A journey through the nephron…

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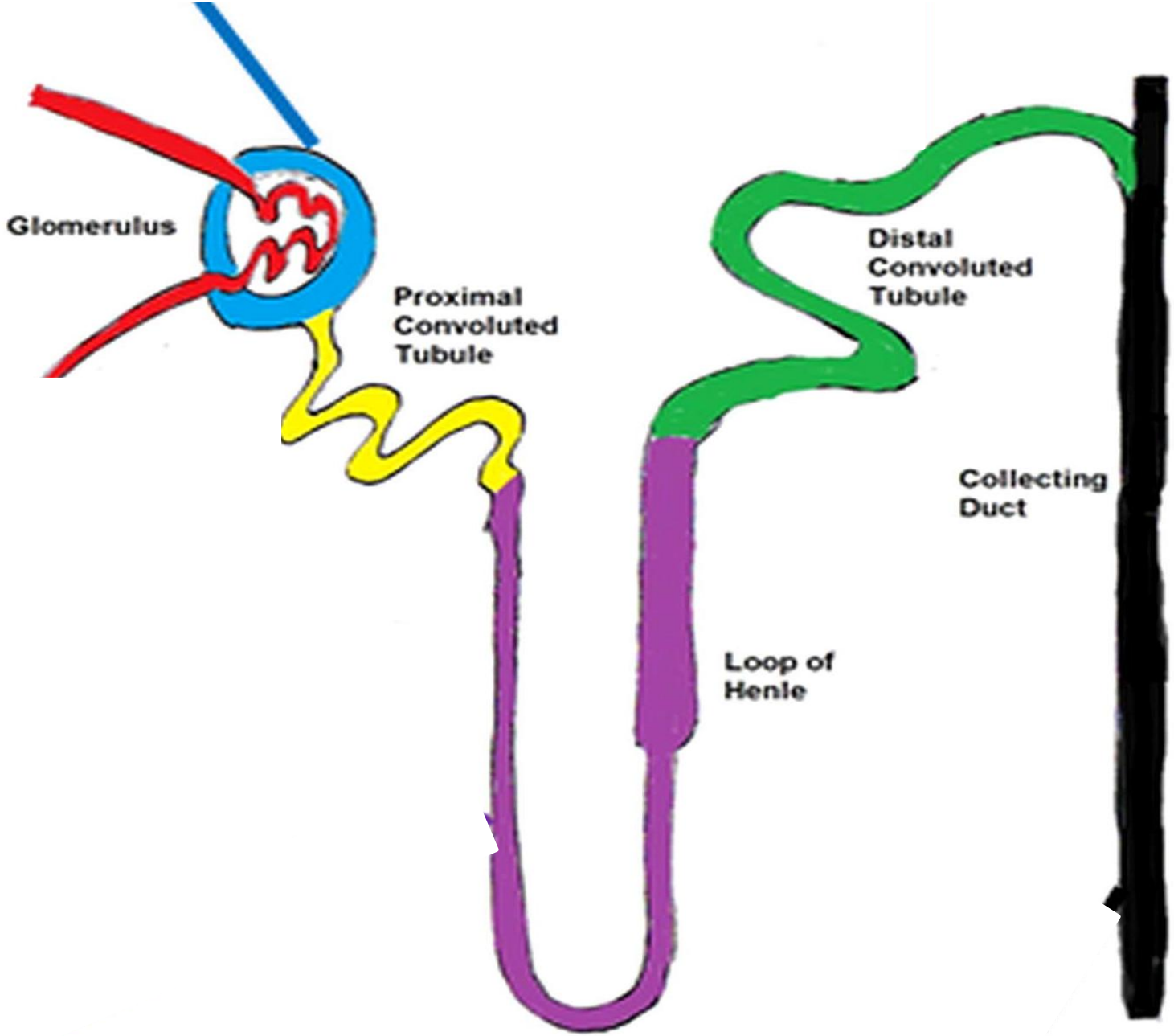
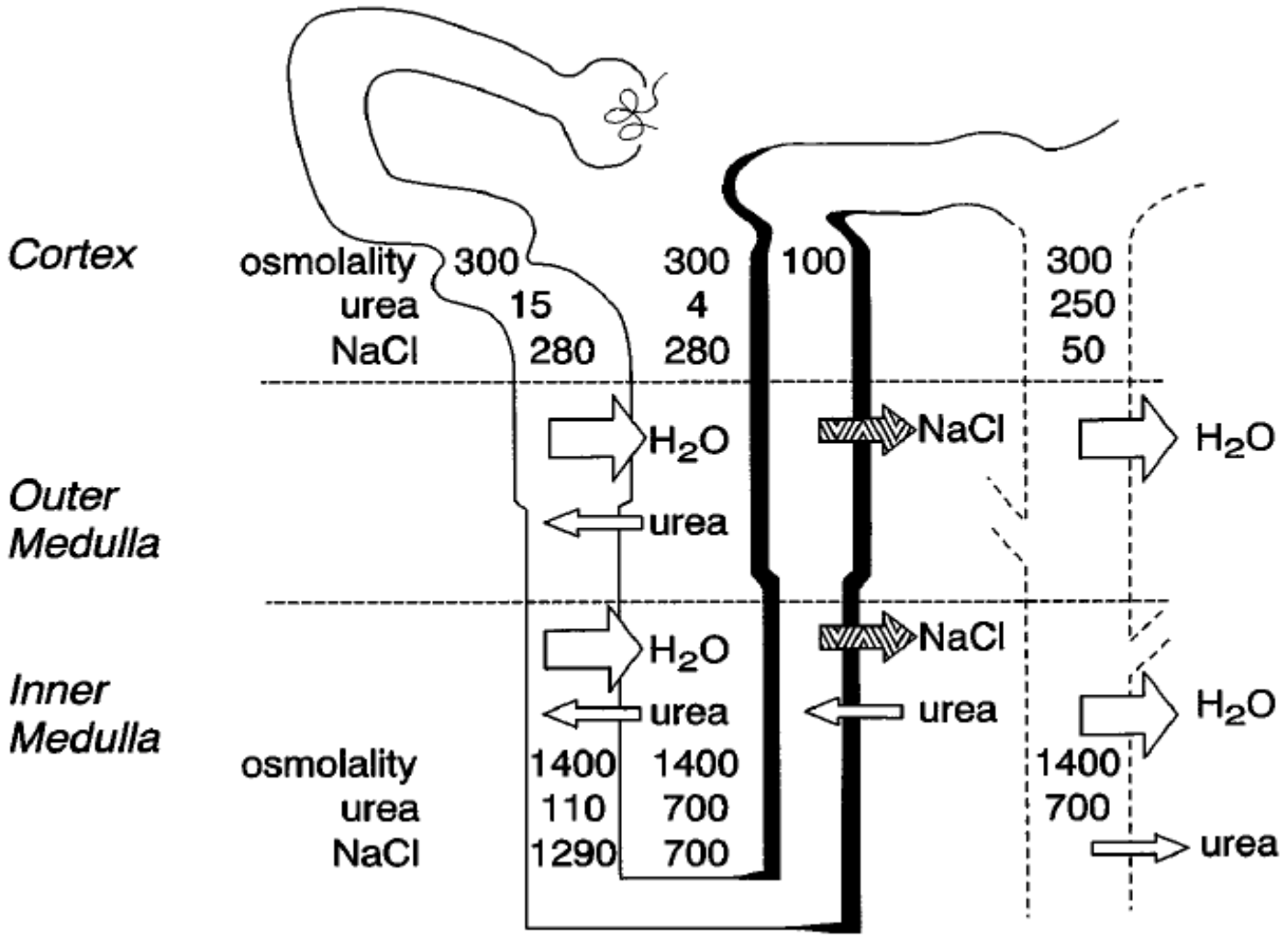
Dealing with a tubulopathy?

- What are the electrolyte abnormalities?
- What is the acid base balance?
- H/o of polyuria or plydipsia?
- Is the child thriving?
- Is there any family history?
- What medication is the child on or been on in the past?
- What does the urine show?
- What does the USS show?


Glomerulus
Proximal Convoluted Tubule
Distal Convoluted Tubule
Collecting Duct
Loop of Henle


Cortex
Outer Medulla
Inner Medulla
osmolality 300 300 100 300
urea 15 4 250
NaCl 280 280 50
H2O
NaCl
H2O
urea
H2O
NaCl
urea
urea
H2O
osmolality 1400 1400 1400
urea 110 700 700
NaCl 1290 700
urea

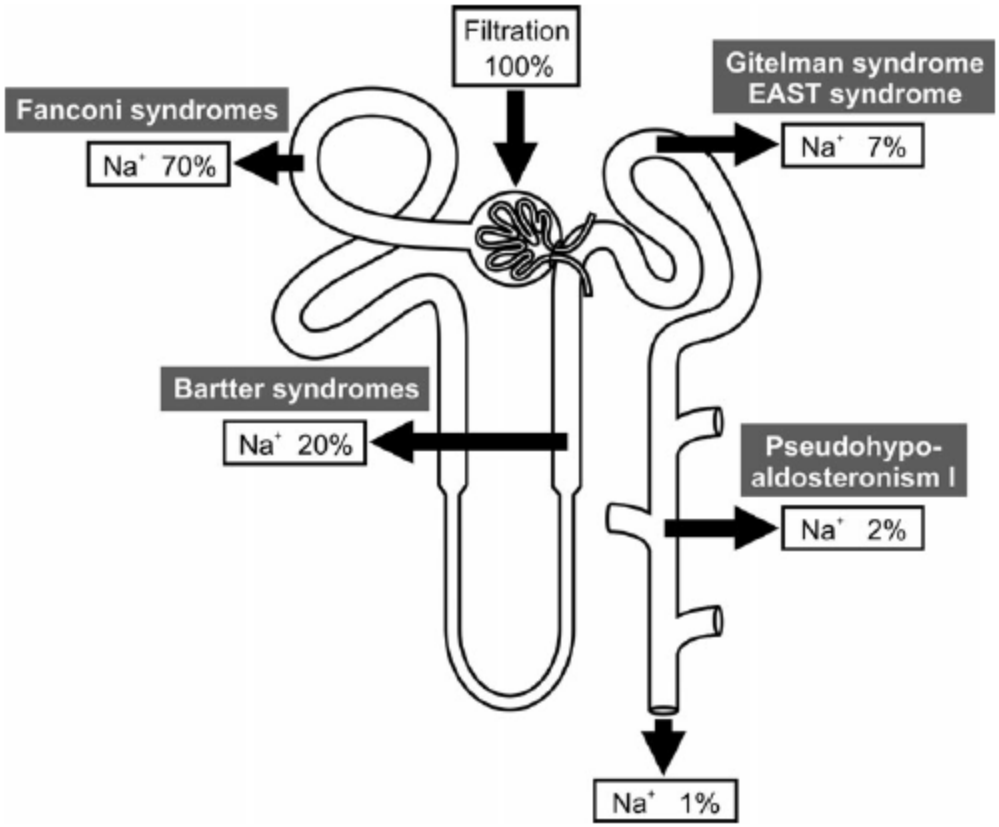
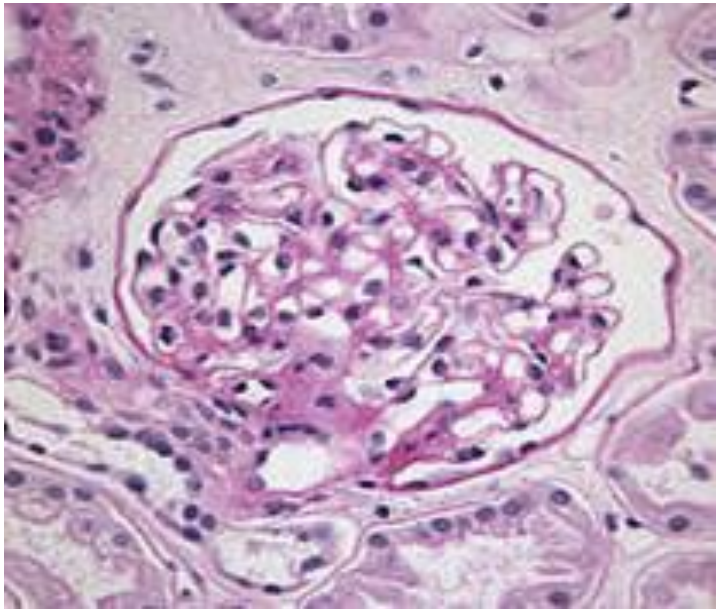
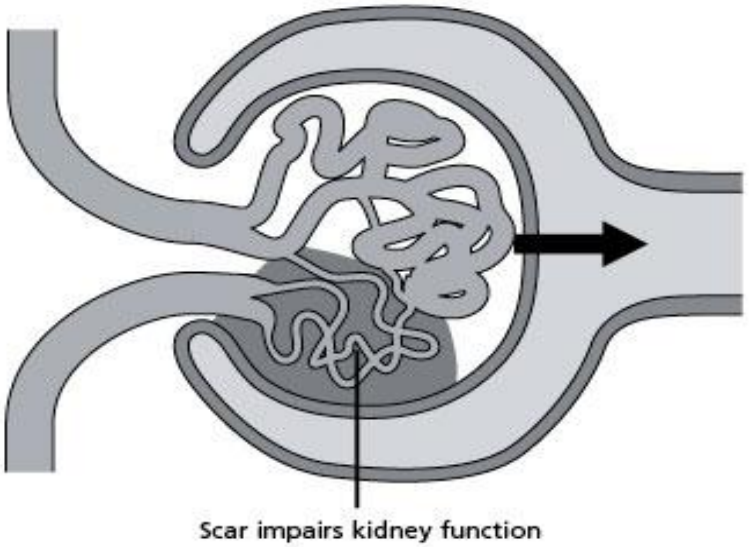
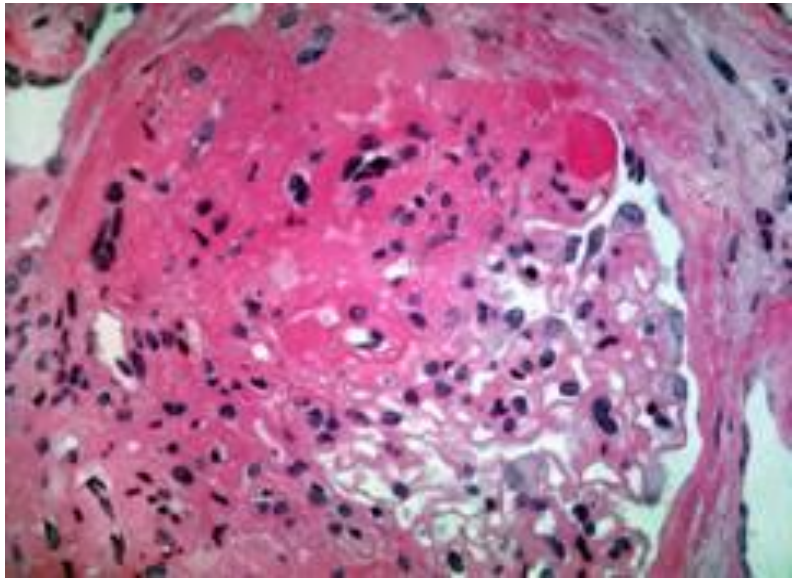


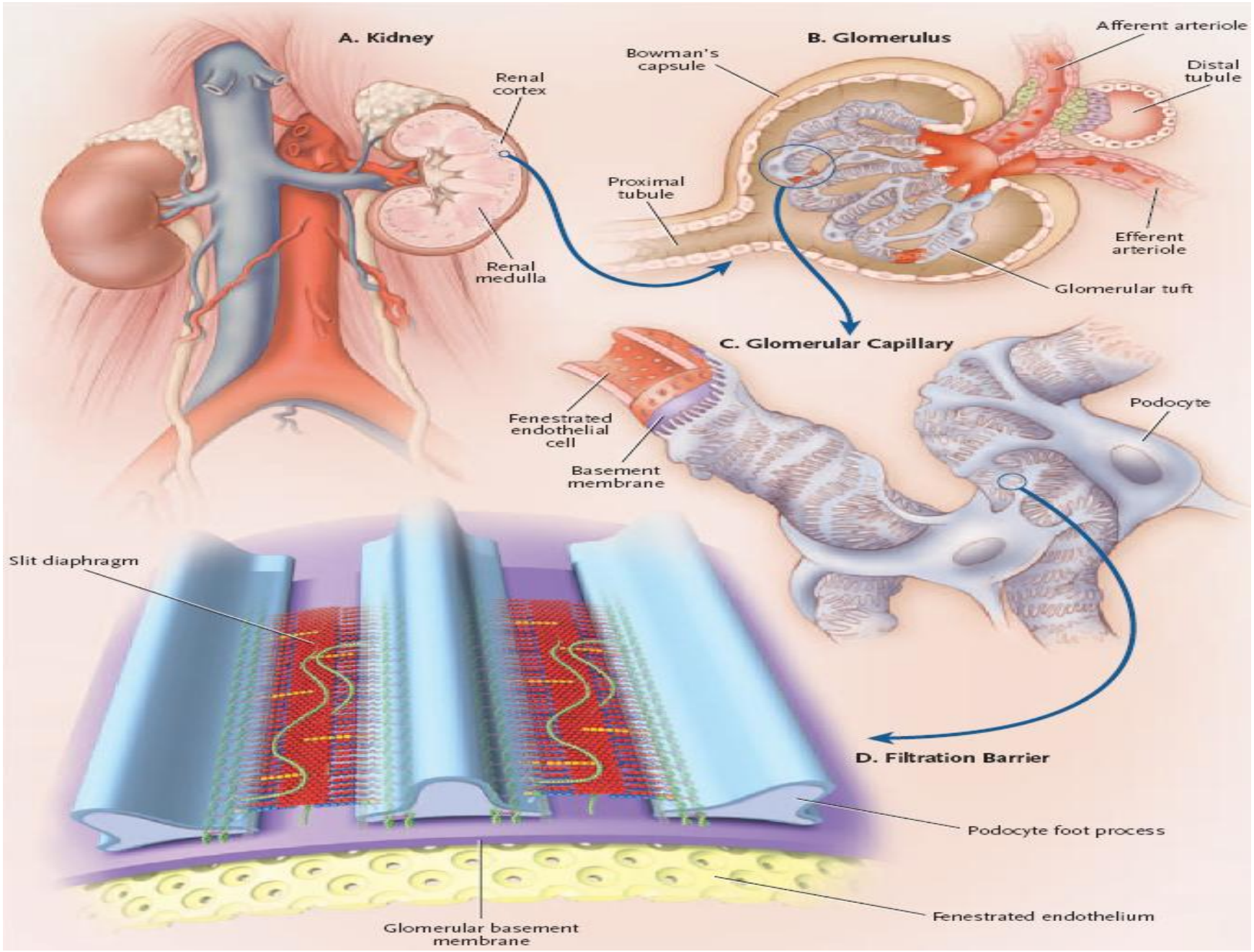
FIGURE 1: Genetic renal tubular diseases caused by failure of sodium reabsorption in individual nephron segments.

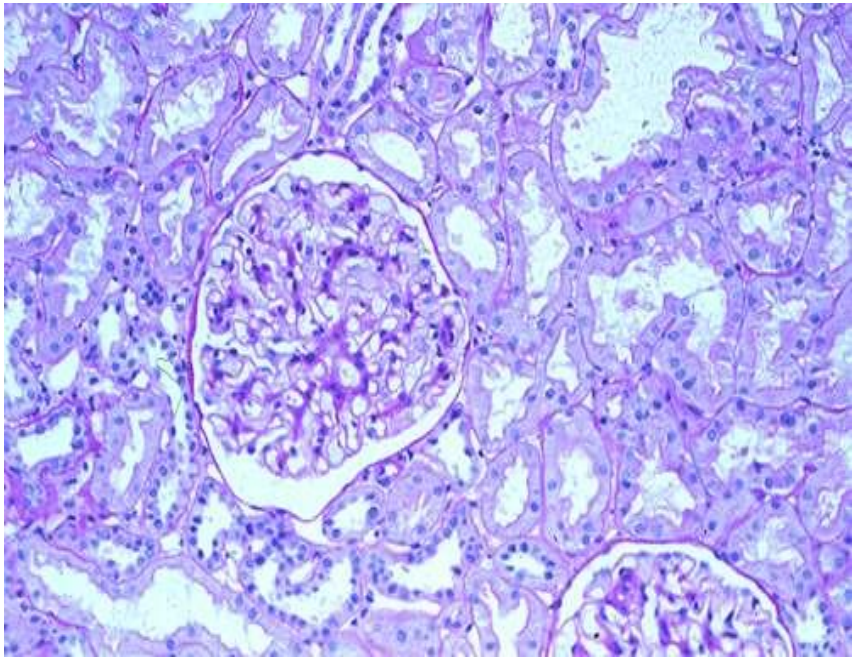
- 6 yr old
- Pr/cr ratio 1200 mg/mmol
- Alb 10
- Normal renal function
- Normotensive
- No response to steroids
- Renal biopsy

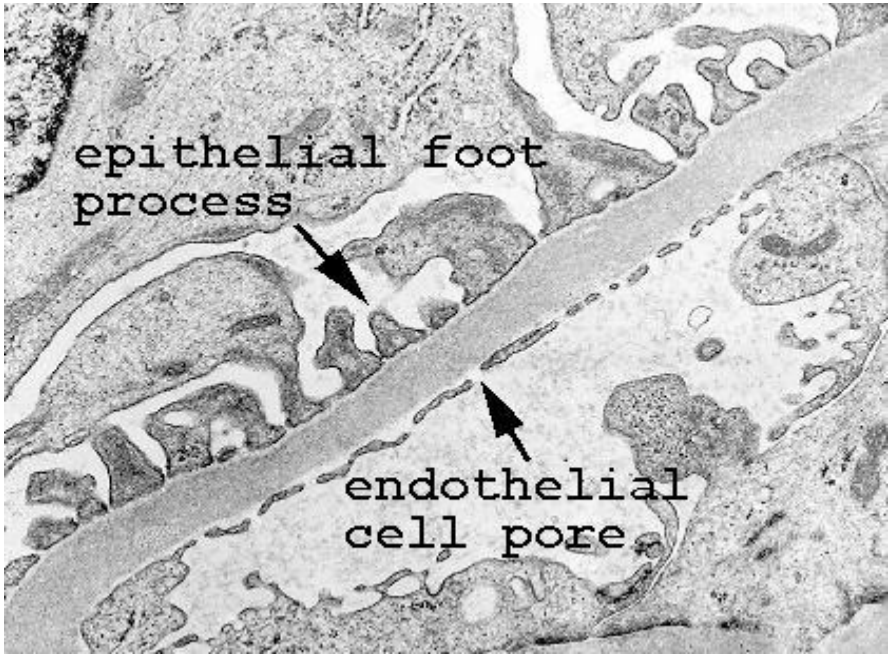


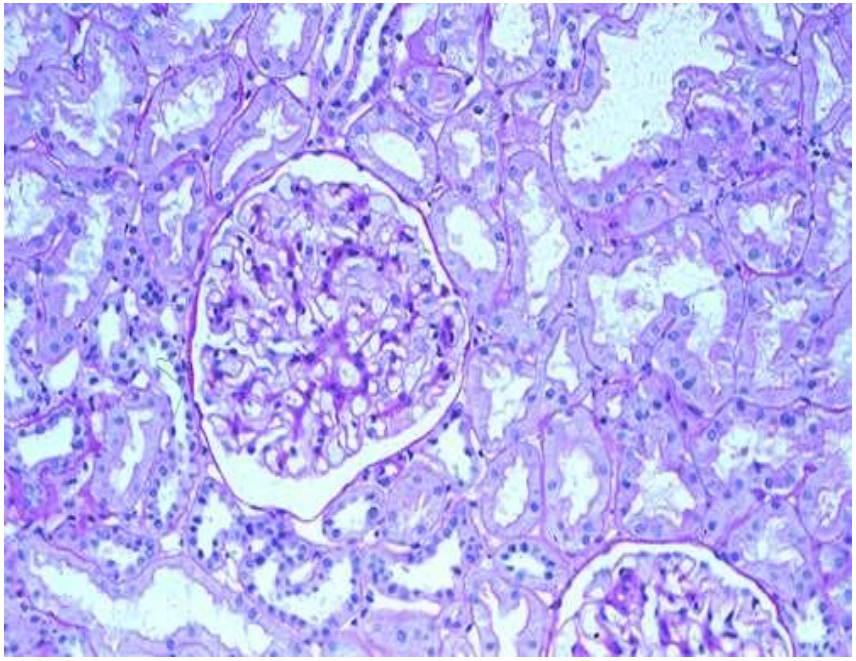

Scar impairs kidney function




A. Kidney
Renal cortex
Renal medulla
B. Glomerulus
Bowman's capsule
Afferent arteriole
Distal tubule
Proximal tubule
Efferent arteriole
Glomerular tuft
C. Glomerular Capillary
Fenestrated endothelial cell
Basement membrane
Podocyte
Slit diaphragm
D. Filtration Barrier
Podocyte foot process
Fenestrated endothelium
Glomerular basement membrane




epithelial foot process
endothelial cell pore



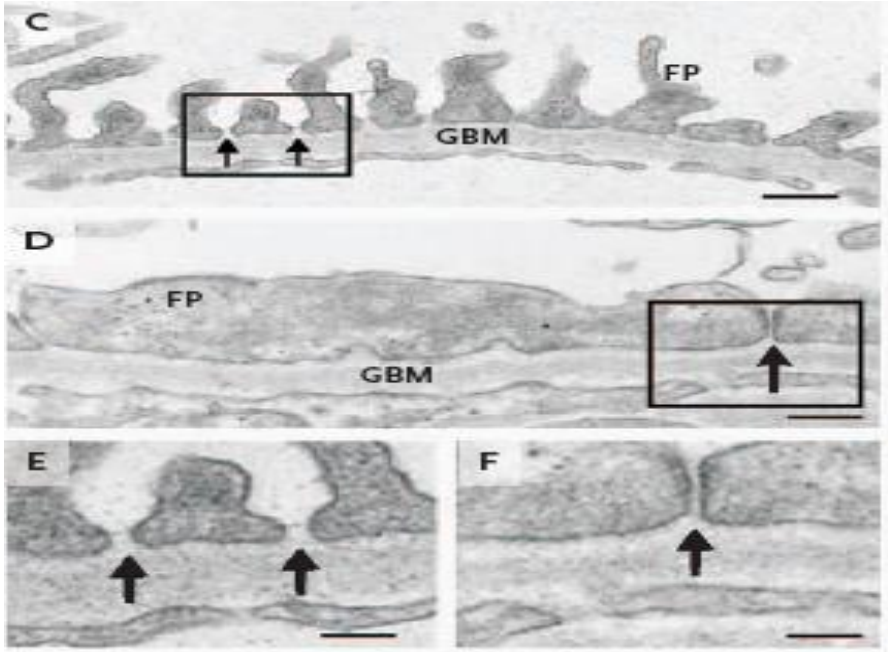
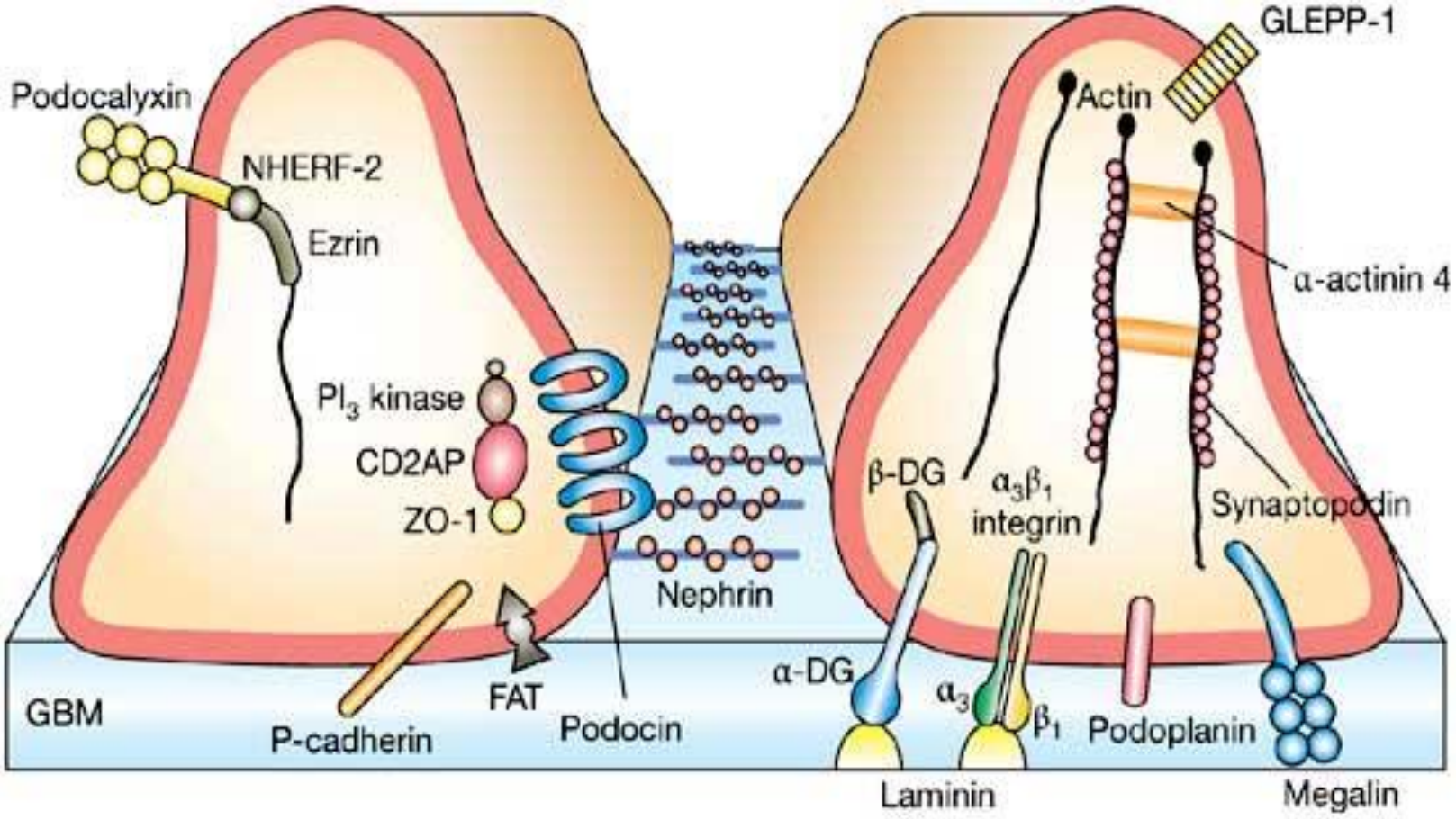

C
FP
GBM
D
FP
GBM
E
F

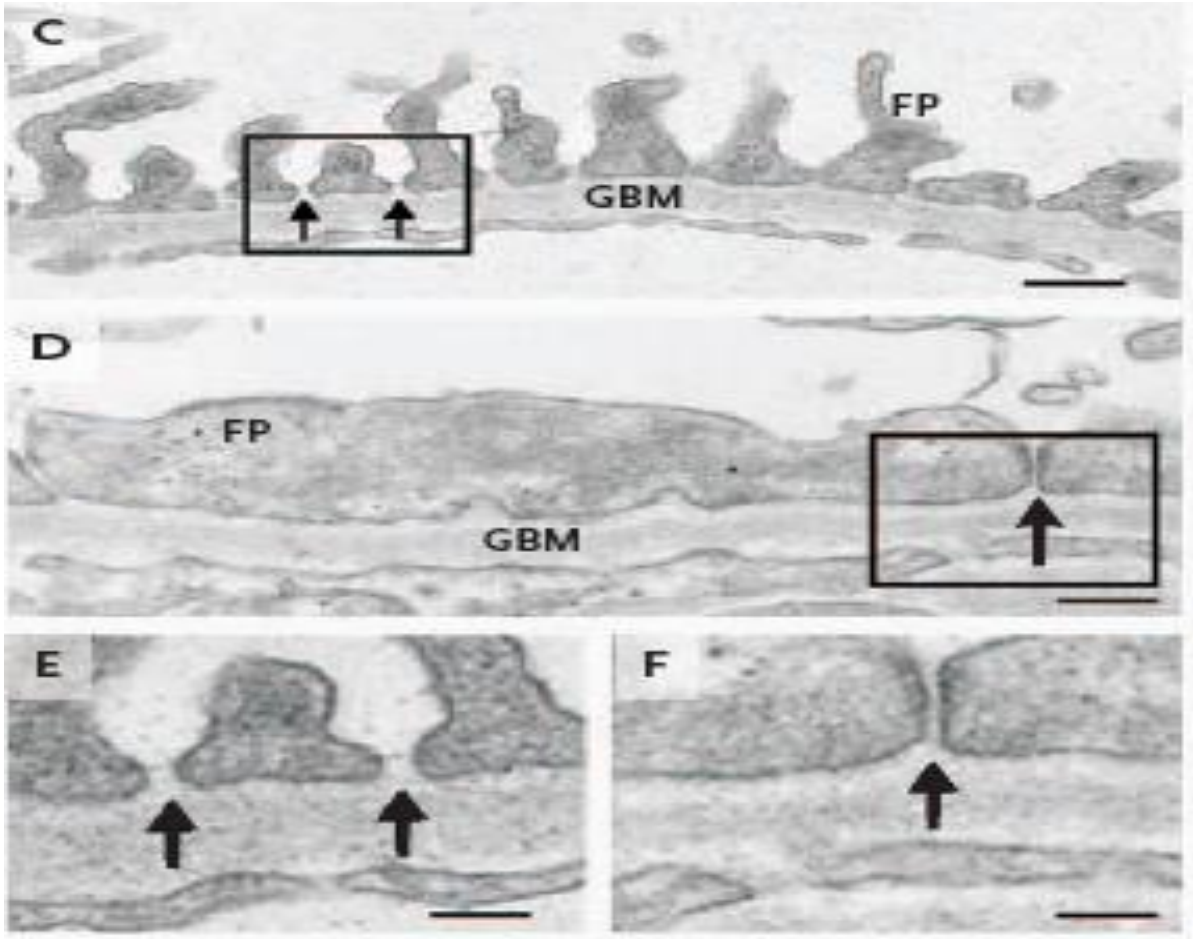
Table 1 Genetic causes of glomerular disease, arranged by site affected in glomerulus (see figure 1)

Site affected in glomerulus	Disease	Gene	Gene product	Inheritance	Phenotype OMIM number
Podocyte slit diaphragm	Congenital nephrotic syndrome	NPHS1	Nephrin	Autosomal recessive	256300
Podocyte slit diaphragm	FSGS	NPHS2	Podocin	Autosomal recessive	600995
Podocyte actin cytoskeleton	FSGS	ACTN4	α-actinin-4	Autosomal dominant	603278
Podocyte calcium flux	FSGS	TRPC6	Cation channel C6	Autosomal dominant	603965
Podocyte nuclear proteins	Denys-Drash syndrome, WAGR syndrome, Frasier syndrome	WT1	Wilm's tumour 1	Autosomal dominant	194080
Type IV collagen, basement membrane	Alport syndrome	COL4A5	α5 chain, type IV collagen	X-Linked (most commonly*)	301050
Glomerular basement membrane	Pierson's syndrome	LAMB2	Laminin-β2	Autosomal recessive	609049
Transcription factor regulating podocyte genes	Nail Patella syndrome	LMX1B	LMX1B transcription factor	Autosomal dominant	161200

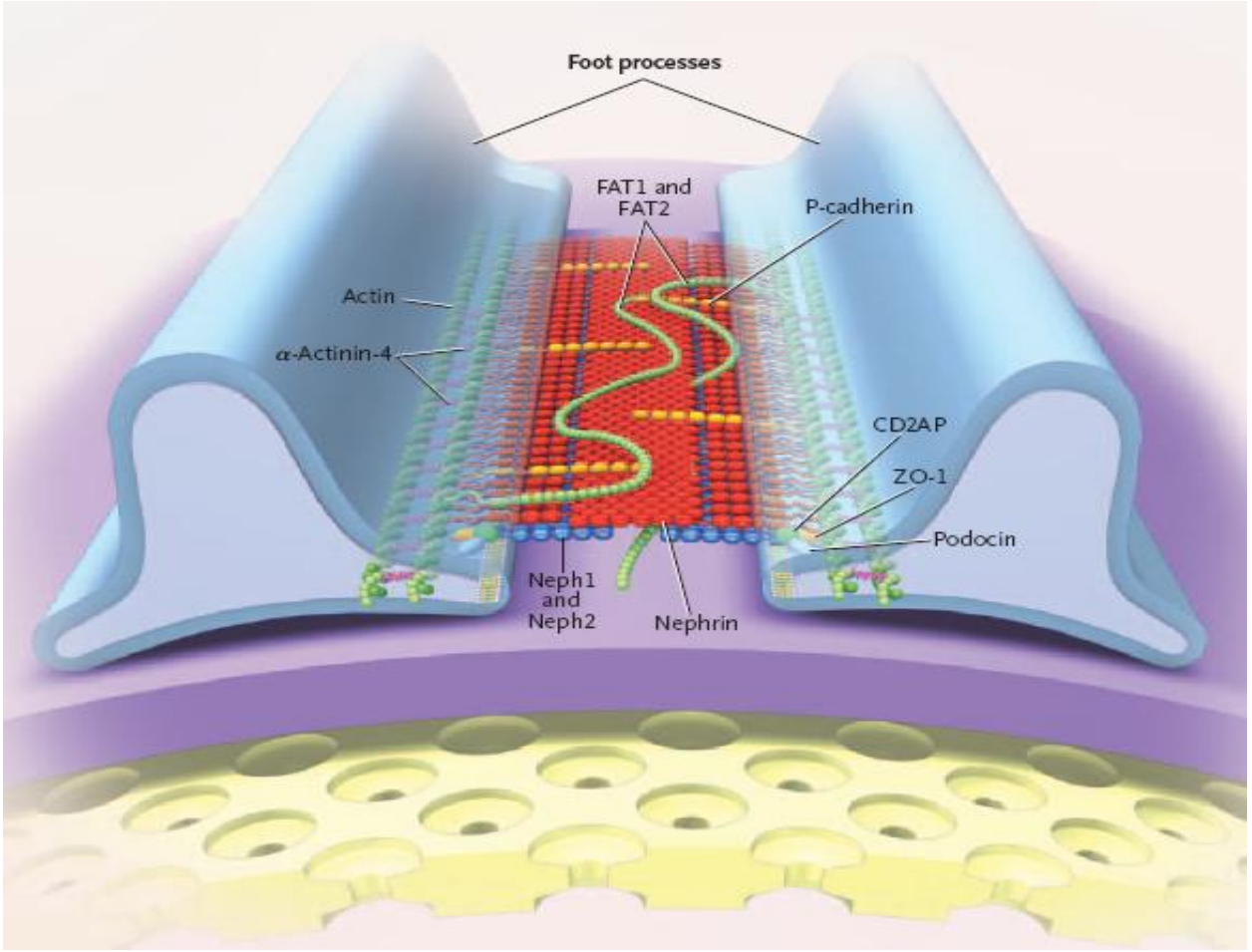
Genetics

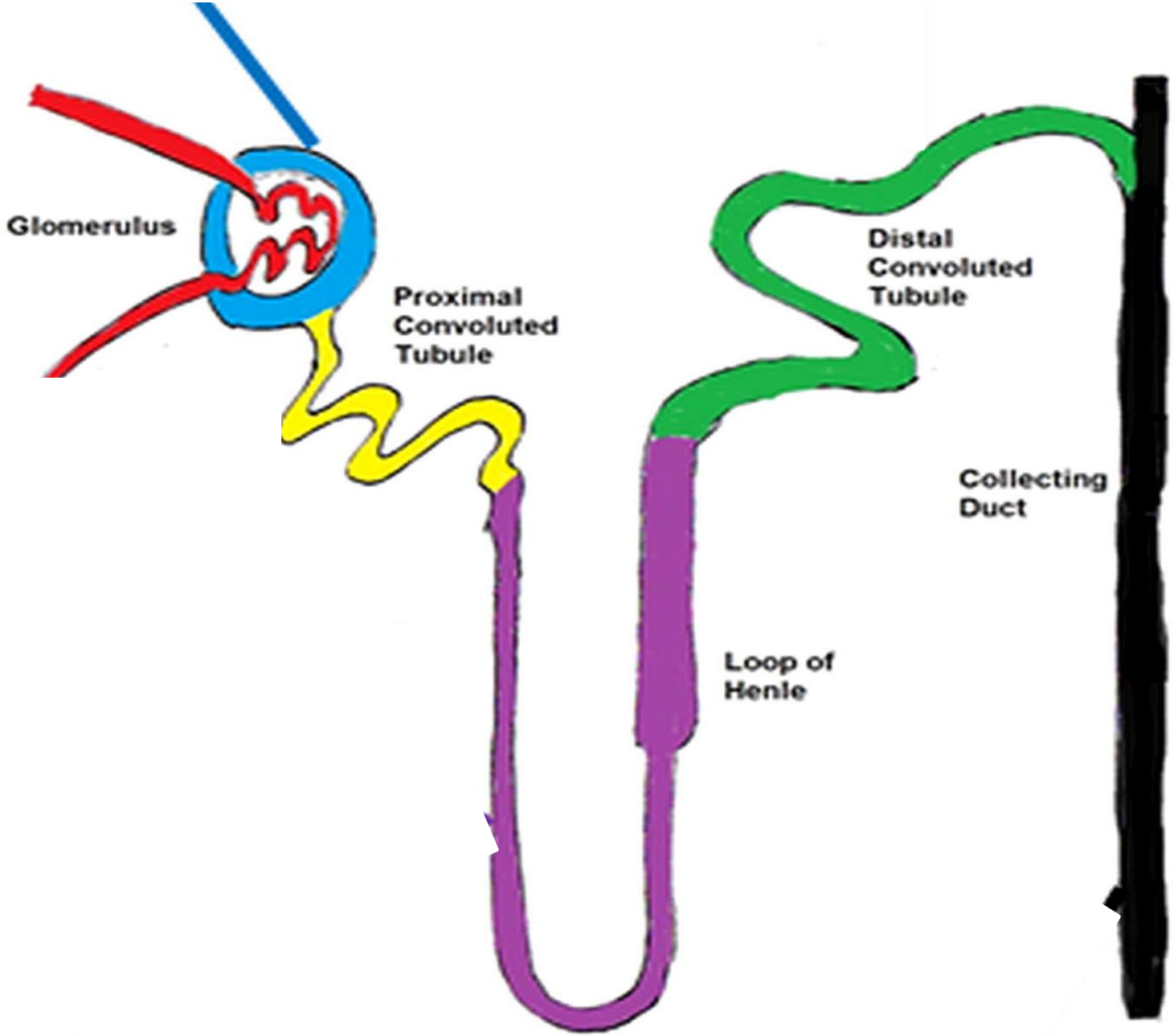

Podocalyxin
NHERF-2
Ezrin
PI_3 kinase
CD2AP
ZO-1
Nephrin
GBM
P-cadherin
FAT
Podocin
GLEPP-1
Actin
α-actinin 4
β-DG
$\alpha_3\beta_1$ integrin
Synaptopodin
α-DG
α_3
β_1
Podoplanin
Laminin
Megalin

Genetics



Genetics


Foot processes
FAT1 and FAT2
P-cadherin
Actin
α-Actinin-4
CD2AP
ZO-1
Podocin
Neph1 and Neph2
Nephrin


Glomerulus
Proximal Convoluted Tubule
Distal Convoluted Tubule
Collecting Duct
Loop of Henle

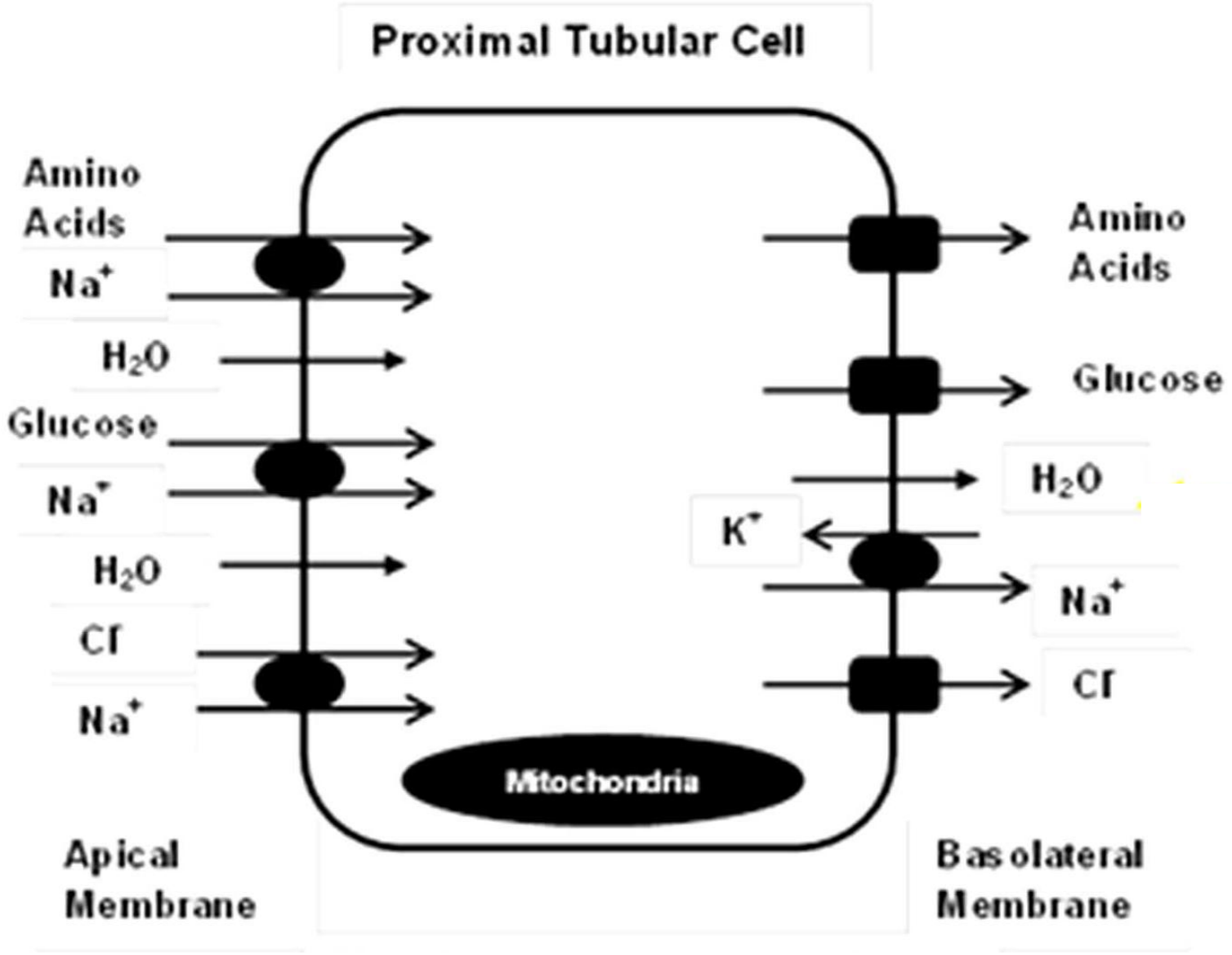
Case 1

- 6 yd old with Asthma
- Normotensive
- Urine dipstix – Glucose +++

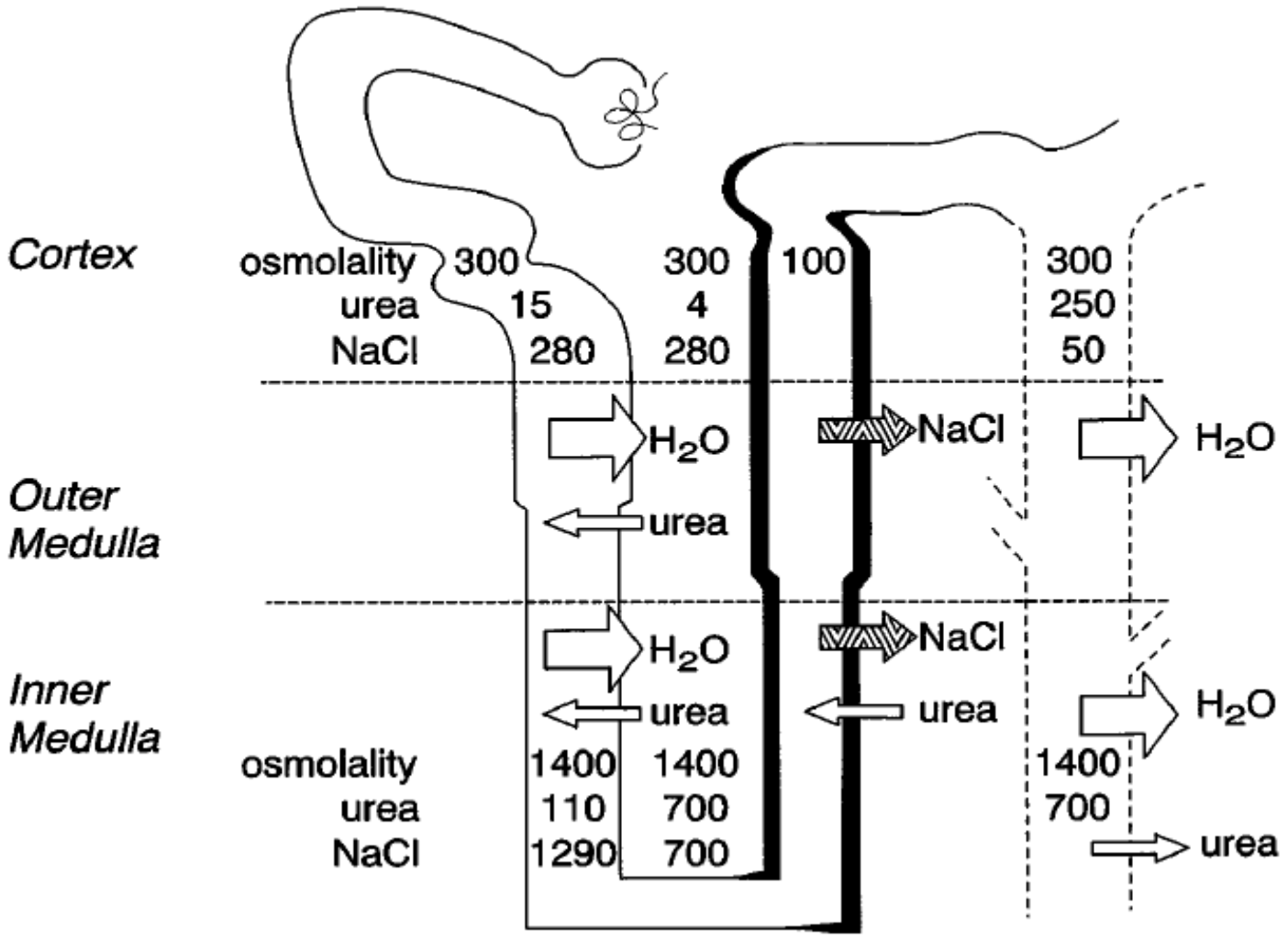
- So what next???

Electrolytes

- Na 128
- K 2.5
- Ca 1.98
- PO4 0.87
- Bic 12
- Aminoaciduria
- Phosphaturia


Proximal Tubular Cell
Amino Acids
Na+
H2O
Glucose
Na+
H2O
Cl-
Na+
Mitochondria
Amino Acids
Glucose
H2O
K+
Na+
Cl-
Apical Membrane
Basolateral Membrane

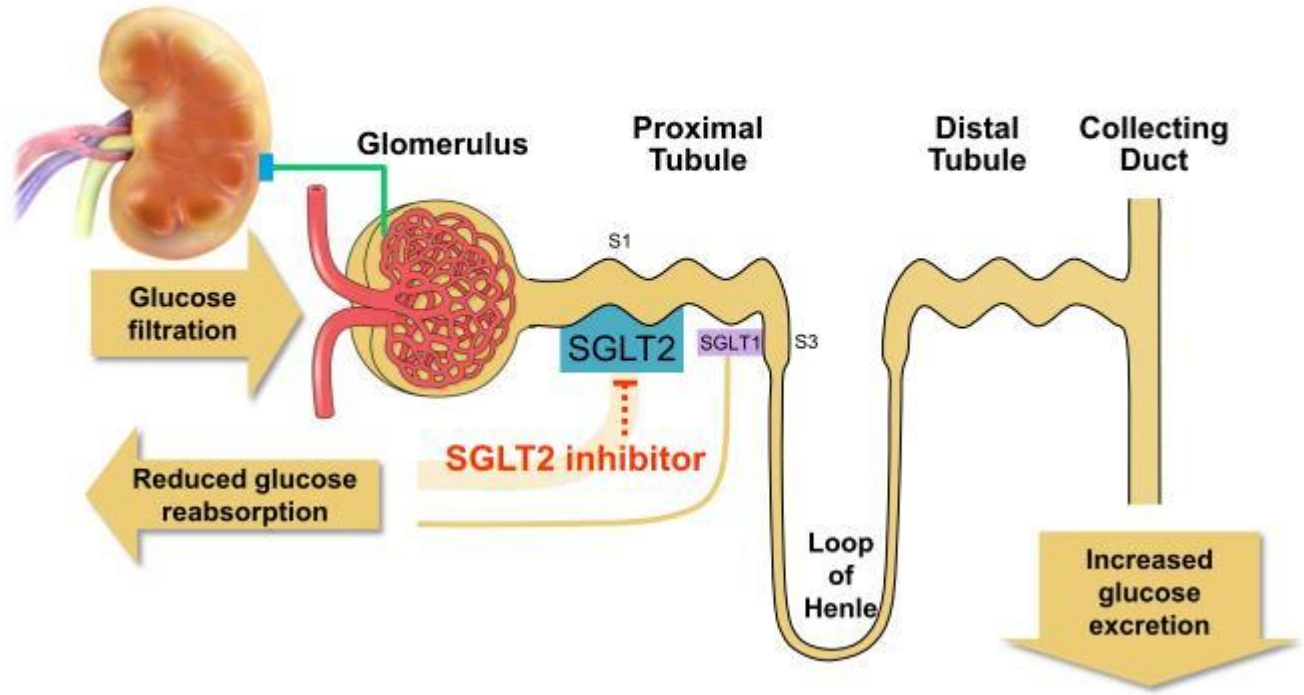
Disease	Gene	Gene product	Inheritance	Extra renal manifestations	OMIM
Cystinosis	CTNS	Cystosin	AR	Fair hair and complexion, hypothyroidism and photophobia	219800
Tyrosinaemia Type 1	FAH	Fumaryl acetoacetate hydolase	AR	Hepatomegaly, progressive live failure, peripheral neuropathy	276700
Galactosaemia	GALT	Gal -1-Phos uridyl transferase	AR	Cataracts, hepatomegaly, seizures, hypoglycaemia	230400
Lowe's syndrome	OCRL	Phosphatidylinositol	X-Linked	Cataracts, hypotonia, developmental delay	309000
Dent's disease	CLCN5	Chloride channel	X-Linked	Nephroclcinosis	300009
Cystinuria Type 1	SLC31	Aminoacid protein	AR	Stones	220100


Cortex
Outer Medulla
Inner Medulla
osmolality 300 300 100 300
urea 15 4 250
NaCl 280 280 50
H2O
NaCl
H2O
urea
H2O
NaCl
urea
urea
H2O
osmolality 1400 1400 1400
urea 110 700 700
NaCl 1290 700
urea

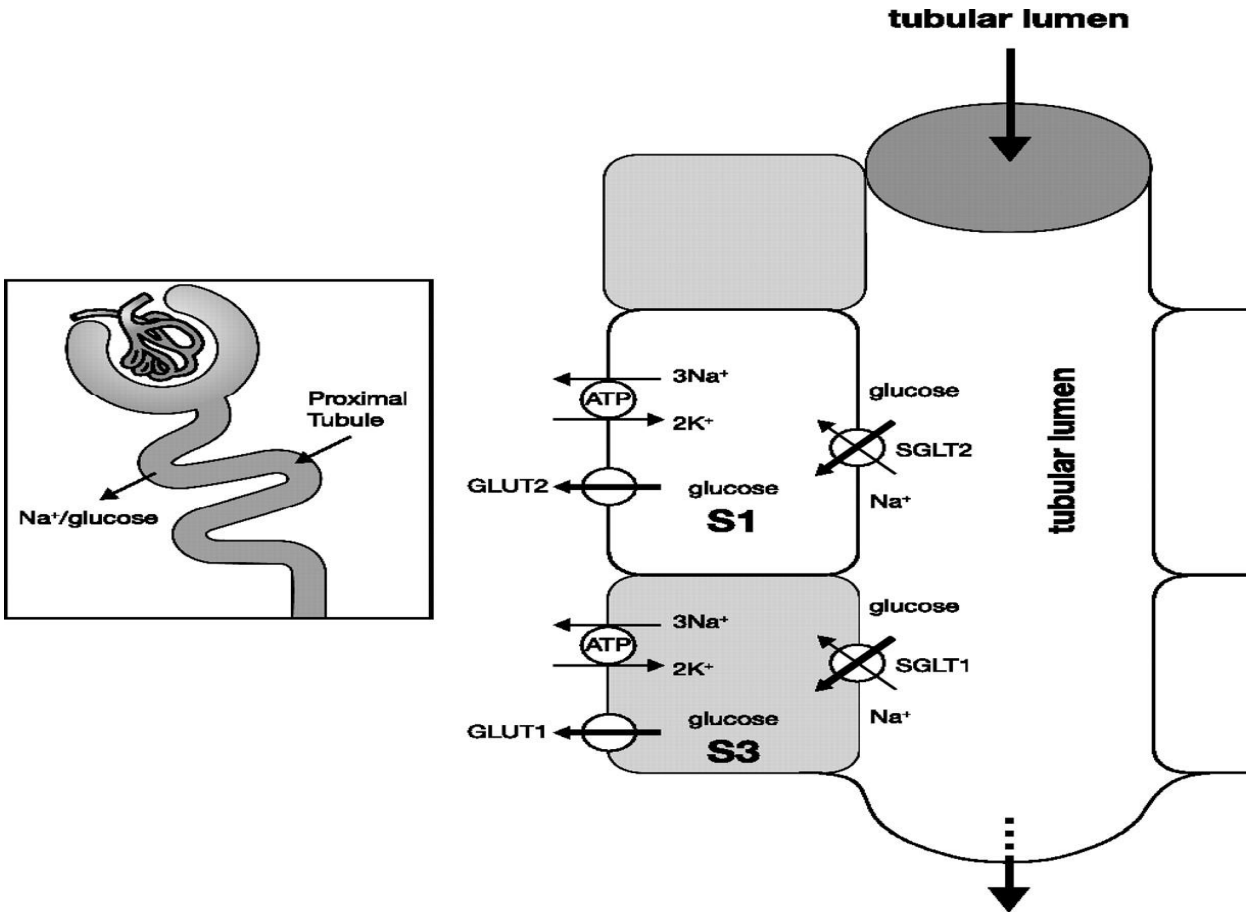
Electrolytes

- Na 128
- K 2.5
- Ca 1.98
- PO4 0.87
- Bic 12
- Aminoaciduria
- Phosphaturia

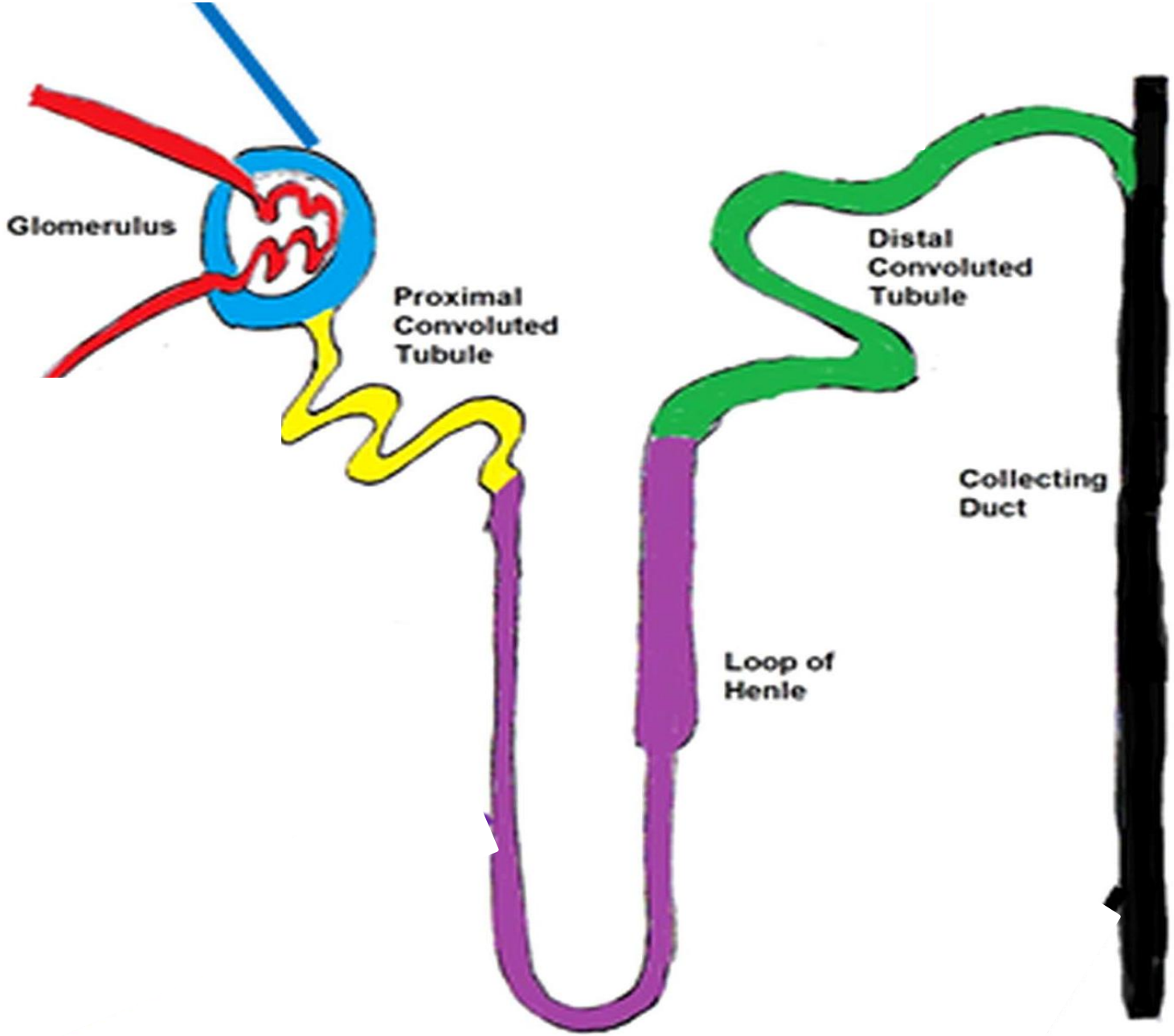
- Normal Electrolytes
- Normal acid base Balance
- So what next??



Canagliflozin
Dapagliflozin
Andempagliflozin



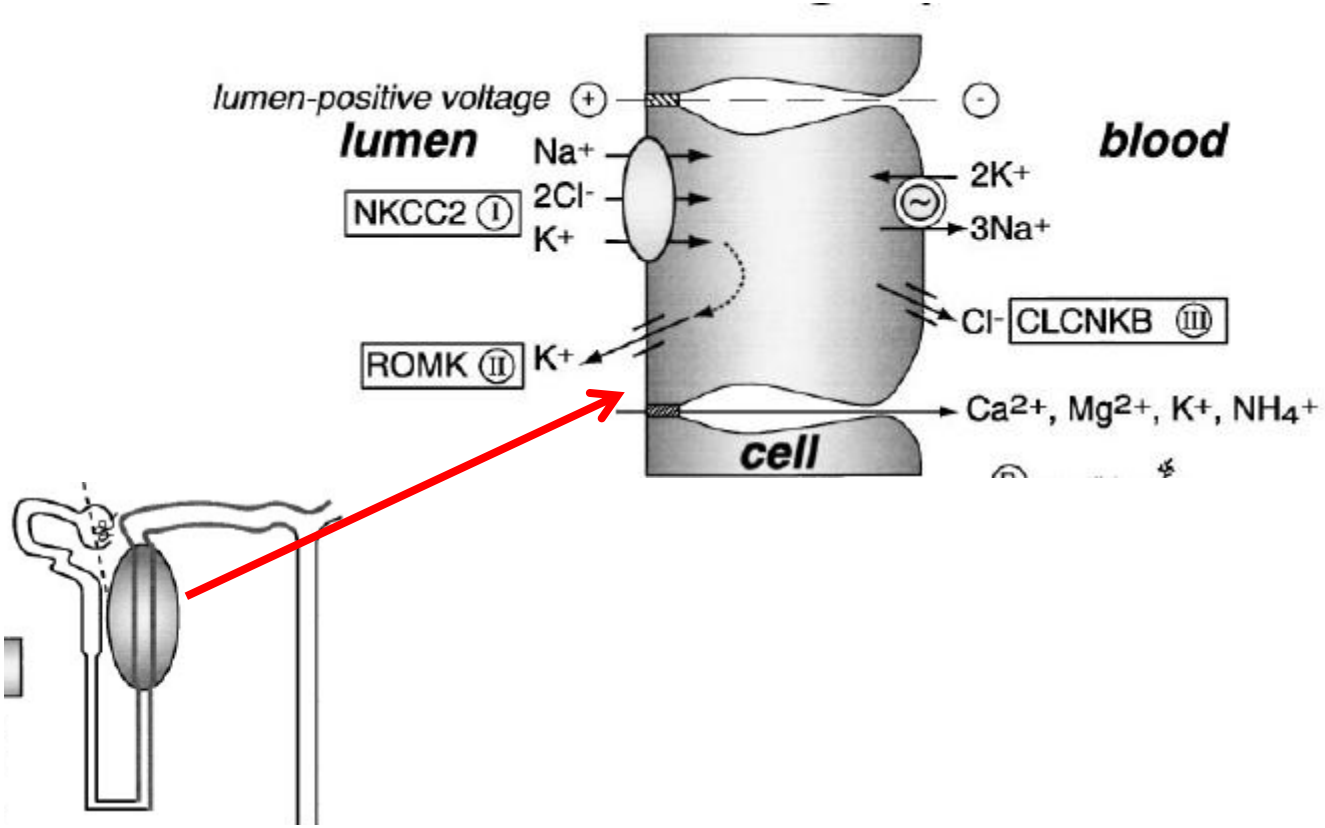
René Santer, and Joaquim Calado CJASN 2010;5:133-141


Glomerulus
Proximal Convoluted Tubule
Distal Convoluted Tubule
Collecting Duct
Loop of Henle

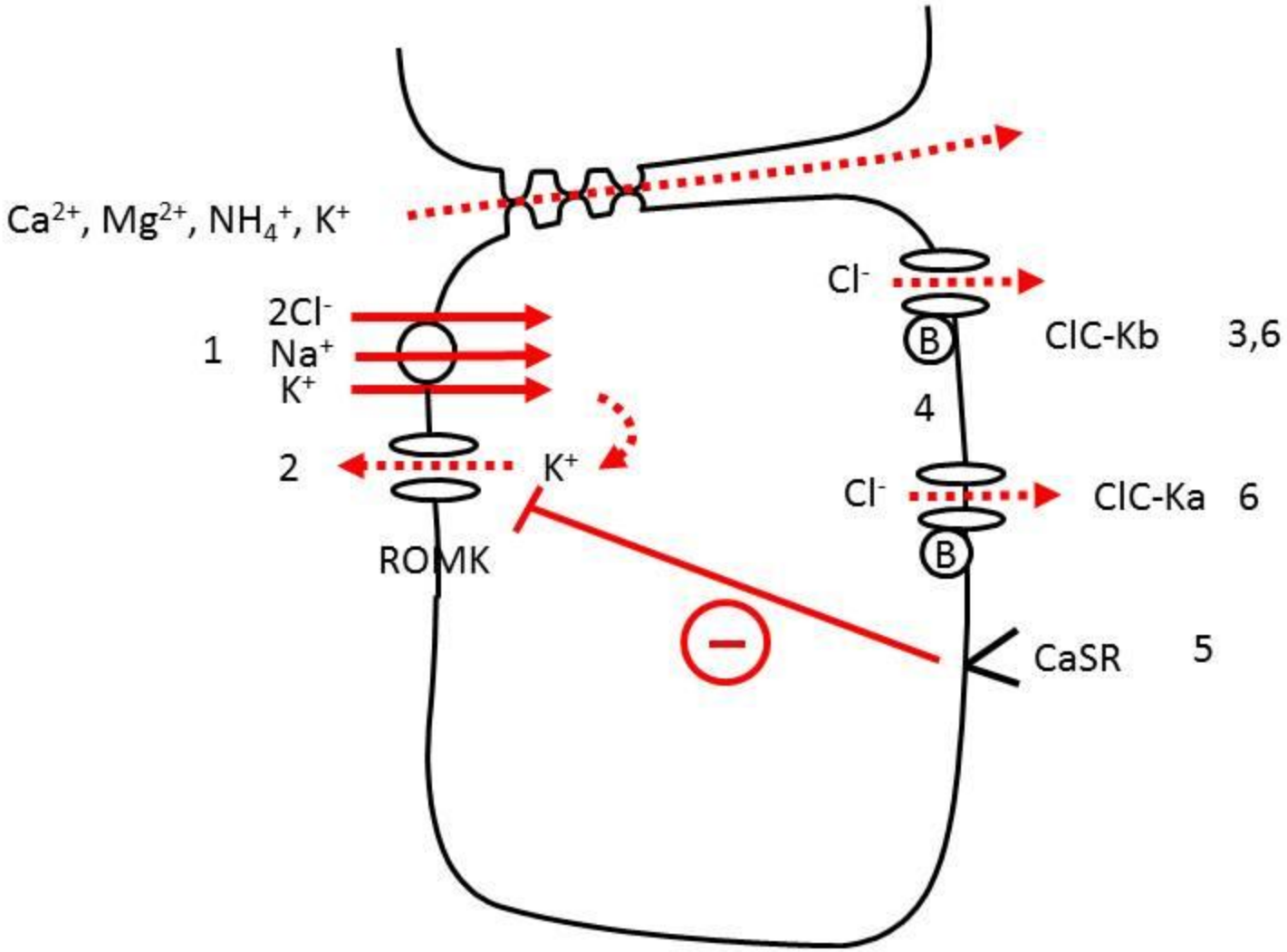
Case 2

- Na 129
- K 1.6
- Ca 2.31
- PO4 1.6
- Mg 0.96
- Bic 29

- Maternal polyhydramnios
- Multiple amniotapping
- Lost > 20% body weight within the first 3 days
- Urine output 8ml/kg/hr
- Normotensive

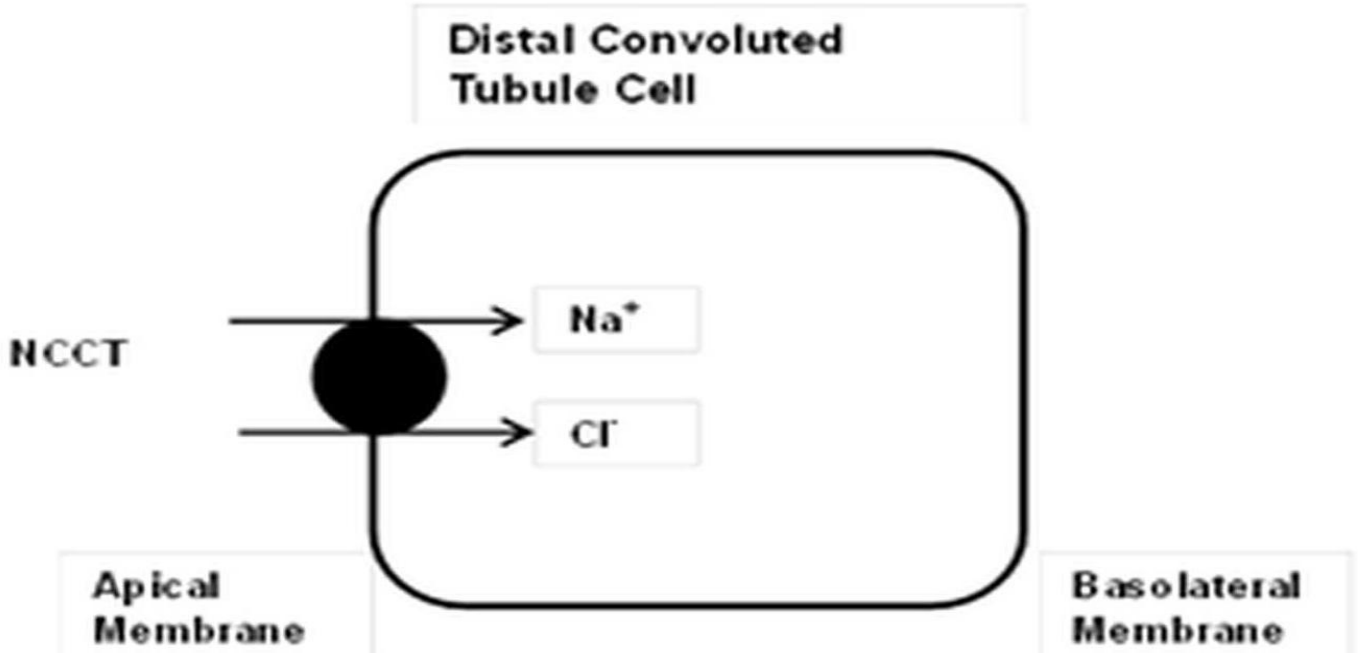

lumen-positive voltage
+
-
lumen
blood
Na+
2Cl-
K+
NKCC2 I
2K+
3Na+
Cl-
CLCNKB III
ROMK II
K+
Ca2+, Mg2+, K+, NH4+
cell

Bartter syndrome



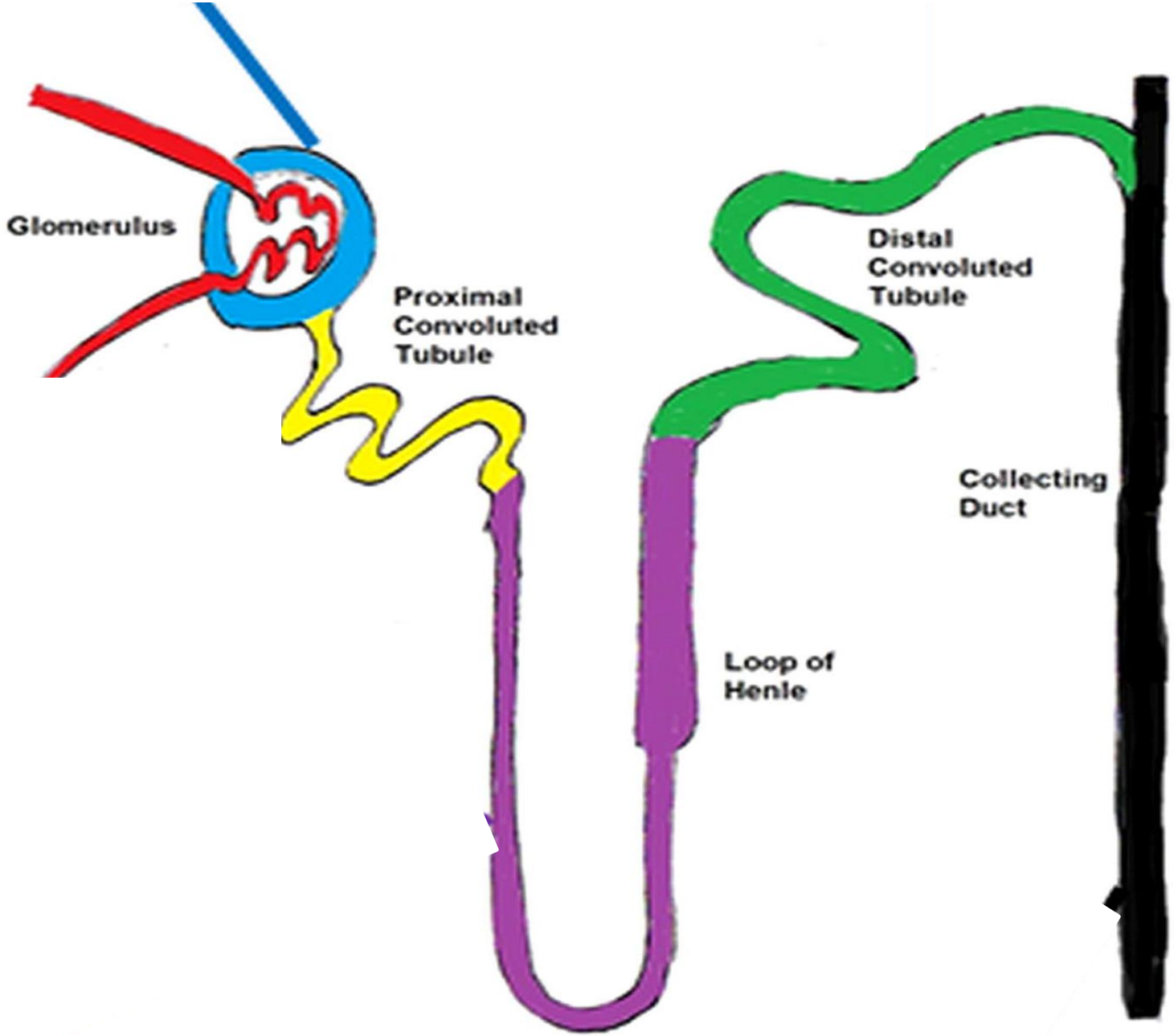
Barrtter's Type	Defective Gene	Clinical Presentation
I	NKCC	Neonatal
II	ROMK	Neonatal Hyperkalemia - initially
III	CLCNKB	Classic
IV	BSND	Neonatal with deafness
V	CLCNKB & CLCNKA	Neonatal with deafness

- Diagnosis
- Treatment options
- Complications


Distal Convoluted
Tubule Cell
NCCT
Na+
Cl-
Apical
Membrane
Basolateral
Membrane

Barterr vs Gitleman

	Bartter	Gitelman
Site	TAL	DCT
Sodium	Low	Low
Potassium	Low	Low
Alkalosis	++	+
Magnesium	Normal	Low
Urine Ca/Cr ratio	High	Low
Nephrocalcinosis	+++	+
Drug similarity	Loop	Thiazide


Glomerulus
Proximal Convoluted Tubule
Distal Convoluted Tubule
Collecting Duct
Loop of Henle

Case 3

Sodium 182 mmol/L *

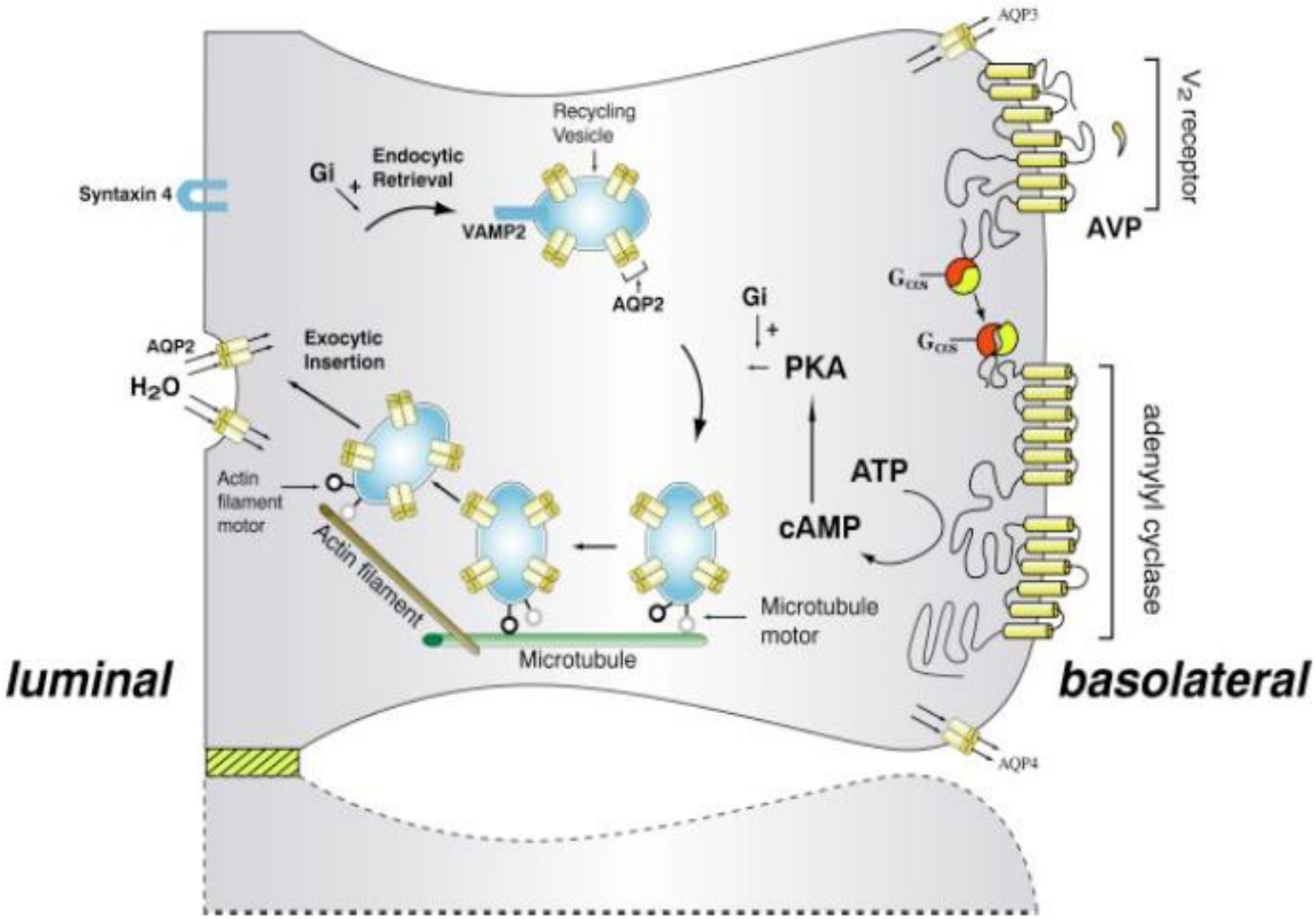
Potassium 4.1 mmol/L

Urea 4.7 mmol/L

Creatinine 59 umol/L *

Serum Osmolality 381

Urine Osmolality 158


AQP3
V2 receptor
AVP
Recycling
Vesicle
Gi
+
Endocytic
Retrieval
Syntaxin 4
VAMP2
AQP2
Gi
+
PKA
Gcas
Gcas
AQP2
H2O
Exocytic
Insertion
ATP
cAMP
adenylyl cyclase
Actin
filament
motor
Actin filament
Microtubule
motor
Microtubule
luminal
basolateral
AQP4

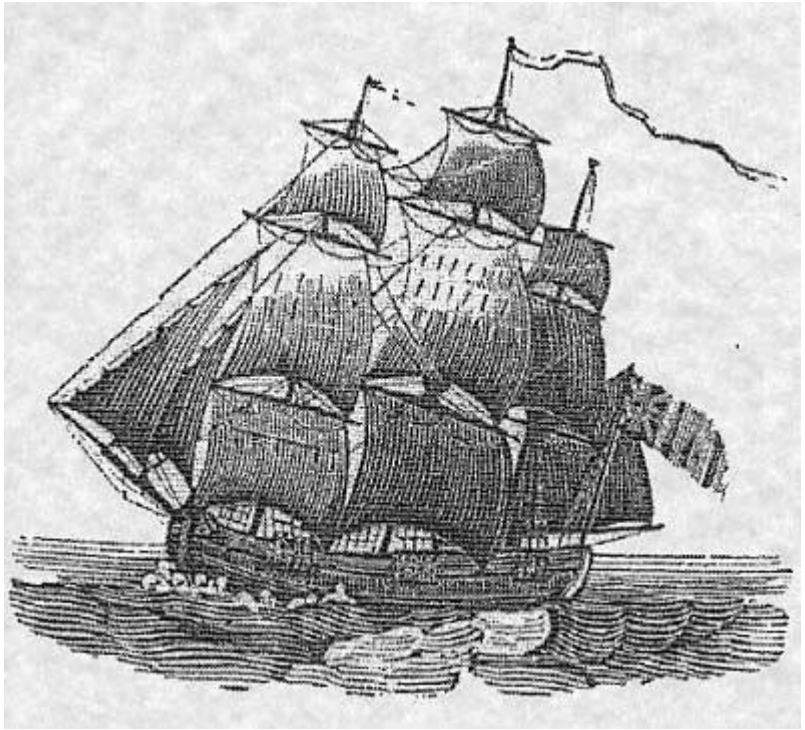
Nephrogenic DI

- Treatment
  - Thiazides
  - Indomethacin
  - Antacids

  - Plenty of water

  - Watch for renal abnormalities

Ship - Hopewell



Case 4

Antenatally detected to have

- Left Duplex Kidney
- LK Hydronephrosis
- Ureterocele
- Right Kidney Duplex - Uncomplicated

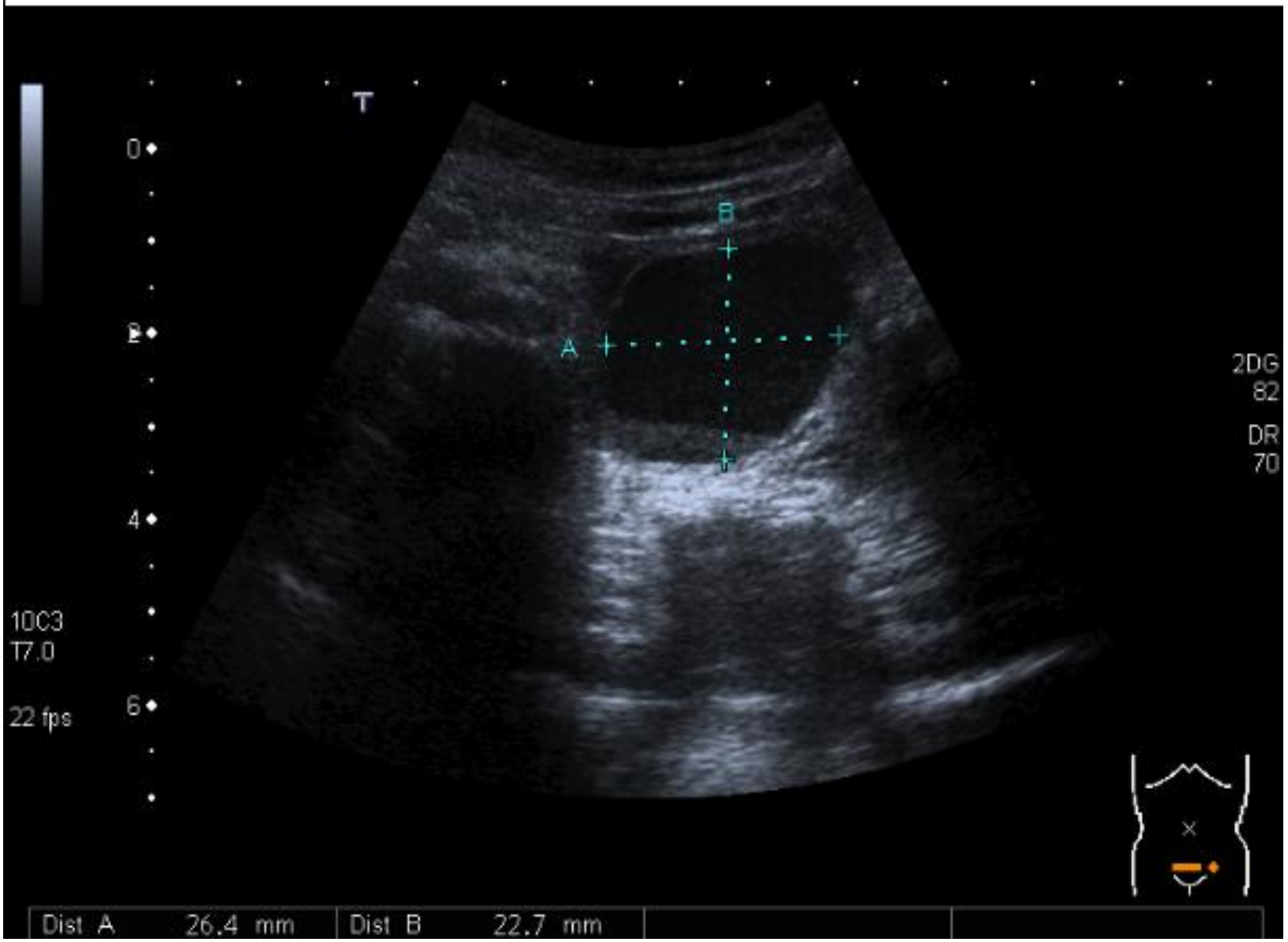
Case 4

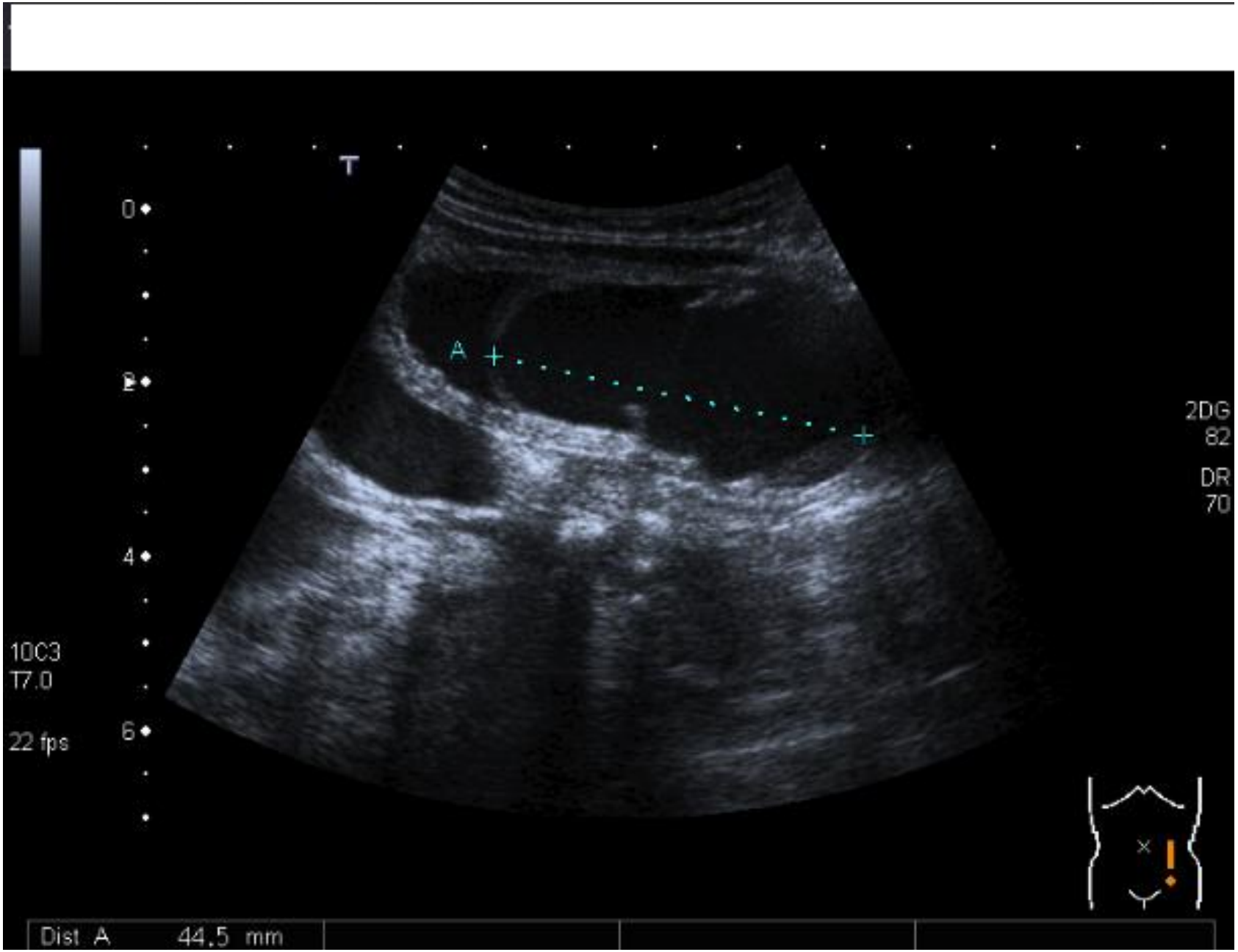
- Born at term NVD
- Follow USS showed
- Duplex left Kidney
- Dilated tortuous left collecting system
- Debris with the left tract and the large ureterocele
- Urine sterile pyuria

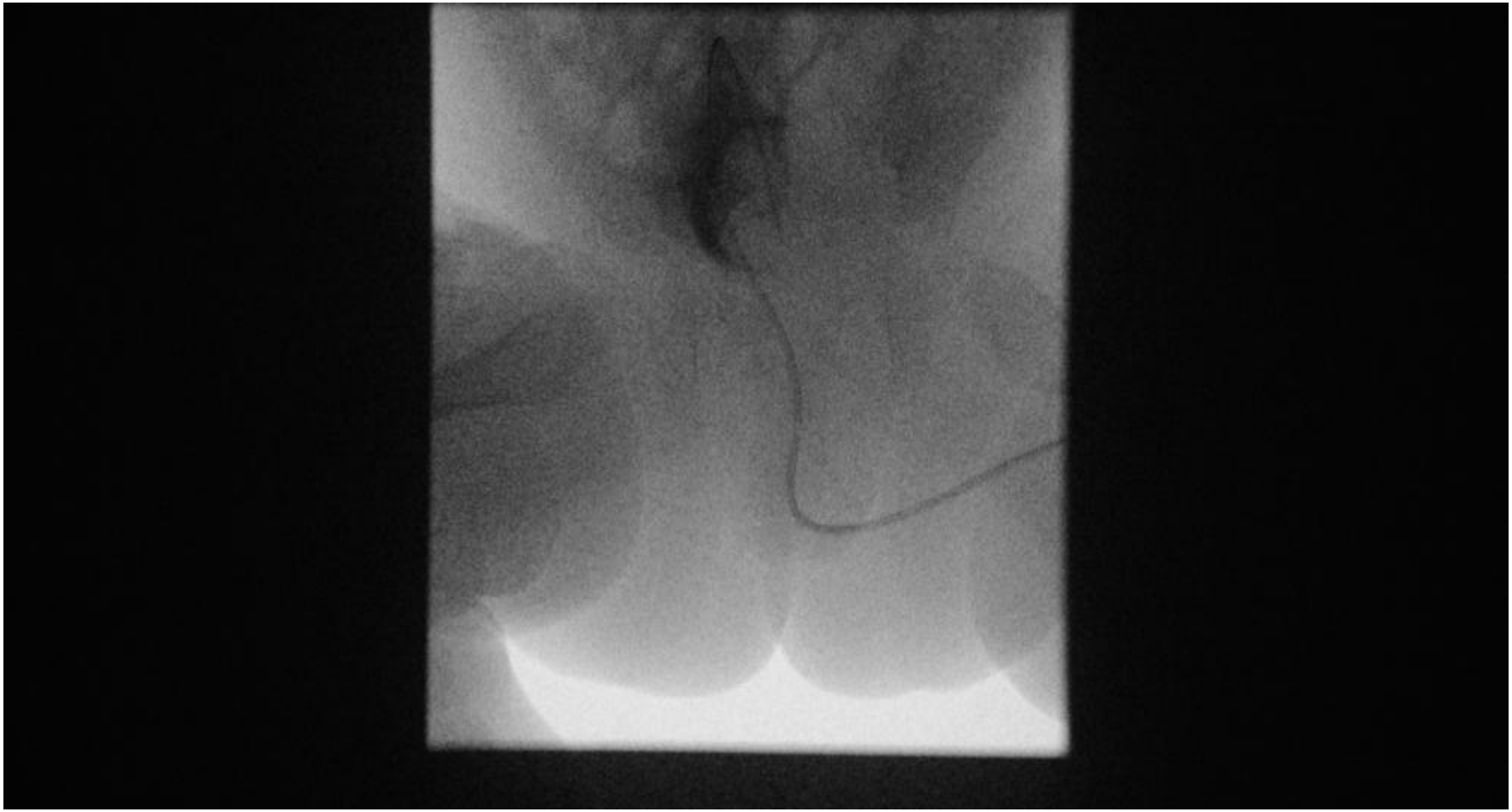
- Brought to UHW
- Looked reasonably well
- At 3 weeks weight just above the birth weight

Bloods showed

- Na 125 K6 Ur 7.3 Cr 47 Bic 12 CRP12
- USS confirmed the findings and it showed a large ureterocele 45 x 26 x 23mm


T
0
2
4
6
A
B
2DG
82
DR
70
10C3
T7.0
22 fps
Dist A 26.4 mm
Dist B 22.7 mm


T
0
2
4
6
A
2DG
82
DR
70
10C3
T7.0
22 fps
Dist A 44.5 mm

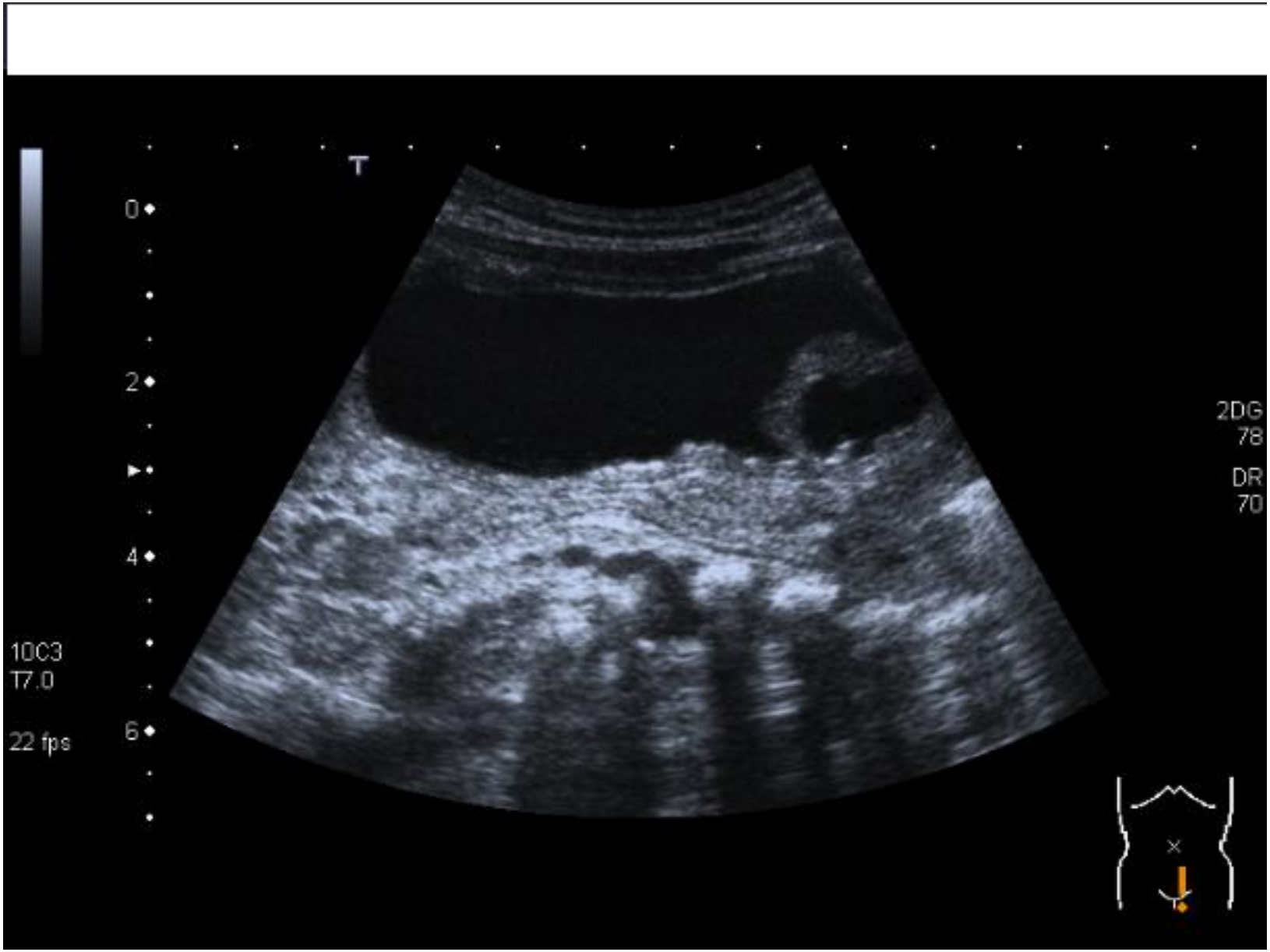


Story continues……..

- Ureterocele punctured
- Na 138 K4.9 Ur 0.8 Cr 35 Bic 23

- Prior to discharge the ureterocele had disappeared the LK UM AP 14, LK LM AP 15 ureter was still dilated

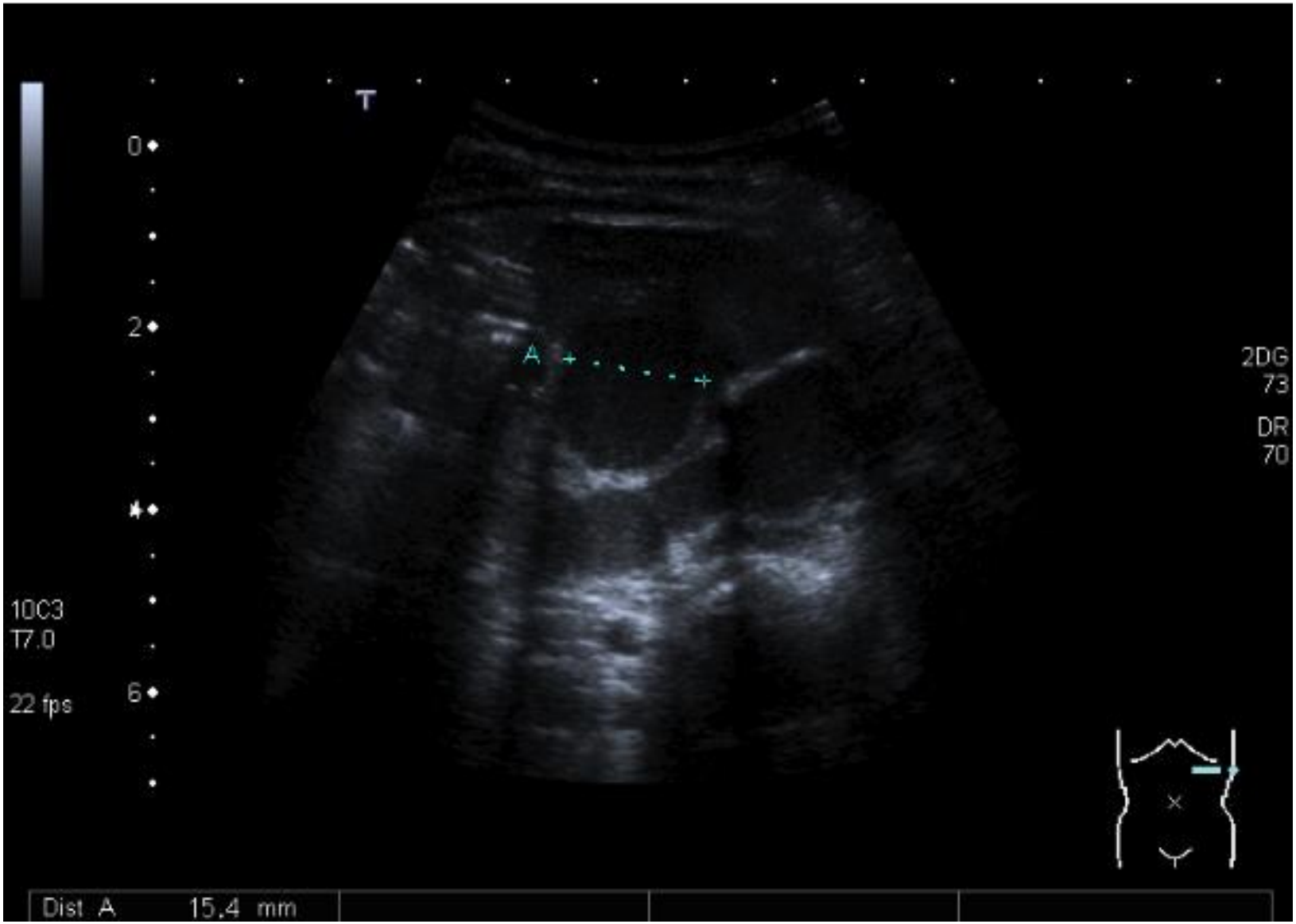
- Cystogram which showed that the Ureterocele had collapsed and there was no reflux demonstrated

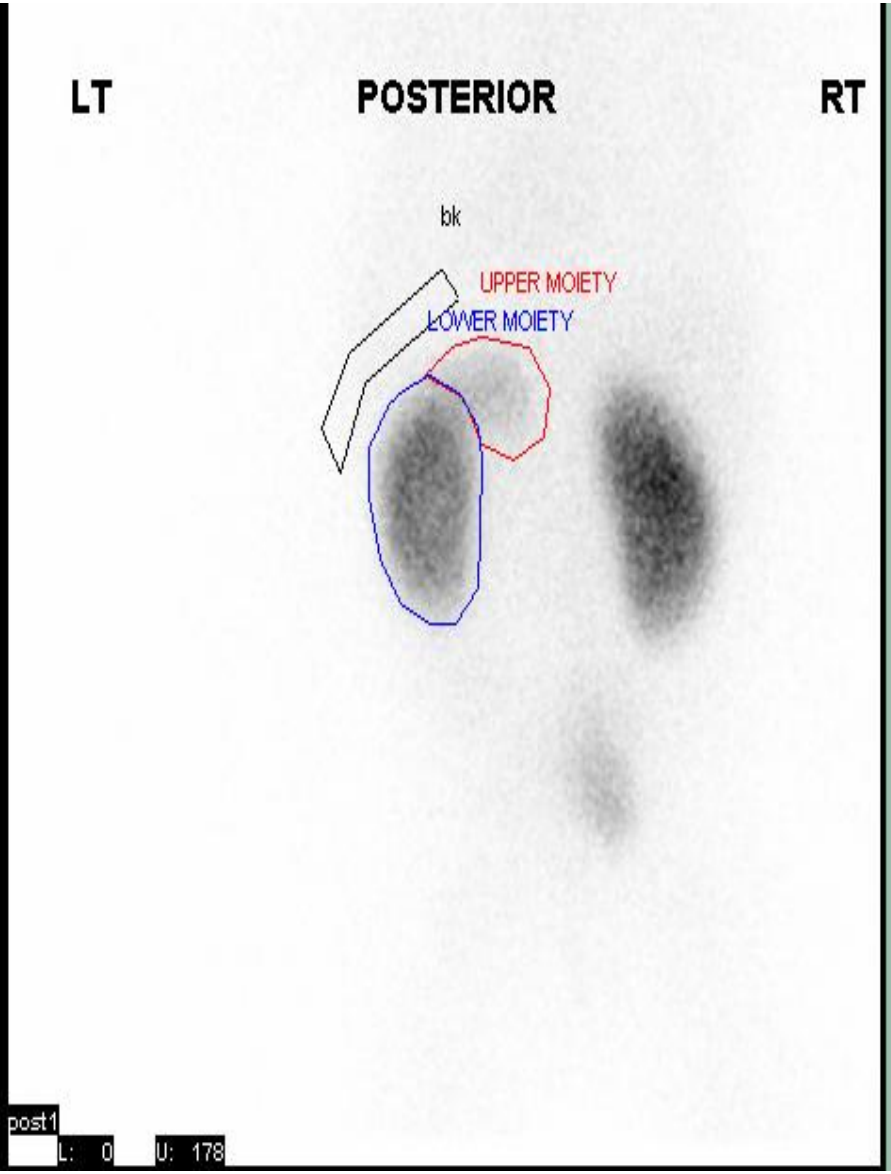

T
0
2
4
6
10C3
T7.0
22 fps
2DG
78
DR
70

Story continues….

- 3/12 months came for a clinic review
- Taking a long time to feed
- No clinical signs of UTI; Urine did show + leucocytes and Nitrates
- Wt down from 25th centile to 0.4th centile
- Bloods showed

  Na 123 K 6 Ur 8.8 Cr 41 Bic 15 CRP 5
- Urgent USS was done - large dense ureterocele with a lot of debris

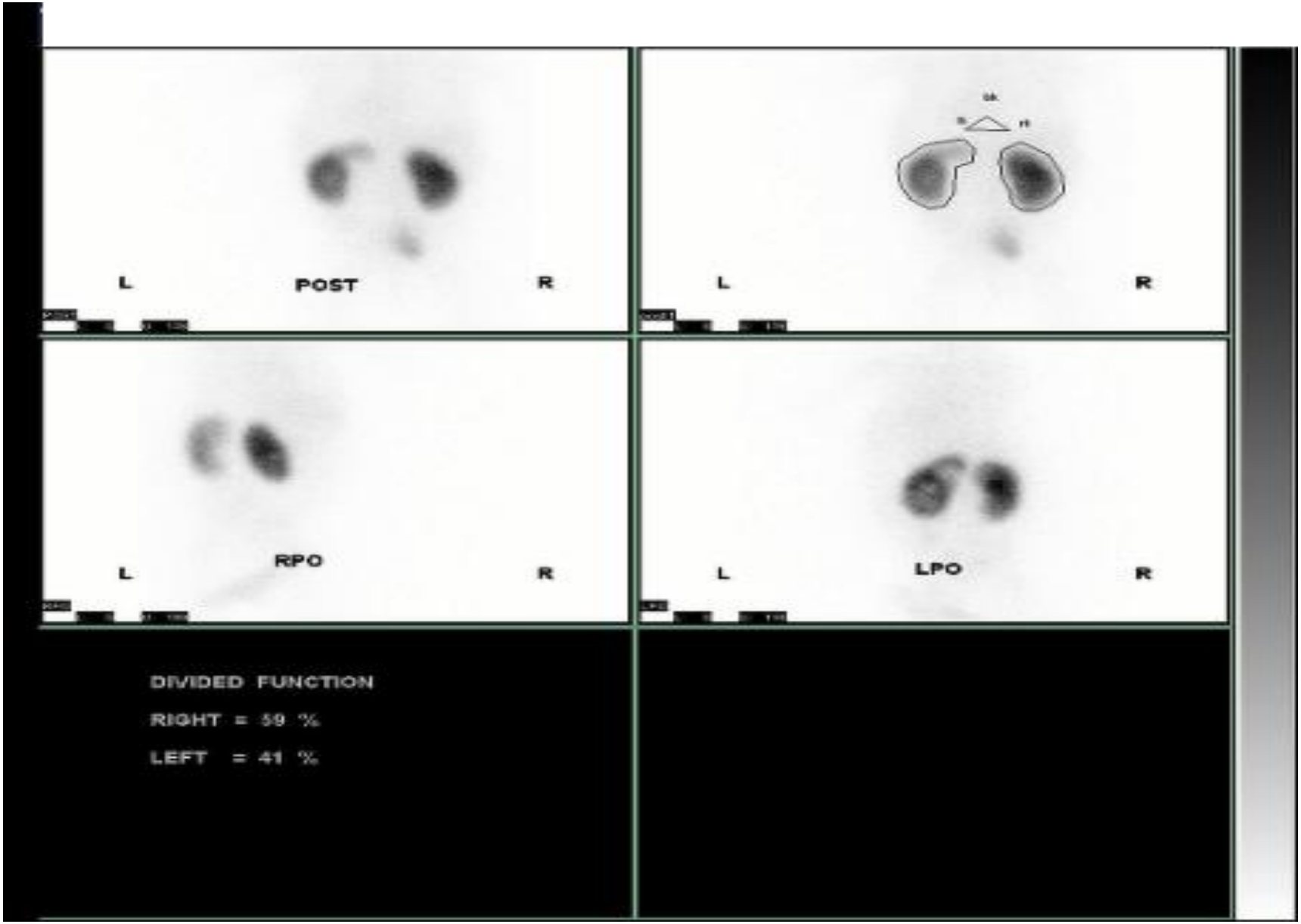

T
0
2
4
6
A
2DG
73
DR
70
10C3
T7.0
22 fps
Dist A 15.4 mm

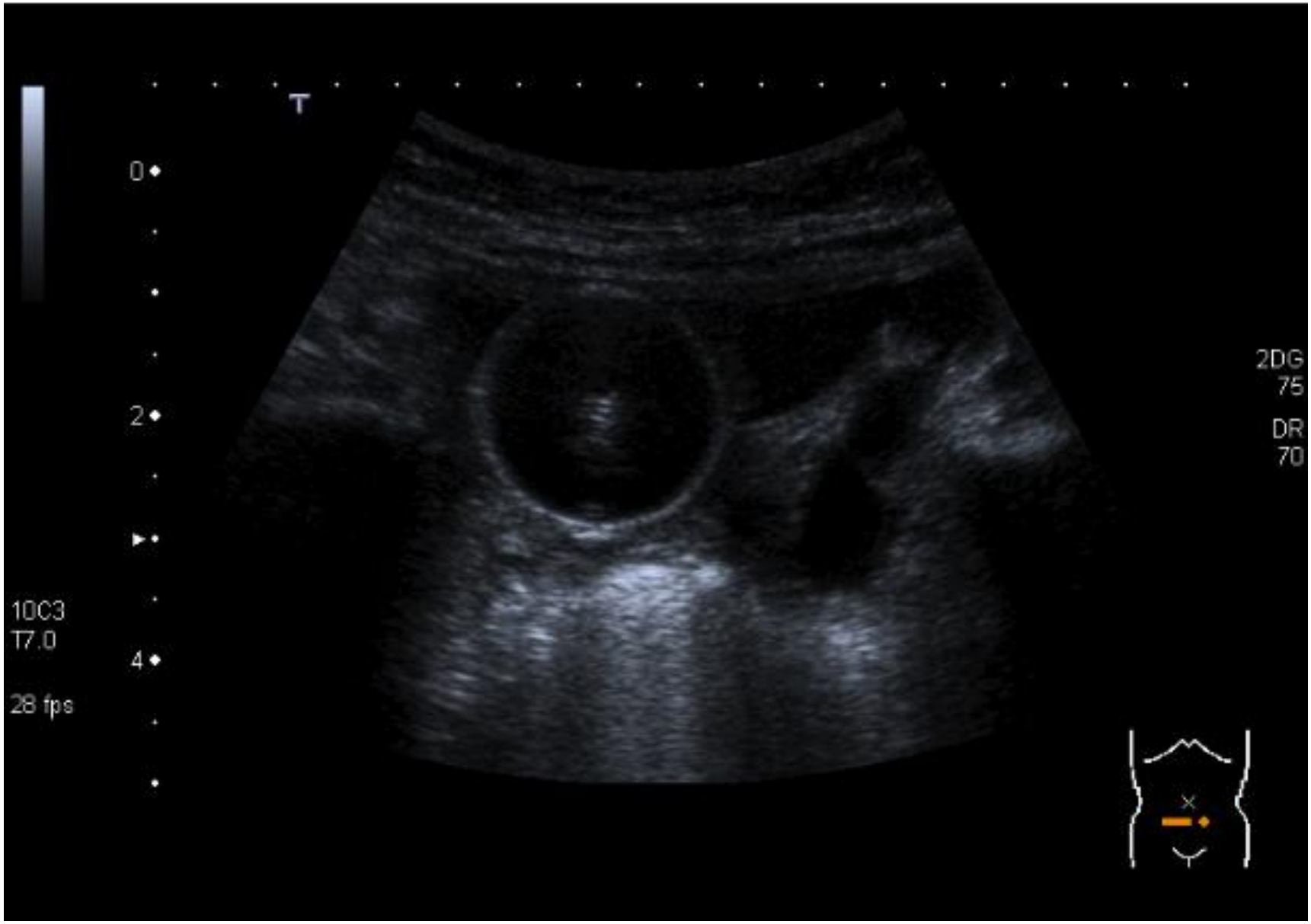


DIVIDED FUNCTION OF LT KIDNEY

UPPER MOIETY = 15%

LOWER MOIETY= 85%


L
POST
R
L
R
L
RPO
R
L
LPO
R
DIVIDED FUNCTION
RIGHT = 59 %
LEFT = 41 %


T
0
2
4
10C3
T7.0
28 fps
2DG
75
DR
70

- Since the ureterocele had recollected
  - Nephrostomy
    - To allow the infection to be treated
    - Achieve weight gain
- Left upper pole heminephrectomy - once clinically stable
- The ureterocele collapsed
- MCUG undertaken to see the degree of reflux

Type 4 RTA

- Early transient – childhood
- Mineralocorticoid deficiency
  - Addison's disease, CAH, Acute GN
- Mineralocorticoid resistance
  - PHA
  - Obstructive uropathies
- Drug induced
  - K sparing diuretics, CNI

Proximal Type 2 RTA

- Hereditary – AD/AR

- Secondary
  - In the context of Fanconi syndrome
  - Acetazolamide, Aminoglycoside, Valproate
  - Associated with other clinical entities

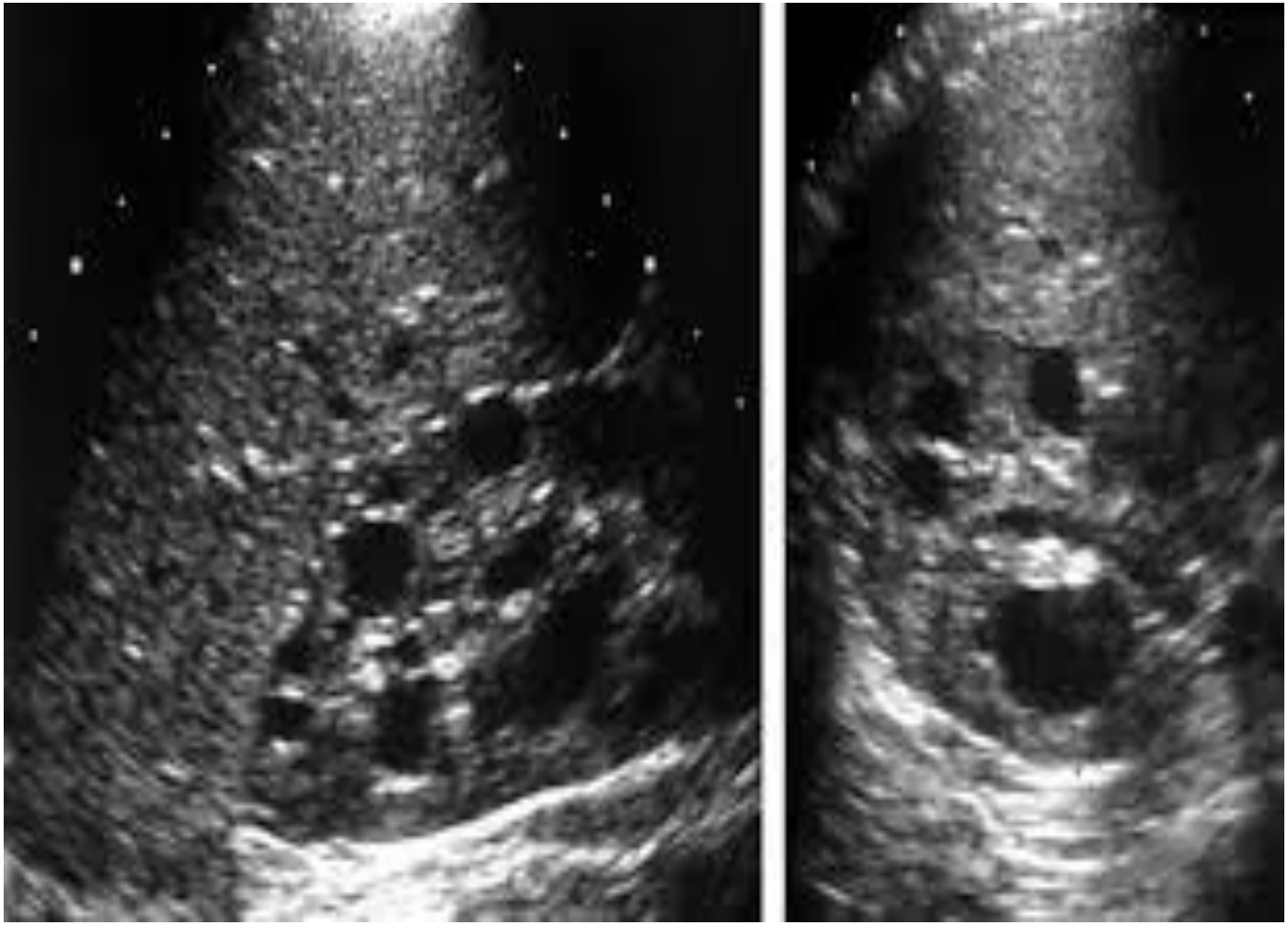
Distal Type 1 RTA

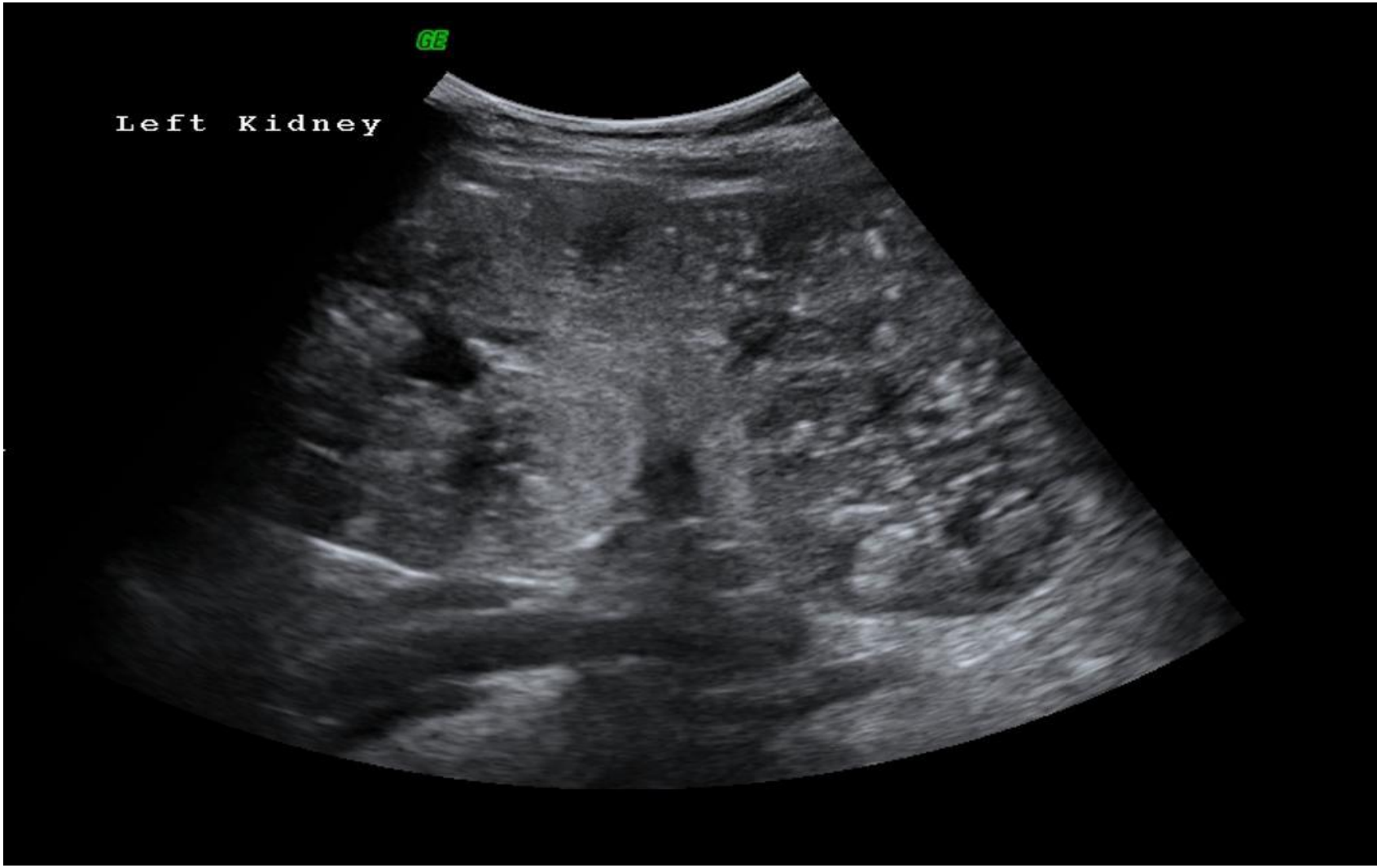
- Primary
  - Sporadic or inherited
  - AD/AR

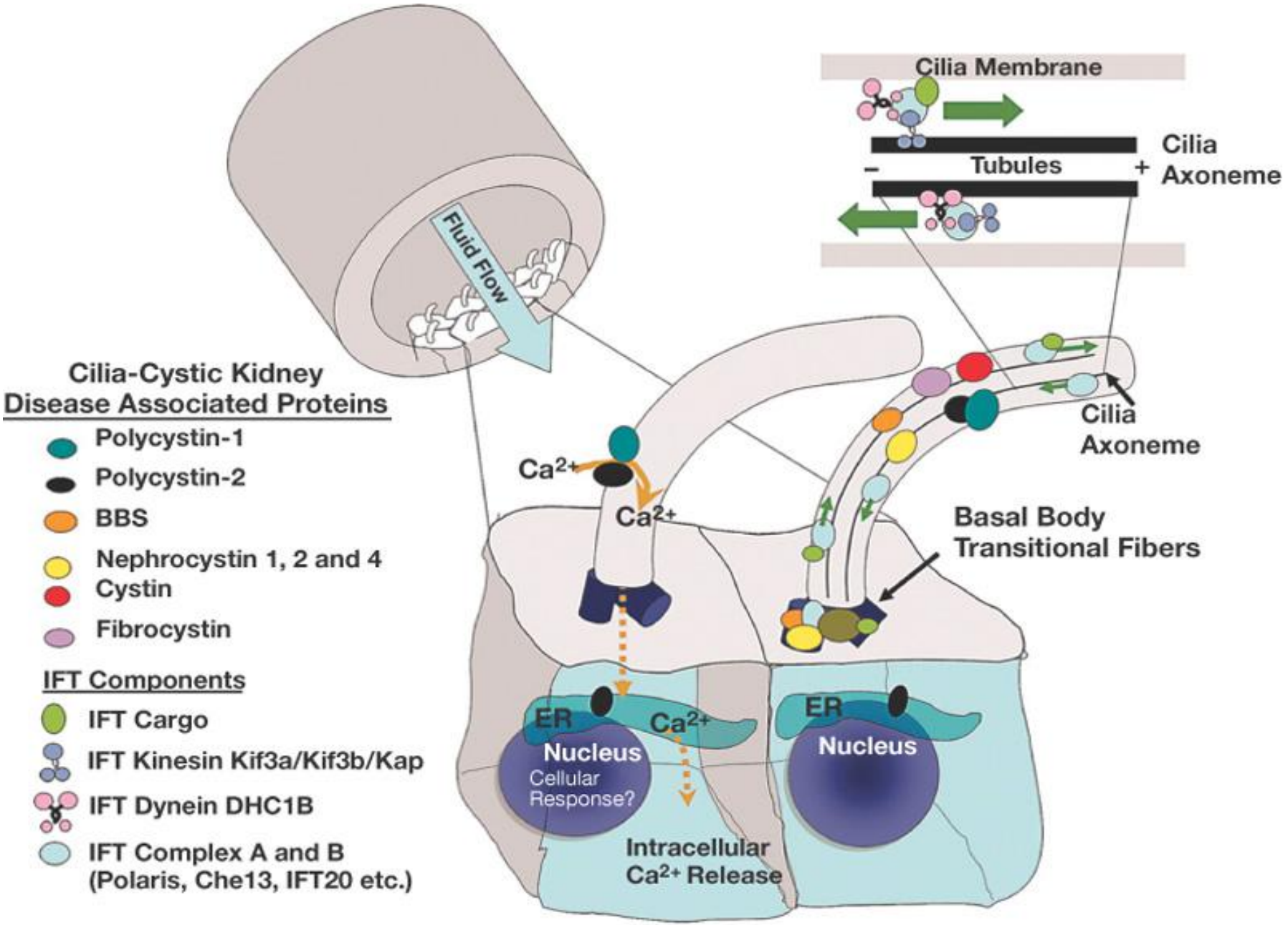
- Secondary
  - Genetic disease – ED syndrome, Wilsons
  - Hepatic cirrhosis, nephrotic syndrome
  - Drugs – Amphotericin B, Lithium.

Renal Tubular Acidosis

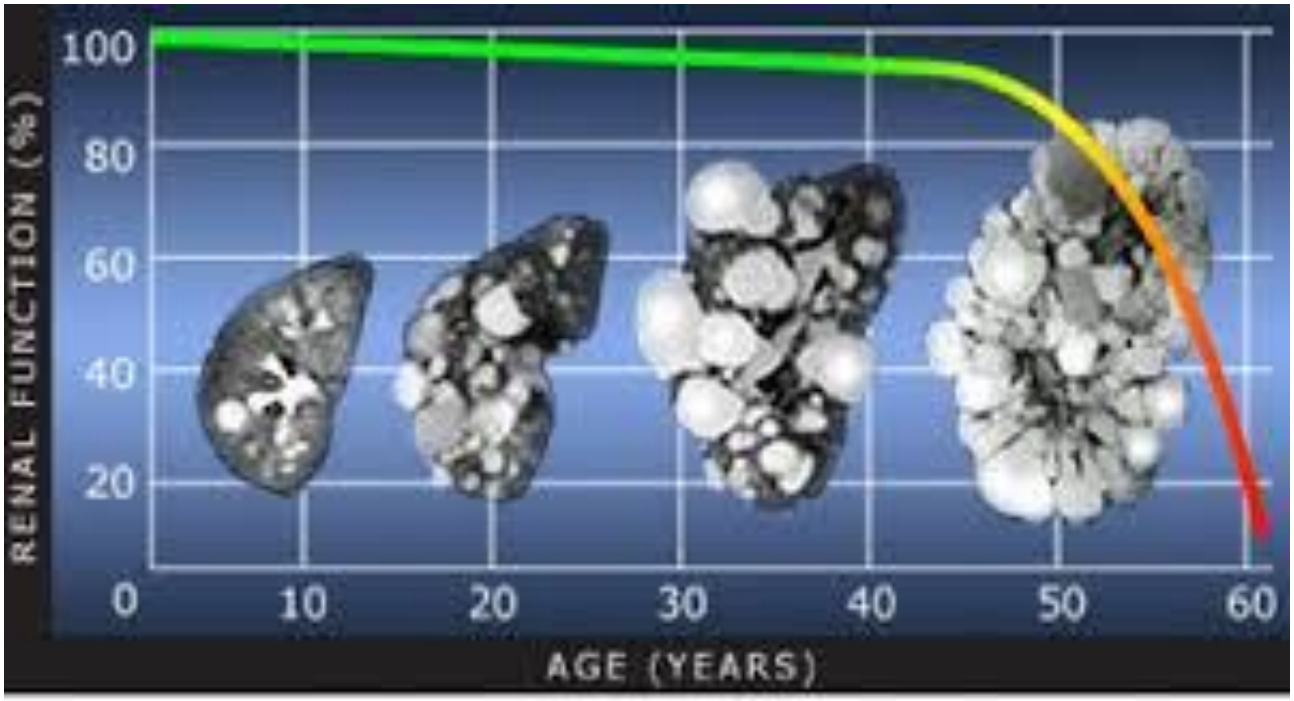
RTA			
	Type 1 (Distal)	Type 2(Proximal)	Type 4
Basic abnormality	Impaired distal acidification	Diminished proximal HCO3 reabsorbtion	Alsosterone reistance or deficiency
Urine pH	<5.5	Lower below 5.5	<5.3
Plasma HCO3	<10 mmol/l	14-20 mmol/l	> 15 mmol/l
Plasma K	Usually normal or reduced	Normal or deduced	Elevated
Other features	Nephrocalcinosis, renal stones	Rickets or osteomalacia	Look for causes




GE
Left Kidney



(From Davenport JR, Yoder BK: An incredible decade for the primary cilium: a look at a once-forgotten organelle. *Am J Physiol Renal Physiol* 289:F1159-69, 2005.)



	ADPKD	ARPKD
Site	All Nephron	CD
Incidence	1:1000	1:10,000 -40,000
Neonatal	+	+++
Oligohydramnios	+	+++
Extrarenal	++	+++ (Caroli's disease)
Mutation	PKD	PKHD
Cyst	Multiple and different shapes and sizes	Small cyst
Treatment	?Tolvaptan	??

Questions