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STUDIES IN RICKETS IN THE CAPE PENINSULA

III. RICKETS OF LATE ONSET ASSOCIATED WITH RENAL TUBULAR DYSFUNCTION

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In 1931 Fanconi[1] first suggested that rickets might be associated with dysfunction of the renal tubules, when he published a report of a child suffering from glycosuria and proteinuria in addition to rickets. In 1935 Lightwood[2] described nephrocalcinosis in 6 children with similar clinical features, and in 1936 Butler *et al.*[3] described the abnormal serum biochemistry which occurred in this syndrome and labelled it briefly 'hyperchloraemic acidosis'. This syndrome is frequently referred to as 'renal tubular acidosis' (RTA). Vitamin-D-resistant rickets is a third syndrome in which rickets is probably associated with renal dysfunction.

All these conditions are familial (RTA less commonly) and are associated with dwarfism. The rickets occurs over the age of 3 years, when ordinary vitamin-D-lack rickets is rare. We have recently had the opportunity of studying 8 patients with these syndromes, and are reporting the clinical and biochemical findings and the results of therapy in 5 of them.

FANCONI SYNDROME WITH CYSTINOSIS

Cases 1 and 2

In October 1958, D.A., a Coloured child, aged 5½ years, was admitted to an orthopaedic hospital with deformities of the lower limbs. Radiographs at this time demonstrated active rickets (Fig. 1A). His urine contained a trace of protein, but no sugar. Serum alkaline phosphatase was elevated, although inorganic phosphorus and blood urea were normal (Table I). An elder sister, M.A., aged 11, had had an osteotomy 5 years previously because of bent legs, and her urine had contained protein at that time. The parents and 4 other siblings were said to be normal, and this was later confirmed by us.

D.A. was treated with large doses of vitamin D (100,000 units daily), and showed radiological evidence of healing over 5 months (Fig. 1B). The serum calcium was not elevated and remained normal. An osteotomy was performed to correct the lower-limb deformity and he returned to his family. Unfortunately, he received no further treatment, and 2 years later he again showed clinical, biochemical and radiological evidence of rickets (Table I and Fig. 1C). He was now aged 7½ years and only 3 feet 2 inches tall (Fig. 2). He had complained of severe photophobia during this period. The urine contained protein and sugar, and cystine crystals were present in his corneae.

In 1960 his elder sister M.A. was sent to us from an orthopaedic hospital because of leg deformities and persistent proteinuria. She was then aged 13, and 4 feet tall, and her only complaint was of mild photophobia. Radiographs demonstrated active rickets (mild) and this was confirmed biochemically (Table I). Other electrolytes and CO_2-combining power were normal, but her blood urea was elevated (64 mg. per 100 ml.) and her creatinine clearance was depressed (60·9 ml. per minute). The urine contained protein, and a general increase of all the amino acids, but no sugar. There were numerous cystine crystals in the bone marrow. These were also seen in her cloudy corneae by slit-lamp examination or by ophthalmoscopy, using a +40 lens. There was no steatorrhoea. Vitamin D was commenced on 12 September 1960, 400,000 units being given daily by injection. Radiological healing and improved tubular re-absorption of phosphorus (Table II) were evident 1 month later.

FANCONI SYNDROME WITHOUT APPARENT CYSTINOSIS

Case 3

A.W., a European boy aged 7½ years, was 3 feet 4 inches tall and lack of stature was his main complaint. A younger brother, aged 4½ years, was already taller. His mother had noticed polyuria and excessive fluid intake for many years, and said that he had suffered from intermittent attacks of muscular weakness on 3 or 4 occasions, each lasting 6-8 hours, during which he was unable to move.

There was no mental impairment or photophobia. Apart

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TABLE I. SERUM BIOCHEMISTRY

Patient	Na	Cl	K	CO_2	Ca	P	Alkaline phosphatase	Urea
D.A. 1958					9·6	4·0	29	
D.A. 1960 (cystinosis)	135	104		19·6	9·3	2·5	51·1	35
M.A. (cystinosis)		104	3·8	21		2·8	47	64
A.W. (Fanconi syndrome)	140	104	3·6	12·5 (28)	8·6	2·9	32	90
S.S. 1956	137	113	2·1	16.9 (38)	8·2	3·3		38
S.S. 1957	137	120	3·7	11.6 (26)	9·6	3·7	12·6	27
S.S. 1960 (RTA)	136	117	3·0	14·7 (33)	8·8	2·8	29·3	27

Units: Na, mEq./l.; Cl, mEq./l.: K, mEq./l.; CO_2, mEq./l., figures in brackets—volumes %; Ca, mg. per 100 ml.; P, mg. per 100 ml.; alkaline phosphatase, Shinowara-Bodansky; and urea, mg. per 100 ml.

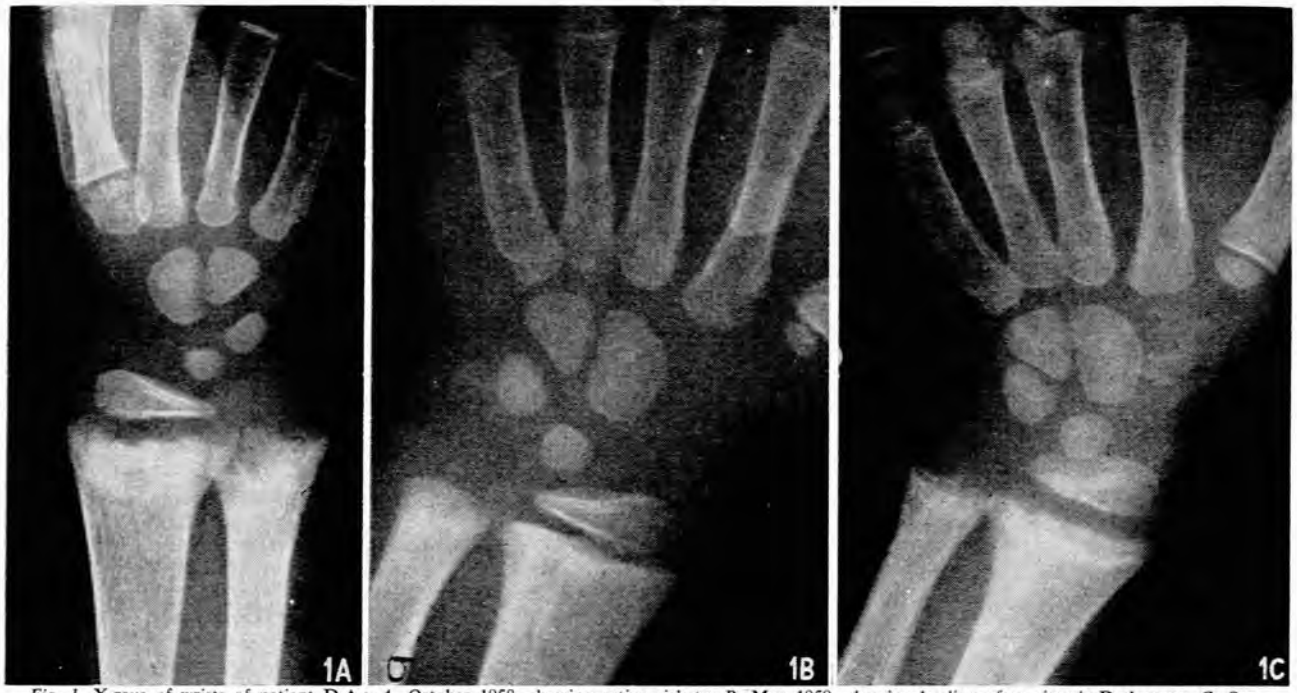

Fig. 1. X-rays of wrists of patient D.A.: *A.* October 1958, showing active rickets; *B.* May 1959, showing healing after vitamin-D therapy; *C.* September 1960, showing recurrence of active rickets — no vitamin-D therapy since May 1959.

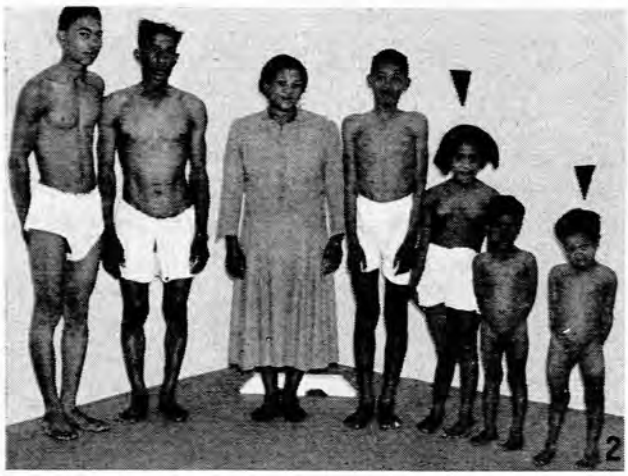

Fig. 2. Family with cystinosis. Patients M.A. and D.A. (indicated by arrows) with parents and 3 normal siblings.

from genu valgum, there was no abnormality on physical examination. There were no cystine crystals in the corneae or the bone marrow.

Active rickets was evident radiologically (Fig. 3A), and his bone age was 3 years. There was no renal calcification. He had glycosuria and proteinuria and there was a general increase in amino-acid excretion. During hospitalization he frequently had a urinary volume above 50 oz. daily — the maximum output was 64 oz. daily. Urine concentration was only 1007 after a 12-hour fast. His biochemistry was typical of active rickets (Table I). The serum-sodium, serum-chloride and serum-potassium levels were normal, but he was markedly acidotic. The renal tubular re-absorption of phosphorus was impaired (Table II).

Daily treatment with calciferol, 400,000 units, and an alkalinizing mixture containing 5 G. of sodium citrate and an equal amount of sodium bicarbonate in 50 ml. of water, was given. The CO_2-combining power remained low (12·5 mEq./l. for the first 2 days, but 4 days after treatment began it was within the normal range — 22·5 mEq./l.). After 5 days on 400,000 units of calciferol daily, the dose was halved and he received

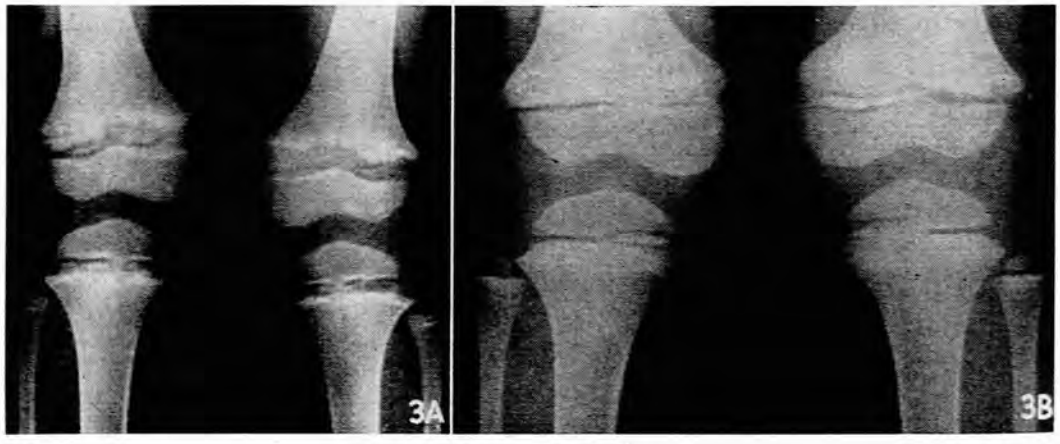

Fig. 3. X-rays of knees of patient A.W.: *A.* Active rickets; *B.* Healing 1 month after vitamin-D therapy.

TABLE II. TUBULAR RE-ABSORPTION OF PHOSPHORUS

Patient		GFR	Fp	UVp	Tp	Phosphorus re-absorbed %
M.A. (Fanconi syndrome)	before treatment	29·9	·78	·43	·35	44·9
		28·1	·83	·39	·44	52·9
	after vitamin-D treatment	15·4	·77	·30	·48	61·7
		17·5	·92	·33	·59	64·6
A.W. (Fanconi syndrome)	before treatment	6·8	·19	·137	·06	30
	after vitamin-D treatment	9·0	·54	·29	·24	46·1
		10·1	·56	·31	·24	43·8
J.D. (vitamin-D-resistant rickets)	before treatment	27	·71	·38	·33	46
		22	·63	·27	·36	57
		22	·59	·33	·26	44
	after vitimin-D treatment	26·8	1·74	·31	1·43	82
		28	1·64	·24	1·4	85
S.S. (RTA)	before treatment	20·6	·72	·41	·30	42·4
		20·0	·64	·37	·27	41·9
	after treatment with citrate	35·6	1·7	·46	1·3	73·7
		33·8	1·5	·44	1·1	70·2

GFR = glomerular filtration rate (ml./min.) (from endogenous creatinine clearance); Fp = filtered phosphorus (mg./min.); UVp = urinary phosphorus (mg./min); Tp = tubular re-absorption of phosphorus (mg./min.).

between 200,000 and 300,000 units daily for 1 month without any toxic effects. The serum phosphorus returned to normal 3 weeks after treatment began. Radiological healing was evident after 1 month (Fig. 3B) and the renal tubular re-absorption of phosphorus improved (Table II).

RENAL TUBULAR ACIDOSIS (HYPERCHLORAEMIC ACIDOSIS WITH NEPHROCALCINOSIS)

Case 4

S.S., a Coloured girl, aged 4½ years, was first seen in 1956, when she weighed 12 lb. 4 oz. and was 2 feet 4 inches tall. Since the age of 7 months she had failed to thrive, and she had never walked. Polyuria and polydipsia were prominent (she frequently drank 20 oz. in 15 minutes). There were 8 healthy siblings, none of whom had skeletal or renal disease.

She had gross rickets clinically, biochemically and radiologically. There was no evidence of cystine deposition in the tissues, but she had quite marked nephrocalcinosis (Fig. 4A). In addition she had biochemical evidence of hyperchloraemic acidosis (Table I), but was not uraemic. There was mild proteinuria, but no glycosuria or aminoaciduria. Her urinary citrate was 30 mg. per day (normal is over 200 mg. per day). Urinary pH varied between 6·8 and 8·0, and after an ammonium-chloride load corresponding to 0·3 G. per kg., the lowest figure obtained was 6·5 (Table III).

Shortly after therapy with an alkalinizing mixture and potassium (5 G. of potassium citrate with 5 G. of sodium citrate and 5 G. of citric acid daily) her acidosis and hypokalaemia were corrected and the CO_2-combining power was maintained between 50 and 60 volumes %. She was given 1 ml. 'ostelin forte' (Glaxo) intramuscularly (= 600,000 units of vitamin D), and 2 months later her rickets had healed.

One year later (1957) she was re-admitted with hyperchloraemic acidosis (Table I), but without radiological evidence of rickets. She had not had treatment for 8 months. On re-instituting therapy with citrate mixtures, the serum biochemistry returned to normal. However, she again failed to take any therapy for the 18 months up to October 1960, when she was next seen. Now aged 8½, she was still only 3 feet 1 inch tall and had gross limb deformities (Fig. 5). There was biochemical and radiological evidence of recurrence of rickets, as well as hyperchloraemic acidosis and increased nephrocalcinosis and lithiasis (Fig. 4B and Table I). She was treated with citrate mixture alone in the same dose as previously. The electrolyte abnormality and acidosis were corrected, but after 3 months the rickets had become worse, so she received, in addition, 2 ml. ostelin forte in 2 separate doses (= 1,200,000 units of vitamin D). Radiological and biochemical evidence of healing rickets was present 1 month later.

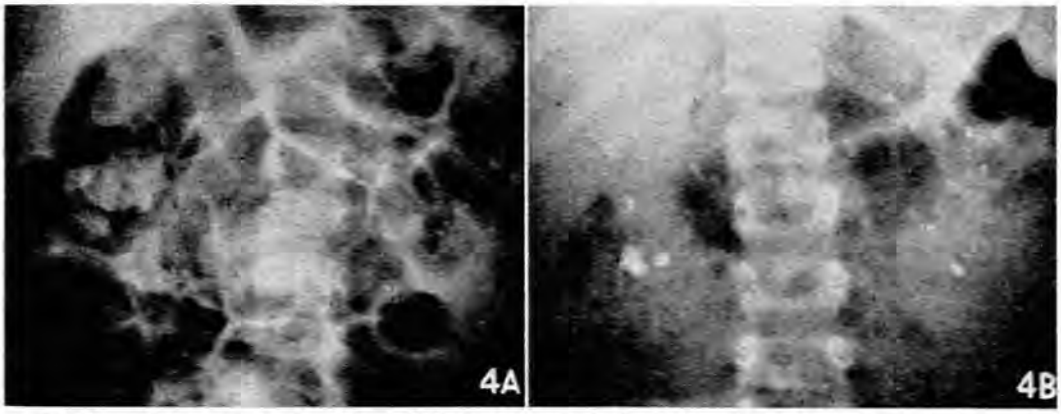

Fig. 4. X-rays of abdomen of patient S.S.: *A.* 1956, showing renal calculi;; *B.* 1960, showing increased calcification.

VITAMIN-D-RESISTANT RICKETS

*Case 5**

J.D., a Coloured male, aged 11 years, was the eldest child in a family of 4 bow-legged children first seen in January 1958 (Fig. 6). There was biochemical and radiological evidence

* Reported in greater detail elsewhere.[12]

TABLE III. ACID-LOAD RESPONSE* (PATIENT S.S.—RTA)

	Period (hours)	Urine: Volume (ml.)	Urine: Ammonia (mEq./min.)	Urine: Titratable acidity (mEq./min.)	Urine: pH	Blood: Cl (mEq./l.)	Blood: HCO_3 (mEq./l.)
	1	70	14	4·7	6·9	109	13·0
Acid load	2	50	10·5	3·75	6·8		
	3	106	14·5	17·7	6·9		
	4	40	7·6	5·5	6·9	111	8·5
	5	190	28·5	21·1	6·6		
	6	172	31·0	27·0	6·6		
	7	100	20·8	10·4	6·5		

* Short-term acid-load response:[18]
Hourly urine collections are made, and 3·5 G. of ammonium chloride are given after period 2.
Normal range[18] 2 - 8 hours after acid load as follows (in mEq./min.):

	Ammonia	Titratable acidity
Normal	33 - 75	24 - 51
RTA	10 - 44	4 - 18

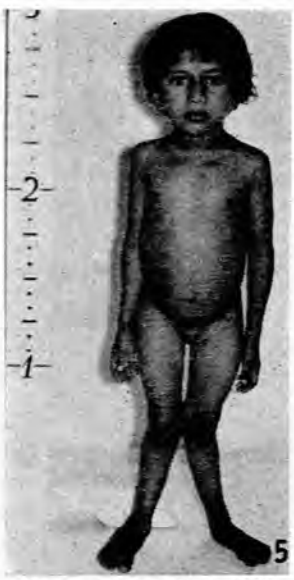

Fig. 5. Patient S.S. in 1960, aged 8½ years (scale in feet).

of rickets in all the children, and their mother had had an osteotomy as a child because of bent legs. There was no glycosuria, proteinuria, aminoaciduria or polyuria, and no evidence of cystine deposition. The renal tubular re-absorption of phosphorus was deficient (Table II) and the gastrointestinal absorption of calcium was impaired.

Both these defects were improved by large doses of vitamin D (1 million units daily for 1 week; 400,000 units daily for 2 weeks; and a maintenance dose of 200,000 units of calciferol daily for 4 weeks). The rickets healed, and bilateral osteotomies were then performed by Dr. H. Bell to correct the deformities. The patient returned home in August 1958 on the inadequate dose of 1,600 units of calciferol daily. By December 1958 the serum alkaline phosphatase had risen from 10 units (in August) to 25 units, but we found no other biochemical or radiological abnormality.

Fig. 6. Family with vitamin-D-resistant rickets.

DISCUSSION

Aetiology

Renal Tubular Acidosis

During normal body metabolism an excess of hydrogen ion is produced, and this must be excreted in the urine against a high gradient. (The average maximal gradient of hydrogen ion between urine and plasma is 800 to 1, corresponding to a urinary pH of 4·6.) The hydrogen ion is eliminated either as free hydrogen ion (measured as urinary titratable acidity) or combined with ammonia. In renal tubular acidosis there is an inability to eliminate hydrogen ions against the plasma/urine gradient. This is demonstrated by inadequate urinary acidification following an acid load (usually given as ammonium chloride, 0·1 G. per kilo, after which the pH should fall well below 5).

The maintenance of the plasma/urine gradient involves enzyme systems, and the basic defect in RTA is probably an enzyme dysfunction or lack. A research stimulus was provided when 'diamox', a carbonic anhydrase inhibitor, was observed to produce hyperchloraemic acidosis. Numerous attempts have been made to demonstrate carbonic-anhydrase deficiency in RTA. However, diamox administration to these patients further increases bicarbonate excretion, implying that further inhibition of carbonic anhydrase has occurred.[4-6]

Jaffe *et al.*[7] demonstrated normal carbonic-anhydrase activity in renal tubular tissue removed at biopsy. They also demonstrated that the activity of triphosphopyridine nucleotide (TPN) diaphorase was abnormally low. This enzyme is active in the tricarboxylic-acid cycle, the integrity of which may be necessary to provide the intracellular energy for maintaining the high plasma/urine hydrogen-ion gradient. Recently, Huth *et al.*,[8] using a 'clearing index' of hydrogen ions, have demonstrated latent RTA in apparently unaffected members of a family in whom 1 sibling had the typical syndrome.

The aetiology of the rickets in this syndrome has not been satisfactorily explained. In our patient (S.S.) there appeared to be a deficient tubular re-absorption of phosphorus, which improved after citrate therapy (Table II). This might have been expected to lead to healing of rickets, but there was no radiological evidence of healing after 3 months.

The cause of the nephrocalcinosis has recently been related to an abnormality in citrate metabolism which occurs in this condition.[9] Low citrate concentration tends to facilitate calcium precipitation which is enhanced in alkaline or near-alkaline media. The citrate excretion in RTA is low, as we observed in S.S.

Fanconi Syndrome and Vitamin-D-resistant Rickets

The mechanism of the biochemical disturbance in vitamin-D-resistant rickets and Fanconi's syndrome is also obscure, but presumably based on enzyme dysfunction. In addition to a defect in tubular re-absorption of phosphorus,[10] an impaired gastro-intestinal absorption of calcium has been demonstrated in both these conditions.[11,12] In vitamin-D-resistant rickets this has been considered to be the main defect by some workers, the phosphaturia being secondary to hyperparathyroidism resulting from deficient calcium absorption.[13,14] In Fanconi's syndrome there is an impaired renal tubular re-absorption of sugar and amino acids in addition to phosphorus. It is also possible that many patients with the Fanconi syndrome have primary defects in the glomeruli as well as in the tubules.[15] The relation of cystine deposition to the tubular defect is obscure. A so-called 'swan-neck' anatomical deformity of the renal tubules has been described in cystinosis.[16]

Inheritance

All 3 of these conditions are genetic. Vitamin-D-resistant rickets is inherited as a sex-linked dominant, and Fanconi's syndrome as an autosomal recessive. Inheritance of RTA, at one time considered to be rare, now appears to occur fairly frequently.[8] This inherited predisposition makes a congenital enzymatic deficiency more probable than a deficiency secondary to some other process (e.g. renal infection).

Diagnosis, Therapy and Prognosis

These 3 syndromes can be distinguished by simple investigations (Tables IV and V). Rickets over the age of 2 years must always suggest a renal aetiology. When present, cystine crystals can easily be visualized in the cornea using a +40 lens.[17] (Not all patients with the Fanconi syndrome have cystinosis, but its presence is diagnostic.) Proteinuria may occur in both the Fanconi syndrome and RTA, but glycosuria and aminoaciduria occur only in the Fanconi syndrome. Nephrocalcinosis occurs only in RTA, and is present in 70% of cases.[18] Defective renal acidification and systemic acidosis are always present in RTA, but both these abnormalities may be present in Fanconi's syndrome.

TABLE IV. A COMPARISON OF THE 3 SYNDROMES OF RENAL TUBULAR DYSFUNCTION

	RTA	*Fanconi*	*Vit.-D-resistant rickets*
Rickets	50%	Most	All
Nephrocalcinosis	70%	—	—
Cystinosis	—	±	—
Glycosuria	—	+	—
Acidosis	+	±	—
Defective urinary acidification	+	±	—
Aminoaciduria	—	+	—
Hypopotassaemia	45%	±	—
Hyperchloraemia	+	—	—
Decreased gastro-intestinal absorption of calcium	?	Present	Present
Prognosis	Good (if treated)	Poor. Death at puberty, usually in uraemia	Good (even if untreated, life span probably normal)
Treatment	Alkalinizing mixtures. Small doses of vitamin D. Potassium	Large doses of vitamin D. Potassium	Large doses of vitamin D
Inheritance	Rarely obviously familial	Autosomal recessive	Sex-linked dominant

TABLE V. A COMPARISON OF THE 3 SYNDROMES OF RENAL TUBULAR DYSFUNCTION ACCORDING TO THE DEFECT PRESENT

	Anatomical and physiological defect	*Important results*
1. Vitamin-D-resistant rickets:		
	Diminished proximal tubular re-absorption of phosphorus	Low-phosphate rickets only
	Deficient intestinal absorption of calcium and phosphorus	Low-phosphate rickets only
2. Renal tubular acidosis (hyperchloraemic acidosis):		
	Inability to acidify urine (? exact mechanism)	Low-phosphate rickets Hypokalaemia Metabolic acidosis
3. Fanconi syndrome:		
	Swan-neck proximal tubule deformity with diminished re-absorption of phosphorus, glucose, amino acids, water	Low-phosphate rickets
	Frequent inability to acidify urine	Hypokalaemia
	Later glomerular damage	Metabolic acidosis
	Organ cystinosis (not in the 'adult form')	'Diabetes insipidus' Photophobia Uraemia and death

Hypopotassaemia may also occur in both conditions, but hyperchloraemia only occurs in RTA.

RTA is treated by means of alkalinizing mixtures and, in addition, potassium supplements if necessary. These must be administered for the remainder of the patient's life. Both healing of rickets and diminution of nephrocalcinosis have been reported on this therapy.[19,20] If the patient discontinues treatment (as in S.S.) rickets recurs, nephrocalcinosis increases and uraemia results. One hesitates to use vitamin D in the presence of nephrocalcinosis, but we were unable to observe any healing in S.S. after 3 months on citrate mixtures and therefore had to do so. We did not employ the massive doses necessary to effect healing in Fanconi and vitamin-D-resistant rickets. Orthopaedic correction of deformities will be necessary later.

Both in Fanconi's syndrome and vitamin-D-resistant rickets, high dosage of vitamin D is necessary to produce healing (in one case up to 1 million units daily). In addition, alkalis and potassium supplementation may be necessary in the Fanconi syndrome depending on the biochemical abnormalities. Although the therapeutic dose of vitamin D is high, the toxic dose remains similar to that in normal subjects, so that careful control is necessary when massive doses are used. Relapse of the rickets occurs if therapy is discontinued (as in D.A.), so that vitamin D must either be given continuously in smaller doses, e.g. 50,000 units daily, or in intermittent courses using high doses. In addition to increasing the tubular re-absorption of phosphorus in Fanconi's syndrome, vitamin-D therapy may cause diminution in glycosuria and aminoaciduria.[21,22]

The prognosis of these 3 conditions differs. In spite of adequate therapy all that can be achieved in Fanconi's syndrome (with or without cystinosis) is healing of rickets and correction of acidosis and hypopotassaemia. The children usually die of uraemia at puberty. Provided that therapy with alkalinizing mixtures is commenced early enough, before irreparable renal damage has ensued, patients with renal tubular acidosis can probably live a normal life span. Patients with vitamin-D-resistant rickets may survive to adulthood, even without treatment. There is no evidence that their life span is shortened.

SUMMARY*

We have discussed the case histories of 5 children suffering from rickets of late onset associated with renal tubular dysfunction. Fanconi's syndrome (with or without cystinosis), renal tubular acidosis (RTA), and vitamin-D-resistant rickets are all distinct syndromes. Nephrocalcinosis occurs only with RTA; the mode of inheritance, the prognosis and the treatment differ in the 3 conditions. There are, however, certain features common to 2 or all of them, notably systemic acidosis and failure to acidify the urine, which may occur in both Fanconi's syndrome and RTA; a defect in the gastro-intestinal absorption of calcium present in Fanconi's syndrome and vitamin-D-resistant rickets; and a low-phosphorus rickets with a diminished tubular re-absorption of phosphorus occurring in all 3. A better understanding of the association between these conditions must await elucidation of the basic enzyme defects, which are probably responsible for the disordered renal tubular and gastro-intestinal function.

We should like to thank Prof. F. Ford for enabling us to investigate most of these patients; S.S. was originally investigated by Dr. B. Zilberg. We thank Prof. J. Kench and the Department of Clinical Pathology, Miss M. Lloyd and Mrs. E. King for biochemical estimations; Mrs. E. Orkin for preparing the manuscript, and Mr. B. Todt for the photographs.

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ADDENDUM

Methods

Biochemical methods used were those reported previously by us [Jackson and Dancaster (1959): J. Clin. Endocr., 19, 658]. The phosphorus re-absorption was estimated from timed urinary collections with midway serum determinations, using endogenous creatinine clearance as a measure of the glomerular filtration rate. Phosphate intakes and times of day were kept near-constant.

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* This paper is presented mainly as a brief clinical account of the conditions described and does not attempt to enter into the complicated biochemical difficulties (e.g. cause of hypercalciuria, serum amino acids, parathyroid hyperplasia etc.). We have wittingly oversimplified the matter herein.