

## LETTERS TO THE EDITOR

### RA sex ratios, HLA-DR, and testosterone

Sir: We would like to support some points arising from the interesting review article entitled 'Sex hormones in HLA related rheumatic diseases',<sup>1</sup> and recent correspondence arising from this.<sup>2,3</sup> The author suggests that because parental sex hormones may influence the sex of their offspring, and HLA genes exert some sort of control over both sex hormones and rheumatic diseases such as rheumatoid arthritis (RA), one might expect to see unusual sex ratios among the sibs of rheumatoid probands.

We have analysed our data on rheumatoid probands to see if they agree with the observation that probands with RA are more likely to have an excess of sisters.<sup>1</sup> Twenty five families with multiple cases of RA, who have been described elsewhere,<sup>4</sup> were analysed for the ratio of sisters and brothers of the proband. Forty six siblings were female and 36 male. Although this is not significantly different from random ( $\chi^2 = 1.8$ ,  $p > 0.05$ ), the trend is in the same direction as those studies quoted by James<sup>1</sup> - that is, an excess of female siblings. Interestingly, the offspring of affected parents from the same pedigrees were 16 female to seven male. This was significant ( $\chi^2 = 4.0$ ,  $p < 0.05$ ) and supports the hypothesis that there is an interaction between parental and proband sex hormones, HLA haplotypes, gender of first degree relatives, and RA.

We have also measured testosterone and calculated free testosterone concentrations in postmenopausal female rheumatoid sibships (methodological details in ref 5). For some of these we had obtained HLA-DR types by a standard serological technique. The table shows the total and derived free testosterone concentrations in HLA-DR4 positive and negative rheumatoid and non-rheumatoid women. In both patient groups the mean concentrations of both total and derived free testosterone were lower in the HLA-DR4 positive women, though these differences were not significant. Analysis of potential confounding demographic and reproductive variables did not suggest any other variables to account for the differences in testosterone concentrations. Owing to the small numbers available, the lack of significance may represent a type II statistical error, and would require larger study groups to confirm the

possibility that HLA-DR4 is associated with lower testosterone concentrations. Low testosterone concentrations have consistently been associated with RA in male patients,<sup>6</sup> and the association between RA and HLA-DR4 is well established.

If both inherited HLA haplotypes and HLA-DR alleles are important in sex hormone profiles, and sex hormones in some way partially explain the predisposition to RA, these observations support the possibility that within the major histocompatibility complexes (MHCs) are not only gene products involved in antigen presentation that increase susceptibility to RA but also linked genes that govern potentially predisposing sex hormone profiles. The MHC contribution to RA may therefore be multifaceted.

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### Dorsal vertebral fractures with 'normal' bone mineral density

Sir: We have read the article by Bhambhani *et al* on the differential involvement of the dorsal and lumbar spine in osteoporosis.<sup>1</sup> In their study they reported 11 patients with dorsal vertebral fractures and 'normal' lumbar bone mineral density (BMD) - defined as a BMD value greater than one standard deviation below the age and sex matched reference value. From these data the authors suggested that spinal osteoporosis in some patients might be a focal disorder. However, the fact that the 'normal' age matched BMD values in these patients, who

had a mean age of 65 years, are close to the reported fracture threshold values<sup>2,3</sup> was overlooked. Therefore, an increased risk for dorsal or lumbar fractures could not be disclosed using the reported criteria. Maybe, a consensus of densitometric criteria for osteoporosis is needed. On the other hand, in this study three patients had corticosteroid induced osteoporosis. It has been previously shown that patients receiving corticosteroid treatment may have vertebral fractures with normal BMD. Thus, for example, 30% of steroid dependent asthmatic patients had vertebral fractures even though their BMD was above the fracture threshold.<sup>4</sup>

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**AUTHOR'S REPLY** The relation between osteopenia and fracture risk clearly depends upon the definition of osteopenia. We agree with Peris *et al* that in elderly women 'normality' of bone density with respect to age matched reference data does not imply absence of fracture risk as most elderly women have bone density values close to or below the notional fracture threshold. These considerations have led to a wide consensus that osteopenia should be defined in relation to values obtained in healthy young adults.<sup>1</sup> Nevertheless, densitometric criteria for treatment are poorly defined and few physicians would advise treatment for the elderly, asymptomatic woman with a bone density greater than one standard deviation below the age and sex matched reference value.

It is well documented that bone loss in osteoporosis is heterogeneous and it would therefore not be surprising if differential changes occurred in the lumbar and dorsal spine. Our findings are consistent with this hypothesis but do not prove it. The main implication of our study is that dorsal spine fractures may be missed if 'normal' bone mineral density values in the lumbar spine are assumed to exclude clinically significant spinal osteoporosis.

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Total and derived free testosterone concentrations in HLA-DR4 positive and negative women with rheumatoid arthritis and healthy postmenopausal women. Results are shown as mean (SEM)

Patient group	HLA-DR4 status	Number	Testosterone concentration (SEM)	
			Total (nmol/l)	Free (pmol/l)
RA	+	23	0.73* (0.09)	9.85† (1.07)
RA	-	8	0.94* (0.20)	13.45† (2.87)
Healthy	+	13	0.85‡ (0.16)	10.37§ (1.98)
Healthy	-	7	1.26‡ (0.15)	15.81§ (1.88)

t tests: \* $t=1.07$ ,  $p=0.38$ ; † $t=1.47$ ,  $p=0.15$ ; ‡ $t=1.66$ ,  $p=0.11$ ; § $t=1.79$ ,  $p=0.09$ .