A FAMILIAL TUBULAR ABSORPTION DEFECT OF GLUCOSE AND AMINO ACIDS*

BY

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The above title was used (Luder and Sheldon, 1955) to describe a family in which a renal tubular reabsorption defect involving glucose and amino acids appeared in three successive generations (female twins then aged 5, their father and his father). The purpose of this communication is to correct the impression given in the previous paper, to report some further investigations and to discuss the management of these cases in the light of recent treatment.

In the case of the grandfather, who was known to have had renal glycosuria for many years, an amino acid leak could not be demonstrated because the necessary technique was not known during his lifetime. But its existence is strongly suggested because he was very short and thin (weighing 98 lb.), and had an unexplained osteoporosis of his vertebrae.

This family thus provides strong evidence of a combined renal tubular reabsorption defect transmitted as a Mendelian dominant, a point of considerable interest to which we shall return later.

In 1955 a third daughter was born. Her urine was free of reducing substances and showed a normal amino-acid chromatogram, so that she did not suffer from the disease that affected her twin sisters. She died at 4 years of age from tuberose sclerosis, the autopsy also showing multiple hamartomata in the heart and kidneys and nephrocalcinosis. We are grateful to Dr. Darmady for microdissecting the kidneys; the 'swan's neck' deformity of the proximal tubule, as described in the de Toni-Fanconi syndrome, was not present.

The family were discovered because one twin (Lindsay) had been brought for advice regarding thirst and poor growth. She was found to be nearly 5 in. shorter than the other twin (Glynis) and this was attributed to a greater amino acid leak, although the blood group findings showed almost conclusively that the twins were uniovular. Neither twin showed any radiological evidence of rickets, and their serum phosphorus levels were 4.2 mg.% (Lindsay) and 5 mg.% (Glynis). These levels were considered normal, and the possibility of a tubular phosphate leak was not further pursued.

Both children had raised serum alkaline phosphatase levels (Lindsay) 31.9 King Armstrong units and (Glynis) 27.2 King Armstrong units, but in the absence of clinical or radiological rickets and in view of the normal phosphorus levels, the raised phosphatase levels were tentatively attributed to a disturbance of liver function, rather than being regarded as a warning of potential rickets. The subsequent history of the children shows this view to have been incorrect, for when they were seen after an interval of three years the smaller twin had developed rickets, and the serum alkaline phosphatase had risen from 31.9 to 83 King Armstrong units; the other child still showed no rickets and the phosphatase level was unchanged. In both we have now been able to demonstrate a renal tubular defect of phosphate reabsorption and an acidosis of renal tubular origin.

Summary of History and Previous Findings

The twins, although apparently uniovular, were of different birth weights, Lindsay weighing 4 lb. 15 oz. and Glynis 5 lb. 14 oz. The smaller twin was seen at the age of 5 years because of stunting, thirst and poor appetite. Her height was 36 in., weight 23 lb. 14 oz. (both below the 3rd percentile), but no other physical abnormalities were present in any system, including the skeleton. The skeletal age was 3 to 3½ years. Blood chemical findings were normal except for the raised alkaline phosphatase, already mentioned. The only abnormal findings were in the urine, which contained an excess of many amino acids in a typical 'renal tubular' pattern, a small amount of protein and an excess of glucose.

The other twin, who was taller and heavier showed similar chemical findings, though the excretion of amino acids and glucose was rather less.

The father was tall and well built and excreted glucose and amino acids, but in slightly smaller amounts than...
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The twins. He had a serum phosphorus level of 3·2 mg.% No radiological abnormality was seen in the bones, and the serum alkaline phosphatase level was normal (10 units % King Armstrong).

Lindsay

The smaller twin was not seen from 1954 until 1957 when, at the age of 8½ years, she was brought on account of gradually increasing genu valgum. Although active and alert, she was very small for her age, measuring 42 in. (107 cm.) in height and weighing 33 lb. (15 kg.). The degree of genu valgum was such that with the knees touching, the medial malleoli were 4½ in. (12 cm.) apart, but there were no clinical signs of rickets. Radiological examination, however, showed typical rachitic changes at the ends of the long bones, and the bone age was retarded to 5 to 6 years. The heart was normal; blood pressure 115/75 mm. Hg. The other systems were normal and the urine contained a variable amount of protein and, as on the previous occasions, both glucose and amino acids, the amino acid chromatogram being very similar to that seen in other types of renal tubular defect. There were no Kayser-Fleischer rings and no cystine crystals in the cornea.

Blood chemistry. Analysis revealed calcium 9·5 mg.%: inorganic phosphorus 3·0 mg.%: alkaline phosphatase 83 King Armstrong units %: urea 37 mg.%: sodium 148 mEq/litre: potassium 3·8 mEq/litre: chloride 112 mEq/litre: bicarbonate 17 mEq/litre.

Renal investigations.

ACIDOSIS STRESS TEST. (1). This was carried out in July, 1958. The pH of urine before the test was 7·0 and 6·72. Ammonium chloride 6 mEq/kg./24 hr. was given in six-hourly doses for 48 hours. Urinary pH levels were then as follows: after 16 hours, 6·42; after 22 hours, 5·14; after 40 hours, 4·82. Plasma bicarbonate after 38 hours was 10 mEq/litre.

ACIDOSIS STRESS TEST. (2). This was carried out in November, 1958 using the technique described above. The results tabulated below show the levels at six-hourly intervals after the test dose.

<table>
<thead>
<tr>
<th>Urinary pH</th>
<th>Ammonia N. (mg./24 hr)</th>
</tr>
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<tbody>
<tr>
<td>6·56</td>
<td>49</td>
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<tr>
<td>5·14</td>
<td>78</td>
</tr>
<tr>
<td>5·16</td>
<td>76</td>
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<td>5·52</td>
<td>70</td>
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<tr>
<td>5·76</td>
<td>74</td>
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</tbody>
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Blood pH before test was 7·26 and 48 hours after test dose, 7·28.

UREA CLEARANCE. This revealed 34·6 ml./min./1·73 m.² or 63% average standard normal; blood urea, 50 mg.%.

GLomerular Filtration Rate. This was 120 ml./min./1·73 m.², about 65% of normal.

PHOSPHATE CLEARANCE (endogenous). This was at a rate of 63 ml./min.

PHOSPHATE REABSORPTION. This was estimated by the method described by Anderson (1955) and showed the following results:

October, 1957, TmP = 2·2 mg./min./1·73 m.² and in November, 1958, TmP = 2·15 mg./min./1·73 m.².

(Normal 4·0-4·5 mg./min./1·73 m.².)

INTRAVENOUS PYELOGRAM. Both kidneys were investigated when just 9 years old. Like her sister she was an active and alert child, her height being 48½ in. (124 cm.) and her weight 46 lb. (20·8 kg.). The urinary findings were similar to those of her twin. Clinical examination was normal, there was no radiological evidence of rickets, and the bone age was normal. Slit-lamp examination of the corneae showed no cystine crystals.

Blood chemistry. Analysis revealed calcium 9·9 mg.%: phosphorus 2·5 mg.%: alkaline phosphatase 30 King Armstrong units %: urea 30 mg.%: sodium 152 mEq/litre: potassium 3·9 mEq/litre: chloride 106 mEq/litre: bicarbonate 20 mEq/litre.

Renal investigations.

ACIDOSIS STRESS TEST. (details as for Lindsay). Urinary pH before test was 6·84 and 6·56. Urinary pH level after 16 hours, was 4·68; after 22 hours, 4·82; and after 40 hours, 4·68. Plasma bicarbonate after 38 hours, was 13 mEq/litre.

PHOSPHATE REABSORPTION. In January, 1958, TmP = 3·6 mg./min./1·73 m.².

INTRAVENOUS PYELOGRAM. The excretion of dye was good and equal on both sides. The appearances were normal.

Urinary Protein Electrophoresis

It has been shown by Butler and Flynn (1958) that electrophoresis of the urinary protein in renal tubular disorders tends to show a distinctive pattern, characterized by a relatively high content of α₂ globulin and sometimes of β globulins as well, especially when the proteinuria exceeds a level of about 15 mg./100 ml. We are indebted to Dr. Flynn for investigating this point in both twins and their father.

The total urinary protein in the father was 40 mg./100 ml.; in Glynis it was 20 mg./100 ml. and in Lindsay 10 mg./100 ml. In all three the electrophoretic pattern was examined by Dr. Flynn, who reported it as being typical of renal tubular disease. Electrophoresis of the serum proteins in both twins showed a pattern normal for their age.

Treatment and Subsequent Progress

Lindsay. It was decided to try to control the genu valgum with walking calipers, while treating the rickets with vitamin D. The dose was initially 25,000 I.U. daily. After a week, some radiological improvement was evident at the wrist and the serum phosphatase level had fallen from 83 to 61 King Armstrong units. After two months, the level was 69 King Armstrong units. At this point the dose of vitamin D was increased to 50,000 units daily and was maintained for four months. She was...
also given an inorganic phosphate mixture by mouth, made up of $\text{NaH}_2\text{PO}_4$, $2\cdot1$ g. and $\text{Na}_3\text{HPO}_4$, 12 $\text{H}_2\text{O}$, 30-0 g. plus water to 1,000 ml. The dose was 500 ml. daily (providing 1.8 g. phosphorus daily).

After four months had elapsed, she was re-examined, and was found to have grown 2 inches. Genu valgum had lessened, and serum alkaline phosphatase had fallen to 40 King Armstrong units. Radiographs of the wrists some weeks earlier showed continuing improvement in the rickets. The plasma phosphorus however was still 2.5 mg.%. She was then changed to another phosphate mixture, made up of $\text{NaH}_2\text{PO}_4$, 4$\text{H}_2\text{O}$, 78 g.; water to 950 ml.; 5N $\text{NaOH}$ to 1,000 ml. ($\text{pH}$ now 7.0). The dose was 40 ml. t.d.s.

This was continued for a further seven months and then stopped; at the same time, the daily vitamin D dose was progressively increased to 60,000 I.U., 75,000 I.U. and finally 90,000 I.U. over the next year.

During this period radiological healing of the rickets occurred and has been maintained until the present time (see Fig. 1). The genu valgum also disappeared. The child has continued to grow and gain weight (during the 18 months of treatment she grew 4 in. and gained 5 lb.). The serum alkaline phosphatase, early in the treatment, had fallen to 25 King Armstrong units, and now fluctuates between 35 and 45 King Armstrong units. The plasma phosphorus has varied between 2-8 mg.%, and 3-5 mg.%, in general remaining stable throughout the period (Fig. 2). In spite of the high doses of vitamin D the serum calcium has remained normal. The blood urea has shown a tendency to rise, the most recent figure being 44 mg.%, while no appreciable change has occurred in the sodium, potassium, bicarbonate, or chloride levels.

Glynis. Bearing in mind our experience with Lindsay, we decided to treat Glynis with an oral phosphate mixture with the object of preventing the onset of rickets, which in view of her raised serum alkaline phosphatase level seemed imminent. We also hoped to gauge the effect of this treatment by its influence on the phosphatase level.

She was given the first inorganic phosphate mixture (see above) for three months, by which time her serum phosphorus level was 3.5 mg.%, and phosphatase level 26 King Armstrong units. She was then switched to the second mixture for a further three months. At the end of this period there was no detectable change in the child; the serum phosphorus was 3.8 mg.%, and phosphatase 32 King Armstrong units. The treatment had exerted no effect on the serum phosphatase level.

Phosphate treatment was then stopped and vitamin D was given in a daily dose of 25,000 units for five months. At the end of this time the serum phosphorus was 2.8 mg.%, having at one time reached 4.6 mg.% and the alkaline phosphatase had fallen to 23 King Armstrong units. Serum calcium remained normal. During the next three months the vitamin D was gradually raised to 50,000 units daily, but the phosphatase level after this course was still 27 King Armstrong units, and serum phosphorus 3.9 mg.% (see Fig. 3). No sign of rickets has appeared.

**Discussion**

It is now apparent that additional tubular disturbances are present in both twins, who were formerly thought to show leaks of amino acids and sugars only. These are (a) a phosphate leak (b) a defect in ammonia formation and possibly in H ion exchange.

This development raises several questions: (1) Are these tubular disturbances part of the original hereditary tubular reabsorption defect? (2) If so, why was their appearance so delayed? (3) Why has one twin developed rickets already, whilst the other has so far failed to do so?

The fact that serum phosphorus levels were normal at the age of 5 years is evidence against the existence of tubular phosphate leaks at that time. These must, therefore, have developed between the ages of 5 and 8 years, whilst the other leaks were probably congenital, to judge from the failure to thrive and the symptoms of thirst which dated from an early age. Such a delayed appearance of one of a number of tubular leaks is unusual, though not unknown. We have examined the records of 18 cases of low phosphate rickets, with or without other tubular leaks, seen at Great Ormond Street in recent years, and in no case could it be shown that the development of the various tubular leaks was separated in time. The first estimation of serum phosphorus was performed in all the cases before the age of 3 years, and in the majority before the age of 18 months. In all cases the level was abnormally low at the first estimation and continued to remain low thereafter. Nor have we any personal experience of the consecutive appearance of other leaks.
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Fig. 2.—Lindsay; serum alkaline phosphatase and serum phosphorus levels during treatment with vitamin D and oral phosphate.

Fig. 3. Glynis; serum alkaline phosphatase and serum phosphorus levels during treatment with vitamin D and oral phosphate.
in cases of inherited renal tubular defects, though, of course, it is well known that the clinical manifestations arising from these leaks may be delayed for a considerable time. The other possible origin of the phosphate leak is from acquired damage to the renal tubules. Tubular reabsorptive defects can, of course, result from damage to the tubules by disease processes, infective, degenerative or toxic, or from lack of an essential substance. Thus pyelonephritis and chronic nephritis may result in leaks of sodium, chloride, potassium, amino acids, phosphate, glucose, bicarbonate and water. Toxins that may cause various leaks include lead, uranium, chloridzin and phenol compounds. In metabolic disorders such as Wilson's disease and galactosaemia, tubular amino-aciduria also occurs in the early years of life, presumably due to the toxic effects on the tubules of copper and galactose respectively. Vitamin D deficiency may cause a fall in phosphate reabsorption, and anti-diuretic hormone deficiency causes a water leak. In the absence of any history or urinary findings suggestive of kidney disease, the possibility must be considered that the damage has been caused by the long-standing amino acid leak, especially the essential amino acids. It had previously seemed likely to us that this constant depletion accounted for the dwarfing of one of the twins. Any kidney damage of this nature is likely to affect glomeruli as well as tubules, and it may be significant that the blood urea of the rachitic twin has tended to rise since 1954. The other renal function tests, namely the urea clearance, glomerular filtration rate and intravenous pyelogram all show evidence of diminished glomerular efficiency. The acidosis stress tests also indicate impaired ability to acidify the urine after a load of an acid salt. The other twin, Glynis, who had a lower amino acid excretion in 1954, is less dwarfed, has a better phosphate reabsorption (though still abnormally low) and her glomerular function tests are normal.

The tests of ability to acidify the urine after doses of ammonium chloride indicated considerable impairment in the case of Lindsay, particularly in the second test (November, 1958). Her plasma bicarbonate concentration and blood pH were both low before the test, and the test showed that the power to form ammonia was much decreased. In the case of Glynis the results were less striking, but her plasma bicarbonate concentration was slightly low before the test and fell considerably during it. Lindsay therefore has an acidosis and Glynis an 'incipient' acidosis, due to a defect in the tubular mechanism for H ion exchange and ammonia formation. It is conceivable that these tubular disturbances could be explained by the effects of the original amino acid leak, though it must be confessed that there are strong arguments to the contrary. The total loss of amino acids in the urine in these cases is small compared with the dietary intake and is unlikely to have any adverse clinical effects unless it comprises mainly the 'essential' amino acids (Dent and Walshe, 1954). These are certainly present in the urine of our cases, but not in gross excess compared to other amino acids. It would also be difficult to explain why the effect of amino acid leak is greatest upon the mechanisms for phosphate reabsorption and ammonia formation, whilst other electrolytes and water continue to be reabsorbed normally. The question of aetiology must therefore be considered an open one.

It should also be noted that a phosphate leak and radiological rickets do not run pari passu, and in fact the phosphate leak may precede the rickets by a matter of years. Thus the larger twin, Glynis, was shown to have a low blood phosphorus level and a diminished tubular phosphate reabsorption in January, 1958 and it is not possible to say how long before that they had been abnormal; however, no rickets was present, nor has it developed since. Again, one of the Great Ormond Street cases, noted previously, was found to have a low serum phosphorus level (2.7 mg./100 ml.) at the age of 1½ years, but she remained free of rickets until she was 4½ years old. During this period the serum alkaline phosphatase level remained normal. The reason for the delayed appearance of rickets is not clear, but may depend first on the degree of phosphate leak, and secondly, as in the development of true renal rickets, on the rate of growth of bone, being more likely at times of rapid growth. This, in turn, will depend on many other factors apart from tubular leaks.

Nevertheless, apart from the larger twin mentioned in this paper, we know of no other case in which a tubular phosphate leak, once demonstrated in a child, has not been followed in a shorter or longer time by rickets and it should, therefore, be regarded as a definite warning. We are less certain of the value of the serum alkaline phosphatase in this connexion. Several of the Great Ormond Street cases already quoted (including the child mentioned above) had normal phosphatase levels during the period preceding and even during the development of rickets. In most of the cases, however, the level was elevated and remained so even after the rickets was healed. It seems, therefore, that in children with a tubular absorption defect for phosphorus, the serum alkaline phosphatase is a poor guide of the imminence of rickets, and also of its cure under vitamin D therapy. This
is in contrast to the situation in vitamin D deficiency rickets, in which a rise of serum alkaline phosphatase is an early and certain diagnostic indication, and an early fall of serum alkaline phosphatase a good indication of cure.

The treatment used in our cases was influenced by a report by Fraser, Jaco, Yendt, Munn and Liu (1957) that healing of vitamin D-resistant rickets could be demonstrated within a few days of setting up a continuous intravenous infusion of an isotonic sodium phosphate solution at a rate sufficient to maintain the serum inorganic phosphorus level above 5 mg./100 ml., without recourse to vitamin D therapy. A reversion to active rickets took place when the infusion was discontinued. The beneficial effect of this experimental therapy was due to a temporary restoration of the serum phosphorus to a normal level. Theoretically, if sufficient phosphorus could be fed by mouth and absorbed to achieve a normal serum phosphorus level, a comparable benefit to the rachitic process should be achieved, although against a background of renal tubular wastage of phosphorus, this possibility seemed remote. This has unfortunately proved to be the case. The smaller twin, Lindsay, began to heal her rickets on vitamin D alone and this process continued after she began her oral phosphate solution. In spite of this healing, however, her serum phosphorus level remained abnormally low. After the phosphate solution was discontinued in October, 1958, her rickets has remained healed under the influence of a large dose of vitamin D and her serum phosphorus level is unchanged.

Glynis was started on the oral phosphate solution alone, without vitamin D, as a prophylactic measure after a tubular phosphate leak and a raised serum alkaline phosphatase level had been demonstrated. It was hoped at that time to gauge the effect of the treatment by the alkaline phosphatase level, but we now realize that in the type of endogenous rickets with which we were dealing the phosphatase level is of much less value for this purpose than it is in vitamin D deficiency rickets. Her serum phosphorus and alkaline phosphatase levels did not alter materially during this treatment or during subsequent treatment with vitamin D alone.

Though neither case was a wholly clear-cut experiment, we have concluded that oral phosphate solutions in the doses used were without effect, and that the healing of rickets in the rachitic twin was due to the influence of vitamin D alone.

This family also demonstrates another point of unique interest, namely the dominant inheritance of this multiple renal tubular defect. Most other renal tubular defects are inherited by recessive, incomplete recessive or sex-linked mechanisms and the only other example of a tubular defect inherited by dominant autosomal means is renal glycosuria.

**Summary**

The development of a renal tubular phosphate leak and an acidosis is described in twins who were reported in 1955 to leak glucose and amino acids only.

The possible aetiology of these fresh tubular disturbances is discussed. The consequent rickets in one twin has healed under treatment with large doses of vitamin D, while oral phosphate solution has been ineffective. The dominant mode of inheritance of this condition is most unusual.

We wish to record our thanks to Professor C. H. Gray and Professor C. E. Dent for their help and advice; to Dr. M. Rinsler for estimating the phosphorus Tm; and to Dr. F. V. Flynn for the electrophoretic study of the urinary protein.

**References**


