Pyleonephritis in Patients with Leprosy

Significance of Bacteriemias and Asymptomatic Bacteriurias[1, 2]

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By definition pyelonephritis is a nonspecific infection of the renal parenchyma which usually involved the pyelocalyceal zone and is provoked by local invasion of pyogenic and other bacteria ([23]). Acute and chronic pyelonephritis are in rank second in frequency to respiratory infections ([23]). Studies by Weiss and Parker ([31]) and Brod ([4]) in large autopsy series have shown a total incidence of pyelonephritis in the order of 6 per cent. One-third of deaths in uremia are related to pyelonephritis making this an important cause of death higher in frequency than glomerulonephritis.

Clinically, pyelonephritis presents as a disease characterized by progressive parenchymal destruction associated with functional insufficiency. Arterial hypertension is an important complication. The course of the disease is highly variable being slowly progressive in some cases while in other cases it is accelerated.

1 Received for publication 5 June 1970.

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Several factors are related to the speed of progression. Some of these are: (1) the bacterial strain involved, (2) the frequency of reinfections and exacerbations, (3) the nature of any predisposing anatomic malformations, (4) the presence of associated diseases such as arterial hypertension, diabetes and gout ([3, 28]).

The high incidence of chronic albuminuria in patients with leprosy concomitant with commonly associated infections such as skin ulcers and osteomyelitis suggested that pyelonephritis is a frequent renal disease in these patients. Initially this proved to be true because pyelonephritis was diagnosed in several such patients both with and without generalized amyloidosis ([22]), and in a previous study ([20]) we had been impressed by the high frequency of positive urine cultures in leprosy patients.

The purpose of the present presentation is to present the results of bacteriologic studies of ulcers, osteomyelitic fistulae, blood cultures, and urine cultures. As an additional fact, our experience on the importance of the renal elimination of the leprosy bacillus is presented.

MATERIALS AND METHODS

Two hundred and fifty-eight patients were studied, of which 217 had urine cultures, to determine the incidence of urinary infection, (Tables 1 and 2). In another 41 patients with skin ulcers and/or osteomyelitis, cultures of exudates and blood were made (Tables 3 and 4).

The age, sex, clinical form of leprosy, skin bacteriology are shown in Tables 1 and 2. The patients were not selected and all stages of the disease were included.

Sixty-seven patients with leprosy had chronic renal disease (amyloidosis, chronic glomerulonephritis and pyelonephritis) with persistent albuminuria. No definite diagnosis of the renal disease was made other than "chronic renal disease."

One hundred and twenty-eight had localized chronic infections (ulcers or osteomyelitis).

Urine collection. Wide mouthed sterile flasks were used for both sexes. The external genitalia were cleaned and a mid-urine specimen was collected. All samples were stored in a refrigerator for 24 to 36 hours until microscopic examination and cultures were taken.

TABLE 1. *Age groups of patients with incidence of urinary infection.*

Age group (yrs)	No. patients
10–19	2
20–29	20
30–39	41
40–49	40
50–59	40
60–69	47
70–79	25
>80	2
TOTAL	217
SEX	
Male	188
Female	29

TABLE 2. *Clinical forms of leprosy of patients included in the study.*

Type of leprosy	No. patients
Lepromatous	201
Positive bacilloscopy	109
Negative bacilloscopy	92
Indeterminate	4
Tuberculoid	11
Borderline	1
TOTAL	217

TABLE 3. *Age groups of patients with skin ulcers and/or osteomyelitis.*

Age group (yrs)	No. patients
20–29	2
30–39	4
40–49	7
50–59	9
60–69	11
70–79	7
Not specified	1
TOTAL	41

TABLE 4. *Clinical forms of leprosy in patients with ulcers and/or osteomyelitis.*

Type of leprosy	No. patients
Lepromatous	36
Indeterminate	1
Tuberculoid	2
Borderline (intermediate)	0
Not specified	2
TOTAL	41

The bacteriologic examination consisted of the following: (a) bacteriologic diagnosis—typing, and differential cultures, (b) tube dilution sensitivities in 71 pure strains (Table 11), (c) search for acid-fast bacilli (Ziehl-Neelsen method) in the sediment of 217 urine samples, and (d) no colony count was made.

For discussion purposes, positive cultures were those in which the urine sediment showed bacteria. Negative cultures were those in which the sediment contained no bacteria or else only contaminants such as Doderlein's bacillus and pseudodiphtheria.

In 41 patients (36 males and 5 females) with chronic skin ulcers and/or osteomyelitis cultures of the exudates and blood cultures (one every 24 hours x 3) were made (Tables 3 and 4). The blood was collected under aseptic conditions using a dry syringe and collecting 10 ml. of blood in a sterile test tube with sodium citrate. The blood was cultured in nutrient broth, sodium thioglycolate broth, and blood agar. Cultures were regarded as negative when no growth occurred at the end of 15 days.

The exudate from skin ulcers and fissures was taken with cotton swabs moistened with sterile normal saline. The smears were stained by Gram and Ziel-Neelsen stains and cultures made on nutrient broth, rabbit's blood agar, sodium thioglycolate broth, Levine's EMB medium, and Chapman's medium. Wherever bacteria were found these were typed. The Chi-square [31] method was used to statistically evaluate the results obtained.

TABLE 5. *Relation between urinary infections and ulcers and/or osteomyelitis.*

	Urine cultures	
	Positive	Negative
Patients with complications	46 (36%)	82 (64%)
Patients without complications	35 (39%)	54 (61%)
TOTAL	81 (37%)	136 (63%)

p = no significance.

TABLE 6. *Relation between urinary infections and presence of proteinuria.*

	Urine cultures	
	Positive	Negative
Patients with proteinuria	27 (40%)	40 (60%)
Patients without proteinuria	46 (30%)	104 (70%)
TOTAL	73 (34%)	144 (66%)

p = no significance.

TABLE 7. *Relation between sex and positive urine culture.*

	Urine culture	
	Positive	Negative
Males	60 (32%)	128 (68%)
Females	17 (58%)	12 (42%)
TOTAL	77 (36%)	140 (64%)

p = 0.01.

RESULTS

Incidence of urinary tract infections. (Tables 5, 6, 7, and 8). Thirty-seven per cent of the patients studied had pathogens in the urine samples. There was no evidence that chronic infections (Table 5) nor albuminuria (Table 6) exerted a definite influence in the incidence of infections. Likewise age (Table 8) did not seem to play a definite role. Sex apparently does play a definite role since the incidence of positive urine cultures was significantly higher in females than in males $p < 0.01$ (Table 7).

TABLE 8. *Relation between urinary infection and age.*

Age group	No. of cases	Urine culture	
		Positive	% Negative
10–29	22	6 (27%)	16 (73%)
30–49	81	26 (32%)	55 (68%)
50–69	87	32 (37%)	55 (63%)
70–89	27	8 (30%)	19 (70%)
TOTAL	217	72 (33%)	145 (67%)

TABLE 9. *Isolated microorganisms of urine cultures.*

	No. cultures
No. of u ine cultures	230
No. of positive urine cultures	95 (41.2%)
Positive to one microorganism	72
Positive to 2 or 3 microorganism	23
PURE INFECTIONS	
Staphylococcus aureus	24
" *epidermis*	9
Escherichia coli	8
Paracolon bacilli	1
Proteus m rabilis	10
Streptococcus faecalis	13
Klebsiella pneumoniae	4
Aerobacter aerogenes	2
MIXED INFECTIONS	23
Staphylococcus aureus	7
" *epidermis*	3
Proteus	4
Escherichia coli	11
Pseudomonas aeruginosa	1
Aerobacter aerogenes	1
Gaffkya tetragena	2
Sarcina lutea	1
Candida albicans	3
Corynebacterium pseudodiphtheriticum	1
Streptococcus faecalis	10
Proteus morganii	1

In 217 urine sediments of patients with leprosy stained by Ziehl-Neelsen technic no acid-fast bacilli were found.

Most common organisms in urinary tract infections. All cultured organisms, pathogens and saprophytes, are taken into consideration. Two-hundred and seventeen urine cultures plus 13 reexaminations are evaluated. In the 230 total urine cultures there were 95 positives (41.2%). Of these, 72 were due to a single strain of bacteria and 23 to two or three strains (Table 9). The most frequently found organisms were *Staphylococcus aureus* and *Streptococcus faecalis* of the gram-positives and *Escherichia coli* and *Proteus vulgaris* of the gram-negatives.

Sensitivity of the cultured microorganisms, (Tables 10 and 11). Furadantine was the most effective drug. Less effective were aminocidine, gentamycine, novobiocin, etc. It should be noted that the most commonly used antibiotics such as tetracycline and chloromycetin of the wide spectrum and erythromycin, penicillin and streptomycin of reduced spectrum type proved to be ineffective because of a great number of resistant strains.

Incidence of infection in ulcers and in osteomyelitis. (Tables 12, 13 and 14). In 41 examined lesions pathogens were found in 39. The infections were due to many bacteria, in some cases up to four strains. The predominant bacteria were *Streptococcus faecalis, Staphylococcus aureus, Pseudomoras aeruginosa* and *Proteus mirabili.*

Incidence of bacteriemias. (Tables 12, 13, 14 and 15). One hundred and twenty-three blood cultures were taken from 41 patients. There were 19 positive blood cultures in eight patients (18%). In two patients one of three blood cultures were positive, in one, two blood cultures were positive and in five patients three blood cultures were positive. The cultured bacteria in decreasing frequency were: *Streptococcus faecalis, Staphylococcus aureus* and *Streptococcus hemolyticcus.* The significance of these bacteriemias is not clear.

DISCUSSION

Bacteriurias due to pathogens are frequent in patients with leprosy. These bacteriurias are equally as frequent in patients with or without chronic albuminuria and they appear at any age but are more frequent in females than in males.

Patients with chronic ulcers and/or osteomyelitis usually have pathogens in the lesions.

Nineteen per cent of patients with ulcers and/or osteomyelitis have bacteriemias as evidenced by positive blood cultures.

Bacteriemias. The incidence of bacteriemias in hospitalized patients with severe illnesses, in pregnant patients, and following dental extractions has been described by several authors. Baker and collaborators (1) mention that puerperal bacteriemias vary between 0 to 5 per cent of all cases and between 10 to 83 per cent in cases of postdental extractions. Cuestas Carnero

TABLE 10. *Microorganism sensitivity to antibiotic and chemotherapeutic drugs.*

Antibiotics-Chemotherapeutics	No. of strains			% Sensitive strains	
	Total	Gram positive	Gram negative	Gram positive	Gram negative
Tetracycline	71	46	25	30%	20%
Chloramphenicol	71	46	25	38%	36%
Kanamycine	71	46	25	42%	8%
Erythromycin	71	46	25	46%	0%
Rifamycin	71	46	25	67%	24%
Streptomycin	71	46	25	23%	20%
Novobiocin	71	46	25	73%	28%
Colistin	71	46	25	10%	12%
Aminocidin	71	46	25	63%	68%
Penicillin	71	46	25	34%	0%
Cephaloridine	71	46	25	55%	36%
Gentamycine	71	46	25	51%	68%
Spiramicine	71	46	25	15%	4%
Sulfas	71	46	25	6%	4%
Wyntomilon	71	46	25	42%	52%
Furadantine	71	46	25	80%	92%

and collaboratores ([6]) found postdental extractions bacteriemias in 27 per cent of cases.

Rogers and collaborators ([25]) after urologic manipulations in hospitalized patients with severe affections described bacteriemias in 70 to 90 per cent of all cases.

Hauviller and Acerbo ([12]), in leprosy patients with chronic skin ulcers, mention seeing a high incidence of bacteriemias and postulate that the properdin system could be altered in these patients which would cause a diminution of the bacteriostatic power of the serum and would facilitate bacteriemias in patients with chronic infections.

Our studies show an incidence of bacteriemias of 19 per cent, this is notably less than the incidence presented in patients subjected to urologic procedures and similar to the incidence seen in postdental extraction. It is probable that the 19 per cent incidence doesn't give an exact idea of the number of patients with bacteriemias since these patients had chronic infections. It is probable that multiple repeated blood cultures would reveal a higher incidence of positive cultures.

The observed bacteriemias are generally asymptomatic even though in some cases they are persistent enough to produce positive cultures on three successive days. The significance of these bacteriemias is not clear.

Bacteriurias. The significance of bacteriurias in healthy individuals has been determined by several authors. Kunim ([16]) found an incidence of 0 to 0.03 per cent in children of school age. Switzer ([29]) in healthy individuals age 30 to 69 found an incidence of 0.2 per cent. Kass ([15]) in patients from outpatient departments found an incidence of 4 per cent and in hospitalized patients of 12 per cent. Hansen ([11]) in healthy individuals found an incidence of 3 to 3.7 per cent.

Significant increase in bacteriurias has been found in several conditions: pregnancy, benign prostatic hypertrophy, diabetes, renal lithiasis, previous infections, surgical procedures, instrumental manipulations, etc. Wolfson and collaborators ([34]) in males aged 21 to 91 years, with an average of 63 years, who were hospitalized in a general hospital found a significant bacteriuria in 15 per cent of all cases. The inci-

TABLE 11. *Microorganisms sensitivity to antibiotics and chemotherapeutic drugs—(71 studied strains).*

		Staph. aureus	*Staph. epiderm.*	*Str. faecal.*	*Esch. coli*	*Para-choli*	*Prot. mirab.*	*Klebs. pneum.*	*Aerob. aerog.*
Tetracycline	VS	3	4	0	0	0	0	0	0
	S	2	3	3	3	0	1	1	0
Chloramfenicol	VS	4	1	0	1	0	1	0	0
	S	6	3	8	3	1	2	1	0
Erythromycin	VS	1	0	0	0	0	0	0	0
	S	10	7	6	0	0	0	0	0
Wyntomilon	VS	6	1	2	3	0	0	0	0
	S	5	5	7	3	1	4	2	0
Kanamycin	VS	4	2	1	0	0	0	1	0
	S	8	4	1	1	0	0	0	0
Rifamycin	VS	3	0	3	0	0	2	0	0
	S	14	6	6	0	0	3	0	1
Streptomycin	VS	0	0	1	1	0	3	2	0
	S	7	2	1	2	0	0	0	0
Novobiocin	VS	3	2	3	1	0	1	2	0
	S	14	6	7	0	0	2	0	1
Furadantine	VS	1	1	0	1	0	2	2	0
	S	17	8	11	7	1	8	2	0
Colistin	VS	0	0	1	2	0	0	1	0
	S	3	1	0	0	0	0	0	0
Aminocidine	VS	1	4	1	3	0	4	2	1
	S	17	5	2	2	1	4	0	0
Penicillin	VS	5	1	3	0	0	0	0	0
	S	4	2	1	0	0	0	0	0
Cephaloridine	VS	2	1	6	3	0	1	1	0
	S	14	2	1	2	0	1	0	1
Sulfas	VS	1	0	0	0	0	0	0	0
	S	0	2	0	0	0	0	0	0
Gentamycin	VS	1	0	2	1	0	1	0	0
	S	12	3	6	4	1	5	3	2
Spiramycin	VS	2	0	0	0	0	0	1	0
	S	3	0	2	0	0	0	0	0

VS = very sensitive.
S = sensitive.

TABLE 12. *Positive cultures in infectious areas (ulcers-osteomyelitis), urine and blood.*

No. cases	Ulcers-osteomyelitis	Blood
41	39 (95.2%)	8 (19.5%)

TABLE 13. *Bacteriology in infectious areas (ulcers-osteomyelitis) and blood.*

	Ulcers osteomyelitis	Blood
Unbacterians	2	33
Monobacterians	2	5
Polibacterians	37	3
Bi	19	3
Tri	16	0
Tetra	2	0

TABLE 14. *Isolated bacterias.*

	Ulcers	Blood
Streptococcus faecalis	29	5
Staphilococcus aureus	23	3
Pseudomonas aeruginosa	19	0
Proteus mirabilis	13	0
Streptococcus β-hemolyticus	4	3
Candida albicans	4	0
Bacillus subtilis	3	0
Staphylococcus epidermis	1	0
Cornybacterium pseudo-diphtheriticum	1	0

TABLE 15. *Positive blood cultures: Positive cultures with relation to the total blood cultures taken from each patient*[a]

Positive blood cultures	No. cases	Percentage
One of three	2	25.0
Two of three	1	12.5
Three of three	5	62.5

[a] Three blood cultures were done to each patient (one each 24 hours).

dence increased with age. Hansen ([11]), in diabetics, found an incidence of bacteriuria of 7.5 per cent in females and 18.5 per cent in diabetic males. The same figures for nondiabetic individuals were 3 and 3.7 per cent respectively.

The incidence of bacteriurias due to pathogens in our present patient population is much higher than those previously reported (32% in males and 58% in females). This high incidence is apparently not influenced by age, chronic infections in other parts of the body and chronic albuminuria. Wilkinson *et al.* ([32]) found high incidence of bacteriurias due to pathogens also in patients with leprosy. The pathogens cultured by these authors generally coincide with those found by us. The lack of correlation between renal disease and bacteriuria makes difficult the interpretation of the significance of the bacteriuria.

Infections in ulcers and fistulae. These areas in patients with leprosy are generally infected with a rich and varied bacterial flora. Our results are in accordance with those of Hauvillier and Acerbo ([12]) and Wilkinson and collaborators ([33]). The significance of the growth of these pathogens in these areas explains the frequency of local supurations and perhaps (because of the flora) the relatively frequent bacteriemi's described above.

Urine as a means of elimination of Hansen's bacillus. Manzi *et al.* ([17]) have described in the urine of patients with leprosy the presence of acid-fast bacilli microscopically similar to Hansen's bacilli. One of the authors (J.G.M.) has had personal communication with Lefevre, his collaborator, who reiterated these findings and noted that similar findings have also been reported by Waisman *et al.* ([30]).

In 217 urinary sediments stained by the Ziehl-Neelsen technic we have not found acid-fast bacilli. These observations coincide with those of Wilkinson *et al.* ([32]). The data presented here, plus the fact that the kidney and the urinary tract are not affected by *M. leprae* ([2, 10, 13, 14]) make highly improbable that the bacillus described by other authors in the urinary sediment were leprosy bacillus.

Renal diseases in patients with Hansen's disease. Pyelonephritis. In previous papers

([19, 21]) one of us, in collaboration with other authors, pointed to the significance of albuminuria as an expression of chronic renal disease in patients with leprosy. In these papers it was pointed out that the most frequent cause of albuminuria was amyloidosis and that it was probably precipitated by prolonged lepromatous reactions and chronic infections secondary to the neurotropic processes ([5, 18, 19, 21]).

The data mentioned above have been confirmed in autopsy material by Bernard ([2]) who in 40 autopsies found 22 amyloid nephroses (55%), eight nephrosclerosis (20%), four pyelonephritides (10%), four renal cysts (10%), two tuberculosis (5%), two hydronephroses (5%) and one glomerulonephritis (2.5%).

In a previous study ([20]) we believed the most frequent renal disease in patients with leprosy was pyelonephritis. However, according to Bernard ([2]) the frequency of pyelonephritis in patients with leprosy is not higher than in the general population. Finally, according to Weiss and Parker ([31]) and to Brod ([4]), the incidence of pyelonephritis in a general hospital is 6 per cent and in patients with leprosy it is 4 per cent.

DISCUSSION

In spite of our previous impression we have not found an increased incidence of pyelonephritis in patients with leprosy over that found in general population. This observation we believe should not be considered definitive since in leprosy several conditions which predispose to pyelonephritis are present. This apparent contradiction has been repeatedly observed by other authors. This makes even more obscure the significance of certain bacteriemias and bacteriurias. According to Dontas ([8]) the role of asymptomatic bacteriuria in the course of nonobstructive renovascular disease and the development of intrarenal infections is not yet clear.

Smythe ([26]) stated that the experimental observation that hypertension favors the development of pyelonephritis ([7]) does not have a clinical counterpart.

An editorial in the *British Medical Journal* ([9]) states that "Although the relationship between pyelonephritis and urinary infection is not completely understood, bacteriuria should be considered potentially dangerous." Wolfson *et al.* ([34]), in an extensive study of the epidemiology of bacteriurias in old people could not understand the significance of bacteriurias seen in 9 per cent of patients 60 years old and in 42 per cent of patients 81 years old. Similar doubts exist in humans with respect to the significance of asymptomatic bacteriurias despite the fact that in experimental animal studies renal infections have been produced by intravenous injections of pathogens ([3, 28]).

The contradictions presented in this paper with reference to our previous report ([20]), despite bibliographic support, should not be taken as definitive and should have further confirmation.

SUMMARY

Previously published data led to the belief that pyelonephritis was a common renal disease in patients with leprosy. In the present study bacteriologic studies in 217 patients with or without kidney disease and 41 blood cultures and bacteriologic studies of exudates from ulcers and osteomyelitic fistulae are presented.

The results obtained raise doubts about pyelonephritis being more frequent in patients with leprosy than in the general population. However other findings such as chronic albuminuria, bacteriuria and positive blood cultures suggest that further studies are needed.

RESUMEN

Datos publicados con anterioridad hicieron pensar que la pielonefritis era una enfermedad renal frecuente en pacientes con lepra. En el presente estudio se presentan estudios bacteriológicos de 217 pacientes con y sin enfermedades renales y 41 hemocultivos y estudios bacteriológicos de exudados de úlceras y fístulas osteomielíticas.

Los resultados obtenidos hacen dudar que la pielonefritis sea más frecuente en pacientes con lepra que en la población en general. Sin embargo, otros hallazgos tales como albu-

minuria crónica, bacteriuria y hemocultivos positivos sugieren la conveniencia de estudios posteriores.

RÉSUMÉ

Les données publiées antérieurement portent à croire que la pyélonephrite est une affec ion rénale commune chez les malades souffrant de la lèpre. On présente dans cette étude les résultats des investigations bactériologiques menées chez 217 malades avec ou sans atteinte rénale, ainsi que les données provenant de 41 cul ures de sang et d'échantillons bactériologiques d'exsudats obtenus dans des ulcères et dans des fistules ostéomyélitiques.

Les résultats obtenus permettent d'émettre certains doures quant à la théorie qui veut que la pyelonéphtite soit plus fréquente chez les malades souffrant de lèpre que dans la population générale. Certaines autres observations, telles que la présence d'une albuminurie chron que, une bactéroiurie, ou des cultures de sang positives, suggèrent que des études complémentaires sont toutefois nécessaires.

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