Table 42-1
Causes of Fanconi syndrome

Hereditary
• Dent disease
• Lowe syndrome
• Mitochondriopathies
• Cystinosis
• Galactosemia
• Hereditary fructose intolerance
• Glycogen storage disease type I (von Gierke disease)
• Fanconi-Bickel syndrome
• Tyrosinemia
• Wilson disease
• Idiopathic Fanconi syndrome
Acquired
• Nephrotic syndrome
• Myeloma
• Sjögren syndrome
• Renal transplantation
• Acute tubulointerstitial nephritis with uveitis (TINU) syndrome
• Autoimmune interstitial nephritis and membranous nephropathy
• Anorexia nervosa
• Untreated condition of distal renal tubular acidosis
Exogenous substances
• Drugs
• Chemical compounds
• Heavy metals

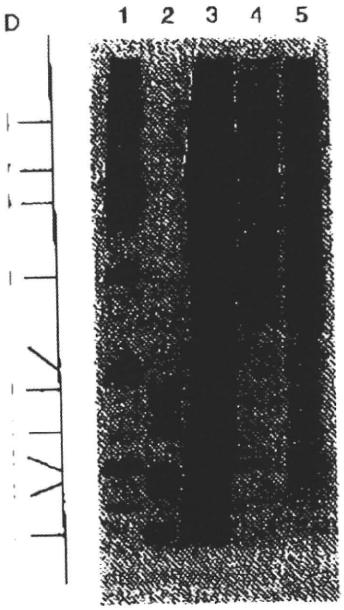
Dent disease is associated with inactivating mutations in *CLCN5* gene, which encodes 746 amino acids renal specific chloride channel-5 (ClC-5) (8, 47–49). ClC-5 belongs to the family of voltage-dependent chloride channels, which function as homodimeric proteins. ClC-5 is co-expressed with the vacuolar H^+-ATPase and plays a key role in endosomal acidification that is a crucial function in the receptor-mediated endocytic pathway (50). More than 80 distinct *CLCN5* mutations are reported in patients with Dent disease. They are nonsense, missense, frameshift, splice-site, insertional, and deletional mutations, which result in total or partial loss of function. There are no genotype-phenotype correlations as various mutations are associated with different clinical phenotypes, even within the same family.

Numerous filtered proteins are bound to megalin and cubilin in the luminal membrane of proximal tubules, and the protein-receptor complex is incorporated into the endosome. The ligand and receptor are disassociated in the endosome; the receptor is recycled back to the luminal membrane and the reabsorbed proteins go into lysosome for further processing. This disassociation is dependent on acidification of the lumen of endosome by increased concentration of H^+ and Cl^- due to the function of H^+-ATPase and ClC-5 chloride channel. An abnormal endocytosis pathway due to ClC-5 dysfunction disturbs the recycling of megalin and cubilin, the back to the luminal membrane, and the expression of megalin and cubilin in the luminal membrane of proximal tubules, leading to LMW proteinuria, hypercalciuria, hyperphosphaturia, and nephrolithiasis. Proper acidification is also important for protein degradation in the endosome. Immunohistochemical analysis of proximal tubule cells in patients with Dent disease revealed an inverted polarity of the H^+-ATPase, with redistribution to basolateral regions, suggesting that the loss of ClC-5 channel alters the function of components that co-distribute and physically interact with it (51).

Total urine protein ranges from 0.5–2.5 g a day, but may reach 4 g or higher in patients with Dent disease (45, 52). More than 60% of the filtered proteins are LMW proteins with molecular weight less than 45 KD (◉ *Fig. 42-3*). Nephrotic syndrome does not occur. LMW proteinuria is the most consistent and one of the earliest presenting abnormalities. Urinary beta 2-microglobulin, a LMW protein (MW = 11.6 KD), is excreted in amounts 100–300 times the upper limit of the normal. Albumin is also excreted in the urine. The pattern of proteins representing the increased excretion of several LMW proteins as well as albumin (MW = 65 KD) is termed as *tubular proteinuria* (52, 53). The terms of LMW proteinuria and tubular proteinuria have usually been used interchangeably (53).

Patients with Dent disease manifest hypercalciuria in the range of 4–10 mg kg^{-1} of body weight a day in children and 4–6 mg kg^{-1} of body weight a day in adults (54). Nephrocalcinosis is also found in children (◉ *Fig. 42-4*). Defective endocytosis of parathyroid hormone (PTH) in patients with Dent disease resulting in its persistence in the lumen of the proximal tubule stimulates 25-hydroxyvitamin D3 1-hydroxylase to produce more 1,25-dihydroxyvitamin D3 resulting in the increased serum levels of this vitamin. 25-hydroxyvitamin D3 is presented to 25-hydroxyvitamin D3 1-hydroxylase in the form of a complex with the vitamin D3-binding protein. As this complex is lost in the urine as a result of defective endocytosis leading to LMW proteinuria, the precursor

of urine from the family members of Dent polyacrylamide gel and stained by sliver /W proteinuria. Lanes 1 and 2, molecular , 12-year-old boy with Dent disease; Lane 4, e 5, his father.



nin D3 could be in short supply. The e of increased 1, 25-dihydroxyvitamin depend on the delicate balance between The slightly elevated serum levels of 1, amin D3 in patients with Dent disease eased intestinal Ca^{2+} reabsorption result- ciuria (*absorptive hypercalciuria*). In fact, tients with *CLCN5* mutations manifest even though some of these do exhibit s (55). This may be explained by the out mice model; ClC-5 disruption pro- rystal agglomeration, as well as a redistri- rystal-binding molecule annexin A2, in pithelial cells (56).

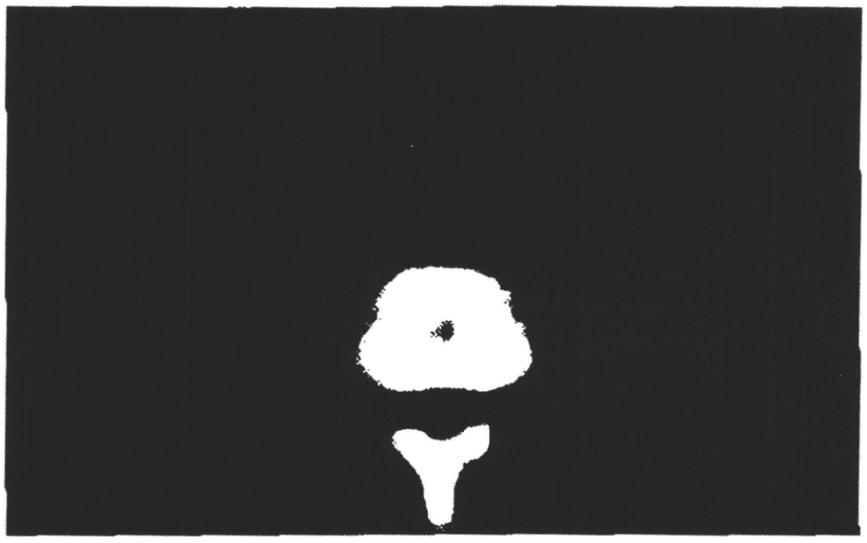
f renal insufficiency and progression to failure are quite variable. Significant de- ular filtration rate is seen in children with ıd the patients fall into end-stage renal d of the age of 40s. Renal biopsy demon- or focal global glomerulosclerosis with tubular dilatation, and interstitial infil- ocytes. Medullary nephrocalcinosis is a re in patients with Dent disease. Patients of age manifest medullary nephrocalci- e mechanism of progressive renal failure is not known in patients with Dent disease. Nephrocalcinosis can be a candidate to disturb the glomerular filtration rate. High urinary concentrations of potentially bioactive proteins including insulin, insulin like growth factor-1 (IGF-1), and the chemokine monocyte chemoattractant protein-1 (MCP-1) may contribute to interstitial fibrosis that will lead to progressive renal failure in patients with Dent disease (57). Generalized proximal tubule dysfunction is associated with increased cell proliferation, dedifferentiation, and oxidative stress resulting in interstitial fibrosis and eventual renal failure (58). Patients and carrier females often manifest nephrolithiasis, and renal stone is calcium phosphate stone that is also seen in patients with distal renal tubular acidosis.

Dent disease is genetically heterogeneous. Mutations in the *OCRL1* gene are identified in a subset of patients with the Dent disease phenotype (59). Unlike patients with typical Lowe syndrome, typical facial features, mental retardation, metabolic acidosis, and ocular abnormalities are usually absent in patients with Dent disease who have *OCRL1* mutation. The phosphoinositol 4,5-bisphosphate phosphatase (PIP_2 5-phosphatase) activity is markedly reduced in skin fibroblasts cultured from patients with Dent disease due to *OCRL1* mutations, and protein expression, measured by Western blotting, is reduced or absent. PIP_2 5-phosphatase participates the trafficking and recycling of endosome in the proximal tubules. Defective PIP_2 5-phosphatase activity can lead to endosomal dysfunction leading to LMW proteinuria. Unlike the patients with typical Lowe syndrome, none of patients have metabolic acidosis. These observations and findings suggest that *OCRL1* mutations can cause the isolated renal phenotype of Dent disease and affected individuals lack the cataracts, typical facial features, renal tubular acidosis, and neurologic abnormalities that are characteristic to Lowe syndrome. It is difficult to explain that *OCRL1* mutations can cause the isolated renal phenotype of Dent disease. However, it is possible that another phosphatase, *INPP5B*, which shares amino acid homology with *OCRL1*, can compensate phosphatase activity in patients with Dent disease due to *OCRL1* mutations.

There are no specific interventions at present that will change the natural course of renal manifestations and progressive renal failure in patients with Dent disease. Hypercalciuria is corrected by thiazide diuretics therapy in doses similar to effective doses for idiopathic hypercalciuria, presumably by stimulating the reabsorption of calcium in the distal convoluted tubule, where ClC-5 channel is not expressed (60). However, this is not a long-term study which provides the evidence that it is

Figure 42-4

Abdominal CT demonstrating bilateral medullary nephrocalcinosis in a 12-year-old boy with Dent disease.



effective to prevent or delay the progression of end stage renal failure. In animal experiment using *clcn5* (mouse chloride channel 5 gene) knock-out mice, high citrate diets can delay the progression of nephrocalcinosis and end stage renal failure (61, 62). Treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) may delay progression of end stage renal failure (63).

Lowe Syndrome

The oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked disorder that is characterized by a complex phenotype that involves major abnormalities of the eyes (particularly congenital cataracts), central nervous system abnormality and FS (64). Cataracts are recognized in all the male patients. Lens opacities are present in all carriers of females by slit-lamp examination and this is a reliable screen for carriers (65). Other ocular abnormalities include glaucoma, microphthalmos, and corneal keloid formation. Visual acuity is frequently disturbed. Central nervous system abnormalities include infantile hypotonia (floppy infant), areflexia, and mental retardation. The patients manifest mild ventriculomegaly and cysts in the periventricular regions in the brain. Status epilepticus is sometimes recognized. FS is a major clinical feature and occurs in the 1st year of life, but the severity and age of onset vary. The patients manifest LMW proteinuria, glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, hypophosphatemic rickets, hypercholoremic metabolic acidosis, and progressive renal insufficiency (66). Renal insufficiency progresses at variable rate among patients, and it progresses to end-stage renal failure by 30s or 40s.

Like in patients with Dent disease, megalin is nearly absent from the urine in patients with Lowe syndrome suggesting of the decreased expression of megalin in the luminal membrane of the proximal tubule cells. Thus, urinary excretion of retinol-binding protein and the lysosomal enzyme N-acetyl-glucosaminidase are significantly increased in young boys with OCRL (67).

The gene (*OCRL1*) that is responsible for OCRL encodes a 105 KD Golgi protein with phosphoinositol 4,5-bisphosphate phosphatase (PIP_2 5-phosphatase) activity (68). PIP_2 5-phosphatase is mainly a lipid phosphatase that may control cellular levels of a critical metabolite, phosphatidylinositol 4,5-bisphosphate, and is involved in the inositol phosphatase signaling pathway (69). PIP_2 5-phosphatase is present in cultured skin fibroblast and it is not present in peripheral blood cells. PIP_2 5-phosphatase activity is markedly reduced in fibroblasts from patients with Lowe syndrome (70). However, this biochemical test for carrier diagnosis is not reliable; lyonization produces a highly variable pattern of tissue expression in females.

Deficiency of PIP_2 5-phosphatase leads to cellular accumulation of its substrate PIP_2. PIP_2 accumulates in lysosomal membrane (71). PIP_2 is involved in signal transduction, vesicle trafficking and actin polymerization. Absence of PIP_2 5-phosphatase activity leads to a reduction in the number and length of actin stress fibers, a tendency of actin fibers to depolymerize when provoked,

nal distribution of two actin-binding pro-
nd alpha-actinin. This disruption of actin
significant effects on epithelial function
pting cell–cell contacts such as tight junc-
rent junctions or by altering membrane
h as transport proteins (72). Trans-Golgi
r altered actin polymerization can explain
with Lowe syndrome. PIP_2 5-phosphatase is
dosome and Golgi membranes along with
tin, the mannose 6-phosphate receptor,
d the early endosomal antigen 1 marker.
hatase interacts with clathrin terminal
the clathrin adaptor protein AP-2. This
for PIP_2 5-phosphatase in endosomal re-
ng and sorting (73, 74). OCRL1 is present
e early endocytic pathway, including in
hirin-coated pits, and demonstrate a
tween OCRL1 and adaptor molecules
he endocytic trafficking of receptor in the

; a C-terminal RhoGAP domain. *OCRL1*
5-phosphatase activity that binds to Rac
ted Rac GTPase stably associates with the
AP domain. In this sense, the protein
RL1 can play a bifunctional role. Loss of
P domain and the resulting alteration in
may contribute to mental retardation in
e, as observed in other forms of X-linked
ion (76).

tations can cause the isolated renal pheno-
lisease and affected individuals lack the
al facial features, renal tubular acidosis,
abnormalities that are characteristic to
e. It is difficult to explain that *OCRL1*
cause the isolated renal phenotype of
However, another phosphatase, *INPP5B*,
mino acid homology with *OCRL1*, can
osphatase activity in patients with Dent
OCRL mutations.

'0 *OCRL1* mutations have been described
Lowe syndrome; nearly all are clustered in
specially exon 15, and almost none are
1–9 (70).

; supportive and includes taking care of
ations, anticonvulsants, speech therapy,
plications. The eye abnormalities usually
arly in life. Bicarbonate therapy is usually
se of 2–3 mmol kg^{-1} of body weight a day
ium or potassium phosphate can be given
–4 g a day for phosphate depletion and if
amin D can be given.

Mitochondriopathies

The mitochondria (mt) have a major role in fatty acid oxidation, tricarboxylic acid cycle, urea cycle, and ATP production through the process of oxidative phosphorylation. Oxidative phosphorylation occurs at the level of the respiratory chain in the inner membrane of the mt (77). The respiratory chain comprises five components (● *Fig. 42-5*). Complex I (NADH-coenzyme Q reductase) carries reducing equivalents from NADH to coenzyme Q and consists of different polypeptides, seven of which are encoded by mitochondrial DNA (mtDNA). Complex II (succinate-coenzyme Q reductase) carries reducing equivalents from $FADH_2$ to coenzyme Q and contains five polypeptides that are all encoded only by mtDNA. Complex III (reduced coenzyme Q-cytochrome c reductase) carries reducing equivalents from coenzyme Q to cytochrome c and contains 11 subunits, one of which is encoded by mtDNA. Complex IV (cytochrome c oxidase) transfers reducing equivalents from cytochrome c to oxygen. This complex is composed of cytochromes a and a3, and 13 protein subunits, three of which are encoded by mtDNA. The fifth complex is ATP synthetase.

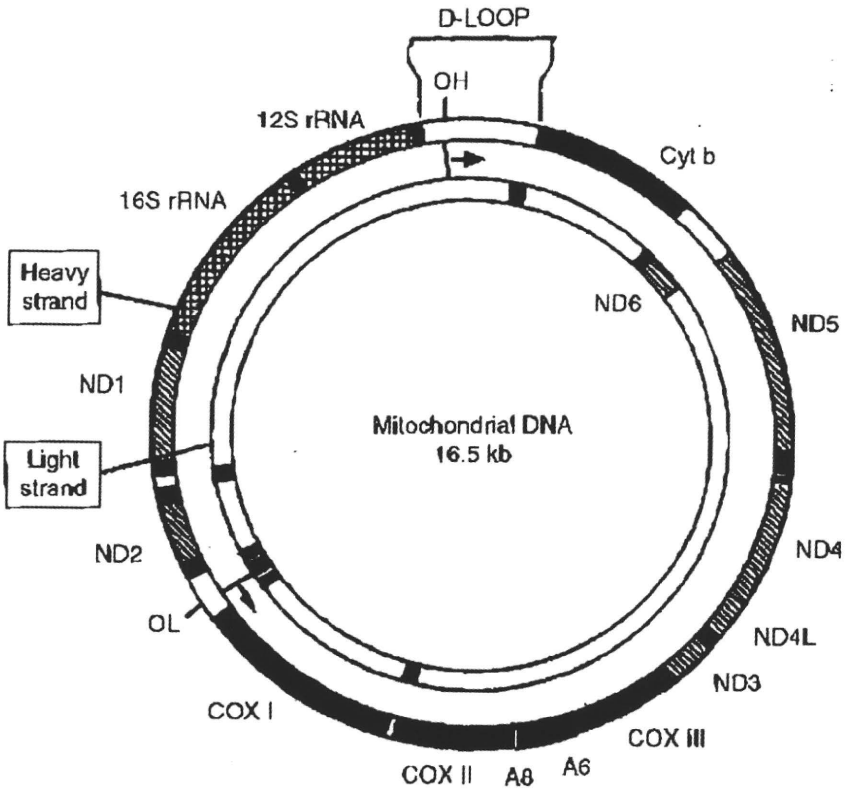
Oxidative phosphorylation consists of oxidative reactions that lead to oxygen consumption and phosphorylation of ADP to ATP. Each mt have its own 2–10 mtDNA. MtDNA genome is a 16.5 kb circular double stranded DNA with an asymmetrical base composition. The heavy strand contains more guanine residues while the light strand contains more cytosine residues. The mtDNA contains 37 genes; 13 encode for polypeptides of the respiratory chain, 2 for the ribosomal RNAs and 22 for transfer RNAs (78). Mitochondrial injury is due to congenital insults or may be the result of secondary events. Genetic defects of one or several polypeptide enzyme complexes of the oxidative phosphorylation system in the mt DNA or nuclear DNA which encodes structural or functional mitochondrial proteins can give rise to mitochondriopathies (mitochondrial cytopathies, mitochondrial diseases) (79).

Mitochondriopathies are multi-systemic disease and may begin at any age. Affected organs are diverse including central nervous system, muscle, liver, heart, kidney, gut, endocrine system, bone marrow, ear, eye, and skin (● *Table 42-2*). They display extreme heterogeneity, and make unpredictable the extent and manifestations of disease presentation (80). With the course of the disease, the numbers of organs involved are increased.

The screening for mitochondriopathies includes the determination of plasma lactate, pyruvate, keton bodies and their ratios in fasted and fed patients, polarographic, and spectrometric studies to evaluate the different

Figure 42-5

Map of mitochondria genome. Regions encoding cytochrome b (ctb b), various subunits of NADH-coenzyme Q reductase (ND), cytochrome c oxidase (COX), ATPase, and ribosomal RNAs (rRNA) are indicated (Niaudet P, Rötig A. The kidney in mitochondrial cytopathies. *Kidney Int* 1997;51:1000–1007).



enzymatic complexes of the respiratory chain, muscle histologic studies, and genetic analysis (4).

Renal disease may be the first sign of mitochondriopathies, or it may appear simultaneously with neurological and neuromuscular signs (81). FS is particularly frequent in newborns, infants, and young children (82–84), whereas tubulointerstitial nephropathy is more frequent in children and young adults (85, 86), and can be associated with hereditary focal segmental glomerulosclerosis due to the mitochondrial transfer RNA gene mutation (87–89) and collapsing glomerulopathy due to the mutations in the gene *COQ2* encoding the parahydroxybenzoate-polyprenyl-transferase enzyme of the CoQ10 synthesis pathway (CoQ2 nephropathy) and in the gene *PDSS2* encoding for decaprenyl diphosphate synthase (90, 91).

Most patients with FS due to mitochondriopathies manifest moderate FS including failure to thrive, dehydration, aminoaciduria, glucosuria, proteinuria, LMW proteinuria, phoshaturia, uricosuria, hypercalciuria, and bicarbonaturia. Many patients manifest FS by the age of 2 years. Extra-renal manifestations including neurological symptoms, myopathy, hepatic dysfunction, clinical features of Pearson syndrome, partial adrenal insufficiency, cardiac involvement, diabetes mellitus, deafness, and ophthalmoplegia often manifest in the patients (12, 92, 93). Patients who manifested proximal tubular acidosis with hypercalciuria or Bartter syndrome were described (94, 95). Some patients manifest progressive renal failure (96). Histological analysis reveals tubular dilatations, tubular atrophy and cytoplasmic vacuolization of the tubules. Bizarre giant mitochondria are frequently observed (97).

No satisfactory treatment is presently available to alter the course of mitochondriopathies. The treatment is mainly symptomatic: supplements of sodium bicarbonate, potassium, vitamin D3, phosphate, and water are necessary. Carnitine is given in case of secondary carnitine deficiency. It includes avoidance of drugs that interfere with the respiratory chain such as valproate and barbiturates, or that inhibit mitochondrial protein synthesis such as tetracyclines and chloramphenicol. Dietary recommendations include a high lipid and low carbohydrate diet in patients with complex I deficiency. Hypercaloric diet and parenteral nutrition should be avoided in these patients.

ms in patients with mitochondriopathies

ıs	Symptoms
s system	Apnea, lethargy, hypotonia, coma, pshycomotor retardation, cerebellar ataxia, stroke-like episodes, myoclonus, seizures, dementia, spasticity, headache, hemiparesis
	Myopathy, poor head control, limb weakness, myalgia, exercise intolerance
	Hepatomegaly, liver dysfunction
	Cardiomyopathy, arrhythmia
	Fanconi syndrome, tubulointerstitial nephropathy, nephrotic syndrome (focal segmental glomerulosclerosis, collapsing nephropathy), renal failure
	Vomiting, diarrhea, villous atrophy, cholonic pseudoobstruction, pancreatic dysfunction
	Diabetes mellitus, growth hormone deficiency, hypoparathyroidism, hypothyroidism, adrenal insufficiency
	Sideroblastic anemia, neutopenia, thrombocytopenia
	Hearing loss
	Progressive extrarenal ophthalmoplegia, pigmentary retinal degeneration, ptosis, diplogia, cataract
	Mottled pigmentation, trichothiodystrophy

eviewed in detail in Chapter 41 of this herefore only a short description is includ-

ıosis is an autosomal recessive lysosomal r characterized by an accumulation of cys-fide of the amino acid cysteine, in the s, notably kidney, cornea, bone marrow, nodes, liver, and spleen (98). Renal man-ıinate the clinical presentation and course stinosis. Cystinosis is the most common of the FS in Western countries. Many ularly in North America, have blonde or hair. Other organs frequently affected in-a and thyroid, causing painful photopho-yroidism respectively.

nical forms of the disease exist and are at onset and severity of the symptoms . The most severe form, infantile cystinosis, ıy failure to thrive, polyuria, polydypsia, fluid and electrolyte loss, aminoacid-ia, phosphaturia, renal tubular acidosis 12 months of age. Some of the patients itamin D-resistant rickets due to phos-ıanifest severe growth failure. Renal func-ılly normal at presentation. However, ımerular impairment leads to focal seg-ulosclerosis and eventually to end stage 10 years of age without treatment (99).

Patients with infantile cystinosis manifest FS, including hyperchloremic metabolic acidosis, aminoaciduria, hypokalemia, hypophosphatemia, glucosuria, and phosphaturia. There have been several patients of nephropathic cystinosis presenting with features of secondary Bartter syndrome (hypokalemia, hyperchloremic metabolic alkalosis, hyperreninemia, and hyperaldosteronism), suggesting abnormalities of Na^+ and Cl^- reabsorption (100, 101). Patients with cystinosis often manifest medullary nephrocalcinosis (102).

Renal histopathologic changes in infantile cystinosis include severe lesions of proximal tubules; typical alterations to the glomerular podocytes, which become multinucleated giant cells; and the presence of cystine crystals, mostly in interstitial cells and podocytes (103). The proximal tubule is the first clinical target of the disease, but cystine crystals are rarely found in the tubular cells of patients with cystinosis. Cystine crystal deposition in the cornea leads to photophobia. Continuous widespread cystine accumulation eventually leads to rickets and retinal, endocrinologic (hypothyroidism and impaired glucose tolerance), hepatic, gastrointestinal, muscular, and neurological abnormalities.

Two less severe and less common form of cystinosis are juvenile (or late-onset) and ocular cystinosis. Patients with juvenile cystinosis manifest glomerular impairment between 12 and 15 years of age but do not suffer from severe tubulopathy or growth failure. Progression to end stage renal failure is slow and occurs at

■ Table 42-3
Clinical manifestations of infantile cystinosis

At presentation
Common
Failure to thrive
Polyuria and polydipsia
Fanconi syndrome
Vitamin D resistant rickets
Progressive renal failure
Photophobia
Hypothyroidism
Uncommon[a]
Bartter syndrome
Nephrotic syndrome
Diabetes insipidus
Pot-renal transplantation
Dysphagia
Myopathy
Exocrine pancreatic insufficiency
Diabetes mellitus
Central nervous system deterioration
Primary hypogonadism

Adapted from Gahl et al. (114)
[a]may be transient and coexist with common manifestations

variable ages (104). Patients with ocular cystinosis do not involve kidney.

Infantile cystinosis is caused by mutations of the *CNTS* gene encoding cystinosin, a lysosomal transport protein, leading to complete abolition of cystine transport (105). Cystinosin has 367 amino acids and seven transmembrane domains. Cystine transport is dependent on the pH gradient, and the transport of cystine out of the lysosome is driven by the high H^+ content within the lysosomal lumen that is produced by the activity of the H^+-ATPase. A range of mutations in *CNTS* gene has been described, but a single mutation, a 57-kb intragenic deletion, accounts for as many as three quarters of all European cases (105). The adolescent and ocular forms have one severe and one mild *CTNS* mutation, leading to reduced transport activity. The sparing of the kidney in patients with ocular cystinosis reflects tissue-specific expression of splicing factors, or the increased endogenous level of *CTNS* mRNA normally seen in the kidney (106). Individuals who are heterozygous for severe *CTNS* mutations reveal elevated levels of leukocyte cystine but are completely asymptomatic.

The pathophysiology of tubular cystine transport defects in patients with cystinosis is poorly understood, reflecting of an animal model for the disease. Knock-out mice model lacking cystinosin gene do not manifest signs of FS, despite accumulation of lysosomal cystine in the proximal tubules (107). Cystine-loaded proximal tubular cells demonstrate loss of free phosphate and defective ATP production and inhibition of Na^+-dependent transporters (108). ATP depletion can reduce proximal tubular Na^+, K^+-ATPase activity leading to increased Na^+ delivery into the distal tubules and Bartter syndrome (101). A cell culture demonstrated that cells accumulated with intracellular cystine undergo apoptosis at a rate two- to four-fold higher than controls (109). Another works suggests that increased oxidative stress and altered redox status in proximal tubule cells cultured from the urine of patients with cystinosis are associated with proximal tubule dysfunction (110).

The diagnosis of cystinosis is confirmed by demonstrating elevated cystine levels in peripheral leukocytes (97). Corneal crystals detected by slit-lamp examination are diagnostic in childhood cystinosis because these crystals are not seen in patients with other hereditary FS. However, this finding is not sensitive for early diagnosis. The renal pathologic findings in infantile cystinosis consist of a chronic tubulointerstitial nephropathy, with characteristic multinucleated podocytes and intracellular crystalline inclusions in interstitial histiocytes (111). Although numerous multinucleated podocytes are the most characteristic pathologic findings, they are not found in the sclerotic glomeruli and detected only in low frequency (<4%). The cystine crystals are birefringent under polarized light in only alcohol-fixed tissue or in unfixed frozen tissue, because they are water-soluble and not retained in the tissue after routine histologic preparation with aqueous solutions (112).

The management and treatment for infantile cystinosis involve supportive therapy to maintain fluid balance and replace electrolyte losses at initial presentation. Early diagnosis and oral cysteamine, a cystine-depleting agent, can delay the progression of end stage renal failure and other organ involvement. Oral cysteamine therapy given at doses of 60–90 mg kg^{-1} of body weight (or between 1.3 and 1.95 g m^{-2}) a day divided every 6 h generally achieves approximately 90% depletion of cellular cystine, as measured in circulating leukocytes (<1.0 nmol half-cystine/mg protein) (113). The dosage recommended for adults is 500 mg every 6 h, but higher dosages are often required to achieve satisfactory cystine depletion. On the basis of its beneficial effects in maintaining thyroid function and depleting muscle of cystine, oral cysteamine

d continue in patients after renal transplan-
› preserve other organs. Administration of
nine eye-drops, given 6–12 times a day, can
eal cystine crystals and lessen visual symp-
)ther therapies to supply potassium, alkali-
including citrate or bicarbonate, phosphate,
D3 are required. When the growth velocity
›ved and the patient remains below the 3rd
height after one year of therapy, growth
'apy may be considered.

nia

is an autosomal recessive disease of galactose
Nursing infants must move large amounts of
›ugh Leloir pathway in order to utilize the
›ns for energy (◆ *Fig. 42-6*). Galactose is the
›on source in mammalian neonates, since it
ed into glycogen more efficiently than is

frequent form is classic galactosemia that is
leficient activity of galactose-1-phosphate
rase (GALT) encoded by *GALT1* (116).
es the reaction of galactose-1-phosphate
s uridine diphosphate glucose to uridine
galactose plus glucose-phosphate. Uri-
ıate galactose can be further metabolized
ose or CO_2 and H_2O via glycolysis. Milk is
e of galactose. Accumulated gal-1-p due to
T and exposure to galactose lead to acute
of multiple organ systems, including liver,
, brain, and eye. Affected infant patients
iting, diarrhea, failure to thrive, develop-
liver dysfunction, coagulopathy, renal tubu-
›n, cerebral edema, vitreous hemorrhage,
a coli sepsis. They sometimes manifest jaun-
›njugated hyperbilirubinemia and may have
sis. Liver damage leads to hepatomegaly and
is potentially lethal. Neonatal screening
udes galactosemia, anticipating that early
l intervention would prevent long-term
such as mental retardation, premature
e, and speech delay. Although a galactose-
:t prevents the neonatal death, many
›atients continue to develop debilitating
(117, 118). Clinically evident speech delay
signs are more frequent than other findings.
arian failure is nearly universal in females
mia. The predominant manifestation due to kidney damage is FS including hyperaminoaciduria, LMW proteinuria, hyperphosphaturia, and bicarbonaturia (118). Patients placed on a galactose-restricted diet are never truly free of galactose insult, as a significant amount of galactose is found in non-dairy foodstuffs such as vegetables and fruits (119, 120). More importantly, galctose moieties can be produced endogenously from UDP-glucose via the UDP-4-galactose epimerase reaction, and natural turnover of glycoproteins/glycolipid; the rate of endogenous galactose synthesis ranges from 0.53–1.05 mg kg^{-1} of body weight a day (121, 122). Once the lactose is formed intracellularly, it will be converted to gal-1-p by GALT. The less common form of galactosemia is a deficiency of galactose kinase (GALK), which forms gal-1-p from galactose. These patients do not manifest either the acute toxicity syndrome or chronic complications seen in patients with classic galactosemia. They manifest cataracts. Since GALK-deficient patients do not accumulate gal-1-p in their tissues, gal-1-p is considered to play a significant role in the pathogenesis of classic galactosemia (123, 124). GALT deficiency results in accumulation of toxic galactose leading to the unfolded proteins, altered calcium homeostasis and subsequently endoplasmic reticulum (ER) stress (125). ER stress caused by GALT-deficiency might contribute to accelerated apoptosis seen in the granulose cells maturing follicles in galactosemic females, leading to premature ovarian failure (126). Formation of galactitol from galactose by aldose reductase has been proposed as a pathogenetic mechanism and is at least responsible for cataract formation.

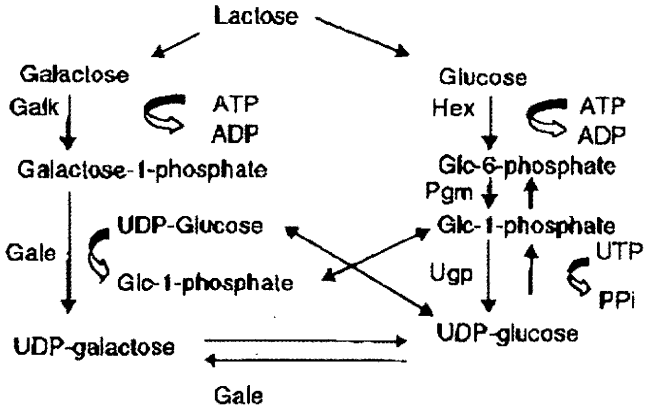
The diagnosis is suggested by galactose or galactose 1-phosphate in serum, or in the urine. The diagnosis is confirmed by demonstrating deficient GALT activity in red blood cells, fibroblasts, leukocytes, or hepatocytes.

Treatment of this disorder is elimination of galactose from the diet. Acute symptoms and signs resolve within a few days after starting the diet therapy. However, developmental delay, speech disturbance, ovarian dysfunction, and growth retardation are common outcomes in this disorder (127).

Hereditary Fructose Intolerance

Hereditary fructose intolerance (HFI) is an autosomal recessive disorder caused by a deficiency of aldolase B, an enzyme of liver, intestine, and renal cortex catalyzing the metabolism of fructose of exogenous origin (128). Frequency of HFI is estimated at 1 in 20,000 live births. Aldolase B catalyses the specific and reversible cleavage of

Figure 42-6
Composite diagram of the Leloir pathway and uridine diphosphate (UDP)-glucose pyrophosphorylase pathway. *Galk*, galactokinase; *galt*, galactose-1-phosphate uridyltransferase; *Gale*, UDP-galactose 4-epimerase; *Hex*, hexokinase; Pgm, phosphoglucomutase; *Ugp*, UDP-glucose pyrophosphorylase (Leslie ND. Insights into pathogenesis of galatosemia. *Annu Rev Nutr* 2003;23:59–80).



fructose-1,6-bisphophate (FBP) and fructose-1-phosphate (F1P) into dihydroxyacetone phosphate and D-glyceraldehyde-3-phophate, or D-glyceraldehyde, respectively. Aldolase B is equally active with FBP and F1P, whereas aldolase A and aldolase C, the other two vertebrate isozymes, are more active with FBP than with F1P. Aldolase B is encoded in Aldolase B gene (*ALDOB*) mapped to chromosome 9q21.3–q22.2 (129, 130). Missense and nonsense mutations, large and small gene deletions and mutations in the splicing region have been identified in *ALDOB* of HFI patients (131).

Affected individuals manifest symptomatic hypoglycemia, vomiting and life-threatening episodes shortly after the intake of fructose or related sugars including sucrose and sorbitol (132). Prolonged ingestion leads to failure to thrive, hepatomegaly, jaundice, hepatic cirrhosis, and nephrocalcinosis, and may lead to convulsions, coma, and death from severe liver and kidney failure. Symptoms of HFI appear during infancy when infants with HFI are fed a formula or foods including fruits, vegetables, and sweetened cereals that contain sucrose. Patients with HFI may develop a protective aversion to sweets and fruits, which is a reason that diagnosis is frequently missed, and which also explains that reliable prevalence numbers for different populations do not exist.

HFI is associated with proximal tubule dysfunction leading to aminoaciduria, bicarbonaturia, phosphaturia, and lactic acidosis. These manifestations appear rapidly after the ingestion of fructose (133, 134). The development of lactic acidosis adds significantly to the metabolic acidosis (135). Chronic fructose ingestion leads to nephrocalcinosis and impaired distal tubular function. In contrast, resolution of proximal tubule dysfunction can take days or weeks with strict restriction of fructose and sucrose (136).

Aldolase B coexists abundantly in endocytosis zones of the proximal tubule cells with H^+-ATPase (137). Nonfunctional aldolase B impairs the coupling of H^+-ATPase to glycolysis and endosomal acidification that will lead to FS.

Diagnosis includes the metabolic response to an intravenous fructose load or an enzymatic assay of liver or intestinal biopsy samples. However, both of them are bothering and invasive (138). Fructose breath hydrogen test is one of the standard procedures for the diagnosis. However, it can develop life-threatening adverse effects during the test (139). Molecular analysis is available for the diagnosis.

Strict avoidance of foods or drugs containing fructose, sucrose, and sorbitol is the predominant treatment.

Glycogen Storage Disease Type I (von Gierke Disease)

Glycogen storage disease type I (GSD-I) is a group of autosomal recessive disorders with an incidence of 1 in 100,000. There are two major subtypes. Glycogen storage disease type Ia (GSD-Ia, von Gierke disease) is common and is caused by s deficiency in glucose-6-phosphatase-alpha (G6Pase-alpha), a key enzyme in glucose homeostasis that catalyzes the hydrolysis of glucose-6-phosphate (G6P) to glucose and phosphate in the terminal step of gluconeogenesis and glycogenolysis (140). G6Pase-alpha is a hydrophobic endoplasmic reticulum-associated transmembrane protein. Glycogen storage disease type Ib (GSD-Ib) is caused by a deficiency of microsomal glucose-6-phosphatase transporter (G6PT). G6PT translocates G6P from cytoplasm to the lumen of the endoplasmic reticulum. Therefore, G6PT and G6Pase-alpha work in concert to maintain glucose homeostasis. Whereas G6Pase is exclusively expressed in gluconeogenic cells, G6PT is ubiquitously expressed and its deficiency generally causes a more severe phenotype.

Patients with GSD-Ia manifest a phenotype of disturbed glucose homeostasis characterized by fast life-threatening hypoglycemia, hepatomegaly, nephromegaly, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, lactic acidemia, neutrophilia, and growth retardation (141, 142). Infants with GSD-Ia typically present with

epatomegaly at 6–8 months of age. Approx- of adolescent and adult patients develop adenoma (HCA), which can lead to con- ıidity and mortality (143). The incidence of tocellular carcinoma is recently increasing tients can live longer than before (144). The SD-Ia and GSD-Ib are associated with re- of life, independent functioning, and ele- f internalizing distress, and parental stress lthy peers.

ıplications include renal enlargement, gout enal stones, nephrocalcinosis, Fanconi-like chronic renal disease leading to renal insuf- Hepatomegaly is a common finding in ruricemia and uric acid stone in GSD-Ia by a combination of increased synthesis of competitive inhibition of renal tubular ex- c acid (urate) by lactate (146). Proximal ıction has been observed in patients with its manifest proximal renal tubular acidosis bicarbonate in the urine, hyperphospha- ted aminoaciduria and increased excretion oglobulin which are ameliorated by inten- ıpy (147, 148). This finding suggests that c control can prevent proximal tubular dys- nic renal disease is a long-term complication. reveal interstitial fibrosis, tubular atrophy, ıental glomerulosclerosis with marked glo- nent membrane (GBM) thickening and patients with GSD-Ia (149–151). Glycogen resent in the areas of abnormal GBM. The nt in the mesangium and in the epithelial, endothelial cells is increased. Recent treat- ficantly alleviated the metabolic abnormal- ed the clinical manifestation of chronic and renal insufficiency in patients with ver, glomerular hyperfiltration, hypercal- raturia that worsens with age, and urinary tion still occur in metabolically compen- with GSD-Ia (152, 153). Although the hanism responsible for chronic renal dis- rly understood, activation of the angioten- ıggested to have an important role for the sion (154). The expression of TGF-beta 1 ıe is increased in a patient with GSD-Ia oteinuria, interstitial fibrosis, and tubular

ve of treatment is to maintain normogly- id metabolic complications and lactic ıoglycemia is accomplished at night with ding of glucose or with orally administered uncooked cornstarch (156). A single dose (1.75–2.5 g kg^{-1} of body weight) of uncooked cornstarch will maintain serum glucose concentration higher than 3.9 mmol L^{-1} for 7 h in most young adults (157, 158).

Liver transplantation is indicated in the patients when medical treatment fails to control the metabolic problems or when HCA or hepatocellular carcinoma develops. Living-donor liver transplantation is a viable option to restore normal metabolic balance and keeping normal renal function (159). Hepatocyte transplantation can be a potential therapeutic intervention to prevent hypoglycemia despite the discontinuation of cornstarch meals (160).

Fanconi-Bickel Syndrome

Fanconi-Bickel syndrome (FBS) is an autosomal recessive disorder characterized by failure to thrive, "doll-like" face, hepatomegaly, nephromegaly, and severe rickets. Patients with FBS manifest glycogen accumulation in hepatocytes and proximal tubular cells, fasting hypoglycemia, galactose intolerance, and FS including glucosuria, aminoaciduria, hyperuricosuria, hyperphosphaturia, proteinuria, and sodium and potassium wastage (161, 162). Some patients manifest cataracts in neonatal period (163). Overall prognosis of FGS is considered as favorable (164). However, some patients manifest neonatal diabetes mellitus and galactosemia and die of hepatic failure during infancy (165).

FBS is caused by the mutations in facilitative glucose transporter gene (*SLC2A2*, also referred to as *GLUT2*) expressed in liver, kidney, intestine, and pancreatic islet cells (166). Over 60 mutations in *SLC2A2* were reported (167). This facilitative glucose transporter is expressed in hepatocytes, pancreatic beta cells, and renal and intestinal epithelial cells and is important for the exchange of glucose between these cell types and the bloodstream (168). Renal histology reveals an increase in mesangial cellularity, glomerulosclerosia, and patchy swelling of epithelial foot process and irregularly thickened lamina rara interna in the glumeruli, and vacuolization of epithelial nuclei in the proximal tubule cells suggesting the presence of glycogen in a 7 year-old patient with FBS (169).

The therapy for FBS is directed at the renal solute losses including sodium bicarbonate and potassium-sodium phosphate; treatment of rickets including active vitamin D3; and frequent feeding including night-time supplementation to prevent ketosis. Uncooked cornstarch has been shown to lessen hypoglycemia and improved growth (170). Galactose–free milk is also used for infant patients (165, 171).

Tyrosinemia I

Hereditary tyrosinemia type I (TI) is an autosomal recessive disorder of an amino acid metabolism. TI is due to the defect in the fumarylacetoacetate hydrolase (FAH) gene (172, 173). FAH is the last enzyme in the tyrosine catabolic pathway.

Patients with TI display a variety of clinical symptoms, such as liver damage from infancy that advances to cirrhosis, reduced coagulation factors, hypoglycemia, high plasma concentrations of methionine, phenylalanine, and aminolevulinic acid, high risk of hepatocellular carcinoma, and tubular and glomerular renal dysfunction (174).

Progressive renal damage begins from early infancy in severe form. Chronic liver damage with a high incidence of hepatoma (hepatocellular carcinoma) is characteristic in milder form (175). Even a patient without clinical manifestations of TI can manifest hepatoma during childhood (176). Accumulated fumarylacetoacetate in the patients with TI is pathogenic for hepatoma. Patients with milder form of TI are at risk for acute exacerbation of liver dysfunction. A common presentation mode is the "acute hepatic crisis" in which ascites, jaundice, and gastrointestinal bleeding are precipitated by an acute event such as an infection. Acute hepatic crises usually resolve spontaneously but on occasion progress to complete liver failure and encephalopathy. Acute, painful peripheral neuropathy may appear and can lead to transient paralysis. Autonomic dysfunction with hypertension and tachycardia can be associated with this acute neuropathy (177). Plasma tyrosine and methionine levels usually are elevated in untreated patients. The presence of succinylacetone in plasma and urine is diagnostic of TI. A rapid ultra performance liquid chromatography tandem mass spectrometric method is used for mass screening of tyrosinemia (178).

FS and developmental hypophosphatemic rickets are features of the kidney involvement. Generalized aminoaciduria, renal tubular acidosis, and mild proteinuria are also often seen, whereas glucosuria is less common because plasma glucose levels are low. Kidney enlargement is common, and nephrocalcinosis can be seen (179). FS leads to carnitine deficiency (180). Glomerulosclerosis and impaired GFR may be seen with time.

Disturbances in tyrosine metabolism lead to increased levels of succinylacetone and succinylacetoacetate. However, the mechanisms causing liver failure, cirrhosis, renal tubular dysfunction, and hepatocarcinoma are still unknown. Apoptosis of hepatocytes and renal tubular epithelial cells are characteristic features of this disease and the apoptotic signal in this disease seems to be initiated by fumarylacetoacetate (181, 182). Accumulated maleylacetoacetate and fumarylacetoacetate in affected tissues can react with free sulfhydryl groups and reduce intracellular levels of glutathione. They may be capable of acting as alkylating agents. Maleylacetoacetate and fumarylacetoacetate are not detectable in plasma or urine but are converted to succinylacetoacetate. Succinylacetone, a metabolite of succinylacetoacetate, is structurally similar to maleic acid, which is known to induce FS and may be the cause of tubular dysfunction of HI. Experimentally, succinylacetone administration to rats leads to FS (183, 184).

Treatment with a low-phenylalanine and low-tyrosine diet dramatically improves the renal tubular dysfunction (185). However, this treatment cannot necessarily improve the hepatic involvement. Moreover, there is a risk of inducing deficiencies of phenylalanine or tyrosine. The formation of pathogenic fumarylacetoacetae is prevented by 2- (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). NTBC is used for the patients with TI during the first 6 months of life in addition to a diet low in tyrosine and phenylalanine. NTPC clearly improves the vital prognosis and quality of life in the patients (186). However, some patients with NTBC treatment develop hepatoma. A rise of alpha-fetoprotein (AFP), a slow AFP decrease, and never normalizing levels of AFP are important predictors of hepatoma development (187). Liver transplantation has been used for patients with liver failure and to prevent the development of hepatoma (174). Liver transplantation leads to rapid correction of FS (188).

Wilson Disease

Wilson disease (WD, progressive hepatolenticular degeneration) is an autosomal recessive inborn error of copper (Cu) metabolism that affects numerous organ systems (189). Biliary excretion of Cu and incorporation into ceruloplasmin is impaired, leading to liver damage, neuronal degeneration, and impairment of other organs from accumulation of Cu in patients with WD.

The majority of patients with WD presents with either predominantly hepatic or neuropsychiatric symptoms, and with either clinically asymptomatic or symptomatic liver involvement. Approximately 40% of patients presents with liver disease, 40% with extrapyramidal symptoms, and 20% with psychiatric or behavioral abnormalities. Symptoms rarely occur before 6 years of age. Hepatic involvement includes acute hepatitis, fulminant hepatic failure, or progressive chronic liver disease in the form of either chronic

is or cirrhosis of the macronodular type. Neu- involvements are variable. The most common tation is bulbar symptoms characterized by th speech and swallowing, and drooling. They anifest dysarthria and coordination defects movements accompanied by involuntary One third of the patients with WD manifest listurbances. The remaining patients with ient with symptoms including hemolytic ane- acture, arrhythmias, FS, hyperpigmentation, er ring, cataract, and gynecological problems utable to the involvement of the organs.

used by a mutation in the gene *ATP7B* that type Cu transporting ATPase beta polypep- ATP7B) (190). This ATPase is targeted to the ı, suggesting that its role in Cu dependent kes place in this organelle. The disease estimated to be between 1 in 5,000 and 1 in the carrier frequency is approximately .

orbed by the intestinal cells and stored with ein in a non-toxic form. The Cu is later ı the circulation by a Cu transporter 15,000 protein, Cu-transporting P-type ATPase 1 ich is located on the membrane of entero- 42-7) (192). It is then transported to the liver lbumin, from where it is accepted by hepa- ATOX1 chaperone protein directs Cu to its ts in the hepatocytes. Some of Cu bounds to ein for storage, and the remainders are ex- ATP7B-regulated biliary canaliculi. ATP7B the transfer of Cu to apoceruloplasmin to Cu binding protein, ceruloplasmin (193). n is released into the blood, carries 90% of nt in the plasma, and acts as a source for gans. Mutations of the *ATP7A* gene result in f Cu in enterocytes, preventing entry of Cu ulation and thus causing a complete Cu enkes kinky hair disease) (192).

ı in *ATP7B* gene lead to a reduction in the of apoceruloplasmin into ceruloplasmin, lly present at low levels in the patients of e to excrete Cu into the biliary canaliculi effect to hepatocytes. Excess Cu damages , which produce oxidative damage to the ws spillage of Cu into the blood, thereby other tissues including the brain, kidney, l cells, initiating toxic effects.

accumulation of Cu in the kidney leads to dysfunction in patients with WD. Patients eatures of FS before the onset of hepatic failure and is characterized by intermittent glucosuria, aminoaciduria, hyperphosphaturia, hyperuricosuria, and proteinuria (194–196). Patients can manifest rickets or osteomalacia, hypercalciuria, urolithiasis, nephrocalcinosis, decreased urine concentrating ability and distal renal tubular acidosis are reported (197). Glomerular function decreases as the disease progresses, but death from extrarenal causes occurs before the onset of renal failure.

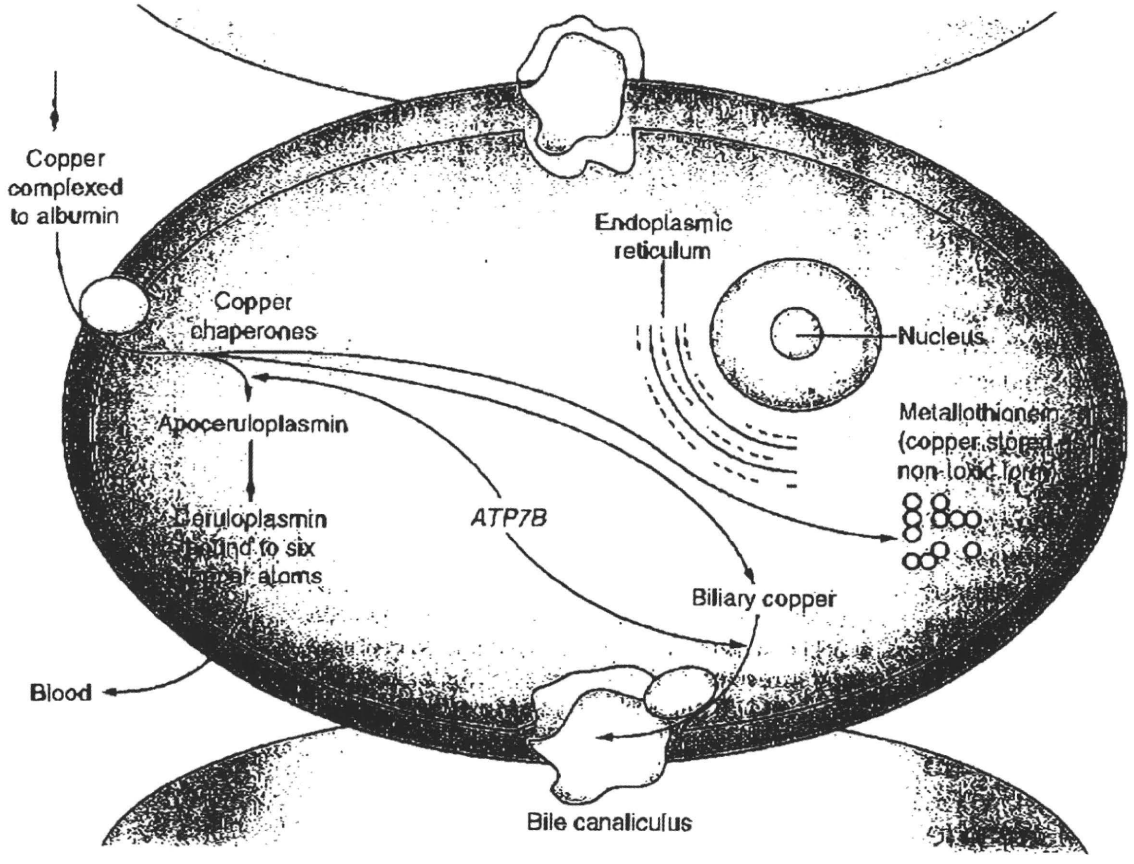
Histological analysis of the patients with WD revealed no alteration on light microscopy or only flattened proximal tubule cells without recognizable brush border (198). Electron microscopy disclosed loss of the brush borders, electron dense deposit in the subapical region of tubular cytoplasm probably representing metalloproteins, and cavitation of the mitochondria with disruption of the normal cristae pattern (199).

All subjects presenting with symptomatic or asymptomatic liver disease with no apparent causes or with extrapyramidal features along with a past or family history of similar hepatic or neurological illnesses in other siblings should be screened for WD (200). Measurement of the serum ceruloplasmin is valuable for diagnosis. Any value below 200 mg L^{-1} is abnormal, and reduced levels are seen in up to 95% of the patients with WD. An estimation of 24 h urinary Cu excretion is another reliable test for the diagnosis of WD. Normal excretion is between 20 and 50 µg a day, and Cu excretion is increased to in excess of 100 µg a day in patients with WD. Serum free Cu is a measure of nonceruloplasmin toxic Cu in the blood, and normal value range from 1.3 to 1.9 µmol L^{-1} (8–12 µg dL^{-1}) in parallel with the increased urinary Cu excretion, because of saturation of the hepatic storage of Cu. A hepatic biopsy and a measurement of its Cu content are helpful for diagnosis. 80% of the patients manifest increased hepatic Cu (>250 µg/g of dry tissue weight). Genetic analysis of *ATP7B* gene is a helpful confirmation of WD. Brain MRI is a very sensitive method for revealing abnormalities in patients with WD. Generalized brain atrophy and hyper-intensity in the basal ganglia, white matter, thalamus, or brainstem are common findings in the patients. Patients exhibit characteristic features on MRI; "face of the giant panda" is seen in the midbrain and "face of the miniature panda" is seen in the tegmentum region of the pons in T2-weighted images (201, 202).

WD has a fatal outcome if not treated appropriately and in a timely manner. The aim of treatment for WD is to remove the toxic deposit of Cu from the body to produce a negative Cu balance, and to prevent its re-accumulation (190, 203). Successful therapy is measured in terms of a restoration of normal levels of free serum Cu and its excretion in the urine. The average daily diet

Figure 42-7

Schematic representation of cooper metabolism within a liver cell. *ATP7b*, causative gene for Wilson disease. (Das SK, Ray K. Wilson's disease: an update. *Nat Clin Pract Neurol* 2006;2:482–493).



contains 2–4 mg of Cu, and 0.8 mg is normally lost into the feces. Patients should avoid Cu-rich foods including chocolate, nuts, shellfish, mushrooms, and liver. D-penicillamine therapy (20 mg kg^{-1} of body weight a day) has been the most commonly used chelating agent that may reverses multiple tissue dysfunction including FS. However, use of D-penicillamine has been questioned, because of reported side effects. The side effects from D-penicillamine can occur both early and late in the treatment period. Early side effects include a hypersensitivity reaction characterized by fever, skin rash, and lymphadenopathy. Delayed side effects including Goodpasture's syndrome, polymyositis, systemic lupus erythematosus, and bone marrow suppression are caused by immunological reactions. Trientine is another effective chelating agent (750–2,000 mg a day for adults). Ammonium tetrathiomolybdate (2–3 mg kg^{-1} of body weight a day in six doses along with meals and in the interval between meals) is a potent agent in removing Cu from the body and may be the drug of choice for patients with neurologic disease to prevent the immediate worsening of symptoms that can occur with D-penicillamine therapy. Zinc acetate or sulfate induces intestinal metallothionein and helps in the prevention of Cu absorption from the gut (3–5 mg kg^{-1} of body weight a day in three divided doses before meals). D-penicillamine should be taken 2 h after meals to avoid any interaction with the zinc. Zinc acetate or zinc sulfate has been used successfully in asymptomatic or presymptomatic affected family with WD, and is equally as effective as D-penicillamine in a group of patients predominantly with neurological disease (204, 205). The use of trientine, tetrathiomolybdate, and zinc has been advocated, although results of long-term trials are awaited. The best therapeutic approach remains controversial and there is no universally accepted regimen. Liver transplantation is effective for the patients with progressive live failure or acute liver failure. Liver transplantation is also indicated for patients with WD in whom medical therapy is ineffective. Symptomatic patients with WD require lifelong treatment, because an interruption to therapy or inadequate treatment can lead to fatalities within 9 months to 3 years (189, 203).

Fanconi Syndrome

ignificant numbers of genetic causes for the ing to FS are identified, there exist patients ic FS. Idiopathic FS should be diagnosed r known causes have been excludes. Idio- be inherited as an autosomal dominant tosomal recessive (212, 213), and X-linked lowever, most of the familial forms are minant inheritance.

vith idiopathic FS manifest failure to thrive, s of dehydration, and rickets. They often tures of FS, including polyuria, polydipsia, hypophosphatemia, proximal renal tubular noaciduria, glucosuria, and proteinuria. tration rate is usually normal during child- r, some develop chronic renal insufficiency nal failure 10–30 years after the onset of)8, 209, 213). Nephrocalcinosis and *genu* k knee) are seen in some patients (213). ne fracture, and scoliosis due to osteomala- ie serious complications in adult patients c FS (● *Fig. 42-8*).

tology reveals chronic tubulointerstitial interstitium demonstrates patchy fibrosis tubular atrophy and focal collections of mononuclear inflammatory cells. Occasional cystically dilated tubules are seen containing eosinophilic proteinaceous material that stains positive for PAS (213).

Treatment for idiopathic FS remains symptomatic. Careful follow-up of these patients is necessary to prevent recurrent bouts of dehydration, electrolyte imbalance, and metabolic bone diseases. Glomerular function and nephrocalcinosis must be checked regularly. Renal transplantation has been done in a few patients who had end-stage renal failure (209).

wing scoliosis and osteopenia in a 35-year-h idiopathic Fanconi syndrome.

Acquired Fanconi Syndrome

Nephrotic syndrome is associated with FS (215). The renal pathology is focal segmental glomerulosclerosis. Although the true pathogenesis is not clarified, mitochondriopathies can manifest FS, focal segmental glomerulosclerosis leading to nephrotic syndrome, and both (79–84).

Immunological or hematological disorders are associated with dysproteinuria leading to FS. They are multiple myeloma, Sjögren syndrome, and amyloidosis. Almost all of the patients with theses diseases are adults. In early stages of myeloma, light chain nephrotoxicity often presents with proximal tubular functional abnormalities leading to FS. Proximal tubule dysfunction is the most common mode of renal involvement and it can manifest in a variety of ways. Endocytosis in the proximal tubules is overloaded and cell stress responses that include phosphorylation of MAPKs, prominently, p38 MAPK, and nuclear transcription factors NF-kappa B, AP-1 are activated resulting in production of inflammatory and proinflammatory cytokines, TNF-alpha, interleukin-6, 8 and monocyte chemo-attractant protein-1 (216). These proximal tubule alterations often progress to a severe tubulointerstitial nephritis and end stage renal failure.

Sjögren syndrome is an autoimmune connective tissue disorder that affects exocrine glands. Renal involvement of Sjögren syndrome is mainly manifested as tubular disorders; 70% of the patients manifest distal renal tubular acidosis (217). Urinary concentration defect, proteinuria and LMW proteinuria are often seen in the patients. Only 4% of the patients manifest FS (217). Patients with FS and Sjögren syndrome manifest osteomalacia including bony deformities of rib cage, bilateral humeral shaft fractures, and marked cortical bone thinning (218). Characteristic histological feature of Sjögren syndrome is chronic interstitial nephritis, with diffuse or focal plasmacytoid lymphocytic infiltration. In the late stage of the disease, tubulointerstitial fibrosis is severe. Corticosteroid or/and immunosuppressant therapy can improve the prognosis.

FS has appeared rarely after renal transplantation (219). Acute tubular necrosis, chronic rejection reaction, and nephrotoxic drugs can induce the progression of FS in the patients.

Acute tubulointerstitial nephritis with uveitis (TINU) syndrome is an immunological disease that leads to tubulointerstitital nephritis and anterior uveitis (220). Patients with TINU syndrome manifest asthenia, malaise, weight loss, nocturia, and thirst. Patients also manifest incomplete or complete FS including proteinuria, LMW proteinuria, glucosuria, aminoaciduria, bicarbonaturia, phosphaturia, and uricosuria due to proximal tubule dysfunction and acute renal failure (221). Urine concentration is decreased in the patients. Corticosteroid therapy can improve renal and eye manifestations.

Autoimmune interstitial nephritis and membranous nephropathy is a distinct disorder. The patients manifest failure to thrive, multiple renal tubular disorders including FS and proteinuria (222, 223). Renal biopsy revealed interstitial nephritis with lymphocytic infiltration and fibrosis, and membranous nephropathy. In advanced stage, focal segmental glomerulosclerosis and tubular atrophy develop. Immunofluorescence analysis shows linear staining of IgG along the glomerular capillaries and the tubular basement membrane. These renal lesions result from an autoimmune response to the 58-kD tubular basement membrane autoantibody (224). This disorder is genetically related to HLA B7 serotype (224).

A patient with anorexia nervosa is described to manifest reversible FS like condition including glucosuria, phophaturia, and uricosuria, although the precise pathogenesis is not known (225). These manifestations subside with nutritional recovery.

Untreated patients with distal renal tubular acidosis manifest LMW proteinuria, generalized aminoaciduria, phosphaturia, uricosuria, and hypercalciuria (226, 227). These proximal tubular abnormalities are transient and disappear by the alkali and potassium therapy. Although the precise pathogenic mechanisms underling the development of proximal tubular dysfunction remains unclear, decreased pH in the cytoplasm of the proximal tubule cells resulting from the intracytoplasmic accumulation of H^+ due to luminal membrane H^+-ATPase dysfunction can disturb trafficking of endosome.

Exogenous Factors

Drugs

Numerous drugs and herbs are implicated in the pathogenesis of FS. Drugs and herbs are usually filtered from the glomerulus and reabsorbed in the proximal tubules. They include outdated tetracycline (228), aminoglycosides (229, 230), salicylate (231), valproic acid (232, 233), and Chinese herbs (234, 235). Aminoglycoside antibiotics reduce glucose reabsorption in kidney tissue by reducing mRNA, protein expression, and function of the Na^+-dependent glucose transporter, which is located in the luminal membrane of the proximal tubule (236). Covalent binding of salicylate or its metabolites to mitochondria in proximal tubule cells alters the function of mitochondria (231). Valproic acid produces the defects of mitochondrial respiratory chain and lysosomal enzyme activity in the proximal tubule cells leading to multiple renal transport abnormalities (13, 237). Chinese herbs containing aristolochic acids cause proximal tubular injury, and this is called as aristolochic acid-related nephropathy.

A number of cancer chemotherapy agents are associated with renal glomerular and tubular dysfunctions including FS. The nephrotoxicity of cancer chemotherapy agents is dose dependent and often irreversible. Ifosfamide is an alkylating agent widely used in the treatment of various solid tumors. Chloroacetaldehyde (CAA), one of the main metabolites of ifosfamide, contributes to inhibit endocytosis in the proximal tubule cells (238). CAA decreases total glutathione and ATP levels in the proximal tubule cells. CAA also inhibits endosomal H^+-ATPase activity, which disturbs intracellular vesicle trafficking (239). Patients receiving ifosfamide who have received prior cisplatin are at significantly higher risk of developing FS than are those who have received no prior nephrotoxic therapy (240). When the patients manifest FS, renal sonography reveals hyperechogenicity of the parenchyma with good corticomedullar differentiation (241). Taurine can protect against ifosfamide-induced renal dysfunction without compromising its anti-tumor activity (242). Cisplatin also reduces glucose reabsorption in kidney tissue by reducing mRNA, protein expression, and function of the Na^+ dependent glucose transporter (243). Cisplatin inhibits various types of amino acid transporters in the proximal tubule cells leading to a generalized aminoaciduria (243).

Imanitib mesylate is a specific tyrosine kinase inhibitor that is the first line therapy for patients with chronic myeloid leukemia. This agent induces partial FS including phosphaturia and uricosuria with mild renal failure. Combined blockade of both platelet-derived growth factor receptor and c-Kit receptor tyrosine kinase in proximal tubules causes partial FS (244).

Nucleotide reverse transcriptase inhibitors that are used as anti-human immunodeficiency virus (HIV) agents including adefovir, cidofovir, and tenofovir induce

nic diabetes insipidus, and acute renal failure defovir and cidofovir interact with organic orters (OAT); these drugs enter into proxi-lls by activated OAT located in the basolat-ne. However, their efflux into the tubular reased by inactivated multidrug-resistance-RP 2) located in the luminal membrane. rugs are accumulated in the proximal tubule o mitochondrial damage and tubular toxici-ty of adefovir and cidofovir is proportional AT expression (246). Histologic and ultra-amination reveals tubular degenerative oximal tubules with swollen and dysmorphic . In tubular cells, respiratory chain compo-d by mitochondrial DNA (cytochrome oxi-I) are selectively deficient in renal tubular ochondrial DNA is quantitatively reduced rast to adefovir and cidofovir, renal toxicity is much less frequent. Tenofovir has little l toxicity and it does not interact with herefore, the precise mechanisms of neph-tenofovir remain unknown.

Compounds

on-selective herbicide, and colloidal bismus use FS (251, 252). Large amount of these re usually ingested in a suicide attempt. ifest FS and acute renal failure. Treat-e chelating agent sodium 2,3-dimercapto-onate in combination with hemodialysis is e in reducing the serum bismus level. Meth-e (diachrome) (253), 6-mercaptopurine uene also lead to FS (255).

als

such as lead, cadmium, mercury, chromi-num are a major environmental and occu-d. They are very toxic at very low doses. The first target organ of heavy metal toxicity. renal damage by heavy metals depends on se, route, and duration of exposure. Both nic intoxication have been demonstrated to athies, with various levels of severity rang-lar dysfunctions like acquired FS to severe 256). Lead poisoning leads to FS, predomi-dren (257). As lead is non-biodegradable ng biological half-life, aminoaciduria and glycosuria persist up to 13 years after childhood severe lead poisoning (258).

Cadmium intoxication leads to FS after a long exposure (259). The industrial waste contaminating cadmium in the Jinzu River basin in Toyama prefecture in Japan produced a lot of patients with *Itai-Itai* (*ouch-ouch*) disease that is compatible to FS with severe osteomalacia. Patients complained severe bone pains that are derived from advanced non-traumatic multiple bone fractures. Cadmium produces free radicals that alter mitochondrial activity or induce mitochondrial gene deletion in the proximal tubules (260, 261). Cadmium inhibits H^+-ATPase, which results in a Fanconi-like syndrome (6).

Therapy

Identification of the underling cause for FS is a first step and is critical to direct specific therapy. Avoidance of offending nutrients in galactosemia, HFI, and tyrosinemia and avoidance of Cu-rich foods in WD are therapeutically critical. Specific treatments with Cu-chelating agents including D-penicillamine, trientine, and ammonium tetrathiomolybdate, and zinc are effective for WD. Imuunosuppressive drugs are used for immunologically induced disorders including Sjögren syndrome, TINU syndrome and autoimmune interstitial nephritis and membranous nephropathy. These treatments can completely resolve FS.

When specific therapy does not exist, therapy is directed at the biochemical abnormalities secondary to renal solute and fluid losses and the metabolic bone diseases. Proximal renal tubular acidosis usually requires large amount of alkali (2–15 mEq kg^{-1} of body weight a day) divided into four to six daily doses. High dose of alkali can produce volume expansion, further bicarbonate wasting and potassium loss in the patients with FS. 1–3 mg kg^{-1} of body weight a day of hydrochlorothiazide can reduce the dose of alkali by preventing the volume expansion. Administration of potassium salt of citrate, bicarbonate, or acetate fulfills the dual purpose of treating acidosis and preventing hypokalemia. Sodium wasting and dehydration are treated with combination of sodium bicarbonate, citrate, and chloride, depending on the degree of acidosis. Ensuring adequate fluid and electrolyte intake is essential, especially in the case of infants or gastrointestinal diseases. Early intervention with intravenous replacement therapy is required for the patients with FS who manifest vomiting and diarrhea.

Hypophosphatemia and impaired renal vitamin D3 metabolism in patients with FS lead to rickets and other metabolic bone diseases. 1–3 g of phosphate supplementation

is necessary as neutral phosphate (the mixture of sodium phosphate dibasic 1.94 g and potassium phosphate monobasic 0.34 g contains 0.5 g of phosphate) divided into four to six daily doses. Supplementation of 1,25-dihydroxyvitamin D3 or dihydrotachysterol is effective to treat or prevent rickets and osteomalacia. Vitamin D3 therapy improves the hypophosphatemia and lessens the risk of hyperparathyroidism. Hypercalcemia and hypercalciuria are toxic side effects of vitamin D3 therapy. An adequate amount of physical activity, as well as appropriate diet with calcium, phosphate, and vitamin D3, is necessary to prevent bone deformations, non-traumatic fractures leading to bone pain, deterioration of motor development and disability (262).

Aminoaciduria, glucosuria, proteinuria, LMW proteinuria, and uricosuria usually do not induce clinical symptoms and do not require specific treatments.

Growth failure is a major complication in FS. Despite correction of electrolyte abnormalities, some patients manifest severe growth retardation, especially those with cystinosis and Fanconi-Bickel syndrome. A patient with FS was reported to have growth hormone deficiency (263). Supplemental growth hormone has been used successfully in a few patients with FS.

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