appropriate evaluation of synovial fluid be carried out in all such patients.

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Acquired antithrombin III deficiency and systemic lupus erythematosus

Sir,

We read with interest the report by Gladman and Urowitz on thromboembolic disease and systemic lupus erythematosus (SLE).¹ The thrombotic diathesis in this group of patients was, however, not explained. It has been well established that familial antithrombin III deficiency is associated with a thrombotic diathesis.² Kauffman and coworkers have linked an acquired antithrombin III deficiency in patients with the nephrotic syndrome to their development of renal vein thrombosis and extrarenal sites of thrombosis.³ They demonstrated a highly significant negative correlation between serum antithrombin III concentration and urinary protein excretion ($r = -0.58$, p 2-sided <0.001). Their findings suggested that the low antithrombin III levels were due to loss of the molecule in the urine. Because renal disease with proteinuria is a frequent complication of SLE, we decided to determine plasma antithrombin III levels in a group of SLE patients.

Plasma antithrombin III concentration was assayed by radial immunodiffusion (Behring Diagnostic Corp., La Jolla, CA) on 33 plasma samples from 27 patients with documented SLE, i.e., meeting at least 4 ARA criteria for SLE.⁴ Twenty-four hour urine collections for creatinine and protein excretion were obtained on all patients within 1 week of the plasma sample. Creatinine clearances in all patients studied were greater than 30 ml/minute (mean = 68 ml/minute). Protein excretion ranged from 0 to 24.13 g per 24 hours (mean = 3.15 g per 24 hours).

There was a significant inverse correlation of antithrombin III level and urinary protein excretion ($r = -0.413$, p 2-sided <0.05). Antithrombin III levels were below normal in 5 patients, on at least 1 determination. Four of these patients had a rise in antithrombin III level to normal on serial determinations. In 2 of these patients there was a simultaneous dramatic decrease in urinary protein excretion of at least 6 g of protein per 24

hours. In the other 2 patients urinary protein excretion did not change during the period that their antithrombin III levels normalised. Both of these patients had clinical and serological evidence of active SLE at the time their antithrombin levels were low. Follow-up samples during disease remission showed normal antithrombin III levels. During the study period thromboembolic disease was not documented in any of the patients.

In conclusion, we have demonstrated that patients with SLE can have an acquired antithrombin III deficiency. There is a significant inverse correlation of antithrombin III level and urinary protein excretion. However, the normalisation of the antithrombin III levels in 2 patients occurred when their SLE became inactive, suggesting that low antithrombin III levels in SLE patients may be related to factors other than urinary protein excretion. Only a long-term prospective study of SLE patients with serial antithrombin III assays will determine if there is a relationship between and acquired antithrombin III deficiency and thromboembolic disease in SLE.

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Beta-2-microglobulin in RA

Sir, In 2 recent studies on serum beta-2-microglobulin ($\beta_2\mu$) in rheumatoid arthritis (RA)^{1,2} the results are somewhat divergent with regard to the correlation between $\beta_2\mu$ and the disease activity. We have studied the same subject and would like to report our findings.

Our material consisted of 51 consecutive inpatients with classical RA (ARA criteria 1958). One patient was excluded because of paraproteinaemia.

The clinical examination showed that the 50 patients could be separated into 2 distinct groups with regard to the disease activity. In 39 patients (mean age 53.8 ± 12.0 years, range 25-72 years) no more than a few joints were actually inflamed. Their disease was considered

slightly or moderately active. In contrast, 11 patients (mean age 51 ± 10.2 years, range 33–63 years) had widespread active arthritis with systemic symptoms such as fever and/or rheumatoid complications (amyloidosis 3, significant Sjögren's syndrome 2, neuropathy 1, necrotising nodules 1). These patients were felt to suffer highly active or complicated rheumatoid disease. The 2 groups were termed groups I and II respectively. $\beta_2\mu$ was determined by a radioimmunoassay, Phadebas β_2 -micro test (Pharmacia Diagnostics AB, Uppsala, Sweden).

Serum IgG, IgA, IgM, α_1 -antitrypsin, orosomucoid, and haptoglobin were analysed by a turbidimetric immunoassay using an Aminco Rotochem II centrifugal fast analyser. Other routine parameters determined were erythrocyte sedimentation rate (ESR), blood lymphocyte count, and serum creatinine.

A quotient was calculated between the obtained $\beta_2\mu$ value and the $\beta_2\mu$ value calculated from the linear regression line between $\beta_2\mu$ and serum creatinine.³ The equation was corrected for the present standard of $\beta_2\mu$, which gives 1.25 times higher values than that previously used for calculation of the regression line. The quotient was calculated in order to correct the $\beta_2\mu$ levels for a decreased glomerular filtration rate (GFR), which always gives higher values of the protein. In this way it was possible to minimise the influence of a decreased kidney function as a cause for elevated $\beta_2\mu$ values. Student's *t* test was used for testing the difference between the mean values in groups I and II.

The mean $\beta_2\mu$ concentration was significantly higher in group II than in group I (3.90 mg/l, SD 1.76, and 2.41 mg/l, SD 0.622 respectively; $p < 0.01$). In group I 41% of the patients had an increased $\beta_2\mu$ (> 2.4 mg/l) and 73% in group II.

Of the other laboratory parameters listed above only ESR and α_1 -antitrypsin were significantly higher in group II than in group I ($p < 0.01$). Serum levels of haptoglobin, orosomucoid, and IgM tended to be higher in group II ($p < 0.05$). The blood lymphocyte count was slightly lower in group II than in group I (mean 1.27×10^9 /l, SD 0.714×10^9 , and 0.732×10^9 /l, SD 0.694×10^9 respectively; $p < 0.1$).

The mean serum creatinine values did not differ significantly between the groups (group I $73.3 \mu\text{mol/l}$, SD 15.8; group II $81.1 \mu\text{mol/l}$, SD 32.7; $p > 0.1$).

Four of the 50 patients had serum creatinine values above the normal limits, $100 \mu\text{mol/l}$ in women and 115 in men. Three of these were found in group II. To eliminate an influence on $\beta_2\mu$ of a decreased GFR the 2 groups were compared with respect to the quotient $\beta_2\mu$ found/ $\beta_2\mu$ calculated. The difference was still significant (group II 1.44 mg/l, SD 0.304, group I 0.987 mg/l, SD 0.275; $p < 0.01$). If the 4 patients were excluded, the mean $\beta_2\mu$ value in group II, 3.16 mg/l, SD 1.06, was likewise significantly higher ($p < 0.01$) than in group I, mean 2.39 mg/l, SD 0.620.

Correlation coefficients were calculated between $\beta_2\mu$ and the ESR, blood lymphocyte count, and the serum values of orosomucoid, α_1 -antitrypsin, haptoglobin, IgA, IgG, IgM, and creatinine in all 50 patients. Only the correlations to ESR ($r = 0.41$) and creatinine ($r = 0.65$) were significant, $p < 0.01$. There was no correlation

between serum $\beta_2\mu$ and the duration of disease. In healthy subjects a correlation has been observed between serum $\beta_2\mu$ and age.⁴ In this material a tendency to higher $\beta_2\mu$ values with increasing age was observed, $r = 0.30$, $p < 0.05$. This agrees with the findings of Sjöblom *et al.*²

Manicourt *et al.*¹ reported a positive linear relation between $\beta_2\mu$ and Hollander's 'joint count' ($r = 0.898$). In the study of Sjöblom *et al.* there was no such close association with the clinical status measured with 'Ritchie index' ($r = 0.34$). Both indices indicate the number of joints actually painful to pressure or movements. To get a more comprehensive expression of the disease activity Sjöblom *et al.* also considered the physicians' overall assessment on a 10-point scale. The relation to $\beta_2\mu$ was weak ($r = 0.29$).

In both studies RA patients with elevated serum creatinine were omitted and in that of Manicourt *et al.* also those with other complications. Our material was unselected except for 1 case of malignant disease. Elevated values were found in several individuals with mild or moderate clinical activity but were more frequent among those with highly active or complicated disease. The mean $\beta_2\mu$ value was significantly higher in this last group. This group also contained most of the few patients with elevated serum creatinine. However, neither exclusion of these latter patients nor use of a $\beta_2\mu$ quotient, correcting for elevated creatinine values, changed the result.

Our findings support those of Sjöblom *et al.* in showing only weak correlations of $\beta_2\mu$ with the acute-phase-reactants and with the immunoglobulins in RA. The highest correlations were found with ESR ($r = 0.41$), IgM ($r = 0.29$), α_1 -antitrypsin ($r = 0.24$). This low correlation between $\beta_2\mu$ and accepted laboratory parameters of inflammation or 'activity' was also stressed by Manicourt *et al.* The tendency to a negative correlation between $\beta_2\mu$ and total blood lymphocyte count in our patients is contradictory to the last-mentioned authors' findings. If it does not depend on the sampling of patients or the relatively small number of patients in the study of Manicourt *et al.* this point needs further investigation.

We do not feel that $\beta_2\mu$ in RA is just a function of the inflammatory activity at a given time. In our opinion it may be suggested that, from unknown causes, elevated $\beta_2\mu$ in RA expresses an inherent trait of the disease in such cases to greater aggressivity or to extra-articular involvement. Long-term controlled studies of patients with elevated $\beta_2\mu$ values are needed to clarify the relationship between $\beta_2\mu$ and the clinical and radiological evolution of the rheumatoid disease as well as the relation between $\beta_2\mu$ and various forms of drug treatment.

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Obituary

Ralph Consden

Dr Ralph Consden, formerly biochemist to the Medical Research Council's Rheumatism Unit at Taplow, died in November 1980 at the age of 69. His name will forever be associated with the technique of paper chromatography which he developed with his colleagues Gordon and Martin while at the Wool Research Centre in Yorkshire. Although the technique was originated for the separation and identification of amino acids in hydrolysates of proteins, it was rapidly extended to other complex mixtures such as sugars and lipids. Its application played

a major part in the unravelling of the many unborn errors of metabolism, notably the mucopolysaccharidoses, many of which have rheumatological implications.

Dr Consden was essentially a practical chemist who excelled and delighted in doing things with his own hands. A major stroke from a cerebral thrombosis some 12 years ago was therefore a shattering blow, depriving him not only of his pleasure in work but also of his two major pastimes, cricket and the piano. He was a fine colleague, enjoyed everyone's confidence, and his gifts as a cartoonist will long be remembered by his many friends at Taplow.

L. E. G.

Notes

Twelfth Course on Foot Disorders

This course will take place on 18–22 May 1981 in Barcelona. Further information from the secretary of the course, Dr J. C. Gonzalez Casanova, Hospital de San Rafael, Pso. Valle de Hebron, Barcelona 35, Spain.

Symposium on crystalline deposits in human tissues

This symposium will be held at Mount Sinai Hospital, Toronto, Canada, on 13–14 August, 1981. It is an associated meeting of the XIIth Congress of the International Union of Crystallography. The topics include apatite, pyrophosphate, lipid, and other nonproteinaceous crystalline deposits. Details from Dr P.-T. Cheng, Department of Laboratories, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario, Canada M5G 1X5.