

Cases	Age (yrs)		Metacarpal bone density	
	Mean	Range	Per cent. above 50th and 90th percentile	
OA + osteotomy (100)	56	27-76	91	49
OA + replacement (100)	65	50-83	87	51

Bone density in 51 of the osteotomy patients was measured again between 2 and 6 years later. Changes in metacarpal bone density were:

Increased	10 cases
Parallel to percentile line	16 cases
Decreased	25 cases

Although the patients were asked about the effect of the osteotomy, and most (80 per cent.) were satisfied, no proper assessment such as would allow correlations with the above findings was made.

These findings suggest the hypothesis that an increase in bone density precedes the development of OA. The evidence is clearly inconclusive; a longitudinal study in which bone density from childhood is measured from hand x rays would show whether, as we think, those with a very high bone density go on to develop OA in later years and would be a test of the postulate that there is a direct cause and effect relationship between an abnormally high bone density and the development of OA. There are reasonable prospects that such a study is feasible, as x rays taken of the hands of 120 schoolboys 20 years ago are available and have been measured for bone density. The subjects can be readily traced for further study concerning the development of OA in the future.

*Discussion*

DR. C. F. HAWKINS (*Birmingham*) Can you correlate the density of bone with physical activity in the jobs that people are doing?

DR. FOSS I have no accurate information, but one thing that has struck me in examining the bone density of schoolboys is that those who were above the 90th percentile group were the very keen rugby playing, boxing types, whereas the idle fellows were down at the bottom of the scale.

DR. A. J. PALFREY (*London*) As I understand this work, the measurements of bone density have been done on a single metacarpal which is, of course, an upper limb bone, whereas the diseases we're talking about are in the lower limbs. Now I'm sure that Dr. Exton-Smith checked the correspondence of upper limb and lower limb bone density (Exton-Smith, Milland, Payne, and Wheeler, 1969). Do you not think it might be advisable to check on the lower limb bone as well?

DR. FOSS Yes. In fact, where low bone density is concerned, the effect of low bone density in a metacarpal is associated with a sub-capital fracture of the femur so that there is obvious correlation there. One indication that high bone density in a metacarpal goes with high bone density in, for instance, a femur is that a fracture of the neck of the femur is extremely rare in cases of osteoarthritis of the hip.

DR. D. A. PITKEATHLY (*Manchester*) I wonder if perhaps the correlations might be somewhat different if we excluded the subjects with generalized osteoarthritis

(GOA). It seems to me that osteoarthritis in the hip in GOA may develop by a different mechanism than idiopathic osteoarthritis.

DR. FOSS There are those who hold the view that there is no such thing as idiopathic osteoarthritis of the hip. However, we examined the question whether the 200 patients in our series had monarticular or polyarticular osteoarthritis. They were randomly distributed. Some of them had both hips, some one hip, and some multiple joints involved.

DR. R. GRAHAME (*London*) It seems that the whole hypothesis rests very much on the validity of Exton-Smith's data. Can you tell us a little more about this data—what population they were drawn from and so forth—because what may be abnormal in Camden may be normal in Stanmore?

DR. FOSS That is absolutely right. They had a series of nearly a thousand individuals who turned up at the casualty department for unrelated injuries and happened to have had their hands x-rayed, and inmates of a geriatric home, and various people like that. They have correlated their radiological findings with bone ash measurements on *post mortem* studies and they agree apparently very accurately using this particular form, more so in fact than the various other formulae.

DR. J. BALL (*Manchester*) Have you data on osteoarthritis of the hip in the control (Exton-Smith) group used for bone density comparisons?

DR. FOSS No. His survey was of a group of normal people. The hips were not x-rayed to exclude osteoarthritis, but then again his cases were of all ages from 5 years upwards.

DR. J. BALL (*Manchester*) Yes, but not making age-matched comparisons? I am suggesting that the true situation requires a knowledge of the distribution and severity of osteoarthritis of the hip in your bone density control group.

DR. FOSS There may be a lot of osteoarthritis in the older members of his sample, but in the younger members I think it is no more likely than the incidence would be in this room. That may be a criticism that I have used his figures inaccurately, but in fact the various other formulae for the calculation of bone density have been used in this study to cross-check all the cases, and they agree that those who are osteoporotic or osteoarthrotic by one method of measurement are so by another and *vice versa*.

*References*

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**Controlled Trial of Azathioprine in Rheumatoid Vasculitis.**  
 By A. NICHOLLS, M. L. SNAITH, R. N. MAINI, and J. T. SCOTT (*Kennedy Institute of Rheumatology, London*)

There are numerous case-reports of beneficial effects from cytostatic drugs in rheumatoid arthritis, but controlled trials are few and may be listed as follows (overleaf):

Drug	Author	Date	Daily dose	Mean duration	No. of patients	Conclusions
(A) Azathioprine	Mason <i>et al.</i>	1969	2.5 mg./kg.	1 yr	49	36 per cent. reduction in steroid dose
	Levy <i>et al.</i>	1972	3.0 mg./kg.	6 mths	18	'Marked improvement' in 39 per cent.
	Urowitz <i>et al.</i>	1971	2-3.5 mg./kg.	16 wks	10	'Statistically significant' improvement
(B) Cyclophosphamide	A.R.A.	1970	Up to 150 mg. (Control up to 15 mg.)	32 wks	48	Greater reduction in activity in high dose group
	Lidsky <i>et al.</i>	1972	0.7-1 mg./kg.	1 yr	22	No benefit
	A.R.A.	1972	Up to 150 mg. (Control up to 75 mg.)	32 wks	82	High dose better than low dose
	Townes <i>et al.</i>	1972	117 mg.	9 mths	24	Effective

None of these trials has been concerned specifically with vasculitis for which an immune basis has been suggested. Cytostatic drugs possess both immunosuppressive and anti-inflammatory properties, but improvement in the features of vasculitis might be interpreted as indicating that a specific immunosuppressive effect was taking place.

The use of potentially hazardous agents of unproven value was considered to justify a double-blind controlled trial involving fifteen patients with vasculitis complicating rheumatoid disease. Seven patients were randomly selected for treatment with azathioprine (2.5 mg./kg. body weight) and compared with a matched group of eight subjects who received inert tablets. Treatment of patients in both groups (corticosteroid hormones, analgesics, etc.) was continued individually as seemed necessary.

The mean duration of therapy was 27 weeks. There were two withdrawals (one a patient taking azathioprine who had severe vomiting; the other a patient receiving placebo who developed septicaemia), but no other toxic effects. There were three deaths, one in the azathioprine group and two in the placebo group. Clinical improvement in vasculitis was considered to have taken place in three patients receiving azathioprine and four patients receiving placebo; deterioration in two patients on azathioprine. One control patient remained unchanged.

The striking fact to emerge from the study is that the very variable natural history of vasculitis in rheumatoid disease makes therapeutic assessment extremely difficult. From this limited but closely studied group of patients, it was certainly not possible to discern a beneficial action attributable to azathioprine.

### Discussion

DR. A. K. THOULD (*Truro*) I should like to ask why you chose azathioprine rather than for instance chlorambucil which is said to be a better cytotoxic and immunosuppressive agent?

DR. NICHOLLS This trial was started about 4 years ago and at that time we had more experience with azathioprine than with any of the other cytotoxic agents.

DR. P. J. L. HOLT (*Manchester*) You described these drugs as immunosuppressive and anti-inflammatory. They also are very strong suppressors of fibroblastic action. I can visualize that this latter action might impede the repair of ulcers. The second point is the use of these drugs. As shown in the Tables, varying doses have been

used and I wonder if its justifiable to do these trials without having any idea of what is happening. We do not know how to measure immunosuppression, so if one is using what amounts to blind and arbitrary dosage, one ought to take the opportunity to try and assess the effect using some other parameters, presumably immunological.

DR. NICHOLLS We did lymphocyte transformation to phytohaemagglutinin and purified protein derivative before treatment and during treatment and there was no consistent difference in these.

DR. P. J. L. HOLT (*Manchester*) These are quite crude parameters.

DR. MAINI (*London*) I am not sure what Dr. Holt is after. This paper is concerned with an evaluation of the possibility that azathioprine has clinically recognizable efficacy in the management of rheumatoid vasculitis rather than with the assessment of a possible mode of action. Although it would be of interest to be able to assess the immunological function of patients on azathioprine and to know whether this was related to the success or failure of the drug, it is immaterial to the conclusions of this study.

DR. G. HOLDEN (*Worthing*) It has been reported with azathioprine that the effect is potentiated in patients receiving steroids. You say that the concomitant treatment was continued. Is there any difference in the numbers of patients in your two groups with regard to steroids?

DR. NICHOLLS No. All the patients but one were receiving steroids, and the mean steroid dosage at the onset in both groups was 9.8 mg. prednisone daily. So there was in fact no difference at all.

DR. M. K. JASANI (*Horsham*) Perhaps I can throw some light on the problem outlined by Dr. Holt and the counter argument put by Dr. Maini. It is true to say that cytotoxic agents do in fact have an immunological effect quite separate from any anti-inflammatory effect; and it may therefore be quite possible to observe a substantial anti-inflammatory effect, *e.g.* improvement in joint pain, without having to alter the underlying immunological disorder (Swanson and Schwartz, 1967). But in relation to the present study, the important point is to know of some objective measurement that could enable us to judge whether the amount of drug employed was sufficient to induce the desired therapeutic effect, *i.e.* the arrest of recurrent vasculitis. In my view serially-obtained platelet counts might be one such criterion.

DR. A. ST. J. DIXON (*Bath*) Have you done any studies on platelets?

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  $215.6 \pm 25.9$  min. and in the unsuccessful group  $123.0 \pm 13.1$  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