THE ULTIMATE PROGNOSIS OF NEPHRITIS IN CHILDHOOD

TOGETHER WITH A STUDY OF THE INCIDENCE OF ANAEMIA
IN THE VARIOUS STAGES OF THE DISEASE

BY

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The ultimate prognosis of acute nephritis in children has always been a subject of interest to the paediatrician. The relative frequency of acute nephritis in childhood and the fact that many cases of renal failure in adult life cannot be explained, have led to repeated attempts to correlate the childhood illness with the adult renal failure. Until recent years and with traditional methods of examination these efforts have failed, but Addis (1925) gave clinicians a sign by which they can distinguish between those children who have fully recovered from acute nephritis and those who appear equally healthy, but are actually in the latent stage of nephritis, and will ultimately die of renal failure or its complications.

After many years' work he devised a method by which a quantitative estimation can be made of the urinary protein and the cellular elements in the sediment and gave the upper limits of normal in adults and the conditions under which reliable results can be obtained. By using this method he had followed cases of Bright's disease from the acute stage through the latent stage in which they were apparently normal, although quantitative examination of their urine showed that the renal lesion was still active, and through the active or subacute stage to the terminal stage of chronic nephritis. In this way he established the connection between acute nephritis in childhood and degenerative or chronic nephritis in adult life. He suggested the following diagram as depicting the course of nephritis :

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Since that time various workers (Lyttle, 1933 ; Snoke, 1938) have applied Addis's method to the examination of the urine of children and established the upper limits of normal for albumin and cellular elements. Their results are all very similar. Those given by Snoke are reproduced here since they have been used in the present series of cases.

CELLULAR ELEMENTS AND PROTEIN IN TWELVE HOURS NIGHT
URINE IN NORMAL CHILDREN (SNOKE)

RANGE	MEAN VALUE	STANDARD DEVIATION	
Casts 0-29000	1230	3900	95 per cent. under 9000. All were hyaline or granular.
R.B.C. 0-800000	8600	116300	Above 600000 suspicious.
Protein 5-90 mgm.	28.5 mgm.	13.2 mgm.	95 per cent. under 55 mgm. 55 mgm. suggested as upper limit of normal.

Scope of enquiry

For the purpose of this investigation, all the children who had been in the general wards of this hospital with nephritis at any stage of the disease since 1934 and a few unselected cases from 1933 were requested to report to the hospital. Out of a hundred and forty-eight such cases, a hundred and twenty (eighty-one per cent.) reported. These were subjected to a general clinical examination, including measurement of blood pressure, and the mother was given typed instructions for the collection of a twelve hours' specimen of urine for examination by the Addis method.

The albuminuria was estimated by the Kjeldahl method since it had been found in the examination of the urine in cases of acute haemorrhagic nephritis with gross haematuria and albuminuria that the method of Shevky and Stafford as modified (Peters and Van Slyke, 1932) and used by Addis and Snoke, gave results which were considerably higher than those given by the Kjeldahl method. In any case in which the albuminuria was near the upper limit of normal it was estimated by both methods and the results obtained by the method of Stafford and Shevky were accepted in order that the results should be comparable with those of Snoke and other workers. At least two specimens were examined. The urines were usually satisfactory as regards volume, specific gravity (above 1020) and acidity to litmus. If two such specimens could not be collected at home, either the child was admitted to the ward for twenty-four hours or the case was discarded. If the first showed an obvious abnormality, a second specimen was not always examined. If one specimen was normal and one was abnormal, the renal lesion was considered to be active at the time of the abnormal specimen. If either specimen was suspicious, further examinations were made, if possible, until a definitely abnormal result was obtained. It is possible that the number of cases that were actually in the latent stage was higher than the figures show, as Snoke considers that consistently normal results over at least a year are necessary before the child can be regarded as cured. No result was considered abnormal because of an excess of white blood cells, epithelial cells or casts alone. The majority of cases in the latent stage excreted an excess of red blood corpuscles, a few had albuminuria and haematuria, and a few had albuminuria only. I can confirm Snoke's statement

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that in the presence of heavy albuminuria it may be difficult to detect haematuria, and repeated examinations may be necessary before an abnormal count is obtained.

When the urine was found to be abnormal or suspicious, the blood non-protein nitrogen or urea was estimated whenever possible. If the urine was abnormal, but both the blood pressure and non-protein nitrogen were normal, the child was considered to be in the latent stage. If the urine and either the blood pressure or the non-protein nitrogen were abnormal, the child was considered to be in the terminal stage. Only those children who were constantly or frequently in a state of generalized oedema were considered to be in the active stage. The plasma proteins were estimated by the method of Folin and Wu in as many cases as possible.

Clinical features

The latent stage was in most cases characterized by good health and freedom from symptoms, but in a few cases the mother reported that the child's face occasionally became puffy with a cold. Of thirty-eight cases in the latent stage, only five had any subjective symptoms referable to renal disease. Of these, four were known to have had renal disease for more than two years and one for one year and ten months, so that it is possible that they were all passing into the terminal stage of renal failure. These five children, together with five out of six who were found to be in the terminal stage complained of recurrent attacks of headache, nausea and vomiting in the mornings. The attacks varied in frequency from once weekly to once in several months. In some cases they were migrainous in character and when the vomiting was over the child felt perfectly well and attended school in the afternoon.

None of the children in the terminal stage was free from symptoms. Five suffered from recurrent attacks of morning vomiting and headache, two complained of tiredness which was worst in the mornings, and one had recurrent abdominal pain without vomiting. All except one, however, were attending school, and this one had severe renal failure which caused her death eight weeks after the onset of symptoms.

The four children who were in the active stage were all oedematous either constantly or with short periods of freedom. Three were free from symptoms apart from the oedema, and the remaining case, who was approaching renal failure, complained of headaches and lassitude in the mornings.

These findings confirm the general impression that in children with chronic nephritis, subjective ill health does not occur until renal failure is advanced. It is therefore not advisable to place much reliance on the presence or absence of symptoms in assessing the state of the kidneys.

Results and discussion

The plasma proteins in the various stages of nephritis.

The plasma proteins were estimated by the method of Folin and Wu in as many cases as possible. The results were as follows :

TYPE OF CASE	NO. OF CASES	PLASMA ALBUMIN (GM. PER CENT.)		PLASMA GLOBULIN (GM. PER CENT.)		TOTAL PROTEIN (GM. PER CENT.)	
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Healed or normal control	5	3.10-4.4	3.68	2.52-3.28	2.81	5.87-7.58	6.58
Latent ..	16	1.95-4.23	3.12	1.56-3.34	2.57	4.30-6.90	5.70
Active ..	4	1.47-2.82	1.91	1.51-2.94	1.97	2.98-4.71	3.88
Terminal ..	8	1.82-3.8	3.25	1.44-2.71	2.07	4.14-6.28	5.29

The values for the plasma albumin in the healed and normal cases are slightly below the values given as normal by Rappaport (1935). It is possible that the plasma albumin is easily and frequently depressed in children, especially when the diet is low in first-class protein, as it is in most working-class children.

One child who had completely recovered from acute nephritis was interesting in this respect. On first examination of his blood the following results were obtained—plasma albumin 3.55 gm. per cent., plasma globulin 4.17 gm. per cent., total protein 7.58 gm. per cent. It was found that the child had been on a low protein diet for the three years which had elapsed since his attack of acute glomerular nephritis. The mother was therefore instructed to give him a full diet with one pint of milk and meat or fish daily for six weeks, at the end of which time his blood was re-examined with the following results—plasma albumin 4.4 gm. per cent., plasma globulin 2.52 gm. per cent., total protein 6.92 gm. per cent., showing a rise in plasma albumin and a fall in the globulin.

In the majority of cases in which dietary restrictions had been continued for a long time after the recovery from nephritis, only red meat and occasionally eggs had been withheld, so that close questioning showed that the child had been receiving the usual amount of protein for his age and social position. This case indicates the possible ill-effects of severe dietary restriction even when there is no loss of albumin by albuminuria. In the latent stage about half the cases had plasma proteins within the range shown by the normal cases, and all the cases in which the total proteins were greatly reduced showed persistent albuminuria. All the cases in the active stage showed greatly reduced plasma albumin and total plasma protein values, which is consistent with the heavy albuminuria and oedema found in these cases. This is the only stage of the disease in which a typical and gross deviation from normal was constant. In the terminal stage all except one case had normal plasma albumin, four out of the eight cases examined had normal total protein. The only case with greatly reduced plasma albumin and total protein had persistent heavy albuminuria and occasional slight oedema for several months at least, but was grouped with those in the terminal stage because of nitrogen and phosphorus retention. The absence of correlation between the level of plasma proteins and the occurrence of oedema was striking in some cases, the critical level of total plasma proteins at which oedema developed apparently being between 4.0 gm. per cent. and 5.0 gm. per cent. in most cases. That some other factor must be involved is shown by the following cases which were examined on different

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occasions so that values were obtained when oedema was present and when they were free from oedema.

CASE	OEDEMA PRESENT			OEDEMA ABSENT		
	PLASMA ALBUMIN (GM. PER CENT.)	PLASMA GLOBULIN (GM. PER CENT.)	TOTAL PROTEIN (GM. PER CENT.)	PLASMA ALBUMIN (GM. PER CENT.)	PLASMA GLOBULIN (GM. PER CENT.)	TOTAL PROTEIN (GM. PER CENT.)
O.K. ..	2.0	1.96	3.96	1.82	2.32	4.14
R.T. ..	1.47	1.51	3.98	1.80	4.04	5.84
G.D. ..	2.82	1.53	4.35	3.00	2.20	5.20
C.A. ..	1.77	2.94	4.71	1.55	2.55	4.10
C.C. ..	0.75	2.94	3.69	2.20	2.10	4.30

1. Cases with acute haemorrhagic nephritis at onset.—A hundred and two cases of acute haemorrhagic nephritis have been studied. Of these nine died during the acute stage of various septic complications and not primarily of nephritis. They were therefore discarded. Another five were examined, but satisfactory specimens could not be obtained and they were discarded. Eighty-eight cases remained. Of these three died in the acute stage. Two cases were found to be in the terminal stage with hypertension or nitrogen retention. No case was found to be in, or to have passed through, the active or subacute stage. The remaining cases were examined six months to six years after the onset with the following results :

TIME AFTER ONSET	$\frac{1}{2}$ –1 YR.	1–2 YR.	2–3 YR.	3–4 YR.	4–5 YR.	5–6 YR.
Healed	5*	12†	13‡	10	12	4
Latent	2	14	3	4	2	2
Percentage of total which were healed	70	46	81	71	86	68

In the first two years the percentage of the total which were healed was 51.5. After the first two years the percentage of the total which were healed was 75. It will be seen that after the first two years from the onset the percentage of healed cases does not rise, which supports the statements of K. de Leeuw (1937) and Snoke (1937) that healing rarely occurs, if it has not already done so, after the first two years. Of all the cases seen two years or more after the onset, seventy-five per cent. are healed. It is probable that none of the cases which are in the latent stage two years or more after the onset and only seventy-five per cent. of the cases in the first two years will recover. Of the total eighty-eight cases, the results are as follows :

DEAD IN ACUTE STAGE—3 cases	..	..	..	..	..	3.4 per cent.
IN TERMINAL STAGE—2 cases	..	..	..	..	..	2.3 per cent.
IN LATENT STAGE—28 cases	..	..	..	..	..	32 per cent.
HEALED—56 cases	..	..	..	..	..	64 per cent.
ESTIMATED TOTAL ULTIMATE MORTALITY	..	..	..	..	..	27 per cent.

* 2 suspicious

† 2 suspicious

‡ 1 suspicious.

Previous investigators have given varying reports on the ultimate prognosis in this condition, the severity of the prognosis given largely depending on the methods used to determine whether or not complete healing of the renal condition had occurred. Smellie (1926) reviewed nine cases of acute nephritis six months to eight years after the onset, and found that one had died, apparently of an acute exacerbation of the initial attack, seven appeared normal (77·7 per cent.), and one was apparently in the chronic stage, although the urine was normal. Of thirty-nine cases he reviewed at an average time of sixteen years after the onset, all were symptomatically well. Sixteen were examined. Of these eleven had either raised blood urea and low urea concentration tests or enlarged hearts and raised blood pressure, but it was difficult to assess the significance of these findings in view of the normal urinary findings. Smellie came to the conclusion that the ultimate prognosis in acute nephritis was good when the treatment of the initial attack was efficient, and that the cases of renal failure in adult life were accounted for by subclinical and therefore untreated attacks in childhood. Lyttle and Rosenberg (1929) reported the results of observations on ninety-nine cases which had been followed for several years after the onset of acute nephritis. They were observed in the out-patient department, and regular clinical and routine urine examinations were made. Of seventy-four cases of acute glomerular nephritis, the immediate mortality was 5·4 per cent. and 5·4 per cent. of the cases became chronic. The remaining 89·2 per cent. appeared to be in good health. K. de Leeuw (1937) reported his findings in eighty cases of nephritis which had been seen in the previous seventeen years. Of sixty-nine with an observed initial attack of acute glomerular nephritis, sixty-three or ninety-one per cent. had completely recovered, but a few of these showed 'negligible quantities of albumin or sporadic red blood corpuscles' in the urine, which findings were not considered abnormal. Only one had chronic nephritis, one had orthostatic albuminuria, and one had some form of chronic renal infection. In all these investigations the percentage of cases of acute nephritis which appeared to become chronic was small, and apparently complete recovery occurred in ninety per cent. of the cases in the series of K. de Leeuw and Lyttle and Rosenberg.

Two series of cases have been reported in which the Addis method has been used for the assessment of recovery. Boyle et al. (1937) reported on a series of twenty-five cases which were clinically recovered from acute post-infectious nephritis six months to eight years after the onset. The cases were selected from a series of two hundred and fifty such cases in order to include more than the correct percentage of severe initial attacks with acute cerebral manifestations or prolonged albuminuria. The urine of each case was examined once by the Addis technique. All except one of the cases gave results within the upper limit of normal as defined by Lyttle for children, and the remaining case was found to have a chronic infection of the renal tract. The authors concluded that children who have clinically recovered from acute haemorrhagic nephritis, i.e. have no known symptoms or signs of nephritis and in whom the routine urinalysis is completely negative, do not have subacute or latent nephritis. In the same year Snoke (1937) published the results of a hundred and fifty-four cases which either he or Addis had followed for a period of ten years after the onset. All the cases had been examined at regular intervals clinically, and their urine by the Addis method. No case was considered to be healed unless the urine was consistently normal when examined by the Addis method for at least one year. Briefly his results showed that out of a hundred and three cases with an acute haemorrhagic onset, forty-four (42 per cent.) were healed, fifty-two (50 per cent.) were still active, and seven (6·8 per cent.) had died in advanced renal failure. He estimated that at least 33·3 per cent. would ultimately die of renal failure.

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It is clear that the more stringent the criterion of cure, the worse is the prognosis. The contradiction between the results given by Boyle et al. and by Snoke may be only apparent, since of sixteen cases in the present series which were actually in the latent stage, but in whom clinical and routine urine examination gave normal results, eleven or sixty-nine per cent. gave normal results on one or more occasions when examined by the Addis method. It is therefore possible that if repeated examinations of the urine had been made in the cases reported by Boyle et al., cases of latent nephritis would have been found although clinical and routine urinalysis and one examination by the Addis method gave normal results.

The results of the present series are in general agreement with those of Snoke except that the percentage of healed cases is higher (sixty-four as compared with forty-two per cent.), the percentage of cases in the latent stage is lower (thirty-two as compared with fifty per cent.), and the estimated ultimate mortality, largely based on these figures, is lower (twenty-seven as compared with thirty-three per cent.). This discrepancy may be due to the criterion of cure in this series, which, although more strict than in those in which the urine was not examined by the Addis technique, was not as strict as in Snoke's, repeated examinations over at least one year being impossible. With such repeated examinations some cases appearing normal on two occasions might have been found to be latent. That none of the cases died in advanced renal failure is probably due to the short interval between the initial attack and the period of review, and that no case was found to be in, or to have passed through, the active stage was probably fortuitous, as both Addis (1925) and Snoke (1937) report cases which they have observed to pass into this stage after an acute haemorrhagic onset.

Effect on ultimate prognosis of various factors.

1. SEPTIC FOCI, most commonly enlarged tonsils, were present in sixty-nine cases at the time of onset. Their removal before the child's discharge from the hospital had little, if any, effect on the ultimate prognosis, as shown by the following figures :

Septic foci were present at onset in sixty-nine cases. Now healed forty-four. Now latent twenty-five.

REMOVED WITHIN 3 MONTHS OF ONSET—41 cases.	NOW HEALED	63·5 per cent.
REMOVED 3–12 MONTHS AFTER ONSET—10 cases.	NOW HEALED.	50 per cent.
REMOVED 1–2 YEARS AFTER ONSET—3 cases.	NOW HEALED.	.. 100 per cent.
SEPTIC FOCUS STILL PRESENT—15 cases.	NOW HEALED	.. 67 per cent.

This is difficult to correlate with the general impression and with the statement of Lyttle and Rosenberg (1929) that the persistence or recurrence of infections is the most potent factor in producing chronic nephritis. Perhaps these figures are too small to be reliable. Or the removal of the apparent source of infection may not be enough to protect the individual from small subclinical infections. Kellett (1936) has shown that at the onset of acute haemorrhagic nephritis complement almost completely disappears from the blood, probably due to the premature production of antibody and a reversed anaphylactic reaction by which many, if not all, the cells of the body are injured. In spite of the removal

of the apparent source of infection, small infections of the skin or nasopharynx may occur, sufficient to upset the antigen-antibody balance, thus causing further renal damage. That this may often happen is shown by the case P.R. who was in hospital with acute haemorrhagic nephritis and reported ten months later. Her tonsils had been removed three weeks after the onset. Though she seemed perfectly well, examination of her urine by the Addis method showed haematuria. The mother was therefore instructed to keep her in bed and watch her carefully if she should have a cold or sore throat. Five months later the mother brought a small bottle of urine which was smoky and contained albumin, and stated that the child had had a sore throat two days previously, and had apparently completely recovered, but had passed this urine on her return from school that day. The private doctor examined the urine that evening and daily for a week and reported nothing abnormal. This undoubted, but mild, exacerbation following the sore throat, and in spite of tonsillectomy, would have been missed if the mother had not been watching for it. The removal of septic foci alone does not prevent exacerbations.

2. BED AND DIETARY TREATMENT.—The cases have been grouped according to the duration of bed treatment and dietary restriction during the acute attack. Results were as follows :

IN BED LESS THAN 6 WEEKS—21 cases.	HEALED	..	..	67 per cent.
IN BED 6–12 WEEKS—27 cases.	HEALED	..	..	74 per cent.
IN BED 12 WEEKS OR MORE—29 cases.	HEALED	..	..	65.5 per cent.
LOW PROTEIN DIET LESS THAN 6 WEEKS—21 cases.	HEALED	..	..	75 per cent.
LOW PROTEIN DIET 6–12 WEEKS—23 cases.	HEALED	..	..	65 per cent.
LOW PROTEIN DIET 12 WEEKS OR MORE—39 cases.	HEALED	..	..	61.5 per cent.

The length of bed treatment and dietary restriction are usually proportional to the severity of the attack, but do not seem to have any significant effect on the ultimate prognosis. When the cases are grouped according to the severity of the initial attack the same result is shown.

3. TYPE OF INITIAL ATTACK

ACUTE FOCAL—21 cases.	HEALED	..	..	..	67 per cent.
ACUTE DIFFUSE. MILD—27 cases.	HEALED	..	..	..	74 per cent.
ACUTE DIFFUSE. MODERATE—28 cases.	HEALED	..	..	..	64.5 per cent.
ACUTE DIFFUSE. SEVERE—7 cases.	HEALED	..	..	..	57 per cent.

In view of the small number of cases which had severe initial attacks, the fall in the percentage of cured cases is probably not significant. These conclusions are in agreement with those of Lyttle and Rosenberg (1929) and of Snoke (1937), all of whom concluded that the liability of the disease to become chronic is not proportional to the severity of the initial attack.

2. Cases with subacute, or acute tubular onset.—Fourteen children have been admitted to hospital in the last four years in the active or subacute stage of nephritis with no history of acute glomerular nephritis. Six of them have died in the active stage with or without a superimposed infection, and one died at home five and a half years after the onset. The actual mortality has thus been fifty per cent. Of the remaining seven, none are normal. Five are latent and apparently in good health, but with excess of either red blood corpuscles or protein in the urine. Two of these have had pneumococcal peritonitis

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since the onset of the nephritis. Four of them having had nephritis for more than two years are unlikely to recover. The remaining two are still in the active stage. The ultimate mortality will be seventy-nine per cent. even if these two patients and the two who have been latent for less than two years after the apparent onset recover.

These results again give a worse prognosis than those of Lyttle and Rosenberg (1929) in whom the urine was not examined by the Addis method. They reported that of twenty-five cases of acute glomerulo-tubular or acute tubular nephritis, the immediate mortality was twenty-eight per cent. and another twenty per cent. became chronic, the remaining fifty-two per cent. being apparently normal. The results of the present series are in fairly close agreement with those of Snoke (1937) who found that of fourteen cases first seen in the degenerative stage with no history of acute haemorrhagic nephritis, one had recovered, one was in the latent stage, two were still in the degenerative stage and six (forty-two per cent.) were dead of renal failure.

That children can remain in apparently good health for many years after the active stage and yet ultimately pass into the terminal stage is shown by a case O.K., not included in the above figures, because she was first admitted before the period of this review.

She was in this hospital eight years ago with subacute nephritis. After several months she apparently recovered and attended school for eight years. She then had an attack of cramps in her hands and feet and was examined by a doctor who found albuminuria. A few months later she was readmitted and found to be in the terminal stage with nitrogen and phosphorus retention.

The ultimate prognosis in this type of nephritis is grave. The probable explanation is that these children have already had unnoticed acute glomerular nephritis, so that although the onset of the nephritis appears to be with the onset of the oedema, actually they have had nephritis for some time previously and their kidneys are already seriously damaged when they are first seen.

This was suggested by Parsons (1926) ; since then the evidence has grown much stronger. Lyttle (1933) reported fourteen cases of scarlet fever without symptoms or signs of nephritis, who all showed excess of protein, cells and casts in the urine by Addis counts between the eighth and forty-eighth day of the disease. Gram (1936) found that of eight cases of scarlet fever without manifest nephritis, all excreted excess of red blood cells and casts in the urine at some time during the disease, and concluded that the majority of cases with scarlet fever have latent or, as Snoke would term it, 'micro'-nephritis. Goldring (1931) showed that thirty-eight out of forty-four previously healthy patients with acute lobar pneumonia excreted excess of albumin or formed elements in the urine during the acute stage of the disease. Albuminuria, cylindruria and excess of white and epithelial cells occurred so commonly that he concluded that they indicated only minimal renal damage, but haematuria occurred in sixteen cases and was thought to indicate more serious renal damage.

Thus evidence accumulates of kidney injury in most acute infections, and although the majority are left without serious renal damage, the high mortality in those children who are first seen with subacute or acute tubular nephritis may be due to serious renal damage acquired during a previous infection, or perhaps a series of subclinical attacks. There is a tendency to refer to these

cases as mixed types when they apparently start as pure nephrosis and are later found to have haematuria. I think that they are actually cases of nephritis from the onset, and that their prognosis is that of subacute nephritis.

As Snoke (1937) pointed out, it may be extremely difficult to demonstrate haematuria in the presence of heavy albuminuria. It is generally agreed that cases of nephrosis do not develop renal failure, and there seems to be no reason why they should develop a superimposed nephritis. As Kellett showed, the development of nephritis is probably due to a certain state of resistance of the body to an infection, and is not a local condition apt to develop in previously damaged kidneys.

3. Cases with insidious onset.—Ten children in whom the onset of nephritis was insidious have been followed. The presenting symptom in five cases was malaise, or loss of appetite, in two it was puffiness of the face, and in three there were no symptoms, but albuminuria was discovered in routine examination of the urine during an acute infection (measles, two cases ; scarlet fever, one case). In most cases there was no known preceding infection ; in three cases the albuminuria followed or accompanied scarlet fever, and in two cases measles. In none was there gross haematuria or oedema. In a few there was slight nitrogen retention at the time of the discovery of the renal lesion. Of these ten cases, four are now healed. Of the remaining six, one has been in the active or subacute stage for more than two years, three are in the terminal stage with hypertension, and the remaining three have had the renal disease for three to five years, being still in the latent stage and are unlikely to recover. These results are similar to those of Snoke (1937) who found that of eleven such cases, five had recovered and of the remaining six, one had died and four were unlikely to recover. Such cases, in which the ultimate prognosis is graver than the mild and unimpressive symptoms at the onset indicates, seem to pass into the terminal stage almost unnoticed. These probably include two types : (1) cases which after a mild unnoticed initial attack are already when first examined in the convalescent stage and may recover spontaneously, and (2) cases which, having passed through the initial attack and latent stage unnoticed, are in or approaching the terminal stage when first examined. That they may pass through all the preliminary stages unnoticed is well recognized. Only one such case was found in the present investigation, and she died in the terminal stage three months after the onset of symptoms.

Anaemia

References in the literature to anaemia in nephritis are few. With a view to determining the incidence and degree of anaemia in each stage of nephritis, blood examination was made in as many cases as possible in the present series, and on cases of acute nephritis in the wards during the past nine months. These have been supplemented by any blood counts which have been available on the cases during their previous admissions.

In the acute stage of haemorrhagic nephritis, during the first three weeks of the disease half the blood counts gave a haemoglobin reading below eighty per cent. In the second three weeks twenty-five per cent. of the counts gave haemo-

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globin values below eighty per cent. and the haemoglobin at a later stage was almost invariably about eighty per cent. (fig. 1). Severe anaemia in the acute stage was unusual except in the presence of sepsis or immediately after tonsillectomy. The rise of haemoglobin in the majority without iron medication, although the diet was still restricted, suggests that the slight anaemia in the first three weeks was due to the infection associated with the nephritis rather than to blood loss, a suggestion in keeping with the fact that the colour index was rarely below normal in the first three weeks. In three cases out of seven in which iron was not given and no complication was present, the haemoglobin remained below normal or actually fell after the toxæmia had passed off, the colour index being lower at the end of the period of observations than at the beginning (average 0.86 to average 0.78). This together with the rise in haemoglobin in those patients anaemic in the early stages, who received iron

FIG. 1.—Chart showing haemoglobin of cases of acute nephritis plotted against the day of the disease. Cases with obvious sepsis or recent tonsillectomy have been excluded.

Dots indicate that no iron was being given at the time of the blood examination. X indicates that iron was being given at the time of the blood examination. Solid line is the mean between the crosses and indicates mean course of the cases receiving iron.

medication, suggests that in some cases the loss of blood by the kidneys and the restricted diet is sufficient to cause a mild deficiency anaemia. Mild anaemia (haemoglobin sixty-six to seventy-eight per cent.) was present in all five patients who were examined within a week of tonsillectomy, but recovery was rapid in all except one, in whom a septic focus persisted. In the child in whom sepsis was present at the time of the first examination, anaemia was severe (haemoglobin fifty per cent.).

These results are at variance with those of Gladys Boyd (1937) who stated that secondary anaemia is a constant complication of acute nephritis and is proportional to the blood lost by the kidneys. She found that a diet high in vitamin E, including milk, fruit and vegetables as early as possible after the onset appeared to prevent severe anaemia.

It is difficult to reconcile these apparently contradictory findings except by the suggestion that the cases to which she referred were more severe than most of the cases in this series.

The blood counts of twenty-nine patients completely recovered from acute nephritis, and thirty-six patients still in the latent stage without nitrogen retention or hypertension (table 1) show no evidence of anaemia in the latent stage of nephritis. There was no deviation from normal in those children in whom the nephritis having been latent for more than two years was unlikely to recover completely.

TABLE 1

	HEALED		LATENT	
	RANGE	AVERAGE	RANGE	AVERAGE
Haemoglobin, per cent.	76-98	87	80-104	89
Red blood cells, millions per c.mm. ..	4.5-5.58	5.12	4.5-6.2	5.33
Colour index	0.77-0.97	0.85	0.75-1.05	0.84
Haematocrit, per cent.	32.1-42.1	37	35-47	38.2
Mean corpuscular volume	64.8-81.5 μ^3	72 μ^3	62.5-81 μ^3	72 μ^3

Blood counts in five cases in the subacute or active stage with oedema, but no nitrogen retention or sepsis results were as follows :

	RANGE	AVERAGE
Haemoglobin, per cent.	90-96	91
Red blood cells, millions per c.mm. ..	4.16-5.96	5.33
Colour index	0.76-0.91	0.85
Mean corpuscular volume	65.8-73 μ^3	69.5 μ^3

A Price-Jones curve in a typical case was normal (fig. 2). One child was observed in the active stage of nephritis with oedema and no sepsis and was found to have haemoglobin ninety-eight per cent. and red blood cells 5.8 million per c.mm. About one month later she was readmitted with pneumococcal septicaemia which caused her death twelve days later. On readmission her haemoglobin had fallen to eighty per cent. and it fell rapidly to seventy per cent. before death. These results suggest that anaemia is apparent rather than real in the majority of cases with uncomplicated subacute nephritis, but develops in the presence of sepsis.

Only six children have been examined in the terminal stage of chronic nephritis with either hypertension or nitrogen retention, but blood counts are available for other children with renal failure and renal rickets (table 2). None of the children had obvious sepsis at the time of the blood count, and all had apparently had renal failure for several months or years (table 2).

Anaemia was present in five out of nine cases, severe in three. With one exception it was orthochromic and normocytic. A Price-Jones curve in a typical case was normal (fig. 3). The reticulocyte count was consistently low and the van den Bergh reaction negative. Anaemia was present in only one case (O.K.) with blood urea under 100 mgm. per cent. and was present in all except one of those with blood urea above 100 mgm. per cent., but its severity was not proportional to the degree of nitrogen retention (fig. 4). Neither was the severity

TABLE 2

CASE	HAEMO- GLOBIN PER CENT.	RED BLOOD CELLS, MILL. PER C.MM.	COLOUR INDEX	HAEMA- TOCRIT PER CENT.	MEAN CORP- USCULAR VOLUME	BLOOD UREA MGM. PER CENT.	CA. MGM. PER CENT.	P. MGM. PER CENT.	BLOOD PRESSURE MM. HG.
J.Fen...	110	6.77	0.81	48	$71\mu^3$	26.7 (N.P.N.)	—	—	154/100
B.H. ..	104	5.63	0.92	41.2	$73\mu^3$	44	—	—	120/80
W.J. ..	100	5.41	0.92	42	$77.5\mu^3$	37.5 (N.P.N.)	—	—	156/120
J.F. ..	84	5.20	0.81	34	$65.4\mu^3$	50	—	—	190/150
J.D. ..	80	4.46	0.90	—	—	239	5.8	13.0	—
N.Y. ..	74	4.58	0.81	33	$72\mu^3$	105	—	—	160/110
D.N. ..	74	4.12	0.90	29	$70.5\mu^3$	195	8.1	6.82	104/74
O.K. ..	60	3.80	0.79	26	$68.5\mu^3$	70	8.4	9.04	124/84
C.H. ..	52	3.23	0.81	25	$77.5\mu^3$	179	10.1	5.7	128/110
D.H. ..	52	3.48	0.74	—	—	148	8.95	6.67	100/70

FIG. 2.—Price-Jones curve in case of active or subacute nephritis. RBC 5.5 mill./c.mm. Hb 90 per cent. C.I. 0.82. Mean corp. vol. 69.4μ . Mean diameter 7.0μ $\pm 0.59\mu$. V 8.4 per cent. Microcytosis 0.8 per cent.

FIG. 3.—Price-Jones curve in case (C.H.) of chronic renal failure. RBC 3.23 mill./c.mm. Hb 25 per cent. C.I. 0.81. Mean corp. vol. $77.5\mu^3$. Mean diameter 7.37μ $\pm 0.66\mu$. V 8.4 per cent. Microcytosis 0.8 per cent.

FIG. 4.—Chart showing haemoglobin of cases of chronic nephritis and renal rickets plotted against blood urea or NPN—see table.

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of the anaemia proportional to the degree of hypertension, the depression of the serum calcium or the elevation of the serum phosphorus. Anaemia did not occur with depression of the serum proteins in the cases of nephritis in the active stage of the disease.

These findings do not support the statement of Osgood et al. (1932) that anaemia is so constant in chronic nephritis that it is useful in the differential diagnosis of this condition from hypertensive renal disease in which anaemia rarely occurs. On the other hand, when Mitchell (1930) in reviewing cases of chronic interstitial nephritis, especially when complicated by renal rickets, stated that in practically every instance in which the blood was examined, secondary anaemia was found, he was probably dealing only with severe and late cases similar to those with renal rickets and anaemia in the present series.

The chart (fig. 5), showing the principal findings in a case of chronic nephritis over a period of four and a half months, demonstrates several of the many factors which complicate the study of anaemia in this condition.

FIG. 5.—Chart showing main findings on blood examination in the case O.K., 14 years of age, over a period of 4½ months—see text.

The child is the one (O.K.) previously referred to, who was known to have had subacute nephritis eight years previously, but who had remained in apparent good health and attended school until three months before admission. She then had an attack of tetany and remained at home on a meat-free diet. For two weeks before admission she had a painful swelling behind the right ear. On admission she was pale, slightly puffy, undersized and with no signs of puberty, and had acute mastoiditis. The chief blood findings are shown on the chart. Her serum calcium was 5.9 mgm. per cent., serum phosphorus 10.4 mgm. per cent., and phosphatase 2.4 units. Her urine was dilute and contained red blood corpuscles and 13.8 gm. of protein daily. The albuminuria fell to an

average of 7 gm. daily during the last month in hospital. Three days after admission she had a diuresis of sixty-three ounces daily for three days. At the end of that time her haemoglobin and non-protein nitrogen had risen slightly, but they both fell rapidly to their previous level. A small blood transfusion had no effect on the anaemia. A mastoid operation was performed three weeks after admission and was followed by a slight temporary fall in the haemoglobin and red blood cell count, and rise in the blood non-protein nitrogen. For the next three weeks the mastoid wound was unhealthy with offensive sloughs and much discharge. The child was given three blood transfusions, each of which was followed by a slight rise in the haemoglobin, but in spite of the transfusions the plasma albumin tended to fall and the wound remained unhealthy. By this time her dietary protein had been raised to sixty grammes daily (1 gm. per pound body weight), and she was taking a diet high in vitamin C with added vitamin B. She was then given an additional thirty grammes of protein daily in the form of serum protein prepared in the biochemical laboratory under the direction of Dr. Hickmans. This was followed by an immediate improvement in her general condition and in the mastoid wound, and in a rise of plasma albumin and fall in plasma globulin, the total protein remaining practically stationary. At the same time the blood non-protein nitrogen and haemoglobin began to rise. After ten days of this treatment, an equivalent amount of protosol was substituted for the serum protein. The plasma albumin fell slightly, but the total plasma proteins rose because of a rise in the globulin, the non-protein nitrogen continued to rise, the haemoglobin remained stationary, and it was the opinion of the ward sister and of the house physician that the child did not seem quite so well. She was therefore given the serum protein again, but she was discharged home three days later and took only about fifteen grammes daily for a fortnight. When next seen, her general condition was about the same, the mastoid wound was granulating, but still discharging a little thin sero-pus, the anaemia was improving slowly, and the blood non-protein nitrogen had fallen to below 100 mgm. per cent. The plasma albumin had risen slightly but was still lower than the globulin, and the total plasma proteins were unchanged. She was then given serum protein thirty grammes daily for two weeks. At the end of this time the mastoid wound was about the same, and she complained of anorexia. It was found that the non-protein nitrogen had risen to 146 mgm. per cent. The plasma albumin had fallen slightly, but the total plasma proteins had risen to 5.8 gm. per cent. and the haemoglobin to sixty per cent. In view of the anorexia and rise in non-protein nitrogen, the extra protein was discontinued, and she was given a liberal diet including meat with about sixty grammes of protein daily. After three weeks on this diet her appetite had improved and she felt better, the non-protein nitrogen had fallen to sixty-nine mgm. per cent. the haemoglobin was stationary at sixty per cent., but the red blood cells had risen to 3.8 millions per c.mm. The plasma proteins had fallen to their original low level, and the mastoid wound was still about the same.

The following are the chief points which emerge from this case :

(1) The severity of the anaemia was not proportional to the depression of the plasma proteins or the elevation of the non-protein nitrogen, but it was most severe at the time of severe sepsis and gradually improved as the sepsis cleared up. It is not suggested that sepsis is the only cause of the anaemia in such cases, but it clearly aggravated the anaemia in this case. It was unfortunately not possible to follow the case further, but the rise in the red blood cell count during the last three weeks, which coincided with a marked fall in the

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nitrogen retention, suggests that the high non-protein nitrogen also had had a depressing effect on the bone marrow. In view of the renal failure this child is unlikely ever to be free from anaemia, even in the complete absence of sepsis. The administration of iron had no apparent effect on the course of the anaemia.

(2) The first administration of serum protein was accompanied by a marked and rapid rise in plasma albumin and improvement in general condition ; its continued administration only maintained the same level of plasma albumin, but caused a gradual rise in total plasma proteins, a good effect counterbalanced by a rise in non-protein nitrogen. In such a case, unusual in its combination of gross albuminuria with severe nitrogen retention, sufficient serum protein to replenish plasma proteins can probably not be administered without increasing the nitrogen retention. The quick initial response of the plasma proteins to feeding with serum proteins, followed by the later gradual response, resembles the findings by Weech and Goetsch (1938) in dogs to whom they fed serum protein after prolonged depletion of plasma proteins, and may be due, as they suggest, to the slow recovery of the organ—probably the liver—which is responsible for the regeneration of plasma albumin. The less marked improvement in general condition when the equivalent amount of protein was administered as protosol, and the return to the abnormal albumin : globulin ratio, appear in the light of later developments to have been fortuitous only, or due to the increasing nitrogen retention.

Summary

Prognosis.—A hundred and twenty cases of nephritis which had been in the Children's Hospital, Birmingham, were examined, and were grouped into healed, latent, active, or terminal cases according to the urinary findings and blood chemistry. Those in the latent stage were usually free from symptoms with normal blood chemistry, but a few exceptions were noted. There was no change in the plasma proteins which could be considered typical of any one stage of the disease, but they were abnormal in all the cases in the active or subacute stage.

Eighty-eight cases of acute haemorrhagic nephritis who were first admitted in the initial attack, have been examined six months to five years after the onset. The mortality in the acute attack was 3·4 per cent. Two cases were found to be in the terminal stage with hypertension. Thirty-two per cent. of the cases were in the latent stage, and sixty-four per cent. were healed. The estimated ultimate mortality was twenty-seven per cent.

The liability of the disease to become chronic was not affected by the removal of the apparent focus of infection, usually infected tonsils, in the acute stage of the disease nor was it related to the severity of the initial attack, nor to the length of bed or dietary treatment in the initial attack.

Fourteen cases who were first seen in the active or subacute stage of nephritis were examined. The actual mortality was fifty per cent. and the probable ultimate mortality was at least seventy-nine per cent.

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Ten cases of nephritis with insidious onset have been examined. Four have recovered and the remaining six are unlikely to recover.

Anaemia.—Cases in the initial acute attack, healed, latent, active and terminal stages have been investigated for anaemia.

In the acute initial attack the anaemia was slight, tended to recover spontaneously, and was probably due to the infection associated with nephritis. In a few cases there was evidence of mild hypochromic anaemia, probably due to a combination of haematuria and restricted diet.

No anaemia was found in the latent stage of nephritis.

No anaemia was found in the subacute or active stage of nephritis except in the presence of sepsis.

In the terminal stage, anaemia was found to be a late complication and was nearly always accompanied by marked nitrogen retention. It was orthochromic and normocytic with no evidence of haemolysis. One case is discussed in detail.

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