaction to tattoo pigments, and microorganisms. In fact, there is increasing evidence that environmental factors, such as microorganisms and trauma, may induce or exacerbate psoriasis and psoriatic arthritis in genetically predisposed individuals [6, 7].

In our case, however, since microorganisms were not found, it is possible to hypothesize the responsibility of the trauma or tattoo pigments. The presence of HLA Cw6 and DR7, frequently associated with psoriasis [8], and of B39, a split of HLA-B16 strongly associated with psoriatic arthritis in the north-eastern Italian population [9], confirms the importance of genetic predisposition. Moreover, our observation further indicates the variety of complications related to tattooing procedures. As tattooing is more frequent in the population than is commonly believed [10], it must be officially recognized as a profession requiring serious training and standards of hygiene in order to limit the risks.

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Chlamydia pneumoniae Antibodies in Myalgia of Unknown Cause (Including Fibromyalgia)

Sir—The recent report by Moling et al. [1] on Chlamydia pneumoniae (ChP) infection in reactive arthritis is an important addition to our search for aetiological agents in different rheumatic diseases. At the last rheumatology seminar here (Seventh International Seminar on the Treatment of Rheumatic Diseases, 1995) we reported findings regarding the frequency of ChP antibodies in 101 unselected rheumatic patients, as compared to the incidence of antibodies to Chlamydia trachomatis (ChT). Antibodies to ChP were found in 67.4% and to ChT in 37.5%. The respective incidences for each type of antibody were 7/10 and 5/11 for rheumatoid arthritis, 5/7 and 3/8 for reactive arthritis, and 5/5 and 2/6 for tendinitis. The most interesting figures were those for myalgia of undetermined cause, including fibromyalgia (FM). The incidence of ChP antibodies in these cases was 18/23 (78.3%) and that of ChT antibodies was 12/21 (57.1%) [2].

The high incidence of antibodies to both Chlamydia species, but especially to ChP, could of course reflect a high incidence of this infection within the general population. Nevertheless, the often ‘mysterious’ aetiology of different cases of myalgias on the one hand and the presence of ChP antibodies in all of our (small group) patients with tendinitis (anatomically: a part of a muscle) on the other, calls for a deeper look into the possibility of a connection between Chlamydia infection in unexplained cases of myalgia and of soft-tissue rheumatism in general. Fibromyalgia has been reported following Borrelia and parvovirus infection [3–5], both infections seemingly not as frequent as ChP. We witness here a frequent, clinically a mostly mild, infection and a very common syndrome, FM, in which ChP antibodies were found in 78.3% of cases. The possible aetiopathogenetic connection of both should be considered.

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Diagnostic Criteria for Work-Related Upper Limb Disorders

Sir—I read with interest Helliwell’s Editorial on this topic [1] and found myself in agreement with many of the points made. In particular, I would agree that the phenomenon of individuals presenting with upper limb pain, which they or others attribute to their occupation, has social, psychological and economic facets. Cleland’s review of the Australian ‘epidemic’ describing the phenomenon as a form of ‘social iatrogenesis’ is recommended to anyone seeking to avoid repeating the Australian experience [2]. It is perhaps worth pointing out that the problem has now largely disappeared in Australia, largely it seems through a change in medical, social and political attitudes. I would like to make some additional points.

Firstly, it is worth stating the obvious point that disease is not a discrete phenomenon and has social, economic, political and even legal dimensions. Illness, i.e. the human behavioural response to real or imagined disease, is likewise multidimensional. My point, though, is that the practical solutions to disease and illness are not always medical and may lie in the hands of others, and this is particularly relevant to this issue.

Helliwell [1] discusses the use of the term repetitive strain disorder (RSD) and quotes published data on whether doctors ‘believe it is genuine or not’. This, however, misses the point—no one doubts that the phenomenon (i.e. limb pain, as described above) exists; what is really at issue is why does it happen, is there an aetiological relationship with the subject’s occupation and, finally, should the phenomenon fall into the purview of medicine and be studied using the ‘medical model’ at all? The problem with the labels RSD and work-related upper limb disorder (WRULD) is that both imply a universal aetiological relationship with work which is not justified and, moreover, RSD implies a mechanism, i.e. that repetitive mechanical forces cause pain and tissue damage, which is unproven. This, as Cleland [2] and Hadler [3] point out, runs counter to the purposes of conventional scientific taxonomy and, in so doing, misleads us and confounds our attempts to understand the phenomenon.

A further observation is that patients to whom the label RSD or WRULD has been attached seem to
fall into two broad but sometimes overlapping categories. The first comprises those who have clearly identifiable and often treatable pathology which has been overlooked for want of simple clinical examinations (e.g. epicondylitis, undiagnosed polyarthritis, cervical radiculopathy, carpal tunnel syndrome, mood disorder). Sometimes these are related to the subject's occupation. The second group have no identifiable problem other than their musculoskeletal symptoms and their distress; some have discomfort related to poor trunk and limb posture which improves with simple advice, others are harassed and unhappy in their workplace or are economically distressed; sometimes their distress has been displaced from their domestic life to their workplace. Some, of course, overlap between these two groups and have some minor musculoskeletal pathology which has become the focus for distress and which really has its origin elsewhere in their lives. All these individuals are equally deserving of medical attention, but the solution to their problems is not necessarily strictly medical. Giving an unjustified and all-embracing medical diagnostic label is of no practical utility, and runs the risk of reinforcing illness beliefs, disability and handicap.

The problem with the starting point suggested by Helliwell, namely that we need agreed ‘diagnostic criteria’ for the phenomenon, is that we then start with the assumption that the medical model is the most appropriate for its study. If the phenomenon is to be studied, it should not be constrained by a set of diagnostic criteria, but should be studied as a social phenomenon defined as ‘subjects who present to a doctor complaining of limb pain which has been attributed to work’, or something similar. This is the only criterion needed. Testable hypotheses may then be set up about the relationship or otherwise of the phenomenon to putative social, psychological, economic, medical, ergonomic and other aetiological factors. Suitably controlled experimental and epidemiological designs can then be used to test these hypotheses.

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Reply
Although I accept that my background may have given the impression of a bias towards the medical model of illness, my suggestion should not constrain the user to adopt such beliefs. Agreed ‘criteria’ are required so that we can proceed with epidemiology and so that we can explore associated features of this phenomenon (be they physical or sociopolitical, or both). The problem with Dr Hurst’s criteria (1. presentation to doctor; 2. limb pain; 3. attributed to work) is that they are too narrow for the workplace and would exclude large numbers of people with arm symptoms who have not yet consulted about their problem. At this stage, the criteria must be sensitive enough to detect all cases: more specific criteria will follow a better understanding of this phenomenon. As mentioned in my Editorial, the Health and Safety Executive has recently convened a ‘consensus’ meeting on diagnostic criteria for upper limb disorders, the results of which should soon be available.

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The Contribution of the Rabin Medical Center to the Field of Rheumatology

SIR—In a recent article [1], Ehrenfeld et al. reviewed the clinical and research activity of rheumatology in Israel. The authors omitted more than a generation of clinical and research work performed in Israel in the field of gout and uric acid metabolism, as well as clinical and experimental studies in the field of environmental factors influencing arthritis. One of the leading physicians in Israel, the late Professor Andre De Vries, was involved in numerous publications on gout, uric acid stones and hypouricaemia. Some of these publications are still cited in textbooks of rheumatology [2, 3].

Uric acid metabolism has been intensively studied at the Rabin-Beilinson Medical Center. The research group headed by Professor O. Sperling is a well-known centre for purine metabolism in man [4, 5]. Professors De Vries and Sperling, who both served as deans of the Sackler Faculty of Medicine, Tel Aviv University, organized the First Symposium on Purine Metabolism in Israel in the early 1960s.

Professor De Vries’ research was also a great contribution to the history of gout [6].

Indeed, ignoring all the above intensified work performed at the largest medical centre in Israel, which has a total of 1300 beds, leads one to the conclusion that this paper was not adequately prepared. Moreover, errors such as Weisenbik instead of Wysenbeek, or that the Department of Rheumatology at the Rambam Medical Center is known centre for purine metabolism in man [4, 5].

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Reply
We apologize that the subject of gout and purine metabolism was omitted from our review, and indeed deserved publication. Yet, being limited in space, not every contribution to rheumatology in Israel could be mentioned in the article. A spelling mistake in a name does not necessarily indicate that the whole article was not prepared properly.

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