Idiopathic Fanconi Syndrome with Progressive Renal Failure: A Case Report and Discussion

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Fanconi syndrome is a complex of renal tubular dysfunctions defined by glycosuria without diabetes, aminoaciduria, phosphaturia, and renal tubular acidosis. It is often associated with hypokalemia, hypophosphatemia, and rickets or osteomalacia. Although it is usually found in the setting of other well-established non-renal diseases, Fanconi syndrome may present without identifiable etiology or association. Very infrequently a patient with idiopathic Fanconi syndrome will progress to chronic renal failure. This case report details the course of such a patient over the 20 years since his diagnosis and discusses the syndrome's genetic background, clinical features, putative pathophysiology, and therapeutic options, including transplantation.

INTRODUCTION

DR. M.J. BIA: The Fanconi syndrome (FS) is a metabolic disorder characterized by renal glycosuria, phosphaturia, and generalized aminoaciduria in association with hypophosphatemia and rickets or osteomalacia. Systemic acidosis, hypouricemia, and hypokalemia from renal wasting of bicarbonate, uric acid, and potassium are other common features. A variety of genetically determined disorders, systemic diseases, or exogenous toxins can produce this complex of renal tubular abnormalities, or the syndrome may be idiopathic without identifiable etiology. Although the syndrome is relatively rare, knowledge of its metabolic consequences is important for proper patient management. Furthermore, continued work with experimental models designed to evaluate the etiologies of the syndrome has shed new light on the physiologic functions of the proximal and distal nephron. The following case, recently presented at Renal Grand Rounds at Yale, provides an opportunity to review the salient clinical aspects of Fanconi syndrome and discuss the most recent theories concerning its etiologies.

CASE HISTORY

DR. W.S.. LONG: The patient's disease was first detected in 1968 at age 21 during his evaluation for the Navy, when his urine contained both protein and glucose, although his blood sugar was normal. Two years earlier as a university student, the patient had a

TABLE 1
Laboratory Data

	Serum							Urinary Excretion/24 Hours			
Date	Na mEq/L	K mEq/L	Cl mEq/L	HCO$_3$ mEq/L	Creat[a] mg/dL	BUN[a] mg/dL	Urate mg/dL	Glucose g	AA[b] mM	Protein[c] mgm	GFR[d] ml/minute
1968	147	4.1	109	24	1.8–2.3	22–42	2.2–5.2	19	65	900	42–53
1979	141	4.0[e]	114	16	2.3	14					
1983	143	3.9[e]	114	10	2.9						
1988	144	5.4	114	17	5.0	48	2.7	23	65	1,600	20

[a]Creat, creatinine; BUN, blood urea nitrogen
[b]AA, amino acids (normal, <10 mM/day)
[c]Normal, <150 mg/day
[d]GFR, glomerular filtration rate, estimated as creatinine or inulin clearance
[e]Values obtained on potassium supplements

urinalysis as part of a routine physical; the results caused no comment and he presumes that it was normal. In 1968 the patient appeared robust and had a normal physical exam when examined by his local physician; however, laboratory values at that initial evaluation included an elevated serum creatinine of 1.8 mg/dL, serum phosphate 2.6 mg/dL, "massive aminoaciduria," proteinuria, and glycosuria (3 g/day) with a normal blood glucose.

His local physician referred him to Dr. Leon Rosenberg at Yale's Department of Human Genetics, where a thorough history for hereditary disorders or systemic diseases provided few clues. He was currently taking bicarbonate supplements prescribed by his local physician. He denied hematuria, dysuria, polyuria, frequency, or edema. During the summers he had worked as a camp counselor, mailman, waiter, and as a sorter in the sample room of a battery factory.

Family history revealed hypertensive cardiovascular disease on both sides of his family and a paternal uncle with adult-onset diabetes mellitus. His parents and one of his sisters subsequently tested negative for Fanconi's syndrome with a urinary amino acid screen. His remaining sister was not screened but has not been reported to have renal disease.

On his initial exam at Yale (July 1968), he was five feet eight inches tall with normal posture, weighed 150 pounds, and had a blood pressure of 130/90. Except for bilateral sustained clonus of unknown etiology, his physical exam was unremarkable. Laboratory values at the time of first evaluation here are included on Tables 1 and 2. The normal bicarbonate level was maintained with supplementation. His urinalysis showed severe generalized aminoaciduria, 2+ proteinuria, and 2–4+ glycosuria despite normal serum glucose levels. Tests within normal limits included complete blood count (CBC), calcium, phosphate, ceruloplasmin, serum protein electrophoresis (SPEP), audiometry, and urinary mercury, arsenic, and lead. Intravenous pyelogram (IVP) revealed normal-sized kidneys with a 1 cm stone on the left and a 2 mm stone on the right. Bone radiographs showed general demineralization. Bone marrow was unremarkable, and neither bone marrow nor eye exam revealed cystine crystals.

On renal biopsy in 1968, many tubular cells were swollen and distorted with granular vacuolated cytoplasm. Elsewhere tubular epithelia were flattened. Some glomeruli were hyalinized; most appeared normal. Interstitial fibrosis was more striking in the medulla than in the cortex.

TABLE 2
Calcium, Phosphorus, and Bone Studies

Date	Ca mg/dL	P mg/dL	Alk Phos[a] mU/ml	$U_{Ca}V$[b] mg/day	U_pV[c] mg/day	PTH[d] pM/L	1,25 Vitamin D_3[e] pg/ml	25 Vitamin D_3[e] pg/ml
1968	9.7	2.6	126	732	1,298			
1979	8.9	1.9						
1987	7.6	4.3	142					
1988	8.8	5.6	37	119	1,460	145	46	51

[a]Alk Phos, alkaline phosphatase (normal, 30–135 mU/mL)
[b]$U_{Ca}V$, urinary calcium excretion per day (normal <300 mg per day; decreases with renal failure)
[c]U_pV, urinary phosphorus excretion per day (normal <800 mg per day; increases with renal failure)
[d]PTH, parathyroid hormone (immunoassay of intact PTH) (normal, <25 pM/L)
[e]1,25 $(OH)_2$ Vitamin D_3 (normal, 20–65 pg/ml)
25 (OH) Vitamin D_3 (normal <5 pg/ml)
Levels of Vitamin D_3 and of PTH measured while patient on Vitamin D_3 supplements

The patient was thought to have idiopathic Fanconi syndrome because of the absence of known causes of acquired Fanconi syndrome (Table 3). He was followed twice a year and remained stable except for a modest decrease in glomerular filtration rate (GFR) and an increase in excretion of glucose, phosphate, and amino acids. On X-ray in 1976, he had slight demineralization of the spine and extra-articular bones in his hands. Overall, his mineral status had improved, and his bone pain had resolved. An abdominal X-ray (KUB) showed no change in his stones. He was maintained on bicarbonate, phosphate, potassium chloride (KCl), and a thiazide diuretic for hypertension.

The patient married, and in 1981 a son was born. In 1983, the patient complained of thirst, polyuria, and occasional nocturnal cramps. Figure 1 illustrates persistent worsening of his azotemia, starting about ten years after his diagnosis. At this time he was also acidotic, due to episodic noncompliance with bicarbonate supplements. Renal scan revealed kidneys of normal size and without obstruction but with some diminution of flow in the right kidney. In 1987 the patient was evaluated for a renal transplant because of progressive azotemia (Fig. 1). Although he was still a robust athletic man, working full-time as a high school teacher and exercising several times a week in the gymnasium, he noted increased muscle pain and weakness. The patient was now on calcium and 1,25$(OH)_2$ Vitamin D_3 therapy along with potassium phosphate, atenolol, and bicarbonate. He was normotensive and weighed 149 pounds. Laboratory values at that time are included in Tables 1 and 2.

Despite decreased glomerular filtration rate, he still had markedly elevated excretion rates of amino acids and proteinuria, which consisted mainly of proteins of small molecular weight on urine electrophoresis. Bone densitometry in 1987 was 137 mg/cm³, at the lower limits of normal. A computed tomogram (CT) of his wrist showed marked decreases in both cortical and trabecular bone mass.

Bone biopsy demonstrated mixed renal osteodystrophy with moderate signs of both osteitis fibrosa cystica from hyperparathyroidism and osteomalacia with increased inactive osteoid surfaces. Repeat IVP now revealed persistent kidney stone only in the left kidney with no obstruction. Both kidneys were reduced in size.

TABLE 3
Etiologies of Fanconi Syndrome[a]

Genetic [2]	Acquired [3,4]
Wilson disease (AR) [5]	Heavy metals [22,23] (cadmium, uranium, lead, mercury)
Glycogen storage disease (Type 1) (AR) [6,7]	Toxins (Lysol [24], toluene [25], paraquat [26])
Galactosemia (AR) [8]	Drugs (outdated tetracyclines [27], cisplatin [28])
Hereditary tyrosinemia (Type 1) (AR)[9]	Nephrotic syndrome [29,30]
Hereditary fructose intolerance (AR) [10]	Vitamin D deficiency/secondary hyperparathyroidism [31]
Cystinosis (AR) [11]	Immunoglobulin disorders (multiple myeloma [32], amyloid [33], light chain disease [33], monoclonal gammopathy [34])
Oculo-cerebro-renal syndrome (XLR) [12]	Rejection episodes post-renal transplant [35–38]
Idiopathic (AD) [13–20]	Anti-tubular basement membrane antibodies [39]

[a]Figures in brackets denote reference numbers.
  AR, autosomal recessive trait
  AD, autosomal dominant trait
  XLR, X-linked recessive trait

In summary, the patient is a 42-year-old white male with a 20-year history of Fanconi syndrome and progressive renal failure. With appearance of Fanconi syndrome in his son (see below), a familial cause for his primary Fanconi syndrome seemed likely.

FANCONI SYNDROME IN THE PATIENT'S SON

DR. N.J. SIEGEL: The child was first seen at Yale in July 1986, when he was five years of age. He had been previously hospitalized in Newington for orthopedic problems related to cerebral palsy. During that hospitalization, he was noted to have 3+ glucose with a blood glucose of 110 mg/dL. Other than glycosuria and cerebral palsy, the child appeared perfectly healthy. He was normotensive and quite active.

He had diffuse aminoaciduria, renal glycosuria, and uric acid of 2.5 mg/dL, which is low even for a child. His phosphate was 3.5 mg/dL; for a five-year-old this would be a slightly low value, since phosphate tends to run a little higher in children during their growth period. The most common cause of Fanconi syndrome in children is cystinosis [1]. It was clear that at his age he didn't have infantile nephropathic cystinosis, but there is an intermediate form, which is not as severe as the nephropathic form, and we thought that he might fall into that category. So we re-evaluated the child for cystinosis but found no evidence for that disease. When the father's record was reviewed, it became clear that the child had a familial form of idiopathic Fanconi syndrome.

GENETICS OF FANCONI SYNDROME

DR. M.R. SEASHORE: There are a limited number of cases in the literature with transmission of Fanconi syndrome over two, three, and, maybe in one family, over four generations. The "classic" Fanconi syndrome shows increased renal excretion of amino acids, phosphate, proteins, and uric acid, along with type 2 renal tubular acidosis; however, people can present without all those findings.

What are the known single gene disorders with associated renal tubular damage that can present as Fanconi syndrome? What are the genetic disorders with which the
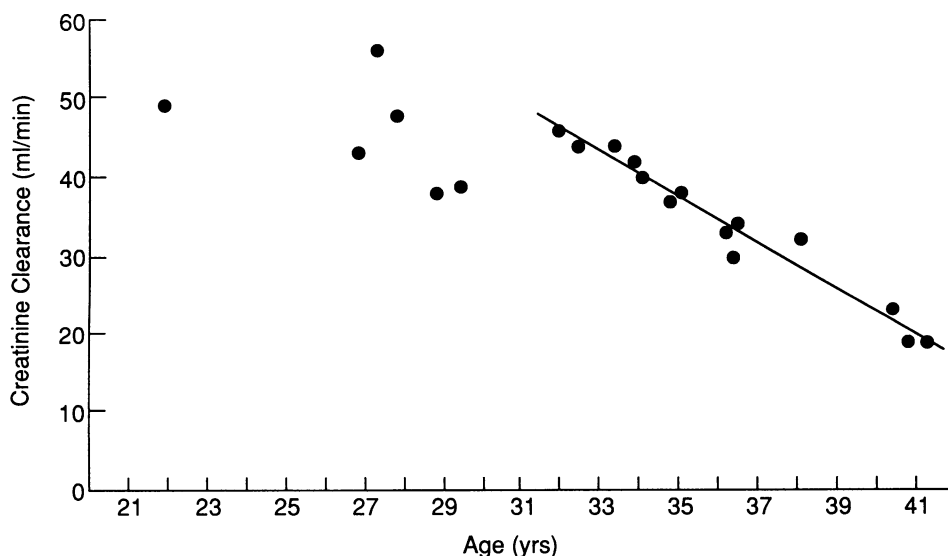
FIG. 1. Glomerular filtration rate estimated as creatinine clearance versus year of measurement. Clearance was calculated from patient's weight, age, and serum creatinine by the formula of Cockcroft and Gault [61]. No statistically significant change occurred in estimated creatinine clearance during the first ten years of the patient's follow-up; the decline noted in the last decade is significant ($p < 0.01$).

Fanconi syndrome, as a collection of renal tubular dysfunctions, is associated [2]? Table 3 presents a list of those best known and reported. I think we can exclude all of them in this patient and his family, but their review is worthwhile.

At the top of the list is Wilson's disease, a disorder of copper metabolism [5]. Copper is stored in various body tissues and leads to toxicity not only in the kidney but in the liver and central nervous system as well. The basic defect is as yet unknown, but the damage is reversible with decoppering, using chelating agents such as penicillamine. Wilson's disease has been excluded in this patient by the normal blood ceruloplasmin concentrations, the absence of Kaiser-Fleischer rings, and the absence of central nervous system deterioration without any specific therapy. Wilson's disease is a rare autosomal recessive disorder. It would be unusual for a parent and a child to have a rare autosomal recessive disorder, because it would require that the affected parent be married to an individual heterozygous for the same gene in order for the child to be homozygous for the same mutation, which can occur in disorders that are common or in consanguineous families.

Glycogen storage disease is a disorder that one must consider in the pediatric age group, particularly Type 1 glycogen storage disease, due to glucose-6-phosphatase deficiency [6,7]. These patients have storage of glycogen in liver but also in the kidney, resulting in renal tubular damage. This condition is reversible with maintenance of normal blood glucose, formerly by continuous nasogastric suction and now with cornstarch every six hours by mouth. There is no reason to think that this family has glycogen storage disease.

Galactosemia, due to galactose-1-phosphate uridyl transferase deficiency, is another recessively inherited disorder in which renal tubular damage is prominent [8]. Toxicity is probably due to either galactose or galactose-1-phosphate. This patient's initial

presentation is quite inconsistent with galactosemia, because classical galactosemia, if untreated, is usually fatal within the first four weeks of life.

Hereditary tyrosinemia is a very rare disorder of amino acid metabolism in which the basic defect is a deficiency of the enzyme fumaryl acetoacetase, an important component of the tyrosine catabolic pathway [9]. This condition is also an autosomal recessive disorder, and afflicted individuals succumb in early infancy if not treated. The only successful treatment at the present time is liver and renal transplantation. This condition is not a consideration for this patient.

Hereditary fructose intolerance (HFI) due to deficient fructoaldolase is another rare, recessively inherited disorder of carbohydrate metabolism [10]. Fructose and/or fructose-1-phosphate are toxic to the renal tubule, but this condition is reversible with a fructose-free diet. It would be unusual to find a parent and child who are both affected with this disease. It is possible to find a child with this disorder who develops symptoms in later childhood. Because patients become symptomatic with vomiting and diarrhea only when they have a fructose load, such an individual could self-limit fructose intake and not present until a later age. Usually those who do present at later ages have had small fructose intakes and present with hepatomegaly as well as renal insufficiency or renal tubular damage. I think it is a very unlikely explanation for this patient.

Cystinosis is an interesting autosomal recessive disorder in which cystine is stored within lysosomes, probably because of abnormal cystine transport [11]. The infantile form presents with conjunctivitis, renal insufficiency, failure to grow, and developmental delay in young infants. Obviously, that's not the explanation here. There is, however, an intermediate form with onset in adolescence and a less severe course. In the adult-onset form, renal tubular function is usually spared. It has not been proven that these three are all due to different mutations at the same locus, but that is the leading hypothesis. Absence of cystine crystals in bone marrow or in the renal biopsy of this patient excludes this diagnosis.

The last relatively common genetic disorder associated with Fanconi syndrome is the oculo-cerebral-renal syndrome described by Charles Lowe [12]. It is the only X-linked disorder reported. The mechanism of that disorder is completely unknown, and the gene has not been defined. There is no successful therapy that I know of, and those children die in early infancy. It would be untenable to think that a father and a son would have the same X-linked disorder because the gene is on the X chromosome, so father-to-son transmission excludes an X-linked disorder.

What do we know about the familial occurrence of the Fanconi syndrome in patients without any of the recognized genetic disorders? There are several families now reported in the literature over the last 20 years where there are multiple family members with isolated Fanconi syndrome, unexplainable by any of the other mechanisms just reviewed.

The earliest case involving more than one generation was a family reported in 1959 by Sheldon, Luder, and Webb [13]. Twin girls presented with the Fanconi syndrome in childhood. When the father was then examined, he had glucosuria, phosphaturia, and skeletal problems. The children had frank rickets. Review of the medical record of the paternal grandfather (then deceased) showed glucosuria, thought to be renal glucosuria. He had been a very short, slender man diagnosed with osteoporosis. He died before quantitative amino acid measurement was available, and so he never had amino acids measured in blood or urine. Sheldon and colleagues postulate that this family represents three generations of proximal renal tubular dysfunction, presenting in the

twins as classical Fanconi syndrome. In 1981, Patrick et al. [14] provided follow-up information about the family described by Sheldon and Luder, and noted that renal failure necessitating renal transplant had occurred in the father; the twins at that time had less severe renal failure. Although their renal failure has continued to progress, neither twin had begun dialysis or been transplanted by early 1988 [Cameron JS: personal communication].

In 1961 Ben-Ishay and his colleagues [15] reported three generations in a family with low serum uric acid concentrations and phosphaturia but without renal failure. Hunt [16] in 1966 reported a mother and three children with aminoaciduria, glucosuria, proteinuria, and hypophosphatemia. The mother had skeletal manifestations which improved after treatment with phosphate and vitamin D. In 1981, Brenton and colleagues [17] provided extensive data about the occurrence of idiopathic Fanconi syndrome in two generations of the families of the siblings reported in 1951 by Dent and Harris and believed to have a recessive form of Fanconi syndrome. This 30-year follow-up revealed the occurrence of idiopathic Fanconi syndrome in a total of five individuals in two generations. The cases reported by Friedman and his colleagues [18] in 1978 were father and son, each with relatively early renal failure; both underwent renal transplantation. The Wisconsin group has recently reported another family in which both mother and son have generalized aminoaciduria, glycosuria, and impaired renal function [19].

Some of the cases just reviewed were reported prior to 1968, the date we first saw this patient. The rarity of the reported cases at that time and the lack of family history in our case mitigated against the initial diagnosis of inherited Fanconi syndrome. Today, however, with further cases reported, we would raise the possibility of a 50 percent risk to offspring, since dominant inheritance has been demonstrated in some families.

The question of environmental influences arises. I think this is always a serious problem, but in the Sheldon and Luder paper, at least, there are three generations affected. The various reports summarized above have come from different parts of the world: Hunt's report from Iowa City, Friedman and Chesney's from the University of Wisconsin, Ben-Ishay's from Israel (the patient was Tunisian), and Sheldon and colleagues from Great Ormond Street in London. So, although we cannot conclusively rule out environmental effect in these cases, it seems either unlikely or worldwide in distribution.

Much variability occurs from one case to another, both within families and among the families reported in the literature. This fact, of course, is not an unusual feature of dominantly inherited disorders (if indeed this is a disorder involving a single gene). A great deal of clinical variability occurs within and among families in most autosomal dominant disease.

Is this an autosomal dominant disorder? At present, there is no proof for that hypothesis. No linkage to any other known genes has been demonstrated. For Fanconi syndrome, no mapping to a specific chromosomal location has been done, but the pedigree evidence speaks for autosomal dominant inheritance. Within the families described, the affected parents have had both normal and abnormal children, which is compatible with autosomal dominant inheritance. There have been affected fathers with affected sons, also compatible with autosomal dominant inheritance and incompatible with X-linked inheritance.

In summary, we have evidence for a few families in the literature where there is vertical transmission compatible with autosomal dominant inheritance (but certainly

TABLE 4
Characteristics of Fanconi Syndrome

Cardinal Features	Clinical Consequences
1. Generalized aminoaciduria	1. May contribute to failure to thrive in infants and children; no known effects in adults
2. Glycosuria	2. Hypoglycemia and ketonuria only if severe; usually without marked clinical effect
3. Phosphaturia	3. Bone disease
4. Renal tubular acidosis (RTA Type II > I)	4. Metabolic acidosis; probably contributes to bone disease
Other Less Frequent Abnormalities	Clinical Consequences
5. Hyperuricosuria	5. None known
6. Proteinuria	6. None known
7. Potassium wasting	7. Hypokalemia, weakness
8. Sodium wasting	8. Volume contraction and hyponatremia if severe
9. Polyuria	9. Dehydration and electrolyte abnormalities if severe

not proven) and clinical variability within and among families. This list is a very small number of families from which to construct a genetic model, and the reports do not contain full pedigrees. Nevertheless, Fanconi syndrome is now listed as an autosomal dominant disorder by McKusick in the seventh edition of his catalog, *Mendelian Inheritance in Man* [21].

CLINICAL FEATURES

DR. W.S. LONG, AND DR. M.J. BIA: Clinical features of Fanconi syndrome involving both renal and musculoskeletal systems are listed in Table 4. Cardinal features, present in all patients with Fanconi syndrome, include glucosuria, general aminoaciduria, and phosphaturia [1,3,4,40]. Although glycosuria and aminoaciduria appear to have few clinical consequences, renal phosphate wasting is thought to play a major role in the development of the metabolic bone disease which invariably develops in untreated cases and is an important cause of morbidity. Development of renal tubular acidosis (RTA) may also contribute to bone disease, which is usually Type II RTA from proximal tubular bicarbonate wasting, but patients with Type I (distal) RTA have also been described [5,23,29,30], especially in acquired Fanconi syndrome. Hyperuricosuria and proteinuria (usually tubular proteinuria consisting of proteins of small molecular weight) are also frequent features. Although potassium wasting, polyuria, and salt wasting are less frequently observed, they can have profound clinical consequences if not recognized and treated appropriately. Children may present dramatically with vomiting, polydipsia, polyuria, and volume depletion, or more subtly with failure to thrive. Presentation with rickets will depend on whether the child is walking or crawling (or neither) but may include frontal bossing and hypotonia as well. Bone films show widened epiphyses, frayed metaphyses, and demineralization. Children will eventually develop severe rickets if left untreated [1].

In adults, presentation may by symptomatic, e.g., bone pain, proximal muscle or generalized weakness, polyuria with polydipsia, and myalgias, or it may be fortuitously detected by abnormal laboratory values, as in our patient, before the disease becomes symptomatic. Although untreated adults do not present with growth retardation, they

invariably develop osteopenia, due to both osteomalacia and osteoporosis. Back, hip, and sacroiliac pain and weakness are common complaints, with X-rays showing pseudofractures, even in asymptomatic locations. Although phosphate wasting and acidosis are thought to be the most important contributors to the metabolic bone disease, more recent evidence indicates that deficient $1,25\text{-}(OH)_2$ Vitamin D_3 production in these patients may contribute as well [31,41].

Our patient manifested all the classic features of Fanconi syndrome with phosphaturia, aminoaciduria, glycosuria, proteinuria, and acidosis. Furthermore, he had radiologic evidence of marked osteopenia on initial presentation. Although we cannot date the onset of the syndrome in our patient, it appears to have begun after the age of puberty, since he had attained adult stature and skeletal maturation.

Of particular interest in our case is the presence of asymptomatic renal disease at initial presentation. There are few reliable early clues in patients with idiopathic Fanconi syndrome to ascertain if a given patient will progress to chronic renal failure. Although renal failure was reported to be rare in early reports of patients with Fanconi syndrome [42], later studies showed that this condition does occur. Thus there are at least eight reports [14,16,18,23,38,41,43,44] involving 14 patients with idiopathic Fanconi syndrome associated with significant decreases in GFR. Interestingly, the syndrome was genetically transmitted in ten of these patients, which raises the question of whether such patients inherit both the predisposition for renal failure as well as that for idiopathic Fanconi syndrome. Chronic interstitial nephritis, as demonstrated in our case, with atrophy and dilatation of tubules and interstitial fibrosis has been demonstrated in all cases where renal tissue was examined [14,16,18,23,44]. There are at least four reports demonstrating that the renal failure has progressed to end stage, requiring dialysis or transplantation [14,18,38,43]. Both nephrocalcinosis, resulting from the hypercalciuria and hyperphosphaturia, and renal stones, present in our patient, are rare in the cases described. The etiology of the interstitial nephritis and subsequent renal failure is currently unknown.

PATHOPHYSIOLOGY

DR. W.S. LONG: The wide range of tubular, especially proximal tubular, derangements in Fanconi syndrome suggests that some generalized defect in cellular function underlies its presentation. Although a naturally occurring canine model of Fanconi syndrome exists [45], most experimental work [3,4,40,46] has used models of Fanconi syndrome induced in laboratory animals or in patients with hereditary fructose intolerance (HFI) to investigate two major explanations: *(1)* changes in energy supply and utilization, and/or *(2)* changes in membrane permeability.

1. *Energy Hypothesis:* The energy hypothesis speculates that the etiologies of Fanconi syndrome have in common a diversion of biochemical energy from its usual paths, with consequent disruption of directly and indirectly coupled membrane transport. Support for this hypothesis is derived from observations in patients with HFI, due to defective fructose-1-phosphate (F1P) aldolase. In these patients, ingestion of fructose causes F1P to accumulate primarily in proximal tubular cells, where it serves as an intracellular sink for phosphate. It is also associated with an almost immediate, dose-dependent, increased excretion of amino acids, protein, bicarbonate, and hypophosphatemia without phosphaturia. Glycosuria is usually not found in these patients [4,40].

Given a fructose load, normal dogs [47] and rats [46] produce a urine similar to that found in patients with HFI ingesting fructose or with Fanconi syndrome of other etiologies. This model of Fanconi syndrome, readily established in laboratory animals, has served to study the etiology of Fanconi syndrome. Rats given a fructose load accumulate F1P in renal proximal tubules, small bowel mucosa, and liver, with consequent depletion of intra- and extracellular inorganic phosphate. The resulting depletion of free intracellular phosphate in turn activates adenosine monophosphate (AMP) deaminase, shunts adenine nucleotides into oxypurines (inosine, hypoxanthine, xanthine), reduces total cytoplasmic adenine nucleotide pool including adenosine triphosphate (ATP), and promotes the hyperuricemia and increased excretion of oxypurines observed in HFI [40,46]. Pre-loading with inorganic phosphate attenuates these responses in fructose-loaded rats [40]. (With fructose loading, normal humans appear to develop a syndrome [48] similar to those in laboratory animals, albeit at much higher doses of fructose than those used to produce Fanconi syndrome in patients with HFI.)

The other major model of Fanconi syndrome involves maleic acid (MA), the cis-isomer of fumarate [46,49]. Studies of both the energy and permeability hypotheses in Fanconi syndrome have used MA. This compound induces a reversible, dose-dependent urinary wasting of glucose, phosphate, amino acids, bicarbonate, sodium, and potassium when administered to rats and dogs; under some conditions it may induce acute renal failure [50,51]. The mechanism(s) is(are) unclear. MA blocks both protein and non-protein sulfhydryl groups [46], as well as amino groups [52], and so may have widespread effects on multiple cellular processes. Many studies have shown development of Fanconi syndrome in association with defective energy metabolism after exposure to MA [53,54,55,56]. Rats treated with MA have significantly reduced activities of both Na-K- and Mg-ATPases, as well as decreased ATP concentrations [54,55]. MA inhibits O_2 uptake and phosphorylation in rat kidney mitochondria oxidizing CoA-dependent compounds such as pyruvate and acetoacetate; the effects can be diminished by high concentrations of inorganic phosphate [56]. *In vivo,* phosphate infusion in dogs before MA exposure attenuated increases in urine flow and in clearances for bicarbonate, amino acids, and potassium [48].

Electron microscopy of renal tissue exposed to MA shows dose-dependent changes consistent with effects on both transport and energy systems. Several investigators have shown dense cytoplasm, focal loss of microvilli, and the accumulation of apical vacuoles in proximal tubules [51,55,57]. Christensen and Maunsbach demonstrated decreased uptake and lysosomal degradation of lysozyme in MA-treated rats, attributed in part to diminished supply of ATP [51]. Verani and colleagues [57] showed the histologic changes only in the late proximal convolution and pars recta, while others demonstrate leakage of inulin and histological changes beyond the proximal convolutions [50,55].

These investigations in laboratory animals and in humans [4,40] make it reasonable to implicate disruption of energy metabolism at one or more sites in the multiple transport abnormalities observed in Fanconi syndrome. For example, Al-Bander and his colleagues have attempted to combine experimental data and speculation into a clear formulation of the action of MA [47]. MA disrupts proximal tubular mitochondria and consequently oxidative metabolism, as discussed above. This condition in turn could promote the increase in glycolysis and glucose uptake, observed in rats [60], with increased concentrations of phosphorylated intermediates of glycolysis found in tissue

studies. In a manner analogous to that described for HFI, intracellular phosphate depletion would then lead to diminution of adenine nucleotide pools and inadequate energy stores for membrane transport. Pre-treatment with phosphate protects against the effects of MA.

2. *Permeability Hypothesis:* This hypothesis proposes that primary changes in membrane permeability, whatever their causes, explain many findings in experimental Fanconi syndrome. This hypothesis stems from the microinjection, microperfusion, and stop-flow experiments in maleate-treated rats by Bergeron and his colleagues [58,59]. They interpret their studies to show that MA increases membrane permeabilities (luminal > basal) in both proximal and distal tubular cells with otherwise intact transport mechanisms on both sides of the cell. According to this model, the proximal tubule still reabsorbs glucose and amino acids despite its increased membrane permeabilities. From the interstitium, these compounds enter distal tubular cells and tubular fluid across its cellular membranes, made abnormally permeable by MA. Because distal tubular cells lack reabsorptive mechanisms for glucose and amino acids, they are excreted in the urine before inulin, even though filtered simultaneously, as observed in their experiments with radioactive compounds. The increased permeabilities of both proximal and distal tubular cells to glucose and amino acids but not to inulin create this short circuit across the interstitium.

Most experimenters feel that the findings of experimental Fanconi syndrome cannot be explained solely by one of these two hypotheses. Nonetheless, the energy hypothesis does allow us, by uniting data from histologic, physiologic, and biochemical experiments, to imagine how distortion of energy metabolism could give rise to the many transport abnormalities of Fanconi syndrome with their clinical consequences. Evidence for the permeability hypothesis is not as wide-ranging or as various.

Readers interested in an extensive review of the experimental analysis of pathogenesis in Fanconi syndrome are referred to the article of Gonick and Kramer [46].

THERAPY

DR. W.S. LONG AND DR. M.J. BIA: In cases associated with exposure to an exogenous toxin or with a systemic disease, treatment of the underlying problem will often result in resolution or improvement of the tubular defects. In some secondary cases and in idiopathic cases, however, Fanconi syndrome persists, and the effects of electrolyte and fluid imbalances require direct treatment.

Replacement of phosphate losses is mandatory to prevent progression of bone disease, which constitutes the major morbidity associated with the syndrome. Oral supplementation of 1–3 g neutral phosphate per day is usually required, although prolonged treatment may be limited by intestinal discomfort and diarrhea experienced at these doses. High doses of vitamin D or $1,25\text{-}(OH)_2$ vitamin D_3 should also be used in cases with documented rickets or osteomalacia. Therapy with both phosphate and vitamin D has been shown to promote growth in children and improve symptoms and radiologic evidence of rickets in children and osteomalacia in adults [1,4]. If renal failure develops, phosphate wasting diminishes, and supplementation is no longer needed, as in our patient's case. Sodium may be used to replace urinary losses and to aid in volume repletion. Potassium supplements are frequently needed; bicarbonate, acetate, citrate salts (2–10 mEq/kg/day) are used as anions in these supplements to control the acidosis of Fanconi syndrome. Replacement of organic solutes like amino acids or glucose is not necessary.

Our patient's initial therapy (1968) consisted only of bicarbonate supplements, to which phosphate (1969) and potassium (1978) supplements were later added, as well as antihypertensive (1981) medications; however, with progressive renal failure phosphate and potassium supplements are no longer needed.

Accounts concerning transplantation for idiopathic Fanconi syndrome are few. The group of J.P. Merrill reported a maternal allograft in a 14-year-old boy diagnosed with idiopathic Fanconi at age five [38]. Although Fanconi syndrome can develop de novo during transplant rejection [35–37], his two early episodes of rejection showed no signs of it. Five weeks after transplantation (creatinine, 1.6 mg/dL percent), however, he developed proximal tubular acidosis with subsequent glycosuria and aminoaciduria. Thus, in this case Fanconi syndrome appears to have recurred. At the time of publication, the patient was two years beyond his transplantation, had mild renal insufficiency attributed to further episodes of rejection, and required bicarbonate supplements to control his acidosis [38].

Friedman and his associates have reported two more cases of transplantation for idiopathic Fanconi's syndrome [18]. Both father and son had aminoaciduria, glucosuria, phosphaturia, and renal insufficiency. At age 29, he received a cadaveric renal transplant without nephrectomy. In 1988, six years after transplantation, the patient's allograft continued to function well with no signs of recurrent Fanconi syndrome. In 1965, the patient's three-year-old son presented with Fanconi syndrome and at age 16 received a maternal allograft which functioned without sign of recurrent Fanconi syndrome for about a year. This allograft and a subsequent cadaveric kidney were eventually rejected, and he (the patient's son) is now on dialysis [Friedman A: personal communication].

In summary, we have three published cases of idiopathic Fanconi syndrome receiving renal allografts with at least one year of follow-up. In only the first case does Fanconi syndrome appear to have recurred. It will be interesting to follow our patient's case after transplantation to determine if his Fanconi syndrome recurs.

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