Successful use of cyclosporin A for the treatment of acute interstitial pneumonitis associated with rheumatoid arthritis

Sir. The interstitial lung disease associated with rheumatoid arthritis (RA) is characterized by slow and insidious progression up to 10 yr [1]. However, it infrequently shows rapid progression, resulting in death within a short time after the onset of pulmonary symptoms [2]. This form of the disease is known as acute interstitial pneumonitis (AIP). Although oral corticosteroids have been used as the standard treatment for AIP, high-dose steroid therapy is frequently associated with serious side-effects without any improvement of the lung disease [3]. In this report, we describe a patient with AIP due to RA, who was successfully treated with the combination of cyclosporin A (CyA) and corticosteroids.

A 60-yr-old woman with a 15-yr history of seropositive RA developed low-grade fever and a dry cough in December 1998. She had been treated successfully with gold injections and bucillamine for 10 yr; these were discontinued in 1994 because the disease became inactive. Six months before admission, she developed a sustained flare of her arthritis, she underwent treatment with loxoprofen sodium (120 mg/day), indomethacin (50 mg/day, suppository) and prednisolone (0.1 mg/kg per day; 5 mg/day). She was admitted to the community hospital on 4 January 1999 because of worsening symptoms, including high fever, cough and exertional dyspnoea. The chest X-ray showed a fine reticular shadow in both lung fields that had developed during the last 2 weeks. The patient was a non-smoker and reported no history of exposure to hazardous chemicals or dust. Since pulse therapy with 1000 mg methylprednisolone i.v. produced no effect, the patient was referred to our hospital for further evaluation and treatment. On admission, the patient complained of general fatigue and dyspnoea. No finger-clubbing, peripheral cyanosis, heart murmur or lymphadenopathy were noted, but fine crackles were audible over both sides of the chest. Laboratory data showed a white blood cell count of 14.7×10^3/mm^3 (neutrophils 89%, lymphocytes 10%), haemoglobin 9.2 g/dl, platelet count 287×10^3/mm^3, aspartate aminotransferase 30 IU/l, lactate dehydrogenase (LDH) 848 IU/l (normal range; 236–455), creatinine kinase 13 U/l, C-reactive protein 3.9 mg/dl and erythrocyte sedimentation rate 87 mm/h. The rheumatoid factor level was 64 IU/ml by nephelometry (normal range 0–18), and antinuclear antibodies were not detectable. A tuberculin skin test was negative. Arterial blood gas analysis on breathing oxygen (12 l/min) showed a partial pressure of arterial oxygen (PaO_2) of 71.1 torr and PaCO_2 of 43.4 torr, with pH 7.42. The chest X-ray (Fig. 1, top left) demonstrated reticular shadows in both lung fields. High-resolution computed tomography (CT) of the chest (Fig. 1, lower left) showed bilateral and patchy high density areas and partial pleural thickening, but no obvious honeycombing. The interstitial ground-glass appearance suggested active inflammation of the lungs. Cultures for bacteria and mycoplasmas were negative. No cytomegalovirus antigenaemia was detected. A diagnosis of AIP was made on the basis of the acute clinical course, laboratory data, chest CT findings and the resistance to steroid pulse therapy. Her condition deteriorated, including worsening of the interstitial shadow on the chest X-ray, progression of hypoxaemia and hypercapnia, and a progressive rise in serum LDH up to 889 IU/l. Accordingly, treatment was begun with CyA at a dose of 5 mg/kg per day (250 mg/day) was begun on 7 January 1999, with an increasing dose of prednisolone up to 1.2 mg/kg per day (60 mg/day). This treatment resulted in a dramatic improvement, within 3 weeks, in her symptoms and clinical findings such as serum LDH and PaO_2. In April, the abnormal shadow on chest X-ray had disappeared (Fig. 1, top right), and only irregular thickening of the pleura without obvious honeycombing was still noted on the high-resolution chest CT (Fig. 1, lower right). Shortness of breath improved further and stabilized, and CyA was tapered to 2 mg/kg per day (100 mg/day) 3 months later, because the trough level of whole blood was maintained between 100 and 200 ng/ml. Prednisolone was also tapered gradually during the same period. Soluble interleukin (IL)-2 receptor, which is a marker of activated T cells [4], was reduced from 2080 to 589 U/ml (normal range 220–530 U/ml) after initiation of CyA therapy. These findings indicated a good response to immuno-suppressant therapy with CyA. The patient was discharged on April 19, 1999, and was followed up in the outpatient clinic of our hospital. She remains well without any symptoms. One year after the initiation of the combination therapy, the patient was still being treated with CyA (100 mg/day) and prednisolone (5 mg/day).

Although the mechanisms of action of CyA are incompletely understood, CyA is known to reduce IL-2 synthesis by activated T cells and to disrupt lymphokine-dependent T lymphocyte-macrophage interaction [5], and thus prevents fibroblast-mediated fibrosis in patients with pulmonary interstitial fibrosis [6]. This may be the explanation for its apparent efficacy in interstitial lung disease, in the pathogenesis of which activated alveolar macrophages are thought to be important [6]. In addition to the suppression of IL-2, it is reported that CyA also inhibits IL-2 receptors [7]. In our case, administration of CyA suppressed soluble IL-2 receptor levels, and this was closely related to the therapeutic effect and disease activity of AIP. To our knowledge, there are only two reports of successful treatment of RA-associated AIP with CyA [2, 3]. Since
Fig. 1. Chest X-ray and CT before (left) and after (right) the initiation of combined CyA+prednisolone therapy. (Top left) Chest X-ray showing diffuse reticular infiltrates in both lung fields. (Lower two panels, left) Chest CT demonstrating bilateral patchy areas of ground-glass appearance in the outer and inner zones. Note the lack of honeycombing. (Top right) Chest X-ray showing remarkable improvement (compare with left side). (Lower two panels, right) The ground-glass appearance disappeared on chest CT 3 months after initiating the combination treatment. Note the presence of slight irregular pleural thickening but no obvious honeycombing.

The level of soluble IL-2 receptor was not examined in the previously reported cases [2, 3], this is the first report providing objective biochemical data to demonstrate the effectiveness of CyA against RA-associated AIP. The lack of reports describing the use of CyA for the treatment of RA-associated AIP warrants caution in its use; nevertheless, in our opinion, the poor prognosis of this complication of RA justifies treatment with this agent.

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Lack of evidence for an association between hantavirus infections and Wegener’s granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome and giant cell arteritis

Sir. Systemic vasculitides are a heterogeneous group of disorders characterized by inflammation of vessel walls. Much progress has been made in understanding their pathophysiology and pathogenesis, but the cause remains unclear in the majority of the cases. Associations with distinct viral infections have been demonstrated [1]. Among agents that have been implicated are hantaviruses, the infectious causes of haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome [2]. HFRS occurs worldwide and may be clinically inapparent. Hantaviruses are known to infect endothelial cells in vitro and in vivo, inducing acute vascular inflammation [3]. Moreover, there is evidence that they can generate the formation of immune complexes [4]. However, it remains obscure whether hantavirus infections are involved in the development of chronic vascular inflammation. We therefore investigated the prevalence of hantavirus-specific antibodies in a large group of patients with well-defined forms of systemic vasculitides.

The sera studied were collected from patients attending the Departments of Rheumatology in Bad Bramstedt (Rheumaklinik) and Lübeck (University of Lübeck), Germany, between 1994 and 1998. These were 101 patients with Wegener’s granulomatosis (WG) and 30 patients with microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS) and giant cell arteritis (GCA), classified according to the definitions of the Chapel Hill Conference and the classification criteria of the American College of Rheumatology [5, 6]. Control sera were obtained from 69 patients with rheumatoid arthritis (RA) who fulfilled the American College of Rheumatology criteria [7], and from 238 healthy blood donors (Table 1). Patients and controls were resident in northern Germany. Antineutrophil cytoplasmic antibody titres >1:8 determined by indirect immunofluorescence were regarded as positive.

The enzyme-linked immunosorbent assay (ELISA) for the detection of hantavirus-specific IgG antibodies was performed as described previously [8]. Briefly, microtitre plates (Nalge Nunc International, Albertslund, Denmark) were coated overnight at 4°C with a basic buffer detergent extract of Puumala or Hantaan-infected Vero cells inactivated with 2×10⁶ rad from a ⁶⁰Co source. Standard methods were followed, and uninfected antigen controls were run for each serum. Subsequently, wells were incubated with human serum followed by a polyclonal antibody against human IgG conjugated to horseradish peroxidase (Dako, Hamburg, Germany), each for 1 h at 37°C. Substrate solution (Kirkegaard & Perry Laboratories, Gaithersburg, USA) was added for 30 min at 37°C and signals were measured by spectrophotometry [optical density at 410 nm (OD₄₁₀)]. To yield the adjusted OD (adOD) value, the reading of the negative control antigen was subtracted. The cut-off was defined as adOD 0.100. All sera reacting positively in a 1:100 dilution were tested again in a twofold serial dilution. Serum titres ≥1:400 were considered as seropositive if the added adOD₄₁₀ values of positively reacting serum dilutions exceeded 1.0.

A total of 191 sera obtained from patients with different forms of systemic vasculitides were tested,

| Blood donors | 238 | 46.6 | 18–74 | 32.0 | NT | NT | 0 |
| Rheumatoid arthritis | 69 | 72.5 | 21–90 | 57.0 | 0 | 2 | 0 |
| Wegener’s granulomatosis | 101 | 50.5 | 26–77 | 55.0 | 75 | 2 | 0 |
| Microscopic polyangiitis | 30 | 60.0 | 17–86 | 59.0 | 0 | 16 | 0 |
| Churg–Strauss syndrome | 30 | 53.3 | 22–70 | 43.0 | 2 | 0 | 0 |
| Giant cell arteritis | 30 | 90.0 | 41–80 | 66.5 | 0 | 0 | 0 |

NT, not tested. ANCA, antineutrophil cytoplasmic antibodies.
including 30 from patients with localized WG. None of them displayed IgG antibodies to Puumala or Hantaan viruses. This was also true for 69 sera from patients with RA and 238 sera from healthy blood donors (Table 1). Control measurements of sera from patients with clinically apparent Puumala or Hantaan infections confirmed the validity of the assay used.

To the best of our knowledge, this is the first comprehensive study investigating the prevalence of hantavirus-specific antibodies in patients with systemic vasculitides. In our well-defined population of 191 patients with WG, MPA, CSS and GCA, we found no serological evidence of an association between hantavirus infections and the development of systemic vasculitides. The lack of positive sera among patients and controls suggests a low prevalence of hantavirus infections in the northern German population in general. However, the specific rodent reservoirs (*Clethrionomys glareolus, Apodemus agrarius*) are present and clinical cases of acute hantavirus infections (Puumala and Dobrava) are seen at the Lübeck University Hospital.

Antibody titres may decrease after the infection has resolved. Thus, we might have missed previous hantavirus infections in some cases. To minimize this bias we investigated sera from patients with short-term as well as those with longstanding disease. The lack of positive cases in both groups suggests that a time-dependent decrease in antibody titres was not a major problem. Moreover, previous studies have shown that elevated antibodies to hantaviruses generally persist for many years [9].

Our findings contrast with the results of a recent small uncontrolled study conducted in Bavaria, Germany. Among 26 patients with WG or MPA, Hierl *et al.* [10] detected antibodies to hantavirus in 15%. This high prevalence may be explained by their use of an immuno-fluorescence assay (Progen, Heidelberg, Germany), while we performed an internationally recognized ELISA [8]. Moreover, Hierl *et al.* used a cut-off titre of 1:16, resulting in relatively low specificity. In fact, none of their patients had a hantavirus antibody titre above 1:32.

In summary, our data indicate that hantavirus infections are not associated with the development of WG, MPA, CSS or GCA. Serological or molecular approaches might identify other infective agents in rheumatological disorders in the future.

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The effects of dothiepin on subjects with rheumatoid arthritis and depression

Sir, We read with great interest the paper by Ash *et al.* [1], and would like to bring to readers’ attention our own similar study, presented to the British Society of Rheumatology in 1989 [2].

One hundred and eighty-four patients with rheumatoid arthritis (RA), stable on second-line therapy, were screened for anxiety and depression using the Hospital and Depression scale (HAD); 91% (45%) met the entry requirements (HAD > 7 on the subscales or > 11 on the combined score), of whom 58 were recruited to receive dothiepin 75 mg or matched placebo for 6 weeks. Exclusions were as in the Ash *et al.* study, with the addition of patients with severely impaired hand function, who were unable to perform physical measurements (grip strength and finger joint circumference) unaided. These measurements, together with a diary of patients’ assessments (visual analogue scale (VAS)) of duration of morning stiffness (EMS), mood, pain on waking, early evening and bedtime, and quality and duration of sleep (minutes), were done for all or part of the study. Assessments by investigators were done at baseline, 2 weeks (when the medication could be increased to 150 mg if the HAD score was still high).
and 6 weeks, and were: global assessment score, a five-
point scale of the clinical change in RA signs and
symptoms; duration of EMS; and overall assessment of
the study medication. The HAD scale was repeated at
2 and 6 weeks.

Our groups were well matched, with the exception of
the initial HAD scores: group means for total HAD and
the anxiety score were significantly higher ($P < 0.05$) in
the patients randomly selected to receive dothiepin; 11
patients withdrew (five on dothiepin, six on placebo).
The mean HAD scores fell in both groups; within-
treatment changes were highly significant ($P < 0.01$) but
between-group differences were not. Improvements at
2 weeks in mood, pain, sleep and grip strength occurred
in both groups, but were more rapid in the treatment
group. At 6 weeks, there was a significant improvement
in the evening grip strength; mean pain scores fell in
the dothiepin group but were consistent over time in the
placebo group, although this did not reach significance
owing to the higher entry scores in the dothiepin group.

Although the study of Ash et al. [1] was of slightly
longer duration than ours (11 weeks on therapy), this
was still not an accurate reflection of usual practice;
long-term, low-dose tricyclic medication has now
become an accepted part of chronic pain management.
Their numbers were small at entry and had a high
dropout rate (nearly half), reflecting the problems of
high-dose tricyclics. We do not feel that they have
acknowledged adequately the major placebo effect of
regular frequent contact with health professionals,
which, together with active patient participation (as in
our study), was partly responsible for the high placebo
response.

Ash et al. [1] maintained that few studies had
examined the effects of antidepressants on mood in
RA patients (they cited only four that were adequately
controlled), specifically examined patients with depres-
sion, and included measures of anxiety and/or depres-
sion. Our study qualified on all three counts. We feel
that the use of the HAD questionnaire as a screening
tool in rheumatology clinics provides a quick and
sensitive method of assessing undeclared psychological
problems, and that treatment with tricyclic antidepress-
ants or greater support improves both physical and
psychological symptoms.

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1. Ash G, Dickens F, Creed FH, Jayson MIW, Tomenson B. The
effects of dothiepin on subjects with rheumatoid arthritis and
treating anxiety and depression in rheumatoid arthritis [abstract].

Rheumatology 2000;39:1426–1427

Reply

We would like to thank Chuck and co-authors for
bringing the findings of their own study to our attention.
We agree that the methods and findings of the two
studies are broadly similar, other than that the mood
assessment in our study included an observer-rated
scale, the Hamilton Rating Scale for Depression (HRSD) in addition to a self-report scale (Hospital
Anxiety and Depression Scale), and that the fall in pain
scores observed in the study of Chuck et al. did not
reach statistical significance. With the limited details
of the trial presented in their letter it is not possible to
speculate why our findings should have differed in
this way.

It is of interest that both studies demonstrate improve-
ment in mood ratings with time in both active drug and
placebo groups, yet neither study was able to demon-
strate a significant difference between drug and placebo
groups, i.e. an antidepressant effect of dothiepin. We
feel that this primarily reflects the relatively low thresh-
old for severity of mood symptoms for entry into our
study, and we presume that the same would hold for the
study of Chuck et al. Severity of depressive symptoms
is a predictor of response to antidepressant medication
[1], and in our study the mean HRSD scores on entry
(15.3 for dothiepin, 15.7 for placebo) were relatively
low in comparison to those of psychiatric populations,
although they were above the threshold for
antidepressant effect.

We accept the comments of Chuck et al. that a drug
trial lasting 11 weeks is not an accurate reflection of
usual practice. However, this is a fairly typical dura-
tion of treatment for a placebo-controlled trial. It is
possible that a more prolonged trial might demonstrate
a significant effect of dothiepin on pain and depres-
sion since the placebo effects seen are likely to be
short-lived.

Long-term low-dose tricyclic medication is becoming
an accepted part of pain management. However, the
approach to treatment of depression with antidepress-
ants in subjects with rheumatoid arthritis remains
distinct from that for analgesic augmentation. Doses of
150–225 mg should be prescribed if the aim is to
effectively treat depression in normal adults. This dose
should be continued for at least 6 months after the mood
has completely returned to normal. Medication should
then be reduced and stopped over a period of 4–6 weeks
unless continued analgesic augmentation is required,
when it can be continued at doses of 25–50 mg daily. We
feel this is an important point, and clinicians should
have clear in their mind what they aim to achieve by
using antidepressants to avoid inadequate treatment of
pain or depression.

We dispute the fact that we have failed to recognize
adequately the importance of the placebo response in
our subjects, and would direct attention to the last
paragraph of our discussion, where we note ‘the subjects
included in this study would be likely to benefit from the detailed attention and sympathetic listening involved in repeated assessments ... .

We fully endorse the view of Chuck et al. that the HADS questionnaire is a useful screening tool in rheumatology clinics to indicate where treatment of depression will reduce distress and improve quality of life, and may improve coping with physical symptoms.

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Rheumatology 2000;39:1427–1428

Diagnosis and therapy monitoring of Whipple’s arthritis by polymerase chain reaction

Sir, Whipple’s disease is a multisystem bacterial infection usually characterized by malabsorption syndrome with diarrhoea and weight loss, low-grade fever and lymphadenopathy. Arthritis is often the first sign of Whipple’s disease and may begin years before typical intestinal manifestations occur. Examination of joint fluid and tissue might therefore provide an opportunity for an early diagnosis. Diagnosis of Whipple’s disease is usually established by the presence of periodic acid-Schiff (PAS)-positive, rod-shaped inclusions in macrophages of biopsies of the small bowel and other involved tissues and/or the identification of bacteria by electron microscopy. The non-cultivable Tropheryma whippelii has been identified by the polymerase chain reaction (PCR) based on the 16S rRNA gene sequence [1]. Recently, positive PCR tests either of synovial fluid (two patients) or membrane (one patient) were demonstrated in Whipple’s disease patients with arthritis [2, 3].

Only in one patient with chronic and erosive arthritis PAS-positive macrophages were demonstrated in small bowel biopsies. There was no evidence of T. whippelii by PAS staining or by PCR testing in the upper gastrointestinal tract in the other two cases. No post-treatment examinations of joint specimens have been reported. Similarly, patients with Whipple’s endocarditis negative in histopathology and by PCR in duodenal biopsies have been described recently [4].

We describe two middle-aged Caucasian males presenting with arthritis who were admitted for diagnostic needle arthroscopy. Synovial fluid and tissue as well as small bowel biopsies were T. whippelii-positive by PCR and became negative after 1 yr of treatment with trimethoprim-sulphamethoxazole. Specific detection of T. whippelii DNA was performed using primer combinations TW-1/TW-3, resulting in a 141-base pair (bp) fragment, or TW-1/TW-2 followed by seminested reamplification with TW-4/TW-2, resulting in an amplicon of 229 bp [5]. Both patients became asymptomatic and no relapse occurred over a period of 22 and 18 months respectively. Neither by histology nor by electron microscopy were Whipple bacilli detected in joint and small bowel specimens. For PCR results see Table 1.

Patient 1 presented with an 8-yr history of arthralgia and intermittent arthritis of the small and large joints, which responded well to anti-inflammatory drugs. He had no gastrointestinal or neurological manifestations. Radiography revealed joint space narrowing of the knees but no erosions. Laboratory findings included an erythrocyte sedimentation rate (ESR) of 16 mm/h, C-reactive protein (CRP) of 37 mg/l, a normal blood cell count and a negative test for rheumatoid factor. Synovial fluid from the left knee showed 2100 leucocytes/mm³, mainly mononuclear cells; there were no crystals. Histologically, mononuclear infiltration was seen in the synovial biopsy, and stains for microorganisms, including PAS-positive organisms, were negative. All conventional cultures for bacteria remained negative. Because of T. whippelii-positive PCR results of joint specimens, a small bowel biopsy was taken by upper gastrointestinal endoscopy. No PAS-positive macrophages were demonstrated by light and electron microscopy but PCR was positive. Ten weeks after the onset of antibiotic therapy, the patient was asymptomatic and remained without relapse for at least 22 months after 1 yr of treatment with trimethoprim-sulphamethoxazole. In the follow-up examination after 1 yr of treatment, no synovitis was found and PCRs of synovial fluid, synovial tissue and small intestine biopsy were negative.

Patient 2 reported episodes of abdominal pain and diarrhoea without weight loss over the previous 6 yr. During the 8 months before admission for needle arthroscopy, he suffered from arthralgia and intermittent arthritis of the shoulder, wrist, knee and ankle joints. There was normal radiography of the joints, and

<table>
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<tr>
<th>Source of specimen</th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
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<tr>
<td>Joint</td>
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<tr>
<td>Synovial fluid</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Synovial tissue</td>
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<tr>
<td>Gastrointestinal tract</td>
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<td>Stomach</td>
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<td>Duodenum</td>
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Post-treatment, after 12 months of trimethoprim-sulphamethoxazole therapy; n.a., not available.
laboratory findings were normal, including ESR, CRP, blood cell count, stool cultures for bacteria and fungi, and special tests for parasitic infection. Synovial fluid contained 12,200 leukocytes/mm³ with 75% polymorphonuclear cells, and the synovial tissue showed monocytic inflammation without PAS-positivity. Bacterial DNA was found by amplification in synovial fluid, biopsy material and duodenal biopsies. Its sequence was identical to that of *T. whippelii*. This result was confirmed by *T. whippelii*-specific PCR. The histology of the mucosa revealed non-specific inflammation without demonstration of *T. whippelii* by PAS staining or electron microscopy. Antimicrobial therapy with trimethoprim-sulfamethoxazole was given for 1 yr, with improvement of the gastrointestinal symptoms. PCR results of joint and intestinal samples were all negative after this time.

The availability of the DNA sequence of the 16S rRNA gene from *T. whippelii* has facilitated the development of relatively specific and sensitive diagnostic tests for Whipple’s disease [1, 6]. This report underlines the usefulness of PCR in Whipple’s patients presenting with arthritis. In the absence of convincing histological findings, PCR of joint samples or intestinal biopsies may be an important diagnostic tool. The presence of the pathogen in small intestine biopsies without histological confirmation was demonstrated by PCR in patients with a strongly considered diagnosis of Whipple’s disease [4–7]. All except one presented with intestinal symptoms. Positive PCR results of duodenal samples and gastric juice, however, were found in about 5–12% of patients without clinical signs of Whipple’s disease who were referred for elective gastroscopy [7]. The relationship of *T. whippelii* genetic material detected in the gastrointestinal tract to the pathogenesis and manifestation of disease remains to be investigated.

The arthritic presentation of Whipple’s disease can be associated with the presence of *T. whippelii* DNA in synovial tissue and fluid. In our patients, no erosions were demonstrated by radiography despite an arthritic history over several years. The question whether the identification of Whipple’s bacillus by histology or electron microscopy in synovial tissue relates to erosive changes remains open. Whether PCR of synovial fluid and tissue reveals equivalent results is still to be elucidated. In addition, PCR may be useful for monitoring the response to treatment. Post-treatment small bowel biopsies of five patients with no clinical gastrointestinal relapse were negative, whereas in the remaining seven of 12 patients with persistently positive PCR results, relapses or no response to treatment occurred [6]. Our results suggest that negative post-treatment PCR of synovial specimens may indicate cured disease. PCR may be the only positive diagnostic test in patients with Whipple’s disease and it may be helpful in the follow-up.

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**Rheumatology 2000;39:1428–1429**

**Osteomalacia secondary to renal tubular acidosis masquerading as primary biliary cirrhosis**

SIR, The biochemical abnormalities of osteomalacia can easily be overlooked in patients with primary biliary cirrhosis (PBC). This may develop as a consequence of renal tubular acidosis (RTA), which can be associated with PBC. A 47-yr-old lady with a history of nephrotic syndrome resulting from a minimal-change nephropathy, was referred for a liver biopsy because of elevated serum alkaline phosphatase. She was positive for the anti-mitochondrial antibody (AMA), which had first been identified when she had presented with nephrotic syndrome 4 yr earlier. This had been treated successfully with prednisolone and the serum creatinine had stabilized around 150 µmol/l on a maintenance dose of prednisolone 5 mg on alternate days. Although there were no specific histological features of PBC on the liver biopsy, there was evidence of mild chronic hepatitis, and she was given a trial of antioxidants [Biaontoxy and BioQuinone Q10; both from PharmaNord, Vojens, Denmark] as treatment for PBC.

Over the next 2 yr she developed rib pain and proximal muscle pain, which progressed to the point where her mobility was severely restricted. On referral to the rheumatology department she was found to have a waddling gait with proximal muscle weakness and rib tenderness. The serum bicarbonate was low at 16 mmol/l (normal range 22–29 mmol/l) and the
urine pH 6.0. The serum phosphate was 0.6 mmol/l (normal range 0.8–1.4 mmol/l) and the serum alkaline phosphatase 270 IU/l (normal range 30–120 IU/l). Glycosuria (+ + + +) was found on urinalysis with a normal blood glucose. There were Looser’s zones on radiographs of the femoral neck bilaterally, and a bone scan showed marked uptake at these areas and also numerous hot spots in the ribs, consistent with rib fractures. The serum vitamin D, 25-hydroxyvitamin D, parathyroid hormone and urinary calcium excretion were all within the normal range. The AMA was positive at a titre of 1:40 but the anti-M2 antibody was negative on ELISA. A tetracycline-labelled bone biopsy confirmed severe osteomalacia. The trabecular bone volume was normal but the osteoid was dramatically increased (Fig. 1), and absence of tetracycline labelling indicated failure to mineralize. She was treated with bicarbonate, potassium and phosphate supplements (sodium bicarbonate 9 g daily, Sandoz phosphate 3 tablets daily) together with calcitriol 250 ng daily. Her symptoms resolved over a 9-month period, with an associated reduction in serum alkaline phosphatase concentration and correction of the hypophosphataemia.

Acquired forms of both distal and proximal RTA are associated with PBC. Tubular damage may result from an autoimmune process and tubulointerstitial nephritis may be identified on renal biopsy in these patients [1]. Antibodies to renal tubular cells have also been reported [2] although their contribution to pathogenicity is uncertain. An antibody to a 52-kDa mitochondrial protein extracted from porcine kidney has been described in a patient with tubulointerstitial nephritis and RTA [3]. Although AMA-positive, this patient, like ours, was negative for the M2 antibody reactive against pyruvate dehydrogenase complex, which is a highly specific marker for PBC [4].

Although an elevated alkaline phosphatase in a patient who is AMA-positive will usually be due to PBC, osteomalacia should be considered, especially when the M2 antibody is negative or the liver biopsy is non-specific.

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Erectile dysfunction in Behçet’s disease without neurological involvement: two case reports
Sir, Behçet’s disease (BD) is a unique systemic vasculitis of unknown aetiology, which may affect both veins and arteries of different sizes and localization [1]. Erectile dysfunction, which may be described as the lack of penile erection for successful vaginal penetration, may be due to vascular, neurological, (rarely) endocrinological or psychological factors or various drugs. Recently, erectile dysfunction in BD patients with neurological involvement was reported to have a high prevalence [2]. However, there is no knowledge about erectile dysfunction in BD without neurological involvement. We present two cases of Behçet’s disease with erectile dysfunction but without neurological findings. These two cases are remarkable for having venous leak as the aetiology of erectile dysfunction, one patient being treated successfully by deep dorsal vein ligation.

Case 1 was a 35-yr-old man with a 17-yr history of BD. The main clinical features were recurrent oral and genital ulcersations, erythema nodosum, deep vein thrombosis, subcutaneous thrombophlebitis and intermittent oligoarthritis. There was no ocular or neurological involvement. The pathegy test was positive. He had been receiving colchicine treatment irregularly for the last 12 yr. He described loss of penile erection for the past year. Libido was normal. He was a non-smoker.

Case 2 was a 55-yr-old man with a 23-yr history of BD. The main clinical features were recurrent oral and genital ulcerations, erythema nodosum, deep vein thrombosis and intermittent oligoarthritis. There was no
ocular or neurological involvement. The pathergy test was positive. He had been receiving colchicine treatment regularly (1 mg/day) for the last 4 yr. He described loss of penile erection for the last 2 yr. Libido was normal. He was a non-smoker.

These two patients, both being followed by Ege University Rheumatology Department, were investigated because of their complaints about erectile dysfunction during routine tests. The patients did not have a history of any chronic infection, diabetes mellitus or any other co-existing disease. Both of the patients were normotensive with normal cardiac and pulmonary examinations. There was no organomegaly or lymphadenopathy. Urological physical examinations were normal, except for scrotal scars. The psychiatric and neurological consultations were also normal. Biochemical examinations, including liver and kidney function tests, serum glucose levels, full blood count, urine analysis, serum protein levels and lipid profile, were within normal limits in both patients. Endocrinological tests, including free and total testosterone, oestadiol, gonadotrophins, prolactin, adrenocorticotrophic hormone and cortisol, were also normal. Electromyography was performed in both patients, but polyneuropathy was not detected.

As the next step, penile electrophysiological tests, penile colour Doppler ultrasound and cavernosography were performed. Electrophysiological tests included analysis of the bulbocavernous reflex. Colour Doppler ultrasonography was performed after intracavernosal injection of 60 mg papaverine as a vasoactive agent. In accordance with the literature, arteriogenic impotence is diagnosed when maximum systolic velocities measured in both of the cavernosal arteries are less than 35 cm/s [3]. End-diastolic velocities in cavernosal arteries greater than 7 cm/s with normal maximum systolic velocities are accepted as venous leak [4]. Patients with Doppler findings suggestive of venous leak undergo confirmative cavernosography. During cavernosography, 40 mg papaverine is injected intracavernously. Penile tumescence and rigidity are observed. A 21-gauge intravenous cannula is then inserted and 50% diluted contrast medium with 76% iodeine is injected into the cavernous body. Serial fluoroscopic images are then taken. These last two tests (penile colour Doppler ultrasonography and cavernosography) revealed venous leak in both patients (Table 1).

For treatment of erectile dysfunction, patient 1 underwent deep dorsal vein ligation. During the operation, a biopsy of the cavernous body was also performed; it revealed hypocellular, collagen-rich tissue but no signs of vasculitis. Complete recovery of penile erection was attained in the post-operative period. Patient 2 refused the penile operation.

Since BD is a chronic systemic vasculitis with many different clinical findings, erectile dysfunction may be expected to occur during its course. Besides secondary psychiatric problems, various drugs used in BD may contribute to erectile dysfunction. Neurological involvement (neuro-Behçet disease) is known to be able to cause erectile dysfunction. However, erectile dysfunction in BD, and its prevalence, have not been studied extensively. In the literature we could find only a single study, by Erdor et al. [2], investigating the prevalence of erectile dysfunction in BD with neurological involvement. They found erectile dysfunction in 14 out of 24 (63%) neuro-Behçet patients. With respect to the aetiology of erectile dysfunction, they reported a mixed type of vasculogenic impotence in seven patients, arterial insufficiency in two patients, veno-occlusive dysfunction in two patients and neurogenic impotence in one patient.

The cause of erectile dysfunction in our patients was severe venous leak, detected by penile Doppler ultrasound and cavernosography. Since venous thrombosis is a well-known clinical finding in BD, penile veins may also be affected. The occurrence of venous leak may be related to recanalized microthrombosis. During the recanalization process, the sphincter structure of the veins may be disturbed, causing venous leak.

Although colour Doppler ultrasonography is reported to have high sensitivity in diagnosing arteriogenic impotence, its performance in the diagnosis of venous leak is still debatable [3, 4]. For this reason, we prefer confirmative cavernosography in addition to Doppler results indicating venous leak.

The histological findings of the cavernous body biopsy taken during the operation on patient 1 merit further discussion. The biopsy revealed hypocellular, collagen-rich tissue with no signs of vasculitis. As colchicine has an antifibrinectic effect, [5] fibrosis of the cavernous body may be regarded as interesting. On the other hand, since BD is a chronic vasculitis, one might have expected to find vasculitic signs in this biopsy.

While evaluating the aetiopathogenic factors of erectile dysfunction in BD, one should keep in mind the possible effects of the drugs used in BD. Colchicine, which was used in our patients, is the most widely used drug in BD, and myoneuropathic effect is well known [6]. On the other hand, neither of our patients had used other drugs, such as cyclophosphamide, sulfasalazine, indomethacin and naproxen, which are well known to cause erectile dysfunction [7].

We conclude that erectile dysfunction may be expected even in the absence of neurological involvement.
Venous leak, as in our patients, should be kept in mind as a treatable cause of erectile dysfunction in BD.

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Cyclosporin for sulphasalazine-induced aplastic anaemia in a patient with early rheumatoid arthritis

Sir, Bone marrow aplasia has been described very rarely as a complication of sulphasalazine therapy [1–5]. We report a case in which cyclosporin was used successfully to treat sulphasalazine-induced aplastic anaemia.

A 68-yr-old woman with recent-onset rheumatoid arthritis was admitted with pancytopenia. Four months before admission, treatment had been initiated with sulphasalazine, which she had never received before. At that time the erythrocyte sedimentation rate (ESR) was 75 mm/h and the C-reactive protein (CRP) concentration 32.2 mg/l. The haemoglobin concentration was 7.4 mmol/l, the leucocyte count 9.3 × 10⁹/l and the thrombocyte count 341 × 10⁹/l. The joint symptoms ameliorated after 8 weeks of sulphasalazine therapy. The patient had an unremarkable history, except for mild hypercholesterolaemia, for which she had used pravastatin for more than 1 yr. Other medications were Naprosyn (naproxen) and omeprazole, initiated several months before sulphasalazine was started. There were no complaints suggestive of haemorrhagic diathesis or infection.

After admission, vital signs were normal, body weight was 65 kg, and on physical examination there were no abnormalities. Laboratory testing revealed severe pancytopenia, with a platelet count of 11 × 10⁹/l (normal range 150–10⁹/l to 350 × 10⁹/l), a haemoglobin concentration of 5.4 mmol/l and a leucocyte count of 1.4 × 10⁹/l, with 3% neutrophils, 4% band forms and 88% lymphocytes.

The ESR was 110 mm/h and the CRP concentration 56 mg/l. The serum creatinine concentration was 58 µmol/l, lactate dehydrogenase 128 U/l, iron 26 µmol/l, bilirubin 14 µmol/l, alkaline phosphatase 89 U/l, aspartate aminotransferase 9 U/l and alanine aminotransferase 12 U/l. The vitamin B12 concentration was 146 pmol/l (normal range 145–610 pmol/l) and folic acid 1.7 nmol/l (normal range 6–10 nmol/l). The direct Coombs test was positive and the haptoglobin concentration was 2.05 g/l (normal range 0.40–2.00 g/l). There were no autoantibodies against thrombocytes and the thrombopoietin concentration was raised (266 U/ml, normal range 4–32 U/ml).

Bone marrow examination showed severe aplasia with severe depression of megakaryocytes, myeloid cells and erythroid precursors. Repeated blood, urine and stool cultures showed no growth of pathogens. Serological testing revealed no recent infections with hepatitis A, B or C, parvovirus B19 or Epstein–Barr virus. Chest X-ray, abdominal X-ray and ultrasonic examination revealed no significant abnormalities.

As the results of the physical examination and laboratory tests made infection unlikely, sulphasalazine was considered to be the causal agent of this severe aplastic anaemia. This possibility was strengthened by the gradual decrease in the cell counts in the months before hospital admission. A relationship with pravastatin, omeprazol or Naprosyn treatment was not likely as these had been used for long periods before sulphasalazine. Moreover, aplastic anaemia associated with pravastatin, omeprazol or Naprosyn has not been described before. Although the direct Coombs test was positive, the antibodies detected were non-specific and did not lead to haemolysis, as the haptoglobin, bilirubin and lactate dehydrogenase concentrations were normal and there were no fragmentocytes. We have no clear explanation for the raised CRP concentration and ESR, although the latter could be explained at least partly by the anaemia.

Sulphasalazine was stopped and the patient was treated with repeated erythrocyte and thrombocyte transfusions, and folinic acid and granulocyte colony-stimulating factor were given. There was a gradual recovery of the leucocyte count. However, the haemoglobin concentration and particularly the thrombocyte count remained low (Fig. 1) despite increased numbers of cells of all three lines at the repeated bone marrow examination 5 weeks after admission. Laboratory tests showed no haemolysis. The need for transfusions
Fig. 1. Haemoglobin concentration and thrombocyte count after hospital admission.

Persisted, and high doses of i.v. corticosteroids did not exert any effect on the thrombocyte count or the haemoglobin concentration. Thus, at day 76 cyclosporin treatment was initiated at a dose of 200 mg/day. After 1 month of treatment the thrombocyte count had increased and 4 months after the initiation of cyclosporin treatment it was around 50 x 10^9/l. Cyclosporin had to be stopped at this time because of renal toxicity. Thereafter, the thrombocyte count increased slightly and the creatinine value normalized. The haemoglobin concentration showed a similar pattern (Fig. 1). No bleeding complications were observed during the entire period. At the last laboratory check (October 1999), the haemoglobin concentration was 7.0 mmol/l, the thrombocyte count 76 x 10^9/l and the leucocyte count 8.0 x 10^9/l, with normal differentiation. Repeated bone marrow examination (June 1999) showed almost complete normalization of the bone marrow.

Cyclosporin treatment resulted in sustained (partial) recovery of the thrombocyte count and haemoglobin concentration. As there was a clear time-dependent relationship between the administration of cyclosporin and the recovery of thrombocyte count and haemoglobin concentration, it is unlikely, that this (partial) remission occurred spontaneously [6]. Hence, we suggest cyclosporin as a therapeutic option in (persistent) sulphasalazine-induced aplastic anaemia.

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Churg–Strauss syndrome presenting with visual loss

Sir. Churg–Strauss syndrome (CSS) is a rare form of small vessel vasculitis characterized by asthma, hyper eosinophilia and vasculitis affecting a variety of organs. We report a case of CSS presenting with visual loss due to posterior ischaemic optic neuropathy (PION), a previously unreported neurological complication of this form of vasculitis. A 60-yr-old male with a history of asthma and recurrent sinusitis presented to his general practitioner with 5 days of increasing shortness of breath, malaise and myalgia. An exacerbation of asthma secondary to a viral infection was felt to be the cause of his presentation and a short course of oral corticosteroids was prescribed that resulted in a marked improvement of his symptoms. Shortly after stopping corticosteroids his symptoms recurred; they were now associated with diplopia, jaw claudication, 6 kg weight loss and transient paraesthesias involving the left hand and foot. The patient was admitted to hospital for further investigation. On admission, the significant findings were diplopia with vertical separation of images, mild proximal muscle weakness, sensory peripheral neuropathy and widespread expiratory wheeze in the chest. Shortly after admission the patient developed acute painless loss of vision in his right eye. He was now found to have a right afferent pupillary defect, with a large central scotoma and visual acuity that was reduced to counting fingers. Fundoscopic examination revealed a normal disc with a swollen macula, findings consistent with the diagnosis of PION. Laboratory investigations showed a normal haemoglobin concentration and platelet count, a white cell count of $17 \times 10^9$/l with eosinophilia of $10.5 \times 10^9$/l (57%), normal renal function, creatine kinase of 6054 U/l (RR 0–200), erythrocyte sedimentation rate 38 mm/h (RR 0–20) and a C-reactive protein of 127 mg/l (RR 0–5). Antinuclear antibodies were negative and antineutrophil cytoplasmic antibodies were positive, with a perinuclear pattern of staining on indirect immunofluorescence. Sinus radiography showed opacification of both the maxillary and the ethmoid sinuses. A temporal artery biopsy showed no evidence of large vessel vasculitis involving the temporal artery itself, but did demonstrate a prominent perivascular eosinophilic infiltrate and vascular inflammation involving smaller cutaneous vessels Fig. 1. A muscle biopsy revealed a mixed lymphocytic and monocytic interstitial inflammatory infiltrate consistent with a myositis process. A diagnosis of CSS was made and i.v. methylprednisolone 1 g daily was commenced. There was a rapid improvement in the patient’s visual loss and resolution of his constitutional symptoms. The patient was discharged on oral corticosteroids and azathioprine, with visual acuity of 6/6–2 uncorrected in the affected eye.

In 1951 the pathologists Churg and Strauss reviewed the records of 13 patients with ‘periarteritis nodosa’ who presented with a clinical syndrome characterized by asthma, hypereosinophilia and systemic vasculitis [1]. The three histological features common to these cases that were not present in periarteritis nodosa patients without asthma were extravascular granulomas, tissue eosinophilia and necrotizing vasculitis. Churg and Strauss coined the term ‘allergic granulomatosis and angiitis’ to describe these 13 cases, which was later changed to CSS in recognition of their work in the classification of systemic vasculitis. Recognition that not all patients with CSS had the three pathological features originally described by Churg and Strauss led Lanham [2] to advocate a clinical approach to the diagnosis. Lanham et al. [2] proposed that the diagnosis of CSS could be made in patients with asthma, hypereosinophilia and clinical evidence of vasculitis involving two or more extrapulmonary organs. Another classification system states that the diagnosis of CSS can be made if at least four of the following six criteria are present: asthma, eosinophilia >10% of total white blood count, mono- or polyneuropathy, pulmonary infiltrates, sinus involvement and extravascular eosinophils in biopsy [3]. The unifying feature of patients presenting with CSS is asthma. Although wheeze is the most common reason for presentation, the vasculitic process is often outside the lungs, most commonly involving the peripheral nervous system, heart and gastrointestinal tract. Vasculitis involving the peripheral nervous system is the most characteristic feature of CSS, and mononeuritis

Fig. 1. Inflammatory infiltrate composed of mainly eosinophils around two small vessels.
multiplex occurs in 75% of patients. Other neurological manifestations of CSS described previously in association with CSS include peripheral neuropathy, cranial nerve palsies, stroke, dementia and anterior ischaemic optic neuropathy (ION) [4, 5]. The association of CSS and PION has not been described previously. Involvement of the eye is uncommon in CSS, but can include conjunctivitis, scleritis, uveitis, corneal ulceration and exophthalmos. Most reports of arteritic ION concern patients with temporal arteritis and are associated with permanent visual loss. Similar visual outcomes are seen in the CSS literature, with only one report of reversible visual loss due to PION. In a recently published retrospective study, however, Liu et al. [6] reported that over 30% of patients with visual loss secondary to arteritic ION experienced improvement of vision if treated with high-dose systemic corticosteroids early in the course. Our case report highlights two important aspects of vasculitis management: first, PION can be associated with CSS; secondly, the prompt institution of high-dose corticosteroids in patients with PION is important.

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Links between joint damage and disability
Sir. The review by Scott et al. [1] is very important and useful as it clearly shows, as could be expected, that radiographically detectable joint damage is related to disability. This relation is somewhat obscured in the early phase of the disease because disability is caused by the inflammation of the joints during this period while the consequence of inflammation—destruction—takes time to appear. Later, after 5–6 yr, the relation between damage and disability has become significant. This statement shows the importance of X-ray progression as an outcome parameter of treatment with disease-modifying anti-rheumatic drugs (DMARDs): if progression can be prevented in the early phase, later disability may be avoided.

However, the average progression rates given in the review can be misleading. Apart from the considerable variation in the pattern of progression between individual patients mentioned in the review, the outcome after a longer period may also show huge differences. In an ongoing prospective, longitudinal, one-centre cohort study, 128 patients with active early erosive RA [2, 3] were originally included. They had participated in a clinical trial and were treated with conventional DMARDs (parenteral gold or methotrexate). One hundred and fifteen of these patients were followed over 7 yr; eight had died and five were lost to follow-up. At baseline, the mean radiographic score was 1.6% of the possible maximum score (range 0–10%), after 7 yr it was 13% (range 1–50%), representing an average increase of 1.6%/yr. This is in line with the published data cited in the review, although it has to be taken into account that the patients in this trial were erosive at baseline and therefore had a poor prognosis. The course of the disease was very different between individual patients: only 15/109 patients (14%) reached a score of >20% of the maximum possible score (mean 31%), which translates into an increase of 4.2%/yr. Forty-five of 109 patients (42%) ended with a score between 5 and 20% of the maximum score (mean 9.5%). Their progression per year was 1.1%. Forty-nine of 109 patients (44%) reached a score below 5% of the maximum score after 7 yr (mean 2.1%); their mean progression rate per year was 0.07%, i.e. they had nearly no progression.

Therefore, it is important to know that only a minority of patients treated with conventional DMARDs have a really severe progressive disease, while a large proportion of patients may show a very benign disease course. This fact is obscured by reporting mean progression rates.

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Safety and efficacy of an intravenous loading dose of azathioprine for treatment of non-TPMT-deficient patients with rheumatic diseases

Sir. Azathioprine has been used as a disease-modifying drug in rheumatology for several years. A disadvantage of its application is the delayed onset of the therapeutic response. Intravenous azathioprine has been found to be effective as induction therapy for Crohn’s disease. In a pilot study [1], twelve patients with Crohn’s disease were treated with an i.v. loading dose. Healing of fistulae and improvement of inflammatory disease was seen after 4 weeks of treatment in the majority of patients.

On the basis of this experience, we designed a study with the primary aim of evaluating the safety of an i.v. loading dose of azathioprine followed by maintenance oral azathioprine in patients with different inflammatory rheumatic diseases. This was an open-label, single-centre study involving 11 adult patients (eight women, three men) with different rheumatic diseases [three with myositis, three with systemic sclerosis, three with systemic lupus erythematosus (SLE) and two with rheumatoid arthritis (RA)]. All patients suffered from active disease requiring immunosuppressive treatment. The study protocol was approved by the local ethics committee. All patients gave written informed consent. Before the initiation of treatment, the activity of thiopurinemethyltransferase (TPMT), an inactivating enzyme in the metabolism of azathioprine, was determined. TPMT activities of all patients included in the trial were in a range (9.2–20.7 nmol/ml red blood cells·hour) considered to be safe for azathioprine treatment [2].

As suggested by Sandborn et al. [1] for the therapy of Crohn’s disease, we treated our patients with a loading dose of 1800 mg azathioprine as a continuous infusion over 36 h (50 mg/h). Given the incomplete oral bioavailability of azathioprine (41–50%) [1], 1800 mg of i.v. azathioprine would correspond to an oral dose of 3600–4390 mg of the drug. The dose and the duration of the infusion were as defined by Sandborn et al. following phase I and II studies using an investigational 6-mercaptopurine preparation in patients with solid tumours, assuming a body surface area of 1.73 m² for the average adult [1,3]. Patients were hospitalized for 36 h of i.v. treatment and a treatment-free interval of 36 h for additional safety. Subsequently, oral azathioprine was administered in a dose of 1–1.5 mg/kg body weight per day. After 4 weeks of azathioprine treatment, the daily dose was increased to 2–2.5 mg/kg body weight if treatment was well tolerated and no adverse events occurred. On day 0 and 24, 36, 48 and 72 h after the initiation of treatment, measurements of the concentration of 6-TGN (thioguanine nucleotides) (the effective azathioprine metabolite) in erythrocytes, serum amylase and serum lipase concentrations were determined and liver function tests and blood counts were performed. Erythrocyte 6-TGN concentration, blood count, white blood cell count, creatinine and C-reactive protein were

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Letters to the Editor

determined and liver function tests and urinalysis were performed 1, 2, 4, 6 and 8 weeks after the beginning of treatment. To assess treatment outcome and adverse events, patients were interviewed and physical examinations were performed at the time of inclusion in the trial, before discharge from the hospital and during follow-up visits.

In two of three patients with dermatomyositis, the combination of prednisolone and azathioprine led to a decrease in serum levels of muscle enzymes, leukocytes and inflammatory proteins. Clinical examination showed an improvement in myalgias, muscle weakness and cutaneous manifestations. In all patients with systemic sclerosis we observed a rapid improvement of digital ulcers. In two of three patients with SLE, serum anti-double-stranded-DNA antibody levels decreased slightly after the initiation of treatment with azathioprine. No convincing clinical improvement was seen during the short follow-up period. One patient with RA and detectable anti-nuclear antibodies showed a reduction of joint inflammation during follow-up.

Adverse events following i.v. azathioprine treatment were rare. In two patients we found transient leukopenia as low as 2.1 leukocytes/ml. One of these patients had a history of lymphopenia in the context of SLE with autoimmune haemolytic anaemia and thrombocytopenia. The other patient suffering from dermatomyositis presented with a disease-related leukopenia of 3.4 leukocytes/ml. In both patients the leukocyte count decreased temporarily after the initiation of treatment. One patient with SSc suffered from cephalalgias during the time of azathioprine infusion. Severe adverse events leading to discontinuation of the treatment were not seen in our patients.

In agreement with Matteson et al. [4], who used the same protocol for the treatment of patients with refractory, active RA, i.v. azathioprine was well tolerated in our group of patients. Unlike Matteson et al., we saw clinical or serological improvement in the majority of patients. Peak erythrocyte 6-TGN levels of the two patients not responding to therapy were below the median of the whole group. In order to demonstrate a superior and faster clinical effect of parenteral compared with oral initiation of azathioprine treatment in patients with rheumatic diseases, further studies with a more homogeneous group of patients and azathioprine doses individualized according to erythrocyte 6-TGN concentration should be performed. The promising results of the pilot study on patients with Crohn’s disease [1] disease have been refuted by a larger, placebo-controlled trial in which a loading dose of azathioprine did not decrease the time to response in patients with Crohn’s disease [5].

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Mononeuritis secondary to rheumatoid arthritis responds to etanercept

Sir. We report the effect of etanercept therapy on mononeuritis secondary to rheumatoid vasculitis (RV). A 65-yr-old male, with a 15-yr history of refractory rheumatoid arthritis (RA), had been treated with the following disease-modifying anti-rheumatic drugs (DMARDs): hydroxychloroquine (HCQ), salazosulphapyridine (ASA), azathioprine, gold preparations, methotrexate (MTX), peroral cyclophosphamide, MTX plus ASA plus HCQ, and MTX plus cyclosporin A. Cyclophosphamide had to be stopped because of haemorrhagic cystitis and cyclosporin A because of severe hypertension. The other regimens were ineffective.

In June 1999 the patient was admitted with a highly active polyarthritis (28-joint count: 13 swollen joints) and weakness of the right foot, which had developed within the last few days. Serologically, a state of high inflammation was found: positive for rheumatoid factor (111 U/ml), Westergren erythrocyte sedimentation rate 105 mm/h and C-reactive protein 12.2 mg/dl. The actual therapy during the last 3 months had consisted of MTX 22.5 mg i.v. weekly, 3 g ASA/day, 400 mg HCQ/day and a continuous dose of prednisolone (10 mg daily). Neurological examination revealed right-sided paresis of dorsiflexion and eversion of the right foot (score 2–3 according to The British Medical Research Council). Tendon reflexes were normal. The patient complained of hyperpathy in the dorsum of the right foot. Electromyography (EMG) revealed axonal neuropathy with spontaneous activity (fibrillation potentials and positive sharp waves) in muscles innervated by the common peroneal nerve, and a highly rarefied interference
pattern. Amplitudes of the motor unit potentials were normal (about 0.5 mV). Unsuspicous nerve conduction studies excluded compressive neuropathy of the common peroneal nerve.

Because of the high RA activity and assuming that the mononeuritis was a manifestation of RV, we initiated additive therapy with 25 mg etanercept twice weekly for 6 months. Treatment with MTX, ASA, HCQ and prednisolone 10 mg/day was continued. Clinical and serological assessments were performed before the initiation of treatment with etanercept and were repeated weekly in the first month and once a month thereafter. A neurological examination was performed before treatment began and after 3 and 6 months. X-rays of the joints (hands, feet, cervical spine) were performed before treatment began and after 6 months.

Within 4 weeks, the patient achieved an ACR 70% response, and the effect was sustained over the 6 months of additive therapy with etanercept. The combination treatment was well tolerated, without side-effects. Palsies regressed markedly, reaching a score of 4 after 3 months. EMG now did not show any spontaneous activity. Motor unit potentials became polyphasic and amplitudes increased to 5 mV. There was a slight to moderate reduction in the interference pattern. After 6 months the patient’s clinical status was almost normal. EMG revealed mild signs of residual axonal neuropathy. The joint erosions showed no progress after 6 months.

The rapid improvement of RA following treatment with etanercept is well documented [1, 2]. To our knowledge, we describe the first successful application of etanercept therapy in a patient with mononeuritis secondary to RV. Peripheral nerve involvement is a common presentation in rheumatoid vasculitis [3]. The treatment of RV usually consists of high-dose prednisolone and DMARDs (e.g. azathioprine) [4] or, in severe cases, of cytotoxic immunosuppressive drugs, such as cyclophosphamide [5].

Our patient had characteristics predisposing him to the development of RV: male gender, the presence of rheumatoid factor and a severe course of RA with joint erosions. Furthermore, rapid neurological deterioration within a few days is common in vasculitis. Other relevant causes, such as diabetes mellitus, sarcoidosis, vitamin deficiency, neoplasia and alcoholism, were ruled out.

Because of the rapid progress of motor dysfunction and the high RA activity, we initiated additive treatment with etanercept instead of i.v. cyclophosphamide; the latter had not been tolerated by this patient in the past. Etanercept led to a dramatic improvement of the joints within a few weeks and to almost complete remission of the paresis within several months. Further studies are needed to determine the effectiveness of etanercept in treating RV.

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Novel clinical manifestations associated with antiphospholipid antibodies

Sir. Antiphospholipid antibodies (aPL) are known to be related to other clinical manifestations, such as cardiac valve lesions and haemolytic anaemia, in addition to the major clinical features of antiphospholipid syndrome (APS), such as thrombosis, recurrent fetal loss and thrombocytopenia [1]. Recently, we encountered and reported on patients with reactive haemophagocytic syndrome (HPS) or hypopituitarism (Sheehan’s syndrome), possibly induced by the presence of aPL [2, 3]. Patient 1 was a 27-yr-old woman who showed anaemia and severe thrombocytopenia (white cells 7.0 x 10^3/mm^3; red cells 411 x 10^6/mm^3; haemoglobin 7.0 g/dl; platelets 0.2 x 10^4/mm^3). aPL were detected in the immunological examination (Table 1). Clinical and laboratory examinations allowed us to exclude connective tissue diseases, such as systemic lupus erythematosus (SLE) and autoimmune haemolytic anaemia, and viral infections or malignancies as underlying disorders. Bone marrow smears showed an increase in mature-looking histiocytes scattered among the haematopoietic cells. The histiocytes showed marked phagocytosis of the haematopoietic cells, including megakaryocytes and erythroblasts. On the basis of these findings, the patient was diagnosed with HPS associated with the presence of aPL.

Thrombocytopenia and anaemia improved with steroid treatment, and her haemophagocytic phenomena disappeared during the second bone marrow aspiration 1 month after initiating steroid treatment. We also encountered a similar patient (patient 2 in Table 1), though the details of the patient profile were not described in this letter. In addition to infections and malignancies, autoimmune diseases such as SLE are also known to be causative disorders of HPS [4–6]; however, HPS associated with aPL has not been previously reported. Increases in serum cytokines (such as tumour necrosis factor α and interferon γ), ferritin and body temperature are generally observed in infection- or malignancy-associated HPS. Cytokines are thought to play an important role in the induction of HPS.
However, these findings were not noted in our patients and other reported patients with autoimmune-associated HPS [5, 6]. This suggests that the underlying mechanism of autoimmune-associated HPS is different from that of infection- or malignancy-associated HPS. Binding of aPL-bound haematopoietic cells to the Fc receptor of phagocytes via the Fc portion of aPL may play a significant role in aPL-associated HPS [7].

Patient 3 was a 33-year-old woman who complained of fatigue, failure to lactate and to resume menses after delivery. Hormonal examinations revealed low levels of adrenocorticotropic hormone (<5 pg/ml, normal range 9–52) and prolactin (<1.0 ng/ml, normal range 1.4–14.6) and magnetic resonance imaging examination disclosed empty sella of the hypophysis, which is a neuroradiological finding indicating pituitary necrosis. She showed positive reactions to aPL and thrombocytopenia (Table 1); however, it was not clear whether her thrombocytopenia was associated with HPS (as in the patients 1 and 2) because there was no bone marrow examination. There were no autoimmune connective tissue disorders noted after further investigation. Although it is difficult to prove directly the relationship between empty sella and thrombosis of pituitary vessels, she was thought to have Sheehan’s syndrome associated with the presence of aPL. To date, adrenal insufficiency (Addison’s disease), hyperthyroidism (Graves’ disease) and primary and secondary hypopituitarisms have been reported as aPL-related endocrine disorders [8–10]; however, our patient was the first reported case of Sheehan’s syndrome associated with aPL. Although Sheehan’s syndrome is thought to be induced by ischaemic hypophysal necrosis induced by extensive blood loss associated with delivery, blood loss in this patient was not severe. APS and or the presence of aPL may play an important role in the occurrence of such postparturient hypopituitarisms.

Recently, new criteria for the classification for APS were provided by Wilson et al. [11]. These criteria emphasize the importance of thrombosis and/or recurrent fetal loss but omit thrombocytopenia from the clinical criteria. The new laboratory criteria have more accurate specifications for detecting aPL in order to define the parameters for diagnosing APS, compared with previous criteria [12]. The laboratory findings of our three patients fulfilled the new criteria. However, the clinical findings did not meet the new criteria for diagnosing APS even though these patients were diagnosed with APS according to the previous criteria [12], because these patients have not developed any thrombosis affecting the deep veins or arteries, or recurrent fetal loss. This preliminary criterion for APS seems to be more suitable for confirming a diagnosis. On the other hand, the possibility of novel minor clinical symptoms associated with aPL, especially aPL according to the laboratory criteria given by Wilson et al. (such as those found in our patients), should not be overlooked, since aPL-related aetiological mechanisms, including the development of thrombosis, are not yet entirely clear. Further studies of additional associated features of APS should be encouraged.

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Early therapy is nothing new in rheumatoid arthritis

Sir, It has become fashionable to urge that rheumatologists of today, unlike their predecessors, should treat rheumatoid arthritis (RA) patients with second-line (‘disease-modifying’) therapy ‘early’ in their disease. This view is based on the assumption that patients have traditionally been treated late in their disease. I collect trials of second-line therapy in RA, and I did not recognize a history of such tardiness in initiating treatment, either from my reading or from my recollection of clinical practice 20 yr ago. I therefore reviewed a random selection of the studies of second-line therapy in RA in my collection, and extracted the date of the study, the mean disease duration of those included in treatment, and the range of disease duration. The results are shown in Fig. 1.

It can be seen that rheumatologists have included patients with early disease (less than, say, 5 yr of disease duration) ever since randomized controlled trials were begun in RA. Indeed, where it was possible to extract the range of disease duration there were nearly always patients included who had less than 1 yr of disease. The average disease duration for all trials taken together was 5.7 yr.

Thus, urging early treatment in RA is superfluously preaching to the converted. I am not aware of any substantial change in my own practice, yet in a recent survey of patients in my clinic, 75% of those within 2 yr of disease onset were already taking second-line treatment.

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Fig. 1. Mean (range) patient disease duration in 30 randomized controlled trials of second-line therapy in RA.