PYELONEPHRITIS IN INFANCY AND CHILDHOOD: ITS BACTERIOLOGY AND PATHOLOGY*

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Until about twenty-five years ago it was generally accepted that pyelitis was a disease per se and that infection of the renal tissue proper was as a rule secondary to infection of the pelvis. Recently, however, it has been shown that the lesion is seldom localized in the pelvis and a considerable amount of evidence has accumulated which favours the supposition that the primary focus of infection is in the kidney itself (Thiemich¹, Borrmann-Bremen², Kowitz³, Chown⁴, Wilson and Schloss⁵).

In the present investigation the bacteriological findings in 87 cases of pyuria are recorded. In 25 of these the formation of agglutinins was studied and in 9 complement-fixation tests were carried out. The lesions found at 170 post-mortem examinations are described and in 70 of these the kidneys were examined histologically.

It was found that 78.2 per cent. of the 170 cases occurred in the first year of life. As only fatal cases are dealt with, this figure does not give the true age incidence of pyuria, but it suggests that it is more fatal in infants than in older children. Girls were found to be more frequently affected than boys, in the proportion of 2 to 1, but in children under six months there was little difference in the sex incidence. This finding is in agreement with the observations of others (Kowitz³, Chown⁴, Wilson and Schloss⁵, Spence⁶).

TABLE 1.

AGE AND SEX INCIDENCE OF FATAL CASES OF PYURIA.

AGE GROUPS.	CASES.		PERCENTAGE OF TOTAL CASES.
	Boys.	Girls.	
Up to 26 weeks	33	43	44.7
26 weeks to 1 year	12	45	33.5
1 to 13 years	10	27	21.8
Total	55	115	
Percentage	32.4	67.6	

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Bacteriology.

Cultures were obtained from the urine of 87 cases of pyuria. The greatest care was always taken to avoid contamination of the specimens in the process of collection. The organism was first cultured on MacConkey's medium and on nutrient agar and from the colonies grown subcultures were made in various sugar media and the resulting reactions noted. When streptococci were found their resistance to heat and haemolytic properties were investigated. The organisms of the coli group were further identified by their agglutination reactions to antisera. Some difficulty was experienced in the preparation of the antisera as sometimes the animals rapidly failed after the commencement of the inoculations. This was overcome by injecting 0.5 c.c. colloidal manganese intramuscularly at the same time as the animal was inoculated with the organisms. Further, it was noted that living organisms were tolerated better by the animals than killed ones.

From the urine of 87 cases 9 different types of organisms were obtained, the bacteria most commonly present being the various coliform bacilli. In some of the specimens of urine more than one organism was obtained. Table 2 shows the order of frequency of the occurrence of the different types. From the table it will be noted that coliform bacilli were the organisms most commonly identified and that of these *b. coli communis* and *b. MacConkey 71* occurred most frequently. The fact that these are two of the commonest inhabitants of the bowel (MacConkey⁷ and Mackie⁸) favours the view that lesions of the urinary system are often due to auto-infection from the bowel.

TABLE 2.

TYPES OF ORGANISMS FOUND IN 87 CASES OF PYURIA.

87 cases	{	Pure coliform 51	{	21 <i>B. coli communis</i> .
				17 <i>B. MacConkey 71</i> .
				3 <i>B. paracolon</i> .
				3 <i>B. proteus</i> .
				3 Non-lactose fermenters.
	{		{	2 { <i>B. paracolon</i> .
				<i>B. MacConkey 71</i> .
				1 { <i>B. paracolon</i> .
				<i>B. lactis aerogenes</i> .
				1 { <i>B. paracolon</i> .
	{	Pure streptococcal 11	{	<i>B. acidi lactici</i> .
		Pure staphylococcal 2		11 <i>Enterococcus</i> .
		Mixed 23		2 <i>Staphylococcus aureus</i> .
		Enterococci together with		7 <i>B. coli communis</i> .
				7 <i>B. MacConkey 71</i> .
				5 <i>B. proteus</i> .
				2 <i>B. paracolon</i> .
				1 <i>B. lactis aerogenes</i> .
				1 Non-lactose fermenter.

When the agglutinating properties of the organisms were studied it was found that organisms having identical cultural properties did not correspond serologically. The antisera prepared to *b. coli communis*, *b. MacConkey 71* and *b. paracolon* agglutinated the homologous organisms in dilution of 1 in 3,200, 1 in 6,400 and 1 in 12,800 respectively. When, however, the antiserum to *b. MacConkey 71* was tested against 12 other strains of culturally identical bacilli recovered from the urine of other patients agglutination only occurred in high concentrations of the serum, e.g. 1 in 40. Coliform bacilli giving different sugar reactions, etc., from these obtained with the various strains of *b. MacConkey 71* were not agglutinated at all. Similar findings were obtained with 13 strains of *b. coli communis* and 4 strains of *b. paracolon* isolated from the urine of pyuria cases when tested against the appropriate antisera. Thus, while antisera are of use in identifying individual members of the coliform group, they are, on account of their strict specificity, of limited value for the differentiation of groups of organisms giving the same sugar reactions. This is in accordance with the work of Mackie⁸ and suggests that only autogenous vaccines are likely to be of any benefit in treatment.

Agglutination tests with patients' sera.—In 25 cases of pyuria agglutination tests were carried out with the patients' sera against the organisms isolated from their urine. When agglutination in dilution of 1 in 40 or over was obtained the results were considered to be positive. Thirteen of the 25 cases (52 per cent.) showed positive results, the titre varying from 1 in 40 to 1 in 3,200. Six of these, all under 1 year, died, while there was only one fatal case in the 12 where the serum did not show agglutinins (Table 3). The kidneys of 4 of the patients who died, in whom the sera agglutinated, were examined histologically and abscesses found. Similar lesions were also found in the single fatal instance among those where the sera did not agglutinate.

TABLE 3.
RESULTS OF AGGLUTINATION TESTS WITH PATIENTS' OWN SERA.

INFECTING ORGANISM.	AGGLUTINATION WITH PATIENT'S SERA.			
	Positive.		Negative.	
	Recovered.	Died.	Recovered.	Died.
<i>B. coli communis</i>	6	2	4	1
<i>B. MacConkey 71</i>	1	2	2	0
<i>B. paracolon</i>	0	2	2	0
<i>B. proteus</i>	0	0	2	0
<i>B. lactis aerogenes</i>	0	0	1	0
	—	—	—	—
Total	7	6	11	1
	—	—	—	—

In two of the fatal cases the infecting organism was *b. coli communis* and the agglutination titre was 1 in 80 and 1 in 40 respectively; in two other children the organism isolated was *b. paracolon* and the titre of the patients'

sera was 1 in 2,560 and 1 in 160 respectively. In the remaining two subjects who died, b. MacConkey 71 was present in the urine and the titre of the patients' sera was 1 in 640 and 1 in 160 respectively. In the 7 children who did not die and who gave positive agglutination tests, 6 girls and 1 boy, 3 were under one year and 4 were aged 3, 4, 7 and 8 respectively. Six of these children were acutely ill for several weeks with high fever and then gradually recovered. The seventh child was not acutely ill and the agglutination results were somewhat anomalous, for agglutination was obtained with normal serum in the same dilution as that obtained in the patients' serum. In these 7 cases b. coli communis was present in 6 and in the seventh b. MacConkey 71. The titre of the sera of the patients infected with b. coli communis was 1 in 3,200, 1 in 400, 1 in 320, 1 in 160, 1 in 80 and 1 in 40 and that of the child infected with b. MacConkey 71 was 1 in 40.

Case report.—The patient in whom the highest titre (1 in 3,200) was obtained showed certain points of interest and the following are the chief details:—

The patient was a girl aged 34 weeks. She had been healthy until one week before admission when diarrhoea began. On admission to hospital the child was drowsy, feverish and appeared acutely ill. Both kidneys were palpable, especially the left. The urine contained abundant pus cells and b. coli communis. A fortnight after the onset of the illness an agglutination test was performed when it was found that with a 1 in 3,200 dilution of the patient's serum the infecting coliform bacilli were completely agglutinated. Six weeks later when the child's condition had improved slightly, the test was repeated, but the agglutination titre of the patient's serum had fallen to 1 in 400. An autogenous vaccine was then prepared and given to the patient at weekly intervals. Three days after the first dose the titre was 1 in 160 and a month later, 1 in 80. The child was dismissed well one month later and the urine was free from pus and organisms, while the kidneys were no longer palpable.

This case is of interest because agglutination was at its height when the child was acutely ill and as her condition improved the agglutination titre declined.

Of the 12 cases which showed no agglutination 7 were in children under one year. Of these, 2 (one boy and one girl) showed little constitutional disturbance, while 4 girls were acutely ill with high fever, but the condition cleared up rapidly under treatment with sodium bicarbonate. The seventh case, a boy of 25 weeks, died nine days after the onset of the disease. The blood serum was tested for agglutinins on the fourth day of the illness with negative result. It is to be regretted that the agglutination test was not repeated at a later date as it is probable that when the test was made agglutinins had not had time to make their appearance. There were 5 cases over one year, all females, and in 4 of these frequency and pain on micturition were prominent symptoms. The fifth patient, aged 3 years, was acutely ill on admission with high fever. They all made good recoveries under treatment with sodium bicarbonate.

From the results of the agglutination tests it would appear that neither the type of infecting organism nor the sex or age of the patient seems to affect the agglutination results. The production of agglutinins appears to depend on the general resistance of the patient and on the severity and extent of the lesions. In support of the latter view it was found that all but

one of the fatal cases showed positive agglutination tests whereas other children who were acutely ill on admission, but who recovered quickly, gave negative results.

Complement fixation tests.—In 9 of the 25 cases in which agglutination tests were performed, the sera were also examined for antibodies by complement-fixation tests. Each serum was tested in 8 tubes containing complement varying in amount from 2 to 40 minimal haemolytic doses. One of the early cases showed zonal fixation of complement when doses up to 40 minimal haemolytic doses were added to the antigen-antiserum mixture: accordingly, throughout the experiments both untreated complement and complement treated with charcoal were used to remove the natural immune-bodies to certain organisms of the coli-typhoid group present in guinea-pig's serum (Dunlop⁹). From Table 4 it will be seen that 4 of the 9 sera tested gave positive complement fixation results and 3 of them also agglutinated the infecting organism. On the other hand, of the 5 sera in which the complement-fixation test was negative 2 gave negative and 3 positive agglutination tests. It would appear that the results of the tests do not run strictly parallel with the agglutination findings, nor does the production of complement-fixing antibodies seem to depend on the type of infecting organism. Further, it was found that neither the age, the sex, the general condition of the patient nor the extent of the lesion appeared to influence the results.

TABLE 4.
COMPARISON OF COMPLEMENT-FIXATION AND AGGLUTINATION TESTS.

Organism.	Complement-fixation.	Agglutination.	No. of cases.
B. coli communis	+	+	2
	—	+	2
	—	—	1
	+	—	1
B. MacConkey 71	+	+	1
	—	+	1
	—	—	1

Pathology.

At post-mortem examination definite inflammatory lesions were noted in the kidney substance in 84 of the 170 cases investigated, and of these the pelvis was congested in 58 and the bladder in 39. In the remaining 86 cases there were varying degrees of congestion and cloudy swelling in the kidneys, with congestion of the pelvis in 66 and of the bladder in 32. As the post-mortem findings in patients dying of pyogenic infection of the urinary tract probably only show the most advanced stages of the inflammatory process, it was thought that earlier changes might be found in patients dying of some other disease but who had pus in their urine. Sixteen cases of this nature were studied. In all of these the kidneys showed congestion or cloudy swelling, with congestion of the pelvis in 9 and of the bladder in 8.

Histology.—Of the cases coming to autopsy portions of the kidneys, pelvis, ureters and bladder of 70 were examined histologically, and were divided into four groups according to the severity of the microscopic lesions present. In the first group there were 18 children, in 16 of whom pyuria, often of only a few days' duration, arose during the course of some other illness and was not directly the cause of death. In the remaining two cases the pyuria was primary. In all of these little change was noted in the kidneys, apart from congestion of some of the glomeruli and cloudy swelling in the epithelial cells of the convoluted tubules. The pelvis in 14 showed varying degrees of acute inflammatory reaction, and similar changes were noted in the bladder in 7. These minor lesions in the kidneys, such as

FIG. 1.—Section of kidney from case of pyelonephritis. (Female, aged 7 months.) In the cortex a small perivascular area of round-celled infiltration is present. Haematoxylin and eosin. $\times 60$.

congestion of the glomeruli and cloudy swelling in the tubules, may represent the earliest stage of the reaction to the infection. In 14 of the cases coliform bacilli were cultured from the urine and in one this organism was actually seen in sections of the glomeruli. Although the infection of the urinary tract in these cases was mostly of a secondary nature, it is unlikely that the reactive changes to the infection would be different from those met with in primary cases and they probably represent the earliest phase of the inflammatory process.

The second group was composed of 4 cases in which more marked histological changes were found in the kidney substance than in the first group. Small foci of dense, round-celled infiltration (Fig. 1) were present in the interstitial tissue as well as the slight changes, e.g., congestion of the glomeruli and cloudy swelling in the epithelial cells of the tubules, which were noted in the first group. The pelvis was congested in all 4 cases, but the bladder in only one. In all of the cases coliform bacilli were isolated

from the urine. The cases in the second group were considered to have died at a more advanced stage of the disease than those in the first group.

The third group, in which there were 16 cases, showed definite acute inflammatory lesions in the kidney substance and other parts of the urinary tract. In the kidney there were widely separated foci of polymorphonuclear infiltration of the interstitial tissue and frequently these formed actual abscesses. In these areas, which were often wedge-shaped with the base of the wedge towards the surface of the kidney, the tubules were distended with polymorphonuclear leucocytes and desquamated epithelial cells. The glomeruli showed varying degrees of congestion. These inflammatory foci were situated chiefly in the cortical regions. The pelvis in only 3 of these

FIG. 2.—Section of kidney from case of chronic pyelonephritis. (Female, aged 4½ months.) In the cortex there is an area of round-celled infiltration in the interstitial tissue. Haematoxylin and eosin. $\times 90$.

16 cases showed definite inflammatory change, and in one of these a similar lesion was noted in the bladder. In the other two cases, in addition to the lesions in the kidneys, foci of inflammation were found in the bladder microscopically, but not in the pelvis. In 15 of these cases coliform bacilli were isolated either from the urine during life or from the kidney abscesses post mortem. In the sixteenth staphylococcus aureus was grown from the abscesses in the kidney.

The 32 cases comprising the fourth group showed a less acute course and more chronic lesions than in any of the foregoing groups. These lesions consisted of widely separated foci of round-celled infiltration of the interstitial tissue (Fig. 2) and, in some cases, areas of early fibrosis. Some of the tubules in these areas contained polymorphonuclear leucocytes and desquamated epithelial cells, and the glomeruli showed only minor degrees of congestion. The lesions were often wedge-shaped with their bases along the surface of the cortex, causing small irregular, vascular, depressed areas

on the surface of the kidney (Fig. 3, 3a, and 4). Such areas corresponded roughly in shape and distribution to the areas of polymorphonuclear infiltration noted in the acute cases. Scattered through the kidney substance

FIG. 3.—Surface view of kidney from case of chronic pyelonephritis. Numerous irregular small vascular depressed areas are present. The larger depressions are due to foetal lobulation. Natural size (Museum of Royal Hospital for Sick Children Glasgow).

FIG. 3A.—View of cut surface of chronic pyelonephritis. (Same kidney as Fig. 3.) Many small irregular depressed wedge-shaped areas are present in the cortex. Natural size (Museum of Royal Hospital for Sick Children, Glasgow).

FIG. 4.—Section of kidney from case of chronic pyelonephritis. (Female, aged 5½ months.) The cortex shows a depressed vascular area on the surface. There is slight round-celled infiltration of the interstitial tissue immediately under the capsule and some early fibrosis. Haematoxylin and eosin. $\times 67$.

in some of these cases were foci of polymorphonuclears but these probably represented a recrudescence of infection. In only 8 of these were there inflammatory lesions in other parts of the urinary tract. The pelves were affected in 4, the bladder in 2 and in the remaining 2 both the pelves and bladder were affected. In 30 of the cases coliform bacilli were found in the urine and streptococci in 8. In one staphylococcus aureus was found.

From the morbid anatomical and histological findings it is evident that in the fatal cases of pyuria in infancy and childhood the kidney substance is often the seat of an inflammatory change more marked than that found in the pelvis. Indeed, the pelvis frequently shows no lesion either on naked eye or on histological examination. In 70 cases in which the kidneys were shown histologically to be affected the pelvis showed inflammatory lesions in 27 and the bladder in 15. The common lesion in such cases is therefore suppurative nephritis rather than simple pyelitis. This is in agreement with the findings of many other workers. Death occurs in many cases when the lesion is in the acute stage, yet in some there is evidence of an attempt at healing as shown by areas of fibrosis, while in others death may occur when the condition has become subacute as shown by the presence of scattered patches of round-celled infiltration. It is possible that, in cases where the infection is overcome, the only permanent damage may be widely separated foci of fibrosis in contradistinction to the diffuse fibrosis of chronic interstitial nephritis.

Pathway of infection.—A study of the present series of cases brings out some points in favour of the descending route of infection. The fact that in infants under six months of age, a time of life when the vulva is specially exposed to infection, the proportion of males affected is almost equal to that of females is evidence that in young children at any rate the route of infection is not up the urinary passages. This point has been commented on by other workers^{3, 4, 5}. In older children, however, females are more commonly affected than males and it is possible that in some of these infection spreads from below. It is known that primary pneumococcal peritonitis is more common in females than in males (McCartney and Fraser¹⁰) and it is probable that in this disease the organisms frequently gains access to the peritoneum via the genital passages; similarly in the underclad children of the poorer classes renal infection may spread upwards from the vulva.

In 70 cases of the present series in which histological examination of the kidney, renal pelvis and bladder was made only 35 showed lesions outside the kidney and of the 48 cases with gross renal damage only 13 showed pelvic or bladder lesions. It seems improbable that if the infection spreads upwards inflammatory reaction in the lower urinary passages should be so relatively infrequent, for one would have to assume either that the inflammatory changes in the pelvis and bladder had healed, leaving no trace, or that infection could reach the kidneys without producing changes in the intervening tissue; both of these explanations seem improbable. Lastly, the histological appearance of the lesions is in favour of a haematogenous spread. In the early cases the glomeruli and convoluted tubules showed the most notable changes while in the more advanced cases the cortex of the

kidney was as a rule more seriously damaged than the tissue adjacent to the pelvis. If infection had spread from below it is probable that the tissues furthest removed from the pelvis would be least affected.

Conclusions.

1. The post-mortem findings of 170 cases of pyuria in infants and children are recorded. In 70 of these the kidneys were examined histologically. In 87 cases the bacteriological results are recorded. In 25 of these the formation of agglutinins was studied and in 9 complement-fixation tests were carried out.

2. Coliform bacilli were the organisms most commonly isolated suggesting that pyuria is due to auto-infection from the bowel.

3. Great specificity to agglutination was shown by the coliform organisms. For this reason only autogenous vaccines are likely to be of benefit.

4. Agglutination of the organisms isolated from the urine with the patient's serum occurred much more commonly in the fatal cases than in those that recovered. Acutely ill patients whose serum did not agglutinate recovered quickly. Probably the development of agglutinins depends on the extent and severity of the lesions in the kidneys and on the general resistance of the patient.

5. The power of fixing complement did not run strictly parallel to the agglutinating properties of the serum.

6. The morbid anatomical and histological findings indicate that the lesion is a suppurative nephritis affecting especially the renal cortex and that these lesions may either heal leaving scar tissue or become subacute and show scattered foci of round-celled infiltration.

7. The cortical distribution of the lesions and the relatively infrequent infection of the pelvis and bladder point to a blood infection in most cases.

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