Cystinosis is a rare autosomal recessive metabolic disorder characterized by cellular accumulation of cystine crystals in many organs and tissues. Ocular complications of this disorder include photophobia (light sensitivity) as well as corneal erosions and later a form of corneal degeneration called band keratopathy with visual loss; all caused by increasing cystine crystal accumulation within the cornea. Crystal accumulation is also noted in other anterior ocular tissues including the conjunctiva, iris, ciliary body, as well as important posterior ocular structures such as the retina and optic nerve. These crystals begin to accumulate in the first months of life and their presence is helpful diagnostically during evaluation of infants for poor growth, or kidney problems. Figure 1 illustrates the ground-glass hazy appearance of the cornea in a three year old child with cystinosis who already has marked light sensitivity as well as intermittent pain and foreign body sensation, and decreased corneal sensitivity.

Crystal accumulation also occurs in the optic nerve and is associated with optic nerve edema (swelling) and increased pressure within the brain known as pseudotumor cerebri. Crystal accumulation in the retina results in retinal pigmentary retinopathy which begins with patchy peripheral depigmentation but later causes changes in the central vision area (macula) which can result in visual loss later in life.

The development of oral cysteamine therapy as well as successful kidney transplantation has significantly changed the natural history of this disease. However, with increased longevity, ocular symptoms and complications have become more clinically significant, especially in
patients who do not take their recommended oral cysteamine treatment regularly and from an early age. Large clinical studies by William Gahl, MD and others at the National Institutes of Health (NIH) have clearly demonstrated improvement in posterior ocular signs and symptoms such as retinopathy in patients who fully comply with oral cysteamine therapy. But oral cysteamine does not reach the cornea well and so does not eliminate the corneal cystine crystals or the resulting severe light sensitivity and corneal irritation.

To treat the corneal problem, the NIH developed a formula for topical cysteamine eye drops that were shown to be safe and effective in several clinical trials. The NIH protocol eye drops clearly dissolve the corneal crystals in young and older patients to reduce or eliminate the photophobia, blepharospasm (frequent blinking), and eye pain caused by cystine crystal corneal irritation. Figure 2 shows the marked corneal crystal reduction and clearing in young and older patients treated with the drop. But, unfortunately, although the NIH drug protocol works well, lifelong continued compliance is difficult requiring frequent, 10-12 x/day, dosing with drops that are unstable at room temperature, requiring them to be shipped and stored frozen. By supporting a large clinical trial in which I was involved, Sigma-Tau Pharmaceuticals attempted to develop an improved eye drop formulation that would have been more stable and easier to use. But the new formula proved to be less effective than the original NIH protocol. Fortunately, however, Sigma-Tau has made the investment to bring the original NIH drops to market in the United States and just recently obtained scientific approval from the U.S. Food and Drug Administration, now only awaiting approval of a manufacturing plant to produce the drug for distribution. We are all looking forward to this exciting development that will improve local access to this eye drop treatment for cystinosis patients.
Finally, at the recent 6th International Cystinosis Congress meeting in Lignano Sabbiadoro, Italy, we heard from many outstanding international cystinosis researchers and clinicians about the exciting future with possible new treatments for the eye complications of cystinosis. They presented new research to develop therapies and drug delivery systems that could improve and simplify treatment of the debilitating ocular complications of cystinosis. Studies were presented for discussion on techniques to improve ocular treatment using gel delivery systems, delivery of the medication in the form of a stable “pro-drug” which can be stored easily and would require less frequent dosing, that would then be activated within the ocular tissue. Evidence was also presented on gene therapy or stem cell replacement therapies that may potentially even further revolutionize the way cystinosis eye problems are treated in the future. I am encouraged that this continued research will result in new therapies which are more stable, easier to use and more long lasting.