Papers and Originals

Clinical Observations Relating to Incidence and Aetiology of Urinary-tract Infections in Children

J. M. STANSFELD,* M.A., M.D.

Brit. med. J., 1966, 1, 631–635

Sometimes the mother of a child with a urinary-tract infection will ask how it occurred and whether there was anything in her management that could be faulted. It may be difficult to answer her, and this study was undertaken in an attempt to seek further information concerning the incidence of urinary-tract infection and the circumstances in which it occurs in childhood.

Material

Observations have been made on 350 children with urinary-tract infections, all having significant pyuria and bacilluria and some also with radiological or histological evidence of pyelonephritis. Of these, 193 were seen at a urological clinic for children held in the Royal Victoria Infirmary, a teaching hospital in Newcastle upon Tyne, and 157 at Dryburn, a non-teaching hospital in Durham. The experiences at the two hospitals differed. Cases were selected in both, but in different ways, those at the teaching hospital being mainly referred by paediatricians because of suspected or revealed abnormalities in the renal tract, while those at the peripheral hospital were referred by family doctors. Certainly the cases seen at the teaching hospital were more severe, with frequent abnormalities, and were both more difficult to control and more liable to relapse.

Incidence

The patients in the teaching hospital came from too wide an area and were too selected to allow an estimate to be made of the incidence of hospital referrals. A better idea of this was obtained at the peripheral hospital, which dealt with over 90% of the children sent to hospital with urinary infections in its area. When first diagnosed all such cases were admitted for investigation and initial treatment. There were 125 new cases among a total of 10,162 admissions to the paediatric wards during the eight years 1957–64, giving a yearly average of 15.6 and a rate of 12.3 per 1,000 admissions. It was difficult to number the population from which these cases were drawn, as some doctors at the periphery of the hospital catchment area used the hospital and others sent their patients elsewhere. Moreover, a few doctors varied in their patronage, almost haphazardly sending cases to any of a number of hospitals.

Nevertheless, allowing for the known habits of the doctors in the vicinity, it was estimated that the population served by the paediatric department was in the region of 233,000, including 55,000 children up to 14 years of age (28,000 boys and 27,000 girls), with an error of probably not more than 15%. If these figures are approximately correct the yearly incidence of children seen at hospital with urinary-tract infections was 0.17 per 1,000 boys and 0.4 per 1,000 girls.

Such an incidence of urinary-tract infection seen at hospital may be very much less than that found in general practice, but a comparison of the two can be valid only if the same criteria are used for diagnosis. In this series the presence of infection has been confirmed by the finding in a clean uncentrifuged specimen of urine of 10 or more leucocytes per c.mm. and 100,000 or more organisms per ml. when plated within two hours of being voided. Bacterial counts and prompt testing are essential in order to distinguish true bacilluria from growth of contaminants after the urine has been passed. The only survey of urinary-tract infection in general practice in this country based on bacterial counts is one reported by Mond *et al.* (1965), who, remarkably, in a practice of 3,460 persons, during 18 months found no case of infection in children. Loudon and Greenhalgh (1962) accepted as evidence of infection an unspecified amount of pyuria and a "positive" culture of the urine without mention of bacterial counts or the time taken for the specimen to reach the laboratory, and found in a practice of 4,905 persons a yearly incidence of urinary infections in children up to 14 years of age of 2.3 per 1,000 boys and 10.8 per 1,000 girls. These rates are similar to those found by Fry *et al.* (1962), who also based their diagnosis on routine laboratory microscopy and cultures, but it is likely that both surveys included some patients erroneously thought to have urinary-tract infections because of false-positive urine cultures caused by growth of contaminants.

Family Incidence

The 350 children with urinary infections included four pairs of sisters and one pair of brothers. Two other children had sisters with proved infections but not included in the series, and a further two had sisters and one a brother with probable infections. Thus, certainly seven and possibly 10 siblings of 345 cases were affected.

In order to determine if this incidence of infection in families was greater than in the rest of the population the total number of siblings at risk needed to be known as well as their sex and ages. There were in fact 741 siblings, but the sex and ages were recorded in only 613 of them, being 322 boys of average age 7.96 years and 291 girls of average age 7.81 years. At the rates of the sample the 741 children would represent 3,098

TABLE I.—*Estimated Yearly Rates of Urinary-tract Infections Per* 1,000 *Children*

	Hospital	Siblings of Hospital Cases	General Practice*
Boys	0·17	0·33	2·3
Girls	0·4	2·18	10·8

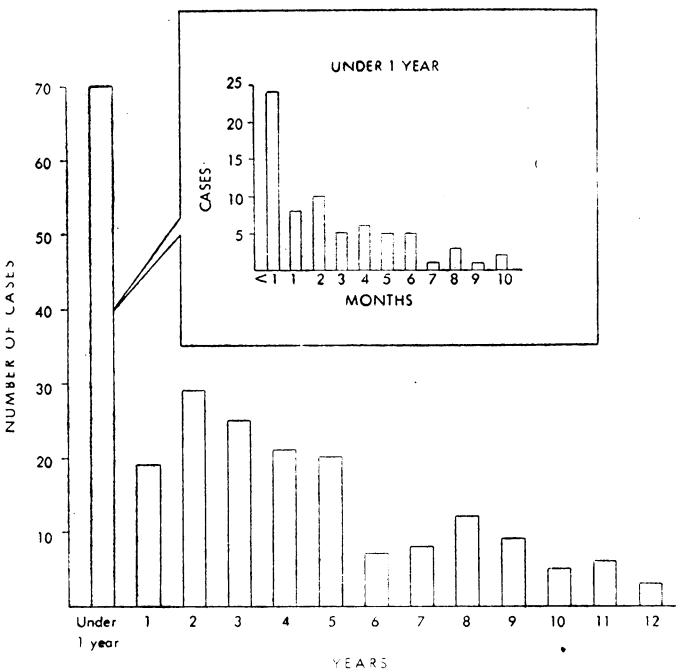
* Loudon and Greenhalgh (1962) with different criteria for diagnosis.

* Consultant Paediatrician, Durham and North-west Durham Hospital Management Committees; Associate Physician, Child Health Department, the Royal Victoria Infirmary, Newcastle upon Tyne.

child-years for boys and 2,749 child-years for girls; among them one boy and six girls were found to be infected. The yearly family rates of infection worked out as 0.33 per 1,000 boys and 2.18 per 1,000 girls, being greater than the incidence of hospital referrals but probably less than the incidence in general practice (Table I). The series thus did not appear to reveal any enhanced family susceptibility to infection in the urinary tract.

Age at Onset and Sex

By the time that a child with a urinary infection reaches hospital symptoms have often been present so long that it cannot be remembered when they started. A reasonably accurate time of onset could be obtained in only 234 of the 350 cases. From these it was, however, quite clear that, as was found in a different series of cases (Stansfeld, 1954) and confirmed since by others (Smellie *et al.*, 1964), the disease starts most often in the first year of life and particularly in the first month (see Chart). Indeed, symptoms were occasionally present at birth, and it was suspected that infection might even have occurred inside the uterus.



Age at onset of symptoms of 234 children with urinary-tract infections.

For the whole series girls were affected more than twice as often as boys (2.6:1) and three times as often in the less selected peripheral hospital component. The female preponderance was smaller in infancy (1.5:1), while among the 24 cases starting in the first month of life boys outnumbered girls (1.6:1). A male preponderance in the newborn was also found by Sauer (1925), Craig (1935), Porter and Giles (1956), and Lincoln and Winberg (1964). Ursula James (1959) found a more equal sex distribution (19 girls:13 boys), but even this was strikingly different from the marked female preponderance in older children.

Family Background

The different sex distribution of cases at various ages raises the possibility that urinary infections throughout childhood may not be homogeneous. Those contracted during the first month or even in the first year of life might be caused in a different way from those in older children. With such a possibility in mind cases have been divided into three groups according to whether the symptoms started in the first month, between one month and one year, or after the child's first birthday.

In older children the first symptoms are commonly those of a cystitis, and it would seem likely that infection, particularly in the female, occurs by ascent of organisms up the urethra. It might be expected that such infections would occur more readily in children whose hygiene was less good and who were more liable to get vulval contamination with faeces. Though many of the mothers were particularly fastidious over their daughters' cleanliness it was thought worth while to investigate how the cases were distributed in social groups as determined by the fathers' occupations. These were known in 318 of the 350 cases, and Table II gives the number of cases falling into each social group, together with their percentage distribution and that found in the 1951 census for Durham, Northumberland, and Newcastle upon Tyne for comparison. Clearly the social-group distribution does not support any hypothesis that the disease might be less frequent in the more affluent groups. The numbers in social class IV were higher than expected, and those in classes III and V correspondingly lower, though this may be due to the large proportion of cases from Durham rural area, where there are many miners.

TABLE II.—*Social Class of Fathers of Patients with Urinary-tract Infection Compared with* 1951 *Census Figures for Region*

	Social Class					Total Classified
	I	II	III	IV	V	
No. of urinary-tract infections	9	39	130	113	27	318
% of total classified	2·8	12·3	40·9	35·5	8·5	100·0
1951 census for region. % distribution	2·1	10·8	51·4	22·7	12·3	99·3

An index of the nutrition of the children, and so indirectly of their home conditions, may be got by a comparison of their heights with the normal. Height measurements were made on 267 of the cases, and when plotted on Tanner and Whitehouse charts 180 were the 50th percentile or less and 87 above the 50th percentile. Such a distribution is significantly different from a 1:1 ratio ($\chi^2=32.38$, n=1, $P<0.01$). However, many of the height measurements were made after infection had been present for some time, and it might well be that growth had been impaired because of the disease itself. In order not to be misled by this it would have been preferable to measure the heights of their brothers and sisters rather than those of the affected children, but this was not done. Instead, only height measurements made within three months of the onset of symptoms were examined.

There were 70 of these measurements, all of children starting their illness after 1 year of age. Forty-seven were the 50th percentile or less and 23 more than the 50th percentile—a distribution still significantly different from that expected ($\chi^2=8.23$, n=1, $P<0.01$). Thus it seemed that the height of the children starting urinary-tract infections tended to be less than the height of normal children in London and Oxford, where the data used by Tanner and Whitehouse were obtained.

TABLE III.—*Distribution of Heights of Children with Urinary-tract Infections Compared with that for Children Admitted for Hernia Repair or Acute Appendicitis*

	Height Percentiles								Total Classified
	−3	−10	−25	−50	−75	−90	−97	97+	
Urinary tract-infections within 3 months of onset:									
No.	4	9	15	19	14	6	2	1	70
%	5·5	12·8	21·4	27·1	20·0	8·6	2·9	1·4	99·7
Other children in hospital:									
No.	8	34	33	70	62	29	10	4	250
%	4·1	13·6	13·2	28·0	24·8	11·0	4·0	1·6	100·3

This might be because the average height of children in the north-east of England is lower than in the south, and in fact the heights of the children with urinary-tract infections differed little from those of 250 children from the same area admitted to hospital for repair of herniae or for acute appendicitis (Table III).

If faulty hygiene is a factor in the production of urinary-tract infections in children then the inexperienced mother or the mother harassed by a large family might be more likely to have children affected. The mean maternal age at birth of 320 of the children in the series was 28.25 years and the paternal age 30.6 years. These means do not differ significantly from the population average, nor is the distribution of maternal ages unusual (Table IV).

TABLE IV.—*Mothers' Age at Birth of 320 Children with Urinary-tract Infections*

Mothers Age in Years	Percentage Distribution in Series	Percentage Distribution England and Wales, Registrar-General 1961
Under 20	3·4	6·0
20–29	64·1	62·0
30–39	29·4	29·0
40 and over	3·1	Nearly 3

The place in the family was recorded in all but nine of the cases, and the birth order for the series was estimated by the method used by Slater (1962). Thus when an individual comes m^{th} in a sibship of n individuals, the expression $\frac{m-1}{n-1}$ will vary between 0 if he is the first-born and 1 if he is the last. The mean value in a random collection of families will tend towards 0.5 if the series is large enough. A higher figure will be found if there is an unusual proportion of late births and a figure less than 0.5 if there are more early births. In this series it came to 0.5028, which clearly does not differ significantly from the expected mean. The position in the family thus did not appear to influence the liability to develop urinary-tract infection. The size of the family did not seem to matter either, for at the time when the histories were taken it averaged 3.17 children—little more than the average of 2.90 for the families of the 250 children admitted for hernia repair or appendicitis.

It thus appeared that the incidence of urinary-tract infections in childhood did not show any correlation with social class, height, age of parents, birth rank, or size of family. Moreover, all these factors, except height, still revealed nothing significant when analysed for groups of cases divided according to age at onset.

Structural Abnormalities

When children who have urinary-tract infections are investigated many are found to have abnormalities in their renal tract which often cause some obstruction to the flow of urine. Opinions differ widely on how often such abnormalities occur, and would seem to depend upon what is considered to be abnormal and how extensively cases are investigated. In an attempt to define the situation in this series cases have been put into one of the following six groups:

1. *Normal renal tract* as visualized by both satisfactory intravenous pyelograms and micturating cystourethrograms.

2. *Apparently normal renal tract but incompletely investigated.* (*a*) Only intravenous pyelograms. (*b*) No radiology.

3. *Obstruction or dilatation in part or all of urinary tract due to major abnormalities*—for example, pelvi-ureteric, ureteric, or uretero-vesical obstructions, mega-ureters, urethral valves, calculi, absent abdominal muscle syndrome, paralysed bladders, duplications with ureteroceles, etc.

4. *Other major abnormalities but without obstruction*—for example, horseshoe kidney, hypoplastic or incompletely ascended kidneys, ectopia vesicae, duplications without ureteroceles.

5. *Vesico-ureteric reflux and/or bladder-neck obstruction* without other abnormalities apart from dilated upper urinary tract.

6. *Minimal or doubtful abnormalities*—for example, incomplete duplication of kidney, caliceal abnormalities, etc.

Changes such as scarring of the kidneys or reduction in width of cortex, which are secondary to pyelonephritis, were not included. Vesico-ureteric reflux or bladder-neck obstruction also occurred in some of the cases included in groups 3 and 4. Duplications associated with dilated ureters or ureteroceles were included in group 3, but without such evidence of obstruction they were put in group 4.

The numbers of cases in each group are given in Table V together with their percentage frequency. The distribution of cases in the various groups according to sex and time of onset of symptoms is shown in Tables VI and VII. Abnormalities causing obstruction appeared to be much commoner in males and occurred in 62% of those fully investigated, a frequency about three times that found in females. They were also more frequent in those whose symptoms started during the first month of life, and most neonatal infections occurred in boys with severe obstructive lesions in their renal tracts.

TABLE V.—*Classification of 350 Children with Urinary-tract Infections According to Radiological Findings*

Group	No. of Cases	Percentage of All Cases (350)	Percentage of Investigated Cases (246)
1. Normal renal tract	38	11	15
2. Apparently normal—incompletely investigated:			
(*a*) I.V.P. only	98	30	—
(*b*) No radiology	6		
3. Major abnormalities with impaired flow	79	23	32
4. Other major abnormalities ..	31	9	13
5. Vesico-ureteric reflux and/or bladder-neck obstruction only	88	25	36
6. Other abnormalities ..	10	3	4

TABLE VI.—*Abnormalities of Urinary Tract Related to Age at Onset of Symptoms and Sex*

Group as in Table V	−1 Month		−1 Year		Over 1 Year		Uncertain		Total	
	M	F	M	F	M	F	M	F	M	F
1	—	1	2	2	1	19	4	9	7	31
2	5	4	4	12	13	44	1	20	23	80
3	9	2	11	7	15	14	11	11	46	34
4	—	—	2	4	4	13	2	6	8	23
5	1	2	1	5	7	34	3	35	12	76
6	—	—	—	—	1	4	—	5	1	9

TABLE VII.—*Percentage Distribution of Abnormalities for Various Ages at Onset of Symptoms*

Group as in Table V	Age at Onset			
	−1 Month (15 Investigated)	−1 Year (34 Investigated)	Over 1 Year (112 Investigated)	Uncertain (86 Investigated)
1	7%	12%	18%	15%
3	73%	53%	26%	26%
4	—	18%	15%	9%
5	20·0%	18%	37%	44%
6	—	—	4%	6%

Preceding Events

Most urinary infections in childhood appear to arise without any obvious cause, and only a minority of them are associated with any happening that might be of aetiological importance. Among the 234 cases whose times and details of onset are reasonably well known, infection began in two soon after trauma —one in a 4-year-old boy who fell off an outhouse roof, injuring his loin and developing urinary symptoms the next day, and the other in a 12-year-old boy who ruptured his kidney after being hit in the flank by a swing and who had haematuria the next two days, together with anorexia and frequency, which continued until a urinary-tract infection was discovered two

weeks later. In seven cases the onset followed instrumentation or operation upon the urinary tract, and in one it started during the course of a Henoch-Schönlein purpura. A larger group of 31 cases began within a week of an acute respiratory infection, and a further 18 followed other infections, including four each of measles, gastro-enteritis, and skin sepsis.

It was notable how often a respiratory infection preceded a urinary-tract infection. At first sight it would seem unlikely that the two could be causally related, for they are usually due to different organisms, and, moreover, both are so common that they might by chance sometimes coincide. Even so, other authors have observed such an association. Thus Woodruff and Everett (1954) found an acute respiratory infection in 25 of their 76 cases of urinary-tract infections, Burke (1961) noticed that 30% of her 100 cases of urinary-tract infections also had an acute infection of the respiratory tract, and Smellie *et al.* (1964) mentioned that an upper respiratory infection co-existed with a urinary-tract infection in eight of their 44 cases aged between 2 and 5 years.

In the present series a respiratory infection immediately preceded the onset of the urinary-tract infection in 13% of the cases. As it was not known how often respiratory infections occurred among the population at risk, it could not be shown whether there was anything more than a chance association between respiratory and urinary-tract infections. However, there is some circumstantial evidence. The incidence of respiratory infection varies with the time of year, being greater in the winter months. If there is any link urinary infections should show a similar seasonal variation. In Table VIII the month of onset is shown for 226 cases where this is accurately known. Symptoms do in fact more often start in the winter than in the summer, the maximizing dichotomy being October–March and April–September. Thus symptoms started in 129 cases in the six winter months, and in 97 in the summer, though such a difference could well be due to chance. When seasonal comparisons were made for different age groups at onset it was found that there was no significant difference between

TABLE VIII.—*Age and Month of Onset in 226 Cases*

Age at Onset	Month of Onset											
	1	2	3	4	5	6	7	8	9	10	11	12
−1 month	1	—	2	2	5	3	—	1	1	3	2	4
−1 year	2	5	5	4	3	4	5	4	7	2	4	3
1+ year	17	10	11	5	11	11	12	10	9	22	18	18
Total	20	15	18	11	19	18	17	15	17	27	24	25

summer and winter for cases starting in the first month or the first year of life, but in the large group which became infected later 96 started in the winter and only 58 in the summer, a difference which is significant at 1% level (David and Newell, 1966). Thus if respiratory infections play any part in the development of urinary-tract infections they probably do so only after infancy.

Discussion

It is not easy to infect the urinary tract in healthy animals. The introduction of organisms into the urethra or bladder appears to do little harm, and even the intravenous injection of *Escherichia coli* or *Proteus vulgaris* usually fails to cause any pyelonephritis. Only coagulase-positive staphylococci given intravenously can be relied upon to infect the kidneys when the renal tract is normal. If, however, it is not normal the situation is quite different. If the urine-flow from the kidney has first been obstructed by clamping a ureter, or the kidney has previously been damaged by diathermy or a preceding staphylococcal pyelonephritis, even though it be healed, the kidney becomes susceptible and an intravenous injection of *E. coli* or *Proteus vulgaris* will readily infect it.

Although experimental work has mainly been done on rats and rabbits, it is tempting to speculate on how it may explain some of the findings in this series. Perhaps bacteraemia occurs more often than is generally supposed and organisms become filtered off by the kidneys and washed out in the urine. In a normal tract they probably cause no harm, but when the kidney is diseased or the flow of urine impeded they have a chance to settle and multiply. A newborn infant with a congenital obstructive lesion would be particularly susceptible and rapidly become infected. The high incidence of staphylococcal infections in the newborn may be another reason for the prevalence of urinary infections at this time, since a staphylococcal pyelonephritis might open the pathway to a subsequent *E. coli* invasion. Rupp (1958) found a high incidence of staphylococcal pyelonephritis in newborn infants with staphylococcal skin lesions, and Neumann and Pryles (1962) noted that infection in neonates was often associated with sepsis. After infancy it seems that infection of the urinary tract is more likely to occur by an ascent of organisms up the urethra to the bladder and subsequently by reflux to the kidneys. The seasonal variation and the possible relationship to respiratory infection cannot be explained, but it may be significant that in a study of pus-cell counts from 2,000 children in hospital (Stansfeld, 1962) a temporary pyuria was frequently found in girls who had acute respiratory infections.

Summary

A study was made of 350 children seen at hospital with urinary-tract infections.

The yearly rates of referral to a non-teaching hospital amounted to approximately 0.17 per 1,000 boys and 0.4 per 1,000 girls.

There was no evidence that the incidence of infection in families with affected children was any greater than in the general population.

Infection most often started in infancy, particularly in the newborn. Girls were more often affected than boys except in the first month of life, when the reverse occurred.

The incidence of infection in the neonate infant or older child did not appear to be related to the social class of the family, age of parents, birth order, or size of the family. If the height of the children is taken as an indication of their nourishment those in whom infections started after infancy would seem to have been as adequately fed as other children in the community in which they lived.

Major structural abnormalities of the urinary tract were found in 45% of the cases investigated, and a further 36% had vesico-ureteric reflux or obstruction of the bladder-neck.

Gross abnormalities, especially those causing obstruction, were particularly prevalent in males and in infants whose symptoms began in the first month of life.

An acute respiratory-tract infection was noted within a week before the onset of the urinary-tract infection in 13% of the cases.

Infection after infancy started more often in the winter than in the summer.

I would like to thank Professor S. D. M. Court for his help and interest. I am grateful to Mr. R. A. McNay for advice concerning the statistical analysis, and to Mrs. M. Jackson for editorial assistance.

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Relapses of Urinary-tract Infections in Children

J. M. STANSFELD,* M.A., M.D.

Brit. med. J., 1966, 1, 635–637

It is one thing to clear the urine of a child with a urinary-tract infection but quite another to keep it clear, and relapses are both common and ill-understood. This paper records their frequency, connexion with treatment, and time of occurrence in a group of 350 children with urinary-tract infections. The cases were seen at two hospitals, and details, including sex, age, and incidence of anatomical abnormalities, are given elsewhere (Stansfeld, 1966). All have been kept under continued observation. After initial hospitalization the children were at first seen every one or two months, but later the intervals were lengthened up to a year, depending on the progress in each case. The period of observation, average number of times seen, and frequency of visits are given in Table I. Treatment has varied over the years, but antibiotics have been selected throughout in accordance with the sensitivity of the organisms recovered from the urine and usually given in full dosage for one or two weeks followed by a reduced amount given for months or even years. Surgical relief of obstructive lesions has been undertaken whenever possible, and most cases have been seen at a combined medical and surgical clinic.

TABLE I.—*Details of Follow-up of 350 Cases of Urinary-tract Infection in Children*

	No. of Cases	Observed less than 6 Months	Monthly under Observation		Average No. Times Seen	Average Interval between Visits (Months)
			Range	Average		
Hospital A	193	25	1–131	27¾	10	2¾
„ B	157	19	1–178	44	9½	4¾

A relapse or a reinfection—no distinction has been made between these two—has been taken to be a return of significant pyuria or bacilluria, with or without symptoms, after the urine had previously been clear. In a few cases infection could not be controlled, and though there might be exacerbations these were not counted as relapses. Some who had responded to treatment became unwell between their visits to the hospital, and, without their urine being examined, had further treatment from their family doctors and thus were well again when they returned to the follow-up clinic. Whether these episodes were relapses or not was decided on the history of the symptoms and the special knowledge the family doctor and the mother had of the child. When there was any doubt treatment was stopped and the child was watched to see what happened. No attempt was made to number the relapses which had occurred before the child was first seen in hospital, but they were known to be frequent.

* Consultant Paediatrician, Durham and North-west Durham Hospital Management Committees; Associate Physician, Child Health Department, the Royal Victoria Infirmary, Newcastle upon Tyne.

Relapse Rate

In 28 of the 350 cases treatment failed. In spite of all that was done their pyuria and bacilluria continued unabated. All these patients had gross abnormalities of the urinary tract, such as severe obstruction or paralysed bladder, and the six deaths in the series occurred among them. The remaining 322 responded to treatment, with clearing of their urine, for at least two months. Yet many had relapses (Table II).

TABLE II.—*Relapses Encountered Among 350 Children with Urinary-tract Infections*

	Total Cases	No. of Relapses							Persistent Infection or Death
		0	1	2	3	4	5	6	
Hospital A	193	94	48	18	11	6	1	1	14
„ B	157	108	17	9	2	5	2	0	14

Apart from suggesting that relapses are common the figures in Table II give no indication of their true frequency, which will obviously depend upon how long each case is observed. Taking into account the length of follow-up in each case, the rates for first relapses were worked out in a life-table, from which Table III is derived. This shows how many relapses occurred in each 100 cases during six-monthly intervals over a period of three years after initial control. Many relapsed during the first 18 months, and this should be the minimum follow-up period for all cases. The figures also illustrate how greatly the results at one hospital may differ from those at another. The treatment at the two hospitals concerned was very similar but the cases were quite different. Those at hospital A, a teaching hospital, were referred from a wide area and sent because of anatomical abnormality or because they were not responding to hospital treatment elsewhere, while those at hospital B were solely referred by family doctors.

TABLE III.—*Relapse Rate Per 100 Cases at Intervals After Initial Onset*

6-month period:	1st Year		2nd Year		3rd Year		Total for 3 Years
	First	Second	Third	Fourth	Fifth	Sixth	
Hospital A ..	19·6	13·1	13·0	5·4	3·2	1·3	55·6
„ B ..	9·4	3·1	9·2	2·6	1·5	—	25·8
Combined ..	14·8	8·3	11·2	3·8	2·2	1·0	41·3

Time and Cause of Relapses

About 40% of the relapses occurred during treatment and 60% after it had stopped. Those during treatment were mostly of unknown cause or due to the presence of resistant organisms, some were due to the child failing to take his medicine or pills,