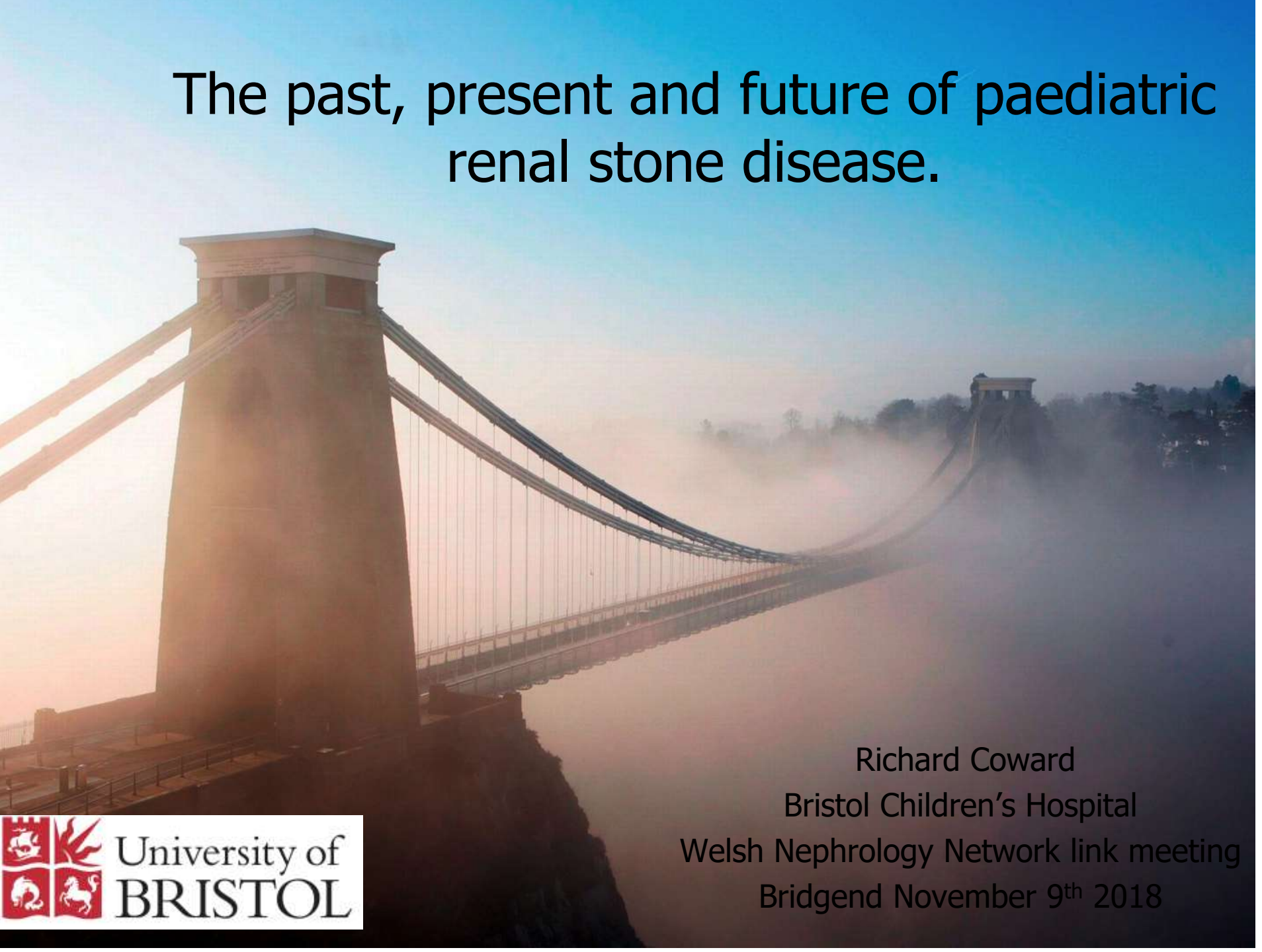
The past, present and future of paediatric renal stone disease.



Richard Coward
Bristol Children's Hospital
Welsh Nephrology Network link meeting
Bridgend November 9th 2018

University of BRISTOL

Background

Fluids

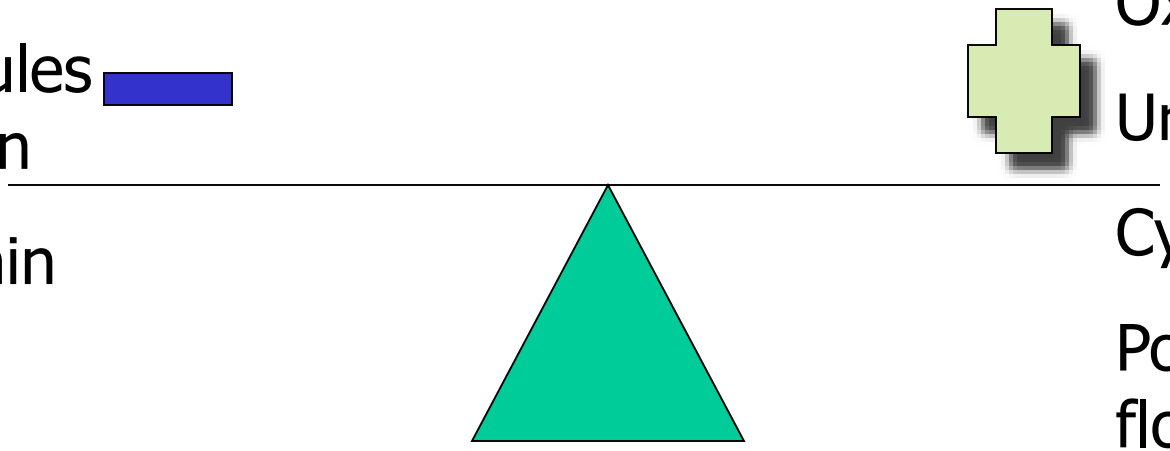
Citrate

Magnesium

Macromolecules
eg TH protein

Nephrocalcinin

H^+



Infection

Ca

Oxalate

Uric acid

Cystine

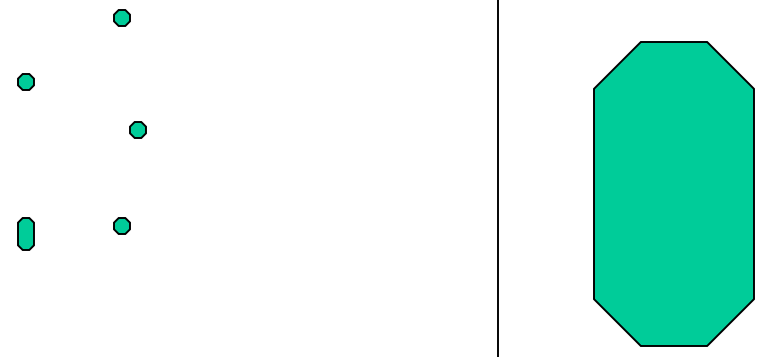
Poor urine flow

H^+

Physical Chemistry

1. Proportion ionised → 2. Activity product

UNDERSATURATED | METASTABLE | LABILE



SOLUBILITY PRODUCT

FORMATION PRODUCT

Childhood urolithiasis in Britain

S. GHAZALI, T. M. BARRATT, and D. I. WILLIAMS

From The Hospital for Sick Children, Great Ormond Street; The Institute of Child Health; and The St. Peter's Hospitals Group, London

Ghazali, S., Barratt, T. M., and Williams, D. I. (1973). *Archives of Disease in Childhood*, **48,** 291. **Childhood urolithiasis in Britain.** 120 children with urinary calculi were treated between 1966 and 1971. 75% were male, and the median age of diagnosis was 3 years. In 34 there were associated urological abnormalities and in 8 a metabolic cause of calculi was identified. 12 of 67 children had hypercalciuria. In 95 children the urine was infected on admission to hospital; in 76, particularly the younger children, this was with *Proteus* species. Calculi recurred after surgery in 13 children, and in 9 the only identifiable factor was failure to eradicate the *Proteus* infection.


BABY

ORIGINAL ARTICLE

Epidemiology of paediatric renal stone disease in the UK

R J M Coward, C J Peters, P G Duffy, D Corry, M J Kellett, S Choong, W G van't Hoff

Arch Dis Child 2003;**88**:962–965

See end of article for authors' affiliations

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Accepted 1 March 2003

Background: The previous epidemiological study of paediatric nephrolithiasis in Britain was conducted more than 30 years ago.

Aims: To examine the presenting features, predisposing factors, and treatment strategies used in paediatric stones presenting to a British centre over the past five years.

Methods: A total of 121 children presented with a urinary tract renal stone, to one adult and one paediatric centre, over a five year period (1997–2001). All children were reviewed in a dedicated stone clinic and had a full infective and metabolic stone investigative work up. Treatment was assessed by retrospective hospital note review.

Results: A metabolic abnormality was found in 44% of children, 30% were classified as infective, and 26% idiopathic. Bilateral stones on presentation occurred in 26% of the metabolic group compared to 12% in the infective/idiopathic group (odds ratio 2.7, 95% CI 1.03 to 7.02). Coexisting urinary tract infection was common (49%) in the metabolic group. Surgically, minimally invasive techniques (lithotripsy, percutaneous nephrolithotomy, and endoscopy) were used in 68% of patients.

Conclusions: There has been a shift in the epidemiology of paediatric renal stone disease in the UK over the past 30 years. Underlying metabolic causes are now the most common but can be masked by coexisting urinary tract infection. Treatment has progressed, especially surgically, with sophisticated minimally invasive techniques now employed. All children with renal stones should have a metabolic screen.

Issler et al. BMC Nephrology (2017) 18:136
DOI 10.1186/s12882-017-0505-x

BMC Nephrology

RESEARCH ARTICLE Open Access

Epidemiology of paediatric renal stone disease: a 22-year single centre experience in the UK

Naomi Issler[1,3†], Stephanie Dufek[1,3†], Robert Kleta[1,2,3], Detlef Bockenhauer[1,2,3], Naima Smeulders[1,2] and William van't Hoff[1,2*]

Abstract

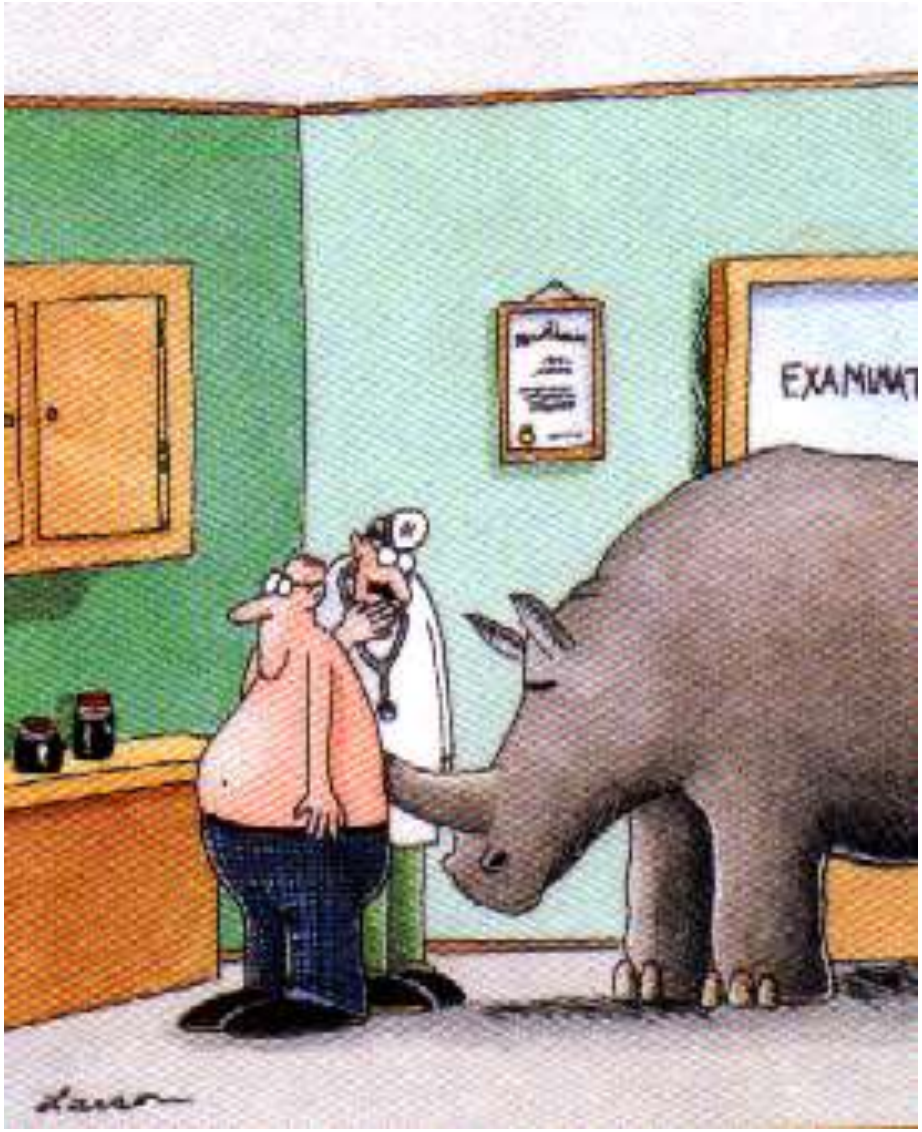
Background: Whilst still rare, the incidence of paediatric stone disease is increasing in developed countries and it is important to evaluate the aetiology. We set up a dedicated renal stone service for children combining medical and surgical expertise in 1993 and now have a large case series of children to investigate the epidemiology.

Methods: A retrospective hospital note review of children presenting with kidney stones during the last 22 years (1993–2015) was conducted. All patients had a comprehensive infective and metabolic screen and were classified as metabolic, infective or idiopathic stone disease.

Results: Five hundred eleven patients (322 male) were reviewed. The median age of presentation was 4.4y for males (1 m-16.6y) and 7.3y (1–18.5y) for females with a median height and weight on the 25th centile for male and on 10th and 25th for female, respectively. One hundred seventy five (34%) had an underlying metabolic abnormality, 112 (22%) had infective stones and 224 (44%) were classified as idiopathic.
Of the 175 patients with a metabolic abnormality: 91 (52%) had hypercalciuria (76 persistent and 15 transient), 37 (21%) hyperoxaluria, 38 (22%) cystinuria, 3 (2%) abnormalities in the purine metabolism and the remainder other metabolic abnormalities. Bilateral stones occurred in 27% of the metabolic group compared to 16% in the non-metabolic group (OR 0.2, $p < 0.05$). Urinary tract infection was a common complication (27%) in the metabolic group.

Conclusions: In this paper, we present the largest cohort of paediatric stone disease reported from a developed country giving details on both, clinical and laboratory data. We show that in the majority of the patients there is an identifiable underlying metabolic and/or infective aetiology emphasizing the importance of a full work up to provide adequate treatment and prevent recurrence. Moreover, we show that stone disease in children, in contrast to the adult population, does not seem to be associated with obesity, as children have a weight below average at presentation.

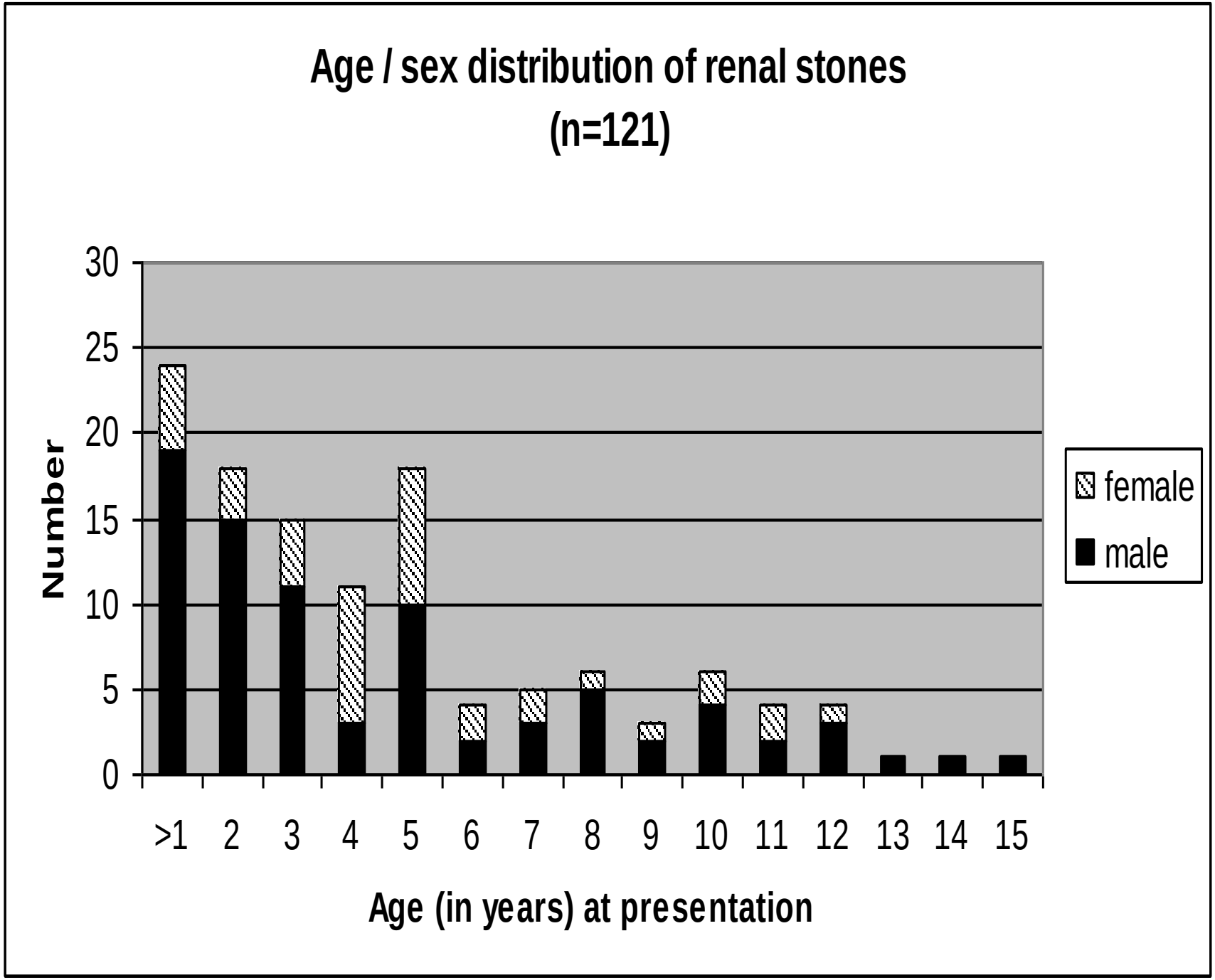
Keywords: Epidemiology, Stone disease, Nephrolithiasis, Hypercalciuria, Growth

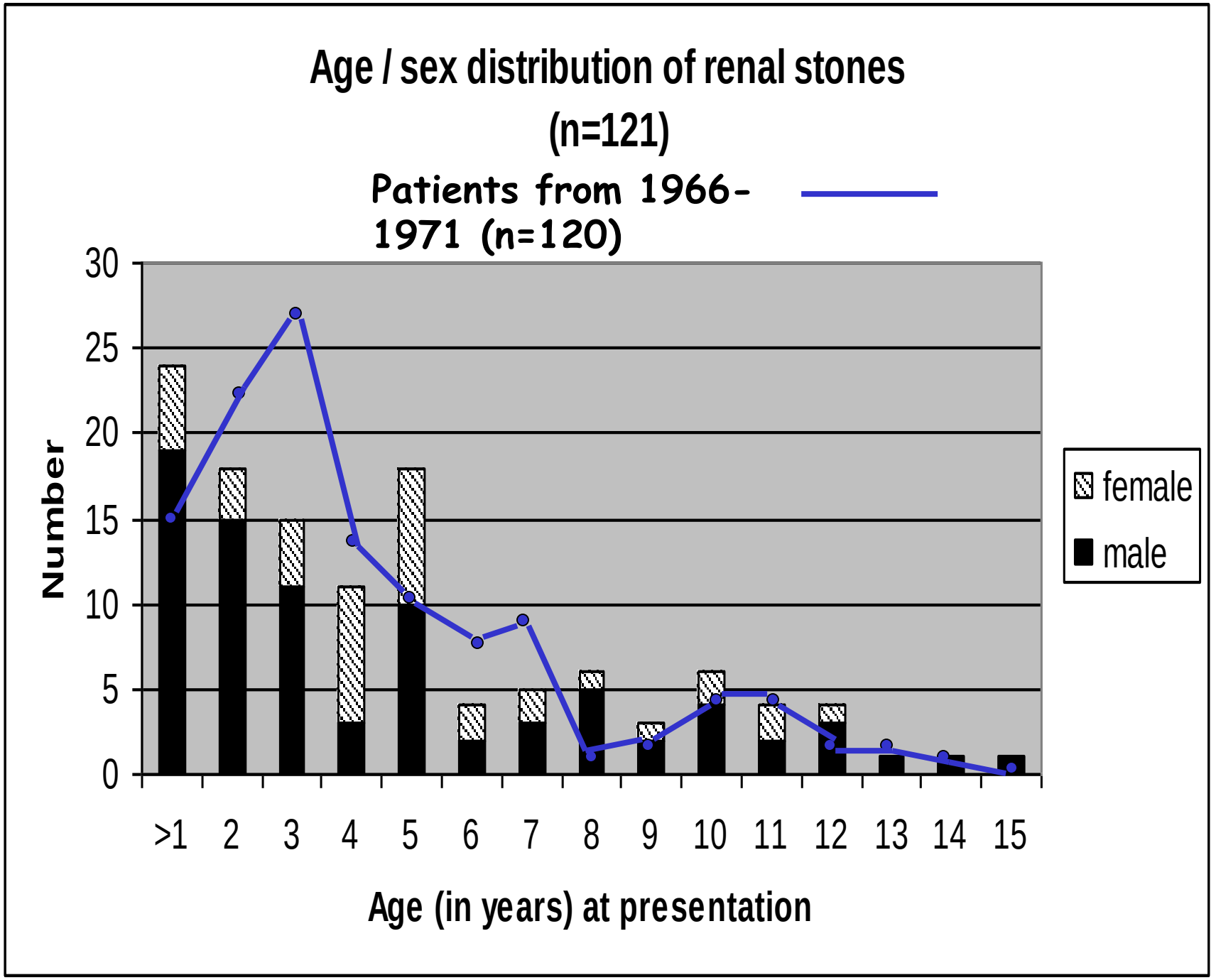


Well Sir, it may not be renal stones after all.

Presenting features

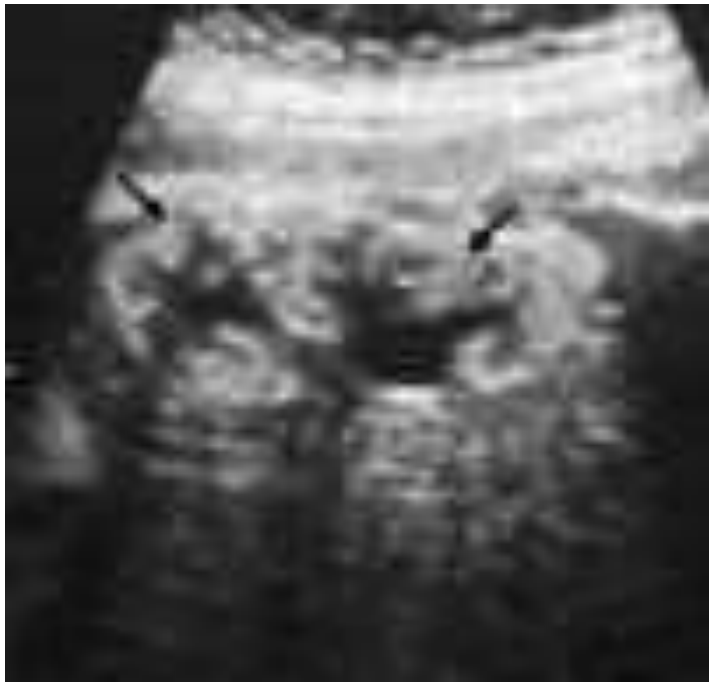
- Haematuria in 60%
- Vomiting in 22%
- Abdominal pain 55%
- Presenting UTI 44%
- Mean Ht and wt 30th C.
- 16% asymptomatic

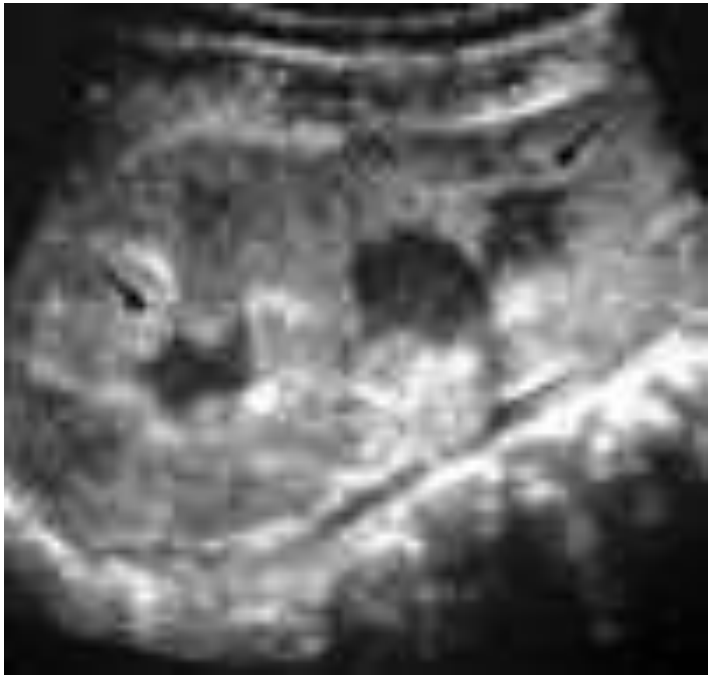

Age / sex distribution of renal stones
(n=121)
Number
30
25
20
15
10
5
0
>1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Age (in years) at presentation
female
male


Age / sex distribution of renal stones
(n=121)
Patients from 1966-1971 (n=120)
Number
30
25
20
15
10
5
0
>1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Age (in years) at presentation
female
male

Risk factors in history

- Family history
  1st degree relatives 19%
  1st or 2nd degree relatives combined 38%
- Prematurity
  15% < 37 weeks
- Immobility
  10%
- PMH UTI
  46%
- Drugs

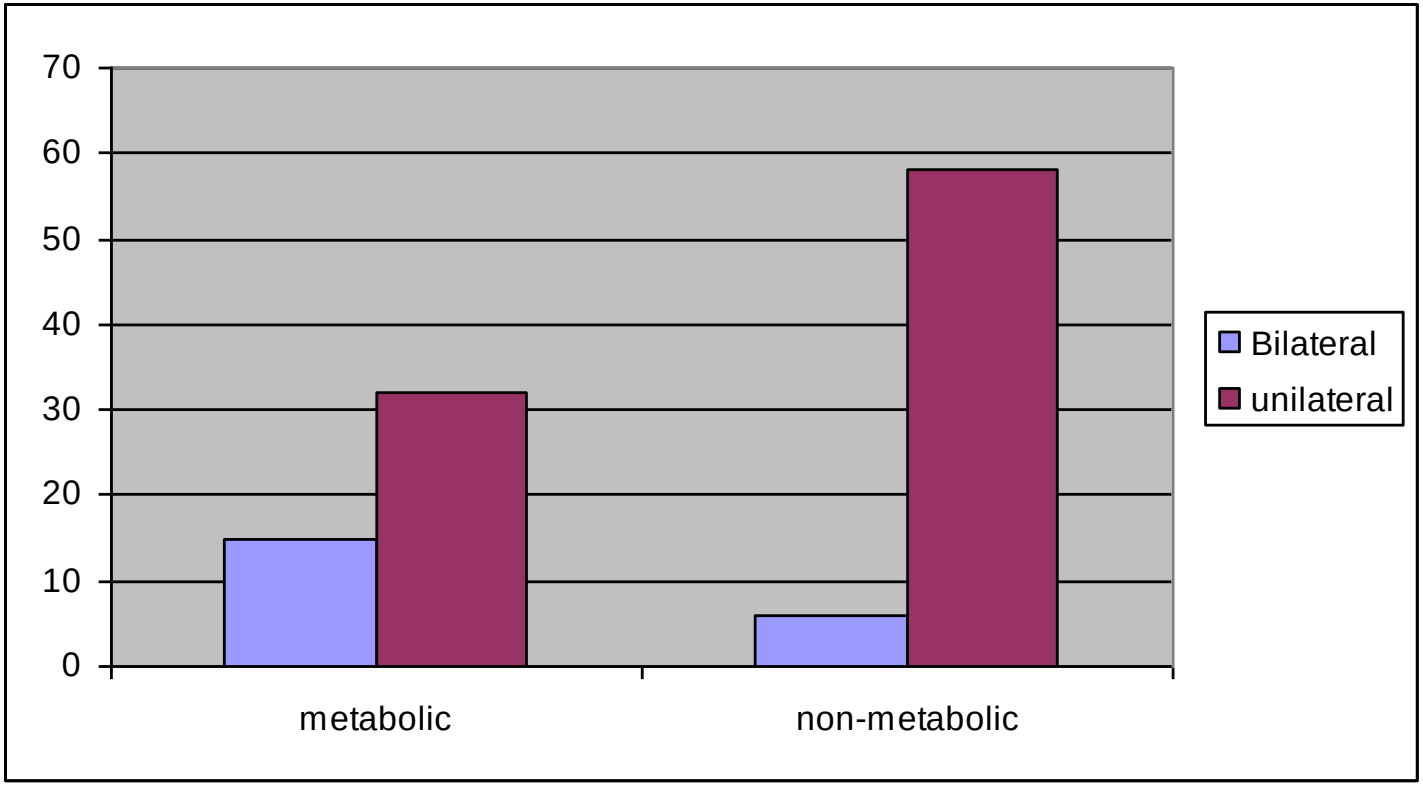




AETIOLOGY

- Infective
- Metabolic
- Unknown

Risk factors- Bilateral stones



Odds ratio = 3.5 . 95% CI = 1.2 → 9.6

Underlying changing aetiologies of renal stones

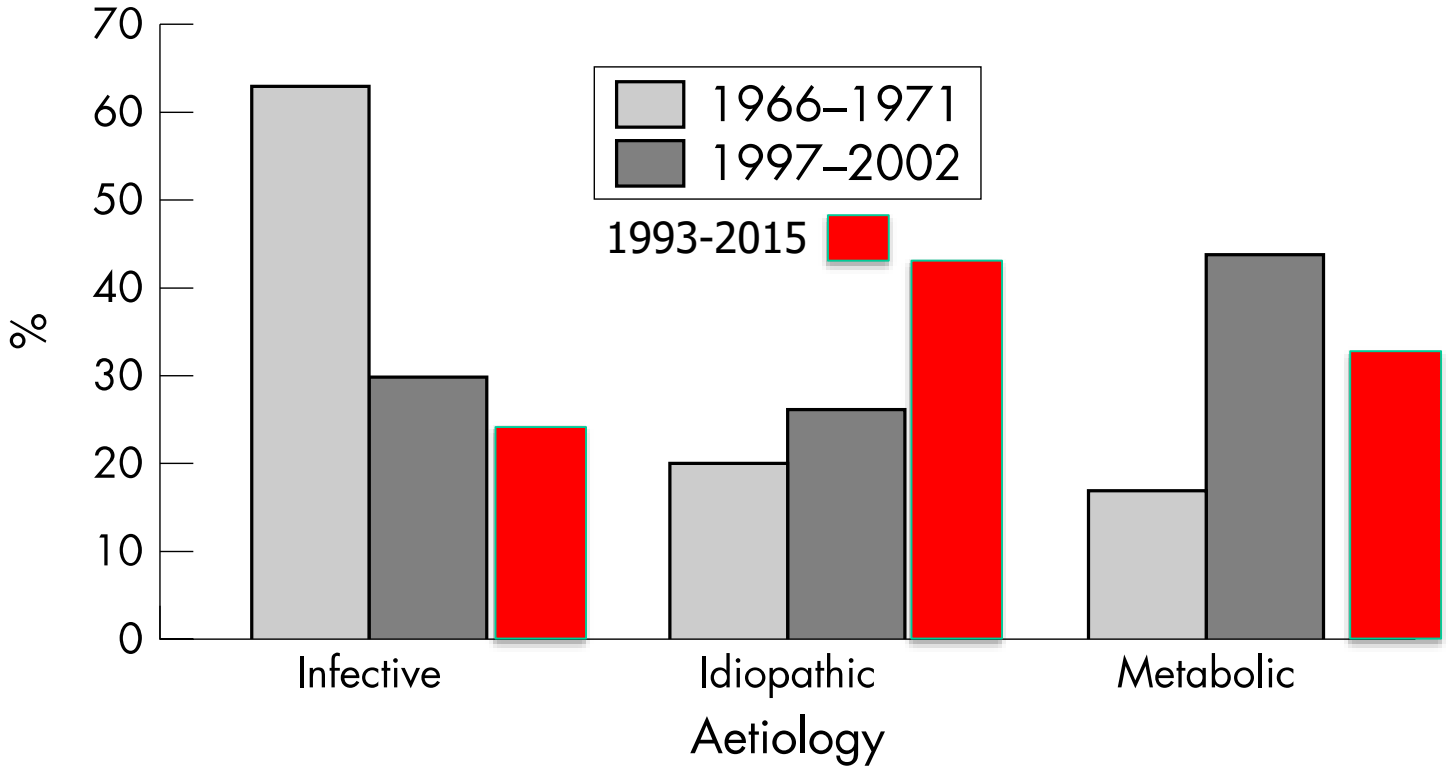
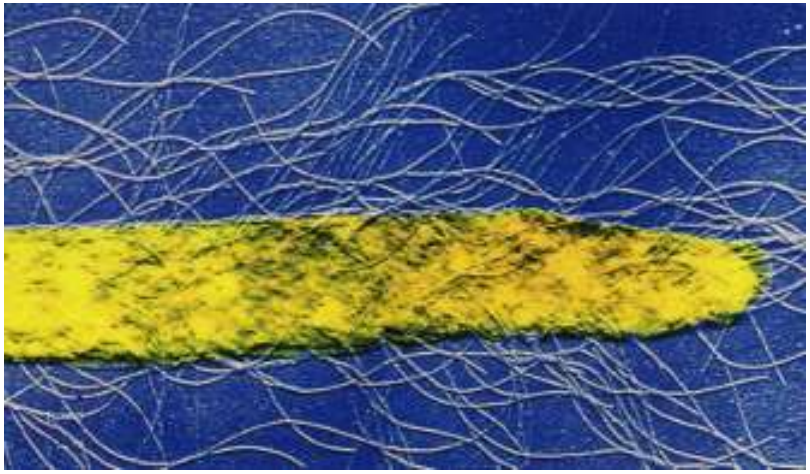
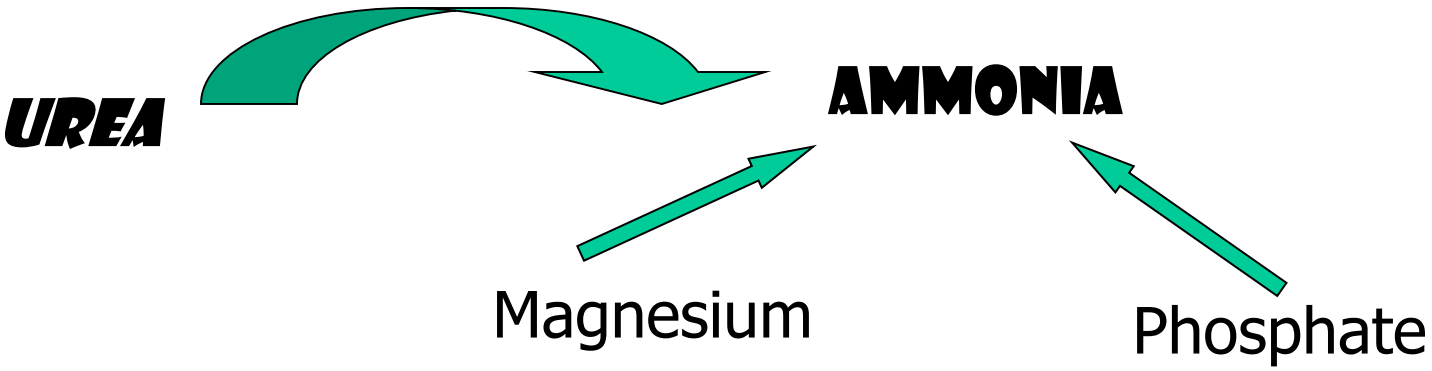


Figure 3 Underlying stone aetiologies. Comparison between previous study (1966–71) and present study (1997–2002).

AETIOLOGY

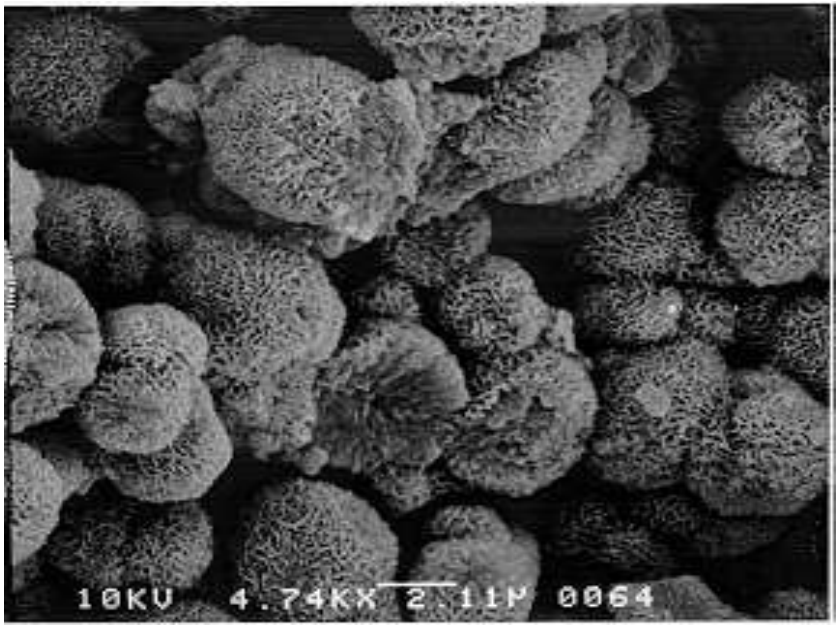
- Infective
- Metabolic
- Unknown




UREA
AMMONIA
Magnesium
Phosphate

AETIOLOGY

- Infective
- Metabolic
- Unknown


10KV 4.74KX 2.11P 0064

Hypercalciuria

- Idiopathic hypercalciuria
- Hypercalcaemia
- Drug related
- Diet (Ketogenic)
- Syndromes Dents, Michaelis- Manz, dRTA, pRTA

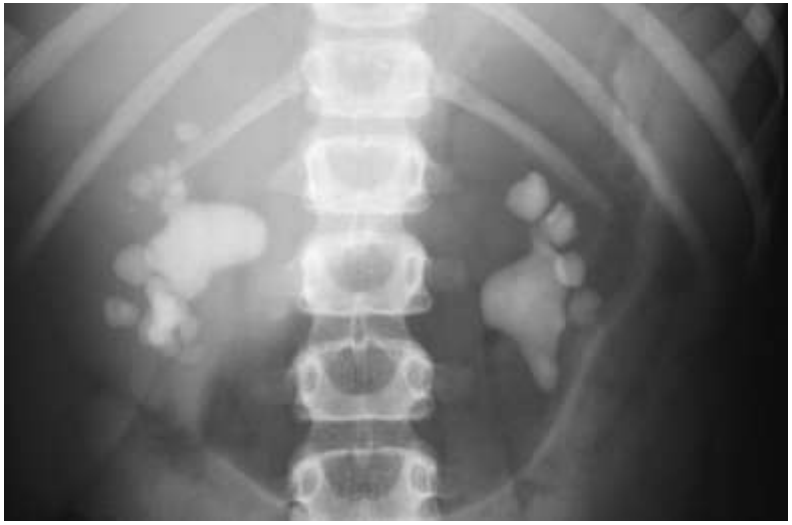
Treatment

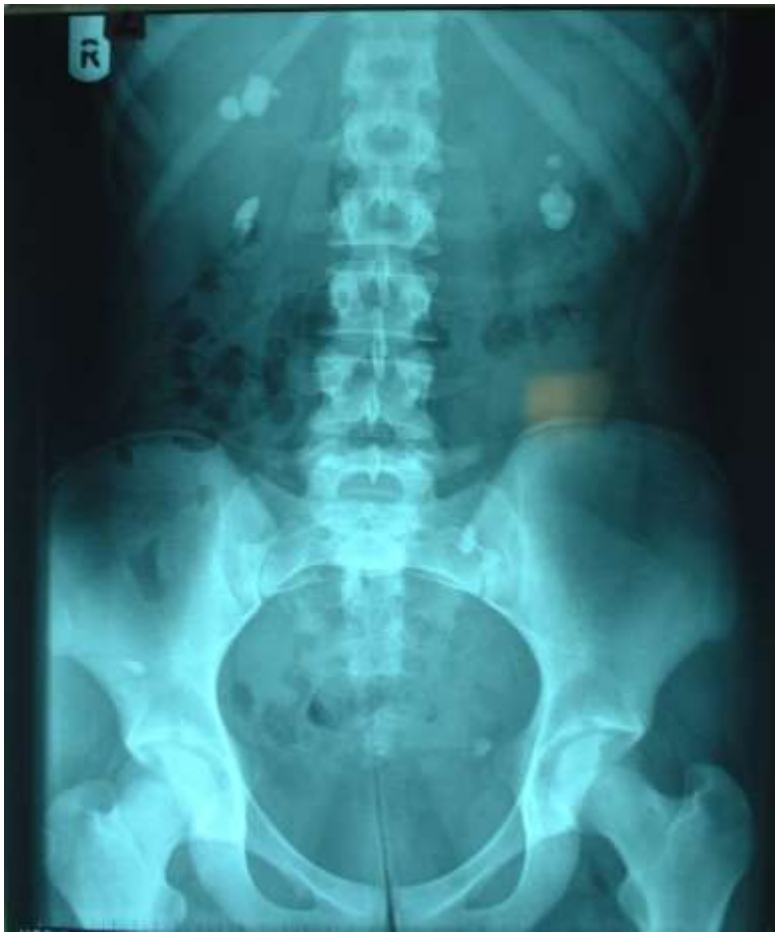
- Increased fluid intake
- Dietary Ca restriction not necessary
- Low Na high K diet may help
- Thiazide diuretic

AETIOLOGY

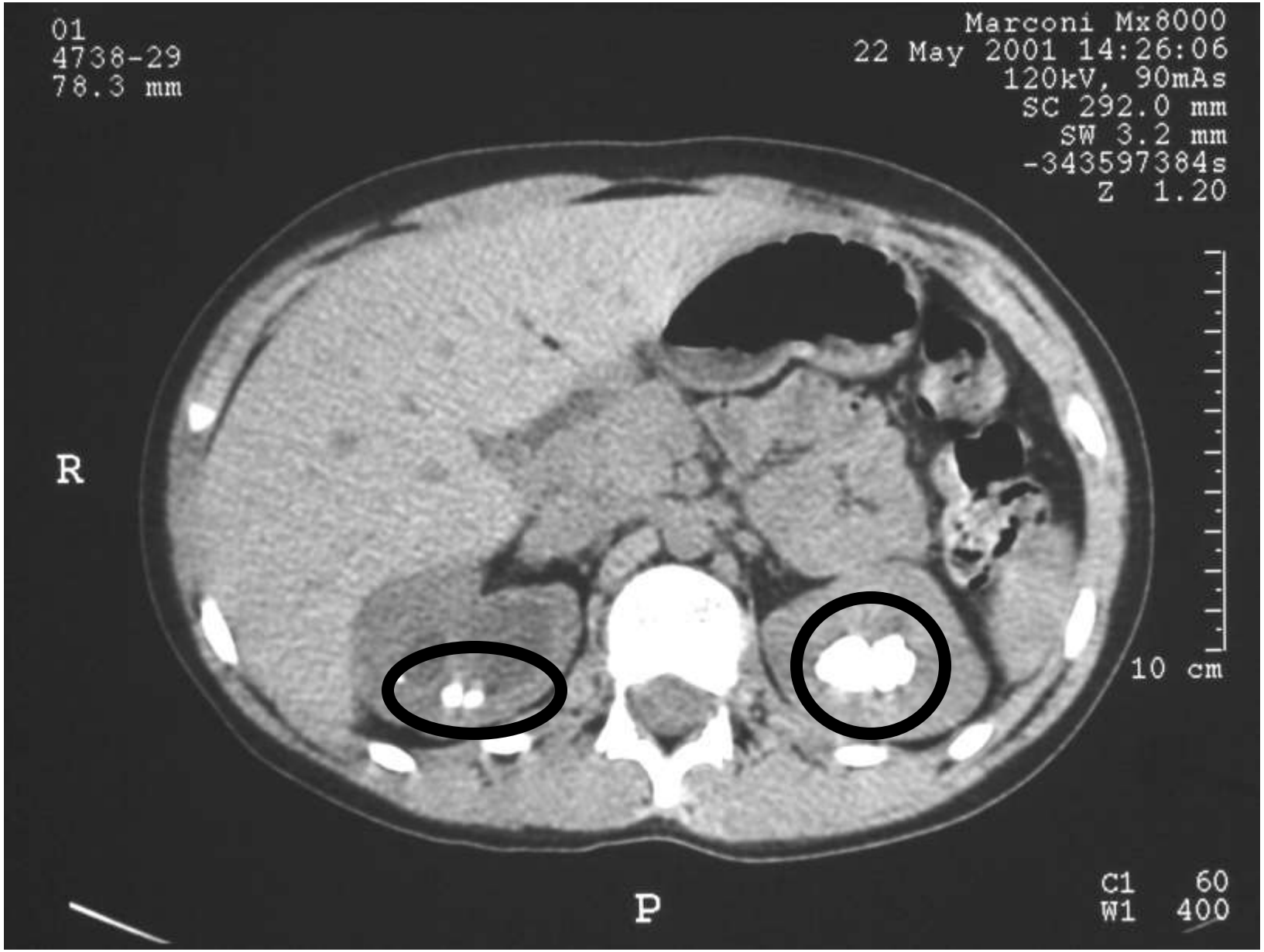
- Infective
- Metabolic
- Unknown

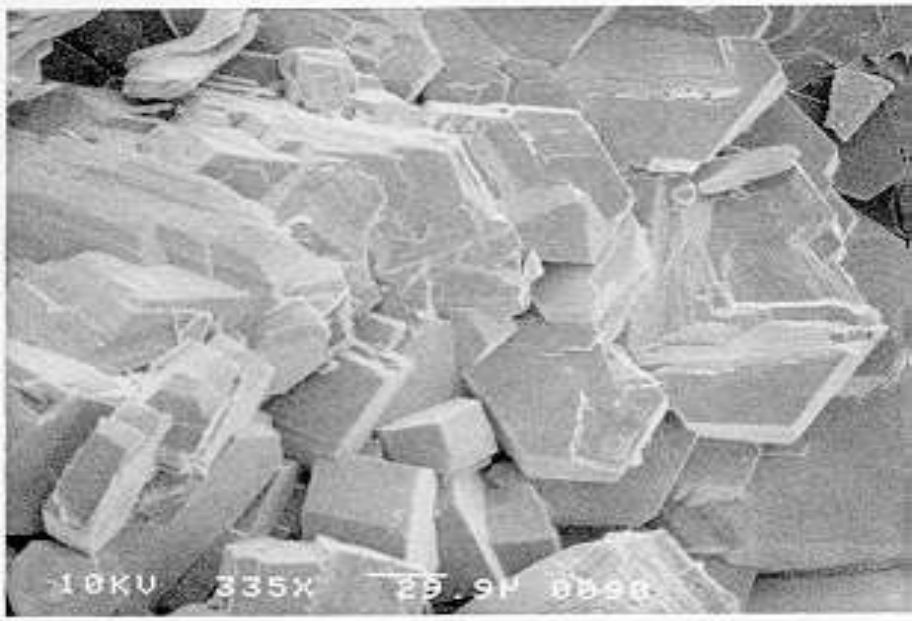
Monogenic conditions



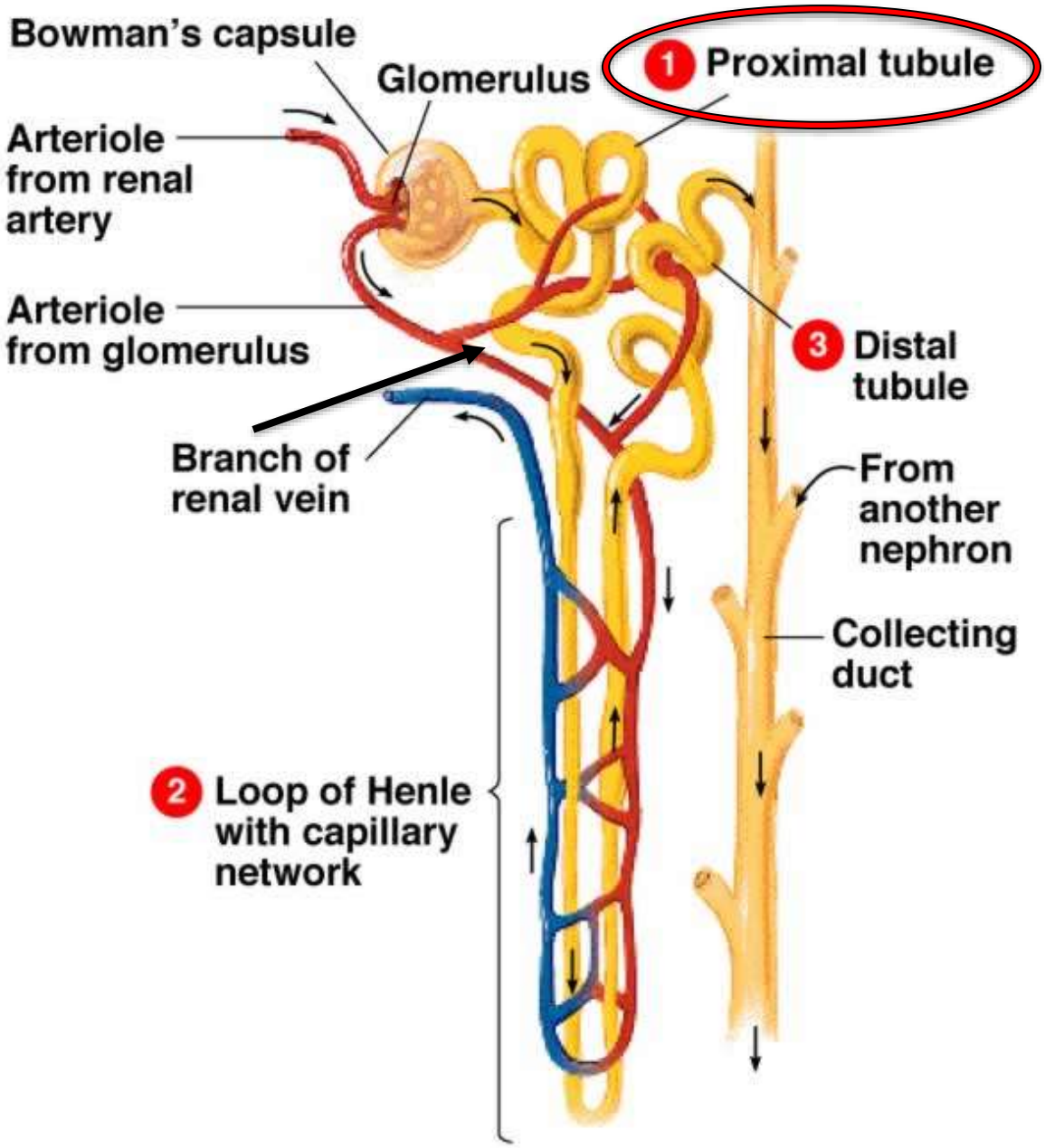

R

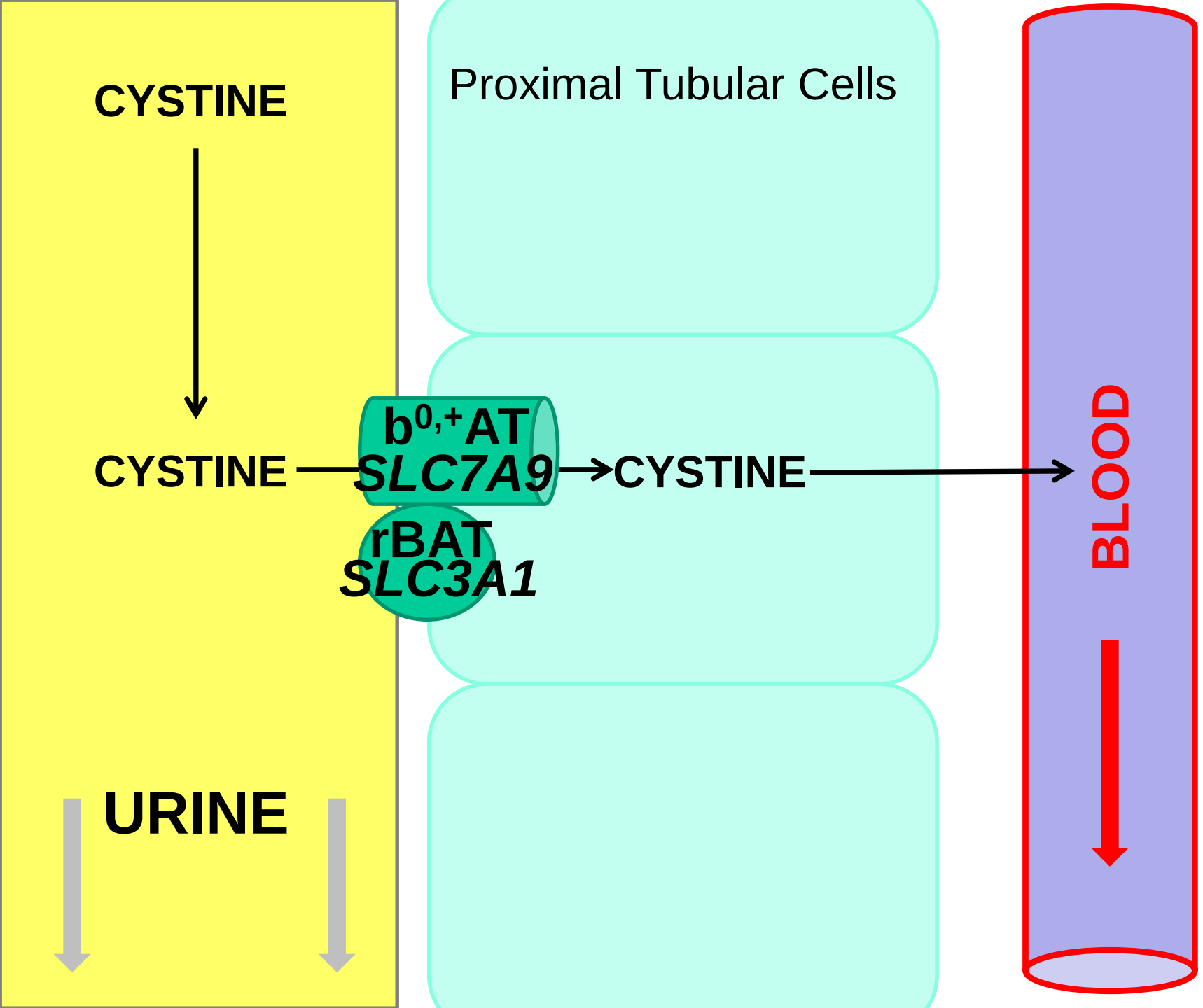

CM
1 2 3 4 5 6 7 8 9 10
PATIENT
DATE

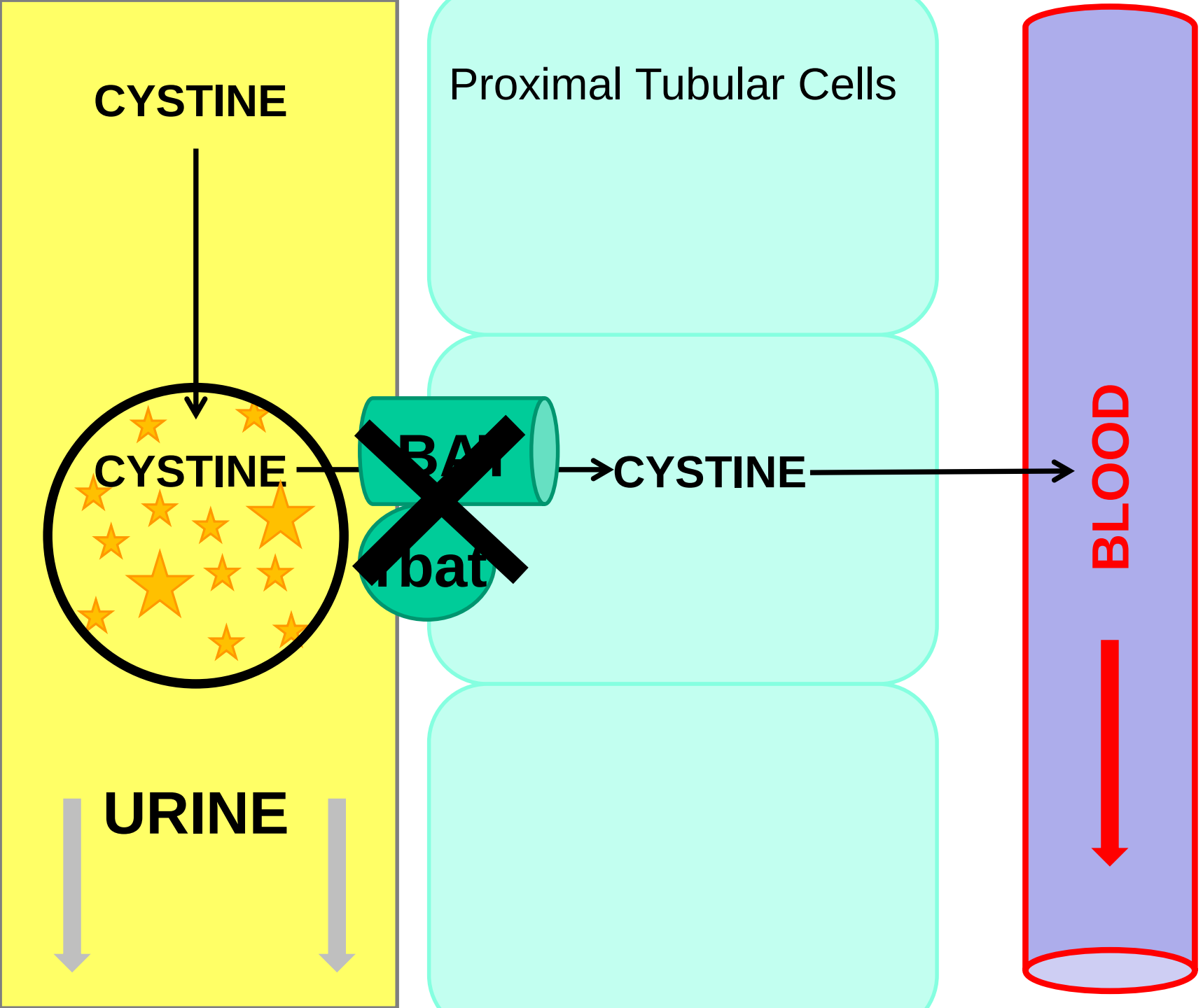

01
4738-29
78.3 mm
Marconi Mx8000
22 May 2001 14:26:06
120kV, 90mAs
SC 292.0 mm
SW 3.2 mm
-343597384s
Z 1.20
R
10 cm
P
C1 60
W1 400


10KV 335X

Cystinuria


Bowman's capsule
Glomerulus
1 Proximal tubule
Arteriole from renal artery
Arteriole from glomerulus
3 Distal tubule
Branch of renal vein
From another nephron
Collecting duct
2 Loop of Henle with capillary network
©Addison Wesley Longman, Inc.


CYSTINE
Proximal Tubular Cells
CYSTINE
b0,+AT
SLC7A9
CYSTINE
rBAT
SLC3A1
BLOOD
URINE


CYSTINE
Proximal Tubular Cells
CYSTINE
CYSTINE
BLOOD
URINE

Clinical and Genetic Analysis of Patients with Cystinuria in the United Kingdom

Hannah L. Rhodes, Laura Yarram-Smith,† Sarah J. Rice,‡ Ayla Tabaksert,‡ Noel Edwards,§ Alice Hartley,‖ Mark N. Woodward,* Sarah L. Smithson,¶ Charles Tomson,**†† Gavin I. Welsh,* Margaret Williams,† David T. Thwaites,‡ John A. Sayer,§†† and Richard J.M. Coward**

Abstract

Background and objectives Cystinuria is a rare inherited renal stone disease. Mutations in the amino acid exchanger System $b^{0,+}$, the two subunits of which are encoded by *SLC3A1* and *SLC7A9*, predominantly underlie this disease. The work analyzed the epidemiology of cystinuria and the influence of mutations in these two genes on disease severity in a United Kingdom cohort.

Design, setting, participants, & measurements Prevalent patients were studied from 2012 to 2014 in the northeast and southwest of the United Kingdom. Clinical phenotypes were defined, and genetic analysis of *SLC3A1* and *SLC7A9* combining Sanger sequencing and multiplex ligation probe–dependent amplification was performed.

Results In total, 76 patients (42 men and 34 women) were studied. All subjects had proven cystine stones. Median age of presentation (first stone episode) was 24 years old, but 21% of patients presented after 40 years old. Patients had varied clinical courses, with 37% of patients having ≥10 stone episodes; 70% had evidence of CKD, and 9% had reached ESRD as a result of cystinuria and its complications. Patients with cystinuria received a variety of different therapies, with no obvious treatment consensus. Notably, 20% of patients had staghorn calculi, with associated impaired renal function in 80% of these patients. Genetic analysis revealed that biallelic mutations were present in either *SLC3A1* (*n*=27) or *SLC7A9* (*n*=20); 22 patients had only one mutated allele detected (*SLC3A1* in five patients and *SLC7A9* in 17 patients). In total, 37 different mutant variant alleles were identified, including 12 novel mutations; 22% of mutations were caused by large gene rearrangements. No genotype-phenotype association was detected in this cohort.

Conclusions Patients with cystinuria in the United Kingdom often present atypically with staghorn calculi at ≥40 years old and commonly develop significant renal impairment. There is no association of clinical course with genotype. Treatments directed toward reducing stone burden need to be rationalized and developed to optimize patient care.

Clin J Am Soc Nephrol 10: 1235–1245, 2015. doi: 10.2215/CJN.10981114

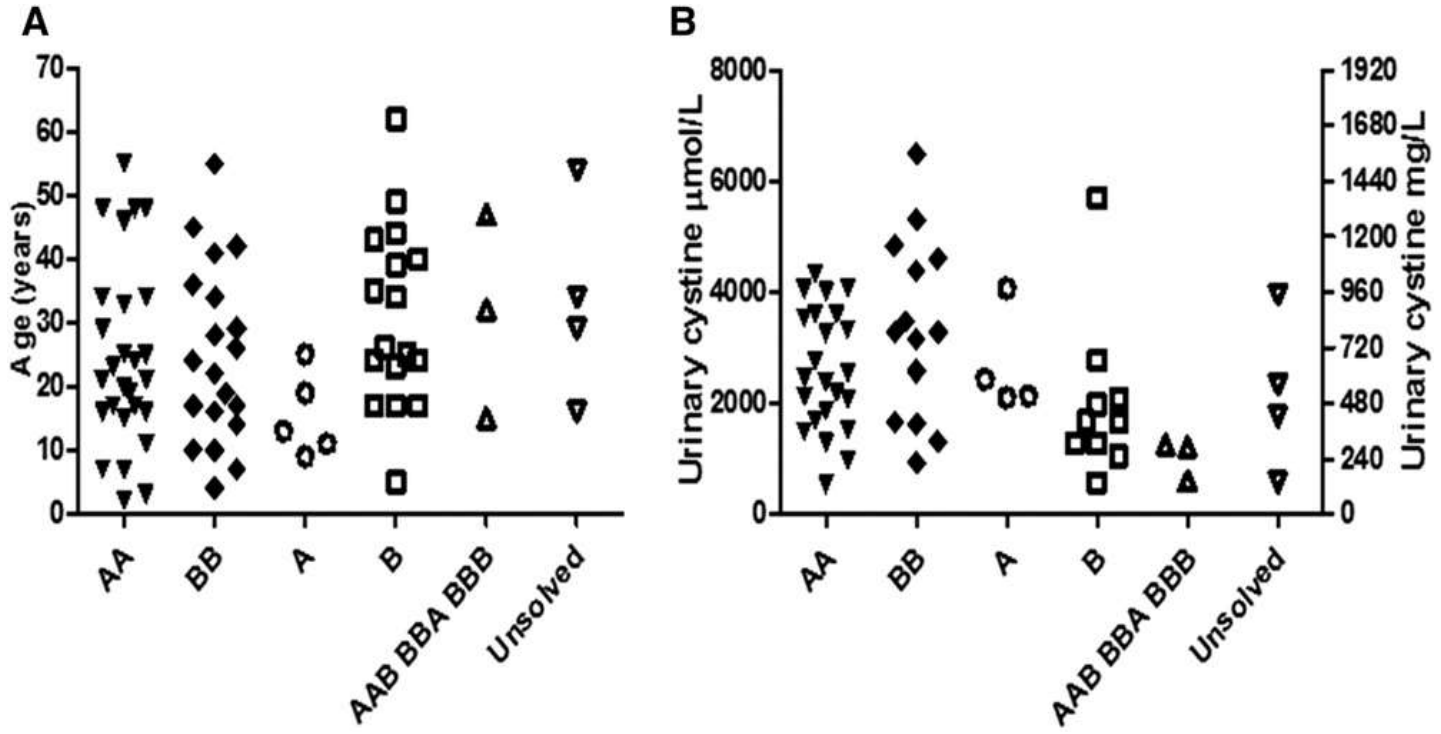

A
Age (years)
70
60
50
40
30
20
10
0
AA
BB
A
B
AAB BBA BBB
Unsolved
B
Urinary cystine µmol/L
8000
6000
4000
2000
0
Urinary cystine mg/L
1920
1680
1440
1200
960
720
480
240
0
AA
BB
A
B
AAB BBA BBB
Unsolved

Table 1. Comparison of renal function by genotype

eGFR (ml/min per 1.73 m^2)	No.	Percent	AA (B)	A	BB (A or B)	B	AB	Genotype Unknown
≥90	23	30	8		6	8		1
60–89	37	49	16	4	7	5	3	2
30–59	9	12	2		3	3		1
<30	4	5	1	1	2			
ESRD with renal transplant	3	4			2	1		

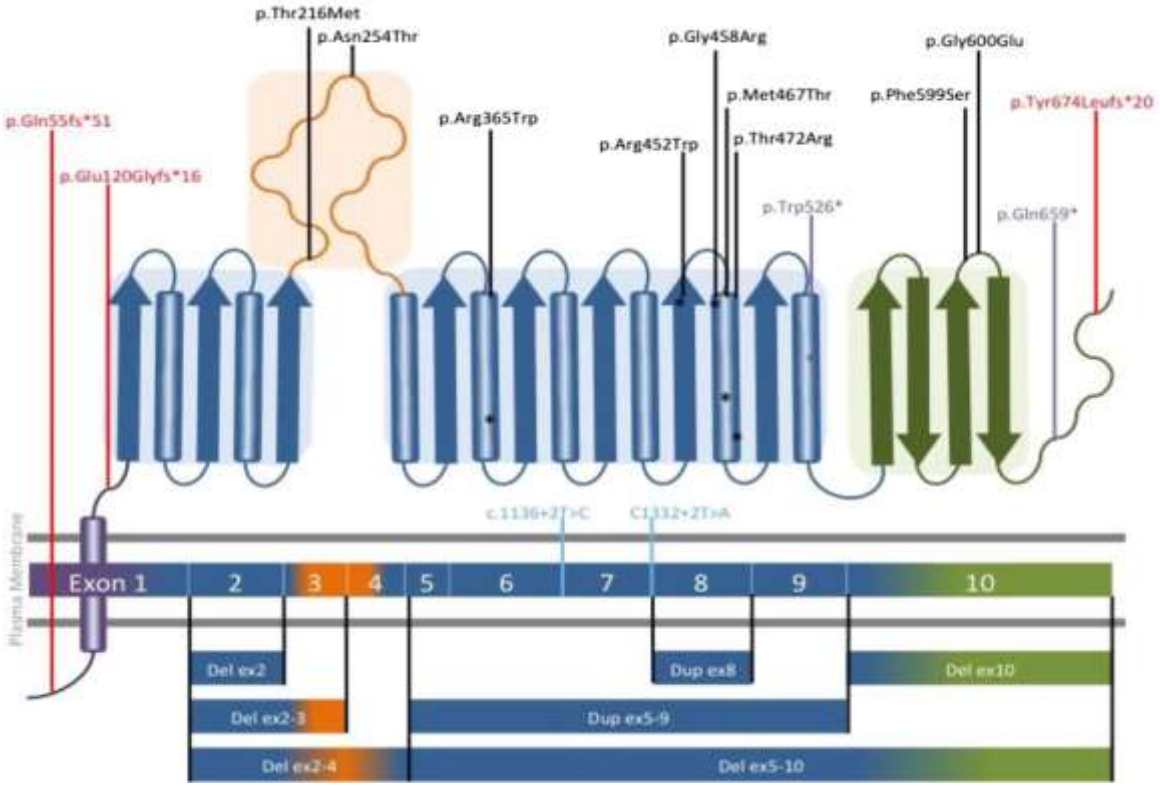


Figure 2. | Distribution of mutations detected in *SLC3A1* (rBAT) throughout the exons and protein domains. Schematic diagram of rBAT and a homology model of the extracellular domain of rBAT on the basis of the crystal structure of oligo-1,6-glucosidase from *Bacillus cereus* (Protein Data Bank ID code 1UOK). The domains of rBAT are shown in purple (TMD), blue (domain A), orange (domain B [subdomain]), and green (domain C). Mutations are labeled as follows: missense in black, nonsense in purple, frameshift in red, and splice site in pale blue. Mutations predicted to fall within α-helices are denoted by asterisks of the appropriate color. TMD, trans-membrane domain.

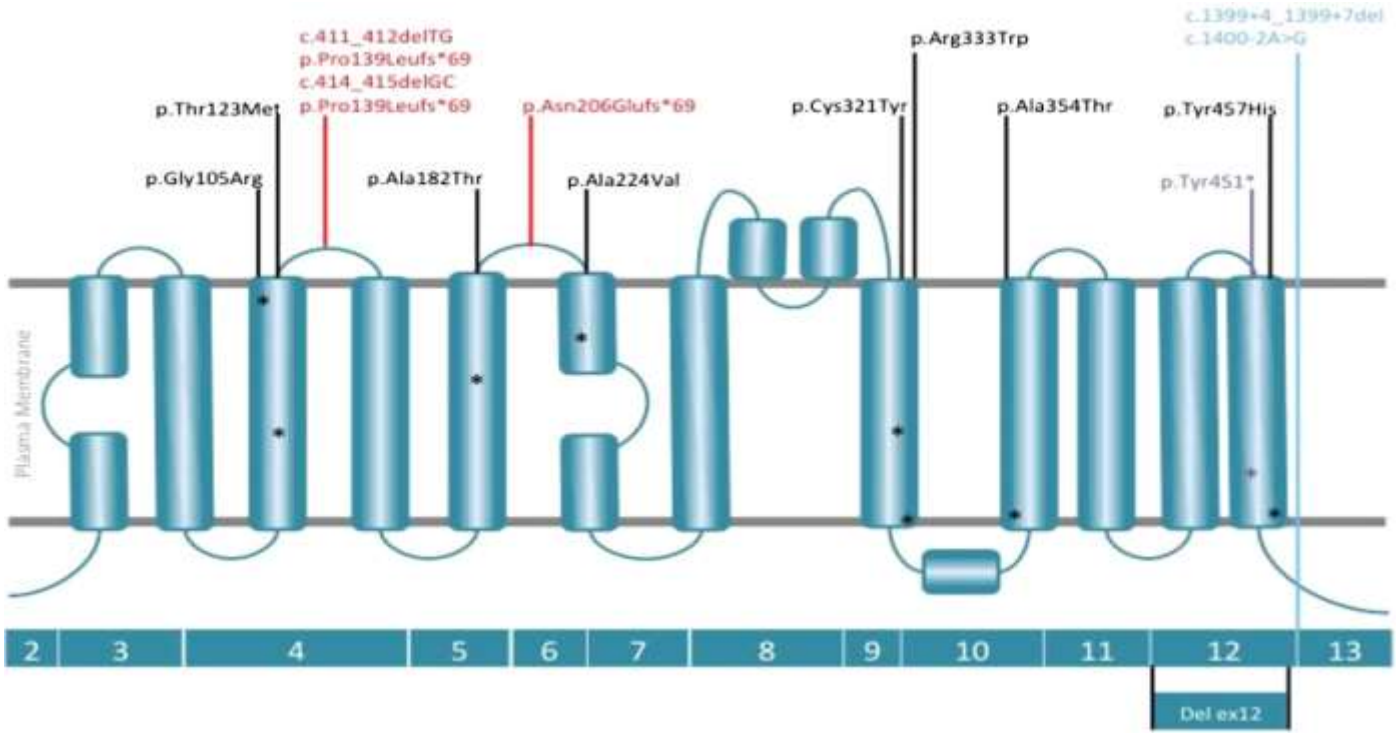
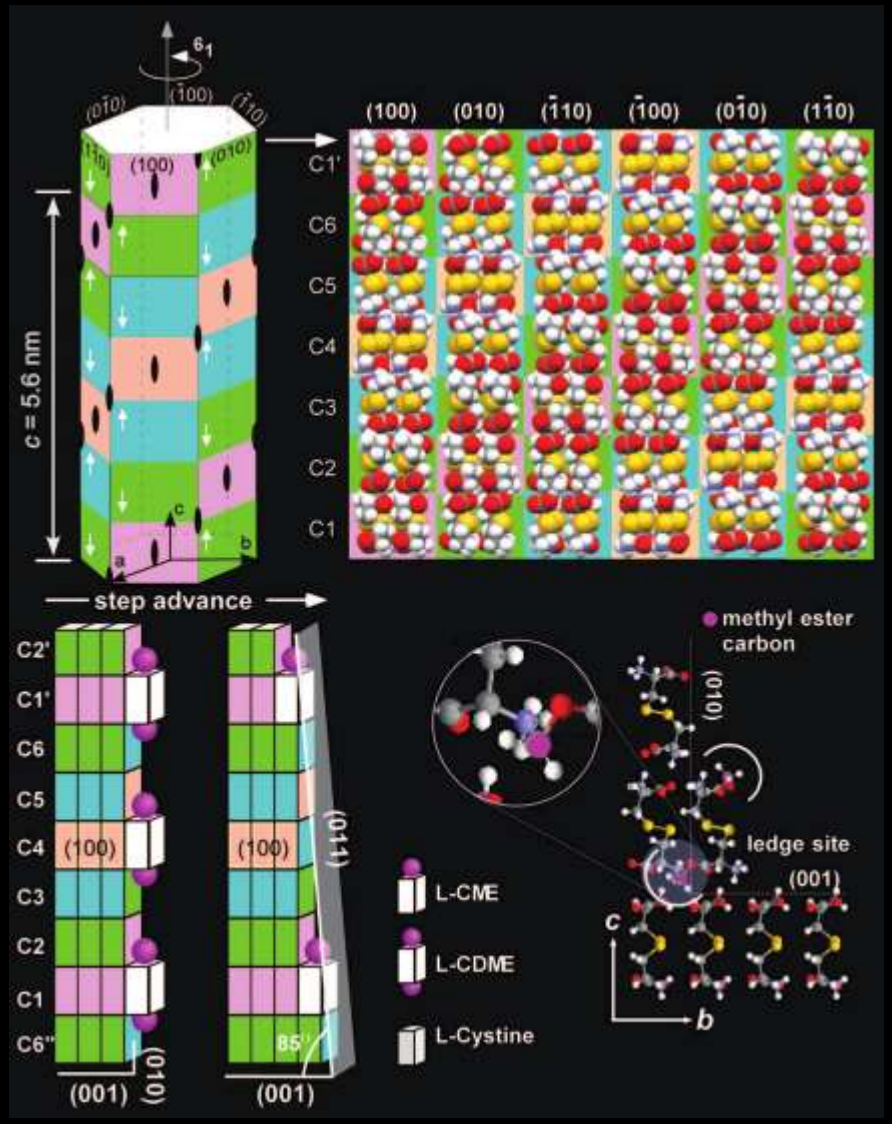


Figure 3. | Representation of the location of mutations detected in *SLC7A9* ($b^{0,+}$AT) throughout the exons and protein domains. Schematic diagram of $b^{0,+}$AT and homology model of $b^{0,+}$AT on the basis of the crystal structure of AdiC protein, an arginine:agmatine antiporter from *Escherichia coli* (Protein Data Bank ID code 3L1L). *SLC7A9* mutations are distributed in exons 4–6, 9, 10, 12, and 13. Mutations are labeled as follows: missense in black, nonsense in purple, frameshift in red, and splice site in pale blue. Mutations predicted to fall within α-helices are denoted by asterisks of the appropriate color.

Treatment

- Surgical
- Increase fluid intake
- Alkalinise urine (pH >7.5)
- Chelate D-Penicillamine
  2-mercaptopropionylglycine (MPG)
  Captopril
- Screen sibs



Crystal Growth Inhibitors for the Prevention of L-Cystine Kidney Stones Through Molecular Design

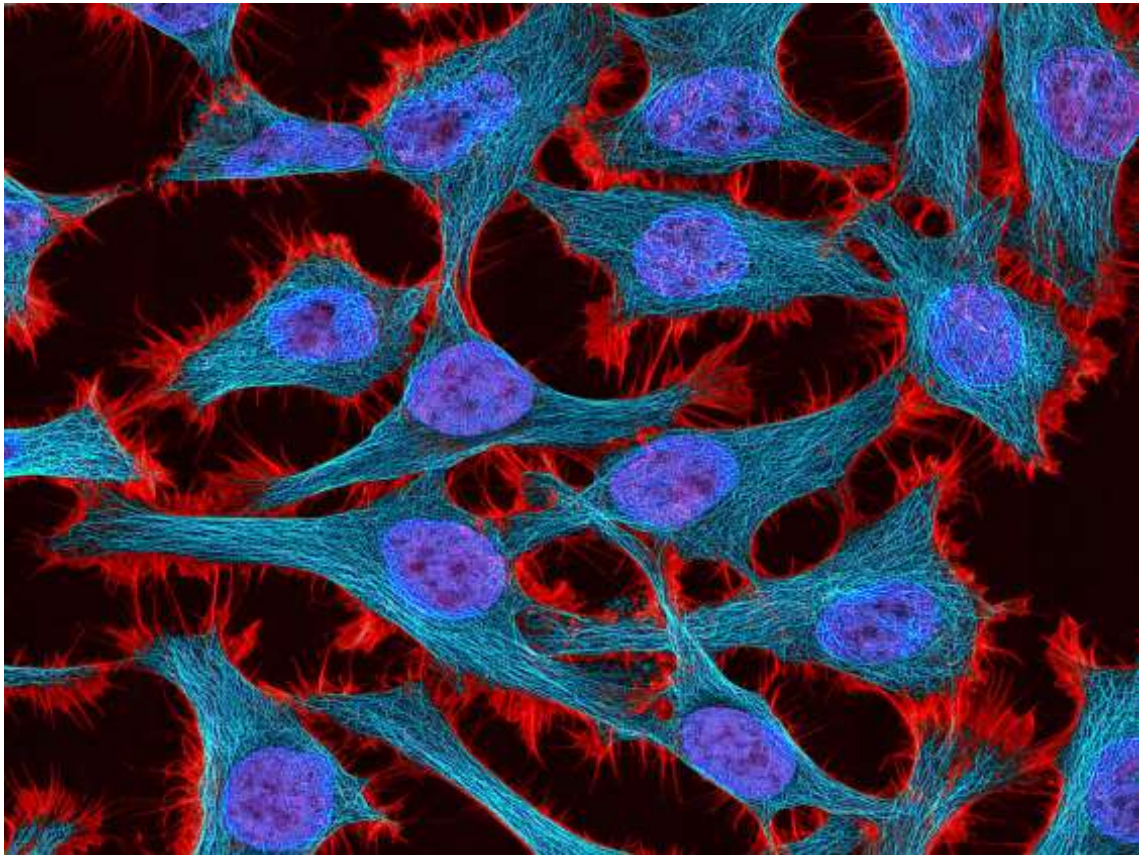
Jeffrey D. Rimer,[1]*† Zhihua An,[1]* Zina Zhu,[1]* Michael H. Lee,[1] David S. Goldfarb,[2] Jeffrey A. Wesson,[3] Michael D. Ward[1]‡

www.sciencemag.org **SCIENCE** VOL 330 15 OCTOBER 2010

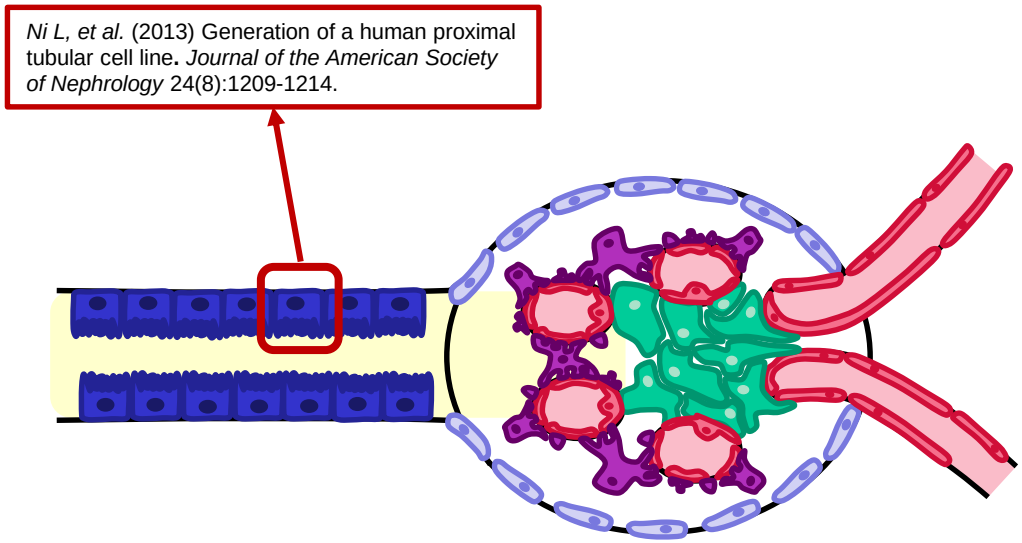
■ Hannah Rhodes sheds new light on the complexities of the rare inherited renal stone disease cystinuria

Cystinuria: an inherited genetic disorder that breaks the rules

CELLS

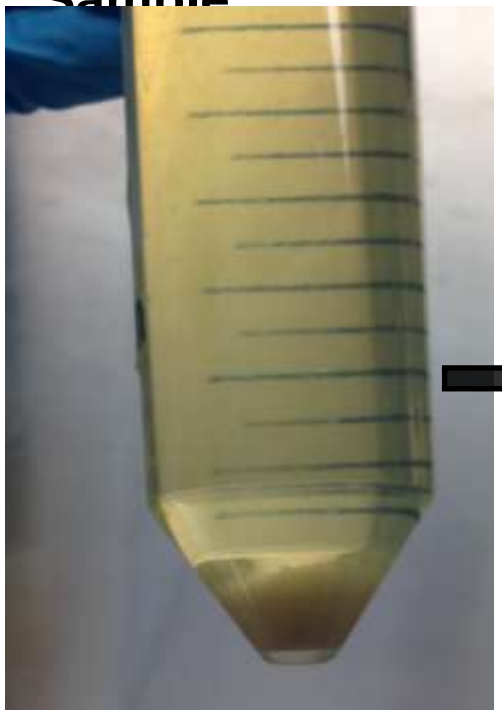


Background

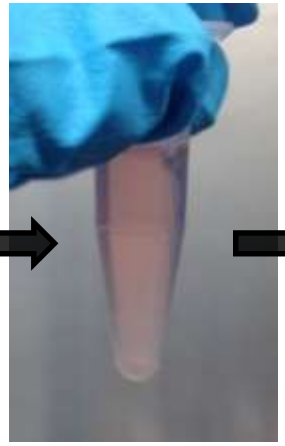

Ni L, et al. (2013) Generation of a human proximal tubular cell line**.** *Journal of the American Society of Nephrology* 24(8):1209-1214.

Preparation of Urinary Cells

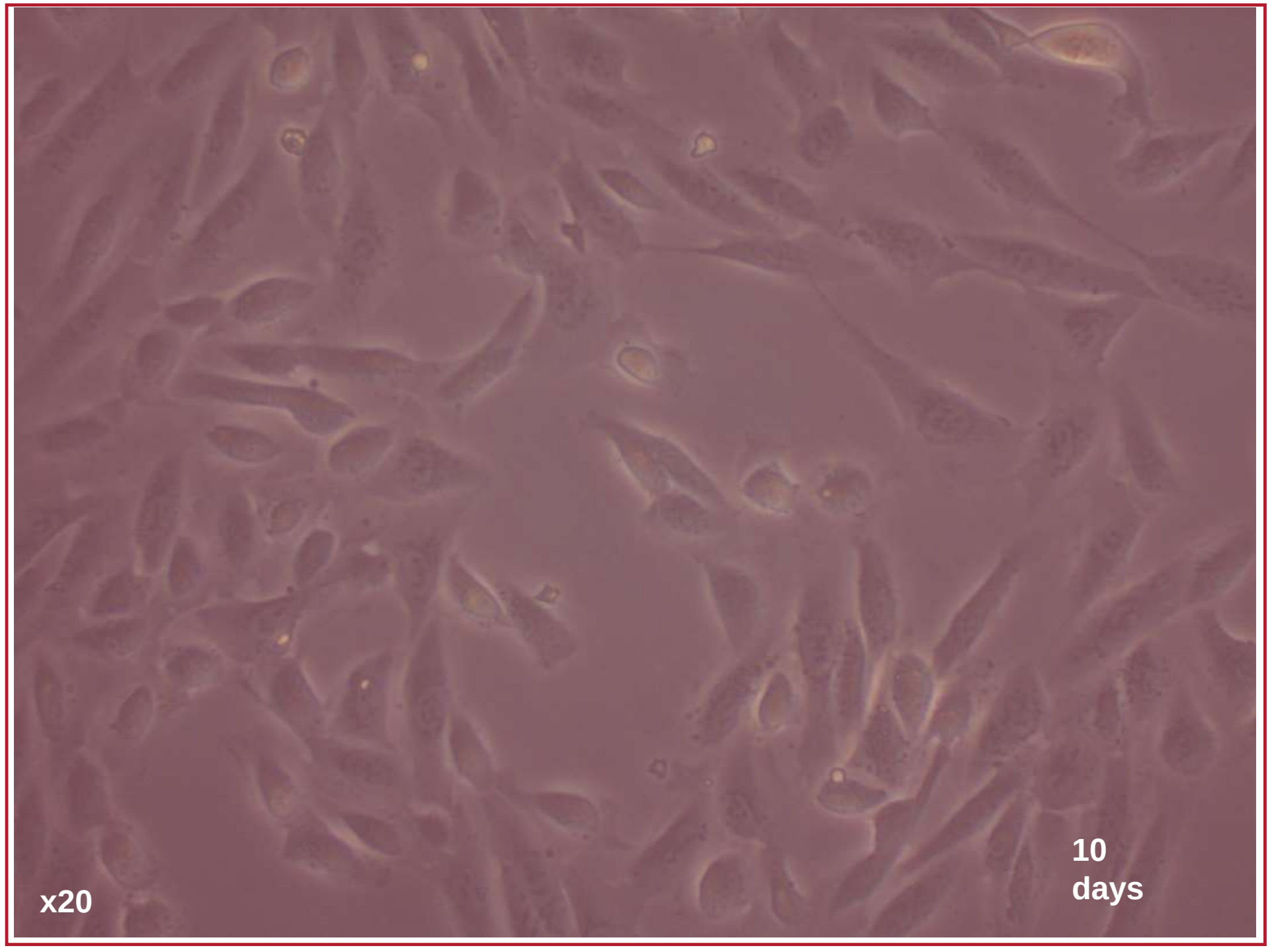
50ml Urine Sample



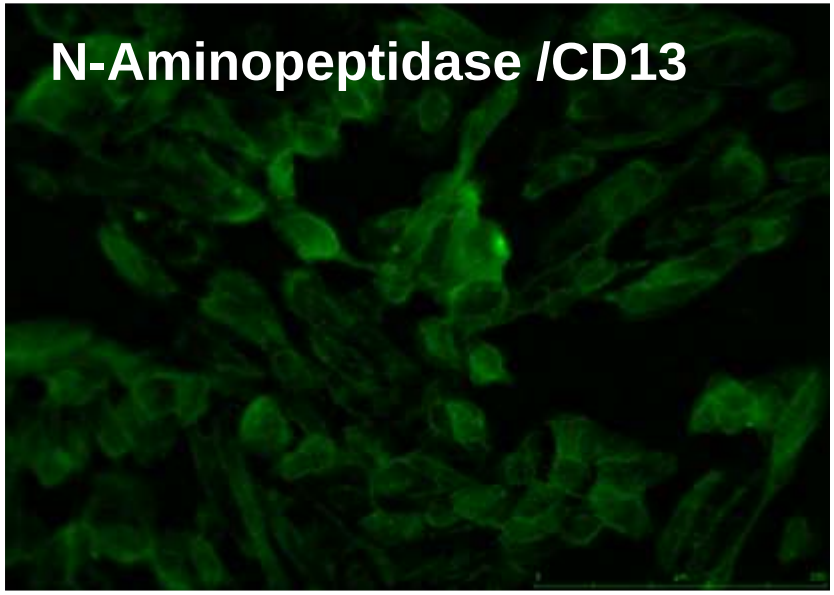
Washed & isolated

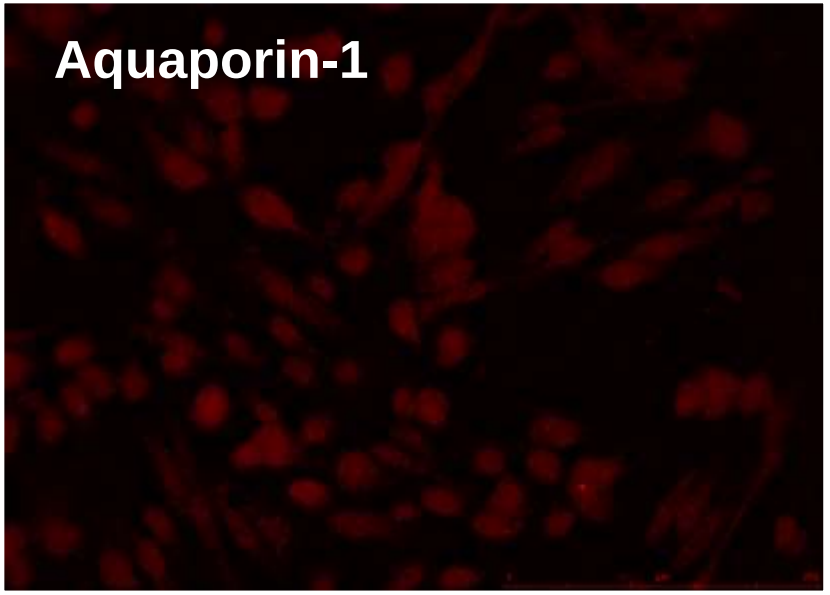


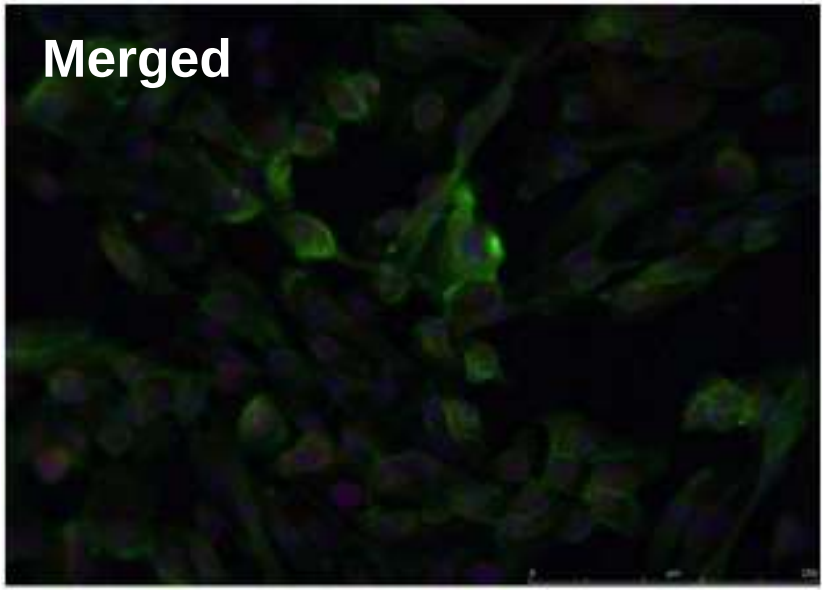
Grown in flasks and dishes

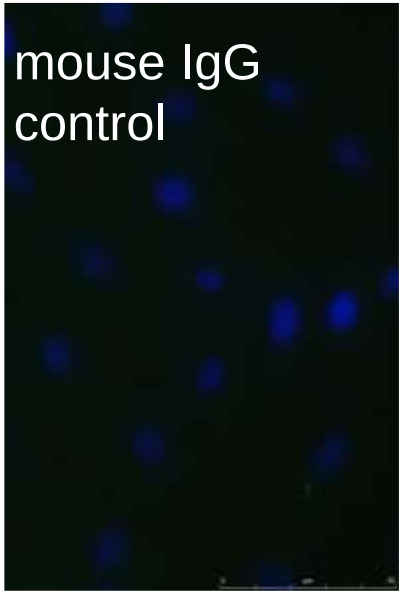

x20
10
days

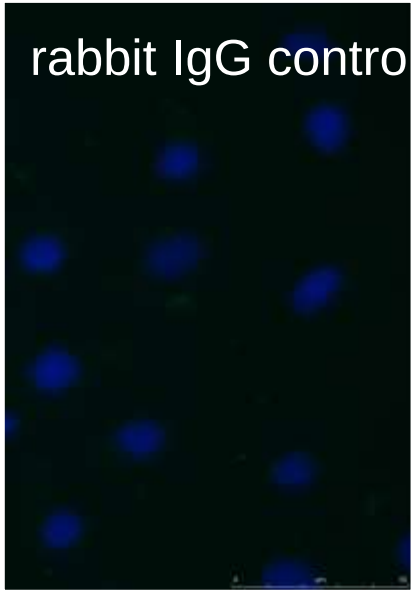
Immunofluorescence for kidney markers



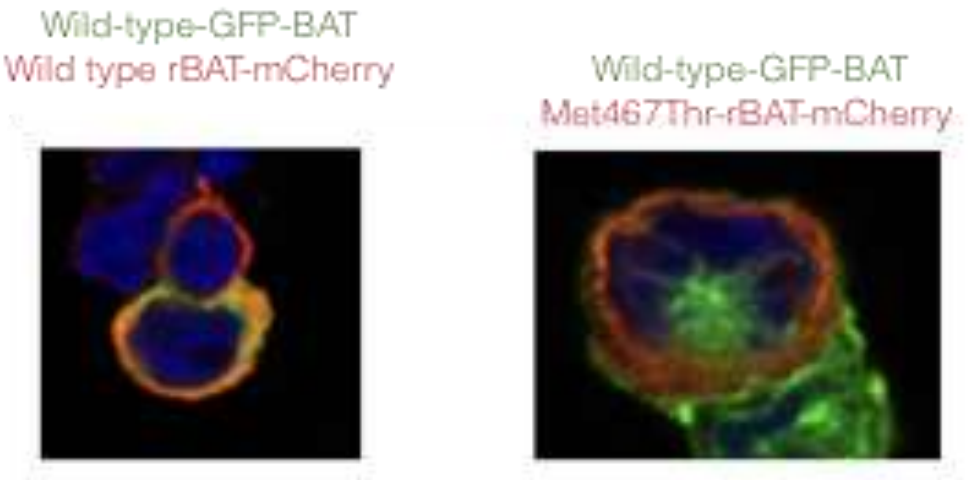




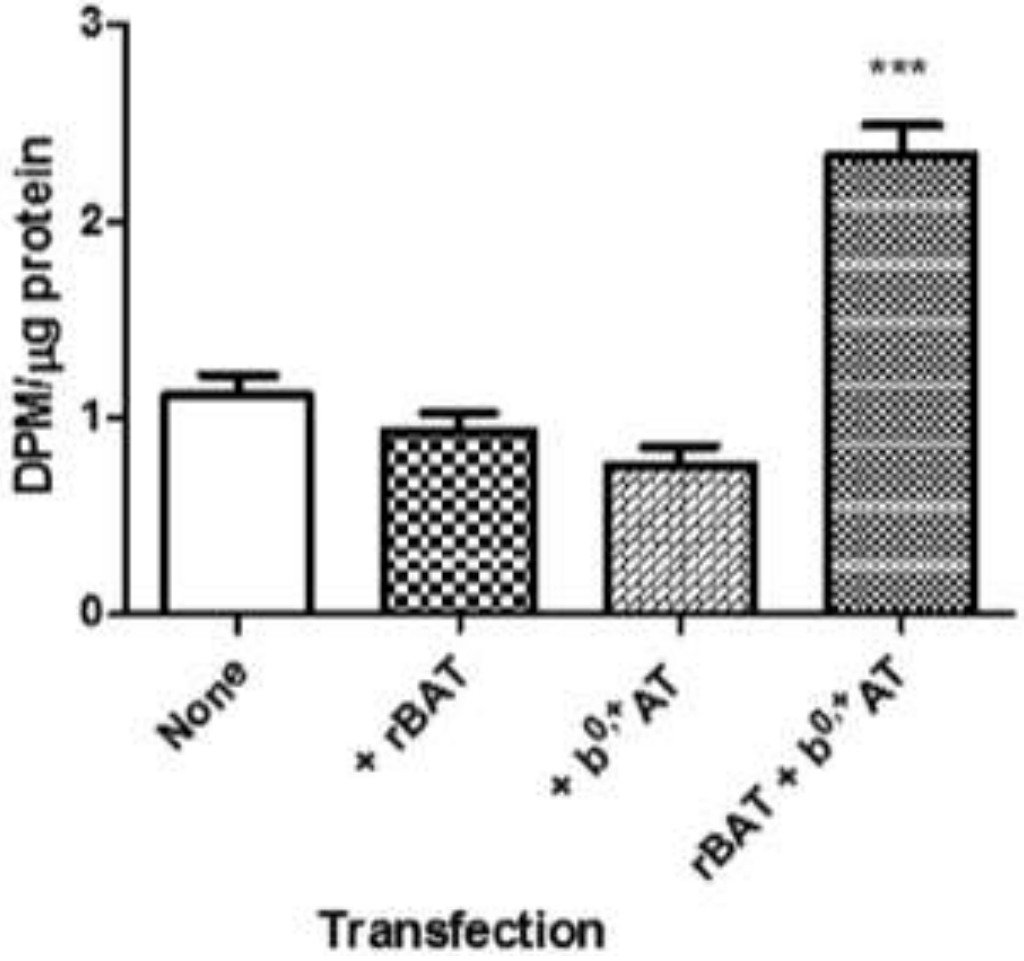




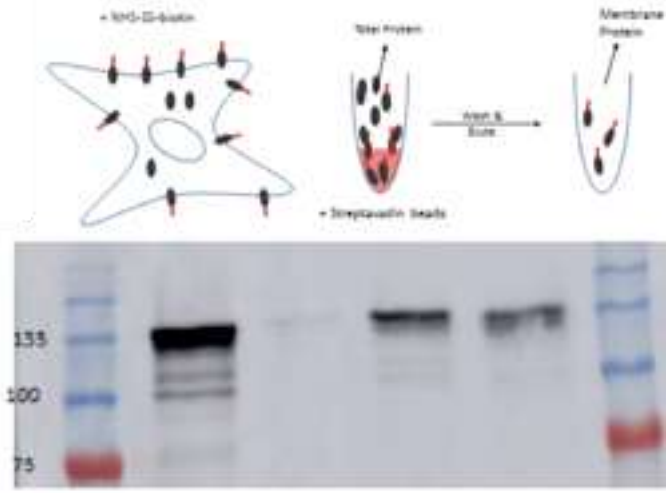
Genetic reconstitution of BAT and rBAT into PTC
Wild type v mutants!!



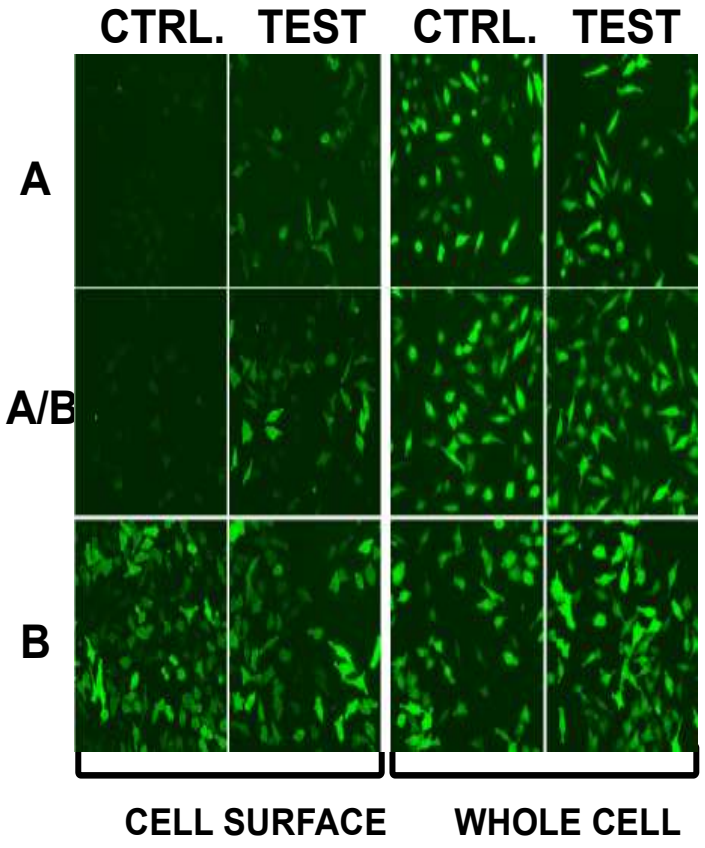
Functional cystine uptake into cells

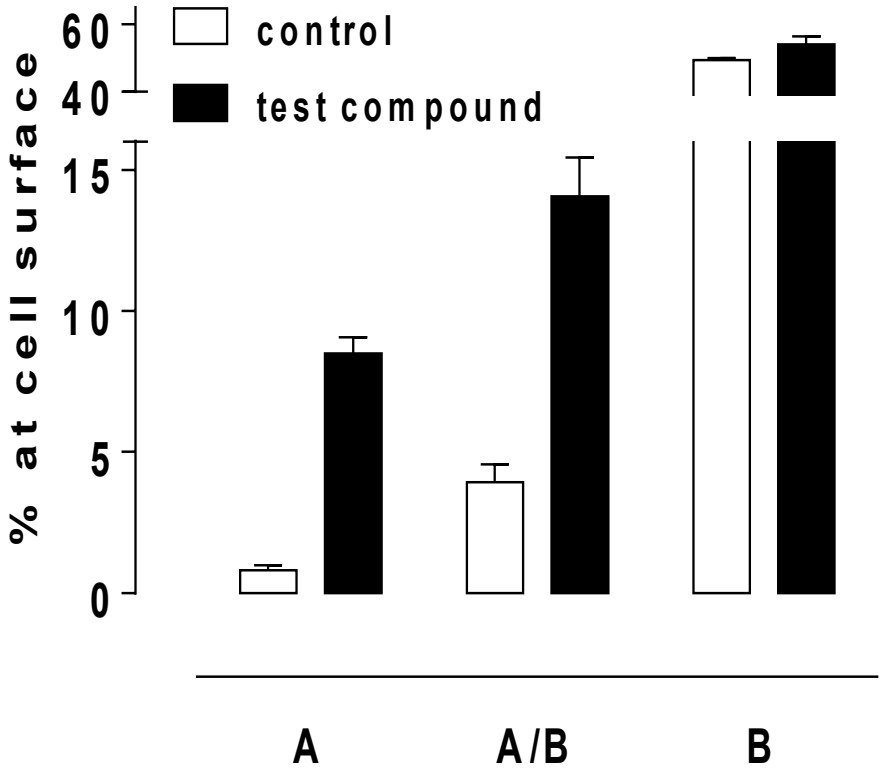


Mapping cell surface location of transporters

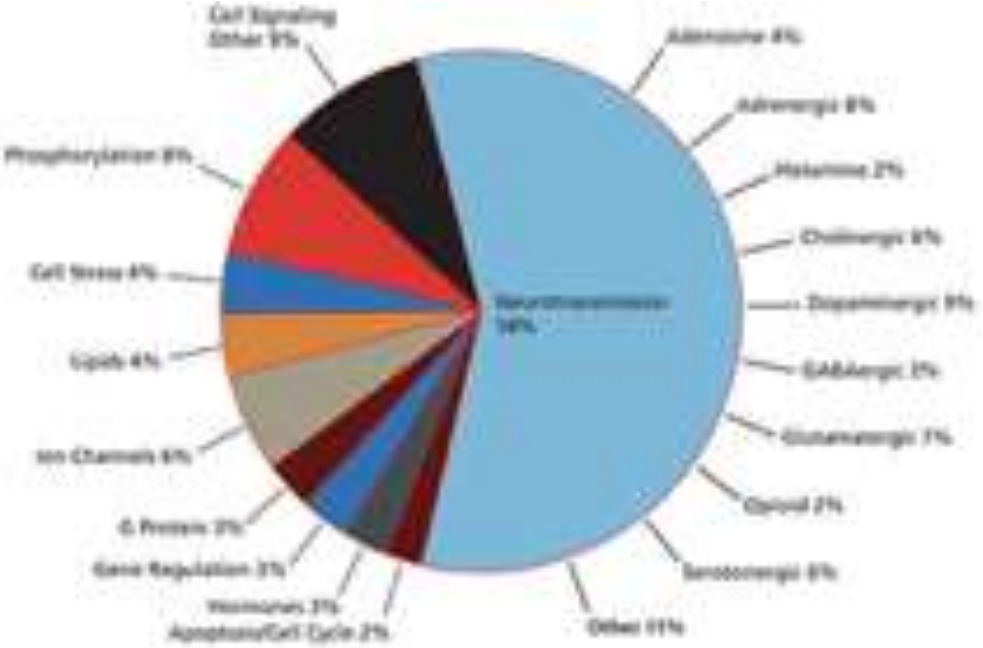


Towards a high throughput system

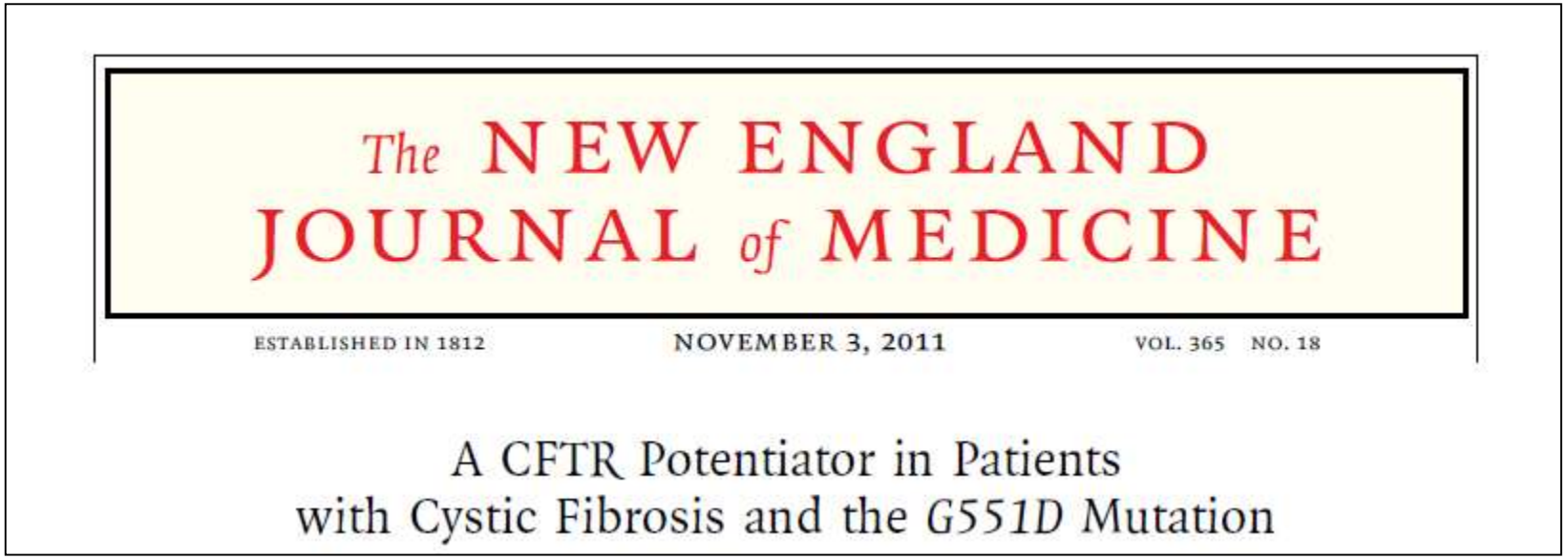




Compound screen



Been done before……



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

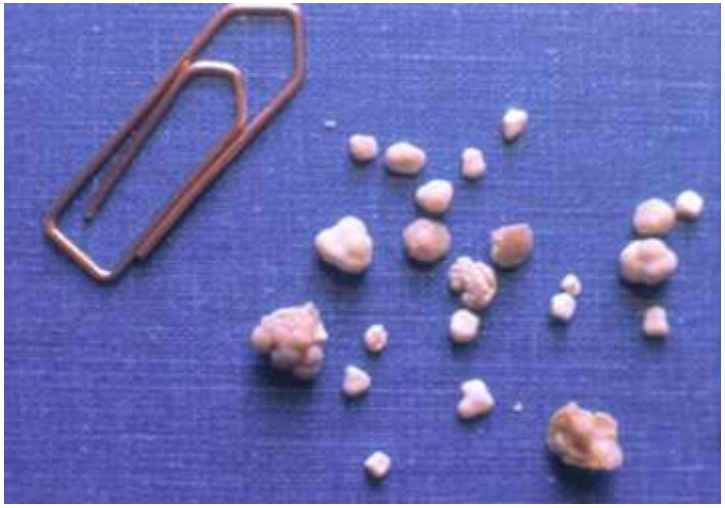
A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

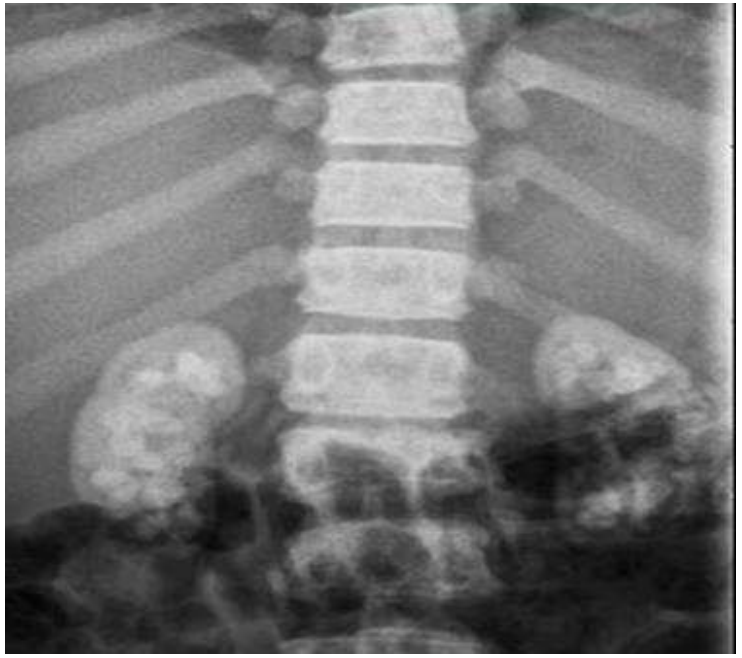
Ivacaftor

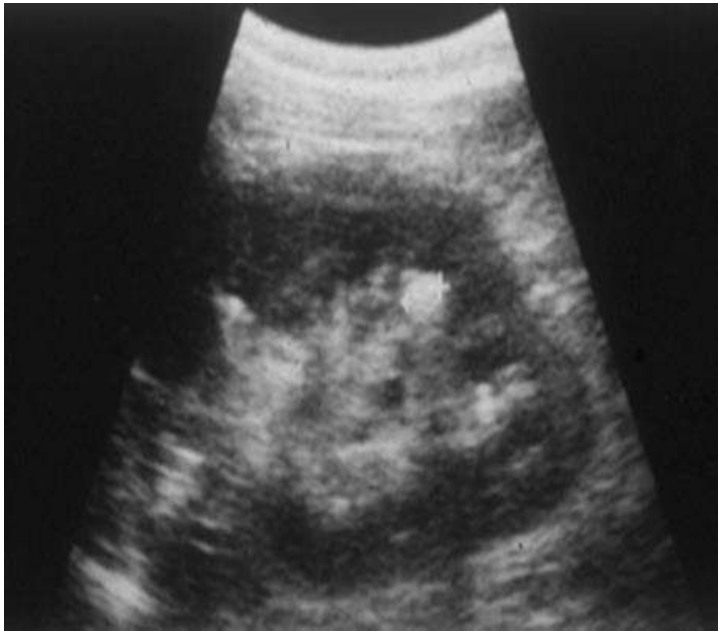
AETIOLOGY

- Infective
- Metabolic
- Unknown

Monogenic conditions







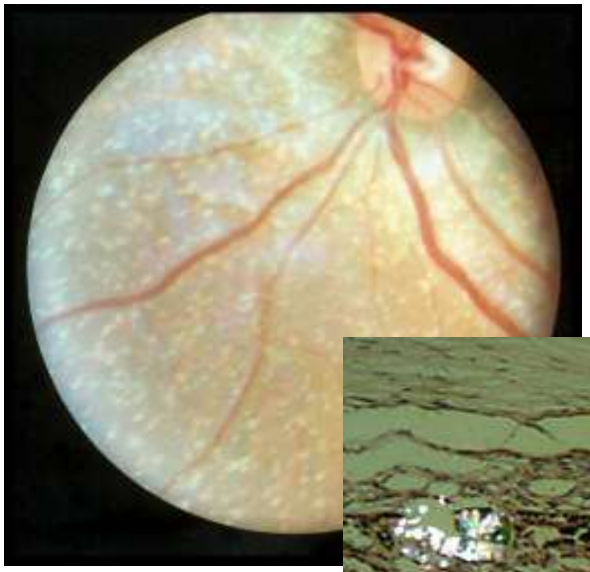
Enzyme deficiency in the liver targets the kidneys

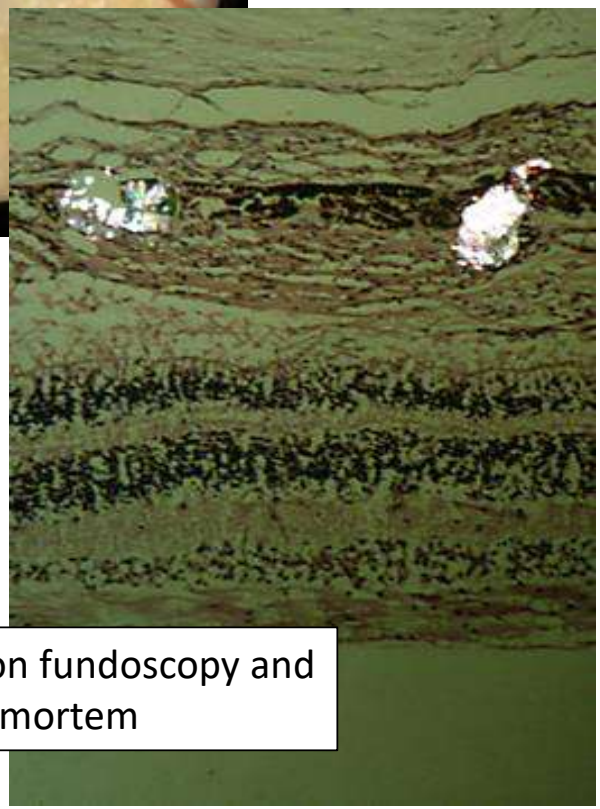
AGT enzyme defect in the ●❀❐□ □ oxalate production

Kidneys normally excrete oxalate

Oxalate deposits in kidneys forming stones + calcification within the kidney (nephrocalcinosis) resulting in kidney failure

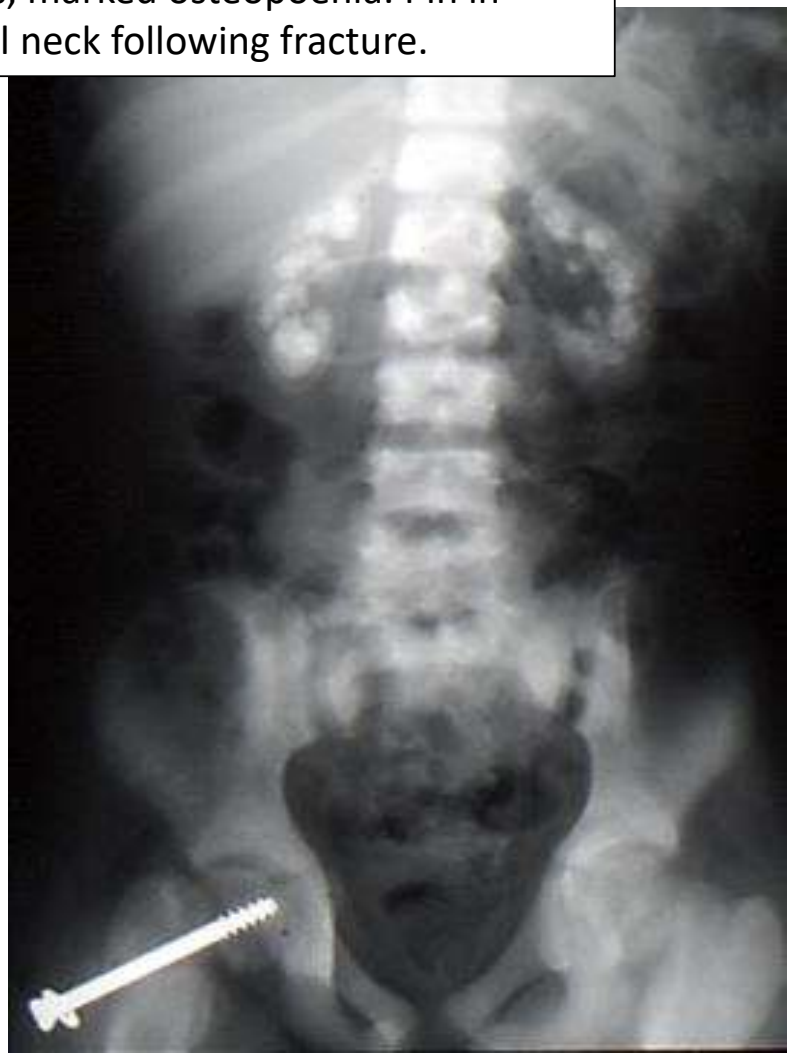
Consequences of PH1



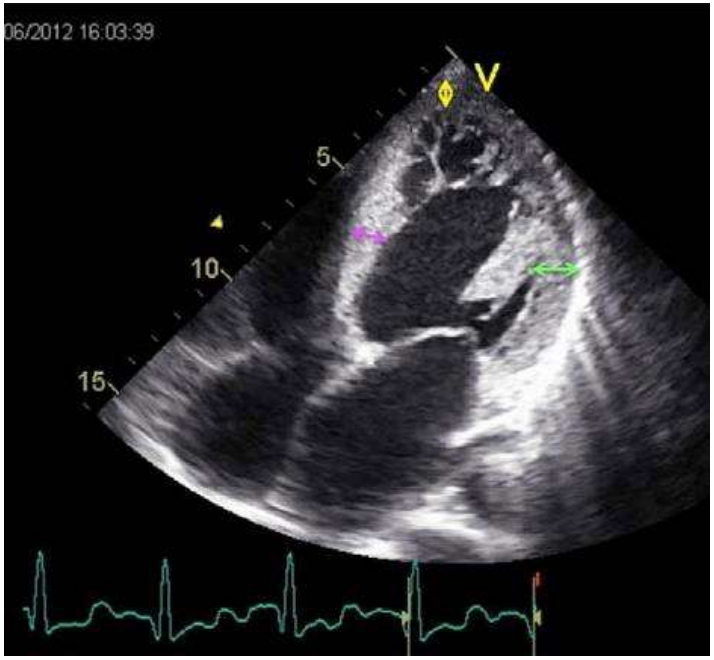


Oxalate crystals on fundoscopy and in retina on post mortem

Female aged 9 years with calcification of kidneys, marked osteopoenia. Pin in femoral neck following fracture.



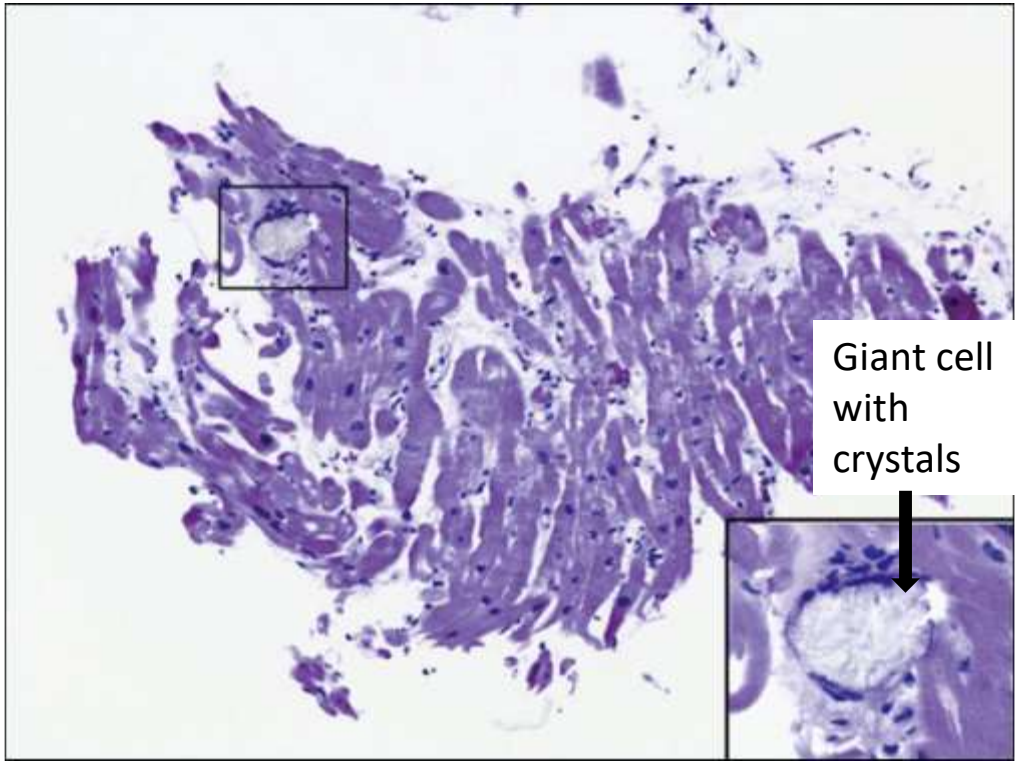
Consequences of PH1



Cardiac echo showing increased wall thickness

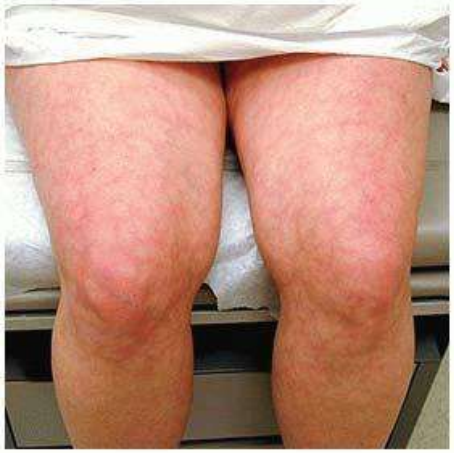
CR Lagies et al: Circ Heart Fail 2013;6: e45-7

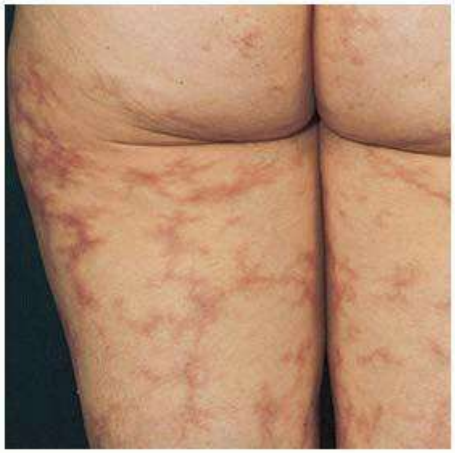
Endomyocardial biopsy right ventricle



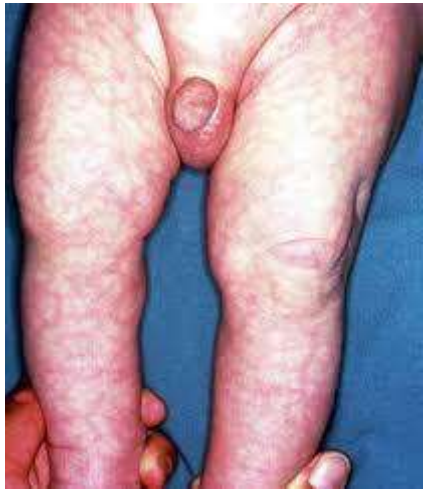
F Mookadam et al: Circ J 2010; 74: 2403 – 2409

Consequences of PH1



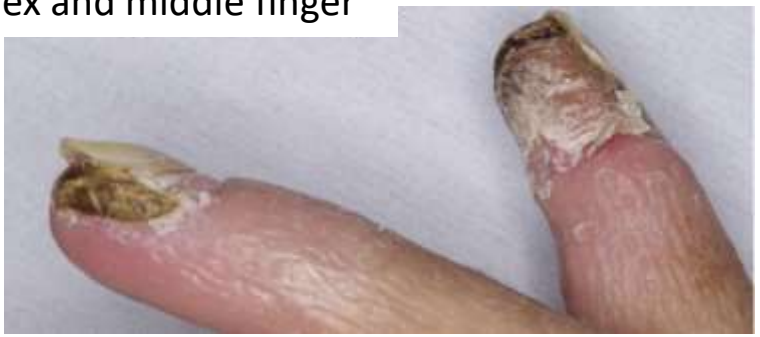


Livedo reticularis of skin



Gangrene of fingers with osteolysis in secondary oxalosis

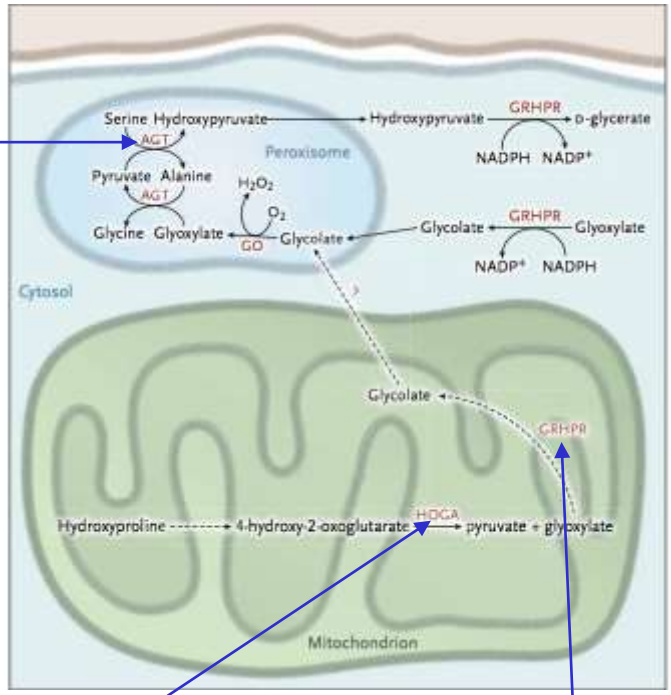
Index and middle finger



Courtesy of S Arampatzis, D Fuster
University Hospital of Bern, Switzerland

PH1: AGXT gene

Pyridoxine co-factor



PH3: chromosome 10

PH2: chromosome 9

Hepatocyte:

Glyoxylate accumulates due to AGT deficiency

Glycoxylate → oxalate by LDH

Oxalate = insoluble

Primarily excreted by kidneys

Crystallises in renal tubules

When eGFR <40 → systemic oxalosis occurs

Oxalate deposits in bone / blood vessels……

PH mutations & diagnosis

- **PH1 AGXT gene *chr 2***
  → plasma oxalate + glycollate
  → urine oxalate

- **PH2 GRHPR gene *chr 9***
  → urine L-glyceric acid (may be absent)

- **PH3 HOGA1 gene *chr10***
  →urine oxalate + glycollate
  → urine Ca + uric acid

Database of pathological mutations + polymorphic variants
http://www.uclh.nhs.uk/phmd

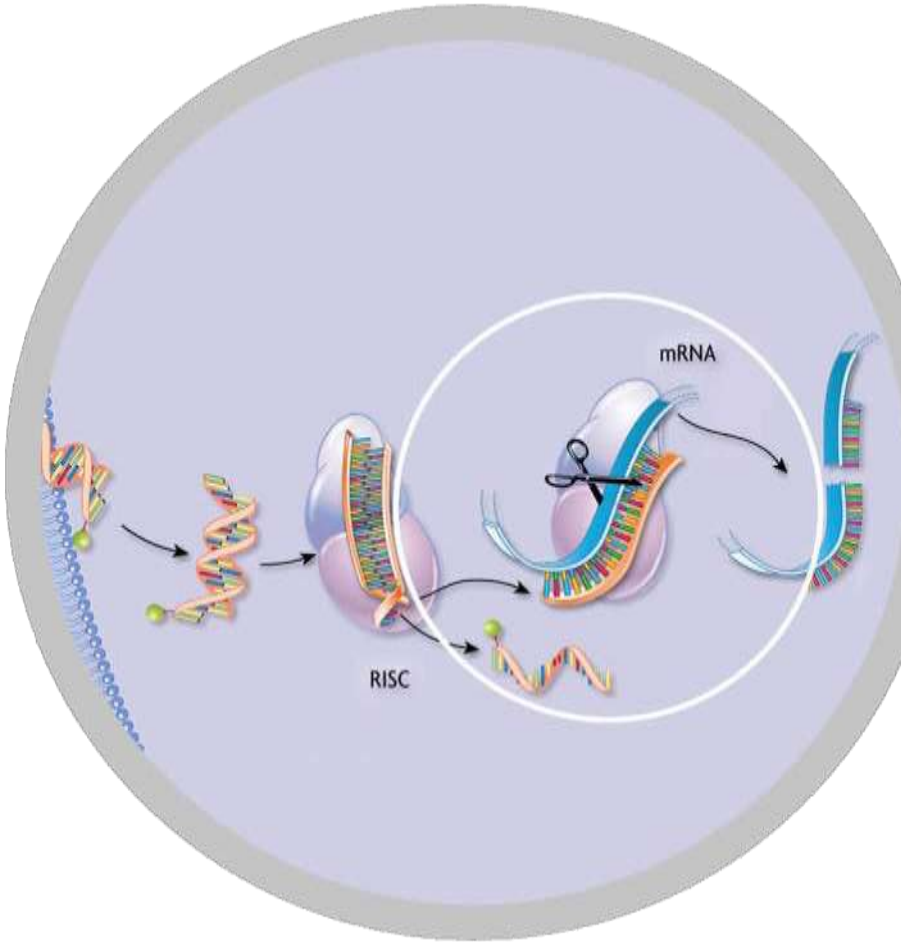
Primary Hyperoxaluria

- Fluids.
- Citrate.
- Pyridoxine for SOME type 1.
- Surgical intervention as necessary.
- Definitive treatment is combined liver kidney transplant.

RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now commercial



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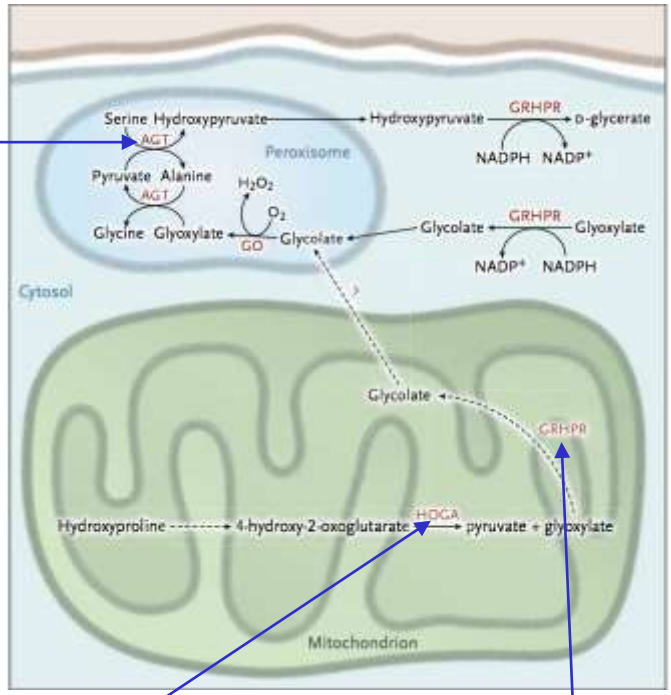

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Oxalate deposits in bone / blood vessels……

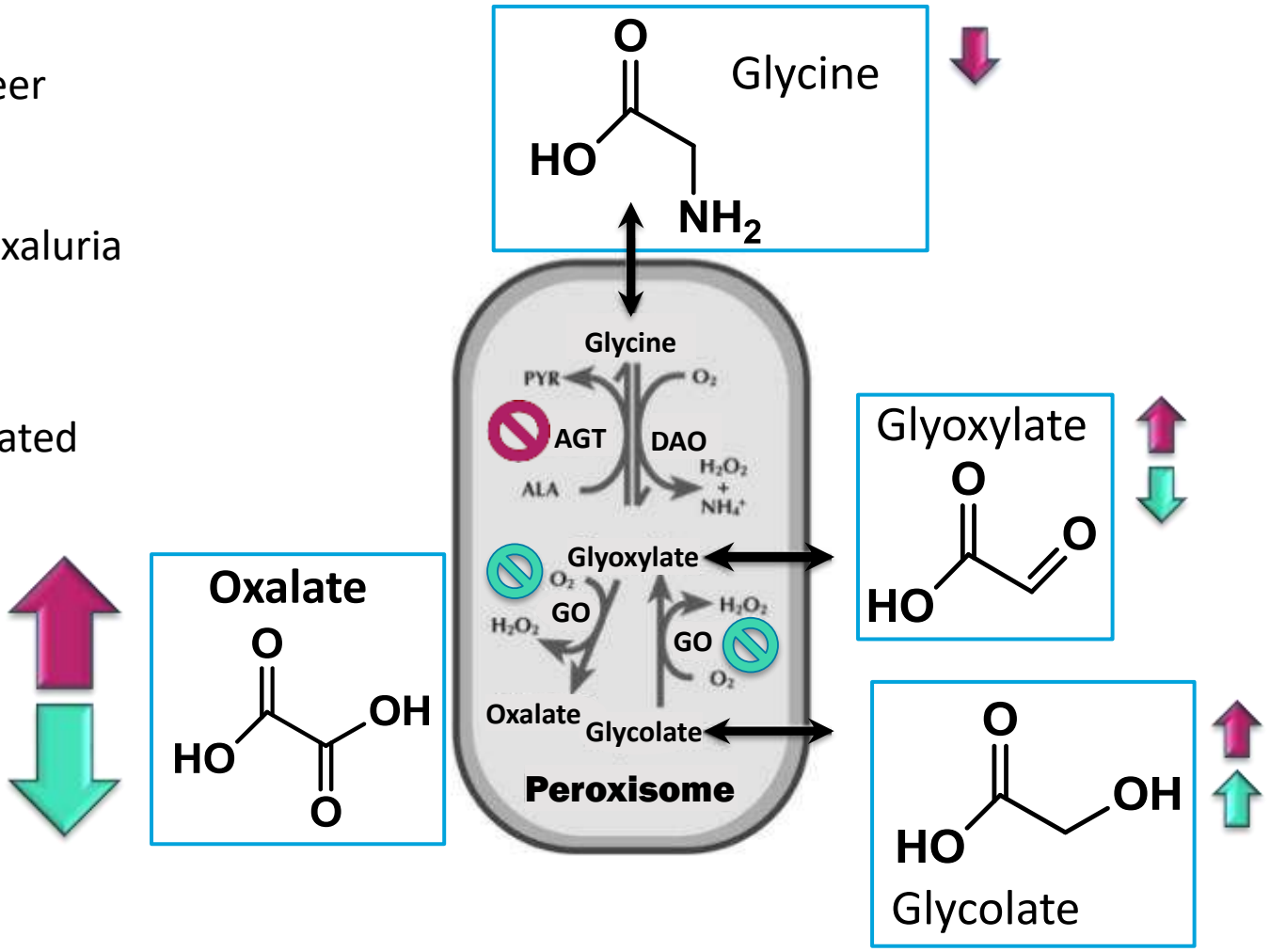
Lumasiran Therapeutic Hypothesis

Knockdown of Liver GO Enzyme to Reduce Oxalate

Healthy Volunteer

Primary Hyperoxaluria Type 1 Patient

PH1 Patient Treated with Lumasiran

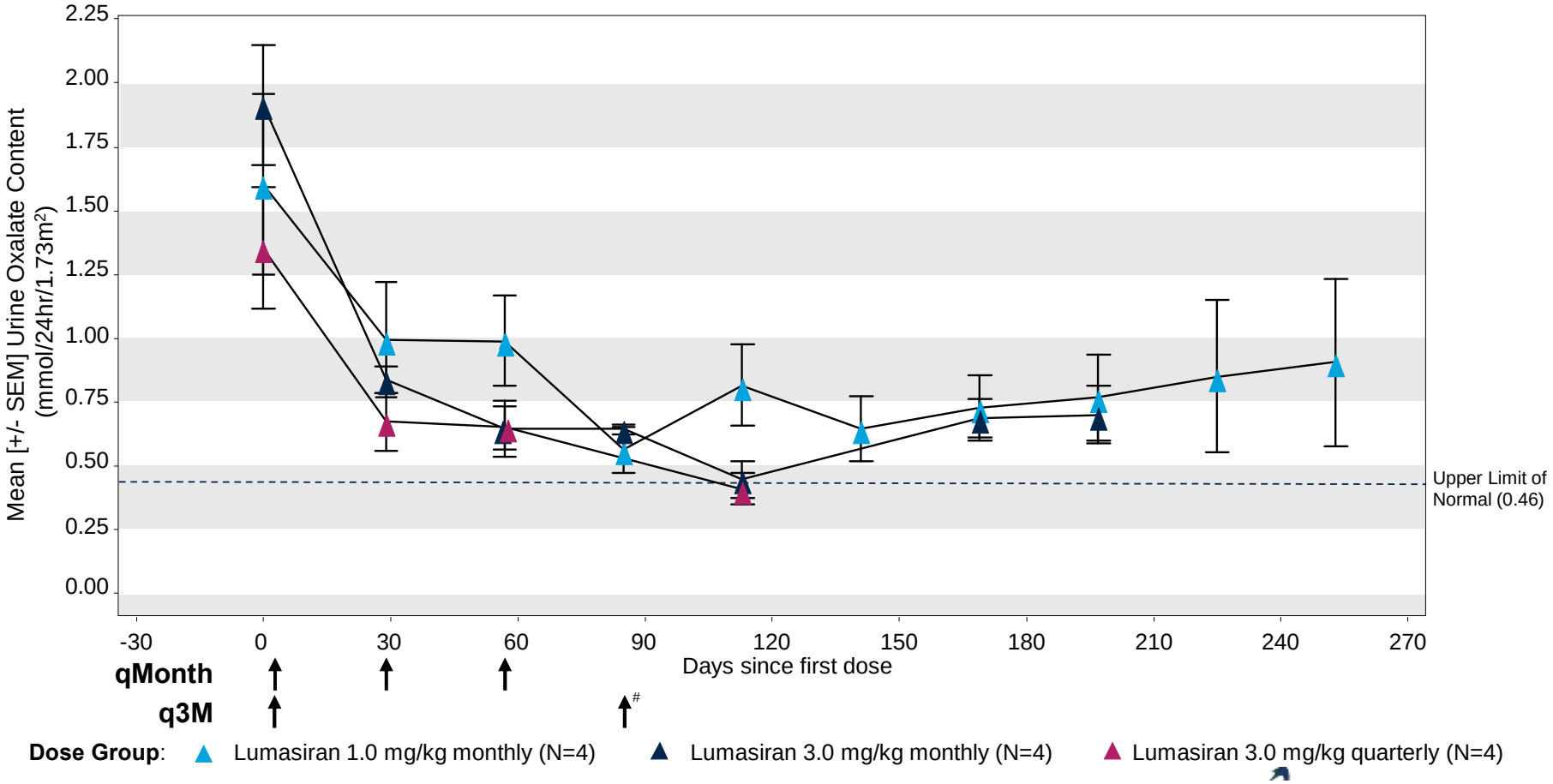


Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Part B (Patients with PH1)

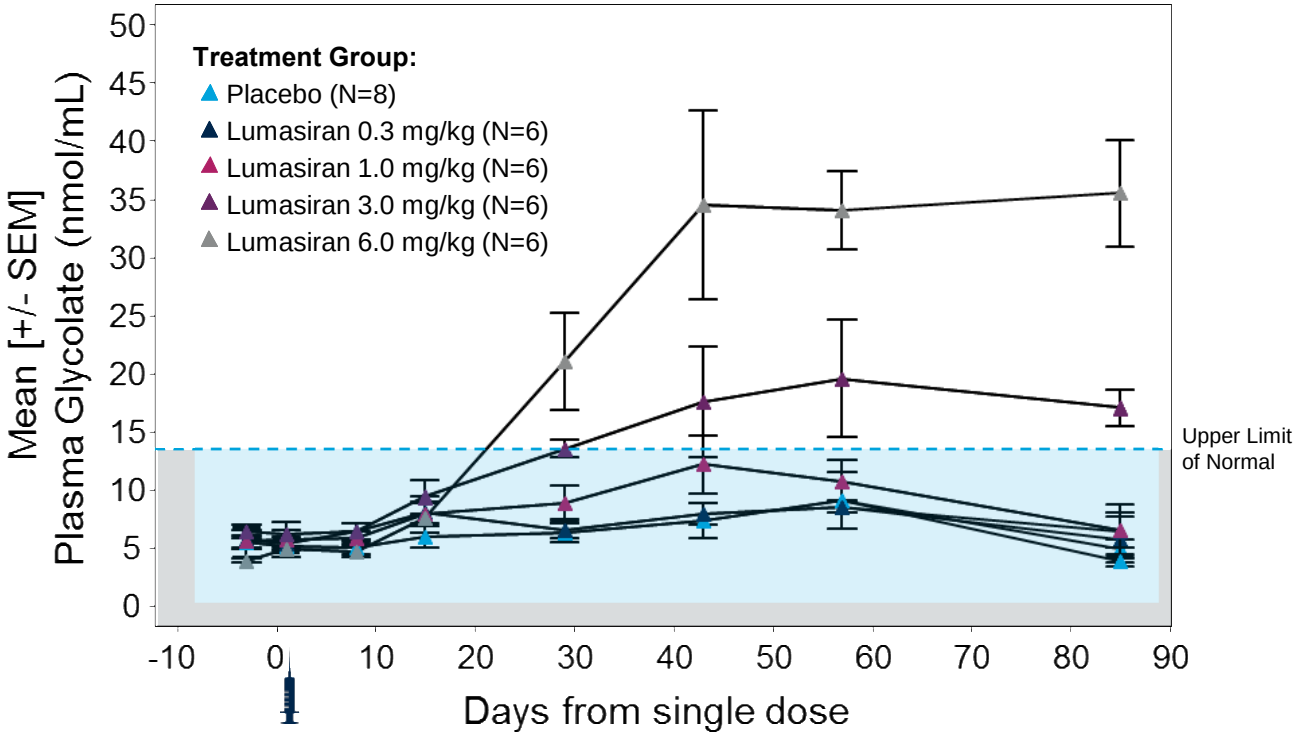
Mean maximal reduction in urinary oxalate of 64% relative to baseline after lumasiran dosing in patients in Cohorts 1-3 (n=12)

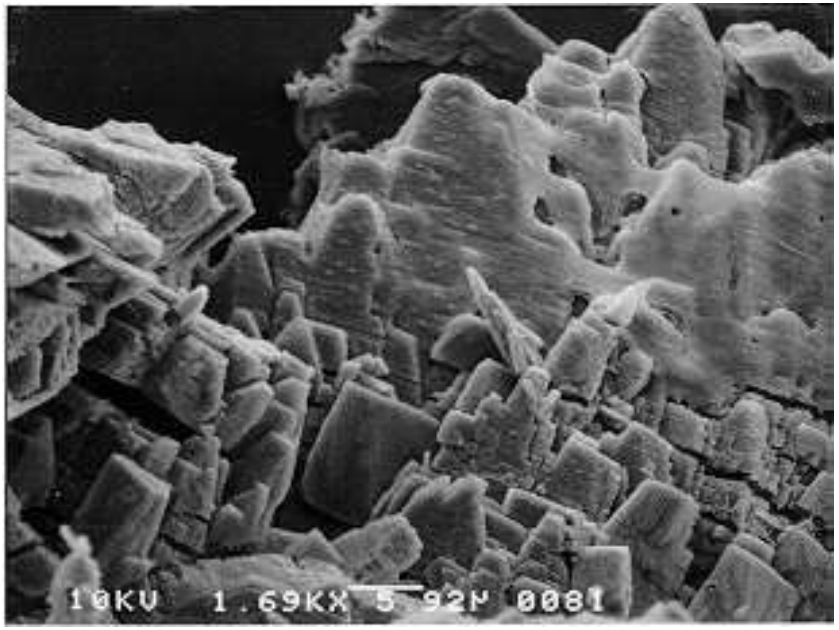
- Mean 63% urinary oxalate reduction relative to baseline observed at day 85 (n=9†)



Lumasiran Phase 1/2 Part A Study Results: Plasma Glycolate Levels in Healthy Volunteers

Dose-dependent increase in plasma glycolate levels in healthy volunteers after single dose of lumasiran[1]



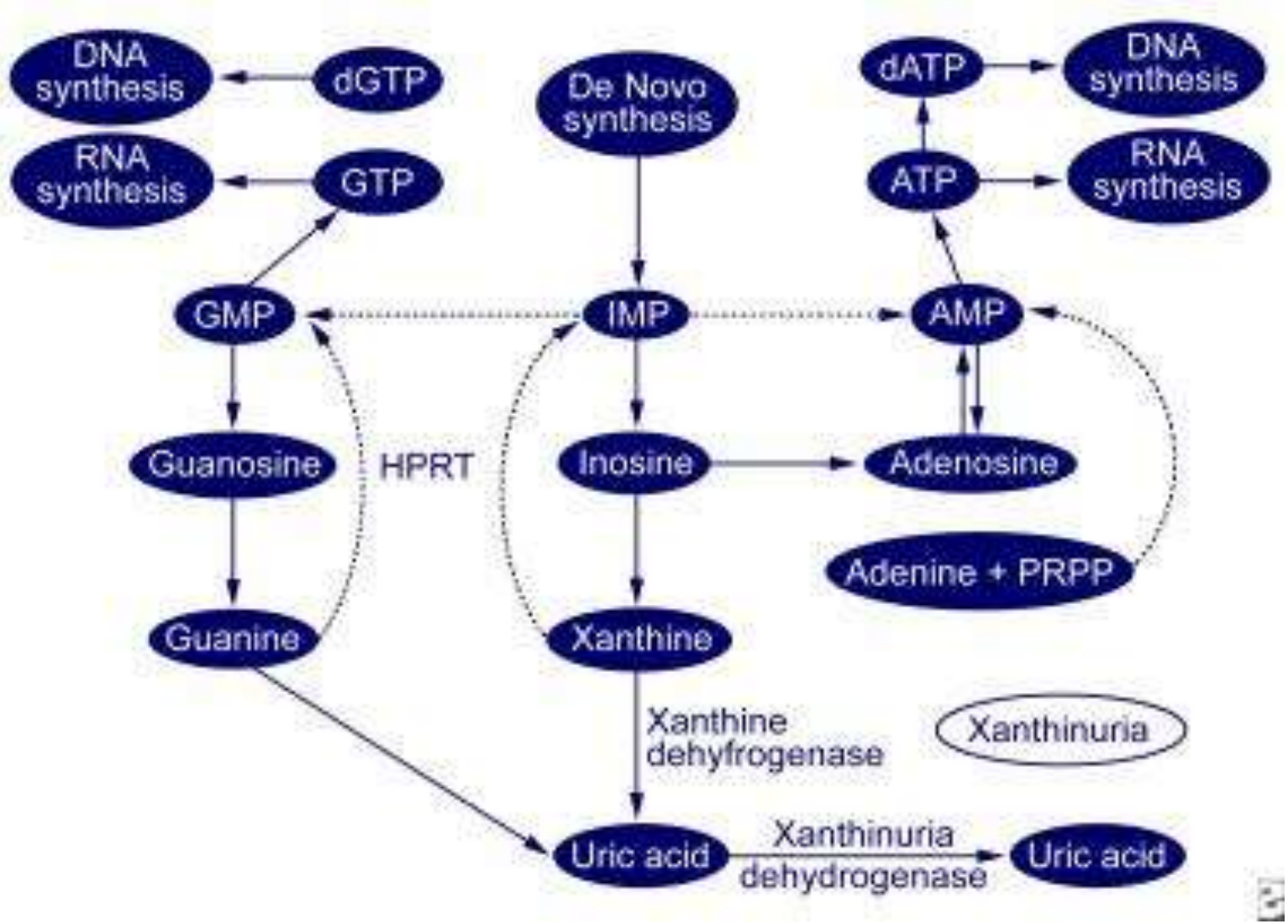


High cellular turn over states

Lesch-Nyhan syndrome

Uric acid stones - treatment

- Increased fluid intake
- Alkalinise the urine
- Allopurinol


DNA synthesis
dGTP
RNA synthesis
GTP
De Novo synthesis
dATP
DNA synthesis
ATP
RNA synthesis
GMP
IMP
AMP
Guanosine
HPRT
Inosine
Adenosine
Adenine + PRPP
Guanine
Xanthine
Xanthine dehyfrogenase
Xanthinuria
Uric acid
Xanthinuria dehydrogenase
Uric acid

Treatment

- High fluid intake
- Low purine diet
- Alkalinisation does not effect solubility
- NB LOW URIC ACID LEVELS IN SERUM AND URINE.

Investigations

- KUB X-ray
- Renal USS
- Urine

Ca:Cr , Ox:Cr , Urate:Cr, Citrate:Cr ratio

Cystine chromatography. 2nd void screen. X 3

- Blood

  Na, K, Urea, Cr, HCO3, urate, Ca, Mg, albumin and alkaline phosphatase. Vit D and PTH may be necessary as 2nd line

- Stone

  Should be sent to biochem → Middlesex

Never forget!

- Involve surgical team early especially if obstruction.

Take home messages

- Renal stones in children commonly metabolic
- Always perform a metabolic stone screen
- Remember Cystinuria and Primary Hyperoxaluria
- New potentially exciting therapies on the horizion

Thank you and any questions?