dose of sodium aurothiomalate of less than 200 mg. The larger group of patients (39) developed blood abnormalities at a total dose of sodium aurothiomalate in excess of 450 mg. The reactions developed between the tenth and twentieth week of treatment in 23 cases, at total doses ranging from 450–900 mg. sodium aurothiomalate.

There were 15 fatalities associated with marrow aplasia; the immediate cause of death was haemorrhage in 9, infection in 2, and a combination of both in the remaining 4. Blood counts were infrequent during chrysotherapy in several of the fatal cases.

Reviewing the details of all 55 cases *retrospectively*, it was possible to identify features which might have been useful indicators in the 'high-dose' patients. In particular, there was in some patients a progressive fall in total white blood counts, polymorphs, or platelets during treatment. In others, blood abnormalities developed when sodium aurothiomalate was continued without dose reduction after clinical remission of rheumatoid arthritis. It is concluded that marrow depression and thrombocytopenia are rare but serious complications of chrysotherapy. It is suggested that the dangers of blood dyscrasias can be further reduced if full blood counts are undertaken regularly and the dose level of sodium aurothiomalate reduced when clinical remission has been achieved. There remain a few patients, particularly in the 'low-dose' group, in which there appears to be no warning of impending blood disorders.

Discussion

PROF. E. G. L. BYWATERS (*Taplow*) What was the value of eosinophil counts?

DR. KAY It would be very helpful if more people did differential counts earlier in the course of gold treatment. We might then be really in a position to say what the value was. They are infrequently done.

DR. J. T. SCOTT (*London*) The extent of marrow damage bears some relation to the total dose of gold administered. Some years ago Dr. Michael Denman, while at the Hammersmith Hospital, did a literature search and found that the total dose which had been given to patients developing thrombocytopenia was 0.65 g.; in patients with leucopenia 1·32 g.; and in patients with complete marrow aplasia 3·51 g. Of course, ranges and overlap were wide. Mortality in the three groups was 20, 35, and 76 per cent respectively.

DR. KAY I think that the total dose should be seen in relation to the time during which it has been given.

DR. P. J. L. HOLT (*London*) You did not comment on the erythrocyte sedimentation rate and clinical response. One of the biggest causes of toxicity, I think, is overtreatment —that is putting patients on to a course of treatment. There seems to be no rationale for specifying ten or twenty injections of 50 mg. We do not do it for anything else and I think that continued reassessment of the ESR and clinical response are important in regulating treatment.

DR. KAY I completely agree that we should assess the dose response relationship more carefully in these patients.

PROF. E. G. L. BYWATERS Can I ask about re-treatment? Does a second course carry a greater danger of marrow depression?

DR. KAY It was not apparent in the series.

DR. R. GRAHAME (*London*) Do you have any information on the relationship between marrow toxicity with gold and blood levels of gold or evidence of cell-mediated immunity to gold?

DR. KAY I have no information but understand that, regarding serum levels, there is no absolute correlation.

DR. T. C. HIGHTON (*New Zealand*) Dr. Palmer and I are doing some work along these lines but so far have been unable to find any relationship.

PROF. J. J. R. DUTHIE (*Edinburgh*) Have you any idea of the total number of treated patients from whom these figures of toxicity arose?

DR. KAY This is very important, but I cannot think of any way of getting this information.

DR. A. G. S. HILL (*Stoke Mandeville*) Do you think the traditional test dose is anything more than a gesture?

DR. KAY I would not think so. Perhaps we should use lower doses up to a total of 200 mg. Myocrisin.

DR. P. D. FOWLER (*Macclesfield*) I should like to stress what Dr. Kay says about the difficulties of retrospective surveys of this type. In my experience it is often extremely difficult to determine the relationship between drug and reaction. There is a very interesting parallel to blood dyscrasias with phenylbutazone in that leucopenias arise early in treatment and aplasias of the sort described here after long periods of treatment. Did you try to relate the annual frequency rate of dyscrasias with the manufacturers' annual turnover of the drug? This *might* give you some clues as to whether they are related.

DR. KAY It does correlate to a certain degree.

DR. J. GLYN (*London*) Do you consider that it is a malpractice to give phenylbutazone and gold simultaneously?

DR. KAY Many people over the years have used this combination of drugs without ill-effects.

DR. D. N. GOLDING (*Harlow*) May I make a comment on behalf of those working on D-penicillamine in a multicentre trial? It has been our impression that patients are more likely to get thrombocytopenia on penicillamine if they have had gold treatment during previous months.

Reference
British Medical Journal (1971) **1**, 471 (Gold for rheumatoid arthritis)

A Study of Renal Disease in Rheumatoid Arthritis. By A. V. CAMP, A. G. MOWAT, W. B. FLETCHER, M. S. DUNNILL, and A. G. MCIVER (*Nuffield Orthopaedic Centre and United Oxford Hospitals*)

The only clearly recognized renal abnormalities associated with rheumatoid arthritis are amyloidosis and drug nephropathy (Burry, 1971), but it has been suggested that there may be a specific renal lesion in rheumatoid disease. Accordingly, thirty unselected patients with definite or classical rheumatoid arthritis were studied by a variety of

renal function tests, infusion pyelography, and percutaneous renal biopsy (informed written consent was obtained from all patients). Sections of renal tissue were examined by light and electron microscopy and immunofluorescent techniques.

The creatinine clearance was reduced below 70 ml./min. in 25 patients and the maximum urinary concentration after water deprivation was below 700 osmol./litre in sixteen patients. Proteinuria in excess of 30 mg./100 ml. was found in five patients and a white cell count of over 10cu./mm. in five patients. All other tests of renal function were normal. There was no correlation between poor glomerular function and drug intake or duration of disease, but there was a positive correlation with seropositivity and the presence of nodules and vasculitis. There was no correlation between poor tubular function and any of these factors or between glomerular and tubular function.

The five patients with proteinuria showed a definite renal lesion. Two had minimal membranous glomerulonephritis, one had amyloidosis, one had tubular nephrosis secondary to gold therapy, and in one the changes were consistent with systemic lupus erythematosis. One biopsy from a patient with membranous glomerulonephritis secondary to penicillamine therapy and one with gold nephropathy contained IgG on the capillary basement membrane of the glomerular tufts. One other biopsy with no histological abnormality showed similar deposits. No patient was found to have evidence of analgesic nephropathy, pyelonephritis, or renal vasculitis.

The findings support the theory that renal lesions in rheumatoid arthritis are either coincidental or secondary to the disease or drug therapy and are not a systemic manifestation of rheumatoid disease.

Discussion

DR. H. C. BURRY (*London*) You seem to be left with the paradox of a normal-looking kidney which does not work. Approximately 122 renal biopsies in rheumatoid arthritis have been reported in the literature (Burry, 1971). About a third of these showed changes in the blood vessels variously described as arteriosclerosis or obliterative endarteritis. About a fifth of the biopsies have shown changes which might be described as pyelonephritis or chronic interstitial nephritis. It is therefore surprising that your series has shown such a low incidence of these changes. Further, in view of the work of Bywaters (1957) and Scott, Hourihane, Doyle, Steiner, Laws, Dixon, and Bywaters (1961), showing obliterative endarteritis in other parts of the vascular anatomy, I wonder if you would comment on the suggestion that fall in the blood flow from the nephrons might cause the low glomerular filtration rate and account for the pathological features we have seen.

PROF. E. G. L. BYWATERS (*Taplow*) Might I add that we have seen what we call 'rheumatoid vasculitis' in the kidney *post mortem*. In one case in particular, there was multiple aneurysm formation which had burst, producing death from haemorrhage. It is not unusual to see some slight degree of renal vasculitis at autopsy in patients with vasculitis elsewhere.

DR. CAMP I was very surprised myself because we found glomerular changes in only one of the six patients with severe vasculitis. There were a few with changes of arteriosclerosis but we thought when comparing these with renal biopsies from other patients, that the changes were compatible with age and nothing else. I cannot comment on any theories because there have been so many postulated. It is a consistent finding that creatinine clearance is reduced in patients with severe and long-standing rheumatoid arthritis and no-one has been able to explain this.

PROF. BYWATERS A renal biopsy is a very, very small piece of the kidney and these vascular changes are often very localized.

DR. CAMP I think this is a problem. We did start off with the idea that we might perform arteriography but dropped this rather hurriedly.

PROF. J. J. R. DUTHIE (*Edinburgh*) We collected 65 *post mortem* kidneys and found significant renal disease in over 70 per cent. In thirteen there was papillary necrosis and interestingly only one of these had not taken phenacetin. Patients who had had high doses of aspirin alone showed no papillary necrosis.

DR. J. M. GUMPEL (*London*) I am interested in the two patients with chronic pyelonephritis and the one with chronic interstitial nephritis. This is often found in patients with Sjögren's syndrome. Did they have a reduced urine concentration?

DR. CAMP No, they did not. None of the three had diminished concentrating power although two had diminished creatinine clearance. Certainly the acidification tests were normal.

References

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Scott, J. T., Hourihane, D. O., Doyle, F. H., Steiner, R. E., Laws, J. W., Dixon, A. St. J., and Bywaters, E. G. L. (1961) *Ibid.*, **20**, 224 (Digital arteritis in rheumatoid disease)

Successful Treatment of Patients with Systemic Lupus Erythematosus, including Nephritis, using Chlorambucil. By M. L. SNAITH, J. M. HOLT, D. O. OLIVER, and A. STEPHENSON (*Nuffield Orthopaedic Centre, Radcliffe Infirmary, Churchill Hospital, and M.R.C. Population Genetics, Oxford*)

It is becoming accepted that drugs which modify immune response can control the manifestations of systemic lupus erythematosus and improve the outlook in patients with nephritis. Of the drugs selected hitherto, azathioprine often leads to marrow suppression and cyclophosphamide frequently causes distressing alopecia. In this report we present a group of patients who have been treated with chlorambucil which we believe to possess advantages over agents previously advocated because of its freedom from side-effects.

Six female patients whose ages ranged between 23 and 45 years are described. In five, nephritis proven by renal biopsy was the dominant feature and the decision to use chlorambucil followed failure to control the manifestations of renal disease with corticosteroids. Moreover, three had developed hypertension and two serious depression. After the introduction of chlorambucil, renal function improved