- (4) Simple tables may be included. This is an excellent method of summarizing data.
- (5) Accepted abstracts will be published as such with the proceedings of the Society in the *Annals of the Rheumatic Diseases*, so must be received in a form suitable for publication. In particular, statements such as 'The data will be discussed' are entirely unacceptable. Abstracts may be revised for publication after the meeting.
- (6) Abstracts should be sent to the Senior Honorary Secretary, The Heberden Society, c/o Arthritis and Rheumatism Council, Faraday House, 8-10 Charing Cross Road, London, W.C.2. Abstracts received at least 2 weeks before each Executive Meeting (normally held on the same day as scientific meetings of the Society) will be assessed at that meeting.
- (7) When submitting abstracts, authors must state whether the communication has been or is about to be read at another meeting; or has been or is about to be published.
- (8) The normal length of time for presentation of papers is 10 minutes. However if authors would prefer a longer (15 minutes) or shorter (5 minutes) time, this should be stated when submitting abstracts. The final allocation of time will however rest with the Executive Committee.
- (9) Authors will be notified (i) when an abstract is received, (ii) when it is either accepted or rejected, (iii) when it is placed on a programme for a particular meeting.
- (10) It is the author's responsibility to keep the Senior Hon. Secretary informed of the date of publication of any paper submitted to the Society.

Clinical meeting

The following papers were presented at the Annual General Meeting on November 23 and 24, 1973.

Penicillamine or Gold for Rheumatoid Arthritis? Multi-centre Trial Using 'Blind' Observers. The First Six Months. By E. C. HUSKISSON, T. J. GIBSON, H. WYKEHAM BALME, H. BERRY, H. C. BURRY, R. GRAHAME, F. DUDLEY HART, D. R. F. HENDERSON, and J. A. WOJTCULEWSKI (*St. Bartholomew's Hospital, Guy's Hospital, and Westminster Hospital, London*)

Penicillamine has been shown to be effective treatment for Rheumatoid Arthritis (Multicentre Trial Group, 1973). In this study, the effectiveness and toxicity of penicillamine and gold are compared.

Eighty-six patients at 3 centres were given either gold or penicillamine according to a randomized schedule, stratified for age, sex, and therapy with steroids and other drugs. Dosage regimens were as follows: gold, 10, 20, 30, and 40 mg weekly for the first 4 weeks, then 50 mg weekly for 18 weeks, then 50 mg monthly; penicillamine base 250 mg daily (or 300 mg daily of hydrochloride) for 2 weeks, increasing by 250 mg or equivalent fortnightly, the maximum dose being determined by the response, but in most cases being 1 to 1.8 g daily. Anti-inflammatory and analgesic drugs were standardized before the beginning

of the trial and kept constant as far as possible. The patients were treated by a physician at their own centre; assessments were made by a 'blind' observer from another centre. All assessments reported were made by 2 observers, the same observer measuring the same patients on all occasions. The following measurements were made after 3 and 6 months of treatment: pain (visual analogue and descriptive rating scales), an assessment of progress, duration of morning stiffness, grip strength, articular index, and proximal interphalangeal joint size. Nodules were counted. Side effects were recorded by the physician treating the patients, who were asked not to mention them to the observer. ESR, Latex test, and SCAT were measured at 3-monthly intervals and x-rays taken 6 monthly.

Improvement in clinical measurements and ESR were seen in most patients and the effects of gold and penicillamine were comparable. There was a reduction in the titres of tests for rheumatoid factor but this bore no relation to changes in the disease. In the first few months of treatment, gold was discontinued more often than penicillamine, reflecting the high incidence of rashes.

Penicillamine is a useful alternative to gold therapy in patients with active rheumatoid arthritis.

Trial of Azathioprine, Cyclophosphamide, and Gold in Rheumatoid Arthritis. By J. WOODLAND, R. M. MASON, J. HARRIS, A. St. J. DIXON, H. L. F. CURREY, A. M. M. BROWNJOHN, J. DAVIES, and B. D. OWEN-SMITH (*The London Hospital and Royal Hospital for Rheumatic Diseases, Bath*)

A double blind, between patient, two-centre trial of azathioprine (A), cyclophosphamide (C), and gold (G) was presented. Patients were selected for the trial on the following criteria—they had seropositive (latex 1/80), erosive, definite rheumatoid arthritis which had reached a stage when a clinical decision to prescribe gold therapy would normally have been taken. 121 patients satisfied these criteria and were admitted to the trial.

All received apparently identical tablets and injections, one of which contained the active substance. Patients were randomly allocated to A (2.5 mg/kg/day), C (1.5 mg/kg/day), or G (standard regimen of 50 mg injections). 62 patients completed 48 weeks, and 36 patients completed 72 weeks.

Clinical results

Joint score, joint number grip strength, functional capacity, early morning stiffness, and subjective grading were recorded. The three treatment groups were comparable at entry into the trial, and all showed a general trend of improvement. However, the Mann Whitney U test revealed some significant differences between treatments in certain criteria.

Functional capacity at 6 mths	A > G	P < 0.05
	C > G	P < 0.01
Joint score at 18 mths	C > A	P < 0.05
	C > G	P < 0.05
Joint number at 18 mths	C > A	P < 0.05
	C > G	P < 0.002

X-rays

No differences between treatment groups were found until 18 months, when significantly more patients on G showed serious worsening of their x-rays compared with those on A or C.

Laboratory tests

LATEX More patients on C and G showed a reduction in latex titre than those on A, but these results did not reach significance.

ESR Similar falls were shown in all of the treatment groups.

Steroid reduction

While patients on A and C showed a reduction in steroid dosage, those on G did not. Due to small numbers, the only statistically significant difference between treatments was that at 1 year showing C to be better than G ($P < 0.03$).

Toxicity

A was associated with fewer withdrawals due to toxicity than C or G, but not significantly so. Of 6 male patients on C who had a male fertility test, all showed azoospermia, an effect not shown by a similar number of patients on A or G.

Discussion on above papers

DR. J. T. SCOTT (London) As the authors have pointed out, azoospermia and amenorrhoea are now well documented accompaniments of cyclophosphamide therapy. I think this is related partly to dosage and duration, and although some patients recover, this is not always the case. Biopsy studies have shown persistent testicular atrophy for up to 14 months after discontinuing the drug, so that the relevance of this to benign forms of rheumatoid arthritis is, of course, obvious. I would like to ask Dr. Woodland what has happened to the reproductive function of his patients since stopping the cyclophosphamide?

DR. WOODLAND We have not followed them up subsequently, but the male patients had fertility tests performed at varying intervals. One patient on cyclophosphamide was sterile after 14 weeks of treatment and one remained sterile 76 weeks after stopping treatment.

DR. G. R. V. HUGHES (Hammersmith) Aptekar, Atkinson, Decker, Wolff, and Chu (1973), at the N.I.H., have recently reported continuing bladder fibrosis in patients who had ceased taking cyclophosphamide many months before. I would be interested to know if you are following up these patients urologically?

DR. WOODLAND They are not being followed up specifically, but most patients are still attending the Department and are under supervision.

DR. P. J. L. HOLT (Manchester) I wonder about the medicolegal situation. We know that cyclophosphamide produces azoospermia and presumably we ought to get all our patients to give written consent.

DR. MASON It has been very interesting talking to these patients because their only concern is to distinguish between potency and fertility and as long as you explain

to them that they are not fertile but remain potent they go away perfectly happy, or almost happier.

DR. W. C. DICK (Glasgow) I would like to ask if the authors of the first paper have thought of looking for relative efficacy of their different assessments within their system. It seems that this is a chance which should not be missed. In the second paper I am less acquainted with the different methods used and I would like to ask if these have been subjected to intra- and inter-observer error variability measurements, day-to-day repeatability and reproducibility. For example, I notice your functional capacity shows a significant improvement. We find, in general, that functional capacity is one of the most resistant parameters in any test situation and I would like to be sure that this is a real change. I notice also you use a χ^2 with a zero in one box which is quite unacceptable in statistical terms. Finally, the more stringent the classification and standardization the more homogeneous, but the less representative of the whole, is the group studied. In our laudable efforts towards the former I am concerned that we are selecting for study more and more exotic rheumatoid arthritis which is becoming less and less representative of the disease as we know it in the common or garden outpatient clinic. This is entirely acceptable provided that we state clearly that the results relate only to the subgroup studied, and I think that all of these studies should be entitled 'Effects of drug X on patients with advanced progressive rheumatoid arthritis' to avoid any confusion in a nonspecialist audience.

DR. HUSKISSON We have looked at the relative values of the different measures; the inescapable conclusion is that most of them are measuring quite different things and the intercorrelations of the different measurements are on the whole very disappointing. For instance, changes in the ESR correlated with nothing other than reduction in nodules.

DR. A. G. S. HILL (Stoke Mandeville) With regard to pregnancy I think perhaps one may be able to except from what has been said any hazard from penicillamine. Although experience in rheumatoid arthritis may be limited, it has been used of course extensively over the years in Wilson's disease and cystinuria. I think that there is only one instance of a suspected deleterious effect of penicillamine on the fetus (the mother was taking large doses for cystinuria), so it may not be in the same category as the other drugs.

DR. D. A. H. YATES (London) Being relatively content with the effects of gold and azathioprine to date, I would like to ask both authors if they were treating either their mother or their wife for rheumatoid arthritis, which immunosuppressive or antimetabolic agent would they choose?

DR. WOODLAND Azathioprine.

DR. HUSKISSON Unless my mother was a gourmet I would give her penicillamine.

DR. M. THOMPSON (Newcastle) I should like to ask Dr. Huskisson whether he noticed within his groups that penicillamine had any particular beneficial effect on those patients suffering from vasculitis and also whether among the patients who showed a remarked reduction in latex or

SCAT titre that those were the patients who benefited most. May I also briefly mention one additional side effect. One of our patients who developed loss of taste was a man of 66, he also developed a remarkable sustained state of priapism of which he was extremely proud. He told a friend of mine, who rang me up urgently in the middle of lunch one day and said, 'What is this wonderful drug that you have given with this truly remarkable effect which also apparently relieves the symptoms of arthritis and can you spare some for me'?

DR. HUSKISSON We had a patient who illustrated another interesting new measurement for rheumatoid arthritis; when she started to get better with penicillamine she asked for the contraceptive pill. Our patients did not have vasculitis as far as we could tell. We did not have any patients with vasculitic skin lesions in this group. The latex test had no relevance to response, and there was no particular tendency for patients who had large falls in latex test to get better. We have not seen any patients with the side effect that you mention.

References

- Aptekar, R. G., Atkinson, J. P., Decker, J. L., Wolff, S. M., and Chu, E. W. (1973) *Arthr. and Rheum.*, 16, 461
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Influence of Tubercle Aggregate Size on the Severity of Adjuvant Arthritis in the Rat. By S. P. LIYANAGE, H. L. F. CURREY, and B. VERNON-ROBERTS. (*The London Hospital and the London Hospital Medical College*)

It is known that adequate grinding of the dead tubercle aggregates before incorporation into Freund's complete adjuvant (FCA) is essential for producing polyarthritis in the rat, suggesting that the actual size of aggregate is critical. Our data support the conclusion that smaller aggregates are arthritogenic by virtue of their influence on the development of cellular immunity.

A series of metal sieves was used to separate ground tubercle aggregates into different sized ranges. Aggregates smaller than 90 μm proved essential to produce arthritis, larger aggregates failing to induce arthritis in any rats. Between 90 and 45 μm , there was no evidence that smaller aggregates produced more intense arthritis. Severe arthritis could be induced by the injection of volumes of FCA as small as 0.1 ml if the FCA contained small aggregates at a concentration of 6 mg/ml.

Cell mediated immune responses to tuberculous antigens studied by the delayed skin test, production of macrophage migration inhibition factor, and PHA-induced blast transformation showed that the smaller, arthritogenic aggregates clearly induced delayed hypersensitivity, while with the larger nonarthritogenic aggregates (180–250 μm) this effect was much less marked and variable. In contrast, small as well as large aggregates produced equal titres of antimycobacterial antibodies. Smaller aggregates also produced a significant reduction of peripheral blood lymphocytes bearing surface membrane immunoglobulin (B-cells) but no significant change in cells without surface immunoglobulin.

Incorporation of human serum albumin (HSA) in FCA revealed that tubercle aggregates of either size augmented the humeral antibody and the delayed skin re-

sponses (conventional adjuvanticity) to HSA to an equal extent.

Discussion

DR. P. A. BACON (Bath) It is an interesting piece of work, but I wonder if you have taken it far enough. Pearson, Koga, Narita, and Kotani (1973) in Los Angeles, have been looking at soluble fractions obtained from mycobacteria which can induce adjuvant arthritis. They, moreover, dissociated the arthritogenic fraction from the adjuvant fraction. If you go to a soluble fraction then you cancel out the effect of aggregate size.

DR. LIYANAGE Although we have not been able to split the aggregate into separate components, our results show that the arthritogenic effect is in fact different to the adjuvant effect, thereby confirming the findings you mention.

DR. I. C. M. MACLENNAN (Oxford) Is there any difference in antigenicity of the two fractions or are you splitting different types of antigens? That is, do small particles contain one type of antigen, large particles another type of antigen? Can you grind down your 180–250 μm sized particles and get the 45–63 effect?

DR. LIYANAGE I use the word aggregate rather than particle to point out that one aggregate is a collection of bacilli.

DR. H. BERRY (London) It is a very interesting piece of work and I enjoyed very much the way you presented it. I wonder, though, whether this isn't just a reflection of particle size related dissemination. Have you had a chance to look at radioactive-labelled bacillae to see whether you were not just dealing with altered dissemination?

DR. LIYANAGE We have not done radioactive studies. We have looked at the lymph nodes histologically, and even on day + 1 the abdominal lymph nodes of animals injected with large aggregate adjuvant show tubercle bacilli, albeit within the adjuvant droplets. Further, the equal titres of antimycobacterial antibody to the small as well as the large aggregates signifies that aggregates of both sizes are being transported. The adjuvanticity experiments showed that there was no difference between the small and the large aggregates in augmentation of humoral antibody response and delayed skin response, again signifying that the large aggregates also are getting through.

DR. I. M. ROITT (London) I wonder to what extent you are considering studying the two possible phases of production of arthritis by inducing low sensitivity to the mycobacteria in a different way, say with BCG or by passive transfer or sensitized cells in an inbred strain and then against this background of induced delayed sensitivity injecting different types of antigen microbacterial preparations.

DR. LIYANAGE We haven't considered that line yet.

References

- Pearson, C. M., Koga, T., Narita, T., and Kotani, S. (1973) *Arthr. and Rheum.*, 16, 563