

Review Article

Medical Progress

CYSTINOSIS

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CYSTINOSIS is an autosomal recessive disorder with an estimated incidence of 1 case per 100,000 to 200,000 live births. The gene for cystinosis, *CTNS*, was mapped to chromosome 17p13 in 1995¹ and was isolated in 1998.² In nephropathic cystinosis, free cystine accumulates continuously in lysosomes, eventually resulting in intracellular crystal formation throughout the body. In a parallel fashion, the acquisition of clinical and basic information about cystinosis over the past four decades has crystallized our understanding of the cause and treatment of this previously enigmatic disease. Since therapy has proved extremely effective, early diagnosis and treatment are critical aspects.

HISTORICAL ASPECTS

Although cases of cystinosis were first reported in 1903 by Abderhalden,³ clinical understanding of the disorder did not mature until the early 1930s, when Fanconi in Switzerland, deToni in Italy, and Debré in France each described young children with renal glucosuria, proteinuria, acidosis, and hypophosphatemic rickets. This generalized renal tubular disorder, called the deToni–Debré–Fanconi syndrome, or simply Fanconi’s syndrome, characterized nephropathic cystinosis. By the late 1940s, Dent⁴ had quantified the extent of polyuria, glucosuria, phosphaturia, and proteinuria and had noted a generalized aminoaciduria in spite of normal plasma amino acid concentrations in affected patients. In 1952, Bickel et al.⁵ described the association between Fanconi’s syndrome and progressive glomerular damage in a large series of patients. A more detailed review of the early studies of cystinosis is available elsewhere.⁶

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The modern era of clinical investigation into cystinosis began in 1967, when amino acid analysis by ion-exchange chromatography became sensitive enough to measure minute amounts of cystine in tissue samples from small children. This technique revealed normal plasma cystine concentrations in patients with cystinosis but markedly elevated amounts of intracellular, free (nonprotein) cystine.⁷ Since cystine inhibits several essential cellular enzymes, investigators hypothesized that cystine must be compartmentalized within cells.⁸ Indeed, a variety of techniques showed that cystine was stored within the lysosomes of cells in affected persons.^{6,9} Subsequent studies showed that the basic defect in cystinosis was an impairment of lysosomal membrane transport.^{10,11} These studies were greatly aided both by the development of a rapid and sensitive assay for cystine that involved the use of a specific cystine-binding protein¹² and by techniques for loading normal cells with cystine.¹⁰

The course of research on cystinosis has been dramatically altered by two medical innovations. First, renal transplantation has proved extremely successful in patients with this disease.^{6,13} Second, cysteamine (β -mercaptoethylamine), which depletes cells of cystine both *in vitro* and *in vivo*,¹⁴ has dramatically improved the prognosis for children with nephropathic cystinosis.

CLINICAL CHARACTERISTICS

As is the case with many lysosomal storage diseases, the initial manifestations of cystinosis generally appear several months after birth. The signs and symptoms are protean (Table 1), but kidney involvement remains the foremost clinical characteristic of the disorder.^{6,15}

Renal Findings

The initial symptoms of cystinosis result from the failure of renal tubules to reabsorb small molecules, causing Fanconi’s syndrome. Cystinosis is the most common identifiable cause of Fanconi’s syndrome in children, although tyrosinemia, Wilson’s disease, Lowe’s syndrome (the oculocerebrorenal syndrome), galactosemia, and glycogen storage disease are included in the differential diagnosis.⁶ Fanconi’s syndrome results in excessive urinary loss of low-molecular-weight protein, glucose, amino acids, phosphate, calcium, magnesium, sodium, potassium, bicarbonate, carnitine, water, and undoubtedly, other small molecules. Children with cystinosis may initially receive a diagnosis of Bartter’s syndrome, diabetes mellitus, or nephrogenic diabetes insipidus.^{6,16,17}

TABLE 1. AGE-RELATED CLINICAL CHARACTERISTICS OF UNTREATED NEPHROPATHIC CYSTINOSIS.

AGE	SYMPTOM OR SIGN	PREVALENCE IN
		AFFECTED PATIENTS
		%
6–12 mo	Renal Fanconi's syndrome (polyuria, polydipsia, electrolyte imbalance, dehydration, rickets, growth failure)	95
5–10 yr	Hypothyroidism	50
8–12 yr	Photophobia	50
8–12 yr	Chronic renal failure	95
12–40 yr	Myopathy, difficulty swallowing	20
13–40 yr	Retinal blindness	10–15
18–40 yr	Diabetes mellitus	5
18–40 yr	Male hypogonadism	70
21–40 yr	Pulmonary dysfunction	100
21–40 yr	Central nervous system calcifications	15
21–40 yr	Central nervous system symptomatic deterioration	2

The polyuria, consisting of obligate daily excretion of 2 to 6 liters of dilute urine (<300 mOsm per liter), may lead to persistent enuresis or even death from dehydration and electrolyte abnormalities in infants with cystinosis who have acute gastroenteritis. Dehydration in such infants progresses rapidly and may be associated with a mild, chronic fever. Phosphaturia leads to hypophosphatemic rickets, with characteristic metaphyseal widening, rachitic rosary, frontal bossing, genu valgum, failure to walk, and elevated serum alkaline phosphatase levels. A generalized aminoaciduria results in the excretion of amino acids at concentrations that are 10 times the normal values.¹⁸ The urinary cystine concentration is elevated to the same extent as the concentration of other amino acids, and cystine stones do not form as they do in cystinuria,¹⁹ because of the dilute and alkaline urine. Many patients with cystinosis have medullary nephrocalcinosis in late childhood.²⁰

When cystinosis is diagnosed in infancy or early childhood, the serum creatinine concentration is generally not greatly elevated, despite a deficit in the glomerular filtration rate. In fact, the serum creatinine concentration seldom exceeds 1 mg per deciliter (88 μ mol per liter) before the age of five years. Many patients have granular casts and microscopical hematuria. In the absence of treatment, creatinine clearance decreases inexorably from infancy. Among 205 European patients studied before cysteamine therapy was available, the mean age when end-stage renal disease (i.e., advanced uremia, with the initiation of dialysis or transplantation) developed was 9.2 years.²¹ Many patients have an improvement in Fanconi's syndrome

as renal function fails, but some continue to excrete large volumes of fluids and electrolytes. Some patients have unexplained plateaus in their renal function, lasting for a period of months to years; others have a rapid deterioration triggered by an acute infection, an acute renal injury from a urinary tract infection, post-infectious glomerulonephritis, or, in infants, hypoperfusion due to dehydration.

Systemic Involvement before Renal Transplantation

The typical North American child with cystinosis has blond hair (Fig. 1A), although patients who are members of ethnic groups with dark hair have a normal degree of pigmentation. Patients with cystinosis are of normal length at birth, but their height falls to the third percentile by one year of age, and they subsequently grow at only approximately 60 percent of the normal rate^{6,22} (Fig. 1B). In the absence of treatment, children with cystinosis rarely achieve a height that exceeds the 50th percentile for a three-year-old. Weight and bone age are consistent with height, but head circumference increases at a normal rate.

If not treated, the formation of cystine crystals in the cornea causes photophobia between mid-childhood and adolescence. Cystine storage in thyroid tissue leads to the formation of crystals and fibrosis, with hypothyroidism developing at 10 years of age, on average.²³ Children with cystinosis do not sweat, salivate, or tear normally,²⁴ and feeding difficulties abound. Specific cognitive dysfunction has been reported in persons with cystinosis and even in their heterozygous siblings.²⁵ Impaired visual and spatial cognition with preserved visual-perceptual, language, and general intellectual function is typical.²⁵ Nevertheless, overall intelligence appears to be normal in patients with cystinosis, and heterozygotes have no other signs or symptoms of the disease.⁶

Systemic Involvement after Renal Transplantation

After renal transplantation, patients often have side effects of immunosuppressive medications, as noted in the cushingoid facies of the patient shown in Figure 1C. However, the recent avoidance of the use of long-term, high-dose corticosteroids and newer antirejection medications may avert many of these post-transplantation problems. Many patients with cystinosis also have the characteristic complications of long-standing kidney failure (e.g., renal osteodystrophy). Other patients have debilitating complications of cystinosis itself, including ophthalmologic problems (posterior synechiae, iris crystals, retinal blindness, and blepharospasm)²⁶; a progressive, distal, vacuolar myopathy with muscle wasting^{27,28} (Fig. 1D); primary hypogonadism in males²⁹; swallowing difficulties³⁰; pulmonary dysfunction³¹; diabetes mellitus³²; central nervous system deterioration^{33,34}; and

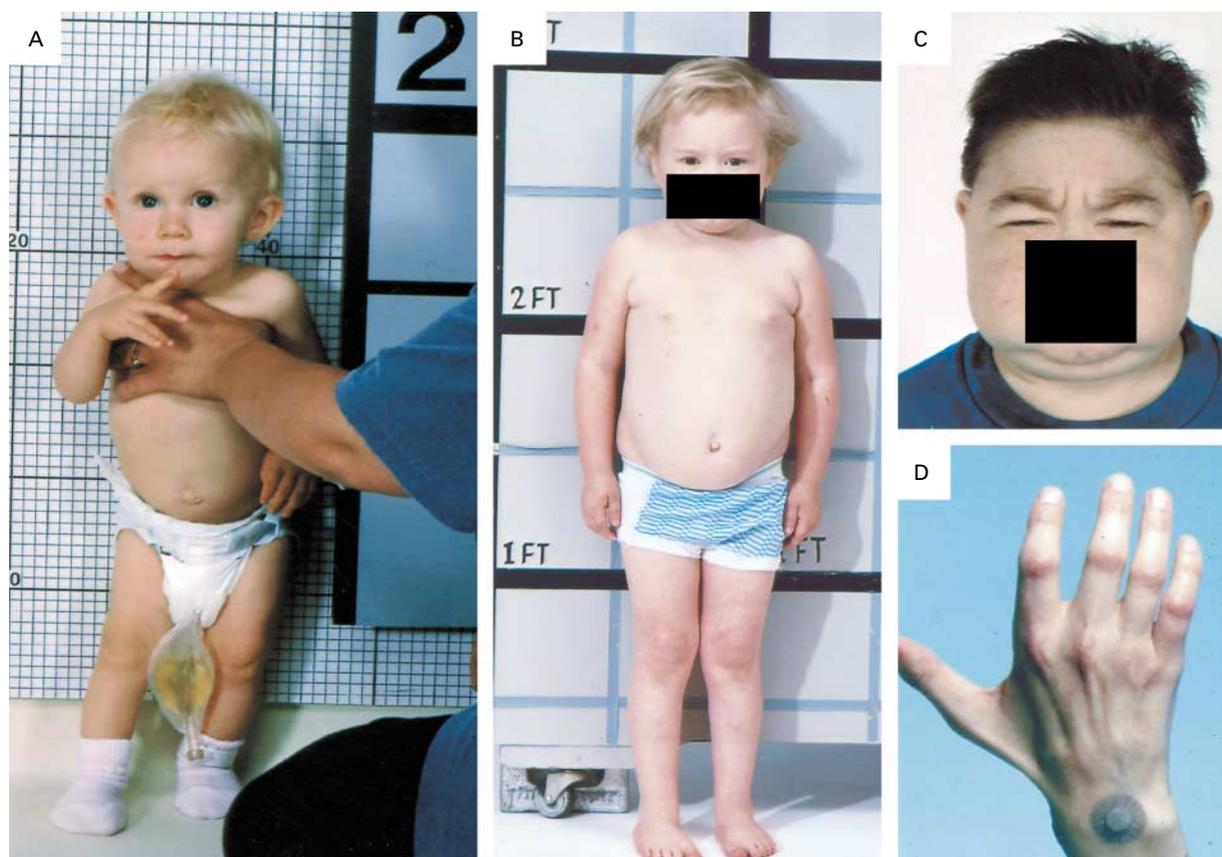


Figure 1. Patients with Nephropathic Cystinosis.

Panel A shows an 11-month-old girl with the blond hair and blue eyes that are typical of patients of northern European descent. Panel B shows a seven-year-old boy with short stature and poor muscular development. Panel C shows the same patient at the age of 25 years, after renal transplantation, with cushingoid features and severe photophobia with blepharospasm. The patient died at the age of 28 years. Panel D shows muscle wasting in the hand of a 23-year-old man with cystinosis who had undergone renal transplantation.

pancreatic exocrine insufficiency.³⁵ Seldom does a patient reach the late 30s without a major, life-altering medical complication of cystinosis.³⁶ The oldest patient with nephropathic cystinosis, the first who underwent transplantation (at the age of 10 years in 1968), is now 44 years old. A few women with cystinosis have given birth to normal, healthy children after undergoing successful renal transplantation.³⁷

PATHOLOGICAL FEATURES

The predominant pathological finding in cystinosis is the presence of cystine crystals in almost all cells and tissues (Fig. 2A through 2F), including the conjunctivae, corneas, liver, spleen, lymph nodes, kidneys, thyroid, intestines, rectal mucosa, muscle, brain, macrophages, and bone marrow.⁶ The crystals have hexagonal, rhombohedral, or polymorphous configurations and are detectable under polarizing prisms if

precautions are taken to avoid dissolution by aqueous solvents. Since the solubility of cystine in plasma at a temperature of 37°C and a pH of 7.3 is 1.7 mM,³⁸ the concentration in tissue lysosomes probably exceeds this level. Corneal crystal accumulation increases with age,³⁹ and episodes of pain occur when Bowman's membrane is perforated. Healing occurs normally. Inexplicably, cystine crystals have never been seen in cultured fibroblasts from patients with cystinosis, despite lysosomal cystine concentrations that are 100 times the normal value.

The kidneys of patients with cystinosis have a characteristic narrowing of the proximal renal tubule, or swan-neck deformity, which is seen in other disorders as well. First described in 1953, the swan-neck deformity develops early in the course of nephropathic cystinosis and appears to correspond temporally to the development of Fanconi's syndrome.⁴⁰ After the

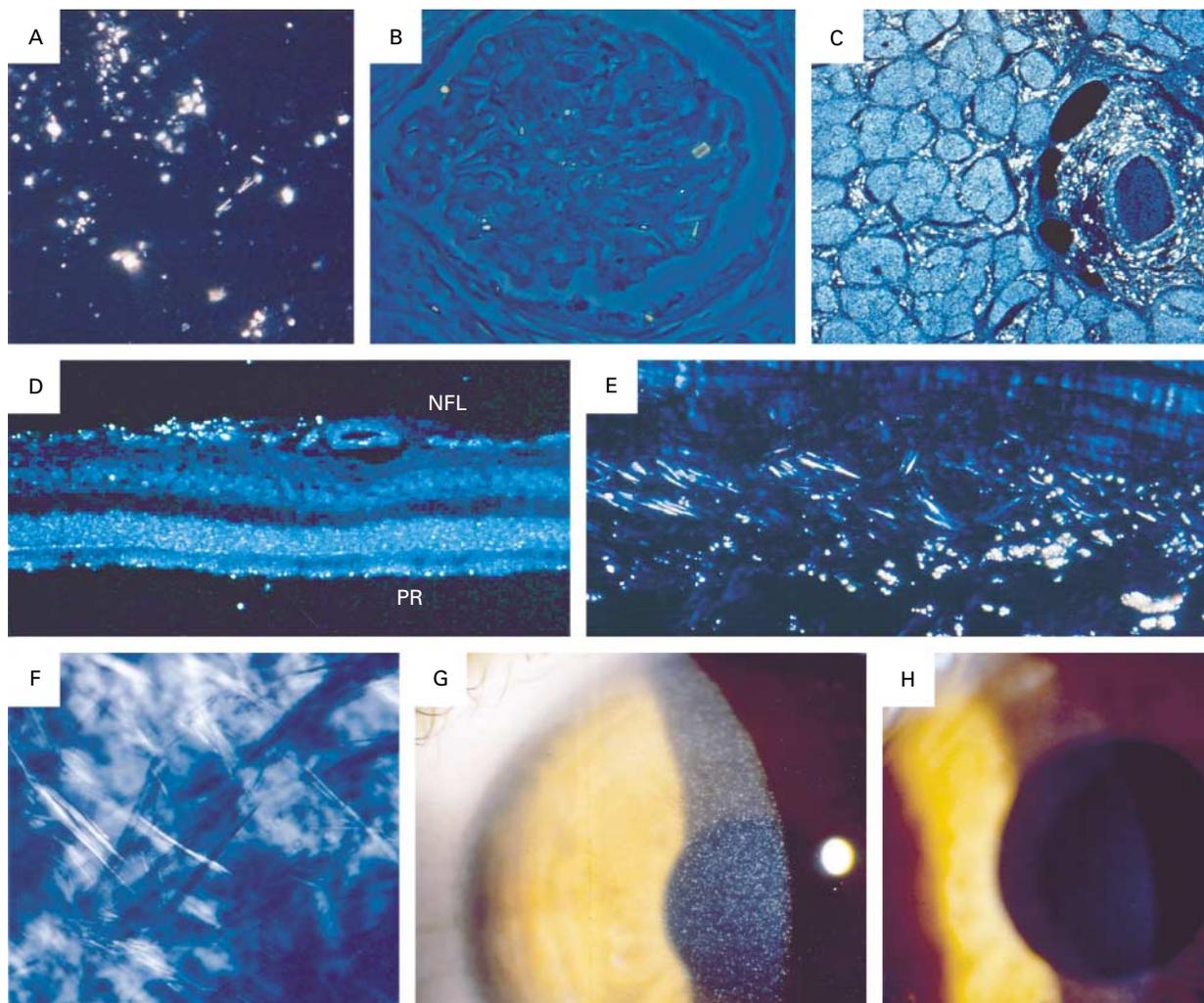


Figure 2. Cystine Crystals in Tissues from Patients with Cystinosis.

Panels A through F show postmortem specimens from an eight-year-old boy with nephropathic cystinosis (from the collection of the late Dr. David Cogan, courtesy of Dr. Carl Kupfer, National Institutes of Health). In Panel A, cystine crystals in a fresh liver specimen exhibit birefringence under cross-polarizing light ($\times 100$). In Panel B, a dark-field photomicrograph of an unstained, paraffin-embedded kidney specimen shows cystine crystals scattered in a renal glomerulus ($\times 200$). One crystal exhibits the natural, undissolved rectangular shape. In Panel C, a dark-field photomicrograph of an unstained, alcohol-fixed cross-section of optic nerve and central retinal artery shows crystals packing the spaces between nerve bundles ($\times 400$). In Panel D, a dark-field photomicrograph of an unstained, alcohol-fixed specimen shows abundant crystals in the nerve-fiber layer and fewer crystals at the level of the photoreceptors ($\times 100$). In Panel E, an alcohol-fixed thick section of the corneal-scleral junction shows sharp, pointed crystals in the stroma (left-hand side) and irregularly shaped crystals in the conjunctiva overlying the sclera ($\times 400$). In Panel F, an alcohol-fixed, thick corneal section shows pointed crystals resembling shards of glass ($\times 400$). In Panel G, slit-lamp examination of a 32-month-old boy shows packed corneal cystine crystals ($\times 17$). In Panel H, slit-lamp examination of the same eye after 25 months of treatment with cysteamine eye drops shows that the crystals have dissolved ($\times 17$). (Panels G and H provided courtesy of Dr. M.I. Kaiser-Kupfer, National Eye Institute.)

onset of the tubulopathy, children with nephropathic cystinosis have chronic interstitial nephritis, further tubular degeneration, endothelial proliferation in the glomeruli, glomerular necrosis and hyalinization with arteriolar thickening, and multinucleated giant cells, as the disorder progresses to end-stage renal disease.

All these changes may be seen in the absence of obvious cystine crystals in the kidneys.

THE BASIC DEFECT

Cystinosis is a lysosomal storage disease that results from the impaired transport of cystine, which forms

after protein degradation, from the lysosome into the cytoplasm. The lysosomal-membrane system for the transport of cystine, characterized most extensively in human polymorphonuclear leukocytes, exhibits saturation kinetics,¹⁰ counter-transport,⁴¹ a gene-dosage effect,⁴² stereospecificity,⁴¹ and a high degree of ligand specificity.⁴¹ The transport of cystine out of the lysosome serves as a prototype for other lysosomal systems that transport amino acids, carbohydrates, and other small molecules.⁴³ Disorders of sialic acid transport (such as Salla disease and infantile free sialic acid storage disease) and cobalamin transport (cobalamin F disease) have joined cystinosis as lysosomal storage disorders caused by defects in the transport of small molecules.⁴⁴

GENETIC FEATURES

CTNS, the gene for cystinosis, encodes the protein cystinosin and maps to chromosome 17p13.¹ The gene contains 12 exons distributed across approximately 23 kb of genomic DNA.² All patients with cystinosis appear to have mutations in *CTNS*. Cystinosin has 367 amino acids, 7 transmembrane domains, and 8 potential glycosylation sites. The protein has recently been shown to transport cystine and has kinetic properties similar to those reported nearly two decades ago.⁴⁵

To date, more than 50 different *CTNS* mutations have been described, but the most common is a 57,257-bp deletion,⁴⁶ easily detected by a multiplex polymerase-chain-reaction assay.^{47,48} The mutation is found in the homozygous state in approximately 50 percent of patients of northern European descent who have cystinosis. This founder mutation, which removes the first 10 exons of *CTNS* and eliminates expression of the protein, apparently occurred in Germany in approximately A.D. 500⁴⁹ and spread by migration to neighboring regions, including Iceland. Patients with classic nephropathic cystinosis have two severe *CTNS* mutations, involving alterations in the promoter region, leader sequence, transmembrane domains, or non-transmembrane regions.^{2,49,50-52} Reported mutations include small deletions and insertions and nonsense, missense, and splicing mutations (Fig. 3).

DIAGNOSIS

Approximately 15 new cases of cystinosis are diagnosed each year in the United States, but this number probably represents only half to two thirds of actual cases. The diagnosis is made by measuring the leukocyte cystine content. Polymorphonuclear leukocytes are prepared from as little as 3 ml of heparin-treated blood by acid citrate-dextran sedimentation, followed by hypotonic lysis of erythrocytes.⁵³ Cystine levels are measured with the use of a specific and

sensitive assay involving cystine-binding protein and isotopic dilution or with the use of ion-exchange column chromatography, which is less sensitive.^{12,53} In normal persons, mixed leukocyte preparations contain less than 0.2 nmol of half-cystine per milligram of protein, whereas in patients with nephropathic cystinosis, the values exceed 2.0 nmol of half-cystine per milligram of protein. (Cystine content is expressed in units of half-cystine because initial methods of quantification involved a reduction of cystine followed by an assay for cysteine.) The presence of typical corneal crystals on slit-lamp examination is also diagnostic of cystinosis, although crystals may be absent before one year of age.³⁹ Performing a skin biopsy to measure cystine in fibroblasts or a tissue biopsy to look for cystine crystals is unnecessarily invasive and is considered outdated.

Although heterozygous patients can be identified by measuring the cystine content of polymorphonuclear leukocytes,⁵⁴ the procedure is tedious and not suitable for general screening. If a family is known to have the 57-kb deletion in *CTNS*,⁴⁸ molecular studies are preferable for identifying family members who are heterozygous for the deletion. DNA assays are not yet practical for the detection of other mutations.

Prenatal diagnostic testing can be performed on either cultured amniocytes⁵⁵ or samples of chorionic villi.⁵⁶ In our experience, many parents of offspring who are at risk for cystinosis eschew prenatal detection but request diagnostic testing immediately after birth so that treatment with cysteamine can be initiated if the diagnosis is confirmed. Neonatal diagnosis can be based on the measurement of placental cystine,⁵⁷ as well as on the measurement of leukocyte cystine.

TREATMENT

Successful treatment of nephropathic cystinosis requires early diagnosis. If the condition is not identified and appropriately treated in infancy, chronic renal failure may develop at an early age, with the attendant need for dialysis and transplantation. The therapeutic needs of an affected child depend on the stage of the disease and fall into two categories: supportive and specific therapy.

Supportive Therapy

Supportive therapy addresses the enormous loss of fluid and solutes due to impaired renal tubular reabsorption. The affected kidneys waste a panoply of nutrients, including water, sodium, chloride, potassium, bicarbonate, calcium, amino acids, glucose, and carnitine.⁶ Thirst and salt-sensing mechanisms are intact, and unrestricted intake of water and salt is essential. Many children crave the four P's of salt-rich foods: pizza, pickles, pretzels, and potato chips.

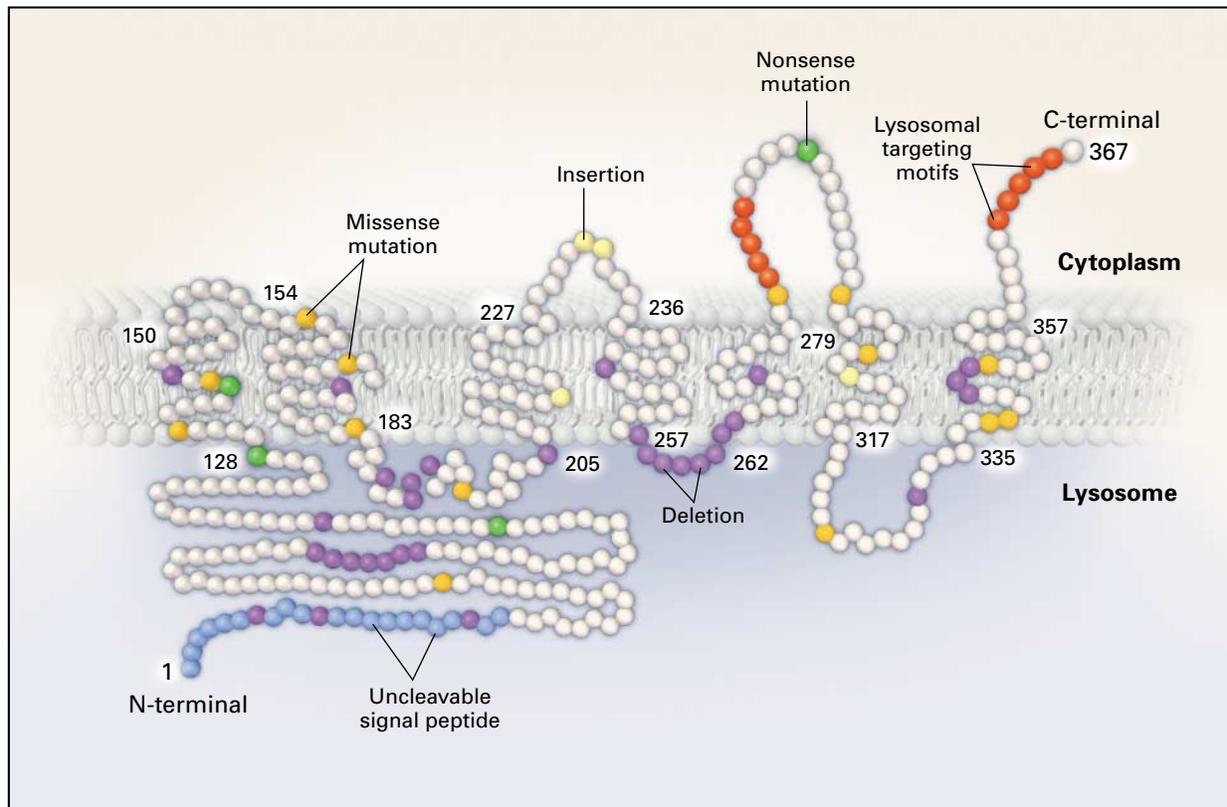


Figure 3. Cystinosis in the Lysosomal Membrane.

Each circle represents 1 of the 367 amino acids in cystinosis. The N-terminal, containing a signal peptide, resides inside the lysosome, and the C-terminal, containing one of two lysosomal targeting motifs, resides in the cytoplasm. Seven transmembrane regions contain missense, nonsense, insertion, and deletion mutations resulting in cystinosis. Some mutations occur in non-transmembrane regions as well. Splicing and promoter mutations are not shown.

Formal electrolyte replenishment is accomplished by administering oral solutions of sodium bicarbonate or sodium–potassium citrate, which is more palatable.^{6,15} Oral calcium supplements may be required, and to prevent renal rickets, sodium phosphate and 1,25-dihydroxycholecalciferol must be administered, beginning in early childhood. Carnitine replacement raises low plasma carnitine levels,⁵⁸ but studies have not been performed to demonstrate that this change is accompanied by clinical improvement. Satisfactory nutrition may be difficult to achieve because of the feeling of satiety that results from the mandatory ingestion of large volumes of fluids and also because of dysgeusia, if cysteamine is being administered. Some centers place gastrostomy tubes to aid in nutrition and drug administration, although controlled trials have not been performed to evaluate the benefit of this procedure, and care must be taken to avoid loss of masticatory function. Although growth

hormone is not deficient in patients with cystinosis, treatment with growth hormone provides a spurt in growth that often allows patients to achieve and maintain normal height for their age.⁵⁹ Hypothyroidism is easily controlled with levothyroxine therapy, and testosterone replacement may be helpful for selected men with hypogonadism.

If renal failure occurs, patients are treated with peritoneal dialysis or hemodialysis until a renal allograft can be transplanted, or preemptive transplantation is performed without antecedent dialysis. Renal allografts in patients with cystinosis do not undergo the functional changes of cystinosis but do accumulate cystine of host origin.^{60,61}

Specific Therapy with Cysteamine

Specific treatment with cysteamine, an aminothioliol, results in long-term depletion of lysosomal cystine. Clinical trials have demonstrated that the institution

of such therapy early in life retards renal glomerular deterioration and improves linear growth.^{22,62} A graph of reciprocal serum creatinine concentrations according to age in patients treated with oral cysteamine and in untreated patients shows the remarkable salutary effect of early, prolonged cystine depletion in patients with cystinosis (Fig. 4).

Many patients have survived into the third decade of life without the need for renal transplantation. If the diagnosis is established and cysteamine therapy is started before symptoms develop, the prognosis for glomerular function is especially good, but tubular dysfunction still develops at an early age. Cysteamine therapy has been shown to obviate the need for levothyroxine replacement in patients with cystinosis,⁶³ indicating that it has a beneficial effect on at least one nonrenal organ, the thyroid. This suggests

that cysteamine should be useful in preventing post-transplantation complications in patients with cystinosis. Oral cysteamine therapy is already recognized as the treatment of choice for patients throughout the world who have nephropathic cystinosis and have not undergone transplantation.

The mechanism of lysosomal cystine depletion involves entry of cysteamine into the lysosomal compartment through a specific transporter, reaction with cystine to form the mixed disulfide cysteamine–cystine, exit of that compound from the lysosomes through an intact lysine transporter^{6,64} (Fig. 5), and reduction to cysteamine and cysteine by glutathione in the cytoplasm. This process permits the cycling of cysteamine between lysosomes and cytoplasm, with each cycle removing 1 mole of half-cystine per mole of cysteamine.

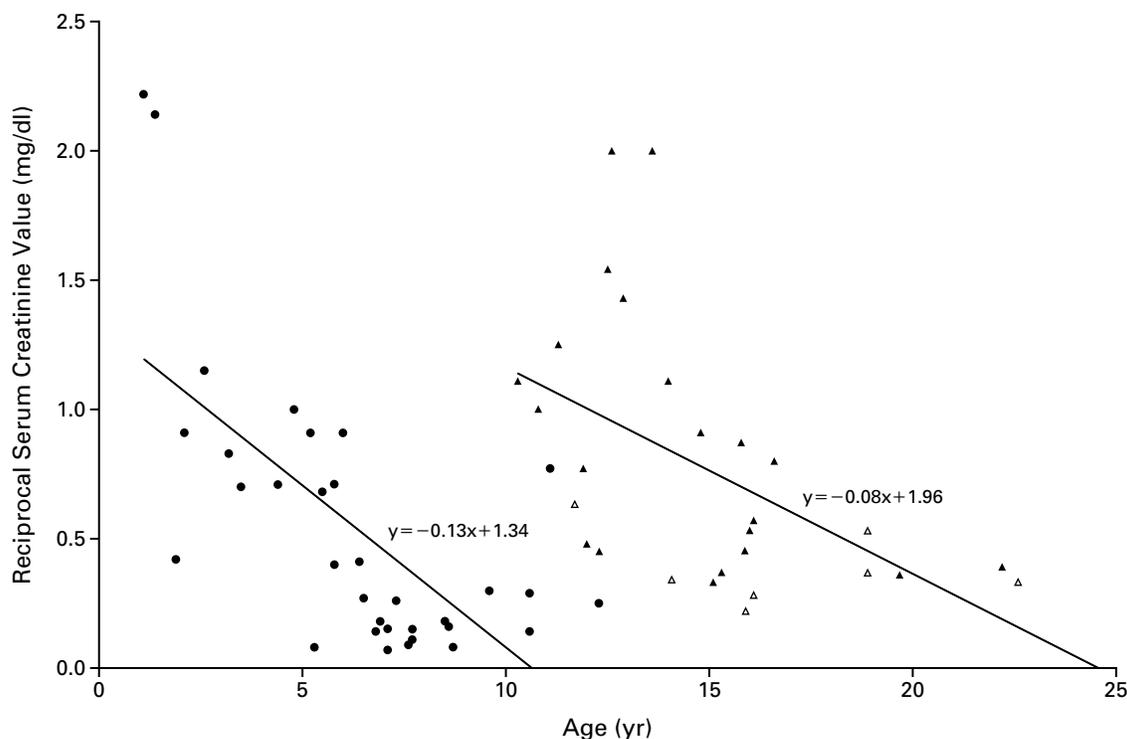


Figure 4. Renal Function in Patients with Cystinosis Treated with Cysteamine and in Untreated Patients, According to Age.

The circles represent 33 patients who were seen at the National Institutes of Health Clinical Center between 1960 and 1992 and who did not receive cysteamine. The triangles represent 28 patients who received oral cysteamine for at least 10 years, beginning before the age of 3 years (mean age, 17 months), and the open triangles those known to have subsequently undergone renal transplantation. The values shown are the most recent available data, and the lines show the best-fit regression curves ($r = -0.67$ for the untreated group, and $r = -0.51$ for the treated group). Serum creatinine values are expressed as reciprocals (1 divided by the creatinine value, in milligrams per deciliter). To convert serum creatinine values to micromoles per liter, multiply by 88.4. Long-term cysteamine therapy has shifted the point at which serum creatinine reaches 10 mg per deciliter from 10 years to 23 years and has lowered the rate of decline of reciprocal serum creatinine values.

Cysteamine has the marked odor and taste of thiols, and it binds to oral mucosa and dental fillings. For this reason, capsules of cysteamine bitartrate (Cystagon, Mylan) are preferable to aqueous solutions when children are old enough to swallow capsules. For infants, the contents of the capsule can be dissolved in juice and can be given with other medications. Often families will make up an entire day's supply at one time and store it in the refrigerator.

Cysteamine should be started at a daily dose of 10 mg of free base per kilogram of body weight per day, given in divided doses every six hours and increased weekly by 10 mg per kilogram per day until a target dose of 60 to 90 mg per kilogram per day (or 1.3 to 1.95 g per square meter of body-surface area per day) is reached. In some patients, much higher doses are required to obtain satisfactory cystine depletion because of poor absorption or rapid drug inactivation. The target leukocyte cystine content is less than 1.0 nmol of half-cystine per milligram of protein. If this is not achieved, the dose of cysteamine should be gradually increased until cystine depletion is satisfactory or side effects limit further increases.

Side effects are usually restricted to nausea and vomiting, although in rare cases, allergic rash, seizures, and neutropenia have occurred because of failure to increase the initial dose incrementally.⁶⁵ These adverse events all resolved when the drug was withdrawn. Approximately 14 percent of patients are unable to tolerate cysteamine therapy because of nausea and vomiting.^{22,62} An overdose of oral cysteamine can cause drowsiness. When given to pregnant rats at very high doses, cysteamine causes developmental defects in the offspring.⁶⁶

Corneal cystine crystals do not dissolve with oral cysteamine therapy but do respond to the administration of cysteamine eyedrops (Fig. 2G and 2H).^{39,67,68} Ocular symptoms regress within a period of weeks, and the corneas clear within months. Approval of cysteamine eyedrops as a new drug is being sought from the Food and Drug Administration.

Two organizations^{69,70} offer support to patients with cystinosis and their families.

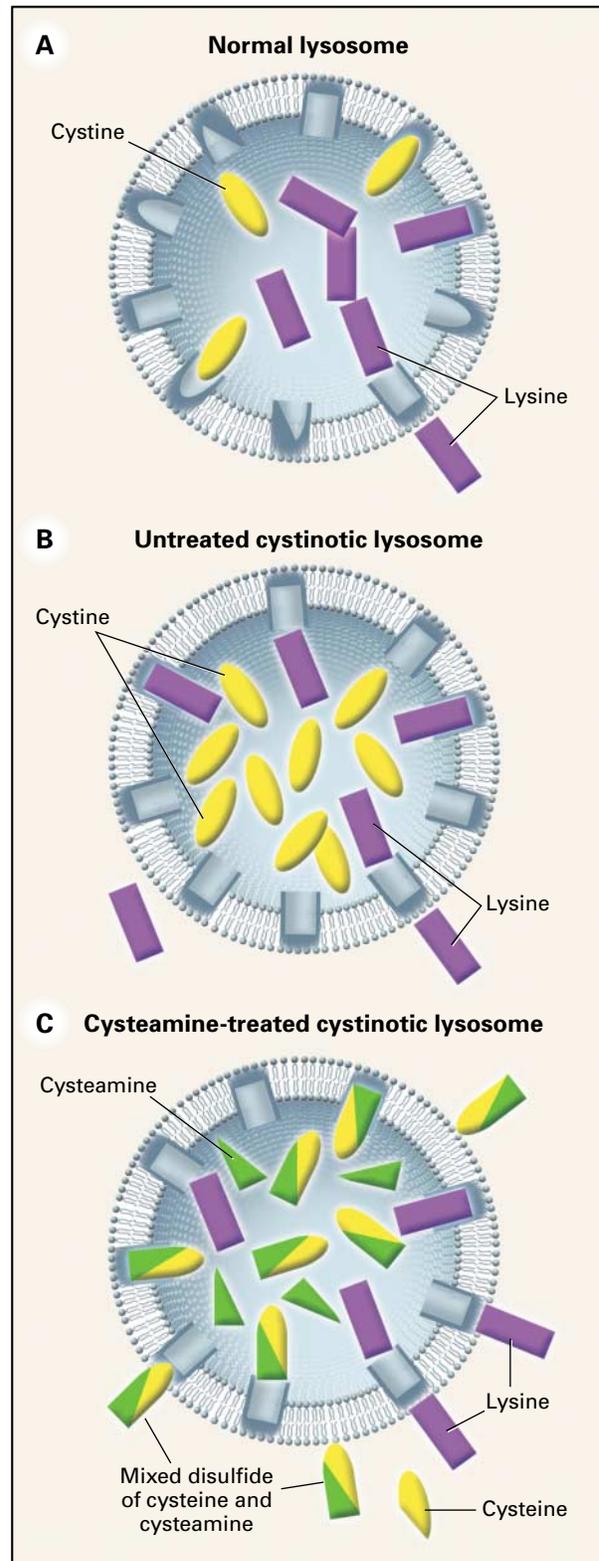


Figure 5. Mechanism of Cystine Depletion by Cysteamine.

In normal lysosomes (Panel A), cystine and lysine freely traverse the lysosomal membrane. In cystinotic lysosomes (Panel B), lysine can freely traverse the lysosomal membrane, but cystine cannot, and it therefore accumulates inside the lysosome. In cysteamine-treated lysosomes (Panel C), cysteamine combines with half-cystine (i.e., cysteine) to form the mixed disulfide cysteine–cysteamine, which uses the lysine transporter to exit the lysosome.

CLINICAL VARIANTS

As with other rare diseases, underascertainment of cases of cystinosis is a problem, and the full spectrum of clinical variants has not yet been described. Classic nephropathic cystinosis accounts for perhaps 95 percent of the approximately 400 reported cases in North America. Less severe forms of cystinosis probably form a continuum, but two distinct subtypes have been emphasized in the literature: intermediate and ocular cystinosis.

Intermediate cystinosis, also called "late-onset" or "juvenile" cystinosis, has the same features as the nephropathic form but with a markedly slower rate of progression.^{6,71} Patients with intermediate cystinosis may retain renal function into their 30s, and growth is only moderately impaired. Cystine crystals accumulate in the corneas at a relatively slow rate. Two siblings in Taiwan with intermediate cystinosis had linear growth and weight gain within 2 SD of the mean for their ethnic group until the ages of 13 and 14 years, when their plasma creatinine concentrations were 1.2 mg per deciliter (106 μ mol per liter) and 3.3 mg per deciliter (292 μ mol per liter), respectively.⁷²

Ocular, or non-nephropathic, cystinosis, previously called "benign" or "adult" cystinosis,⁷³ is characterized by the ocular findings typical of other types of the disease.⁶ All systemic manifestations are lacking.

Patients with intermediate⁷² or ocular⁷⁴ cystinosis generally have one severe *CTNS* mutation (e.g., the 57-kb deletion or a nonsense mutation) and one mild mutation, so that part of the transport function of cystinosin is retained. For example, three patients with intermediate cystinosis were heterozygous for a premature termination codon (W138X) and a splice-site mutation (IVS11+2T→C).⁷² However, the Taiwanese siblings with intermediate cystinosis were homozygous for a mutation of a conserved amino acid (N→K). Presumably, this mutation allowed for some residual cystine transport, accounting for the mild clinical presentation. Patients with ocular cystinosis are often hemizygous for a 928 G→A mutation in *CTNS*.⁷⁴ In one patient who had ocular cystinosis with a leukocyte cystine content similar to that in patients with nephropathic cystinosis, a splicing mutation (IVS10-3C→G) was identified, which may have allowed for some properly spliced *CTNS* expression in the kidney, accounting for the absence of renal disease.⁷⁴

FUTURE DIRECTIONS

Although recent findings have solved many of the mysteries of cystinosis, several questions remain. One important step toward a fuller understanding of the disorder is to determine how the accumulation of cystine causes cellular damage. Cystine should not

be toxic when isolated within the lysosomal compartment, and the disulfide amino acid is reduced to the benign free thiol, cysteine, once it reaches the cytoplasm. Recent data suggest that lysosomal cystine increases the rate of apoptosis in cultured cells,⁷⁵ and a similar process may occur in vivo. Differences in the intrinsic rate of apoptosis among patients may account in part for phenotypic variations. We also need to know whether cysteamine can enter the central nervous system to prevent neuronal damage and whether it crosses the placenta at doses that cause cystine depletion. These issues may be addressed by studies of *CTNS*-knockout mice, which apparently have elevated tissue cystine levels.⁷⁶ This mouse model may also be used to determine whether gene replacement in certain tissues such as the kidney will prove safe and effective.

For now, clinicians rely on cysteamine therapy, which has dramatically changed the course of cystinosis. Cysteamine therapy must be used to the fullest extent possible, which means establishing the diagnosis early through increased awareness of the disorder and, eventually, neonatal screening. Cysteamine therapy should also be considered for every patient with nephropathic cystinosis who has undergone transplantation, with the hope of preventing nonrenal complications of the disorder. Such possibilities make cystinosis one of the most treatable metabolic disorders.

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