

Tubulopathies

Nephropathic cystinosis

the „textbook example” of complex tubular damage, the „Fanconi syndrome”

Outline

1. Disease presentation - Diagnosis at a glance
2. Pathomechanism
 - Why the kidney first?
 - Not just crystals
3. Clinical features
4. Treatment
 - Rationale
 - How successful is the treatment?
 - Multidisciplinary approach
 - Transition to adulthood
5. New therapeutic prospects

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Fanconi syndrome



- Diagnosis of proximal tubular damage at the age of 6 mo
- ESRD at 8 years
- Successful kidney Tx at 9 years

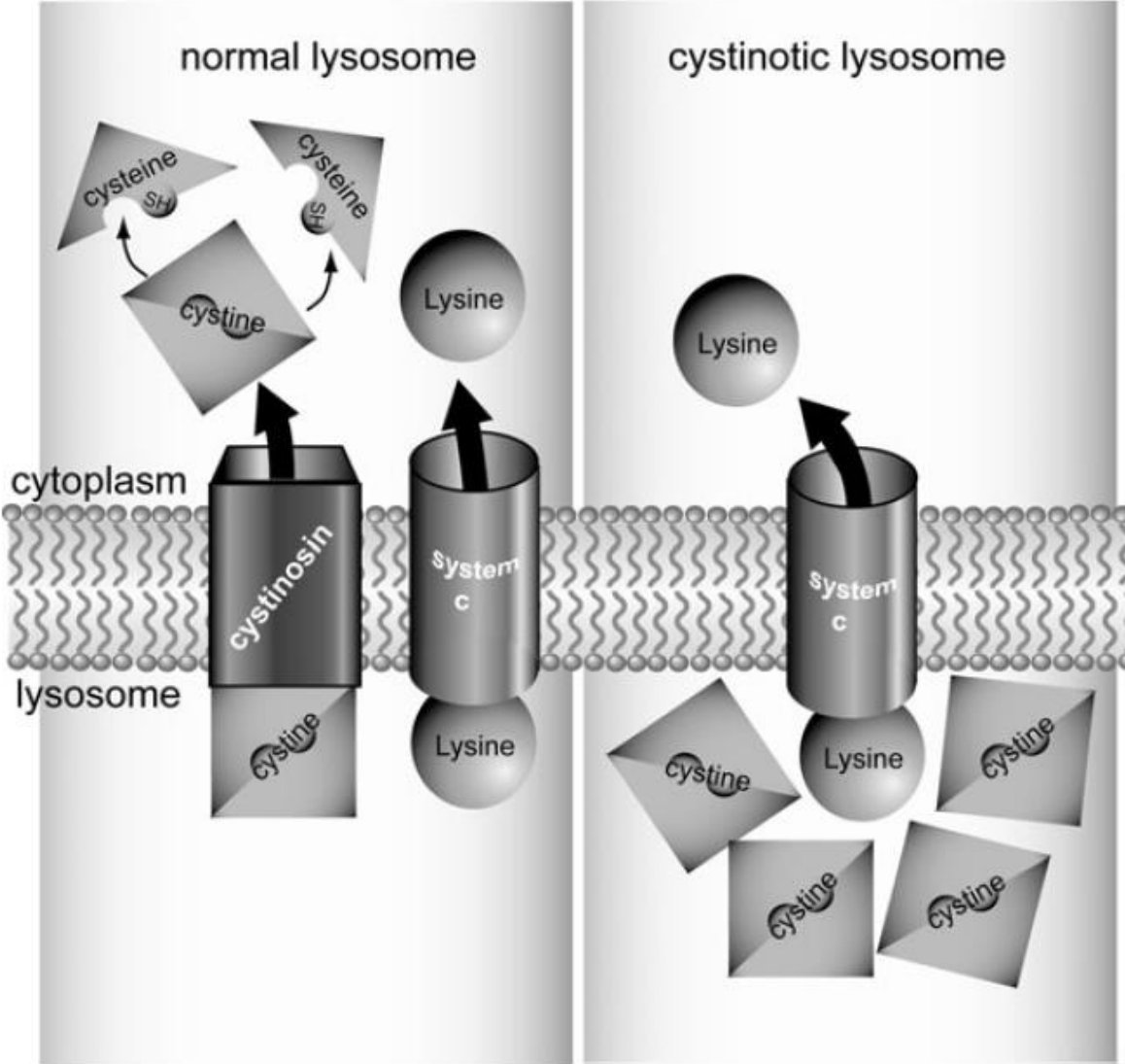
- Diagnosis of cystinosis at 10 years

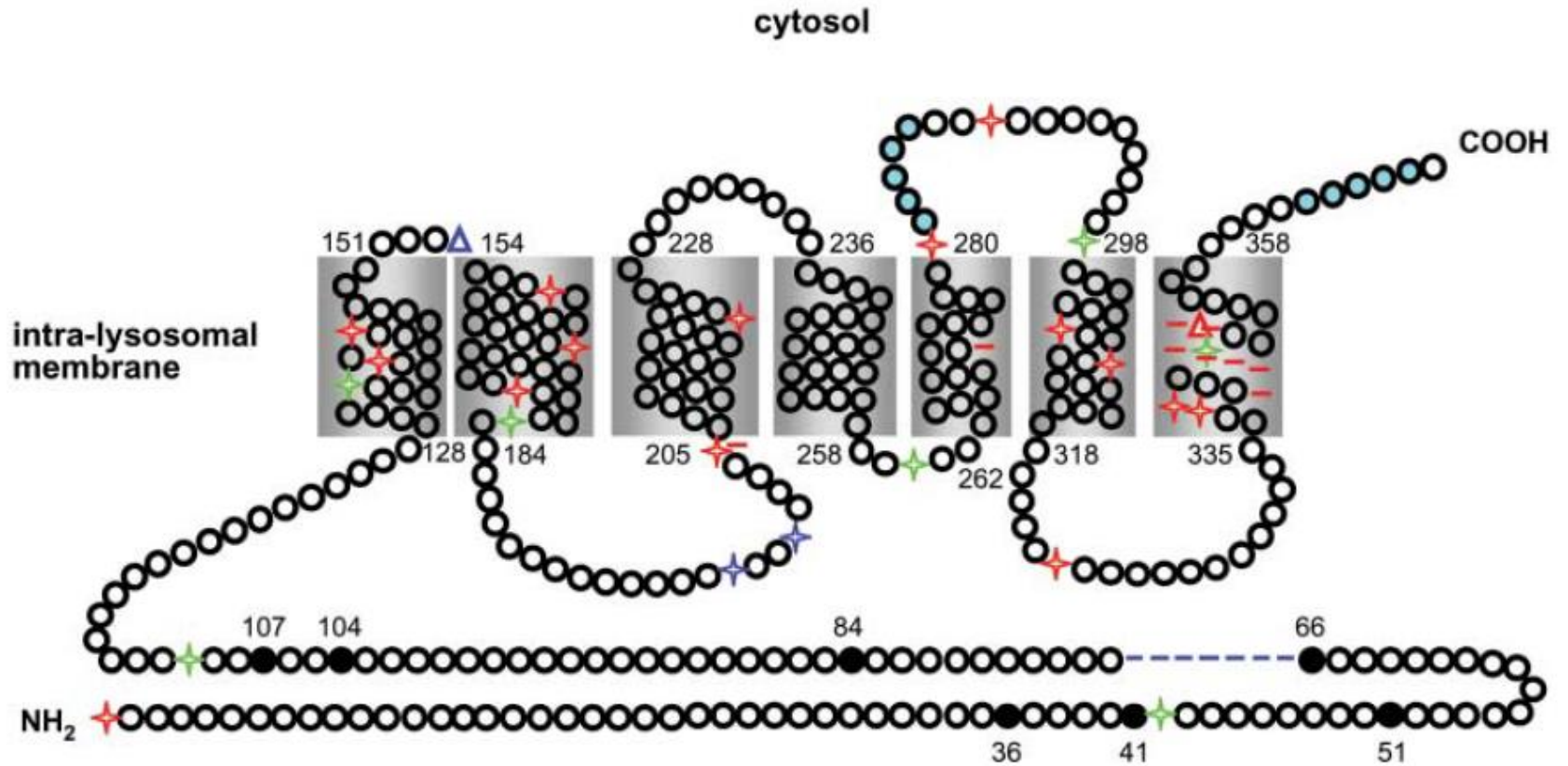
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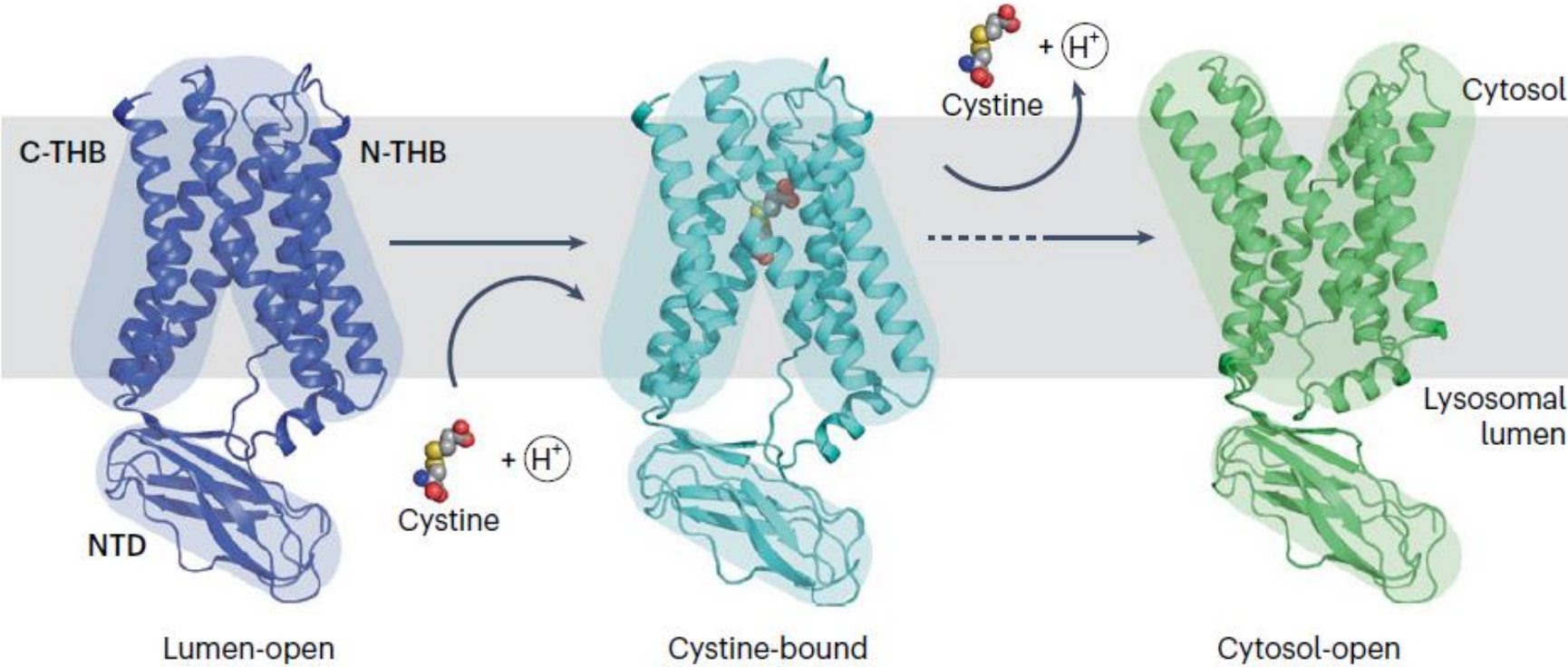
Cystinosis

- a lysosomal membrane transport defect
 - storage disease
- due to defective or missing cystinosine, cystine is trapped in lysosomes and forms crystals
- a disease that affects every cell in the body

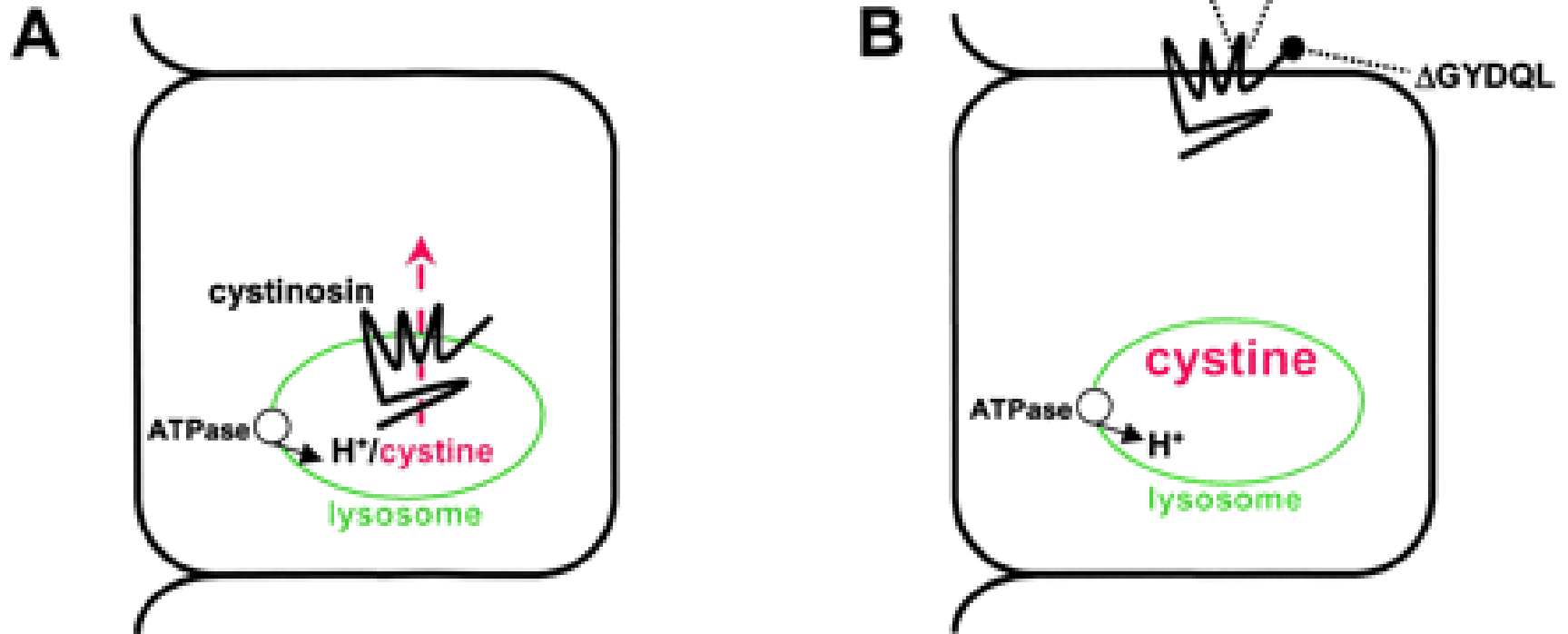




Human cystinosin transport mechanism



Renal Epithelial Traffic Jams and One-Way Streets

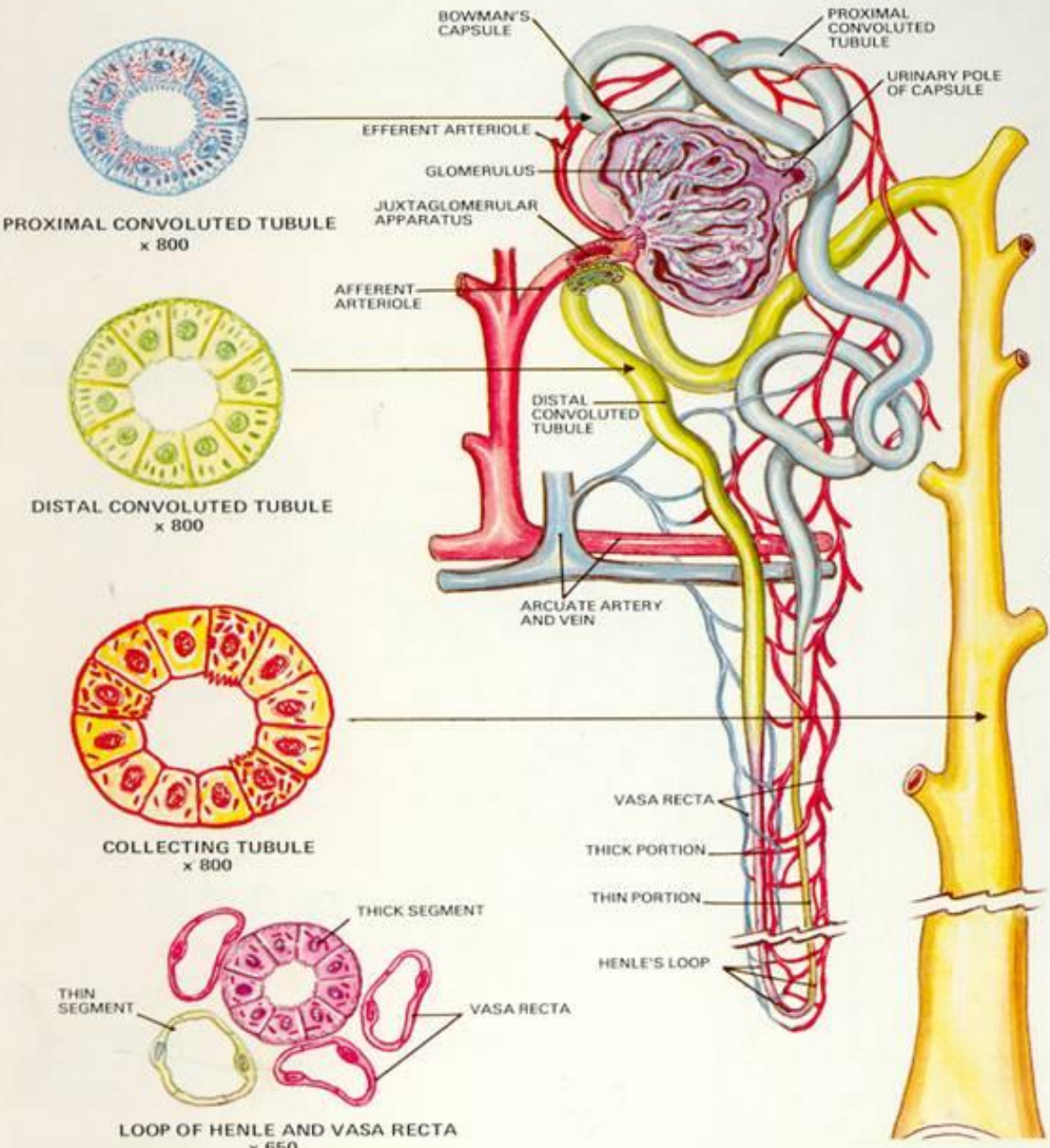


Mark A.J. Devonald and Fiona E. Karet . Am. Soc. Nephrol., Jun 2004; 15: 1370 - 1381.

Cystinosis

- a lysosomal membrane transport defect
 - storage disease
- due to defective or missing cystinosine, cystine is trapped in lysosomes and forms crystals
- a disease that affects every cell in the body
- **Why the kidney first?**

Structure of the kidney



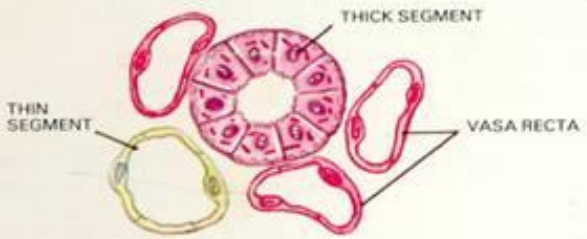
PROXIMAL CONVOLUTED TUBULE x 800



DISTAL CONVOLUTED TUBULE x 800



COLLECTING TUBULE x 800

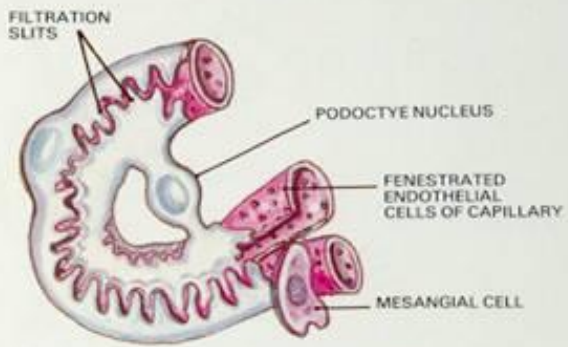


LOOP OF HENLE AND VASA RECTA x 650



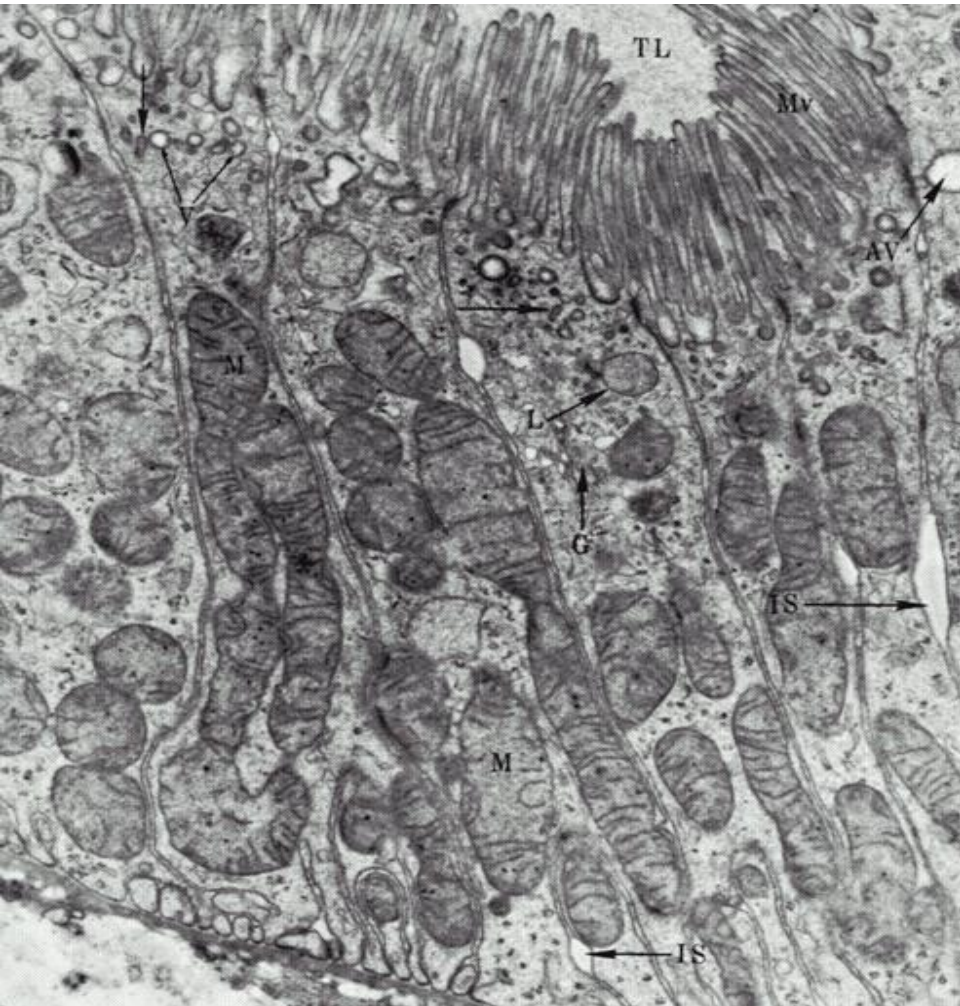
- 1. DISTAL TUBULE
- 2. MACULA Densa
- 3. GRANULAR JUXTAGLOMERULAR CELLS
- 4. EFFERENT ARTERIOLE
- 5. AFFERENT ARTERIOLE
- 6. MESANGIAL CELLS
- 7. GLOMERULAR CAPSULE

ORGANIZATION OF JUXTAGLOMERULAR COMPLEX AND MACULA Densa

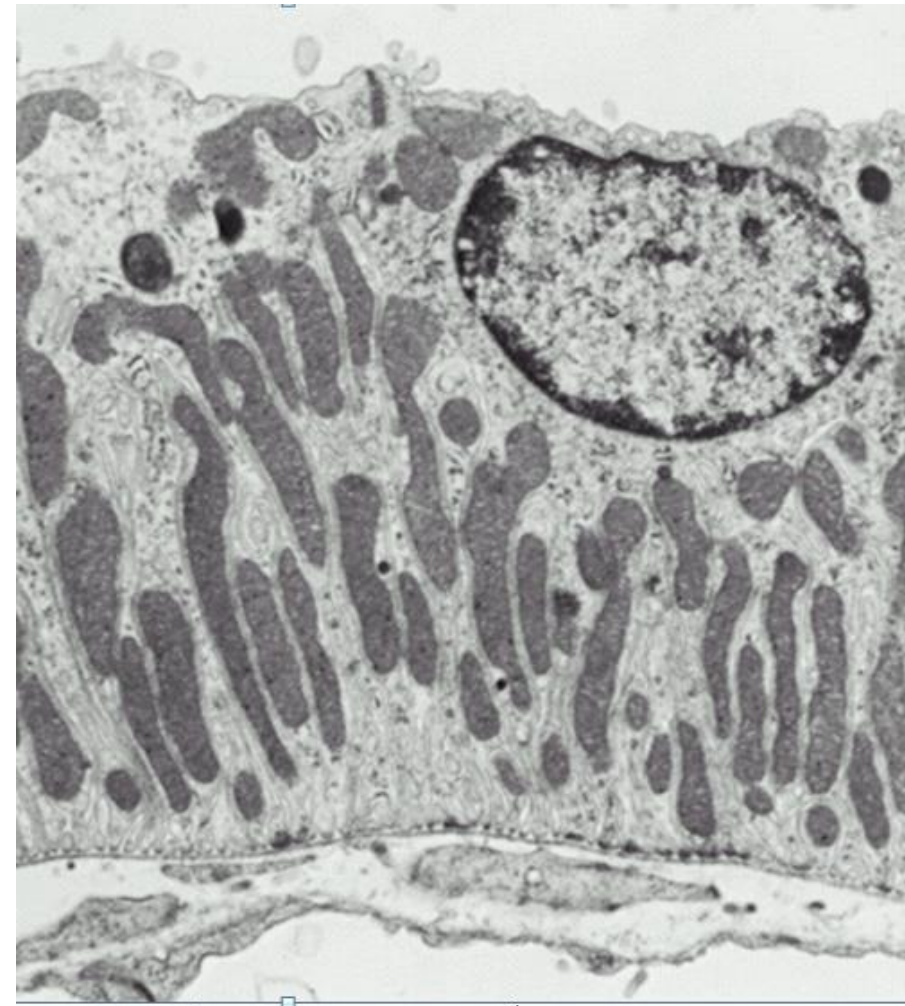


SEGMENT OF CAPILLARY FROM RENAL CORPUSCLE WITH PODOCYTES

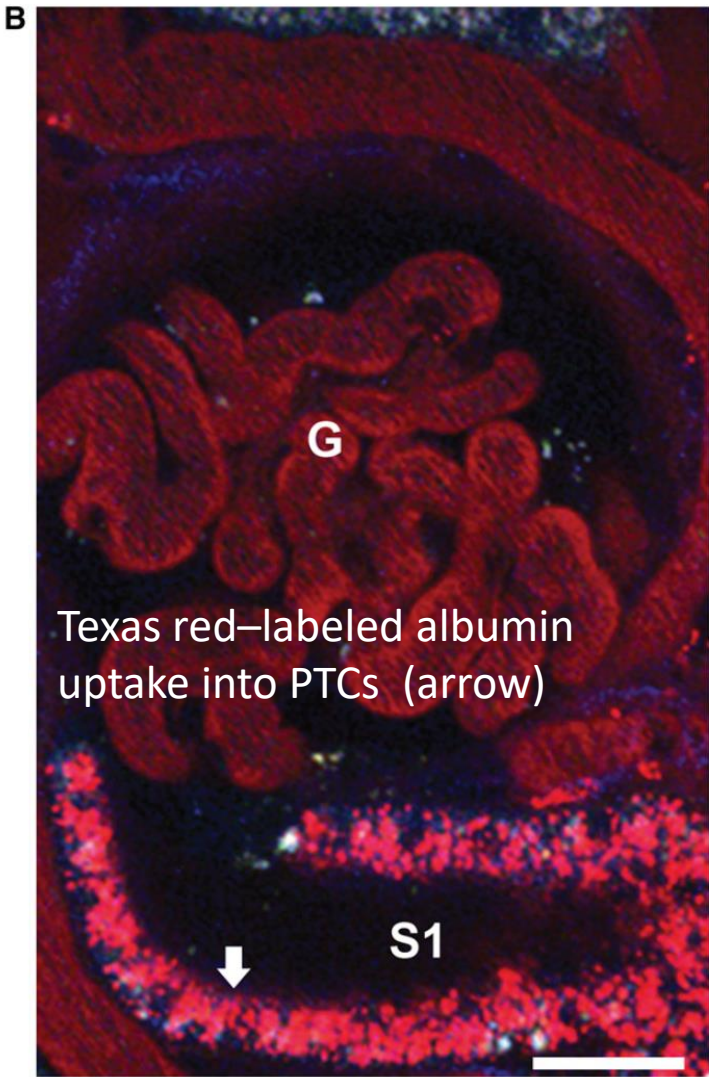
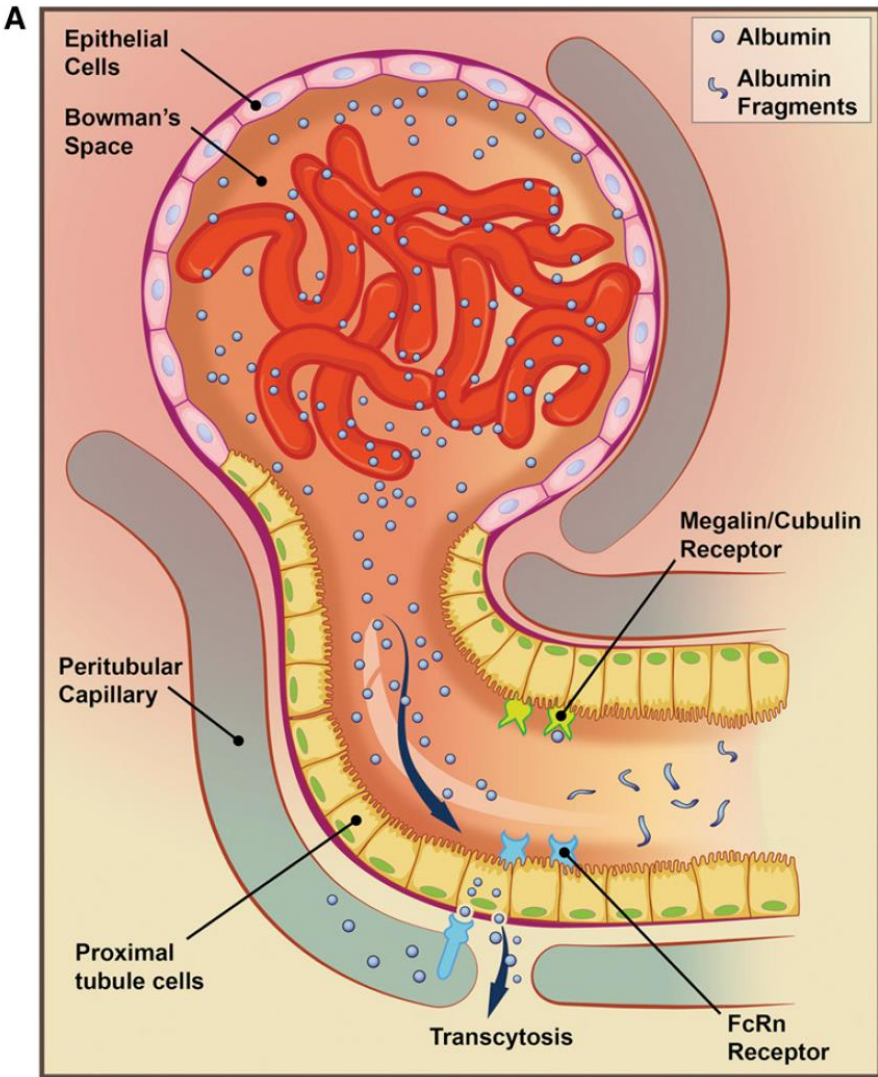
Structure of the proximal tubule



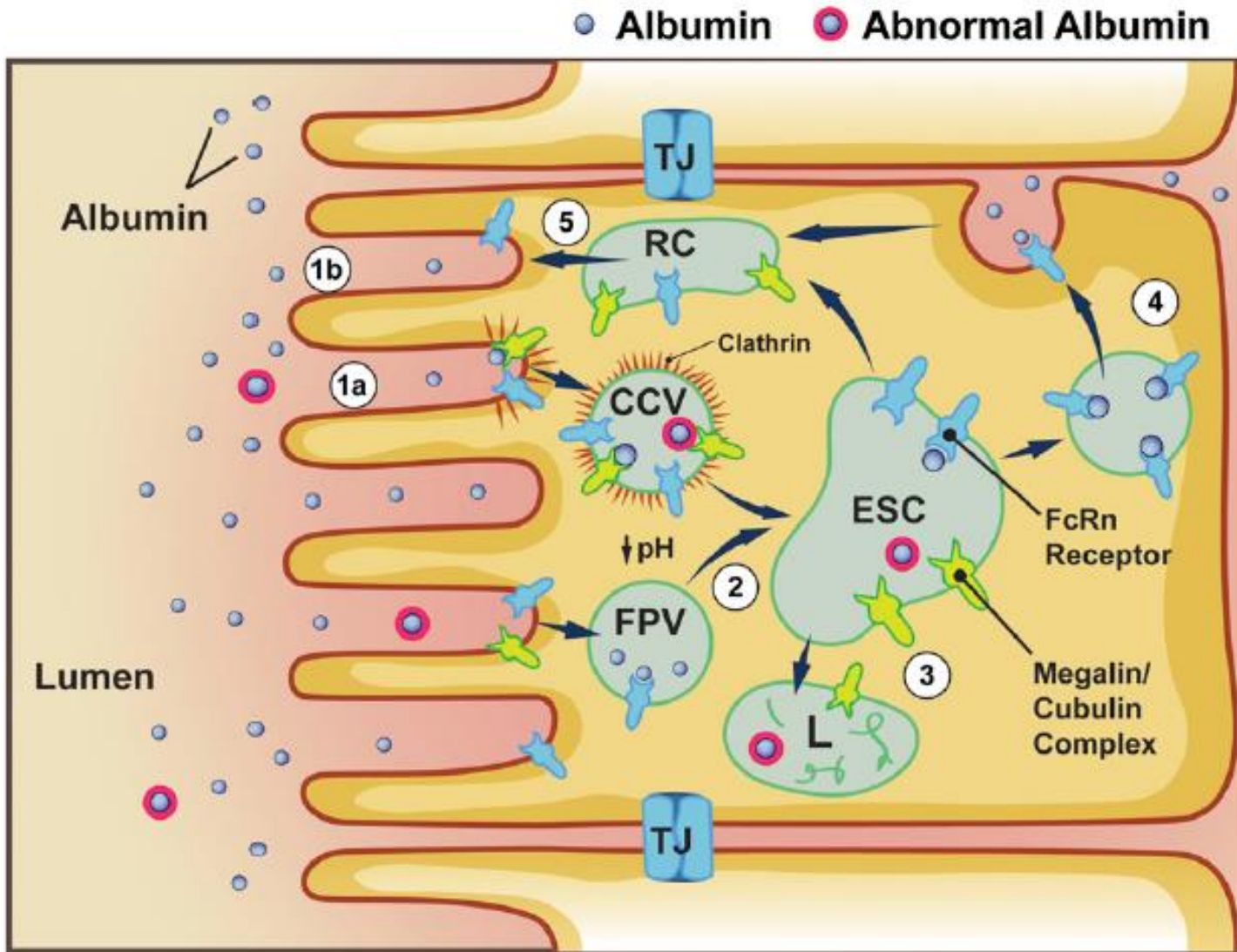
Structure of the distal proximal tubule



Albumin reabsorption in the kidney



Albumin reabsorption in the kidney



ESC: endosomal-sorting compartment

RC: recycling compartment

CCV: clathrin-coated pits into vesicles

L: lysosome

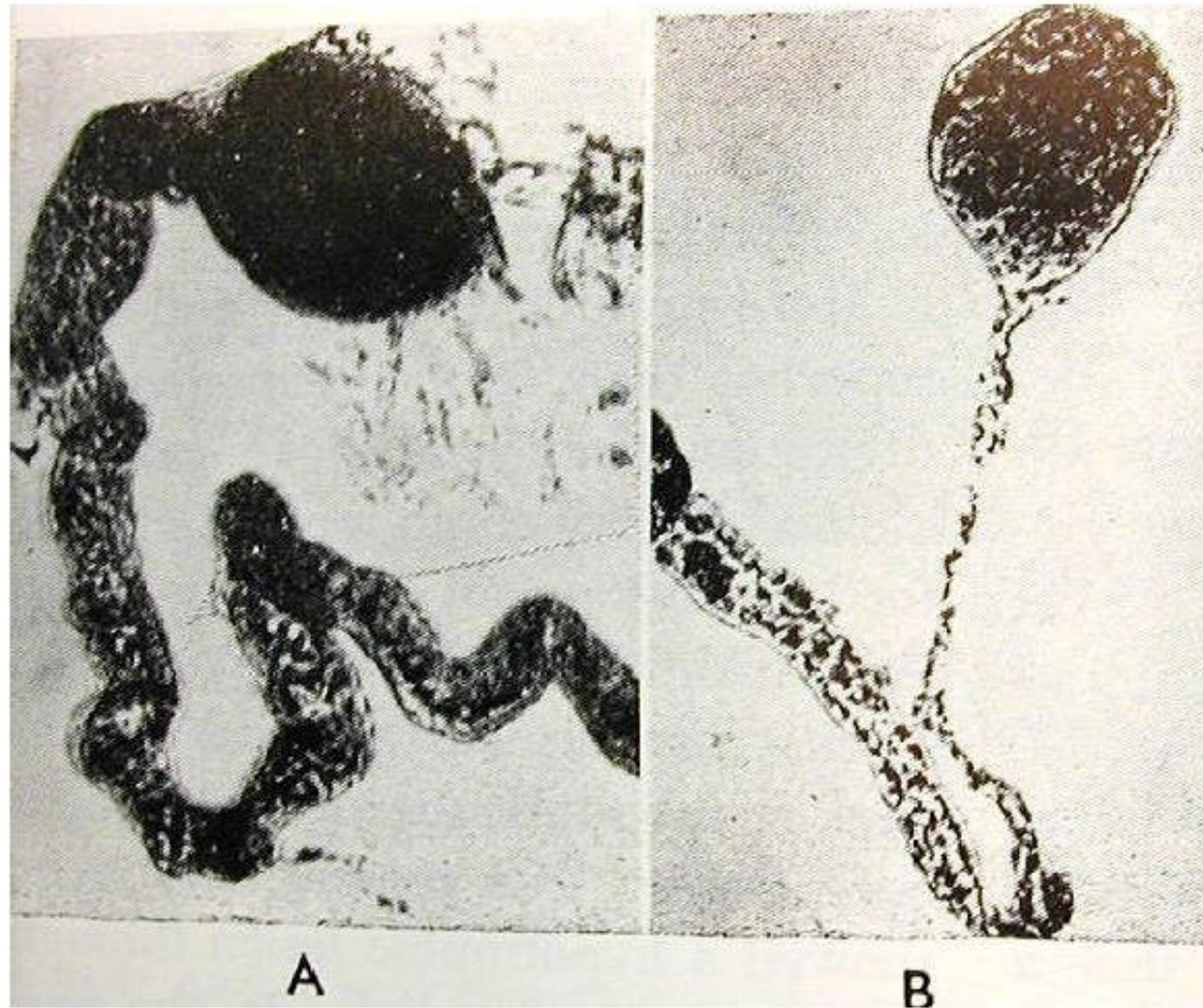
Cystinosis

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 - storage disease
- due to defective or missing cystinosine, cystine is trapped in lysosomes and forms crystals
- a disease that affects every cell in the body
- **Due to massive (immense, enormous...) transcellular protein transport and consequent intracellular protein catabolism, proximal tubule cells are among the first to be damaged in nephropathic cystinosis**

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"Swan-neck Deformity"

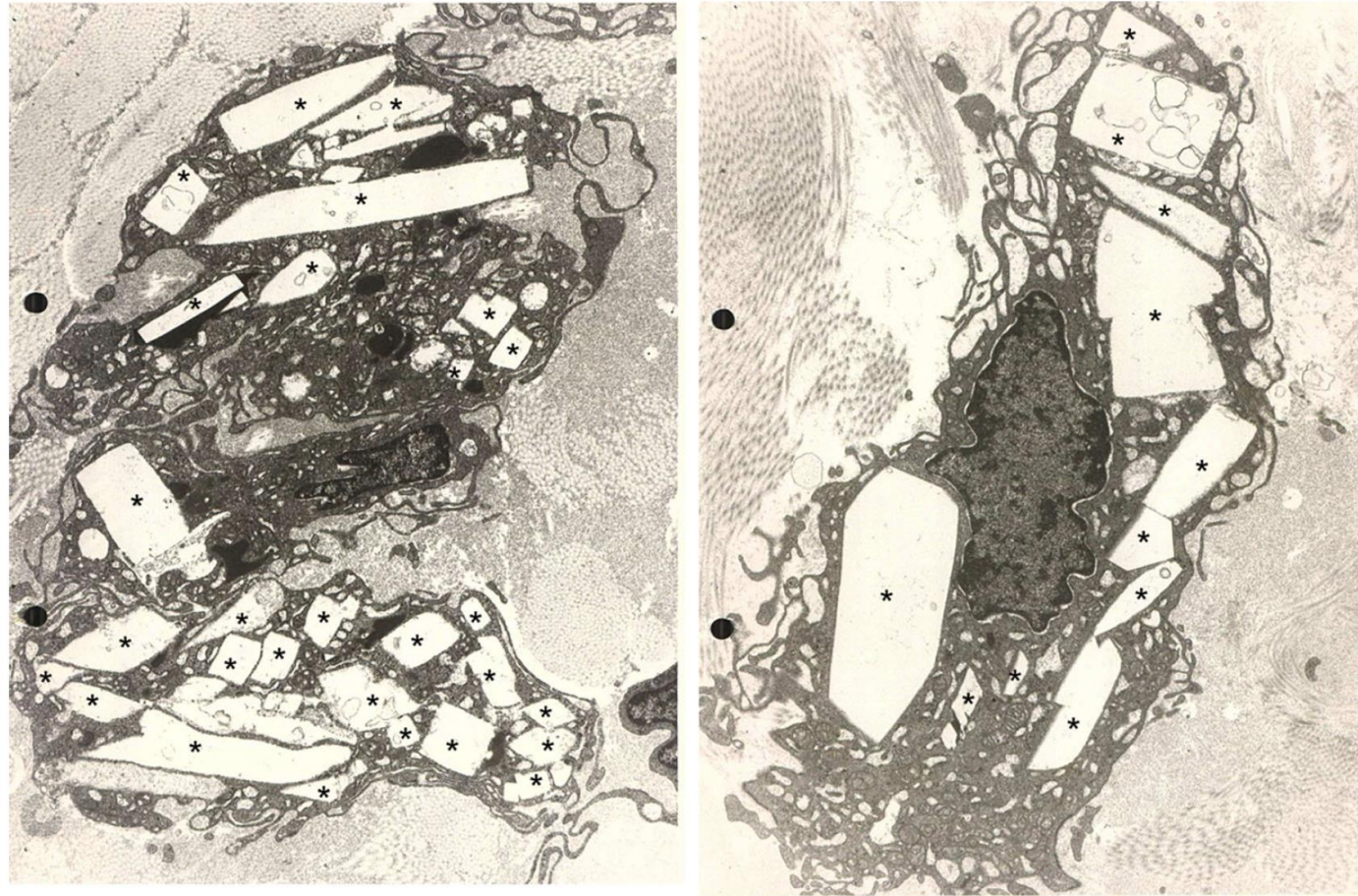


Cystinosis Tissue Repository Study of Atubular Glomeruli

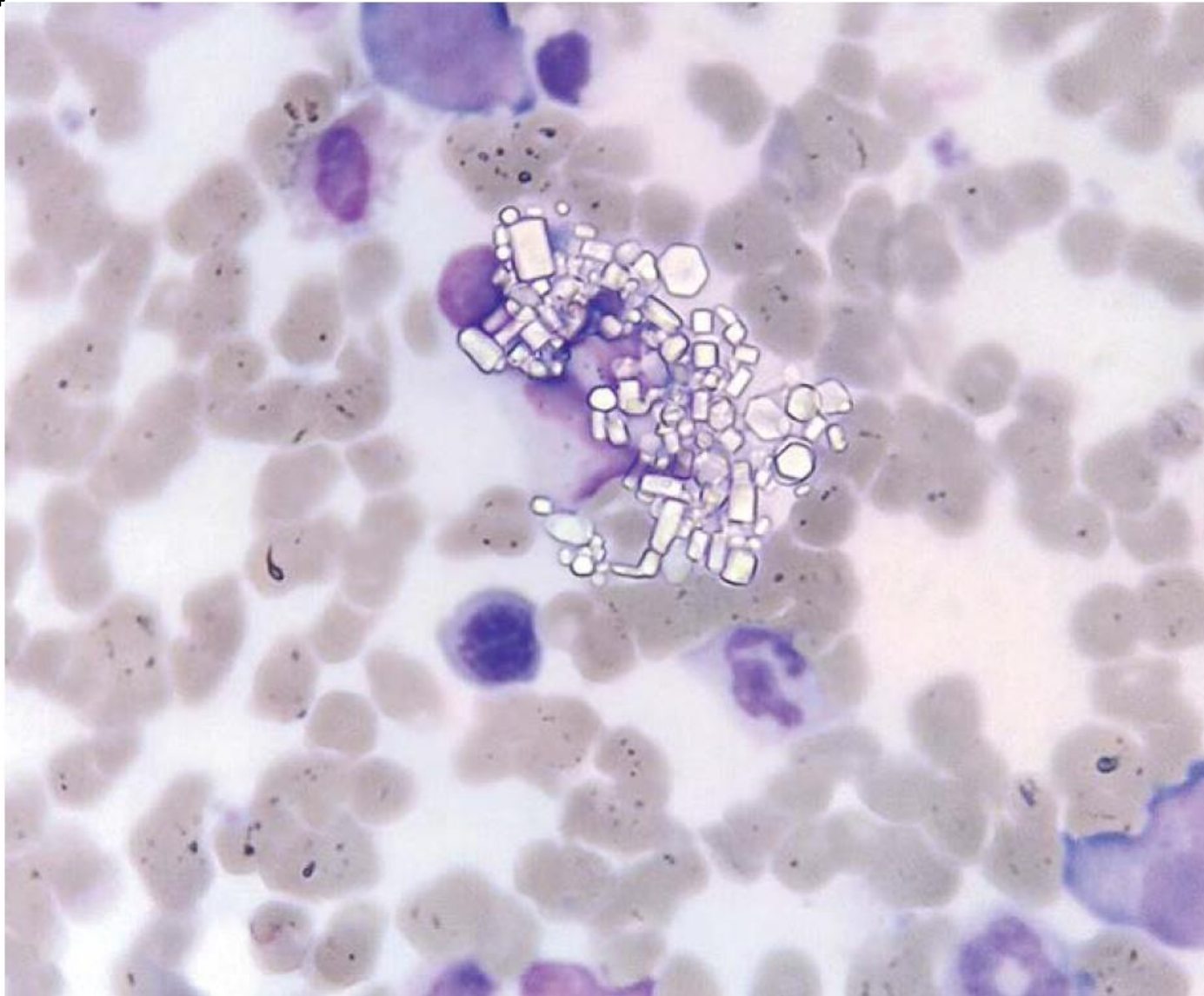
<http://www.slideshare.net/ringer21/cystinosis-tissue-repository-study-of-atubular-glomeruli>

Cystin crystal deposition

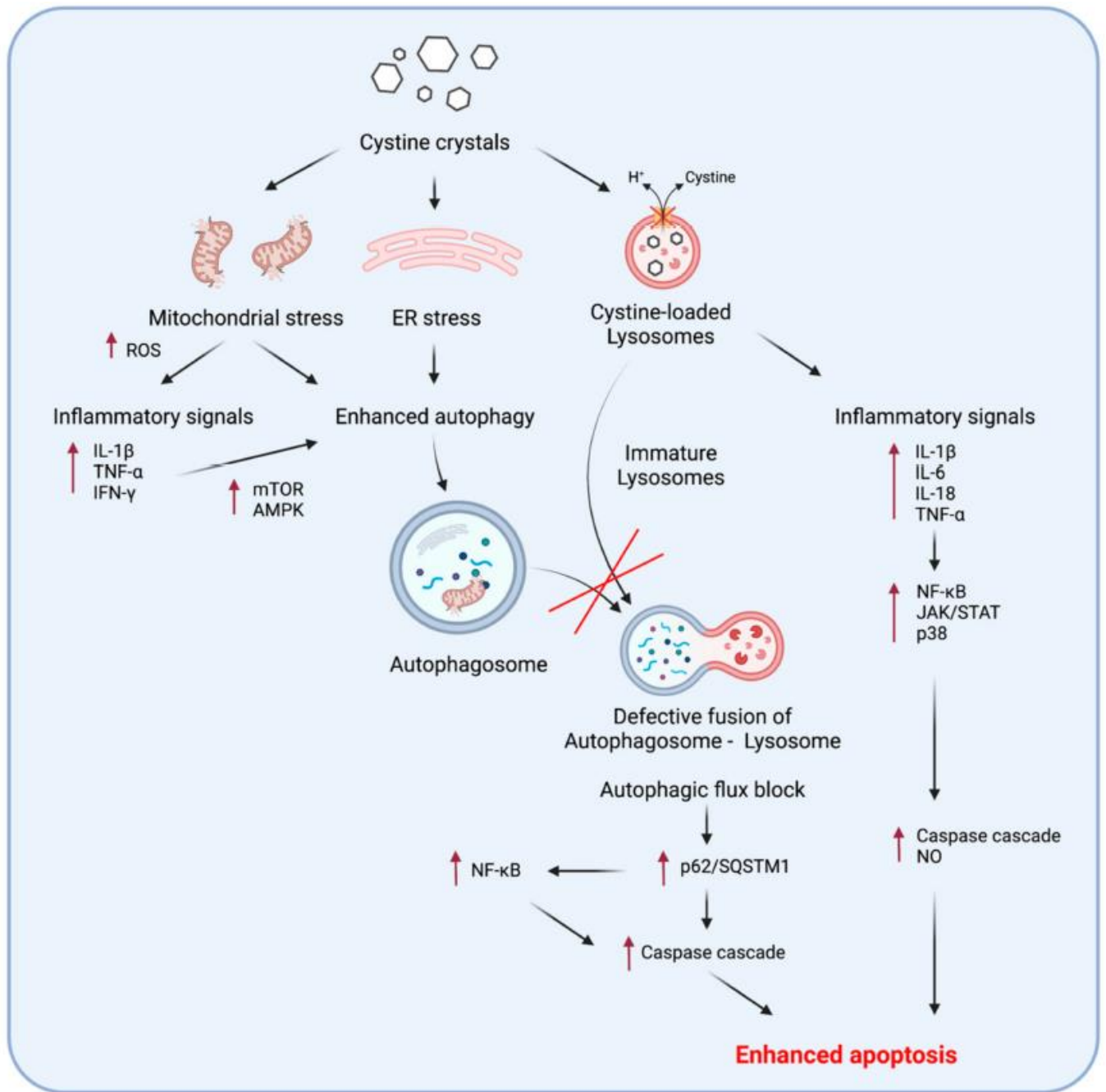
Fig. 2 Electron microscopy of fibroblasts obtained from conjunctival biopsy of the index patient. Fibroblasts can be seen to be packed with cystine crystals (asterisks)



Cystin crystals in bone marrow



Mechanisms of apoptosis and inflammation in nephropathic cystinosis



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Fanconi syndrome

de Toni, Debré and Faconi

renal rickets+glycosuria+hypophosphatemia
=proximal tubular defect=

bicarbonate loss

hypokalemia

decreased urine concentrating capacity

hyperphosphaturia-hypophosphatemia

aminoaciduria

glycosuria

proteinuria

Incidence: 1 - 100,000 Bretagne: 1 - 26,000

Clinical manifestation:

polyuria, dehydration, growth retardation, rickets, + symptoms
specific to the underlying disease

Fanconi syndrome. Etiology:

inherited

- **cystinosis**
- galactosemia
- fructose intolerance
- tyrosinemia
- Wilson' s disease
- Lowe sy
- glycogenosis
- cytochrome-c oxidase def.
- idiopathic

acquired

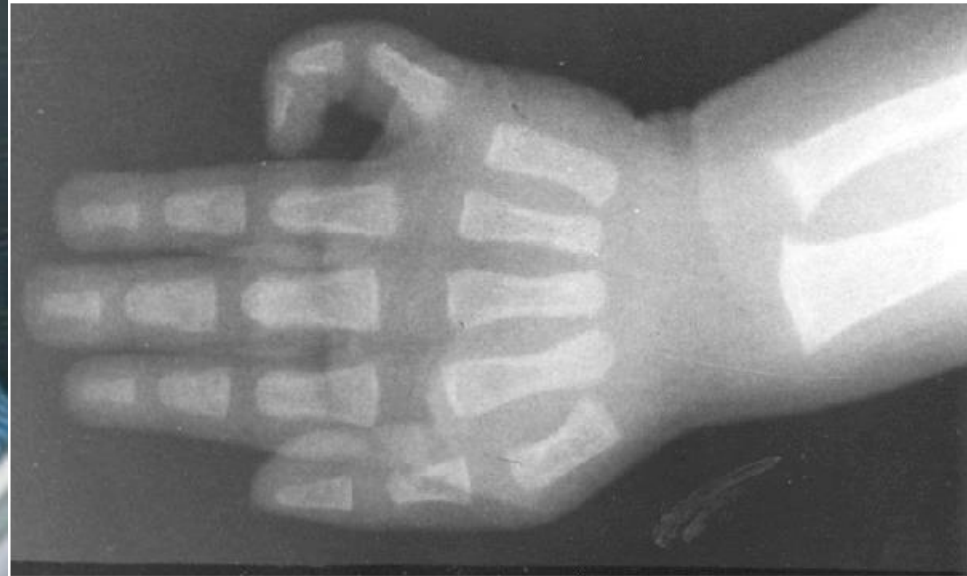
- heavy metal
- Glue-solvent inhalation
- Azathioprine
- Gentamicin streptozocin induced
- Myeloma multiplex
- Sjögren sy
- Amyloidosis
- Cysplatin
- Iphosphamid
- Transplantation

Cystinosis.

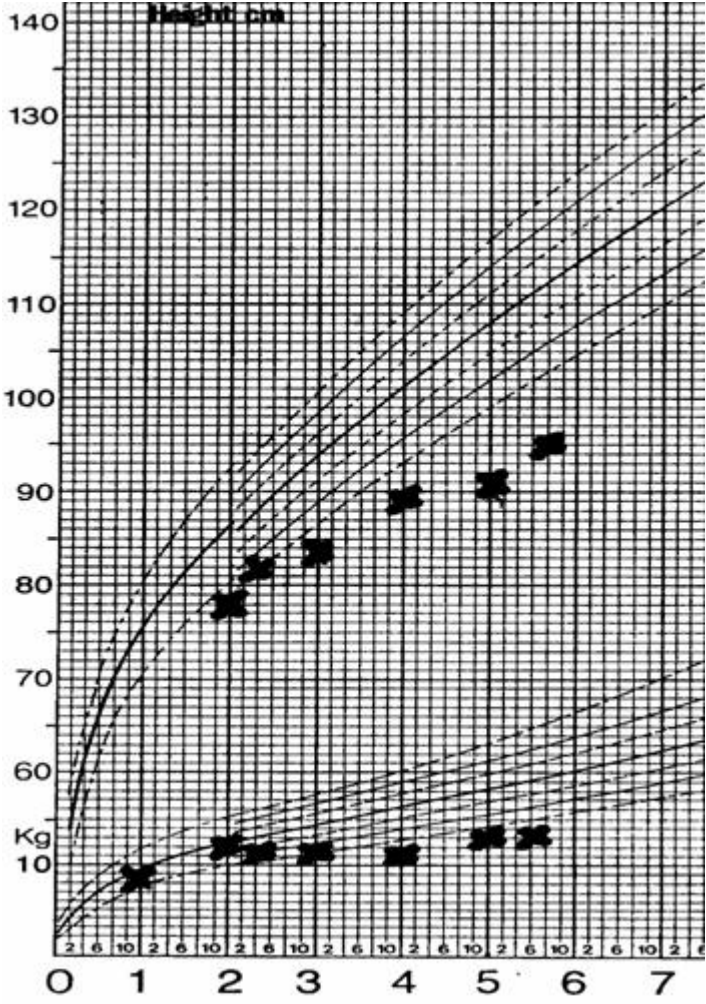


0/20/2023

Rickets



Cystinosis.

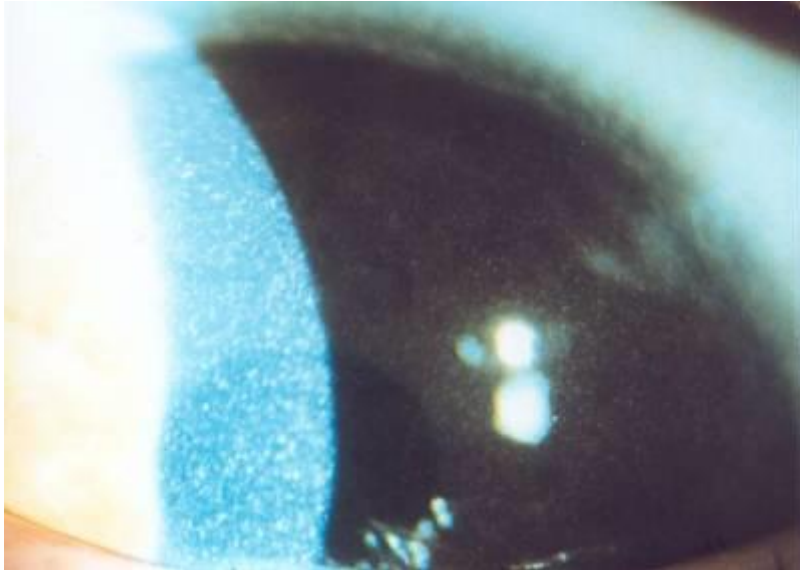


- Growth delay

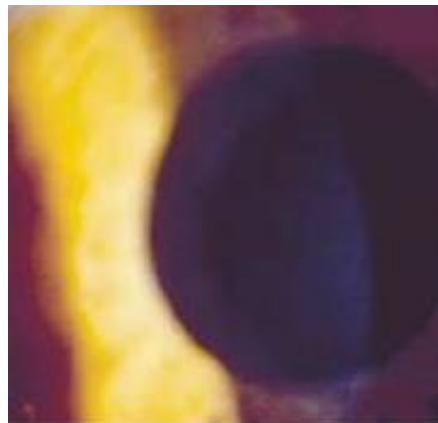
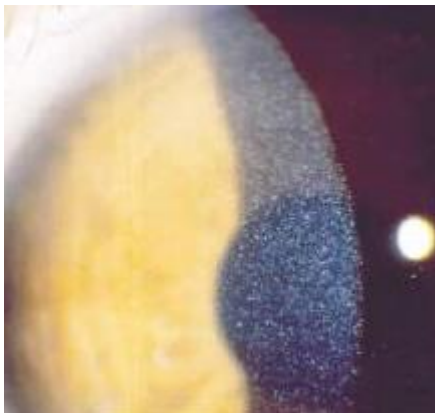
Cystinosis photophobia.



Cystinosis.



- Cystin crystals in the cornea



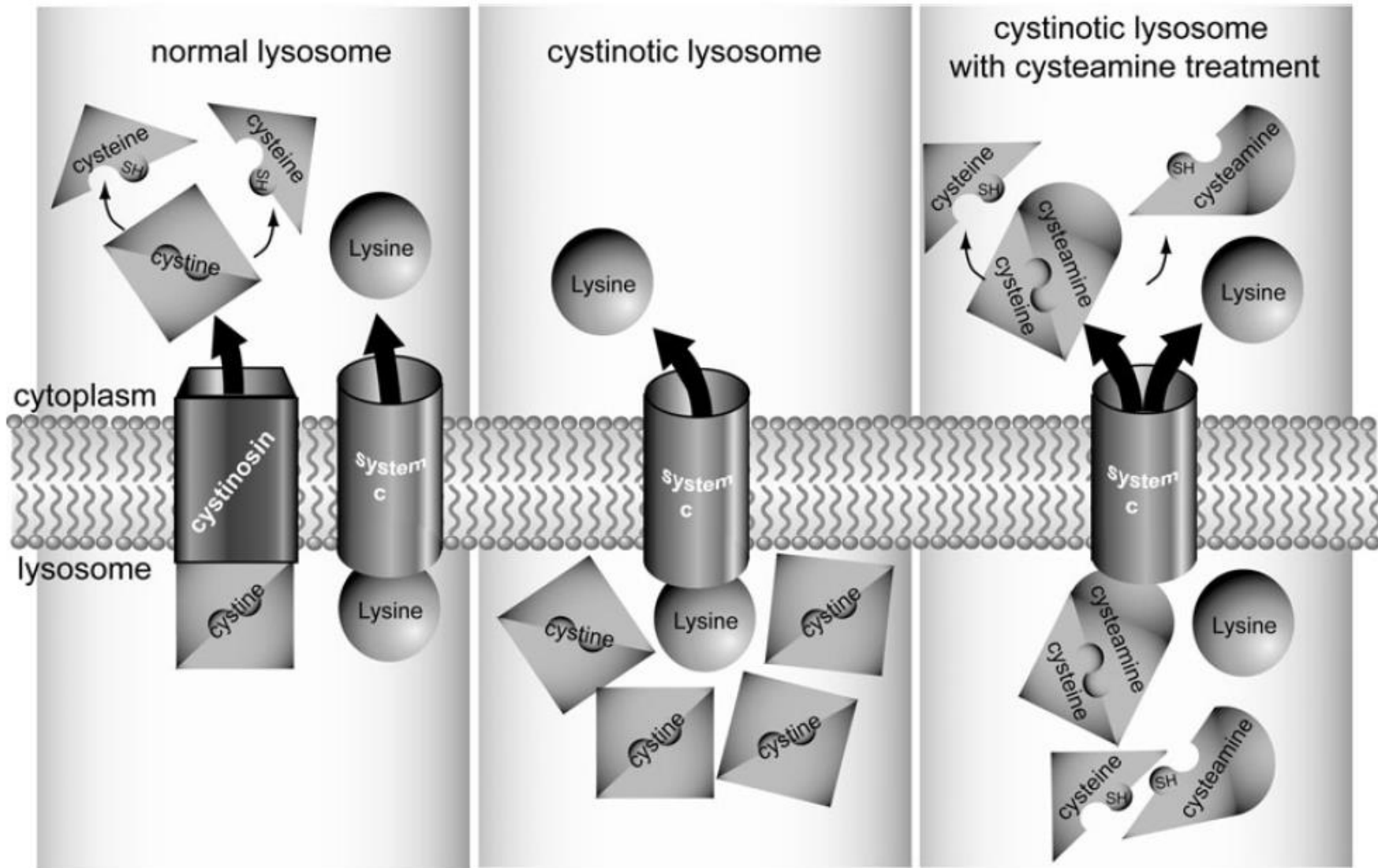
Cystinosis. Natural history of the disease



- 7-8 y: ESRD
- 5-10 y hypothyreosis
- 12-40 y myopathy, difficulty to swallow
- 13-40 y degeneration of the retina, blindness
- 18-40 y diabetes mellitus
- 18-40 y male hypogonadism
- 21-40 y lung dysfunction
- 21-40 y CNS involvement
- -- late outcome ??

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Medical treatment(3.5 y 14 kg)

- Fluid intake: 3-3.5 l = cca. 250 ml/kg
- K 350 mmol/day = 25 mmol/kg
- HCO₃ 300 mmol/day = 21.5 mmol/kg

- Ca Sandoz 2x250 mg
- P Sandoz 4x500 mg
- Alpha-D3 50 mikrogramm/day
- Amilorid 1.25 mg
- HCTZ 12.5 mg

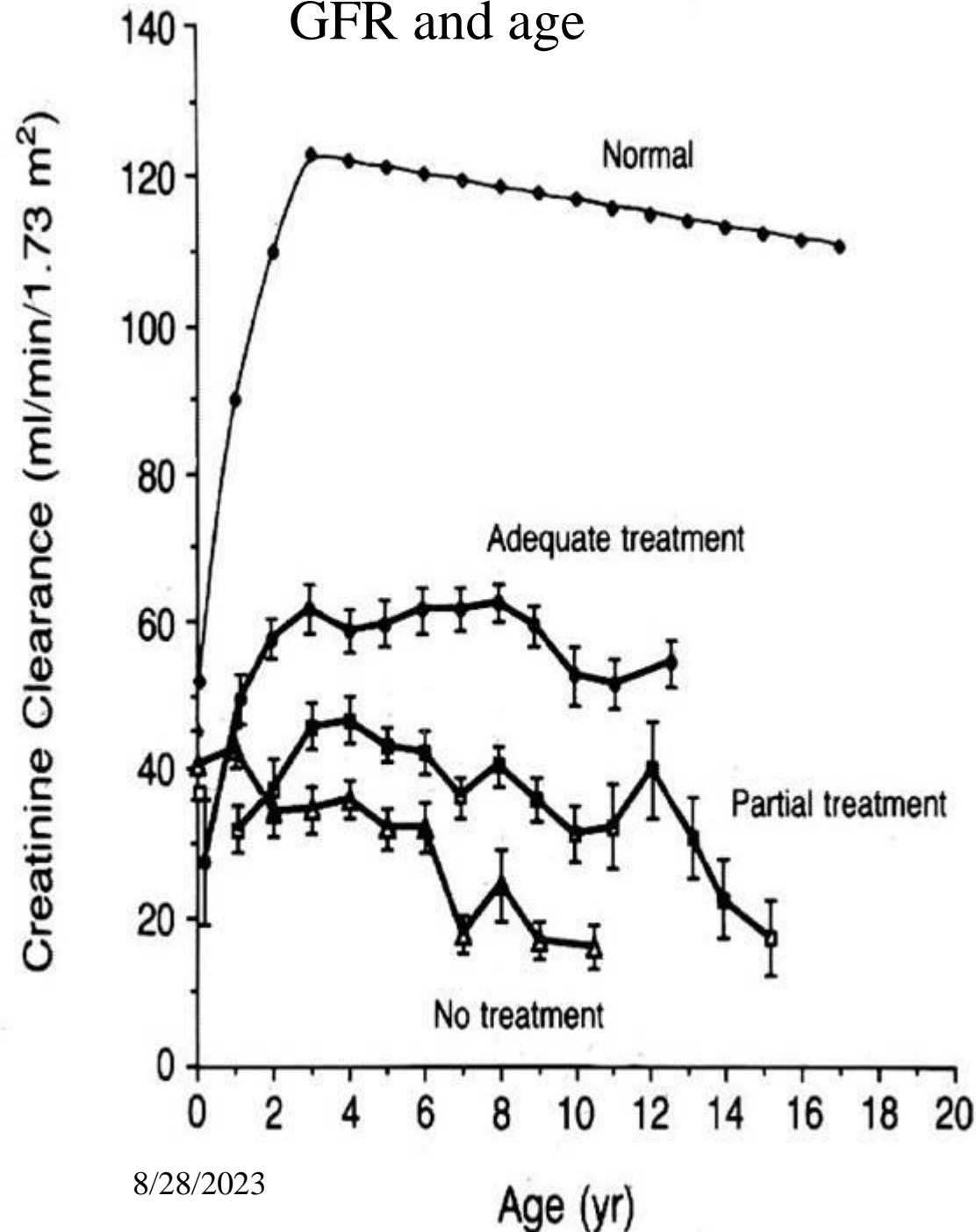
- L-Thyroxin 25 mikrogramm
- Folic acid/iron supplementation

- *Cystagon 6x250 mg*
- *Cysteamin eye drops 4-6x daily*

Aims of treatment

- To conserve kidney function
- Growth
- To stop extrarenal manifestations
 - Eye
 - Thyroid
 - Glucose metabolism
 - Gonads
 - Muscle
 - CNS

GFR and age



Follow-up:
Intracellular cystin level

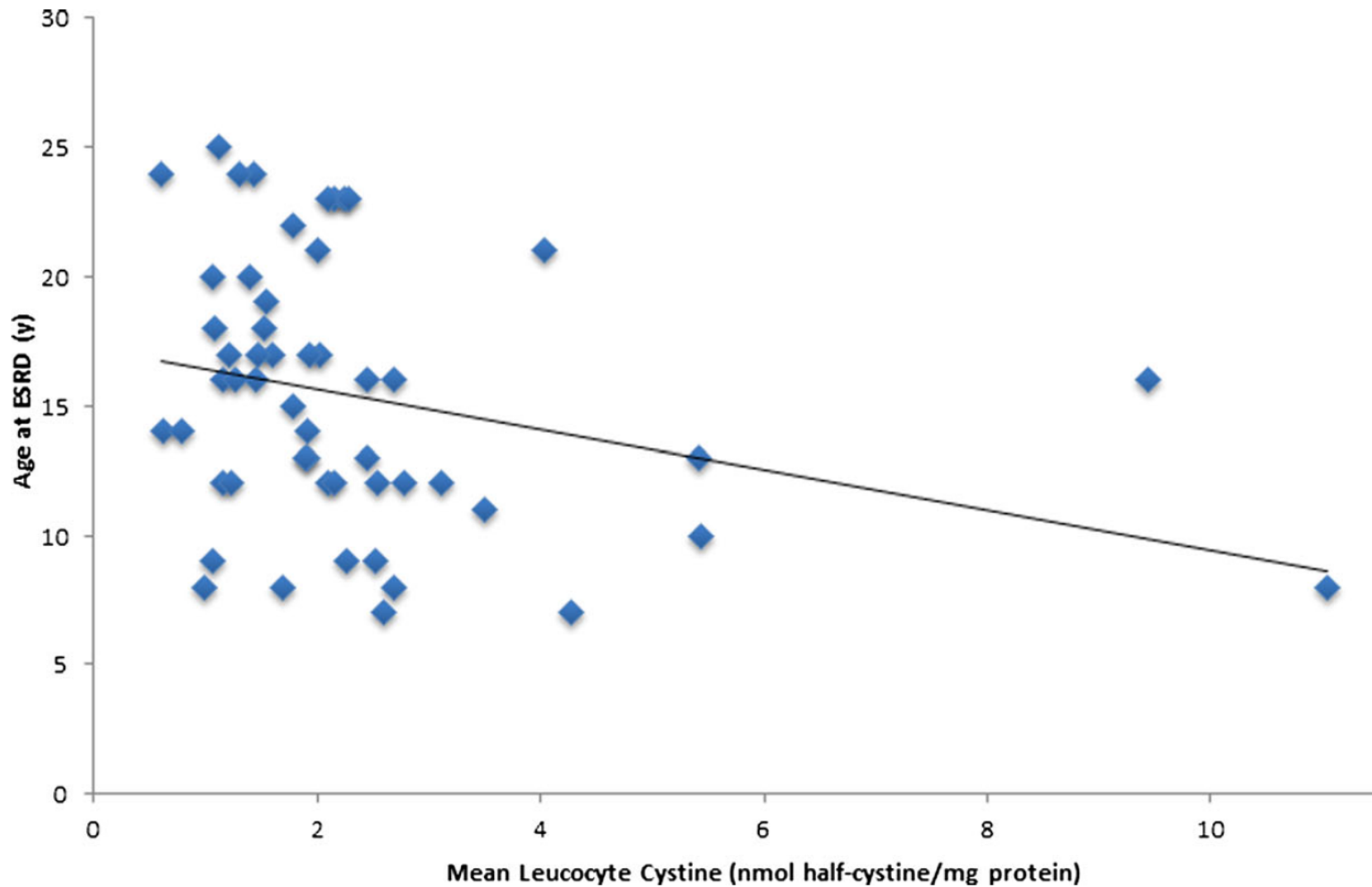
On treatment: n= 17
Partially successful tr: n= 32
Off treatment: n=67

Markello: N Engl J Med,
328: 1993.1157-1162

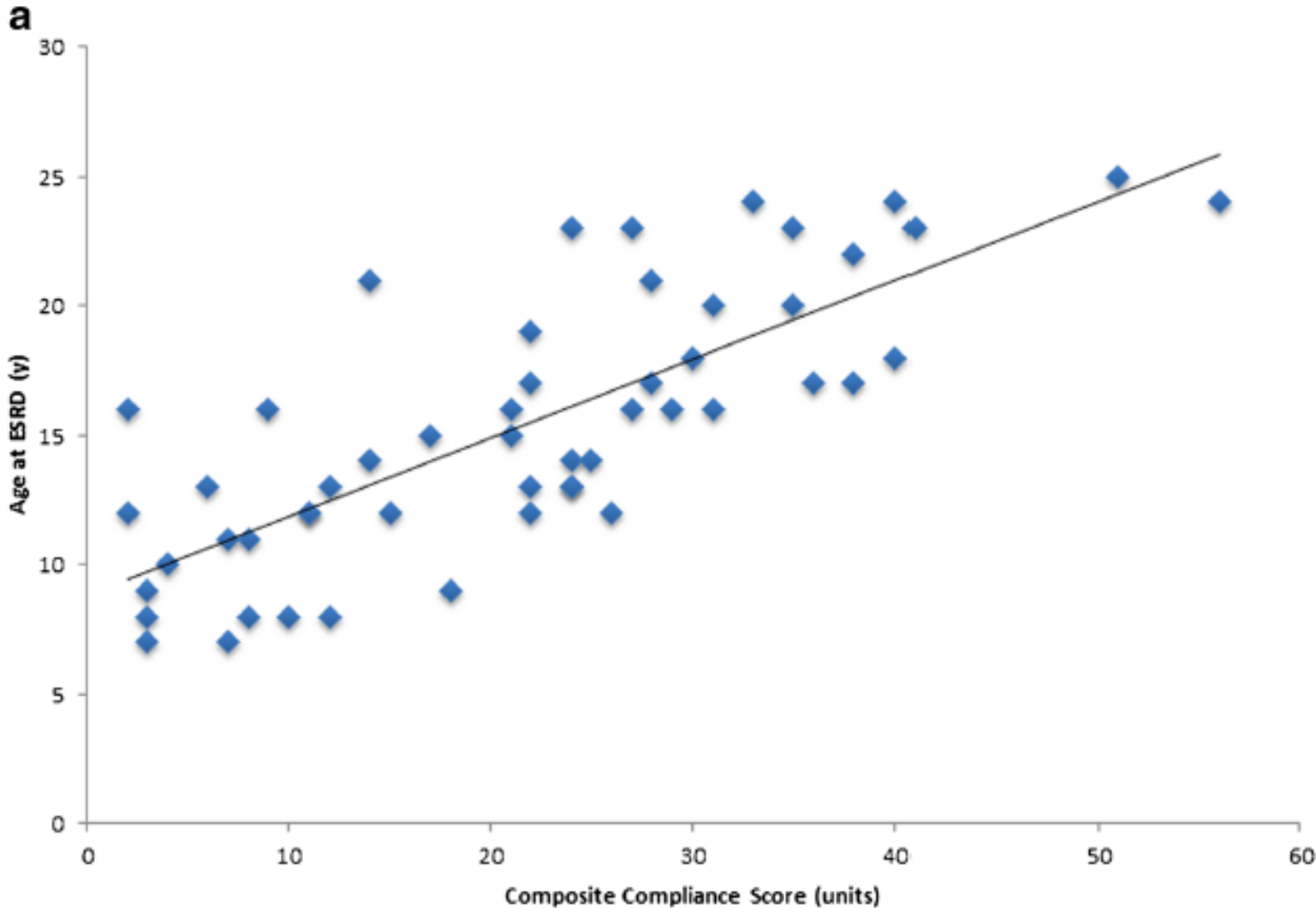
The clue to successful treatment: compliance and monitoring (?)

- Monitoring
 - Measuring intracellular cystine (IC)
 - complex sample preparation
 - rare disease – IC is measured in few certified laboratories
- Compliance
 - frequent dosing is required (6x)
- Foul breath
 - smells like bad eggs because of hydrogen sulfide
- Gastrointestinal complaints
- Treatment should be continued after successful transplantation
- Adolescence

Leucocyte cystin level and CKD



„Compliance score” and evolution to ESRD

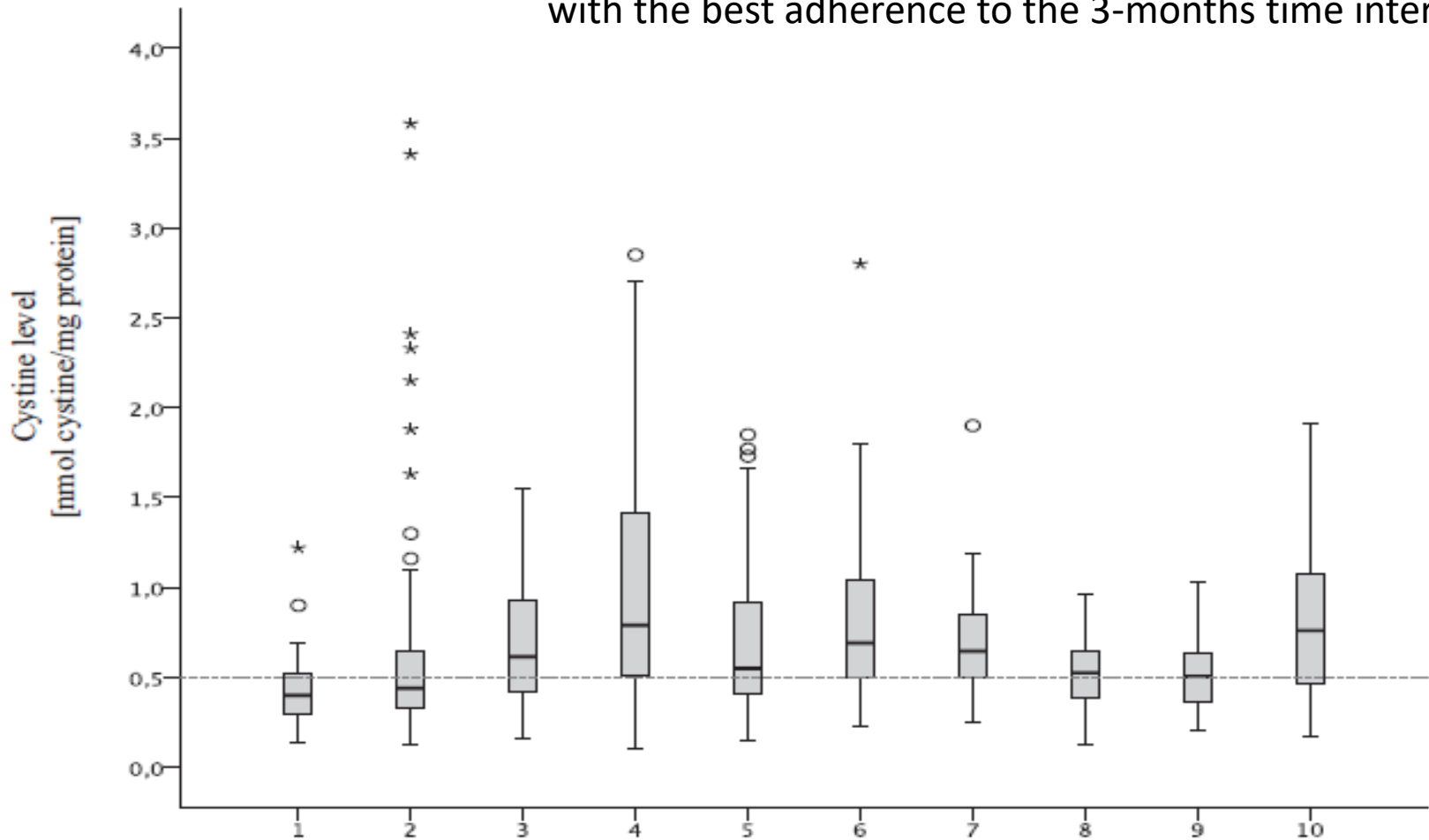


Monitoring treatment

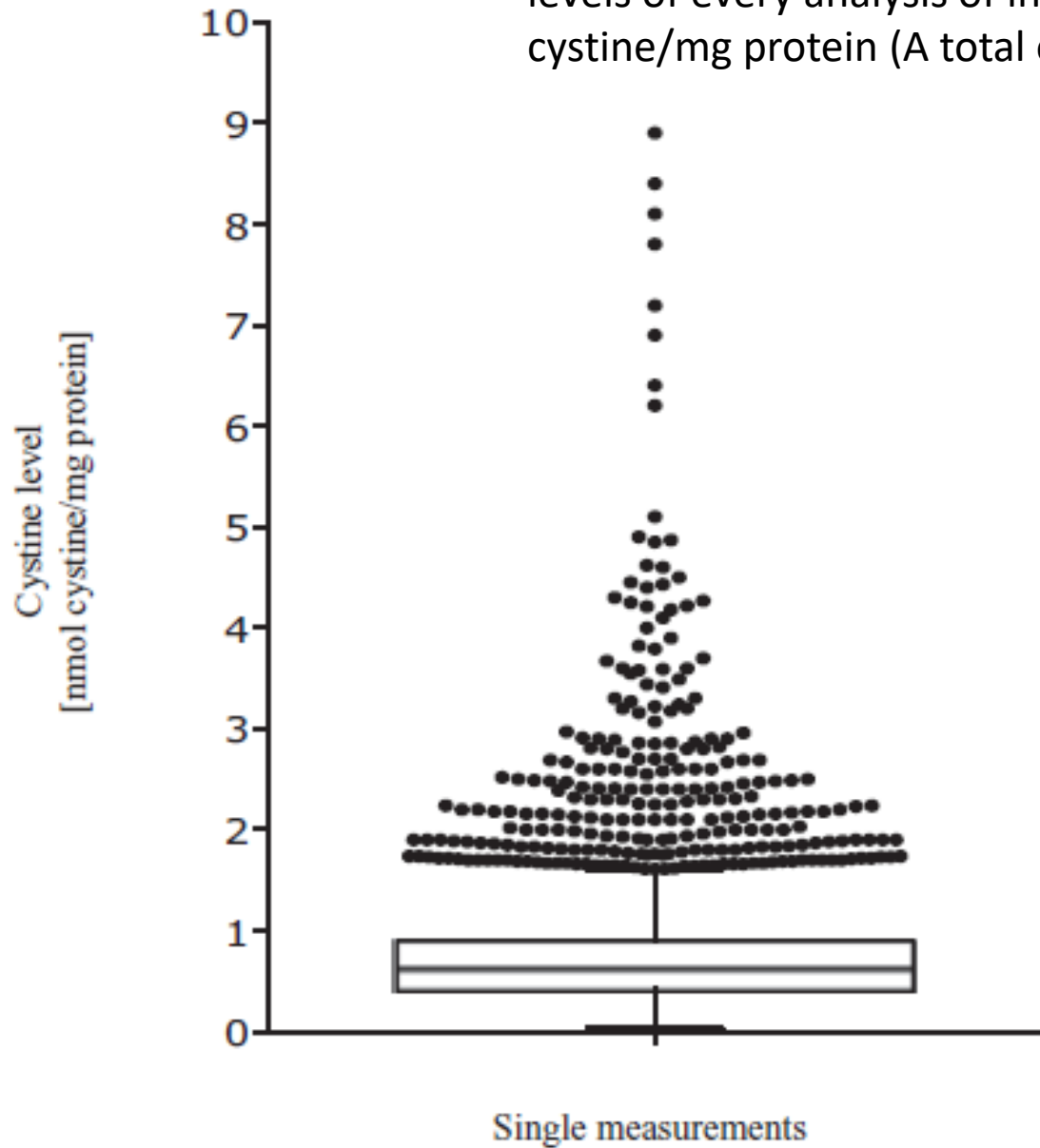
Intracellular cystine level

S. Linden, et al.

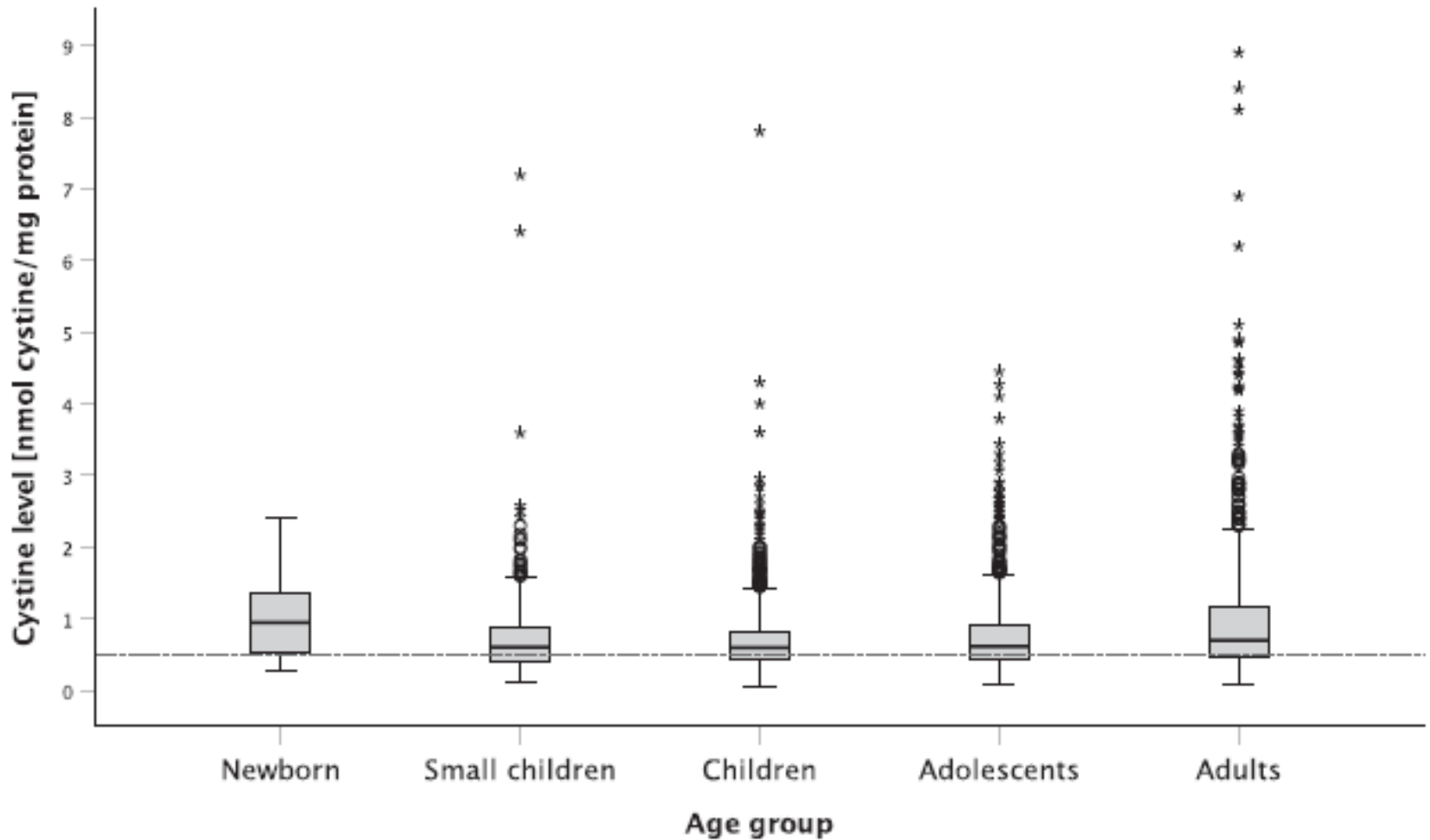
Intracellular WBC cystine levels of the ten patients with the best adherence to the 3-months time intervals



levels of every analysis of individual patients in nmol cystine/mg protein (A total of: 3349 blood samples).






Levels by age groups

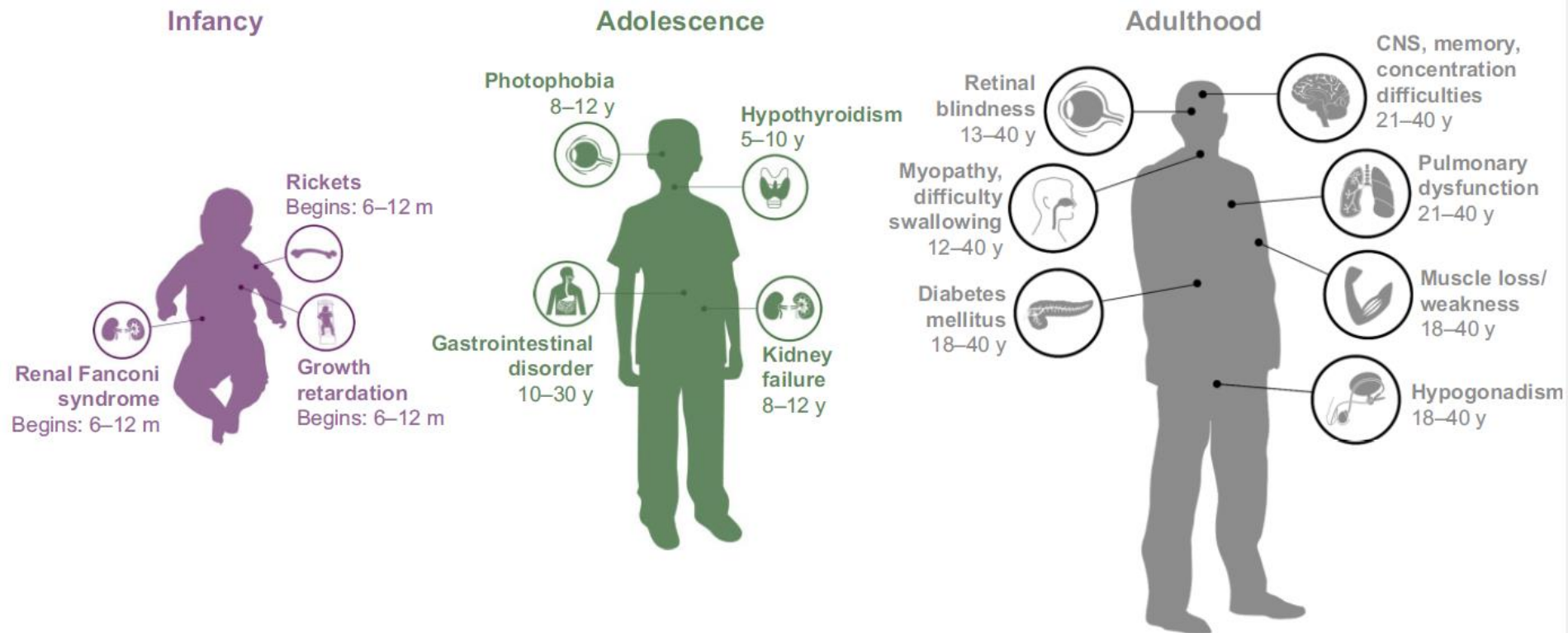


Unmet aims of treatment

- To conserve kidney function
- Growth
- To stop extrarenal manifestations
 - Eye
 - Thyroid
 - Glucose metabolism
 - Gonads
 - Muscle
 - CNS

Expert guidance on the multidisciplinary management of cystinosis in adolescent and adult patients

Elena Levtchenko¹, Aude Servais², Sally A. Hulton³, Gema Ariceta⁴, Francesco Emma ⁵, David S. Game⁶, Karin Lange⁷, Risto Lapatto⁸, Hong Liang⁹, Rebecca Sberro-Soussan¹⁰, Rezan Topaloglu ¹¹, Anibh M. Das¹², Nicholas J.A. Webb¹³ and Christoph Wanner ¹⁴



Expert guidance summary

Table 1. Recommended frequencies of review by key members of the multidisciplinary team

| Multidisciplinary team member | Frequency for review |
|-------------------------------|---|
| Nephrologist | From 2 times/year to more if required |
| Metabolic specialist | At least annually, more frequently if required |
| Ophthalmologist | At least annually, more frequently if required |
| Specialist renal nurse | Always present to help coordinate and assist with patient queries and offer support (where available) |
| Cardiologist/cardiology input | As appropriate |
| Neurologist | At least annually, more frequently if required (unless no problem identified) |

Expert guidance nephrology ... etc.

Table 2. Recommendations for renal monitoring and management in specific patient populations

| Patient population | Monitoring/management recommendations |
|---|--|
| Patients with Fanconi syndrome | <ul style="list-style-type: none">• Use of supplements is recommended to control acidosis, chronic hypokalemia, hypophosphatemia and carnitine deficiency, if present• The use of indomethacin in adults is not recommended |
| Patients on dialysis | <ul style="list-style-type: none">• Both dialysis modes are suitable depending on the medical and social situation of the patient• For patients on haemodialysis, tailoring the ultrafiltration and monitoring of potassium and phosphate levels by adapting supplementation accordingly is advised• Closely monitor electrolytes and acidosis, residual urine volume and other late complications of the disease• Make patients aware that transplantation may be their best treatment option• Cysteamine treatment should be continued in patients on dialysis to protect extra-renal organs<ul style="list-style-type: none">◦ There is no evidence to support the need to adjust cysteamine dose in these patients |
| For patients after kidney transplantation | <ul style="list-style-type: none">• Follow current guidance on post-transplant kidney function monitoring with specific attention to polyuria immediately post-transplantation• Begin cysteamine treatment as soon as oral medication can be administered<ul style="list-style-type: none">◦ Implement strategies to promote patient adherence post-transplant |

Clinical presentation and causes of Cystinosis Metabolic Bone Disease CMBD

1- Renal Fanconi syndrome

resulting in rickets due to

- Hypophosphatemia
- Metabolic acidosis
- 1,25-D deficiency
- Hypocalcemia

2- Deficiency in nutrition and micronutrition

- Malnutrition
- Copper deficiency

3- Hormonal disturbances

- Hypothyroidism
- Hypogonadism
- Hypoparathyroidism
- GH and IGF1 resistance

4- Myopathy

Cystinosis metabolic bone disease (CMBD)

- Short stature
- Osteomalacia
- Bone deformities
- Bone pain
- Osteoporosis

Children: - Rickets

Adults: - Long bone fractures
- Incidental vertebral fractures
- Scoliosis
- Low bone mass
- Cortical impairment

5- Intrinsic and treatment associated bone lesions

- Intrinsic osteoblast/ osteoclast defect due to *CTNS* mutation
- Cysteamine toxicity

6- Mineral and bone disorders due to CKD (CKD-MBD)

- Hyperphosphatemia
- Secondary hyperparathyroidism
- 1,25-D deficiency
- Hypocalcemia
- 25OH-D deficiency

7- CKD-MBD post transplantation

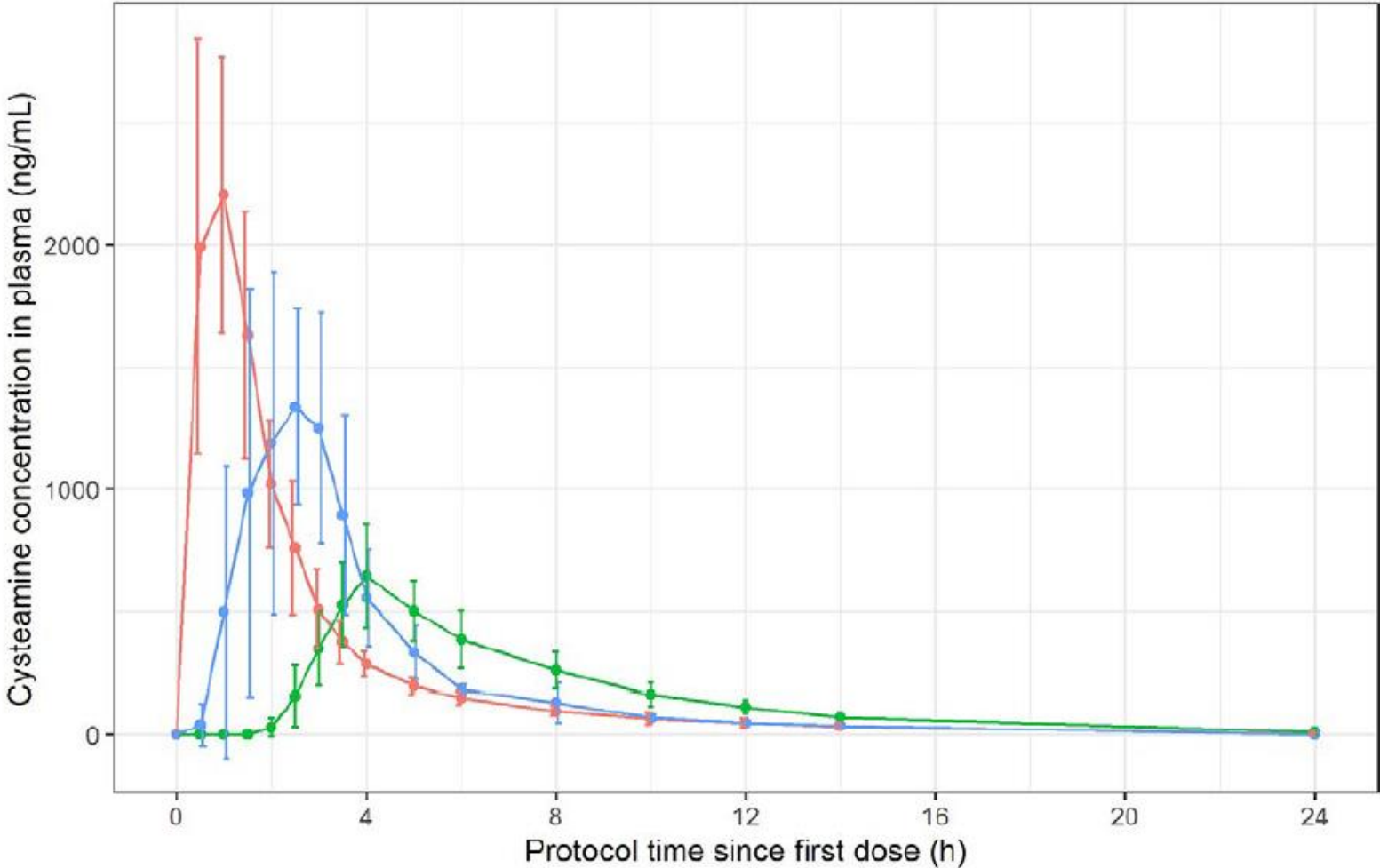
- Glucocorticoid and CNI treatment
- Hypophosphatemia due to persistent Fanconi syndrome
- Mineral and bone disorders related to transplant dysfunction

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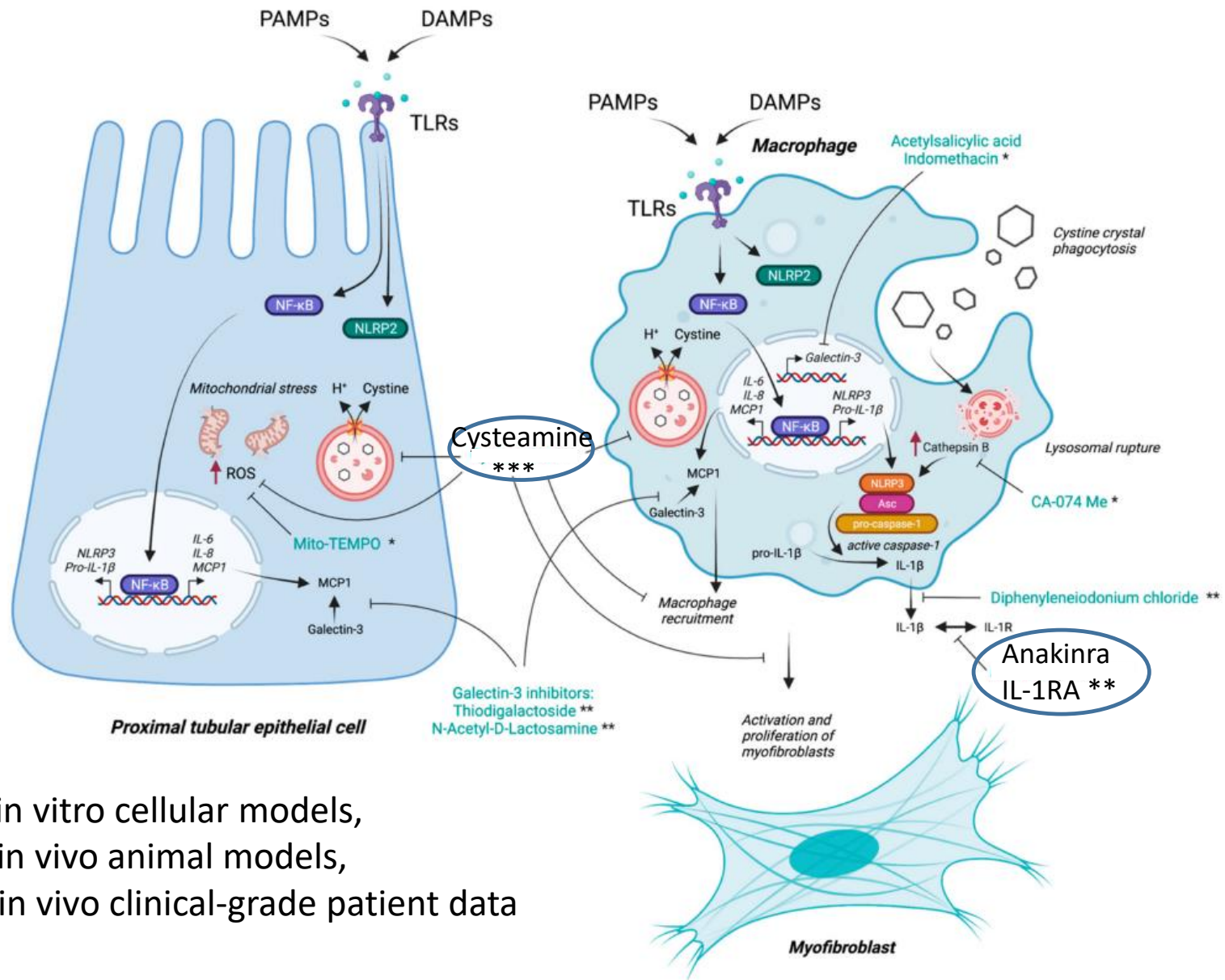
Novel sustained-release cysteamine bitartrate formulation for the treatment of cystinosis

Pharmacokinetics and safety in healthy male volunteers



600mg Cystagon 600mg PO-001 600mg Procysbi

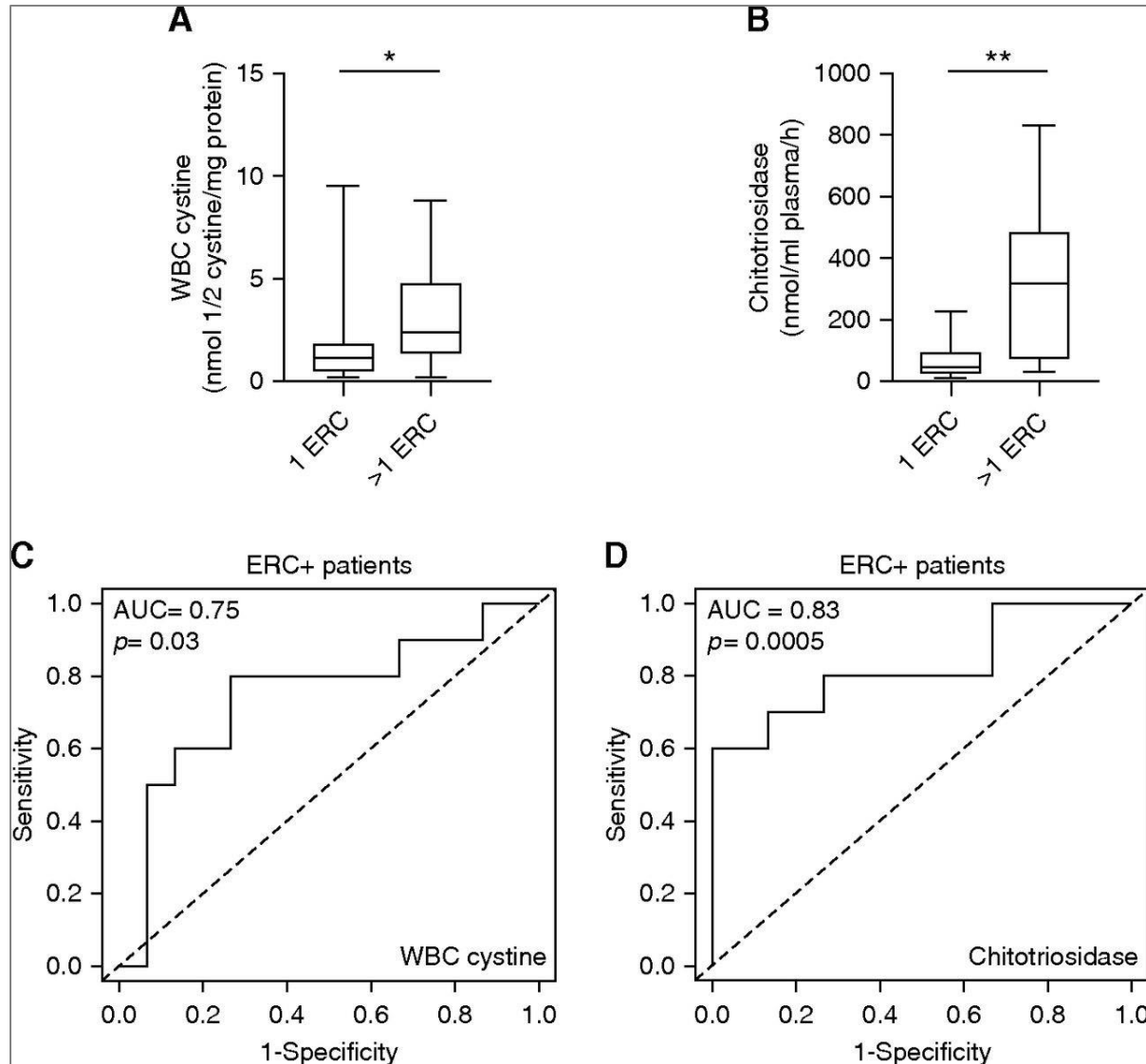
New potential therapeutic targets



*: in vitro cellular models,
 **: in vivo animal models,
 ***: in vivo clinical-grade patient data

ERC: extrarenal complication

Figure 3.



Chitotriosidase as a Novel Biomarker for Therapeutic Monitoring of Nephropathic Cystinosis

Veys, Koenraad R.P.; Elmonem, Mohamed A.; Van Dyck, Maria; Janssen, Mirian C.; Cornelissen, Elisabeth A.M.; Hohenfellner, Katharina; Prencipe, Giusi; van den Heuvel, Lambertus P.; Levtchenko, Elena

Journal of the American Society of Nephrology 31(5):1092-1106, May 2020.

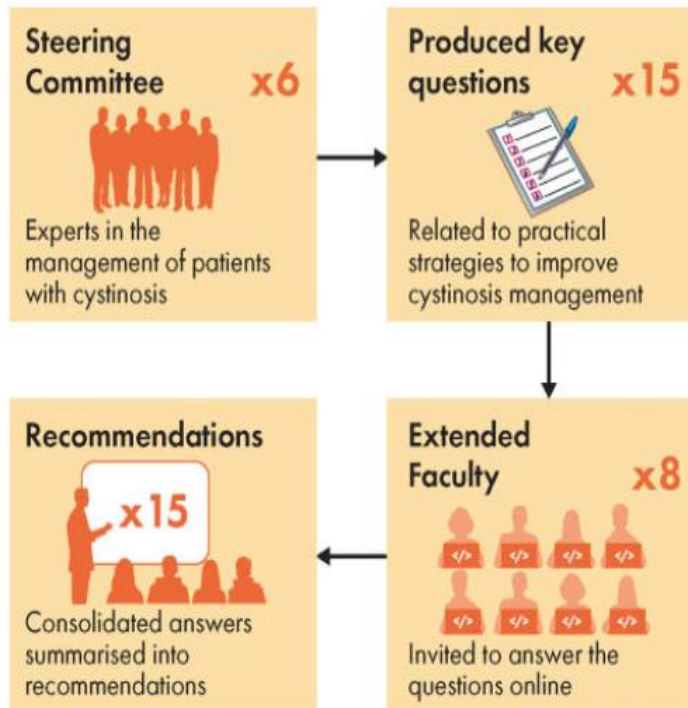
doi: 10.1681/ASN.2019080774

Plasma chitotriosidase enzyme activity performs better than WBC cystine levels and other tested biomarkers of macrophage activation, in distinguishing the presence of one versus multiple ERCs in patients harboring at least one ERC. (A and B) Box and whisker plots for the 2-year average WBC cystine level and plasma chitotriosidase enzyme activity levels in patients harboring at least one ERC, stratified according to the presence of one versus multiple ERCs. (A) *P=0.04. (B) **P=0.006. (C and D) ROC curve analysis of 2-year average WBC cystine and plasma chitotriosidase enzyme activity levels demonstrating the superior performance of chitotriosidase for distinguishing the presence of multiple versus a single ERC. AUC, area under the curve.

Expert guidance on the multidisciplinary management of cystinosis in adolescent and adult patients

Cystinosis is a rare autosomal recessive lysosomal storage disorder that causes abnormal cystine build-up in body organs and tissues. Renal symptoms develop in early life and extra-renal manifestations develop over the next 10-20 years requiring coordinated multidisciplinary care. Here we describe a consensus-based guidance to support the management of adolescents and adults living with cystinosis.

Methods



Results

15 recommendations on cystinosis management and the creation of a cystinosis consultation checklist

1 Multidisciplinary approach



2 Established guidance



3 Cystinosis lead



4 Family planning



5 Renal monitoring



6 Neurology assessment



7 Muscle involvement



8 Ophthalmology assessment



9 Cardio-respiratory review



10 Endocrine screening



11 Liver and pancreas function



12 Skin examination



13 Dental care



14 Psychological support



15 Balanced diet and lifestyle



Summary: This work outlines recommendations and a checklist for clinicians with a vision for improving and standardizing the multidisciplinary care for patients with cystinosis.