In the first series (CJE), 150 sera from patients with 'suspected' rheumatoid arthritis were tested; 48 per cent. were positive by the slide test and 39 per cent. by the SSCT. 3 per cent. of 83 sera from patients with other inflammatory or non-inflammatory disorders of connective tissue were positive with both tests.

In the second series (DP), 117 sera collected consecutively from all patients with 'classical' or 'definite' rheumatoid arthritis attending the follow-up clinic were tested; 79 per cent. had a positive slide test and 63 per cent. a positive SSCT. 5 per cent. of 140 sera from patients with other diseases had positive slide test; 3 per cent. had a positive SSCT. 107 sera collected from a population sample of persons over the age of 65 were tested; 14 per cent. were positive by the slide test and 4 per cent. by the SSCT. This high incidence of positivity in the slide test in the elderly is in keeping with the observations of Heimer, Levin, and Rudd (1963). The increased sensitivity in the slide test in rheumatoid arthritis was not due to weighting by age. The ratio of positive slide tests to positive sheep cell tests was unchanged by the exclusion of patients aged 65 years or over.

These results suggest that the new slide test is more sensitive than the SSCT as done in this laboratory. In the rheumatoid sera the slide test was found to be 1.20 times more sensitive than the SSCT by CJE and 1.24 times more sensitive by DP. In all but the elderly the specificity of the SSCT was only slightly greater than that of the slide test.

The slide test was easy to read, on either venous or capillary blood, and could be set up quickly. DP managed to set up and read forty tests per hour. It is considered that these advantages are sufficient to justify further work with this test.

Discussion

DR. R. BLUESTONE (*London*) What is the effect on the sensitivity of your new test when you heat inactivate all sera before testing?

DR. EASTMOND We have not attempted to do this at all.

DR. BLUESTONE (*London*) I think you should do this, because there is no doubt that a large number of false positive latex tests using the orthodox technique can be excluded by previous heat inactivation at 55°C. for 30 minutes.

Reference

HEIMER, R., LEVIN, F. M., AND RUDD, E. (1963) *Amer. J. Med.*, 35, 175, 274, 133.

Juvenile Rheumatoid Arthritis: A Serological Survey of 200 Consecutive Patients. By R. H. BLUESTONE, L. S. GOLDBERG, R. KATZ, J. M. MARCHESANO, and J. J. CALABRO (*Department of Medicine and Pediatrics, UCLA Center for the Health Sciences, Los Angeles, California, and Department of Medicine, Jersey City Medical Center, N.J.*)

Rheumatoid factor (RF), antinuclear antibodies (ANA), and aberrations in quantitative immunoglobulins are among the serological abnormalities noted in juvenile

rheumatoid arthritis (JRA). We have studied the immunological features of 200 consecutive unselected patients with JRA, irrespective of disease activity, and have attempted to correlate abnormalities with the clinical features of the disease.

RF was detected in 24 patients (12 per cent.) and ANA in eight (4 per cent.). Elevation of serum IgG was noted in 49 patients (25 per cent.), of IgA in 34 (17 per cent.), and of IgM in twenty (10 per cent.). Low levels of IgG was found in five patients (2.5 per cent.) and of IgM in another five (2.5 per cent.). Complete absence of IgA was found in two patients (1 per cent.) and subnormal levels in two others (1 per cent.).

Children with RF, ANA, or raised immunoglobulin levels tended to differ from the group as a whole, with poorer functional status and an increased incidence of hip involvement, subcutaneous nodules, and generalized lymphadenopathy. There was no correlation with age at onset of disease. Children with low immunoglobulin levels showed no clear clinical correlates. The incidence of selective IgA deficiency is less than that reported by Cassidy and Burt (1967), but greater than the expected incidence in the normal adult population.

The incidence of abnormalities is generally lower than that previously reported. This discrepancy may reflect the fact that almost 60 per cent. of patients are at present in complete remission. Thus, the incidence of serological abnormalities in any group of patients with JRA will largely depend on the selection and clinical status of the patients under study.

Discussion

DR. B. M. ANSELL (*Taplow*) It is interesting that, irrespective of the stage taken (*i.e.* 5-year, 10-year, or 15-year follow-up), our overall incidence of positive rheumatoid factor tests, using DAT and latex tests combined, varies between 10 and 12 per cent., which is very similar to yours. I would disagree with you on one point, because we have found that those patients with a high age at onset tend to have a slightly increased frequency of positive rheumatoid factor tests, particularly the DAT, and also a rather prolonged activity of the disease process. I should like to ask one question on the immunoglobulins: we have found a fairly marked increase in all the immunoglobulins in the majority of cases, and this too correlates fairly closely with the disease activity. Could you comment on the disease activity in relation to your various tests?

DR. BLUESTONE We also found a high incidence of immunoglobulin abnormalities, although I must stress that most of our patients were in clinical remission: it is therefore not surprising that your incidence of immunoglobulin abnormality would be even higher, perhaps in following up a group of more severely affected patients. Is it possible that the reason for our low incidence of rheumatoid factor in the older patients is that in our patients the disease was comparatively inactive?

DR. B. M. ANSELL (*Taplow*) I can not comment without knowing more about your series. The group Dr. John Calabro told me about, which I think is the group you have been studying, does differ slightly from ours. It

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 P³²-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 rate 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 thiotepea 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.