There is evidence for the presence of conformational anomalies in the serum IgG of patients with rheumatoid arthritis. Such evidence stems mainly from catabolic studies of normal IgG (from healthy volunteers) and rheumatoid IgG in man and in mouse; direct physico-chemical evidence has been lacking. Recently we have studied the circular dichroic (CD) spectra of serum IgG isolated from two healthy volunteers and from two patients with seropositive RA (volunteers E.S. and D.W.; IgG catabolic studies described previously (Watkins and Swannell, 1973)), together with IgG samples isolated from pools of normal and rheumatoid sera respectively. Some significant differences were observed between the normal and the rheumatoid IgG proteins and these observations are presented in this communication.

Circular dichroism (CD) spectra measure the unequal absorption of right and left circularly polarized light by optically active compounds. The main feature of the spectra of human IgG is a large negative maximum at 217 nm, which has been demonstrated to be characteristic of the β-structure of the protein (Doi and Jirgensons, 1970). At higher wavelengths there are smaller, but still characteristic, absorptions resulting from transitions in aromatic amino acid residues and from the asymmetric environment of disulphide linkages.

Using a Cary 61 recording spectropolarimeter, we found that the spectra of rheumatoid and normal IgG differed only in two regions, at 280 nm. and 294 nm. Rheumatoid IgG appears to have a decreased negative maximum at 280 nm. and an increased positive maximum at 294 nm. The variation in the spectra at 280 nm. is particularly interesting, since the hinge region is implicated in this transition from our parallel studies on the CD spectra of the IgG subfragments, Fab and F(ab')2: only the latter fragment contains the hinge region.

From this it would appear that rheumatoid patients have a conformational anomaly in the hinge region of at least a proportion of their serum IgG molecules.

The observation that these spectral differences could be enhanced by multiple freezing and thawing of rheumatoid sera before fractionation of the IgG protein lends weight to a hypothesis that the structural anomaly occurs as a natural molecular ageing process in vivo and that abnormal quantities of these altered molecules are retained in the serum of rheumatoid patients where they may stimulate a variety of immune phenomena.

Discussion

DR. EVANS (Bath) Have you measured the CD spectra of normal IgG under denaturing conditions such as freezing and thawing?

DR. JOHNSON Yes. Limited denaturation by multiple freezing and thawing will produce a marked reduction in the negative absorption at 280 nm. of both normal and rheumatoid IgG. We have also studied grossly denatured IgG samples that have been heated at 60°C. for 15 minutes. In these cases the CD spectra are drastically altered, indicating gross conformational changes.

DR. P. A. BACON (Bath) The thing most likely to produce structural alterations in IgG is antigen binding. Have you had a chance to look at antibody after binding with specific antigen?

DR. JOHNSON We have not looked at the spectra of specific antibody, nor of antibody dissociated in vitro from an antigen-antibody complex. Any conformational changes in antigen binding may depend on the antigen used. However, our previously reported catabolic studies do indicate some difference between 'normal' and 'antibody' IgG; but there is no evidence of excessive and specific IgG antibody production in the RA patient.

PROF. K. W. WALTON (Birmingham) In relation to the two slides comparing normal and rheumatoid IgG, you pointed out that in both there was an anomaly at 289 nm. which you interpret as being in the hinge region; I noticed that in the second of the paired comparisons there also appeared to be quite a marked anomaly in the region of 295 nm. Would you like to comment on that? I think the second of your suggested explanations was that there might be binding by another molecule. Gamma G globulin acts as a substrate for plasmin. Isolated gamma G in our laboratory does show slight alterations on storage as a result of the action upon it of traces of plasmin still present in the isolated preparation. Little is known about the site of attack of plasminogen but I think it is reasonable to suppose that it may attack in the hinge region.

DR. JOHNSON We believe that the changes in the 280 nm. region of the CD spectra are more significant than those at 294 nm. because the former represent almost a complete disappearance of a peak. The changes at 294 nm. represent small changes within a peak. We have not emphasized this part of the spectra since, during a study of the CD spectra of IgG subclass proteins, we found good reproducibility except in this region at 294 nm. To answer your second point, we have no evidence of plasmin in our IgG preparations, but in view of your comments we shall have to look for plasmin more critically. However, the changes in the CD spectra involve the whole of one peak, suggesting that most of the IgG molecules are involved, whereas the effects of plasmin should involve only a small proportion of the molecules.

Criteria for Classification of Systemic Lupus Erythematosus.

By P. Davis and G. R. V. Hughes (Department of Rheumatology, Royal Postgraduate Medical School, London)

This paper was published in full in the British Medical Journal (1973), 3, 90.

Discussion

DR. P. A. BACON (Bath) It seems to me that in many ways you do agree with the conclusions of Fries and Siegel.
(1973) that the A.R.A. criteria (Cohen, Reynolds, Franklin, Kulka, Ropes, Shulman, and Wallace, 1971) fit a classical population only. You chose a highly classical population by selecting those with DNA-binding, and you demonstrated that other patients whom you thought had S.L.E. did not fit the criteria. This is exactly what Fries and Siegel were saying. So there criteria may be very useful in selecting other patients in whom there is disagreement?

**DR. DAVIS** I think there is a significant difference in total percentages between those of Fries and Siegel and those in our reports. First of all we found a 91-8 per cent. correlation in cases of SLE as opposed to their 73 per cent. Theirs was, of course, a more sophisticated technique, using a computer bank and far more numbers. The second point is that, although our data are not yet complete, we have had the opportunity of analysing a number of cases of other connective tissue disorders and we have not found the number of false positives as high as that reported by Fries and Siegel; they found that approximately 19 per cent of cases of rheumatoid arthritis satisfied the criteria.

We have not found that, with the one exception of a case of Felty's syndrome. I think that our findings are that these criteria are a useful basis on which further revisions can be made and that their specificity would be enhanced if DNA antibodies and complement levels were included as criteria.

**PROF. V. WRIGHT (Leeds)** One always feels about criteria like this that what one really needs is weighting; it is not meaningful to give equal weight to every criterion and there are statistical techniques which are available to do this. I wonder if either you or the American series have in fact done this?

**DR. DAVIS** No. When the criteria were drawn up they were specifically designed not to be weight-specific.

**References**


---

Use of the MacIntosh Knee Arthroplasty in Patients with Rheumatoid Arthritis. By B. BLUM, A. G. MOWAT, G. BENTLEY, and J. R. MORRIS (The Rheumatology Unit, University Departments of Medicine and Orthopaedic Surgery, University of Oxford, Nuffield Orthopaedic Centre, Headington, Oxford)

Published in full in this issue of the *Annals* (1974) 33, 1.

---

Gout, Hypertriglyceridaemia, and Alcohol Consumption. By T. J. GIBSON and R. GRAHAME (Department of Rheumatology, Guy's Hospital, London)

Attention has been drawn to an apparent association between hypertriglyceridaemia and gout (Feldman and Wallace, 1964; Darlington, Shaw, and Scott, 1971).

Since there is a known relationship between hypertriglyceridaemia on the one hand and obesity and excessive intake of alcohol on the other, the question arises whether the hyperlipidaemia seen in gouty subjects is related to their gout *per se* or whether it can be explained on the basis of the obesity or drinking habits that many of them display (Grahame and Scott, 1970).

In either case the pathogenic mechanism might be fatty infiltration of liver as reported in gouty subjects by Hennecke and Südhof (1970). This finding could explain the high incidence of abnormal bromsulphthalein retention seen in gout sufferers (Grahame, Haslam and Scott, 1968).

The present study was undertaken to investigate the problem further. Fasting triglyceride and cholesterol values in forty gouty subjects were compared with those observed in an equal number of abstemious controls matched for age, sex and ponderal index. Estimations of bromsulphthalein retention and urinary uric acid excretion on a low purine diet were also performed on the gouty patients.

A significant inverse correlation was found between serum triglyceride values and ponderal index in the gouty subjects ($r = -0.355$; $P < 0.05$). The mean fasting serum triglyceride level of the gouty subjects as a whole, however, was not significantly higher than that of the controls ($r = 1.72$; $P < 0.1$). Abnormal bromsulphthalein retention was found in fourteen (35 per cent) of the gouty patients, but there was no correlation between the percentage of bromsulphthalein retained and the serum triglyceride level.

Of the gouty subjects seventeen (42 per cent) were excessive drinkers of alcohol (defined as the consumption of more than 3 pints of beer daily or equivalent). The heavy drinkers had significantly higher triglyceride levels than both their matched controls ($r = 2.69$; $P < 0.025$) and the moderate or non-drinking gouty subjects ($r = 3.16$; $P < 0.01$). There was no correlation between abnormal bromsulphthalein retention and alcohol consumption, but the uric acid values of the gouty subjects showed no correlation with serum triglyceride levels, alcohol consumption, or abnormal bromsulphthalein retention.

The results suggest that the fasting serum triglyceride values of gouty patients increase with obesity but do not differ from those of healthy subjects who have a similar range of adiposity. However, those gouty subjects who drink excessively do seem to have relatively higher triglyceride levels than non-drinking subjects with and without gout. This difference is not necessarily related to abnormal liver function.

**Discussion**

**DR. G. R. V. HUGHES (London)** Did you re-test your patients after a period of abstinence for urate and for triglyceride levels?

**DR. GIBSON** Its not easy to encourage the heavy drinkers of this world to give up their sustenance. Six patients volunteered to abstain from alcohol for 2 weeks or 4 weeks; three were frankly hypertriglyceridaemic and three had normal triglyceride levels. The three who abstained for 3 weeks showed quite definite falls in the levels of serum triglyceride. One resumed drinking and his triglyceride level rose again.

**PROF. K. W. WALTON (Birmingham)** In relation to the kind of correlation you were looking for between either obesity or drinking habits and triglyceride levels, surely it