Controversies Conference on Nephropathic Cystinosis
Lisbon, Portugal
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OPENING REMARKS

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Disclosure of Interests

Consultant to Alexion; Janssen; Genzyme-Sanofi; Eli Lilly; Raptor honoraria paid to Kid‘s Kidneys Inc.

Why Study "Rare Diseases"

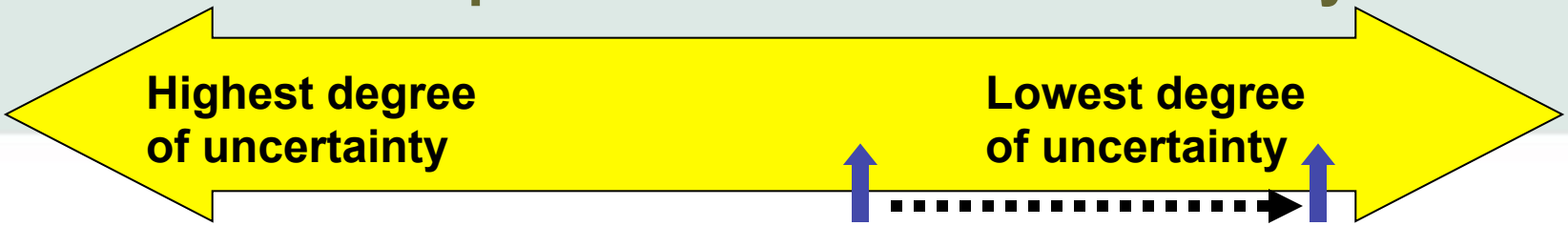
NIH Director, Francis Collins

- 25 million Americans affected with 6000 rare diseases
- Only ~ 200 rare diseases have treatments
- Bridge molecular understanding into Rx
- Repurposing of Drugs

Why Have a Controversy Conference on Cystinosis

- Increase awareness to the professionals
- Increase awareness to those affected
- Coalesce anecdotal experiences
- Promote worldwide databases
- Improve outcomes
- Bridge gap from molecular etiology to patient-centered outcomes
- Provide a framework for investigations and trials going forward
- Increase the patient-professional relationships

The spectrum of clinical uncertainty



Disease condition recognized and defined pathologically

Animal studies, physiological explanation, laboratory evidence

Observational population studies, epidemiological evidence

Well designed clinical trials or a systematic summary of the evidence

Mechanism for Disease hypothesized

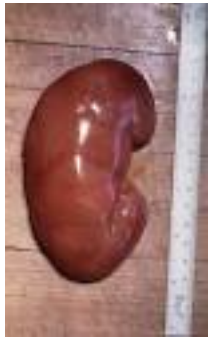
Hypotheses generated

Hypotheses proven or not

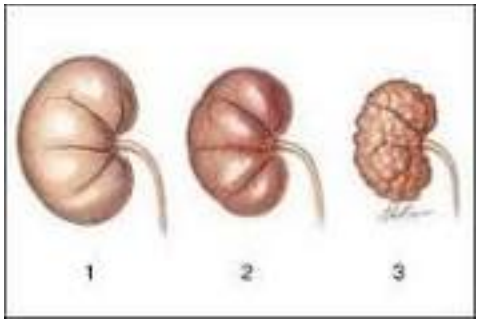
Bias

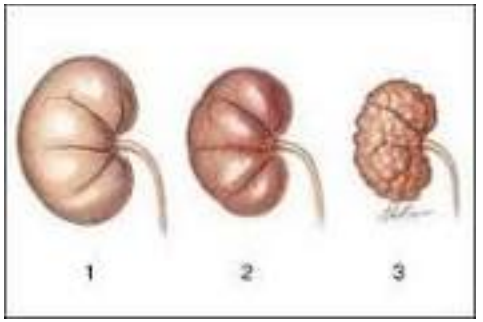
Highest opportunity for introduction of bias into conclusions

The Natural History of Cystinosis has Changed



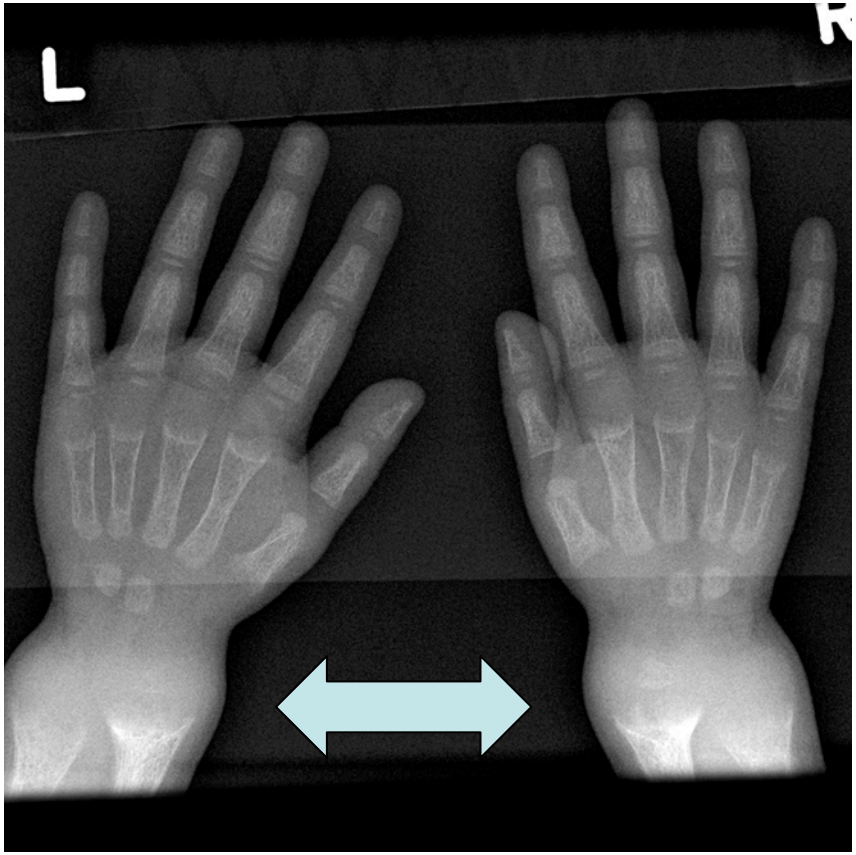
Preserved GFR
Poor tubular Fx

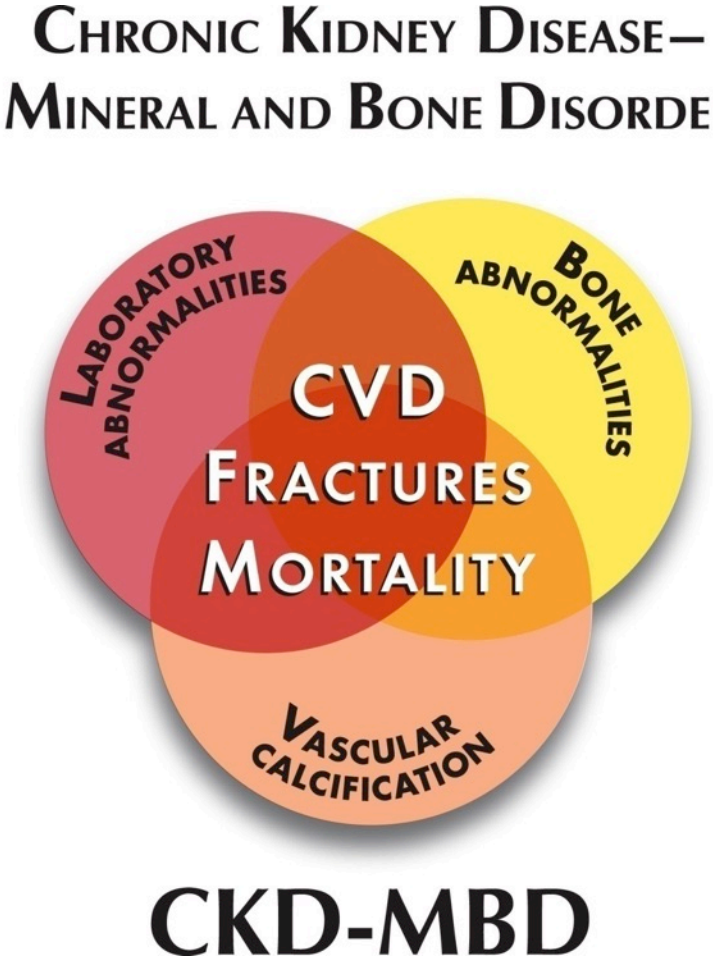




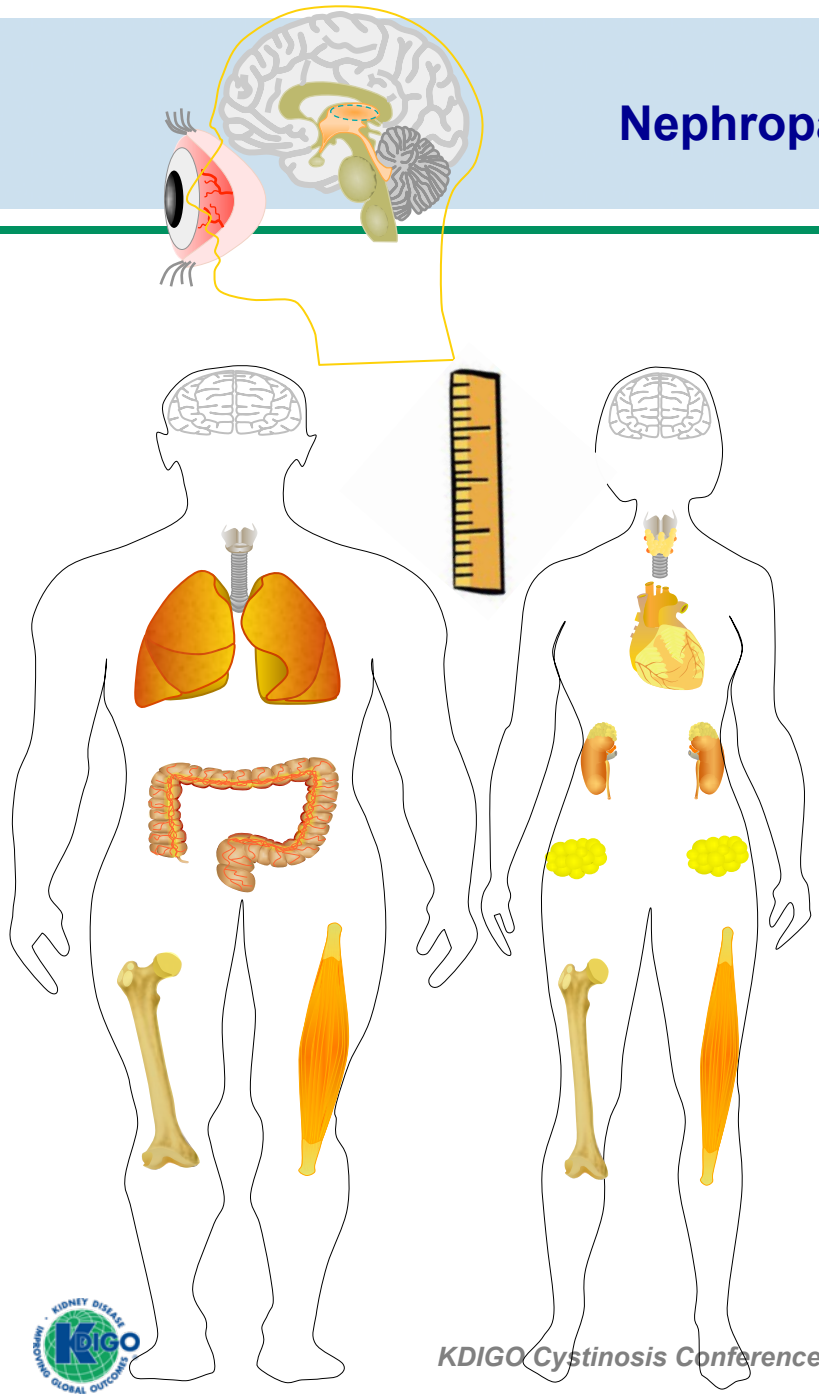
But Why **Exactly?**

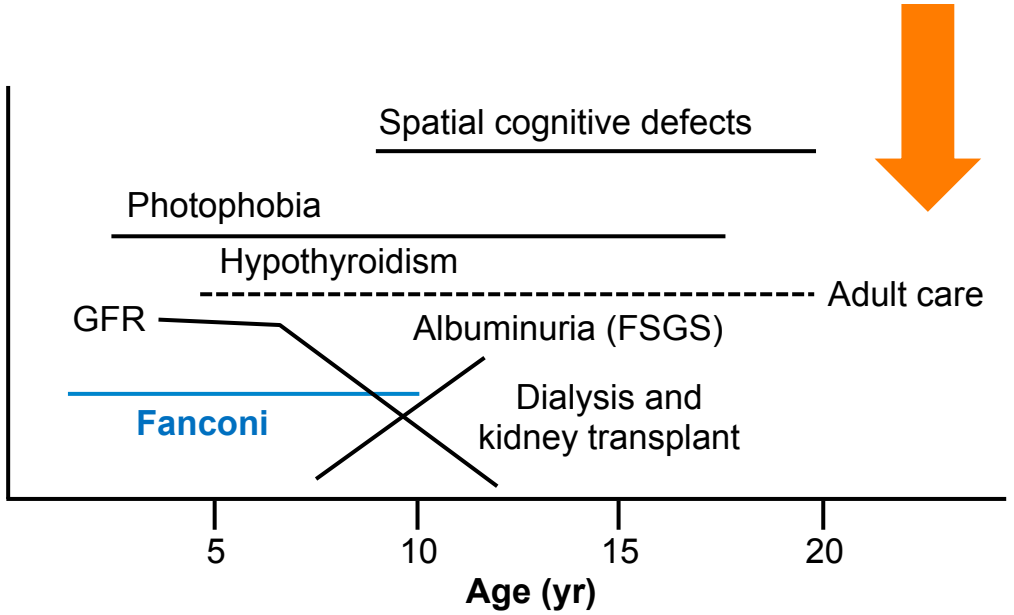
The Natural History of Cystinosis has Changed





Nephropathic Cystinosis Is a Systemic Disease





Goodyer P. *Int J Nephrol.* 2011;2011:929456.
doi:10.4061/2011/929456

Adapted by Langman, 2014

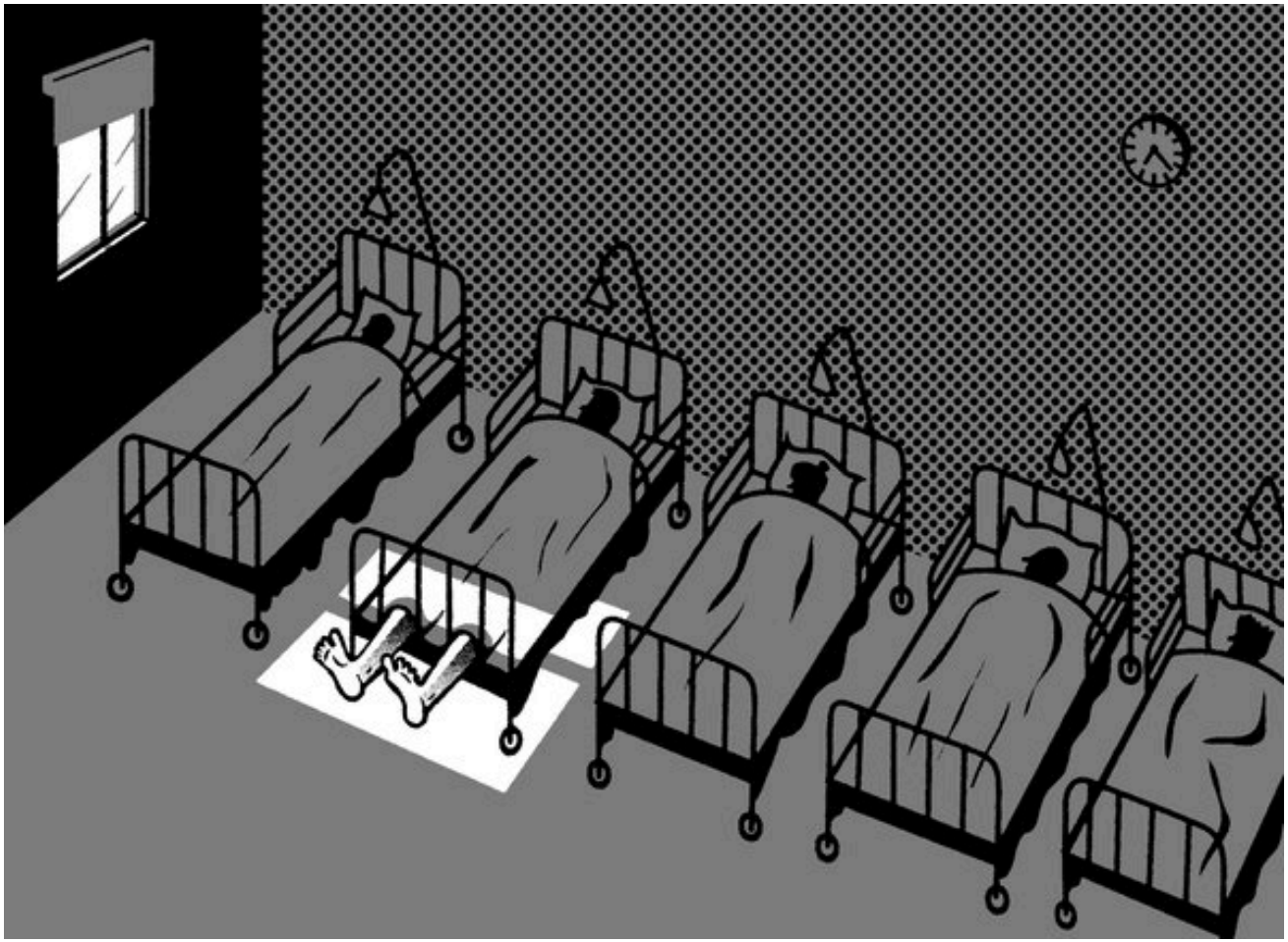
Methods of this Controversy Conference

- Workgroups based on sub-topics
  - Basic & Translational Science
  - Optimal Diagnostics
  - Infant & Young Child
  - Adolescent
  - Adult Years
- Topic Lectures from our Experts
- Deliberations to help 'crystallize' the areas of known and unknown
- Presentations & Group Discussions to refine consensus
- New deliberations to further define what we don't know.

Rules

- Listen to your colleagues.
- Contribute your deep knowledge.
- Work towards consensus.
- Accept some disagreements.
- Think creatively.
- Act with both passion and reason.
- Remember the scientific method.
- Think in a patient-centered manner.

What we are Not!



As We Begin

- We give many thanks to KDIGO
  - John Davis
  - Tanya Green, Michael Cheung, Danielle Green
- We give many thanks to our subgroup leaders
- We give many thanks to our professional participants
- We give many thanks to our lay participants
- We give thanks to friends who could not join us
- We give many thanks to our patients who teach us so much!

NEPHROPATHIC CYSTINOSIS

from History to Future

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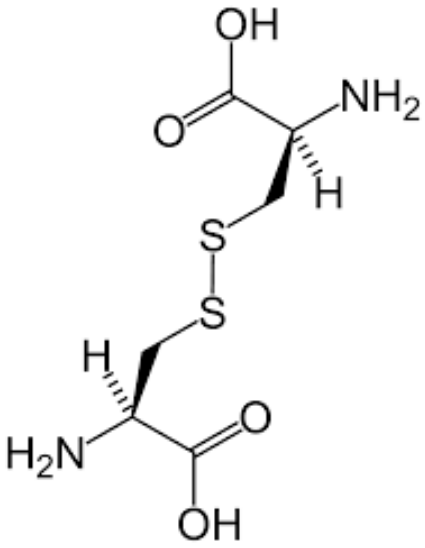
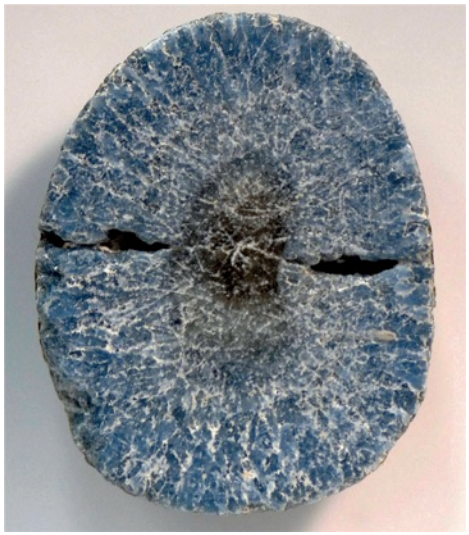
Disclosure of Interests

E. Levtchenko performed consultancy for Raptor Pharmaceutical.

Cystine: first described amino acid

William Hyde Wollaston
(1766-1828)





Gordon Museum, King's College London

The first cystine stone found in a 36-year-old male patient with cystinuria (weight 18 g)

Thomas, K. *et al.* (2014)
Cystinuria—a urologist's perspective

nature REVIEWS UROLOGY

Wollaston W. On cystic oxide: a new species of urinary calculus. *Philos. Trans. R. Soc. Lond.* 100, 223–230 (1810).

First description of cystinosis

Emil Abderhalden
1877 - 1950

Abderhalden E.
Familiäre Cystindiathese.
Z. Physiol Chem 38: 557-561, **1903**

Autopsy of a 21-months-old child:

- Failure to thrive
- Cystine crystals in the liver and spleen

- Confusion between cystinuria and cystinosis

Clinical presentation of cystinosis

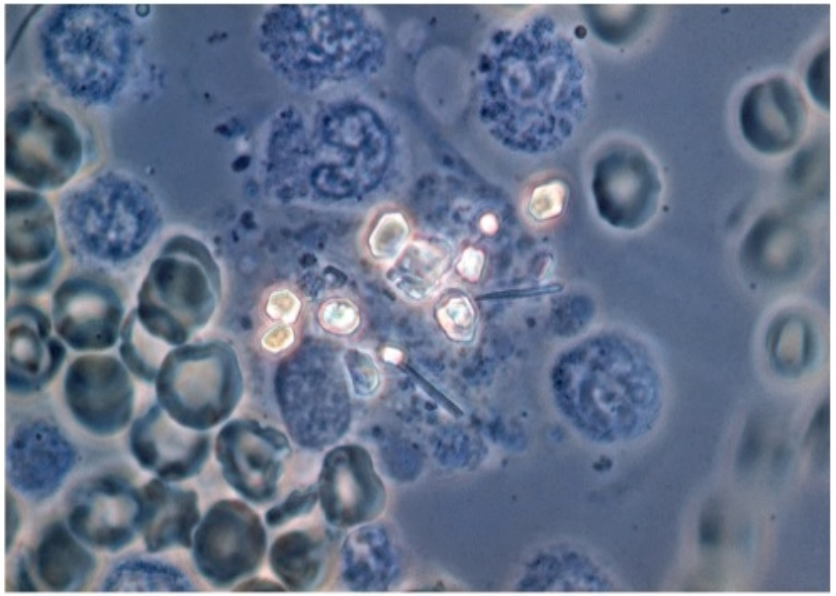
- **Lignac G**: Über storung des cystinstoffwechsels bei kindern
  Deutsch Arch Klin Med 145: 139, 1924

- **deToni G:** Remarks on the relation between renal rickets (renal dwarfism) and renal diabetes
  Acta Paediatr 16: 479, 1933

- **Debré R** *et al:* Rachitisme tardif coexistent avec une néphrite chronique and glucosurie
  Arch Méd Enf 37: 597, 1934

- **Fanconi G**: Der nephrotisch-glykosurische zwergwuchs mit hypophosphtämischer rachitis
  Dtsch Med Wochenschr 62: 1169, 1936

Biochemical basis of cystinosis



Bone marrow aspirate from 5 m old cystinosis patient. Seen unstained with phase microscopy.

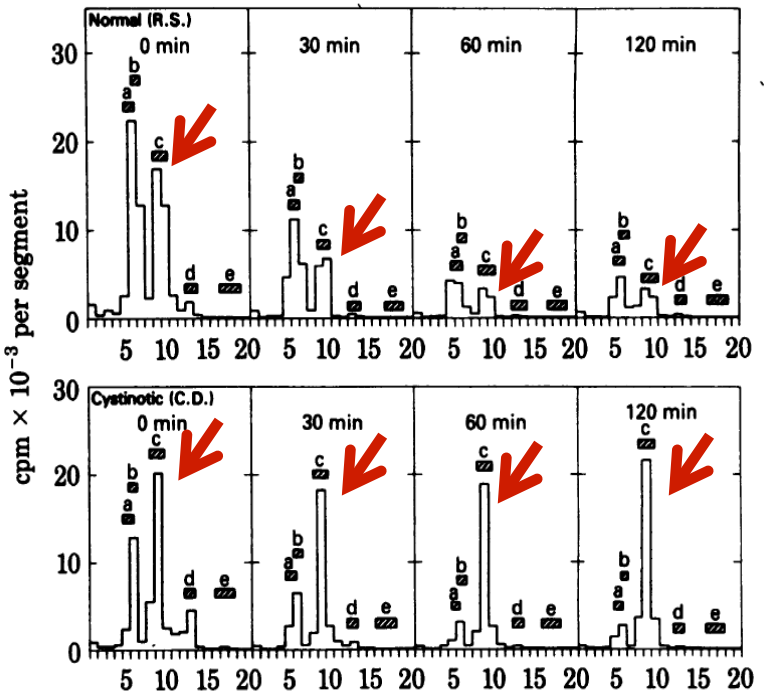
Schneider J *et al.*
Increased cystine in leukocytes from individuals homozygous and heterozygous for cystinosis

Science 157: 1321, ***1967***

Jerry Schneider "A personal History of Cystinosis" KDIGO 2014

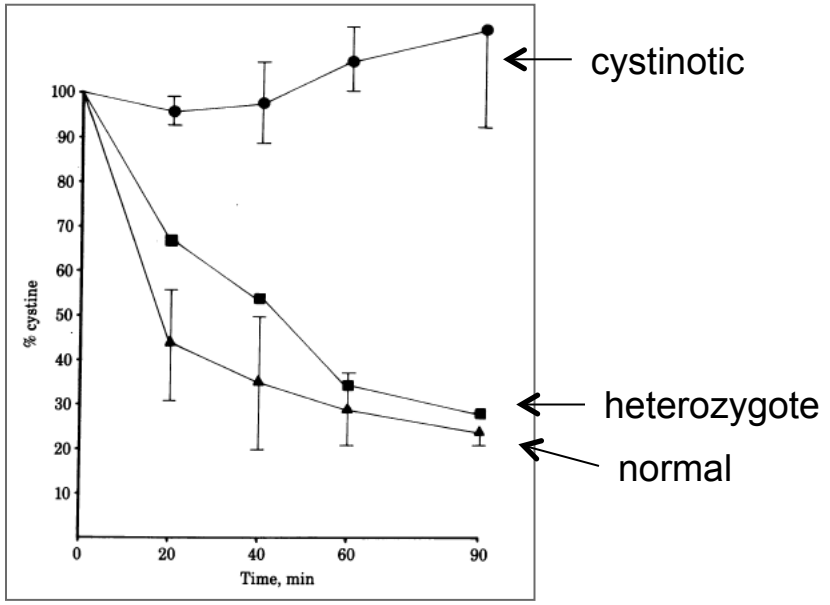
Altered lysosomal cystine transport in cystinosis

Leukocytes



Steinherz R, Tietze F, Gahl WA, Triche TJ, Chiang H, Modesti A, Schulman JD.
Cystine accumulation and clearance by normal and cystinotic leukocytes exposed to cystine dimethyl ester
Proc Natl Acad Sci U S A. 1982, 79 : 4446

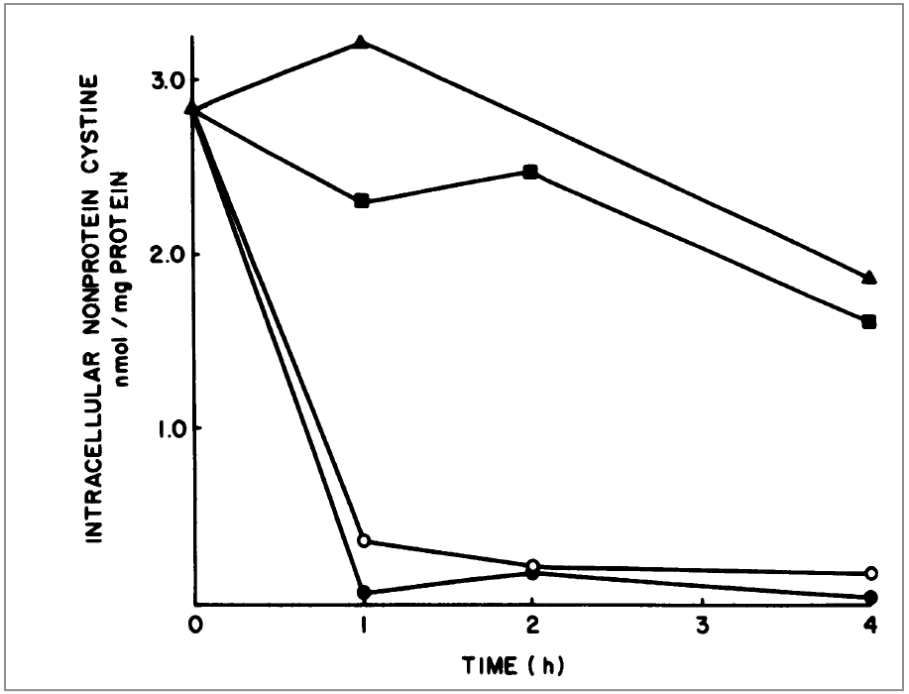
Fibroblasts



Jonas AJ, Greene AA, Smith ML, Schneider JA
Cystine accumulation and loss in normal, heterozygous, and cystinotic fibroblasts

Proc Natl Acad Sci U S A. 1982 , 79 :4442

Cysteamine depletes intra-cellular cystine accumulation

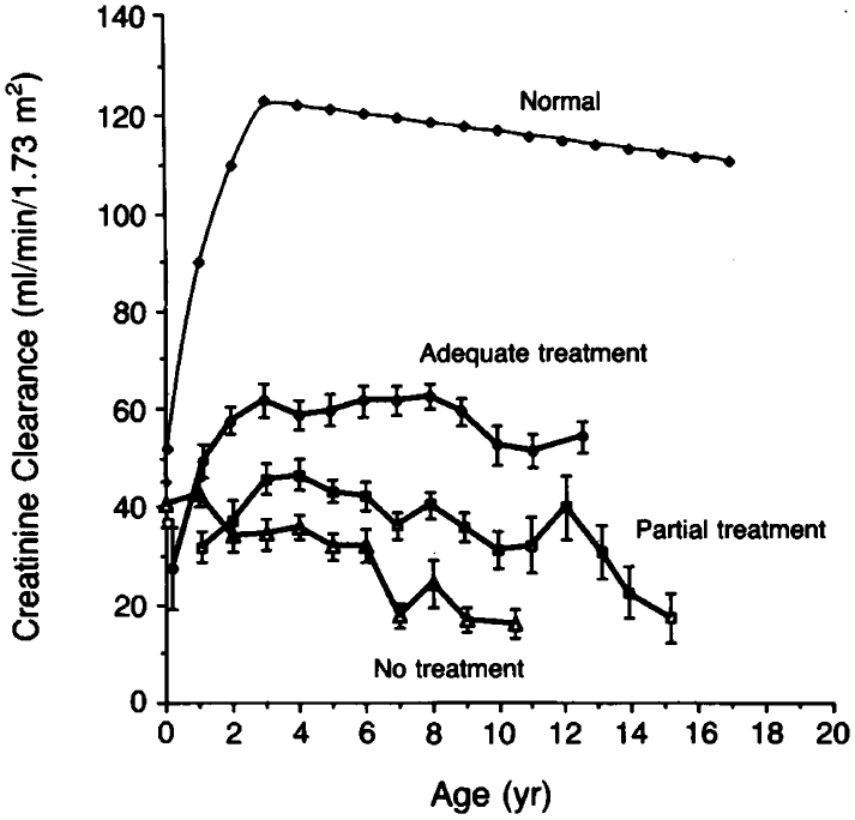


Cysteamine concentrations

- 1 mM
- 0.1 mM
- 0.01 mM
- control

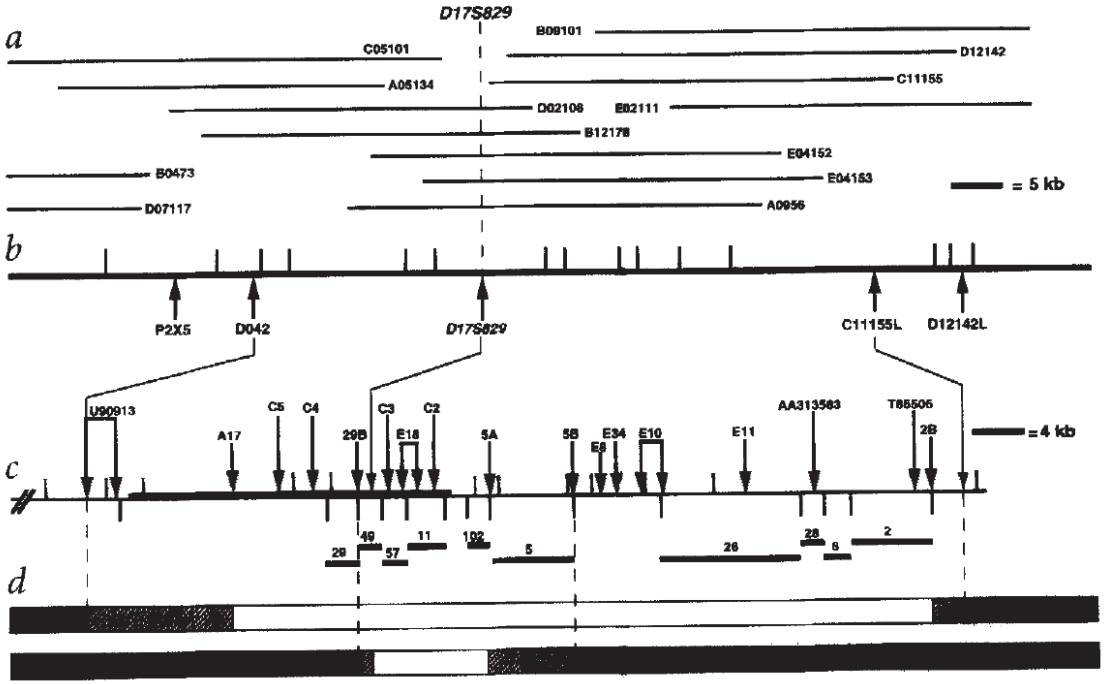
Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA
Cystinosis. Intracellular cystine depletion by aminothiols in vitro and in vivo.
J Clin Invest. 1976, 58: 180

Cysteamine treatment protects renal function



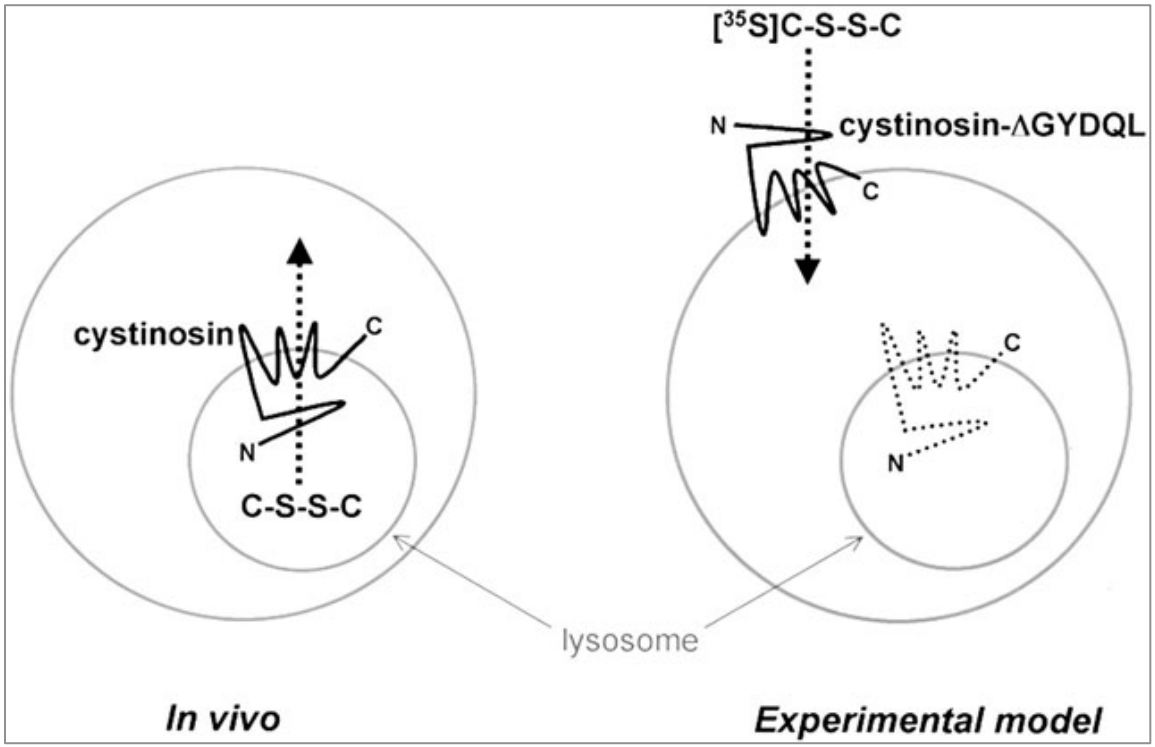
Markello TC, Bernardini IM, Gahl WA.
Improved renal function in children with cystinosis treated with cysteamine
N Engl J Med. 1993 ,1157

Genetic basis of cystinosis: *CTNS gene*



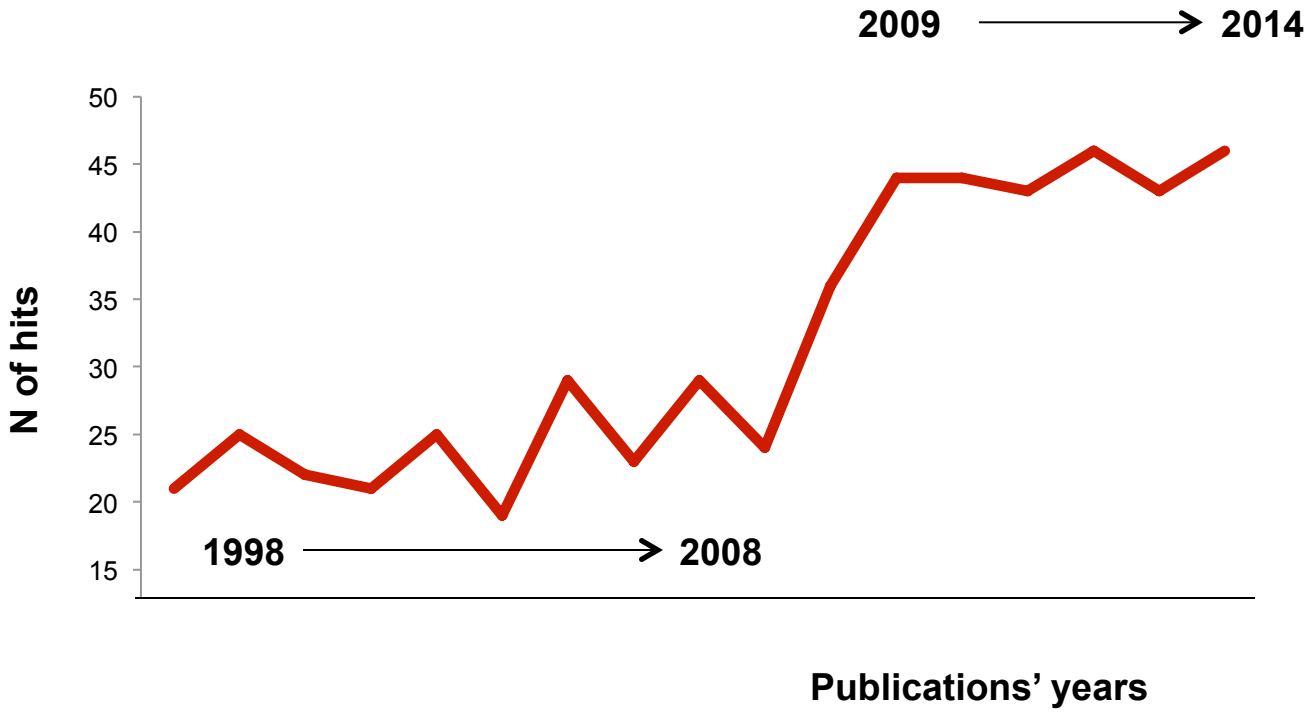
Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitmore SA, Callen DF, Gribouval O, Broyer M, Bates GP, van't Hoff W, Antignac C.
A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis.
Nat Genet. 1998, 18:319

Molecular basis of cystinosis: cystinosin



Kalatzis V, Cherqui S, Antignac C, Gasnier B.
Cystinosin, the protein defective in cystinosis, is a H(+)-driven lysosomal cystine transporter.
EMBO J. 2001, 20: 5940

PubMed hits on cystinosis



2014

CONTROVERSIES IN NEPHROPATHIC CYSTINOSIS

Improving the Future