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Alternatives to allopurinol

SIR, In their letter to the *Annals* Kelsey *et al* state that there is 'no available alternative to allopurinol with its unique mode of action'.¹ There are at least two alternatives²: tiopurine (1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thiol (C₅H₄N₄S)) and oxypurinol (1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-diol(C₅H₄N₄O₂)). Neither are available in the United Kingdom.

In the treatment of gout, tiopurine has been shown to reduce effectively both the plasma and urinary uric acid levels of hyperexcretors, but plasma levels only of normal excretors.³ These effects were shown without a concomitant increase in urinary hypoxanthine and xanthine excretion.³⁻⁶ Tiopurine is only one tenth as active as allopurinol (1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol(C₅H₄N₄O)) as a xanthine oxidase inhibitor *in vitro*,⁷ and is ineffective in lowering uric acid levels in gout associated with a partial deficiency of the enzyme hypoxanthine guanine phosphoribosyl transferase.^{3,5} Therefore, tiopurine reduces uric acid concentrations by interfering with the early stages of its synthesis, thus avoiding increased blood concentrations of hypoxanthine and xanthine. There is no evidence that there is a cross reactivity between tiopurine and allopurinol. The dose range is from 200 to 400 mg daily.

Oxypurinol is the active metabolite of allopurinol *in vivo*. Its half life is about eightfold longer than that of allopurinol.⁸ Allopurinol is the more effective administered orally in view of the relatively poor absorption of oxypurinol from the gastrointestinal tract.⁹ Although several patients with a history of untoward reactions to allopurinol have received oxypurinol without cross reactivity,¹⁰ others do cross react, and in some the reaction may have an immunological basis.¹¹

Rheumatology Department,
The London Hospital

A S M JAWAD

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Hyper-responsiveness to EBV in ankylosing spondylitis

SIR, Recently, Drs Robinson and Panayi reported a deficient control of *in vitro* Epstein-Barr virus (EBV) infection in patients with ankylosing spondylitis (AS).¹ Under blind study control, using peripheral blood mononuclear cells from B27+ spondylitic patients, we have observed a similar hyper-responsiveness to EBV. Cultures were set up in quadruplicate in 96-well, flat bottomed microtitre plates. Virus supernatant, obtained from a 10 day culture of B95-8 marmoset cells, was titrated and mononuclear cells were added to each well to give a final concentration of 5×10^5 cells/ml. Fig. 1 shows the minimum virus concentration required to immortalise the blood B cells of patients with either clinically active AS or rheumatoid arthritis (RA). In these experiments, cells from 90% (9 of 10) of the spondylitic patients and 69% (11 of 16) of the rheumatoid patients formed permanent cell lines and the range of minimum concentrations was similar; the results are based on six week cultures.

Since we have shown previously an increased responsiveness to EBV of rheumatoid blood B cells² we extended the experiments further to evaluate the role of the spondylitic B cell in this observed hyper-responsiveness. Non-T cells, negatively selected using 2-aminoethylisothiouonium bromide hydrobromide (AET) treated sheep erythrocytes, were infected with EBV supernatant at a dilution of 1/10. Work from our laboratory has previously shown this dose to be effective in the measurement of hyper-responsiveness in RA.² Infected and uninfected cells were set up in 24-well, flat bottomed plates at a concentration of 5×10^5 cells/ml. The results of six week cultures are shown in Table 1. In this study no healthy individuals were used and the number of rheumatoid patients was small. The results for the rheumatoid patients, however, were in agreement with our previous data from a larger study.² There, we reported that no B cells from healthy controls spontaneously grew into cell lines as compared with 22% of the B cell samples from rheumatoid patients and only 40% of infected healthy B cells were maintained in culture for six weeks; some of the 'normal' controls carried the

B27 antigen. All superinfected rheumatoid B cells formed permanent cell lines. In this study B cells from approximately 80% of the spondylitic patients were actively dividing after six weeks in culture and B cells from two of these patients spontaneously transformed into cell lines.

Fig. 1 The minimum EBV concentration necessary to initiate cell line formation by peripheral blood mononuclear cells from rheumatoid or spondylitic patients is shown. Cultures were set up in quadruplicate and R denotes cultures where two or more wells showed regression and no cell lines were formed. The results at six weeks are shown.

Table 1 Results of six week cultures using a limiting viral dose (1/10 dilution)

Mononuclear cell population	No of cell lines/total No of patients (%)	
	AS	RA
Unfractionated	1/15 (7)	1/5 (20)
Unfractionated + EBV	6/15 (40)	4/5 (80)
Non-T	2/14 (14)	2/5 (40)
Non-T + EBV	11/14 (79)	5/5 (100)

Taking the results of our two studies together, we conclude that patients with AS, like those with RA, show a B cell defect. Whether this implies similar disease mechanisms, as suggested by Dr Robinson, requires further study since AS, unlike RA, is predominantly HLA class II associated and in our studies reported here, with respect to hyper-responsiveness to EBV, the patients with AS formed a separate group, intermediate between rheumatoid and healthy.

Bone and Joint Research Unit, VIVIENNE R WINROW
The London Hospital J DAVID PERRY*
Medical College
and *Rheumatology Department,
The London Hospital,
London E1 2AD

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The costoclavicular syndrome

SIR, De Silva has described costoclavicular syndrome (a variant of thoracic outlet syndrome) due to traction from brassières in large breasted women.¹ Dr De Silva's claim that this is a 'hitherto undescribed cause of the condition' is not true. In 1972 Kaye reported sensory and motor changes in the upper extremities of women with macromastia, which he felt to be 'a variant of the syndrome of thoracic outlet compression'.² In 1979 McGough, Pearce and Byrne describing their non-operative treatment of thoracic outlet syndrome wrote 'Large-breasted women were urged to be fitted with an underwire support brassière, so that the weight of the breast would be supported around the thorax rather than over the shoulder'.³

We are also concerned by De Silva's contention that normal blood tests and x rays are sufficient investigation to rule out other conditions. In our experience the most common cause of upper extremity pain is carpal tunnel syndrome. Thoracic outlet syndrome was diagnosed much more frequently in the first half of this century than it is now, and it is becoming apparent that many of these earlier patients actually had carpal tunnel syndrome.⁴ All patients suspected of thoracic outlet syndromes should undergo electrodiagnostic studies to rule out carpal tunnel syndrome.^{3 5 6}

Division of Rehabilitation Medicine, KENNETH C WRIGHT
University of Pittsburgh, JOHN J NICHOLAS
Pittsburgh, PA 15213,
USA

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