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RENAL ABNORMALITIES IN RHEUMATOID ARTHRITIS*

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The subject of renal disease in rheumatoid arthritis has recently been reviewed (*Lancet*, 1966), and the usual opinion that renal lesions are uncommon in rheumatoid arthritis has been disputed by studies such as that of Lawson and McLean (1966) who found significant kidney disease in 44 of 61 patients at autopsy examination.

Various types of renal abnormalities have been described. Vascular lesions similar to those in systemic lupus erythematosus and polyarteritis are unusual in rheumatoid arthritis. Amyloidosis affecting the kidney is a complication of long-standing rheumatoid arthritis and has been reported in 15 to 20 per cent. of most series. The association between interstitial nephritis, papillary necrosis, and excessive use of analgesics, particularly phenacetin, has directed attention to the possibility that such renal lesions may occur in patients with rheumatoid arthritis, many of whom take large amounts of these drugs for prolonged periods.

We have studied renal function in 42 ambulatory patients with definite rheumatoid arthritis by means of standard renal function tests, attempting to correlate the findings with the nature and duration of the patients' rheumatoid arthritis and the medications they have received. Abnormalities of these tests (urine analysis, endogenous creatinine clearance, and concentrating ability) were present in 22 of 42 patients. Only two of these patients, neither of whom had renal abnormalities, admitted to taking any phenacetin-containing compounds.

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Material and Methods

Patients

The patients studied were adults attending the Arthritis Clinic of the University Hospital. No selection was made other than to choose those who were able to cooperate in the renal studies described below. There were eight men and 34 women aged 19 to 73 years (mean 50). All had definite rheumatoid arthritis by the criteria of the American Rheumatism Association with disease duration ranging from 2 to 42 years (mean 12). Onset of the illness had occurred before age 15 in three women. Disease activity was sustained in all patients, except for two men, who each had a 2-year episode followed by a long remission. No patient had systemic lupus erythematosus (SLE), diabetes, hypertension, or one of the syndromes that fall between rheumatoid arthritis and the other "autoimmune" diseases such as SLE or polyarteritis.

History

Each patient was seen by one of us (L.A.H.) and information was recorded on a standard form in the following order:

(1) The evidence for rheumatoid arthritis and the duration of active disease.
(2) The medications taken for rheumatoid arthritis and an approximate amount of each one.

Salicylates were recorded as the average number of 5 gr. tablets taken daily for a period of years. A total figure called "tablet-years" was then determined.

E.g.: 12 tab./day for 5 years = 60
6 tab./day for 10 years = 60

Total Tablet-years = 120

This is obviously a rough approximation and there is no evidence that 12 tab./day for 5 years is actually equivalent to 6 tab./day for 10 years. It is recognized as an arbitrary method of comparison which was applied to each patient.

Approximate total amounts of gold salts and daily doses of steroids, chloroquine, and other antirheumatic drugs (phenylbutazone, indomethacin) were recorded

from the patients' charts or histories. All patients were questioned in detail about phenacetin and phenacetin-containing proprietary compounds.

(3) A detailed history regarding the genito-urinary system, including a history of kidney disease, haematuria, or stone; previous urine analyses and proteinuria; pregnancies and complications; urethritis or prostate disease; urethral instrumentation or catheterization.

Renal Tests

The following tests were performed in all patients:

(1) Routine urine analysis.

(2) Two separate examinations of the urinary sediment by one of us (R.J.B.) according to the method suggested by Relman and Levinsky (1963).

(3) Two urine cultures and colony counts.

(4) Urine concentrating ability following a 12-hour fast, as measured by specific gravities; repeated if the specific gravity was less than 1·022.

(5) 24-hour urine protein content.

(6) 24-hour urine creatinine content.

(7) Serum creatinine, sodium, chloride, potassium, and bicarbonate.

(8) Creatinine clearance calculated from (6) and (7); corrected for individual height and weight; repeated if less than 80 ml./min.

On the basis of these tests, the patients were divided into the categories in Table I by one of us (R.J.B.) without knowledge of their medication or the duration of their rheumatoid arthritis.

Results

Of the 42 patients studied, 22 showed evidence of renal disease. Results of renal tests are shown in Table I. From these findings, the patients were grouped into four separate classifications, which reflect clinical diagnosis deemed likely by a trained observer and are not to be construed as absolute anatomic diagnoses:

A. Eleven patients were considered to have interstitial nephritis.

All of them were unable to concentrate the urine (specific gravity less that 1·018) after 12 hours of fluid deprivation on at least two occasions. All had characteristic urine analyses with little or no protein and sediments showing increased numbers of white cells (> 8 per high-power field), white cell casts, and coarsely granular casts. None of these patients had bacteriuria. On repeated testing, nine of them had decreased 24-hour endogenous creatinine clearances which ranged from 52 to 75 ml./min. (mean 64).

B. Two patients were given the diagnosis of glomerulonephritis.

This was because of heavy proteinuria, red blood cells, and red blood cell casts in the sediment. Both had diminished creatinine clearances (65 and 71 ml./min.).

C. Nine patients were considered to have renal disease of uncertain aetiology.

In five, the creatinine clearances were low, ranging from 61 to 79 ml./min. (mean 72). Their urine analyses were characterized by normal or non-diagnostic sediments and little or no protein. Of these five, three were unable to achieve urine specific gravities in excess of 1·012 after 12 hours of water deprivation and, therefore, may have had interstitial nephritis. All four patients in Group C with normal creatinine clearances were unable to concentrate the urine and three of them had an abnormal number of white blood cells (> 8 per high-power field) in the urine sediment. These patients may also have had interstitial nephritis.

D. Twenty patients showed no evidence of kidney disease.

They were able to concentrate the urine beyond the specific gravity of 1·025 and had normal creatinine clearances and urine analyses.

TABLE I
GROUPING OF PATIENTS ACCORDING TO RENAL ABNORMALITIES

Diagnostic Group	No. of Patients	24-Hour Endogenous Creatinine Clearance Corrected (< 80 ml./min.)	Concentrating Ability (< 1·018)	Abnormal Sediment	Red Blood Cell Casts	Coarsely Granular and White Blood Cell Casts	Finely Granular and Hyaline Casts	Proteinuria	Bacteriuria (> 10^5 ml.)	Clinical Diagnosis
(A)	11	9	11	11	0	11	4	3	0	Interstitial nephritis
(B)	2	2	1	2	2	0	2	2	0	Glomerulo-nephritis
(C)	9	5	7	3	0	0	1	2	0	Unclassified renal disease
(D)	20	0	0	0	0	0	0	0	0	No renal disease
Total	42	16	19	16	2	11	7	7	0	

A history of lower urinary tract infection or of urethral catheterization in the past was obtained from twelve of the 22 patients with evidence of renal disease and from ten of the 20 patients without evidence of renal disease. One of the patients considered to have glomerulonephritis (Group B) gave a classic history for an episode of acute glomerulonephritis occurring 4 years previously.

After decisions had been reached regarding renal status, the patients were divided into two groups (22 with renal disease, and 20 without) and the characteristics of the two groups were compared. The results are shown in Tables II and III.

TABLE II
DESCRIPTION OF PATIENTS

Renal Disease		Present	Absent
No. of Cases		22	20
Sex	Male	5	3
	Female	17	17
Mean Age (yrs)		51·3	49·2
Rheumatoid Factor Present		19	17
Mean Duration of Arthritis (yrs)		14·8*	10·8

*P < 0·45.

TABLE III
MEDICATION

Renal Disease		Present	Absent
No. of Patients		22	20
Medication	Chloroquine	6	8
	Indomethacin	4	3
	Phenylbutazone	7	3
	Corticosteroids	15	14
	Gold Salts	15	9†
	Phenacetin	0	2
	Aspirin	22	20
Amount of Aspirin (mean tablet-years)		93·3	65·7*

*P < 0·05.
†P < 0·2.

Reference to Table II reveals that the two groups do not differ significantly in the sex ratio, mean age, or presence of the rheumatoid factor. Patients with evidence of renal disease had active rheumatoid arthritis for a longer period of time than those without; a mean of 14·8 years as against 10·8 years, but when compared by Student's "t" test, this difference is probably not significant (P < 0·45).

The medications taken by the two groups are shown in Table III. There is no real difference between them in the number who received corticosteroids, phenylbutazone, indomethacin, or chloroquine. Fifteen of the 22 patients with renal disease had received a series of gold salt injections as had nine of the twenty without renal disease (χ^2 value of 2·36; P < 0·2). None of the patients in either group had taken a significant amount of phenacetin or phenacetin-containing compounds in the course of their disease. All the patients in both groups took salicylate; however, the groups with renal disease had taken more aspirin for a longer period of time than the group without evidence of renal disease. The mean calculation of tablet-years for the group with renal disease was 93·3 as against 65·7 for those without (P < 0·05).

Furthermore, the nine patients with diminished creatinine clearances (suggesting bilateral disease) and the clinical diagnosis of interstitial nephritis had a mean aspirin intake of 122 tablet-years.

Discussion

Evidence of renal disease, as manifested by a decreased creatinine clearance, defect in concentrating ability, or abnormal sediment, was found in 22 of 42 patients with rheumatoid arthritis. Glomerulonephritis was diagnosed in two of these patients on the basis of heavy proteinuria and sediments showing red blood cells and red blood cell casts. The most likely clinical diagnosis for most of the remainder of the group is considered to be "interstitial nephritis". This term, usually used interchangeably with "chronic pyelonephritis", is preferred in this instance because there was no evidence of bacterial infection in our patients. In eleven cases, this diagnosis was considered likely because of diminished concentrating ability and the presence of white blood cell casts without either bacteriuria or significant proteinuria. White blood cell casts or coarsely granular casts were not demonstrated in the additional nine patients; and, therefore, their renal disease was unclassified, although it is considered probable that some of these also may have an interstitial nephritis.

Previous studies of renal disease in patients with rheumatoid arthritis were based on autopsy or renal biopsy (Pollak, Pirani, Steck, and Kark, 1962; Lee, Dushkin, Eyning, Engleman, and Hopper, 1965; Lawson and McLean, 1966). The lesion commonly found at autopsy, particularly in patients dying in renal failure, has been amyloidosis (Allander, Bucht, Lövgren, and Wehle, 1963). Renal vasculitis and glomerulonephritis are unusual in rheumatoid arthritis. Renal biopsies were not performed in our study and we may have missed some patients with glomerulonephritis or amyloidosis on this basis. The clinical picture did not suggest amyloidosis in any of these patients and little proteinuria was found, but this diagnosis is difficult

to make without tissue examination. Rectal biopsies were performed in two patients with renal disease and one without and no amyloid was present.

There were few differences between the patients with renal disease and those without it. The patients with renal disease were not significantly older; they did not have more severe rheumatoid arthritis or a greater (or lesser) incidence of rheumatoid factor; nor did they take different medicines. On the average, they had had active rheumatoid arthritis for a slightly longer period (14·8 *v.* 10·8 years), but this difference was not great ($P < 0·45$).

The only detectable difference between the two groups was that those with renal disease had consumed more aspirin than those who did not have abnormal function tests. Based on our approximation of total dosage, patients with renal disease had a mean intake of 93·3 tablet-years as opposed to a mean of 65·7 tablet-years for those without evidence of renal abnormality. This difference is significant at the 95 per cent. level of confidence. In the Figure, the creatinine clearance is shown as a function of total aspirin intake for all 42 patients. The correlation coefficient ($r = 0·301$) indicates some relation between aspirin dose and creatinine clearance ($P < 0·05$).

The question of aspirin nephrotoxicity has received considerable discussion. Prescott (1965) demonstrated that the drug may induce renal damage acutely, as manifest by an abnormal sediment containing red blood cells and renal tubular cells. In discussing the nephropathy of phenacetin, Gilman (1964) and Haley (1966) pointed out that in every instance the phenacetin was taken as part of a proprietary analgesic compound containing aspirin and other substances. Lawson and McLean (1966) noted that patients who had taken phenacetin and salicylate had a higher incidence of renal papillary necrosis or non-obstructive pyelonephritis than patients who had taken salicylate only.

The present report provides a useful contrast to previous investigations in that phenacetin consumption is not a habit of our patients. None of those

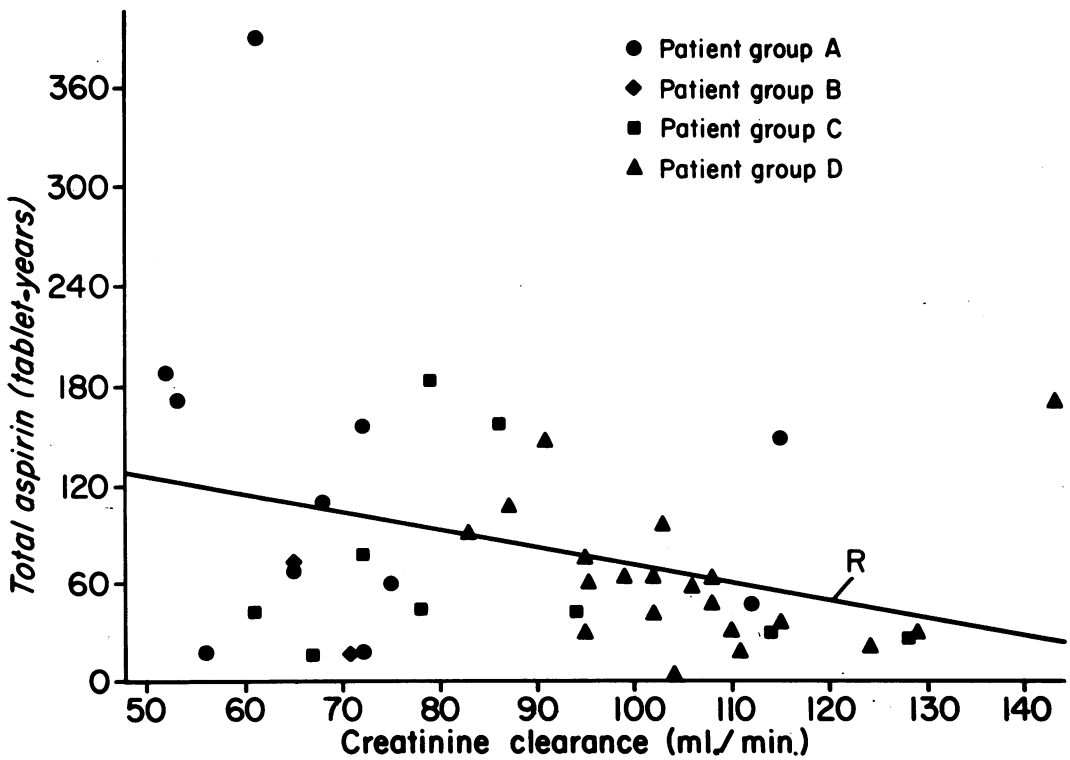

Figure.—The regression line (R) was calculated on the basis of the entire population of 42 patients and has a correlation efficient of 0·301. This shows some correlation between total aspirin intake and creatinine clearance ($P < 0·05$).

with evidence of renal disease admitted to taking any analgesic compounds containing phenacetin, and the two patients who did admit to using them infrequently had no evidence of renal disease. It may be significant that we saw no evidence to suggest renal papillary necrosis nor did any of these patients show clinically significant renal failure despite the abnormalities demonstrated.

The conclusions to be drawn from this study are limited. While the data suggest that chronic high-dose aspirin ingestion is associated with abnormalities of renal function tests, we cannot state that aspirin causes renal failure. The features of this study which limit such a conclusion are:

(1) The inability to separate the possible effects of the rheumatoid disease from the possible effects of salicylate or other medications;

(2) The measurement of salicylate dosage is a rough approximation;

(3) Many patients took high-dose salicylate for long periods without showing abnormalities of renal function;

(4) No patient studied had significant morbidity from renal disease.

The high incidence of renal abnormalities, compatible with the diagnosis of interstitial nephritis in our patients, is consistent with recent autopsy and biopsy studies of patients with rheumatoid arthritis. Although none of our patients showed any morbidity from the renal disease, it may become an important factor in the future.

Summary

Creatinine clearances, tests of urine concentrating ability, careful urine analyses, and urine cultures were obtained for 42 patients with known rheumatoid arthritis. Renal abnormalities were documented in 22 of the patients, sixteen of whom had diminished creatinine clearances. On the basis of these renal abnormalities, eleven patients were felt to have interstitial nephritis, two gave evidence of glomerular disease, and nine had unclassified abnormalities. Some of this last group may have had interstitial nephritis.

Only two of this series of patients admitted to taking phenacetin, and neither of them had renal disease. Only one patient had not taken large doses of aspirin as treatment for rheumatoid arthritis, and she showed no renal abnormalities.

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Les anomalies rénales dans la polyarthrite rhumatoïde

RÉSUMÉ

On étudia chez 42 malades ayant une polyarthrite rhumatoïde connue la clearance de la créatinine, les épreuves de concentration urinaire, et on fit ainsi des analyses d'urine soigneuses et des cultures. On nota des anomalies rénales chez 22 de ces malades, parmi lesquels 16 avaient une clearance de la créatinine diminuée. Partant de ces anomalies rénales, on considéra que 11 d'entre eux avaient une néphrite interstitielle, que deux avaient des signes d'atteinte glomérulaire et que neuf avaient des anomalies non classées. Certains parmi ces derniers auraient pu avoir une néphrite interstitielle.

Deux malades seulement admirent avoir pris de la phénacétine et aucun n'avait d'atteinte rénale. Un malade seulement n'avait pas pris de grosses doses d'aspirine comme traitement de sa polyarthrite et elle n'avait pas d'anomalies rénales.

Las anomalías renales en la poliartritis reumatoide

SUMARIO

Se investigaron en 42 enfermos con poliartritis reumatoide conocida la clearance de la creatinina, los tests de la función concentradora de la orina y se hicieron analisis cuidadosos y culturas de la orina. Se notaron anomalías renales en 22 enfermos, 16 de los cuales revelaron una clearance de la creatinina disminuida. De estas anomalías renales se juzgaron once como casos de nefritis intersticial, dos como casos de lesión glomerular y en nueve pacientes las anomalías quedaron sin clasificar. Algunos de los últimos pudieron haber sufrido de una nefritis intersticial.

Sólo dos enfermos reconocieron haber tomado fenacetina y ninguno de ellos tuvo una lesión renal. Una sola enferma no había tomado fuertes dosis de aspirina para su poliartritis y ella tampoco acusaba anomalías renales.