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 erythematosus. 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 arterio-

sclerosis 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 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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- Bywaters, E. G. L. (1957) *Ann. rheum. Dis.*, 16, 84 (Peripheral vascular obstruction in rheumatoid arthritis and its relationship to other vascular lesions)
- 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

in all. In four with nephrosis, proteinuria fell from more than 8g. per 24 hrs to less than 0.5g. per 24 hrs in three, and 2g. per 24 hrs in the fourth, with return to normal of serum albumin concentration. Two of these patients agreed to a second renal biopsy which showed a significant reduction in cellular infiltration. In the fifth patient renal function deteriorated, necessitating dialysis, but during treatment with chlorambucil creatinine clearance improved from less than 10 to 62 ml./min. The disease remains quiescent in all after 5, 5, 4, 2, and 1½ years. The sixth patient was treated with chlorambucil because corticosteroids alone had failed to keep her peripheral vascular manifestations under control. She remains well 4 years afterwards.

No adverse effect from treatment has yet occurred in these patients, but there is an increasing unease concerning the risk of malignant disease in patients undergoing immunosuppressive therapy. In an investigation into chromosomal abnormalities associated with chemotherapeutic drugs, abnormalities have been observed after cyclophosphamide, but so far not in patients taking chlorambucil.

Discussion

DR. H. L. F. CURREY (*London*) Have you encountered any herpes zoster? Kahn and de Sèze (1971) have most experience with this drug in rheumatoid arthritis and they found a very high incidence of herpes zoster. Interestingly, they suggest that there is a correlation between the clinical response and the incidence of herpes zoster.

DR. SNAITH There was one patient who had this condition but she developed it before she started chlorambucil.

A PHYSICIAN: Did you monitor the serum complement or DNA binding and were you able to show any changes?

DR. SNAITH At the time the DNA binding was not available, but we did look at the complement. This was rather variable and, as the results went back over nearly 10 years, we feel rather doubtful about the reliability of the test. Sometimes it was low and sometimes it was normal.

DR. K. T. RAJAN (*Cardiff*) In view of the teratogenic action ascribed to the drug, did you look at the infant of one of your patients who delivered soon after starting treatment?

DR. SNAITH Yes, we looked and the infant was normal.

Reference

Kahn, M.-F., and Sèze, S. de (1971) 'INSERM Colloque', Hôpital Cochin (Paris) 3-5 November (Polyarthrite chronique rhumatoïde et immunodépression)

Effect of Weight Reduction on Levels of Uric Acid in Plasma and Urine.* By A. NICHOLLS, H. YABLONSKY, and J. T. SCOTT (*West London Hospital and Kennedy Institute of Rheumatology*)

There is now considerable evidence of a relationship between body weight and plasma urate levels. Such an association has been found in epidemiological surveys (Healey and Hall, 1970) and many gouty patients tend to be overweight (Grahame and Scott, 1970). The nature of this association is unknown. The present study was designed

to determine whether weight reduction in individuals has any effect on plasma and urinary urate.

Fifteen subjects were studied, 10 men (5 of them with untreated hyperuricaemia and gout) and 5 women (one with hyperuricaemia). Three 24-hr urate and creatinine clearance estimations were made on a low-purine diet before and after a period of weight reduction.

Mean weight loss was 8 kg. (range 4 to 22). In 12 of the 15 subjects, the plasma urate fell, and in the group as a whole this was significant (mean fall 0.8 mg./100 ml.; $P < 0.01$). There was no consistent change in urinary urate levels (mean fall 82 mg./24 hours; not significant), although four subjects with the highest urinary levels showed a marked fall after weight loss. Creatinine clearance remained unchanged.

The results show clearly that weight reduction produces a fall in plasma urate and therefore suggest that plasma urate levels are influenced by body weight. The mechanism of this fall in urate remains uncertain; a decrease in urinary urate seen in some subjects may mean that urate production is diminished, but this was not a consistent finding and it is possible that other additional (*i.e.* renal) factors may be operating. Total body water is relatively greater after weight loss, which may be a factor in producing a lower level of uric acid in the plasma.

Discussion

DR. B. D. OWEN-SMITH (*Reading*) I should like to confirm these findings. We placed four obese males on alternate 15-day periods of fasting followed by 15 days re-feeding with a low purine metabolic diet, for a total of 60 days. Weight loss (25 kg. average) was similar for all subjects. Hyperuricaemia recurred during fasting and was corrected by re-feeding. There was a fall in the average and peak serum uric acid levels with successive fasts and also in the average and basal levels with successive feeding periods. There was no significant change in renal function as measured by creatinine clearance during the study to account for the fall in serum uric acid level with weight loss.

DR. J. D. GOODE (*Hull and East Riding*) Have you any information on alcohol intake before and after the period of weight reduction?

DR. NICHOLLS These patients were all on a low purine, alcohol-free diet at the time of urine collections, and for a week before, so this should not have affected our results.

DR. J. MATTHEWS (*London*) It would be helpful in assessing the degree of hyperuricaemia if we know the upper limit of normal of your laboratory. You also did not tell us whether you actually observed a reduction in the number of gouty attacks.

DR. NICHOLLS The six patients that we were studying with gout were not, in fact, having treatment at the time because the attacks were infrequent. They did not have any attacks during the time they were losing weight but the numbers were too small to draw any conclusions.

DR. SCOTT The mean value of plasma uric acid in our laboratory for normal adult men on a low-purine diet is 5.1 mg./100 ml. with a standard deviation of 1.0, so that you could define the upper limit as about 7.0 mg./100 ml. This is not really relevant to the present study, however, since we are concerned with changes in particular indi-

* A more detailed account of this work has been published in the *Lancet* (1972) 2, 1223