RICKETS AND OSTEOMALACIA FROM RENAL TUBULE DEFECTS *

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The diagnosis of "renal rickets" is often made uncritically in any patient who has clinical and radiological signs of rickets and evidence of renal damage. The rickets in these cases is also characterised by being "Vitamin D resistant," that is, irresponsive to vitamin D in doses (1,000–10,000 units a day) which rapidly cure ordinary "classical" rickets. Histologically, however, the appearances of renal rickets may be either identical with those of ordinary rickets or complicated and obscured more or less by the fibrosis of secondary hyperparathyroidism. The renal failure nearly always shows the chemical changes characteristic of chronic nephritis. These changes (retention of urea, phosphate, creatinine, etc.) are the direct consequences of a slowing of glomerular filtration. Defects of kidney tubule function are not usually easy to demonstrate apart from the poor ammonia formation and the inability to pass an acid urine which are almost invariably present.

Recent studies of "renal rickets" have now tended to separate off a group of cases in which the renal damage does not take this more common form, and in which the prognosis and response to treatment may be altogether different. In this group the emphasis is on renal tubular damage rather than on defective glomerular filtration. There is no, or only slight, retention of urea and creatinine. This is shown by the normal or only slightly raised blood levels and normal or only slightly lowered clearance for these substances. The plasma phosphate is usually abnormally low. The urine may contain large quantities of substances (glucose, amino-acids) which under normal circumstances are almost completely reabsorbed by the tubules from the glomerular filtrate and so do not appear in the urine to any appreciable extent.

The literature on this subject has become somewhat confused, partly for the reason that the same word "renal rickets" has been indiscriminately applied to a group of quite different diseases, and partly because too many new words have been coined to describe some of the variations. Perhaps better names for the two main types would be "glomerular rickets" and "tubular rickets."† It must be granted that some cases of "tubular rickets" terminate in a uraemic stage and are then almost indistinguishable from cases of primary "glomerular rickets," and also that there is probably tubule damage in all cases of "glomerular rickets." Nevertheless, recent biochemical advances perhaps justify the attempt to be made here to reclassify the forms of "tubular rickets," namely those forms of rickets resistant to vitamin D in which the kidney dysfunction is mainly concerned with the various known actions of the renal tubule. The "tubular osteomalacias" are considered at the same time, because there appear to be adults with kidney tubule dysfunction almost identical biochemically with each of the types found in children.

CLASSIFICATION

Radiographically, the diseases shown in Table I may be indistinguishable from each other. They are divided into six types. Each type may occur at almost any age, in either sex and in acute or chronic form. It is important to distinguish them from each other as they have different treatments and prognoses. Differential diagnosis is largely a biochemical

* From a paper read at the Annual Meeting of the British Orthopaedic Association in London, October 1950.

† The tendency in the more recent literature has been to restrict the term "renal rickets" to the "glomerular" form and to use various new names for the "tubular."

matter. I have tried in the Table to represent this difficult group of cases in a tidy manner which suggests that the first four types can be classified in a way that illustrates an increasing severity of tubule damage affecting one after another the various tubule functions. This suggestion may be found misleading because in other diseases many other combinations of individual tubule dysfunctions may also occur. "A high renal clearance"* for phosphate, presumably due to defective tubular reabsorption, occurs in all the conditions listed in Table I, but this is because we are dealing here only with bone diseases, and it is the low plasma phosphate level which more than anything else is the cause of the bone disease and must therefore be present. We should remember, however, that a high clearance for glucose, for instance, can occur without the phosphate defect, as in ordinary renal glycosuria. A high clearance for amino-acids may also occur without the glucose or phosphate defect, as in some cases of hepatolenticular degeneration, as in all cases of cystinuria (Dent and Rose 1951) and as in some apparently healthy people. Indeed almost any permutation and combination of

TABLE I
RICKETS OR OSTEOMALACIA ASSOCIATED WITH DEFECTS OF TUBULE FUNCTION
(and sometimes with other metabolic defects)

Type	Tubule reabsorption defect				Tubule function defect		Names used in literature to describe these syndromes
1	Phosphate						Resistant (or refractory) rickets, raised late rickets, resistance to vitamin D (RRD), essential hypophosphataemic rickets, idiopathic osteomalacia, Milkman's syndrome
2	Phosphate	Glucose					
3	Phosphate	Glucose	Amino-acids	Water*			Fanconi syndrome, Debre-de Toni-Fanconi syndrome, Lignac's disease, cystine rickets, cystinosis, rickets with cystinuria, amindiabetes, diabetes aminicus et acidaminicus, "renal rickets," (?) hepatic rickets, hypophosphataemic glycosuric rickets
4	Phosphate	Glucose	Amino-acids	Water*	Potassium*	Urine acidification	
5	Phosphate				Potassium*	Urine acidification	Nephrocalcinosis with renal rickets and dwarfism, hyperchloraemic nephrocalcinosis, Butler-Albright syndrome, renal tubular acidosis
6	Phosphate				Potassium*	Urine acidification	Ammonia formation

* Defect not always conspicuous.

tubule defects may be met in clinical practice. Another misleading feature in Table I is that "amino-acids" are grouped in one category as if one substance only was involved. In fact there are over twenty amino-acids commonly found in body fluids, and the individual amino-acids involved are not the same in all cases. Finally, the six categories are not in fact clearly separable from each other except (so far) into two main sub-groups, namely, the first four (Types 1 to 4) and the last two (Types 5 and 6). Within each of these sub-groups the categories are not easily distinguishable and cases occur which it is difficult to place in a distinct category.

A hereditary tendency in all the diseases in the first four categories links them not only with one another but also with most of the tubule reabsorption defects not associated with bone disease which are usually hereditary. In contrast, the last two categories are never

* This term is used in preference to the older term "low threshold" because the existence of sharp kidney thresholds for most substances is now largely discredited.

hereditary; seemingly the cause here is not genetic but environmental, for instance an acquired infection or some kidney toxin.

It is hoped that, in spite of its shortcomings, the classification in Table I makes the various syndromes more comprehensible. An important prognostic feature to be drawn from it is the much greater chance of fatal kidney failure as one proceeds from Type 1 to 4. It seems that the more extensive the affection of the tubule, the greater is the associated glomerular damage, although this is always relatively inconspicuous early in the disease. This is shown, among other things, by the presence of proteinuria and of a lowered urea clearance. It is Type 4 that often terminates in uraemia.

I am hesitant to attempt the imposition of a rigid nomenclature in the group of diseases discussed here. Some objection may also be raised to the classification in "Types." An alternative classification that is more in keeping with previous usage and that would not wander too far from the aims of the present paper would be to reserve the term "resistant rickets" for my Types 1 and 2, "Fanconi syndrome" for my Types 3 and 4, and "renal tubular acidosis" for my Types 5 and 6.

CLINICAL TYPES

Type 1. Defective phosphate reabsorption only—Thirty-three cases were studied.* These comprise most of the cases commonly classed as "vitamin D resistant rickets." This term describes well a condition clinically indistinguishable from rickets which occurs in spite of adequate vitamin D in the diet. Moreover, it can be cured by increasing the intake to the enormous level of hundreds of thousands of units of the vitamin daily. It appears therefore at first sight as if the patient's "vitamin D requirement" is raised but that he is otherwise normal.

I should like to postulate here a different conception of the immediate mechanism of the disease process, namely, that the low plasma phosphate level which is generally conceded to be the cause of the bone disease is the result of an inherited defect of the renal tubule, namely of its ability to reabsorb phosphate from the glomerular filtrate. This does not cause a "phosphaturia," because the urine contains only slightly more phosphate than usual. That this occurs however at a plasma level often maintained for long periods below that (about 2.0 milligrams per cent) at which minimal phosphate excretion normally occurs, clearly indicates the presence of a higher phosphate clearance than normal. According to this view vitamin D in massive doses cures because it is able to increase phosphate reabsorption by the tubule. This explanation does not involve the parathyroid gland and is therefore quite different from the more usual view vigorously put forward by Albright and his co-workers (Albright and Reifenstein 1948). In favour of this theory the following facts are also added: 1) The term "vitamin D resistance" is better avoided, as vague. One could argue that cases of steatorrhoeic rickets and of "glomerular" renal rickets are also "resistant" to oral vitamin. 2) The main action of vitamin D is to facilitate absorption of calcium from the gut. In classical rickets from lack of vitamin D this absorption is markedly impaired so that calcium is practically absent from the urine. In some cases of "resistant rickets" these signs of vitamin D lack are not fully present. 3) The difference between a curative and a toxic dose is far smaller in these cases than in a true rickets. The "resistance" is therefore curiously selective. 4) The concept of "vitamin D resistance" does not help us to explain the frequent association with other congenital tubule defects (Types 2 to 4) which have nothing to do with vitamin D.

These Type 1 cases usually present as a typical but often severe rickets in infants about one to two years of age. Permanent deformity is common in these otherwise healthy

* I should explain that when I say, here and elsewhere, that I have studied "x" cases of this or that rare disease, I have not had most of them under my clinical control.

patients who usually live to adult life. Biochemically identical cases occur occasionally in adolescents and adults, with bone changes typical of osteomalacia. Of the thirty-three patients studied, seven were over twenty years of age. The adult patients are usually in good general health, but may suffer from bone pains, especially in the lower back. Severe muscular weakness may suggest a diagnosis of muscular dystrophy. The difficulty of localising the pain and of producing any clear sign of disease may lead to a diagnosis of neurosis; for instance hysterical paralysis was suspected in one patient, a well built man of fifty-three years who had so much weakness and pain on movement that he lay all day in bed almost motionless. These patients never have proteinuria or disordered glomerular function and the only constant biochemical findings are the low plasma phosphate (often 1-2 milligrams per cent) and, usually, a raised alkaline phosphatase.

FIG. 1

FIG. 2

Figure 1—Pseudo-fracture of the lateral margin of the scapula revealed by an oblique radiograph of the chest of a patient with osteomalacia (Type 1). This is the commonest site, but the lesion may be obscured unless the radiograph is made in a special plane. Figure 2 shows enlarged view of the affected area.

Type 2. Defective phosphate and glucose reabsorption—Four cases were studied. This group is not clearly demarcated from the first, for the glycosuria was only pronounced (above about 0.5 per cent) in one case and was mild and intermittent in the other three. The link with Type 1 is probably close, because my series includes two brothers, one belonging to Type 1 and the other to Type 2. Moreover there are also two cases of osteomalacia associated with von Recklinghausen's neurofibromatosis, a rare condition but one which Albright (private communication) believes to be more than a mere coincidence (see also Gould 1918); one of these belongs to Type 1 and the other to Type 2, the latter being our only case with marked renal glycosuria. It is curious that all four cases have occurred in adults. All the Type 2 cases have otherwise been identical clinically and biochemically with those of Type 1. Milkman's (1934) original case was probably of Type 2 because there was definite renal glycosuria. As far as I am aware the association of renal glycosuria and osteomalacia without

the added features of the Fanconi syndrome (Types 3 and 4) has not been commented on before.

Type 3. Defective reabsorption of phosphate, glucose and many amino-acids—I cannot give figures for this group because its distinction from Type 4 is based largely on the presence or absence of acidosis and it is not possible to draw a clear line between acidotic and non-acidotic cases. The numbers of Types 3 and 4 are therefore taken together (see Table). It seems that the acidotic cases are more common than the non-acidotic, especially in children.

This group shows a spectacular biochemical differentiation from Type 2, namely the occurrence in the urine of large quantities of many (ten to twenty) amino-acids. This "amino-aciduria" occurs in only a few other conditions and is readily detectable by paper chromatography (Dent 1951). It is usually gross, but in one of our cases it was slight. The blood levels of amino-acids are normal or slightly raised; so the mechanism of their excretion is mainly a high renal clearance, just as in the case of glucose. The output of amino-acids and of sugar varies from day to day; so it is well to have several samples of urine analysed. The renal tubule dysfunction is clearly more widespread in Type 3 than in Types 1 or 2. Nevertheless it is consistent with fair general health, although the ultimate prognosis seems poor. One patient, now a boy of eleven years, has been observed for three years and his condition is clinically indistinguishable from Types 1 and 2. Another patient, who had required multiple osteotomies in childhood, presented severe osteomalacia at the age of thirty-four, and died soon afterwards from cirrhosis of the liver with primary hepatoma. I have seen only one other case with this complication, but, as these were the first two cases in my present series, I overstressed its importance in a previous publication (Stowers and Dent 1947). It is common for these cases to show a mild polyuria; this suggests a minor tubular defect of water reabsorption.

Type 4. Defective reabsorption of phosphate, glucose, many amino-acids, often water and sometimes (perhaps often) of potassium, with defective acidification of urine—Twenty-five cases of Type 3 and 4 together have been studied. These types are probably less common in relation to Types 1 and 2 than my figures suggest, because there has been some selection in referring cases to me. Of these twenty-five cases, twenty have been in children under ten years of age; the others have been in adults, one presenting at fifty-one years of age. The essential clinical feature of these acidotic cases is that the symptoms are more marked and the prognosis worse than in any of the other types so far discussed. The biochemical features indicate a renal tubular damage which affects more of its functions than in the other types and progressive glomerular damage is often found.

The children are usually brought for advice at one to two years of age. Often parents have noticed difficulty in making the baby take its food and failure to gain weight. It may vomit its meals; it may be very thirsty; it is usually constipated. At this stage it usually shows rickety deformities, but these may be mild and do not usually affect the skull. The rickets is "resistant" to ordinary doses of vitamin D. On examination the child is wasted, limp and often pot-bellied, and is physically underdeveloped. Radiography reveals rarefaction of the skeleton and rickety epiphyseal changes. The urine is dilute, neutral or alkaline, and contains protein, glucose and large quantities of amino-acids. It may have a high ammonia index. The plasma has a normal fasting glucose content, normal urea, a low phosphate and bicarbonate, and usually a high alkaline phosphatase. One or other of the clinical features may be prominent, so that the obvious sign in the first instance may be rickets, feeding difficulty, failure to thrive, "diabetes insipidus," or even constipation. Other features, even the bone disease, may be absent. The picture is greatly confused by curious febrile attacks, sometimes attributed to dehydration and at other times unexplained, and by episodes of muscular weakness, lethargy or even coma, sometimes with severe acidosis. These attacks may cease spontaneously, or may be fatal. I think that many, if not all, of these symptoms are due to electrolyte disturbances, and also that a high renal clearance for potassium occurs

in many cases and leads to low-potassium attacks which may be the cause of death. High potassium clearance had been demonstrated in the only two of our cases in which the potassium metabolism has been investigated (with Dr A. G. Spencer) and was undoubtedly the cause of death in one of them.

Another curious feature is that some of the children with Type 4 disease had widespread deposits of cystine crystals (cystinosis) in the tissues. The crystals can be best demonstrated in life by examining the cornea with the slit lamp (Bickel and Douglas 1950).^{*} The minute sparkling crystals are seen throughout the cornea and on the conjunctiva. The incidence of these cystine deposits is high in Type 4 cases. Their discovery is of prognostic importance because most patients with them have died before the age of ten years. The formation of cystine deposits is the only feature that cannot yet be explained adequately by any theory involving the renal tubule, or indeed by any other theory.

The cause of death is intercurrent infection, coma (usually called acidotic but possibly often low-potassium) or, when survival is prolonged, uraemia. The rare tendency to cirrhosis and primary hepatoma has been mentioned already. When uraemia develops it is associated with the expected changes in the blood chemistry; that is, the phosphate rises and the calcium may fall even to tetany levels. It may be impossible at this stage, unless cystine deposits are found, to distinguish such a case from "renal rickets" of the type primarily affecting the glomerulus.

Cystine is usually one of the amino-acids that are excreted in large quantities in the urine of these cases. Hence it is easy to apply to them the term "cystinuria" and to confuse this Type 4 syndrome with the more common condition, also called "cystinuria," in which otherwise healthy people constantly excrete large quantities of cystine in the urine and have a tendency to form cystine stones in the renal tract. In fact, these two conditions are distinct from each other clinically, biochemically and genetically (Dent and Rose 1951, Dent and Harris 1951). The correct diagnosis of "cystinuria" is readily made by paper chromatography of the urine (Dent 1951).

The rare adult cases of the Type 4 syndrome may present at almost any age, but mostly between thirty and forty-five years. There is less systemic disturbance than in the children; indeed the general health may be good. Apart from thirst, polyuria and muscular weakness (which may not be present) the illness is dominated by the bone disease, which resembles osteomalacia of any other type. The pain is most commonly felt in the lower back and down the thighs but "rheumatic" pains in the limbs and feet are also common. Early diagnosis is difficult and the history therefore tends to be of several years duration and may include periods of psychiatric treatment. The patient may ultimately become bedridden. On examination there may be tenderness over some of the bones, and there may be evidence of bone deformity or old fracture. Radiographs show gross rarefaction of the skeleton and typical pseudo-fractures or Looser's *Umbauzonen* (Figs. 1 to 3). The plasma has usually normal or only slightly raised urea content, normal glucose, low phosphate, low bicarbonate and usually raised alkaline phosphatase. The urine contains a trace of protein, is always neutral or alkaline, and contains glucose and high concentrations of many amino-acids. No adult case of the

FIG. 3
Pseudo-fractures of ribs in an adult with Fanconi's syndrome (Type 4) and more than thirty pseudo-fractures.

^{*} Personal communication. See also BURKI, E. (1941): *Anales Paediatrici*, 156, 324.

Type 4 syndrome has yet been reported with cystinosis. These patients can be greatly improved by treatment (see later) but as none has been followed long enough we have no idea yet of the ultimate prognosis. One might expect ultimately renal failure.

Types 5 and 6. Defective tubular function with respect to urinary acidification and ammonia formation, the resulting acidosis leading to decreased phosphate (and sometimes potassium) reabsorption—Five cases were studied. This syndrome has been described by Albright and Reifenstein (1948), who were the first to stress the concept of tubular-insufficiency-without-glomerular-insufficiency in these cases. The original cases were associated with calcification in the renal tubules ("nephrocalcinosis"), readily detectable in a plain radiograph (Fig. 4). It was later found that this probably corresponded to a late stage of the disease and that all the other signs and symptoms could occur without renal calcification. (Nephrocalcinosis can also occur in other conditions associated with a high calcium output in the urine.) The disease can present at almost any age. In the child the

FIG. 4

Nephrocalcinosis in a case of renal tubular acidosis (Type 5).

bone disease appears as typical rickets; in the adult as osteomalacia. There are additional symptoms from the associated acidosis. In children attacks of vomiting with anorexia dehydration and prostration may occur, with aggravation of the acidosis. In adults the chronic acidosis may lead to considerable dehydration, with lassitude, and, occasionally, to attacks of low-potassium paralysis. On examination the usual concomitants of rickets or osteomalacia may be observed, with radiographic changes also of the usual types. The plasma usually shows marked acidosis, with low phosphate and sometimes low potassium. Often the plasma chloride is unusually high. The urine is nearly always neutral or alkaline, but may be acid in a severe exacerbation of acidosis. It is usually said to show a low ammonia coefficient but in some cases the tubules form ammonia reasonably well. As it is not possible to draw a definite line between those with more or less damage to the ammonia mechanism the two types, 5 and 6, have been taken here together. Seemingly the primary defect is inability to pass an acid urine. Since metabolic acids cannot be eliminated adequately by the kidney a

chronic acidosis of the body results. This causes an increased excretion of phosphate and of the fixed bases in the body, calcium, sodium and potassium being the most important. The calcium and phosphate depletion produce the osteomalacia, the sodium is lost with some extracellular fluid and the potassium from within the cells. Since acidosis also increases phosphate excretion, the plasma phosphate is low. The especial point is that as all these effects are secondary to the acidosis: they are all corrected when the acidosis is corrected. The response to alkali treatment is therefore gratifying. Although the kidney damage is usually irreversible, it does not progress greatly over a period of years. It is clear that the defective phosphate reabsorption in Types 5 and 6 is of quite different origin from that occurring without acidosis in Types 1 and 3. In Type 4 the low plasma phosphate is presumably the result of both factors, namely intrinsically defective phosphate reabsorption by the tubule (as in Types 1 to 3) and defective reabsorption acquired only because of the acidosis (as in Types 5 and 6).

It is interesting to comment here on the almost identical renal disturbance in children that was originally described by Lightwood and is usually called "renal acidosis." These children have symptoms like those described before and the biochemical findings may be identical. The main differences are however that bone disease is nearly always absent, that the nephrocalcinosis is less marked and cannot usually be detected in an abdominal radiograph, and that the disease is self limiting, spontaneous cure occurring in a few months. Presumably these children would develop the bone disease eventually if the condition were irreversible and were present long enough, and it is reasonable to believe that such cases would then be true cases of Type 5 or 6. Latner and Burnard (1950) believed that the mechanism involved is that of bicarbonate reabsorption in the proximal tubule.

TREATMENT

Treatment of the six types of "tubular rickets or osteomalacia" shown in Table I—The general principles apply equally to all cases; hence it is convenient to deal with the treatment of all the six types together.

When there is high phosphate clearance without acidosis (as in Types 1 to 3) the clearance can be lowered by the administration of large doses of vitamin D. The response to treatment is determined by the radiographic changes and by the rise in plasma phosphate. The vitamin has the same effect either by mouth or by injection. It is preferable to start with about 50,000 units a day and to raise this gradually until the plasma phosphate has risen to about 2.5–3 milligrams per cent. Then one attempts to find the lowest maintenance dose or one can continue treatment intermittently with larger doses. A dose as high as 500,000 units a day, or even more, may be required. Such large doses are dangerous and can be fatal if continued after signs of toxicity have appeared. The plasma calcium should be determined every two weeks at first and never less often than at six-weekly intervals. The patient should be warned to stop the drug at once and come to hospital for a blood test if he loses his appetite, feels nauseated, or has polyuria or dysuria. Sometimes the high calcium content is observed before the phosphate has had time to rise. If the calcium level is over 11.5 milligrams per cent all vitamin treatment must stop until it is below 11 milligrams per cent. It may take a month or more to fall. When it has done so, one tries again. Although "biochemical cure," a normal phosphate level, is always to be aimed at, one is greatly helped in doubtful cases by the clinical state of the patient. In children the epiphyses should be radiographed regularly. In adults, disappearance of bone pain is usually the best and quickest measure of the success of treatment but if there are pseudo-fractures, their recalcification should be observed radiographically. Muscular weakness, when present, is also cured by the large doses of vitamin D.

When acidosis is present treatment should include the administration of divided doses of sodium bicarbonate or sodium citrate in such quantities as will maintain a plasma

bicarbonate level of 25–27 m.eq. (56–60 vols per cent CO_2). This alkali therapy has to be continued indefinitely. The amount of alkali necessary varies from patient to patient and does not bear much relation to the severity of the acidosis of the patient when first seen. Likely quantities of sodium bicarbonate (in adults) are 5–20 grammes daily. Acidosis of the Type 4 (Fanconi) syndrome is the most resistant to therapy.

When the radiographs show gross rarefaction a strongly positive calcium balance should be promoted without delay by high calcium intake, citric acid by mouth, and extra vitamin D (unless the patient is already taking large doses). The citric acid makes the gut contents more acid and thus facilitates the absorption of calcium. Suggested daily doses are: calcium gluconate 10 grammes, citric acid 5–10 grammes and vitamin D 50,000 units. These extra measures can be discontinued when the patient's skeleton is no longer grossly rarefied.

In the Type 4 (Fanconi) disease, if water and other electrolytes are being lost in the urine in excessive quantities, they must be replaced. Further work is required on this aspect of the problem. The importance of replacing lost potassium has already been stressed.

PROGNOSIS

The results of treatment are usually satisfactory. Disease of Types 1 to 3 always responds to large doses of vitamin D. The difficulty lies in the long period of observation necessary under this potentially dangerous treatment. Relapse after cessation of vitamin therapy may take many months to appear; so prolonged gaps in treatment can be allowed from time to time. Type 4 cases present many difficulties. In children temporary improvement may be observed but death within a few years from one of the complications is usual. Adults may be completely relieved of symptoms and signs, but so far no long follow-up has been reported. It is important to study the urines of close relatives, who, even though symptomless, may show the characteristic amino-aciduria (Dent and Harris 1951). In this way corrective measures can be applied at the very earliest stage of the disease. Types 5 and 6 are the most gratifying of all. Spectacular improvement always occurs with the alkali treatment and may be long lasting. Maintenance therapy with alkalis is harmless, even though it has to be continued indefinitely.

SUMMARY

1. Cases of rickets and osteomalacia caused by kidney tubule defects have been classified into six sub-groups according to the various disturbances of tubule function concerned.
2. The manifestations, treatment and prognosis appropriate to the sub-groups have been considered.
3. The name "tubular rickets" (or osteomalacia) is suggested for these cases of mainly tubule dysfunction in contrast to "glomerular rickets" (or osteomalacia) which might be used to distinguish cases in which defect in the glomeruli overshadows and precedes that in the tubules.

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