Alterations in Renal Cortical Blood Flow in Infants and Children with Urinary Tract Infections

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Extract

The present studies were designed to elucidate renal functional changes in infants and children with urinary tract infections. Twenty-three infants and children ranging in age from 4 months to 13⁶/₁₂ years with urinary tract infections were studied. Four children ranging in age from 2 to 6¹⁰/₁₂ years without documented urinary tract infections served as controls. Inulin clearances (C_I) were utilized for measurement of glomerular filtration rate. Renal plasma flow and tubular maximum excretory capacity were ascertained by the intravenous administration of para-aminohippurate (PAH). Second determinations performed in eight patients and a third determination in one patient provided longitudinal follow-up. Renal plasma flow measurements were low in 4 of 6 infants and in 6 of 17 children on initial testing; these decreased values were associated with normal glomerular filtration rates except in 3 subjects. In the 4 patients without documented urinary tract infections, C_{PAH} values were within the normal range. C_{PAH} values obtained initially in all subjects were compared on a surface area basis to those characteristic of normal children. Of the 27 experimental points, 21 were below the line representing the normal average C_{PAH} for children. In this small series, only one of three infants failed to recover this function at the time of repeat testing. The recovery rate was less in the children studied. The data indicate that a decrease in renal plasma flow occurs prior to significant alterations in the other renal functional parameters measured.

Twenty-two subjects were tested for both C_{PAH} and Tm_{PAH} . The ratio (C_{PAH}/Tm_{PAH}) was lower in all three groups than the reported normal value of 7.7. In those patients demonstrating an initially reduced value, 13 of 16 showed normal C_{PAH} values. These findings could represent renal ischemia of proximal tubular tissue.

The persistence of renal vascular changes in the face of absent clinical and/or laboratory evidence of urinary tract infections emphasizes the need for caution in identifying the prognosis of children with pyelonephritis and the need for careful long-term evaluation.

Speculation

Although it has been well documented that the renal medulla is the primary site of involvement in pyelonephritis, the current data suggest that the post-glomerular capillaries and tubular structures in the renal cortex are also early sites of involvement in infants and children. A question raised by the study is the relation of reduced renal plasma flow measurements to the natural history and pathogenesis of recurrent pyelonephritis. It is suggested that agents promoting a change toward normal renal circulation may reverse the pathologic process.

Introduction

Acute pyelonephritis is a relatively common illness in children. Unsuspected urinary tract infections occur in 1.1 % in young girls and 0.03 % in young boys [18]. The recurrence rate in patients with overt disease following therapy varies from 32 to 60 % [8, 17, 20]. Notwithstanding the relative frequency of pyelonephritis, data on renal functional measurements in children with acute urinary tract infections are sparse.

The presence of diminution in renal concentrating ability has been reported in children with acute non-obstructive urinary tract infections [28]. The present studies were designed to elucidate changes in kidney function in children with urinary tract infections. The majority of the patients studied had had recurrent urinary tract infections; the remainder had had either a single episode of infection or persistent infection. The latter two groups comprised one-fourth and one-twelfth, respectively, of the patients investigated. The data indicate that a decrease in renal plasma flow occurs prior to significant alterations in the other renal functional parameters measured.

Material

Twenty-three infants and children with urinary tract infections who were from 4 months to 13⁸/₁₂ years of age were studied. Of these patients, one (patient No. 7) with untreated acute infection was studied within three weeks of onset; six (patients Nos. 1-4, 8, 9) with no recurrences had received chemotherapy for several months prior to study; and sixteen (patients Nos. 5, 6, 10-23) with recurrent urinary tract infections had received prolonged chemotherapy prior to investigation. Four patients (Nos. 24-27) without documented urinary tract infections who were 2 to 2¹⁰/₁₂ years of age were also studied.

Of the 23 patients with urinary tract infections, five were males; in three of these, the infections were detected during the newborn period. The urologic abnormalities found in the males were as follows: posterior urethral valves in two; bladder neck contracture and meatal stenosis in one; and a post-traumatic neurogenic bladder in one. The urologic findings demonstrable in females were: bladder neck obstructions in seven; meatal stenosis in two, combined bladder neck contractures and meatal stenosis in six; a complex of bladder neck contracture, meatal stenosis and urethral stenosis in one; and a double collecting system in one. In all, obstructive lesions of the urinary tract were found in 21 of the 23 patients.

The urologic findings in the four patients without documented urinary tract infection were as follows:

bladder neck contracture in one; urethritis in one; megacystis in one; and no demonstrable abnormality in one.

Body weights for the 27 patients ranged from 5.5 to 45.4 kg; estimations of surface area made on the basis of height and weight were between 0.32 and 1.62 m².

A diagnosis of urinary tract infection was made when, in two or more consecutive urine cultures, the same organism was isolated and quantitative colony counts were at least 10⁵ per milliliter of urine.

Microscopic examination of a portion of the urine collected for culture usually revealed more than 50 WBC/mm³ in the unspun specimen or 5 WBC/HPF in the centrifuged sediment.

At the onset of their disease, approximately one-half of the patients demonstrated the usual symptomatology referable to the urinary tract; the remainder had either vague general complaints or were asymptomatic. The same pattern of symptomatology was present at the time renal function tests were conducted. The initial episode was usually treated with oral administration of sulfisoxazole at a dosage level of 120 mg/kg/day for six weeks. After discontinuation of the drug, the therapeutic regimen was considered successful if the following conditions were fulfilled: three negative urine cultures taken at biweekly intervals; clearing of the urinary sediment; and disappearance of symptomatology. Following the initial infection, the patients were reevaluated monthly. Recurrences or relapses were treated with an appropriate antimicrobial agent, usually sulfisoxazole or nitrofurantoin, for a period of six months or longer.

Renal functional measurements were determined in subjects in whom bacteriuria had been present for as short a period as two weeks and in patients with intermittent bacteriuria for a period as long as 3⁸/₁₂ years. Specific antimicrobial therapy had been given before measurements of renal function were made, except in patients Nos. 7, 24, and 27. A second series of determinations were obtained in eight patients, Nos. 1, 2, 5, 6, 16, 17, 18, and 22, at intervals of 5 to 29 months. A third series of studies was completed in patient No. 2 to provide further long-term evaluation.

Methods

Inulin clearance (C_I) was used to measure glomerular filtration rate. Renal plasma flow and tubular maximum excretory capacity were ascertained by the intravenous administration of para-aminohippurate (PAH). During the first equilibration period, the infusion rate was calculated to produce plasma values greater than 25 mg % for inulin and 1 to 3 mg % for PAH. The techniques employed for sedation of the patients and collec-

tion of samples during each period were essentially the same as those previously reported [10]. Following the three clearance periods of 10 to 15 minutes, PAH administration was increased to maintain plasma values above 40 mg/100 ml; three additional collection periods were then obtained for determination of the tubular maximum for PAH transport (TmPAH).

Inulin was determined chemically by the method of HUBBARD and LOOMIS [15] and para-aminohippurate by the method of SMITH and FINKELSTEIN [25]. Solutions of inulin and para-aminohippurate with known concentrations were utilized for construction of a calibration curve for each set of determinations. All determinations, standard and unknown, were assayed in duplicate.

The clearance protocol in patient No. 17 is shown in table I. The steady state plasma values, the consistency of urine flow, and the agreement between values for each collection period are representative of the data acquired in this study. The significant decrease observed in glomerular filtration rate during TmPAH studies is characteristic [19].

The 100-percent value for glomerular filtration rate was 117 ml/min/1.73 m² for girls and 131 ml/min/1.73 m² for boys [9, 22, 24, 27], with a standard deviation of ± 15.6 for girls and ± 21.5 for boys.

The 100-percent value used for para-aminohippurate clearance (C_{PAH}) was 594 ml/min/1.73 m² for girls and 697 ml/min/1.73 m² for boys [9, 22, 24, 27], with a standard deviation of ± 102.4 for girls and ± 135.9 for boys.

The 100-percent value utilized for the tubular maximum excretory capacity for para-aminohippurate (TmPAH) was 77.5 mg/min/1.73 m² for both sexes with a standard deviation of ± 12.9 [9, 22, 24, 27].

The mean value for the relation of C_{PAH} to TmPAH was 7.7 for normal children [9, 22, 24, 27].

Results

Pertinent data on clinical course, urologic findings, renal function, urinary sediment, and bacteriologic cultures are presented in tables II, III, and IV. Abbreviated chronological case histories may be found in tabulated form in an appendix.

Infants

Data on the six infants studied are presented in table II. The glomerular filtration rates were within one standard deviation of the normal with the exception of that of patient No. 2, in whom the inulin clearance remained low even at the age of 2⁸/₁₂ years but was normal at the age of 3³/₁₂ years. The existence of hydronephrosis did not appear to influence the inulin clearances in these patients.

Renal plasma flow was decreased by greater than one standard deviation in patient No. 2 and in three others. When studies were repeated, C_{PAH} showed no

Table I. Clearance protocol—patient No. 17

Period	Time (minutes)	¹ P _{inulin} mg/ml	¹ P _{PAH} mg/ml	Urine flow ml/min	C _{inulin} ml/min/1.73 m ²	C _{PAH}	TmPAH mg/min/ 1.73 m ²
0	0	0	0	0	0	0	0
Equilibration No. 1 65							
1	15	0.26	0.013	1.2	102	466	
2	10	0.26	0.012	1.6	111	504	
3	10	0.26	0.012	1.6	105	467	
Equilibration No. 2 60							
4	12	0.43	0.82	2.5	89	202	105
5	8	0.45	0.84	2.5	90	200	105
6	10	0.47	0.87	2.4	82	186	102

¹ The plasma values given in periods 1–6 are concentrations of inulin and PAH at the mid-point of each period.

improvement in patient No. 5, a rise to normal levels in patients Nos. 1 and 2, and no change from normal values in patient No. 6. Bacteriuria of greater than 10^5 colonies/ml of urine was associated with both normal and diminished renal plasma flow. Vesicoureteral reflux, though present in all infants having a decreased renal plasma flow, appeared to have no influence on the glomerular filtration rate.

TmPAH values in the infants tested were all within one standard deviation of normal with the exception of those in the initial study of patient No. 5.

The relation of C_{PAH} to TmPAH was determined in five of the infants. The mean value, 6.4, is diminished in comparison with the normal mean, 7.7.

Children

Renal function data in the 17 children with documented urinary tract infections are listed in table III. Glomerular filtration rates were within one standard deviation of normal values except in patients Nos. 15 and 21. These latter patients did not have the serious obstructive uropathy demonstrated in the patients with normal renal clearance values, for example, patient No. 8. Renal plasma flow more than one standard deviation below normal was demonstrated on initial testing in six patients (Nos. 7, 9, 13, 15, 17, and 23); in three others (Nos. 14, 18, and 21), the values were borderline. Patient No. 7 was the only subject studied within three weeks of the onset of urinary tract infection. Eight patients had normal values for renal plasma flow. Determinations were repeated on four patients $1\frac{5}{12}$ to $2\frac{4}{12}$ years after the initial studies. Patient No. 17 had a rise to normal values; in patients Nos. 16, 18, and 22, the values fell from normal or borderline normal levels to those significantly below normal. Bacteriuria of 10^5 colonies/ml of urine at the time of the studies was associated with both normal and decreased values for C_{PAH} .

TmPAH was determined in 13 of the 17 subjects with the exception of patient No. 15; values within $\pm$ one standard deviation were found in all. In eight patients, values greater than one standard deviation above the mean were present upon initial or subsequent testing.

The relation of C_{PAH} to TmPAH was determined in 13 patients. The mean value was 5.3, compared to the normal of 7.7.

Four children without documented urinary tract infection but with possible urinary tract obstruction were also studied. Renal function data on these patients are recorded in table IV. All subjects had normal values for glomerular filtration rate and renal plasma flow. In three children, TmPAH was greater than one standard deviation above normal; the mean ratio of C_{PAH} /TmPAH was 5.1.

Discussion

The use of PAH for measurement of renal plasma flow is predicated on the assumption that greater than 90 % of PAH is removed in one circulation through the kidney. Studies [10] have shown that the extraction of PAH by the kidney of the normal newborn is considerably less than that of the adult. During the first half year of life, PAH extraction (E_{PAH}) increases and reaches adult values by six months of age. In the present study, all but one of the patients were six months of age or older. PAH clearance may therefore be used as a reasonable approximation of true renal plasma flow, provided the E_{PAH} is complete in children with urinary tract infections. Such data are not yet available. Renal plasma flow measurements and E_{PAH} have been found to decrease in adults with chronic pyelonephritis; this change is thought to be due to destruction of renal parenchyma [4, 21].

When urine flow is very low, storage of PAH in the kidney may occur [1, 2]. In the present study, the urine volumes achieved were sufficient to prevent this (see table I). Storage of PAH in erythrocytes in children is not a factor in these studies since diffusion rates of red cells to plasma studied previously in three subjects between 2 weeks and $5\frac{6}{12}$ years of age failed to change the renal extraction of para-aminohippurate (E_{PAH}) [10]. Determination of concentrations of PAH in the lymph of dogs was very close to those present in the renal artery and vein [7]. This finding supports the conclusion that the presence of PAH in renal lymph could not be a cause of significant error in renal plasma flow measurements [24]. Nevertheless, studies in experimental pyelonephritis are needed to further clarify this question.

Back pressure from obstruction of urine flow sufficient to result in renal intrapelvic pressures as high as 73 mm Hg has been shown to reduce renal plasma flow [16]. While, in the dog, ligation of one ureter reduced renal blood flow by 40 % on the obstructed side, the contralateral side demonstrated a compensatory increase in renal plasma flow so that the total flow measurements were increased [23]. None of the patients in this study demonstrated a degree of obstructive uropathy sufficient to explain the low PAH clearances observed.

Renal plasma flow measurements were low in 4 of 6 infants and in 6 of 17 children at the time of initial testing; these decreased values were associated with normal glomerular filtration rates except in three subjects. In the four patients without documented urinary tract infections, C_{PAH} was within the normal range. Figure 1 shows that the initial values for C_{PAH} obtained in all subjects was similar to known normal childhood values. It will be noted that 13 of 23 values were one

Table II. Clinical and renal function. Data on infants with urinary tract infections

Patient No.	Sex	Age years	Weight kg	S.A. ¹ m ²	C _I ^{2,8} ml/min/ 1.73 m ²	C _{PAH} ^{3,8} ml/min/ 1.73 m ²	TmPAH ^{4,8} mg/min/ 1.73 m ²	C _{PAH} / TmPAH	At time		
									On Rx	Symptoms	Urine sediment
1	F	4/12	5.5	0.32	102 (87 %)	323 (54 %)			+	failure to thrive, persistent bacteriuria	negative
		11/12	7.4	0.37	133 (114 %)	606 (102 %)	130 (167 %)	4.9	+	none	20-30 WBC/ HPF ⁶
2	M	6/12	9.4	0.41	64 (49 %)	259 (37 %)			+	none	20-30 WBC/ HPF
		21/12	13.0	0.54	90 (69 %)	372 (53 %)			—	none	negative
		3 ⁸ /12	15.0	0.60	152 (115 %)	615 (88 %)			—	none	negative
3	M	6/12	5.6	0.30	160 (122 %)	697 (100 %)	82 (106 %)	8.4	+	failure to thrive dribbling on urination	negative
4	M	6/12	10.0	0.42	154 (118 %)	421 (60 %)	89 (148 %)	4.7	+	negative	negative
5	F	8/12	7.2	0.41	162 (138 %)	422 (71 %)	55 (71 %)	7.4	+	negative	negative
		1 ³ /12	10.0	0.43	125 (107 %)	387 (65 %)	88 (135 %)	4.4	—	negative	negative
6	F	2	10.9	0.48	212 (181 %)	848 (143 %)	121 (156 %)	7.0	—	failure to thrive	10-20 WBC/ HPF
		2 ⁵ /12	11.6	0.55	102 (87 %)	876 (148 %)	135 (174 %)	6.7	+	negative	negative

¹ Surface area² Inulin clearance³ Clearance of para-aminohippurate⁴ Renal tubular transport maximum for para-aminohippurate⁵ Bladder neck contracture⁶ White blood cells per high power field⁷ Uretero-pelvic⁸ Figures in parentheses indicate percent of normal function

of study			Antimicrobial therapy		Recurrence or reinfection	Asymptomatic period	Comments
Urine culture	Urologic findings	Duration from onset	On	Off			
2000 col.* /ml	BNC ⁵ , rt. ureteral reflux	4 months	4 months	0		none	
100,000 col./ml enterococci	BNC, rt. ureteral reflux, mild rt. hydronephrosis	13 months	8 months	1		6 months	
18,000 col./ml <i>E. coli</i>	meatal stenosis BNC, lt. U-P ⁷ holdup mild lt. hydronephrosis, lt. ureteral reflux	5 months	5 months	0		5 months	ureteral dilatation and circumcision at 6 months of age
negative	mild BNC, mild lt. hydronephrosis	25 months	1 month	19		18 months	
negative	mild BNC, mild lt. hydronephrosis	38 months	0	13		13 months	
100,000 col./ml <i>E. coli</i>	rt. hydronephrosis rt. hydroureter	4 months	4 months	0		none	suprapubic cystotomy at 2 months of age. At 4 months of age resection of posterior urethral valves and Y-V plasty performed
negative	rt. ureteral reflux	6 months	6 months	0		2 months	at 4 months of age urethral dilatation and circumcision performed
100,000 col./ml aerobacter, enterococci <i>E. coli</i>	BNC, gaping ureters. No reflux	6 months	4 months	2 months	1	6 months	8 months urethral dilatation performed
negative	rt. ureteral reflux	13 months	4 months	3 months	0	5 months	
negative	mild BNC; retention of contrast media in collecting system for 2 hours	22 months	6 months	16 months	2	none	urethral dilatation at 2 years
negative	negative	27 months	5 months		0	5 months	

* Colonies

Table III. Clinical and renal function. Data on children with urinary tract infections¹

Patient No.	Sex	Age years	Weight kg	S.A. m ²	C _I ml/min/ 1.73 m ²	C _{PAH} ml/min/ 1.73 m ²	TmPAH mg/min/ 1.73 m ²	C _{PAH} TmPAH	At time		
									On Rx	Symptoms	Urine sediment
7	F	2 ¹¹ / ₁₂	13.7	0.58	114 (97 %)	423 (71 %)	78 (101 %)	5.3	—	anorexia, irritability	numerous WBC
8	M	2 ⁶ / ₁₂	12.5	0.55	184 (157 %)	602 (86 %)	82 (106 %)	7.3	+	none	numerous WBC
9	M	5	18.2	0.72	124 (95 %)	538 (77 %)			+	none	TNTC ² WBC
10	F	5 ⁸ / ₁₂	13.9	0.62	109 (93 %)	497 (84 %)	115 (148 %)	4.3	+	none	negative
11	F	4 ⁸ / ₁₂	16.7	0.69	150 (128 %)	512 (86 %)	92 (119 %)	5.6	—	none	negative
12	F	5 ⁴ / ₁₂	15.5	0.67	134 (115 %)	518 (87 %)			—	frequency, urgency	negative
13	F	5 ⁹ / ₁₂	16.0	0.69	133 (114 %)	479 (80 %)			—	frequency, flank pain, dysuria	TNTC WBC
14	F	6 ¹¹ / ₁₂	16.0	0.68	143 (122 %)	491 (83 %)	128 (165 %)	3.8	—	frequency	negative
15	F	5 ³ / ₁₂	18.2	0.75	76 (65 %)	193 (32 %)	61 (79 %)	3.2	—	recurring frequency	5-10 WBC
16	F	6	15.9	0.66	145 (124 %)	560 (94 %)	83 (107 %)	6.7	+	enuresis	WBC 3 × 10 ⁶ (Addis)
		8 ⁴ / ₁₂			102 (87 %)	476 (80 %)	102 (130 %)	4.7	+	none	negative

of study			Antimicro- bial therapy		Recurrence or reinfection	Asymptoma- tic period	Comments
Urine culture	Urologic findings	Duration from onset	On	Off			
100,000 col./ml <i>E. coli</i> and <i>proteus vulgarus</i>	meatal stenosis, bladder trabeculations	3 weeks	0	0	0	0	first attack requiring medical care
negative	rt. hydronephrosis rt. hydroureter rt. ureterocele bilateral reflux posterior urethral valves	6 months	6 months	0	0	5 months	removal of posterior urethral valves and rt. ureteral reimplantation following clearance studies
100,000 col./ml <i>E. coli</i> <i>pseudomonas</i>	'cord bladder'	5 months	3 months	2 months	0	0	traumatic injury and neurogenic bladder
100,000 col./ml <i>E. coli</i>	BNC, meatal stenosis	9 months	9 months	0	2	0	Nephrotic syndrome confirmed by renal biopsy; no pyelonephritis on biopsy. Urethral dilatation and meatotomy after clearance test
negative	BNC	17 months	9 months	8 months	2	none	Therapy: urethral dilata- tion and long-term antimicrobial therapy
negative	double collecting system (left)	10 months	3 months	7 months	1	none	short-term antimicrobial thera py (S). Renal biopsy at time of clearance. Failed to reveal evidence of infection
100,000 col./ml coliform	BNC	24 months	0	12 months	2	12 months	previous short-term anti- microbial therapy (S) for 2 culturally proven previous urinary tract infections
48,000 col./ml <i>E. coli</i>	BNC	12 months	4 months	8 months	1	none	urethral dilatation and meatotomy done at age 6 ³ / ₁₂ years. Renal biopsy at time of clearance failed to reveal infection of kidney
aerobacter 13,000 col./ml	BNC, meatal stenosis rt. upper tract dilated	3 months	2 months	1 month	1	none	urethral dilatation and meatotomy done at time of clearance
22,000 col./ml <i>E. coli</i>	meatal stenosis	16 months	9 months	7 months	2	4 months	urethral dilatation and long-term antimicrobial therapy
negative	meatal stenosis	44 months	10 months	18 months	1	12 months	

Table III. (Continued)

Patient No.	Sex	Age years	Weight kg	S.A. m ²	C _I ml/min/ 1.73 m ²	C _{PAH} ml/min/ 1.73 m ²	TmPAH mg/min/ 1.73 m ²	$\frac{C_{PAH}}{TmPAH}$	At time		
									On Rx	Symptoms	Urine sediment
17	F	7 ⁴ / ₁₂	35.0	1.08	106 (91 %)	479 (80 %)	104 (134 %)	4.6	—	frequency	negative
		9 ⁶ / ₁₂	44.5	1.31	157 (134 %)	680 (114 %)			—	none	negative
18	F	6 ⁹ / ₁₂	33.2	1.05	129 (110 %)	489 (82 %)	72 (93 %)	6.8	—	none	negative
		8 ² / ₁₂	40.0	1.20	125 (107 %)	457 (77 %)			—	none	negative
19	F	6 ⁹ / ₁₂	20.7	0.85	148 (126 %)	623 (104 %)	100 (129 %)	6.2	—	none	negative
20	F	7 ⁸ / ₁₂	25.9	0.98	140 (120 %)	574 (97 %)	122 (157 %)	4.7	—	frequency	negative
21	F	13 ⁴ / ₁₂	30.0	1.05	56 (48 %)	485 (82 %)	100 (129 %)	4.9	—	frequency	negative
22	F	13 ⁶ / ₁₂	36.8	1.22	131 (119 %)	744 (125 %)			+	fatigue	15–20 WBC/ HPF
		15 ¹¹ / ₁₂	42.0	1.50	173 (148 %)	394 (66 %)	68 (88 %)	5.8	—	fatigue	negative
23	F	12 ⁴ / ₁₂	45.4	1.62	165 (141 %)	426 (72 %)			—	fatigue	5–10 WBC

¹ See table II for abbreviations ² Too numerous to count

standard deviation below or at the borderline for the adult mean value for C_{PAH}. The average value of these experimental clearances is 82 %, excluding patients without documented urinary tract infections, and 86 % when these patients are included; this is in contrast to the 'normal' of 100 %. Of the 27 experimental points (fig. 1), 21 are below the line representing the average C_{PAH} for children. The difference between 100 % and 86 % is highly significant, with $p < 0.001$. The lower C_{PAH} value could not be related to the frequency of recurrence nor to the duration of the urinary tract infection. In addition, several patients with reduced C_{PAH} measurements failed to demonstrate morbid

symptoms, abnormal urinary sediment, or bacteriuria.

The restudy of four infants revealed a return to normal values in two in whom values had previously been low, a continued low value in one, and a persistent normal value in the other. In this small series, therefore, only one of three infants failed to recover this function at the time of retesting. In contrast, recovery was less impressive in the children studied. Six of 17 children were observed to have decreased initial C_{PAH} values. If borderline values for C_{PAH} are also included, then initial testing revealed 9 of 17 or 52 % had decreased renal blood flow. In four children, clearances were

of study			Antimicrobial therapy		Recurrence or reinfection	Asymptomatic period	Comments
Urine culture	Urologic findings	Duration from onset	On	Off			
negative	BNC, meatal stenosis	22 months	10 months	12 months	0	0	repeat urethral dilatations and long-term antimicrobial therapy
negative	none	48 months	18 months	8 months	0	14 months	
negative	BNC	9 months	1 month	8 months	1	8 months	dilatation and long-term antimicrobial therapy
negative	none	26 months	12 months	5 months	0	17 months	
negative	negative	11 months	5 months	6 months	1	5 months	single attack, renal clearances after one year therapy
100,000 col./ml <i>E. coli</i>	BNC, meatal stenosis. Rt. kidney enlarged with blunting of superior calyx	8 months	questionable		1	0	
negative	mild BNC, dilatation and blunting of rt. upper calyx	40 months	3 months	0	4	0	repeat urethral dilatation and sporadic antimicrobial therapy
30,000 col./ml <i>E. coli</i>	mild BNC	35 months	24 months	0	0	0	
negative	negative	64 months	0	30 months	0	0	renal biopsy: minimal changes consistent with acute pyelonephritis
40,000 col./ml <i>E. coli</i>	rt. ureteral reflux. Mild BNC	26 months	24 months	2 months	4	0	renal biopsy: minimal changes consistent with acute pyelonephritis

remeasured, and three demonstrated decreased or low values in comparison with values which had been normal or borderline; function in one patient returned to normal. These data suggest that infants, in comparison with children, may have a greater potential for reversing abnormal C_{PAH} values. Further experiments in both infants and children will be needed to verify and determine the significance of this preliminary observation.

PAH clearances were found to be reduced by 22 % in infected rats inoculated repetitively with enterococci every three weeks for 21 weeks, even though the creatinine clearance was unchanged throughout the course

of infection [13]. On the basis of their experimental results, these investigators related the functional alterations to a progression of ischemic reaction in the cortex and the medulla. This reaction ultimately became a pathologic process resembling that found in advanced chronic pyelonephritis in man.

An experimental model utilizing microangiographic and histologic techniques to study experimental pyelonephritis in rabbits and rats revealed that the primary injury occurred at the post-glomerular level [14]. The acute inflammatory phase of the infection was associated with irregular constriction of intertubular capillaries and destruction of cortical tubules. The presence

Table IV. Clinical and renal functional data on children without documented urinary tract infection but associated with possible urinary tract obstruction¹

Patient No.	Sex	Age years	Weight kg	S.A. m ²	C _I ml/min/ 1.73 m ²	C _{PAH} ml/min/ 1.73 m ²	TmPAH mg/min/ 1.73 m ²	C _{PAH} / TmPAH	At time		
									On Rx	Symptoms	Urine sediment
24	F	2	11.0	0.46	111 (95 %)	536 (90 %)	88 (135 %)	6.1	—	none	negative
25	F	3 ⁶ / ₁₂	16.0	0.66	158 (135 %)	557 (94 %)	137 (177 %)	4.1	+	urinary frequency	negative
26	F	3 ⁷ / ₁₂	16.3	0.64	222 (190 %)	750 (126 %)	132 (170 %)	5.7	+	none	negative
27	F	6 ¹⁰ / ₁₂	24.5	0.95	185 (158 %)	747 (126 %)	122 (157 %)	6.1	—	megacystis revealed during	

¹ See table II for abbreviations.

of diminished renal plasma flow in the infants and children observed in the present study appears comparable to the experimental findings noted in the rabbits and rats.

Three subjects in this study demonstrated a reduction in both glomerular filtration rate and renal plasma flow. Impaired renal function due to bacterial endotox-

in has been shown to reduce renal plasma flow, glomerular filtration rate, E_{PAH} , and urinary output. All these changes appeared secondary to renal vasoconstriction [12]. In the one infant with a possible diminished glomerular filtration rate, *E. coli* were present at the time of testing, and in one of two children, enterococci were isolated from the urine at the time of study. The cause of reduced renal function in these two subjects with bacteriuria is moot.

Data on tubular excretory capacity for para-aminohippurate in children with urinary tract infections are not available. In normal growing infants, adult values were obtained by 18 months of age [24]. The finding of values greater than one standard deviation above the mean in 3 of the 4 children without documented urinary tract infections and in 8 of the 14 subjects tested raises several questions concerning the specificity of PAH as a measure of tubular mass in these patients. In the group with urinary tract infections, the following possibilities exist:

(1) Acetate and lactate are substances known to increase PAH transport *in vitro* and *in vivo* [26]; however, no information is available on the urinary excretion rates or renal vein concentration of these metabolites in pyelonephritis.

(2) The early pathologic findings in experimental pyelonephritis in animals include marked hypertrophy and hyperplasia of the collecting duct epithelium. After repetitive infections, cellular hypertrophy is less marked, but an increase in stromal tissue is apparent; this is associated with dilatation of the lumina. Hyperplasia has been demonstrated in response to active loss of tissue or to increased nutrition of the organs through hypervascularity [11]. The TmPAH data in the pres-

Fig. 1. C_{PAH} obtained in infants and children with documented urinary tract infections (UTI) and children without proven infection. The solid line presents the 100-percent value for normal children. The dotted lines are $\pm$ one standard deviation of the average value for normal children. Twenty-one of twenty-seven points are below the solid line. By the binomial test, the difference between 100 % and 86 % is highly significant with $p < 0.001$.

of study			Antimicrobial therapy		Recurrence or reinfection	Asymptomatic period	Comments
Urine culture	Urologic findings	Duration from onset	On	Off			
negative	BNC	6 months	0	5 months	2	5 months	two previous undocumented urinary tract infections treated with urethral dilatations and short-term chemotherapy
negative	urethritis, meatal stenosis	9 months	9 months	0	0	0	
negative	negative	30 months	6 months	24 months	0	24 months	urethral dilatation at 37 months of age
study of genitourinary tract following acute glomerulonephritis 2 years previously							

ent study are in agreement with the pathologic data obtained in rats subjected to experimental pyelonephritis. In these animals, hyperplasia was observed during the first week of the disease [13].

An examination of renal plasma flow per unit of tubular mass may help in some instances to define the nature of the renal disorder. Twenty-two subjects in this study were tested for both C_{PAH} and $TmPAH$. The mean ratios of $C_{PAH}/TmPAH$ were: infants, 6.4; children, 5.3; and children without documented urinary tract infection, 5.1. The ratio ($C_{PAH}/TmPAH$) is lower in all three groups than the reported normal value of 7.7. The most plausible explanation for the decreased ratios is the high values of $TmPAH$ which averaged 87, 95, and 120 mg/min/1.73 m² in the three groups respectively. In initial renal functional studies in those patients demonstrating a reduced ratio, 13 of 16 showed normal values of C_{PAH} . These findings may reflect renal ischemia in individual units of proximal tubular tissue. The renal clearance of PAH is believed to measure cortical blood flow, which in turn accounts for 90 % of the total kidney blood flow. Animal studies have shown that the medulla, papilla, capsule, and perirenal fat account for the remaining 10 % [3]. Assuming that PAH measures renal plasma flow and tubular excretory capacity, the data in the current study of pyelonephritis support the view that the post-glomerular capillaries and tubular structure within the cortex are involved early in urinary tract infections.

It is possible that some infants are born with a defect in cortical blood supply rendering them susceptible to urinary tract infections. Alternatively, cortical ischemia could be secondary to either obstruction or infection. In the patients studied, none had an obstructive

lesion of such a nature as to make this a likely possibility. Rather, the renal ischemia would appear to be a consequence of the acute reversible inflammatory process. Infants, in comparison with children, may have a greater tendency to or capacity for reversal of diminished renal plasma flow, although this speculation requires further observation and documentation.

The localization of chronic pyelonephritis in the medullary portion of the kidney, with a concomitant reduction in the urinary concentrating capacity, has received careful documentation [5, 6]. All of our patients showed a urinary specific gravity of greater than 1.020 in randomly collected urine specimens; in 22 patients, the values were greater than 1.025. Published data [28] on 22 children with acute pyelonephritis in whom a urinary concentrating defect persisted for four to six weeks after subsidence of fever are not comparable to those of the present study since, with one exception, the present subjects were tested after subsidence of their symptoms. At that time, no decrease in urinary concentrating capacity was found in any.

The renal vascular changes demonstrated in this study to persist in the absence of clinical and/or laboratory evidence of urinary tract infections emphasize the need for caution in identifying the prognosis of children with pyelonephritis and the need for careful long-term evaluation.

Summary

(1) Thirteen of 23 infants and children with urinary tract infections were found to have a significant reduction in renal plasma flow as measured by para-aminohippurate clearance ($p < 0.001$). The variations ob-

tained were more than one standard deviation below the normal values for their appropriate ages.

(2) In longitudinal studies obtained 5 to 29 months after initial determinations, 1 of 4 infants and 3 of 4 children continued to show a reduction in C_{PAH} .

(3) Inulin clearance was normal in all patients except those in whom a reduction in both PAH and inulin clearances was demonstrated.

(4) TmPAH was reduced in only 2 of the 18 subjects with urinary tract infections. Approximately 50 % of the 18 subjects had TmPAH values greater than one standard deviation above the normal.

(5) The mean ratio of $C_{PAH}/TmPAH$ in these subjects was reduced, in comparison with the normal value for children.

(6) These observations suggest the presence of renal ischemia in individual units of proximal tubular tissue during the course of urinary tract infection.

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APPENDIX

Case Histories

Patient No.	Age	Comments
1	6 days	Negro female with unexplained jaundice associated with bacteriuria 100,000 col./ml <i>E. coli</i> . Clearing of urinary findings with antimicrobial therapy. Therapy continued for 4 months. Failure to thrive.
	3 months	Cinecystogram normal. No ureteral reflux. Urine cultures persistently positive in spite of therapy.
	4 months	Renal clearances demonstrated a reduced C_{PAH} . Cystoscopy and cystogram revealed severe bladder neck contracture with reflux up right ureter. Urethral dilatation and sulfisoxazole therapy instituted and continued.
	13 months	Repeat clearances, cystoscopy and cystogram. Bladder neck contracture and right ureteral reflux persisted. Mild right hydronephrosis. C_{PAH} clearances normal Y-V plasty repair and right ureteral transplant performed. Discharged on antimicrobial therapy (S)* for 2 months. Child has been well during the past two years. Urinalysis and cultures continue to be negative. <i>Conclusion</i> BNC*, reflux and right hydronephrosis. Clearances showed initial lowered C_{PAH} values, increasing to normal at 13 months despite presence of pyuria and bacteriuria. Antimicrobial therapy given for 12 months continuously.
2	3 weeks	Negro male. Onset with fever and pyuria, proteinuria and bacteriuria. IVP*: left hydronephrosis with a partial obstruction at right uretero-pelvic junction. Sulfisoxazole therapy for 5 months.
	6 months	Cystoscopy and cystogram revealed meatal stenosis, mild BNC and left ureteral reflux. Dilatation and circumcision performed. IVP: left hydronephrosis and uretero-pelvic hold up of contrast media. C_{PAH} clearances were reduced. Antimicrobial therapy given for one additional month, followed by no therapy for 19 months. Urinalysis and cultures negative.
	16 months	During this interval, weight gain adequate even without antimicrobial therapy. IVP still showed mild hydronephrosis on left. Prompt emptying of left uretero-pelvic junction noted.
	25 months	Mild BNC, no reflux. C_{PAH} clearances still reduced. Urine sediment and culture were negative.
	39 months	Repeat studies revealed normal C_I and C_{PAH} . Mild left hydronephrosis and BNC persisted. Off therapy for total of 32 months. <i>Conclusion</i> BNC, left hydronephrosis, left ureteral reflux, and lowered values for C_{PAH} clearances at 6 months. Dilatation and circumcision at 6 months. No antimicrobial therapy for 19 months. Repeat studies at 25 months revealed continued reduced C_{PAH} clearances with improvement in urologic findings: less left hydronephrosis, disappearance of left ureteral reflux and less BNC. Patient asymptomatic for 18 months; urinalysis and cultures continued to be negative. Normal clearances at age 39 months.

* See page 351 for abbreviations

Patient No.	Age	Comments
3	2 months	Negro male with fever and palpable abdominal mass. Urine sediment showed pyuria, proteinuria and white blood cell casts. Urine culture 100,000 col./ml of proteus. IVP: right hydronephrosis with hydroureter and minimal blunting of the left calyceal system. Voiding cystogram showed large bladder with posterior urethral valves and marked right ureteral reflux. Suprapubic cystotomy performed. Antimicrobial therapy (S) administered for next 4 months.
	3 months	Persistent fever and urinary tract infections with pseudomonas and aerogenes.
	4 months	Resection of posterior urethral valves and Y-V plasty repair was performed. Antimicrobial therapy (S) continued.
	6 months	Renal functional clearances were normal. IVP showed decrease in right hydronephrosis with complete disappearance of left calyceal dilatation. Symptomatology continues with dribbling on urination and persistent bacteriuria 100,000 col./ml <i>E. coli</i> . <i>Conclusion</i> Posterior urethral valves, right hydronephrosis and hydroureter with blunting left calyceal system. Surgical repair at 4 months. Clearances done two months later revealing normal values.
4	3½ weeks	Negro male with fever of unknown origin. Urinalysis showed numerous WBC and urine cultures showed over 100,000 col./ml of <i>E. coli</i> and enterococci. IVP outlined normal renal contours. Antimicrobial therapy (S) was administered for 6 months.
	4 months	Cystoscopy and cystogram revealed BNC, meatal stenosis with right ureteral reflux. Circumcision and urethral dilatation were performed. Antimicrobial therapy (S) was continued.
	6 months	Renal functional clearances revealed reduced C_{PAH} . Cystoscopy and cystogram showed normal urinary outlet, but right ureteral reflux still present. Repeat urinalysis and cultures continue to be negative during the past 2 years. <i>Conclusion</i> Meatal stenosis, BNC and right ureteral reflux. Following dilatation, circumcision and antimicrobial therapy (S) for 2 months, urologic findings improved yet C_{PAH} was reduced.
5	2 months	Negro female found to have pyuria and bacteriuria of 100,000 col./ml of coliform organisms on routine examination. IVP normal. Cinecystogram: 20–40 % retention post voiding. Antimicrobial therapy (S) for two weeks.
	3 months	Recurrence of pyuria and bacteriuria 80,000 col./ml coliform. Improvement of bacteriuria with antimicrobial therapy (N)*, pyuria persist in sediment.
	8 months	Renal functional clearances show lowered values for C_{PAH} . Urine cultures 100,000 col./ml of aerobacter, enterococci and <i>E. coli</i> . Cystoscopy revealed BNC and gaping ureters, but no ureteral reflux. Urethral dilatation performed and antimicrobial therapy (T)* instituted and continued for 4 months.
	15 months	Repeat functional clearances continued to show reduced C_{PAH} value. Cystoscopy and cystogram revealed a normal urinary outlet but demonstrated reflux up the right ureter. Antimicrobial therapy (S) continued for one additional month.
	16 months	Cystoscopy and cystogram were normal.
		Patient was normal during past year. No medications required since last visit. Urinalysis and cultures were negative. <i>Conclusion</i> Post voiding retention, BNC, gaping ureters, right ureteral reflux, clearing with dilatation and antimicrobial therapy (S). Two sets of clearances done seven months apart reveal reduced C_{PAH} values.
6	2 months	Negro female found to have pyuria and bacteriuria (100,000 col./ml coliform) in association with malnutrition. Antimicrobial therapy (S) given for 11 days.
	13 months	Returned to Emergency Room for malnutrition, fever, and urinary tract infection (over 100,000 col./ml of coliform). IVP showed normal kidneys and ureters. Post voiding film revealed 25 % retention of contrast media. Cystoscopy was normal. Antimicrobial therapy (S) was given for 6 months. The patient was followed in the renal clinic monthly where she showed adequate weight gain and negative urinalysis and cultures.
	19 months	Therapy discontinued. During the following 6 months, weight gain was inadequate. Urine cultures continued to be negative.
	24 months	Renal functional clearances were normal. Urine culture was negative. IVP showed normal upper collecting systems, but with retention of contrast media after two hours. Cystoscopy and cystogram revealed mild BNC. No ureteral reflux noted. Urethra was dilated and patient was given antimicrobial therapy (S) for an additional 5 months.
	29 months	Repeat renal functional clearances were still normal. Cystoscopy was normal. Urinalysis and cultures were normal. She has continued to be asymptomatic without medications and free of urinary findings during the past year. <i>Conclusion</i> Mild BNC. Renal functional clearances normal on two occasions.

Patient No.	Age	Comments
7	2 ¹¹ / ₁₂ years	White female with first acute attack of urinary tract infection with symptomatology of 3 weeks duration. Pyuria, proteinuria and bacteriuria 100,000 col./ml of <i>E. coli</i> and proteus vulgaris. IVP revealed normal upper collecting tracts. Cystoscopy showed meatal stenosis with bladder trabeculations. Cystogram did not show any reflux. Renal functional clearances indicated a reduced C _{PAH} value. Antimicrobial therapy (N) was administered in addition to a meatotomy. Child lost to follow-up. <i>Conclusion</i> Meatal stenosis with bladder trabeculations suggestion of urologic obstruction at outlet. Three-week history of symptoms. First clinical expression warranting medical care. Reduced C _{PAH} associated. No follow-up.
8	24 months	Negro male admitted with pain and burning on urination, fever and dehydration. Pyuria and bacteriuria (100,000 col./ml <i>E. coli</i>) demonstrated. Antimicrobial therapy (S) given for six months. Significant bacteriuria persisted.
	28 months	Cine IVP revealed right hydronephrosis and hydroureter, reflux up left ureter and right ureterocele.
	30 months	Clearance performed and revealed normal C _{PAH} value. Cystoscopic examination showed presence of posterior urethral valves and bilateral reflux. Following clearance test, posterior urethral valves were removed and right ureter was reimplanted. Urinary tract infection cleared. <i>Conclusion</i> Two-year-old child with right hydronephrosis and hydroureter and bilateral ureteral reflux. C _{PAH} values normal level. Infection difficult to eradicate for 6 months with antimicrobial therapy (S); however, surgical intervention was successful with resultant negative urine cultures and sediment.
9	4 ⁷ / ₁₂ years	Negro male in automobile injury resulting in transection of spinal cord at T5 with paraplegia and neurogenic bladder. Pseudomonas 100,000 col./ml found repeatedly in urine. Pyuria and proteinuria associated. Antimicrobial therapy (C)* given intermittently during the ensuing 5 months.
	5 years	Renal functional clearances showed a reduced C _{PAH} value. IVP normal. Cystogram revealed small and trabeculated bladder. The child's ureters were transplanted into a loop of ileum (Bricker Procedure). <i>Conclusion</i> Neurogenic bladder secondary to cord transection. Urinary tract infection documented. Five months later C _{PAH} found significantly depressed.
10	4 ¹¹ / ₁₂ years	Negro female with known nephrosis for 20 months which responded well to steroid therapy. Relapse associated with pyuria and bacteriuria: 100,000 col./ml coliform and enterococcus. Antimicrobial therapy (S) for 3 months.
	5 ² / ₁₂ years	IVP normal. Antimicrobial therapy (S) continued with good response and complete urine clearing after another month's therapy. Sulfisoxazole continued.
	5 ⁶ / ₁₂ years	Relapse 100,000 col./ml proteus. Antimicrobial therapy (N) given for 2 months without improvement. Bacteriuria persisted.
	5 ⁸ / ₁₂ years	Clearances showed borderline normal C _{PAH} values. Cine IVP showed blunting of right calyceal system. Cystoscopy and cystogram revealed meatal stenosis, moderate bladder neck contracture. No ureteral reflux. Marked trabeculations of bladder mucosa noted. Light and electron microscopy showed changes consistent with nephrosis and no evidence of pyelonephritis. Urethral dilatation and meatotomy were performed. <i>Conclusion</i> Child with nephrosis developed urinary tract infection. Urologic examination revealed meatal stenosis and BNC. After 9 months of unsuccessful medically treated urinary tract infection, low borderline values for C _{PAH} were obtained.
11	3 ³ / ₁₂ years	White female seen for urgency and urinary frequency. Pyuria and bacteriuria 100,000 col./ml <i>E. coli</i> . Antimicrobial therapy (S) for 3 months with slight improvement.
	3 ⁴ / ₁₂ years	IVP normal.
	3 ⁶ / ₁₂ years	Cystoscopic examination showed urethral and meatal stenoses which were dilated.
	3 ⁸ / ₁₂ years	Relapse with symptomatology, pyuria and bacteriuria 100,000 col./ml of <i>E. coli</i> . Cystoscopy and dilatation with improvement.
	4 years	Repeat dilatation. Cystoscopy showed BNC and persistent urethral stenosis. Antimicrobial therapy (S) initiated and continued for 6 months.
	4 ⁶ / ₁₂ years	Relapse with frequency, urgency associated with pyuria and significant bacteriuria 100,000 col./ml <i>E. coli</i> .
	4 ⁸ / ₁₂ years	Renal functional studies showed normal C _{PAH} clearances. Cystoscopy following these studies revealed a slight BNC. Cystogram showed normal bladder and no ureteral reflux. Follow-up for one year without medications. No relapses and urine free of WBC and bacteria.

Patient No.	Age	Comments
		<p><i>Conclusion</i> Child with meatal and urethral stenosis associated with BNC and urinary tract infection for 17 months. Pyuria and bacteriuria associated with two relapses. In between relapses, child never really symptom-free. Renal functional clearances after 17 months showed normal C_{PAH} values. Therapy consisted of repeat dilatation and long-term antimicrobial agents.</p>
12	<p>4⁶/₁₂ years</p> <p>4⁸/₁₂ years</p> <p>5 years</p> <p>5¹/₁₂ years</p> <p>5⁴/₁₂ years</p>	<p>Negro female with frequency, fever associated with pyuria, proteinuria and significant bacteriuria 100,000 col./ml of coliform and paracolon. Antimicrobial therapy (S) for 2 months.</p> <p>IVP showed double collecting system on left.</p> <p>Cystoscopic examination did not show any obstruction or reflux.</p> <p>Relapse of pyuria and significant bacteriuria. Antimicrobial therapy (S) continued for 1 month.</p> <p>Renal functional clearances showed borderline normal for C_{PAH} values. Urine culture negative. Left renal biopsy did not show evidence of acute or chronic infection.</p> <p><i>Conclusion</i> Child without urinary obstructive uropathy associated with urinary tract infection. Antimicrobial therapy cleared urinary sediment and culture findings but symptomatology persisted with lesser intensity. Renal function tests done after 10 months. Short-term antimicrobial therapy given on two occasions.</p>
13	5 ⁹ / ₁₂ years	<p>White female with dysuria, frequency, flank pain, fever associated with pyuria, proteinuria and bacteriuria 100,000 col./ml coliform. Two previous acute episodes documented in the previous two years. Both episodes treated with short-term antimicrobial therapy (S). IVP normal. No ureteral reflux demonstrated with cystogram. On cystoscopic examination, she was found to have BNC. Renal functional clearances showed low C_{PAH} clearances.</p>
14	<p>5¹¹/₁₂ years</p> <p>6²/₁₂ years</p> <p>6³/₁₂ years</p> <p>6¹¹/₁₂ years</p>	<p>Negro female with abdominal pain, anorexia associated with pyuria, proteinuria and bacteriuria 100,000 col./ml coliform. Antimicrobial therapy (S) for 3 months with improvement and clearing of urinary sediment and culture.</p> <p>Four days after therapy stopped, relapse occurred with symptomatology and urinary findings. Antimicrobial therapy (S) continued for one additional month.</p> <p>IVP revealed normal upper tract. Cystoscopy showed urethral and meatal stenosis with moderate BNC. No reflux demonstrated with cystogram. Dilatation and meatotomy performed.</p> <p>Renal functional clearance revealed a low borderline normal C_{PAH} value. Renal biopsy of right kidney failed to reveal evidence of infection.</p> <p><i>Conclusion</i> Child who one year previous to renal clearances showed two documented attacks of urinary tract infection. These were associated with meatal stenosis and BNC. Antimicrobial therapy (S) given for the first 4 months; meatotomy and urethral dilatation done 4 months after initial infection. Symptoms and urinary findings continued. Antimicrobial therapy (S) not given by parents for the following 6 months. Renal function tests show low C_{PAH} values one year after onset.</p>
15	<p>5 years</p> <p>5¹/₁₂ years</p> <p>5²/₁₂ years</p> <p>5³/₁₂ years</p>	<p>Negro female with abdominal pain, fever, pyuria and bacteriuria 100,000 col./ml of <i>E. coli</i>. Antimicrobial therapy (S) for two weeks.</p> <p>IVP revealed dilatation right superior calyceal system.</p> <p>Relapse with pyuria and bacteriuria 100,000 col./ml of enterococci and aerobacter. Antimicrobial therapy (C) for three weeks.</p> <p>Renal functional clearance showed reduced values for C_I, C_{PAH} and $TmPAH$. Cystoscopy and cystogram revealed a marked urethral and meatal stenosis with an edematous bladder neck, bladder mucosal trabeculations and cystitis. Urethral meatotomy done with urethral dilatation. Two monthly follow-up visits revealed normal urinary sediment and cultures.</p> <p><i>Conclusion</i> Child with a known 3-month history of urinary tract infection and x-ray evidence of dilatation of right calyceal system, plus obstruction of the lower urinary outlet. Renal clearances reduced.</p>

Patient No.	Age	Comments
16	4 ⁸ / ₁₂ years	Negro female with gross hematuria associated with pyuria, proteinuria and bacteriuria. 100,000 col./ml coliform. Antimicrobial therapy (S) for 4 weeks with clearing of symptoms, urinary sediment and culture. IVP normal.
	4 ¹¹ / ₁₂ years	Relapse with proteinuria, pyuria and bacteriuria 100,000 col./ml <i>E. coli</i> . Antimicrobial therapy (S) for 6 months initiated.
	5 ⁵ / ₁₂ years	Therapy discontinued. Urinary sediment and cultures negative.
	5 ⁸ / ₁₂ years	Relapse with pyuria, proteinuria and bacteriuria.
	6 years	Renal functional clearance showed normal values for C_{I_1} , C_{PAH} and $TmPAH$. Cystoscopic examination revealed meatal stenosis; no ureteral reflux noted. Antimicrobial therapy discontinued by mother after 3 months.
	6 ⁶ / ₁₂ years	Dilatation.
	7 ⁴ / ₁₂ years	Relapse with frequency and enuresis associated with pyuria and significant bacteriuria 100,000 col./ml <i>E. coli</i> .
	7 ⁵ / ₁₂ years	Dilatation plus antimicrobial therapy (S) for 5 months.
	7 ¹¹ / ₁₂ years	Pyuria and significant bacteriuria persist. Antimicrobial therapy changed from (S) to Polycillin.
	8 ⁴ / ₁₂ years	Repeat renal functional clearances showed reduced C_{PAH} but increase in $TmPAH$. Meatal stenosis dilated once again. Urine cultures were negative.
		<i>Conclusion</i> Child with a known history of urinary tract infection for 3 years and 8 months. No x-ray evidence of uropathy. Urologic finding of urethral and meatal stenosis treated with repeat dilatations and appropriate antimicrobial therapy (long-term). Renal clearance done at 16 months after onset were normal but reduced after 44 months.
17	6 ⁶ / ₁₂ years	Negro female seen because of a history of three previous urinary tract infections during the previous year. This episode of dysuria and history of weight loss associated with proteinuria, pyuria, hematuria and bacteriuria (<i>E. coli</i> greater than 10,000 col./ml). Antimicrobial therapy (S) given for 10 months with symptomatic improvement and clearing of urinary sediment and urine cultures.
	7 ⁴ / ₁₂ years	Renal functional clearances showed reduced C_{PAH} values. Cine IVP showed partial double collecting system on the right side, otherwise urinary tract normal. Cystoscopic examination revealed meatal stenosis and bladder neck contracture with marked bladder trabeculations. No ureteral reflux noted. Antimicrobial therapy (S) given for 6 months.
	7 ¹⁰ / ₁₂ years	Bladder neck contracture still present. Bladder trabeculations. Urethra dilated. Antimicrobial therapy (S) continued for another 6 months.
	8 ⁴ / ₁₂ years	Dilatation. Antimicrobial therapy (S) continued for another 6 months.
	9 ⁶ / ₁₂ years	Repeat functional clearances showed improvement in the previously low C_{PAH} to normal values. Asymptomatic for 14 months.
		<i>Conclusion</i> Child with a documented history of repeat urinary tract infection for 4 years. Associated urologic findings were meatal stenosis and BNC with trabeculations. After 22 months of illness, renal functional clearances showed a reduced C_{PAH} value. Antimicrobial therapy continued for 18 months. Dilatation of urethra every 6 months. Repeat clearance 26 months later showed normal value for C_{PAH} .
18	6 years	Negro female with left flank pain, fever, vomiting associated with pyuria and bacteriuria. Antimicrobial therapy (S) for one month. Symptoms and urinary findings cleared.
	6 ³ / ₁₂ years	Cine IVP demonstrated left renal pelvis contracted with ureteral reflux up to left superior calyx.
	6 ⁴ / ₁₂ years	Cystoscopic examination demonstrated bladder neck contracture.
	6 ⁸ / ₁₂ years	Relapse with pyuria.
	6 ⁹ / ₁₂ years	Renal functional clearances demonstrated a low borderline value for C_{PAH} . Cystoscopic examination still showed bladder neck contracture; no reflux noted. Antimicrobial therapy (S) for 1 year. She continued symptom-free.
	7 ⁹ / ₁₂ years	All medications discontinued.
		8 ² / ₁₂ years Repeat functional clearances showed a further reduction in the C_{PAH} value.
		<i>Conclusion</i> History of documented urinary tract infection 2 years previously. X-ray showed contracted left renal pelvis with ureteral reflux up left ureter. Cystoscopic examination revealed bladder neck contracture. Antimicrobial therapy (S) for one year. During this period patient was symptom-free and urinary sediment and cultures were negative. Repeat renal clearances done at 9 months and 26 months after onset of disease demonstrated reduced C_{PAH} values.

Patient No.	Age	Comments
19	5 ¹⁰ / ₁₂ years	Negro female with malnutrition, enuresis, fever associated with pyuria and bacteriuria (<i>E. coli</i> 100,000 col./ml). IVP normal. Antimicrobial therapy (S) for one month. One relapse after 7 months. Antimicrobial therapy (S) for another 4 months.
	6 ⁹ / ₁₂ years	Renal clearances showed normal C _{PAH} values. Cystoscopic examination negative. No ureteral reflux noted. <i>Conclusion</i> Single documented urinary tract infection 12 months previously. No uropathy demonstrated. Renal clearances normal.
20	7 years	Negro female with frequency of urination, fever, vomiting associated with proteinuria, and pyuria. Urine culture showed 4,000 col./ml paracolon. IVP showed right kidney enlarged with blunting superior calyx. Antimicrobial therapy (S) unknown (question as to whether child took medicine).
	7 ⁷ / ₁₂ years	Relapse with fever, enuresis, frequency of urination associated with aerobacter and enterococci, 100,000 col./ml.
	7 ⁸ / ₁₂ years	Renal functional clearances showed normal values for C _I and C _{PAH} . <i>Conclusion</i> Urinary tract infection for 8 months. Bladder neck contracture and meatal stenosis found in addition to blunting right superior calyx. Antimicrobial therapy for 8 months. Renal clearances revealed normal values.
21	10 years	Negro female with pyuria, and bacteriuria 100,000 col./ml <i>E. coli</i> . Cystoscopic examination showed BNC with bilateral ureteral reflux. Urethra dilated and antimicrobial therapy (S) given for 4 weeks. IVP showed dilatation of right superior calyx.
	10 ⁸ / ₁₂ years	Relapse. Antimicrobial therapy (S) for 4 weeks.
	10 ¹⁰ / ₁₂ years	Cystoscopy showed BNC but no ureteral reflux. Dilated.
	10 ¹⁰ / ₁₂ years—	
	13 ⁴ / ₁₂ years	Three relapses all treated with urethral dilatation and antimicrobial therapy (followed by private physician). Renal functional clearance showed a reduced C _I and low borderline normal C _{PAH} values. Cystoscopy showed mild BNC. No reflux. IVP persistence of dilatation and blunting of right superior calyx. <i>Conclusion</i> Child with history of repeated urinary tract infection associated with bladder neck contracture over a period of 3 ⁴ / ₁₂ years. Renal clearance revealed a reduced C _I and C _{PAH} value. No long-term therapy.
22	10 ⁷ / ₁₂ years	White female found to have asymptomatic pyuria at age 6. During the next three years several antimicrobial agents were used (S), (N) with intermittent clearing of pyuria. Cystoscopic examination three times during the period revealed slight bladder neck contracture. Complaint of fatigue became noticeable during the end of her third year of illness.
	13 ⁶ / ₁₂ years	Renal functional clearances revealed normal C _I and C _{PAH} values. Urinary culture demonstrated 30,000 col./ml <i>E. coli</i> . Cine IVP studies showed normal kidneys and urinary tract. Antimicrobial therapy continued even though urinary sediment and cultures were negative.
	15 ¹¹ / ₁₂ years	Repeat renal functional clearances showed a reduced C _{PAH} value. Urine culture and sediment during the performance of these clearances were negative. Renal biopsy showed minimal changes consistent with acute pyelonephritis. <i>Conclusion</i> Child with asymptomatic pyuria for 3 years. Her only complaint was fatigue. A reduction in C _{PAH} value was found on repeat testing 2 ¹ / ₂ years after the first clearance studies.
23	12 ⁴ / ₁₂ years	White female with a two-year history of urinary tract infection with pyuria and bacteriuria 100,000 col./ml <i>E. coli</i> . and treated with several antimicrobial agents (S), (C), (N). Renal functional clearances demonstrated reduced C _{PAH} values. Cinecystogram showed reflux up right ureter with BNC. Biopsy of kidney showed minimal changes consistent with acute pyelonephritis. Urine culture 40,000 col./ml <i>E. coli</i> . Urinary sediment contained WBC and granular casts. <i>Conclusion</i> Child with a three-year history of urinary tract infection associated with right ureteral reflux and reduced C _{PAH} values.

Patient No.	Age	Comments		
24	2 years	White female with history of two previous undocumented attacks of acute urinary tract infection with pyuria and proteinuria 5 and 6 mos previously. Both episodes treated with short-term antimicrobial agent (S) and dilatation of urethra. Cystoscopic examination showed BNC. Normal renal function clearances obtained 6 months after first attack. Child followed for two years without evidence of urinary tract infection. <i>Conclusion</i> Child without documented urinary tract infection, i.e. no urine culture obtained. Clearance data obtained 5 months after second attack of apparent urinary tract infection revealed normal values.		
25	33 months	Negro female child with fever, convulsions, urinary frequency, dysuria and pyuria. Urine culture negative. IVP showed normal upper tracts. Antimicrobial therapy (S) for 9 months. Urinalysis and cultures continued to be normal in spite of complaints of urinary frequency and dysuria.		
	42 months	Clearances performed were in normal range. Cystoscopy and cystogram revealed meatal stenosis and urethritis. No ureteral reflux demonstrated. Meatotomy performed. <i>Conclusion</i> Symptom primarily of urethritis. Clearances normal. No true obstructive uropathy.		
26	13 months	Negro female with failure to thrive and diarrhea. Urine culture 50,000 paracolon. Pyuria and proteinuria present. IVP normal.		
	37 months	Readmitted for shigella infection, diarrhea, fever and convulsions. Cystoscopic examination revealed BNC. No ureteral reflux. Urethra was dilated and patient given antimicrobial therapy (S) for 6 months.		
	43 months	Clearances performed showed normal values for C_{PAH} . IVP normal. Cystoscopy normal. <i>Conclusion</i> Forty-three-month-old female with shigella infection of intestine at age 37 months; no true infection of kidneys documented. On sulfisoxazole 6 months.		
27	5 ¹⁰ / ₁₂ years	Negro female with history of acute glomerulonephritis 2 years previously who was found to have a large bladder, double collecting system on left, bifid right renal pelvis and blunting of the superior calyx. Megacystis syndrome was presumptive diagnosis. Child seen monthly for 4 months for cystoscopy and dilatation of urethra.		
	6 ¹⁰ / ₁₂ years	Renal functional clearances revealed normal values for C_I and C_{PAH} . <i>Conclusion</i> Child with megacystis. No urinary tract infection. Renal clearance values normal.		
IVP	Intravenous pyelogram	(N) Nitrofurantoin	Col.	Colonies
BNC	Bladder neck contracture	(T) Tetracycline		
(S)	Sulfisoxazole	(C) Chloramphenicol		