Clinical Aspects of Renal Tubular Disorders*

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When most clinicians consider problems in renal disease, they think in terms of levels of blood, urea, nitrogen, and creatinine, and the presence of red cells, white cells, or protein in the urine. In essence, they think primarily of disease of the glomerular filter or loss of total nephron mass. Indeed, most of the signs and symptoms of patients with commonly recognized renal diseases are related to retention of various noxious materials which cannot be adequately cleared because of the reduced glomerular filtration rate.

Despite the overwhelming frequency of diseases involving the glomerulus, I would like to discuss a number of interesting clinical renal problems that are primarily characterized by insufficiency of one or more tubular functions in the presence of continuing adequate glomerular operation. These conditions are not common but are of great importance, because several are amenable to therapy and because each is an experiment in nature displaying the profound physiologic consequences of anatomical abnormality or biochemical dysfunction of a particular portion of the renal tubule.

The diseases that I plan to discuss are listed in Table 1 and can be divided into groups according to localization of disorder within the tubule and the specificity of defect. Specific defects localized to the proximal tubule include: renal glycosuria; phosphate diabetes; cystinuria, which until recently was considered to be solely a defect in dibasic amino acid reabsorption; and Hartnup disease, which is a defect in monoaminomonocarboxy amino acid reabsorption. Generalized defects of tubular transport are included under Fanconi syndrome. The distal tubular problems to be discussed include renal tubular acidosis and nephrogenic diabetes insipidus. Study of patients with these disorders has shed much light on the normal function of the renal tubule.

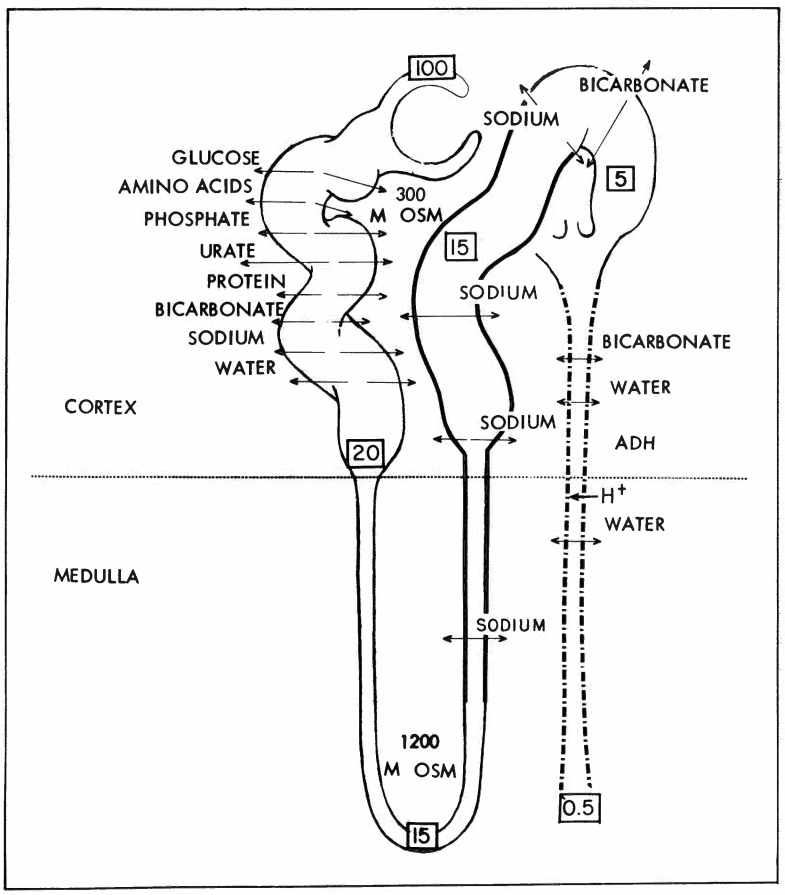

Fig. 1—Schematic representation of a nephron with reabsorptive sites for various substances indicated. The water-impermeable portion of the tubule is indicated by the solid line. The broken line indicates the site of action of ADH.

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Review of Renal Tubular Physiology

It is evident that the renal tubule profoundly alters the volume and composition of the 100 cc of filtrate entering Bowman's space before it appears in the bladder as 0.5 cc of urine (Fig. 1). The filtrate, as it enters Bowman's space, contains large quantities of glucose, amino acids, phosphate, bicarbonate, urate, sodium, and many other filterable constituents of plasma. All or most of these substances are reabsorbed by the renal tubules. Most reabsorption of these materials and water occurs in the proximal portion of the nephron with only about 20% of the isotonic filtrate entering the descending limb of Henle's loop. Reabsorption of glucose, amino acids, and filtered protein is virtually complete in the proximal tubule. About 80% of the filtered bicarbonate is reabsorbed there; the remainder is reabsorbed more distally in association with the formation of titratable acid, ammonium and a maximally acid urine. It is also in the more distal portion of the tubule that the remaining filtrate is initially made hypotonic by sodium extraction from the tubular fluid as it passes through the water-impermeable, thick ascending limb of Henle's loop. The residual tubular fluid is then finally made concentrated by action of antidiuretic hormone in the collecting duct cell, allowing back diffusion of water into the hypertonic interstitium of the medulla.

Since glucose and amino acids are reabsorbed by movement from a lower tubular concentration to a higher peritubular concentration, their transport must be considered to be "active" and require an energy-dependent transport mechanism. It has been learned that the capacity

TABLE 1

Disorders of Renal Tubular Function

1. Specific Disorders of Proximal Tubular Function
   - A. Renal Glycosuria
   - B. Phosphate Diabetes (Vitamin D-Resistant Rickets)
   - C. Cystinuria
   - D. Hartnup Disease
2. Generalized Disorder of Proximal Tubular Function (Fanconi Syndrome)
3. Disorders of Distal Tubular Function
   - A. Renal Tubular Acidosis
   - B. Nephrogenic Diabetes Insipidus

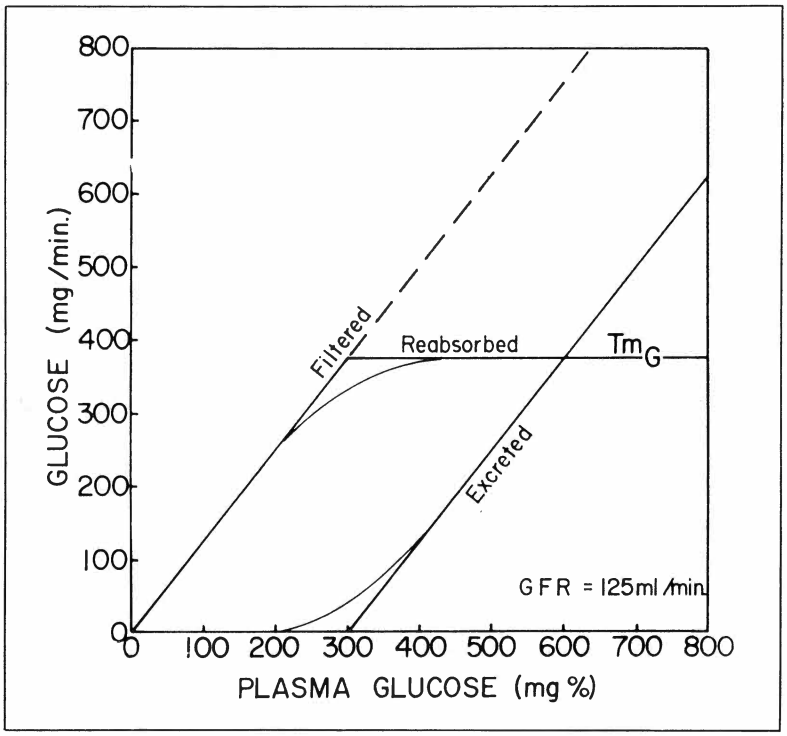

Fig. 2—Schematic representation of the reabsorptive titration curve for glucose. (From *Physiology of the Kidney and Body Fluids,* 1st edition, by Robert F. Pitts. Copyright © 1963, Year Book Medical Publishers, Inc. Used by permission of Year Book Medical Publishers.)

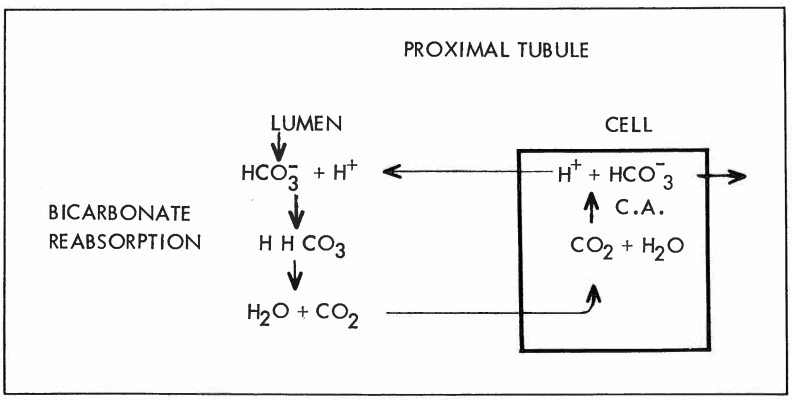

Fig. 3—Schematic representation of the mechanism of bicarbonate reabsorption and H^+ ion secretion in the proximal tubule.

of the transport systems for these substances is limited, and that, when the reabsorptive load of material in the filtrate reaches a certain value, no more can be reabsorbed, the excess being excreted in the urine. This limiting quantity is expressed as the tubular maximum (Tm) for a given substance. A typical Tm curve for glucose is shown in Figure 2. Such a curve is obtained by progressively increasing the filtered load of glucose by raising the plasma level. Reabsorption is complete until a threshold level is reached, at which point a little glucose appears in the urine. As the load is raised further, the transport mechanism becomes saturated at the Tm level. The deviation of the reabsorptive curve from the line of theoretical complete reabsorption is known as the splay of the reabsorptive curve.

Reabsorption of bicarbonate is also characterized by a Tm limitation, but its origin is somewhat different. Bicarbonate reabsorption in both the proximal and distal tubules is linked to and dependent upon H^+ ion secretion into the tubular lumen. Thus, as seen in Figure 3, bicarbonate reabsorption in the proximal tubule depends on adequate production of H^+ ion by carbonic anhydrase catalytic hydration of CO_2 within the cell, followed by movement of H^+ ion into the lumen. Such activity in the proximal tubule represents most of the total H^+ ion secretory capacity. Bicarbonate is regenerated in the distal tubular cell as hydrogen is secreted into the tubular lumen, where titratable acid and ammonium are formed (Fig. 4). It is evident that maximal excretion of these substances is dependent on the establishment of an H^+ ion gradient across the tubule of sufficient magnitude to lower the urine pH and allow for formation of titratable acidity and ammonia diffusion from the tubule cell. Figure 5 shows a normal Tm curve for bicarbonate. Such a curve is a reflection of the total H^+ ion secretory capacity of

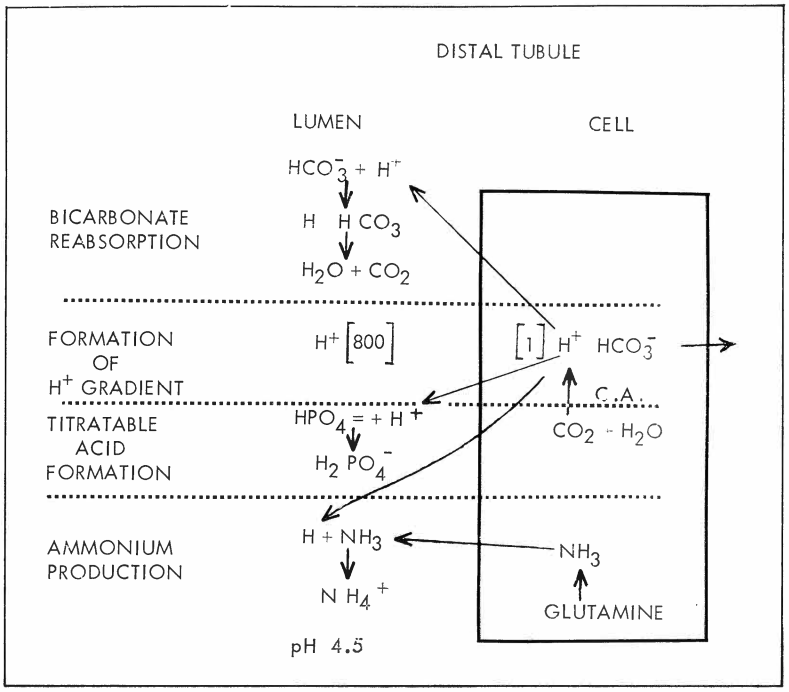

Fig. 4—Schematic representation of the mechanisms of bicarbonate reabsorption, H^+ ion secretion, bicarbonate regeneration, titratable acid formation, ammonia trapping, and H^+ ion gradient establishment by the distal tubule.

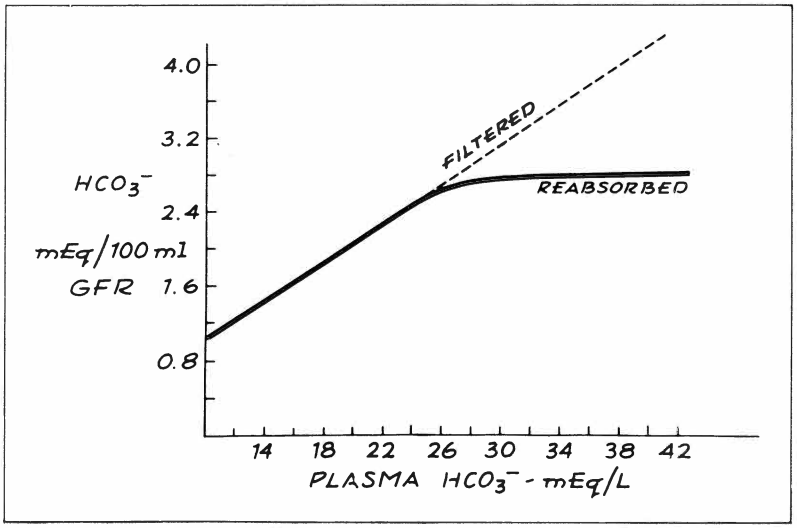

Fig. 5—Schematic representation of the bicarbonate titration curve in normal man (Adapted with permission from *J. Clin. Invest.* 28:37, 1949).

both proximal and distal tubules of the kidney.

Clinical Clues to Diagnosis of Tubular Disorders

There are seven practical clinical clues to the presence of a renal tubular disorder (Table 2).

First, the presence of renal stones or nephrocalcinosis should alert one to the possibility of renal tubular acidosis or cystinuria.

Second, abnormalities of bone, such as rickets, osteomalacia or pseudofractures, may be the first indication of a defect in tubular secretion of H^+ ion or reabsorption of phosphate.

Third, visual problems, particularly in infancy or early childhood, should suggest the possible precipitation of cystine crystals in the cornea. This, we shall see, may occur in generalized cystinosis with Fanconi syndrome.

TABLE 2
Clinical Clues to Renal Tubular Disorders

Clue	Disorders
1. Renal Stones or Nephrocalcinosis	Cystinuria or Renal Tubular Acidosis
2. Rickets, Osteomalacia, Pseudofractures	Phosphate Diabetes, Fanconi Syndrome, Renal Tubular Acidosis
3. Visual Difficulty in Childhood	Fanconi Syndrome with Cystinosis
4. Pellagra	Hartnup Disease
5. Glycosuria	Renal Glycosuria or Fanconi Syndrome
6. Hyperchloremic Acidosis	Fanconi Syndrome or Renal Tubular Acidosis
7. Low Serum Phosphate	Phosphate Diabetes or Fanconi Syndrome

Fourth, a pellagra-like rash should suggest the possibility of an abnormality of tryptophan metabolism, as seen in Hartnup disease.

Fifth, the presence of glycosuria should suggest the possibility of renal glycosuria. When associated with an alkaline urine and proteinuria in a patient without a family history of diabetes mellitus, glycosuria should suggest a generalized defect in renal tubular reabsorption, as seen in Fanconi syndrome.

Sixth, unexplained hyperchloremic acidosis along with an alkaline urine should suggest a defect in bicarbonate reabsorption or H^+ ion secretion, as seen in Fanconi syndrome or renal tubular acidosis.

Seventh, an unexplained low serum phosphate in the presence of adequate food intake and a normal serum calcium should raise the possibility of Vitamin D-resistant rickets or Fanconi syndrome.

Renal Glycosuria

Renal glycosuria, depending on definition, is a relatively common clinical disorder. When defined in broadest terms, it may be characterized by an increased splay in the Tm titration curve, by a lowered Tm for glucose, or by both. It is usually noticed by finding a random positive urine sugar. It is primarily of importance to be differentiated from true diabetes mellitus in order that hypoglycemic agents not be given. Renal glycosuria may occur in patients with true diabetes mellitus, in which case it may make management more difficult, with a tendency to hypoglycemic reactions.

Phosphate Diabetes (Vitamin D-Resistant Rickets)

Phosphate diabetes is a well-defined clinical entity. It characteristically presents in early childhood as rickets, unresponsive to Vitamin D. Figure 6 shows the typical bone changes of rickets including widening of the epiphysis with cupping and ragged mineralization of the metaphyseal plate. Such changes may lead to severe residual deformities in adolescence and adulthood. Typical serum chemistries include a normal calcium, low phosphate, and normal or high alkaline phosphatase, depending on the activity of disease. The low serum phosphate is caused by an increased phosphate clearance. This condition is inherited as a sex-linked dominant trait with a varying propensity for bone disease in the heterozygous female. Mother-to-son and son-to-daughter transmission but no father-to-son transmission is seen, as is characteristic of X-linked inheritance.

The etiology of this condition remains doubtful. There is controversy as to whether there is a primary defect in calcium absorption from the gut, with secondary hyperparathyroidism and parathyroid stimulation of phosphate urinary excretion, or a primary defect in renal tubular reabsorption of phosphate. Recent evidence of Avioli et al. (1967) suggests that Vitamin D metabolism may be defective with production of water soluble metabolites which are ineffective in enhancing calcium absorption from the gut and have no effect on bone. Whether or not such metabolites have a renal effect that blocks phosphate reabsorption is unknown. Recent studies (Wilson et al., 1965) have suggested that the bone disease may be healed by a vigorous and sustained combination of moderate daily doses of Vitamin D (50,000 units) in conjunction with frequent administration of buffered phosphate supplements.

Cystinuria

Cystinuria is an unusual renal tubular defect that usually presents with the passage of a renal stone or gravel. The course is variable, and the first stone may be passed at any time of life from early childhood

to old age. Untreated cases may suffer all the complications of renal calculi, including urinary tract obstruction with the development of hydronephrosis, chronic pyelonephritis, and progressive renal insufficiency.

Defective epithelial transport of the amino acids arginine, ornithine, and lysine in this condition results in both diminished absorption from the gut and decreased reabsorption in the renal tubule, leading to increased concentrations in the urine. Until very recently, cystine transport was also felt to be defective in both the gut and the kidney, but new data (Thier et al., 1965) have demonstrated that transport of this amino acid is normal in the kidney and may be so in the bowel. The high levels of cystine in the urine seem to be a result of intra-urinary oxidation of abnormally large quantities of excreted cysteine to cystine. Because of the limited solubility of cystine in the urine, particularly when it is acid, precipitation of cystine in characteristic hexagonal-shaped crystals occurs. Observation of such crystals should alert the clinician to the possible presence of this condition.

Cystine crystals are radiopaque, and cystinuria should be considered in any stone-forming patient. The cyanide-nitroprusside screening test for cysteine can easily be done in any lab. Analysis of a stone will usually reveal the presence of some cystine, although calcium and phosphate may be integral parts of the calculus.

Recent studies (Rosenberg et al., 1966) have indicated that cystinuria is a hereditary disease. Stone formation is seen in patients homozygous for one of three possible genes which may or may not be alleles.

Moderately good results with prevention of stone formation have been reported in the past in some cases with a low methionine diet, chronic alkalinization of the urine, and production of a continuous water diuresis. The therapy of cystinuria has been revolutionized, however, by the introduction of penicillamine, which chelates the urinary cystine, making it more soluble in the urine. In addition, by some unexplained mechanism the penicillamine also decreases total cystine excretion. Thus, optimal therapy in the chronic cystine stone-former would seem to combine penicillamine with a copious fluid intake, alkalinization of the urine, and low methionine diet to decrease the intake of cystine precursors.

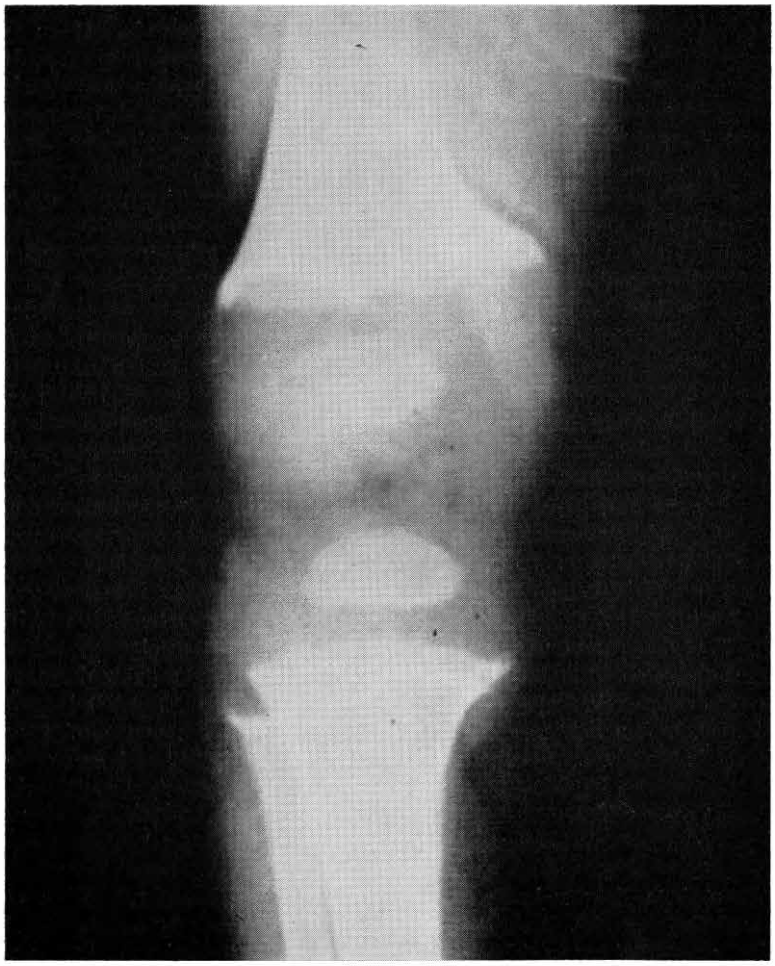

Fig. 6—Characteristic roentgenographic picture of rickets with widening of the epiphysis, associated with ragged, irregular calcification of the developing osteoid. There is a tendency toward cupping of the ends of the long bones.

Hartnup Disease

This is an extremely rare but interesting abnormality of mono-amino-monocarboxy amino acid transport. Clinically, it is characterized by the occurrence of a pellagra-like skin eruption, cerebellar ataxia, and, in some cases, mental deficiency appearing early in life and remitting in late adolescence or adulthood. The basic pathogenic mechanism is considered to be abnormal absorption of tryptophan from both the bowel and the renal tubule. As a consequence of these abnormalities, serum tryptophan levels are low, leading to a decreased production of its important metabolites nicotinamide and serotonin. It may be a deficiency of these metabolites that leads to the integumen-

TABLE 3
Urinary Amino Acid Excretion in a Patient with Adult Fanconi Syndrome

	Patient	Normal
Amino Acid	mg/24 hr	mg/24 hr
Lysine-Ornithine	962	7–100
Histidine	650	113–246
Glycine	756	68–200
Alanine	786	20–70
Serine	766	27–73
Glutamine	2489	
Phenylalanine	430	9–31
Threonine-Leucine	961	9–77

TABLE 4
Results of Glucose Tolerance Test in an Adult Patient with Fanconi Syndrome

Period	Blood Sugar	Urine Sugar
Fasting	96	3+
1 Hour	62	3+
2 Hours	107	3+
3 Hours	87	3+
4 Hours	95	N.S.
5 Hours	87	N.S.

TABLE 5
Causes of the Fanconi Syndrome

1. Child:
   - A. Cystinosis
   - B. Lowe's Syndrome
   - C. Hereditary Fructose Intolerance
   - D. Galactosemia
   - E. Idiopathic
2. Adult:
   - A. Heavy Metal Intoxication
   - B. Multiple Myeloma and Other Tumors
   - C. Wilson's Disease
   - D. Outdated Tetracycline Ingestion
   - E. Transplanted Renal Allograft
   - F. Lysol Ingestion
   - G. Idiopathic
3. Experimental: Maleic Acid

tary and central nervous system disorders. Hartnup disease is inherited as an autosomal recessive gene.

Therapy is directed to avoidance of sunlight and administration of large supplements of nicotinamide during the years of rapid growth. With such measures, improvement has been noted in several patients, leading to sustained remission in adulthood.

Generalized Defects in Proximal Tubular Function

The generalized defects in proximal tubular function are usually grouped under the heading of Fanconi syndrome. This syndrome frequently presents clinically by the occurrence of severe rickets or osteomalacia with fractures and pseudofractures. Laboratory findings include the characteristic hyperchloremic acidosis with a low CO_2 and high Cl content in the serum; low serum phosphate; low serum uric acid; and alkaline urine with proteinuria, aminoaciduria, and glycosuria. Table 3 demonstrates the diffuse aminoaciduria in a patient with adult Fanconi syndrome. Determination of the total amino acid content can be done by measuring the alpha amino nitrogen; individual acids must be separated by chromatography. A typical glucose tolerance test with persistent glycosuria in the face of normal blood sugars is shown in Table 4. Despite the frequent presence of an alkaline urine, occurrence of renal stones in this syndrome is distinctly unusual.

Much evidence points to either an anatomic or functional defect in the proximal tubule as the primary source of difficulty in patients with Fanconi syndrome. Microdissection studies have revealed anatomical damage to the proximal tubular region in patients with both the childhood and adult form of the disease. Recent work of mine (unpublished data) demonstrating a decreased bicarbonate Tm (Fig. 7) indicates that total H^+ ion secretory capacity is reduced and that the acidosis is secondary to a persistent leak of HCO_3 from the proximal tubule. When considered with evidence of an intact distal acidification mechanism, this finding further supports the suggestion that a primary defect in proximal tubular function is the basis of the abnormality observed.

The causes of Fanconi syndrome are outlined in Table 5. It is frequently seen in association with an underlying disease process but, in both children and adults, may be of idiopathic origin. Childhood cases are most frequently seen in association with a generalized metabolic disorder (cystinosis) characterized by deposition of cystine crystals in numerous organs, including the cornea, liver, spleen, lymph nodes, and kidneys.

Diffuse proximal tubular dysfunction has also been seen in children with hereditary fructosuria and galactosemia and as a part of Lowe's syndrome. Adult cases have been described in association with a variety of conditions including the transplanted renal allograft, Wilson's disease, multiple myeloma, poisoning from ingestion of outdated tetracycline, and intoxication from heavy metals such as uranium and bismuth. Experimentally, a similar functional lesion has been seen in animals that have been fed maleic acid.

Patients with Fanconi syndrome must first be carefully evaluated to determine an underlying etiology, if possible. When an underlying cause such as multiple myeloma is found, it should, of course, be treated. Whether or not an underlying cause is determined, several of the metabolic disturbances can be treated. The bone disease may respond to oral phosphate supplements, Vitamin D administration, and large doses of oral bicarbonate or Shohl's solution. Hypoglycemia is not a usual occurrence, despite persistent glycosuria. A large protein intake should be encouraged in an attempt to provide for the

amino acids lost in the urine and the demands of gluconeogenesis. Recent unpublished data of mine suggest that the renal abnormalities may be markedly improved by administration of hydrochlorothiozide and potassium supplements.

Renal Tubular Acidosis

As mentioned in our review of renal acidification mechanisms, the distal tubule reabsorbs the small amount of bicarbonate remaining in the tubular lumen and establishes a high H^+ gradient across the tubular wall, allowing for the formation of titratable acid and trapping of large quantities of ammonia. In the absence of establishment of such a gradient, neutral phosphate is excreted, and ammonia diffusion into the tubular lumen is limited. Such an abnormality is seen in renal tubular acidosis, with the result that patients with this syndrome are unable to form an acid urine and, consequently, develop a hyperchloremic metabolic acidosis. Thus, the defect in this disorder lies not in the limitation of total H^+ ion secretion but in the inability to transfer H^+ out of the distal tubular cell into the urine against a very low H^+ gradient.

Presumably because of the systemic acidosis, calcium is leached from the bones as H^+ ion is buffered by the alkaline bone salts. Osteomalacia develops, and the liberated calcium is excreted in a persistently alkaline urine. Under such circumstances calcium phosphate precipitation occurs, either within the collecting ducts leading to nephrocalcinosis (Fig. 8), or in the renal pelvis producing renal stones. Most patients with this syndrome present with either renal calculi, bone disease, or progressive renal insufficiency secondary to nephrocalcinosis or pyelonephritis.

Because of the important occurrence of renal stones in renal tubular acidosis, it is essential that it be seriously considered in the patient with renal calculi or unexplained hematuria. The presence of a urine pH that is persistently 6.0 or greater indicates that investigation of the systemic acid-base status should be undertaken. The presence of hyperchloremic acidosis in the absence of other tubular abnormalities confirms the diagnosis. Partial defects may occur, however, and, in the questionable case, the response to an acid load of ammonium chloride or a sodium sulfate infusion should be determined. Under such stimuli, the urinary pH in the patient with renal tubular acidosis will not be lowered to the normal range of 5.0 or below.

Renal tubular acidosis occurs in children without apparent genetic cause. An association between adult renal tubular acidosis and a number of disease processes—including a variety of dysglobulinemic states, lupus erythematosus, phenacetin nephropathy, and amphotericin toxicity—has been documented.

Treatment is usually effective in the full-blown case and consists of the administration of sufficient sodium bicarbonate orally to correct the systemic acidosis. Under such circumstances, decalcification is inhibited and hypercalciuria disappears. The urine remains alkaline, but further nephrocalcinosis or stone formation usually does not occur as long as an adequate water diuresis is maintained by large oral intake.

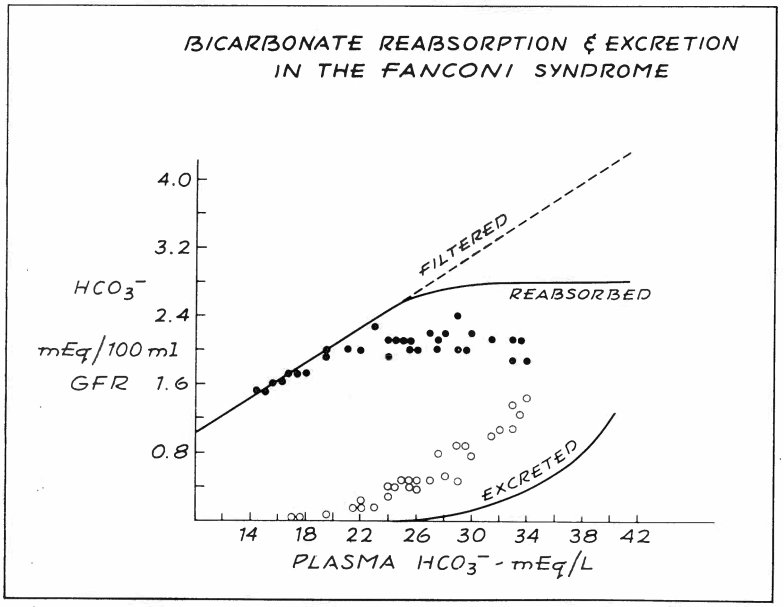

Fig. 7—Bicarbonate titration curve in a patient with Fanconi syndrome, demonstrating a decreased Tm for bicarbonate.

Nephrogenic Diabetes Insipidus

As we noted previously, a concentrated urine is produced by action of antidiuretic hormone on the collecting duct cell, allowing back diffusion of water into the interstitium.

Polyuria unresponsive to vasopressin administration has been described in a number of clinical situations. Infant males may present with severe dehydration and fever and, on investigation, be found to have a persistently hypotonic urine in the face of an elevated serum osmolality. Administration of vasopressin does not correct the defect. Polyuria with a subnormal ability to concentrate the urine may be seen in patients with hypercalcemia, hypokalemia, sickle cell disease, or amyloidosis as well as in patients with any type of severe chronic renal insufficiency.

The male infants mentioned above are afflicted with an X-linked genetic defect that causes them to be unresponsive to either exogenous or endogenous antidiuretic hormone. If their problem is recognized, and adequate hydration is maintained, life can be sustained.

In some older individuals with a recognizable cause for vasopressin-unresponsive polyuria, correction of the underlying disorder, such as lowering the serum calcium or raising the serum potassium, will result in return of ability to adequately concentrate the urine. In those patients whose nephrogenic diabetes insipidus is idiopathic or genetic, improvement in the polyuric state may be seen following a decreased dietary solute load or the administration of hydrochlorothiozide. After the diuretic produces an initial saline diuresis, reduction in the extracellular fluid volume occurs. This in turn reduces glomerular filtration, causing enhanced reabsorption in the proximal tubule with consequent reduction in the amount of solute presented to the loop of Henle and the distal tubule. As a result, less dilute urine is formed and excreted. The patient must strictly adhere to a low sodium diet while on this regimen in order that the glomerular filtration rate not be increased.

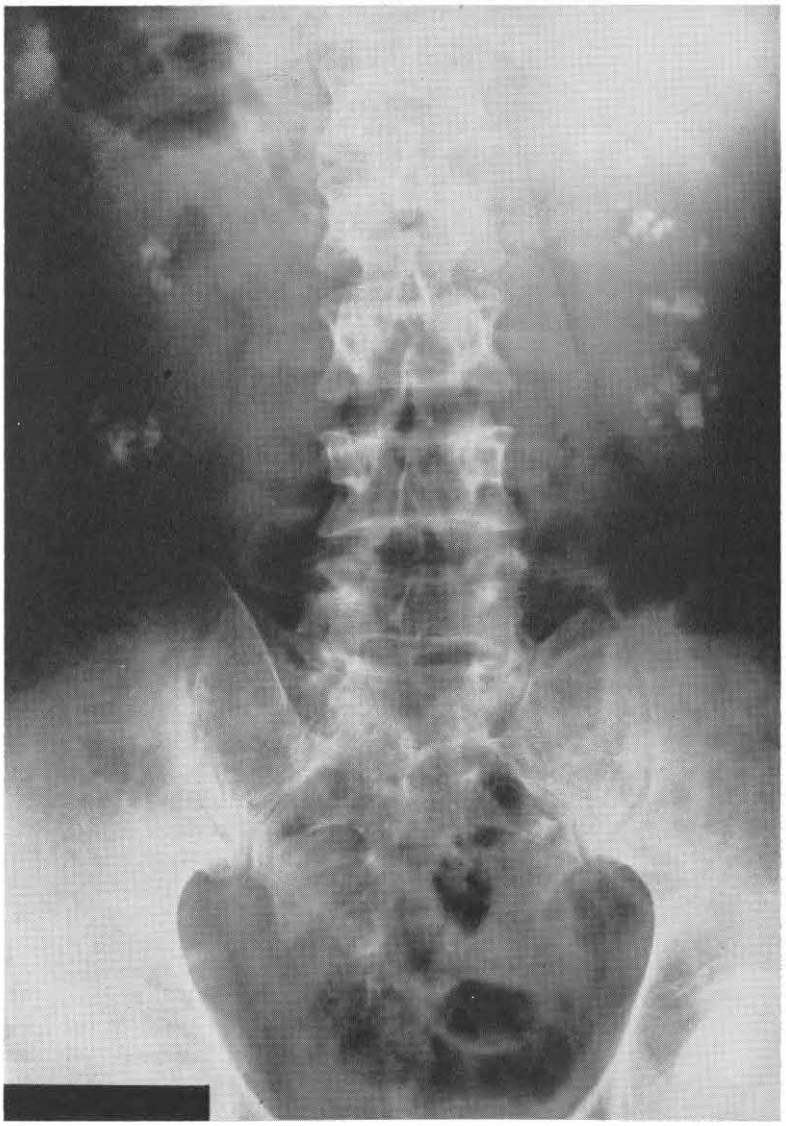

Fig. 8—Roentgenogram of the abdomen, showing nephrocalcinosis and renal calculi.

Summary

I have tried to briefly outline aspects of the presently recognized disorders of tubular function that are of clinical importance. I would like to stress again that, although such disorders constitute a minute portion of the total health problem in this country, they are of great importance as experiments of nature, study of which is opening the way for a clearer understanding of fundamental transport mechanisms in the renal tubule. Additionally, for those individuals afflicted with any of the disorders I have mentioned, the availability of relief is of paramount importance. Such relief can be obtained in some cases by correct diagnosis and proper application of physiologically oriented therapy.

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