LETTERS TO THE EDITOR

Negative antineutrophil cytoplasmic antibodies in Behçet's disease

Sir: Antineutrophil cytoplasmic antibodies have been detected in patients with idiopathic necrotising and crescentic glomerulonephritis, active Wegener's granulomatosis, and microscopic polyarteritis nodosa.¹

Behçet's disease, an inflammatory disorder of unknown cause, is characterised by oral and genital ulcerations associated with systemic manifestations due to large and small vessel vasculitis. Ocular, cutaneous, and central nervous system involvement are often the translation of small vessel vasculitis.² Crescentic glomerulonephritis has also been reported.³ Polymorphonuclear leucocytes have been incriminated in the pathophysiology of Behçet's disease. Lesions are characterised histologically by acute inflammation and an intense infiltration of polymorphonuclear leucocytes with small vessel necrosis, especially at mucosal and cutaneous sites.⁴ The increased chemotaxis and random motility of polymorphonuclear leucocytes in Behçet's disease have been confirmed in several studies, and it has been suggested that a cytoplasmic polymorphonuclear leucocyte factor, serum or lymphocytic factor is responsible for this increased activity.⁵ To appreciate better the role of polymorphonuclear leucocytes in this disease we looked for the presence of antineutrophil cytoplasmic antibodies in patients with active and inactive Behçet's disease.

Twenty eight patients (27 male, one female) with a mean (SD) age of 40 (3) years (range 29-56) were studied. Disease duration was 6.8 (1.9) years (range 2-25). All patients had buccal aphthosis associated with at least two of the following criteria: genital aphthosis, cutaneous lesions, uveitis, and positive pathergy testing. The incidence of clinical manifestations with reported vasculitis is as follows: uveitis (12 cases), central nervous system disease (six cases), thrombophlebitis (six cases), erythema nodosum-like lesions (five cases), and arterial aneurysm (one case). The disease was active in 15 patients and inactive in 13.

Indirect immunofluorescence on human neutrophils was used to detect antineutrophil cytoplasmic antibodies, according to the method of Van der Woude.⁶ None of the 28 serum samples from the patients with Behçet's disease was positive for these antibodies (titres >1/10). The fluorescence was negative in 27 patients and positive in one at a titre of 1/10.

This study strongly suggests that antineutrophil cytoplasmic antibodies cannot be incriminated as contributing to the abnormalities of polymorphonuclear leucocytes in Behçet's disease.

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Pregnancy loss, menopause, and the onset of rheumatoid arthritis

Sir: Spector and Silman suggest that spontaneous abortion may have a protective effect on the development of rheumatoid arthritis (RA).¹ This seems at odds with a previous study from the same group reporting that first degree relatives of women with RA who are destined to develop RA themselves have more frequent adverse pregnancy outcomes in the form of perinatal deaths.² The authors attempt to reconcile the two studies by suggesting that late reproductive loss is only important in those 'particularly genetically susceptible to rheumatoid arthritis'. Although this is an interesting concept, further information to support this hypothesis has not been obtained. In the first study the obstetric histories of the female probands were not given, yet it may be informative to know how they compared with those reported for their relatives who were either affected or non-affected with RA. In the second study the family histories of the patients with RA were not stated, although presumably some first degree relatives are likely to have RA. A study performed by us supports the findings of the second study. After interviewing a large number of women with RA and other connective tissue disorders we found that pregnancy loss is not a risk factor for the later development of RA.³

Undoubtedly, pregnancy loss has an ameliorating effect on the activity of RA. Most women develop RA having completed their pregnancies, however.³ The influence of other hormonal factors, such as the menopause, deserves more attention. From an interview of 117 women with RA in our previous study it was noticeable that a large number had onset of their arthritis about the time of menopause,

Figure 2 Onset of arthritis in relation to the menopause.

an observation not included in our paper. Age of onset of first symptoms of RA and age at menopause (for this purpose defined as cessation of menses) were obtained from all women at the time of interview, in different sections of a questionnaire, with confirmation by recourse to hospital notes when possible. Seventeen women who had undergone hysterectomy and 17 women who were premenopausal were excluded from this analysis.

There seemed to be a broad peak of age of onset of arthritis coinciding with the expected age of menopause (fig 1). When the onset of arthritis was analysed in relation to the menopause in individual patients there were a larger number reporting onset of arthritis and menopause within an encompassing five year interval (fig 2). Undoubtedly this finding is due partly to an unconscious bias in relating major life events to each other, especially considering our crude definition of the menopause. Nonetheless, it is biologically plausible that hormonal fluctuations occurring during the menopause may trigger onset of RA in some women, perhaps by the same mechanism as that occurring in postpartum flares of arthritis in younger women.

These observations at least merit a prospective study, including appropriate assays for hormonal function in women developing RA. Our epidemiological colleagues may also be able to tell us eventually whether hormone replacement therapy is more advantageous than imagined, or perhaps the opposite.

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Figure 1 Age of onset of arthritis.

Sir: Dr McHugh makes some interesting points which we would like to consider in turn. It is correctly pointed out that the results of our two studies are at odds with each other with regard to perinatal death and risk of RA. The second study was much larger and had greater power than the first, and was set up to explore the preliminary findings of the initial first study based on RA multicase families. As stated in the paper the results of the family study were based on small numbers of cases and perinatal episodes, and results could not be generalised to the wider sporadic RA population. Although these findings might

Figure 1 Relation between onset of rheumatoid arthritis and menopause in 191 postmenopausal women in a case-control study.

have arisen by chance, we tentatively suggested that other unknown genetic factors might have been responsible. We would be grateful for any other interpretations of the data. Unlike Dr McHugh we are unaware of the conclusive clinical evidence that pregnancy loss ameliorates existing disease, though this remains a possibility.

Dr McHugh suggests that the effect of the menopause should be given wider consideration owing to the age of onset in women. Dr McHugh's study showed a peak age of onset around the menopause, as did our larger case-control study (fig 1). There are a number of problems that have to be considered before a direct correlation can be postulated. Firstly, the age of onset distribution seen in hospital outpatient studies is not representative of all women with RA. This is because hospital case groups tend to contain those with more severe, longstanding disease, and patients developing RA at an older age will be underrepresented (fig 2). Population surveys are the only accurate way of determining ages of onset. In the United Kingdom these have confirmed that prevalence does indeed increase at the menopause, but remains at this level thereafter.¹ Another study of incidence related to age at the Mayo clinic found that this increased steadily in women and men.² If the menopause were a major factor one might expect differences in prior age of menopause or incidence of artificial menopause and these have not been found in studies.³⁻⁵ As well as the mentioned bias due to recall of disease onset, it should be remembered that surveys have shown that up to 50% of women with

Figure 2 Distribution of age at onset of women with rheumatoid arthritis from a case-control study. (Source: Spector TD. Hormonal and reproductive factors in the aetiology of RA. MD thesis, University of London, 1989.)

menopausal symptoms have joint pain,⁶ and this is likely to be confused with early RA.

A number of studies have looked at hormonal status of women with RA, and, unfortunately, no consistent abnormalities have been detected.⁷ We are just completing a prospective study examining the hypothesis that hormone replacement therapy (HRT) is protective against the development of RA. The data on the possible protective effects of HRT are patchy and contradictory at present and suffer from many of the methodological problems outlined above. Although hormonal change at the menopause may be a factor in RA, current evidence suggests that prior pregnancy and oral contraceptive use at an earlier age may be of more importance.⁸

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Sternoclavicular erosions in polymyalgia rheumatica

Sir: We read with interest the article by Kyle *et al* about the rarity of synovitis in polymyalgia rheumatica.¹ In their work sternoclavicular erosions were seen in only 2/19 of the tomograms obtained. Our experience contradicts these results.²

From 1984 to 1987 tomography of sternoclavicular joints was carried out in 21 patients (12 female, nine male) with active untreated polymyalgia rheumatica, seven of whom also had giant cell arteritis. Their mean age was 68.8 years. All had a negative Rose-Waaler test. In addition, control tomograms were obtained from 18 volunteers (mean age 69.2 years) who had no clinical evidence of inflammatory arthropathy. The films were all examined by one consultant radiologist and two rheumatologists with no knowledge of clinical data.

The incidence of erosions was significantly higher ($p < 0.05$) in patients with polymyalgia rheumatica (9/21) than in control subjects (1/18). Erosions were found more often in patients who had had symptoms for more than six months. There was no correlation between local pain elicited by pressure and the presence of articular erosions.

Our findings support the existence of an erosive arthropathy in polymyalgia rheumatica and are in agreement with the study of Paice *et al* previously published in the *Annals*.³

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Immunological indices of patients with rheumatoid arthritis after methylprednisolone pulse therapy

Sir: In a previous letter to the *Annals* we reported the favourable clinical results obtained by high dose intravenous methylprednisolone treatment in active rheumatoid arthritis.¹ We now present the changes in the immunological indices for these same patients.

The discovery of monoclonal antibodies has enabled the determination of different lymphocyte subgroups.²⁻⁹ We investigated the cellular and humoral immune response of 10 patients with active, classical rheumatoid arthritis. The total lymphocyte count (OKT3), the inducer/helper (OKT4) and suppressor/cytotoxic (OKT8) subgroups were determined with Orthomune monoclonal antibodies by the immunoperoxidase method according to Erber.¹⁰ Concentrations of C3, C4, and the immunoglobulins were measured by Mancini's radial immunodiffusion. Determination of immune complexes was by polyethylene glycol precipitation and cross electrophoresis. Blood samples for determinations were taken before infusion and after 2, 6, 24, and 48 hours.

Before infusion we found a high level of helper cells: mean 69.1% (range 59-78%), absolute number 1921/ μ l (1120-3321), and a low concentration of suppressor cells: mean 25.8% (21-34%), absolute number 808/ μ l (352-1700), in agreement with published data.^{2-4 6 7 11-15} The so-called immunoregulatory ratio—the helper/suppressor quotient—was increased to 2.65 (normal 1.55), as found by others.^{2-4 6 11} This disequilibrium of the immune response was favourably influenced by high dose intravenous methylprednisolone pulse therapy, which decreased the centile proportion: mean 45.3% (24-63%) and the absolute number: mean 418/ μ l (135-715) of T4 cells, thus leading to a normal helper/suppressor ratio. According to Bertouch the cause of selective diminution of helper cells is the remigration of the circulating lymphocytes into the peripheral lymph nodes and bone marrow.^{2 16 17} As the lymphopenia was only transitory and the excretion of uric acid did not rise after the pulse treatment the decrease of cell numbers is probably due to a change in the division of circulating cells and not to cell lysis.¹⁸