IDIOPATHIC RENAL ACIDOSIS IN INFANCY

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The present paper describes the clinical picture, the biochemical disorder and the natural history of idiopathic renal acidosis in infancy.

This condition is due to the kidneys failing to regulate the acid-base balance of the body by excreting a sufficiently acid urine. This results in a metabolic acidosis with a urine which is weakly acid or alkaline instead of strongly acid as would be expected. The adjective 'idiopathic' is added to distinguish this condition from the acidosis of patients with chronic nephritis.

The term renal acidosis was used by Hartmann (1939) who described this condition in an infant. He was the first to ascribe it to a disturbance of kidney function. The cases described by Lightwood (1935) under the title of 'nephrocalcinosis infantum' were almost certainly the same condition. German pathologists (Glaserfeld, 1907; Kühn, 1918) had previously described in detail the deposition of calcium in the kidneys of infants, but Lightwood (1935) studied the history of six infants who were found at necropsy to have renal calcification without any detectable cause for their fatal illness and noticed a striking similarity in the clinical picture. He suggested that this was a definite clinical entity. The following year Lightwood, Maclagan and Williams (1936) described an infant with 'persistent acidosis' who had no radiological evidence of renal calcification, and, because of the similarity of the clinical picture to that of infants with nephrocalcinosis, they thought that it might be the same condition. They failed, however, to incriminate the kidneys for the persistent acidosis although they found an alkaline urine in the presence of a low plasma total carbon dioxide content. The infant recovered from his illness. A few months later Butler, Wilson and Farber (1936) described four infants with severe acidosis during life and renal calcification at necropsy. The urine was said to be acid in three but in the fourth the reaction was not mentioned.

Several workers have described similar cases. Most of these (Powell, 1949; Cooke and Kleeman,

1950; Kelsey, Reinhart and Fishel, 1950; Latner and Burnard, 1950; Engel, 1951; Hutchison and Macdonald, 1951) had a weakly acid or alkaline urine in the presence of a marked acidosis, while the other authors either did not mention the reaction of the urine at all (Israels, Muth and Zeavin, 1949) or only recorded it after the onset of the treatment with alkalis (Boutourline-Young, 1949; Peterman, 1945; Stapleton, 1949). Their remaining clinical and laboratory findings suggested, however, that the diagnosis of idiopathic acidosis was correct. It is possible that some of the cases of nephrocalcinosis attributed to overdosage of vitamin D (Putschar, 1929; Thatcher, 1936) were in reality examples of idiopathic renal acidosis.

The demonstration of renal calcification during life or at necropsy cannot be accepted as a reliable criterion for the diagnosis, for there are many causes of renal calcification in infants (Kühn, 1918; Anderson, 1939; Macgregor, 1948) and in adults (Kühn, 1918; Greenspan, 1949). Albright, Burnett, Parson, Reifstein and Roos (1946) and Albright, Consolazio, Coombs, Sulkowitch and Talbott (1940) suggested that the deposition of calcium salts in patients with renal acidosis was only a secondary phenomenon. The diagnosis of renal acidosis should, therefore, only be made by appropriate biochemical findings during life. The present description is based on the study of nine infants suffering from this condition who were admitted to the Professorial Unit of the Sheffield Children's Hospital between August, 1949, and December, 1950.

Material

In all nine infants included in the present study the diagnosis of renal acidosis was established by estimating the plasma and urine total carbon dioxide content. The diagnosis was made by the detection of measurable quantities of bicarbonate in the urine when the total carbon dioxide content was low. The reaction of the urine was not therefore as low as would be expected from the degree of acidosis present.

The figures for the nine infants when the diagnosis was made were:

	Case No.								
	1	2	3	4	5	6	7	8	9
Plasma total carbon dioxide content (mM per litre) ..	12	9	19	19	16	18	10	5	9
Urine total carbon dioxide content (mM per litre) ..	8	5	12.5	15	15	24	12.5	13	9

This range of urine total carbon dioxide content corresponds to a pH of approximately 6.4 or higher. One infant (Case 4) had evidence of impairment of renal function in addition to that concerned with the regulation of the acid-base balance.

Seven of these infants have been followed up for 15 to 30 months after the onset of the symptoms attributed to renal acidosis. Two died during the course of their illness. In one the immediate cause of death was gastro-enteritis and in the other asphyxia from aspiration of gastric contents after a feed.

Methods

The total carbon dioxide content of plasma and urine was estimated with the Van Slyke apparatus. Blood was put under paraffin immediately after collection and urine was either collected by catheterization under paraffin or if collected by spontaneous voiding the collecting tube contained paraffin. In all clearances two or more periods of urine collection were used and the urine was collected through an indwelling catheter. A detailed description of the methods used for the clearances of endogenous creatinine and of inulin is given elsewhere (Doxiadis and Goldfinch, 1952). Serum sodium, chloride, calcium, phosphorus and alkaline phosphatase and urine ammonia were estimated with standard laboratory procedures.

History

Family History. There was nothing in the family history of any of the nine infants which seemed to be related to their present illness. Three were first children, four second children, one third and one eighth child.

Antenatal and Neonatal History. The mothers of all infants had a normal pregnancy. The birth weight varied from 6 lb. 10 oz. to 7 lb. 12 oz. There were no difficulties during delivery or in the neonatal period.

Growth and Development. The development of all infants appeared to have been normal before the onset of their illness. All of them had been weighed shortly before the onset of the symptoms and their weight was within the range expected from their birth weight.

Mode of Onset and Age at Onset. Refusal of

feeds, vomiting or constipation were the main initial complaints. (Constipation in this paper means not only infrequent motions but also hard faeces.) Of these, the first two were more reliable for assessing the time of onset because constipation was present in two infants (Cases 1, 8) for three months before the occurrence of any other symptom and while the general condition and growth were satisfactory. It is doubtful, therefore, if in these two cases the constipation marked the onset of the renal acidosis.

If refusal of feeds or vomiting without any discoverable cause is accepted as the onset of renal acidosis the age of these infants at the onset varied from 1 to 5½ months.

Course before Recognition and Treatment. The time between the onset of the symptoms and the final confirmation of the diagnosis by biochemical methods varied between two weeks and five months. In only three infants (Cases 3, 6, 9) were vomiting and refusal of feeds present from the beginning. In seven refusal of feeds was present from the beginning while the remaining two continued to take their feeds without difficulty. In these two, however, the interval between the onset of symptoms and diagnosis was two and four weeks respectively (Cases 1 and 8). Vomiting was an initial symptom in five infants and in another (Case 2) it occurred only when he was forced to take his feeds. In the remaining three (Cases 4, 5, 7) it occurred one to three months after the onset of the symptoms. The vomiting was never projectile. It occurred after some of the feeds and it was usually one big vomit rather than many small ones. In two infants constipation, as mentioned above, preceded the onset of any other symptom by three months. When the other symptoms indicating the onset of renal acidosis occurred the constipation continued without any appreciable difference. In five other infants constipation was among the initial symptoms and in two (Cases 3 and 7) it developed a month later.

The general condition of seven infants deteriorated markedly when the symptoms appeared. They became listless and disinterested in their surroundings. They looked ill and tended to become ashen grey, especially after vomiting. The experienced mother whose eighth child was affected (Case 2) said that the infant looked at times so ill that she thought he was going to die. The onset of all these symptoms and manifestations was gradual, and the severity varied from day to day. On the whole, however, they tended to increase in severity. Of the two infants whose general condition was not markedly affected, in one (Case 8) the duration of the symptoms was short while in the other (Case 4) the preceding urinary tract infection and the ensuing

evidence of additional renal damage raise doubts as to the exact time of onset of the renal acidosis.

All infants ceased to gain weight satisfactorily after the onset of their illness. The two infants whose illness began at 1 month and 2 months (Cases 6 and 5) had gained only 5 lb. in the first six months of their life. In the remaining seven, whose illness began at or after the fifth month, the weight before any treatment had been given was either the same as or appreciably lower than their highest recorded weight. In one infant (Case 7) there was a loss of 2 lb. 10 oz. in 14 weeks. In three infants (Cases 2, 4, 6) there were reliable weight records for part of the course of their illness before diagnosis was made and treatment given. There was not during that period a steady loss or a persistent failure to put on weight but a succession of quite large gains, up to 12 oz. in one week followed by an equally large loss or by a longer period of loss of weight. Usually these fluctuations coincided with periods of clinical improvement and deterioration. There was no history of excessive thirst in eight infants. For the ninth it was doubtful whether thirst was present or not.

Preceding or Associated Urinary Tract Infection. During the interval between the onset of symptoms and establishment of a final diagnosis an infection of the urinary tract had been suspected in three infants (Cases 2, 4, 5) because of the presence of moderate numbers of white blood cells in the urine. In one (Case 4) the diagnosis was confirmed by repeated bacteriological examinations. A mixed growth of *Bact. coli* and coagulase-positive *Staphylococcus aureus* was obtained. The infection did not respond to a course of streptomycin and sulphadiazine but cleared up after a course of aureomycin. At that time the plasma total carbon dioxide content was normal. The symptoms of refusal of feeds and vomiting persisted and three months later the diagnosis of renal acidosis was made. Another infant (Case 5) had once only 16 white blood cells per high power field and a feeble growth of coliforms in the urine (catheter specimen). The infection cleared up after a course of sulphadimidine but the symptoms persisted and two weeks later the diagnosis of renal acidosis was made. The third infant (Case 2) had once 28 white blood cells per high power field in his urine but these disappeared before any treatment was given, and without any bacteriological confirmation of the presence of a urinary tract infection. The symptoms however, persisted and the diagnosis of renal acidosis was made. In another infant (Case 9) a urinary tract infection was suspected and bacteriologically confirmed (*Bact. coli*—catheter specimen) at the time when the diagnosis of renal acidosis was

made. The infant died shortly afterwards from aspiration of vomitus before the treatment with antibiotics had cleared the infection. Finally 6-16 white blood cells per high power field were found in the urine of one infant (Case 8) when the diagnosis of renal acidosis was confirmed. Bacteriological examination of the urine was not done at that time but five days later a culture showed the presence of *Proteus* and *Bact. coli*. The infection was successfully treated with streptomycin and chloramphenicol.

Preceding Sulphonamide Medication. It has been suggested (Engel, 1951; Greenspan, 1949) that sulphonamide medication may be one of the causes of renal acidosis. Particular attention was given to any history of administration of sulphonamides. In five infants of this series sulphonamides had not been given at any time before or after the onset of their symptoms. One (Case 7) had a four-day course shortly after the onset of the first symptoms. The three infants (Cases 2, 4, 5) who had a suspected or a proved urinary tract infection had received a course of sulphonamides. Two of them received this treatment while attending this hospital and before the diagnosis of renal acidosis was made. It was known in one (Case 4) that at that time there were no biochemical changes suggesting renal acidosis. In the other (Case 2), however, it cannot be stated with certainty whether the administration of sulphonamides preceded the appearance of the biochemical changes. The clinical symptoms had appeared before the course of sulphonamides but it may be argued that these symptoms were due to the urinary tract infection. The third infant (Case 5) had a course one month before the diagnosis was made but 10 weeks after the onset of the symptoms.

Treatment

As the aetiology of this form of renal acidosis is not known, the treatment was of necessity symptomatic and it consisted of the administration of alkalis. With the exception of Cases 1 and 2 who were given M/6 sodium lactate for six and three weeks respectively in the early stages of their illness, all infants in the present series received sodium citrate, while potassium citrate was added to the sodium citrate at a later stage of this study. Citrate salts were chosen in preference to lactate salts because the latter are usually available in a racemic form and only part of the amount given is metabolized (Hartmann, Perley, Basman, Nelson and Asher, 1938). Sodium citrate has been used by previous authors usually in the form of Shohl's*

* This is usually referred to as Albright's mixture, because Albright (Albright *et al.*, 1940) used it first in cases of renal acidosis. This mixture, however, was first suggested by Shohl (1937) for the treatment of rickets and the citric acid was added to facilitate absorption of calcium from the intestine.

mixture. The addition of citric acid was not considered, however, to be essential in this type of acidosis, and it was not used in the present study. The addition of the potassium salt to the sodium salt at a later stage of this study was the result of the recent advances in our knowledge of potassium metabolism in various disorders. It was thought that prolonged administration of sodium alone to patients who had been and still were acidotic might lead to large losses of potassium and replacement of the intracellular cation by sodium.

The initial dose of sodium citrate or sodium and potassium citrate was 5 g. If both were given together the ratio was approximately 2 : 1. In five infants this dose was later increased, the greatest daily dose not exceeding 10 g. of sodium or 10 g. of sodium and potassium citrate. The daily dose divided into five equal parts was given before, after or in the feed dissolved in 1-2 oz. of water.

Administration of alkalis started within 10 days of the confirmation of the diagnosis with the exception of one infant (Case 6) in which it was delayed in order to assess the effect of a course of 'eucortone'.

In six of the seven infants who survived administration of alkalis was stopped when they were clinically well, and their weight had been increasing satisfactorily for two to four months. In the seventh infant (Case 6) treatment was stopped although the weight gain was not satisfactory, because it was thought that other factors were responsible for the poor weight gain.

In addition to the alkalis all infants received 30 drops of 'adexolin' and 50 mg. of ascorbic acid daily. Two infants received a course of injections of 'eucortone', one (Case 3) at the same time as the alkali and the other (Case 6) before the onset of the alkali treatment.

Course

The most relevant biochemical findings, the weight and the treatment of the first eight cases are shown in Tables 1-8. Case 9 died shortly after the diagnosis was confirmed and treatment was started. It is not therefore included in the subsequent description of the course of the illness and of the effects of treatment.

TABLE 1
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 1

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)	Intercurrent Illnesses
1.9.49					11 4		
5.9.49	12	8	141		11 4		
7.9.49	13	13			11 8		
9.9.49	14	11	130		11 6		
13.9.49	22	8	141	92	12 4	Sod. cit. 5	
16.9.49	17	26	147		11 10		
20.9.49	12	31	154		11 15		
21.9.49					12 3		
22.9.49					11 8		
23.9.49	29	3	147		10 15		
27.9.49						M/6 Sod. lac. 200 ml. i.v. daily	Loose stools Gastro-enteritis, parenteral alimen- tation
29.9.49	26	44	150				"
5.10.49	21	16	154				"
9.10.49					11 6		"
10.10.49					11 9		
12.10.49	24.5	24	137		11 10	M/6 Sod. lac. 200 ml. orally daily	
19.10.49		16			12 9		
24.10.49	28	18	134		12 8		
2.11.49	14.5	48	143		13 1		
6.11.49					12 12	Sod. chlor. 1.8	
7.11.49					12 1		
8.11.49					12 14	Sod. cit. 5	
9.11.49					13 8		
10.11.49					13 2		
11.11.49					13 7		
12.11.49					14 12		
15.11.49	28	21	177	113	15 12		
24.11.49	23	19		96	17 4		
8.12.49	14	21	150	93	15 12		
29.12.49	13	32	148	118	15 12		
3.1.50					15 12	Sod. cit. 7.5	Gastro-enteritis
9.1.50	19	36	150	111	19 4		"
6.2.50	17.5	49.5	141	108	20 2		
13.2.50					20 12		
28.2.50	16	4	173	101	21 12	Sod. cit. 5	
13.3.50	17						
11.4.50	19	17	140	102	22 13		
24.4.50					24 4		
9.5.50	14	15	137	96	24 8		
11.7.50	19	0	143	109	25 10		
8.8.50	18				29 2		
25.10.50	15	2	149	105	30 4		
25.7.51	18	0	148	108			
31.10.51							

TABLE 2
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 2

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)
7.9.49					11 12	
14.9.49					12 1	
21.9.49					12 13	
6.10.49	9	5	152		11 10	
9.10.49					11 5	
11.10.49						M/6 Sod. lac. 200 ml. daily orally
13.10.49	17	5	157		11 14	
16.10.49					12 4	
18.10.49	18.5	48	167		12 4	
21.10.49					12 4	
25.10.49	29	16	144		12 8	
1.11.49					11 14	
3.11.49						Sod. cit. 5
4.11.49	14	41			12 4	
6.11.49					12 4	
7.11.49						Sod. cit. 7.5
9.11.49					13 4	
12.11.49					12 8	
14.11.49					12 17	
16.11.49	22	18	157	111	12 8	
26.11.49					13 8	
29.11.49					12 14	Sod. cit. 5
30.11.49	20	32	157		12 14	Sod. chl. 1.5
1.12.49					12 14	Sod. cit. 7.5
16.12.49	14	34	145		14 3	
23.12.49					13 13	
6.1.50	18	56	143	107	14 10	
24.1.50					14 11	Sod. cit. 10
2.2.50					15 4	
3.2.50						Sod. cit. 7.5
17.2.50					15 17	Pot. cit. 2.5
3.3.50					16 1	
31.3.50	18		140	111	18 4	Sod. cit. 5
28.4.50					18 7	Pot. cit. 1.75
12.5.50	15	36	137	106	20 6	Sod. cit. 3.6
4.8.50	19	1	143	106	22 5	Pot. cit. 1.4
27.10.50	15	12	154	113	25 12	
28.9.51	20.5	1	139	97	30 2	

TABLE 3
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 3

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)	Intercurrent Illnesses
27.10.49					12		
31.10.49	19	12.5	150		12 4		
1.11.49					12 1		
2.11.49	23	8	145		12 3	Sod. cit. 5	
3.11.49					12 6		
7.11.49	23	109	154		13 5		
11.11.49					13 1		
12.11.49					13 6		
14.11.49	27	37	167	110	13 7		
20.11.49					13 14	Sod. chlor. 2.75	
21.11.49					13 13		
22.11.49	24	7	163	112	12 12	Sod. cit. 5	
23.11.49					13 4		
30.11.49					14 4		
16.12.49	13	31	147		14 7		
23.12.49					14 7		
28.12.49					14 8	Sod. cit. 7.5	
2.1.50	15	24	140	106	13 8		
5.1.50					13 7		
11.1.50	22	55	140	100	14 4		
15.1.50					13 10		
19.1.50	19	50	172	100	13 12	Sod. cit. 10	
20.1.50					13 12		
27.1.50	21	52	167	108	14 3		
31.1.50					14 5		
2.2.50					13 6	Sod. cit. 7.5	Occasional loose stools
10.2.50	17.5	27	198		13 8	Pot. cit. 2.5	"
28.2.50	24	21	147	104	14 4		"
8.4.50					16 5		Chickenpox
1.5.50	23	34	146	100	15 6		"
9.5.50							"
18.5.50	22	13	149	105	17 5		
7.7.50	22	0	138	92	18 12		
3.11.50	17	0	150	107	24		
21.10.51	27	0	145	100	27 10		

TABLE 4
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 4

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)
25.8.49					12 12	
30.8.49					11 12	
12.9.49					12 4	
22.9.49	24		148		11 10	
23.9.49		5			11 13	
28.10.49	24	32	148		12 2	
14.11.49					12 5	
24.11.49					11 10	
1.12.49	19	15			11	
4.12.49						Sod. cit. 5
8.12.49	13	7	157	108		
12.12.49					11 15	
16.12.49					11 5	
21.12.49					12 8	
22.12.49					12 3	
28.12.49					12 10	
3.1.50	13	14	151	104	12 1	Sod. cit. 7.5
13.1.50					12 8	
20.1.50	31	60	185	935	12 8	Sod. cit. 10
3.2.50					12 4	
8.2.50	17	37	156		12 8	Sod. cit. 7.5
20.2.50	12.5	27	162	99	13 8	Pot. cit. 2.5
7.3.50					13 7	
14.3.50					13 14	
24.3.50					13 14	
18.4.50					14 15	Sod. cit. 3.75
24.4.50	19	28	127	102	15 9	Pot. cit. 1.25
1.5.50					15 12	
30.5.50					17 2	
9.6.50	19	13	150	104	17 7	
9.7.50					17 9	
14.7.50					16 13	
27.7.50					16 8	
5.9.50	19	2	136	101	18 6	
27.2.51	18	0	148	106	22 4	
10.10.51	19	0	141	99	26 6	

TABLE 5
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 5

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)	Intercurrent Illnesses
15.11.49					12 12		
22.11.49					12 12		
29.11.49	16	15			12 7		
1.12.49					12 1		
2.12.49					11 13		
3.12.49					11 14		
4.12.49					11 10		
5.12.49	17	29	148	102	11 14		
10.12.49					12 5	Sod. cit. 5	
15.12.49					12 3		
20.12.49					12 9		
21.12.49	13	32	132	112			
25.12.49					12 6		
31.12.49					12 14	Sod. cit. 7.5	
1.1.50					13 5		
4.1.50					12 10		
5.1.50					13 1		
6.1.50					12 14		
7.1.50					13 4		
12.1.50	16	14	146	109	13 4		Occasional loose motions
17.1.50					13 4		"
18.1.50	15	44	172	113	13 10	Sod. cit. 10	"
19.1.50					13 12		"
20.1.50					13 15		"
22.1.50					13 9		"
23.1.50					13 14		Gastro-enteritis
26.1.50					13 3		"
28.1.50					12 9		Death
29.1.50							

TABLE 6
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 6

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)
14.10.49					11 1	
21.10.49					11 6	
26.10.49					12 5	
2.11.49					12 4	
16.11.49					12 12	
30.11.49					12 12	
7.12.49					12 12	
20.12.49					12 10	
22.12.49	18	24	145		12 10	
24.12.49					12 10	
26.12.49					12 4	
28.12.49					12 10	
31.12.49					12 12	
1.1.50					12 9	
2.1.50	19	2	144	98	12 15	
4.1.50					12 15	
9.1.50					13 2	'Eucortone' 2 ml.
11.1.50	18	3	148	108	13 12	
18.1.50						
20.1.50	19	4	148	111	14 2	
21.1.50						Sod. cit. 5
26.1.50	21	8	139	101	14 5	
3.2.50	14	60	139	96	14 7	
24.2.50	15		137	104	14 13	
10.3.50	20	30	135	102	15 9	Sod. cit. 3.5
14.4.50	20	25			16	
21.4.50					15 9	Pot. cit. 1.5
8.5.50	19	15	136	102	17	
22.6.50					17 4	
25.7.50	24	9	157		17 5	
20.9.50	22	2	143	105	18 2	
20.12.50	19	3	143	105	19 10	
27.6.51	21	0	138	104	21 8	
15.2.52					25 1	

TABLE 7
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 7

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight (lb. oz.)	Alkalis (g./day)	Intercurrent Illnesses
8.2.50					11 6		
15.2.50					11 10		
21.2.50	10	12.5			11 5		
25.2.50					11 9		
1.3.50	27	13.5	203	99	11 10		
2.3.50					11 12	Sod. cit. 3.5	
7.3.50					12 8	Pot. cit. 1.5	
8.3.50					11 15		
9.3.50	21	12	153	118	12 3		
10.3.50					11 12		
11.3.50					12 6		
15.3.50					12 6		
17.3.50					11 12		
19.3.50					12 3		
22.3.50	17	29	141	112	11 8		
26.3.50							
27.3.50		10				M/6 Sod. lact.	Gastro-enteritis
28.3.50		18				200 ml. alternate	"
29.3.50		17				days intravenously	"
3.4.50	12	15	158	101	12 4		"
5.4.50					12 5		
10.4.50					13 5	Sod. cit. 3.5	
12.4.50	14	12	157	109		Pot. cit. 1.5	
14.4.50					12 6		
17.4.50					13		
25.4.50					13 1		
2.5.50					13 8		
16.5.50					14 9		
31.5.50	20	60	150	103	15		
5.7.50	21	42	138	107	16		
29.8.50	13	2	146	103	18 4		
1.11.50	24	3	142	104	19 9		
28.10.51	27	1	145	103	26 7		
20.11.51					26 5		

TABLE 8
BIOCHEMICAL FINDINGS, WEIGHT AND TREATMENT IN CASE 8

Date	Plasma CO ₂ (mM/l.)	Urine CO ₂ (mM/l.)	Serum Sodium (mM/l.)	Serum Chloride (mM/l.)	Weight lb. oz.	Alkalis (g./day)	Intercurrent Illnesses
21.12.50	5	13		120	12 14		
26.12.50					13 3		
31.12.50					12 12		
1.1.51					13 2		
2.1.51					12 13		
3.1.51					13 5		
4.1.51	10	8	140	115	12 14	Sod. cit. 3.5	Urinary tract
5.1.51					12 14	Pot. cit. 1.5	" [infection
6.1.51					12 11		"
8.1.51							Gastro-enteritis
9.1.51							"
10.1.51						I.V. therapy, blood-	"
11.1.51					13 8	plasma M/6	"
15.1.51	11	11	146	110	13 12	Sod. lact.	"
18.1.51						Sod. cit. 3.5	
20.1.51					13 10	Pot. cit. 1.5	
22.1.51			149		14 1	Sod. cit. 3.5	
31.1.51	13	8	148	111	14 1	Pot. cit. 1.5	
5.2.51					14 4		
12.2.51			143		14 12		
20.2.51					16 5		
7.3.51					17 14		
20.3.51	22	13	150	110	18 11	Sod. cit. 2.75	
						Pot. cit. 1.25	
3.4.51					19 2		
17.4.51	23	2	147	108	19 10		
19.9.51	25.2	1	148	103	24 9		
27.11.51					26		

Physical Condition

When the first physical examination took place in this hospital the symptoms had already lasted from two weeks to three months. At that time no infant appeared to be really well, although in some it was difficult to give the reason for this impression. All had an anxious and apprehensive expression and pallor or an unhealthy greyish colour. There were no signs of dehydration in five and doubtful signs in three. One (Case 3) was moderately dehydrated. Seven appeared to be thin, with evidence of recent loss of weight. In three (Cases 1, 8, 9) hard faeces were palpable in the descending colon. The degree of severity of their condition was not related to the duration of symptoms or to the level of the total carbon dioxide content of their plasma.

The general condition of all the infants showed some improvement in the first few days after admission and before alkalis were given. Feeds were taken more easily than one would have expected from the history. The infant who was moderately dehydrated on admission (Case 3) had partly rehydrated himself before treatment by taking adequate fluids by mouth. It is likely that the improvement after admission was due to the change from the feeding in a tense atmosphere by a very anxious mother to the different attitude of an experienced nurse.

The onset of treatment with sodium and potassium citrate had no striking effect on the general condition of the infants with the exception of the above

mentioned infant (Case 3) in whom the improvement, already apparent before treatment was begun, was accelerated. In another infant (Case 4) it was noticed that the appetite improved when sodium citrate was given.

On the whole and over long periods of time the general condition of the infants was closely related to the weight curve. On individual days, however, there was sometimes considerable discrepancy between the two, losses or gains of 8 oz. in 24 hours not being associated with any change in the clinical condition. There was sometimes a recurrence or exacerbation of the vomiting and of the refusal of feeds. When this recurrence was not due to an intercurrent infection it usually lasted for three to five days and it subsided without any change in the treatment or diet. All the infants had, even during their good periods, capricious appetites and very skilled nursing was required to overcome this difficulty.

In the seven surviving infants when administration of alkalis was stopped no change in their condition was noticed and their progress continued uninterrupted.

Weight. As a result perhaps of better food intake, the weight of five infants was already increasing between the time of admission and the onset of treatment. With the exception, however, of one infant (Case 6), this interval was short. Similar short periods of weight gain were known to have occurred even before admission. In the first 10

days after the onset of treatment the weight increased in seven of the eight adequately treated infants, while in the eighth (Case 7) there was a gain followed by a loss so that at the end of 10 days the weight was the same as when treatment started. In four of the five who had gained weight in the immediate pre-treatment period the rate of gain was more rapid after treatment and in one it was the same.

The initial favourable response of the weight to the administration of alkalis was not consistent for the whole of the treatment period. In only two infants (Cases 1 and 8) was the weight curve similar to that of a normal, thriving infant, allowance being made for intercurrent illnesses. These two infants had the shortest duration of symptoms before treatment was given. In the remaining six infants, the weight curve showed sudden and unexplained fluctuations or remained for long periods at the same level in the absence of any intercurrent illness. On the whole, however, the weight increased and after treatment was discontinued the rate of gain was satisfactory in all.

In two infants (Cases 1 and 3) sodium chloride instead of sodium citrate was given for 48 hours. In both cases the effect was quite alarming. The infants looked ill and dehydrated, vomited copiously and lost 1 lb. in weight.

Increase of the initial dose of 5 g. of sodium citrate to 7.5 g. and to 10 g. in two infants (Cases 2 and 5) resulted in a rapid but temporary weight increase. The same change did not seem to influence the weight curve of two other infants appreciably (Cases 3 and 4).

Two infants (Cases 1 and 5) received only sodium salts (lactate and citrate) during the whole of their illness but in two others (Cases 2 and 6) the replacement of part of the sodium citrate by potassium citrate was made while the infant was gaining weight slowly and no difference was seen. In two other infants (Cases 3 and 4) this replacement took place while their weight was either falling or had been stationary for a long period. The change coincided in both with the onset of a new period of weight gain. Finally in two infants (Cases 7 and 8) both potassium citrate and sodium citrate were given from the beginning. The impression has been gained that the course of the illness of these two infants was less stormy and less unpredictable and that the weight gain tended to become constant earlier after the onset of treatment than in the remaining infants. There are so many factors which influence the course, however, that it is impossible to reach a final conclusion.

Two infants received a course of 'eucortone', one (Case 6) before and one (Case 3) during administration of sodium citrate. The weight and the

general condition were not influenced by this course.

Biochemical Findings. In addition to the estimation of the total carbon dioxide content of plasma and urine, the serum sodium, chloride, calcium, phosphorus and alkaline phosphatase were also estimated at various intervals during the course of the illness.

The serum sodium was estimated in eight infants before the onset of treatment, but in one (Case 7) the value was so high that an error in the estimation cannot be excluded. In the remaining seven infants the serum sodium level was within normal limits or slightly raised. As it is mainly sodium which determines the total concentration of cations, it may be concluded that this and the osmolality of the extracellular fluid in general is not altered in renal acidosis.

There was a definite rise of the serum sodium to abnormal levels in three of the infants (Cases 1, 2, 3) when sodium citrate was given. The serum sodium level rose again later in these and in two other infants (Cases 4 and 5). These high levels sometimes followed an increase in the dose of alkali. The high levels were not associated with either an abnormal increase in weight or with any change in the clinical condition. The rise in the serum sodium level did not lead to any change in treatment and the high figures became normal again later.

The initial response of the plasma total carbon dioxide content to the administration of alkalis was not the same in all infants. Of the four with a very low initial value (12 mM per litre or less), there was a definite rise in two (Cases 1 and 2), in one (Case 8) the rise which had started after admission continued when treatment was given and in the fourth (Case 7) the plasma total carbon dioxide content had reached normal levels before alkalis were given. In the remaining four infants with initial values between 16 and 19 mM per litre there was either no change or a very slight rise or fall. Later in the course of the illness the plasma total carbon dioxide content remained on the whole either around the 20 mM per litre level or just below it. In only one infant (Case 8) was there a steady rise from the initial value of 5 to 25 mM per litre.

After the initial period values of the total carbon dioxide content of the order of 18 to 20 mM per litre were compatible with a good general condition and satisfactory weight gain. The increase in the dose of the sodium citrate was usually followed by a rise of the plasma total carbon dioxide content but this was not marked nor was it maintained. When the citrate salt or the citrate mixture was eventually discontinued the plasma total carbon dioxide content did not fall. In four of the eight infants

there was some relation between the rise of the plasma total carbon dioxide content and the rise of the serum sodium level and this was particularly noticeable immediately after the onset of the treatment in one of them (Case 8). In four infants this relationship was not noted.

The serum chloride was estimated before the onset of treatment in five infants. In only one infant (Case 8) was the chloride level definitely raised.

During the course of the disease the serum chloride level usually varied between 100 and 110 mM per litre, slightly exceeding the level of 110 only once or twice in each infant. These values fall within the normal range for this age (Overman, Etteldorf, Bass and Horn, 1951). There was occasionally an inverse relation to changes of the plasma total carbon dioxide content. In one infant (Case 8) this relation was very marked, so that although the values for these two ions changed considerably from the first to the last estimation their sum remained remarkably constant.

The initial values of the total carbon dioxide content of the urine, which were high in relation to the low plasma total carbon dioxide content and constituted the main criterion for the diagnosis of renal acidosis, have already been presented. In the subsequent course of the disease similar high values were repeatedly observed in all infants, thus confirming the initial diagnosis. It must be emphasized that these values are considered as high only in relation to the low plasma total carbon dioxide content when this is estimated at the same time, indicating the inability of the kidney to form a urine sufficiently acid for that degree of acidosis. For example, in all infants there were occasions when the total carbon dioxide content of the urine exceeded 15 or 20 mM per litre while the plasma total carbon dioxide content was at or below the level of 20 mM per litre.

With the onset of the treatment the urine total carbon dioxide content increased even further in five infants. In four of the five this effect became obvious not at the first but at the second estimation which was made one week or longer after the onset of treatment. It must be noted, however, that these estimations were made on isolated specimens of urine and minor variations may not be significant. In the five infants in whom the dose of the alkali was increased during the course of the illness the total carbon dioxide content rose. Study of the levels of the plasma and the urine total carbon dioxide content and the dosage of alkali in Tables 1-8 suggests that at the time of each estimation there is a level of the plasma total carbon dioxide content which cannot be exceeded and most of the administered base is excreted in the urine, thereby sustaining

or increasing the already relatively high urine total carbon dioxide content. When the administration of alkali was discontinued the urine total carbon dioxide content fell and remained low, as one would have expected from the plasma total carbon dioxide content, thus confirming the clinical impression gained that the child had recovered.

The serum calcium was estimated in only one infant (Case 8) before the onset of treatment. It was slightly low (8.8 mg. per 100 ml.) and it rose during the administration of sodium and potassium citrate and remained at the same level after the treatment had been discontinued. In all the remaining infants the values for serum calcium during and after treatment were mostly within normal limits or so slightly outside the normal range that the deviations were of no significance.

The serum inorganic phosphorus was estimated in four infants before the onset of treatment and levels found to be within the normal range for their age (Cases 5, 6, 7 and 8). In these and in the remaining four infants the values during and after administration of citrates were within normal limits, with a slight tendency to remain above the average. A few values exceeding 7 mg. per 100 ml. were recorded but these were too isolated to be of significance.

The serum alkaline phosphatase was normal in the four infants (Cases 5, 6, 7, 8) in whom it was estimated before treatment. In one of these (Case 7) and in the remaining four infants the values during and after treatment were mostly within normal limits. Occasional high values were found but they were not constant. In two infants (Cases 6 and 8) with a normal initial value there was a rise later in three and four consecutive estimations and finally a return to normal levels. In only one infant (Case 1) was the serum alkaline phosphatase level persistently elevated during and after treatment in the absence of any clinical or radiological evidence of rickets.

The ammonia content of the urine was estimated in most of the specimens obtained for estimation of the total carbon dioxide content. The variations in each infant were great and had no relation to the urine total carbon dioxide content or to any other factor. It is likely therefore that contamination and formation of ammonia after the urine was passed was not avoided. In one case, however (Case 8), particular precautions were taken to minimize this risk and it is thought that the results are reliable. The values in this infant varied from 7.4 (January 15, 1950) to 18 mM per litre (April 17, 1951). They were not therefore unduly low for that range of urinary acidity.

Urine Specific Gravity. The specific gravity of the urine after fluid had been withdrawn for eight to 15 hours was estimated in four infants before

citrates were given and in all of them during or after treatment. Values of over 1010 were obtained in all cases. In the six infants (Cases 1, 2, 3, 4, 7, 8) in whom the specific gravity of the urine was estimated more than once it was found to be above 1010 in all stages of the disease. The specific gravity of the urine of 22 infants whose renal function was normal was also determined under similar conditions of fluid withdrawal, and the range of the values obtained from these controls was the same as that of the infants suffering from renal acidosis.

Formed Elements in the Urine. The presence in some infants of urinary tract infection has been mentioned above. A striking finding in the microscopical examination of the urine was the presence of spherical vacuolated cells, presumably renal epithelial cells. Their significance could not be properly evaluated when other signs of infection of the urinary tract were present.

In three infants, however (Cases 1, 3, 7), moderate to great numbers of these cells were present in the urinary deposit on more than one occasion in the first few weeks of observation. There was no sign of infection of the urinary tract in these infants. These cells were only present in a few specimens of urine examined during that period. In another infant (Case 2), in whom a urinary tract infection had been suspected but excluded, these cells subsequently appeared in the urine.

Radiological Examination. There was no radiological evidence of renal calcification either at the time of diagnosis or at the time of the last examination in the seven infants who survived. In the two infants who died, radiological examination 14 and four days before death did not reveal calcification but at necropsy deposits of calcium salts were found in the kidneys.

In six infants radiological examination of the long bones at the onset and later in the course of the illness showed no abnormality. One infant (Case 3) had a slight degree of generalized osteoporosis at the first examination, but later the radiological appearance of the bones returned to normal. Finally, two infants had definite rachitic changes in the wrists. One (Case 4) had these changes three months before the diagnosis of renal acidosis was made and while the total carbon dioxide content of plasma and urine were within normal limits. When the biochemical changes of renal acidosis were found, however, the radiographs of the wrists indicated that the rickets had healed. The other infant (Case 8) had rachitic changes at the time of the diagnosis of renal acidosis and the rickets had healed five months later.

Other Investigations. Estimations of the urea clearance were done four to seven times during the

course of their illness in the seven infants who survived and once in one of the two infants who died. In six the values (corrected for surface area) fell within normal limits. In one (Case 3) after an initial low figure of 18% of the average normal, the following values were observed: 75%, 46%, 63%, 66%, 35% and 28%. The last two low values were obtained when all the other biochemical findings had returned to normal, and the child's general condition was satisfactory. The blood urea was 39 mg. per 100 ml. at the time. In one infant (Case 4) the first estimation of the blood urea was done three months after the confirmation of the diagnosis of renal acidosis and it was then 130 mg. per 100 ml. The values remained high (see Appendix). In this infant the values for urea clearance (corrected for surface area) were as follows: February 20, 1950, 18.5%; June 9, 38%; September 5, 47%; February 27, 1951, 48% of the average normal. In the last estimation (October 10) the values for urea clearance of the four collection periods were 41%, 83%, 77% and 59% of the average normal. In the last three collection periods, however, very high urine values were attained (7.02, 11.1 and 6.6 ml./min./1.73 sq.m.) and it is doubtful whether the values can be relied upon.

Numerous estimations of endogenous creatinine clearance were also performed during the course of the illness. Subsequent experience, however, (Doxiadis and Goldfinch, 1952) has convinced us that the clearance of the endogenous creatinine is not an accurate measure of the glomerular filtration rate and therefore no more details are given here.

Inulin clearance tests were performed on four infants but only after there had been complete clinical recovery from their illness and when there was no longer any biochemical evidence of renal acidosis. In three of them (Cases 2, 6, 8) the average inulin clearance exceeded 100 ml./min./1.73 sq.m., thus falling within normal limits. In the fourth (Case 4), in whom there was already evidence of renal dysfunction other than renal acidosis, the average inulin clearance of four collection periods was 81 ml./min./1.73 sq.m. It is likely, therefore, that in this infant there was some renal lesion affecting more than one of the functions of the kidney. The disorder which caused the picture of renal acidosis subsided, but the glomerular lesion persisted, causing the raised blood urea and the reduced glomerular filtration rate.

Last Examination

At the time of writing 15 to 30 months have passed since the onset of the symptoms in the seven surviving infants and 10 to 21 months since treatment with alkalis was discontinued.

The growth of all seven infants is satisfactory and their weight is within normal limits for their age. On physical examination no abnormality is detectable. Radiological examination does not show any calcification in the kidneys or any rachitic or porotic changes in the bones. The plasma total carbon dioxide content is 19 mM per litre or more and the urine is acid with a pH of 6.1 or less and it does not therefore contain significant amounts of bicarbonate. Values of serum calcium and phosphorus are within normal limits. The alkaline phosphatase is normal in six infants, while in one (Case 1) it is definitely raised. The specific gravity of the urine is above 1010 in all infants and there are no formed elements.

In one infant (Case 4) the blood urea is still slightly raised (50 mg. per 100 ml.) and the inulin clearance is reduced.

Cause of Death and Necropsy Findings

In one infant (Case 5) the immediate cause of death was gastro-enteritis. There can be little doubt, however, that the renal defect and the ensuing metabolic disorder made recovery much more difficult than in an otherwise normal infant. In the other infant (Case 9) the immediate cause of death was inhalation of the stomach contents, which were vomited immediately after a feed. In this case again the debilitated condition of the infant due to the metabolic disorder increased the risk of such an event. The histological changes in the kidneys of these two infants are described by Dr. J. L. Emery. The rest of the necropsy report is summarized in the Appendix.

Case 5. The glomeruli showed normal vascularity and membranes. A few involuting glomeruli were present but in normal numbers for the age of the child. The proximal tubular cells almost completely filled the tubules and showed no gross abnormalities. The cell cytoplasm in the distal tubules stained considerably less deeply than in the proximal tubules. The cells were smaller and the lumen correspondingly larger than that of the proximal tubules. No abnormality was seen in the loops or in the collecting tubules other than some slight dilatation. Many foci of calcification were present, situated almost entirely in the deepest part of the medulla, namely next to the cortex. The foci appeared to be outside and beside dilated and distorted tubules which appeared to be tubules of the loops of Henle. No inflammatory lesions and no gross vascular lesions were seen.

Case 9. The glomeruli appeared normal. Involuting forms were present but in normal numbers. The appearance of the convoluted tubules was very like that of Case 5, the proximal tubules probably being normal while the distal ones were pale. There were, however, a number of dilated tubules containing acellular colloidal material (hyaline casts). The tubules which were involved did not appear to be all distal ones or collecting

tubules but were proximal and distal tubules in about equal numbers. There were many foci of calcification, chiefly in the deeper layers of the papilli and in the cortical medullary zone. The lesions appeared to be beside dilated distorted tubules and did not involve primarily the tubular epithelial cells. No inflammatory foci were seen. The blood vessels showed no gross abnormality and there did not appear to be an increase in connective tissue.

Discussion

Diagnosis. The diagnosis of renal acidosis was suspected when an infant in whom there was no evidence of infection or mismanagement of the feeding started to refuse his feeds or vomit and he failed to gain weight satisfactorily. The diagnosis was, however, confirmed only by estimating the plasma and the urine total carbon dioxide content and by finding that the urine total carbon dioxide content was too high and therefore that the urine was not sufficiently acid for the degree of acidosis shown by the plasma total carbon dioxide content. Payne (1948) considered that the presence of 'an alkaline urine with persistent acidosis is a point of diagnostic value'.

It is difficult to decide what degree of urinary acidity to expect in an infant without renal disorder in relation to the degree of acidosis present. Pitts, Ayer and Schiess (1949) have shown that in adults when the plasma bicarbonate is below 24 mM per litre only minute amounts of bicarbonate appear in the urine. Similar experiments have not been done in infants. Estimation, however, of the plasma total carbon dioxide content and simultaneously or within a short period of time of the urine pH has been made by Hoffman, Parmelee and Grossman (1948) and by Branning (1942) in premature infants whose renal function was presumably normal. Simultaneous estimation of the plasma total carbon dioxide content and of the pH of the urine was also made in this hospital on nine patients with normal renal function, aged 3 weeks to 23 months, using the same methods as those used for the infants with renal acidosis. With values of plasma total carbon dioxide content varying from 16 to 25.9 mM per litre (Hoffman *et al.*, 1948), or 9 to 16 mM per litre (Branning, 1942) or 20.6 to 25 mM per litre (own controls) the urine pH was 5.75 or lower. At such a range of pH in the urine only negligible quantities of bicarbonate are present. Infants with normal renal function form therefore a urine of a pH well below 6 and as low as 4.8 when the plasma total carbon dioxide content is below 26 mM per litre. In the nine infants with renal acidosis the plasma total carbon dioxide content was between 5 and 19 mM per litre, while simultaneously collected specimens of urine had a total carbon

dioxide content of 5 to 25 mM per litre corresponding to a pH of 6.4 or higher. Three of the infants had plasma total carbon dioxide contents which may be within normal limits (18 and 19 mM per litre) for their age. Their urine was not however, sufficiently acid and it is this discrepancy and not the absolute values of their plasma total carbon dioxide content which confirmed the diagnosis. It is suggested that such a discrepancy alone justifies the diagnosis of renal acidosis. As a working rule, it may be taken that a plasma total carbon dioxide content below 20 mM per litre with a urine containing measurable amounts of total carbon dioxide content (more than 1 to 2 mM per litre) or having a pH above 6 makes the diagnosis very likely.

Aetiology. In none of the infants of this study nor in any case previously reported with the exception of that reported by Engel (1951) has there been any family history of the complaint. Engel excluded familial disease because the x-ray examination of the kidney region of other members of the family did not show any calcification.

The role of infection of the urinary tract in the aetiology of renal acidosis is obscure, but this possibility should be borne in mind. In five of the nine infants of this series an infection of the urinary tract had been suspected. In only one infant (Case 4), however, did a proved urinary tract infection precede the development of the biochemical changes characteristic of renal acidosis. This was also the only infant in whom the blood urea level was persistently raised and this elevation persists many months after the renal acidosis subsided. Of the remaining four infants, in two the diagnosis of urinary tract infection was not confirmed bacteriologically and in two it was discovered just before or at the time of the establishment of the diagnosis of renal acidosis. It is not, therefore, certain that the infection preceded the renal lesion. It is difficult to assess the incidence of infection in most of the previous reports as there is either no mention that the urine was bacteriologically examined (Butler *et al.*, 1936; Engel, 1951, Case 2; Hartmann, 1939; Hutchison and Macdonald, 1951, Cases 1 and 2; Kelsey *et al.*, 1950, Case 2; Stapleton, 1949) or the nature of the specimen from which an organism was grown was not stated (Powell, 1949). However, in one of the two infants studied by Kelsey *et al.*, in two of Latner's and Burnard's (1950) six cases and in the case reported by Peterman (1945) there was undoubted infection of the urinary tract. Even in these cases it is impossible to state either that the infection preceded the development of acidosis or that it was aetiologically significant.

Finally administration of sulphonamides has been suspected as the cause of this condition in some

cases. Engel (1951) thought that a toxic nephritis due to sulphadiazine caused renal acidosis and nephrocalcinosis in one infant and possibly in his sibling. He also stated that six of the seven patients described by him had received sulphonamides. Of the nine infants of this series, five had never received any sulphonamide, while in four a course of sulphonamides (sulphathiazole, sulphadiazine or sulphadimidine) was given after the onset of the symptoms but before the biochemical confirmation of the diagnosis. No toxic effects had been observed during the administration of the drug. Less than half of the previously reported cases had received some sulphonamide, usually after the onset of the symptoms which led to the diagnosis of renal acidosis. Nevertheless in those patients who had received sulphonamides it is difficult altogether to exclude sulphonamide toxicity as a cause of their illness. It should be noted that most of the evidence in favour of such a hypothesis, which has been summarized by Greenspan (1949), refers to the development of nephrocalcinosis. It is likely, however, that calcification of the kidney in renal acidosis is only a secondary phenomenon. The only link connecting sulphonamides to the biochemical disorder of renal acidosis is the demonstration by McChesney, Sprague and Marshall (1941) and by Pitts and Alexander (1945) that administration of sulphanilamide in dogs produced acidosis with an alkaline urine. The latter authors suggest that this is due to the inhibition by sulphanilamide of the action of carbonic anhydrase and therefore to interference with the mechanism of acidification of the urine in the distal tubules. The two main reasons against a similar explanation in the aetiology of idiopathic renal acidosis are the fact that this action of sulphanilamide on the carbonic anhydrase is not shared by other commonly used sulphonamides and the demonstration by Latner and Burnard (1950) that the defect in renal acidosis lies in the proximal and not the distal tubules.

Pathogenesis. Hartmann (1939) was the first to suggest that loss of bicarbonate in the urine leading to severe acidosis was the cause of the syndrome he described. All later authors (Peterman, 1945; Albright *et al.*, 1946; Stapleton, 1949; Kelsey *et al.*, 1950; Latner and Burnard, 1950; Hutchison and Macdonald, 1951) agreed with this suggestion although Albright and his colleagues and Stapleton thought that another explanation might be the failure of the kidneys to form ammonia. This possibility can, however, be rejected, because failure to form ammonia in the absence of other renal defect would lead to loss of fixed base and not to excretion of an alkaline urine. Furthermore, Latner and Burnard (1950) have shown that the

kidneys of the affected infants can form ammonia as well as those of normal infants. The values for ammonia in the urine obtained in Case 8 of this series are in accordance with this finding.

The work of Pitts and his team (Pitts, Ayer and Schiess, 1949) on the reabsorption and excretion of bicarbonate has made possible a clearer understanding of the disorder in renal acidosis. These workers have shown that when the plasma bicarbonate of normal adults is below 24 mM per litre essentially all bicarbonate is reabsorbed by the tubules from the glomerular filtrate. It is not known if this threshold is the same in infants. Even assuming that it is lower and as low as 20 mM per litre, it would not be expected that for values of plasma total carbon dioxide content below this figure any bicarbonate would appear in the urine at all. In all nine infants, however, measurable amounts of urine total carbon dioxide were found when the plasma total carbon dioxide content was below 20 mM per litre, which would mean that the plasma bicarbonate was even lower. This was considered to be the primary defect and it was used as the main criterion for the confirmation of the diagnosis. The fact that the urine total carbon dioxide content and not the bicarbonate has been estimated does not introduce any appreciable error, since the urine $p\text{CO}_2$ may be above 50 mm. Hg only in urines in which the total carbon dioxide content is higher than that found in the urines of the infants of the present series (Pitts *et al.*, 1949). With the present range of values subtraction from the total urine total carbon dioxide content would therefore be small and would not significantly lower its value.

No less important than the values of the plasma and urine total carbon dioxide content before treatment are those obtained during the administration of sodium citrate or of sodium and potassium citrate. As is seen in Tables 1-8, in all infants and on more than one occasion, large amounts of bicarbonate were excreted in the urine while the plasma total carbon dioxide content was still below 20 mM per litre. Similar observations were made in adults suffering from renal acidosis and osteomalacia (Burnett, Burrows and Commons, 1948; Towery, 1951). This persistent disorder provides additional confirmation of the diagnosis in those infants whose initial values may be equivocal, for example, Case 7, and demonstrates again that the essential defect is a lowering of the renal threshold for bicarbonate. Which part of the nephron is the site of the defect it is not possible to say from the present study. There is nothing, however, in this series that is in disagreement with the conclusion of Latner and Burnard (1950) that the proximal tubule is the site of the biochemical disorder. The

previously expressed opinion that the nephrocalcinosis in adults or children is due to a pure lower nephron nephrosis (Greenspan, 1949) or distal tubular dysfunction (Cooke and Kleeman, 1950) is untenable after the elegant demonstration by Latner and Burnard (1950) of the ability of the distal tubules to form both ammonia and an acid urine. Furthermore, one of the reasons for incriminating the distal tubules (Cooke and Kleeman, 1950) was the presence of a low urinary specific gravity. In all the cases of this study, however, the specific gravity of the urine has been within normal limits, demonstrating that a fixed low specific gravity is not one of the essential features of renal acidosis.

It has been shown by Albright *et al.* (1946) and subsequently confirmed by Cooke and Kleeman (1950) and Israels *et al.* (1949) that in renal acidosis administration of an acidifying salt or the intake of an acid-ash diet increases the excretion of calcium in the urine, while administration of an alkalinizing salt reduces it. These observations have been taken to mean that because of the inability of the kidney to form an acid urine there is a drain on the base stores of the body and calcium is mobilized from the bone and excreted in the urine. This excessive amount of calcium in the urine leads to deposition of calcium salts in various parts of the nephron and to nephrocalcinosis. If it is accepted that the nephrocalcinosis is only a secondary manifestation, the result of a renal acidosis of long duration, its absence in the infants of the present series, at any rate to any marked degree, is easily explained. In all infants the disease was recognized and treated a few weeks or at the most five months after its onset. In most of the previously reported cases the disease had been of longer duration. Further evidence in support of the hypothesis that nephrocalcinosis is not one of the main features of the disease is the absence of thirst and polyuria and of a low urine specific gravity in the infants of this series. It is therefore postulated, as suggested by Albright and his colleagues (1946), that all these manifestations of a distal tubular lesion are the result of the nephrocalcinosis and they are therefore absent in the early stages of the disease or during its whole course if nephrocalcinosis does not take place.

Course and Outcome. Two infants died, one from an intercurrent illness and the other from inhalation of vomitus. Although their metabolic disorder contributed to the fatal outcome it was not the main cause of death. Furthermore the histological changes of the kidney were not so severe as to be incompatible with life and perhaps with ultimate recovery. The seven survivors are clinically in excellent condition and they have all

recovered from their renal acidosis, their plasma total carbon dioxide content being normal and their urine acid (pH below 6.1). The only abnormalities are a high serum alkaline phosphatase level in one infant in the absence of clinical and radiological evidence of rickets and a slightly raised blood urea level in the other. The cause of the high alkaline phosphatase level is unknown. The elevation of the blood urea is associated with a reduced glomerular filtration rate. It is likely that both the glomerular lesion and the defect resulting in renal acidosis were due to the same cause, perhaps a pyelonephritis, but the glomerular lesion persists while the renal acidosis has subsided. The defect causing renal acidosis was therefore a self-limiting process in the seven who survived and perhaps it would have been the same in the two infants who died.

The survival of patients with renal acidosis has been reported before, but in most cases the presence of severe nephrocalcinosis demonstrated radiologically makes complete recovery very unlikely (Albright *et al.*, 1946; Engel, 1951; Greenspan, 1949; Payne, 1946; Israels *et al.*, 1949; Powell, 1949; Cooke and Kleeman, 1950). In a few infants calcification was not visible in the radiographs at the time of the publication of these reports (Hutchison and Macdonald, 1951; Kelsey *et al.*, 1950, Case 2; Hartmann, 1939) but the infants were still acidotic and were receiving treatment. Case 1 reported in the paper by Kelsey *et al.* seemed to have made a complete recovery, but values for the acidity of the urine after the end of treatment are not given. Thus, the only other case of renal acidosis in infancy with complete recovery is that described by Stapleton (1949) in this hospital, but in this child the last estimation of the plasma and urine total carbon dioxide content took place only two months after the end of treatment. Through the kindness of Professor R. S. Illingworth I had the opportunity to examine the child reported by Stapleton three years after her illness, at the age of 4 years and 5 months. She was physically very well. She had no polydipsia or polyuria. There was no radiological evidence of nephrocalcinosis, rickets or osteoporosis. The plasma total carbon dioxide content was 23.5 mM per litre and the urine total carbon dioxide content 19.8 mM per litre with a pH of 7.07.

The effect of treatment on the course and outcome of renal acidosis in infancy is not clear. It is certain that the intake of base in the form of sodium and potassium citrate decreased the degree of acidosis and perhaps replaced the previous losses of the main cations. The infants were therefore able to survive the critical period until recovery took place. It may be that nephrocalcinosis was also prevented in this way. The treatment was directed

against the results of the renal defect and there is no reason to believe that it had any effect on the renal defect itself. It is, however, the only treatment likely to help the infant and it should be started immediately the diagnosis is made and continued until the plasma total carbon dioxide content returns to normal and the urine on withdrawal of the alkali becomes acid.

When the food and vitamin D intake are adequate there is no need to add citric acid to the sodium citrate. The addition of potassium citrate is, however, desirable in order to avoid undue losses of this ion and retention of sodium. The clinical impression in the present study has been in favour of adding potassium citrate to the treatment. The arbitrarily chosen dose of 5 g. of citrate salts per day seemed to be adequate. Higher doses resulted usually in excretion of larger amounts of bicarbonate in the urine without a sustained rise of the plasma total carbon dioxide content. If higher doses are to be given, however, both sodium and potassium salts should be used, as excessive amounts of sodium are likely to cause or accentuate potassium deficiency.

It is impossible to say whether all cases of renal acidosis if adequately treated will recover without permanent damage to the kidneys. The fact that previously reported cases (Greenspan, 1949; Cooke and Kleeman, 1950; Albright *et al.*, 1946; Baines, Barclay and Cooke, 1945) still had renal acidosis many years after the onset of their symptoms is against it, unless the development of nephrocalcinosis, which is a secondary phenomenon, tends in some unexplained way to perpetuate the primary renal defect. The uncertainty on this point creates doubts as to whether the condition described in this paper and the established nephrocalcinosis of children and adults are the same entity.

In the literature reviewed I have only been able to find three cases of renal acidosis after infancy without radiologically demonstrable nephrocalcinosis (Cases 23 and 24 of Albright and Reifenstein, 1948, and Case 1 of Pines and Mudge, 1951). In all three the degree of renal acidosis was less than that seen in infants, in that levels of plasma total carbon dioxide content of 25 mM per litre or higher were easily attained on giving alkali. The duration, however, as assessed from the clinical history, was much longer, and perhaps as a result of this the skeletal involvement was severe in spite of the mildness of the renal defect. In the present series the acidosis was more severe, in that the plasma total carbon dioxide content remained low in spite of alkali therapy, but it lasted for a comparatively short time and there was no skeletal involvement. At this stage of our knowledge any

final decision on the identity of the condition in infants and adults is unwarranted.

Conclusion

There exists in infancy a disease characterized by inability of the kidneys to form a sufficiently acid urine to preserve the acid base balance of the body. The inability results in excessive loss of bicarbonate in the urine. Other renal functions are unaffected. The disease is self-limited and spontaneous recovery takes place if intercurrent illnesses do not cause death and if extreme degrees of acidosis are avoided. Alkali therapy assists in the survival during the period of acidosis. It is likely that under certain circumstances and in untreated cases the deposition of calcium salts takes place in the kidneys. Inability of the kidneys to concentrate the urine is then added to the main defect. The relation of this entity to renal acidosis with nephrocalcinosis or nephrolithiasis of adults is still a matter of speculation.

Summary

Nine infants suffering from idiopathic renal acidosis were followed up for 13 to 29 months and the clinical picture, the laboratory findings and the course of the disease have been described.

The presence of renal acidosis was suspected when an infant refused his feeds or vomited and failed to thrive in the absence of any detectable cause.

The diagnosis was confirmed when the plasma total carbon dioxide content was low and the urine alkaline or weakly acid instead of strongly acid. It is suggested that a plasma total carbon dioxide content below 20 mM per litre with a urine of a pH above 6 makes the diagnosis of renal acidosis very likely.

The disorder which resulted in the discrepancy between the plasma bicarbonate and the degree of acidity of the urine was thought to be the primary defect in renal acidosis.

There was no loss of the concentrating capacity of the kidney in the seven survivors and no radiological evidence of nephrocalcinosis.

One infant died from an intercurrent illness and another from inhalation of vomitus. The seven survivors have fully recovered from the renal acidosis, but in one there is still evidence of glomerular damage.

Treatment with alkalis helped the infants during the period of acidosis. The recovery from the main defect was considered, however, to be spontaneous.

It is not possible to decide whether the idiopathic renal acidosis of infants described here and the fully established nephrocalcinosis of older children and adults are the same condition. It is likely that in some cases renal acidosis of the type described precedes the development of nephrocalcinosis.

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APPENDIX

Case 1. This was a boy, the second child of healthy parents. The first child died with convulsions when 1 month old. The patient was born on April 14, 1949. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. 12 oz. The baby was partly breast-fed with complements till the age of 11 weeks, and then completely bottle-fed. No vitamins were added to the diet. He became constipated at the age of 1 month, but his growth was otherwise normal. The highest known weight was 12 lb. 3 oz. at the age of 4 months. At this age he began vomiting and became irritable and restless. The symptoms became progressively worse and the general condition of the child deteriorated. He looked ill, particularly so after a vomit. One week later he was admitted, having lost approximately 1 lb. of weight. On admission he was not dehydrated but there was evidence of recent loss of weight. Hard faeces were filling the colon. There were no other abnormal physical findings. The constipation was relieved with enemata. He continued to vomit one to three times daily and he took his feeds badly. The plasma and urine total carbon dioxide content were then estimated six days after admission and the diagnosis of renal acidosis was made. The initial response to the administration of 5 g. of sodium citrate daily was satisfactory. Seven days later he began to pass loose stools, and in another week he had severe gastro-enteritis. He recovered from the gastro-enteritis after a very stormy course, during which he was on parenteral alimentation for 11 days and was receiving 200 ml. of M/6 sodium lactate daily intravenously. He continued to receive the same amount of sodium lactate orally and later this was changed to 5 g. of sodium citrate. His progress since then has been satisfactory and may be followed on Table 1. There were two further periods of weight loss. The first was due to the substitution of sodium chloride for sodium lactate for 48 hours (November 7-8, 1949); the second was due to another attack of gastro-enteritis (end of December, 1949).

Case 2. This was a boy, the eighth child of healthy parents. The health of the siblings has been good. He was born on April 3, 1949. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. 8 oz. He was breast fed till the age of 4 months. He then began to refuse his feeds and became constipated and listless. He was taken off the breast and a variety of proprietary milks was tried. There was no improvement and he would vomit if forced to take his feeds. Sometimes, especially after a vomit, he looked so ill that his mother thought he was going to die. At the beginning of his illness there were days when the symptoms were much less marked. Later, however, the refusal of feeds and the listlessness became permanent features. One month after the onset of symptoms he was seen at the out-patient clinic for the first time. He was then ill, pale and wasted. His weight on September 7, 1949, was 11 lb. 12 oz., his best weight having been 12 lb. 3 oz. There were no other abnormal physical findings but his urine contained 28 white blood cells per high power field

and when he was brought back on September 14, a course of sulphadimidine was prescribed. The urine of that day was subsequently reported as normal and the diagnosis of urinary tract infection was never confirmed. As a result probably of better feeding technique there was some improvement at the next visit on September 21, but he subsequently deteriorated, lost weight and he was admitted on October 5. The diagnosis of renal acidosis was made the following day. The further course and the response to treatment are illustrated in Table 2.

Case 3. This was a boy, the third child of healthy parents. The health of the two elder siblings and of a subsequently born infant was good. He was born on February 26, 1949. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. The baby was breast fed for three weeks and then on a preparation of dried milk. Vitamins were added in adequate amounts. His general condition and growth were satisfactory until the age of 5½ months when his weight was 14 lb. 4 oz. Then he began to refuse his feeds and to vomit. The onset of these symptoms was gradual and there were days when he would be quite well. His condition deteriorated and he refused to take any solids. One month after the onset of the vomiting he became constipated. At the age of 8 months when he was seen at the out-patient clinic he was wasted and moderately dehydrated and his weight had fallen to 12 lb. He was admitted four days later and the diagnosis of renal acidosis was confirmed. The initial response of the weight to the administration of 5 g. of sodium citrate was very satisfactory. When, however, on November 21, 1949, sodium chloride was substituted for sodium citrate for 48 hours a catastrophic loss of weight occurred, the weight falling by more than 1 lb. within two days. Resumption of sodium citrate restored the normal gain and the infant was discharged on December 17. For a short time the satisfactory progress continued at home, but quite unexpectedly and while still receiving sodium citrate, he began to refuse his feeds and he was readmitted on January 2, 1950, having lost 12 oz. since discharge. The dose of sodium citrate was increased to 7·5 g. and later to 10 g. but twice the weight fell by over 8 oz. in a short time, the second time probably because of a period of loose stools lasting for nearly the whole of February. A new constant rise in weight coincided with the change of the alkali intake from 10 g. of sodium citrate to 7·5 g. of sodium citrate and 2·5 g. of potassium citrate. On this mixture the infant was discharged on March 24, 1950, to be readmitted one month later because of loss of weight following an attack of chickenpox. When gain in weight was resumed administration of alkalis was stopped and progress has since been uninterrupted.

Case 4. This girl was the second child of healthy parents. The older sister has been well. The baby was born on March 12, 1949. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. She was breast fed for six weeks and then on dried milk. Cod liver oil and orange juice were added to the diet. Her progress continued satisfactorily until the age of 4½ months when her weight was 13 lb. 7 oz. Then she

began to refuse her feeds and she became constipated. As these symptoms persisted she was seen two weeks later in the out-patient department. Her weight had fallen to 12 lb. 12 oz. but there was no other abnormality with the exception of the presence in her urine of 5 leucocytes per high power field (catheter specimen). As her mother was over-anxious and tended to force the infant to eat, it was decided to admit the infant to regulate the diet and to enable her to gain weight. She stayed in hospital from August 28 to September 12 and she gained 8 oz. in the period. She was readmitted, however, on September 22 because the refusal of feeds, vomiting and constipation had recurred and the weight had fallen to 11 lb. 10 oz. During her stay in hospital the plasma and urine total carbon dioxide content were estimated twice and the results were not compatible with the diagnosis of renal acidosis. She had, however, a persistent infection of the urinary tract with *Bact. coli*. This eventually cleared up after a course of aureomycin. During the whole of this second period of observation in the wards she was very difficult with her feeds, even after the urinary infection had cleared up. She was taken home by the parents on November 14. The extreme refusal to take feeds continued and the weight fell again so that on December 3 blood and urine were again collected for the estimation of the total carbon dioxide content and this time the diagnosis of renal acidosis was made. Even after the onset of the treatment there were still great fluctuations in the weight but there was a tendency for it to rise. The most spectacular rise followed the substitution of potassium citrate for one fourth of the dose of sodium citrate. Since then, even when treatment was discontinued, her progress has been satisfactory, although for the whole of 1950 she still had periods of refusing food. Vomiting and constipation did not, however, recur. On February 20, 1950, the blood urea level was estimated for the first time. It was 130 mg./100 ml. and it is a matter of considerable regret that this important estimation was not done at an earlier stage in this infant in whom it proved to be important. Subsequent estimations of the blood urea were 130 mg./100 ml. (7.3.50), 132 mg./100 ml. (2.5.50), 92 mg./100 ml. (5.9.50), 70 mg./100 ml. (3.10.50), 56 mg./100 ml. (3.11.50), 48 mg./100 ml. (27.2.51), 50 mg./100 ml. (10.10.51).

The urine contained traces of albumin and spherical epithelial cells for six months after the urinary tract infection but has been clear for the last 18 months. Finally an inulin clearance test performed on October 10, 1951, showed a decrease in the glomerular filtration rate, the average of four successive periods being 81 ml./min/1.73 sq.m. In this case, therefore, although the renal acidosis subsided and although the child is clinically very well there is evidence that there is still some renal damage and the outcome is doubtful.

Case 5. This was a girl, the second child of healthy parents. The health of the sibling is good. The baby was born June 4, 1949. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. 8 oz. She was breast fed until the age of 6 weeks. Then the mother thought that her milk was insufficient and changed to a dried milk. From that time onwards

the baby showed a reluctance to take all the feeds and she became constipated. She continued to gain some weight and her last known weight before the age of 5 months, when she was sent to the hospital for the first time, was 12 lb. 7 oz. A few days before her first attendance she started vomiting and reluctance to take her food increased. She was seen on November 15, 1949. Her weight was then 12 lb. 12 oz., and apart from some wasting and perhaps slight dehydration there were no other abnormal physical signs. The urine contained, however, 16 leucocytes per high power field and on culture a growth of *Bact. coli* was obtained. A course of sulphadimidine was given one week later, but although the urinary infection cleared up, the infant continued to refuse feeds and to vomit and the weight remained stationary. She was admitted on November 29 and the diagnosis of renal acidosis was made the same day. With treatment there was initially some gain in weight. There were, however, large fluctuations, a spectacular rise following increases in the dose of sodium citrate and being followed by catastrophic falls. Unfortunately, the importance of adding a potassium salt to the diet was not at the time realized. In the light of the subsequent experience with other cases it is felt that the addition of potassium salt might have made growth more constant. The infant developed loose motions on January 7, 1950, and severe gastro-enteritis on January 23 and she died six days later. In addition to the histological changes in the kidney the only other notable finding was seen in the liver, which showed extreme fatty changes in the lobules. These changes were attributed to the preceding under-nutrition and gastro-enteritis.

Case 6. This was a girl, the second child of healthy, elderly parents. The much older sibling has been well. The baby was born on June 20, 1949. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. 3 oz. She was breast fed for 10 days, then complementary feeds of dried milk were given until the end of the first month when she was taken off the breast altogether and fed on various brands of dried milk. The first symptoms occurred when she was 1 month old and was taken off the breast. She then began to refuse feeds and to vomit and she became constipated. These symptoms continued with varying intensity until the age of 4 months when she was seen in the out-patient clinic. Her weight was then 11 lb. 1 oz., but, with the exception of slight wasting, there were no abnormal physical findings. She was kept in hospital for eight days but the diagnosis of renal acidosis was not suspected and biochemical investigations were not done. She was seen at frequent intervals in the out-patient clinic but after a great gain in weight following her discharge the weight remained stationary and the refusal of feeds, vomiting and constipation persisted. At the age of 6 months she was admitted for a second time and the diagnosis of renal acidosis was made. Treatment with alkalis was, however, withheld for a whole month because the infant, apart from the failure to gain weight since the last admission was otherwise very well. During this month 2 ml. of 'eucortone' were given daily for 13 days. Both before and during the administration of 'eucortone' the weight increased and the infant was very active and

lively although always difficult with her feeds. The initial discrepancy between the total carbon dioxide content of the plasma and urine on which the diagnosis was based was not found again during that month, so that doubts were entertained as to the validity of the diagnosis. After, however, the daily administration of 5 g. of sodium citrate the total carbon dioxide content of the urine rose again while the total carbon dioxide content of the plasma remained low. This response confirmed the diagnosis beyond any reasonable doubt. Treatment was discontinued during an episode of watery motions, and it was not resumed later because the child's general condition was satisfactory and the plasma total carbon dioxide content above 20 mM per litre. The progress of this child since then has been satisfactory regarding development and absence of any symptoms or signs but the weight gain has been below average and on occasions there is some refusal of feeds but no vomiting or constipation. This is attributed to a behaviour problem which developed at the beginning because of the mother's anxiety and later because of long periods when the mother and child were separated due to the mother's frequent admissions to hospitals for gynaecological operations.

Case 7. This was a girl, the first child of healthy parents. She was born on July 11, 1950. The pregnancy, delivery and neonatal period were normal. The birth weight was 6 lb. 10 oz. The baby was breast fed until the age of 3½ months when her weight was 14 lb. Breast feeding was then complemented with various brands of dried milk. At about the same time she became listless and began to refuse her feeds. The stools were loose at the beginning but one month later she became constipated. Vomiting did not occur until the sixth month. She was then seen in the out-patient clinic. She was not ill but her weight had fallen to 11 lb. 6 oz. She was observed as an out-patient for one month and various changes were made in her diet and the feeding technique. She failed, however, to improve and her weight remained stationary. The diagnosis of renal acidosis was then suspected and on admission at the age of 7 months the diagnosis was confirmed. Even before sodium and potassium citrate were given the plasma total carbon dioxide content rose to normal levels. Subsequent estimations, however, while she was receiving the alkali treatment left no doubt about the diagnosis. The response of the weight to the treatment was not good. Wide fluctuations were observed within short periods of time. On March 26, 1951, she developed gastro-enteritis and M/6 sodium lactate was given intravenously instead of the citrate salts orally. Oral feeding was resumed and alkalis were given by mouth again on April 5, but her weight still showed wide fluctuations although she was clinically very well. She was discharged on April 18 on sodium and potassium citrate and her weight has been increasing steadily since then. Alkalis were stopped in July, 1951, but the rate of weight gain remained unaffected.

Case 8. This was a boy, the first child of healthy

parents. He was born on July 11, 1950. The pregnancy, delivery and neonatal period were normal. The birth weight was 7 lb. He was breast fed for six weeks, then put on a full cream dried milk with adequate additions of cod liver oil and orange juice. He became constipated at the age of 1 month, but he was otherwise well and gaining weight at an average rate of 5 oz. weekly until the age of 4½ months. He then began to vomit all his feeds, though he did not refuse his food. These symptoms continued until he was seen in the out-patient department two weeks later. He did not seem wasted and he was only slightly dehydrated if at all. Masses of hard faeces were felt in the colon. He was suspected of having renal acidosis and the diagnosis was confirmed on admission the following day. The response of the total carbon dioxide content of the plasma and of the weight to the administration of sodium and potassium citrate was most satisfactory in spite of the occurrence of a urinary tract infection and of gastro-enteritis. He recovered quickly from these infections and he has had a continuous satisfactory weight gain without the fluctuations seen in the other infants.

Case 9. This was a boy, the first child of healthy parents. He was born on April 29, 1950. The pregnancy, delivery and neonatal period were normal. Birth weight was 7 lb. He was breast fed for two weeks, then on a half-cream and later on a full cream dried milk with inadequate vitamin supplements. The first symptoms appeared at the age of 5 months when the infant began to refuse his feeds and vomit them and he became constipated. His weight at the time was not known but one month later it was 12 lb. 7 oz. These symptoms were not constant at first but they increased in frequency and severity. His general condition was then affected and he became very listless. Refusal of feeds was never, however, a prominent feature. He was first seen in the out-patient clinic on December 31, 1950, at the age of 8 months and his weight was then 12 lb. 5 oz. He looked obviously small for his age but he was lively and not dehydrated. Hard faecal masses could be felt in the abdomen. The diagnosis of renal acidosis was confirmed the same day and the infant was admitted one week later. The plasma total carbon dioxide content was 14 mM per litre on December 29. Three days after admission he did not look very well, but no abnormal physical signs could be found. He was then given 3·5 g. of sodium citrate and 1·5 g. of potassium citrate and he improved, but on January 3, 1951, a catheter specimen of urine contained albumin, 190 mg./100 ml., leucocytes 15 per high power field and spherical epithelial cells six per high power field. *Bact. coli* was grown in the culture. A course of streptomycin was started the following day, but 24 hours later the infant aspirated his vomitus immediately after a feed and died within a few seconds. The histological changes in the kidneys at necropsy have already been mentioned. The only other significant finding was the inhaled vomitus in the trachea and bronchi.