Heberden Society

Clinical Meeting, February, 1974

At a clinical meeting held at King's College Hospital, London, on February 22, 1974, the Heberden Round was conducted by Dr. E. B. D. Hamilton and the following papers were presented.

Evaluation of Hospital Inpatient Treatment in Management of Acute, Active Rheumatoid Arthritis. By P. LEE, A. C. KENNEDY, J. ANDERSON, and W. W. BUCHANAN (*The Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow*)

A controlled trial comparing the benefits of inpatient hospital treatment with outpatient management in thirty patients with active rheumatoid arthritis was reported. The patients were alternately allocated to one of two treatment groups. Sixteen patients were admitted to hospital and received a modified bed-rest (minimum 13 hrs bed rest daily) regimen for 4 weeks, and fourteen patients were treated on an outpatient basis as controls. Both groups received indomethacin 100 mg orally daily, and progress was assessed at weekly intervals.

At the end of the 4-week period the hospital inpatient group showed significant improvement in pain severity, severity and duration of morning stiffness, articular index of joint tenderness, and grip strength, whereas in the outpatient group no significant improvement was observed in any of the indices measured. In an analysis of covariance significant differences between hospitalized and non-hospitalized patients were found for both the mean (average of the scores over the period of study) and final scores for the severity of pain ($P < 0.025$ and $P < 0.05$, respectively) and articular index ($P < 0.05$ and $P < 0.025$, respectively). In addition, significant differences were found in the mean scores for the severity of morning stiffness ($P < 0.025$) and technetium (^{99m}Tc) uptake in the left knee ($P < 0.025$), right knee ($P < 0.05$), and right wrist ($P < 0.025$).

It is concluded that hospitalization is of benefit to patients with acute, active rheumatoid arthritis, and this clearly must be taken into account if hospital inpatients are used in short-term clinical trials of nonsteroidal antirheumatic drugs.

Discussion

PROF. E. G. L. BYWATERS (*Taplow*) Perhaps I might ask the authors whether they would draw the corollary that 13 hrs minimum bed rest a day is good for the rest of the rheumatoid's life, because as far as I remember in two previous studies (Partridge and Duthie, 1963; Mills and others, 1971), although there was some improvement during the period of hospitalization, within 2 or 3 months after they had returned home there was no difference between the two groups.

DR. LEE I agree that we need to extend the study. I have seen most of the patients subsequently and although many

have remained in remission for some time, a number have relapsed. I tried to confine the patients to bed for a greater period than 13 hrs but many objected to staying in bed all day, particularly when the disease activity was reduced and they became more active.

DR. R. M. MASON (*London*) There are no data after say, a year's time?

DR. LEE No.

DR. J. A. HICKLIN (*Crawley*) I must say that I am very relieved that what we have always believed to be true really is true, particularly as Goldberg and I went out on a limb at Brighton and said that this effect was a major reason for not doing drug trials on inpatients. What worries me is that such a canny race as the Scots should only use this medicine (bed rest) for 13 hrs a day. I would have thought that you would have got very much better results, very much quicker, by using it for longer. I keep mine in bed for 24 hrs a day, apart from allowing them to the toilet in a Sanichair. I expect to get the kind of results which you achieve in 4 weeks in 2 weeks.

DR. LEE I agree it would have been desirable to keep them in bed longer, but as I explained the problem was that of keeping them in bed. We had to toss up whether it was better to keep them in bed for shorter periods or for longer periods in an agitated state.

DR. R. M. MASON (*London*) More bed rest in a shorter time.

DR. P. J. L. HOLT (*Manchester*) The Glasgow group now have a lot of experience of different ways of measuring inflammation and for practical purposes this is quite a heavy barrage of tests to perform on every patient. Would you like to give us a best buy, as it were, of which tests, if we want to cut corners, we ought to use for practical purposes? It seems to me that your articular index and your period of morning stiffness, for instance, give as good a differential as your technetium scan; admittedly one is very subjective and one is an objective test.

DR. LEE Following the corticosteroid era of Hench and others (1949) there was a craving for objective measurement, but one must remember that these are the most insensitive measurements that we have. We (Deodhar and others, 1973) found the patients' assessment of their own pain response, the articular index, and morning stiffness to be the more sensitive criteria. It is very important when measuring differences in nonsteroid anti-inflammatory drugs to employ the most sensitive criteria available, whether these be subjective or objective. Since these medications are very similar, in that they are all relatively impotent when compared with corticosteroids. I have not found the technetium index to be particularly sensitive.

DR. E. GLICK (*London*) I think we have to be careful about interpretation. This was not a trial of bed rest, it was a trial of hospitalization, as the wording of the summary makes clear. All the outpatients had a minimum of 8 hrs bed rest, so you were comparing 8 and 13 hrs which are not very different. It is hospitalization and avoidance of a lot of the minor trauma that goes with looking after houses and so on, that you have been testing and not bed rest alone.

DR. LEE Yes, it is hospital inpatient treatment versus outpatient treatment. I think hospital inpatient treatment involves more than bed rest because the patient is actually removed from the burden of domestic and business worries as well.

References

- Deodhar, S. D., Dick, W. C., Hodgkinson, R., and Buchanan, W. W. (1973) *Quart. J. Med.*, **42**, 387
 Hench, P. S., Kendall, C. E., Slocumb, C. H., and Polley, H. F. (1949) *Ann. rheum. Dis.*, **8**, 97
 Mills, J. A., Pinals, R. S., Ropes, M., Short, C. L., and Sutcliffe, J. J. (1971) *New Engl. J. Med.*, **284**, 453
 Partridge, R. E. H., and Duthie, J. J. R. (1963) *Ann. rheum. Dis.*, **22**, 91

A Double-blind Comparative Trial of Cyclophosphamide and Gold in Rheumatoid Arthritis. By J. M. GUMPEL, A. HALL, and B. ANSELL (*M.R.C. Rheumatism Unit, Canadian Red Cross Memorial Hospital, Taplow*)

A comparative study of gold and cyclophosphamide was started in this unit in December 1969. Sixty-seven patients with rheumatoid arthritis whose disease activity was not controlled by conventional therapy and who would, in the ordinary course of events, have been treated with gold have entered the study. All had completed their families, and were willing to enter a trial of this nature. By random selection the patient received either cyclophosphamide and dummy gold injections, or gold and dummy cyclophosphamide. The therapy was controlled by one physician, while the clinical state of the patient was regularly assessed by a second physician without knowledge of the active drug or of any side effects that had occurred. This report is on the first year of treatment of fifty patients.

There was statistically significant improvement in functional state in patients on gold and on cyclophosphamide. The results for decrease of joint pain, increase in grip strengths, and improvement in walking time were significant for the patients on cyclophosphamide but not for those on gold. The ESR improved in both groups, the significance being greater ($P=0.001$) with gold than with cyclophosphamide. Side effects were more common with cyclophosphamide but no patient was withdrawn from cyclophosphamide because of drug-related side effects, whereas three patients were withdrawn from gold therapy because of severe gold rash.

Discussion

DR. H. L. F. CURREY (*London*) Can you correlate the dose of cyclophosphamide with the response of the patients? Two trials have shown what appears to be a threshold effect and I wonder whether you have looked for this? Secondly, comparing your results with ours from The London Hospital, I am impressed that your results with cyclophosphamide are better than ours, from the

point of view of both toxicity and clinical response, and I think the reason for this is that you tailored the dose, whereas we had to use a fixed dose.

DR. GUMPEL A special feature in the design of this study and the reason for having an independent assessor was that it gave us this freedom to tailor the dose to suit the patient. This was very important, and we think that if we had used a fixed dose as you mention in your study, we would have had more toxicity.

DR. J. KAKAKI (*Holland*) Have you studied some parameters of cell mediated immunity in your group of patients treated with cyclophosphamide?

DR. GUMPEL Initially we studied at the beginning of treatment and after 3 months, but abandoned this because of our concern about the reproducibility of the results and especially with staff shortages and changes.

DR. P. A. BACON (*Bath*) I think your study very nicely confirmed that cyclophosphamide is one of the most effective drugs for rheumatoid arthritis around at present and that the chief problem is controlling the toxicity. I have recently been giving a large dose, 2 mg/kg, but as an intermittent dose, 1 week on and 1 week off or variants of this regimen. My initial impression is that one can get a good effect with this sort of intermittent therapy and I think toxicity may be less. Have you any experience of this sort of regimen?

DR. GUMPEL No, but the regimen you mention has many theoretical attractions.

DR. C. BARNES (*London*) Were there any radiographic differences comparing films taken at the beginning and end of the trial?

DR. GUMPEL Yes, in many patients we have seen healing of erosions both on gold and on cyclophosphamide. We have spent considerable amounts of time looking at the radiographs, and have just recently worked out a system that will allow us to produce a meaningful score to compare before and after treatment.

On the Relationship Between Inflammatory Joint Disease and the Foregut Hormones, Gastrin and Secretin. By P. J. ROONEY, J. MILLAR, J. R. HAYES, K. D. BUCHANAN, and W. C. DICK (*The Centre for Rheumatic Diseases, University Department of Medicine, Royal Infirmary, Glasgow; University Department of Medicine, Queen's University of Belfast*)

Serum immunoreactive gastrin levels have been found to be raised in approximately one-third of patients with rheumatoid arthritis. No increase in serum gastrin levels has been noted in eight patients with psoriatic arthritis, twenty-three patients with systemic lupus erythematosus, seventeen patients with ankylosing spondylitis, and twenty-five patients with osteoarthritis. In addition, no rise in immunoreactive gastrin was observed in sixteen patients with active pulmonary tuberculosis and ten patients with recent myocardial infarction (within 48 hrs).

Studies have been conducted in patients with rheumatoid arthritis in which fasting immunoreactive gastrin was