

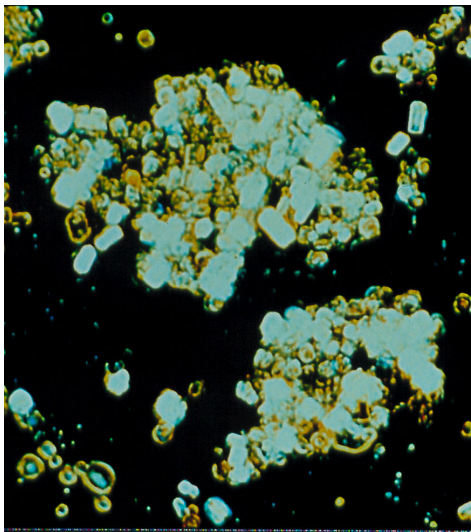
Cysteamine Eyedrops for Cystinosis

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NIH, DHHS**



CYSTINOSIS

- **AR; 1 in 200,000 births**
- **Storage of cystine in cells because of genetic defect in transport of cystine out of lysosomes.**
- **Crystals form in cells and destroy tissues.**



CYSTINOSIS NATURAL HISTORY

Age

Clinical Manifestation

Birth

None

Infancy

Renal tubular Fanconi syndrome

Growth retardation

Early childhood

Photophobia

Late childhood

Renal failure

Adolescence and
adulthood

Cerebral calcifications, diabetes

mellitus, retinal blindness,

myopathy, swallowing difficulty

Treatment of Cystinosis



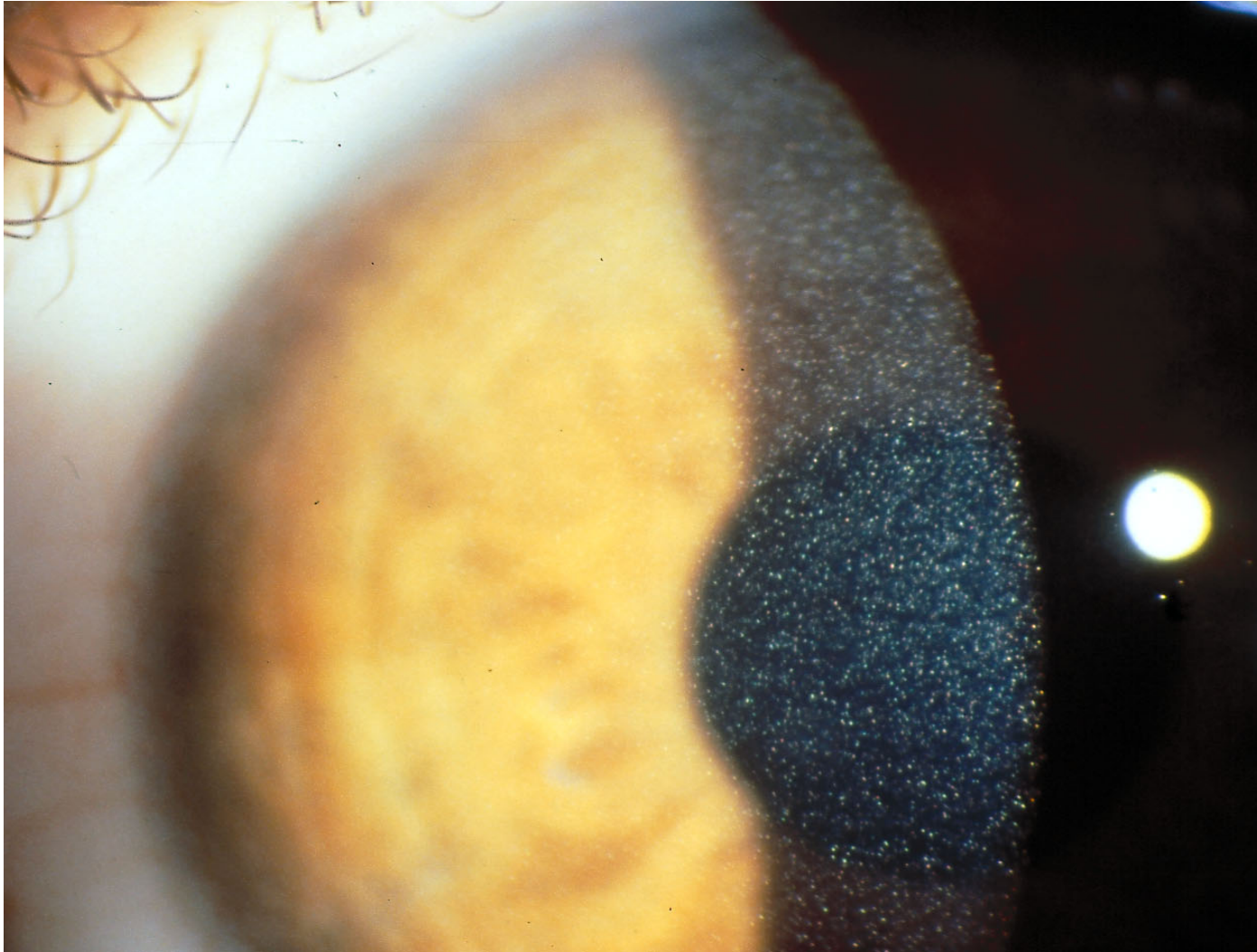
CYSTEAMINE

Chemically reacts with cystine to form products that can exit the lysosome and the cell.

Effects of Oral Cysteamine

- **Lowers cystine content of cells and tissues by 90%.**
- **Retards renal deterioration.**
- **Enhances growth.**
- **Prevents late complications of cystinosis.**

Oral cysteamine does not dissolve corneal cystine crystals.



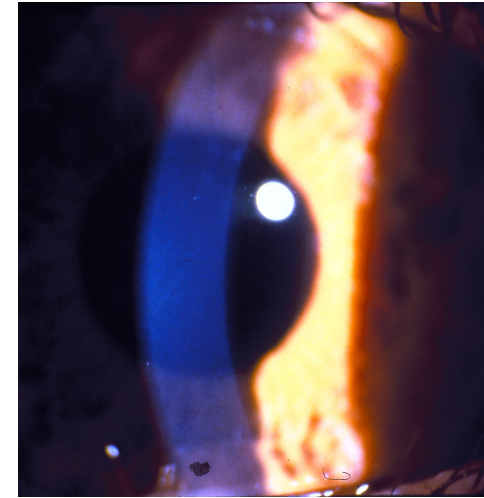
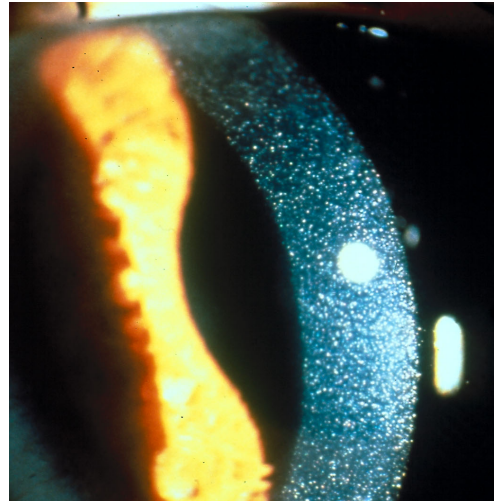


Cysteamine eyedrops do dissolve corneal crystals.

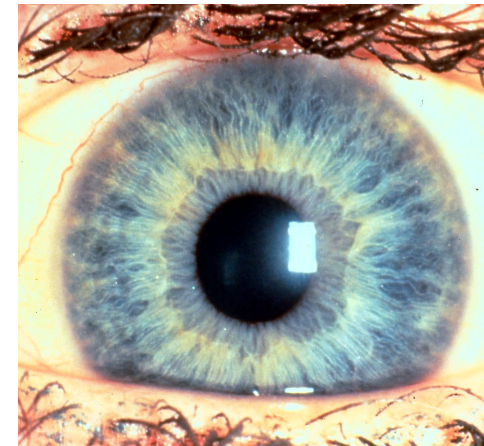
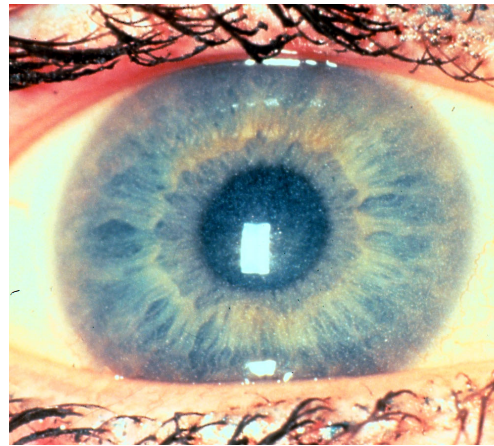
Untreated

Treated

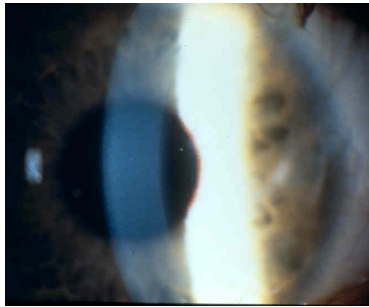
3-year old



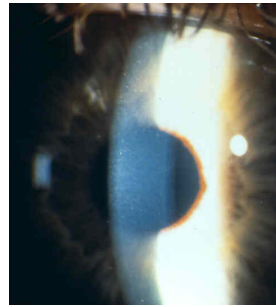
20-year old



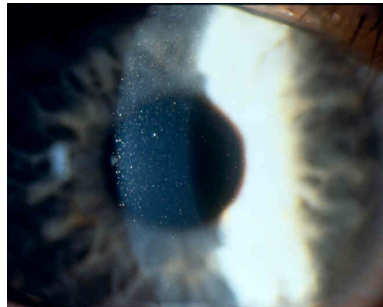
Library of Corneal Crystal Densities



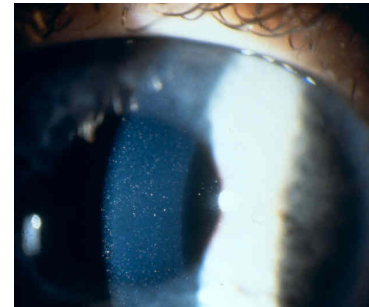
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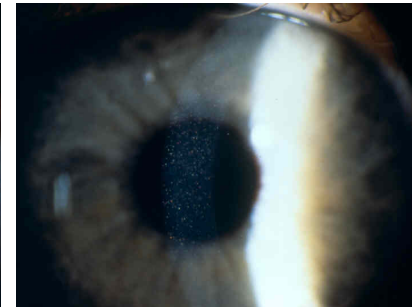
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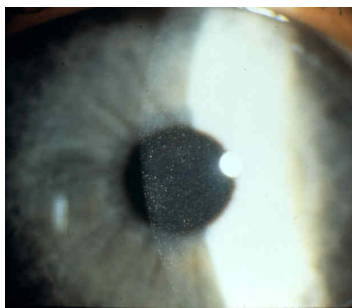
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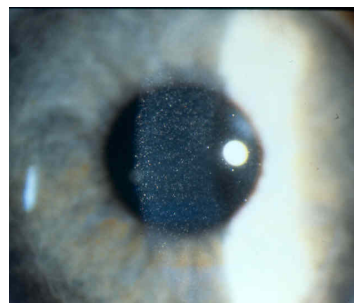
0.75



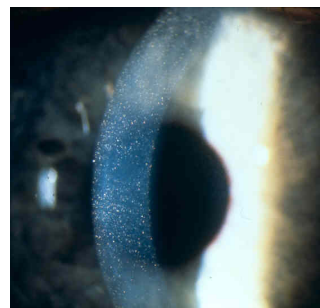
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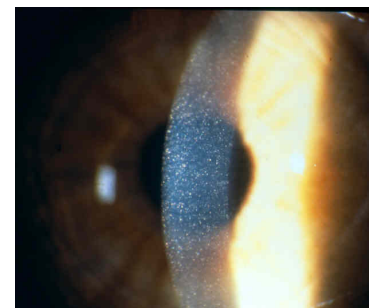
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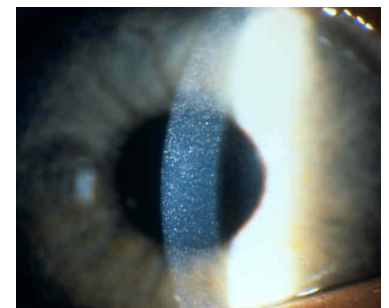
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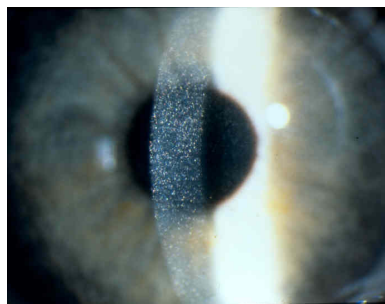
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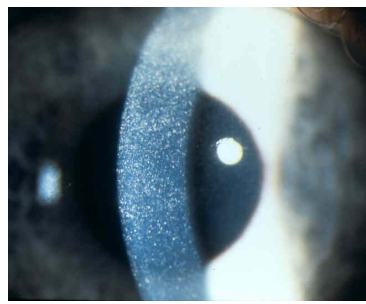
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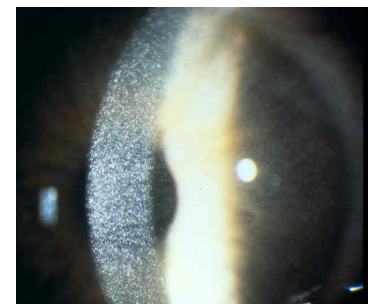
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2.50

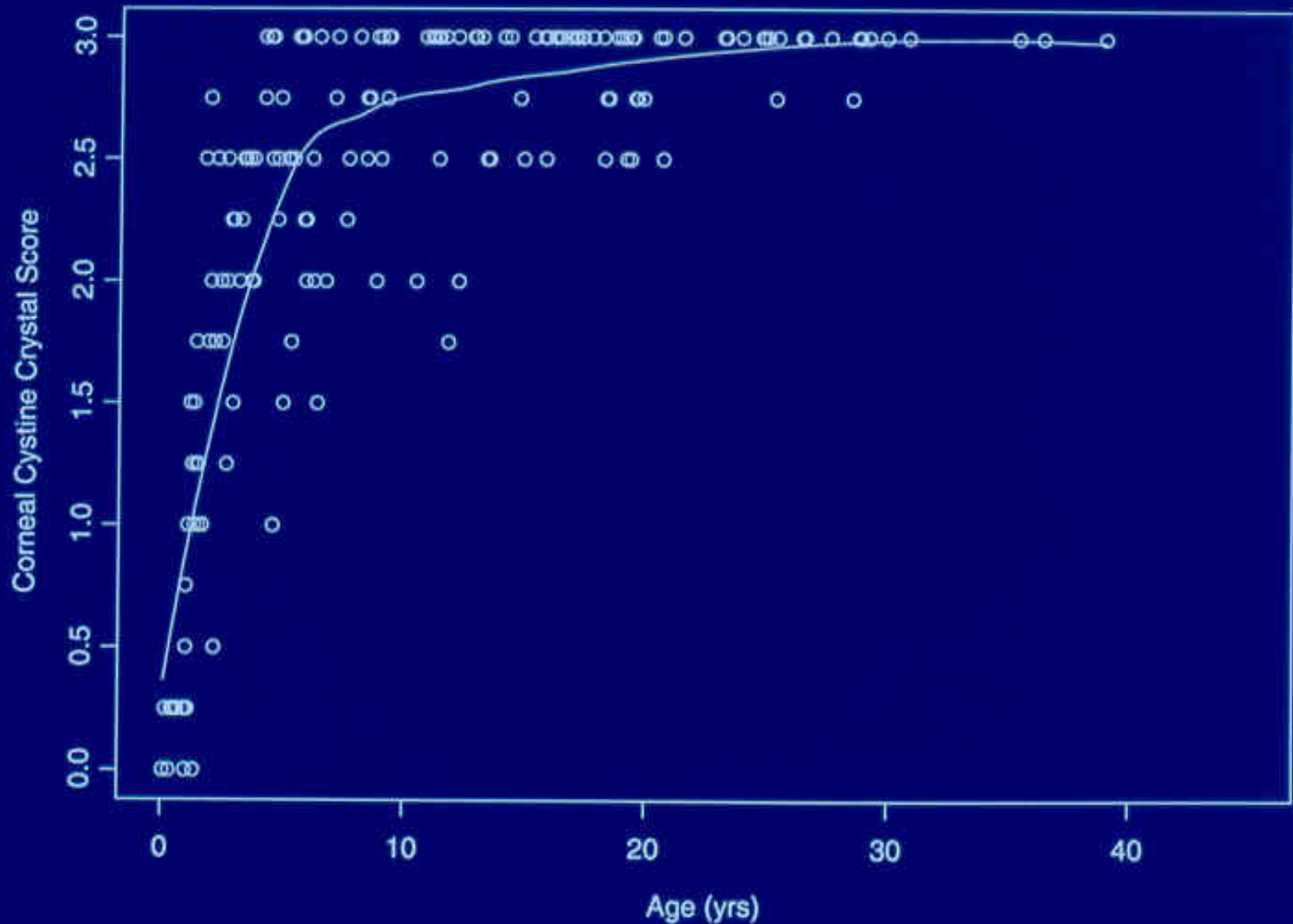


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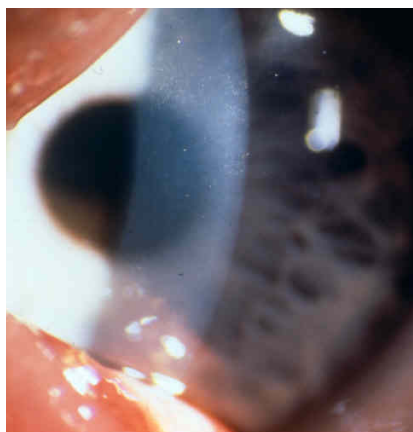
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Corneal Crystal Accumulation



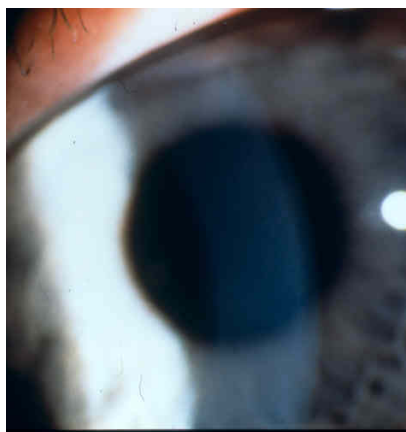
Cysteamine Eyedrop Therapy

12 mo



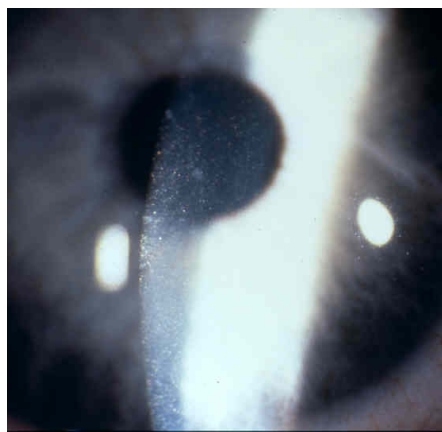
0.25

20 mo



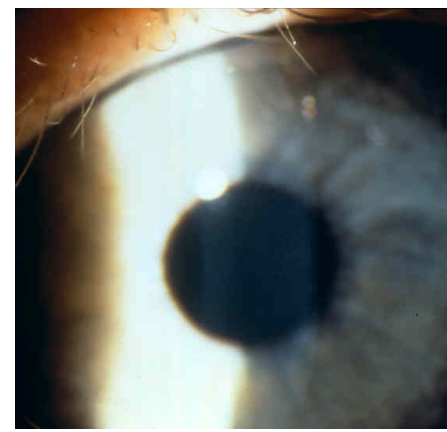
0.00

32 mo



2.00

57 mo



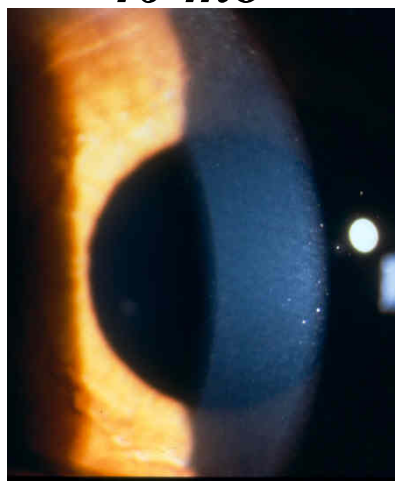
0.00

15 mo



1.00

40 mo



0.00

43 mo



0.50

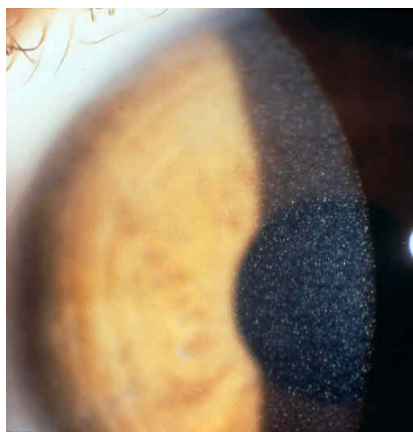
56 mo



0.00

Cysteamine Eyedrop Therapy

69 mo



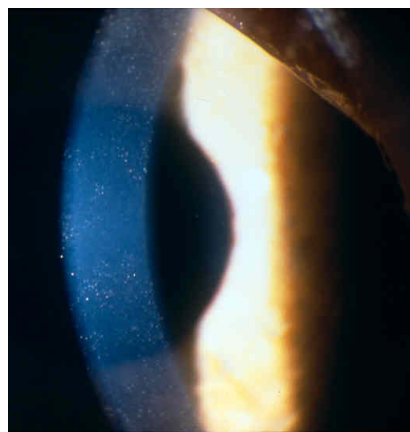
3.00

85 mo



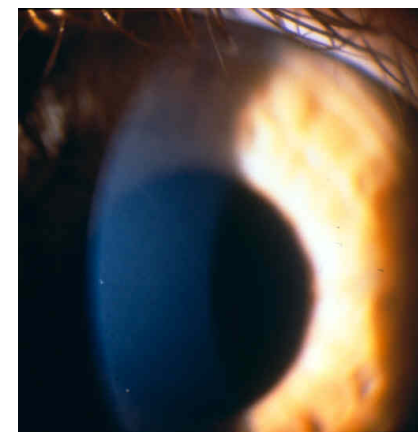
0.00

133 mo



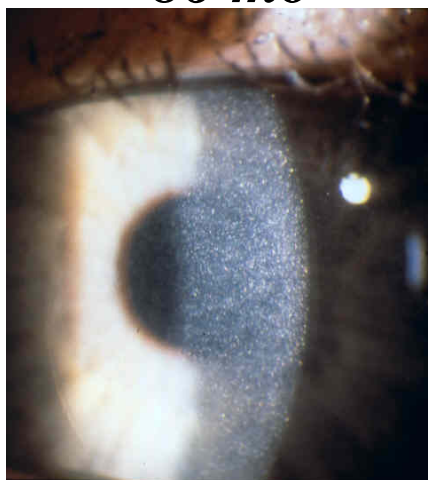
3.00

157 mo



0.00

86 mo



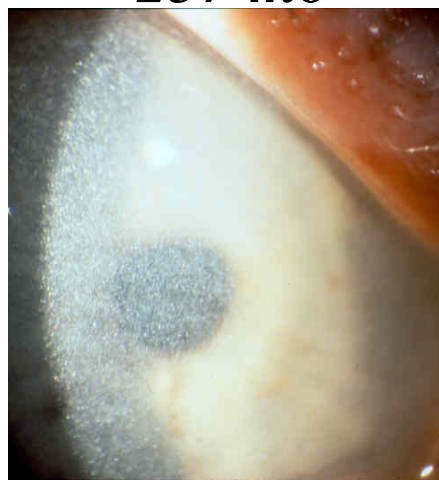
3.00

109 mo



0.00

237 mo



3.00

249 mo



0.25

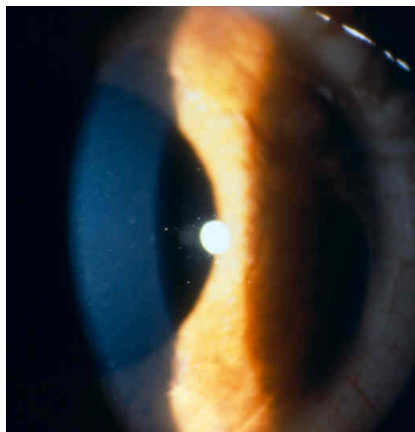
Cysteamine Eyedrop Therapy

262 mo



3.00

303 mo



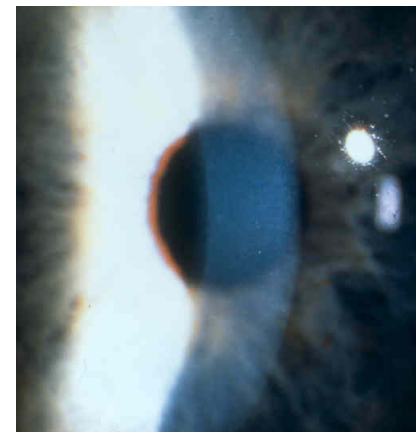
0.25

342 mo



2.50

354 mo



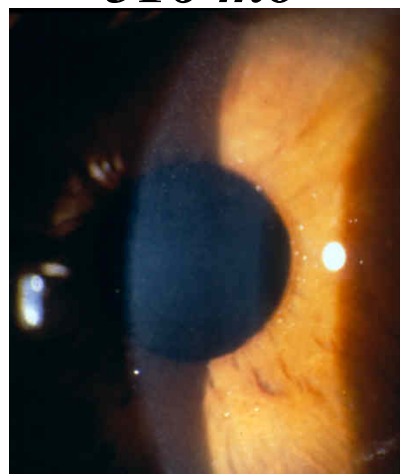
0.25

304 mo



3.00

316 mo



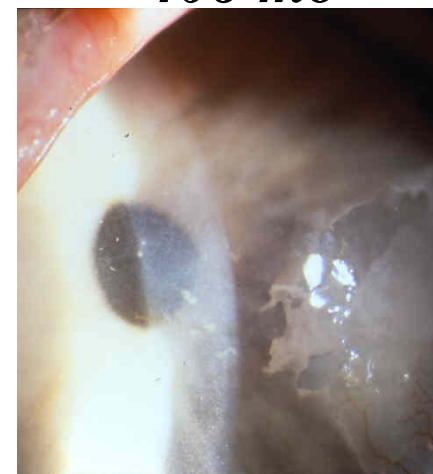
0.25

394 mo



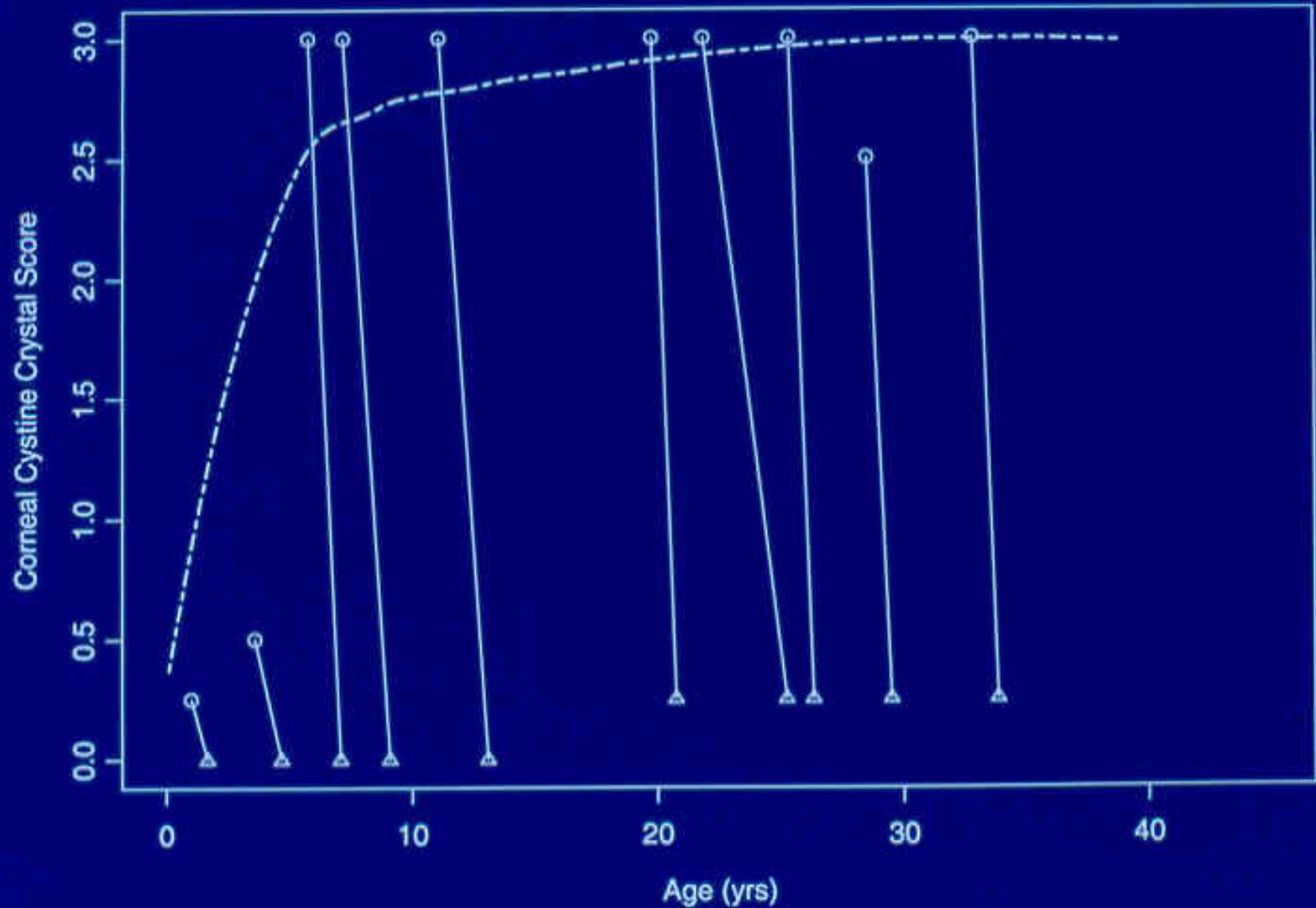
3.00

406 mo



0.25

Cysteamine Eyedrop Therapy



Cysteamine Eyedrops: Timeline

1986: NEI/NICHD show safety and efficacy of cysteamine eyedrops in two children (NEJM).

1986-present: NIH physicians provide eyedrops to cystinosis patients under protocol and IND.

1995-present: Sigma-Tau Pharmaceuticals sponsors drug development.

- Provides human-use drug to NIH for patients.
- Prepares NIH clinical data for FDA.
- Large investment in personnel and money.

2000: NIH publishes natural history of eye crystals.

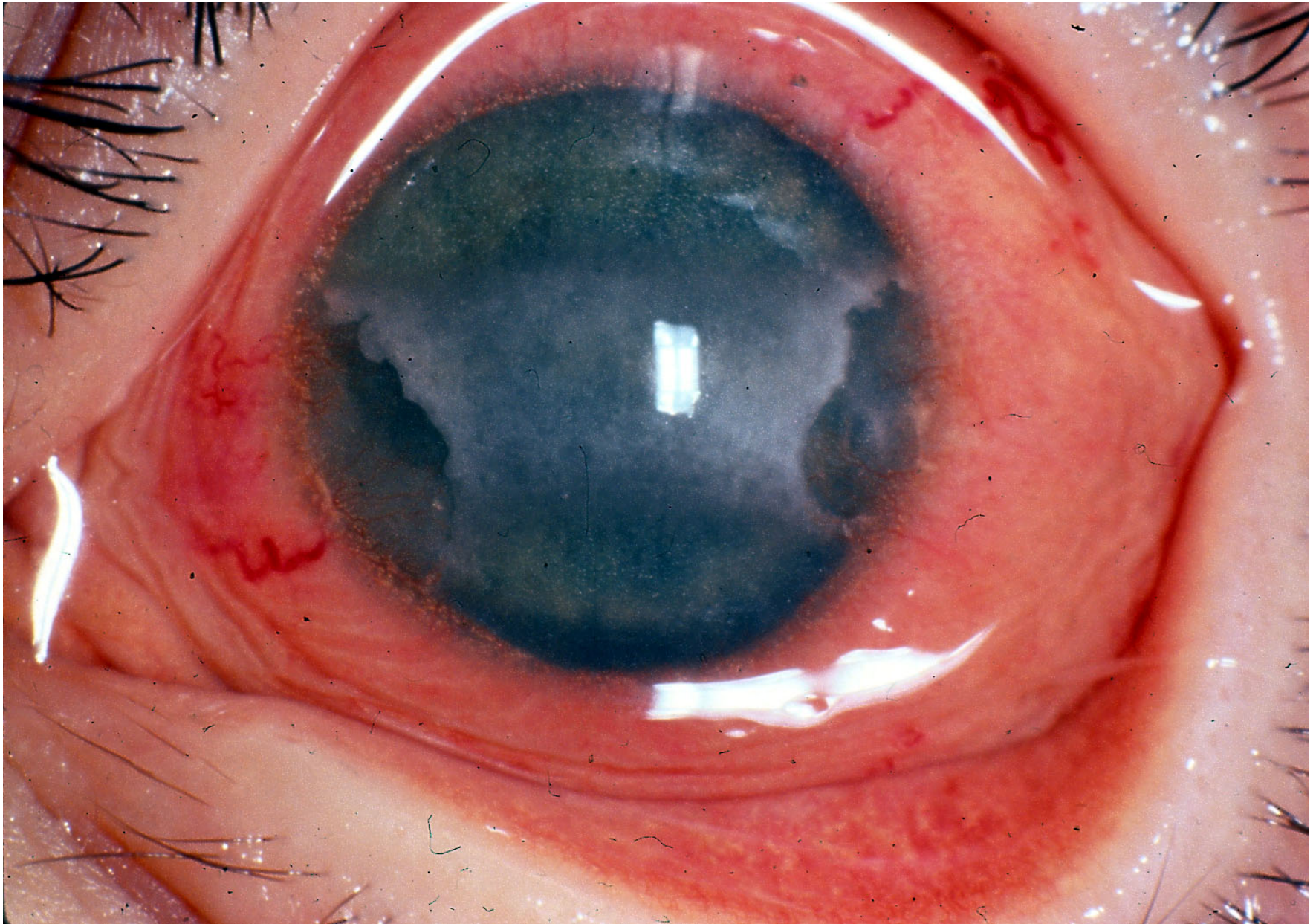
**2010: Sigma-Tau submits IND; FDA fast-tracks it.
NIH records now being inspected.**

Lessons

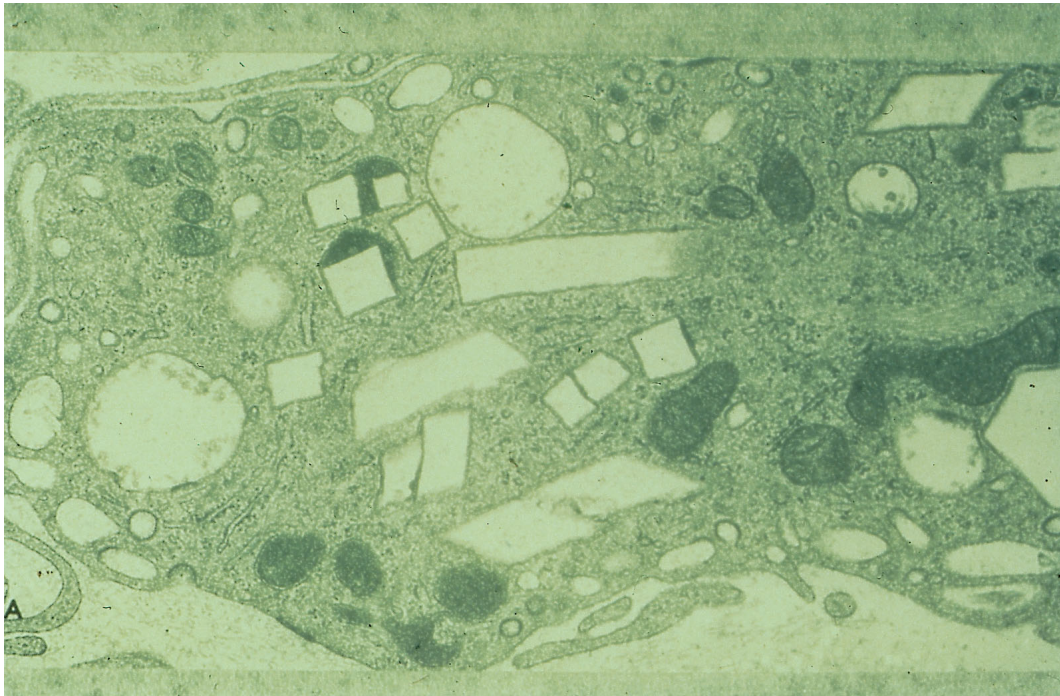
- **Clinical research is a partnership of investigators, patients, and pharmaceutical companies.**
- **The FDA cannot approve a drug unless a New Drug Application is filed.**
- **Knowing the natural history of a disease is an integral part of obtaining approval for a drug.**
- **There do exist pharmaceutical companies that address the niche market of rare or orphan diseases.**

Cysteamine Eyedrops

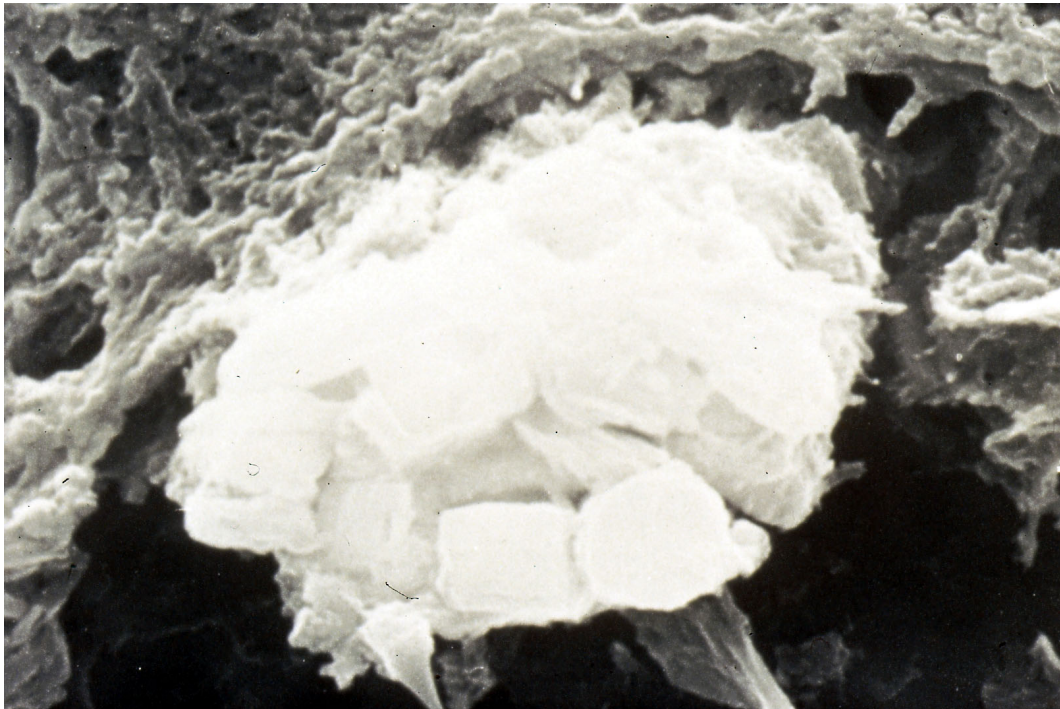
- **Dissolve corneal crystals if begun at any age.**
- **Cannot treat the band keratopathy once it occurs.**
- **Relieves the photophobia of cystinosis.**
- **Moving to New Drug Approval.**



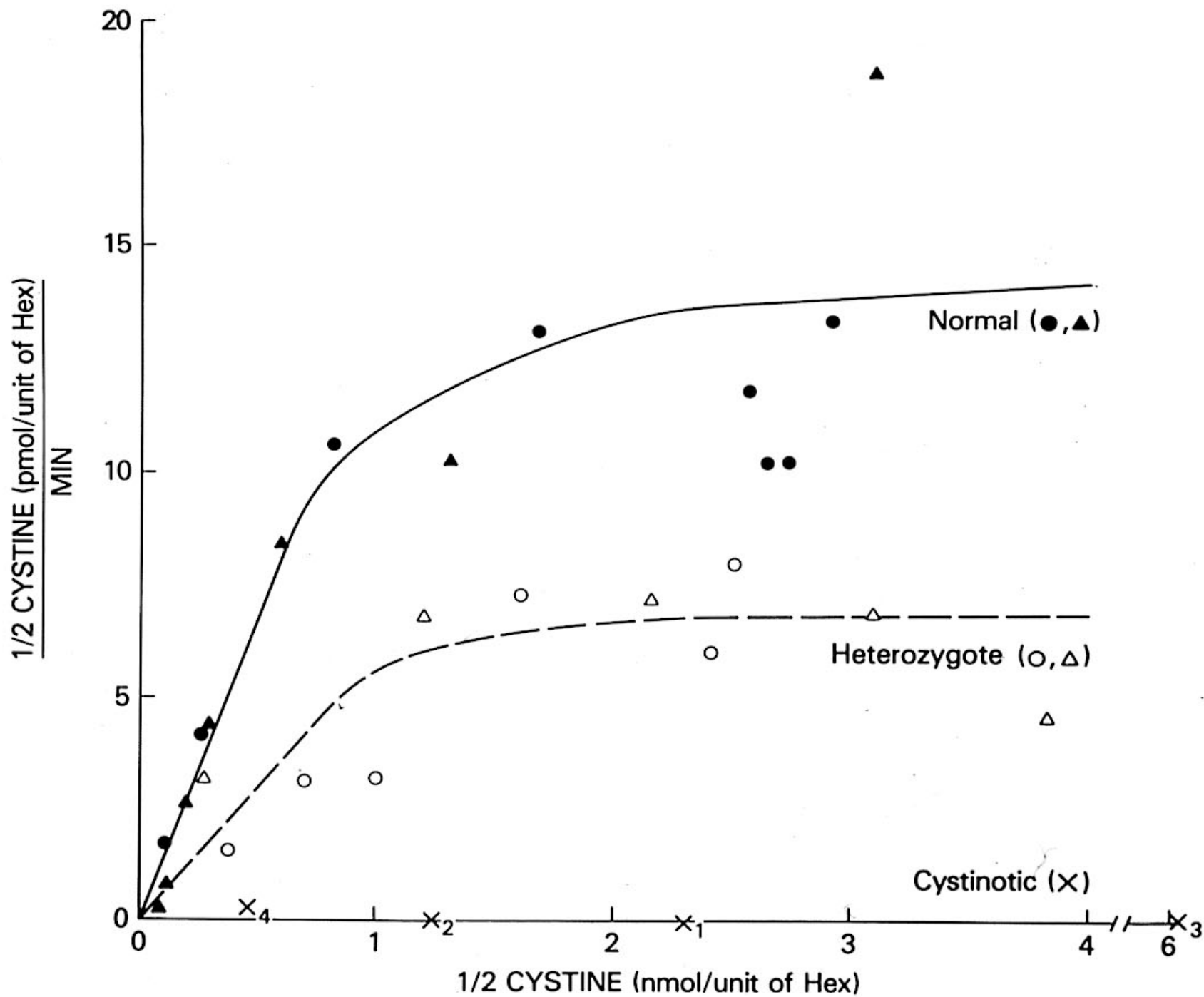
**Band keratopathy in
a 14-year old girl**

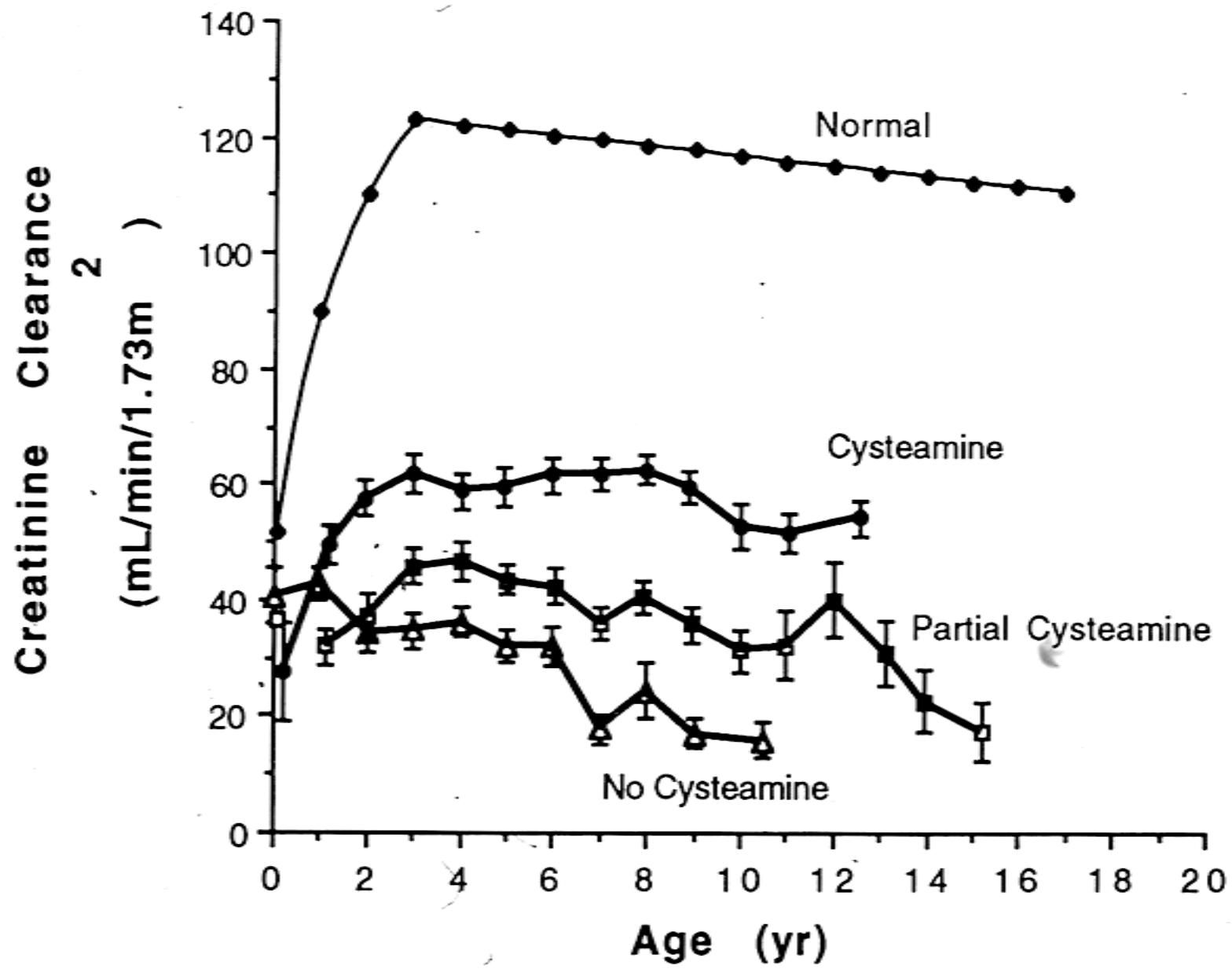


**Transmission EM
of conjunctival cell**
(Dr. T. Kuwabara)

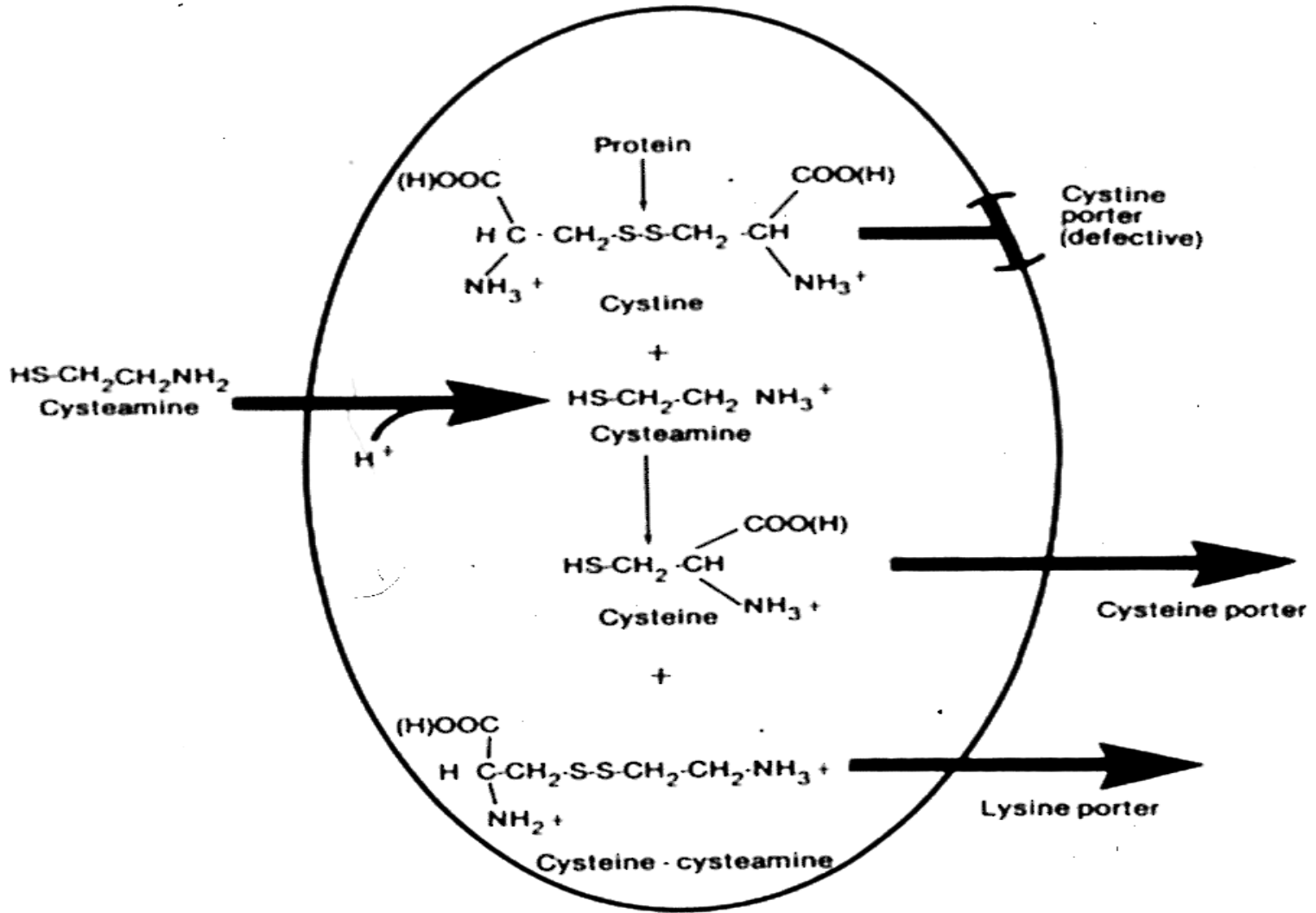


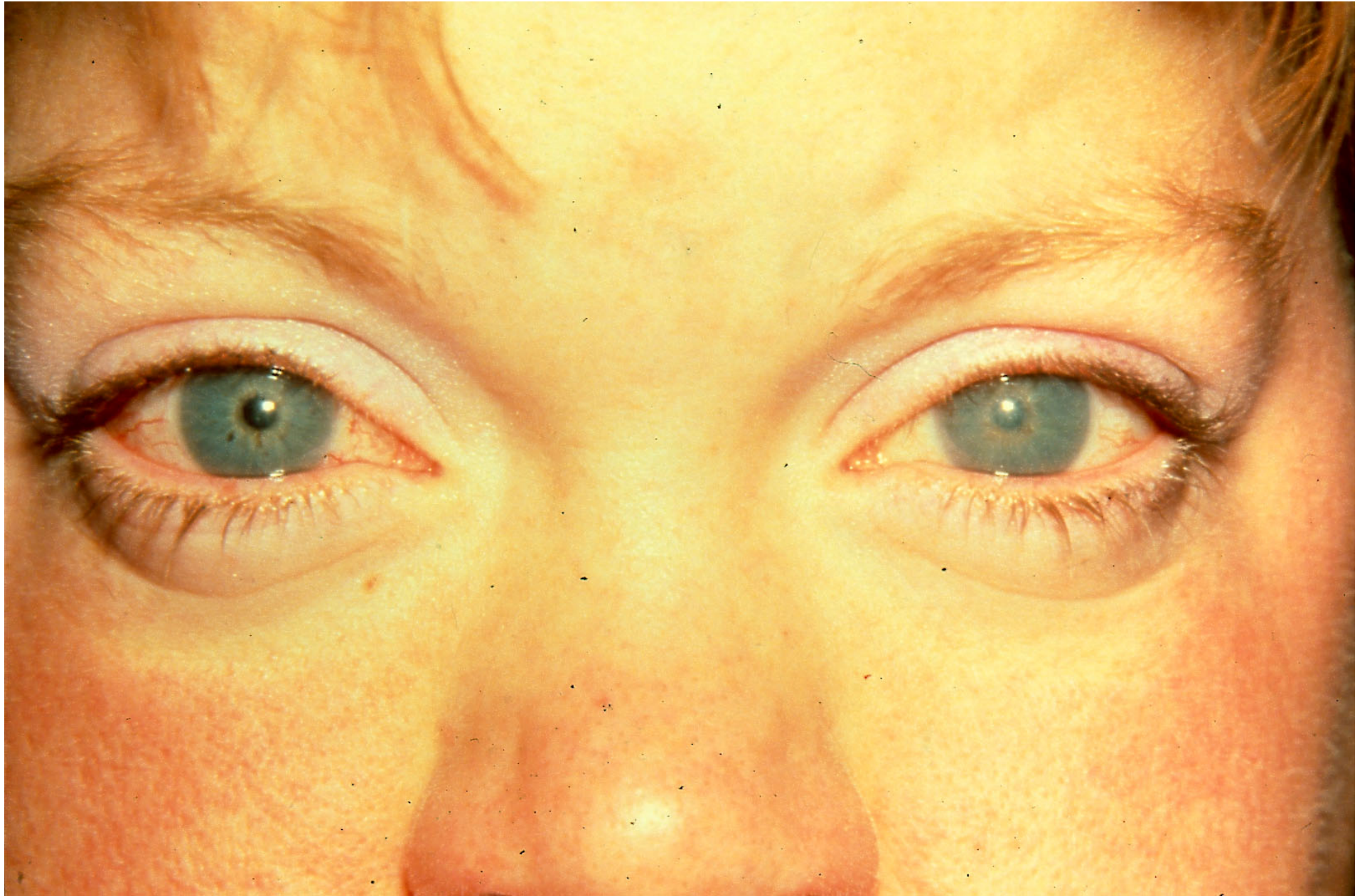
**Scanning EM of
liver Kupfer cell**
(Dr. Kamal Ishak)





Cystinotic Lysosome







Approved August 15, 1994