Correspondence

Plasma von Willebrand factor in connective tissue disease

SIR, Vascular endothelial cells synthesise von Willebrand factor (VWF), a high molecular weight protein that plays a part in the interaction of platelets with the subendothelium.^{1,2} The VWF is stored in the endothelial cells, and it can be released by a number of biological stimuli, including thrombin.³ If VWF release occurred in vivo as part of the endothelial response to damaging stimuli, a raised plasma level of VWF might indicate ongoing endothelial damage; this concept is supported by observations that plasma VWF is modestly raised (mean increase around two- to fourfold) in connective tissue disease associated with microvascular pathology.⁴⁻⁸ The mechanisms of VWF release in these conditions have not been determined, and the relation between VWF levels and the course of the disease is not clear, but experimental studies have shown that VWF can be an acute phase reactant in animals.⁹ If the increase in VWF in connective tissue disease reflected acute inflammatory episodes it

should correlate with levels of a recognised acute phase reactant.

To investigate this we measured VWF by enzyme linked immunosorbent assay (ELISA), and C reactive protein by radial immunodiffusion, in plasma from 34 patients with scleroderma, 18 patients with systemic lupus erythematosus (SLE), 39 with rheumatoid arthritis (RA), and 37 normal controls. The mean level of VWF in the patients with scleroderma (1.42 (SD 0.66)) was significantly ($p<0.03$) greater than that of the control group (1.13 (0.41)), though only six patients had levels above 2 IU/ml. Levels in the groups with RA and SLE were also significantly raised, with mean values of 1.95 (0.97) and 2.45 (1.08) respectively (see Fig. 1). There was no correlation between levels of VWF and C reactive protein in the scleroderma and SLE groups, but positive correlation was found in the patients with RA (Spearman's rank correlation coefficient 0.39; $p<0.02$). Increase of VWF in the RA group was not associated with vasculitis.

Our results indicate that an increase in plasma VWF is common in SLE, RA, and, to a lesser extent, in scleroderma. This may reflect endothelial damage (in the

Fig. 1 Levels of VWF in the plasma of patients with connective tissue diseases. The horizontal bars show the mean for each group and the mean values (SD) are indicated.

absence of another cause such as renal failure or liver disease), as has been previously suggested; however, it can also be associated with an acute phase reaction, and this should be borne in mind when interpreting the significance of VWF measurements.

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HLA antigens Dw4 and Dw14 in rheumatoid arthritis

SIR, In a recent study in the *Annals of Rheumatic Diseases* we assayed the differences in HLA system of 62 patients with rheumatoid arthritis (RA) with various toxic effects of gold salts and 23 RA controls without gold toxicity.¹ The findings included higher Dw4 and Dw14 and lower Dw1 incidences in the controls with classical rheumatoid arthritis (RA) when compared with the gold toxicity

Table 1 Phenotypes of Dw4 or Dw14 positive patients, or patients positive for both

	Patients without toxic effects (n=23)	Patients with toxic effects (n=61) ^a
Dw4/x or - [†]	6	13
Dw14/x or -	2	6
Dw4/w14	5 [‡]	0

^aD typing missed in one patient.
[†]x means any other HLA-D specificity found.
[‡]In DR typing only DR4 was found.

group, which was more heterogeneous as to the American Rheumatism Association criteria.²

Although we emphasised the differences in Dw4 and Dw1 frequencies between the groups, the higher Dw14 prevalence in the RA controls with classical RA was disregarded in the discussion.

Recently, Dr Nepom and colleagues identified HLA-Dw4/w14 heterozygosity by allele specific oligonucleotide probes in five out of seven phenotypically DR4 homozygous (RA) patients who were found among 45 selected Caucasian RA patients with classical and seropositive disease.³ They proposed that their report was the first to describe high Dw14 in adult RA and suggested that the Dw14 allele may play an important part in susceptibility to RA.

We have now re-evaluated our series with regard to Dw4/Dw14 status. The table shows the phenotypes of Dw4 or Dw14 positive patients, or patients positive for both, in each group. The five Dw4/w14 heterozygotes in the group with classical RA without gold toxicity was significantly more than the expected number of 2.09 calculated from the phenotype frequencies ($\chi^2=4.05$, $p<0.05$). Instead, none of the patients with gold toxicity was Dw4/w14 heterozygous. Our results obtained with cellular HLA-D typing thus agree with those of Dr Nepom and colleagues concerning classical RA. Although the Dw4 and Dw1 genes both may be associated with disease susceptibility (gene), their effect on the clinical picture of RA may be even stronger.

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