INBORN DEFECTS OF THE RENAL TUBULE

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There is a small group of conditions considered to be due to dysfunction of the renal tubule. They have been sub-divided below according to the nature of the function involved, but often more than one disturbance may occur in the same case.

1. Acid-base regulation
   - Infantile Renal Acidosis (Lightwood type).
   - Hyperchloaemic nephrocalcinosis (Albright type).
   - De Toni-Fanconi-de Bray syndrome.
   - Lignac-Fanconi syndrome (Cystinosis).

2. Glucose re-absorption
   - Renal glycosuria.
   - Cystinosis.

3. Amino-acid re-absorption
   - De Toni-Fanconi-de Bray syndrome.
   - Cystinosis. Cystinuria.

4. Phosphate re-absorption
   - Vitamin D. resistant rickets.

5. Base re-absorption not due to adrenocortical disturbance
   - 'Salt losing' Nephritis:
     A Sodium Chloride losing condition found in infancy.
     Hypokalaemia in cystinosis.

6. Water regulation — not due to pituitary dysfunction
   - 'Pitressin Resistant Diabetes Insipidus.'

1. Acid-base Regulation

   Renal control of the pH of the plasma is effected by two mechanisms. One is the formation of ammonia, which replaces fixed base. This is in all probability regulated by the degree of acidity of the urine within the tubule. The second relies on the filtration of bicarbonate and phosphate mainly in combination with fixed base. These dissociate into R’ and ‘HCO₃⁻ and R’ and ‘R HPO₄²⁻. The fixed base R’ can be exchanged by an ion exchange mechanism in the tubule cell for an H’ ion. The H’ ion is obtained by the ionization of H₂CO₃ present universally in the tissues initially as CO₂, the rate of formation of H₂CO₃ from H₂O and CO₂ being greatly accelerated by carbonic anhydrase. This ion exchange produces H RHPO₄⁻ (RH₂PO₄) and H HCO₃⁻ (H₂CO₃). The H₂CO₃ will decompose to CO₂ and H₂O, the CO₂ returning to the kidney. If, however, so much H₂CO₃ is formed that it is not fully decomposed to CO₂ and H₂O by the time it leaves the nephron the excess CO₂ will be found in the urine, if it is collected under paraffin.

   In the Lightwood type of nephrocalcinosis—infantile renal acidosis—the condition does not usually show itself until about the fourth or fifth month of life. Then a previously apparently healthy infant begins to vomit, lose its appetite and fail to grow. Later, polyuria and thirst may occur and as the latter is usually not noticed, the infant becomes dehydrated. The condition persists for many weeks resisting the usual simple remedies, and ultimately the child reaches hospital. On examination, a somewhat dehydrated atomic child is found with severe constipation and faecal masses in the abdomen. The urine is alkaline (or weakly acid if the dehydration is severe), but the blood has a lowered pH and the plasma bicarbonate is well below the normal level. Correction of the acidosis brings about a marked improvement and after some months it is possible to cease treatment.

   In about 30 per cent. of cases, X-ray reveals radiopaque areas in the kidney region, and P.M. examination of fatal cases shows this to be due to medullary calcification mainly in the collecting tubules. An explanation of this is that the blood acidosis mobilizes the calcium of the tissues giving rise to an increased excretion. The urine, however, is alkaline and becomes increasingly concentrated as it descends the tubule. Ultimately it is supersaturated with calcium (mainly phosphate) and deposition of calcium phosphate occurs.

   In the Albright type of nephrocalcinosis, a very similar state of affairs exists, but the age of onset is later, and largely owing to the prolonged
acidosis leading to calcium loss, bony changes may occur. The nephrocalcinosis, also, is much more marked. Although alkaline treatment brings about clinical improvement, cure does not occur and the treatment has to be continued indefinitely. Another point of difference lies in the power of ammonia formation. It is probable that the stimulus to ammonia formation is the presence of acid urine in the tubule; so as long as the urine is neutral, but little ammonia is formed. When the urine becomes acid, ammonia is formed in infantile renal acidosis, but not in the Albright type of nephrocalcinosis. Although these two conditions are very similar, they probably have a different pathology. In the Albright type, a lesion in the tubule (acquired or congenital) has been described in microscopical studies of the kidney, and clinically it is irreversible. In the Lightwood type, except in the patches of calcification, no abnormality can be seen in the tubules, and the clinical condition ultimately clears up. It is suggested that in the Lightwood type there is an imbalance in the rate of maturing of the different parts of the nephron in the neonate, leading to a temporary overloading of the distal tubule allowing bicarbonate to be excreted. In the Albright type, there is a functional and strucrtural defect in the tubule.

In the Fanconi type of persistent acidosis, the symptoms vary with the differing pattern of tubular defect, but vomiting, constipation and failure to grow are common. The cause of the acidosis is probably a defect in the tubular mechanism which excretes H⁺ ions. The urine is more frequently acid than in infantile renal acidosis, although it may be alkaline. Ammonia may be formed in normal amounts or occasionally in amounts higher than normal (3).

(2) Glucose Re-absorption

It is generally accepted that glycosuria can be explained by assuming the tubule to be capable of re-absorbing only a limited amount of sugar (maximum tubule re-absorptive capacity, Tm glucose). The amount of glucose presented to the tubule for re-absorption, depends on the glomerular filtration rate, and the plasma glucose level. As in most people the glomerular filtration rate does not vary by a very great amount, it has been customary to use the blood sugar level as the variable causing glycosuria. It has long been known that some people will pass sugar at a lower level of blood sugar than normal, and it has been shown that in most of these cases, Tm glucose is lower than the normal value. In a few, however, glucose re-absorption continues to increase with increasing load (Robertson and Gray).

As long as this is the only tubular defect, there are no symptoms, unless the value Tm glucose is extremely low, when the excessive drain of sugar and the 'osmotic' diuresis attending it may cause ketonuria and dehydration.

Our present knowledge of the cause of the alteration of the 'renal threshold' in diabetes and pregnancy is small, but it is possible that factors other than a simple alteration in Tm glucose level are present.

Glycosuria is present in other conditions in which a tubular defect is postulated—e.g., Cystinosis and some cases of renal rickets, and in these it is probable that Tm glucose is low. In these conditions the glycosuria is usually variable and slight, but it may on occasion be marked.

(3) Amino-Acid Re-absorption

It is at present not possible to give a clear picture of the normal. With so many separate amino-acids of different biological importance, and with different chemical and physical properties, the existence of specific threshold levels (or Tm amino-acid x) can only be conjectured.

It is even less possible to differentiate the various types of amino-aciduria. The pattern and grouping of individual amino-acids varies from case to case and in some cases from time to time and the clinical picture also varies. In recent years as a matter of convenience the whole group, with the exception of cystinuria and of cases with a known pathology has been called 'Fanconi's syndrome.' The work of Bickel and his colleagues have made it clear that cystinosis can be detached from this group and they have called it the Lignac-Fanconi syndrome. In as much as Fanconi's original cases were in all probability examples of cystinosis it is not reasonable to leave the name Fanconi syndrome for the residue of cases. Fanconi himself is developing a classification of these cases and until this has become stabilized it would be simpler to talk of cystinosis and amino-aciduria without cystinosis.

Cystinosis can be sub-divided into two types. In the acute type the infant, after a few more or less normal months of existence, begins to fail to thrive. Vomiting and constipation, loss of appetite, polyuria and thirst develop. Later, signs of active rickets appear, often with marked bowing and liability to fracture. Growth almost ceases, the weight remains stationary. The child appears thin, and frail, but of normal intellect and personality. The blood chemistry shows a marked lowering of the plasma bicarbonate with a slight increase in the chloride, a low inorganic phosphorus, slightly low or normal calcium, and a low serum potassium. The blood urea may be normal or raised. The blood amino-acid is normal, or slightly raised; the urine is dilute and the
pH varies between 6 and 8, and is quite often moderately acid; ammonia formation is usually within the normal range. The amino-acid content is increased many-fold above the normal and most of the biological amino-acids are found in excess, the pattern being approximately similar to that found in the blood. An intermittent glycosuria of varying degree may also be present. Left untreated, these children rarely survive many years, dying of intercurrent infection or of acute hypokalaemia.

In the chronic type, the first symptoms observed are slow growth and polyuria, in an otherwise apparently normal child. The blood shows but little alteration from the normal, except for a slightly raised blood urea. The urine appears normal except for its low specific gravity, and the large volume, unless amino-acids are looked for when the typical pattern may be found to be present.

Untreated, the condition slowly progresses—acidosis, low potassium and all the features of the acute type slowly develop, together with a progressive renal failure and the development of a typical renal rickets.

In both types, confirmation of the diagnosis is found by the demonstration of crystals in the cornea by the slit lamp, or in the marrow or in excised lymph nodes by histological examination.

Individual cases vary in many details from the typical. Any factor may be absent either permanently or temporarily, although amino-aciduria is rarely permanently absent.

There are some cases in whom amino-aciduria is associated with rickets, glycosuria, renal acidosis or hypokalaemia without any evidence of cystinosis and often with a pattern of amino-aciduria differing from that commonly found in cystinosis. On the whole these children are not so severely affected as the cases of cystinosis and tend to resemble the vitamin resistant rickets group.

The second type of amino-aciduria includes the well recognized familial cystinuria with cystine crystals in the urine and a liability to cystine calculi. In these cases other amino-acids are usually present in excess—lysine and arginine, sometimes ornithine. The blood levels of these amino-acids are normal. The discovery of this condition was due to the accident of the low solubility of cystine. It is quite possible that other examples of increased excretion of individual amino-acids may be found.

(4) **Phosphate Re-absorption**

It has already been noted in the description of cystinosis that a low plasma phosphate may be present. A similar low plasma phosphate is found in association with rickets not due to vitamin D deficiency. This group, "vitamin resistant rickets," is a familial disease which develops in early life and despite treatment with the usual corrective dose of vitamin D, the rickets persists into adult life. Apart from a raised plasma phosphatase and the low inorganic phosphate, no other abnormality is present, and the general health and nutrition are good. Vertical growth, however, is less than normal even allowing for the effect of the bowing of the limbs.

Occasionally, in this group, intermittent glycosuria is found, but amino-aciduria is absent.

It has been suggested that the lowered plasma phosphate is due to a reduction in the renal threshold. Such studies as have been made are somewhat difficult to translate, but are in general in support of this view. There is no evidence from metabolic balance studies of excessive loss of phosphate in the urine.

(5) **Base Re-absorption**

The renal tubules are influenced by the mineralocorticoids of the suprarenal, and disturbance of the base regulation is usually due to dysfunction of the suprarenal cortex. In some cases, however, the tubule itself may be the seat of the disturbance. Thorn has described a 'salt-losing nephritis' and we have observed in infants a condition in which the apparent renal threshold for sodium falls well below normal and has not been influenced by giving desoxycorticosterone. In infancy, the condition is usually of short duration, a week or so to a few months, but while it lasts it may menace the child's life.

To determine the cause of total body potassium loss or of low serum potassium involves the consideration of many factors and, before accepting a renal origin, loss from the gastro-intestinal tract or transfer to another fluid compartment of the body has to be eliminated.

Renal loss of potassium occurs most commonly in cystinosis in which it can be so marked as to be one of the main causes of death. It is usually found in association with a low plasma bicarbonate. A similar condition has been found during the course of nephrosis again associated with a low plasma bicarbonate.

(6) **Failure of Water Regulation not due to the Pituitary Factor**

In this rare but interesting familial defect, there is a marked polyuria present almost from birth. The infant, unless it is enabled to take much more fluid than is usually offered, suffers from continuous thirst and dehydration. At first growth is normal, but later on, owing partly to refusal of food, growth is deficient. There may be also mental retardation. The blood is hypertonic, with
raised sodium and chloride. The bicarbonate is raised, giving rise to mild alkalosis. Despite the large volume of urine, the blood urea is usually raised. Unlike the classical cases of diabetes insipidus, pitressin has no effect on these children, except for a vasoconstrictor effect when large doses are given.

The only way of preventing a chronic state of hyperelectrolytaemia is to give large quantities of fluid. Over five pints a day has had to be given in some cases to toddlers and infants. It is not wise, however, to give too great a quantity of fluid as symptoms of water intoxication can be obtained when the sodium level is reduced too sharply even before it reaches the normal value. (W. Wallace, personal communication.)

Discussion

In the foregoing brief account of some of the more noteworthy examples of inborn tubular deficiency, the main clinical results of the tubular defect have been described. In an endeavour to relate the chemical lesions to the clinical manifestations, examples of disturbance of a single function can be examined.

Acidosis

The effect of prolonged acidosis are seen in Hyperchloaraemic nephrocalcinosis (Albright type), and to a less degree in the Lightwood type; vomiting and loss of appetite appear to be caused directly by the acidosis (Lightwood et al., 1953). The polyuria and dehydration can be due to this also, but may be a secondary symptom following the disturbance of tubular function by calcium deposition.

The rachitic lesions in the Albright type are due to the prolonged loss of calcium caused by the acidosis. The nephrocalcinosis is an accidental occurrence due to the insolubility of calcium salts in an alkaline medium.

Glycosuria

Glycosuria as seen in simple renal glycosuria is symptomless unless the loss of sugar is gross.

Amino-aciduria

It is difficult to believe that amino-aciduria alone could produce symptoms by the quantity lost in the urine, as this is, even in the most extreme cases, only a fraction of the amino-acid intake—in this it resembles glycosuria. If a lowering of the blood level occurred due to a drop in the 'threshold,' it would be understandable that growth might be disturbed, but most observers find a high normal or actually slightly raised blood level. In the only known example of 'simple' amino-aciduria—cystinuria—no symptoms occur, except as a result of the accident of low solubility of cystine in acid urine. Likewise, in cystinuria, Dent has failed to find a raised blood level. As amino-aciduria is known to occur without raised blood amino-acids, in chronic renal disease, it is possible that the amino-aciduria of the cystinosis is a secondary and not a primary lesion, and might be due, for example, to the effects of cystine on the kidney.

Hypophosphataemia

Acute hypophosphatemia appears to be symptomless, but long standing low plasma phosphate is constantly associated with rickets. There are at least two possible explanations, one is the loss of phosphates due to the low renal threshold which gives rise to rickets of the type found experimentally in animals fed a low phosphorus diet. Against this, is the observation that the phosphates in the urine are no greater than in the normal, and there is no evidence of a negative phosphate balance. Observations on two children given large daily doses of aluminium hydroxide (aludrox) to reduce the urinary phosphate in chronic calculus formation, has shown that a very marked reduction in the phosphate intake can be produced together with a regular intermittent lowering of the plasma phosphate without causing any change in normal bony growth. The second explanation is that the solubility quotient (Ca x P) is low, and that this, by itself, is the cause of the failure of normal bone growth. In simple vitamin D resistant rickets the low plasma phosphate is the most striking and constant feature.

Loss of base

The most striking example of this is the severe hypokalaemia which may occur in the cystinosis syndrome, but we have never observed it yet as a simple lesion. It has always been associated with amino-aciduria and acidosis.

Of course, there are many extra-renal causes of hypokalaemia, but these do not concern us. There is no doubt that hypokalaemia, as found in cystinosis, can cause pronounced symptoms, the most important of which are loss of muscular strength and cardiac failure, leading to collapse and death. From the point of view of renal physiology, it is significant that the tendency to lose potassium is not an isolated symptom, but is associated with an acidosis due to a failure to excrete H' ions.

In infantile renal acidosis where the low bicarbonate appears to be due not to a failure to excrete H' ions but to a failure to re-absorb bicarbonate ions, there is no tendency to loss of potassium.

The group of infants in which persistent low
plasma sodium is found, and in which D.C.A. or cortisone does not correct the error, the only common factor is a preceding electrolyte disturbance, such as is caused by an acute gastroenteritis, or an abdominal operation. The sodium loss has been observed to persist for some days or weeks after the rectification of the other plasma electrolyte levels. The more recent studies on potassium and sodium relationship and the difficulty in determining the actual level of the potassium stores at a given moment, especially in infants, makes it possible that these cases are examples of electrolyte imbalance, and not of a primary tubule defect. Polyuria with dehydration in Pitressin resistant diabetes insipidus, is, in all probability, a pure tubular defect presumably of the receptor organ for the antidiuretic hormone. These infants appear to be quite unable to control their osmotic pressure, and if left without water, dehydrate and get hyperelectrolytaemia with alteration of personality or fits and raised temperature. Acidosis, which is often the cause of the polyuria in other tubular defects, is absent in this group—in fact, often there is an unexplained rise in the plasma bicarbonate. As we have no clear idea of the mechanism whereby the final adjustment of the water and salt balance is made, one can only conjecture whether the cause lies, say, in a defect in the loop of Henle, or in its vascular supply or on the other hand in a disturbance of some mechanism of the tubule cell which responds to the antidiuretic hormone by imbibing or rejecting water.

Finally, what connection is there between these various defects? There are some defects occurring alone but more than one may occur in the same case. Glycosuria and hypophosphataemia, hypophosphataemia and simple amino-aciduria are both known to occur. When, however, one turns to the cases included in the syndrome of cystinosis, one finds all sorts of combinations of tubular defects, and when a given case is observed over a period of time, additional defects may become apparent. The pathology of this group of cases is difficult to understand; in particular, the existence of intercellular cystine crystals, almost entirely in the reticuloendothelial system, cannot be easily explained as arising from a primary renal tubular defect. On the other hand, there is experimental evidence to indicate that cystine affects the renal tubules and causes microscopically demonstrable lesions. Darmady has found by the technique of the nephron dissection, similar anatomical deformities (‘swan neck’ and shortening of the proximal tubule) in a case of cystinosis, and in an adult case of amino-aciduria without cystinosis, but with symptoms resembling the ‘Fanconi’ syndrome. The full significance of these findings must await the results of further dissections in a wider range of cases.

The outlook in the group of cases with cystinosis is very different from the other types of tubular defect; few have reached more than 10-14 years of age and many die in early childhood. It is difficult to keep the electrolytes of the plasma within normal limits and even when this is successful the general progress of the child is poor. On the other hand, in the group without cystinosis treatment aimed at correcting the chemical disturbances can give a reasonably satisfactory result, although in the hypophosphataemic group it is usually not possible to obtain normal growth.

In the appendix is a brief description of seven illustrative cases.

I would like to thank my colleagues at The Hospital for Sick Children, Great Ormond Street, for allowing me to study the patients who form the basis for this article, and to Dr. H. Bickel, Dr. C. Dent and Dr. L. I. Woolf for many interesting discussions on these and their own cases.

APPENDIX

CASE 1. R.W.
Present Age: 6 years. Fanconi Syndrome

Normal baby, breast fed till 9 months. When 14 months ceased to gain weight. Clinical rickets developed at 18 months. Always given adequate vitamin D.

He was transferred from an orthopaedic hospital for investigation, aged 20 months, with history of rickets resistant to vitamin D and of amino-aciduria. He was a healthy, well-nourished but bald child with marked rickets both chemically and radiologically. Weight: 18 lb. 13 oz. Height: 28 in. on admission.

His blood chemistry showed a normal calcium, a low phosphorus (1.8-3.2 mg.) and a raised phosphatase (45-75 units). The plasma bicarbonate, chloride and urea were normal.

The urine showed a generalized increase in amino-acids, but no glycosuria. The amino-aciduria varied from a great excess to a normal amount. Slit lamp examinations of the eyes and microscopic examination of the bone marrow failed to show any crystals. He was given 100,000 units of vitamin D daily and a calcium balance was made before and after three weeks’ treatment. There was no material difference; about 200 mg. calcium being retained daily in both periods.

He was given increasing doses of vitamin D, reaching finally 500,000 units, and sent home, reporting at intervals. Seven years later he had gained 2 lb. (weight 21 lb. and his height 31½ in., a gain of 3½ in.). Radiologically, there was improvement in the rickets and a calcium and phosphorus balance showed a daily gain of 1,000 mg. of calcium and 600 mg. phosphorus, but showed an unduly high loss of phosphorus in the urine compared with the faeces.

He has since then been under observation at his local hospital, where the dose of vitamin D has been varied from time to time. There has been steady maintenance of the general improvement.

CASE 2. A.H.
Present Age: 7½ years. A case of Cystinosis

Admitted at the age of 20 months with a history of...
thirst, polyuria and intermittent vomiting. She had been well up to one year of age. She weighed 15 lb. 12 oz. with a height of 29 in. The blood urea was raised slightly (maximum 66 mg.) and the urea clearance was low (26 per cent. and 48 per cent.). Blood chemistry:

Plasma bicarbonate: 40.6 Vols. CO₂ or 18 m. eq/l.
Plasma chlorides: 575 mg./100 ml or 98 m. eq/l.
Plasma potassium: 12.5 mg./100 ml.
Plasma sodium: 338 mg./100 ml or 147 m. eq/l.
Plasma calcium: 11.1 mg./100 ml.
Plasma phosphorus: 3.2 mg./100 ml.

The diagnosis of ‘Renal insufficiency from a congenital renal defect’ was made. Clinically and radiologically no evidence of rickets.

She was readmitted at the age of 4½ for further investigation. Her weight was 17 lb. 40 oz. Height: 32½ in. Crystals were seen in the cornea and in the bone marrow, but no amino-aciduria or glycosuria was found. Blood chemistry:

Blood urea: 96 mg./100 ml.

Fig. 1.—Case 1. R.W. Fanconi syndrome.

Cystinosis

Case 3. M.T.

Present Age: 5 years. A case of Cystinosis

Normal birth and throve fairly well till 9 months, when she was admitted to her local hospital with diarrhoea, vomiting and gross dehydration. She was found to have active rickets and a high blood urea; she subsequently failed to thrive and had bouts of vomiting, anorexia and constipation.

On admission, aged 2 years, she was dehydrated, ill, small and frail for her age (weight, 15 lb. 12 oz.; height, 28½ in.). Blood examination showed:

Plasma bicarbonate: 44 vol. CO₂ per 100 ml. or 19.8 m. eq/l.
Plasma chlorides: 602 mg./100 ml or 103 m. eq/l.
Blood urea: 29 mg./100 ml.
Plasma calcium: 9.7 mg./100 ml.
Plasma phosphorus: 2.3 mg./100 ml.
Phosphatase: 31.4 units/100 ml.

X-ray showed gross osteoporosis and clinical rickets. Slit lamp examination of the eyes showed many crystals.

Fig. 2.—Case 2. A.H. Doubly refractile crystals in the bone marrow. (By polarised light) × 1000.

Plasma bicarbonate: 29.5 vols. per 100 ml or 13.4 m. eq/l.
Plasma chlorides: 563 mg. per 100 ml or 96 m. eq/l.
Plasma phosphorus: 5.7 mg./100 ml.
Plasma calcium: 11.6 mg./100 ml.
Phosphatase: 16.5 units/100 ml.

Potassium at first normal, but later fell to 15 mg./100 ml. She was given potassium citrate, 2 g. a day, and the bicarbonate rose to 39 vols. and the urea fell to 43 and the potassium rose to 23 mg. She has continued on varying doses of potassium and alkali. The present dose is potassium citrate 3 g. daily and her last blood analysis showed:

Plasma potassium: 15 mg./100 ml.
Plasma bicarbonate: 34 vols. per 100 ml or 15.2 m. eq/l.

Blood urea: 55 mg./100 ml.

At the age of 7 years her weight was 24 lb. 10 oz. and her height 34½ in. She is bright, happy and has been attending school for three years and is doing very well, but she complains now that bright sunlight worries her.

There is still no rickets.
and marrow biopsy also showed doubly refractile crystals present.

The urine showed a generalized increase in amino-acids and an intermittent glycosuria. The ammonia coefficient (urine pH 6.7) was 17.3 per cent. Later blood examinations showed a varying blood phosphate, values as low as 1.8 mg. being attained. Potassium varied from 14.5 mg. to 5 mg. and the plasma bicarbonate once fell to 38 vols. CO₂.

She was given 6 g. of sodium citrate and 2½ g. of potassium chloride in divided doses daily and she improved greatly in her well-being. The dose of potassium had to be increased steadily to 4 g., but no increase in the sodium citrate has been necessary. With 10,000 units of vitamin D the rickets has been cured but her growth is very slow. In the last three years she has gained 7 lb. in weight and 3½ in. in height. Thus at the age of 5 years she is only 22 lb. 10 oz. in weight and 32 in. in height, but she is bright and active and attends school.

CASE 4. J.B.

Present Age: 5½ years. 
Fanconi Syndrome

First seen at age of 2½ years (height, 32 in.; weight, 21 lb.). She had a history of moderate progress until 6 months, when she became constipated; admitted to Guy's Hospital, where she was found to be severely constipated with an enlarged liver, but no clinical or radiological evidence of rickets. Since then her progress has been poor, only 1 lb. increase in weight in one year. Constipation was severe, but there was only occasional vomiting. The appetite was fair, but variable.

On examination the liver was enlarged and there was clinical evidence of rickets. The urine gave a moderate reduction of benedicts. The first blood examination was:

- Plasma bicarbonate: 38.5 vols. CO₂/100 ml. or 17.2 m. eq/l.
- Plasma chlorides: 666 mg./100 ml. or 113 m. eq/l.
- Plasma potassium: 17.5 mg./100 ml.
- Plasma calcium: 9.7 mg./100 ml.
- Plasma phosphorus: 1.5 mg./100 ml.
- Phosphatase: 106 units/100 ml.
- Blood urea: 15 mg./100 ml.

The urine showed excessive excretion of amino-acids and a gross excess of tyrosine. The ammonia coefficient was 13.5 per cent. and the specific gravity varied from 1.017-1.007.
Urea clearance test: 149 and 201 per cent. of normal.
The plasma bicarbonate progressively fell to 29.5 vols., and then treatment with sodium citrate and citric acid mixture was started. 500 mg. of vitamin C daily reduced the urinary tyrosine to a much lower level. 75,000 units of vitamin D were given. For a time she improved, but the vitamin D had to be reduced to 40,000 units owing to hypercalcaemia. No evidence of cystinosis was found by slit lamp or in bone marrow. The blood amino-acid was raised above normal level.

The dose of alkali had to be steadily increased and the serum potassium began to fall, levels around 13.5 mg./100 ml. being found when she was about 4 years of age. By the end of 1952 she was receiving about 450 m. eq. of Alkali (equivalent to 45 gm. sodium citrate), of which 185 m. eq. was given as the potassium salt (equivalent to 14 mg. KCl).

This did not control the plasma bicarbonate, which stayed around 35 vols. CO₂ (15.5 m. eq.) except for occasional periods when a normal value was obtained.

Her weight (4½ years) was 24 lb. 6 oz. and the liver was still large. She was happy and walking well.

In January 1953 she fell off a chair and fractured her thigh. The fracture at first began to heal and callus formed although slowly, and by the middle of the year she began to walk with a calliper. Then an increase in the acidosis occurred and even larger doses of alkali were needed. With this a generalized decalcification of the skeleton took place and the callus disappeared.

In January 1954 she is taking 700 m. eq. of alkali (equivalent to 70 gm. sodium citrate) without fully correcting the alkali reserve. The pH of the blood varies between 7.2 and 7.3. There is still gross decalcification. The fracture is not mending.

Case 5. S.P.

Present Age: 8 years. A case of resistant Rickets

Normal birth and she appeared normal till 21 months old when ‘hips appeared stiff.’ Put in plaster and gait improved, but legs became bowed. Growth became slow. Various orthopaedic measures were tried to correct bony abnormality. Normal doses of cod liver oil given since one month of age.

Previous to admission here and before treatment blood chemistry was:

Plasma calcium: 9.4 mg./100 ml.
Plasma phosphorus: 4.4 mg./100 ml.
Phosphatase: 10 units.
Plasma bicarbonate: 53 vols. CO₂ per 100 ml. or 23.6 m. eq/l.
Blood urea: 27 mg./100 ml.
Urine—no albumin, sugar or amino-acids.
Renal function tests—normal.
X-ray—active rickets.

Treated with vitamin D on doses varying from 50,000 to 100,000, but on the higher dose she got hypercalcaemia. Seen here she was a normal, alert child, but under her normal weight and height (33 lb. and 39½ in.) at 7 years of age.

Plasma calcium: 10.6 mg./100 ml.
Plasma phosphorus: 3.5 mg./100 ml.
Plasma bicarbonate: 46 vols. CO₂ per 100 ml. or 20.4 m. eq/l.
Plasma chlorides: 590 mg./100 ml. or 100.5 m. eq/l.
Phosphatase: 11 units (King Armstrong).
Simultaneous phosphate—inulin clearances were performed.
Inulin clearance was within normal range, but phosphate clearance was above normal and calculated; tubular re-absorption was below normal.

On one occasion slight glycosuria was found. Calcium and phosphorus balance was within normal range but urine calcium excretion was somewhat high.

She was given a normal diet and 30,000 units vitamin D for six months. On re-examination she had grown ¾ in. in just over four months.

Her mother had suffered from long-standing rickets as a child and was now only 4 ft. 8 in. and her blood calcium was 10.0 mg./100 ml.; phosphorus, 2.3 mg./100 ml.; and phosphatase, 6 units/100 ml.

Case 6. P.A.

Present Age: 1½ years. Pitressin resistant Diabetes Insipidus

Well until 4 months of age when, after a short febrile illness, he began to vomit occasionally and...
became very constipated and thirsty. His previous normal weight gain ceased. Finally, after an attack of diarrhoea he was admitted acutely dehydrated. His chemistry is shown below:

<table>
<thead>
<tr>
<th>Time</th>
<th>CO₂</th>
<th>Cl⁻</th>
<th>Na⁺</th>
<th>Urinary Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before diarrhoea</td>
<td>24</td>
<td>120</td>
<td>87</td>
<td>oz</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After admission</td>
<td>25.5</td>
<td>144</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>Full dehydration</td>
<td>18.5</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period of vomiting</td>
<td>38.9</td>
<td>102</td>
<td>161</td>
<td>20</td>
</tr>
<tr>
<td>Next day after 300 c.c.</td>
<td>26.9</td>
<td>117</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>Low Na⁺+water added</td>
<td>26.4</td>
<td>119</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Adequate water</td>
<td>23</td>
<td>126</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>No fluid for 6 hrs.</td>
<td>24</td>
<td>136</td>
<td>170</td>
<td></td>
</tr>
</tbody>
</table>

Serum calcium and potassium within normal range.

It was noted that whenever he became acutely dehydrated his temperature rose.

Urea clearance tests at 1 year averaged 66 per cent. of normal.

**Pitressin Tests (Dr. R. H. Wilkinson)**

1. **Dose 0.5 units per sq. m. (0.15 units) given 12 noon.** Hourly feeds during test:

<table>
<thead>
<tr>
<th>Vol.</th>
<th>Sp. gr.</th>
<th>Cl⁻</th>
<th>mgm. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>11—12</td>
<td>67</td>
<td>1004</td>
<td>183</td>
</tr>
<tr>
<td>12—1</td>
<td>60</td>
<td>1003</td>
<td>219</td>
</tr>
<tr>
<td>1—2</td>
<td>63</td>
<td>1003</td>
<td>175</td>
</tr>
<tr>
<td>2—3</td>
<td>73</td>
<td>1003</td>
<td>209</td>
</tr>
</tbody>
</table>

2. **Dose 2.5 units per sq. m. (.75 units) given 12 noon:**

<table>
<thead>
<tr>
<th>Vol.</th>
<th>Sp. gr.</th>
<th>Cl⁻</th>
<th>mgm. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>11—12</td>
<td>66</td>
<td>1007</td>
<td>114</td>
</tr>
<tr>
<td>12—1</td>
<td>29</td>
<td>1005</td>
<td>105</td>
</tr>
<tr>
<td>1—2</td>
<td>64</td>
<td>1006</td>
<td>105</td>
</tr>
<tr>
<td>2—3</td>
<td>80</td>
<td>1005</td>
<td>96</td>
</tr>
</tbody>
</table>

During the first hour after injection signs of over-response to pitressin were present (slight collapse, pallor). On a fluid intake of about 100 oz. daily he maintained a fairly normal blood chemistry and his general condition improved slightly. At the age of one year his weight was 13 lb. 3 oz. and his height 28 in.

**Case 7. B.L.**

**Present Age: 6 years. Infantile Renal Acidosis**

Normal full-term baby, breast fed for six months, reaching 16 lb. in weight. Weaning started and shortly afterwards vomiting and constipation with loss of appetite and refusal of solid food occurred. He ceased to gain weight. After six months struggle he was admitted to this hospital weighing 14 lb. 10 oz. He was a dehydrated, thirsty, irritable child with severe constipation and faecal masses palpable in the abdomen. The urine was alkaline, but the blood showed a definite acidosis. There was no evidence of any physical disease. Clinically and radiologically there was no evidence of rickets, but slight calcium deposits were seen in the kidneys. There was slight albuminuria and a few white cells in the urine. No amino-aciduria or glycosuria was found. Blood chemistry:

- Plasma bicarbonate: 35 vols. or 15.4 m. eq/l.
- Plasma chlorides: 750 mg./100 ml. or 120 m. eq/l.
- Plasma sodium: 359 mg./100 ml. or 156 m. eq/l.
- Plasma potassium: 21 mg./100 ml. or 5.4 m. eq/l.
- Plasma calcium: 10.1 mg./100 ml.
- Plasma phosphorus: 3.9 mg./100 ml.

Blood urea: 78 mg./100 ml.

He was given sodium citrate-citric acid mixture in a maximum dose of 120 m. eq/l a day and immediately began to improve clinically and his weight increase became normal. At the end of six months the treatment was stopped and he was found to be able to maintain a normal blood chemistry and to pass an acid urine. He was re-examined at the age of six and was found to be quite normal except for the persistence of the renal calcification.

### Summary of Cases 1—7

<table>
<thead>
<tr>
<th>Case</th>
<th>Glycosuria</th>
<th>Amino-aciduria</th>
<th>Acidosis</th>
<th>Hypokalaemia</th>
<th>Rickets</th>
<th>Failure to gain weight</th>
<th>Failure to grow</th>
<th>Cystinosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) R.W.</td>
<td>☑</td>
<td>+</td>
<td>+</td>
<td>☑</td>
<td>+</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>(2) A.H.</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>(3) M.T.</td>
<td>+</td>
<td>+</td>
<td>✓</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(4) J.B.</td>
<td>☑</td>
<td>+</td>
<td>☑</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(5) S.P.</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(6) P.A.</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(7) B.L.</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*when cured*

### Bibliography


BICKEL et al. (1952), 'Cystine Storage Disease with Amino-aciduria and Dwarfism,' Acta Paed., 42, 90.


Inborn Defects of the Renal Tubule

W. W. Payne

Postgrad Med J 1954 30: 476-484
doi: 10.1136/pgmj.30.347.476

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