DR. NICHOLLS We obviously did platelet counts, but no other tests of platelet function. There were no total variations.

DR. M. K. JASANI (*Horsham*) In fact, one does not observe a substantial improvement in the vascular complication of homograft rejection in the rabbit until there is a significant fall in the platelet count, a requirement which will, of course, be unethical in clinical trials because it may lead to other complications. This immediately leads one to exclude the use of cytotoxic drugs as a practicable therapy.

DR. A. J. SWANNELL (*Nottingham*) With reference to the three patients who improved on azathioprine, did they relapse when you stopped the drug? Also, did you perform any complement levels during the trial?

DR. NICHOLLS The three patients who improved in the azathioprine group maintained their improvement for about a year, although one did subsequently die from a perforated peptic ulcer. Complement studies were unfortunately not done.

DR. P. J. L. HOLT (*Manchester*) I think it is important to know what you are trying to do. In this case you have given azathioprine in a standard dose. Now no patient responds the same way to a standard dose; therefore you should use different doses, *i.e.* the optimum for each patient. Secondly, there is a probability that rheumatoid vasculitis is an immune complex type of disease. Now, in another vasculitic disease due to immune complexes such as the Australia antigen-associated polyarthritis nodosa, it may be positively dangerous to alter the ratio of antigen and antibody by immuno-suppressive therapy in this disease. In other words, if you do not know what is happening, you may in fact do damage rather than benefit by altering the *status quo* in the ratio of antigen to antibody. So first of all you must have some idea how much of the immuno-suppressive agent each patient needs to obtain the optimum treatment, and you must tailor the treatment to each patient.

DR. NICHOLLS We must defend our giving a standard dose of azathioprine to our patients by reference to previous controlled trials in which two out of three did the same. It is difficult to define the optimum dose for each patient when the effectiveness of the drug is not proven. I accept that it would be nice to know exactly what azathioprine was doing by monitoring complement and so on; it was intended to do this at the start of the trial but unfortunately this was not possible.

DR. SCOTT If one knew exactly what one was doing there would be no need to do a trial. One of our main therapeutic problems at the moment is the treatment of this potentially lethal complication of rheumatoid arthritis by potentially lethal drugs. Our carefully documented experience has emphasized what a very formidable undertaking this is.

DR. C. FELDMAN (*London*) I should like to support Dr. Scott. Surely this is more in the nature of a pilot trial dealing with clinical effects of a drug. Dr. Holt and some other speakers have confused the issue by introducing into the discussion complement and other parameters. It is impossible to deal with the whole vast subject in one paper and this particular paper aims at exploring one aspect of the problem.

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Naproxen—A New Non-steroid Anti-inflammatory Agent. By H. F. HILL (*Stoke Mandeville Hospital, Aylesbury*), B. M. ANSELL (*MRC Rheumatism Unit, Canadian Red Cross Memorial Hospital, Taplow*), J. M. GUMPEL (*Northwick Park Hospital, Harrow*), A. G. S. HILL (*Stoke Mandeville Hospital, Aylesbury*), J. A. MATHEWS and M. SEIFERT (*Department of Rheumatology and Physical Medicine, St. Thomas' Hospital, London*), and A. G. MOWAT (*Nuffield Orthopaedic Centre, Headington, Oxford*)

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Clinical and Laboratory Double-Blind Investigation on the Effect of Fibrinolytic Therapy in Patients with Cutaneous Vasculitis. By W. J. CUNLIFFE, B. DODMAN, and B. E. ROBERTS (*Department of Dermatology and Haematology, Leeds General Infirmary*)

The pathogenesis of cutaneous vasculitis is unknown but recent investigations have suggested that immunological phenomena, such as the precipitation of immune complexes, may be important. As a result of the immunological reaction occurring within the blood vessel wall this may culminate in the formation of a thrombus. Investigation of blood coagulation factors are limited, but studies of fibrinolysis have been more detailed. We have demonstrated that 60 per cent. of patients with cutaneous vasculitis have an impaired fibrinolytic activity and Parish (1972) has confirmed this observation.

It is also established that phenformin and an anabolic steroid (such as ethylestrenol and stanozolol) will enhance fibrinolytic activity. We therefore compared in a double-blind cross-over trial the effects of phenformin and an anabolic steroid with placebo on the clinical state, plasma fibrinolytic activity, and F-R antigen in fifteen patients with cutaneous vasculitis (two of whom had rheumatoid arthritis). Nine patients showed considerable clinical improvement whilst taking phenformin and an anabolic steroid. An impaired fibrinolytic activity before treatment and during the placebo period favoured clinical improvement. The mean activity before treatment in the successful group was $215{\cdot}6 \pm 25{\cdot}9$ min. and in the unsuccessful group $123{\cdot}0 \pm 13{\cdot}1$ min. This difference is significant at the 5 per cent. level.

This double-blind trial underlines further the importance of fibrinolytic activity in the aetiology of cutaneous vasculitis.

Discussion

DR. P. J. L. HOLT (*Manchester*) Am I right in thinking the blood vessel itself has a fibrinolytic activity? If so, to

what extent is this independent of the serum fibrinolytic activity. When you improve the fibrinolytic activity of the serum, does the fibrinolytic activity of the vessel improve and is it dependent or secondary to the serum?

DR. CUNLIFFE We are finding a relationship between tissue activity and plasma fibrinolytic activity. Furthermore, patients with vasculitis have no tissue fibrinolytic activity whatsoever in their lesions, and the skin nearby where there is no rash also shows a reduced fibrinolytic activity. The fibrinolytic activity of the tissues improves with treatment.

DR. H. L. F. CURREY (*London*) In patients with vasculitis and raised euglobulin lysis times, what is the effect on the euglobulin lysis time of giving steroids?

DR. CUNLIFFE I have not done any work on steroids, but we found that in four patients who were on steroids there was some improvement in the fibrinolytic activity and in two there was not; but the patients who had rheumatoid arthritis were also on other drugs.

DR. A. ST. J. DIXON (*Bath*) Would it not be equally logical to conclude from the data that patients who start with a prolonged euglobulin lysis time have a good prognosis irrespective of treatment?

DR. CUNLIFFE This we have not found. We have been studying patients over a period of several years and at the moment one cannot draw this conclusion.

DR. M. I. V. JAYSON (*Bath*) Do you think that the prolonged euglobulin lysis time could be due to excessive fibrin deposition and be the result of vasculitis rather than being concerned in pathogenesis?

DR. CUNLIFFE This is our conclusion.

DR. D. A. PITKEATHLY (*Manchester*) Are you using this treatment as the treatment of choice in patients with severe vasculitis?

DR. CUNLIFFE I should treat the acute vasculitis with steroids, but if the patient has had it for many years and the fibrinolytic activity is impaired then I would go straight on to phenformin and an anabolic steroid.

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Immunohistological Studies of the Kidney in Systemic Lupus Erythematosus and Systemic Sclerosis. By D. G. SCOTT and N. R. ROWELL (*Leeds*)

The kidney specimens examined were obtained from seven patients with systemic lupus erythematosus and eight with systemic sclerosis. Fourteen of the specimens were obtained at autopsy, and one at biopsy from a patient with systemic schlerosis.

Sections from all specimens were reacted in immunohistological staining experiments with antisera to IgG, C'3, and human renal glomeruli. Sections of kidney from three patients with systemic lupus erythematosus and three with systemic sclerosis were reacted also with antisera to IgM, IgA, and fibrinogen.

In systemic lupus erythematosus, granular staining for IgG and C'3 was found in the walls of arterioles in five kidneys and the glomerular mesangium or along glomerular capillary basement membranes in six. In two instances granular basement membranes staining was superimposed on smooth linear staining of the basement membrane. The presence of granular basement membrane staining appeared to correlate with clinical evidence of renal failure, but staining confined to the mesangium did not. This relationship has been previously described by Koffler, Agnello, Carr, and Kunkel (1969).

In systemic sclerosis, IgG was detected in arterioles and in glomerular capillary basement membranes in one kidney and IgG and C'3 in a second. Staining for fibrin was found at these sites in three other kidneys.

In studies with antiglomerulus antisera, systemic sclerosis kidneys showed alterations in the pattern of intimal and medial staining of arterioles in seven instances and broadening of glomerular capillary basement membranes in four. In systemic lupus erythematosus abnormal antiglomerulus staining was not found in the absence of immunoglobulin deposition.

It is suggested that these observations provide further evidence that immunological processes are not involved in the pathogenesis of the renal lesions of systemic sclerosis. They appear to indicate also that the vascular deposition of fibrin in systemic sclerosis occurs in previously damaged vessels.

Discussion

DR. P. J. L. HOLT (*Manchester*) I am not quite sure what your antiserum is raised against, because it does not seem to be basement membrane antigen and it seems to be staining the arterioles rather than the rest of the glomerulus.

DR. SCOTT The antiserum was raised against the whole of the glomerulus. Glomeruli were stained in the sections.

DR. P. J. L. HOLT (*Manchester*) So it is fairly crude.

DR. SCOTT Yes, it is a crude antiserum.

DR. P. J. L. HOLT (*Manchester*) And it stains the arterioles of the kidney in systemic sclerosis. Can you find staining in other organs in systemic sclerosis?

DR. SCOTT The antiserum will produce staining of reticulin in the media of normal arteries. In systemic sclerosis there are abnormalities in the distribution of this staining. These abnormalities are not associated with the deposition of globulin, but may be associated with the deposition of fibrin.

DR. P. J. L. HOLT (*Manchester*) So it is the pattern of the staining rather than the presence or the absence of the staining that is important?

DR. SCOTT Yes.

DR. M. I. V. JAYSON (*Bath*) Dr. Dubois has presented a series of patients with systemic sclerosis which showed the features of S.L.E., and these features responded to steroid therapy, whereas the systemic sclerosis features did not. Were you able to find any S.L.E.-like signs and symptoms in this group of systemic sclerosis patients?

DR. R. N. MAINI (*London*) Was there any correlation with immunoglobulin or complement levels in the pattern of deposition which you saw?

DR. ROWELL This work has been done over about 10 years. Serum complement levels were not available in this hospital in the early days.