INFANTILE RENAL ACIDOSIS IN A CHINESE INFANT

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The term "infantile renal acidosis" is an entity in children characterised by anorexia, vomiting, constipation and failure to thrive and biochemically by the presence of a low plasma bicarbonate, a raised plasma chloride and an alkaline urine.

The diagnosis depends on the finding of a urinary PH on the alkaline side of 6.5 in the face of an acidosis in the blood below 40 volumes of carbon dioxide. The condition occurs in children in the first eighteen months of life and the primary fault is failure of the proximal tubules to reabsorb bicarbonate. It is important to diagnose this condition because treatment with alkalis results in the relief of symptoms and after a period of time ranging from a few weeks to many months in apparent cure.

Historically, Albright and his associates published in 1940, one case of hyperchloraemic acidosis in a girl of thirteen with persistent rickets and dwarfism and radiologically there was nephrocalcinosis. Biochemically, there was hyperchloraemia, a low serum bicarbonate, a normal calcium, a low serum phosphorus and a high serum phosphatase. Albright postulated at this stage that this was due to inability to make ammonia or excrete an acid urine due to renal tubular disease, with consequent loss of sodium, potassium and chloride. In 1946, Albright and his associates described further cases of adults with acidosis, nephrocalcinosis and rickets.

Baines, Barclay and Cooke (1945) next described the condition in a 29 year old English woman and this was characterised by a history of colic, polyuria and thirst over a period of nineteen years. There was extensive bilateral renal stones, a raised serum chloride, a low plasma bicarbonate and a fixed specific gravity and PH of the urine. There were no skeletal deformities. With a sodium citrate-citric acid mixture, the patient regained good health and the blood chemistry became approximately normal.

The first series of medullary calcification in children were described by Lightwood (1935) who discovered six of these cases in 850 consecutive autopsies in children at the Great Ormond Street Children's Hospital, London. Reviewing their clinical picture he found that these six cases conformed to a common clinical story with anorexia, vomiting and failure to thrive. The ages of these children varied form 5 to 11 months and all six patients died from intercurrent infection.

Stapleton (1949) explained the disorder as an inability of the tubules to converse base and Latner and Barnard (1950) discovered that the primary fault in idiopathic hyperchloraemic acidosis appears to be faulty absorption of bicarbonate in the proximal tubules.

The next big series of cases were by Lightwood, Payne and Black (1953) who reviewed 35 cases of renal acidosis from the Great Ormond Street Children's Hospital, London over a six year period and in 1954 Carre, Wood and Smallwood reviewed 17 children with a five year follow-up and they reported that this disorder leaves no serious ill-effect. In Singapore no child with infantile renal acidosis has been reported so far and it is possible that the condition is often missed because these infants resemble very closely any child with failure to thrive, due to malnutrition and other causes. Below is a case-report of a Chinese baby with infantile renal acidosis.

CASE-REPORT

S.H.K.N. was a four month old female Chinese baby admitted to the department of Paediatrics because of failure to thrive. The child is the youngest of three children in the family, the other two siblings being normal.

The baby was a full term baby delivered normally, weighing 6 lbs. 12 ozs. at birth. The baby was brought up on full strength Lactogen feeds and the mother remarked that the baby failed to thrive in spite of proper feeding and advice from the infant welfare clinic. The

child was prone to recurrent chest infection and was admitted to the ear, nose and throat department as a case of laryngeal stridor.

A laryngoscopy done at ear, nose, throat department showed that the arytenoids were injected and the epiglottis was inflamed but there was no congenital malformation of the vocal cords. The child was then transferred over to the department of Paediatrics as a case of failure to thrive.

Physical examination revealed an under weight baby weighing seven pounds; the child was toxic, febrile, dehydrated, acidotic, wasted and pale. (Figure 1). The child was extremely hypotonic and there were palpable faecal masses in the abdomen. The heart and lungs were clinically clear and the kidneys were not palpable.

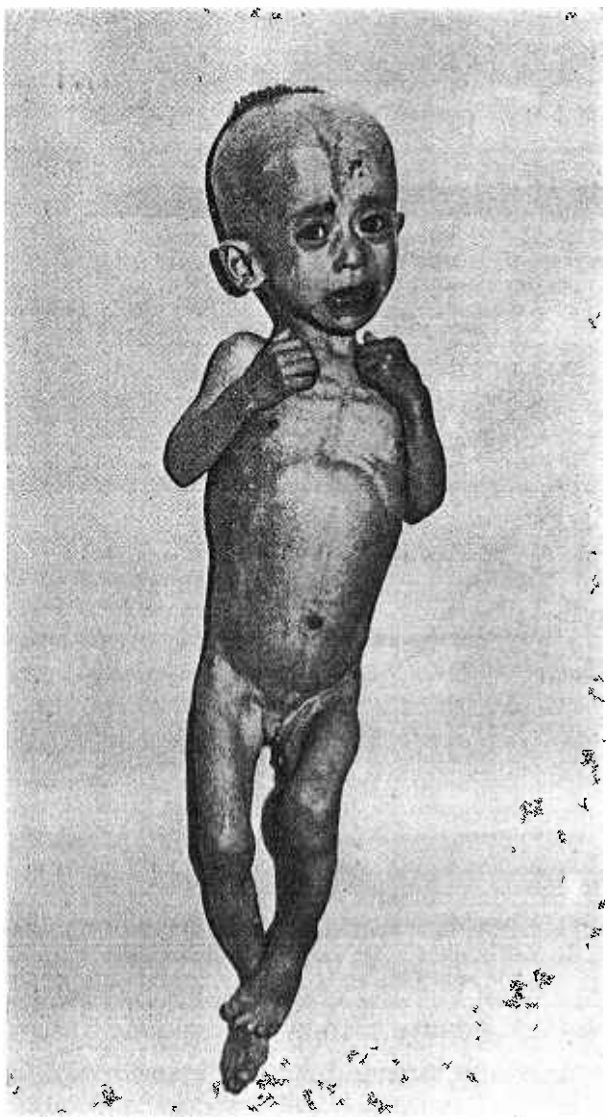


Fig. 1. Note the wasted. marasmic, dehydrated child with sunken eyes.

After an intravenous transfusion of Hartmann's solution and blood, the child improved temporarily and was put on oral milk feeds. However, she vomited all her feeds and became acidotic and dehydrated again. A lumbar puncture done at this stage revealed a normal cerebrospinal fluid with a normal cytology and composition.

As seen in Figure 2 the child had a temperature swinging between 101°F and 103°F and examination of the urine revealed 140 to 150 pus cells per field. At a later date, Bacillus coli was cultured from the urine and the urinary infection finally responded to injections of Penicillin and Streptomycin. Biochemical investigations were done periodically and below is a table of the findings.

As seen in the above table the alkali reserve was persistently low, varying between 18 and 26 volumes of carbon dioxide whilst the reaction of the urine to litmus was alkaline, the PH of the urine being 8.1. In addition, as seen on the table, although the serum sodium and serum potassium were low on admission, being 129 mEq/litre and 3.3. mEq/litre, the serum chloride was high being 116 mEq/litre.

The blood urea was elevated being 55 mgm %. The diagnosis of infantile renal acidosis in this case was quite obvious, with a persistently low alkali reserve, a raised plasma chloride and an alkaline urine. It was not possible to do the PH of the blood at this early stage.

A radiograph of the abdomen did not reveal any calcification of the abdomen, and the intravenous pyelogram was normal.

The child was treated with a mixture of 10% Sodium Citrate with 6% Citric acid, 15 ccs six hourly and gradually there was some improvement. As shown in the above table and Figure 3, there was a rise in the alkali reserve, reaching normal levels of 57 volumes of carbon dioxide at the end of six weeks of treatment.

The pH of the urine which was in the region of 8.4 had dropped to 4.1 by the end of six weeks. The pH of the blood after one month of treatment was normal, being 7.4. The haemoglobin of this patient was in the region of 14.7 Gms %, the high levels being due to haemo concentration due to dehydration.

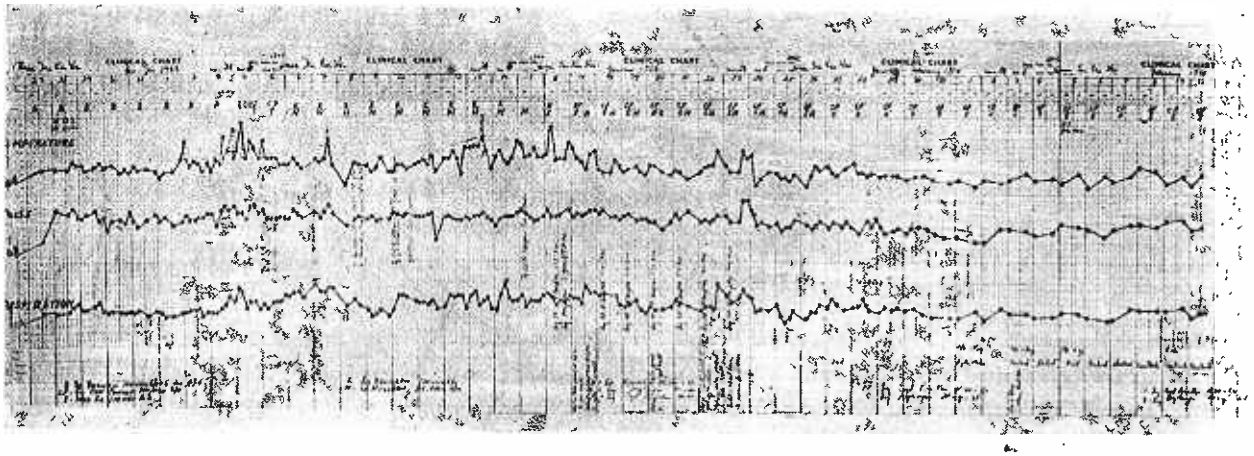


Fig. 2. Note the high swinging temperature of patient which subsided after the administration of Shohl's solution.

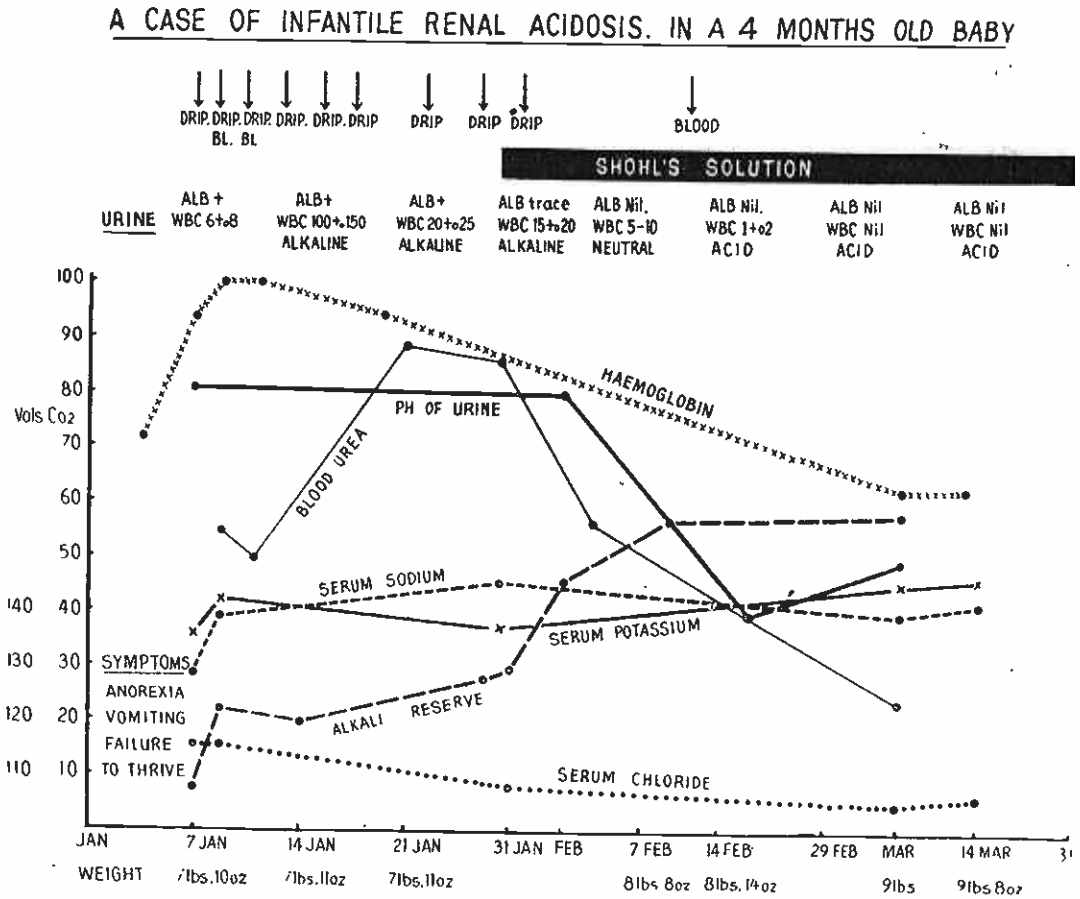


Fig. 3. To show the response of the patient to Shol's solution, note:

(a) the drop in blood urea to normal limits with therapy.

(b) the rise in the alkali reserve to normal limits with therapy.

(c) the drop in the serum chloride to normal levels with therapy.

(d) the weight gain of 2lbs with therapy.

Date	Alkali Reserve Vol. of Co2	Blood Urea (mgm %)	Urine for pus cells per field	Serum Sodium mEq/litre	Serum chloride mEq/litre	Serum Potassium mEq/litre	Weight	Reaction of Urine	PH of Urine	Treatment
7.1.64	18	—	30 - 40	129	116	3.3	7.10	Alkali	8.1	Intravenous therapy
9.1.64	22	55	Numerous	139	116	4.1	7.11	Alkali	—	Intravenous therapy
12.1.64	—	50	100 - 150	—	—	—	7.11	Alkali	8.1	Intravenous therapy
20.1.64	22	87	20 - 25	—	—	—	7.10	Alkali	—	Intravenous therapy
28.1.64	26	86	10 - 15	146	109	4.2	7.11	Alkali	—	Intravenous therapy
4.2.64	46	57	6 - 8	—	—	4.1	8.8	Neutral	4.1	Shohl's Solution
11.2.64	57	—	1 - 2	—	—	—	8.14	Neutral	—	Shohl's Solution
1.3.63	57	24	Nil	140	107	4.7	9.8	Acid	4.1	Shohl's Solution
14.3.64	57	—	Nil	140	107	5.2	9.8	Acid	—	Shol's Solution

With treatment there was a drop in the haemoglobin the anaemia being an iron deficiency anaemia, with the serum iron of 70 mgm %. However with iron therapy and blood, there was a gradual rise in the haemoglobin, as seen in Figure 3. With the continuous administration of Shohl's solution the child was able to retain her feeds and at the end of a month, there was a weight gain of 2 lbs. This child has been followed up for a period of over one month and at present the progress is satisfactory while on Shohl's solution.

DISCUSSION

Among some of the causes of failure to thrive encountered in this country are faulty feeding, malnutrition, recurrent infection and underlying congenital abnormalities.

It is important to recognise this group of biochemical disorders namely infantile renal acidosis. The importance of recognising this condition is because with rehydration and alkalis the condition of infantile renal acidosis can be reversed, which would otherwise have been fatal, probably from intercurrent infection.

The best review of the subject in children is by Lightwood, Payne and Black (1953) where 35 cases were studied at the Hospital for sick children, London from 1946 to 1952. In this review of cases there were 23 males and 12 females. None of the cases in his series showed evidence of consanguity nor was there any proved instance of more than one case occuring in the same family.

The possible aetiological factors have been reviewed by Lightwood, Payne and Black (1953) and by Carre, Wood and Smallwood (1954). The possibility of mercury which is one of the major components of teething powders was investigated into by Lightwood, Payne and Black (1953) and it was found that although mercury in the form of teething powders had been given to some of the cases, no excessive amount of mercury had been administered. Neither was any case associated with a high intake of Vitamin D.

In Carre, Wood and Smallwood's series of 17 cases (1954) 8 of them had been given Milk of Magnesia; however, in a careful enquiry it was found that the symptoms related to the disordered renal function were present even before the onset of the administration of the drug. So that, in short, no definite etiological factors have been found in relation to infantile renal acidosis.

The predominant age group for the onset of symptoms in Lightwood's series of cases was between six to nine months of age. Failure to thrive over a considerable length of time was a constant symptom and often there was loss of weight. However in many patients constipation and vomitting are the commonest early symptoms. These are followed by anorexia, fretfulness and loss of weight. Unlike adult cases where polyuria and thirst were present, in children, polyuria and thirst were rarely noticed by the mother.

Because of the paucity of physical signs, this condition is often missed. Lightwood (1953) states that hypotomia of the skeletal muscles, loss of skin turgor, inelasticity of the skin and hard faecal masses may be palpable. Rickets is not a constant feature and in the cases reported by Lightwood clinical evidence of rickets was seen only in one case. In the Chinese baby reported above there were very few physical signs, except for acidotic breathing, wasting and hypotonia of the muscles.

The urine in the majority of cases reported by Lightwood was alkaline to litmus, the urinary PH being 6.9 to 7.4, while the specific gravity was 1.008.

He reported that the urinary protein may be slightly raised while the miscroscopic deposit may show a few white cells. In the case reported above the pyrexia was initially attributed to a urinary infection due to Bacillus coli, and as seen on the temperature chart (Figure 2) the fever responded to Penicillin and Streptomycin, but the acidosis persisted.

Biochemically in Lightwood's series of cases the plasma bicarbonate was decreased below 40 volumes of carbon dioxide and the plasma chloride was elevated above 110 mEq/litre. The blood urea was commonly elevated while the serum sodium, chloride, alkaline phosphatase and serum protein were normal. The serum calcium was estimated in 20 cases and it was normal in 18 of Lightwood's series. Carre, Wood and Smallwood (1954) found that the serum calcium was high in 5 out of

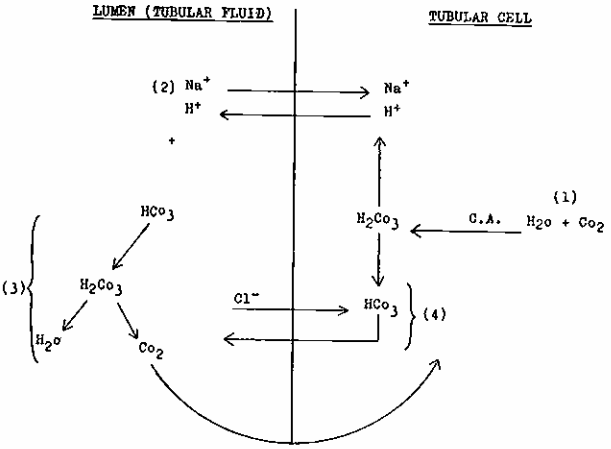
the 17 cases and with treatment with alkalis the values became normal in two cases. However, in the case reported above, the serum calcium was within normal limits. It is interesting to note that in Carre, Wood and Smallwood's cases (1954) in nine cases the average haemoglobin of 60% was found during the course of treatment with alkali. In seven of their cases the drop in haemoglobin occurred over a period of four months while under treatment. The anaemia was a hypochromic anaemia and responded to treatment with oral iron.

In the Chinese baby reported above the child was dehydrated on admission, and the high haemoglobin as seen in Figure 3, could be accounted for by haemo concentration during the period of dehydration. However with oral iron therapy there was a rise in the haemoglobin.

Lightwood, Payne and Black (1953) state that radiology plays an unimportant place in the diagnosis of infantile renal acidosis because the absence of demonstrable nephrocalcinosis does not exclude the diagnosis of infantile renal acidosis. Evidence of radiological calcification was found only in 13 of their 35 cases. The radiological changes described by Lightwood were bilateral and occurred equally on both sides. In the advanced cases described by Lightwood, particulate deposits with a fingerprint appearance were seen in the medullary region, while in less severe cases the calcification was of fine ground glass appearance. The reason put forward for this calcification is due to acidosis which tends to mobilise calcium and therefore increases its concentration in the urine and the alkalinity of the urine which favours precipitation of calcium as the urinary concentration increases during the passage down the tubules.

The differential diagnosis is that of causes of difficult feeding, anorexia, vomiting, failure to thrive and constipation in infants aged six to eighteen months. However difficulties in feeding arising between the child, its food and its mother rarely cause marked illness in the child. Acute or chronic pyelitis is probably the most common cause of difficulty in diagnosis, as the urine frequently yields a positive culture and contains a few white cells. The true state of affairs is shown by a persistent acidosis with a neutral or alkaline urine even after the infection has been cured (Payne 1948). The one condition that can be confused is that of idiopathic hypercalcaemia of infants. In this condition there is no acidosis, an alkaline, acid or neutral urine, raised serum calcium and raised plasma protein in conjunction with the clinical picture of vomiting constipation and failure to thrive. A dense white line will be seen at the epiphyseal junction when the serum calcium has been raised for some time.

Many theories have been put forward to explain the pathogenesis of infantile renal acidosis and it is necessary to understand the normal mechanism of ion exchange in the proximal tubules.



1. First the carbonic anhydrase catalyses the hydration of carbon dioxide in the tubule cell to form carbonic acid which is the source of H and HCo ions.

2. Secondly the H^+ ions pass into the tubular fluid and there is an exchange of Na^+ ions.

3. The H^+ ions combine with HCo_3 to form carbonic acid which in turn breaks to form H_2o and Co_2 which passes back into the cell to start the reaction all over again.

4. More chloride is absorbed back into the cell accounting for the hyperchloraemia.

In infantile renal acidosis there is failure of bicarbonate absorption and less bicarbonate is absorped so that larger amounts are lost in the urine making it more alkaline with less bicarbonate in the blood.

Few hydrogen ions are lost from the cell with resultant acidosis. One of the theories put forward is that of functional immaturity. Rubin et al (1949) have shown that the glomemlus and the tubules mature at different rates. Lightwood postulates that if the ability of the proximal tubules to reabsorb bicarbonate preferentially to chloride and the ability of the distal tubules to secrete hydrogen ions matures later than normal, then an increased output of bicarbonate would occur and account for the acidosis. Such an unbalanced development would account for the delay in appearance of symptoms until the 4th or 6th months and also for the ultimate recovery.

The treatment of infantile renal acidosis consists of the administration of alkalis. Shohl (1937) and Albright (1940) have devised a solution containing 9.8 gms of Sodium and 14 gms of Citric acid in 100 ccs of water. 15 ccs of this mixture four times a day is given and Lightwood et al (1953) claim that satisfactory improvement seldom occurs unless the plasma bicarbornate is kept over 18 mEq/litre. Lightwood, Payne and Black (1953) use two criteria for stopping treatment. First the child should be gaining weight and secondly the plasma bicarbonate should be above 20 mEq/litre for at least three months. The duration of treatment varies with the individual case and the usual period in Lightwood's series was between 9 to 12 months, the shortest being 2 months and the longest being 2 years.

The self-limiting nature of renal acidosis has been assumed from the follow-up studies of individual cases.

Buchanan and Komrower (1958) in a follow-up of renal function in eight children who had renal acidosis has shown that over a period of four-year follow-up there was a complete recovery of the ability to secrete an acid urine, and to form ammonia. The authors therefore conclude that infantile renal acidosis is a different condition from that associated with nephrocelcinosis in older infants and adults and that one does not lead to the other.

However, this does not preclude the possibility that milder cases escaping diagnosis in infancy may not present in later childhood with irreparable renal damage.

Carre, Wood and Smallwood (1954) reviewed 17 cases of infantile renal acidosis from the Birmingham Children's Hospital during the five year period from February 1948 to February 1953 and was able to assess their long term prognosis. In 13 patients treatment with alkalis has been discontinued from 4 to $4\frac{1}{2}$ years. Their results show that the children appear well and show no biochemical abnormality.

Physical development has been satisfactory although the average weight was still below normal.

Their observations confirm the suggestion that the condition is a self-limiting process and that recovery probably complete is likely to follow if these infants can be tided over the phase of disordered renal function.

SUMMARY

1. One case of infantile renal acidosis in a 4 month old baby is described. The clinical presentation of the case was that of failure to thrive, vomiting and anorexia. Physically she showed wasting, dehydration and acidosis and biochemically had a low alkali reserve, a raised blood urea, hyperchloraemia and an alkaline urine. She responded to a mixture of Sodium Citrate and Citric acid.

2. A review of the literature on infantile renal acidosis in children is discussed.

REFERENCES

Albright, F., Consolazio, V., Coombs, F. S. Sulkowith, W., and Talbott, J. H. (1940): Metabolic studies and therapy in a case of nephrocalcinosis with rickets and dwarfism. Bull, John Hopkins Hosp. 66, 7.

Albright, F., Burnett, C.H., Parson, W., Reifenstein, E.C., and Ross, A. (1946): Osteomalana and Rickets, Medicine, 25, 399.

Baines, G.H., Barclay, J.A. and Cook, W.T. (1945): Nephrocalcinosis associated with hyperchloraemia and low plasma bicarbonate. Quarterly Journal of medicine 14, 113.

Buchanan, E.U. and Komrower, G.M. (1958): Arch. dis. of childhood 29, 326.

Carre, I. J. Wood, B. S. B. and Smallwood, W. C. (1954): Infantile renal acidosis in infancy. Arch. dis. childhood, 29. 326.

Latner, A.L., and Burnard, E.D. (1950) Idiopathic Hyperchloraemic renal acidosis of infants. Quarterly Journal of Medicine 19, 285.

Lightwood, R., (1935): Calcium infarction of kidneys in infants. British Paediatric Association Proceedings, Arch. dis. childhood, 10, 205.

Lightwood, R., Payne, W.W., Black, J.A. (1953): Infantile Renal Acidosis, Paediatrics, 12, 628.

Payne, W.W. (1948): "Persistent acidosis in infancy Arch. dis. child, 23, 145.

Rubin, M.I., Brack, E., and Rapoport, M. (1949): Maturation of renal function in childhood. Clearance Studies, J. Clin. Investigation, 28, 1144.

Shohl, A.T. (1937): Effect of acid base content of diet upon production and cure of rickets with special reference to citrates. J. Nutrition, 14, 69.

Stapleton, T., (1949): ..... Lancet, 1, 683.