Urinary tract infection in patients with rheumatoid arthritis

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Pyelonephritis is the commonest disease of the kidneys found at autopsy and was present in between 10 and 20 per cent. of autopsies in several general hospitals (Jackson, Dallenbach and Kipnis, 1955; MacDonald, Levitin, Mallory, and Kass, 1957). In a comparative study of the renal lesions found at autopsy in control subjects and patients with rheumatoid arthritis in this region, pyelonephritis was found in 9 per cent. of the controls (Lawson and McLean, 1966). When chronic pyelonephritis alone is considered, the incidence has been reported as 3·3 to 7·9 per cent. in women, with a slightly lower incidence in men (Jackson and others, 1955; Kleeman and Freedman, 1960; Kimmelstiel, Kim, Beres, and Wellmann, 1961).

The terminal phases of rheumatoid arthritis may be complicated by severe renal disease. Duthie, Brown, Truelove, Baragar, and Lawrie (1964) reported that 17·3 per cent. of 74 patients died of renal disease after suffering from rheumatoid arthritis for 10 or more years. Lawson and McLean (1966) reported that 34·5 per cent. of 61 patients with rheumatoid arthritis died primarily of renal disease and 72·1 per cent. of the 61 patients had evidence of renal disease at autopsy. Pyelonephritis was the renal lesion in 29 (47·5 per cent.) of these patients and the lesion was regarded as chronic in almost half of the cases. Renal papillary necrosis was also present in thirteen (44·8 per cent.) of the patients with pyelonephritis. In those patients taking salicylates alone pyelonephritis was present in five (22 per cent.), but the lesion occurred in 24 (64·9 per cent.) of those patients taking phenacetin-containing drugs. In addition there was a significantly higher incidence of renal papillary necrosis in those patients taking phenacetin-containing drugs than in those taking other drugs. There was little difference in the incidence of pyelonephritis in those who received corticosteroids.

Phenylbutazone and gold therapy appeared to have had no influence upon the incidence of renal disease. Similar results have been reported by Clausen and Pedersen (1961).

Although there may be a chemical basis for some of the renal lesions found in patients with rheumatoid arthritis, the possibility of an increased incidence of renal infection in these patients has not previously been considered. The present study was undertaken to compare the incidence of urinary tract infection in patients with rheumatoid arthritis and in control subjects.

Chronic pyelonephritis may be associated with intermittent bacteruria and therefore it is possible that some of these patients may present with urine specimens containing no organisms (false negative). There is evidence that, when there is renal involvement in cases of urinary tract infection, antibodies to the antigens of the infecting micro-organisms, which in the great majority of instances are strains of Escherichia coli (Gould, 1968), are present in the serum. Therefore it might be expected that patients with rheumatoid arthritis who are suffering from pyelonephritis would have raised serum antibody titres to strains of Esch. coli commonly found in urinary infections (Reeves and Brumfitt, 1968). Accordingly, the sera of the patients and control subjects in this study were examined for antibody to selected strains of Esch. coli to determine whether there was any correlation with bacteruria and also to establish the possibility of renal infection without demonstrable bacteruria.

Material and methods

Patients with rheumatoid arthritis

This group consisted of 85 patients (50 females and 35 males) with classical or definite rheumatoid arthritis according to the diagnostic criteria of the American Rheumatism Association (Ropes, Bennett, Cobb,
Jaco, and Jessar, 1959); 34 (40 per cent.) of the patients (18 females and 16 males) were in-patients in the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh.

Control subjects
This group consisted of 68 healthy subjects (42 females and 26 males) who were members of the hospital staff. The two groups are compared in Table I.

Table I Details of patients and controls

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Number of patients with rheumatoid arthritis</th>
<th>Number of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>10-20</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20-30</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>30-40</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>40-50</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>50-60</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>70+</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>55·98</td>
<td>57·14</td>
</tr>
</tbody>
</table>

Individuals known to have any of the following conditions were excluded from both groups because of their known or suspected association with bacteruria and pyelonephritis (Kleeman, Hewitt, and Guze, 1960):

(a) Congenital abnormalities of the urinary tract
(b) Obstructive lesions of the renal tract other than prostatic enlargement
(c) Pregnancy
(d) Gout
(e) Nephrocalcinosis
(f) Diabetes
(g) Agammaglobulinaemia
(h) Neurological disease involving the bladder.

Details of age, parity, and prostatic symptoms were noted. An enquiry was made of a past history of urinary tract surgery, catheterization, urinary tract symptoms, and any treatment for these symptoms in both groups. Details of drug therapy with particular regard to salicylates, phenacetin-containing drugs, and steroids were noted. For the patients with rheumatoid arthritis the duration of the disease was recorded and an examination made for the presence of rheumatoid nodules and evidence of arthritis. Blood for plasma electrolyte and urea estimations and serum for antibody studies was taken from all subjects and also for the sensitized sheep cell test from the patients with rheumatoid arthritis.

Urine specimens
Standard techniques were used for the collection, storage, and dispatch of the urine samples (Elliott and Sleigh, 1963). No cleaning procedure was carried out in either sex as this was considered unnecessary in terms of obtaining satisfactory urine cultures (Turner, 1961).

At least two and usually three mid-stream specimens of urine were taken from each patient. The time interval between successive specimens was usually 1 or 2 days and never more than 7 days. A diagnosis of urinary tract infection was made on the finding of significant bacteruria and pyuria in at least two specimens. Both the quality and quantity of the organisms isolated from the specimens were assessed (Urquhart and Gould, 1965; Gould, 1968) and generally viable counts of potential pathogens of 100,000 per ml. or greater were regarded as significant (Kass, 1956). A specimen of urine obtained at the same time as the mid-stream specimen was microscopically examined immediately, without centrifugation, on a covered slide. The presence of five or more white blood cells per high power field was designated as pyuria.

Sera for antibody studies were separated at the same time and stored at −20°C for subsequent examination. The antigens used were strains of Esch. coli isolated from the patients and controls and also stock strains of the following 'O' antigen types: 0·1; 0·2; 0·4; 0·5; 0·6; 0·9; 0·11; 0·18; 0·39; and 0·75.

The techniques used were:

(a) Agglutination of suspensions of the whole bacteria with serial dilutions of the sera (Brumfitt and Percival, 1963; Percival, Brumfitt and de Louvois, 1964)
(b) Haemagglutination of fresh sheep red cells sensitized with suspensions of the same bacterial strains (Neter, Bertram, Zak, Murdock, and Arbesman, 1952; Winberg, Andersen, Hanson, and Lincoln, 1963; Reeves and Brumfitt, 1968).

Results
The results are set out in Table II. Five patients (5·88 per cent.) with rheumatoid arthritis and eight controls (11·76 per cent.) had significant bacteruria and pyuria, which was asymptomatic in every case. Seven of the infected controls and all the infected patients were female. There was no significant difference in the infection rate in the two groups. Even when women or out-patients alone were considered, there was still no significant difference in the infection rate. Three of the five infections in the patients were found in in-patients and, although this represents a higher infection rate than in out-patients, the difference is not significant.

The majority of the strains isolated from the infected cases were Esch. coli. Two strains of coliform bacilli, one of Proteus mirabilis, and one Streptococcus species were also isolated and, with the exception of one of the Esch. coli strains, all were sensitive to ampicillin and sulphonamides.

Only five cases (two controls and three patients) with significant bacteruria showed significant antibody titres to either the organism isolated or to the type-specific Esch. coli. A further twenty cases,
Table II  Results in patients and controls

<table>
<thead>
<tr>
<th>Series</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Per cent.</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>10·00</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>16·66</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>5·88</td>
</tr>
<tr>
<td>In-patient Female</td>
<td>3</td>
<td>8·2</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>10·00</td>
</tr>
<tr>
<td>Out-patient Female</td>
<td>2</td>
<td>4·1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>3·92</td>
</tr>
<tr>
<td>Cause of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>B. protens</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Streptococcus</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Coliform</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No. with serum antibody</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>No. with infection and antibody</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Unmarried women</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Total pregnancies</td>
<td>84</td>
<td>10·00</td>
</tr>
<tr>
<td>Pregnancy rate/married woman</td>
<td>2·048</td>
<td></td>
</tr>
<tr>
<td>Urinary tract surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>—</td>
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<td>Catheterization</td>
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<td>*Previous urinary tract symptoms</td>
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<tr>
<td>Female</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>*Previous treatment for symptoms</td>
<td>3</td>
<td>10·00</td>
</tr>
<tr>
<td>Female</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Prostatic symptoms</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes those found to be infected in this study

equally distributed between the patient and control groups, showed significant antibody titres but there was no correlation of titres between the two different techniques carried out. In patients with rheumatoid arthritis there was no correlation between the antibody titres and the titre of the sensitized sheep cell test.

The strains of micro-organism isolated from the patients and controls with asymptomatic bacteruria correspond to the types of bacteria isolated from cases of primary infection (Gould, 1968). They were, with one exception, sensitive to the antibacterial agents usually used and this would seem to confirm that they had been derived from autogenous infection.

When those individuals who reported previous urinary tract symptoms were considered, five patients and twelve controls were found. Since they were all female this represents a previous infection rate for women with rheumatoid arthritis of 10 per cent. and for female controls of 28·5 per cent. The difference is significant ($x^2 = 4·066; P < 0·05$).

No correlation could be shown between drug therapy and urinary tract infection in either group. No correlation could be shown between duration of disease, sensitized sheep cell test titre, the presence of nodules, arteritic lesions, and urinary tract infection for the patients with rheumatoid arthritis.

Table II also shows that the parity of the married women with rheumatoid arthritis was less than that of the married controls. The controls had also undergone more urinary tract surgery and catheterization than the patients.

All subjects had normal serum electrolyte and urea values.
Discussion

The incidence of a significant bacteruria, taken as a viable count of pathogenic bacteria of 100,000 or more per ml. (Kass, 1956), has been reported in a number of populations. Kass (1956) found an incidence of 6 per cent. in 337 female and of 4 per cent. in 102 male out-patients. Similar figures have been noted by Williams, Thomlinson, Cole, and Cope (1969) and by Sussman, Asscher, Waters, Evans, Campbell, Evans, and Williams (1969). Other authors (Freedman, Phair, Seki, Hamilton, and Neffzer, 1965; Miall, Kass, Ling, and Stuart, 1962) have noted an increasing incidence of urinary tract infection with increasing age. Surveys of the incidence of urinary tract infection in general practice provide similar figures, and suggest that 1 per cent. of the population will have an infection each year (Fry, Dillane, Joiner, and Williams, 1962; Loudon and Greenhalgh, 1962; Mond, Percival, Williams, and Brumfitt, 1965).

When the incidence of urinary tract infection in patients admitted to hospital is considered, rather higher figures are found. Whatmore, MacCabe, Ross, and McNair (1966) found that 11 per cent. of men and 37 per cent. of women were infected on admission to a general surgical unit and that two-thirds of them were asymptomatic. Similar findings have been reported by Kaitz and Williams (1960). A much increased incidence has also been noted in patients over 60 years of age on admission to hospital, with 31 per cent. of men and 34 per cent. of women having urinary tract infections (Walkey, Judge, Thompson, and Sarkari, 1967).

In the present series there was no significant difference in the infection rate between patients with rheumatoid arthritis and controls. However, an incidence of bacteruria of 11·76 per cent. in the controls is rather higher than that reported in the other series. In the patients there were no infections in the males and the infection rates for female in- and out-patients of 16·7 and 6·25 per cent. are rather lower than might have been expected from other series for patients in the age groups investigated. The only significant difference noted between the two groups was in the incidence of previous urinary tract symptoms, the higher figure being found in controls. However, since so many subjects have asymptomatic infections of the urinary tract, these findings are probably unreliable. The higher average age of the patients might be balanced by their lower parity and incidence of urinary tract surgery and catheterization to produce these results.

Patients with rheumatoid arthritis are reported to be more liable to infections of all sorts than controls (Cobb, Anderson, and Bauer, 1953). A higher incidence of pulmonary infections in these patients has been reported (Stack and Grant, 1965; Walker, 1967). Kellgren, Ball, Fairbrother, and Barnes (1958) have shown that it is not uncommon for these patients to develop suppurrative arthritis. No comparative study of the urinary tract infection rates in patients with rheumatoid arthritis and controls has previously been carried out, although Bulger, Healey, and Polinsky (1968) found no significant bacteruria in 42 patients. The finding of a low urinary tract infection rate in this study is therefore surprising. It may well be that the increased infection rates in other sites reflects the liability of tissues already damaged by the rheumatoid process to become superinfected with pathogenic organisms. Renal lesions due to rheumatoid disease are rare (Lawson and McLean 1966), and no correlation could be shown between the incidence of urinary tract infection and the sensitized sheep cell test, the presence of nodules or arteritic lesions, and the duration of the disease.

The possibility of intermittent bacteruria in the presence of chronic pyelonephritis cannot be excluded by the extent of the bacteriological examination in the present study. A good correlation between chronic bacteruria and serum antibody to the isolated strain of infecting organism has been reported by several investigators (Brumfitt and Percival, 1963; Winberg and others, 1963; Percival and others, 1964; Ehrenkranz and Carter, 1964). This has not been confirmed in the present study although the number of cases is very small, and may indicate that the patients with bacteruria and no serum antibody are in the early stages of renal disease. A larger number of cases without detectable bacteruria had serum antibody to type-specific Esch. coli strains known to be more frequently associated with renal infection, and these were equally distributed between patients and controls. Only one of these cases had a history attributable to previous urinary tract infection. It is difficult to assess the significance of such a finding but it seems unlikely that it can be interpreted as meaning that larger numbers of patients with rheumatoid arthritis have infective pyelonephritis than indicated by the presence of bacteruria.

Although the relationship of significant bacteruria to pyelonephritis is not clear (MacDonald and others, 1957; Beeson, 1967), it seems likely that some factor other than infection must be implicated to account for the high incidence of renal lesions found at post-mortem in patients with rheumatoid arthritis.

Chronic interstitial nephritis is generally regarded as being a specific lesion associated with renal papillary necrosis (Spühler and Zollinger, 1953; Kincaid-Smith, 1967a) and although these renal changes occur as a result of urinary tract obstruction and in diabetic subjects, most of the lesions can be attributed to analgesic abuse. However, others
have emphasised that a similar lesion occurs in classical pyelonephritis and may appear as a secondary phenomenon to primary vascular disease of the kidney (Sørensen, 1963; Randerath, 1958). It may be difficult therefore to attribute renal lesions found at post-mortem to any specific cause. An association between these renal lesions and the ingestion of phenacetin has been suggested by several authors (Lawson and McLean, 1966; Clausen and Pedersen, 1961; Cochran, Lawson, and Linton, 1967). However, others suggest that the factors involved are complex since other drugs are almost invariably administered simultaneously with phenacetin (Sørensen, 1963; Prescott, 1965; Kincaid-Smith, 1967b; Saker and Kincaid-Smith, 1969).

The present study therefore provides further evidence that drug therapy may be responsible for much of the high incidence of renal lesions found at autopsy in patients with rheumatoid arthritis.

Summary

The incidence of urinary tract infection in patients with rheumatoid arthritis and controls was compared; 5.88 per cent. of patients and 11.76 per cent. of controls had urinary tract infections, but the difference was not significant. These findings are discussed in the light of the high incidence of renal lesions found at autopsy in patients with rheumatoid arthritis. It is suggested that these results provide further evidence of the importance of analgesic abuse in the production of renal lesions.

We wish to thank Prof. J. J. R. Duthie, Dr. R. J. G. Sinclair, and Dr. W. R. M. Alexander for permission to study their patients and for their advice during preparation of this paper.

We also wish to record our thanks to Sister M. Daniel for her careful supervision of the collection and dispatch of the urine specimens.

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 Percival, A., Brumfit, W., and de Louvois, J. (1964) Lancet, 2, 1027 (Serum-antibody levels as an indication of clinically inapparent pyelonephritis).

 Prescott, L. F. (1965) Ibid., 2, 91 (Effects of acetylsalicylic acid, phenacetin, paracetamol, and caffeine on renal tubular epithelium).


 Résumé

 L'Incidence des voies urinaires chez les malades atteints de polyarthrite rhumatoïde

 L'incidence de l'infection des voies urinaires chez les malades atteints de polyarthrite rhumatoïde et chez les témoins a été comparée.

 5,88 pour cent. des malades et 11,7 pour cent. des témoins avaient une affection des voies urinaires, mais la différence n'était pas significative. Ces observations sont discutées à la lumière de l'incidence marquée des lésions rénales trouvées à l'autopsie chez les malades atteints de polyarthrite rhumatoïde. Il est suggéré que ces résultats donnent encore une preuve de l'importance de l'abus de l'emploi des analgésiques dans la production des lésions rénales.

 SUMARIO

 Infeción del tracto urinario en pacientes con poliartritis reumatoide

 La incidencia de infección del tracto urinario en pacientes con poliartritis reumatoide fue comparada con la de testigos.

 Un 5,88 por ciento de pacientes y un 11,7 por ciento de testigos padecían infección del tracto urinario, pero la diferencia no era significativa. Estos descubrimientos se discuten a la luz de la alta incidencia de lesiones renales halladas en la autopsia de pacientes con poliartritis reumatoide. Se sugiere que estos resultados constituyen una prueba más de la importancia del abuso de analgésicos en la producción de lesiones renales.
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