LETTERS TO THE EDITOR

Juvenile Chronic Arthritis: Diagnosis and Management of Tibio-talar and Sub-talar Disease

Sir—We agree with Remedios et al. [1] that guided intra-articular steroid injections to joints of the ankle joint complex (AJC) are likely to give more precise placement of drug and therefore improved effect. We would like to add two comments to their article.

Firstly, in adults, communication between the joints of the ankle is often seen at arthrography and injecting one of these joints is likely to lead to improvement in all of them. How often does this phenomenon occur in children?

Secondly, the cartilage of the tibio-talar joint is subjected to some of the highest stresses in the body [2] and the ankle, in common with many other joints, requires intact ligaments and tendons for stability. In addition, the mechanical requirements of the AJC in walking involve a complex series of three-dimensional movements to enable the transfer of forces from the body to the foot/floor interface. For these reasons, deformity commonly occurs at the AJC in the presence of inflammatory joint disease. Treating the inflammation is of paramount importance (and intra-articular injection is an effective method), but, for the reasons given above, it is equally important to attend to malalignment which is sometimes only apparent when walking. Weight-bearing deformity at the AJC is most effectively treated by the use of individually made functional orthoses and adequate footwear, both of which are an essential part of the management of inflammatory disorders at this site.

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Accepted 5 January 1998


Reply

If there are communications between the ankle and the sub-talar joints in children, they are clinically irrelevant since injections into the tibio-talar joint do not affect talo-calcaneal synovitis, both clinically and on MRI. With regard to orthoses, we routinely provide custom-made orthoses to correct any hindfoot deformities.

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Accepted 5 January 1998
LETTERS TO THE EDITOR

Treatment of Gout After Transplantation

Sir—Byrne et al. [1] have recently reported two cases of the successful control of gout after cardiac transplantation with allopurinol and a reduced dose of azathioprine. Gout may become a problem in cardiac transplant recipients [2] as they are usually treated with cyclosporin A and diuretics. Hyperuricaemia is a common side-effect of cyclosporin therapy [3] and, in patients on cyclosporin A, hyperuricaemia is more frequent in those who are also on diuretic therapy [4]. Both cyclosporin and diuretics induce hyperuricaemia by reducing urinary excretion of urate [4, 5].

In the two patients reported [1], azathioprine was reduced in order to avoid side-effects due to the concurrent administration of allopurinol, and the dose of frusemide was also reduced. One of them suffered a further attack secondary to an increase in the dose of frusemide. Data regarding renal function and renal handling of urate in these patients would be of interest, because they would have probably shown severe underexcretion of urate. Uricosuric therapy would then appear to be preferable to allopurinol, especially in patients in whom the dose of azathioprine or diuretics could not be reduced.

Recent reports have demonstrated the usefulness of benzbromarones such as benziodarone and benzbromarone for the therapy of hyperuricaemia and gout in renal transplant recipient patients despite moderate renal insufficiency [4, 6] and in primary chronic gout [7]. The use of uricosuric drugs is probably a more pathogenic approach to therapy in patients showing underexcretion of urate and will avoid the risks of combing allopurinol and azathioprine (especially myelotoxicity) in transplant recipients. Recently, Cummings et al. [8] have suggested that uricosuric drugs should be considered for treating hyperuricaemia in such cases.

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Antimalarial Drugs in the Treatment of Rheumatological Diseases

Sir—The review by Rynes [1] of the use of antimalarials was timely and, in most respects, extremely helpful. However, the comments about ophthalmological supervision, particularly as far as hydroxychloroquine is concerned, should not be allowed to pass unchallenged. The author produces very little evidence to suggest that there is a true problem with retinal toxicity when using low-dose hydroxychloroquine. Bearing in mind the vast experience of using this drug over 30 yr or so, it is remarkable just how few case reports there are of toxicity, including in longitudinal studies.

The author works in a country where there are a large number of ophthalmologists and where screening is relatively easy. In many countries, this luxury is not available and if Rynes’ advice is followed then patients who would benefit from the drug will be denied it. I would urge that suggestions about unreasonable monitoring are critically appraised and that, as a speciality, we abandon what is, in medical terms, a fairly expensive and relatively useless test.

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Kelley–Seegmiller Syndrome: A Case Report and Review of the Literature

Sir—We would like to report the case of a 26-yr-old man referred to our department with poorly controlled gout in spite of treatment with allopurinol. He was investigated for loin pain and haematuria at the age
of 13 yr, and had a normal cystoscopy and i.v. urogram, although urate crystals were seen on urine microscopy. When aged 16 yr, he was admitted to the hospital with acute renal failure. There was no history of gout and his serum uric acid level was normal. Renal imaging showed non-obstructed kidneys and renal biopsy was normal. A repeat renal biopsy 5 months later showed chronic changes and abnormal areas of giant cell formation around clefts thought to represent sites of crystal deposition, which were considered highly suggestive of urate nephropathy at a subsequent review. A period of dialysis was required, but independent renal function was regained.

Because of the combination of poorly controlled gout and nephropathy at an early age, the possibility of an underlying disorder of urate metabolism was considered and purine metabolic studies were performed at the Guy's Hospital purine metabolism research unit. These revealed absent hypoxanthine-guanine phosphoribosyltransferase (HPRT) in haemolysate, but intact red cells had reduced, but not zero, activity. The purine de novo synthesis intermediates were raised, a finding typical of partial HPRT deficiency.

The partial deficiency of HPRT was first reported by Kelley et al. [1] in some subjects with gouty arthritis in whom the onset of gout occurred earlier and who had an increased incidence of urate renal stones. Up to 25% of these patients may have minor neurological features, but do not self-mutilate as in Lesch–Nyhan syndrome in which the enzyme deficiency is complete [2]. The overproduction of uric acid may not result in hyperuricaemia and gout because there is high uric acid clearance before puberty [3], and may only present with nephrolithiasis. The excessive production of uric acid characteristic of partial HPRT deficiency results from an accelerated rate of de novo purine biosynthesis [4]. The mechanisms involved are illustrated in Fig. 1.

The inheritance of this deficiency is X-linked [5]. Major clinical manifestations are in the affected male with evidence of transmission through carrier females. Pre-natal diagnosis is possible using chorionic villus sampling [6, 7], but not justified in partial deficiency because of the mild nature of the disease. The diagnosis is made by a high serum urate level, a high 24 h urinary production of urate expressed on the basis of body weight, a urinary urate:creatinine ratio of >0.75% unless in renal failure and reduced HPRT activity in erythrocyte lysates (0.01–30% of normal).

This case illustrates that urate nephropathy or gout in childhood is usually genetic and should be investigated in spite of normal serum urate levels [8].

**Letters to the Editor**

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**Sacroiliitis in an HLA B27-negative Patient Following Giardiasis**

Siri—Sacroiliitis is commonly seen in reactive arthritis (ReA) following enteric infections. ReA has been described following infection caused by the flagellated protozoan *Giardia lamblia*. Sacroiliitis has not been previously described as a feature of this arthropathy. We present an HLA B27-negative patient with sacroiliitis and enthesitis following giardiasis.

A 37-yr-old previously healthy man presented to the general physicians in June 1996 with a 5 month history of malaise, abdominal pain without diarrhoea, and increasing low back pain with early morning stiffness of 2 h duration and marked inactivity stiffness. There

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**Fig. 1.** —Mechanisms involved in excessive production of uric acid resulting from an accelerated rate of de novo purine biosynthesis.
was no relevant past medical or family history and systems enquiry was unremarkable. He was a non-smoker, drank 40 units of alcohol per week and was heterosexual with a long-term partner. He worked as a vehicle accessories trader and attended a meeting in Estonia in January 1996.

General physical examination was unremarkable. The ESR was elevated at 53 mm/h and the CRP was elevated at 57 mg/l. The following investigations were normal: FBC, full biochemical profile, serum immunoglobulins, blood cultures, viral serology, ECG, CXR, stool microscopy and culture, sigmoidoscopy with biopsy, urine microscopy and culture, and abdominal ultrasound scan. A standard CT scan of the abdomen was also performed which showed narrowing and sclerosis of the sacroiliac joints bilaterally, consistent with sacroiliitis, but no other abnormality. He was HLA B27 negative.

He was referred to the rheumatology clinic in July 1996 and noted to have pain on stressing the sacroiliac joints, mild reduction in spinal movements (modified Schober flexion 18.5 cm) and tender Achilles tendons bilaterally. Chest expansion was normal (6 cm). The gastrointestinal symptoms had resolved by this stage and there was no weight loss. A clinical diagnosis of ankylosing spondylitis was made; however, in view of the previous abdominal pain and negative HLA B27 status, a jejunal biopsy was requested principally to exclude Whipple’s disease. He was commenced on treatment with sodium diclofenac 150 mg daily and sulphasalazine 2 g daily, and was referred for physiotherapy.

The jejunal biopsy was postponed until December 1996. The appearance of the small bowel mucosa was normal; however, histological examination revealed numerous luminal G. lamblia. At review in January 1997 he had generally improved with no significant morning stiffness, resolution of low back pain and improved spinal movements (modified Schober flexion 26 cm). He was, however, noted to be tender over the iliac crests bilaterally in addition to the previously noted Achilles tendon tenderness. The inflammatory indices had normalized (Figure 1). Metronidazole 2 g daily for 3 days was prescribed and it was decided to withdraw the sulphasalazine and observe his progress closely.

He has been reviewed on a 3 monthly basis and there has been no deterioration in symptoms or spinal measurements. Inflammatory indices have remained normal and the enthesis tenderness has now resolved.

Musculoskeletal manifestations of giardiasis were first described in detail by Goobar [1]. In a series of 66 children aged 2–15 yr, he described an acute, additive polyarthritis affecting principally the large joints of the lower limb. The knee joint was the most commonly affected. The shoulder, elbows and wrist were involved in a significant number of patients, but the small joints of the hands and feet were rarely affected. Subsequent reports by Farthing et al. [2] and Woo and Panayi [3] support this clinical syndrome in children. Invariably, the arthritis was refractory to treatment with non-steroidal anti-inflammatory drugs, but responded to antimicrobial treatment of the giardiasis. Diagnosis was made by stool microscopy or following duodenal aspiration. Unless multiple examinations are performed, stool microscopy may be insensitive as giardia cysts are excreted intermittently in the faeces [4]. It is also emphasized that the gastrointestinal infection is frequently asymptomatic. In one case, the patient was found to be HLA B27 positive [3].

A similar clinical picture is reported in adults. Shaw and Stevens [5] report a maculopapular rash and acute

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**FIG. 1.—Inflammatory indices against time.**

- ESR (mm/hr)
- CRP (mg/l)

<table>
<thead>
<tr>
<th>ESR (mm/hr)</th>
<th>CRP (mg/l)</th>
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<tbody>
<tr>
<td>60</td>
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<td>50</td>
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<tr>
<td>20</td>
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**Jun-96** | **Sep-96** | **Dec-96** | **Mar-97** | **Jun-97** | **Sep-97**
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Metronidazole 2 g daily for 3 days

**Sulphasalazine 2 g daily**
polyarthritis in a 39-yr-old female associated with giardiasis. Arman [6] reports two cases of chronic relapsing polyarthritis in a 30-yr-old female and a 26-yr-old male. Barton et al. [7] report a 29-yr-old HLA B27-positive female with a family history of ankylosing spondylitis who developed an asymmetrical oligoarthritis following giardiasis, but who had no signs of sacroiliitis. All cases responded to antimicrobial therapy.

There are no reports in the literature of axial involvement in the arthropathy associated with giardiasis. Other than as specified the patients were HLA B27 negative or, in the case of the original series, not determined. The patient reported here appears to have developed an axial reactive arthritis with clinical evidence of enthesitis following giardiasis. Although this is a common presentation of ReA, we believe it is the first report secondary to giardiasis. The clinical picture is complicated by the course of treatment with sulphasalazine; however, after stopping this treatment, there has been no recurrence of the arthropathy and the CRP continued to fall and remains normal. Furthermore, the clinical findings of enthesitis resolved after metronidazole, whilst appearing to worsen on treatment with sulphasalazine. It is interesting that our patient is HLA B27 negative; however, at present, there is insufficient information available to determine the relationship between HLA status and the risk of developing ReA following giardiasis.

From a clinical viewpoint, we feel that this case highlights the necessity of taking a detailed history. In the specific case of giardiasis, the intestinal infection may be asymptomatic and the diagnosis may be overlooked in a patient presenting with ReA. This is important as antimicrobial chemotherapy appears to be curative. In our patient, the history of travel to Eastern Europe, where giardiasis is relatively common, might have suggested the diagnosis. We conclude that chronic giardiasis needs to be excluded in patients presenting with a spondyloarthritis, abdominal symptoms and a suspicious travel history.

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TABLE I

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Female</th>
<th>Age (yr)</th>
<th>Duration of RP (yr)</th>
<th>Positive ANA</th>
<th>Positive RF</th>
<th>Abnormal NCM</th>
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<tr>
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<td></td>
<td></td>
<td>&lt;4</td>
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<td>10+</td>
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<tr>
<td>RP only</td>
<td>26</td>
<td>22</td>
<td>39.4 (21–74)</td>
<td>8</td>
<td>7</td>
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<td>Possible</td>
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<td>33</td>
<td>52.2 (28–79)</td>
<td>14</td>
<td>6</td>
<td>16</td>
<td>18 (30%)</td>
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<tr>
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<td></td>
<td></td>
<td>Speckled 8 (Scl-70)</td>
<td>Centromere 4</td>
<td>Homogeneous 4</td>
<td>Nucleolar 2</td>
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<tr>
<td>Definite</td>
<td>13</td>
<td>11</td>
<td>48 (28–69)</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td></td>
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<tr>
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<td>SLE 5</td>
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</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>66</td>
<td>47</td>
<td>25</td>
<td>15</td>
<td>35</td>
<td>29 (38.7%)</td>
</tr>
</tbody>
</table>

DL, dilated loops; TL, tortuous loops.

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CD134/OX40 Expression by Synovial Fluid CD4+ T Lymphocytes in Chronic Synovitis

Sir—Pitzalis [1] has recently reviewed the role of adhesion mechanisms in the pathogenesis of chronic synovitis. The processes leading to the accumulation of CD45R0+ T lymphocytes in synovial fluid (SF) of chronic synovitis were illustrated focusing on the selective adhesion to and migration through the endothelium by activated T cells. The main role in these mechanisms is played by LFA-1 and VLA integrins, but a proportion of the binding of T cells to endothelial cells cannot be inhibited by the addition of combinations of blocking antibodies against known adhesion molecules. Recently, a new molecule has been demonstrated to play an important role in the process of adhesion of activated T cells to the endothelium [2], and it has been identified as the previously described OX40 antigen (now, also termed CD134), a member of the tumour necrosis factor receptor family [3–5]. Anti-OX40 antibodies inhibit the binding of phytohaemagglutinin-activated CD4+ T cells to human vascular endothelial cells, which were found to express OX40-ligand [2]. Moreover, OX40-transfected T cells were shown to bind in an OX40 system-specific way to vascular endothelial cells [2].

In humans, OX40 is detectable in non-malignant tissues only on very rare lymphocytes in the T-cell compartment of lymphoid organs [6] and is virtually absent on peripheral blood resting lymphocytes [6, 7]. However, its expression can be induced upon stimulation in vitro with mitogens, mainly on CD4+ cells, but also on a small number of CD8+ cells [6, 7].

We have studied by flow cytometry the expression of OX40 using the monoclonal antibody L106 (provided by the VI International Workshop for Leucocyte Differentiation Antigens) in eight patients with rheumatoid arthritis (RA) and in six age-comparable normal individuals. On CD4+ cells purified from peripheral blood by means of immunomagnetic beads (Dynal, Oslo, Norway; purity was always >96%), only a moderate difference between the two groups was observed, as far as the number of cells co-expressing OX40 was concerned (mean ± 1 s.d% in RA 13 ± 3% vs 6 ± 2% in healthy controls; P = 0.053; Wilcoxon’s rank sum test).

However, high levels of OX40 expression were observed on CD4+ cells purified from SF of eight patients with RA (49 ± 25%; P < 0.01 vs peripheral blood CD4+ cells from healthy controls), in a patient with psoriatic arthritis (PsA) (29%), and even in two patients with osteoarthritis (OA) of the knee, from whom lymphocytic SF was aspirated (median 30%). On the other hand, only a small number of purified
CD8+ SF lymphocytes expressed OX40 (RA: 10 ± 10%, n = 6; PsA: 9%, n = 1; OA: median = 8.5%, n = 2).

This observation suggests a possible role of OX40 in the process of migration into inflamed synovial joint by activated CD4+ T cells (worthy of future studies), but not by CD8+ cells, thus confirming the preferential expression of OX40 by CD4+ cells in rats [1], mice and humans after optimal stimulation in vitro [6, 7] and in vivo in patients with ongoing immune activation [7].

Moreover, these data add to those that have emerged from recent studies demonstrating on SF T cells from patients with RA (much more than in their peripheral blood) phenotypic features that can be obtained only after T-cell stimulation, such as the expression of CD69, CD70 and the down-modulation of CD27 [8, 9], 13. Thomas R, McIlraith M, Davis LS, Lipsky PE. Rheumatoid arthritis: evidence for ‘frustrated’ activation. J Rheumatol 1987;14:662–6.


Mseleni Joint Disease: Social Priorities

Mseleni Joint Disease (MJD) is a progressive, early-onset arthropathy found in the Maputaland Region of Kwazulu-Natal in South Africa, among the Zulu and Tonga people. The disease was first described by Wittman and Fellingham in the Lancet [1] when many young people were noticed to be suffering from hip problems. Since then, many avenues of research have been followed, but with no definite aetiology attributed to the disease. An expanding database at Mseleni Hospital, monitoring disease progression and treatment, has enabled important questions to be tackled. I visited the hospital for my medical elective. The database contains over 400 entries, obtained from patients who come to the weekly MJD clinic. The average age is 47 yr, with the mean duration of symptoms being 17 yr. Remembering that, in Africa, it takes quite a lot to make people come to the doctor—89% of new arrivals at the clinic had X-rays for hip problems. Since then, many avenues of research have been followed, but with no definite aetiology attributed to the disease. An expanding database at Mseleni Hospital, monitoring disease progression and treatment, has enabled important questions to be tackled. I visited the hospital for my medical elective. The database contains over 400 entries, obtained from patients who come to the weekly MJD clinic. The average age is 47 yr, with the mean duration of symptoms being 17 yr.}

Finally, considering that OX40 can enhance the proliferation and immunoglobulin secretion by activated B cells expressing OX40-ligand [11, 12], this molecule might contribute to the pathogenesis of rheumatoid synovitis, also having a role in the potent helper effect for B cells provided by CD4+ memory cells within the rheumatoid synovium [13].

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have been suggested, from genetics [5] to environmental factors [6], but so far there has been no research into an autoimmune or inflammatory cause, even though biopsy specimens (showing thick, fibrillated cartilage) [7] and molecular genetics (implicating COL2A genes) [8] have hinted at this. Could a rheumatoid-like process be involved? My study of 50 serum samples from MJD patients and 50 from skeletal healthy controls showed no autoantibodies (including rheumatoid factor) to be present at clinically significant levels, and no difference in the levels of inflammatory mediators: serum immunoglobulins, alpha-1-antichymotrypsin and C-reactive protein (unpublished observations). This does not favour an autoimmune aetiology after all.

In an attempt to lay a foundation for future research, the Mseleni team hope to set up a survey, where people will be selected at random from other hospital attendees and given a pelvic X-ray and objective functional assessment. A subpopulation of sufferers with early X-ray changes at presentation has also been identified, and these will be followed more closely in the future. These patients are suitable subjects for drug trials of potential disease-modifying agents, possibly methotrexate or 5-ASA compounds, although cost may well prohibit this.

Although the aetiology is still in doubt, the most pressing concern is the management of current sufferers. THR is fairly effective, but costly, and as such cannot be used to treat everyone. Arthrodesis has been considered, but the disease is usually bilateral, making this impractical. The majority of the resources and energy must be put into community rehabilitation programmes. The problems have been highlighted before—in particular, the low social standing of families with an MJD sufferer, and the effect it has on their children’s education [9]—but there is still a huge lack of social work, disability grants and pensions. Improving the standard of living is necessary for patients who cannot walk far. There is little non-manual employment locally, and water is far away (60% of supplies are more than one hour’s walk away). There have been great strides in this last direction, with wells being dug and pipes being laid over some of the region, but it is still far from ideal. Social workers in the area are focusing on families of MJD patients, but there is also vast need from the rest of the community. Orthopaedic remedies for MJD fall last on the list at present.

To end on a more enjoyable note, the work done by the Mseleni team is having an effect, with the MJD population trusting both the medically based symptomatic relief and the surgeon’s knife, knowing that at least someone is concerned about their future.

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Accepted 17 November 1997


Two Different Drug-Induced Pulmonary Complications in a Patient Suffering from Rheumatoid Arthritis

Sir—Pneumonitis is a rare, but most serious adverse effect of methotrexate (MTX) therapy in RA patients [1, 2]. Its pathogenesis is still not completely understood. Histologically, the most frequent lesion is an extensive acute granulomatous reaction with or without oedema [3]. Several decades ago, aminorex fumarate (Menocil®) caused an epidemic of primary pulmonary hypertension (PPH) in Central Europe [4]. For its development, aminorex was initiated in 1963. In April 1969, increasing shortness of breath led to hospitalization.
Physical examination of the patient (81 kg/174 cm; RR: 120/80) showed normal heart size on percussion, an accentuated second heart sound, clear lung auscultation, mild liver enlargement and extensive oedema of the lower limbs.

Except for hyperlipidaemia and mildly increased eosinophils (6%, normal <5%), laboratory findings were normal. X-rays showed slight heart enlargement with a prominent pulmonary artery, scintigraphy no evidence for pulmonary embolism, and spirometry hyperventilation and acidosis on exercise. ECG revealed abnormal right axis, P pulmonary and right ventricular hypertrophy. On catherization, a dilated pulmonary artery, widened main branches and pulmonary artery pressures of 80 mmHg were found.

PPH due to aminorex was diagnosed. A control in 1970 showed that pulmonary pressure had decreased to 65 mmHg, the ECG axis had returned to normal left, the spirometry had improved and eosinophils normalized (2%)

In 1984, seropositive RA developed. Oral low-dose MTX was introduced (7.5 mg week) in 1989. In September 1991 (total dose 810 mg of MTX), acute mild. Abnormal laboratory findings: ESR 45 mm/h; RF 114 U/ml (normal <40); CRP 27 mg/l (normal <6); borderline creatinine; LDH 340 U/l (normal <240); 7% eosinophils; pO2 54 mmHg. Pulmonary function test revealed decreased respiratory and diffusion capacity, lung X-rays reticulo-nodular infiltration and HR-CT interstitial infiltration, especially in the lower lobes. Echocardiography was normal.

Since seven of the nine Searles and McKendry [7] criteria were fulfilled, MTX pneumonitis was regarded as definite: acute dyspnoea, tachypnoea and non-productive cough, interstitial infiltrates, WBC <15 000/ml, negative cultures, restrictive pulmonary function with decreased diffusion capacity, pO2 <55 mg. MTX was discontinued and adequate treatment including glucocorticoids led to rapid improvement. Within a year, pulmonary function and X-rays improved, and eosinophils became normal.

MTX pneumonitis appears to occur independent of MTX doses [7]. Pre-existing lung diseases, particularly radiographic interstitial infiltrates [8], or impaired bioavailability of MTX, may increase the risk for MTX pneumonitis; however, no predisposing factors can be identified with certainty yet [1]. Although our patient refused bronchoscopy and lung biopsy, an infectious pathogenesis could be excluded by cultures and serological tests. The common hypothesis for MTX pneumonitis is a hypersensitivity reaction, entailed by activated macrophages leading to granulomatous reactions in the pulmonary parenchyma [1]. Similar to MTX pneumonitis, the pathogenesis of drug-induced PPH has not been completely elucidated yet. The hypothesis mostly accepted is a trigger event in genetically predisposed individuals [9]. Serotonin, but also cytokines (IL-1β, IL-6) seem to be involved in the disease process [10]. Activated macrophages are known to produce pro-inflammatory cytokines, indicating some similarities of PPH and RA.

The drug-induced pulmonary disorders may have occurred coincidentally in our patient. Several aspects, however, indicate a relationship. First, in our own cohort of several hundred MTX-treated patients, hitherto only two cases of pneumonitis have occurred, one with a history of drug-induced pulmonary affection. Second, in this patient, elevated eosinophils occurred only with the pulmonary disorders and decreased along with improvement after discontinuation of the causal medication. Thus, this patient’s history and the pathogenetic similarities of both disorders may indicate that drug-induced PPH may constitute a risk factor for MTX pneumonitis. We therefore recommend using MTX particularly carefully in patients with a history of drug-induced pulmonary problems. Moreover, since appetite suppressants may be used more frequently in the future, one should be aware of the potential threats in the context of MTX therapy of RA.

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9. Rubin LJ. Pathology and pathophysiology of primary pulmonary hypertension. Am J Cardiol 1995;75:51A–4A.

Trigeminal Sensory Neuropathy in Systemic Sclerosis

Sin—The occurrence of a trigeminal sensory neuropathy (TSN) in association with connective tissue disease (CTD) is rare, but has been generally accepted as a feature of these diseases [1]. Most cases of isolated
TSN have been reported in diffuse or limited systemic sclerosis (SSc), mixed connective tissue disease and in the undifferentiated connective diseases (UD-CTD).

We report a case where the diagnosis of TSN and UD-CTD was made concurrently with the development of a diffuse SSc 4 months later. The pathogenesis of this association is discussed and the anatomical location of the lesion causing TSN is described with MRI.

A 62-yr-old man was admitted to our hospital with right side facial numbness. The patient had been in excellent health until 2 months earlier, when he began to have gradual right paraesthesiae in the maxillary, mandibular and ophthalmic divisions of the trigeminal nerve, morning stiffness and finger swelling. Six weeks before admission, a CT scan of the brain was normal, and a physician began to treat him with carbamazepine with no clinical improvement. Physical examination revealed sclerodactyly and evidence of sensory loss in the right trigeminal area, with impairment of taste and diminished corneal reflex. The patient denied the presence of Raynaud’s phenomenon and oesophageal dysphagia. The heart and lungs were normal, and there was no lymphadenopathy or enlargement of the spleen or liver. Laboratory analyses on admission, including blood count, ESR, electrolytes, liver and muscle enzymes, were normal. Rheumatoid factor and serological syphilis tests were negative. Antinuclear antibodies were positive (1/640, in a nucleolar pattern), and anti-Scl-70 (antitopoisomerase-I antibodies) were highly positive. Extractable nuclear antigen antibodies (anti-RNP, anti-SSA, anti-SSB, anti-Sm), anticientromere and anti-DNA antibodies were negative. Nailfold capillaroscopy disclosed important dilatation and capillary destruction. Cerebrospinal fluid analysis and chest X-ray were normal. In the lung function tests, reductions in FVC (65%), FEV1 (51%) and diffusion capacity (DLCO) (53%) were found. Contrast-enhanced T1-weighted MRI brain scan showed enhancement and slight enlargement of the pre-ganglionic segment of the right fifth cranial nerve (Fig. 1). Abnormal R1 response was obtained unilaterally on the right side with blink reflex testing. Peripheral neuropathy was not found on nerve conduction studies. Treatment with steroids or NSAID was not administered and the patient was discharged with the same treatment provided previously (carbamazepine). Four months later, he presented with constitutional symptoms, fatigue and arthralgias. Clinical examination revealed widespread skin involvement, with loss of skin creases over the fingers, hands, thorax and abdomen. Pitting oedema was noted on the hands and ankles. The facial numbness had improved and a follow-up contrast-enhanced MRI brain scan showed a normal pre-ganglionic segment of the right fifth cranial nerve. The R1 response on the blink reflex was nearly normal. The patient was discharged to our SSc out-patient clinic on treatment with d-penicillamine.

The differential diagnosis of fifth cranial nerve dysfunction includes bone disease, tumours, infections, vascular abnormalities, and a variety of other disorders [2–4]. The connective tissue diseases most frequently associated with TSN are undifferentiated connective tissue disease (47%), mixed connective tissue disease (26%) and SSc (19%) [5].

TSN is the most common nerve disorder in scleroderma. Other cranial neuropathies have also been reported, including bulbar palsy and glossopharyngeal neuropathy [6]. It has been proposed that the neuropathy in scleroderma results from ischaemic lesions of the peripheral nerves through involvement of the vasa nervorum [7]. Immunological mechanisms may also have a role in the pathogenesis of polyneuropathy in scleroderma patients [8]. One might assume from the above that autoimmune vascular injury due to heightened immune response to basement membrane antigens would be behind the dysfunction of the vasa nervorum and peripheral nerves in patients with scleroderma [6]. Besides these immunological and vascular theories, we propose an alternative theory, taking into account our clinical and radiological findings. The trigeminal nerve is the largest of the cranial nerves and its pre-ganglionic segment, located between its emergence from the anterior aspect of the pons to its entrance through the porus trigeminus into Meckel’s cave, is commonly identified with MRI [9]. Förster

![Fig. 1.—Gadolinium-enhanced axial T1-weighted image shows enhancement and slight enlargement of the right pre-ganglionic segment of the fifth cranial nerve (arrow).](image-url)
et al. [10] reported a patient with TSN and MCTD where MRI suggested a lesion in the cisternal part of the nerve including the Gasserian ganglion.

We speculate that fifth nerve neuropathy in the early stages of SSc (oedematous stage) could be interpreted as an entrapment neuropathy because of the inflammatory reaction with oedema, produced by an increase in the permeability of adjacent vascular structures and increases in extracellular fluid. These changes are reflected on MRI by abnormal contrast uptake and slight enlargement of the pre-ganglionic segment, which resolves with the resolution of oedema.

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Association of Antiphospholipid Syndrome and Chronic Hepatitis C

Sir—The anticardiolipin antibody (ACA) antiphospholipid syndrome is closely associated with arterial or venous thrombosis, recurrent fetal loss and thrombocytopenia [1]. ACA have been described in various pathological conditions, including autoimmune diseases such as systemic lupus erythematosus, infectious diseases or cancer. A group of patients developing the antiphospholipid syndrome who are healthy and harbour no other underlying medical condition are therefore classified as having primary, rather than secondary, antiphospholipid syndrome. Hepatitis C virus (HCV) infection has been shown to induce extrahepatic autoimmune manifestations [2]. In addition, it has been suggested recently that ACA could frequently be found in patients with HCV infection [3]. We report a possible association between antiphospholipid syndrome and HCV infection.

In December 1992, a 40-yr-old man presented with thrombosis of the ilio-femoral vein. The subject’s past medical history included blood transfusion in 1985 and a 2-fold increase in alanine aminotransferase (ALT) serum level, known since 1990. He was treated with s.c. heparin during 3 months, followed by long-term oral anticoagulation with vitamin K antagonists. Despite this therapy, between 1992 and 1994, recurrent thrombotic events with multiple bilateral deep and superficial vein thromboses of the lower limbs occurred. Antiphospholipid syndrome was suspected because IgG anticardiolipin antibodies above 36 GPLU were detected using ELISA (BMD, Paris, France) associated with IgG lupus anticoagulant (ELISA), weakly positive antibodies to β2-GPI and false-positive Bordet Wasermann reaction. Neither serum mixed cryoglobulinaemia nor other autoantibodies were demonstrated (ANA, anti-double-stranded DNA, anti-ENA, anti-smooth muscle antibodies, anti-mitochondrial antibodies). Diagnosis of HCV infection was based on standard serological tests and virus RNA detection by polymerase chain reaction (Amplicor®, Roche Diagnostic Systems, France). HCV genotype was 1a (Inno-Lipa 1®, Innogenetics, Brussels, Belgium). Liver biopsy showed chronic active hepatitis with a Knodell’s activity index at 8.

In October 1994, the patient was treated s.c. with 3 MU of recombinant interferon (Interferon α 2a, Hoffmann-La Roche, Basel, Switzerland) three times a week for 24 weeks. At the end of interferon-α therapy, ALT levels were normal and virus RNA was undetectable. A decrease in ACA level to 28 GPLU, then 13 GPLU, associated with a disappearance of the anti-β2-GPI antibodies and lupus anticoagulant was observed during interferon-α therapy (Fig. 1). In addition, thrombotic disease was considerably improved. Under oral anticoagulation, we could not observe clinically any subsequent recurrence of deep vein thrombosis and this was confirmed by the Doppler ultrasonography controls. During the 2 months following discontinuation of interferon-α therapy, the virological response remained complete and no thrombotic event occurred. Unfortunately, a relapse of viral hepatitis with a rise in ALT level and extensive deep vein thrombosis occurred simultaneously 3 months after the end of interferon treatment despite effective oral anticoagulation. HCV RNA became detectable again and an increased ACA level to 40 GPLU associated with positivity of antibodies to β2-GPI was observed (Fig. 1).

In a recent study, it has been suggested that HCV infection may facilitate the development of antiphospholipid antibodies and probably thrombotic disorders [3]. In our observation, antiphospholipid
Ondansetron Prevents Refractory and Severe Methotrexate-induced Nausea in Rheumatoid Arthritis

Methotrexate (MTX) is one of the most commonly used disease-modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis (RA) [1–3]. Nausea is one of the most frequent side-effects, observed in up to 40% of the patients treated with this drug, leading to discontinuation of MTX in 6.8% of the cases [1–3]. Ondansetron is an anti-emetic drug widely used in chemotherapy for patients with malignancy [4]. Many studies have shown that ondansetron is usually more effective and with less side-effects than other anti-emetic drugs [4–7]. Our aim was to evaluate the effects of ondansetron in preventing refractory and severe nausea induced by MTX in RA.

Patients with RA diagnosed according to the ACR criteria who were receiving MTX on single therapy were studied [8]. All patients were also receiving leucovorin (folinic acid) as previously reported [9]. Ondansetron was prescribed if they fulfilled the following inclusion criteria: (a) good response to MTX (reduction in the number of tender and swollen joints syndrome was observed during the course of chronic hepatitis C infection in the absence of antiviral therapy. Interferon-α therapy of chronic hepatitis C and the patient) in the absence of other side-effects; was followed by a complete biochemical and virological response, along with dramatic improvement of the thrombotic disease. In addition, the relapse of viral hepatitis was immediately accompanied by a recurrence of thrombotic disease. These findings suggest that antiphospholipid thrombosis syndrome might be another HCV-associated autoimmune disease. In addition, both the concomitant response in levels of ACA and HCV RNA clearance under interferon treatment led to the remission of the thrombotic disease, as has been described with other immunological disorders related to HCV infection [4].

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related to ondansetron were written in a diary daily by the patients. Activity due to RA was examined at baseline and at each visit after ondansetron therapy. Full blood count, ESR, blood chemistry profile and urinalysis were performed monthly. A comparative study of the intensity and duration of nausea at baseline (considered as the symptoms observed a week before onset of ondansetron therapy) with observations at 1, 4, 8, 16 and 24 weeks was performed. A non-parametric analysis of the variance for related samples (Friedman’s test) was applied. Statistical significance was defined at $P \leq 0.05$. There was no financial support from or any relationship with the producer of 16 mg of oral ondansetron. Regarding this, a considerable cheaper alternative to MTX and ondansetron may be to swap the patient over to an alternative DMARD. In conclusion, in RA, ondansetron seems to be useful and safe in preventing refractory and severe nausea induced by MTX. A larger controlled and blinded study is needed to support these promising results.

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Three Infected Injections from the Same Organism

Sr—Rheumatologists perform injections daily in the normal routine of treatment. These injections carry a tiny risk of infection, quoted as 0.06% for arthrocentesis [1]. This risk can presumably be minimized by reasonable sterile precautions, but practice in this respect varies widely [2]. I wish to report three cases of infection from the same phage type *Staphylococcus* which was present in the operator’s nostrils.

Case 1 was a woman aged 34 yr with a prolapsed lumbar disc with sciatica. She was treated with three sacral epidural injections of 40–60 mg of triamcinolone acetonide in 20 ml of 0.25% lignocaine, with 2 months and then 3 weeks between injections. Three weeks after the third injection, she was admitted to hospital with fever and a considerable increase in pain in the back and left leg. ESR was 78 mm, WBC 15.4 × 10^9/l with 72% neutrophils. Liver function tests were abnormal. A small amount of thick pus was withdrawn by needle puncture of a tender swelling at the left low back. This yielded a heavy growth of *Staphylococcus aureus* sensitive to most antibiotics. Appropriate antibiotics were given and an MRI scan showed a paravertebral muscle abscess with the suspicion of infection within the lumbar epidural space.

At operation by Mr Robert Bradford, neurosurgeon, a large left paravertebral muscle abscess was drained, but fortunately the epidural space was free from infection. The patient made an uneventful recovery.

It seems likely that the second injection caused the infection, after which some deterioration occurred.

Case 2 was a 63-yr-old woman with an ulnar compression neuropathy at the elbow who was given an injection of 25 mg of hydrocortisone acetate to the ulnar groove. Within 4 days, she developed swelling and pain above the injected area, fever, and increased ulnar nerve dysfunction. A diffuse tender swelling proximal to the ulnar groove in the muscles above the elbow was explored with a needle, but no pus was found. ESR and WBC were normal. A week later, ESR was 84 and WBC 12.3 with 84% neutrophils. Flucloxacillin and fucidin were started, and a little blood clot aspirated from the swelling grew *S. aureus* sensitive to those antibiotics. The patient made an uneventful recovery.

Case 3 was a 55-yr-old man with supraspinatus tendinitis who was given an injection of 25 mg of hydrocortisone with 1 ml of 1% lignocaine to the subacromial bursa. A week later, he complained of increased pain in the shoulder, sweating and headache. ESR was 34 mm, WBC normal. A week later, there was still pain and ESR was 29 mm with WBC 12.4 × 10^9/l with 67% neutrophils. Nothing could be aspirated from the subacromial bursa, but the needle was sent for culture. Flucloxacillin and fucidin were started. Culture from the tip of the needle yielded *S. aureus* sensitive to those antibiotics. The injection in case 3 was just 9 days after the injection which had infected case 2.

After the third infection, nasal swabs were taken from the operator (MFG) and from case number 2. MFG yielded *S. aureus* sensitive to erythromycin, flucloxacillin and penicillin. The swab from case 2 was negative. Phage typing was performed on staphylococci grown from all three infections and from the nasal swab of MFG. These were all identical. MFG then undertook a week’s course of standard treatment for staphylococcal carriers. Further nasal swabs taken then and subsequently were negative.

These infections were all undertaken using the moderately rigorous, but not totally aseptic, technique which the author had used for many years. This involved careful hand washing, the use of sterile towels upon which to place prepared syringes, etc., and prior swabbing of the skin with Mediswabs. On microbiological advice, this technique has now been improved by the invariable use of disposable sterile gloves, and careful preliminary drying of the injection site. Medical accidents such as infections cannot be eliminated completely, and it is not known whether the incidence of infection is altered by the level of aseptic technique [2]. Skin disinfectants have proven efficacy and are recommended [3], although no difference on microbiological testing of the skin has been shown after using different forms of skin swab [4].

The presence of pathogenic *Staphylococcus* in the nose of an operator performing invasive techniques can have dangerous consequences. Perhaps regular checking of doctors performing such techniques should be performed, but this is not routine practice and it is doubtful whether the yield would make this worthwhile. The three patients reported here were not ill or immunocompromised, but were otherwise healthy people. The risk of introducing infection, and the necessity to consider this diagnosis in the event of untoward reactions to injections, must constantly be borne in mind.

I would like to thank Dr Yasmin Drabu for her...
help in searching out the specimens from the three infected patients, and confirming that they and my own nasal swabs were all of the same phage type, and also for her very helpful advice about sterile procedures.

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