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PRESENTATION AND DIAGNOSIS OF CHRONIC PYELONEPHRITIS

BY

H. M. LEATHER, M.D., M.R.C.P.

Consultant Physician, Plymouth Clinical Area; Late Senior Medical Registrar, Medical Unit,
Bristol Royal Infirmary

Chronic pyelonephritis may be very difficult to diagnose. In some large surveys as few as 20% of cases have been diagnosed during life (Kleeman *et al.*, 1960). In recent years new methods of diagnosis have become available and include renal biopsy and the "pyrogen" test. Between July, 1959, and January, 1962, 30 cases of chronic pyelonephritis were diagnosed in the medical unit, Bristol Royal Infirmary. The way these cases presented has been analysed and an attempt made to determine how useful were the new methods of investigation.

Methods

Full clinical details were taken and at least four specimens of urine from each case were examined for proteinuria and centrifuged deposit. Quantitative urine culture was carried out by the loop technique (Gillespie *et al.*, 1960). Infection was considered to be present when the bacterial count exceeded 10,000/ml. A urinary W.B.C. count (Houghton and Pears, 1957) was made in each case and the effect of pyrogen (Pears and Houghton, 1958) or steroid (Katz and Moore, 1960; Katz *et al.*, 1962; Little and de Wardener, 1962) on the output of W.B.C. determined. Renal biopsies were taken by the method of Kark and Muehrcke (1954) with the modification in later cases in the series that an image intensifier was used throughout the course of the biopsy to locate the kidney. Other investigations included excretory urography and, when necessary, cystoscopy and retrograde pyelography.

Diagnosis.—The diagnosis of chronic pyelonephritis was made on any one of the following criteria: (1) a history of infection of the urinary tract together with changes on excretory urography, which included distortion and clubbing of calices with focal parenchymal narrowing; (2) a positive pyrogen or steroid test provided this was associated with other evidence of pyelonephritis obtained from the history, excretory urography, or biopsy; and (3) conclusive histological

evidence of pyelonephritis from renal biopsy. Since the investigations were made five cases have come to necropsy and in three others a nephrectomy has been carried out. In all eight cases the diagnosis of chronic pyelonephritis has been upheld. In one other case a diagnosis of primary hyperparathyroidism has been made subsequent to the diagnosis of pyelonephritis.

Findings

There were 22 women and 8 men; their ages ranged from 5 to 60 years.

Presentation.—Thirteen cases presented with symptoms of infection of the urinary tract. All complained of dysuria and frequency, and eight of them had had loin pain. Only 2 of these 13 cases had hypertension, and in these two dysuria and frequency dated from 7 and 16 years previously. A further case presented with acute epididymitis. There had been no history of infection of the urinary tract prior to this. Sixteen cases showed evidence of intrarenal infection: five with hypertension, seven with renal failure, and four with proteinuria. Only six of these (three with hypertension and three with renal failure) had had dysuria and frequency, which had occurred from 16 to 30 years previously. Hypertension was present in 14 of the 30 cases. Only two of these came with dysuria and frequency; the remaining 12 had hypertension itself (five cases), renal failure (four cases), albuminuria (two cases), and acute epididymitis (one case). The clinical presentation of these 30 cases thus fell into two broad groups. Approximately half complained of symptoms of infection of the urinary tract. The remainder showed evidence of renal damage.

Urinary Findings.—Proteinuria was usually present but never heavy. Three cases were repeatedly protein-free and in these the urinary deposit was also normal. In three other cases proteinuria was absent between acute episodes of urinary tract infection. In eight cases the

urinary deposit was normal; in 18 varying degrees of microscopic pyuria were present; in four microscopic haematuria with a normal W.B.C. content was found. The W.B.C. excretion/hour did not always tally with the findings in the "routine" centrifuged deposit. In four cases with fewer than 10 W.B.C./high-power field (H.P.F.) in the deposit the W.B.C. excretion rate exceeded 1,000,000/hour.

Excretory Urography.—This was performed in 24 cases. In six the findings were characteristic of chronic pyelonephritis; in four cases congenital abnormalities were present; in three a hydronephrosis was demon-

strated; and the remaining 11 were normal, but in one of these with persistent right loin pain micturating cysto-urethrography revealed right ureteric reflux. In four further cases in which the blood urea was raised retrograde pyelography revealed evidence of chronic pyelonephritis in two.

Pyrogen Test.—The pyrogen or steroid test was performed in 29 cases. The result was positive in 17. (In a positive test the urinary output of white blood cells during the hour of maximum excretion following pyrogen or steroid rose to double that of the control period and exceeded 300,000 W.B.C./hour (Leather

Summary of 30 Cases of Chronic Pyelonephritis

Case No.	Sex and Age	Presentation	B.P.	Urine							Blood Urea	I.V.P.	Biopsy Evidence of Pyelonephritis
				Albumin	Deposit		W.B.C./hr.	Culture	Pyrogen/Steroid	Max. Conc.			
					R.B.C.	W.B.C.							
1	F 20	Dysuria, frequency, loin pain—6 years	120/75	Nil	0	<1	23,000	Sterile	+	1019	22	Normal	Suggestive
2	F 25	Dysuria, frequency, right loin pain—5 years	120/70	Trace	0	1-5	8,000	"	+			Right kidney: low malrotated	"
3	F 27	Dysuria, frequency, loin pain—1 year	130/85	+	<1	5-60	9,000,000	<i>B. paracolon</i>	—	1014	39	Bilat. chronic pyelonephritis	—
4	F 21	Dysuria, frequency, rigors, loin pain	130/80	+	<1	10-12	3,200,000	<i>E. coli</i>	+	1020	18	Crossed ectopia left kidney	—
5	F 39	Dysuria, frequency, abdominal pain—3 weeks	145/90	Trace	0	10-15	61,000	Sterile	+		24	Duplex left kidney	—
6	F 11	Dysuria, frequency, right loin pain—7 years	110/70	+	<1	10-15	10,000,000	<i>E. coli</i>	—		25	Normal. Cysto-urethrogram = right ureteric reflux	—
7	F 34	Dysuria, frequency, loin pain—7 years	140/90	Trace	1-3	25-30	220,000	"	—			Right chronic pyelonephritis	Nephrectomy chronic pyelo.
8	M 5	Dysuria, frequency, fever, rigors—2 years	105/75	"	1-3	40-50	12,000	<i>St. aureus</i>	+		46	Left hydronephrosis and hydroureter	Nephrectomy, chronic pyelo.
9	F 25	Dysuria, frequency, loin pain—6 months	130/80	Nil	0	1-2	22,000	Sterile	+	1020	30	Normal	—
10	F 26	Dysuria, frequency, loin pain—9 years	110/65	Trace	0	<1	41,000	"	+	1023	24	"	Suggestive
11	F 23	Dysuria, frequency, 7 years	140/90	"	50-60	4-10	113,000	<i>E. coli</i>	+	1023	24	"	"
12	F 44	Dysuria, frequency, 7 years	170/100	+	<1	8-10	60,000	Sterile	+	1026	19	Horseshoe kidney	—
13	F 60	Dysuria, frequency 16 years	190/100	Trace	<1	4-6	15,000	"	—	1019	25	Right chronic pyelonephritis	Normal
14	M 16	Acute epididymitis. No dysuria, frequency	210/145	"	<1	30-40		"	Not done	1020	38	" "	Nephrectomy, chronic pyelo.
15	F 38	Hypertension (med. exam.). Pyelitis aged 5 years	190/140	"	0	<1	9,000	"	—	1020	29	Bilat. chronic pyelonephritis	Inadequate tissue
16	F 37	Headaches, vomiting, rigors, dysuria, frequency, with pregnancy 16 years previously	200/120	"	<1	5-10	1,500,000	"	+	1007	42	Normal	Chronic pyelonephritis. Nephrocalcinosis
17	M 40	Hypertension (med. exam.)	210/140	+	<1	1-2	56,000	"	+	1012	59	Bilat. hydro-nephrosis	—
18	F 28	"	200/120	Nil	<1	1-2	54,000	"	+		36	Normal	Suggestive
19	F 48	Heart failure. Dysuria, frequency 16 years previously	230/110	+	<1	<1	41,000	"	—		40	Right chronic pyelonephritis	"
20	M 15	Proteinuria (med. exam.)	125/80	+	40-50	1-5	216,000	"	+	1022	28	Normal	"
21	F 24	"	120/80	+	<1	10-15	10,000,000	"	—		51	"	"
22	M 35	"	190/115	+	5-10	4-8	100,000	"	+	1013		"	"
23	M 47	"	160/100	+	40-50	6-8	424,000	"	+	1019	48	"	Chronic pyelonephritis
24	M 41	Renal failure. Proteinuria 18 years previously	150/85	+	1-2	1-2	40,000	"	—		302	—	Necropsy: chronic pyeloneph.
25	M 45	Renal failure, dysuria, frequency 20 years previously	160/115	+	40-50	1-5	60,000	"	—	1007	150	—	Chronic pyelonephritis
26	F 24	Renal failure	165/120	Trace	<1	1-2	63,000	"	+		178	Retrograde normal	" "
27	F 56	"	190/90	+	0	>100	13,000,000	"	—	1005	81	Right hydro-nephrosis	—
28	F 42	Renal failure. Dysuria, frequency, loin pain in pregnancy, 22 years previously	210/130	+	4-10	5-10	202,000	"	—	1010	112	Retro. bilat. chronic pyelonephritis	Necropsy chronic pyeloneph.
29	F 38	Renal failure. Dysuria, frequency with pregnancy, 17 years previously	180/100	+	>100	1-3	1,200,000	"	+	1007	141	" "	" "
30	F 40	Renal failure. Proteinuria, hypertension with pregnancy, 12 years previously	160/90	Trace	<1	10-20	730,000	"	—		400		" "

et al., 1963). In 5 of these 17 cases the diagnosis of pyelonephritis had already been established conclusively by evidence of repeated severe acute pyelonephritis in one, biopsy evidence in three, and x-ray evidence in one. In the remaining 12 cases the pyrogen test was of great value in establishing the diagnosis, as x-ray or biopsy evidence had not been conclusive.

Renal Biopsy.—A renal biopsy was taken in 15 cases (13 percutaneous, 2 at open operation). In four of these conclusive histological evidence of pyelonephritis was obtained. The histological features included interstitial fibrosis with round-cell infiltration, periglomerular fibrosis, tubular dilatation, and atrophy, together with eosinophilic tubular casts and polymorph casts. In nine cases the biopsy findings supported the diagnosis of pyelonephritis but were not conclusive. They were, however, very helpful in excluding other disorders such as glomerulonephritis. From one case only normal renal tissue was obtained. In the remaining case the biopsy specimen was insufficient for diagnosis.

Discussion

Intrarenal infection is notoriously silent (Kleeman *et al.*, 1960) and destruction of the renal parenchyma may proceed to the stage of renal failure before symptoms become manifest. In the present series 16 patients presented as a result of the effects of intrarenal infection (hypertension, renal failure, albuminuria), and the illness in these cases was of long duration as judged by past history of infection of the urinary tract. This group was in marked contrast to those in whom dysuria and frequency were the presenting complaints. In them symptoms had been present for a shorter time, hypertension was uncommon, and renal function as assessed by urine concentrating power and blood urea was rarely impaired. The symptoms in this group probably arose from associated disease of the lower urinary tract or from inflammation of the pelvis of the kidney.

In the present series the most common feature of the urine was a light microscopic pyuria. A measurement of the rate of urinary W.B.C. excretion was of value, for in several cases a raised excretion was found when "routine" centrifuged deposit results indicated a near normal W.B.C. content. The discrepancy may partly be due to delay in the examination of routine specimens with the resultant degeneration in W.B.C. (Houghton and Pears, 1957), and partly to the fact that examination of the urinary deposit does not take into account the degree of concentration of the specimen examined. In several cases haematuria predominated and there was no evidence in these patients that this arose from associated stone formation. Neither was there any evidence of glomerulonephritis. A normal urine occurred in three cases, but this does not exclude pyelonephritis (Kipnis *et al.*, 1955; Hutt *et al.*, 1961).

Excretory urography is useful and simple. Diagnostic evidence was obtained in a quarter of the cases so examined. However, other conditions such as nephrosclerosis and renal infarction may occasionally mimic the appearance of chronic pyelonephritis, and this must be taken into consideration in assessing the radiological findings.

The pyrogen or steroid test was the most useful single diagnostic test employed and was positive in over half the cases. However, it also is not pathognomonic for pyelonephritis, as positive results have been recorded in glomerulonephritis (Hutt *et al.*, 1961; Leather *et al.*,

1963). It should not be regarded as evidence of pyelonephritis in the absence of other features. Moreover, in pyelonephritis it may be negative if antibiotic treatment has been given within the previous three months. The substitution of steroid for pyrogen has materially reduced the discomfort to the patient entailed by this test (Katz *et al.*, 1962; Little and de Wardener, 1962).

Renal biopsy was of only moderate value in diagnosis, for conclusive evidence was obtained in only 4 out of 15 cases. Various factors contribute to this low success rate. Firstly, though the use in the latter part of the series of an image intensifier greatly assisted in taking the biopsy from the affected area, the kidney in pyelonephritis may be small, irregular, and firm, and may not therefore be an easy target for a biopsy needle. Secondly, pyelonephritis is a focal disease and normal renal tissue may be obtained from a diseased kidney. Thirdly, the histological diagnosis of pyelonephritis is not straightforward and many of its histological features are still in dispute (Kimmelstiel *et al.*, 1961). Finally, nephrosclerosis itself may mimic some of the changes attributed to pyelonephritis and therefore in the presence of hypertension conclusive evidence of pyelonephritis may be difficult to obtain from a needle biopsy specimen. However, in eight cases supportive evidence of pyelonephritis was obtained, and this, together with other diagnostic aids, was useful in establishing the presence of the disease.

Occasionally the diagnosis can still not be established during life. In one case in the present series in which chronic pyelonephritis was strongly suspected the urinary deposit was repeatedly normal and the pyrogen test negative. A high blood urea excluded aid from excretory urography and made renal biopsy unjustifiably hazardous. The diagnosis was confirmed at necropsy.

Summary and Conclusions

The presentation and diagnostic features of 30 cases of pyelonephritis are reviewed.

Cases presented in two ways: as a result of infection of the urinary tract or because of intrarenal infection. In the first group dysuria and frequency were the presenting symptoms; hypertension was uncommon and renal functional impairment usually absent. A high proportion of these cases had changes of pyelonephritis or congenital abnormalities on excretory urography. In the second group with intrarenal infection dysuria and frequency were absent or long past. These cases presented with albuminuria, hypertension, and renal failure.

In both groups the most useful diagnostic aid was the pyrogen or steroid test. Excretory urography and renal biopsy was also of value. An absolute count of urinary excretion of white blood cells was more reliable than a single examination of the urinary deposit.

In most cases the clinical features and a combination of diagnostic measures were necessary to establish the diagnosis of chronic pyelonephritis.

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CLINICAL TRIALS OF A NEW AMINOPHYLLINE PREPARATION

BY

NORMAN L. JONES, M.B., M.R.C.P.

Department of Medicine, Postgraduate Medical School of London

Treatment with oral bronchodilator drugs is often of value in supplementing other measures in the management of patients with asthma and bronchitis, where airway obstruction is reversible or partially reversible. Oral preparations of theophylline derivatives are widely used in this way, and several clinical trials (Simon, 1956; Pengelly and Brockbank, 1959; Turner-Warwick, 1957; Gandevia *et al.*, 1957) have shown that, of the preparations tested, aminophylline and choline theophyllinate are the most effective. Both give a plasma theophylline level adequate to produce improvement in airway obstruction (Turner-Warwick, 1957), but they are prone to cause troublesome gastric side-effects; Gagliani *et al.* (1954) found that 24% of a series of patients taking aminophylline and 5% of those taking choline theophyllinate complained of nausea or abdominal pain, and Brown and Clancy (1955) reported an incidence of 14% in a series of 35 patients taking the latter drug.

The new preparation "delaminoph" was produced in an attempt to reduce the frequency of these side-effects, by coating aminophylline with an inert lacquer so that disintegration of the tablet is delayed beyond the stomach. The present study was designed to find out whether this drug produced an adequate blood level and symptomatic response, and whether there was any difference between it and choline theophyllinate in the incidence of side-effects.

Effect of a Single Dose

In a small series of patients in hospital the effect of a single dose of 250 mg. of "delaminoph" on the plasma levels of theophylline and on tests of ventilatory function was obtained. The nine patients were all being treated for an exacerbation of chronic lung disease associated with severe airway obstruction, the average forced expiratory volume in one second (F.E.V.₁) being 860 ml., and vital capacity 2,170 ml. Drugs and food-stuffs known to affect the plasma theophylline level were stopped 16 to 24 hours before the dose of delaminoph. The test was begun at 9 or 10 in the morning to avoid the possibility of a false improvement in the degree of airway obstruction due to diurnal variation in tests of ventilatory function reported by Lewinsohn *et al.* (1960). Heparinized samples of venous blood were taken just before and two, four, and six hours after the dose, and the plasma theophylline levels were estimated by the method of Schack and Waxler (1949); in two cases a final sample was taken after 24 hours. The degree of airway obstruction was assessed at the same intervals by measurements of peak flow rate measured by the Wright peak flow meter (Wright and McKerrow, 1959) and by measurement of the F.E.V.₁ and vital capacity, using a modified Gaensler spirometer (McKerrow *et al.*, 1960).

The results of these investigations are shown in Figs. 1 and 2. A rise in plasma theophylline level was observed at four and six hours after the dose, a mean level of over 1 mg./100 ml. being obtained at these times. This level has been suggested by Turner-Warwick (1957) to be that at which a therapeutic result may be expected, and this has been confirmed by the studies of the F.E.V.₁; the mean improvement was 20% of the initial

FIG. 1.—Plasma theophylline following a single dose of 250 mg. of delaminoph. (Mean values and 2 S.D. shown.)

FIG. 2.—F.E.V.₁ readings following a single dose of delaminoph.

reading at four hours and 30% at six hours. Similar improvement in peak flow measurement (15% at four hours and 25% at six hours) was also obtained, and in general the subjective improvement reported by the patients paralleled these objective measurements. The plasma level recorded is less than that found by Turner-Warwick after oral doses of 790 mg. of choline