Therapies for Two Rare Diseases

ICORD

Stockholm, Sweden

February 15, 2005

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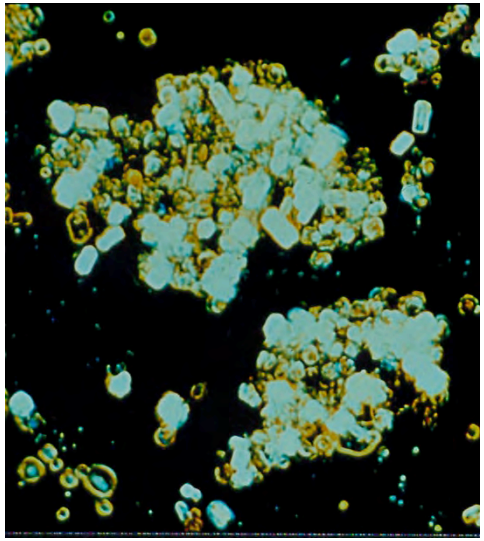
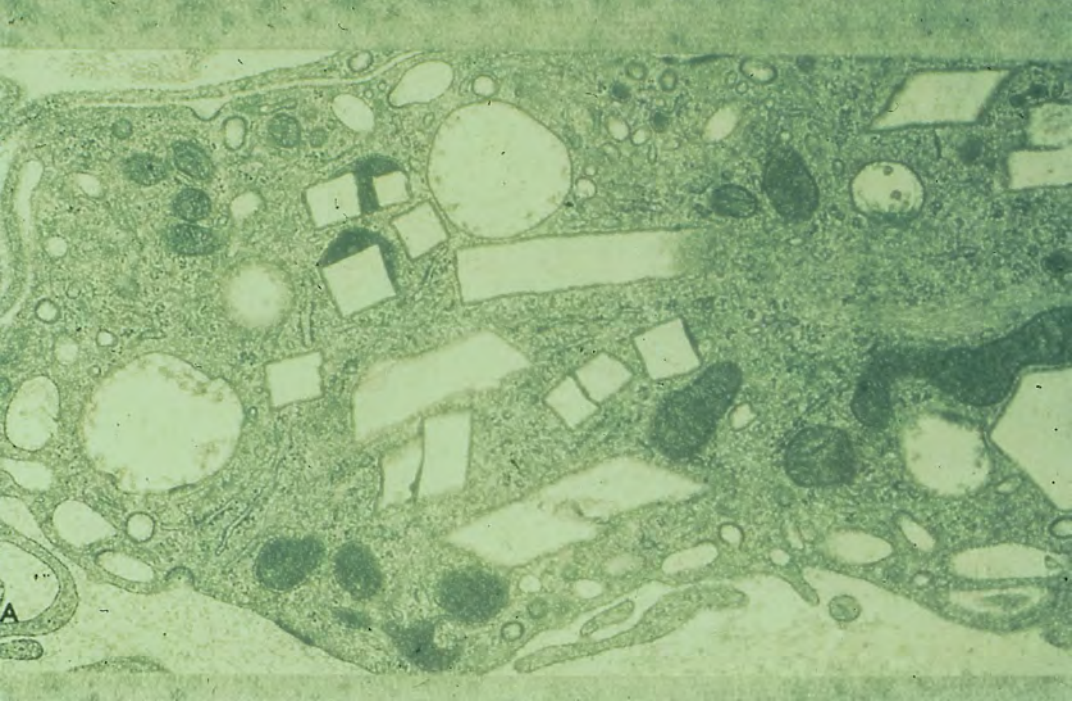
Therapies for Two Rare Diseases

- Cystinosis - Cysteamine
- Alkaptonuria - Nitisinone
- Generalizations - Disease to Therapy



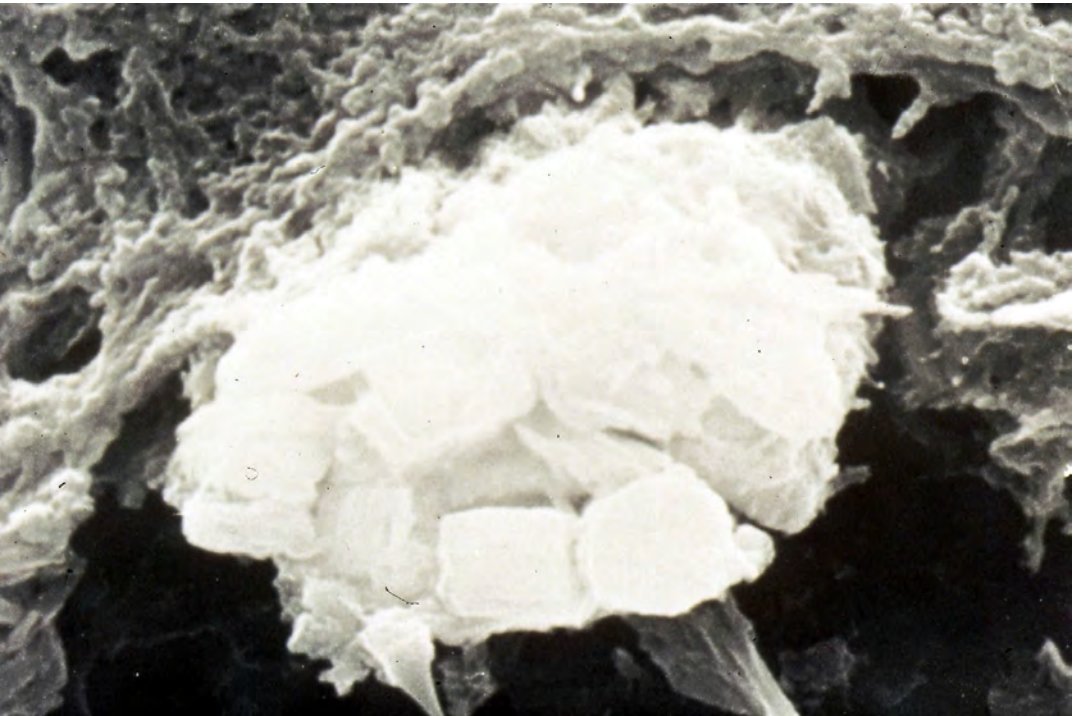
CYSTINOSIS

- Autosomal recessive
- 1/200,000 births
- Lysosomal storage disease due to impaired transport of cystine out of lysosomes.
  - High intracellular cystine content
  - Crystals in many tissues



Transmission EM of conjunctival cell

(Dr. T. Kuwabara)



Scanning EM of liver Kupfer cell

(Dr. Kamal Ishak)

CYSTINOSIS NATURAL HISTORY

Age	Clinical Manifestation
Birth	None
Infancy	Renal tubular Fanconi syndrome
	Growth retardation
Early childhood	Photophobia
Late childhood	Renal failure (age 10 years)
Adolescence and adulthood	Cerebral calcifications, diabetes mellitus, retinal blindness, myopathy, swallowing difficulty

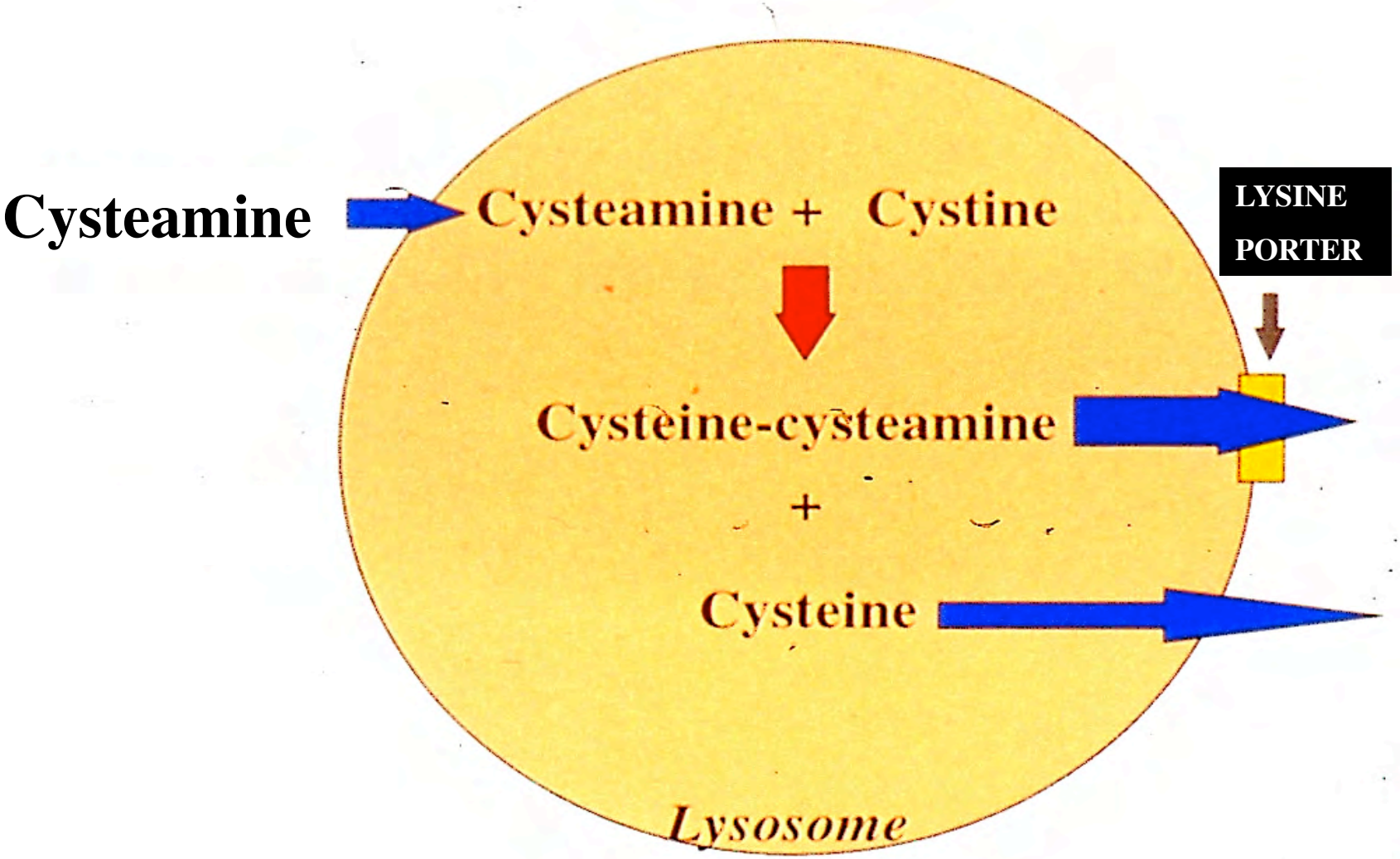
Cystinosis - Therapy

- Symptomatic
  - Replacement of renal losses (citrate, phosphate, potassium, water, calcium)
  - L-thyroxine, testosterone
  - Growth hormone
- Cystine Depletion
  - Oral cysteamine (Cystagon^{R})
  - Cysteamine eyedrops

$HS\text{-}CH_2\text{-}CH_2\text{-}NH_2$

CYSTEAMINE

MECHANISM OF CYSTINE DEPLETION BY CYSTEAMINE

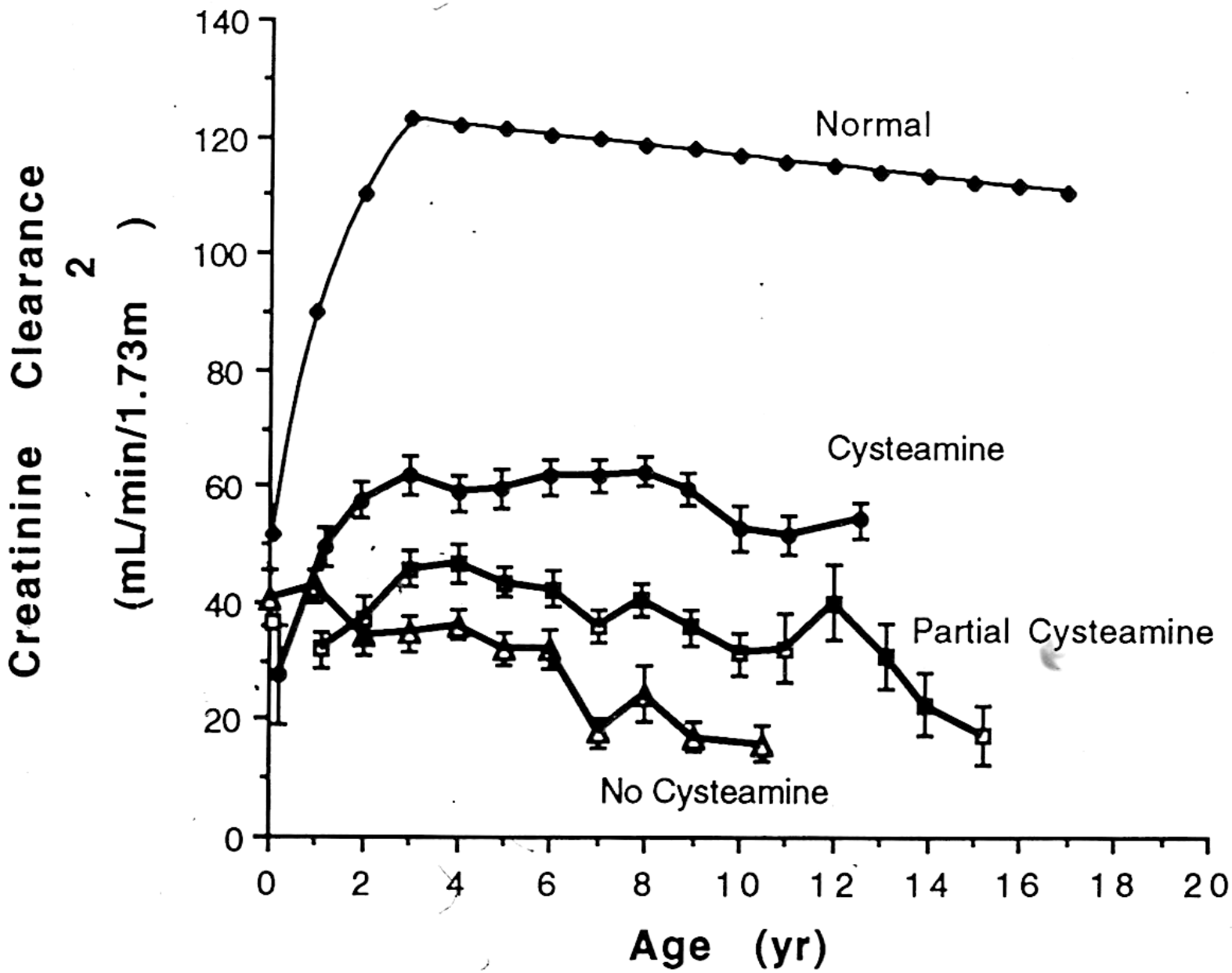


Clinical Trials of Oral Cysteamine

- National Collaborative Cysteamine Study I (1978-1985)
  - San Diego, Michigan, NIH; historical controls
  - Calculated creatinine clearance
  - Cysteamine group did better than controls
- Study of cysteamine doses & forms (1992)
  - No difference: cysteamine and phosphocysteamine; low (60 mg/kg/day) and high (90 mg/kg/day) dose
  - All groups did well (renal function and growth)
- Intent to treat analysis (1960-1992)

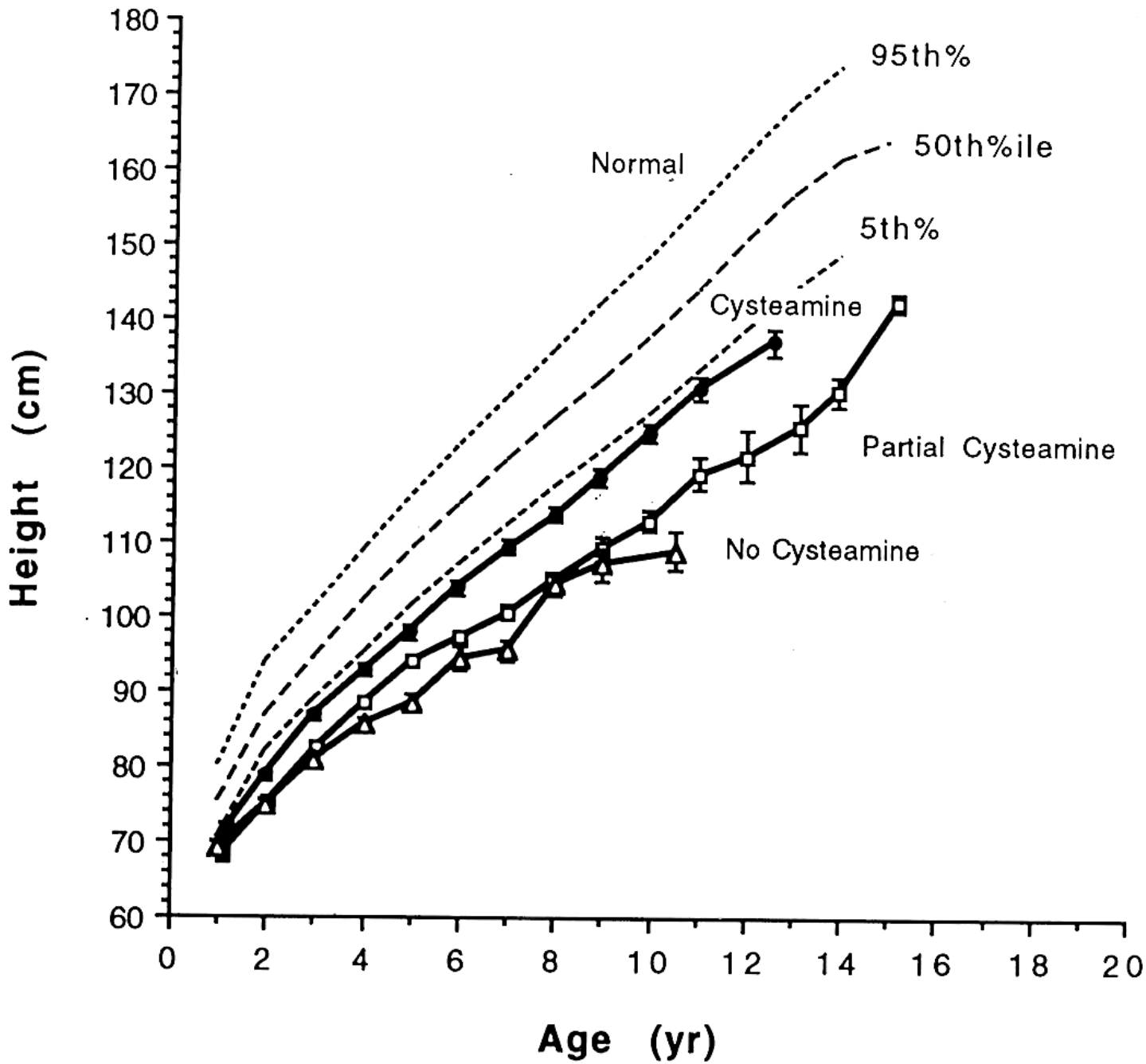
NIH Intent-to-treat Analysis for Oral Cysteamine; All Patients 1960-92

- Cysteamine treatment
  - Excellent (17): Started < age 2 y; median leucocyte cystine <2 nmol half-cystine/mg protein
  - Partial (32)
  - None (67)
- Creatinine clearances measured - based upon repeat serum creatinines and 2025 inpatient 24-hour urine collections


Creatinine Clearance
(mL/min/1.73m 2)
140
120
100
80
60
40
20
0
Normal
Cysteamine
Partial Cysteamine
No Cysteamine
0
2
4
6
8
10
12
14
16
18
20
Age (yr)

NIH Intent-to-treat Analysis for Oral Cysteamine (1960-1992)

Treatment	Predicted age at which creat clearance is zero (years)
No cysteamine	9.5
Partial cysteamine	20.0
Excellent cysteamine	74.3

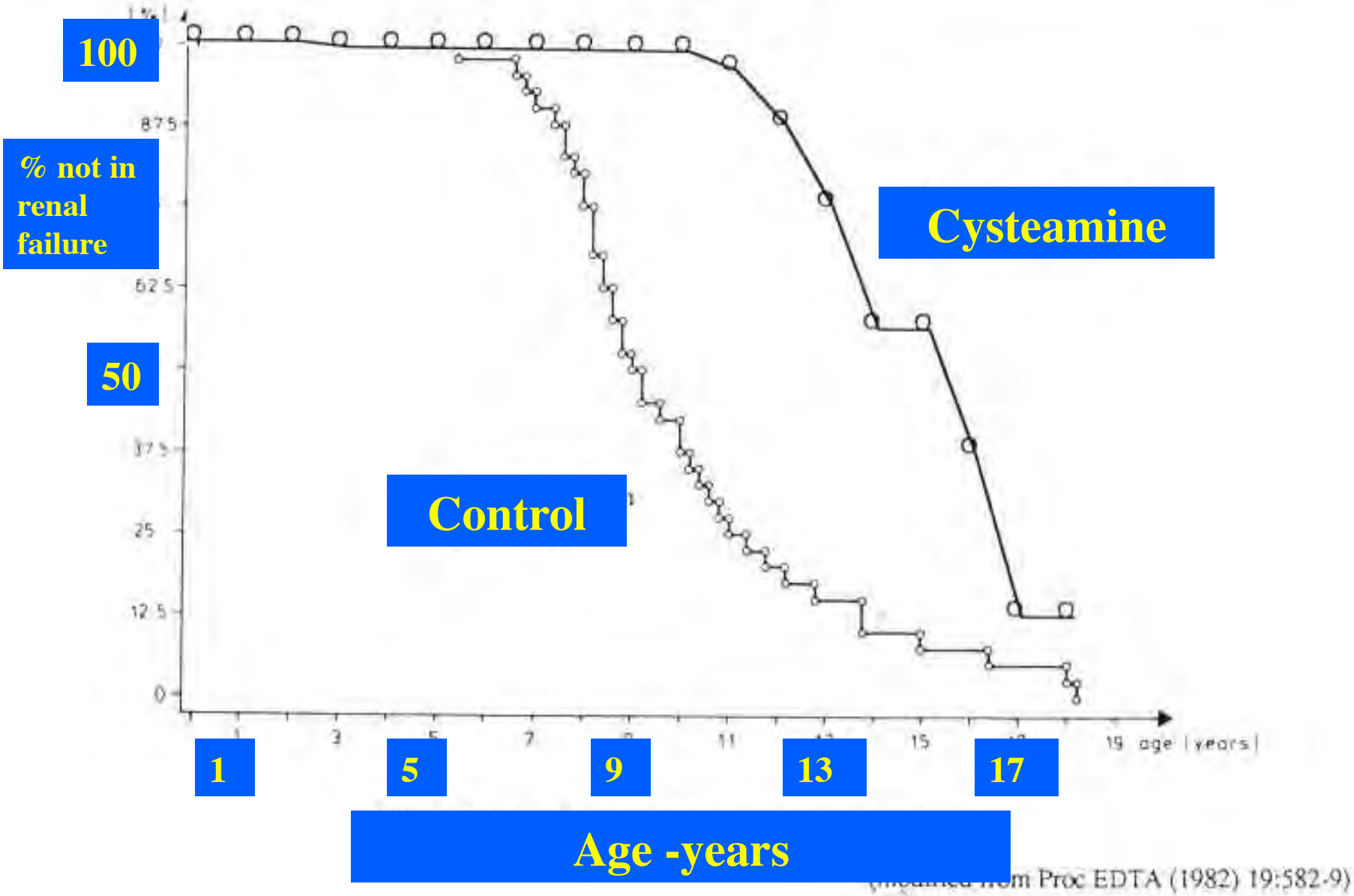

180
170
160
150
140
130
120
110
100
90
80
70
60
Height (cm)
0
2
4
6
8
10
12
14
16
18
20
Age (yr)
95th%
50th%ile
5th%
Normal
Cysteamine
Partial Cysteamine
No Cysteamine

New Drug Approval

- Timetable: Parke-Davis (1-2 y); Mylan (1-2 y); FDA (<1 y)
- FDA Interactions
  - Intent-to-treat study was valued; all patients included.
  - No animal studies required; historical controls accepted. (Nearly all known patients were already treated.)
  - Approved for pre-transplant patients only, since evidence was for prevention of renal deterioration. (Post-transplant use is off-label.)
- Cost remains reasonable.
  - ~$2000-$5000/year
  - Unlike some other orphan drugs

Cystagon: Approved August 15, 1994

Renal Failure in Cystinosis



(modified from Proc EDTA (1982) 19:582-9)

ORAL CYSTEAMINE THERAPY

Age (y)		Height	Creatinine Clearance
MEA	Present	(cm - %)	(mL/min/1.73 m^2)
1.0	12.5	159 - 75%	111
1.1	16.0	164 - 10%	52
1.2	13.6	152 - 15%*	108
1.5	10.3	133 - 15%	67
1.5	12.9	149 - 15%	41
0.5 sib	11.5	143 - 25%	78
1.7	16.7	165 - 10%*	58
1.7	12.9	149 - 25%	62
0.2 sib	6.9	127 - 80%	62

Cystinosis - Outcomes

Born in

- **1955 - Death in infancy/childhood**
- **1965 - Death or transplant, complications**
- **1975 - Death or transplant, complications**
- **1985 to present**
  - **>age 2, delay in transplant**
  - **<age 1, ? No transplant needed**
  - **Expect no late complications**


1952

CYSTEAMINE THERAPY (CYSTINOSIS)

- Oral cysteamine, started early, offers good preservation of renal function and growth.
  - It also helps thyroid & muscle.
  - It does not benefit the cornea, where cystine crystal accumulation continues.
- Proposal: Cysteamine eyedrops could dissolve corneal cystine crystals.

Cysteamine Eyedrop Studies

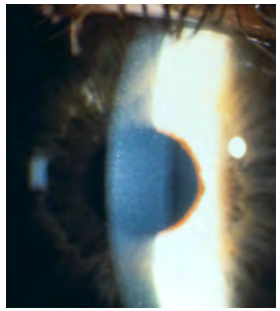
- Double-blind, placebo-controlled trials
  - New England Journal of Medicine, 1987
  - Archives of Ophthalmology, 1990
- Natural history study of corneal crystal accumulation
  - To demonstrate to the FDA that crystals do not spontaneously dissolve.

Cysteamine Eyedrops' Sponsorship

- Sigma-Tau Pharmaceuticals, Inc., began sponsorship ~1996.
  - Most data provided by NIH; one company-sponsored study.
  - Sigma-Tau hired:
    - A company to make human-use cysteamine-HCl.
    - A consultant for NDA submission.
    - A company to put NIH studies in proper format.
- Near to NDA application-early 2005.

Library of Corneal Crystal Densities

0.00



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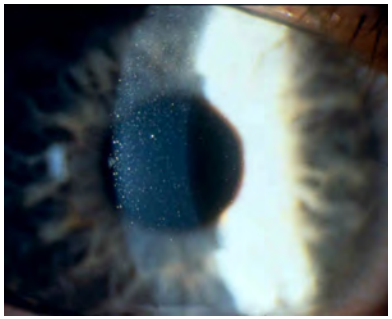

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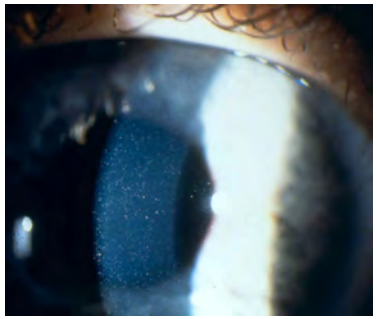

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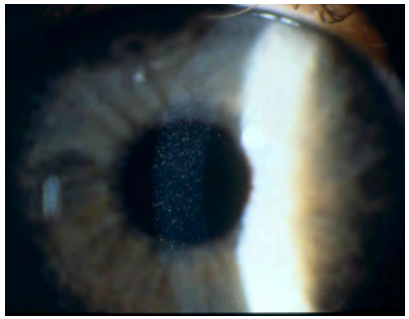
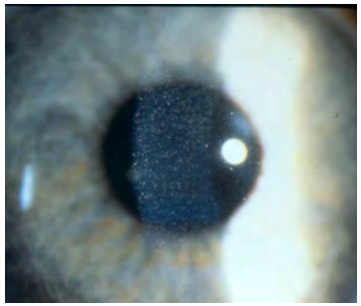


1.00

1.25



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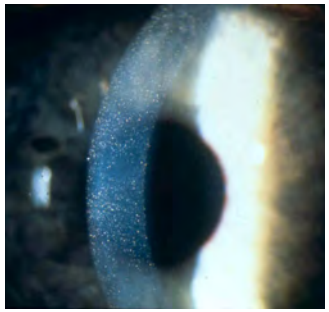

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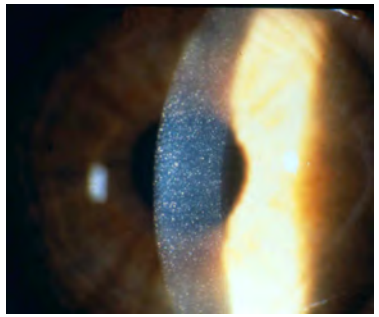

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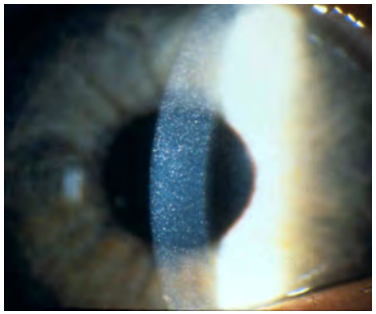

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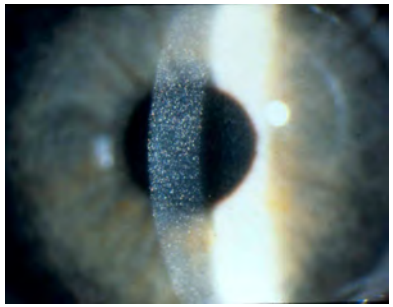

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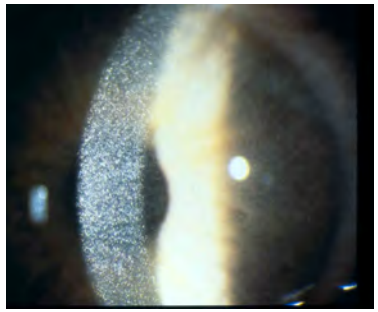
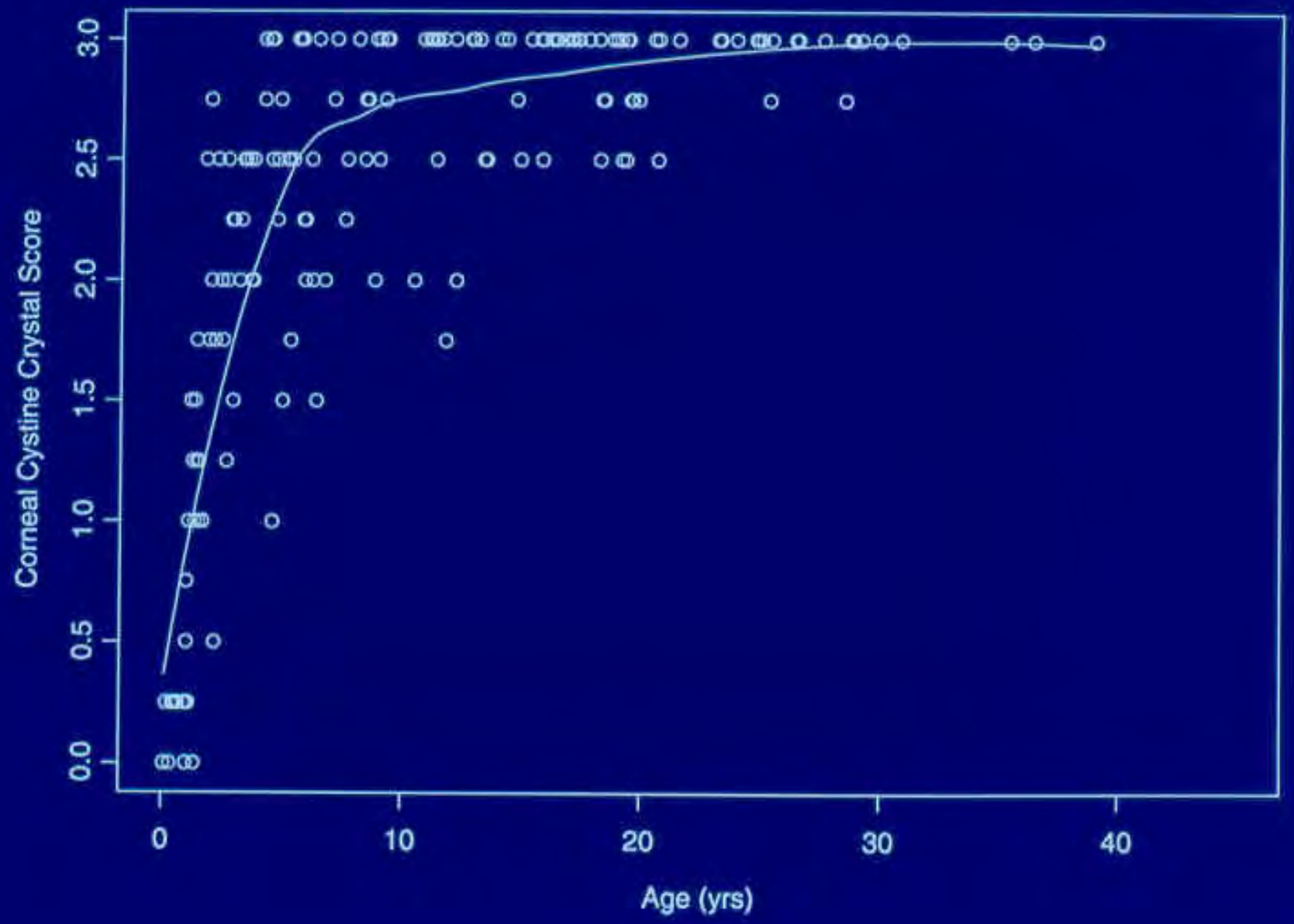
2.75

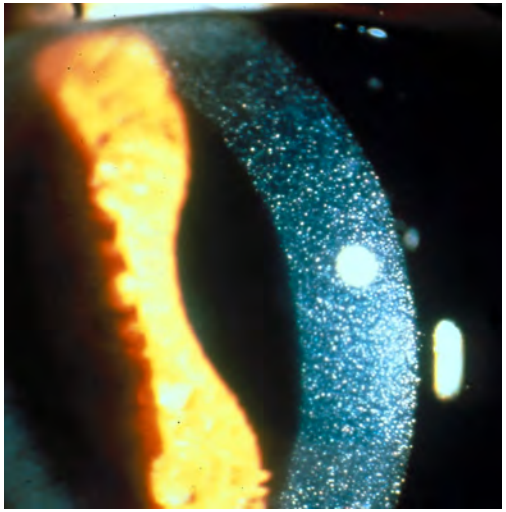
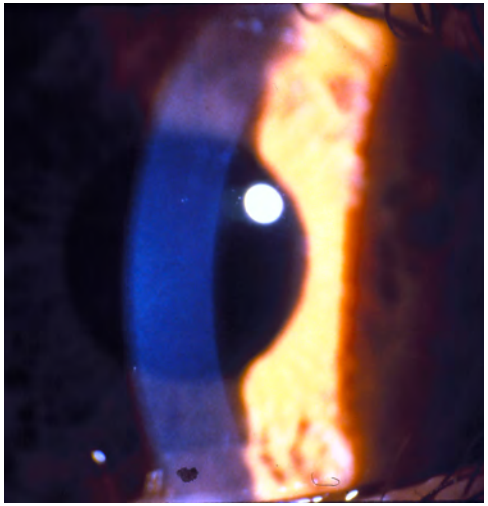
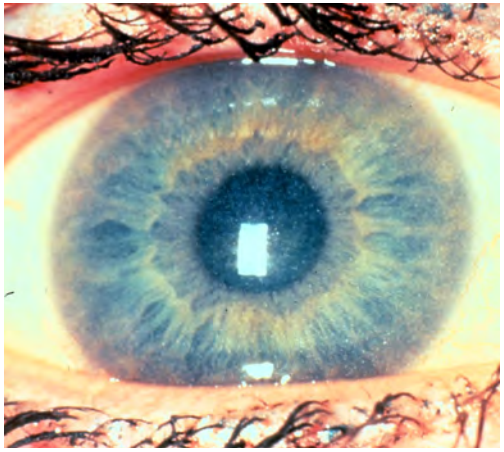
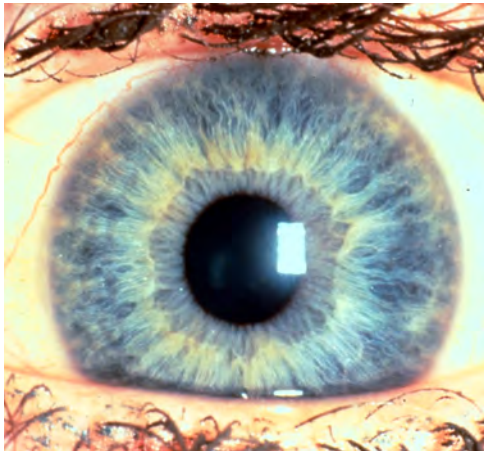


3.00

Corneal Crystal Accumulation

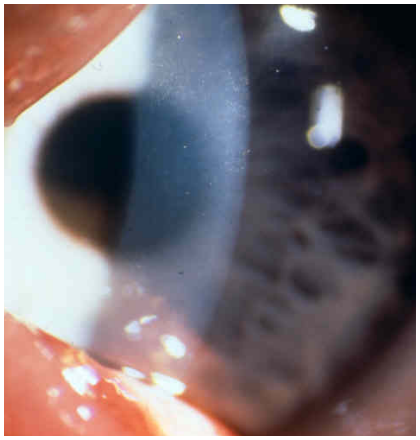


CYSTEAMINE EYEDROPS

	Untreated	Treated
3-year old		
20-year old		

Cysteamine Eyedrop Therapy

12 mo

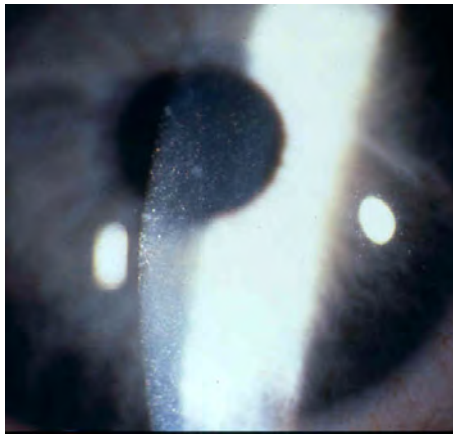


0.25

20 mo

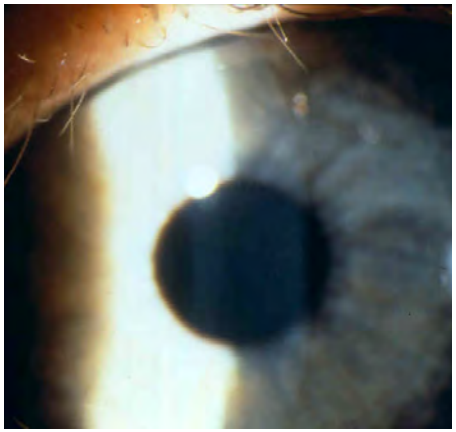
0.00

32 mo



2.00

57 mo

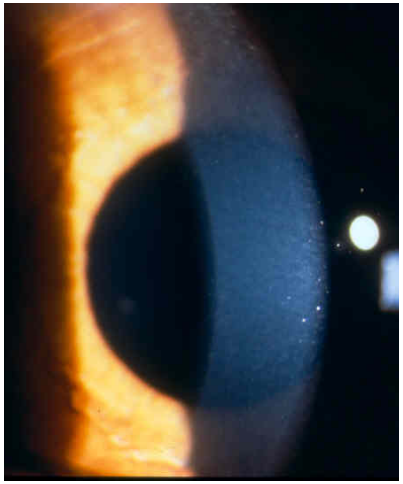


0.00

15 mo

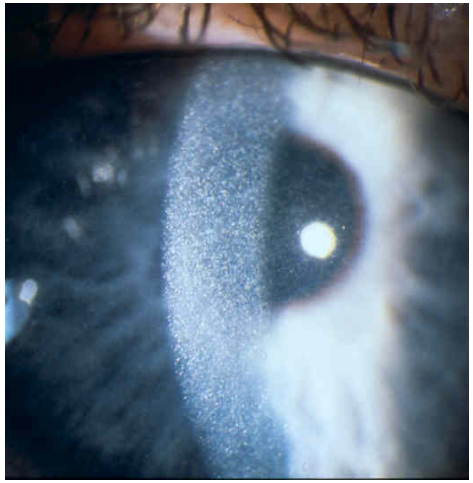
1.00

40 mo



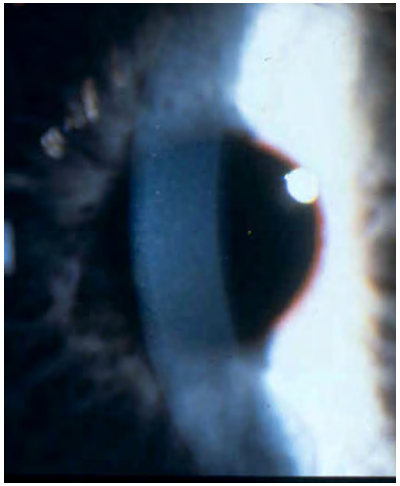
0.00

43 mo



0.50

56 mo



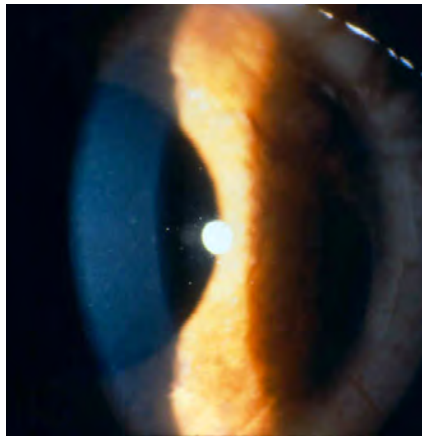
0.00

Cysteamine Eyedrop Therapy

262 mo

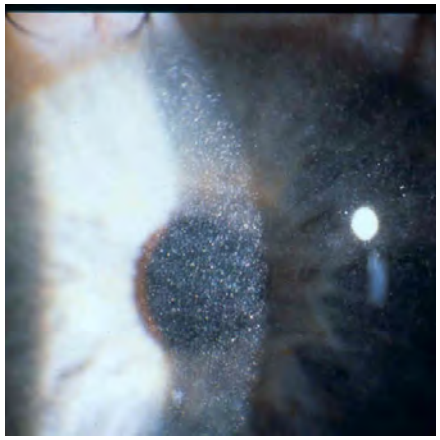
3.00

303 mo



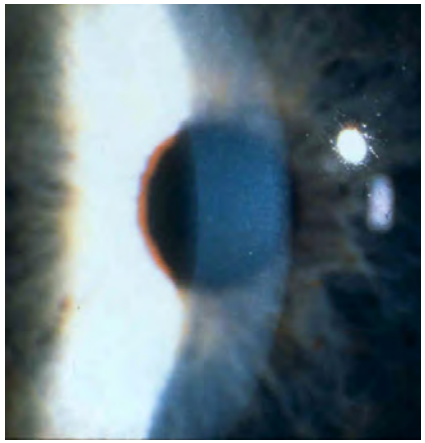
0.25

342 mo



2.50

354 mo



0.25

304 mo

3.00

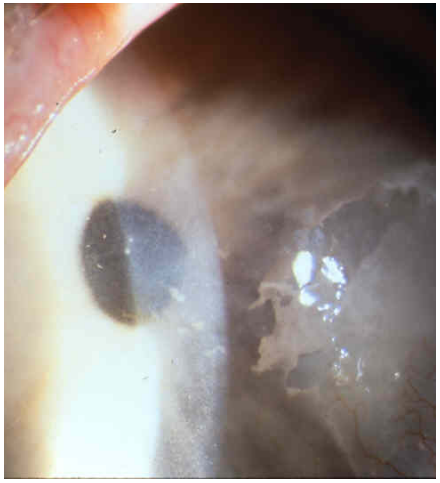
316 mo

0.25

394 mo

3.00

406 mo



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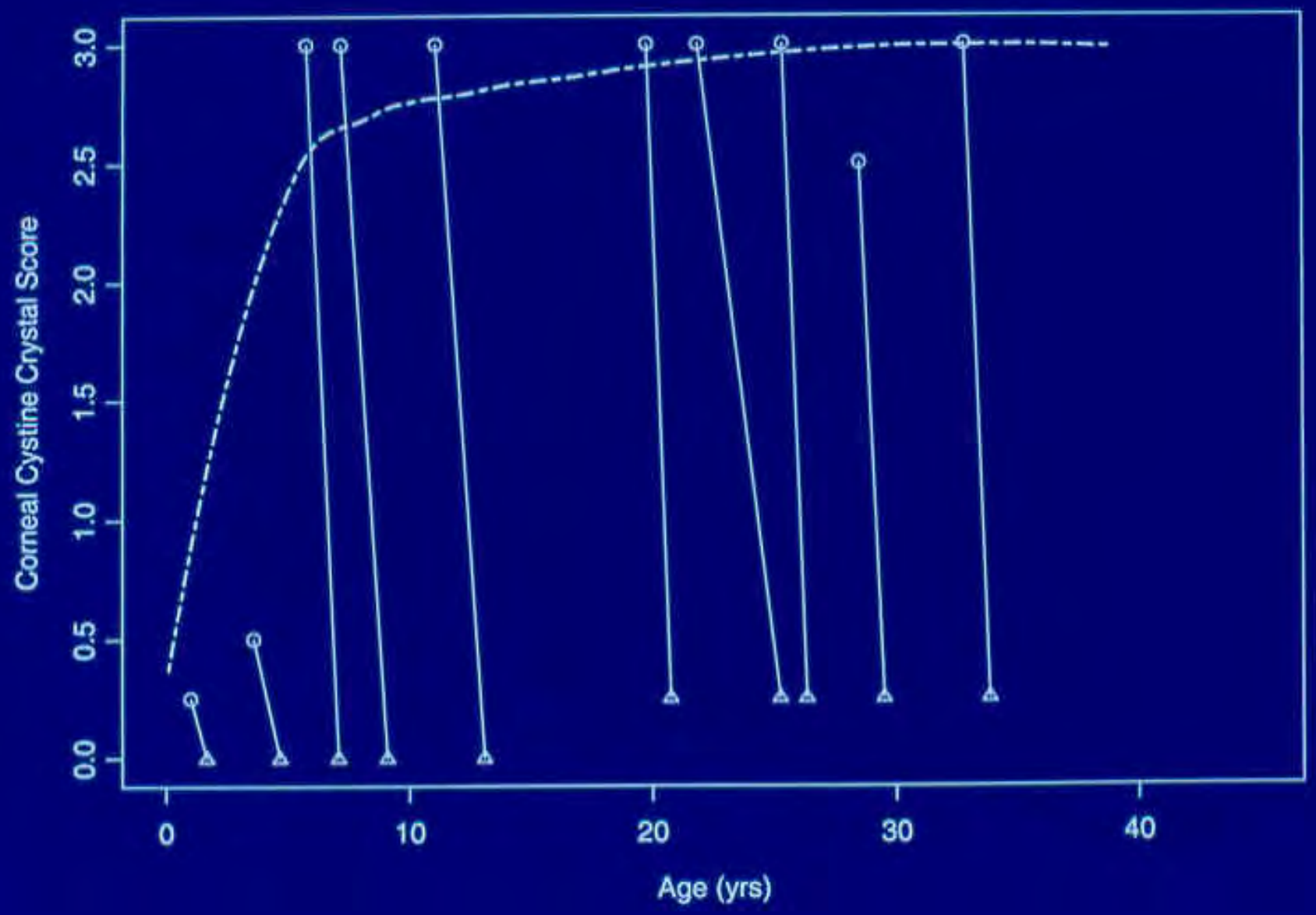
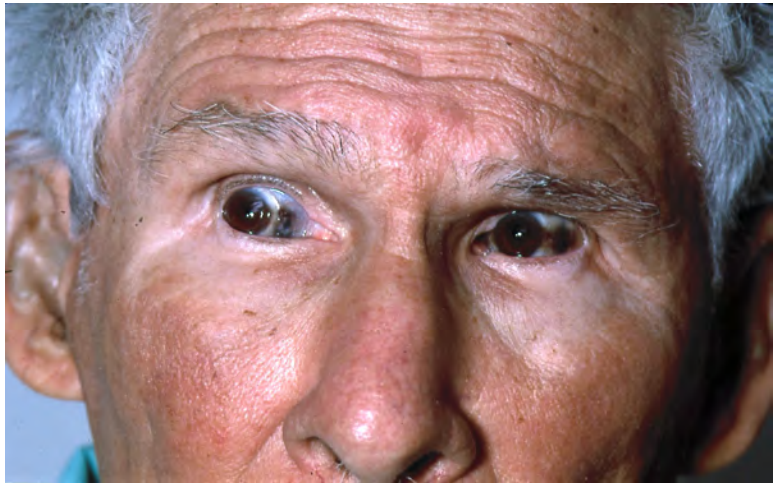
Cysteamine Eyedrop Therapy



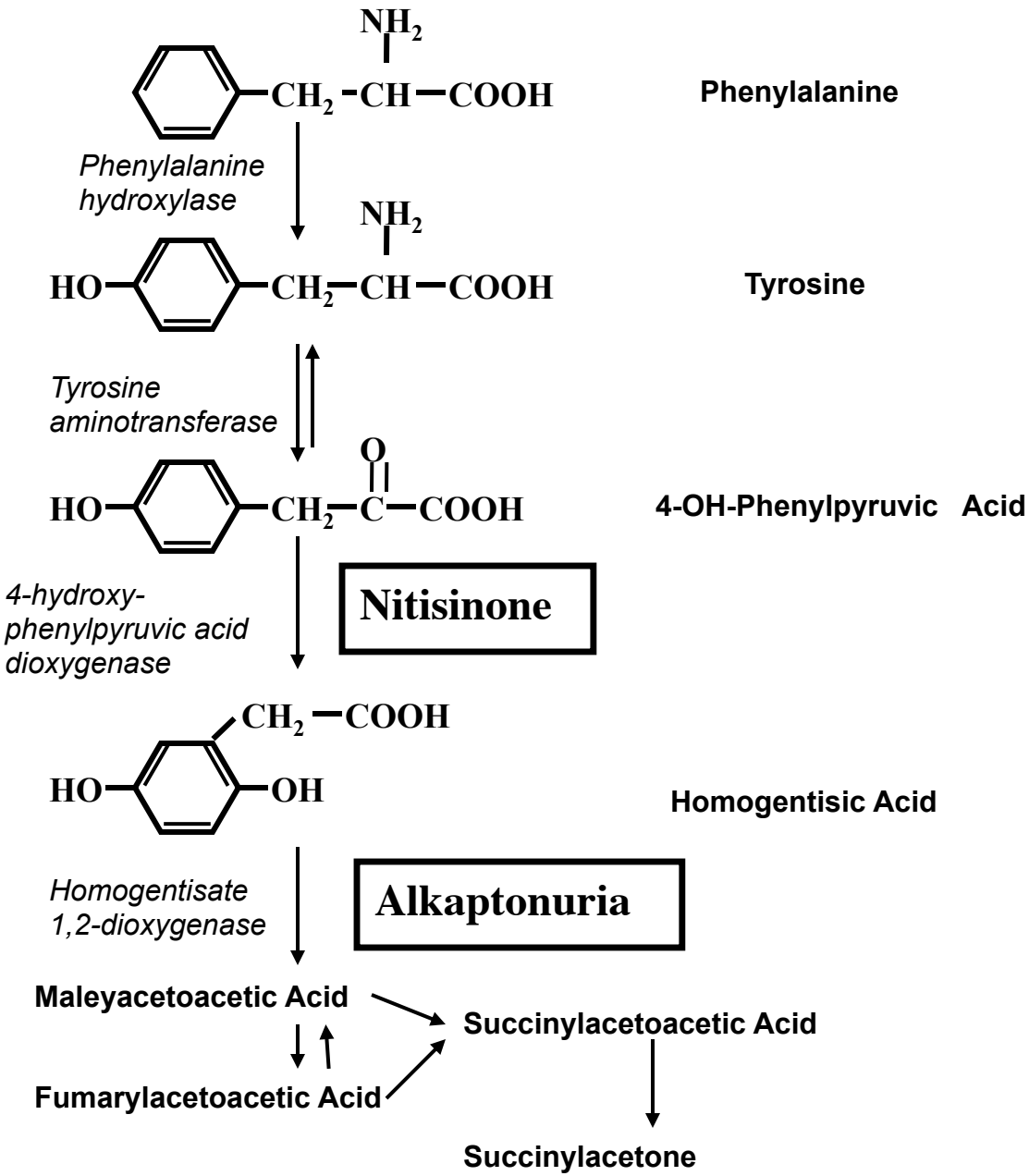
Therapies for Two Rare Diseases

- Cystinosis - Cysteamine
- Alkaptonuria - Nitisinone
- Generalizations - Disease to Therapy



ALKAPTONURIA

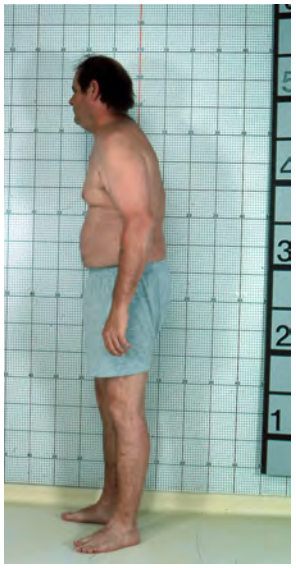
- Autosomal recessive
  - Homogentisic acid dioxygenase deficiency
- HGA accumulation causes ochronosis
  - Blackening and destruction of cartilage and connective tissue
  - Spine, hips, knees, shoulders, aortic valve


NH2
CH2 CH COOH
Phenylalanine
Phenylalanine hydroxylase
NH2
HO CH2 CH COOH
Tyrosine
Tyrosine aminotransferase
O
HO CH2 C COOH
4-OH-Phenylpyruvic Acid
4-hydroxy-phenylpyruvic acid dioxygenase
Nitisinone
CH2 COOH
HO OH
Homogentisic Acid
Homogentisate 1,2-dioxygenase
Alkaptonuria
Maleyacetoacetic Acid
Succinylacetoacetic Acid
Fumarylacetoacetic Acid
Succinylacetone

Alkaptonuria-Natural History

(Sixty-four individuals age 4 to 80 were evaluated.)

34



40

52

58

80

A

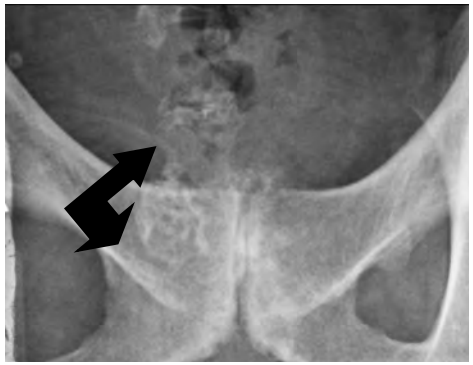
31-40 y

41-50 y

51-60 y

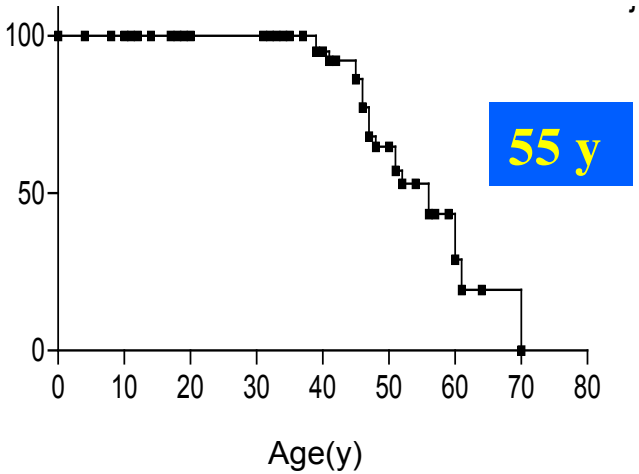
61-80y

B

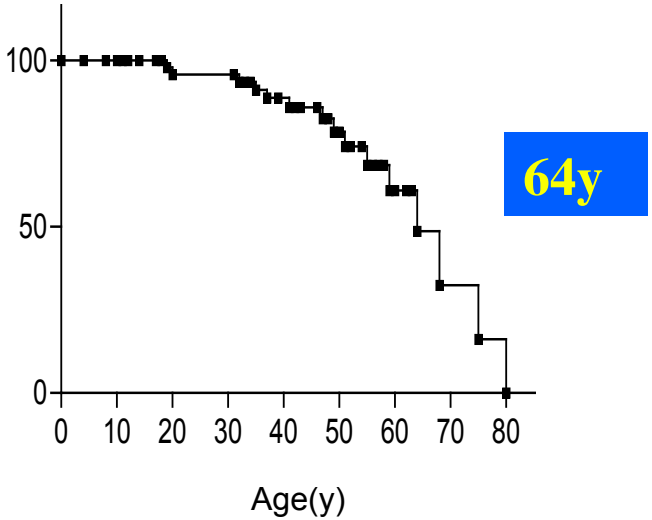


A B C D

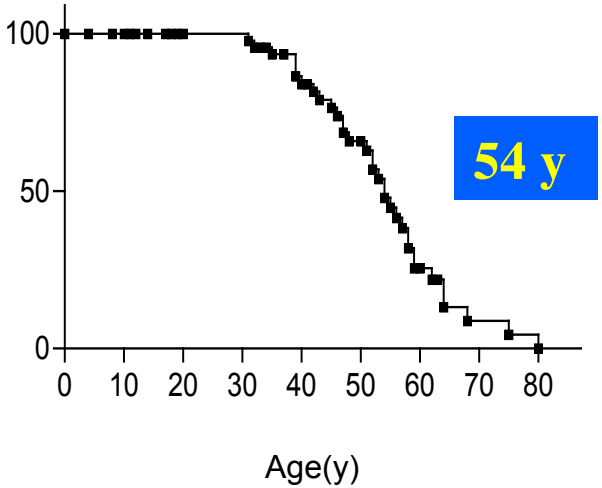
% of patients not manifesting



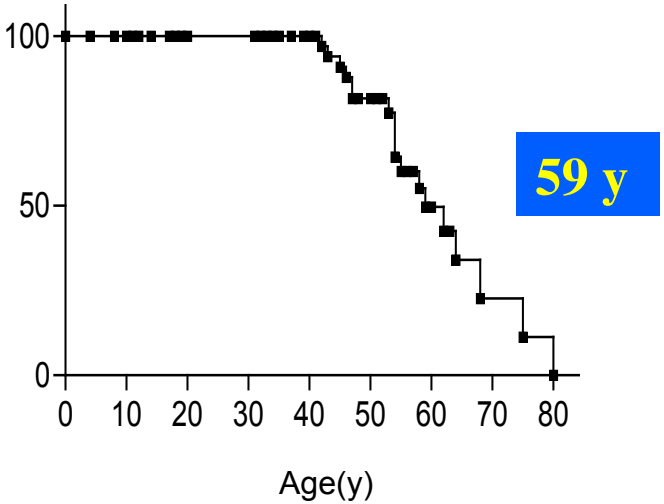
Joint replacement



Renal stones



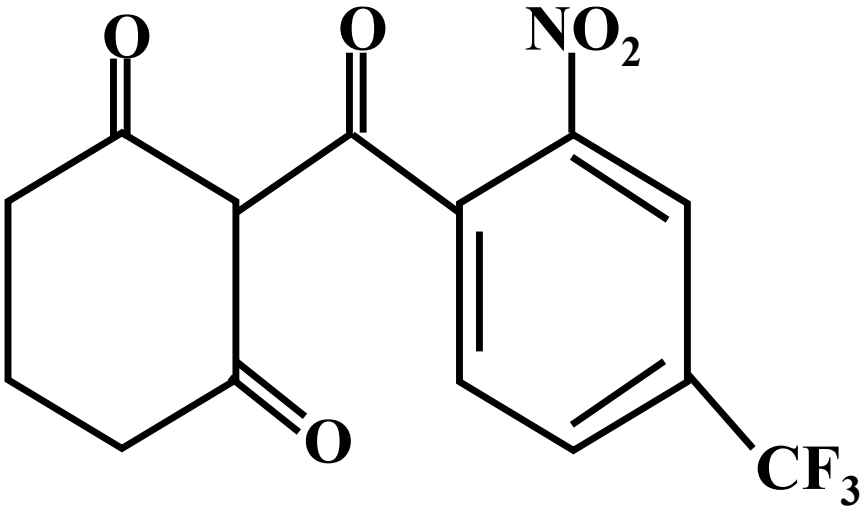
Cardiac valve involvement



Coronary artery calcification

Nitisinone

- 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione.

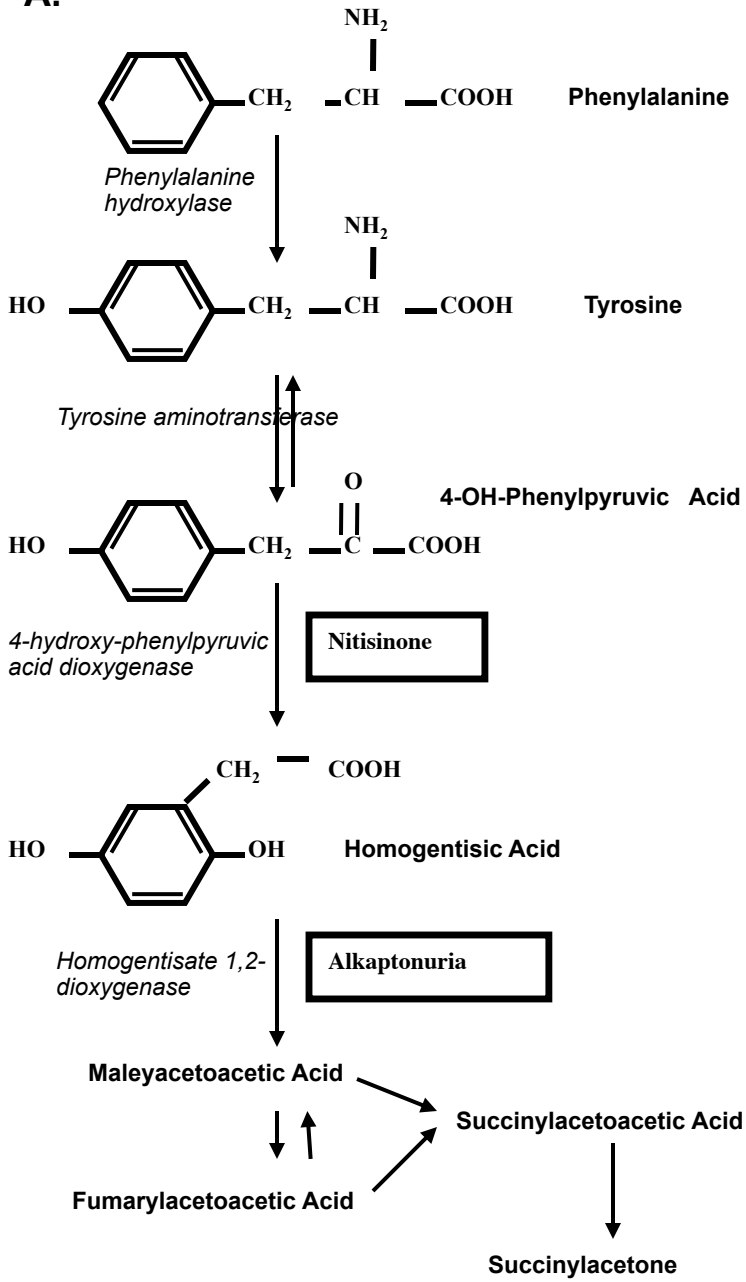


- Licensed to Swedish Orphan International AB.
- Treatment of choice for tyrosinemia type I, a fatal liver disorder of children.
- Approved for human use in the U.S. in January of 2002 as Orfadin.

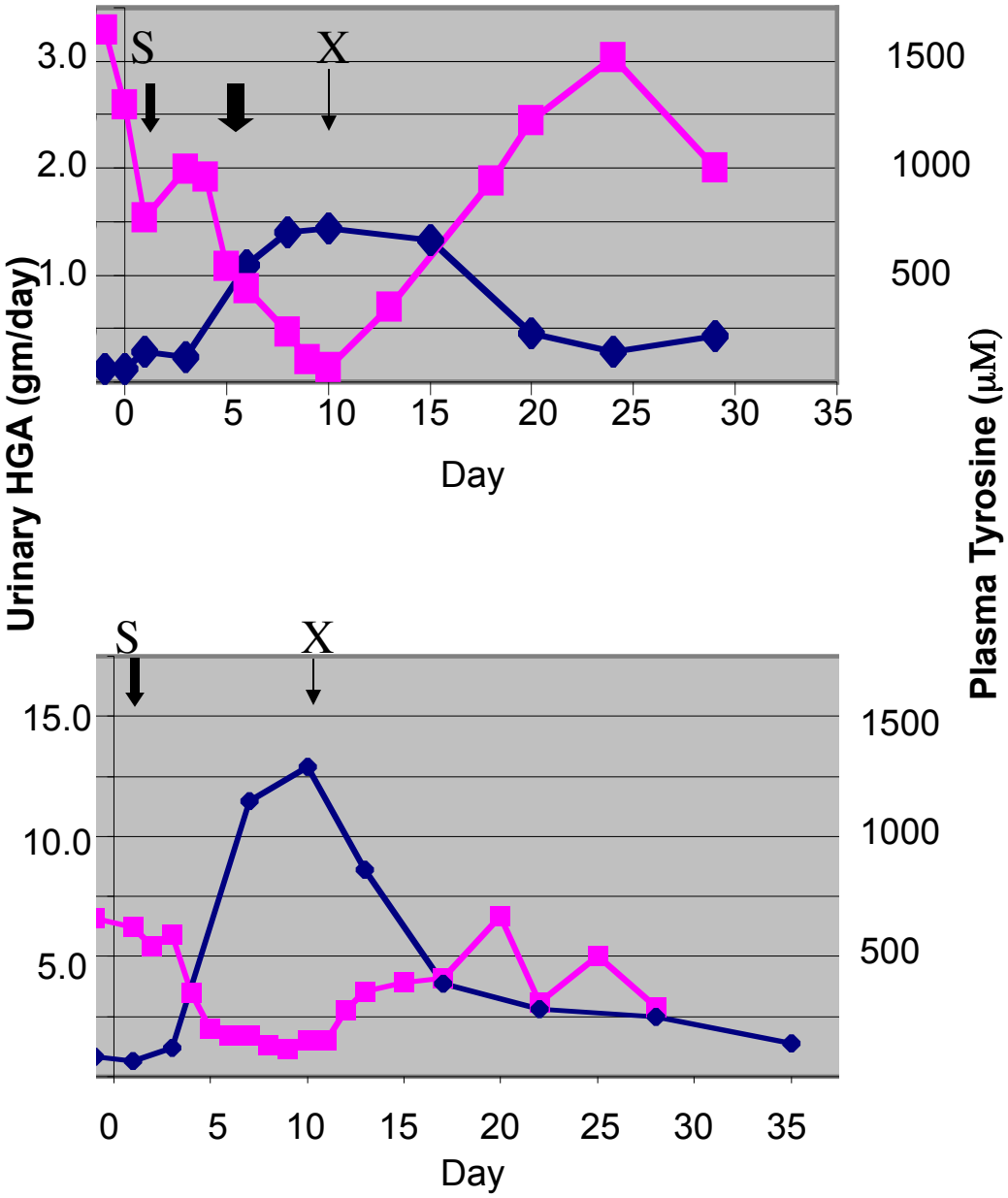
Nitisinone in Alkaptonuria-Study #1

- Two female patients age 51 and 59.
- Initial dosage 0.01 mg/kg/day (divided bid), or one-hundredth the per-kg dose used in tyrosinemia type I.
- One patient received 0.04 mg/kg/day.
- Stop drug if plasma tyrosine > 500 μM.
- Urinary HGA fell by at least 69%.
- No corneal signs or symptoms.

A.


NH2
CH2
CH
COOH
Phenylalanine
Phenylalanine hydroxylase
HO
Tyrosine
Tyrosine aminotransferase
O
4-OH-Phenylpyruvic Acid
4-hydroxy-phenylpyruvic acid dioxygenase
Nitisinone
Homogentisic Acid
Homogentisate 1,2-dioxygenase
Alkaptonuria
Maleyacetoacetic Acid
Succinylacetoacetic Acid
Fumarylacetoacetic Acid
Succinylacetone

B.

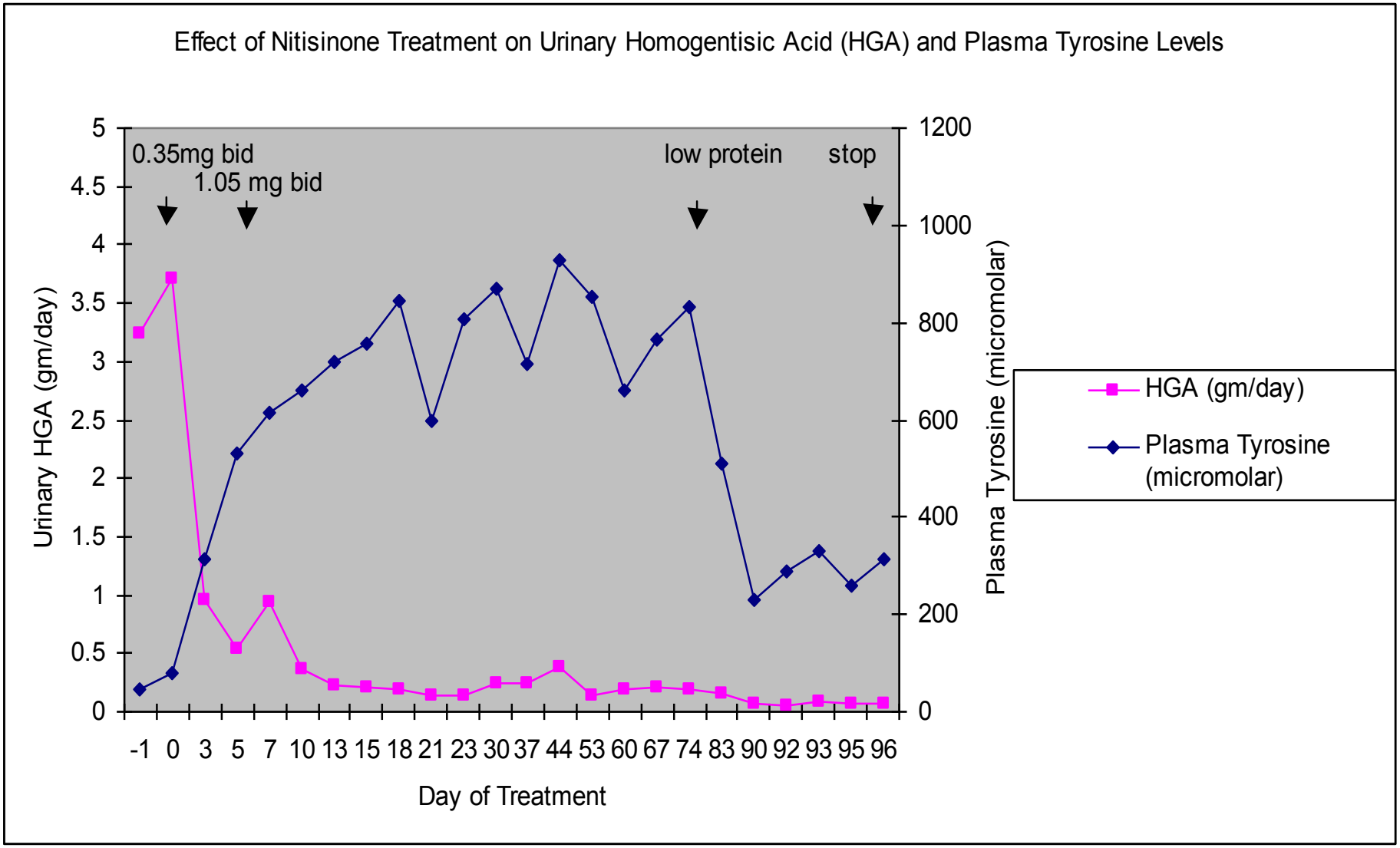

S
X
3.0
2.0
1.0
1500
1000
500
0
5
10
15
20
25
30
35
Day
Urinary HGA (gm/day)
Plasma Tyrosine (µM)
15.0
10.0
5.0

Nitisinone in Alkaptonuria-Study #2

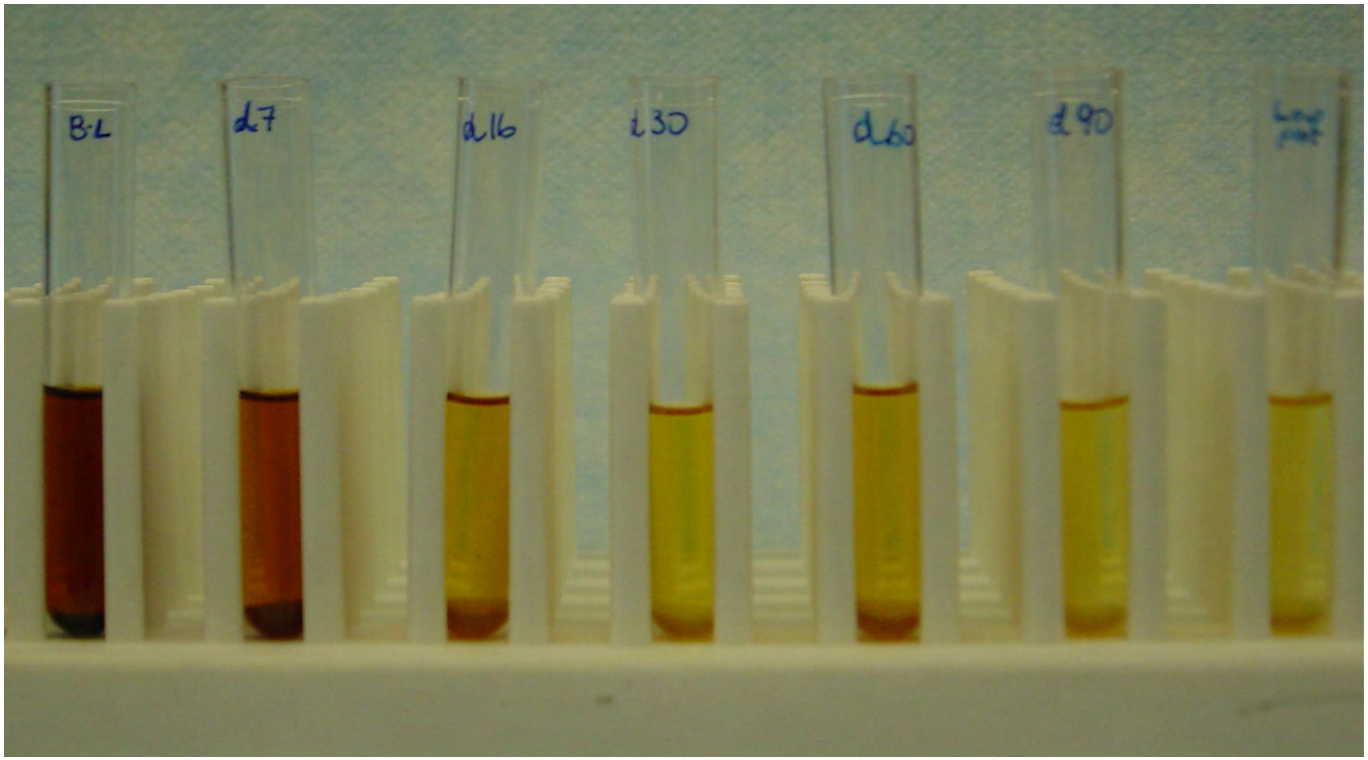
- Incremental dosing regimen (0.35mg, 1.05mg, 4.0mg bid) to see how much nitisinone is required to lower urinary HGA to <0.5 g/day.
- No plasma tyrosine limit; watch for corneal signs and symptoms for 3 months on chosen dose.
- Mild protein restriction final week.
- 10 patients to be enrolled.

Patient #1

Day	NTBC (mg/day)	Urine HGA (mg/day)	Plasma Tyr (μM)
0	0	3474	62
1	0.7	958	312
3	0.7	545	529
5	0.7	944	615
8	2.1	358	662
11	2.1	220	721
13	2.1	214	757
15-21	2.1	140-194	598-844
26-77	2.1	143-375	512-958
84 (diet)	2.1	77	231


Effect of Nitisinone Treatment on Urinary Homogentisic Acid (HGA) and Plasma Tyrosine Levels
0.35mg bid
1.05 mg bid
low protein
stop
Urinary HGA (gm/day)
Plasma Tyrosine (micromolar)
Day of Treatment
HGA (gm/day)
Plasma Tyrosine (micromolar)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
0
200
400
600
800
1000
1200
-1 0 3 5 7 10 13 15 18 21 23 30 37 44 53 60 67 74 83 90 92 93 95 96

Color changes of alkalinized urine in an alkaptonuria patient receiving nitisinone



Summary-Nitisinone

- 2.1 mg per day lowered urinary homogentisic acid by ~95%.
- Plasma tyrosine rose ~10-fold to ~800 μM.
- No corneal side effects.
- Adverse events:
  - Passing of pre-existing renal stones.
  - Recognition of aortic stenosis symptoms.
  - Increased liver function tests.

PLANS

- Perform a long-term trial of nitisinone for safety and efficacy.
  - Primary outcome parameter: Internal + external hip rotation.
  - Secondary outcome parameters: Other ranges of motion, 6-minute walk, etc.
  - Extensive clinical and lab safety measurements.

Therapies for Two Rare Diseases

- Cystinosis - Cysteamine
- Alkaptonuria - Nitisinone
- Generalizations - Disease to Therapy

Rare Disease Therapies: Generalizations

- You must acquire expertise in a disorder before you can treat it.
- Knowing the causative gene may not be necessary.
- Drug therapy remains optimal
  - It reaches ~all tissues.
  - Currently, gene therapy is difficult to target safely.
- It takes a long time:
  - Cysteamine: 1976-1987-1994
  - Cysteamine eyedrops: 1987-2005?
  - Nitisinone: 1998-2002-2008?

Rare Disease Therapies: Generalizations

- Assistance is available from:
  - Office of Rare Diseases
  - Office of Orphan Products Development
  - Family groups, drug companies, metabolic physicians
- Investigational (IND) studies are not enough. New Drug Approval (NDA) is necessary for marketing.
- A pharmaceutical company is needed to make a drug available to the community (NDA).
- Regulatory agencies can be lenient with orphan indications.
- The entire world needs these drugs.