Discussion

DR. J. BENRAAD (*Holland*) Did you measure the concentration of cortisol acetate before and after phenylbutazone?

DR. DOWNIE No.

DR. J. BENRAAD (*Holland*) I asked this question because it has been reported (Wise, Margraf, and Ballinger, 1971) that in rheumatoid arthritis there exists a very high concentration of cortisol acetate in blood as compared to the concentration in normal individuals.

DR. DOWNIE Much has been done on the metabolism of cortisol in rheumatoid arthritis, but one wonders just what the significance of this is.

DR. F. W. J. GRIBNAU (*Holland*) You have already mentioned the work of Stenlake, Davidson, Jasani, and Williams (1968) and you will know the work of the Copenhagen group (Hvidberg, Schou, and Jansen, 1971).

Brodie (1966), speaking on the pharmacological implications of drug transport, speculated about the role of displacement of corticosteroids from transcortine in rat plasma by various compounds and particularly related this to the anti-inflammatory activity of these compounds. Would you like to comment on this?

DR. DOWNIE There have been many suggestions that the anti-inflammatory drugs act by displacement on cortisol-binding sites. The problem with Stenlake's work, and I was associated with it, was that we used rather unphysiological levels. There may be some displacement but it is very difficult to be sure, as it requires measuring micro amounts of cortisol by a radioimmune assay technique and we do not have this available at the present time. One of the problems is that most people look at the plasma proteins and forget that, as far as cortisol is concerned, up to 25 per cent may be bound to the red cells, and it may well be that we split it from these rather than from the proteins.

References

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Mechanism of Action of Some Anti-Rheumatic Drugs in Allergic Blood Diseases. By H. O. NIEWEG, G. S. VAN DER SCHANS, F. BOS-VAN ZWOL, and P. J. STIJNEN (*Division of Haematology, University of Groningen, Holland*)

Some years ago we reported that in some individuals thrombocytopenic purpura may be related to the use of aspirin. This was confirmed by subsequent provocation tests with this drug. Since then we have tried to differentiate aspirin-induced thrombocytopenia from the idiopathic type by laboratory methods such as the platelet factor 3 activation (PF3A) test. The results with normal platelets, patients' serum, and aspirin suggested that 25 out of 34 thrombocytopenic patients were hypersensitive to this drug.

In allergic thrombocytopenia, drugs are generally believed to act as haptens, but this is unlikely in the case of aspirin, because IgG from patients does not bind with this drug. Moreover, the antibodies also injure normal platelets in PF3A tests in the presence of quinine, quinidine, chloroquine, 1,4-naphthoquinone, and especially of PCMBS, a selective inhibitor of membrane SH groups.

Antibodies active in the presence of PCMBS were detected in sera not only from patients with thrombocytopenia induced by various drugs but also from patients with other types of thrombocytopenia. We assume that the various primary factors—known or unknown—apparently induce an identical change of the platelet membrane which makes it antigenic. In drug-induced thrombocytopenia, a sublethal membrane change induced by the drug is made lethal by subsequent antibody action. For this two-step mechanism the term 'spoiled membrane allergy' is used.

A similar final common pathway of minor chemical damage amplified by immunological injury also seems probable in drug-induced aplastic anaemia and agranulocytosis.

Discussion

DR. L. E. GLYNN (*Taplow*) Do the complement components of serum play an important part in this reaction?

PROF. NIEWEG Not necessarily. We have performed complement-fixation experiments with platelets, serum, and PCMBS and about half are positive.

DR. L. E. GLYNN (*Taplow*) In the absence of complement, could you get a positive effect on the stypven time?

PROF. NIEWEG For the normal platelets, we used a platelet-rich plasma so that the complement was present.

DR. L. E. GLYNN (*Taplow*) But in the presence, for example, of cobra venom, would that inhibit the reaction?

PROF. NIEWEG I do not know; we have not tried that.

DR. W. H. D. DE HAAS (*Holland*) Did you study the influence of gold, which is one of our chief tools?

PROF. NIEWEG We have not studied gold *in vitro*. We had some patients with gold thrombocytopenia, but gold is rather difficult to handle *in vitro* as it is oily, whereas quinine and chloroquine are nicely soluble and can be easily handled.

DR. J. KAKAKI (*Holland*) Did you look for specific drug antibodies in other immunoglobulin classes besides IgG.?

PROF. NIEWEG No.

Mobility of the Metacarpophalangeal Joints in Normal Subjects and in Rheumatoid Patients. By W. Y. LOEBL (*Westminster Hospital and Institute of Orthopaedics, London*)

The function of the hand depends to a considerable extent on the function of the metacarpophalangeal (MCP) joints. Ulnar drift in rheumatoid arthritis cannot

develop unless abnormal increased mobility is present in the MCP joints. In the present work two methods were used to study the mobility of MCP joints.

In 108 normal men and 120 normal women aged 18 to 80 years, the angle between the third (middle) and fourth (ring) fingers was measured in both hands. Standardized abducting forces were applied to separate these fingers, with the MCP joints at 90° of flexion. The same was done in thirty rheumatoid patients. In 47 of the normal subjects and in all rheumatoid patients, standardized axial traction was applied across the MCP joint of the third finger and the widening of the joint space was measured from radiographs.

In normal subjects the results of the abduction test showed that the response of the MCP joints was proportionate to the force, and viscoelastic characteristics could be demonstrated. Females were significantly more mobile than males, but there was no appreciable change in mobility with age. The dominant hand was less mobile than the non-dominant. In axial traction the normal subjects showed larger individual variations; otherwise the results were similar.

In rheumatoid patients preliminary results showed a tendency towards a bimodal distribution of mobility. Frank hypermobility was seen in about one-third, and was often present within the first 2 years of their disease. In some patients the collateral ligaments appeared to be weaker on the radial side of the MCP joint.

Discussion

DR. J. D. GOODE (*Hull and East Riding*) Was the hypermobility in any way related to treatment with corticosteroids?

DR. LOEBL None of the hypermobile rheumatoid patients were receiving corticosteroids; in fact, only two of the thirty rheumatoid patients were taking these drugs.

DR. M. I. V. JAYSON (*Bristol and Bath*) At a recent meeting of the Heberden Society Prof. Wright showed some nice x rays of gas induction when the MCP joints were under axial tension. In particular this occurred very suddenly. Did you find that your length change in extension occurred suddenly?

DR. LOEBL None of the joints was heard to 'crack' and in none of the radiographs were there any gas shadows. To make a joint 'crack' it has to be pulled fairly sharply; with my instrument the required traction load was reached gradually over 3 or 4 seconds.

DR. E. N. COOMES (*London*) What happened when you left the 5 kg. weight on the finger? Were there any symptoms due to taking up of the slack in the joint?

DR. LOEBL I think that with these two methods, the slack, if any, is taken up at the smallest force.

DR. E. N. COOMES (*London*) Yes, but presumably that is just as in the experiments that I performed on the knee (Coomes, 1962). There is a slack to start with and there is a further increase when the weight is left on longer. Did you find any increase? If so, at what rate did this occur?

DR. LOEBL Yes, there is a further increase which is due to creep. Its rate diminishes exponentially with time.

DR. E. N. COOMES (*London*) The point I am coming to is that when you draw the finger sideways you must have a fulcrum with two bits of cartilage pushing against each other, and therefore the creep that you are demonstrating could either be pulling the ligaments or compressing the cartilage. I suspect that it is the latter, because at the loads about which you are talking you do not normally get much extensibility.

DR. LOEBL I did take some further x rays during continuous loading and the creep appeared to be mainly, if not entirely, in the various ligaments which are stretched during the procedures.

DR. E. N. COOMES (*London*) I was referring to sideways movement rather than to pulling.

DR. LOEBL It is possible that in sustained abduction there is also progressive compression of articular cartilage. One cannot rely on the x rays, however, because the phalanx shifts to a different region on the metacarpal head where the cartilage may be thinner.

DR. E. N. COOMES (*London*) I was trying to draw comparisons with deflections of the knee joint.

DR. LOEBL Yes, that was a very similar experimental procedure and you showed that, in the knees, the articular cartilage was responsible for the creep. Yet *in vitro*, creep occurs in all types of connective tissues.

DR. J. A. COSH (*Bath*) Among your normal subjects were you able to identify any with hypermobility who were subject to arthralgia?

DR. LOEBL No, I excluded patients with abnormal hypermobility from the study of the normal subjects.

Reference

Coomes E. N. (1962) *Ann. rheum. Dis.*, 21, 378

Rheumatoid Arthritis, Typus Robustus. By W. H. D. DE HAAS, W. DE BOER, F. GRIFFIOEN, and P. OOSTEN-ELST (*Departments of Rheumatology and Anthropobiology, University of Amsterdam, and Department of Psychology, Amsterdam Centre for Rheumatic Diseases, Holland*)

A group was isolated of nine male patients with classical rheumatoid arthritis (RA) who had a striking discrepancy in common. On the one hand, they all had the prognostically unfavourable symptoms of subcutaneous nodules and a high titre in the Waaler-Rose test, while, on the other hand, they were robust, healthy, and working normally. This group, tentatively called robust type (Rob), was compared with two male RA control groups: one group of nine patients in remission (Rem), and the other of nine matched patients in an active phase (Act). The duration of the disease and the kind and number of the joints involved were comparable in the three groups.

This comparative study revealed additional sthenic properties of Rob; nearly all Rob did heavy labour, while all Rem had light adapted work, as had the four Act who