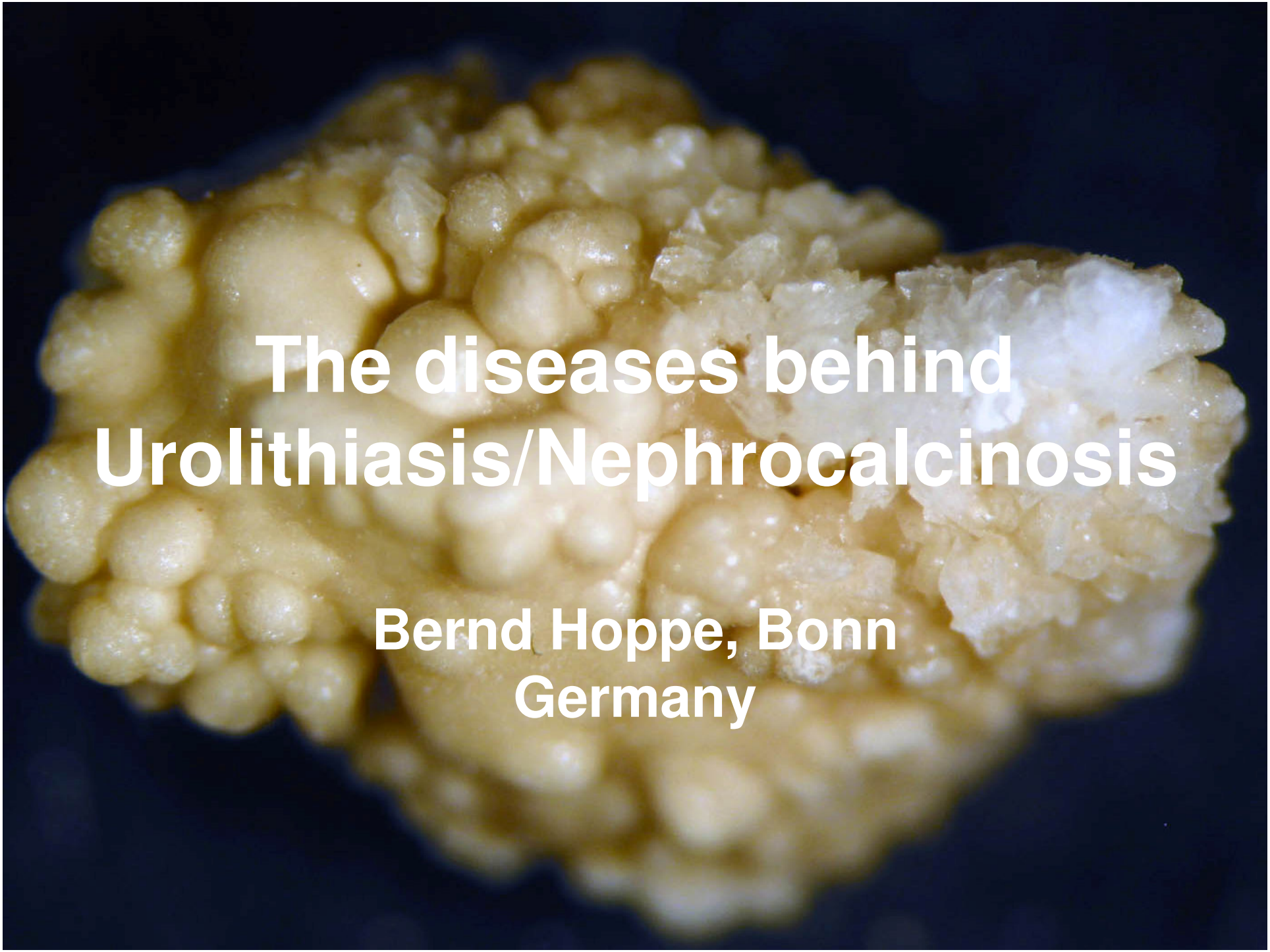


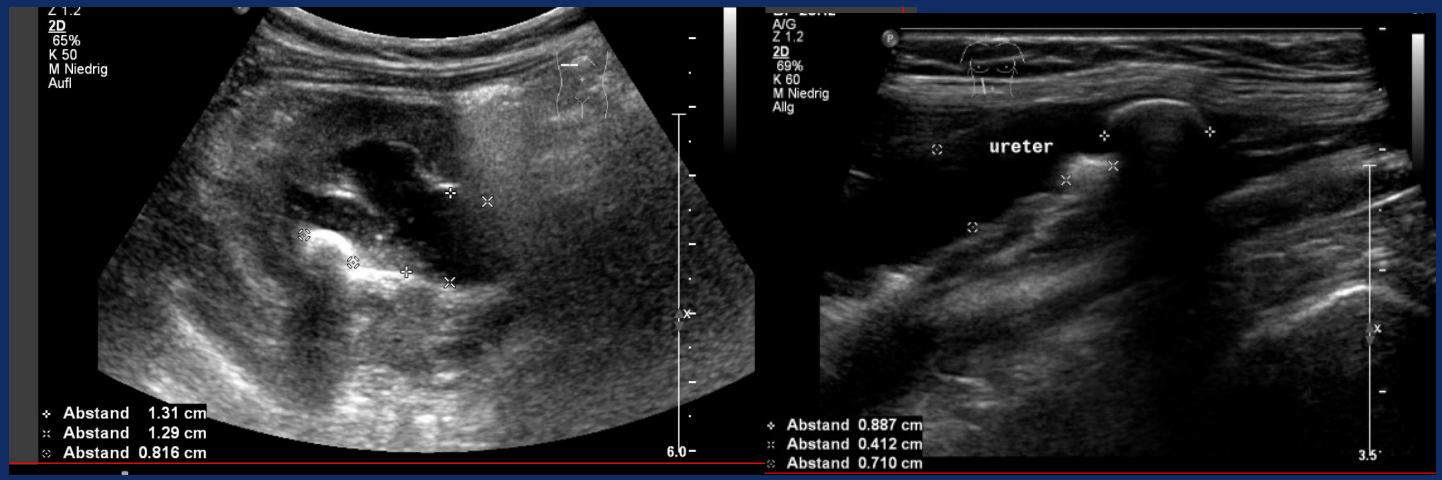
The diseases behind Urolithiasis/Nephrocalcinosis

Bernd Hoppe, Bonn
Germany

ASN breaking news

(from March 27th 2009)

The incidence of childhood urolithiasis is increasing „from seeing a child with stones once in a while to now weekly admitting 1-2 children (or even more) with stones!“ (Uri Alon, dixit).



Incidence/Prevalence UL

- Incidence in pediatrics: ~ 10% of that in adults (5-5.5%)
  - 12 % of men will experience a stone episode
- Increase of children with UL in an emergency room setting from 1996-2007
  - 3.2 to 4.5 per 100.000 African American
  - 10.9 to 26.2 per 100.000 Caucasian children in 2007
  - 5.6 times higher risk in Caucasians

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Sex and Age distribution

- UL and/or NC affect children of all ages
  - Younger children: more renal calculi
  - Older children: more ureteral stones
  - Boys are more affected in first decade of life
  - Girls are more prone in second decade
- NC primarily appears in the first years of life
  - tubulopathies
  - inborn errors of metabolism

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1 stone	2 stones	≥ 3 stones
58 %	18 %	24 %

Early diagnosis and treatment are mandatory

- for the patient
- for the budget

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Late Diagnosis

16.5 year old boy at presentation in Pediatrics

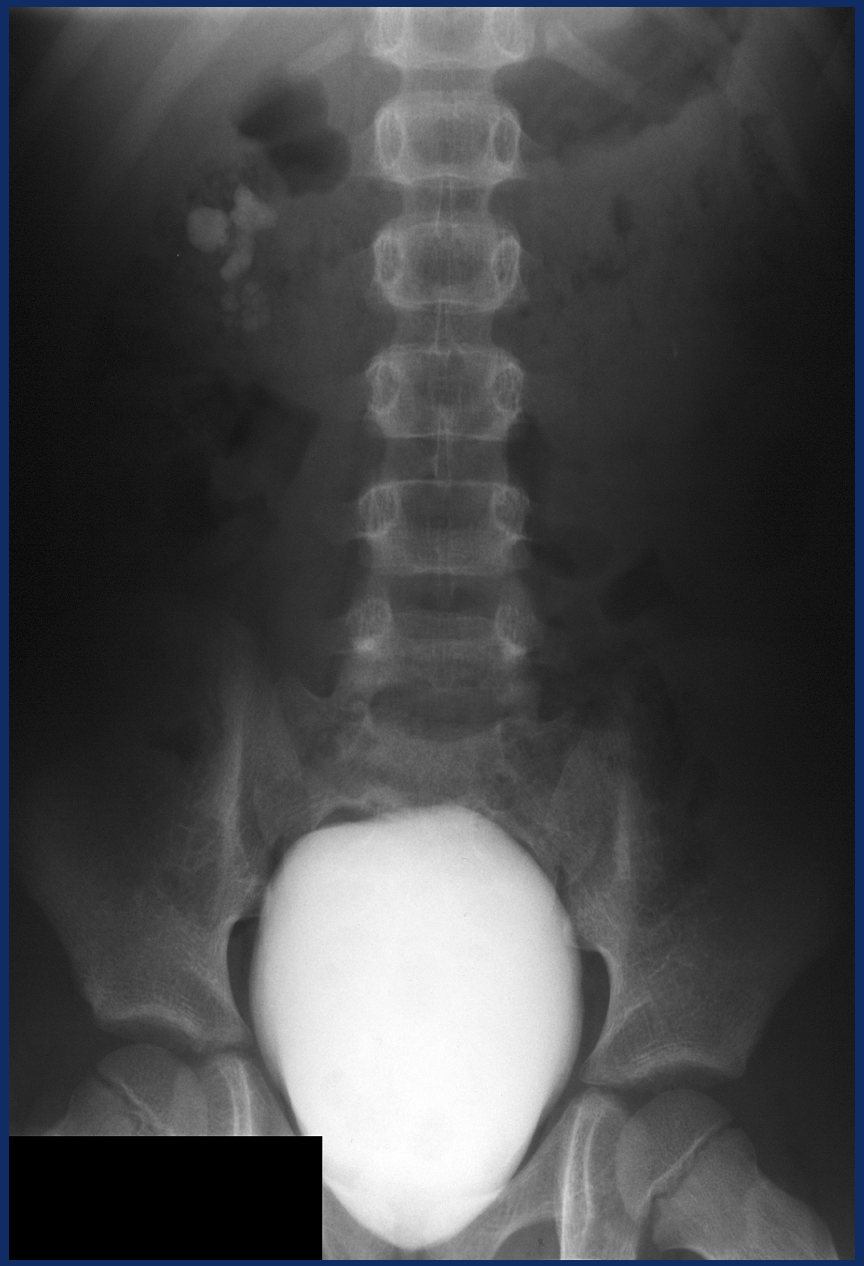
Stones since age 8 years

Repeated Lithotripsy

Repeated open surgery

Nephrectomy right side

Urine was only analyzed for calcium excretion



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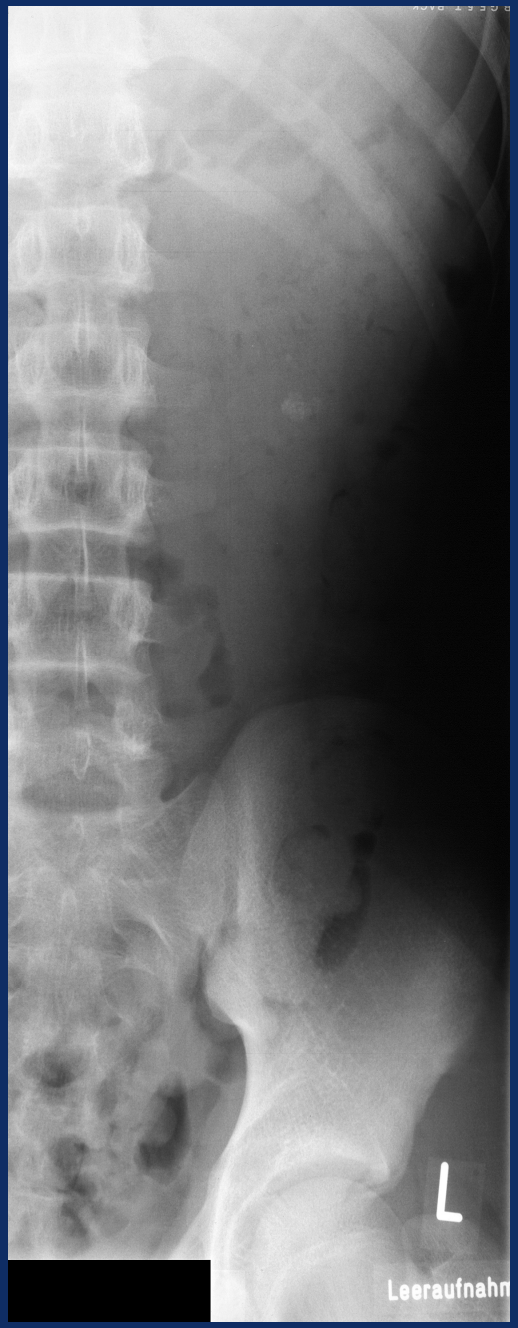
Diagnosis?

- Started with UL left side
- Repeated urine analysis showed severe hyperoxaluria
  - (> 1.5 mmol/1.73m^2/d)
  - L-Glyceric acid excretion was increased
- PH type II => most frequent mutation del103G was found (homozygously)



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Kidney stones are the first

symptoms -

and not the disease itself!

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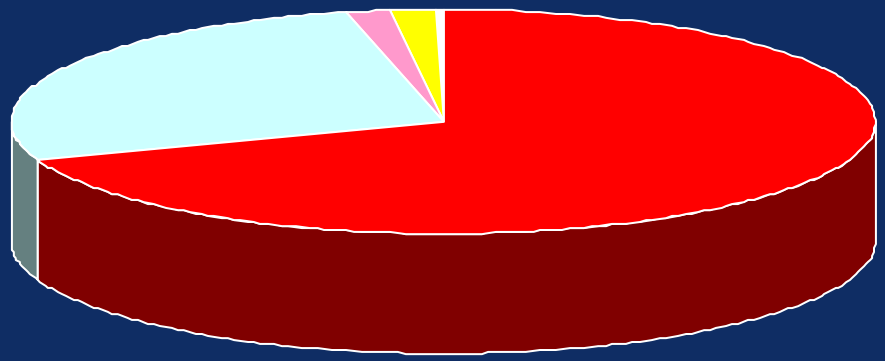
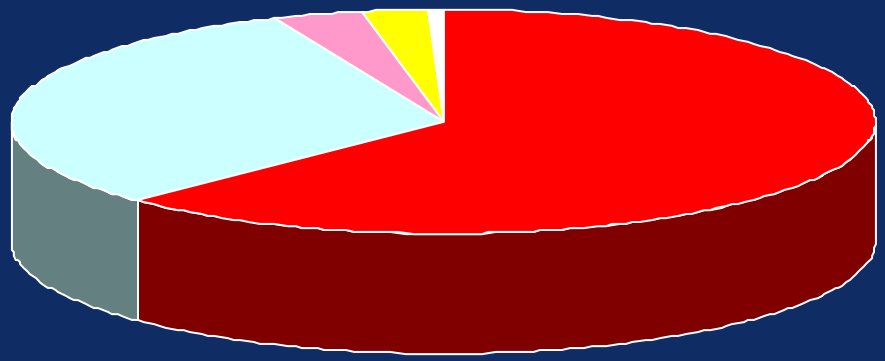
Distribution of kidney stone compositions

Girls



Boys



> 75 % metabolic reason for stone disease!

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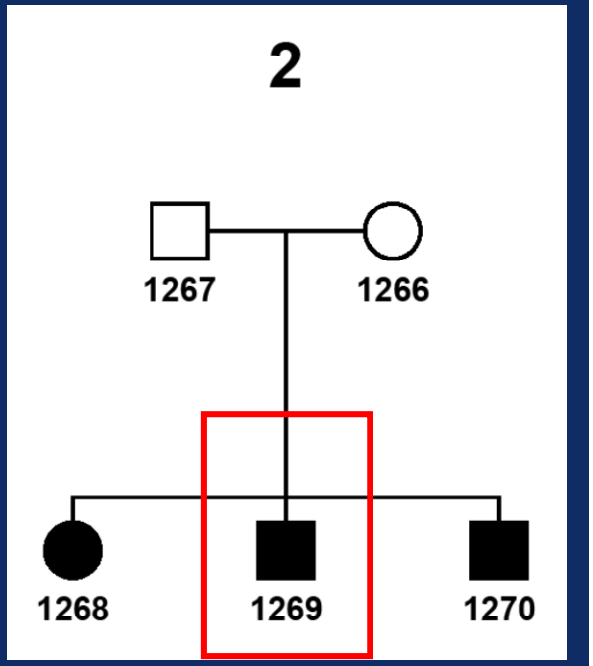
Familiy history

- Stones?
- First, recurrent stones
  - Stone diary
- Chronic Illness
- Urinary tract anomalies
  - Current evaluations
- Recurrent UTI, bacterial spectrum
- Drugs, chemotherapy
- Diet, fluid intake



UL, NC, Hyperoxaluria

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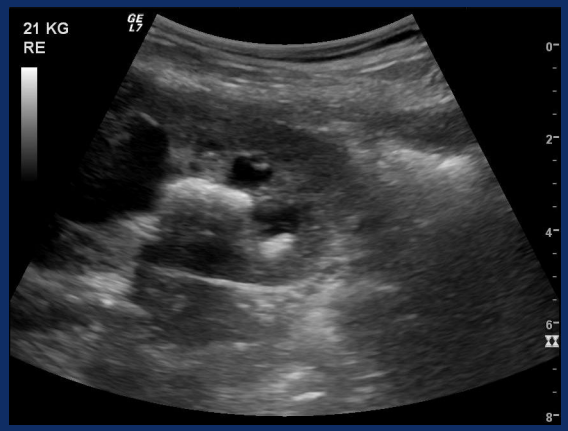
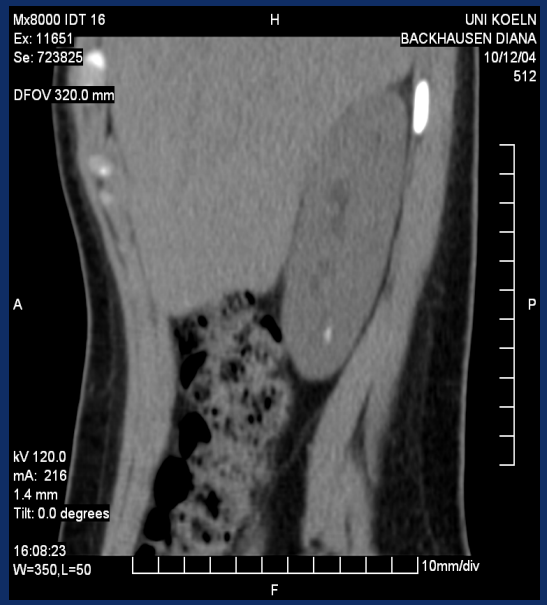
Imaging



- Ultrasound
- Superior for initial evaluation
  - Urine stasis => Necessity of invasive procedures
  - With uncomplicated clinics ultrasound is mostly sufficient as the only imaging procedure
- (no) i.v. Pyelography
  - Pre-lithotripsy
- Low enhanced CT
- (abdominal) x-ray



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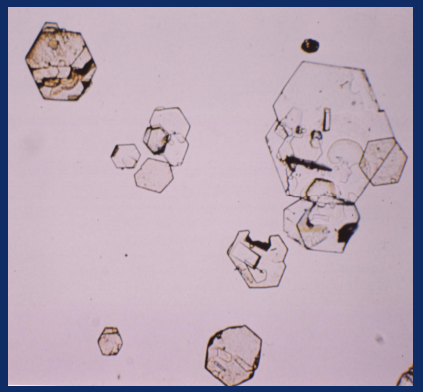
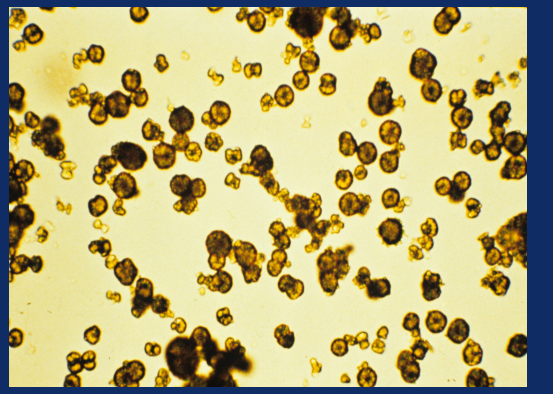
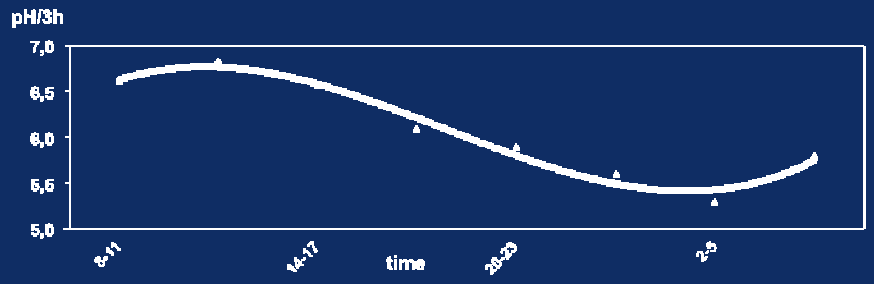
Basic Diagnostic Evaluation







Urine:

- **Status, sediment**
- **Osmolality, pH-daytime profile**
- **Culture**
- **Spot urine or, better, 24 h urines:**
  - **lithogenic and inhibitory substances**

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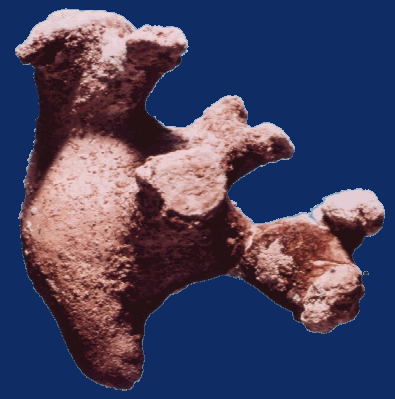
Basic Diagnostic Evaluation



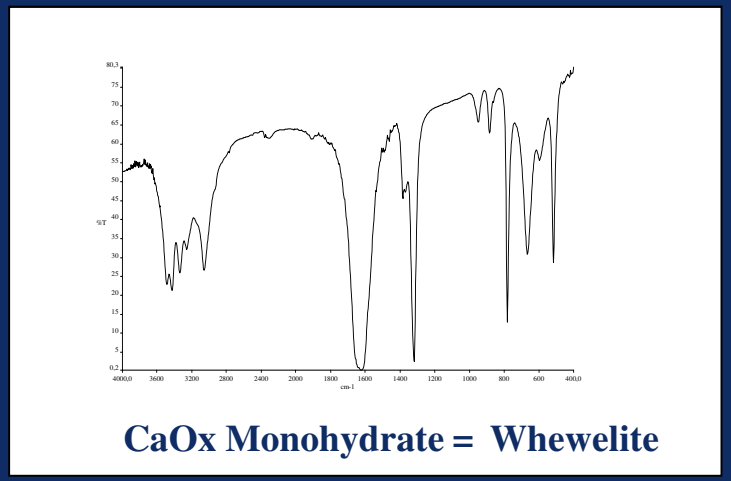
Blood:

- Ca, PO_4, uric acid, Mg, creatinine, urea, alkaline phosphatase, BGA, [oxalate]

Metabolic disease?

Stone analysis

- Infrared-spectroscopy
- X-ray diffraction

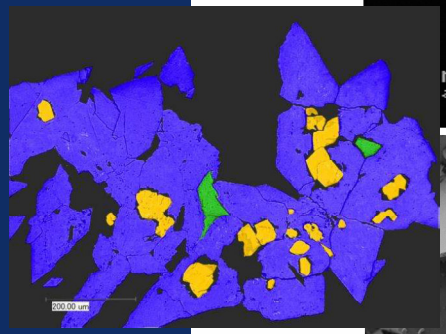


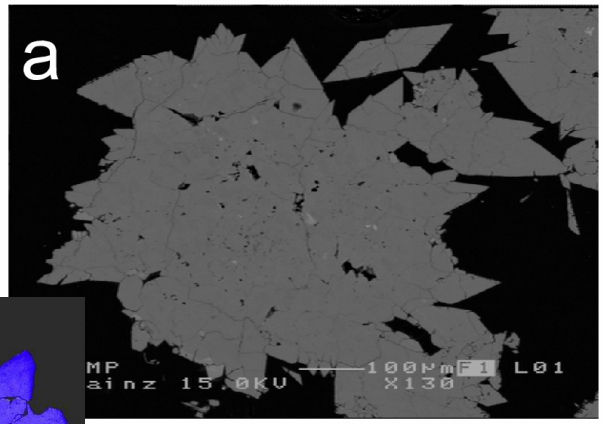
CaOx Monohydrate = Whewelite

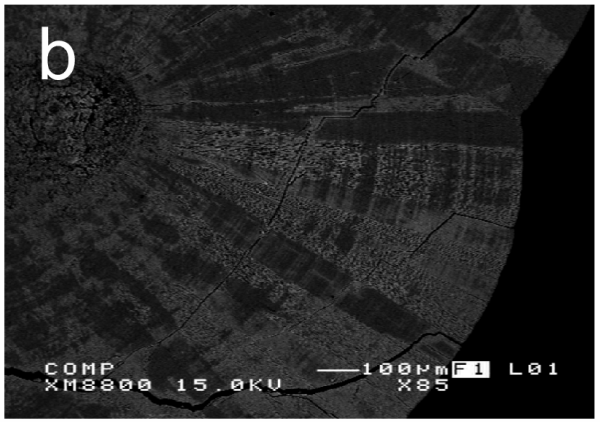
Further stone analysis

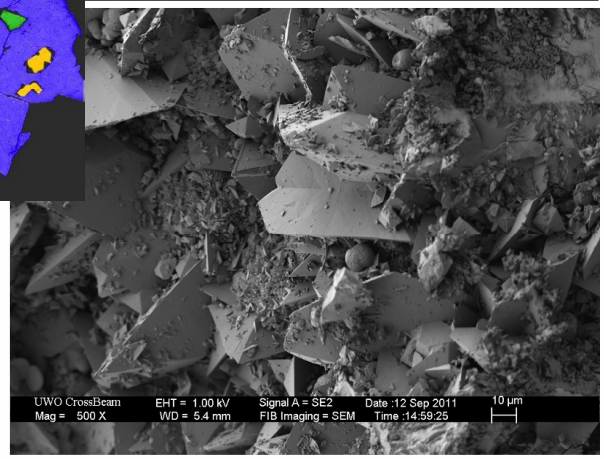
PH III

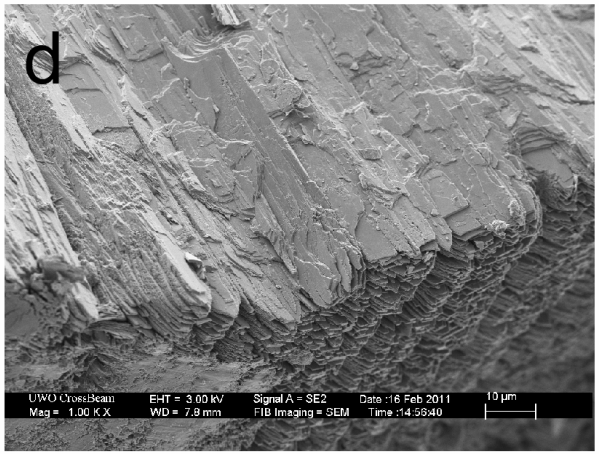
idiopathic CaOx Monohydrate Whewellite











Unregular growth

Monoepitaxial growth

Idiopathic Ca-Ox Monohydrate stones (COM)

- Black colour
- Dense, with rough layering
- Core and rim structure
- High organic content, adhering with minerals

PH stones

- Brighter
- Low organic content
- No core/rim structure
- Porose with big crystals
- Sometimes big crystals with fine lamelation

Bipyramidal COD

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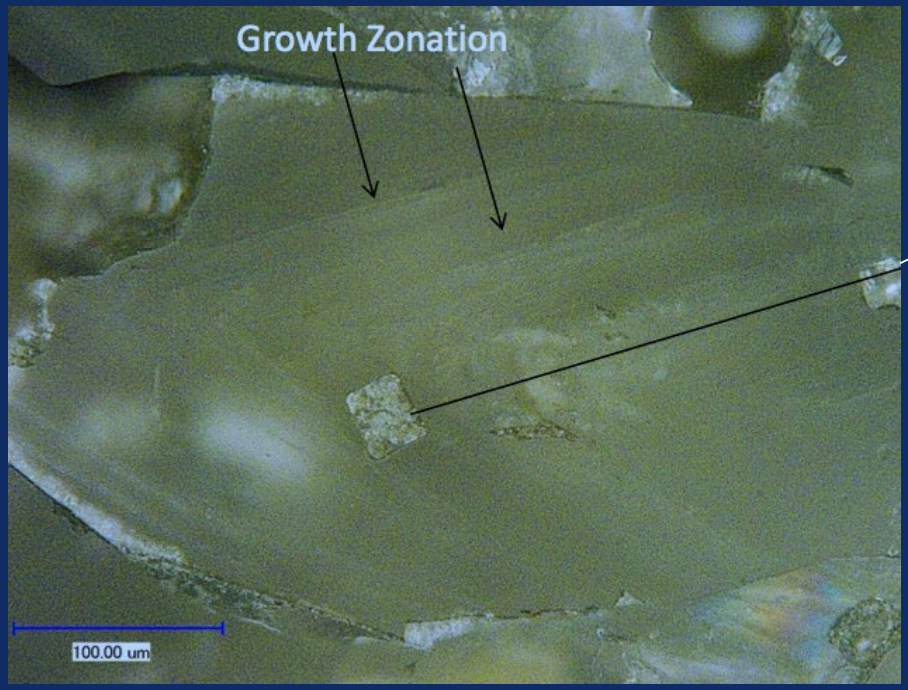
CaOx Stones Hypercalciuria



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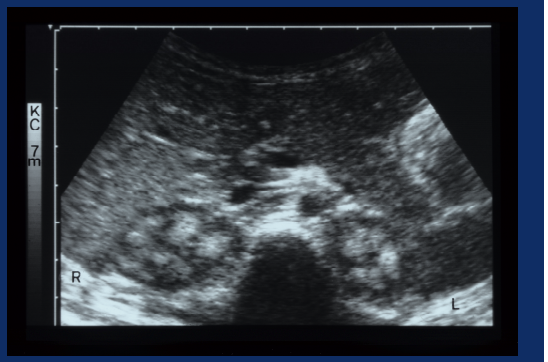
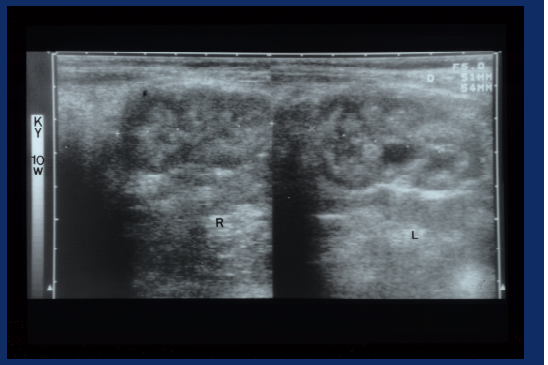
Hypercalciuria





Primary (idiopathic) Hypercalciuria

Autosomal-dominant Hypercalciuria

- Calcium sensing receptor gene mutations

Vitamin D sensible hypercalciuria

- Mutations in CYP24A1 and idiopathic infantile hypercalcemia, (Schlingman P et al, NEJM 2011)

Hypophosphatemic rickets and hypercalciuria

- SLC34A3 Sodium-Phosphate cotransporter (Bergwitz, Am J Hum Genetics 2006)

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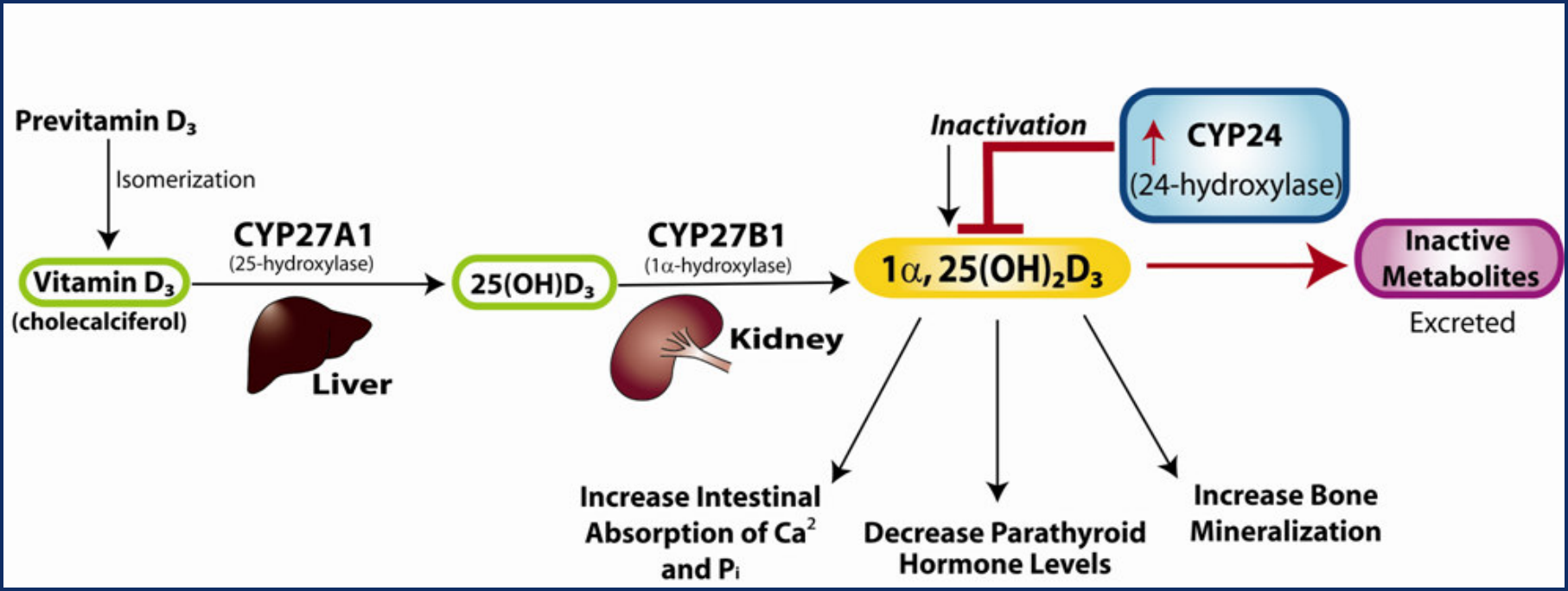
Idiopatic infantile hypercalcemia/hypercalciuria

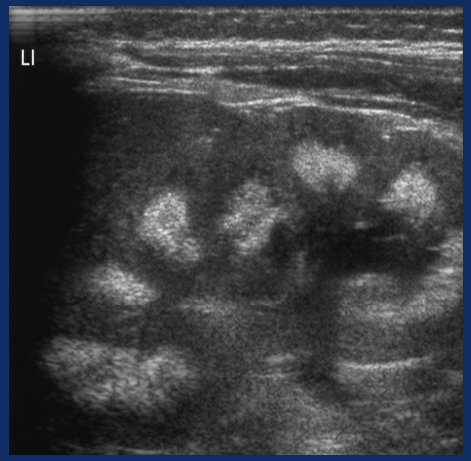
- CYP24A1 mutations => increased Vitamin D sensitivity
- decreased 1,25(OH)$_2$D$_3$ inactivation

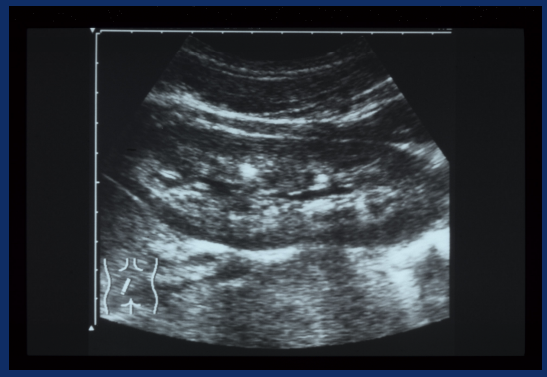


Specific diagnostic steps

- Blood
  - PTH, (FGF23), Vitamin D/A, BGA, (Cortisol), FT3/4
- Imaging
  - Hand x-ray
  - Bone densitometry
- Genetics
  - Not always necessary for diagnosis!
- History
  - Immobilization, medications, ventilation, TPN

Hypercalciuria & Syndromes





+ Nephrocalcinosis in
  - Bartter syndrome
  - Williams-Beuren syndrome
  - Wilson and Lowe syndrom
  - 

, FHHNC
+ Nephrocalcinosis or Ca-phosphate stones in
  - Renal tubular acidosis

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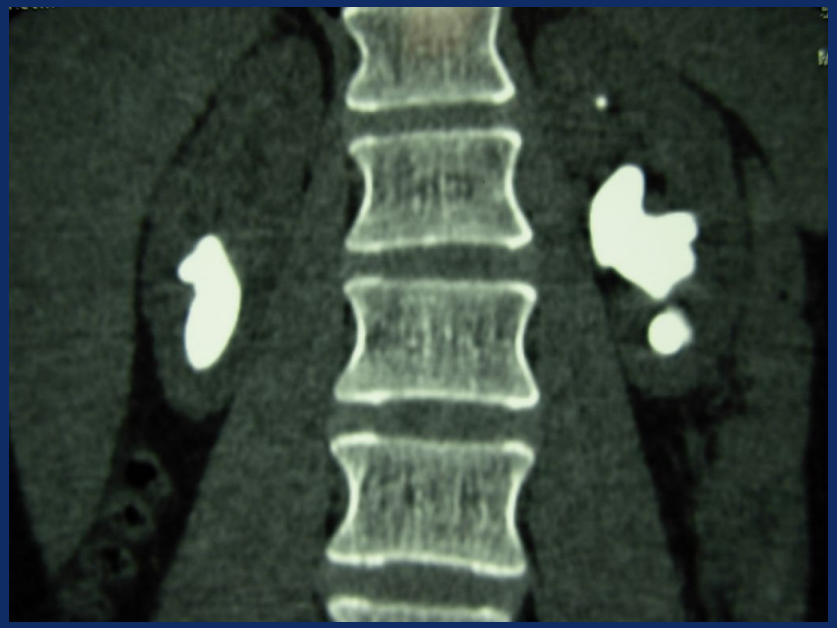
CaOx stones and Hyperoxaluria



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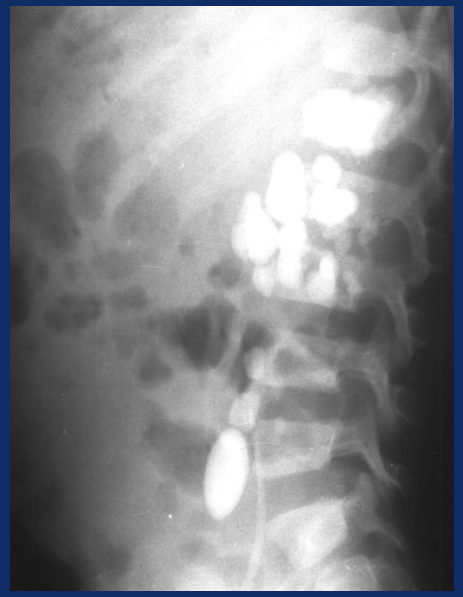
Primary Hyperoxaluria I-III

- Defects of Glyoxylate metabolism with
  - extremely elevated urinary oxalate excretion (> 1 mmol/1.73m^2/24h)
  - Most severe form of kidney stone disease
  - Heterogeneity
  - Often ESRD
  - Multisytemic disease



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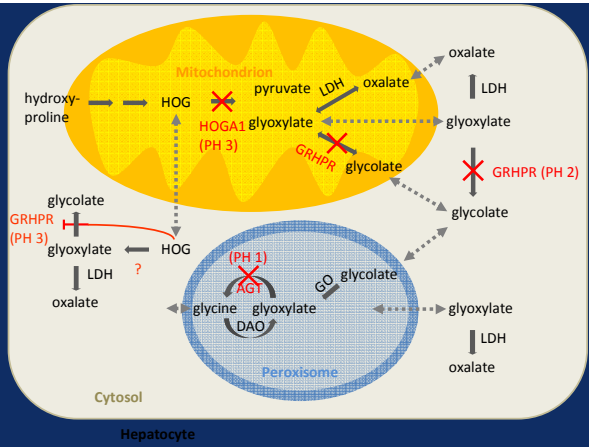
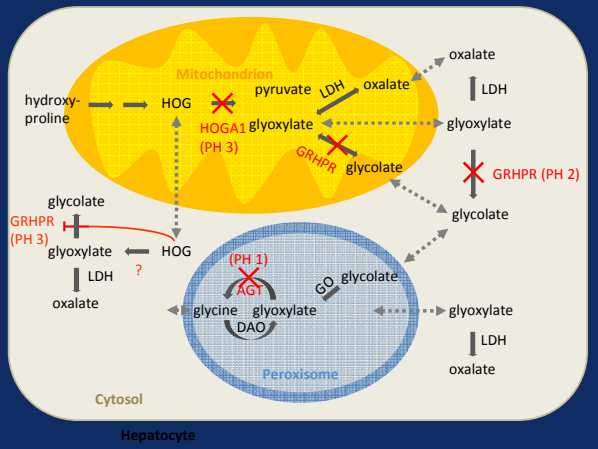
PH I



- Defect of liver specific peroxisomal alanine-glyoxylate aminotransferase (AGT, 2q37.3)
- Prevalence: 1.2-2/10^6
- Increased urinary oxalate excretion
  - > 0.8 mmol/1.73m^2 in 24 h urine
  - > age related normal creatinine ratios

PH II

- Defect of glyoxylate-reductase
  - Not liver specific
- Less often and milder phenotype as PH I
- Increased urinary oxalate (and L-glyceric acid) excretion



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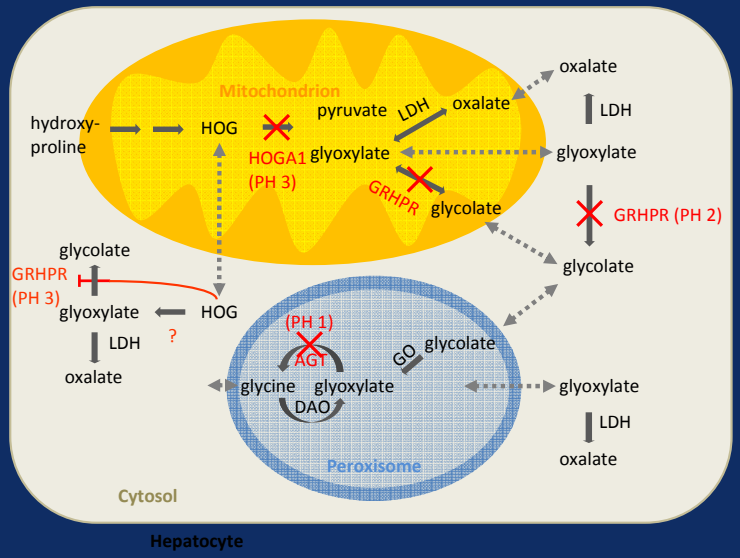
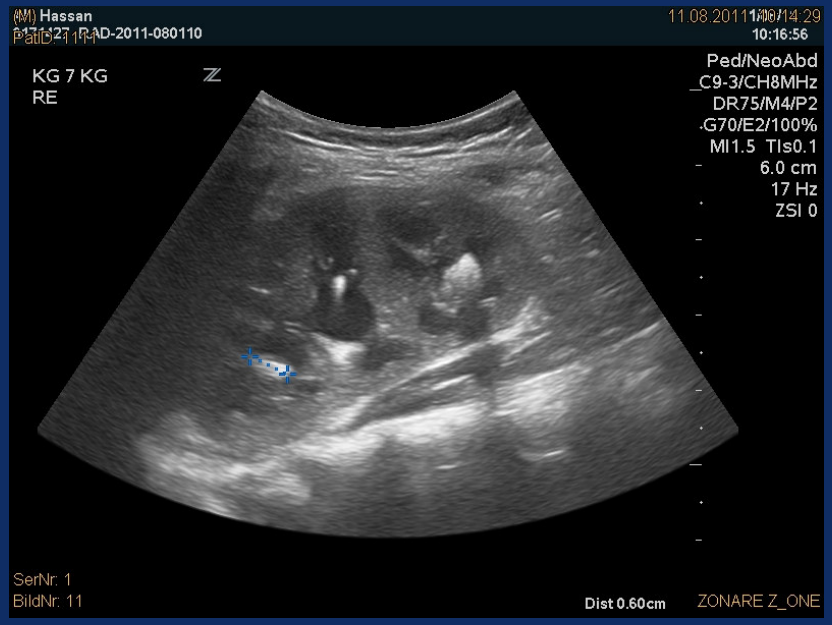
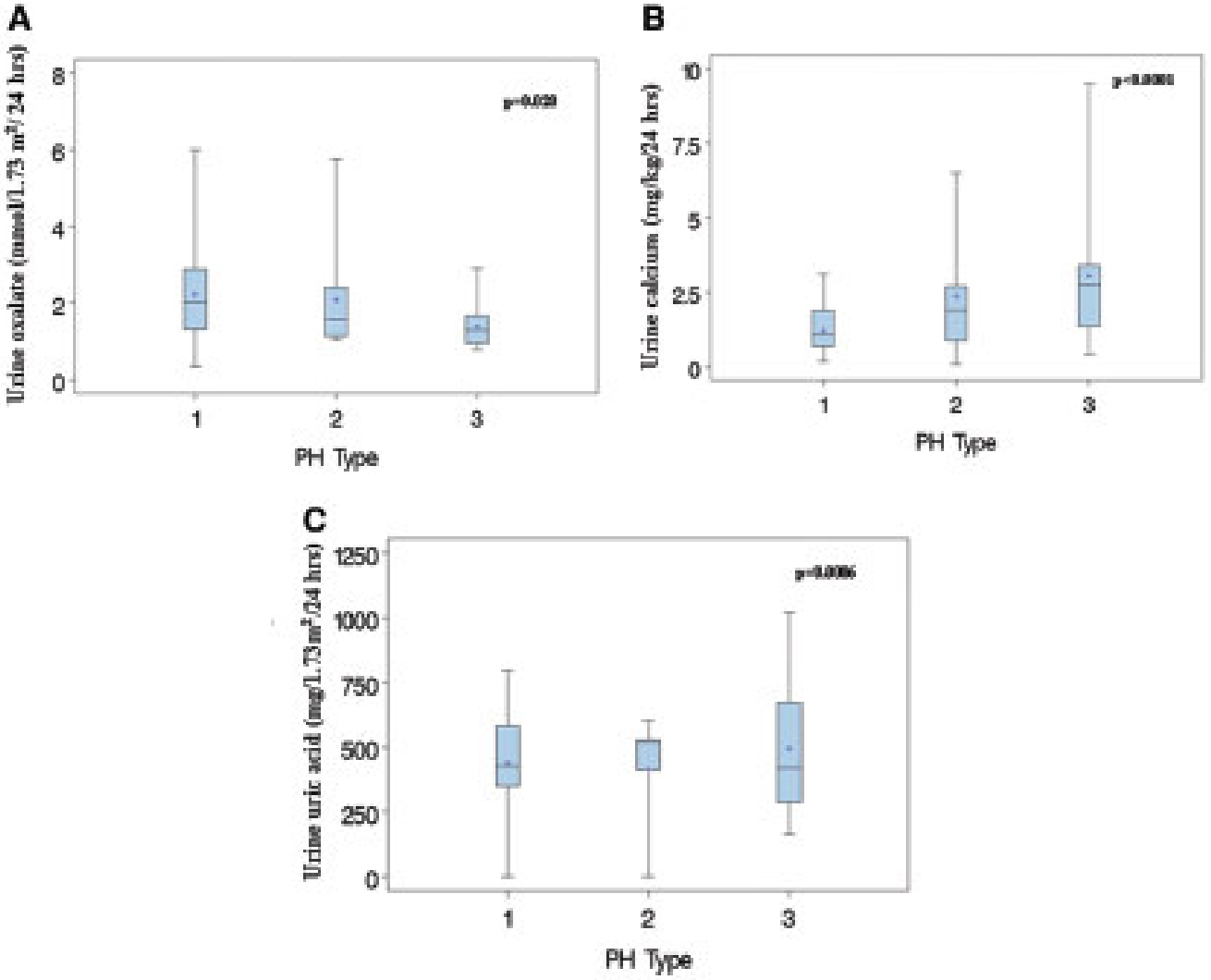
PH III

- Severe Urolithiasis in first years of life
  - Increased HOG
- Normalization of clinical symptoms
  - Ongoing hyperoxaluria
- No ESRD
- Prevalence > PH II





Urinary excretion parameters - Differences -



Monico et al CJASN 2011

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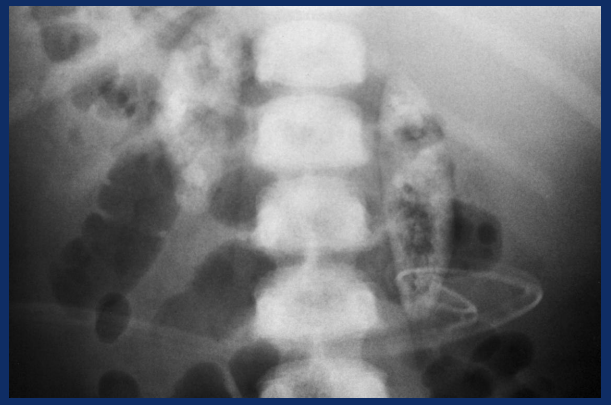
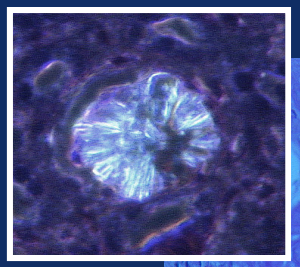
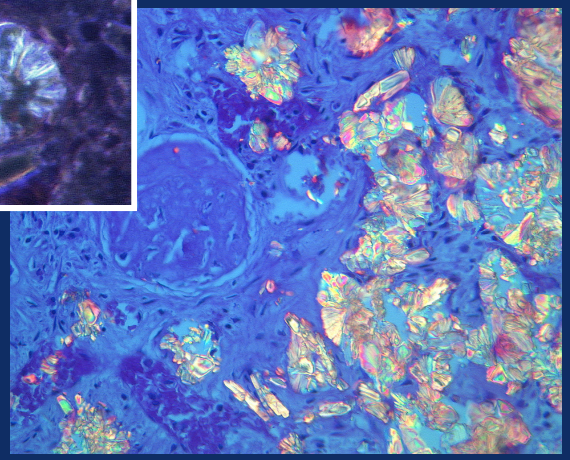
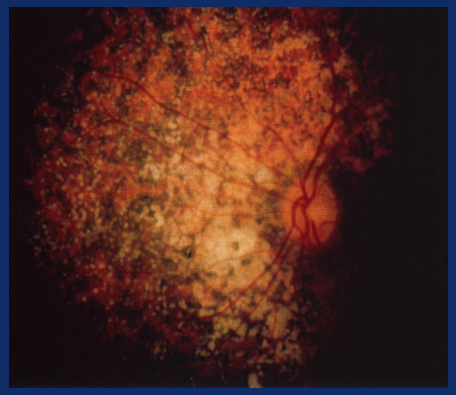
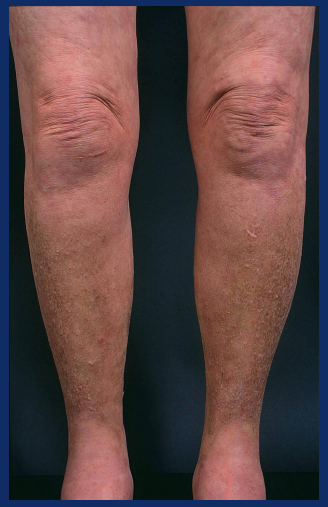
Clinical spectrum PH I

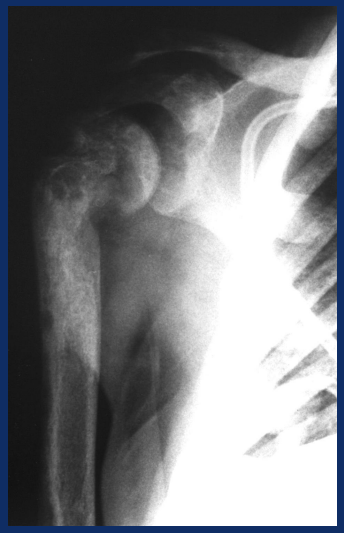


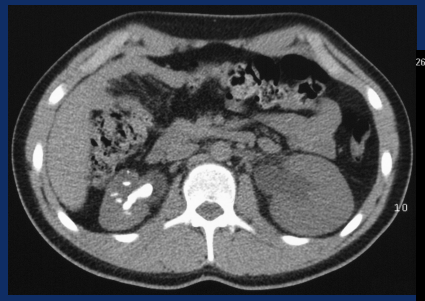


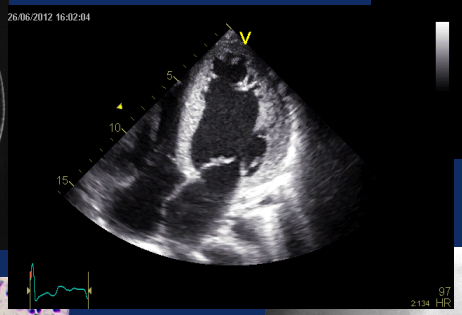


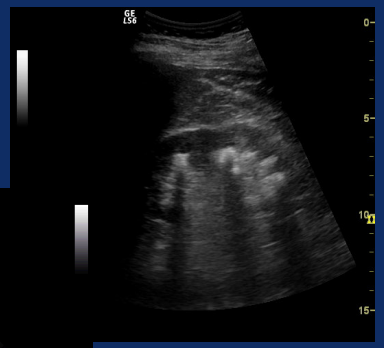


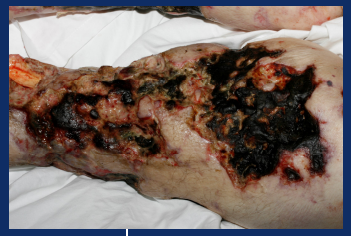


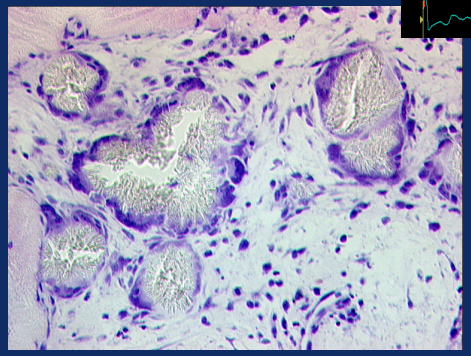


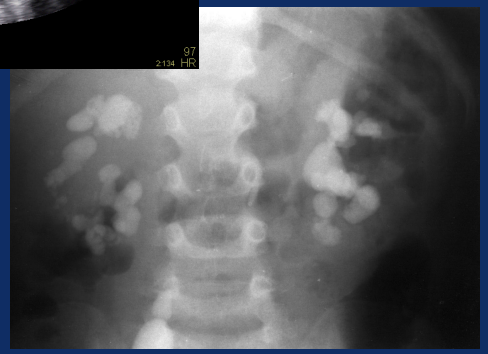


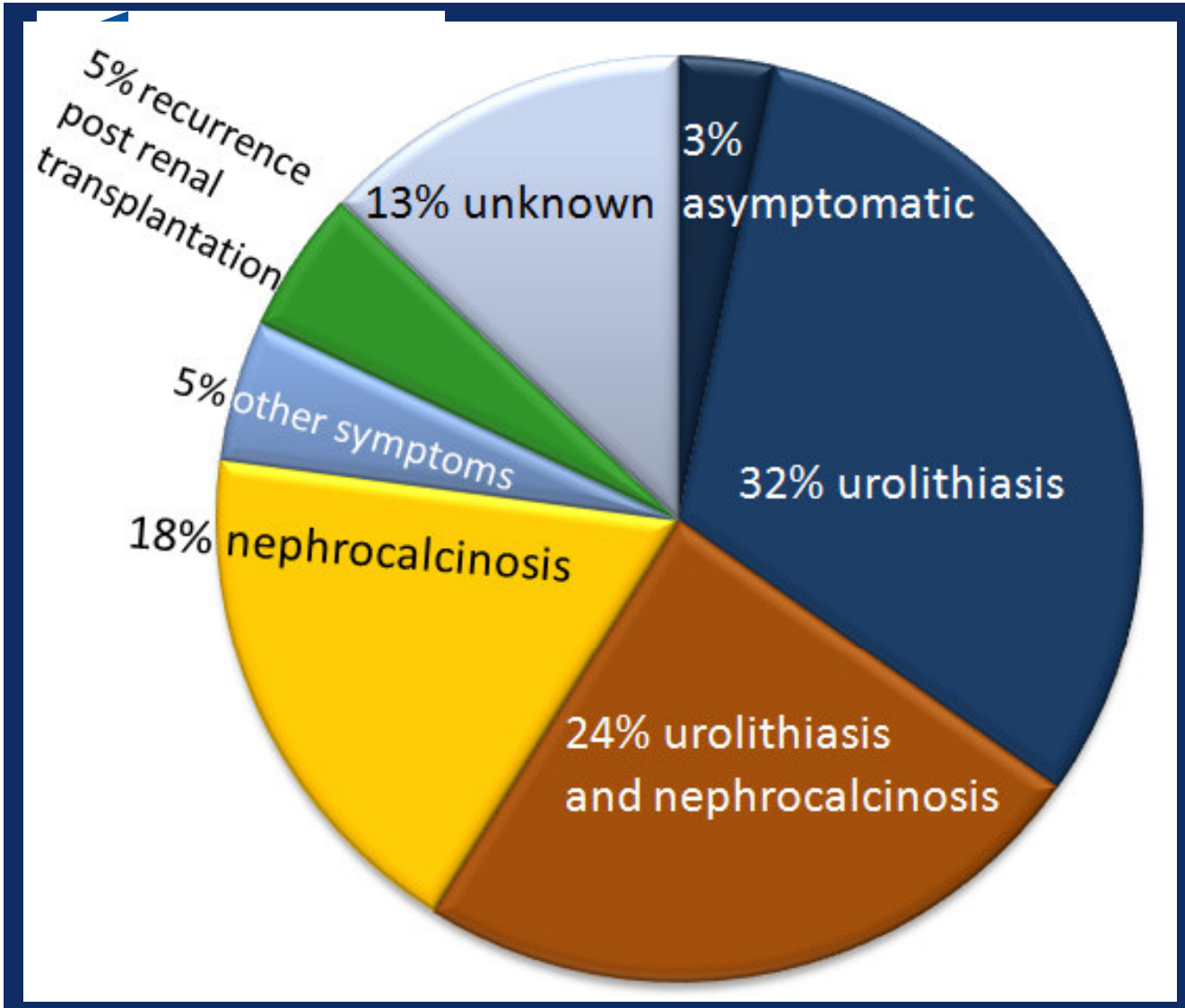


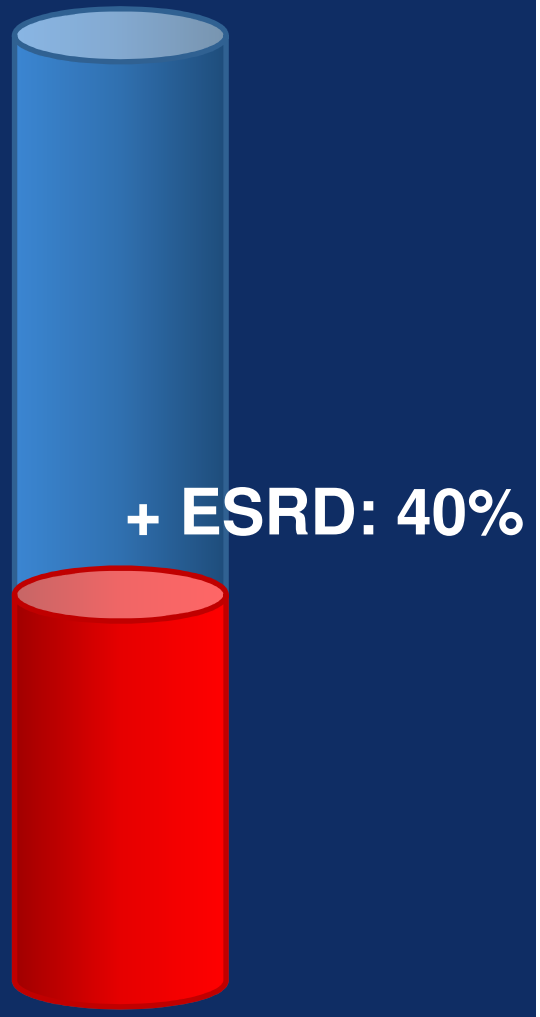










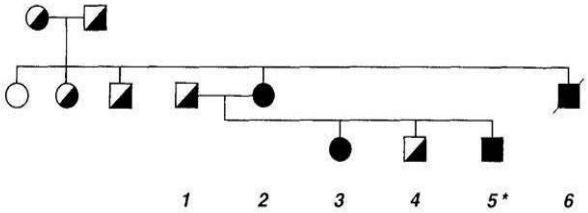


Symptoms at diagnosis

PH type 1 presents itself as a stone disease in half of the patients

Clinical heterogeneity

- Infantile form
  - early end stage renal failure
- Adult form
  - first symptoms later in life
  - ESRF
- Geno-/phenotype correlation?
- Intrafamiliar differences



Pathology						
Clinical severity	unaffected	mild	minimal	unaffected	severe	intermediate
Renal CaOx deposition	none	UL (isolated)	none	none	NC	UL (recurrent) & NC
Age at first symptom	-	23 years	-	-	7 months	15 years
Clinical chemistry						
Urinary oxalate	40.6	195.7	86.6	45.0	131.7	-
Urinary oxalate (+ B6)	-	71.3	-	-	73.1	-
Enzymology						
AGT catalytic activity	-	15.9%	-	-	18.2%	-
AGT immunoreactivity	-	++	-	-	+++	-
AGT subcellular distribution	-	mito & perox	-	-	MITO & perox	-
Molecular genetics						
AGXT allele	*A B*	*B C*	*B B*	*A C*	*B B*	
AGXT cDNA base 154	T T	T C	T T	T C	T T	-
AGXT cDNA base 630	G [A]	[A] G	[A] [A]	G G	[A] [A]	-
AGXT cDNA base 682	C C	C [T]	C C	C [T]	C C	

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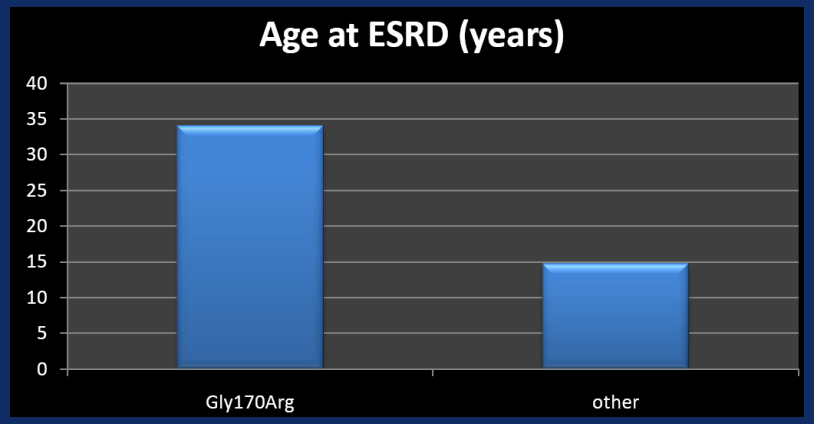
Prediction of outcome (kidney function)

28% Gly170Arg
Phe152Ile

Pyridoxine declines oxalate excretion

Favorable:

AGXT Gene mutation:



Poor:

OXALEUROPE

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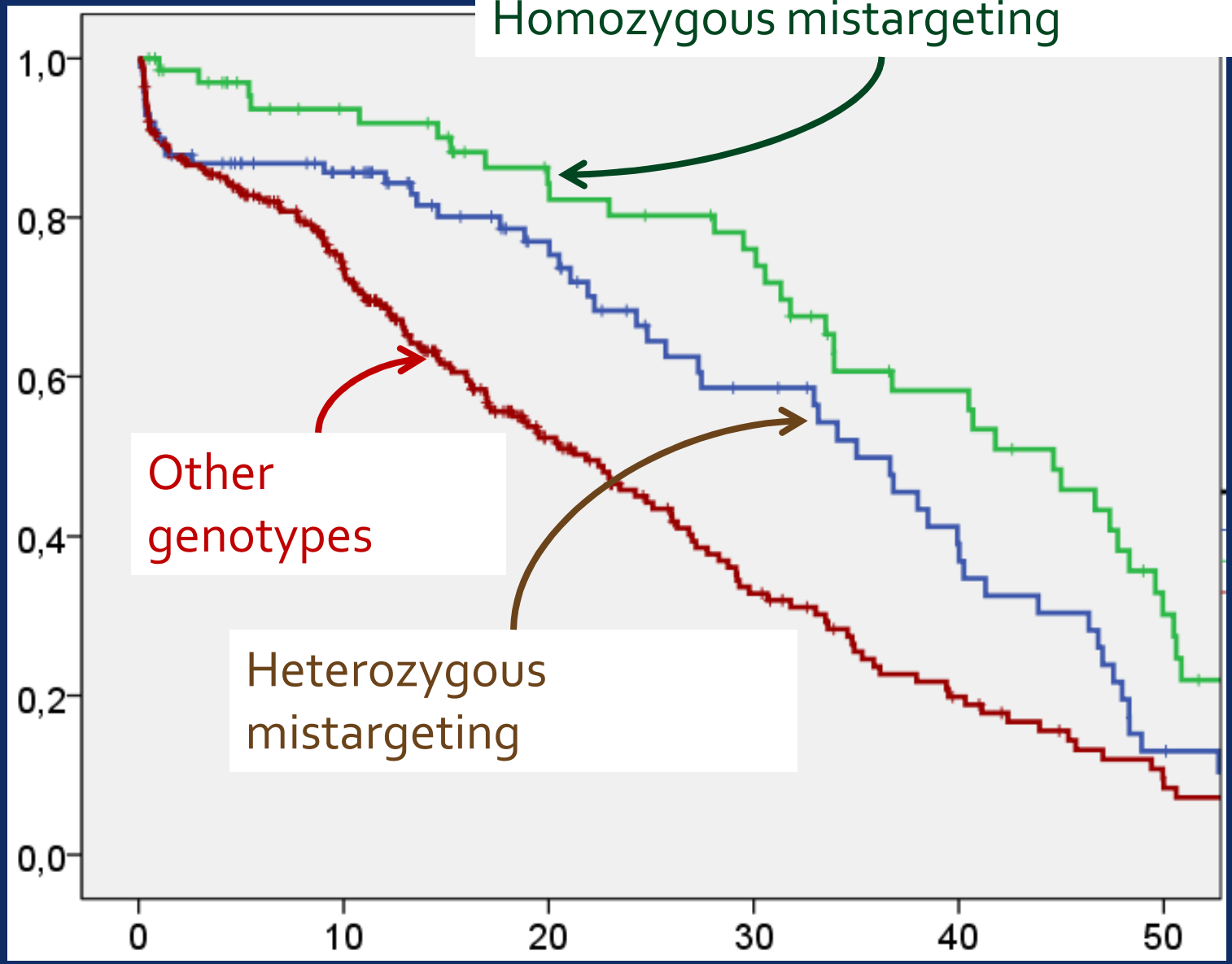
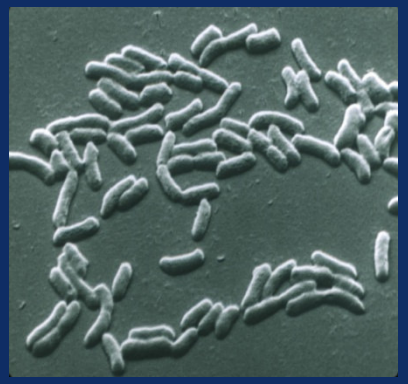
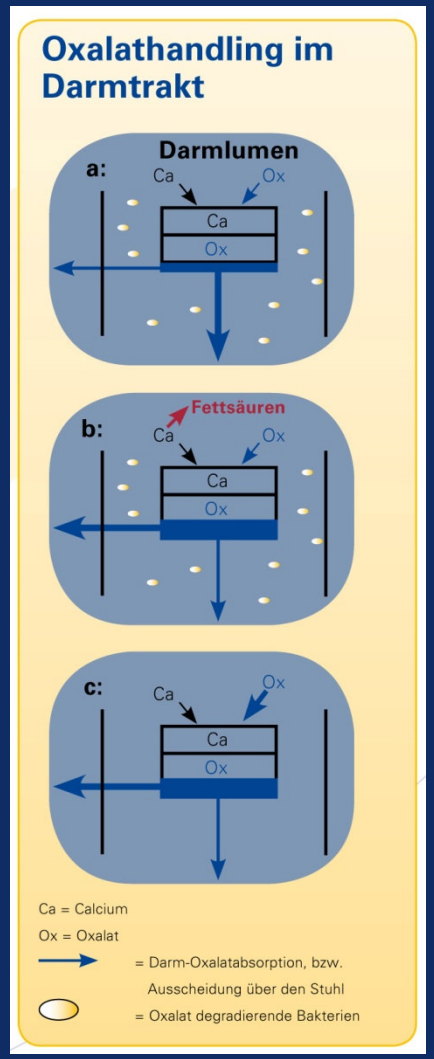
Survival free of ESRD (Kaplan-Meyer) according to genotype



Secondary Hyperoxaluria

- Increased intestinal absorption in
  - Malabsorption syndromes (CF)
  - Crohn‘s disease
  - Short bowel syndrome
  - Lack of intestinal oxalate degrading bacteria
  - High dietary oxalate intake





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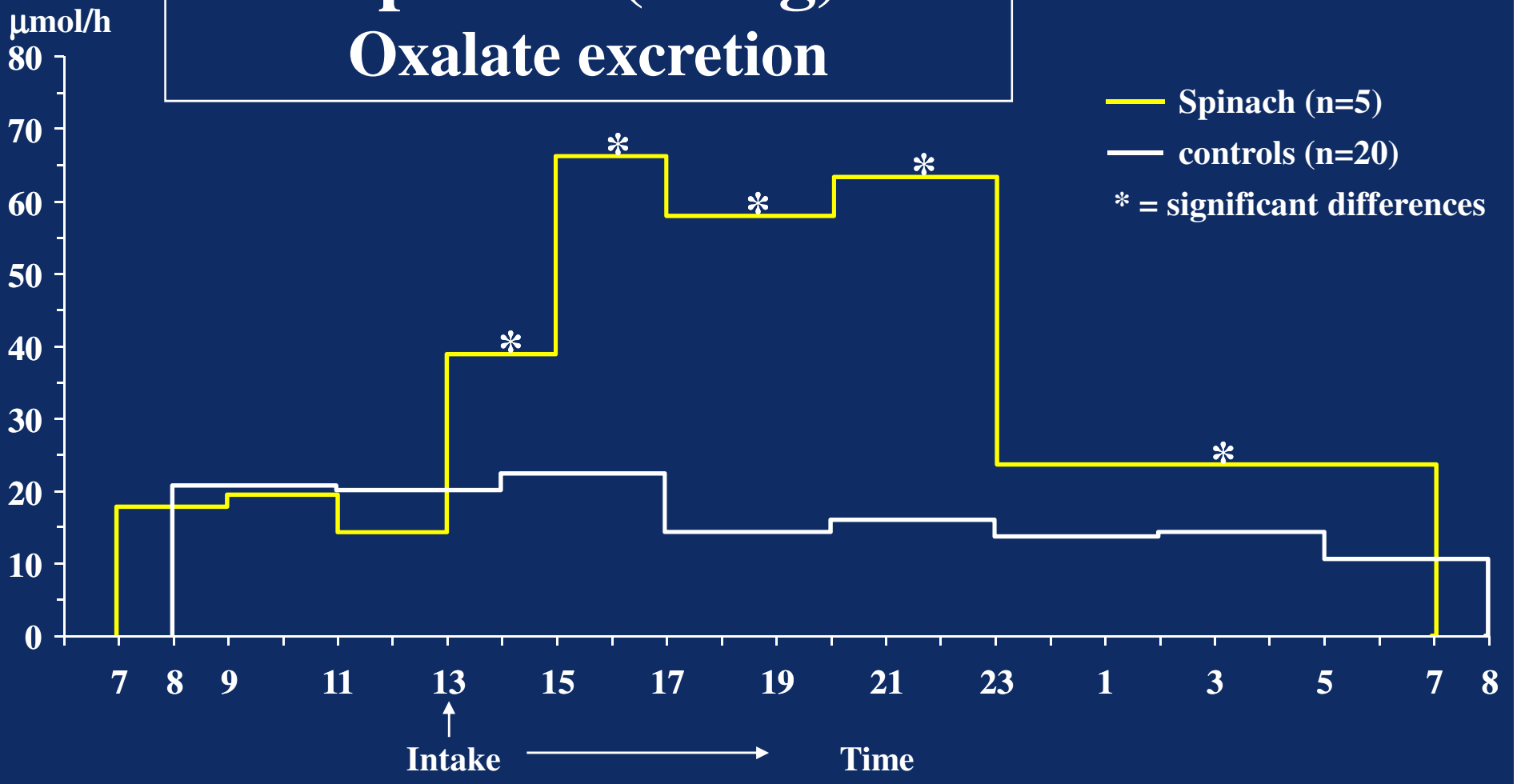
Diet and hyperoxaluria

Spinach (200 g)
Oxalate excretion



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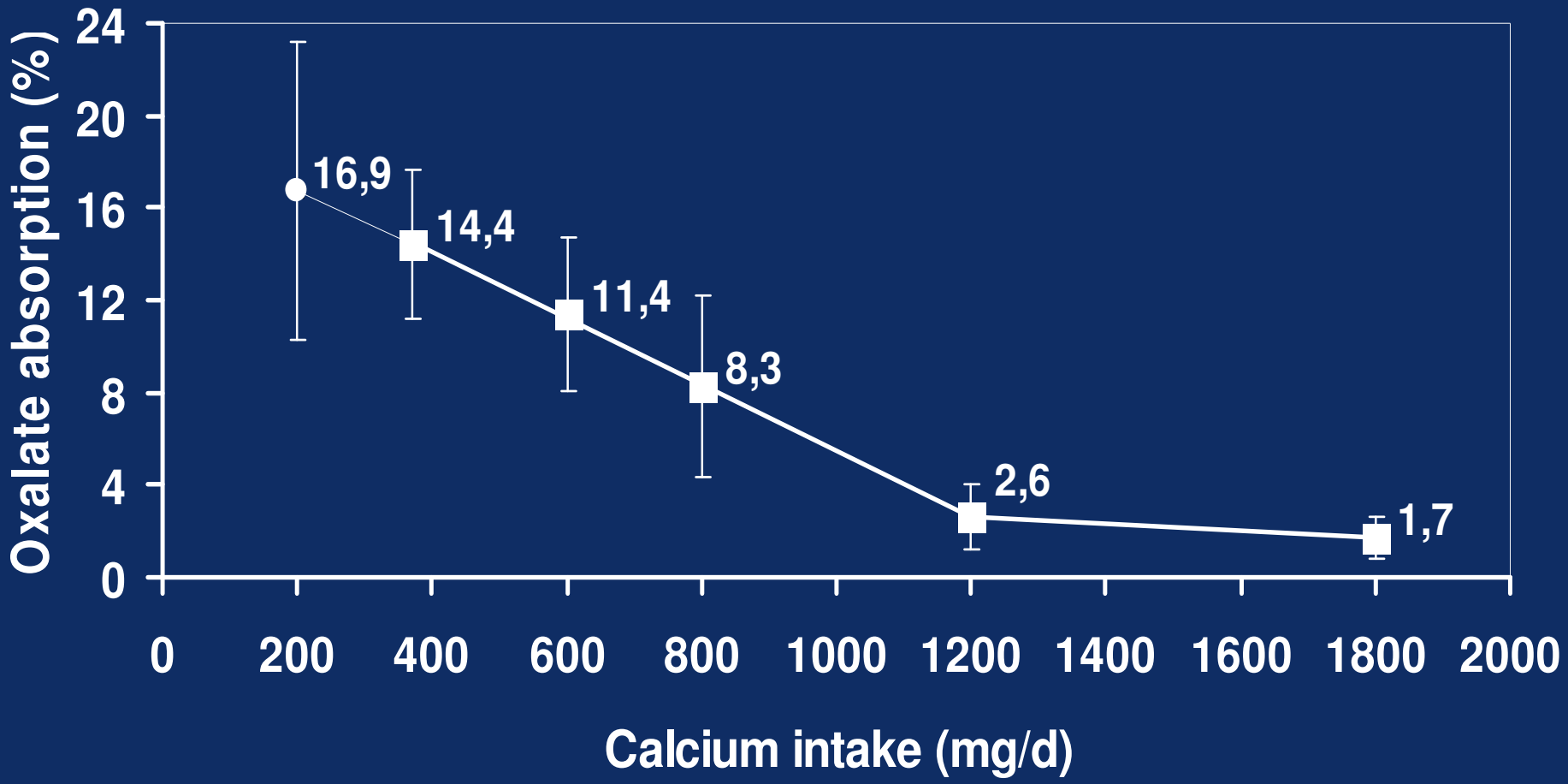
Calcium intake and Oxalate absorption



von Unruh et al. (2004) J Am Soc Nephrol 15: 1567

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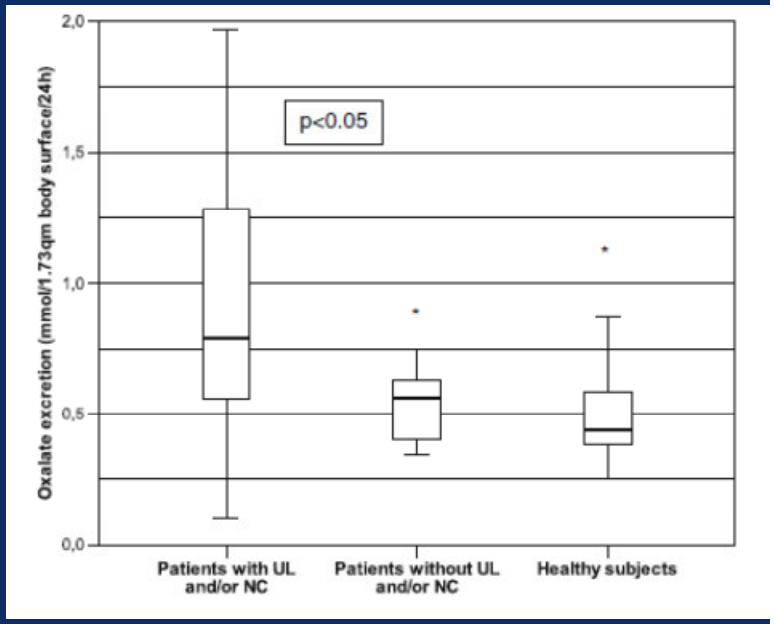
UL/NC Prevalence

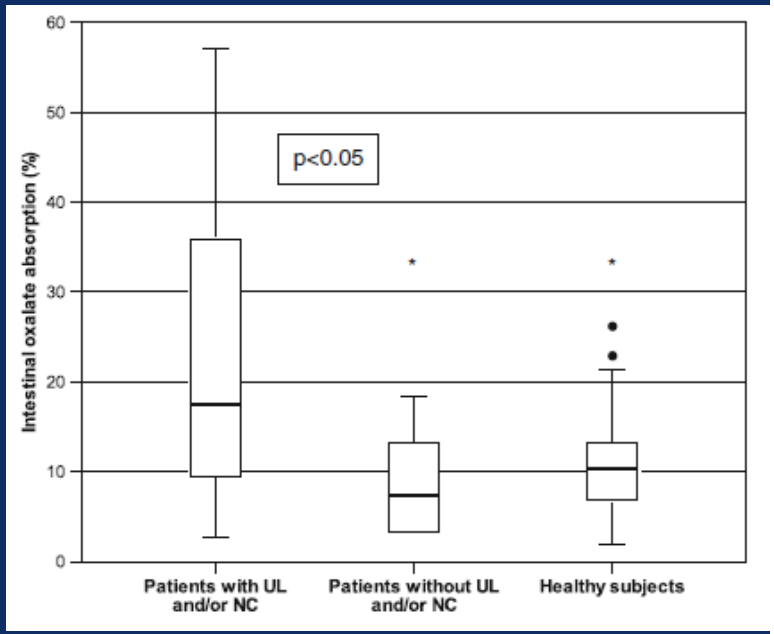
Crohn‘s disease 17.2 %

Normal population ~ 5 %

Patients with CF ~ 11 %

Children < 1 %





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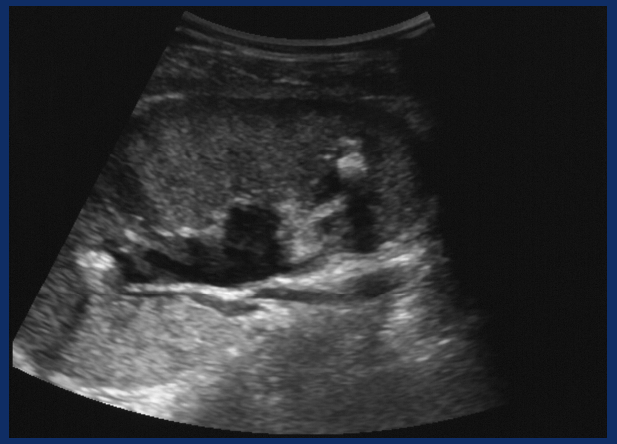
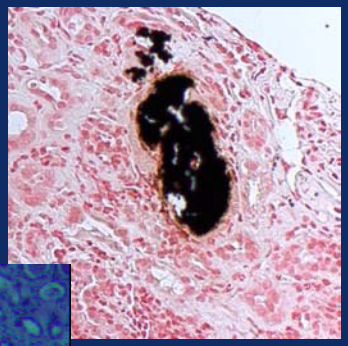
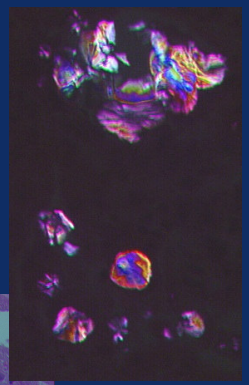
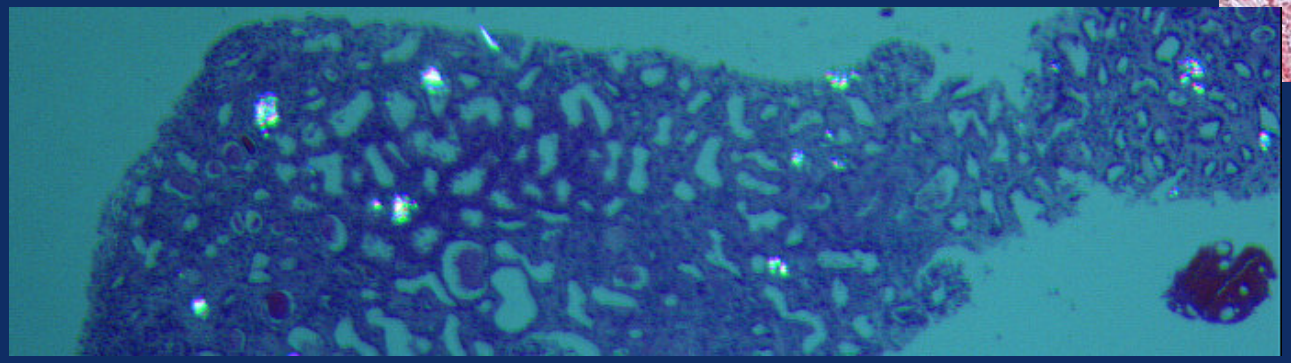
Crohn‘s and UL/NC

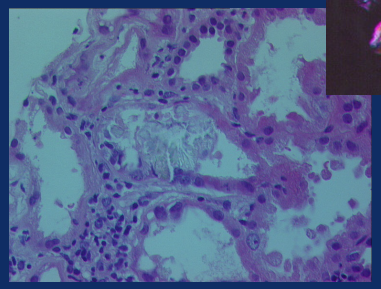
- Severe Hyperoxaluria
- Correlated to bowel resections
- Leads to ESRF
- Systemic Oxalosis like in PH I
- Recurrent disease after KTx











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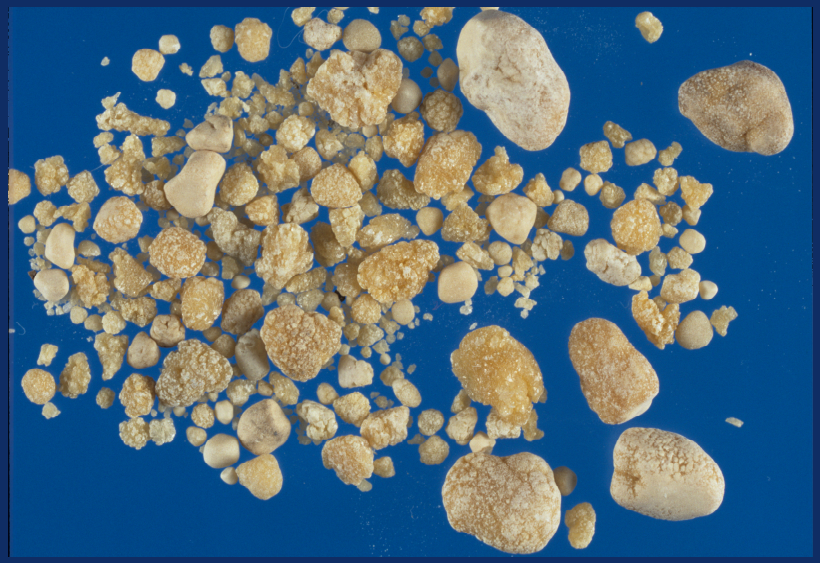
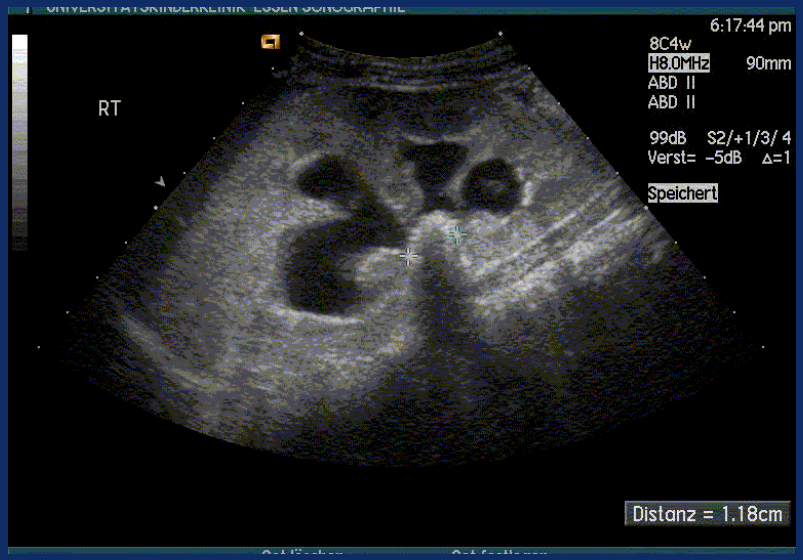
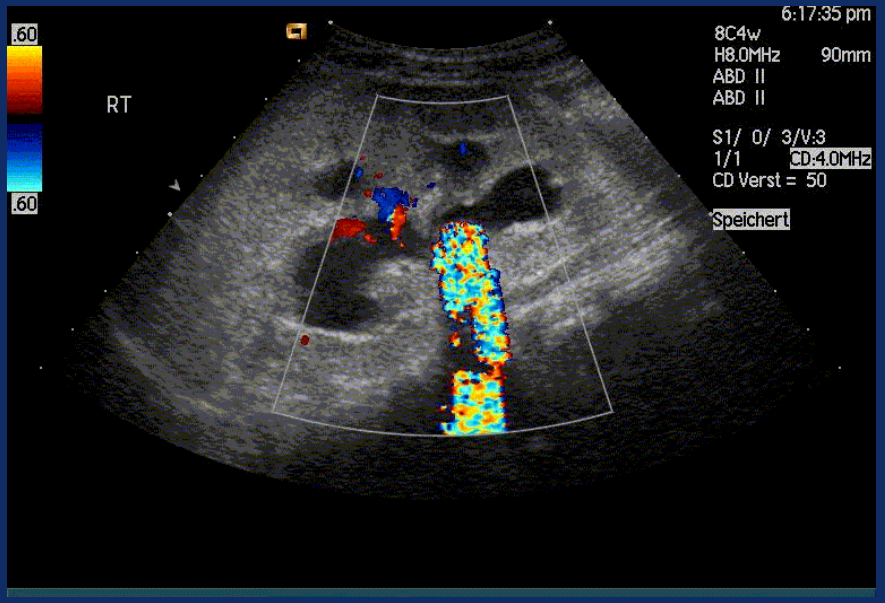
Cystine stones







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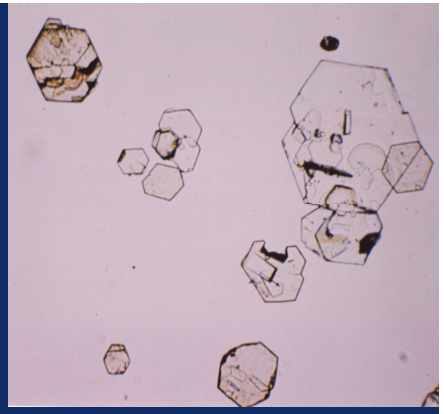
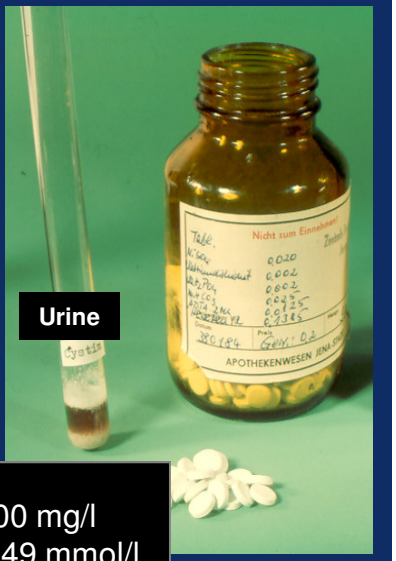
Cystine stones



- Sediment with flat, hexagonal crystals
- 24 h urine excretion:
  - Homocygotes up to 1g/d
  - normal < 80 mg
- Rapid cystine testing
- (Genetics)



Nickel/Dithionite test with semi-quantitative cystine determination

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Problems

- Stones at all ages
- No good genotype/phenotype correlation
- Cystine excretion not diminished by treatment
  - Reduction of dietary salt + protein (methionine) intake
  - Alkaline citrate
  - Penicillamine, alpha-mercapto-propionyl-glycine
    - Excretion of the disulfide derivate cystine + drug
    - Severe side effects
- Solubility reached at 320 mg/l

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Keep in mind:

The stone is the first symptom,

but not the disease itself!

Early diagnosis prevents

disastrous outcomes!