Bacteriuria in rheumatoid arthritis

HUGH C. BURRY

Department of Rheumatology, Guy's Hospital, London, S.E.1.

Pyelonephritis has been noted commonly in patients dying with rheumatoid arthritis (Clausen and Pedersen, 1961; Duthie, Brown, Truelove, Baragar, and Lawrie, 1964). Thus 47.5 per cent. of the patients reported by Lawson and McLean (1966) showed pathological features consistent with this diagnosis. Although not all patients with chronic pyelonephritis are thought to excrete micro-organisms persistently, one would expect that, with an incidence of pyelonephritis at *post mortem* which is so much higher than in the general population, the prevalence of bacteriuria in rheumatoid arthritis would exceed the expected figure of 4 to 6 per cent. (Kass, 1956). Moreover, rheumatoid arthritic subjects have been reported to have an abnormal susceptibility to systemic and particularly pulmonary infections (Cobb, Anderson, and Bauer, 1953; Walker, 1967), and this susceptibility might well be enhanced by treatment with steroid hormones. The present study compares the incidence of bacteriuria in a group of patients with rheumatoid arthritis with the incidence in a control group with particular reference to drug therapy.

Methods

Altogether 254 patients with classical or definite rheumatoid arthritis as defined by the A R A criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were included in the survey. Approximately 90 per cent. of them were in-patients. The control group consisted of 129 patients admitted to the wards, and included patients with spinal disorders, degenerative and monarticular arthritis, and various neurological complaints.

For the purposes of this study it was decided to exclude any patients with known pre-existent chronic renal disease or malformation, and those who had undergone instrumentation of the lower renal tract during the preceding 3 months. Five patients were excluded from the control group to satisfy the latter provision, but there were no exclusions from the rheumatoid arthritis group for either reason.

Patients in the two groups were matched for age and sex. Early morning mid-stream urine specimens were collected by the clean catch technique, after perineal swabbing with sterile water. The specimens so obtained were stored in a refrigerator at 4°C. while awaiting transfer to the laboratory. Colony counts in excess of 100,000 were regarded as significant bacteriuria. Contamination was suspected where a mixed growth was obtained, and the culture was

repeated. The blood urea was estimated in every case, and in 139 the glomerular filtration rate was estimated by means of the endogenous creatinine clearance test. The details of present and past drug therapy with particular reference to corticosteroid hormones, salicylates, and phenacetin-containing analgesics were recorded.

Results

There were 254 patients with rheumatoid arthritis, and 129 controls. The ages of both groups, and of male and females considered separately were very similar (Table I). The male rheumatoid arthritics and the male controls showed an incidence of bacteriuria of 3.9 and 3.5 per cent. respectively (Table II). The corresponding figures for female patients were 10.7 and 11.1 per cent.

Table I Age and sex of patients and controls

Series	Sex	No. of cases	Average age (yrs)
R.A.	Male	77	53.7
	Female	177	54.9
Control	Male	57	51.1
	Female	72	53.6

Table II Bacteriuria

Sex	Series	Total	UTI	
		No.	No.	Per cent.
Male	R.A.	77	3	3.9
	Control	57	2	3.5
Female	R.A.	177	19	10.7
	Control	72	8	11.1

No correlation between bacteriuria and salicylate or phenacetin dosage was seen, but the incidence in those treated with more than 7.5 mg. prednisolone or equivalent, for more than 6 months was significantly greater than in those who had not been treated with steroids (Table III). The ages and sex distribution of those two groups were similar. There was no correlation between bacteriuria and creatinine clearance (Table IV).

Table III *Bacteriuria and steroid therapy*

Therapy	Sex		Total cases	Percentage female	UTI	Percentage incidence
	Male	Female				
Steroids	20	57	77	74	12	15.6*
No steroids	57	120	177	68	10	5.6

* 0.01 < P < 0.05

Table IV *Bacteriuria and creatinine clearance*

Clearance	>80	<80	
		No.	Per cent.
Normal	70	55	44
UTI	6	8	57
Total	76	63	45

Discussion

Asymptomatic bacteriuria has been the subject of extensive investigations in recent years, and its significance, management, and prognosis have been subjects for debate. Kass (1956) defined bacteriuria as a viable count of pathogenic organisms in excess of 100,000 per ml. of a mid-stream urine collected with care to prevent contamination, and either examined immediately or stored in a refrigerator to avoid incubation before culture. He found an incidence of 6 per cent. in 337 asymptomatic females and of 4 per cent. in 102 asymptomatic males. Other surveys, such as that of Williams, Thomlinson, Cole, and Cope (1969), have produced similar results, but Asscher (1970) would put the figure at about 4 per cent. for females and 0.5 per cent. for males in a population aged between 16 and 65. He noted that the incidence increased with age and parity.

The prevalence of bacteriuria appears to be greater in hospital in-patients. Whatmore, MacCabe, Ross, and McNair (1966) reported an incidence of 11 per cent. in males and 37 per cent. in females admitted to a surgical unit. These figures may be even higher in patients over the age of 60 years (Walkey, Judge, Thompson, and Sarkari, 1967).

A survey of renal tract infection in rheumatoid arthritis was carried out by Mowat, Hothersall and Gould (1970), who found no significant difference between 85 patients and 68 control subjects; the figures being 5.88 per cent. and 11.76 per cent. respectively. The present investigation, using a larger sample, confirms this finding, the figures being similar to the expected incidence for the population but lower than figures for inpatients quoted above.

The failure to demonstrate any increased incidence of bacteriuria in patients with rheumatoid arthritis is surprising in view of the known susceptibility of such

patients to systemic infections (Cobb and others, 1953; Walker, 1967). They are even more surprising when contrasted with the incidence of changes reported as 'pyelonephritis' in *post mortem* studies.

The finding of a significantly increased incidence of bacteriuria in patients treated with steroid hormones may reflect the known suppression of immune mechanisms associated with the use of these compounds. Harvald (1962) found a high incidence of papillary necrosis in patients so treated, but the series of Lawson and McLean (1966) did not confirm this association. Nor did the clinical surveys of renal function of Sørensen (1963) and Boye Neilsen, Drivsholm, Fischer, and Brøchner-Mortensen (1963) show any correlation. These studies were concerned with glomerular function. To date, no adequate evaluation of tubular function in rheumatoid arthritis has been carried out.

Death in uraemia is reported to occur in from 17.3 per cent. (Duthie and others, 1964) to 34 per cent. (Clausen and Pedersen, 1961) of patients with rheumatoid arthritis. Pyelonephritis with or without papillary necrosis is a common pathological diagnosis in *post mortem* studies of rheumatoid arthritic patients. The expected incidence of pyelonephritis in all cases examined *post mortem* is approximately 10 to 20 per cent. (Jackson, Dallenbach, and Kipnis, 1955; MacDonald, Levitin, Mallory, and Kass, 1957). Lawson and McLean (1966) found an incidence of 47.5 per cent. in their necropsy series of patients with rheumatoid arthritis, contrasting sharply with an incidence of 9 per cent. in matched controls. Approximately half of the patients with pyelonephritis also had papillary necrosis. Although bacteriuria is known to be intermittent in some cases of pyelonephritis, an increased incidence of bacteriuria might well be anticipated during life. False negatives might in part account for the disparity between clinical evidence of renal infection and pathological findings, but the studies of Mowat and others (1970) of serum antibodies to *E. coli* (the commonest infecting organism) did not show any evidence that this was so.

Chronic pyelonephritis is a difficult pathological diagnosis. Briefly, it consists macroscopically of rather coarse scarring, involving the calyx, cortex, and medulla, and thickening of vessel walls. Microscopically, there is patchy atrophy of tubules and to a

lesser extent glomeruli, with increase in collagen and an infiltrate of chronic inflammatory cells with or without polymorphonuclear leucocytes. The microscopic features may be indistinguishable from those known as chronic interstitial nephritis, and are common to pyelonephritis, papillary necrosis, analgesic nephropathy, ischaemia, and sometimes uric acid nephropathy. Biopsy material (Brun, Olsen, Raaschou, and Sørensen, 1965; Pasternack, Wegelius, and Mäkisara, 1967; Burry, 1971) has shown a high incidence of chronic interstitial nephritis and in many of these cases bacteriuria was not present. Thus it seems unlikely that the changes referred to as pyelonephritis indicate parenchymal infection.

The relationship of interstitial nephritis to drug taking in patients with rheumatoid arthritis is uncertain. Although Lawson and McLean showed a correlation between consumption of analgesics, particularly those containing phenacetin, and the changes they described as pyelonephritis, in their patients with rheumatoid arthritis, the analgesic consumption of their control subjects was not known.

It has been established beyond reasonable doubt that long-continued ingestion of compound analgesics may lead to papillary necrosis with accompanying changes in the medulla and cortex (Spuhler and Zollinger, 1953; Burry, de Jersey, and Weedon, 1966; Kincaid-Smith, 1967), but it remains uncertain whether these changes can occur in the human species as a result of the ingestion of salicylate alone. The majority of the twenty patients with a history of abnormally high and prolonged ingestion of analgesic mixtures investigated by Steele, Gyory, and Edwards (1969) were shown to have deficiencies in both glomerular and tubular function, and one might expect to find such abnormalities in patients with rheumatoid arthritis, since most of them will have taken anti-inflammatory—analgesic drugs, and more particularly salicylates—in large quantities over a protracted period. Although tubular function has not as yet been adequately investigated in patients with rheumatoid arthritis, studies of glomerular filtration rate (Burry, 1972) and urine culture, as in the present

survey, have not shown any correlation with analgesic drug consumption. There is therefore little evidence to incriminate drug-taking habits as the cause of renal abnormalities, apart from an apparently increased incidence of bacteriuria in steroid-treated patients as noted in this study.

Obliterative endarteritis, consisting of a fibrous or mucoid intimal thickening affecting medium-sized arteries including renal vessels, has been described by Bywaters (1957), and confirmed by Scott, Hourihane, Doyle, Steiner, Laws, Dixon, and Bywaters (1961). Mahallawy and Sabour (1959) also reported similar appearances in renal biopsy material from five cases of rheumatoid arthritis, and arterial narrowing has been noted in other renal biopsy studies (Brun and others, 1965; Pasternack and others, 1967).

Patients with rheumatoid arthritis have been shown to have impaired glomerular filtration, the degree of abnormality showing correlation with the severity of disease (Sorensen, 1960; Burry, 1972), and to have an increased incidence of interstitial nephritis at *post mortem*. Vascular insufficiency would explain both the fall in the glomerular filtration rate and the presence of chronic interstitial nephritis in *post mortem* and biopsy material. In view of the lack of evidence of, on the one hand, chronic infection of the renal tract, and on the other of drug-induced nephropathy, there seems to be good reason to suppose that the parenchymal changes and disturbed function may be a vascular complication of rheumatoid disease.

Summary

Evidence of urinary tract infection was sought in 254 patients with classical or definite rheumatoid arthritis. The incidence of bacteriuria was no greater in this group than in a control group of 129 patients matched for age and sex. There was no evidence that treatment with salicylates increased the risk of urinary tract infection, but patients treated with systemic corticosteroid hormones showed a statistically significant increase in the incidence of bacteriuria.

References

- ASSCHER, A. W. (1970) *J. roy. Coll. Physcns Lond.*, **4**, (Screening for urinary tract infection)
- BOYE NIELSEN, J., DRIVSHOLM, A., FISCHER, F., AND BRØCHNER-MORTENSEN, K. (1963) *Acta med. scand.*, **173**, 177 (Long-term treatment with corticosteroids in rheumatoid arthritis)
- BRUN, C., OLSEN, S., RAASCHOU, F., AND SØRENSEN, A. W. S. (1965) *Nephron*, **2**, 65 (Renal biopsy in rheumatoid arthritis)
- BURRY, A. F., DE JERSEY, P., AND WEEDON, D. (1966) *Med. J. Aust.*, **1**, 873 (Phenacetin and renal papillary necrosis: results of a prospective autopsy investigation)
- BURRY, H. C. (1971) *Rheum. phys. Med.*, **11**, 2 (Renal disorders in rheumatoid arthritis)
- (1972) *Ann. rheum. Dis.*, **31**, 65 (Reduced glomerular function in rheumatoid arthritis)
- BYWATERS, E. G. L. (1957) *Ibid.*, **16**, 84 (Peripheral vascular obstruction in rheumatoid arthritis and its relationship to other vascular lesions)

- CLAUSEN, E., AND PEDERSEN, J. (1961) *Acta med. scand.*, **170**, 631 (Necrosis of the renal papillae in rheumatoid arthritis)
- COBB, S., ANDERSON, F., AND BAUER, W. (1953) *Ann. rheum. Dis.*, **12**, 323 (Length of life and cause of death in rheumatoid arthritis)
- DUTHIE, J. J. R., BROWN, P. E., TRUELOVE, L. H., BARAGAR, F. D., AND LAWRIE, A. J. (1964) *Ibid.*, **23**, 193 (Course and prognosis in rheumatoid arthritis: A further report).
- HARVALD, B. (1962) *Nord. Med.*, **67**, 274 (Papillitis necroticans renalis. En klinisk oversigt over 66 tilfælde)
- JACKSON, G. G., DALLENBACH, F. D., AND KIPNIS, G. P. (1955) *Med. Clin. N. Amer.*, **39**, 297 (Pyelonephritis; correlation of clinical and pathologic observations in the antibiotic era)
- KASS, E. H. (1956) *Trans. Ass. Amer. Physcns*, **69**, 56 (Asymptomatic infections of the urinary tract)
- KINCAID-SMITH, P. (1967) *Lancet*, **1**, 859 (Pathogenesis of the renal lesion associated with the abuse of analgesics)
- LAWSON, A. A. H., AND MCLEAN, N. (1966), *Ann. rheum. Dis.* **25**, 441 (Renal disease and Drug therapy in rheumatoid arthritis)
- MACDONALD, R. A., LEVITIN, H., MALLORY, G. K., AND KASS, E. H. (1957) *New Engl. J. Med.*, **256**, 915 (Relation between pyelonephritis and bacterial counts in the urine. An autopsy study)
- MAHALLAWY, N. M. EL, AND SABOUR, M. S. (1959) *Lancet*, **2**, 852 (Renal lesions in rheumatoid disease)
- MOWATT, A. G., HOTHERSALL, T. E., AND GOULD, J. C. (1970) *Ann. rheum. Dis.*, **29**, 143 (Urinary tract infection in patients with rheumatoid arthritis)
- PASTERNAK, A., WEGELIUS, O., AND MÄKISARA, P. (1967) *Acta med. scand.*, **182**, 591 (Renal biopsy in rheumatoid arthritis)
- ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., AND JESSAR, R. A. (1959) *Ann. rheum. Dis.*, **18**, 49 (Diagnostic criteria for rheumatoid arthritis. 1958 revision)
- 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)
- SØRENSEN, A. W. S. (1960) *Acta rheum. scand.*, **6**, 115 (Investigation of the kidney function in rheumatoid arthritis)
- (1963) *Ibid.*, **9**, 122 (Kidney function in relation to drug consumption in patients with rheumatoid arthritis)
- SPUHLER, O., AND ZOLLINGER, H. U. (1953) *Z. klin. Med.*, **151**, 1 (Die chronisch interstitielle nephritis)
- STEELE, T. W., GYORY, A. Z., AND EDWARDS, K. D. G. (1969) *Brit. med. J.*, **2**, 213 (Renal function in analgesic nephropathy)
- WALKER, W. C. (1967) *Quart. J. Med.*, **36**, 239 (Pulmonary infections and rheumatoid arthritis)
- WALKEY, F. A., JUDGE, T. G., THOMPSON, J., AND SARKARI, N. B. S. (1967) *Scot. med. J.*, **12**, 411 (Incidence of urinary infection in the elderly)
- WHATMORE, W. J., MACCABE, A. F., ROSS, J. A., AND MCNAIR, T. J. (1966) *Ibid.*, **11**, 356 (Urinary tract infection in a general surgical unit)
- WILLIAMS, J. D., THOMLINSON, J. L., COLE, J. G. L., AND COPE, E. (1969) *Brit. med. J.*, **1**, 29 (Asymptomatic urinary tract infection in gynaecological outpatients)