Overview of the nephron

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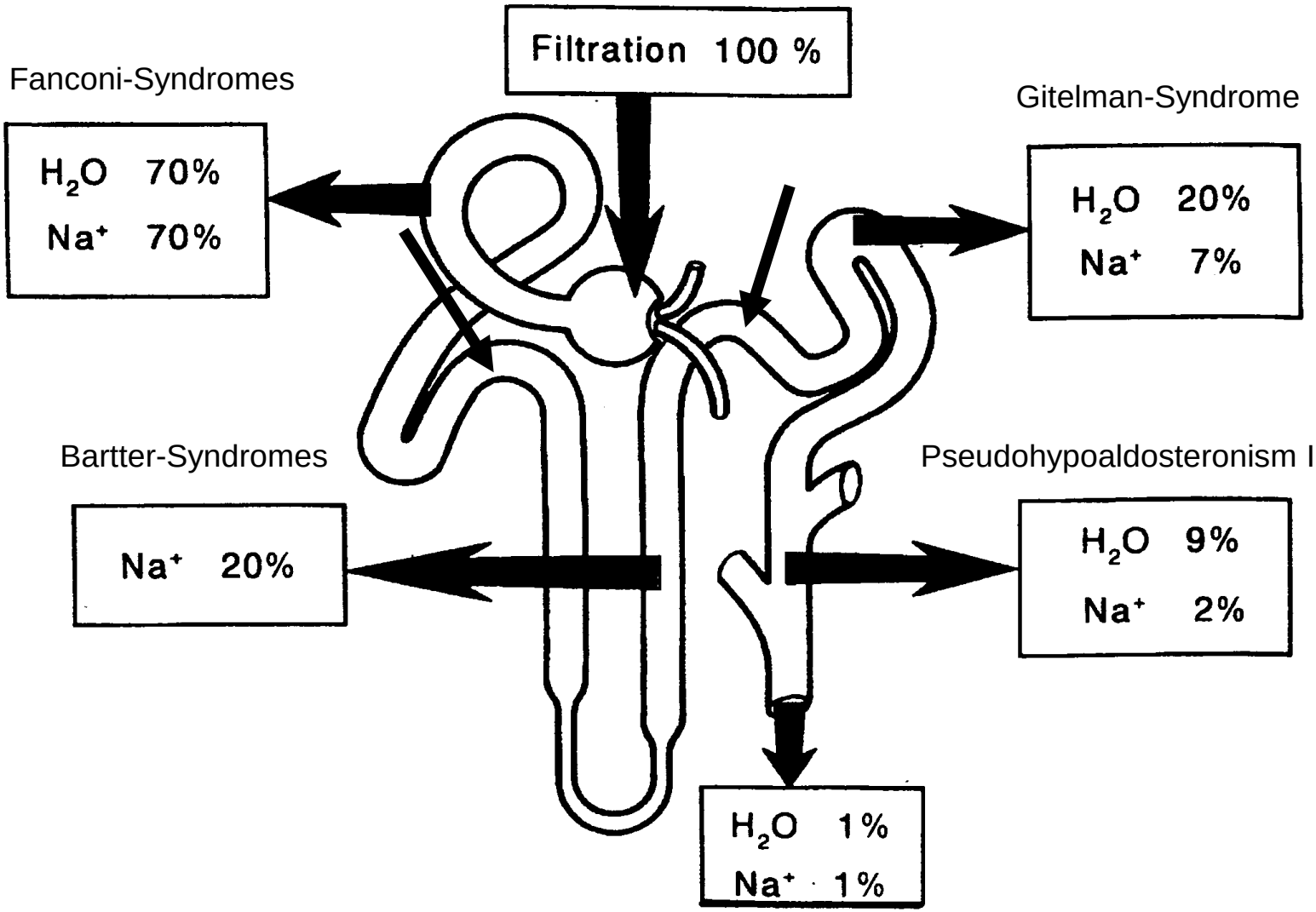
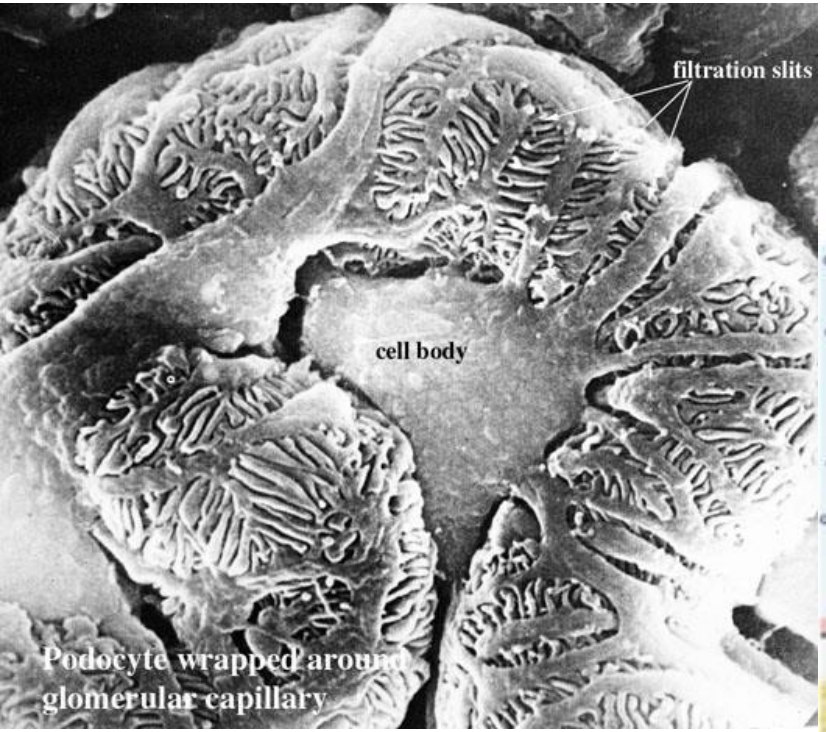
What are the functions of the kidney?

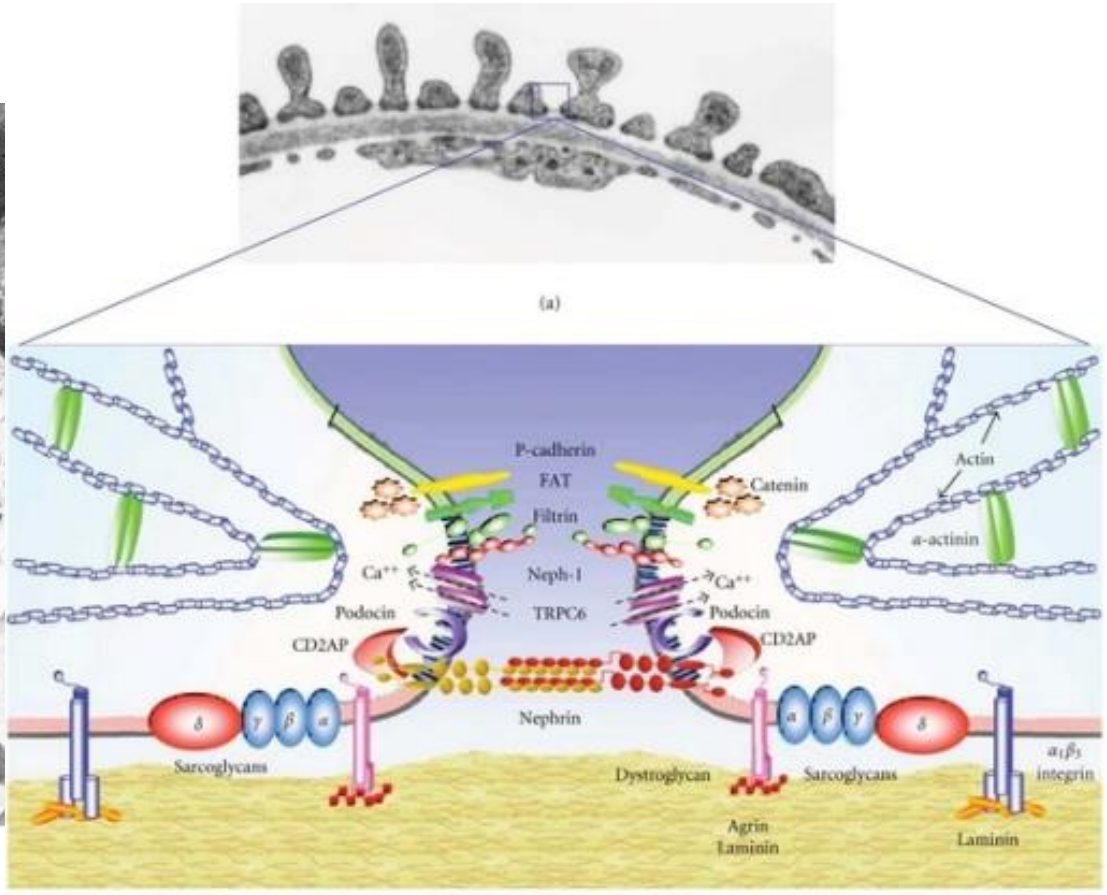
- Elimination of waste products
- Homeostasis
- Endocrine….

Overview of the nephron

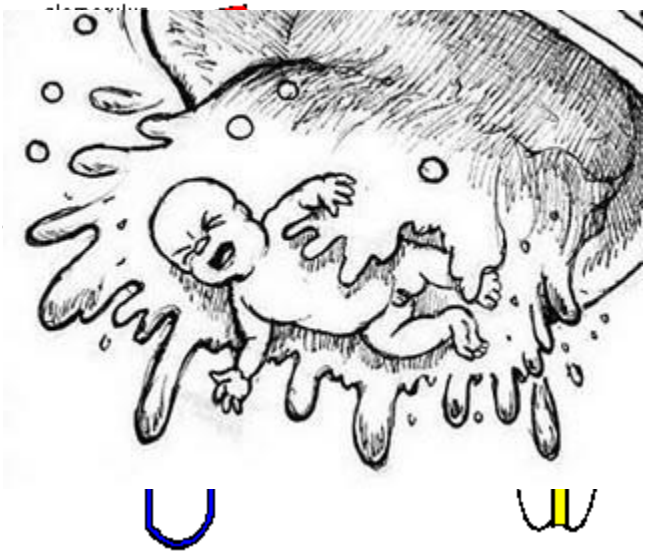


The glomerular view





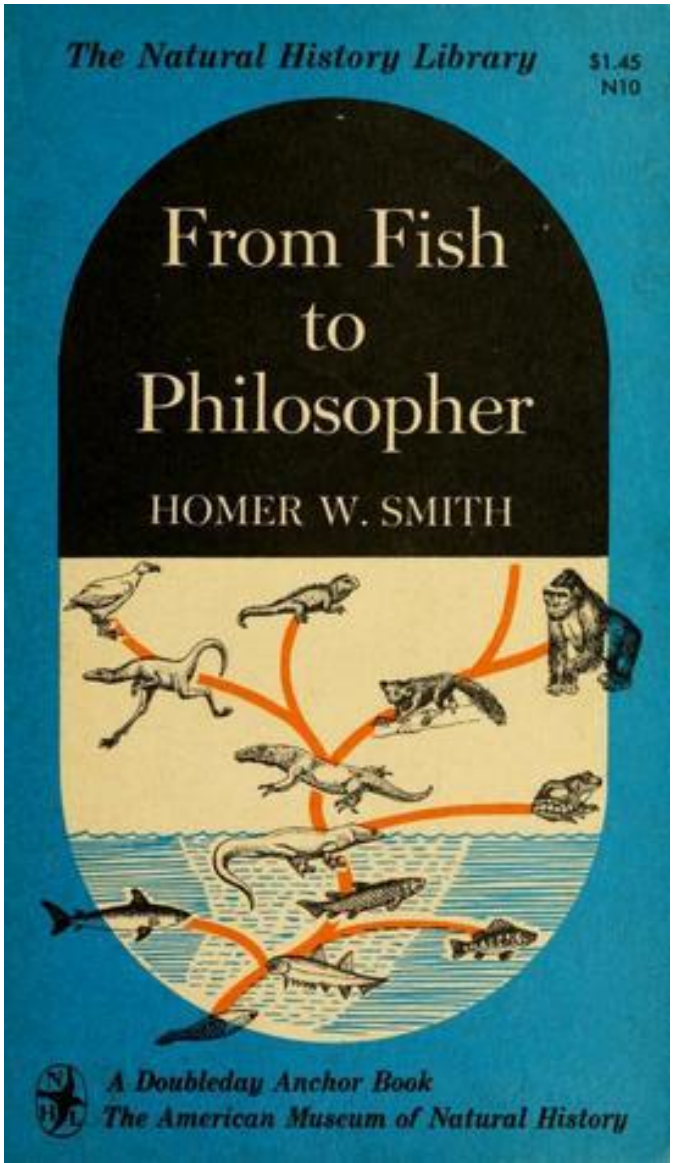
The tubular view



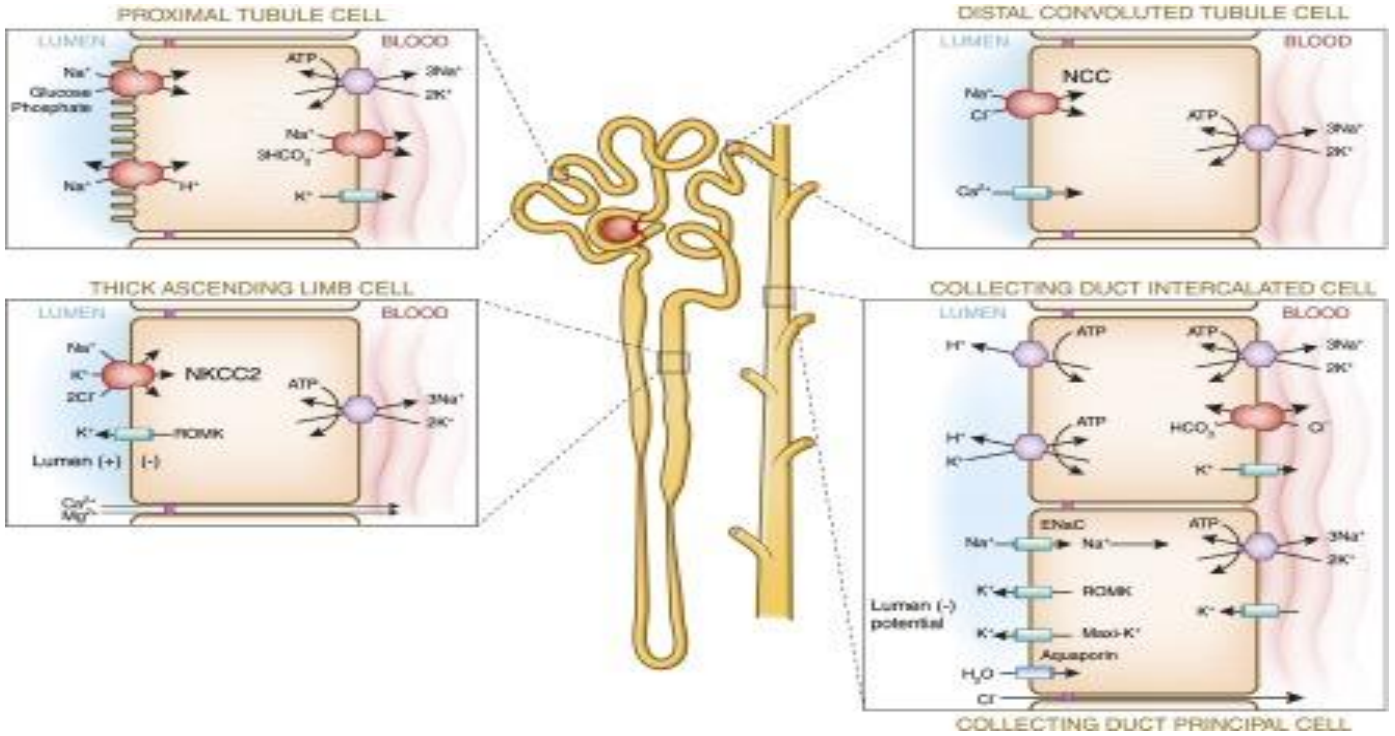
Without the tubules, we would:
1) Pee (and drink) 150 litres per day
2) Pee (and eat) >1 kg of salt each day
3) …..

Tubular function

- Reabsorbs daily:
- ~150 litres of water
- ~22000 mmol Na
- …..
- Maintains “milieu interne”
- Volume
- Acid-base
- Electrolytes



Physiology

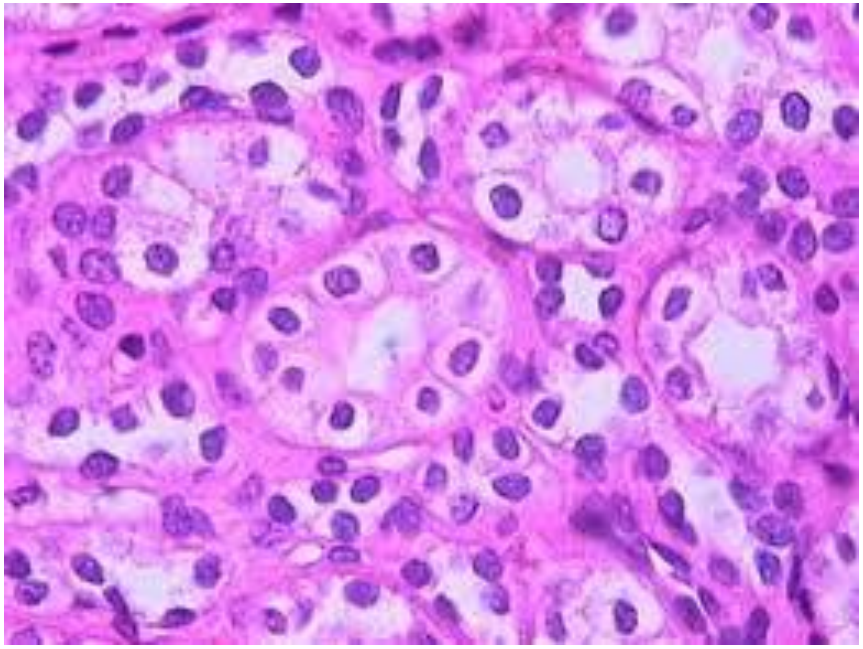


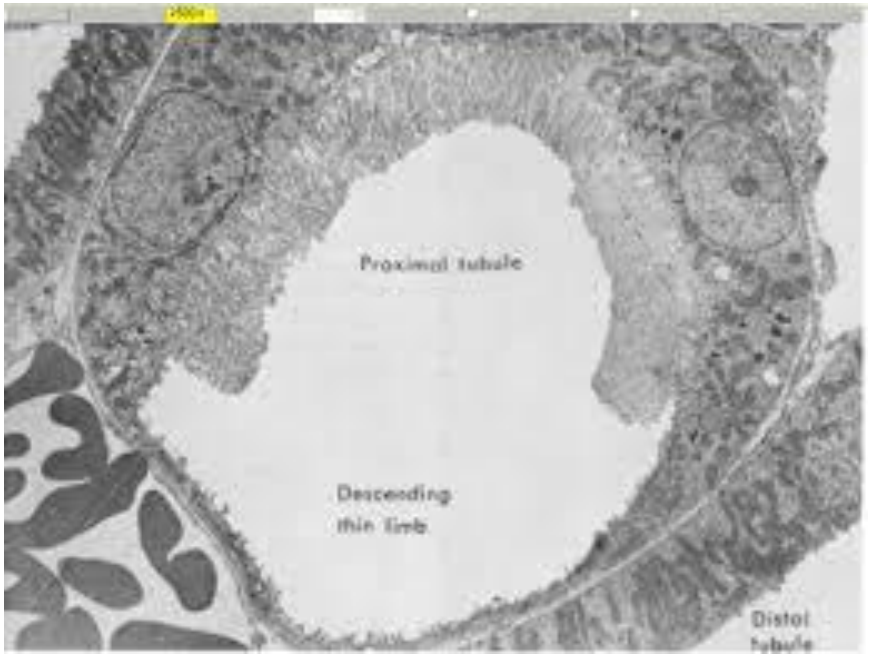
From: Hoenig &Zeidel, CJASN 2014;9(7):1272-1281

Diseases of the proximal tubule

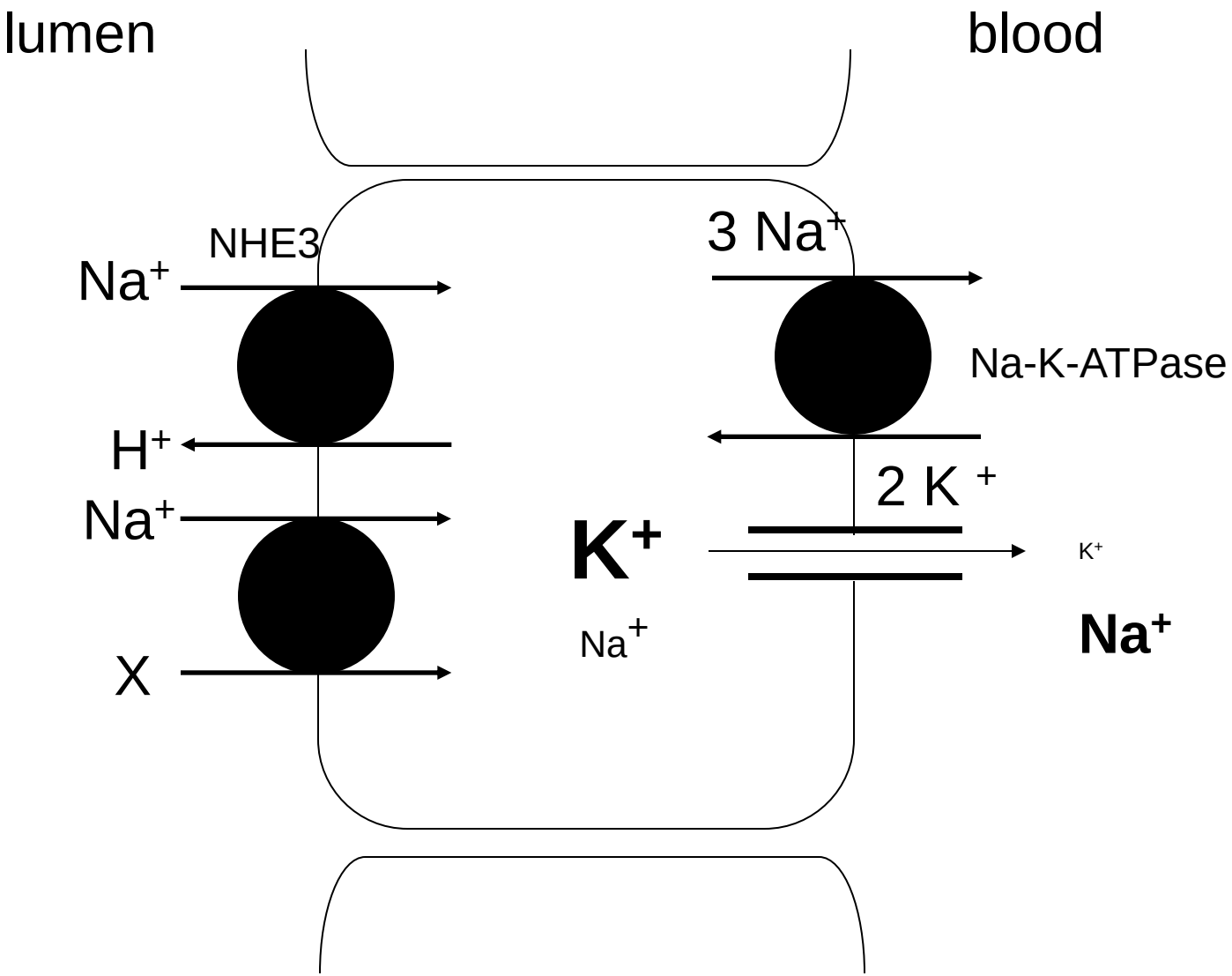
- Renal Fanconi syndrome
- Lowe syndrome/Dent disease
- Proximal RTA
- Immerslund Grasbeck/Donnai-Barrow syndromes
- Specific transporter defects

The proximal tubule

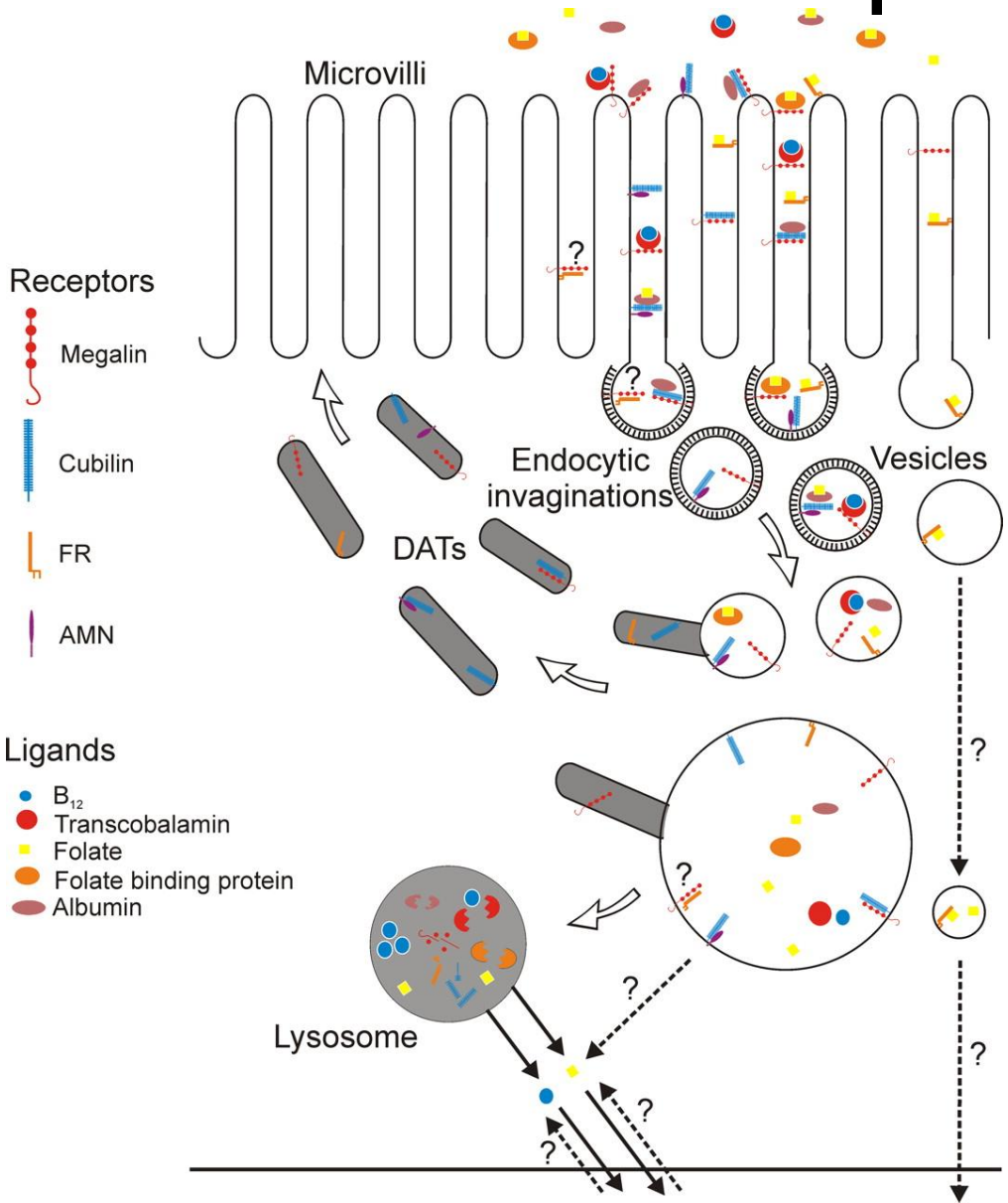


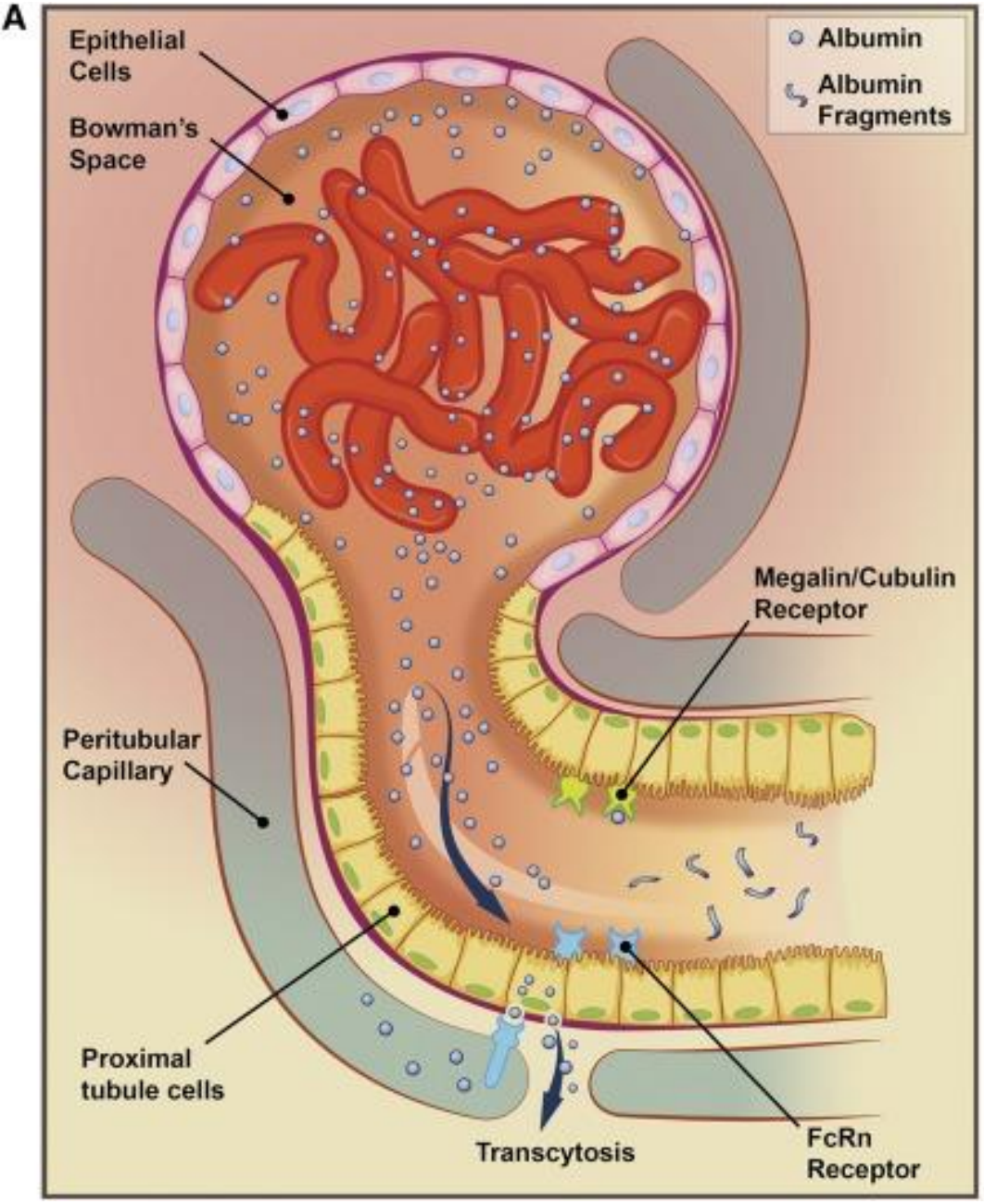


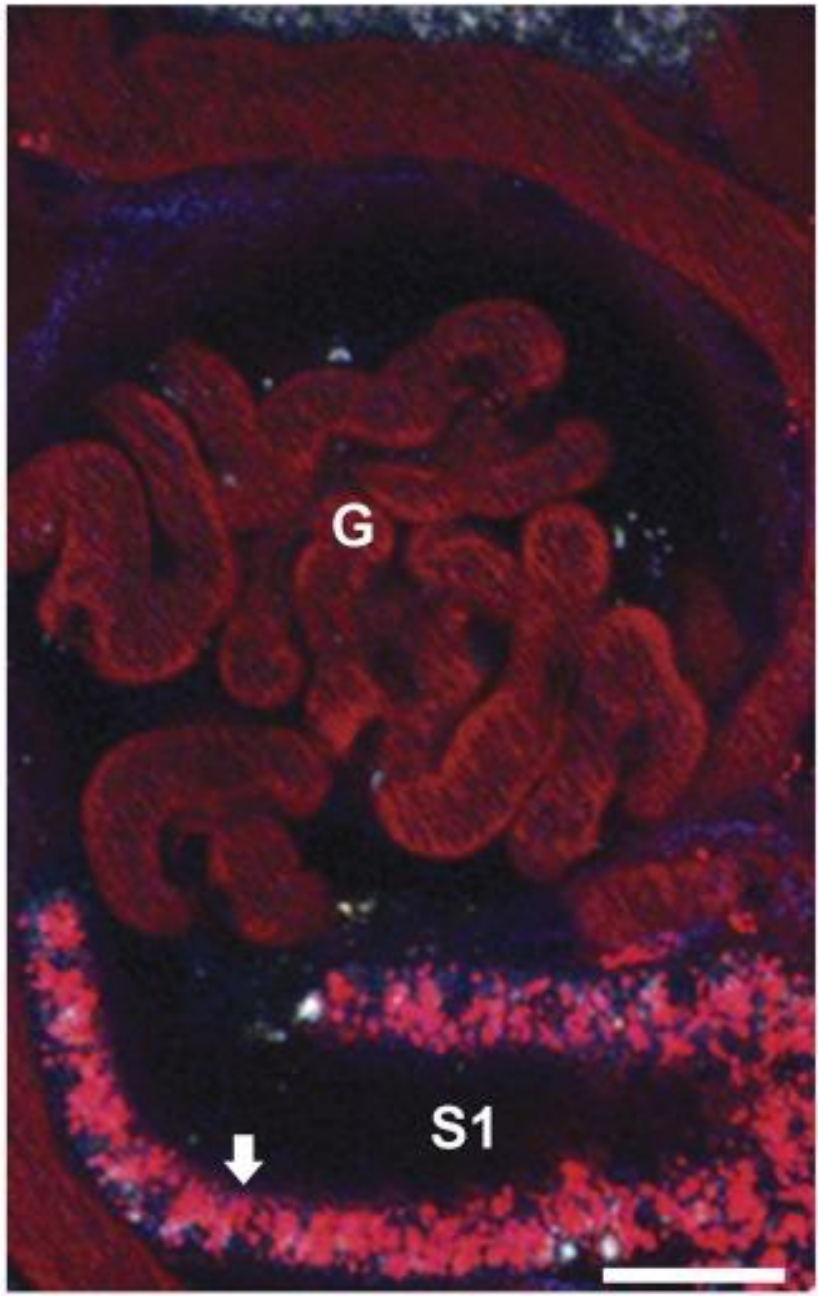
Proximal tubule



Protein-reabsorption




A
Epithelial Cells
Bowman's Space
Albumin
Albumin Fragments
Megalin/Cubulin Receptor
Peritubular Capillary
Proximal tubule cells
Transcytosis
FcRn Receptor


B
G
S1

Proximal tubule

- Work horse: up to 80% of filtered salt and water reabsorbed here
- Exclusive site for reabsorption of phosphate, glucose, LMWP, amino acids, organic acids…..
- Substantial amount of albumin reabsorption (?up to 4 g/day)

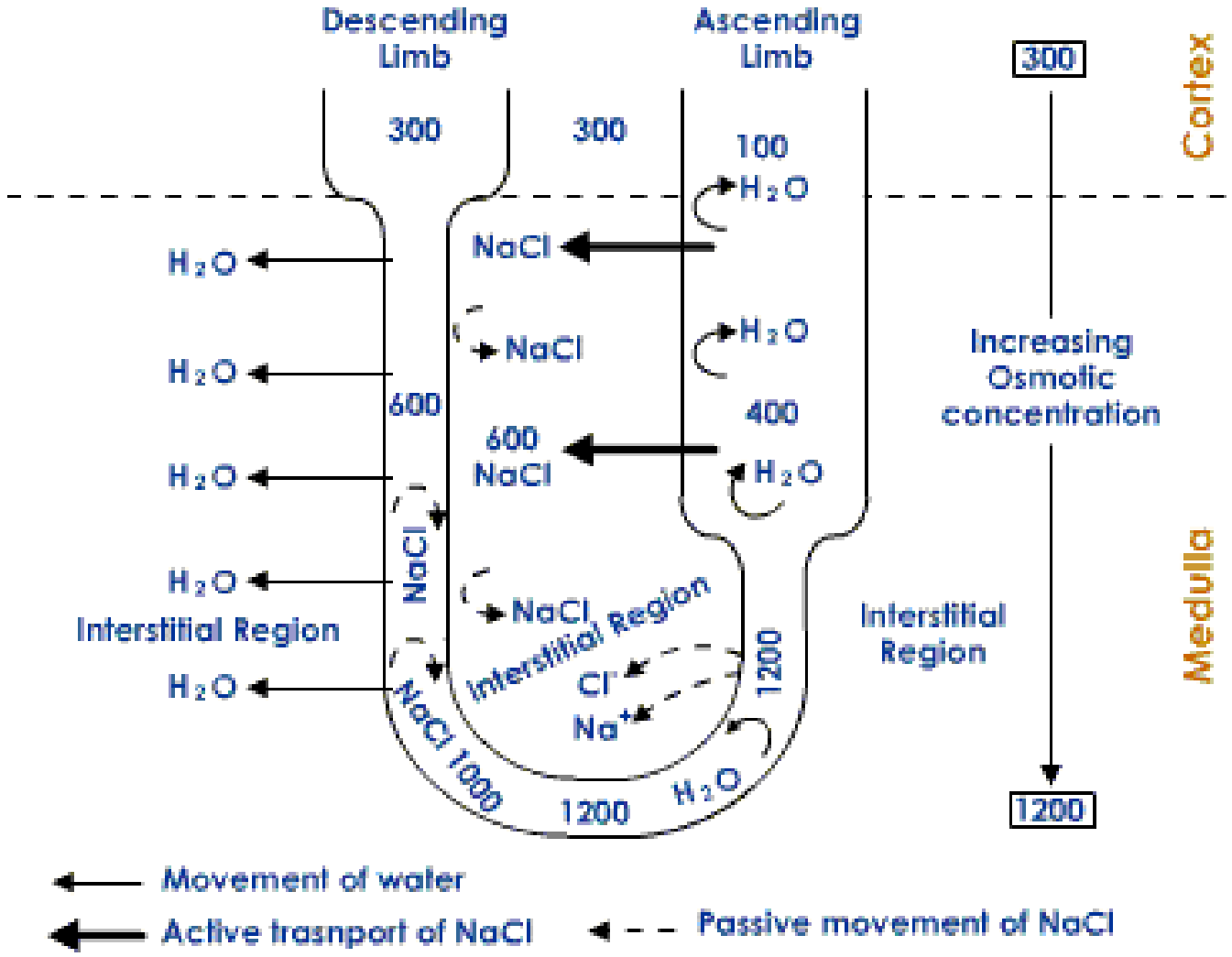
Biochemical Fingerprint (RFS)

	Blood	urine
Na	normal	
K	low	high
Cl	high	
HCO3	low	
Ca	normal	high
Phosphate	low	high
glucose	normal	high
Tub proteins		high

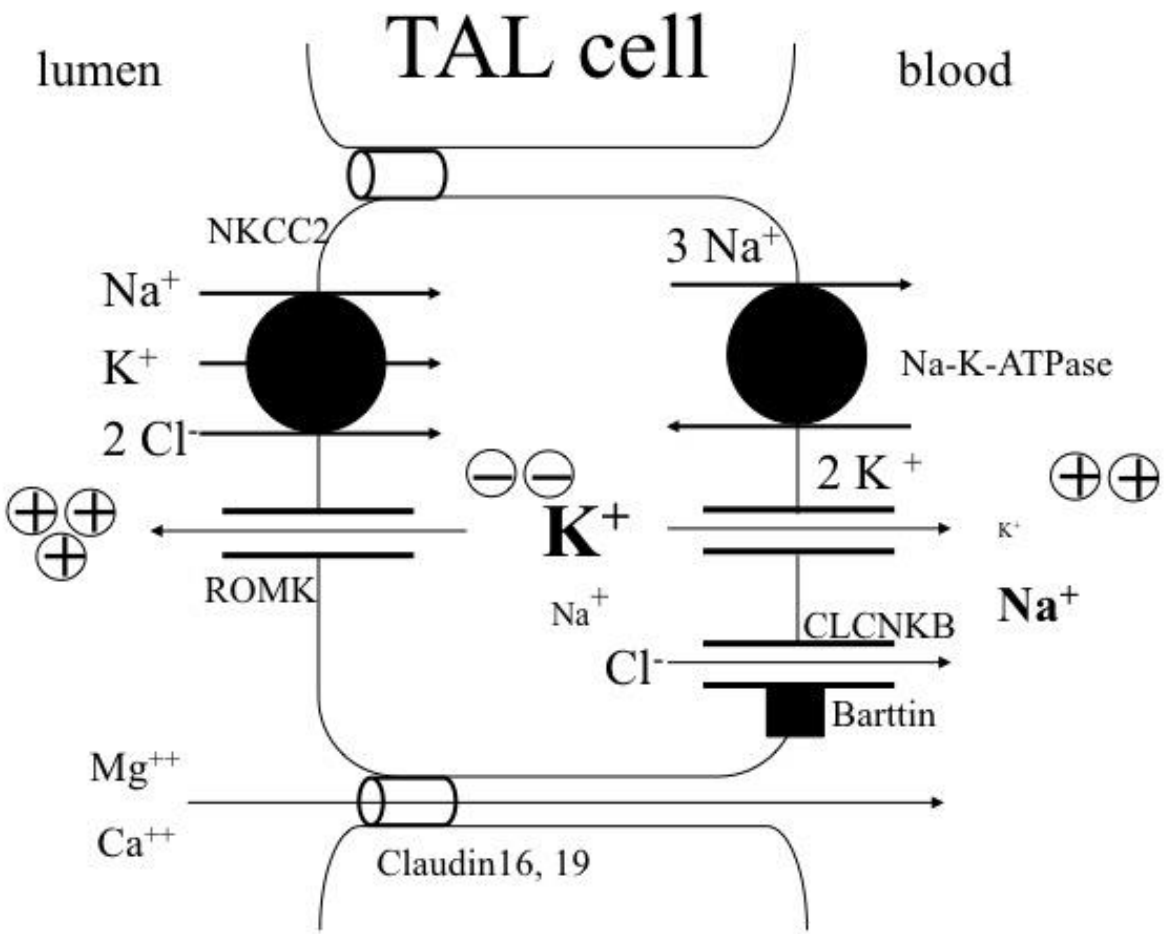
Diseases of the loop of Henle

- Bartter syndrome
- Familial Hypomagnesaemia with hypercalciuria and nephrocalcinosis

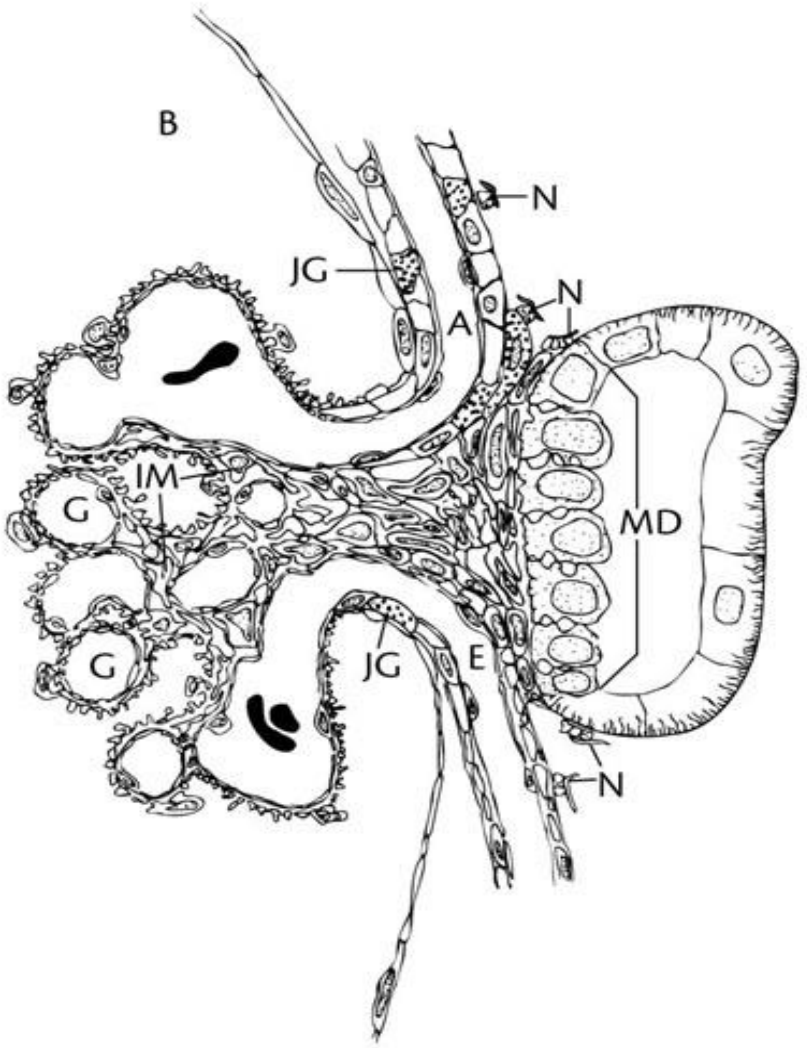
Counter the current



The molecular players



tubuloglomerular feedback



Summary loop of Henle

- Critical for urinary concentration/dilution
- No diseases associated with TDL
- Involved in TGF

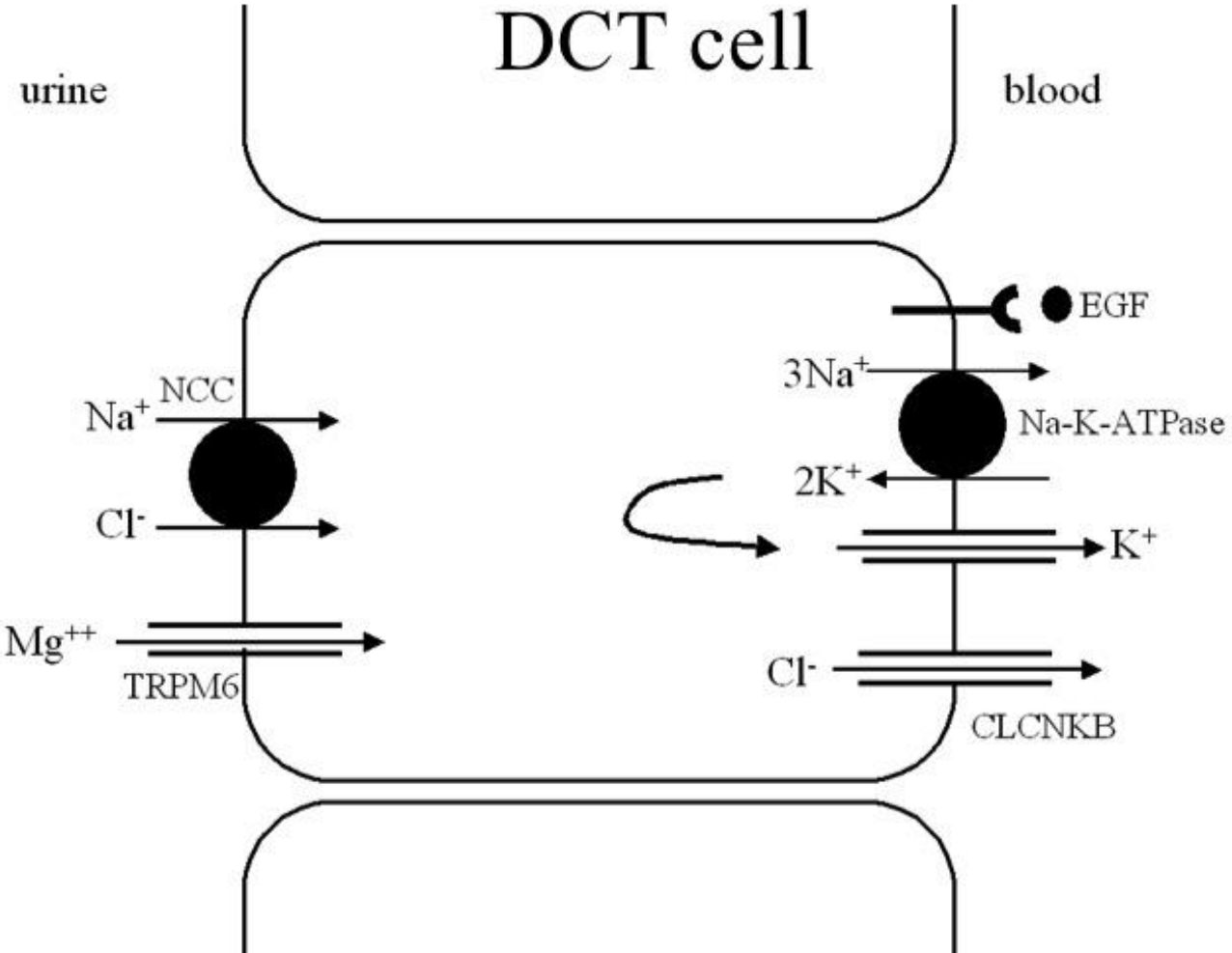
Biochemical Fingerprint (Bartter)

	Blood	urine
Na	normal	
K	low	high
Cl	low	high
HCO3	high	
Ca	normal	high

Diseases of the DCT

- Gitelman syndrome
- EAST syndrome
- Pseudohypoaldosteronism type 2 (PHA2)
- Hypomagnesaemias (HOMG)

The molecular players



Summary DCT

- Key site for regulated Mg reabsoprtion
- K-sensor

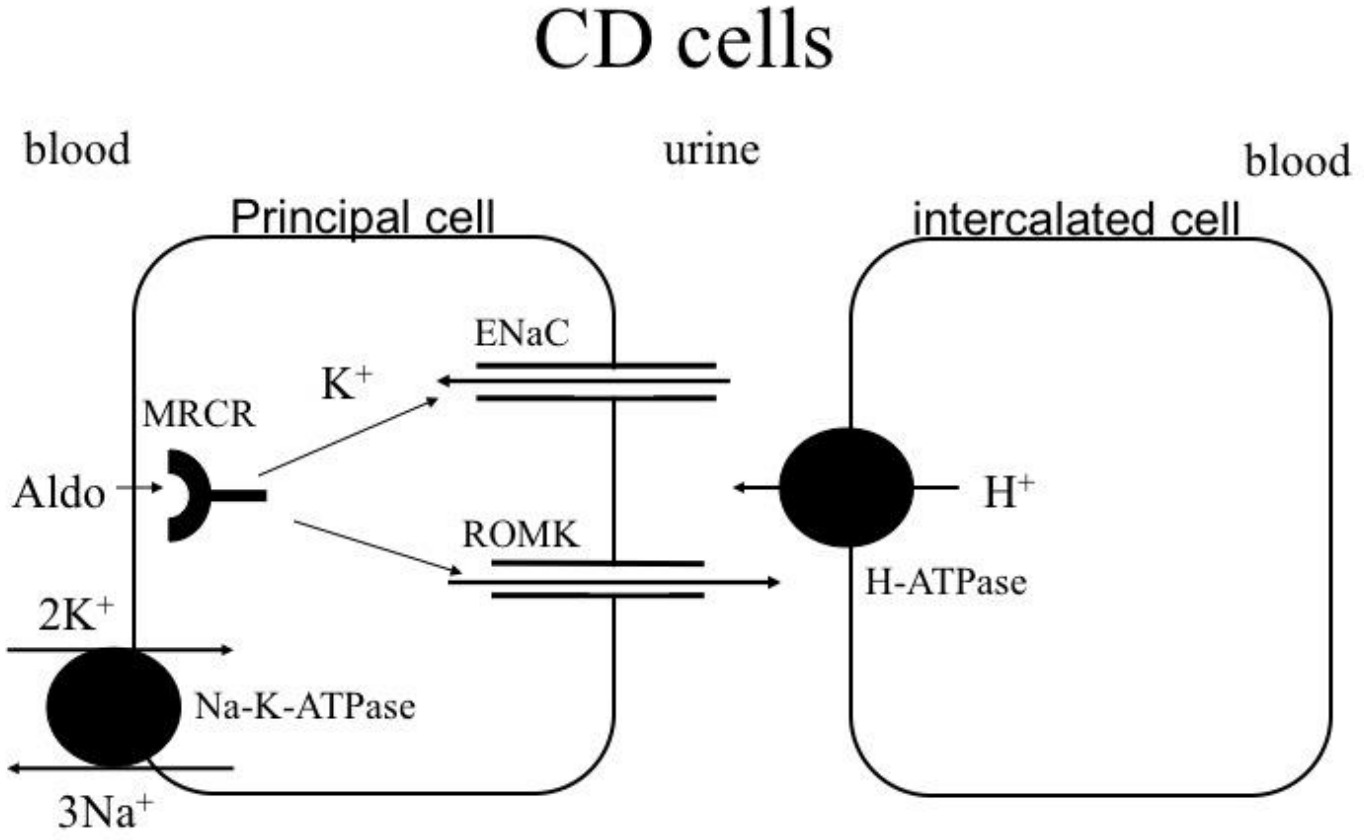
Biochemical Fingerprint (Gitelman)

	Blood	urine
Na	normal	
K	low	high
Cl	low	high
HCO3	high	
Ca	normal	low
Mg	low	high

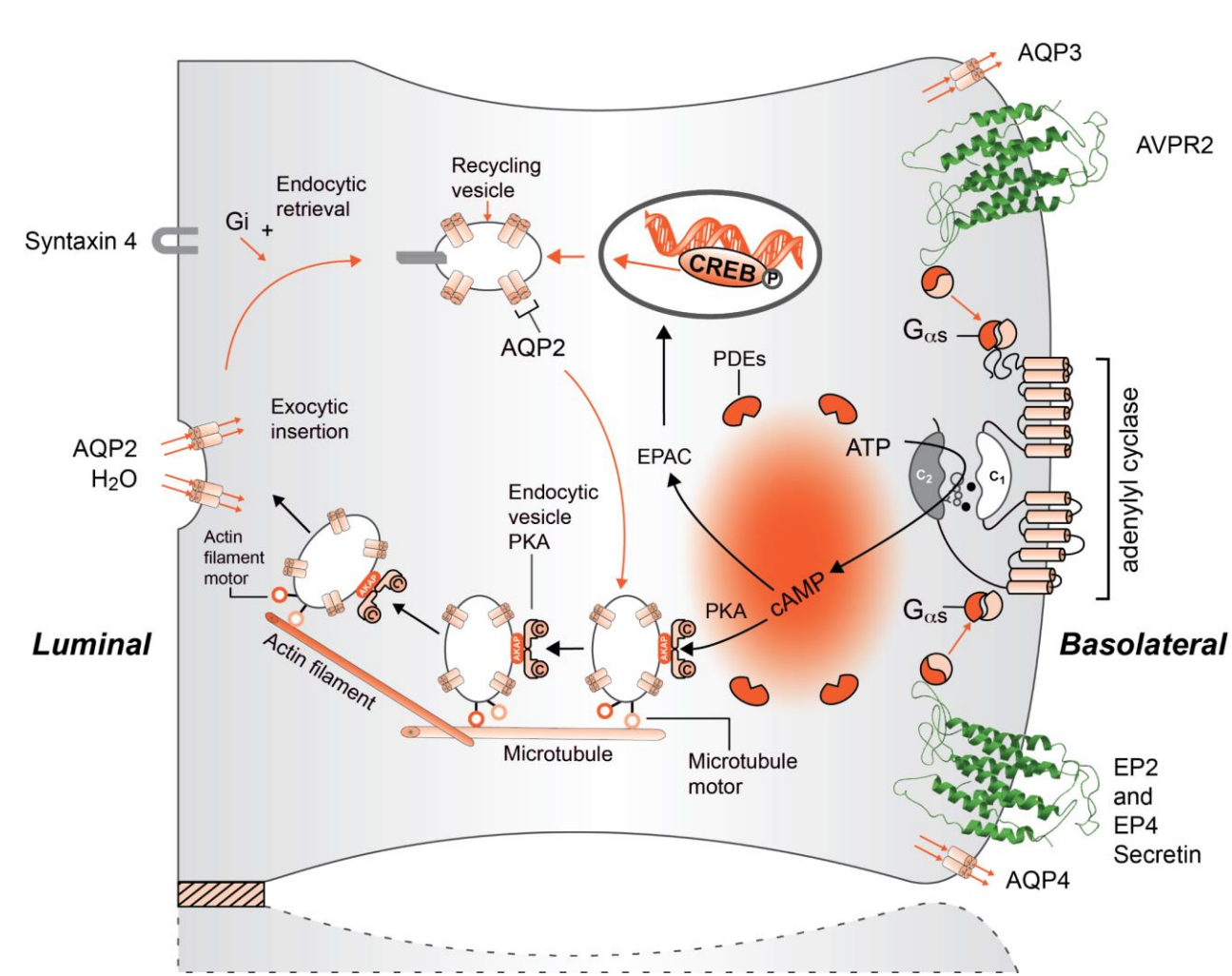
Diseases of the Collecting Duct

- Pseudohypoaldosteronism type 1 (PHA1)
- Nephrogenic Diabetes Insipidus (NDI)
- Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)
- dRTA
- Pendrin syndrome

The molecular players



Urinary Concentration



Summary CD

- Quantitatively, smallest amount reabsorbed
- Highly regulated
- No further compensatory segment
- Critical for urinary acidification
- Critical for urinary concentration

Biochemical Fingerprint (PHA1)

	Blood	urine
Na	low	high
K	high	low
Cl	low	high
HCO3	low	

Conclusion

- The glomeruli ”waste” ~150 litres of water and solutes each day
- A whole orchestra of highly specialised transport molecules enables reabsorption of this primary filtrate
- Based on anatomic and molecular characteristics, specific tubular segments can be distinguished
- Enables homeostasis of volume, water, acid-base and electrolyte homoeostasis

Case 1

- 10-day old baby referred by visiting nurse because of weight loss (2.275 kg, birth weight: 2.280)
- Pregnancy complicated by IUGR
- Born at 37+3 weeks
- Family history: previous pregnancy complicated by maternal hypertension. Two healthy siblings. Parents are first cousins

Laboratory Investigations

	Blood	urine
Na [mmol/l]	133	
K [mmol/l]	7.4	21
Cl [mmol/l]		
HCO3 [mmol/l]	16	
Creatinine [mcmol/l]	40	600
pH	7.25	
Osmolality [mmol/l]	278	128

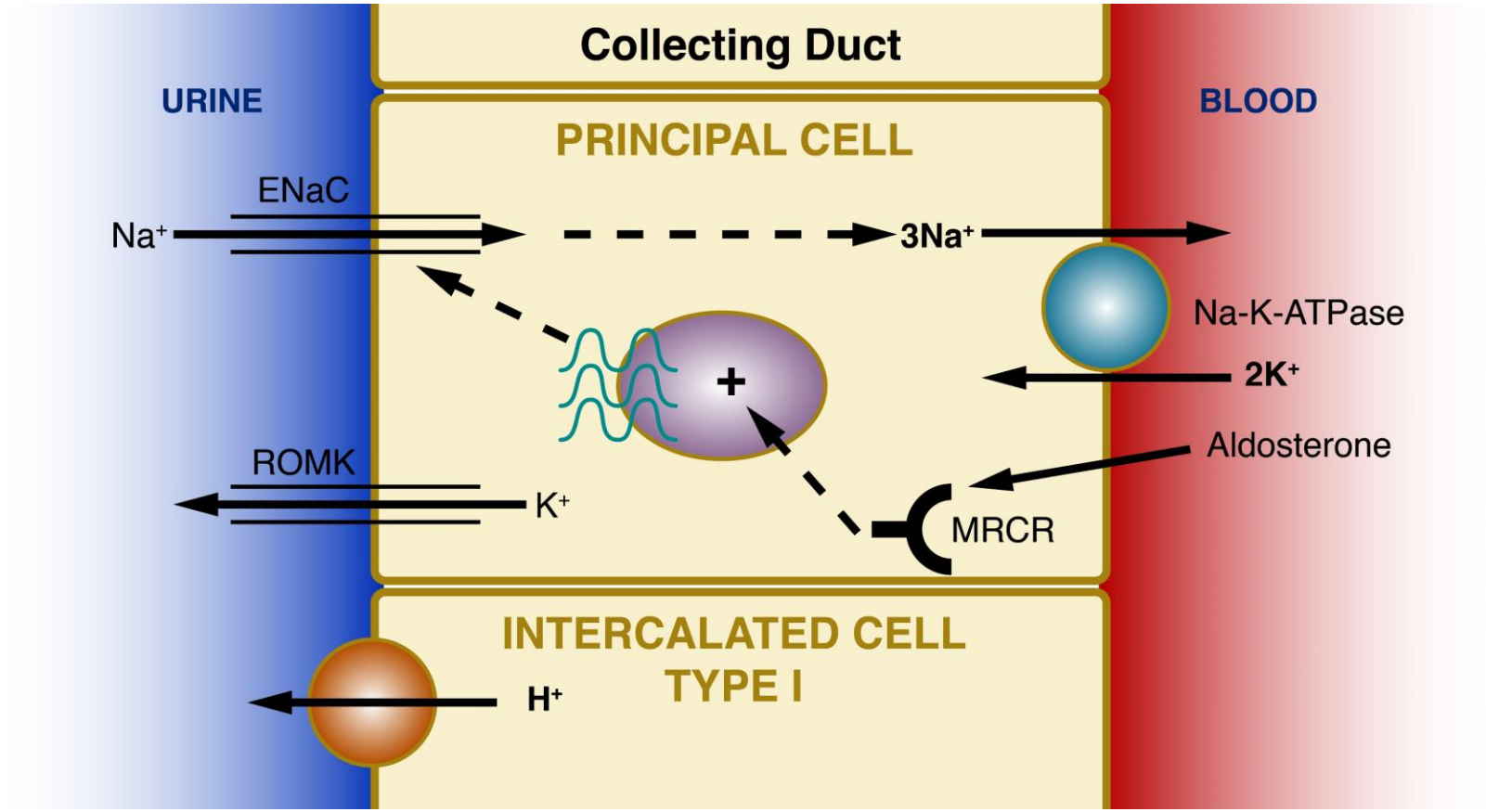
What is your differential diagnosis?

- Congenital Adrenal Hyperplasia
- Pseudohypoaldosteronism

Which part of the tubule is most affected?

- Proximal (PT)
- Thick Ascending Limb of Henle's loop (TAL)
- Distal Convoluted and Connecting Tubule (DCT)
- Collecting Duct (CD)

K-excretion


Collecting Duct
URINE
BLOOD
PRINCIPAL CELL
ENaC
Na+
3Na+
Na-K-ATPase
2K+
+
Aldosterone
ROMK
K+
MRCR
INTERCALATED CELL
TYPE I
H+

Assessing distal K^+ secretion

	formula	low	high
FEK	$\frac{(K_U / Crea_U)}{(K_P / Crea_P)}$	<10%	>30%
TTKG	$\frac{(K_U / osmo_U)}{(K_P / osmo_P)}$	<4	>8

	K	crea	osm	
plasma	7.4	40	278	FEK: 14%
urine	21	800	128	TTKG: 6.2

Initial Treatment

- Initial bicarbonate bolus of 8 mmol/l (“half correction”)
- Milk feed stopped
- Iv 10% glucose @150 ml/kg/d given
- NaCl 10 mmol (3 mmol/kg/d) added to iv fluids
- Fludrocortisone 75 mcg

Subsequent course

- Commenced oral Na-bicarbonate 13 mmol/kg/d
- Na-resonium 450 mg three times daily
- Develops significant hypertension (systolic BP >100 mmHg), but persistent hyperkalaemia (>6 mmol/kg)

- What now?

Transfer to GOSH

- Nabic reduced
- Na-resonium changed to Ca-resonium
- Feed changed to Renastat (low-K)

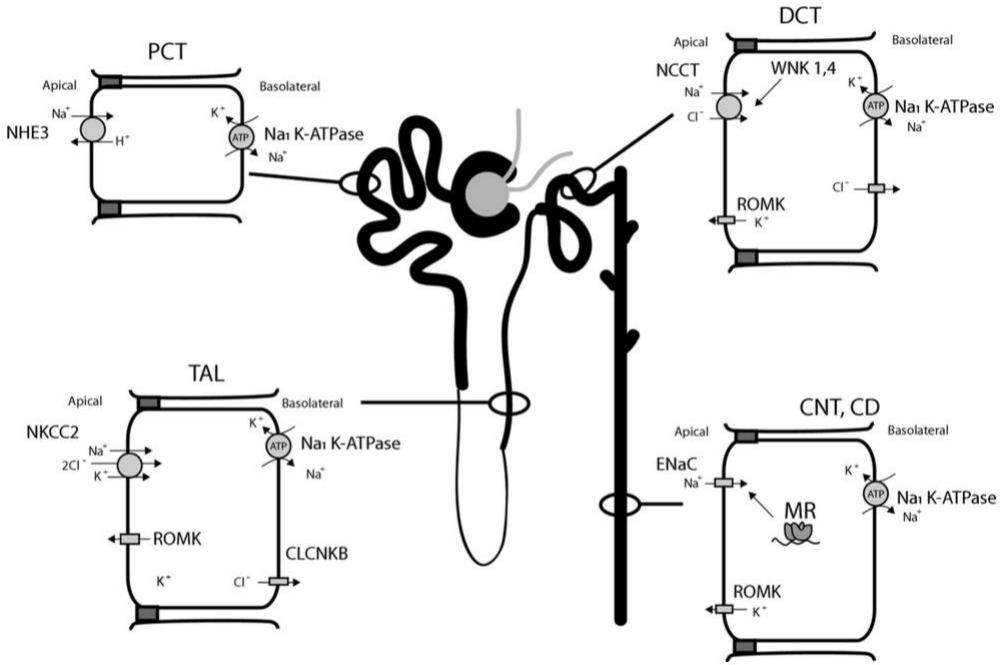
- => persistent hypertension (up to 130 mmHg)

Further investigations

- Normal synacthen test, urinary steroid profile => CAH excluded
- Initial aldosterone level: 3480 pmol/l (normal for neonate: <2000), repeat level (on treatment: 758 pmol/l), renin:<0.3 nmol/l
- Normal renal US, no evidence of UTI

- Diagnosis?

PHA2 (Gordon syndrome)

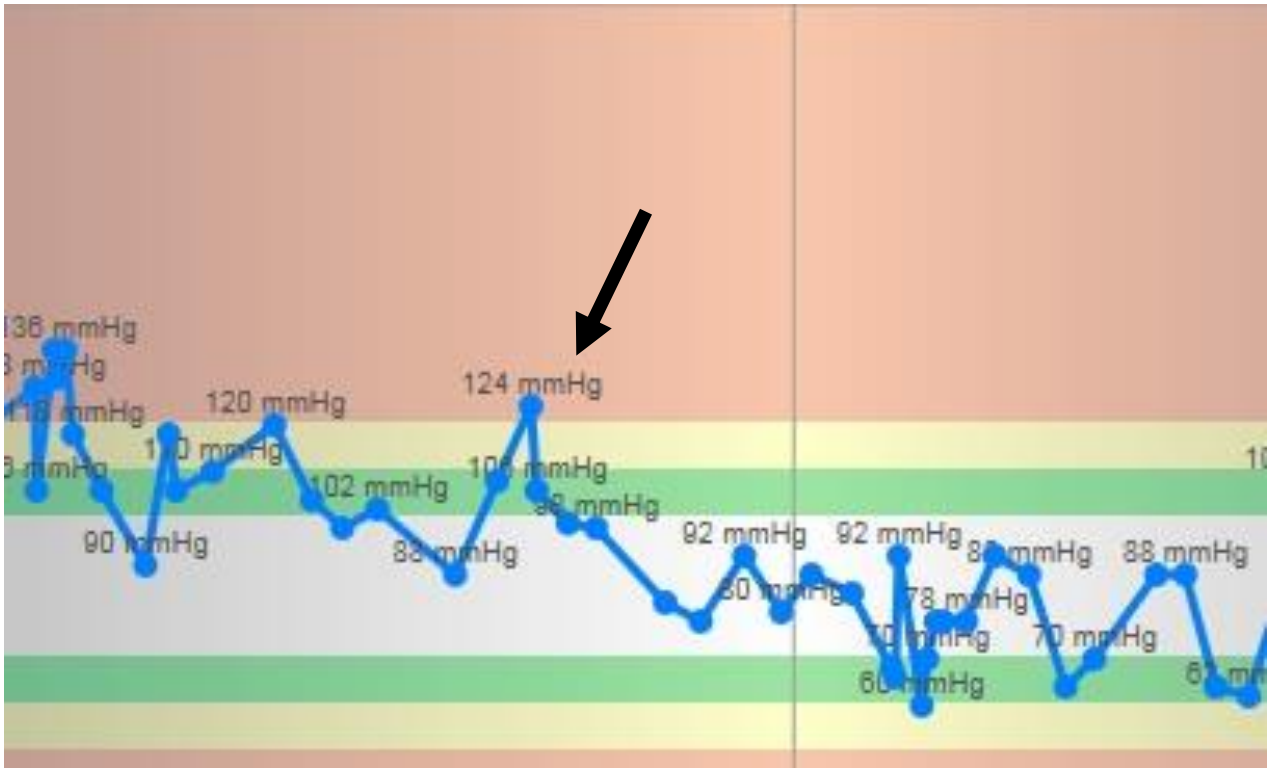


Genetics: homozygous splice site mutation in KLHL3

Trial of Hydrochlorothiazide

	before	On thiazide
Plasma		
Na [mmol/l]	133	134
K [mmol/l]	6.6	3.2

Blood pressure



Case 2

- Second child of consanguineous parents (1º cousins)
- Pregnancy complicated by mild polyhydramnios
  => no intervention required
- Born full term, birth weight 3 kg, discharged home after 2 days. Avid breastfeeder, no diarrhoea
- Travels with parents from 6 - 10 weeks of age

Presentation

- Upon return noted to have failure to thrive
- Exam: “wasted” appearing. Little spontaneous movements, recurrent apneas
  BP: 74 mmHg syst., Pulse: 122/min;
  O2 sat: 84%

Biochemistries

Parameter	Serum	urine
Na (mmol/l)	120	49
K (mmol/l)	1.0	19
Cl (mmol/l)	43	64
HCO_3 (mmol/l)	55	
creatinine (mmol/l)	0.033	0.9
Osmolality (mosm/kg)	251	179
pH	7.62	

Diagnosis?

- Polyhydramnios
- Hypokalaemic alkalosis
- high urinary chloride

  => **Bartter syndrome**: genetic defect in salt reabsorption in TAL
- Homozygous deletion of CLCNKB