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Renal Tubular Disorders in Childhood

Dr. J. S. Cameron, M.D., B.Sc., F.R.C.P.*

The renal tubules are concerned with retrieval of large amounts of filtered metabolic substrates, which would otherwise be entirely lost into the urine in large quantities: and with the regulation of salt, water, potassium and bicarbonate. I shall only briefly mention these latter aspects, nor shall I have space to consider the effects of global renal failure with loss of functioning nephrons. We are concerned here only with what appear to be "primary" tubular disorders, which are not usually (at least in their initial phases) associated with histological changes in the kidney, or loss of glomerular filtering surface.

The transfer of substances from tubular lumen to peritubular capillary is carried out by a series of more or less specific transport mechanisms, many of which (and probably more than we realize at the moment) are under hormonal control. Disorders of this group of transport mechanism are of particular interest to the pediatrician, since many of them are inherited disabilities, either as a direct transport defect, or acquired because a generalized metabolic defect leads to the accumulation of some toxic metabolite.

The main substances which may be affected by tubular disorders are listed in Table I. Those listed in capitals have been the most studied because of their relative importance. In the space available, it is impossible to deal with *all* disorders of tubular function, and I shall give most attention to those that are both relatively common and relatively accessible to treatment.

I shall not consider further the rare conditions which appear to arise from an insensitivity of the renal tubule to normal or increased amounts of circulating hormone and these are summarised in Table II.

* Senior Lecturer in Medicine and Physician in Renal Diseases
Guy's Hospital, London, SE1 9RT.

TABLE I

FILTERED SUBSTANCES WHOSE EXCRETION MAY BE AFFECTED BY TUBULAR DISORDERS

Proximal tubule:	Distal tubule:
AMINOACIDS	HYDROGEN ION
GLUCOSE	WATER
PHOSPHATE	POTASSIUM
urate	sodium
organic acids	
protein	
bicarbonate	
sodium	

TABLE II

INHERITED RESISTANCE TO HORMONES IN THE RENAL TUBULE

Hormone	Part of tubule	Lost in excess	Condition	Inheritance*	ref.
ADH	distal	water	nephrogenic diabetes insipidus	SLR	1
PTH	proximal	phosphate	pseudohypoparathyroidism	SLD	2
Aldosterone	distal	Na^+,Cl	pseudohyperaldosteronism		3
?	proximal	K^+,Na^+ Cl	Bartter's syndrome	?R	4

* SLR sexlinked recessive
SLD seklinked dominant.
D dominant
R recessive

The inclusion of Bartter's syndrome, (familial renal hypoelectrolytaemia) (4) in this group might be contested, since this may be a primary disorder of electrolyte transport. I include it here because of the very high renin and angiotensin levels these patients exhibit.

Disorders of the *proximal tubule* may be primary or secondary, specific or multuple. *Renal glycosuria*[5] is a very common specific transport defect, inherited as a dominant characteristic and affecting perhaps 1% of European populations. Varieties have been described with different types of transport defect. The condition has little clinical im-

portance in children, except that it occasionally contributes to hypoglycemia in infants, it may lead to confusion as to whether diabetes mellitus is present or not when the urine is tested.

AMINOACIDURIAS

All aminoacidurias result in an increased excretion of alpha-amino nitrogen minhydrin-positive material. Individual aminoacids can be separated very simply by 2-dimensional paper chromatography or one-dimensional high voltage electrophoresis, and both these methods can be used for screening. For detailed study and for measurements of plasma levels and clearances, ion exchange resin chromatography is needed, and has greatly increased our knowledge of aminoacidurias.

Specific renal aminoacidurias are rather rare, but at least one *(cystinuria)* is of clinical importance. Aminoaciduria may of course result from the accumulation or overproduction within the body df aminoacids ("overflow" aminoaciduria), in which case the plasma level of the aminoacids concerned is high or normal. I will deal with *generalized aminoacidurias* in the next section.

Specific Aminoacidurias

Study of clinical aminoacidurias, of the maturation of aminoacid tubular transport in infancy, of in vitro transport, and of infusion of single amino acids has lead to the idea that there are five major groups of aminoacids whose transport is inherited in a closely linked fashion, and of which transport defects may be seen (Table III). In at least

TABLE III

GROUPS OF AMINOACIDS WHOSE TRANSPORT IS INHERITED IN A LINKED FASHION

Group	Amino Acids	Clinical transport defect	Inheritance	Ref.
1) Dibasic aminoacids	cystine, ornithine, lysine, arginine	cystinuria	recessive	6
2) Neutral aminoacids	13 in number	Hartnup disease	recessive	7
3) Iminoacids	Glycine, proline and hydroxyproline	Iminoaciduria	recessive	8
4) Dicarboxylic acids	glutamate and aspartate			
5) B-amino acids and taurine				

the first three groups the transport mechanism in the gut is controlled by the same gene and is similarly group specific. However, closer examination of the data suggests that, despite this linked inheritance, an individual transport mechanism for *each* and every aminoacid best explain the observed facts: this point is considered further in the section of cystinuria.

Hartnup Disease[7] and *iminoaciduria*[8] are both excessively rare, and the latter appears to be harmless. Patients with Hartnup disease resemble those with pellagra, having a photosensitive dermatitis and a cerebellar-like ataxia. This may result from faulure to absorb tryptophane whilst losing it in the urine, and nicotinamide should be given for life.

Cystinuria[6] is in contrast relatively common. The incidence of homozygotes has been reported as frequently as 1:2000 n European and North American populations, but a frequency of around 1:20,000 is more likely.[6] In children it forms a higher proportion of calculi than in adults, and is an important cause of stones in Western Europe. In Turkey, with its much higher incidence of renal, ureteric and bladder stones in children, the proportion is much smaller: in a recent series of over 1000 calculi in children studied at Hacettepe[9] *none* were cystine stones, perhaps suggesting a lower carriage for the gene than in Britain, Scandinavia or the U.S.A.

However, all patients with stones should have their urine screened for excess cystine by the simple nitroprusside cyanide test, since cystinurics may form oxalate or uric acid stones, and cystine stones may calcify. Interestingly, several families showing cystinuria associated with hyperuricemia have been described[10]. The bowel defect in aminoacid transport (particularly lysine), may account for the rather small stature of cystinurics.

In general, heterozygote cystinurics have aminoacid excretions indistinguishable from normal, and this has been the case in all the presumed heterozygotes we have examined. There is, however, a less common, incompletely recessive form, characterized by heterozygotes with detectably abnormal aminoaciduria, whilst gut transport in homozygotes is relatively well preserved; and Rosenberg and his colleagues have suggested three genetically distinct forms[11].

Normally, cystine, ornithine, arginine and lysine are all excreted in excess, and it was this observation that led to the suggestion of a common transport mechanism for this group. However, citrulline is a dibasic aminoacid and is not lost in excess in cystinuria, and patients who excrete cystine alone without an excess of any other dibasic amino-

acids have been described. The mixed disulphide of homocysteine and cystine is always present in excess in the urine as well as the classic four aminoacids[12], and recent work in our laboratory[13] shows that cystinurics excrete homoarginine in excess. Excess glycine excretion has been reported in some patients, but we have yet to observe this ourselves. These observations indicate that the simple classification outlined in Table III should not be taken too literally, although it is clinically useful.

Most of the clinical problems associated with cystinuria center around the relative insolubility of cystine in normal urine, and the tendancy to form stones in any part of the urinary tract, leading to infection and obstruction. How many cystinurics exist in the population *without* forming stones is not clear, but all the homozygotes we have studied formed stones: that is, there were no undiscovered homozygotes amongst the siblings of known stone formers. The peak decade for clinical presentation is the 30-40 period, and in one series the average age at death in cystinurics was 37 in males and 54 in females[14]. The condition is thus a serious one.

The *treatment* of cystinuria[15] with stones naturally centers in the first instance around the surgery and chemotherapy of stones and urinary tract infections. Cystinuria, howover, is unique amongst causes of urinary lithiasis in that one can not only present further stone formation but actually dissolve stones already present. This is most efficiently done by maintaining an *alkaline diuresis*[16] throughout the 24 hours of the day. To establish this requires close co-operation between parent, child and doctor. A urine output of 50 ml/kg/day should be obtained throughout the 24 hours of the day. A drink before bedtime, and awakening to pass urine and drink again at 3 or 4 a.m., ensures that-this intake and output is evenly distributed throughout the 24 hours. Meanwhile, $NaHCO_3$ is given to promote alkalinization of the urine and thirst. The amount needed will be found by testing the urine, but to start with 1g four times a day may be tried, and increased as necessary. The dose should be given as capsules or syrup, and if tablets are used should *not* be enteric coated. The urine is tested using pH paper with a range of 5-10 and registering at least 0.5 pH unit)*, and the mother instructed in its use. Cystine is four times as soluble in urine of pH 6.0; and pH readings of 7.5 or 8.0 should be obtained in *all* urine specimens, especially the early morning urine. Once the dose has been adjusted then occasional weekly tests of early morning urine are all that is needed.

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* e.g. Whatman-BDH NR 6-8

Other treatments have also been used. The value of *low methionine diets* has been advocated and disputed[6,17]. We have used this in patients such as a girl who excreted 96% of her filtered cystine. Essentially the aim is one of reduction of animal protein, but at least 1.6-2.0 g/kg/ day of protein should be fed to maintain growth. *D* (+) *Penicillamine* and its n-acctyl derivative solubilize cystine as a mixed disulphide, and have been used[18] in patients in whom alkalinization is unsatisfactory. However, the drug is extremely expensive, and produces proteinuria and a nephrotic syndrome in a high proportion of patients.

Generalized aminoacidurias:

In this group of conditions all, or most aminoacids are detectable in excess in the urine. This is rarely (if ever) the only finding and there is usually an excess of glucose, phosphate and sometimes bicarbonate, urate and other organic acids in the urine. To these *multiple defects of proximal tubular function* the name of "*Fanconi syndrome*" is now firmly attached, often combined with those of others who have studied this condition: Debre and de Toni. It is unfortunate that G. Fanconi's name is also still often associated with *cystinosis (cystine storage disease)*[20] along with that of Lignac, since cystine storage disease is an impotant, but by no means the only cause of this type of multiple tubular defect (Table IV). This table indicates the many primary and other causes of the syndrome, and possible causes should be carefully sought before assuming that the very rare "primary" or "idiopathic" form of the disorder is present. This primary disorder has sometimes been referred to as "benign familial aminoaciduria", but the original family described by Sheldon et al.[19] is now under our care; the father is in advanced renal failure aged 47, and both affected twin daughters show some impairment in glomerular filtration rate in their twenties. In particular careful slit lamp examination of the eyes for cystine crystals should be made, and the lencocyte cystine concentration measured, since cystionsis has such an adverse outlook. Whether or not renal failure can occur after a time has not yet been established clearly for all the circumstances listed in Table IV. Rickets and acidosis are the important clinical manifestations, but are dealt with below together with the more specific tubular disorders causing these states.

The aminoaciduria seen in some bone diseases characterized by raised plasma parathormone levels is also discussed in the next section.

PHOSPHATURIA AND VITAMIN-D RESISTANT RICKETS

Rickets may, of course, occur in association with Vitamin D deficiency in the diet, in gastrointestinal disorders leading to Vitamin D malab-

TABLE IV

CAUSES OF MULTIPLE PROXIMAL RENAL TUBULAR TRANSPORT DEFECT ("FANCONI SYNDROME")

Type	Condition	Toxic substance	Inheritance*	Renal failure eventually	Ref.
Primary	–	?	Usually D some R	Some	19
2° To inborn errors of metabolism	cystinosis	cystine	R	yes	20
	galactosaemia	galactose 1-P	R	no	21
	Wilson's disease	copper	R	no	22
	Lowe's syndrome	?	SLR	?	23
	tyrosinosis	?	R	no	
	glycogen storage disease	glycogen	R	no	24
Acquired in course of other diseases	nephrotic syndrome	? protein	–	some	25 2
	myeloma	? Lr. chain	–	yes	
Acquired from exogenous poisons	heavy metals	Pb, Cd, Au, Hg, U, Bi.	–	some	
	antibiotics	streptomycin	–	no	
		kanamycin	–	–	
		bacitracin	–	–	
		polymyxins	–	–	
		neomycin	–	–	
		degraded tetracycline	–	–	
		amphotericin B	–	–	
	salicylates	salicylates	–	–	

* R recessive
D dominant
SLR sexlinked recessive

sorption, and as a component of renal osteodystrophy from chronic uremia (see P.). Rickets is also seen however, in three disorders which arise from tubular disease, and in each case is resistant to treatment with doses of vitamin D which will heal nutritional rickets:

i. as part of multiple proximal tubular defects (Fanconi syndrome)
ii. in pure phosphaturia
iii. in renal tubular acidosis (see below)

The clinical situation is further complicated by the fact that in nutritional rickets or osteomalacia,[26] and in primary hyperparathyroidism,[27] a reversible aminoaciduria may develop sometimes in association with defects in urinary acidification. These changes appear to be dependent upon raised plasma P. T. H. levels since they can be produced experimentally by injections of the hormone.[28] Careful study of each patient who presents with rickets and aminoaciduria may be necessary before a full diagnosis can be made.

Phosphaturia associated with hypophosphatemia and vitamin D-resistant rickets[29] may be seen as an isolated finding. The condition is inherited as a sex-linked dominant and the gut absorption of phosphate is probably also deficient.

About half the affected males present with rickets in the second year of life. Females may develop osteomalacia later in life. The plasma calcium tends to be normal and tetany is rare, but the alkaline phosphatase is raised. Treatment is with the minimum dose of vitamin D required to produce healing, controlled carefully by plasma biochemistry. Each patient has to be individually titrated, since the dose needed may vary up to 50,000 u/day. A phosphate supplement of 1-4 g/day should also be given either as calcium phosphate or neutral (Na-K) phosphate.

In patients with a Fanconi syndrome and rickets, from whatever cause, treatment with extra phosphate (together with bicarbonate if there is acidosis) may be sufficient to heal the rickets and this should obviously be tried first before resorting to the much more toxic vitamin D. In patients with prominent bicarbonate loss and a proximal tubular type of renal tubular acidosis, hydrochlorothiazide may prove useful (see below).

RENAL TUBULAR ACIDOSIS[30]

The form of tubular acidosis due to bicarbonate wasting in the *proximal tubule*, and usually part of multiple proximal tubular transport defects, has already been mentioned.[31] Much more common, however, is that arising from or an inability of the *distal tubule* to maintain a gradient of hydrogen ions between the blood and tubular fluid and this was the form first described[32] and usually referred to as "classical" or "distal" renal tubular acidosis. Both types may occur rather rarely as

what appear to be primary defects of tubular function. However, both usually occur as a result of other disease. All the causes listed in Table IV may lead to proximal renal tubular acidosis, as well as some others such as fructose intolerance. A great variety of conditions may also be associated with distal renal tubular acidosis: hyperthyroidism, vitamin D intoxication, vitamin D deficiency "idiopathic" hypercal- "idiopathic" hypercalcemia, hyperglobulinemia and intoxication with a number of drugs, particularly amphotericin B, and in association with obstructive uropathy, pyelonephritis with vescicoureteric reflux, potassium depletion and following transplantation.

Th essential difference between the two forms of the condition (which has therapeutic and diagnostic importance) is shown in Figure 1. In the *classical distal form* there is an inability to excrete an acid urine even when the plasma bicarbonate is lowered to 15 mM/l or less. Whether this group *could* acidify their urine if the bicarbonate was taken much lower (say to 5 mM/l) does not appear to have been tested. In contrast, when patients with *proximal renal tubular* acidosis are given ammonium chloride, the urine can be acidified, although at a lower bicarbonate level than that at which the normal person achieves maximum acidification. This means that a standard ammonium chloride

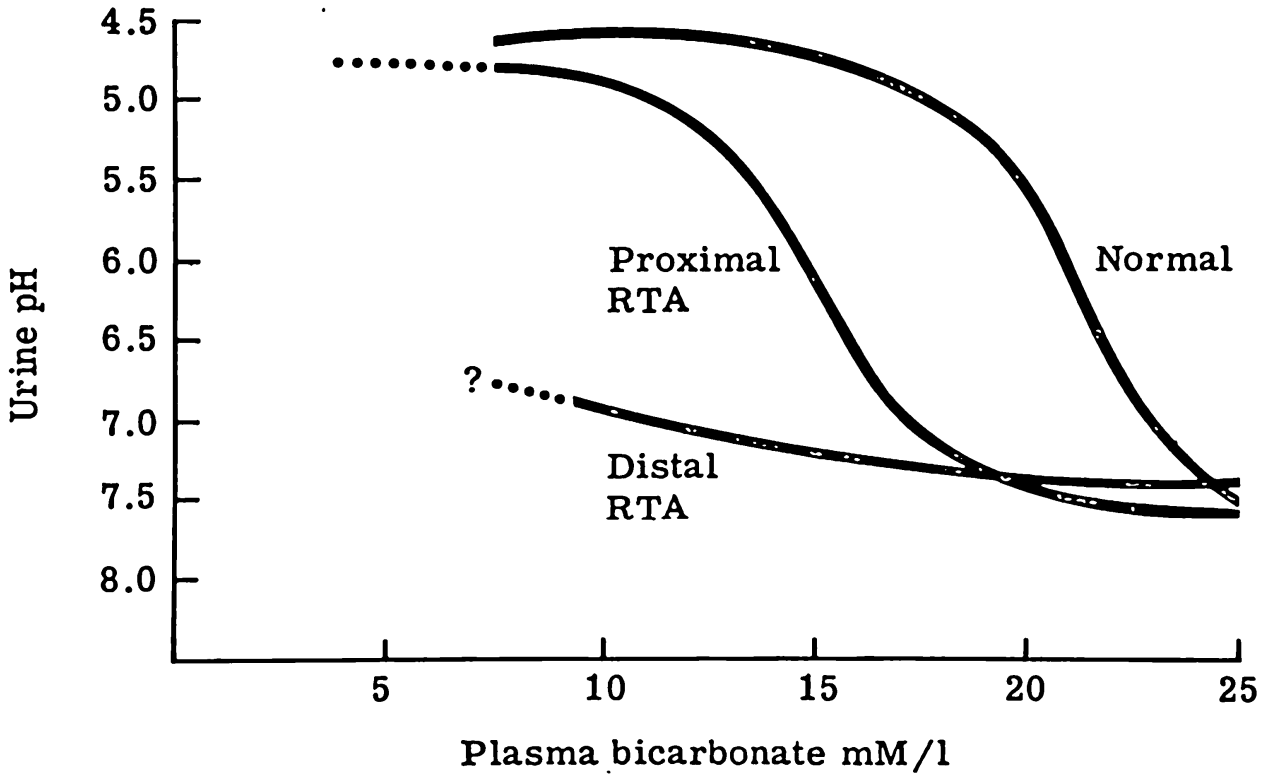

Figure 1

The different behavior of normal children, and children with proximal (bicarbonate wasting) and distal (gradient) renal tubular acidosis. See text for fuller explanation. Adapted from the data of Soriano et al. (31).

load (0.1 g/kg) may show good acidification with a urine pH of 5.3 or less, ev n though proximal renal tubular acidosis is present and the resting plasma bicarbonate is low.

The classical "primary" form appears to be a condition which shows itself in a 6-18 months age group, without any obvious pattern of inheritance, although in the reported series female infants exceed males by 2:1. The commonest picture is a nonspecific one of "failure to thrive" and renal tubular acidosis should be on the diagnostic checklist for such infants. Constipation, dehydration, anorexia, vomiting and som times hypotonia may be seen. Mild, reversibl: uremia may be present.

Investigations should include a plasma bicarbonate (usually below 20 mM/l) and chloride (usually 105 mM/l or more) and a urine pH which usually shows 7.0 or above. A search for glucose and excess aminoacids in the urine should be made, and the plasma phosphate should be measured. A straight x-ray of the abdomen may show nephrocalcinosis in longstanding cases, and x-rays of the bones may demonstrate rickets with an associated raised plasma alkaline phosphatase. An ammonium chloride load sufficient to depress the plasma HCO_3 to 15 mM/l or less will not change the urine pH in patients with distal renal tubular acidosis, but in patients with proximal renal tubular acidosis only the more elaborate bicarbonate titration may reveal the defect. Investigation should of course also be directed towards possible causes for the conditions, and primary disorder be diagnosed only by exclusion. Primary distal renal tubular acidosis is now quite rare in th United Kingdom, and is not found in breast-fed infants. The more cautious use of Vitamin D in dried milk may have contributed to this decline in incidence,[33] as well as the discontinuance of mercury-containing teething powders.

The principal clinical problems which may be encountered are dehydration from the excess loss of cations and water along with bicarbonate in the urine, bone disease of a rickety type, and nephrocalcinosis or stones. The latter finding has still not been properly explained but probably relates to the relative hypercalciuris, alkaline urine and reduced citrate excretion found in these patients. Hypokalemia is much less common in children than in adults.

The *correction of the acidosis* and *maintenance of fluid intake* are the first steps in treatment. Larger amounts of sodium bicarbonate (0. 5-1.0 g/kg/day) will be requried in children with proximal renal tubular acidosis than in the distal form who need only 0.2-0.4 g/kg/day[39]

to correct the acidosis. In the proximal form of renal tubular acidosis, *hydrochlorothiazide* (2 mg/kg/day) has been successfully used in an idiopathic case, and in patients with Lowe's syndrome and cystinosis.[34] The reason why this drug is effective is not yet clear, but the most likely of several possibilities is that the plasma volume contraction induced by the diuretic increases bicarbonate reabsorption. The most interesting effect is that this drug may also heal the rickets of proximal renal tubular acidosis, whether associated with hyperphosphaturia or not. It reduces calcium and phosphate excretion as well as reducing bicarbonate loss, and even if a phosphate supplement is not given as well the rickets may heal.[32] This is especially important, since in patients with renal tubular acidosis administration of *vitamin D* without correction of acidosis could worsen nephrocalcinosis.

In distal renal tubular acidosis, however, there is no reason to suppose that hydrochlorothiazide will help since the bicarbonate threshold is normal. Here, if rickets is present it may often need to be treated with vitamin D: the dose must be carefully controlled and 5-15,000 u/day is usually sufficient. Sodium bicarbonate and oral neutral phosphate should always be tried first, and both continued along with the vitamin D.

The long term prognosis of infantile forms of renal tubular acidosis, and their relationship (if any) to those patients who present similarly in adult life, is still in dispute.[35] Clearly the prognosis in secondary cases will depend upon the primary disorders: the outlook for patients with cystinosis is grim.[17] In the majority of "idiopathic" patients the outlook appears to be good, although long-term studies are very few in number. Adult onset patients may be related to some forms of idiopathic renal tubular acidosis, but rarely have an obvious etiology, and frequently present with nephrocalcinosis, K+ wasting, stone formation and some degree of uremia.

Conclusions

None of these primary r nal tubular disorders is common, but some are treatable and cripple without treatment. Also, they have much to teach us about renal and general physiology, especially in the areas of amino acid, bicarbonate and hydrogen ion transport.

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