Bacteriuria in rheumatoid arthritis

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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

<table>
<thead>
<tr>
<th>Series</th>
<th>Sex</th>
<th>No. of cases</th>
<th>Average age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.A.</td>
<td>Male</td>
<td>77</td>
<td>53·7</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>177</td>
<td>54·9</td>
</tr>
<tr>
<td>Control</td>
<td>Male</td>
<td>57</td>
<td>51·1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>72</td>
<td>53·6</td>
</tr>
</tbody>
</table>

Table II Bacteriuria

<table>
<thead>
<tr>
<th>Sex</th>
<th>Series</th>
<th>Total</th>
<th>UTI No.</th>
<th>UTI Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>R.A.</td>
<td>77</td>
<td>3</td>
<td>3·9</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>57</td>
<td>2</td>
<td>3·5</td>
</tr>
<tr>
<td>Female</td>
<td>R.A.</td>
<td>177</td>
<td>19</td>
<td>10·7</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>72</td>
<td>8</td>
<td>11·1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Sex</th>
<th>Total cases</th>
<th>Percentage female</th>
<th>UTI</th>
<th>Percentage incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>20</td>
<td>57</td>
<td>77</td>
<td>74</td>
<td>12</td>
</tr>
<tr>
<td>No steroids</td>
<td>57</td>
<td>120</td>
<td>177</td>
<td>68</td>
<td>10</td>
</tr>
</tbody>
</table>

* 0.01 < P < 0.05

Table IV  Bacteriuria and creatinine clearance

<table>
<thead>
<tr>
<th>Clearance</th>
<th>&gt;80</th>
<th>&lt;80</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>70</td>
<td>55</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>6</td>
<td>8</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>63</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

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, Thorlinson, 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 Brochner-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. (Claussen 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 micro-
scopic 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 neph-
ritis 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
tissues 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 anal-
gesics may lead to papillary necrosis with accom-
panying 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
cpecies 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 anal-
gesic mixtures investigated by Steele, Gyory, and
Edwards (1969) were shown to have deficiencies in
two 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 anal-
gesic 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,
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 cortico-
steroid hormones showed a statistically significant
increase in the incidence of bacteriuria.

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