has been noted that the patients whose disease becomes and remains inactive tend to have normal tests. In patients whose disease starts later in life (*i.e.* at 10 to 15 years), we have found more positive rheumatoid factor and antinuclear factor tests than in the younger ones, but you do not seem to have found this.

DR. BLUESTONE We did have a fair number of older patients and some in whom the age at onset was 12 to 16 years.

DR. B. M. ANSELL (*Taplow*) That proportion is the same (*i.e.* 10 per cent.)?

DR. BLUESTONE Yes, and this is where our series differs from all the others. Does that answer your question?

PROF. E. G. L. BYWATERS (*Taplow*) You showed functional class grading, but I saw no disease activity grading, so that the correlation of disease activity with sero-positivity is an impression. Is that correct?

DR. BLUESTONE Yes.

PROF. E. G. L. BYWATERS (*Taplow*) May I ask about the significance of the rather, to my mind, small difference shown in the functional class grading between the 24 cases with positive rheumatoid factor and the remainder. Have you done any statistical tests for significance?

DR. BLUESTONE The numbers who were positive were too few to permit a statistical analysis, and that is why I have tried to hedge my comments by referring to 'a trend'.

DR. J. M. GUMPEL (*London*) The use of white cells as a substrate for antinuclear factor tests has led to rather more positive results in many series than the use of, say, liver or calf thyroid. Do you have any comparable control, or figures for antinuclear factor to compare with your 4 per cent. in these children?

DR. BLUESTONE The antinuclear factor test, done in this way in this laboratory, gives if anything a much lower incidence of false positives than other series. Our controls were all negative for ANA.

Reference

CASSIDY, J. T., AND BURT, A. (1967) *Arthr. and Rheum.*, **10**, 272.

Uptake of P^{32}-labelled Cyclophosphamide from Arthritic Knee Joints. By M. I. D. CAWLEY, J. M. MCALLISTER, A. K. THOULD, and H. WYKEHAM BALME (*St. Bartholomew's Hospital, London*) Published in the *Annals* (1969), **28**, 624.

Discussion

DR. A. ST. J. DIXON (*Bath*) This study emphasizes again what an extraordinarily good absorber the joint is. You can get a systemic effect from intra-articular cortisone (I mean *cortisone*) almost 24 hours more quickly than from intramuscular cortisone? Did you give any instructions to your patients about how much exercise they might take after the injection. Did you allow them to walk around or move their limbs? This would alter the rate of absorption very much.

DR. WYKEHAM BALME They were all kept at rest overnight afterwards. Some of them were sent home and some of them were dealt with in hospital. We were as strict and even about this as we could be, but many of them were out-patients.

DR. I. A. WILLIAMS (*Tunbridge Wells*) I am not sure that you should be quite so despondent. A few years ago we gave intra-articular injections of triamcinolone and measured the plasma cortisol levels in the blood, and by measuring the subsequent depression of endogenous cortisol formation we found that it diffused out of the joints very rapidly. In fact the Americans have shown that hydrocortisone can be extracted from one knee 4 hours after injecting it into the contralateral knee.

DR. W. CARSON DICK (*Glasgow*) The rate at which a substance of low molecular weight leaves the joint is related to the degree of lipid solubility or insolubility and of protein binding. Have you any information on either of these points? Your nate of disappearance seemed to me to be rather slow when compared to other substances of low molecular weight, which tend to have half-lives of under an hour. Without more knowledge of its biochemistry it would be difficult to derive useful information on the metabolism of this drug in the knee.

DR. WYKEHAM BALME I am afraid I have no information on the lipid solubility, but there is said to be some protein-binding, and when we studied the excretion curve in more detail the physicists claimed that there were two parts to it, as if there were two different exponentials possibly related to protein-binding in the second and slower component.

DR. P. J. L. HOLT (*London*) You have already mentioned that cyclophosphamide probably has no effect locally. I have two other points. To answer the question about lipid solubility, this substance is, in fact, very strongly lipid soluble. With regard to the question of using hydrocortisone at the same time: some work has been done—admittedly in rat livers, not in human livers —which suggests that prednisone, for instance, competes with cyclophosphamide and this would alter your turnover studied. Anyone using corticosteroids at the same time as cyclophosphamide ought to beware of this. The inference is that, if you are giving prednisone at the same time as cyclophosphamide, cyclophosphamide is broken down less rapidly; as you reduce the prednisone, cyclophosphamide is broken down more quickly, and therefore presumably becomes more effective.

DR. J. H. GLYN (*London*) You mentioned the possibility of using a delayed-action preparation. Did you ever get as far as producing anything effective of this nature?

DR. WYKEHAM BALME No. We talked about it with the drug company but they were not very interested.

DR. J. H. GLYN (*London*) Has anyone carried out a similar study with thiotepa or osmic acid?

DR. WYKEHAM BALME I do not know of any.

Reference

HAYAKAWA, T., KANAI, N., YAMADA, R., KURODA, R., HIGASHI, H., MOGAMI, H., and JINNAI, D. (1969) *Biochem. Pharmacol.*, **18**, 129.