MINIREVIEW

Corneal Crystals in Nephropathic Cystinosis: Natural History and Treatment with Cysteamine Eyedrops

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Although renal disease is the most prominent feature of the lysosomal storage disease cystinosis, corneal cystine crystal formation remains a major complication, leading to photophobia, corneal erosions, and keratopathies. Moreover, the extent of corneal crystal accumulation reflects the course and severity of the disease itself, and the cornea is accessible to direct examination. Therefore, we employed a scoring system, based on a library of slit-lamp photographs of corneas with increasing crystal densities (0.00–3.00), to assess the degree of crystal accumulation in 170 patients with nephropathic cystinosis examined at the National Institutes of Health between 1976 and 2000. None of the patients had received topical cystine-depleting therapy at the time of the evaluation. In this natural history study, infants in the first year of life had absent or minimal corneal crystals, i.e., a corneal cystine crystal score (CCCS) of 0 or 0.25. However, the CCCS increased linearly with age, such that every patient had visible crystals by 16 months of age, and plateaued at approximately 3.00 by early adolescence. Longitudinal studies in representative patients support the cross-sectional results. Individuals homozygous for the common 57-kb deletion involving the cystinosis gene (CTNS) displayed the same course of corneal crystal accumulation as did individuals not bearing the large deletion. Patients with ocular or nonnephropathic cystinosis had CCCSs that were, in general, half those expected for patients with nephropathic cystinosis of the same age. Administration of 0.55% cysteamine eyedrops, given 6 to 12 times per day, dissolved corneal cystine crystals in 10 representative patients with nephropathic cystinosis aged 1 to 32 years within 8 to 41 months.© 2000 Academic Press

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But soft! What light through yonder window breaks.

William Shakespeare

CLINICAL FEATURES OF CYSTINOSIS

The various manifestations of the rare autosomal recessive disease nephropathic cystinosis occur due to accumulation of the disulfide amino acid cystine within cellular lysosomes (1). The disorder results from mutations in the gene CTNS (2), whose protein product, cystinosin, is considered to be the lysosomal membrane transporter responsible for cystine egress. Patients with classic nephropathic cystinosis exhibit a variety of CTNS mutations, but approximately half the mutant alleles contain a 57-kb deletion which was apparently founded in Germany prior to AD 700 (2–8).

In nephropathic cystinosis, intralysosomal cystine crystallizes and destroys several tissues, including the kidney, thyroid, testis, pancreas, muscle, brain,
and eye. Patients appear normal at birth, and develop involvement of different organs at different ages (1,9). Presenting manifestations generally include failure to grow (at 6–9 months of age), persistent polyuria and polydipsia, and episodes of acidosis and dehydration. Hypophosphatemic rickets contributes to the portrait of renal Fanconi syndrome, reflecting destruction of kidney tubules. Glomerular deterioration occurs simultaneously and inexorably, culminating in renal failure at approximately 10 years of age (1,9). Nearly half of all cystinosis patients are also thyroxine deficient by age 10 (10), while photophobia due to corneal crystal accumulation manifests at various ages. After kidney transplantation, nonrenal tissues continue to accumulate cystine, and a variety of complications occur (11). These include a distal vacuolar myopathy (12,13), swallowing difficulty (14), pancreatic exocrine and endocrine insufficiency (15,16), central nervous system deterioration (17,18), primary male hypogonadism (19), and ophthalmic involvement such as posterior synechiae, blephorospasm, and retinal degeneration leading in some cases to blindness (20). Not all patients with cystinosis suffer all these complications, and milder variants of nephropathic cystinosis have been described (1,9,21,22).

Cystinosis is diagnosed by the finding of 50- to 100-fold elevated levels of free, nonprotein cystine within polymorphonuclear leucocytes or cultured fibroblasts (1,9). Symptomatic treatment involves replacement of renal losses and administration of L-thyroxine, as appropriate. However, the mainstay of therapy is the cystine-depleting aminothiol cysteamine, or mercaptoethylamine (23). This simple compound interacts with lysosomal cystine in a disulfide interchange reaction to form cysteine and cysteine–cysteamine mixed disulfide, both of which exit the cystinotic lysosome without requiring a functional cystine carrier (24,25). In this fashion, cysteamine can deplete cells of more than 90% of their cystine content. If administered chronically and diligently beginning prior to age 2 years, oral cysteamine retards or prevents glomerular deterioration and enhances growth in children with nephropathic cystinosis (26,27). Cysteamine, which was approved by the U.S. Food and Drug Administration as Cystagon in 1994, is given to children every 6 h at a daily dosage of 60–90 mg of free base/kg or 1.3–1.95 g of free base/m² of surface area. Chronic oral cysteamine therapy is associated with a delayed requirement for L-thyroxine replacement (28) and with reduction in muscle cystine content (29), but has never been demonstrated to have any effect on corneal cystine crystal accumulation (1,26,30,31). However, topical cysteamine has been shown to dissolve corneal cystine crystals if administered in eyedrop form either every hour while awake (32–34) or six times per day (35), but not four times per day (36).

One clinical aspect of nephropathic cystinosis that has never been reported is the natural history of crystal density progression within the corneas of affected individuals. The cornea, although difficult to photograph in photophobic children, nevertheless remains accessible. We employed a photography-based scoring system to quantitate crystal density, and documented the accumulation of corneal crystals with age by cross-sectional studies in 170 nephropathic cystinosis patients. Longitudinal studies in a sample of 9 individual patients support these results. We include corneal cystine crystal scores for 7 patients with ocular or nonnephropathic cystinosis, in which cystine crystals form only within the cornea and bone marrow (1,22,37). Finally, we illustrate the efficacy of cysteamine eyedrops in dissolving corneal cystine crystals in 10 patients over a wide range of ages.

**METHODOLOGY AND DOCUMENTATION**

**Patients.** All patients were enrolled in protocols approved by the National Eye Institute and the National Institute of Child Health and Human Development to investigate topical and oral cysteamine therapy in nephropathic cystinosis. Written, informed consent was obtained from each patient or a parent. The diagnosis of cystinosis was based on a typical history combined with the finding of a leukocyte cystine level above 1 nmol half-cystine/mg protein for ocular cystinosis and above 3 nmol half-cystine/mg protein for nephropathic cystinosis (normal, <0.2 nmol half-cystine/mg protein). Measurements were performed using the cystine-binding protein assay (1,38). Only nephropathic or ocular (nonnephropathic) patients with slit-lamp photographs were included in this study. These numbered 177 (93 males, 84 females) admitted to the NIH Clinical Center between 1976 and 2000; 170 of these had nephropathic cystinosis.

**Cysteamine eyedrops.** Eyedrops containing cysteamine hydrochloride were administered under protocols approved by the institutional review board of the National Eye Institute, after an Investiga-
tional New Drug exemption was obtained from the Food and Drug Administration. For the first years of the study, beginning in 1986, patients received 0.11% cysteamine solution in normal saline (32). Since 1990, however, all patients have received 0.55% (50 mM) cysteamine in normal saline (33), and since 1993, 0.01% benzalkonium chloride has been present in the eyedrops as a preservative. The eyedrops were prepared steriley by the National Institutes of Health Pharmaceutical Development Service. An ophthalmic nurse taught the parents or the patients how to maintain sterility in administering the eyedrops, and fresh bottles were used every 5 days to reduce the risk of contamination. The patients were instructed to place one drop in each eye every hour while awake, and were given timers to remind them.

**Corneal crystal evaluation.** Slit-lamp biomicroscopy and photography were performed using a Zeiss photo-slit lamp (Carl Zeiss Co., Oberkochen, Germany) with stereoscopic accessories, beam splitters, two camera bodies, and side-arm adapters. The apparatus allowed direct focal illumination using a moderately wide slit beam (5 mm) and 25X magnification. In general, the aperture setting was f22 with a flash intensity of 2. Ektachrome EPD200 film (Eastman Kodak, Rochester, NY) was used.

The density of crystals in the central cornea was evaluated semiquantitatively by comparison with a library of slit-lamp photographs of corneas containing cystine crystals at different densities (Fig. 1). Scores ranged from 0 (clear) to 3.00 (packed with crystals), with increments of 0.25. For the purposes of this study, corneal slides were assigned a corneal cystine crystal score (CCCS) by the most experienced scorer (E.M.K.).

**Statistical analyses.** The best-fit lines of Figs. 4 and 6 were drawn using a weighted, locally quadratic regression line (39) to illustrate the relationship between CCCS and age, and Pearson's $\chi^2$ test was used to test for differences in CCCS by type of CTNS mutation. The Cox–Stuart nonparametric test (40) was used to determine the presence of a trend in the relationship between CCCS and age.

**NATURAL HISTORY OF CORNEAL CRYSTAL ACCUMULATION IN NEPHROPATHIC CYSTINOSIS**

The rate of accumulation of corneal cystine crystals was assessed by both cross-sectional and longitudinal analyses. In each case, comparison of a patient's corneal slit-lamp photograph with the library photographs (Fig. 1) allowed assignment of a CCCS. For the cross-sectional analysis, 170 different patients with nephropathic cystinosis each contributed one data point representing the patient's first available CCCS, always prior to cysteamine eyedrop treatment. These 170 individuals constituted the complete set of patients with nephropathic cystinosis seen at the National Institutes of Health Clinical Center between 1976 and 2000 for whom slit-lamp photographs were available and able to be scored. They were grouped by age in years, i.e., 0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–7, 7–8, 8–10, 10–12, 12–15, 15–18, 18–21, 21–25, and over 25 years, such that, for example, a patient exactly 1 year old would be in the age group 1–2 years. Each group contained between 5 and 21 patients. Corneal photographs showing minimum, median, and maximum crystal density for each age group are presented in Fig. 2, but the complete set of 170 photographs also helped to make several points. First, 2 of 9 infants in their first year of life had no visible corneal crystals, i.e., a CCCS of 0. (Since photographic scoring was performed on the central cornea, some peripheral crystals may have been present and visible on clinical examination.) The highest CCCS in the first year of life was only 0.25. Second, every patient had visible crystals after 16 months of age. Third, corneal crystals accumulated progressively in the first few years of life, but certain patients had more crystals at a young age than other patients had at an older age. For example, each of 3 children had a CCCS of 3.00 before 4 years, 6 months of age (the youngest being 4 years, 2 months), while another child had a CCCS of 1.50 at 6 years, 5 months of age. Finally, the median CCCS for the age group 10–12 years was 3.00, indicating that most corneas are packed with crystals by age 12. No patient over 15 years of age had a CCCS less than 2.50.

A longitudinal analysis of corneal crystal progression in nephropathic cystinosis was also performed. We investigated corneal crystal density in 9 patients who underwent repeated corneal slit-lamp photography over the course of more than 1 year without receiving topical cysteamine therapy. These patients were followed for 12 to 113 months (mean ± SE, 46 ± 12 months), and serial photographs of the corneas of three illustrative patients are shown in Fig. 3. One patient pro-
FIG. 1. Library of slit-lamp photographs showing examples of corneas with corneal cystine crystal scores (CCCSs) of 0 to 3.00, in increments of 0.25.
FIG. 2. Slit-lamp photographs of corneal crystals in patients with nephropathic cystinosis of different ages. Only the first photograph that could be scored was evaluated for each of 170 patients. For each age group, corneas with the minimum, median, and maximum CCCSs are shown. N gives the number of individuals in each age group. Note the increase in median CCCS with age in infancy and early childhood.
<table>
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<th>Median Age</th>
<th>Median CCCS</th>
<th>Maximum Age</th>
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<td>7 years; 1 months</td>
<td>2.75</td>
<td>7 years; 2 months</td>
<td>3.00</td>
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**FIG. 2—Continued**
Minimum

8 years; 10 months  CCCS = 2.00

Median

8 years; 5 months  CCCS = 2.75

Maximum

8 years; 1 month  CCCS = 3.00

8 - 10 years (n = 11)

11 years; 10 months  CCCS = 1.75

11 years; 5 months  CCCS = 3.00

11 years; 4 months  CCCS = 3.00

10 - 12 years (n = 9)

12 years; 3 months  CCCS = 2.00

12 years; 2 months  CCCS = 3.00

12 years; 2 months  CCCS = 3.00

12 - 15 years (n = 13)

15 years; 10 months  CCCS = 2.50

17 years; 4 months  CCCS = 3.00

15 years; 10 months  CCCS = 3.00

15 - 18 years (n = 14)

FIG. 2—Continued
progressed from a CCCS of 0.00 to a CCCS of 1.00 between 2 and 26 months of age (Fig. 3A). A second patient had a CCCS of 0.75 at 14 months of age and a CCCS of 1.75 by 54 months of age (Fig. 3B). A third patient experienced an increase in her CCCS from 0.50 at age 17 months to 2.25 at age 41 months (Fig. 3C). All three patients were receiving oral cysteamine therapy throughout this period of crystal progression, with mean leukocyte cystine depletion to 0.8, 1.0, and 2.6 nmol half-cystine/mg of protein, respectively. Three older individuals in the group of 9 longitudinally studied patients were 6, 14, and 23 years of age, and had CCCS values of 3.00 on their initial examinations (photographs not shown); they could provide no evidence of progression because no scores greater than 3.00 were
FIG. 3. Longitudinal analyses of corneal cystine crystal accumulation in three patients with nephropathic cystinosis. (A) Slit-lamp photographs of a 2-month-old boy, followed for 24 months, during which time his CCCS increased steadily from 0.00 to 1.00. (B) Corneal photograph of a 14-month-old girl showing gradual, persistent progression of CCCS from 0.75 to 1.75 at 54 months of age. (C) Slit-lamp photographs of a 17-month-old girl showing increasing CCCS from 0.50 to 2.25 at 41 months of age. Note 0.50-unit decrease in CCCS between 30 and 33 months of age, with continuation of crystal accumulation to a CCCS of 2.00 five months later. The score at 33 months could have been influenced by photographic parameters such as light bandwidth, light intensity, and focus.

measurable. The 9 patients followed longitudinally for more than 1 year had a total of 59 follow-up visits; on 55 of these repeat examinations, the CCCS either increased or remained the same compared with the previous visit. One patient had a CCCS that fell from 3.00 at 74 months to 2.00 at 83 months, but rose back to 3.00 at 95 months of age. Three other patients had CCCS decreases of 0.25, 0.50, and 0.50. No decrement in CCCS was sustained, meaning that every fall in CCCS was followed by a commensurate rise on a subsequent slit-lamp examination, performed within a year.

The data represented photographically in Figs. 2 and 3 were also expressed graphically. A plot of initial CCCS against age, with a single data point for each of our 170 nephropathic cystinosis patients, gives a nearly hyperbolic curve (Fig. 4A). In this cross-sectional analysis, CCCS increased lin-
FIG. 3—Continued
FIG. 3—Continued

early from 0.00 at birth to 2.5 at approximately 6 years of age, and leveled off at the maximum value of 3.00 shortly after that. By age 15, most patients had corneas packed with crystals, as indicated by a CCCS of 3.00. In Fig. 4B, CCCS values for the 9 patients followed longitudinally for 1 to 9 years are superimposed on the best-fit line derived from the cross-sectional data. The longitudinal data and the cross-sectional data are essentially coincident, suggesting that the cross-sectional data, which represent different individuals of different ages, accurately reflect the crystal accumulation that occurs with time in a single individual’s cornea.

INFLUENCE OF CTNS MUTATIONS ON CCCS

Approximately half of all nephropathic cystinosis patients are homozygous for a 57-kb deletion removing a large portion of the CTNS gene (2–5). Of the 170 nephropathic cystinosis patients in our study, 50 were homozygous for the 57-kb deletion, 43 had no deletion allele, and 77 were either heterozygous for the deletion or not yet analyzed. We compared the CCCSs of the 50 individuals homozygous for the 57-kb deletion (Fig. 4C) with the CCCSs of the 43 cystinosis patients not bearing the deletion in either allele (Fig. 4D). There was no difference between
FIG. 4. Plots of CCCS versus age for various groups of cystinosis patients. (A) Scatterplot showing the relationship between CCCS and age for all 170 patients with nephropathic cystinosis. Each point represents the CCCS of a single individual, based on that patient's first scorable corneal slit-lamp photograph, prior to cysteamine eyedrop therapy. Between birth and 6 years of age, the CCCS increased rapidly; a test for trend found a significant relationship ($P < 0.001$) between increasing CCCS and increasing age. (B) Longitudinal data from 9 patients with nephropathic cystinosis, followed for 1–9 years prior to the initiation of cysteamine eyedrop therapy, superimposed on the cross-sectional data of (A) (dashed line). (C) Scatterplot showing the relationship between CCCS and age for 50 patients with nephropathic cystinosis homozygous for the 57-kb deletion in CTNS. The line provides the best fit to the data. (D) Scatterplot showing the relationship between CCCS and age for 43 patients with nephropathic cystinosis not bearing the 57-kb deletion in either allele. The line was constructed using the same best-fit analysis as for (A) and (C). (E) Relationship between CCCS and age for 7 individuals with ocular or nonnephropathic cystinosis. A single point was used to represent the initial, pretreatment CCCS of 6 patients with ocular cystinosis. The natural history data for patients with nephropathic cystinosis are represented by the dashed line. For the seventh patient with ocular cystinosis, whose leukocyte cystine values were within the range for nephropathic cystinosis, serial values of CCCS are plotted (solid line). This patient’s CCCS approached that of typical patients with nephropathic cystinosis of the same age.
these two groups of patients in the modeled curve relating CCCS to age ($P > 0.5$).

We also investigated the CCCSs of 7 patients with ocular or nonnephropathic cystinosis. These individuals manifest corneal and bone marrow crystals and have photophobia as their only clinical symptom (1,9). Six of the seven patients with ocular cystinosis had leukocyte cystine levels of 1.3, 1.5, 1.7, 1.7, 2.5, and 3.7 nmol half-cystine/mg protein, which are typical values for ocular cystinosis (1). These 6 individuals had initial, pretreatment CCCSs that were approximately half those expected for patients with nephropathic cystinosis of the same age (Fig. 4E). The seventh patient with ocular cystinosis had leukocyte cystine values that varied between 4.6 and 18.6 (mean 10.7) nmol half-cystine/mg protein; he exhibited serial CCCSs that approached those of a typical patient with nephropathic cystinosis (Fig. 4E).
EFFECTS OF TOPICAL CYSTEAMINE THERAPY AT DIFFERENT AGES

Since 1986, 113 NIH patients have received cysteamine eyedrops in at least one eye, with different levels of compliance, for at least 1 year. Of these, 98 began with a CCCS of 1.00 or more and 37 have exhibited a CCCS reduction of at least 1.0 unit with the eyedrop treatment. As examples of therapeutic efficacy, pretreatment and posttreatment slit-lamp photographs of 10 patients who began cysteamine eyedrop therapy at different ages are shown in Fig. 5. Patients from age 1 year, with a CCCS of 0.25, to age 32 years, with a CCCS of 3.00, all showed a reduction in their CCCSs after 8 to 41 months of cysteamine eyedrop treatment. In each of these 10 cases, the final CCCS was either 0 or 0.25, and the reduction in CCCS was sustained for each patient, with follow-up for more than 1 year in every case (data not shown). These 10 patients used the eyedrops, on average, approximately 10 times per day (range, 6–12) during the treatment period represented by the photographs.

The effect of cysteamine eyedrop treatment on CCCS is shown graphically in Fig. 6. The natural history of corneal crystal accumulation indicates no reduction in CCCS with age, but these 10 patients, who adhered to cysteamine eyedrop therapy, experienced a drastic reduction in their CCCSs, regardless of age of initiation of treatment.

THE EYE IS THE WINDOW TO CYSTINOSIS

Clinicians claim that the eye is window to the brain, in part because the retina represents the central nervous system. For cystinosis, however, the eye is window to the entire disorder, at once reflecting severity and revealing physiology through its glassy pane, the cornea.

The physiology flows from the basic defect, i.e., defective transport of the disulfide amino acid cystine across the lysosomal membrane. This discovery, which was made in 1982 (41–43) and which led to the elucidation of a panoply of other lysosomal membrane transporters (44), predicted the existence of an integral lysosomal membrane carrier protein for cystine. That protein acquired the name cystinosin only after its coding gene, CTNS, was isolated and sequenced in 1998 (2). Identification of the cystinosis gene was preceded by laborious linkage and physical mapping studies (45–47).

The discovery of CTNS permitted mutation analysis of nephropathic cystinosis patients, but also allowed confirmation of previous findings (48), indicating that milder variants of the disease were allelic to the classic, nephropathic form. In particular,
FIG. 5. Slit-lamp photographs of patients with nephropathic cystinosis before and after cysteamine eyedrop therapy. Each pair of photographs indicates the change in corneal crystal density for 1 of 10 individuals age 1 to 32 years. Note that regardless of the pretreatment CCCS (0.25–3.00), the posttreatment CCCS was 0.0 or 0.25. The duration of therapy varied from 8 to 41 months, and the drop in CCCS was sustained.
Pre· Treatment

11 years; 1 month
CCC = 3.00

19 years; 9 months
CCC = 3.00

21 years; 10 months
CCC = 3.00

25 years; 4 months
CCC = 3.00

Post· Treatment

13 years; 1 month
CCC = 0.00

20 years; 9 months
CCC = 0.25

25 years; 3 months
CCC = 0.25

26 years; 4 months
CCC = 0.25

FIG. 5—Continued
intermediate cystinosis, in which the onset of renal failure is delayed to the second or third decade (1), results from a combination of different CTNS mutations, one severe and one moderate (21). In ocular or nonnephropathic cystinosis, one allele again carries a severe CTNS mutation, while the other allele has a much milder alteration, commonly an A→G in position 928 (22). The milder mutations in CTNS apparently allow for some residual function of cystinosis; transport studies performed in polymorphonuclear leukocyte granular fractions have demonstrated residual cystine carrying capacities of 9 and 29% for a patient with ocular cystinosis (49).

For ocular cystinosis, the molecular and biochemical findings supported each other. However, the effects of a molecular/biochemical defect on parenchymal tissues and their functions are not always apparent. For example, the renal deterioration in cystinosis almost certainly begins prior to or shortly after birth, since kidney tubules have been shown to be significantly damaged by 6 months of age (50). Yet kidney damage is virtually never seen in the first months of life because biopsies are not performed to demonstrate cystine crystals, and renal parameters appear normal because of the enormous functional reserve of the kidney. Similar situations, in which the clinical manifestations of a molecular defect are clouded, occur in other organs and tissues, notably the thyroid and muscle.

In stark contrast, the eye provides a clear window to the working of the CTNS gene, because the cellular concomitant of a molecular mutation, i.e., crystal accumulation, appears within the corneal stroma on direct visualization. Thus, the CCCS in cystinosis reflects a phenomenon common to most lysosomal storage disorders, i.e., normalcy at birth and gradual progression as the stored material accumulates (Fig. 4A). In fact, longitudinal data, which illustrate the inexorable progression of corneal crystal formation within individuals, support the larger cross-sectional study showing an increase in CCCS with age (Fig. 4B). The increase, which is roughly linear up to approximately age 6, levels off at age 12 with a median CCCS of 3.00. This plateau in CCCS probably occurs because of our inability to distinguish grades of crystal density once the cornea becomes truly packed with crystals. Even into adulthood, the crystals may continue to accumulate, since a haze
CORNEAL CYSTINE CRYSTALS

covering patients' corneas often appears only after adolescence.

The rate of corneal crystal accumulation in cystinosis also reflects the severity of the CTNS mutation. When CCCS is plotted versus age, patients homozygous for the 57-kb deletion (7,8), who as a group have a clinical severity score typical for classic nephropathic cystinosis (3), are indistinguishable from other typical patients not bearing the deletion (Figs. 4C and 4D). In contrast, 6 patients with ocular or nonnephropathic cystinosis, who as a group have no renal disease whatsoever and exhibit leukocyte cystine values approximately 10–50% of those of patients with nephropathic cystinosis (1), have CCCSs half those of patients with nephropathic cystinosis of the same age (Fig. 4E). In these patients with ocular cystinosis, residual cystinosin activity in every cell type may preclude clinical symptoms in all tissues except the cornea, because crystal accumulation does not exceed a critical threshold in the other tissues. The single patient with ocular cystinosis with nephropathic levels of leukocyte cystine, despite entirely normal renal glomerular and tubular function, had CCCSs within the nephropathic range. In this case, the critical threshold for clinical manifestations should be exceeded throughout the body, unless one tissue such as the kidney produces more cystinosin that other tissues such as the cornea. This concept of differential tissue expression provides an alternate hypothesis to explain the phenomenon of ocular, nonnephropathic cystinosis (22).

Whatever the cause or extent of corneal cystine crystal formation, this complication of cystinosis has significant clinical consequences. Photophobia is nearly universal after the first decade of life and, in our experience, corresponds roughly to the time at which a CCCS of 2.50 is achieved, i.e., late childhood (Fig. 4A). Many patients require dark glasses to go outdoors (1,9), and some older patients have intractable blepharospasm from years of squinting. Occasional patients suffer from painful, recurrent corneal erosions (20), which required a penetrating keratoplasty in one unusual case (51). Superficial, filamentous, and band keratopathies have also been observed in patients with nephropathic cystinosis.

It was once hoped that chronic oral cysteamine therapy would prevent these ophthalmic complications of cystinosis. However, several anecdotal reports (26,30,31), including one involving a large number of patients (26), have concluded that oral cysteamine does not improve the photophobia or reduce the corneal crystal density of patients with cystinosis. Furthermore, serial slit-lamp photo-

FIG. 6. Effects of cysteamine eyedrop therapy on CCCS. For each of 10 patients with nephropathic cystinosis, the CCCS before treatment (open circles) and after treatment (open triangles) with 0.55% cysteamine eyedrops is shown superimposed on a plot of the natural history of corneal crystal accumulation in nephropathic cystinosis (dashed line). Regardless of age (1–32 years) and initial CCCS (0.25–3.00), cysteamine eyedrop treatment for 8 to 41 months lowered the CCCS to 0 or 0.25 unit.
graphs of the cornea have documented a steadily increasing CCCS with age in 3 patients, 2 of whom were receiving excellent leukocyte cystine depletion with oral cysteamine throughout the period of investigation (Figs. 3A and 3B). It is believed that the absence of a vascular supply to the cornea mitigates against cystine depletion by orally administered cysteamine in this tissue.

In contrast, direct placement of a cysteamine solution on the cornea can dissolve cystine crystals in less than a year. This was demonstrated to occur for cystinosis patients of all ages (Figs. 5, 6), as evidenced by reductions in the CCCS to 0 or 0.25 that were sustained for at least 1 year. We note that longitudinally studied patients not receiving cysteamine eyedrops exhibited spontaneous reductions at 4 of 59 (7%) of their follow-up examinations. However, these reductions were minimal (0.25–0.50) in 3 of 4 cases, and were not sustained in any case. The documented increases in CCCS on subsequent examinations suggest that a small amount of play exists in our photograph-based scoring system, and that repeat evaluations are helpful.

Nevertheless, the findings of this study indicate that corneal crystal accumulation is reversible by cysteamine eyedrop therapy at any age, unless a band keratopathy has formed. Hence, use of the eyedrops may not be absolutely required in patients who are spared photophobia or corneal erosions. Administration of the eyedrops, which we recommend be performed every hour while awake, constitutes a significant burden for many patients. In fact, we attribute to noncompliance the failure to observe at least a 1.00-unit CCCS reduction in 62% of treated individuals. Patients who responded to cysteamine eyedrop therapy, such as the 10 represented in Figs. 5 and 6, typically take the drops 8–12 times per day. How many drops per day are required to reduce the CCCS has not been rigorously determined, and may vary from patient to patient, but the photographic library (Fig. 1) and the natural history data (Fig. 4A) offer a foundation on which to base future studies. We also expect that future investigations of eyedrop-treated patients will reveal whether this therapy, in addition to dissolving cystine crystals, can completely prevent related ophthalmic complications such as corneal ulcerations and band keratopathies.

For patients with cystinosis, cysteamine eyedrop therapy can change a life of photophobia, squinting, and restricted activity into one of comfort and freedom. The haze that clouds the lives of cystinosis patients is lifted, and with the cornea clearing, neither patients nor students of cystinosis are any longer required to look through the glass darkly.

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