HEMATOGENOUS PYELONEPHRITIS IN RATS. IV. RELATIONSHIP OF BACTERIAL SPECIES TO THE PATHOGENESIS AND SEQUELAE OF CHRONIC PYELONEPHRITIS * †

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Despite the inherent differences in the various bacterial species responsible for human pyelonephritis, little consideration has been given to differences in the characteristics of the renal disease resulting from infection by each species. While it is possible that pyelonephritis is a single disease entity that develops in an identical fashion regardless of the type of bacteria, scattered clinical observations suggest that variations in the pathologic processes are governed to some extent by the properties of the infecting micro-organisms (1–4).

In order to obtain further information on the pathologic differences resulting from renal infection by a variety of bacterial species, pyelonephritis was produced in rats by a method that allows the infection to develop without the confusing effects of surgical hydronephrosis (5). In the study described in the preceding paper in this series, remarkable differences were observed in the character of the acute and subacute renal infection produced by various strains of *Escherichia coli, Proteus, Pseudomonas aeruginosa* and enterococci isolated from patients with pyelonephritis (6). The present study was designed to examine the differential pathological effects of three of these species in chronic pyelonephritis in rats which were followed as long as one year after the onset of renal infection. In addition, the relationship of chronic pyelonephritis to hypertensive vascular disease was studied in an attempt to learn whether differences in bacterial species could account for the inconstant occurrence of hypertension in human chronic pyelonephritis and its absence in experimental chronic pyelonephritis due to *E. coli* (7).

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MATERIALS AND METHODS

Female albino rats of the Holtzman strain weighing 200 to 250 Gm. were used in all studies. Pyelonephritis was established by intracardiac inoculation of either *E. coli, Proteus morganii* or *Streptococcus zymogenes* and massage of the kidney in the manner described previously (5). Each bacterial strain was initially recovered from the urine or blood of patients with pyelonephritis and after growth for 18 hours was frozen and stored in trypticase soy broth at $-22°$ C. Immediate mortality, within the first 48 hours after inoculation was approximately 50 per cent in animals infected with *E. coli* or *P. morganii,* but was absent after *S. zymogenes.* One hundred rats survived initial infection with *E. coli,* 62 rats with *P. morganii* and 73 rats with *S. zymogenes.* Animals infected with each species were then divided into groups which received a second, third or fourth inoculation of the same organism at 10 to 20 week intervals, as indicated in Tables IA through C. Each reinoculation was accompanied by renal massage. Several animals from each subgroup were sacrificed between each inoculation and the remainder approximately one year after the initial infection. A group of 40 control rats were included in the study; 12 of these were sacrificed midway during the experiment and the remaining 28 followed for up to one year (Table ID). All animals were housed in groups of six to 12 in colony cages, fed identical diets of rat chow and allowed tap water for drinking *ad libitum.*

As previously described, the kidneys of each rat were gently but firmly massaged during ether anesthesia for exactly five minutes. In order to minimize subjective factors that might influence the intensity of renal massage, each period of five minutes was divided between any two of us instead of confining the total period for each animal to one person. The kidneys of control animals were not massaged, since it had been demonstrated previously that massage alone does not produce permanent injury (7).

Bacteriological and pathological study of the kidneys and blood cultures were carried out in every rat with the techniques described elsewhere (5–7). Cultures were also made of portions of liver and spleen. All tissues were ground to a pulp with sterile sand, suspended in water and spread across a blood agar plate for culture. Sections for histologic study were made through the kidney

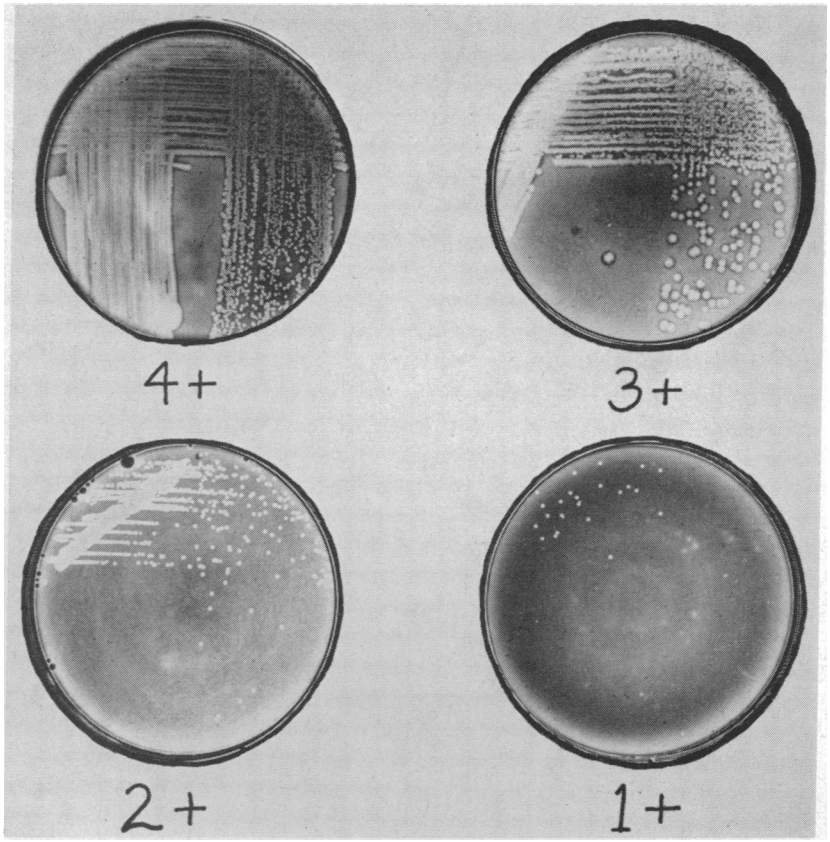

FIG. 1A. SYSTEM FOR GRADING INTENSITY OF RENAL INFECTION FROM GROWTH ON BLOOD AGAR PLATES

at the hilum so that the entire cortex, medulla and pelvis were examined at essentially the same planes in all specimens. The rats were weighed and their systolic blood pressures were determined monthly throughout the study, the latter by the tail plethysmographic method as reported previously (7).

Impairment of renal function was investigated by determining the blood urea nitrogen (BUN) of samples collected by intracardiac puncture upon sacrifice and by measuring the ability of the animals to concentrate urine during the course of the experiment. For the latter purpose the rats were placed in metabolic cages without food or water for 48 hours and the urine collected quantitatively in graduates which contained mineral oil and a small amount of phenylmercuric nitrate. The osmolal concentrations of the urine samples collected between 24 and 48 hours were determined by the freezing point technique with a Fiske osmometer.

RESULTS

1. *Mortality*

Although the immediate mortality after the first injections with *E. coli* and *P. morganii* was approximately 50 per cent, the subsequent combined acute mortality from repeated inoculations of these bacteria was less than 10 per cent. This decrease was attributed to the development of resistance to the endotoxins of the Gram-negative bacteria. The Gram-positive organism, *S. zymogenes,* neither killed the rats nor made them outwardly ill. Aside from the initial inoculation of Gram-negative bacteria, a major cause of death during the course of the study was pneumonia which affected all groups equally, including the controls. Most of these deaths occurred during the last three months of the experiment and were due to Type 2 pneumococci and other primary pulmonary pathogens, but not the bacteria inoculated experimentally. An additional 12 per cent of the rats were killed accidentally.

2. *Bacteriological findings*

Among the rats inoculated with *E. coli,* kidneys of all but four of 31 animals sacrificed 14 weeks or

TABLE IA

Rats infected with E. coli

Group (no. of injections)	No. of rats	Time of sacrifice: Weeks after 1st infection	Weeks after 2nd	Weeks after 3rd	Weeks after 4th	Renal function: Positive kidney cultures (no. of rats)	Infected kidneys with sterile urine (no. of rats)	BUN	Osmolar concentration (wk. of expt.)	Systolic blood pressure: Final BP	No. of rats above 140 mm. Hg	Average elevation above 110 mm. Hg	Heart weight
								mg./100 ml.	*mOsm./Kg.*	*mm. Hg*			*mg./100 Gm.*
E (1)	2	8				1	0	25		98	0	−10	
	2	38				0	0	27		105	0	− 8	
	6*	55				0	0	29	2,660 (33)	124	0	+ 6	274
E (2)	2	9	1 da.			2	0	45		95	0	−15	
	7	10	1			7	2	34		94	0	−11	
	2	22	12			0	0	22		110	0	− 4	
	2	34	25			1	0	28		103	0	− 4	
	6*	56	47			0	0	32	2,798 (39)	117	0	0	277
E (3)	2	20	10	1 da.		2	0	44		115	0	− 3	
	2	23	14	1		2	1	24		105	0	− 5	
	2	29	20	10		0	0	25		100	0	0	
	8*	53	43	33		2	0	28	3,009 (29)	127	1	+ 7	282
E (4)	7*	50	41	33	25	1	1	29	3,106 (33)	119	0	+ 3	270

* Sacrificed at end of study.

TABLE IB

Rats infected with Proteus morganii

Group (no. of injections)	No. of rats	Time of sacrifice: Weeks after 1st infection	Weeks after 2nd	Weeks after 3rd	Renal function: Positive kidney cultures (no. of rats)	Infected kidneys with sterile urine (no. of rats)	Renal stones (no. of rats)	BUN	Osmolar concentration (wk. of expt.)	Systolic blood pressure: Final BP	No. of rats above 140 mm. Hg	Average elevation above 110 mm. Hg	Heart weight
								mg./100 ml.	*mOsm./Kg.*	*mm. Hg*			*mg./100 Gm.*
P (1)	2	13			2	0	2	31		125	1	+10	
	3	24			3	1	1	41		123	0	+12	
	14*	51			8	2	2	35	2,514 (20)	121	0	+13	281
P (2)	2	16	1 da.		2	0	0	50		115	0	+10	
	2	24	3 da.		2	0	0	25		125	0	+14	
	3	17	1		3	0	0	29		105	0	+10	
	2	34	18		2	1	1	32		133	1	+13	
	13*	48	24		10	2	1	33		122	1	+14	283
P (3)	4*	53	37	15	4	1	2	31	2,473 (47)	110	0	+ 1	294

* Sacrificed at end of study.

TABLE IC

Rats infected with Streptococcus zymogenes

Group (no. of injections)	No. of rats	Time of sacrifice: Weeks after 1st infection	Time of sacrifice: Weeks after 2nd	Time of sacrifice: Weeks after 3rd	Renal function: Positive kidney cultures (no.of rats)	Renal function: Infected kidneys with sterile urine (no. of rats)	Renal function: BUN	Renal function: Osmolar concentration (wk. of expt.)	Systolic blood pressure: Final BP	Systolic blood pressure: No. of rats above 140mm. Hg	Systolic blood pressure: Average elevation above 110 mm. Hg	Heart weight
							mg./ 100 ml.	*mOsm./Kg.*	*mm. Hg*			*mg./ 100 Gm.*
S (1)	2	16			2	0	23		123	0	+ 9	
	4	22			4	0	27		117	0	+12	
	8*	44			8	1	24	2,176 (30)	120	0	+11	283
S (2)	3	15	1 da.		3	0	26		113	0	+ 5	
	2	16	1		2	0	26		98	0	+ 8	
	2	24	9		2	0	26		110	0	+ 2	
	2	44	19		2	1	29		128	0	+ 2	
	6*	54	28		6	0	25	2,323 (40)	127	1	+12	274
S (3)	2	24	9	3 da.	2	0	26		115	0	+ 4	
	2	43	28	19	2	0	28		123	0	+14	
	7*	53	38	28	7	0	25	1,957 (40)	118	0	+ 8	272

* Sacrificed at end of study.

TABLE ID

Control group

Group	No. of rats	Time of sacrifice (wks. after start of study)	Renal function: Positive kidney cultures (no. of rats)	Renal function: BUN	Renal function: Osmolar concentration (wk. of expt.)	Systolic blood pressure: Final blood pressure	Systolic blood pressure: No. of rats above 140 mm. Hg	Systolic blood pressure: Average elevation above 110 mm. Hg	Heart weight
				mg./ 100 ml.	*mOsm./Kg.*	*mm. Hg*			*mg./ 100 Gm.*
K-1	12	24	0	24		113	0	+3.0	275
K-2*	11	56	0	25	3,827 (34)	116	0	+6.0	279

* Sacrificed at end of study.

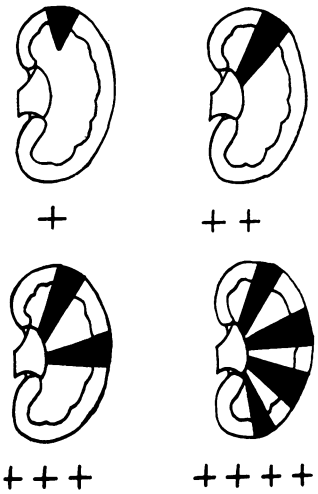

FIG. 1B. SYSTEM FOR GRADING SEVERITY OF GROSS LESIONS IN KIDNEYS WITH CHRONIC PYELONEPHRITIS

longer after their final injection had become sterile. The occasional positive cultures were obtained only from animals receiving two or more inoculations. On the other hand, infection with *S. zymogenes* persisted in the kidneys of all animals, up to the final sacrifice 44 weeks after one or more injections. Infection with *Proteus* was also persistent; up to 24 weeks, kidneys were positive in almost 100 per cent of the rats, while the kidneys in eight of 14 animals receiving only one injection were still infected at the end of a year (Tables IA through D).

Quantitative cultures of the kidneys were performed as previously described (5) and the results recorded according to the scheme in Figure 1A. In Table II, the intensity of the infection in the kidneys obtained from the rats sacrificed at the termination of the experiment are compared for the three species. These data indicate that the infection of the kidneys with enterococci not only persisted longer but that the numbers of bacteria in the kidneys infected with this species also were most numerous.

Neither *E. coli* nor *P. morganii* could be cultured from the blood of animals sacificed one week or later after inoculation or reinoculation of bacteria. With the exceptions of two rats, it was also impossible to isolate *S. zymogenes* from the blood of the 35 pyelonephritic animals examined at any time after the first week of inoculation or reinoculation with that organism. Hence the strongly positive cultures of kidneys from rats with streptococcal or *Proteus* pyelonephritis could not be attributed to bacteremia and the presence of infected blood in the kidneys. Many of the animals with *Proteus* or streptococcal pyelonephritis yielded on culture a few colonies of these bacteria in their liver or spleen. These slightly positive cultures of extrarenal tissue were considered to be secondary to the persistent renal infection, rather than their cause for the following reasons: *1*) Bacteria could be cultured from extrarenal tissues in only 76 per cent of the animals with infected kidneys and never in the absence of renal infection; *2*) only an occasional bacterial colony (less than one in Figure 1A) was recovered

TABLE II

Comparison of intensity of infection in rats sacrificed terminally

Species	No. of injections	No. of kidneys examined	Intensity of infection					"Intensity index"*
			0	1+	2+	3+	4+	
E. coli	1	12	12	0	0	0	0	0
	2	11	10†	0	0	0	0	0
	3	16	13	2	0	1	0	0.08
	4	14	13	1	0	0	0	0.03
P. morganii	1	28	14	5	4	5	0	0.25
	2	26	9	9	8	0	0	0.24
	3	8	0	3	1	4	0	0.53
S. zymogenes	1	16	1	2	4	8	1	0.59
	2	12	0	0	4	2	6	0.79
	3	14	0	1	3	4	6	0.77

* "Intensity index" $= \frac{\text{sum of grades}}{\text{number of kidneys examined} \times 4}$.

† One kidney absent, one kidney infected with *Proteus*.

from extrarenal tissues despite heavy renal infection; *3*) there were no pathologic changes in the liver or spleen while the infected kidneys showed severe inflammatory changes.

In view of the clinical dependence on positive urine cultures to establish the diagnosis of pyelonephritis, it is of interest that sterile urine or bladder cultures were obtained from 13 animals possessing infected kidneys. The renal infection was due to *E. coli* in four of these animals, to *Proteus* in seven and to enterococci in two (Tables IA through C).

3. Blood pressures and heart weights

In Tables IA through D, blood pressure data are expressed in several ways. The mean of the final blood pressure determinations for the rats in each group are listed as well as the number of animals with systolic pressures of 140 mm. Hg or higher. In addition, individual and average monthly deviations from 110 mm. Hg [1] were calculated for each animal, and the means for the groups were determined.

Significant hypertension failed to develop as indicated by the rare occurrence of blood pressure over 140 mm. Hg. Analysis of variance of the blood pressures in animals sacrificed terminally demonstrate that although hypertension did not develop and the final pressures among the various groups were not different, significant elevations above 110 mm. Hg, as compared with the control group of equal age, occurred in the animals inoculated once or twice with *Proteus* ($p = 0.01$, Table III). These small changes in blood pressure in the *Proteus* groups, however, did not lead to a significant increase in heart weight (Table III).

It was not possible to correlate severity of renal involvement or differences in the damage between the two kidneys with the level of blood pressure. However, the highest individual pressure (155 mm. Hg) was found in an animal which at autopsy demonstrated a tiny, atrophic right kidney and a hypertrophied and deformed left kidney. This animal was injected three times with *E. coli* and died spontaneously 12 weeks after the third and 32 weeks after the first inoculation.

In view of the possibility that early deaths may have occurred in those rats with the severest renal disease and that hypertension may have con-

[1] The average systolic blood pressure of a large series of normal young rats in our laboratory is 110 ± 10 mm. Hg with a further rise of approximately 10 mm. Hg with age. Spontaneous pressures of 140 mm. Hg or above are rare in our experience and in those of others employing the same technique (8).

The calculation of "average elevation in blood pressure over 110 mm. Hg" takes into account changes that occur during the entire course of the experiment. It avoids the possibly misleading impression obtained from single terminal determinations in sick hypertensive animals which may develop a fall in blood pressure before death or sacrifice. Normal adult rats with an average elevation of more than + 15 mm. Hg during their lifetime are rare.

TABLE III

Analysis of variance data from animals sacrificed at termination of study

Group	Final blood pressure		Average BP above 110 mm. Hg		Heart weight		BUN		Osmolal concentration	
	Mean	± S. D.	Mean	± S. D.	Mean	± S. D.	Mean	± S. D.	Mean	± S. D.
K-2	115.9	8.6	6.3	5.5	279.2	16.8	24.8	3.3	3,827	837
E (1)	123.8	13.5	6.2	5.4	273.6	18.5	29.2	5.0	2,660*	633
E (2)	116.7	10.8	−0.3*	5.7	277.4	22.2	32.4	9.4	2,798*	387
E (3)	126.9	12.2	7.1	3.6	281.8	11.3	28.0	3.5	3,009†	959
E (4)	119.3	9.3	3.3	6.9	269.5	22.0	28.6	5.2	3,106	592
P (1)	121.4	7.5	12.9*	4.8	280.5	23.4	35.0*	13.2	2,515*	933
P (2)	122.3	6.3	13.5*	5.4	282.8	22.4	32.2*	11.5		
P (3)	110.0	9.1	1.0	6.3	293.7	33.0	30.5	7.9	2,473*	1,000
S (1)	120.0	13.1	10.8	6.3	283.3	24.1	23.9	3.1	2,176*	400
S (2)	127.4	8.8	12.0	5.7	273.5	28.3	25.0	3.0	2,323*	633
S (3)	117.9	6.3	8.4	5.6	272.0	14.7	25.4	2.5	1,957*	412
F	1.53	$p > 0.05$	6.68	$p < 0.01$‡	0.48	$p > 0.05$	2.15	$p = 0.05$‡	4.28	$p < 0.01$‡

* Significant differences from K-2 group; $p = 0.01$ or less.
† Significant difference from K-2 group; $p = 0.05$.
‡ Significant F values.

TABLE IV

Blood pressure in rats which died spontaneously during study

Group	No. of rats	Average time of death: Weeks after 1st infection	Weeks after 2nd	Weeks after 3rd	Weeks after 4th	Systolic blood pressure: Final BP	No. of rats above 140 mm. Hg	Average elevation above 110 mm. Hg
						mm. Hg		
K-2	17	31				119	1	+ 7
E (1)	21	24				115	1	+ 1
E (2)	17	23	14			106	0	− 4
E (3)	9	28	18	9		117	1*	+ 2
E (4)	3	26	17	9	5 da.	117	0	+ 6
P (1)	5	45				120	0	+13
P (2)	9	41	19			117	0	+13
P (3)	3	48	33	10		115	0	+10
S (1)	12	26				116	0	+11
S (2)	14	36	15			121	0	+ 7
S (3)	7	48	32	22		120	1	+12

* Maximum blood pressure in this rat was 155 mm. Hg (see text).

tributed to their demise, similar data were calculated for rats dying spontaneously (Table IV). The blood pressure changes were identical; hypertension failed to develop, but higher blood pressures were indicated in the groups with *Proteus* infection.

4. *Pathologic findings*

The changes of chronic pyelonephritis were present in every rat sacrificed at the termination of the experiment approximately one year after initial infection and were observed as early as 24 weeks. The kidneys of animals sacrificed at the end of the experiment were graded on a scale of 1 + or 4 + according to the severity of gross pyelonephritic changes (Figure 1B and Table V). Gradings were done independently by two different observers and the results were averaged. As in the case of acute pyelonephritis (6), the most severe destruction in the chronic stage resulted from infections with *Proteus*. A striking discrepancy was noted again between renal damage and intensity of infection, when the *E. coli* groups were compared with those infected by enterococci. *E. coli* had disappeared from nearly every infected kidney by the end of one year but the renal damage observed at this time was as great or greater than that in kidneys still heavily infected with enterococci. It is of interest that repeated inoculation usually failed to increase the severity of the lesions.

TABLE V

Comparison of severity of chronic pyelonephritis approximately one year after infection by different bacterial species

Species	No. of injections	No. of kidneys examined	Grade of severity: 1+	2+	3+	4+	"Severity index"*
E. coli	1	12	2	3	3	4	0.69
	2	11	2	3	0	6	0.73
	3	16	6	3	4	3	0.56
	4	14	4	3	5	2	0.59
P. morganii	1	28	4	6	9	9	0.71
	2	26	2	3	8	13	0.83
	3	8	0	2	1	5	0.84
S. zymogenes	1	16	2	6	6	2	0.56
	2	12	2	8	2	0	0.50
	3	14	1	9	4	0	0.55

* "Severity index" $= \frac{\text{sum of grades}}{\text{number of kidneys examined} \times 4}$.

Regardless of bacterial etiology, all animals exhibited at least some of the characteristic changes observed in chronic pyelonephritis in man (Fig-

There was also a remarkable difference in the distribution of lesions produced by the different species (Figures 2A through C). In rats infected with enterococci, cortical lesions were observed microscopically in only 57 per cent of the kidneys but damage to the medulla and pelvic mucosa was invariably present and the severity usually approximated that seen in infections by *E. coli* and *Proteus*. The Gram-negative bacilli, on the other hand, produced lesions in the cortex of almost every kidney (*E. coli* 96 per cent, *Proteus* 100 per cent) but not always in the medulla (*E. coli* 82 per cent, *Proteus* 93 per cent).

FIG. 2A. CROSS SECTION OF KIDNEY INFECTED WITH *E. COLI* (× 15)
Note diffuseness of lesions affecting cortex and medulla.

ures 3 through 6). Kidneys were distorted, lobulated by scars, adhered to surrounding organs and resistant to section. Periglomerular fibrosis was prominent but the glomeruli themselves appeared normal unless destroyed by suppuration. The tubules were distorted, dilated and frequently filled with colloid casts. Interstitial fibrosis and infiltration of mononuclear cells were marked. The renal papillae were thickened and irregular so that on cross section the mucosa appeared to invade the papillae and to produce "polypoid masses" composed of pelvic epithelium and granulation tissue. Occasional pus casts were noted but almost exclusively in infected kidneys.

Kidney stones were found in nine of the 45 animals with *Proteus* infection (20 per cent). These ranged from small concentrations of gravel found near the papillary tip to large, classical "staghorn calculi" filling the entire pelvis of the kidney. Hydronephrosis was noted in association with the stones.

Vascular changes were minimal in all groups. Medial hypertrophy was detected only rarely and was slight. In areas where destruction of renal parenchyma and fibrosis were marked, there was some hyalinization of the media. These changes were most outstanding in the animals infected with *P. morganii*. Intimal thickening was absent and the ischemic type of vascular lesion described in man by Kincaid-Smith was not observed (9).

5. Renal function

The serial data in Tables 1A through C indicate that azotemia occurred immediately after reinfection in the groups infected with *E. coli* or *Proteus* but then tended to subside. A significant elevation of BUN was noted again at the termination of the experiment in two of the groups infected with *P. morganii* ($p = 0.01$, Table III). No elevation of BUN was found in any of the rats infected with enterococci. The group means in the animals infected with *E. coli* likewise were not significantly elevated from normal, but the large standard deviations indicate that some individual animals were azotemic (Table III).

Tables IA through D and Table III also indicate that the osmolal concentration of urine collected after dehydration was reduced below normal in all groups except, paradoxically, those rats receiving four inoculations of *E. coli*. With all of the species, repeated inoculation did not lower the osmolal concentration below that of rats given only one inoculation. It is of interest that osmolal concentration was impaired equally in groups infected with *Proteus* and enterococcus even though

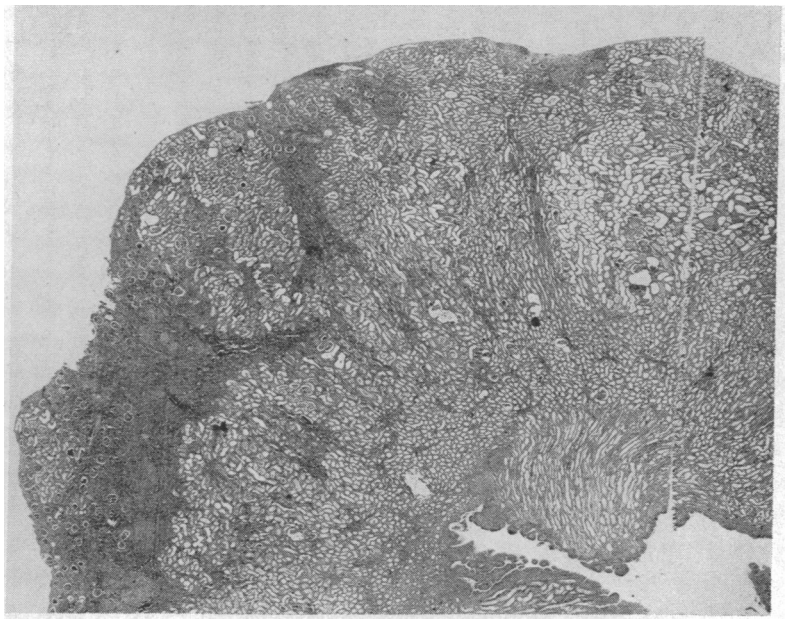

FIG. 2B. CROSS SECTION OF KIDNEY INFECTED WITH *P. MORGANII* (×15)
Lesions are somewhat more localized than in (A) but all parts of the kidney are affected.

azotemia and damage to renal tissue were greater in those infected with *Proteus*. This suggests that with certain bacterial species hyposthenuria may be a more sensitive indicator of impaired renal function in pyelonephritis than azotemia.

DISCUSSION

The different features of pyelonephritis that were attributed in the acute stage to differences in the bacterial species persisted and sometimes progressed as the infections were traced into the chronic stage. As late as one year after the initial infection, *Proteus* remained the sole cause of renal stones and still produced the greatest renal damage. Animals infected with enterococci, on the other hand, continued to show milder renal damage even though their kidneys remained infected with the most bacteria. In chronic *E. coli* pyelonephritis, the discrepancy between renal damage and infection was again the reverse of that with enterococci, and now even more marked than during the acute stage; *E. coli* had vanished from almost every kidney, although the renal damage was extensive and as great or greater than with the enterococcus.

With the passage of time, additional changes were found that were absent in the acute stage. In all three types of infection, the typical histologic features of chronic pyelonephritis became prominent. While the nature of these chronic changes were fundamentally the same for each of the three bacterial species, an important difference was noted between the distribution of lesions in infections by Gram-negative and Gram-positive bacteria. The Gram-negative bacteria produced both cortical and medullary involvement in virtually every kidney, while in chronic enterococcal infections almost 50 per cent of the kidneys were free of cortical lesions despite their invariable development of medullary and pelvic lesions. It was surprising to find that repeated bacterial inoculation did not increase the tissue damage of the kidney or further reduce their function. The first infection produced an obvious increase in resistance to the systemic effects of Gram-negative bacilli, so that mortality from bacteremic shock became negligible after subsequent inoculations. Studies are now in progress to determine whether prior infection also evoked a state of local resis-

tance in the kidney itself through the development of tolerance to the bacterial endotoxins.

The absence of significant vascular disease and hypertension in experimental chronic pyelonephritis, despite the extensive pathologic changes and functional disturbances in the kidneys produced by all three species of bacteria, is not in keeping with the clinical impression that chronic pyelonephritis is a common primary cause of hypertensive vascular disease. It does, however, correlate with the autopsy studies of Shure which indicate that unless pyelonephritis is quite severe, the incidence of hypertension in individuals with chronic pyelonephritis is not greater than that in patients without this renal disease (10). It is thus of interest that a slight increase in blood pressure was found in the animals infected with *Proteus* since they sustained not only the most severe renal damage, but also occasionally suffered unequal damage to the two kidneys because of stones. Heptinstall and Gorrill, who studied the effect of bilateral and unilateral pyelonephritis in rabbits, only noted significant elevation of blood pressure in a few animals with unilateral nephrectomy and severe damage to the remaining kidney (11). It is conceivable, therefore, that with even more severe bilateral renal injury than observed in our experiments, or with a selectively unilateral injury, significant hypertension might develop. However, an alternative possibility for the clinical relationship between hypertension and chronic pyelonephritis is that impairment of renal function by chronic pyelonephritis renders the subject more susceptible to vascular stresses, including those of physical, dietary and behavioral origin, leading eventually to hypertensive vascular disease. This hypothesis is supported by the demonstration that hypertensive vascular disease occurring in rats with other types of renal injury than pyelonephritis can be intensified by steroids, by high sodium diets and by chronic behavioral disturbances (12–14).

Another probable explanation for the clinical relationship between chronic pyelonephritis and hypertensive vascular disease is that the kidney in hypertension, like the kidney in diabetes (15), is more susceptible to infection. Indeed, the frequent occurrence of pyelonephritis in malignant hyper-

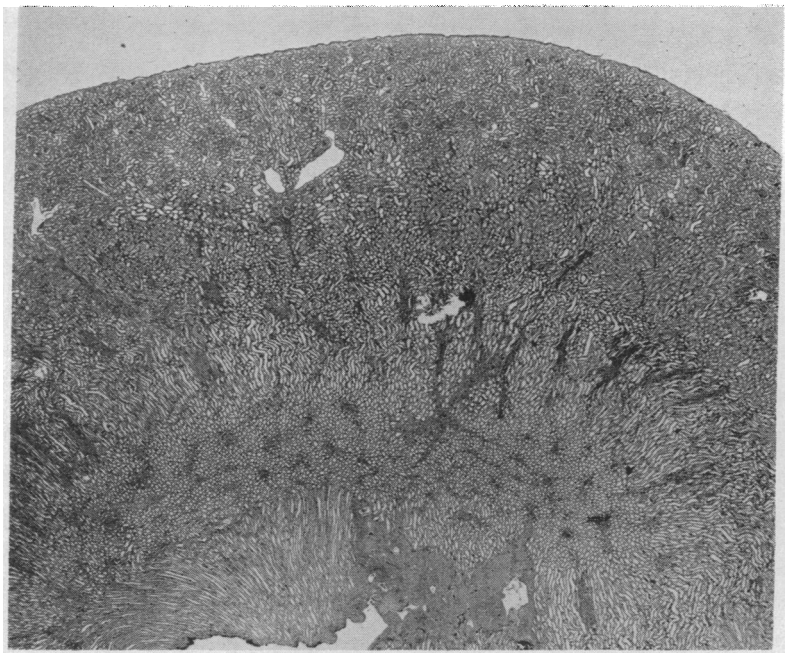

FIG. 2C. CROSS SECTION OF KIDNEY INFECTED WITH *S. ZYMOGENES* (× 15)

Note marked pelvic thickening, dilatation of collecting tubules and infiltrative lesions in medulla, while the cortex is quite free of damage.

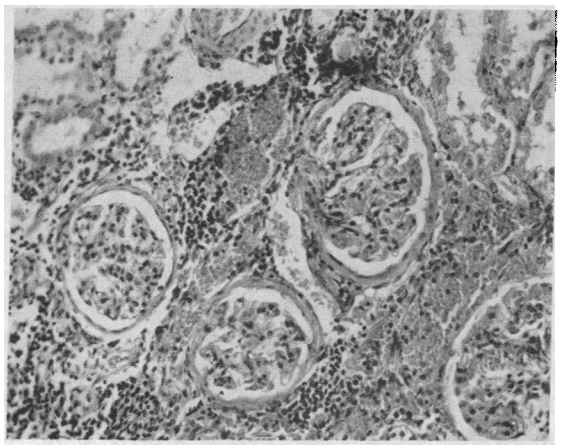

FIG. 3. SECTION THROUGH CORTEX OF KIDNEY INFECTED WITH *E. COLI* (×280)

Note periglomerular fibrosis and otherwise intact glomeruli. Interstitial infiltration of mononuclear cells is present.

tension may represent, as Goldblatt contends (16), the imposition of an infection which then aggravates the hypertensive process. These problems are being investigated in our laboratory and results indicate that desoxycorticosterone acetate hypertension in rats increases susceptibility to acute pyelonephritis induced by *E. coli* (17) and that this infection at least temporarily aggravates the hypertension (18).

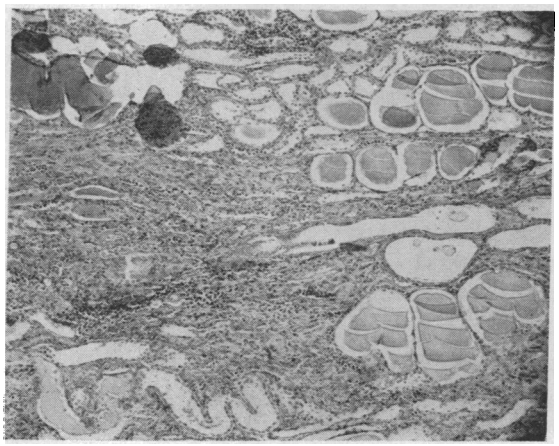

FIG. 4. SECTION THROUGH MEDULLA OF KIDNEY INFECTED WITH *E. COLI* (×140)

Note tubular distortion and dilatation, colloid casts ("thyroid kidney") and interstitial infiltration and fibrosis.

SUMMARY AND CONCLUSIONS

Chronic pyelonephritis was produced in more than 200 rats by combining repeated intracardiac inoculation of either *E. coli, P. morganii* or *S. zymogenes* with renal massage. The animals were observed for as long as one year after initial infection. Since surgical intervention was not necessary to establish pyelonephritis, the resulting pathological lesions of the kidney were purely the product of chronic infection. Although a slight elevation of blood pressure above normal was noted in the rats infected by *Proteus,* significant hypertension did not develop. All groups demonstrated impaired renal function, as measured either by urea retention or by decrease in osmolal

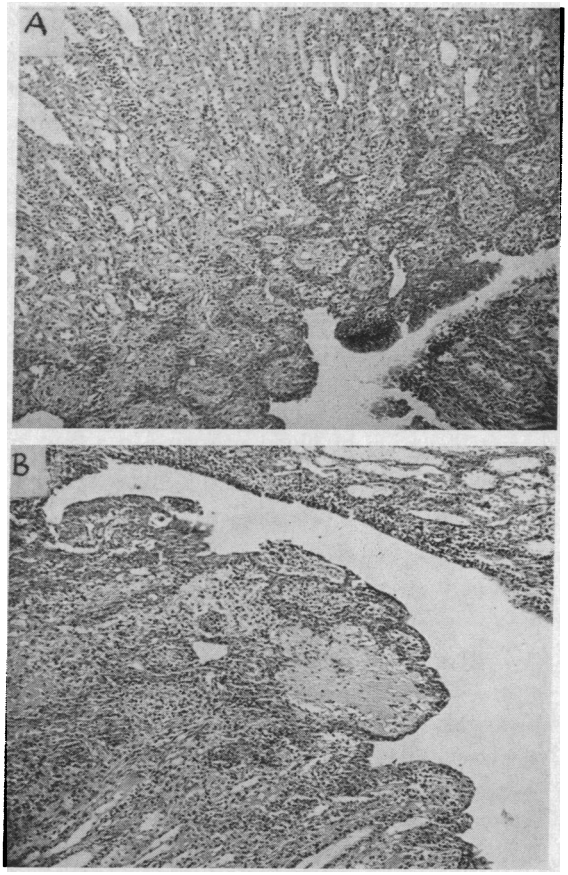

FIG. 5. SECTION THROUGH PELVIS OF KIDNEY INFECTED WITH *S. ZYMOGENES* (×140)

Note "invagination" of pelvic mucosa into papilla in A. A "polypoid mass" in the pelvis consisting of pelvic mucosa and granulation tissue is shown in B.

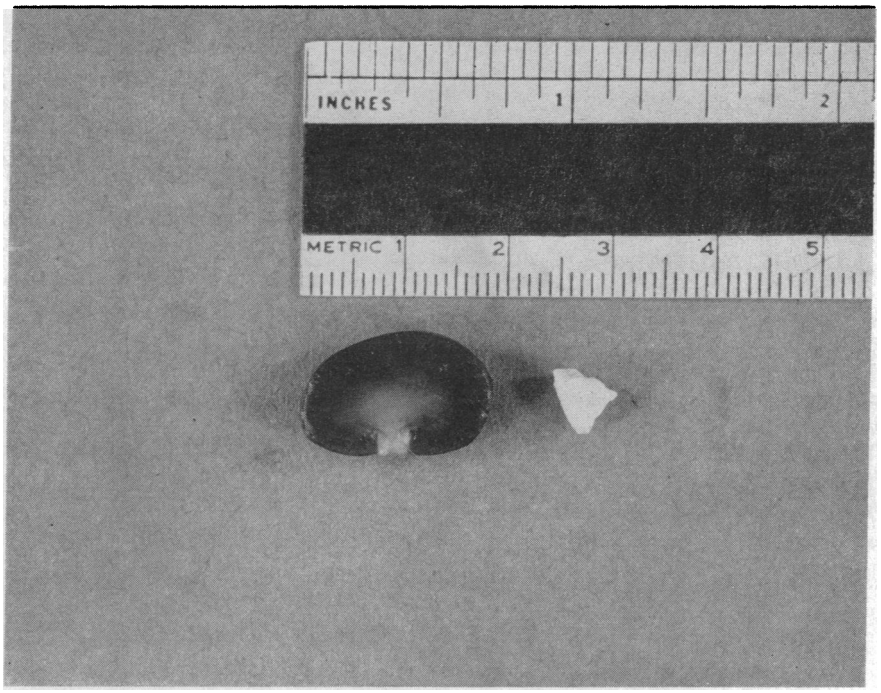

FIG. 6. CALCULUS WHICH FILLED ENTIRE PELVIS OF KIDNEY WITH CHRONIC INFECTION BY *P. MORGANII*

A sagittal section of a normal kidney is shown to illustrate size. Stone was composed of $MgNH_4PO_4$ (analysis by Dr. E. Prien, Boston, Mass.).

concentration of the urine after dehydration. Although the overall pathologic changes produced by all three organisms were basically similar and showed a striking resemblance to chronic pyelonephritis in man, certain features characteristic of each bacterial species were noted. Thus infection with *E. coli* was self-limited, but the inflammatory process that persisted in these sterile kidneys was at least as severe as that in rats with heavily persistent enterococcal infections of the kidney. *P. morganii* produced marked renal destruction, stone formation and hydronephrosis. Infection with *S. zymogenes* was still present in every rat examined at the end of one year, but observable lesions often predominated in the renal medulla.

The results demonstrate the importance of the bacterial species in determining the type and extent of renal injury in chronic pyelonephritis. Moreover, the absence of hypertensive vascular disease suggests several alternative hypotheses to the supposed etiologic relationship of hypertension to chronic pyelonephritis.

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