LETTERS TO THE EDITOR

Antiperinuclear factor in chronic juvenile arthritis

Sir: Nesher *et al* recently described the first comprehensive series considering antiperinuclear factor in juvenile chronic arthritis (JCA). They found an overall positivity of 34%; in patients with the polyarticular type of the disease 16/28 patients were positive.¹ Our results are at variance with these data: in a group of 313 patients only three were positive, all of them children with polyarticular onset (table). Thus our results are more in line with a recently reported Czechoslovakian series (Bardfeld R, IVth Prague international pediatric rheumatology symposium, 1992).

Our material consisted of 49 fresh and 264 frozen serum samples. One of the former and two of the latter were positive. As antiperinuclear factor is predominantly, if not exclusively, of the IgG class, sample preservation would seem unlikely to have influenced the results. A more plausible explanation for the discrepancy lies in the immunofluorescence system. A major confounding factor causing variability in antiperinuclear factor results is the variation in substrate sensitivity, between different donors, of the buccal cells that contain the antigen. This drawback has barred antiperinuclear factor from coming into general use despite the long history of the test.² We used a recently described improved technique that includes detergent treatment of the cells, which is reported to minimise, albeit not to eliminate, donor differences.³ We tested the serum samples at a standard dilution of 1:5,⁴ which is also the titre we recorded for the WHO rheumatoid factor reference preparation that has been proposed by Feltkamp *et al* as the reference standard for antiperinuclear factor, too.⁵ Sixty per cent of serum samples from adult patients with rheumatoid arthritis tested in parallel by this technique were positive (manuscripts in preparation).

In conclusion, antiperinuclear factor seems to be a specific but insensitive marker for the JCA subset with polyarticular onset that resembles adult rheumatoid arthritis. It contributes to the evidence for a basic difference between JCA in general and adult rheumatoid arthritis. The need for a common reference standard in future studies is obvious.

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Patients with juvenile chronic arthritis

Onset type	Antiperinuclear factor positive/ No of patients
Polyarticular	
Rheumatoid factor positive	3/15
Rheumatoid factor negative	0/73
Oligoarticular	0/195
Systemic	0/30
Total	3/313

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- 3 Hoet R M A, Boerbooms A M Th, Arends M, Ruiter D J, van Venrooij W J. Antiperinuclear factor, a marker autoantibody for rheumatoid arthritis: colocalisation of the perinuclear factor and profilaggrin. *Ann Rheum Dis* 1991; 50: 611-8.
- 4 Marmont A M, Damasio E E, Bertorello C, Rossi F. Studies on the antiperinuclear factor. *Arthritis Rheum* 1967; 10: 117-28.
- 5 Feltkamp T E W, Boerbooms A, De Keyser F, *et al*. Antiperinuclear factor—standardization program. *Clin Rheumatol* 1990; 9: 112-3.

AUTHORS' REPLY: We thank Drs von Essen *et al* for their comments. We share their view that there is an obvious need for a common reference standard for antiperinuclear factor studies.

Data from their study point to substantial differences in prevalence of antiperinuclear factor when compared with our results. Possibly, these variant results stem from the different methodologies which were applied: von Essen *et al* treated the buccal mucosa cells with detergents before the incubation with serum samples. This procedure did not decrease antiperinuclear factor antigen-antibody interactions in adult patients with rheumatoid arthritis (RA).¹ It might do so in juvenile chronic arthritis (JCA), however, as characteristics of other autoantibodies in JCA, such as IgM rheumatoid factors, are different from those in adult RA.²

Another possible explanation for the variant frequency of antiperinuclear factor might be a difference in its prevalence among various populations. As an example, preliminary results indicate antiperinuclear factor prevalence in 1:5 diluted serum samples of adult Israeli patients with RA is 40% (Nesher G, unpublished data), compared with 68-86% in European studies.¹ It is possible that such differences exist between Scandinavian and American patients with JCA.

Several drawbacks, some of which are reported in these studies, prevent wider clinical use of antiperinuclear factor. Standardisation of the assay and evaluation of antiperinuclear factor prevalence in various populations might be two steps towards its common use.

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- 2 Dörner R W, Alexander R L Jr, Moore T L. Rheumatoid factors. *Clin Chim Acta* 1987; 167: 1-21.

Diagnostic role of antikeratin antibodies in RA

Sir: We read with interest the article by Paimela *et al*¹ on the diagnostic and prognostic value of antikeratin antibodies in rheumatoid arthritis (RA).

We recently studied two groups with RA using indirect immunofluorescence for antibodies to the stratum corneum of rat oesophagus. In the group of white patients with RA (n=30) we found a seroprevalence for antikeratin antibodies of 53%. In contrast, among the African rheumatoid group (n=54), who had significantly milder disease,² an antikeratin antibody seroprevalence of 6% was seen. Our findings suggest that there may be a wide variation in the incidence of antikeratin antibodies, and even when immunofluorescence is used there is a low sensitivity, low negative predictive value, and a moderate specificity. There is also evidence that immunoabsorption of serum with heterogeneous nuclear RNP core protein A1, in which the C-terminal domain shows a partial homology with keratin, results in a significant reduction of antikeratin antibody titres.³

Our view is that although antikeratin antibodies may be associated with severity of RA, these antibodies are of low discriminating ability when the disease is mild, as is often the case in early RA. Hence they are of limited value for routine diagnostic purposes.

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- 3 Montecucco C, Caporali R, Negri C, *et al*. Antibodies from patients with rheumatoid arthritis and systemic lupus erythematosus recognise different epitopes of a single heterogeneous nuclear RNP core protein: possible role of cross reacting antikeratin antibodies. *Arthritis Rheum* 1990; 33: 180-6.

Sulphasalazine induced hepatitis in adult Still's disease

Sir: We were interested to read the report of sulphasalazine induced hepatitis in juvenile chronic arthritis, noting that one of the two patients had the systemic onset variety.¹

We report an adverse reaction to sulphasalazine in a patient with adult Still's disease and comment on a potential mechanism for enhanced drug toxicity in this disorder.

A 42 year old West Indian woman presented in November 1989 with malaise, weight loss, intermittent fever, and a symmetrical inflammatory polyarthropathy with an erythematous desquamating skin rash. Investigations showed a neutrophil leucocytosis (white cell count $15.8 \times 10^9/l$) and a marked acute phase response (C reactive protein (CRP) 126 mg/l). An extensive screen for bacterial and viral infection was negative. A skin biopsy specimen showed perivascular polymorph infiltrates compatible with a small vessel vasculitis. Carpal erosions were seen on wrist radiographs,

and tests for rheumatoid factor, antinuclear factor, and antibodies to DNA were negative. Liver function tests were normal. After a short course of systemic and intra-articular steroids the skin rash resolved and joint pain improved.

She was readmitted in April 1990 with a recurrence of arthropathy, rash, and fever with a leucocytosis (white cell count $13.9 \times 10^9/l$), raised CRP (226 mg/l), and plasma viscosity of 2.39 mPa.s. She complained of lower abdominal pain and developed peritonism. A limited laparotomy showed sterile peritonitis. Systemic lupus erythematosus was considered unlikely in view of the erosions and negative antinuclear factor, and a diagnosis of adult onset Still's disease was made. She responded to high dose corticosteroids, and sulphasalazine was introduced. By discharge the CRP had fallen (65 mg/l). Five weeks later when taking sulphasalazine 500 mg twice daily, she was noted to be jaundiced. Investigations showed an acute hepatic reaction (aspartate 559 IU/l, bilirubin 57 $\mu\text{mol/l}$, alkaline phosphatase 793 IU/l, γ -glutamyl-transferase 163 IU/l, CRP 62 mg/l), which resolved within two weeks of discontinuing sulphasalazine. No other cause for hepatitis was found. The patient has remained well on a reducing dose of corticosteroid.

This case fulfils the criteria for adult Still's disease proposed by Medsger and Christy.² The hepatitis which developed in our patient was probably due to sulphasalazine, and to the best of our knowledge this is the first reported case of sulphasalazine induced hepatitis in adult Still's disease, though from experience with children sulphasalazine sensitivity in Still's disease may be more common than expected.³⁻⁵

Acetylator status is a major determinant of sulphasalazine pharmacokinetics, but sulphapyridine also undergoes hydroxylation mediated by cytochrome P450. A reduction in hepatic cytochrome P450 induction may occur as a consequence of inflammatory arthritis. Prolongation of sleep times induced by barbiturates (metabolised by P450 pathways) occurs in rats with adjuvant arthritis,⁶ and a role for interleukin 1 in depression of drug metabolism has been proposed.^{7,8} This cytokine is implicated in the pathogenesis of erosive arthropathies.⁹ Furthermore, fever induced by the administration of etiocholanolone or other pyrogens is associated with a decrease in drug metabolism.¹⁰ Thus these studies support the hypothesis that interleukin 1 released during adult onset Still's disease might be capable of reducing hepatic cytochrome P450. Such a mechanism might account for an alteration in drug metabolism and an increased potential for adverse drug reactions.

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Longstanding HLA-B27 associated Achilles tendinitis

Sir: In 1987 we published the case of a B27 positive man who had presented for about four years with bilateral Achilles tendinitis as the only clinical manifestation of a B27 associated disease.¹ We have followed him up since his first visit in December 1986. The Achilles tendinitis went into remission in 1988. No other clinical manifestation of seronegative spondyloarthropathy has developed so far. We have recently seen a similar case, which we report here. A 36 year old man was evaluated at our rheumatic disease unit in November 1990 for bilateral Achilles tendinitis which had persisted for four months.

His medical history showed that he had had a similar episode in 1983, lasting for one month, which was attributed to 10 days' skiing. He denied any inflammatory spinal pain, peripheral arthritis, diarrhoea, urethritis, conjunctivitis, uveitis, psoriasis, cardiac symptoms, or physical injury. His family history was negative for spondyloarthropathy and other B27 associated syndromes.

Physical examination showed warmth, tenderness, and soft tissue swelling along both Achilles tendons and their calcaneal insertions. There was no limitation of spine movement or chest expansion. Laboratory evaluation showed only a C reactive protein of 12 mg/l (normal <5). HLA typing showed the B27 antigen.

Ultrasonography by the technique of Fornage² showed a diffuse thickening of both Achilles tendons, which was more severe on the right side (9 mm v 8 mm) (figure). Sacroiliac joint, lumbar spine, and foot radiographs were normal.

Longitudinal sonogram showing diffuse thickening of both Achilles tendons more marked on the right side (9 mm (A) v 8 mm (B)). Note the peritendinous soft tissue swelling (arrows). C=calcaneus; H=toward patient's head; L=left; R=right.

The Achilles tendinitis subsided after eight months from onset.

The bilateral Achilles tendinitis shown by our patient is consistent with a B27 associated disease process, and the clinical and echographic aspects shown are typical.¹⁻⁵

This case supports our hypotheses about B27 associated peripheral enthesitis—namely, that (a) peripheral enthesitis may for a long time be the only clinical manifestation,^{1-5,8-10} as is true for other clinical features of the B27 associated disease process—that is, peripheral asymmetric oligoarthritis,⁶ dactylitis,⁷ acute anterior non-granulomatous uveitis, and aortic regurgitation and conduction disturbances; (b) it may occur either in childhood^{8,9} or in adulthood^{1-5,10}; (c) Achilles tendinitis may be the only isolated peripheral enthesitis of spondyloarthropathy.¹⁻¹⁰

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