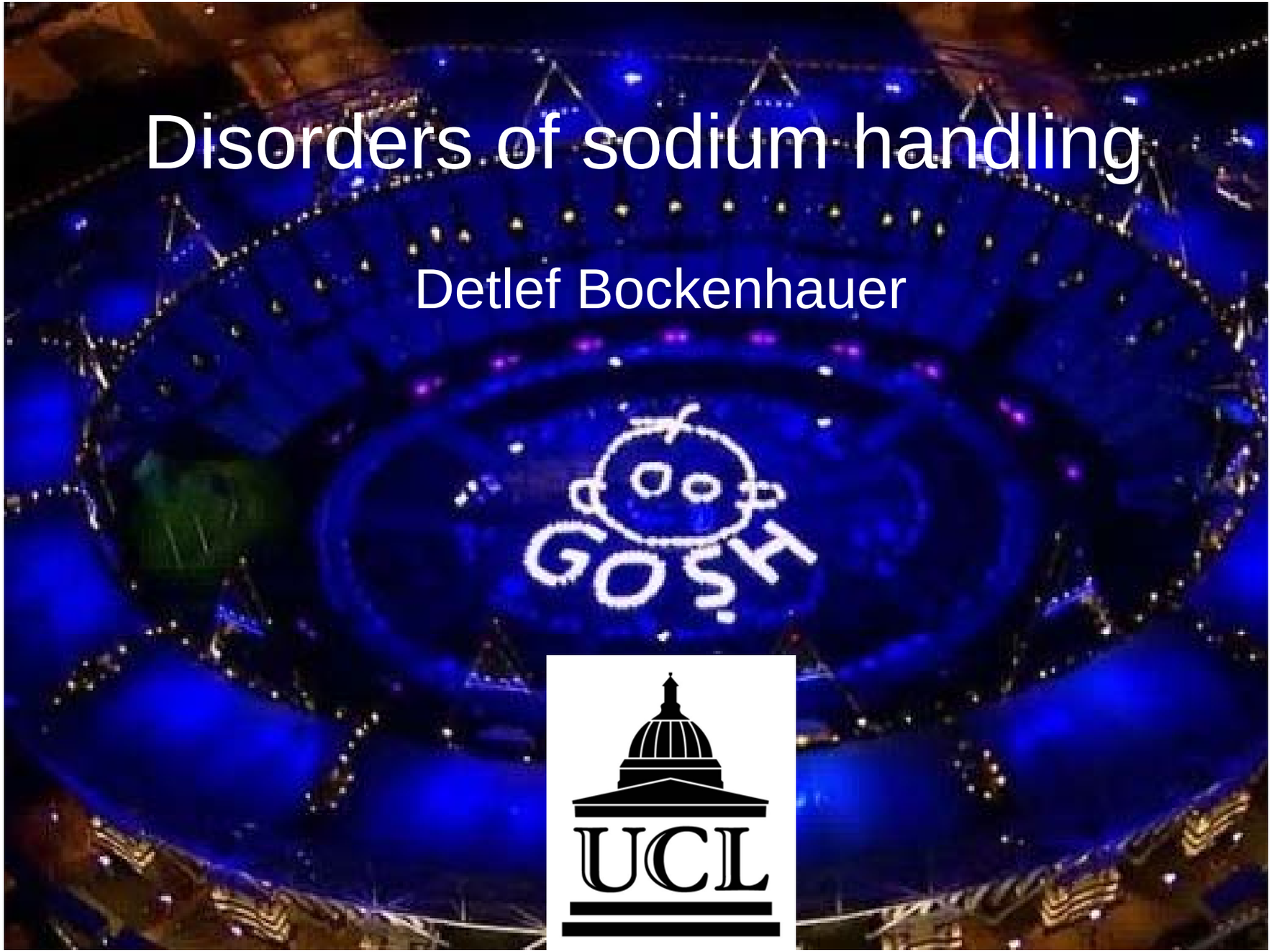
Disorders of sodium handling

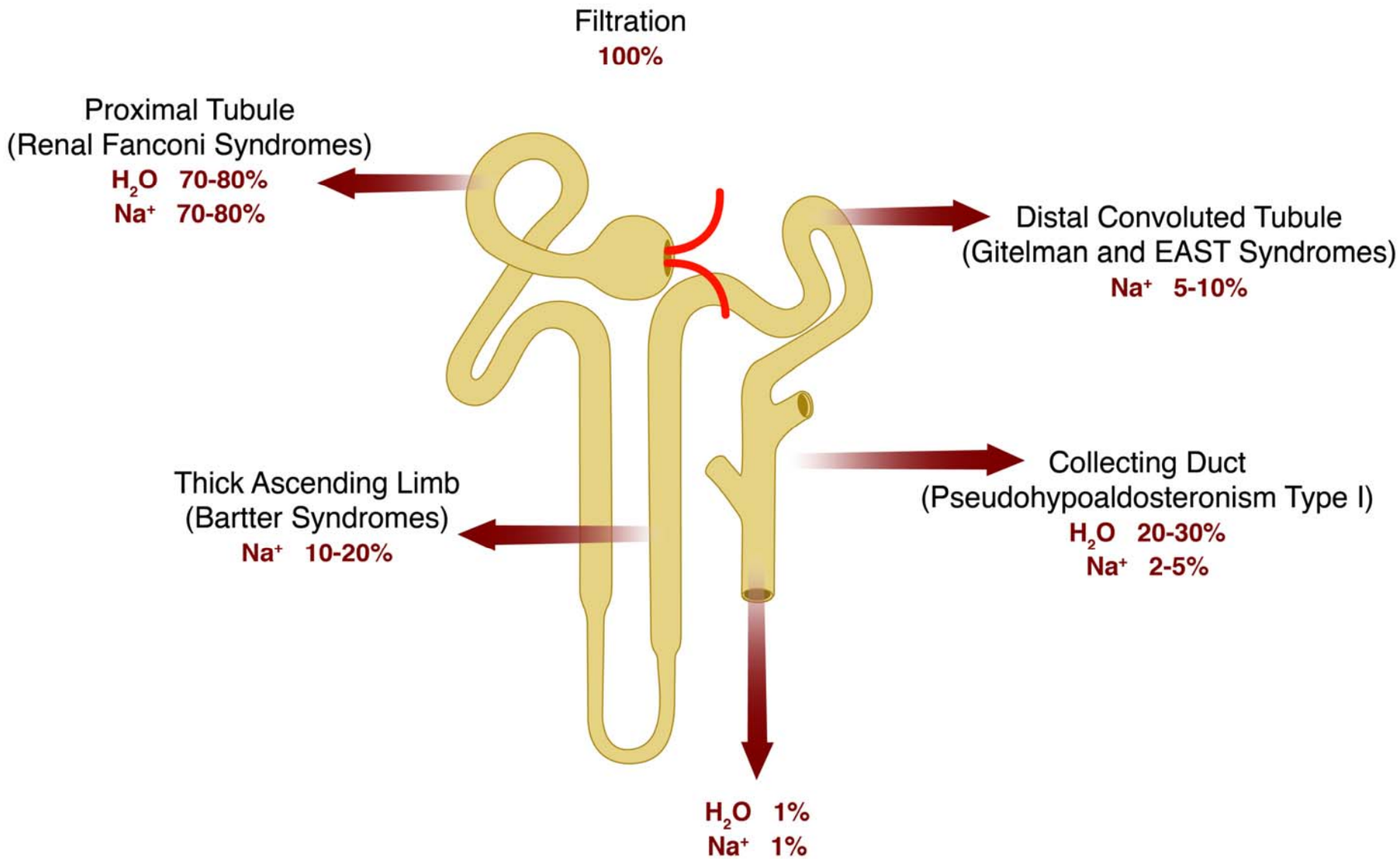
Detlef Bockenhauer



Objectives

- Physiology of sodium transport
- Clinical consequences of disturbed transport

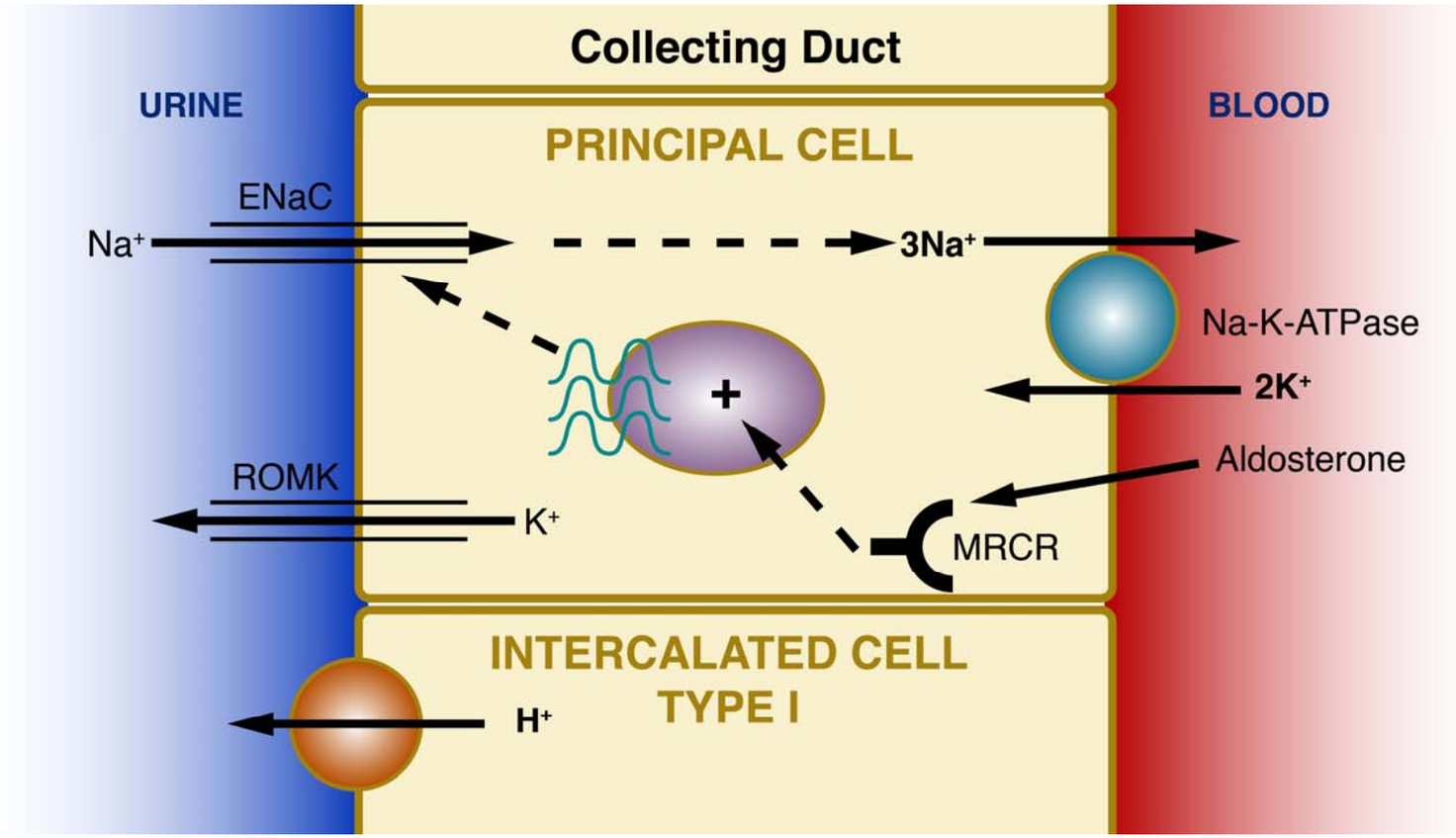
Overview of renal salt handling

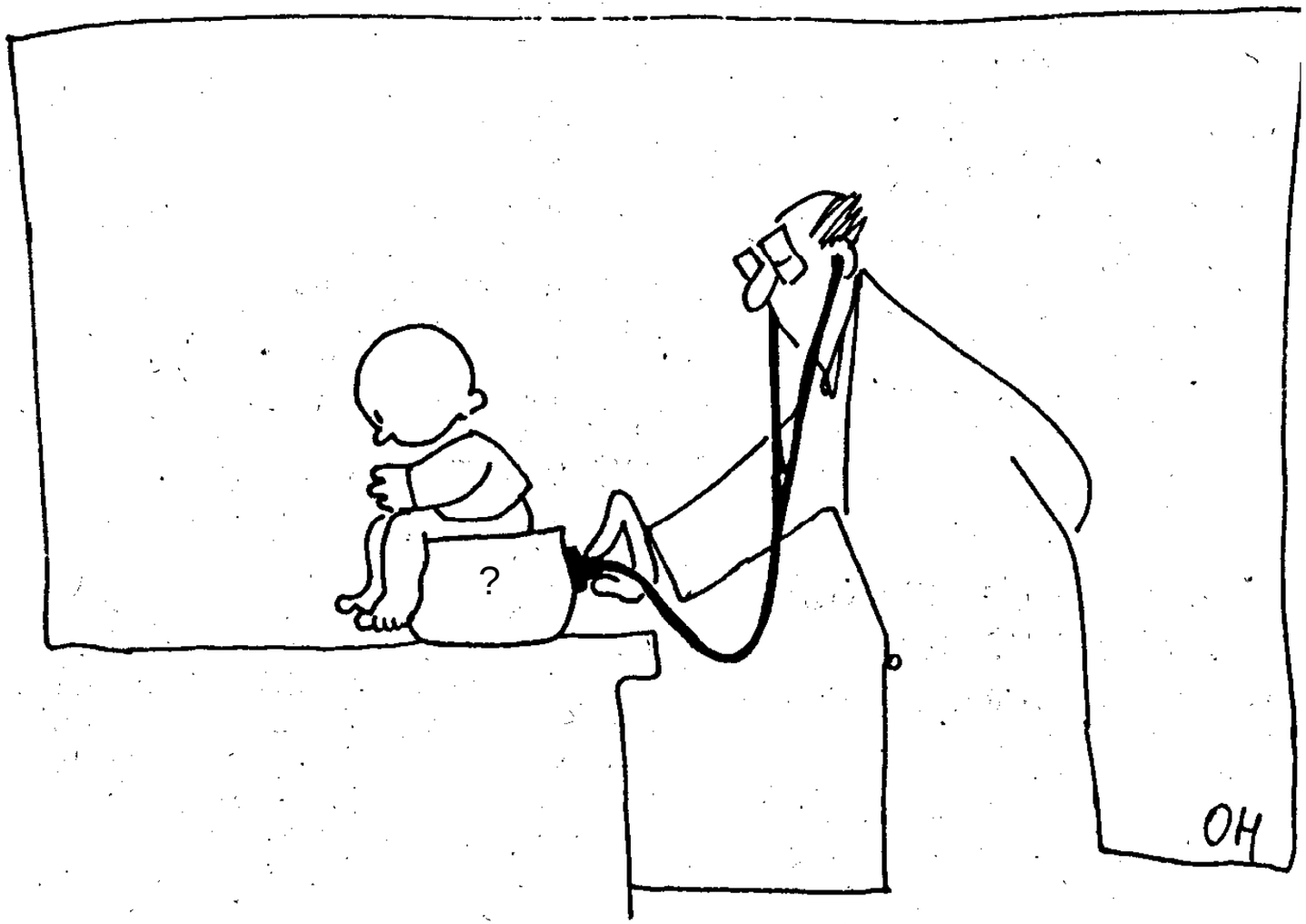


Biochemical “Fingerprinting”

- Disorders of tubular sodium handling are associated with specific biochemical profiles
- Identification of these patterns help establish a specific diagnosis

The “Aldosterone fingerprint”




?
OH

Biochemistry alone is not sufficient

Diagnosis	Bartter	AME
BP (mmHg)	74/46	128/84
Na (mmol/l)	**140**	**142**
K (mmol/l)	2.2	1.9
Cl (mmol/l)	98	95
HCO3 (mmol/l)	27	29

Another case

- 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: Two healthy siblings. Parents are first cousins
- Examination: good peripheral perfusion, BP: ?, no clinical signs of dehydration

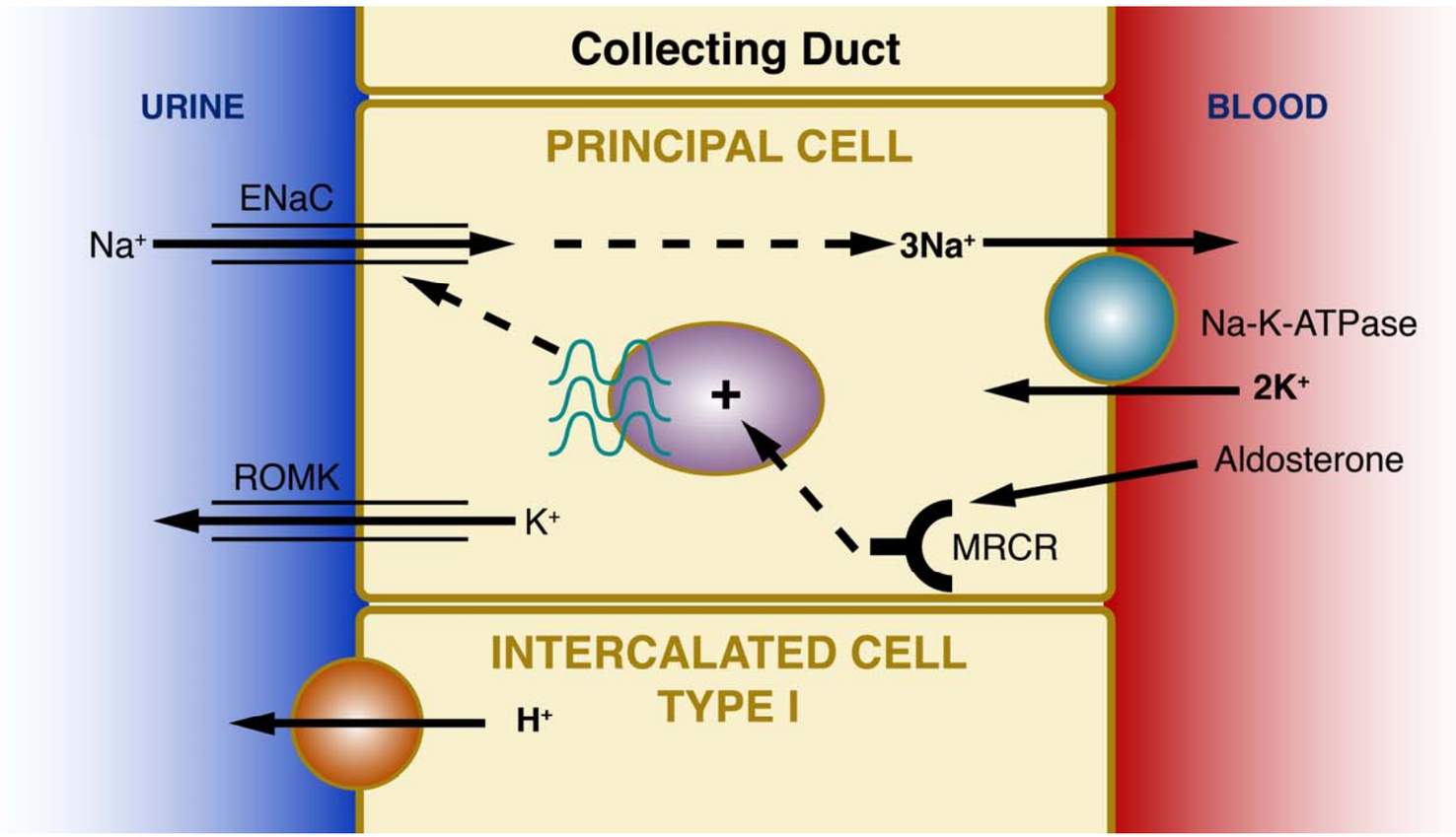
Laboratory Investigations

	Blood
Na [mmol/l]	133
K [mmol/l]	7.4
Cl [mmol/l]	
HCO3 [mmol/l]	16
Creatinine [mcmol/l]	40
pH	7.25
Osmolality [mmol/l]	

Diagnosis?

- Congenital Adrenal Hyperplasia
- Pseudohypoaldosteronism

Sodium transport in CD



Treatment

- Na-bicarbonate 13 mmol/kg/d
- Na-Resonium 450 mg three times daily
- NaCl 10 mmol (3 mmol/kg/d) added to iv fluids
- Fludrocortisone 75 mcg

Subsequent course

- Develops significant hypertension (systolic BP >100 mmHg), but persistent hyperkalaemia (>6 mmol/kg)

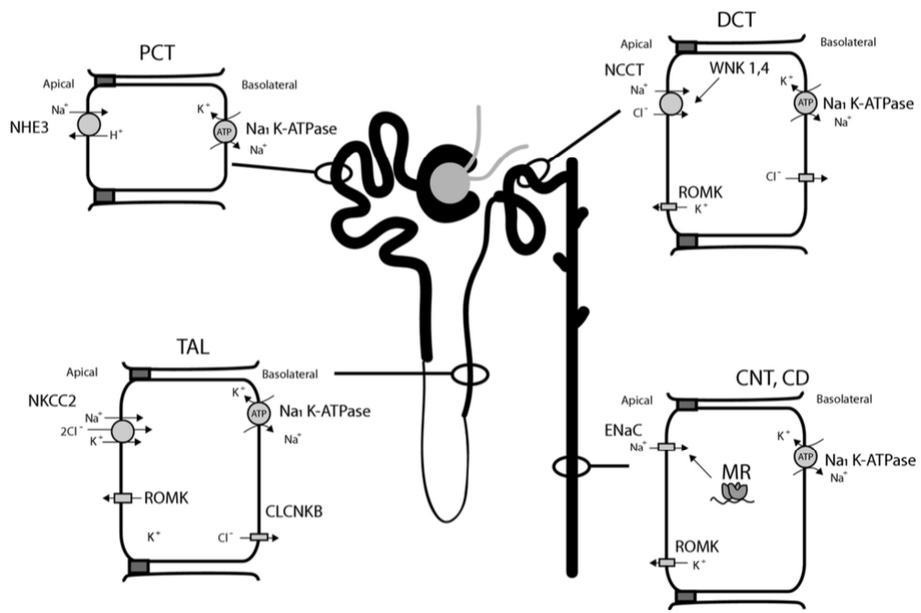
- What now?

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?

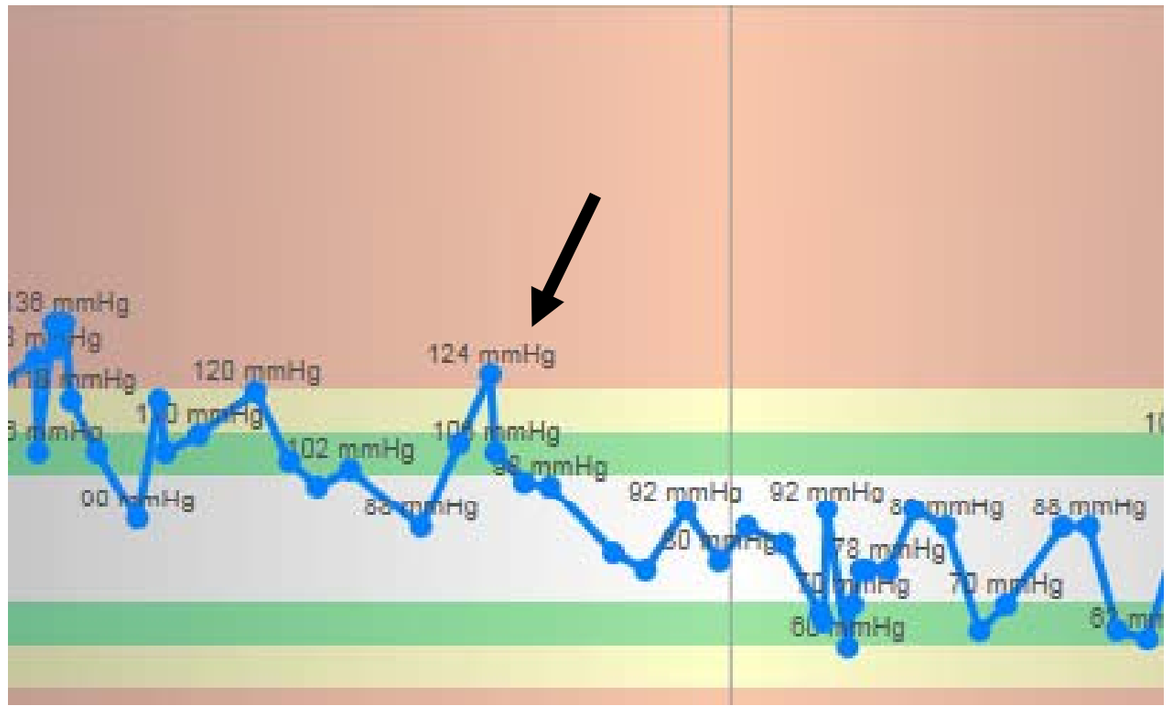
PHA2 (Gordon syndrome)



Trial of Hydrochlorothiazide

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

Blood pressure



Diagnosis?

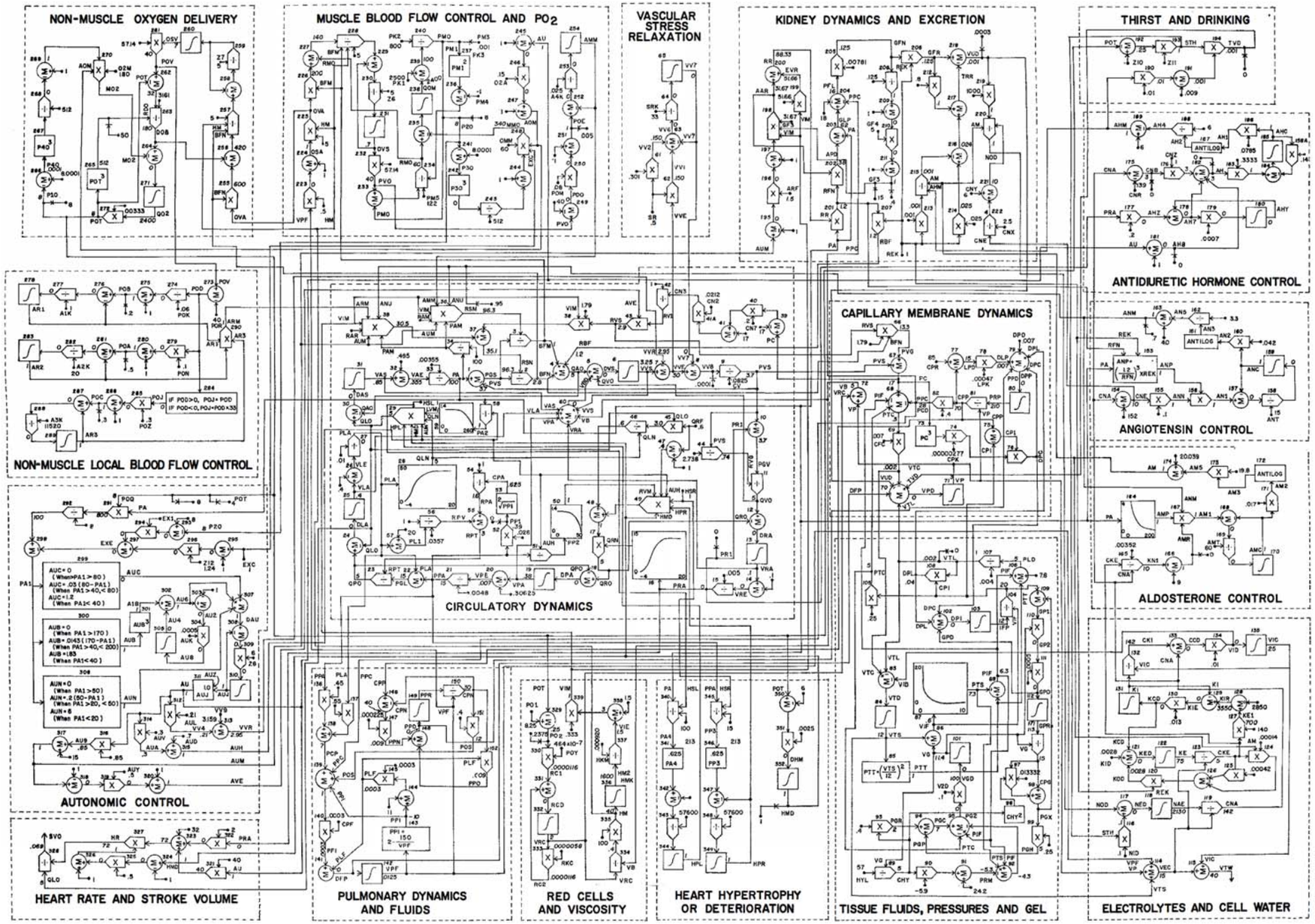
- PHA type 2 (Gordon syndrome)
- Genetics: homozygous splice site mutation in KLHL3: c.903G>A; p.= (last base exon 8)

Disorders of renal salt handling

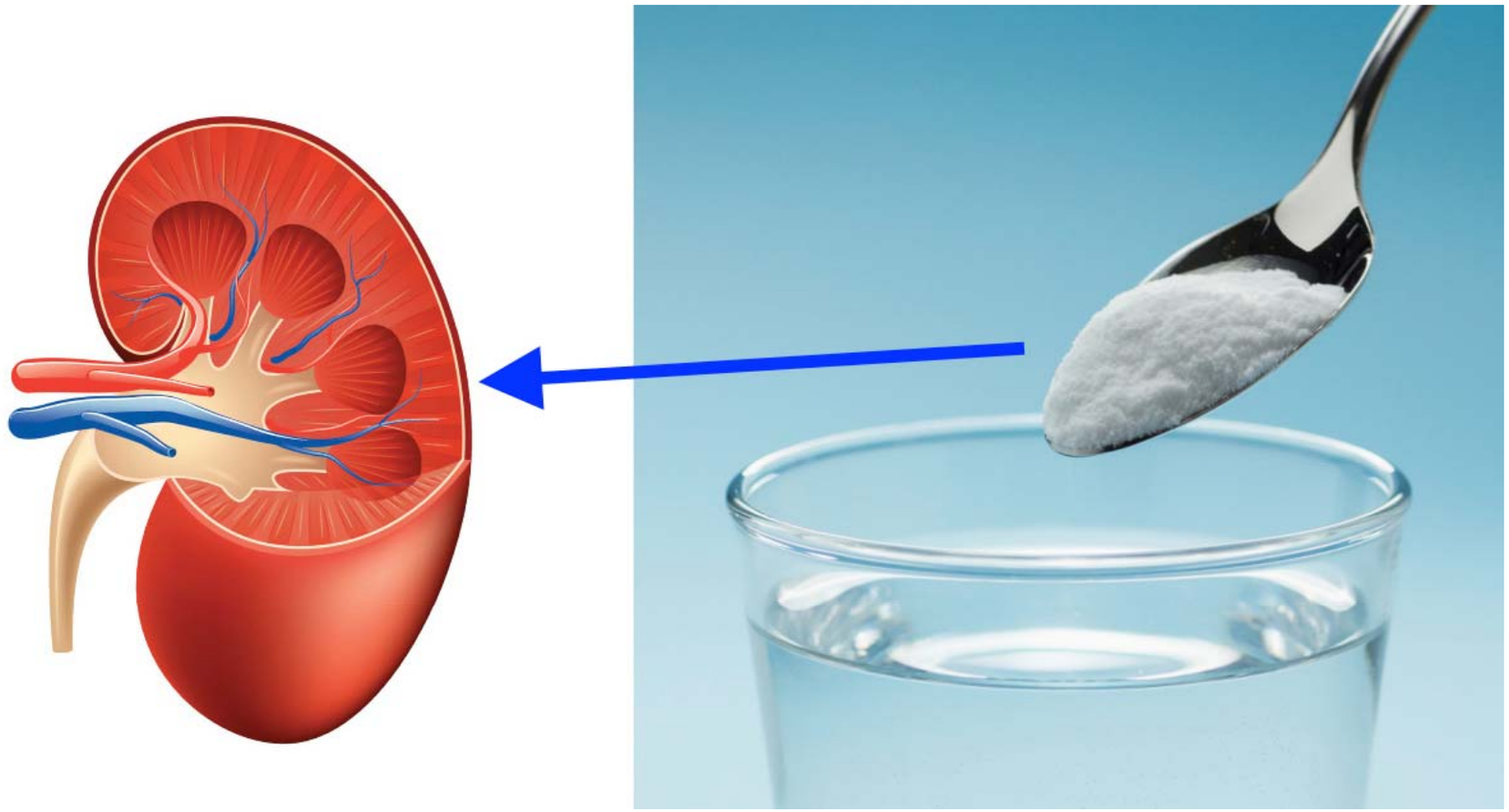
Disorder	Gene(s)	Corresponding drug
Renal Fanconi Syndromes	EHHADH, SLC34A1, ….	
Bartter syndromes	SLC12A1, KCNJ1, CLCNKB, BSND	Loop diuretics
Gitelman	SLC12A3	thiazide
EAST/SESAME	KCNJ10	
PHA1	SCNN1A,B,G, NR3C2	Amiloride/spironolactone
Hypoaldosteronism	CYP11B2,	
PHA2/Gordon	WNK1, WNK4, CULL3, KLHL3	tacrolimus
Liddle	SCNN1B,G	
AME	HSD11B2	licorice
Hyperaldosteronism	CYP11B1, KCNJ5, CACNA1D,H, CYP11B2	fludrocortisone

Key message 1

Sodium transport determines
blood pressure/volume homeostasis

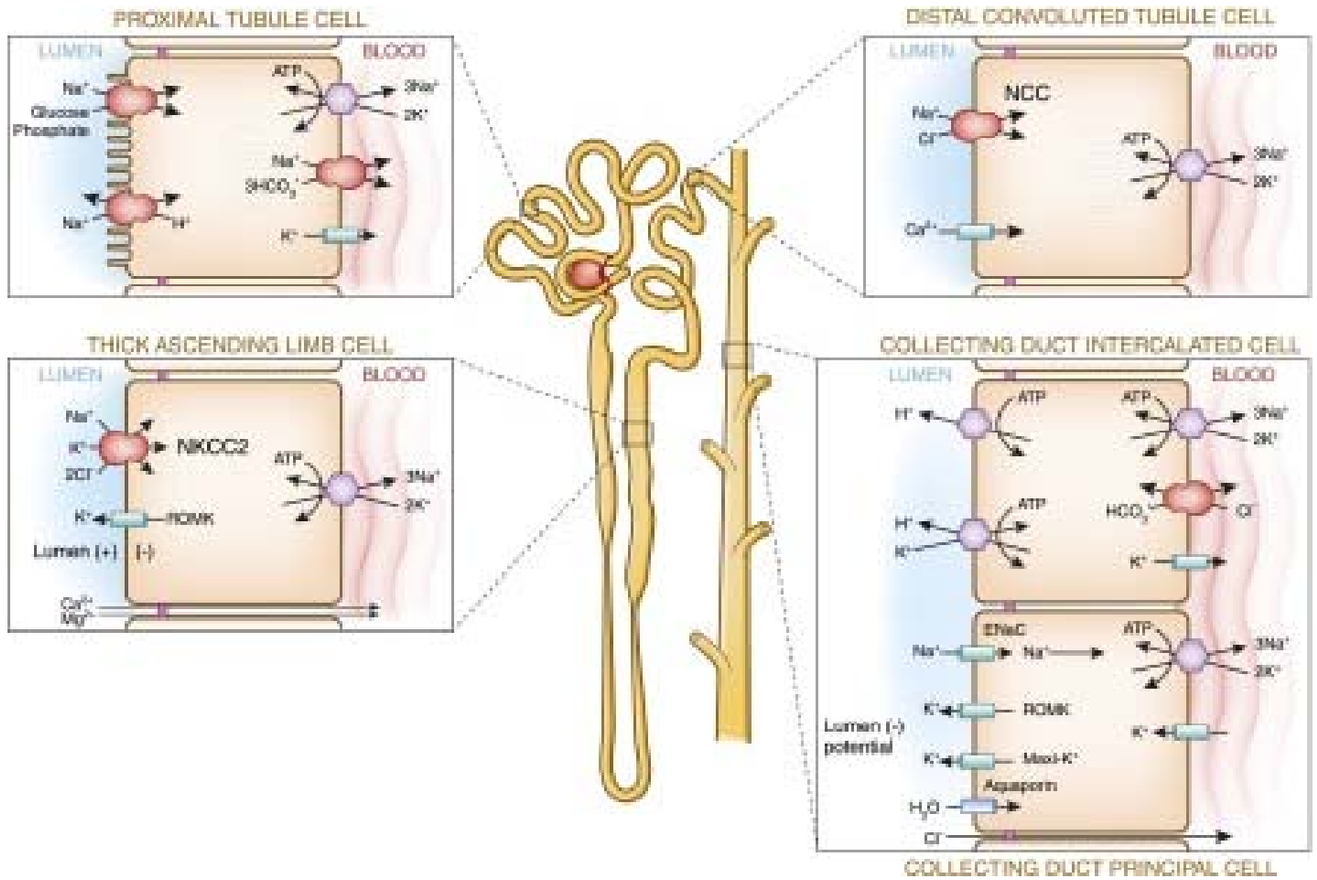

NON-MUSCLE OXYGEN DELIVERY
MUSCLE BLOOD FLOW CONTROL AND PO2
VASCULAR STRESS RELAXATION
KIDNEY DYNAMICS AND EXCRETION
THIRST AND DRINKING
ANTIDIURETIC HORMONE CONTROL
ANGIOTENSIN CONTROL
ALDOSTERONE CONTROL
CAPILLARY MEMBRANE DYNAMICS
NON-MUSCLE LOCAL BLOOD FLOW CONTROL
CIRCULATORY DYNAMICS
AUTONOMIC CONTROL
HEART RATE AND STROKE VOLUME
PULMONARY DYNAMICS AND FLUIDS
RED CELLS AND VISCOSITY
HEART HYPERTROPHY OR DETERIORATION
TISSUE FLUIDS, PRESSURES AND GEL
ELECTROLYTES AND CELL WATER

There is only one organ…



…and it works through salt

Physiology



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

Key aspects of disorders of sodium transport

- Primarily affects volume homeostasis
- Rarely affects plasma sodium concentration
- Molecularly linked to other transport processes

Pathophysiology

- 2-week old neonate transferred to GOSH renal ward
- Born at 32-wk gestation
- Pregnancy complicated by polyhydramnios (2 amniocentesis)
- Postnatal: polyuria (200 ml/kg/d) and severe electrolyte disturbance
- 3rd child of healthy parents, 1st cousins

Examination

- Decreased peripheral perfusion
- Wt: 1.68 kg
- Length: 44 cm
- HC: 29 cm
- BP: 68 mmHg systolic

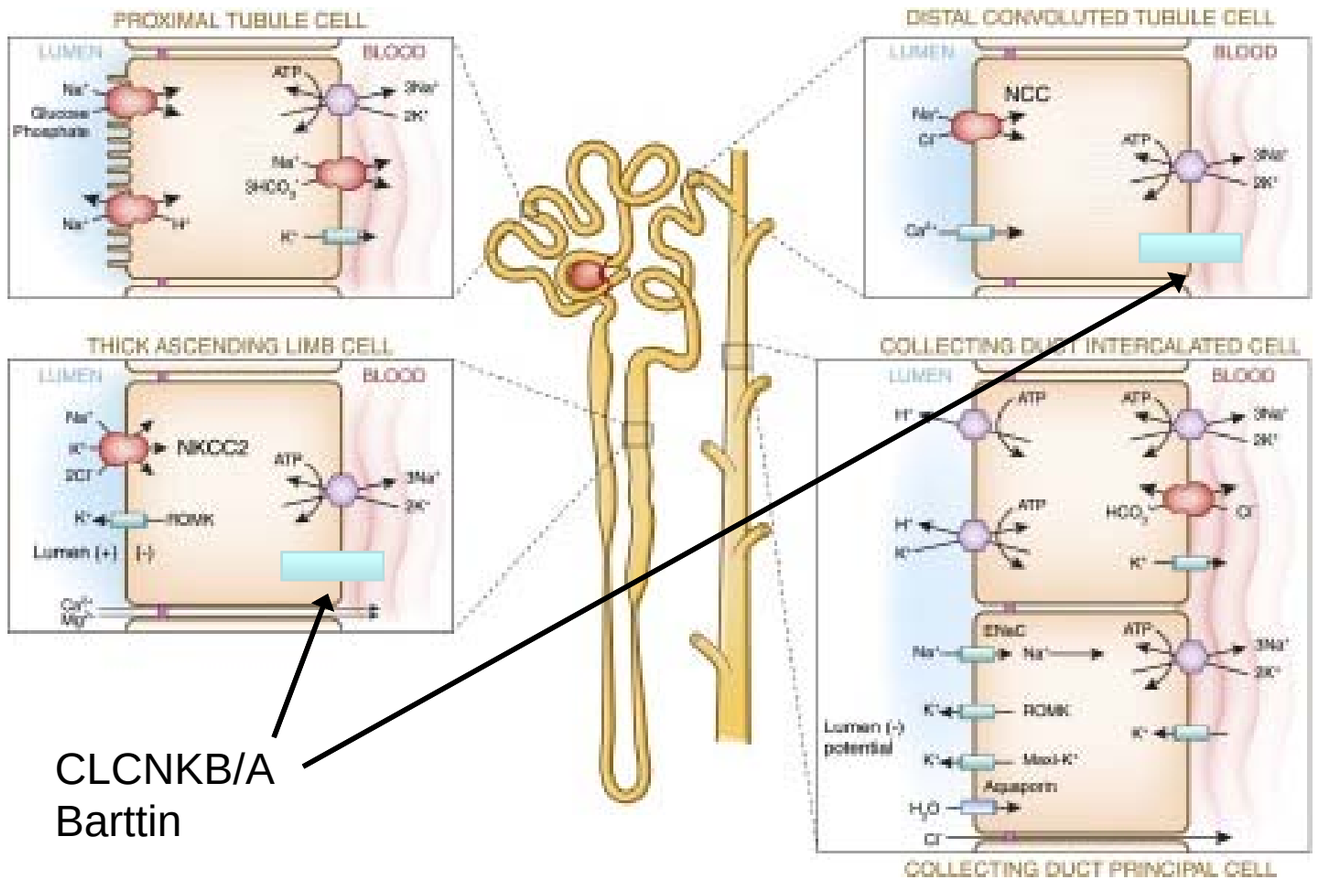
Biochemistries

Parameter	admission	Normal range
Na (mmol/l)	116	133 146
K (mmol/l)	2.1	3.5-5.5
Cl (mmol/l)	59	100-108
	81*	
		7.37-7.43
Ca (mmol/l)	1.99	2.17-2.44
g ( )		
Creatinine (mcmol/l)	116	16-33

Diagnosis

- Bartter syndrome
- Also has sensorineural deafness
- Bartter type 4
- Homozygous mutation in Barttin p.Pro151Leufs*27

Pathophysiology



CLCNKB/A
Barttin

Treatment

- Salt! up to 14 mmol/kg/d
- Potassium up to 13 mmol/kg/d
- NSAID (indomethacin, celecoxib)

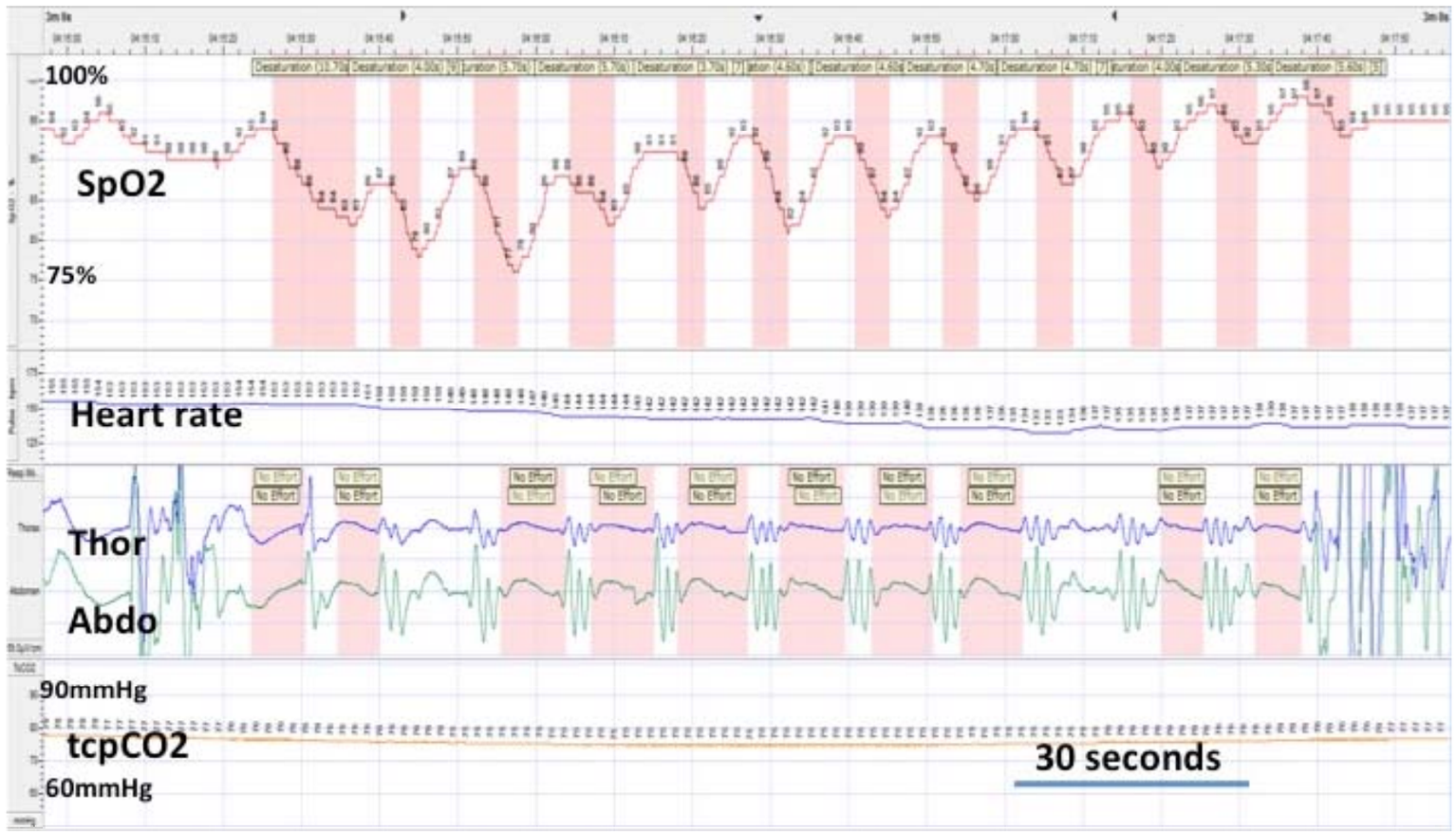
Further course

parameter	min	max
Na (mmol/l)	116	173
K (mmol/l)	1.4	6.9
Cl (mmol/l)	56	125
Creatinine (mcmol/l)	29	182
pH	7.58	7.90

“Renal Apnoea”

- Recurrent desaturations
- Inability to extubate after GA for central line insertion

Polysomnography



More complications

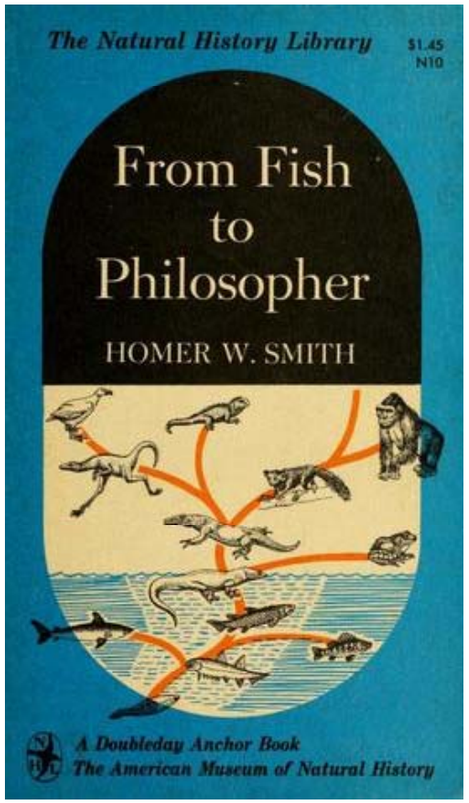
- Hypophosphataemic rickets

test	Value [unit]
PO4	0.3 mmol/l
PTH	56 pmol/l
ALP	1226 IU/l
TmP/GFR	<0.8 mmol/l

….and more complications

- Severe developmental delay
- Failure-to-thrive
- Stuck in hospital

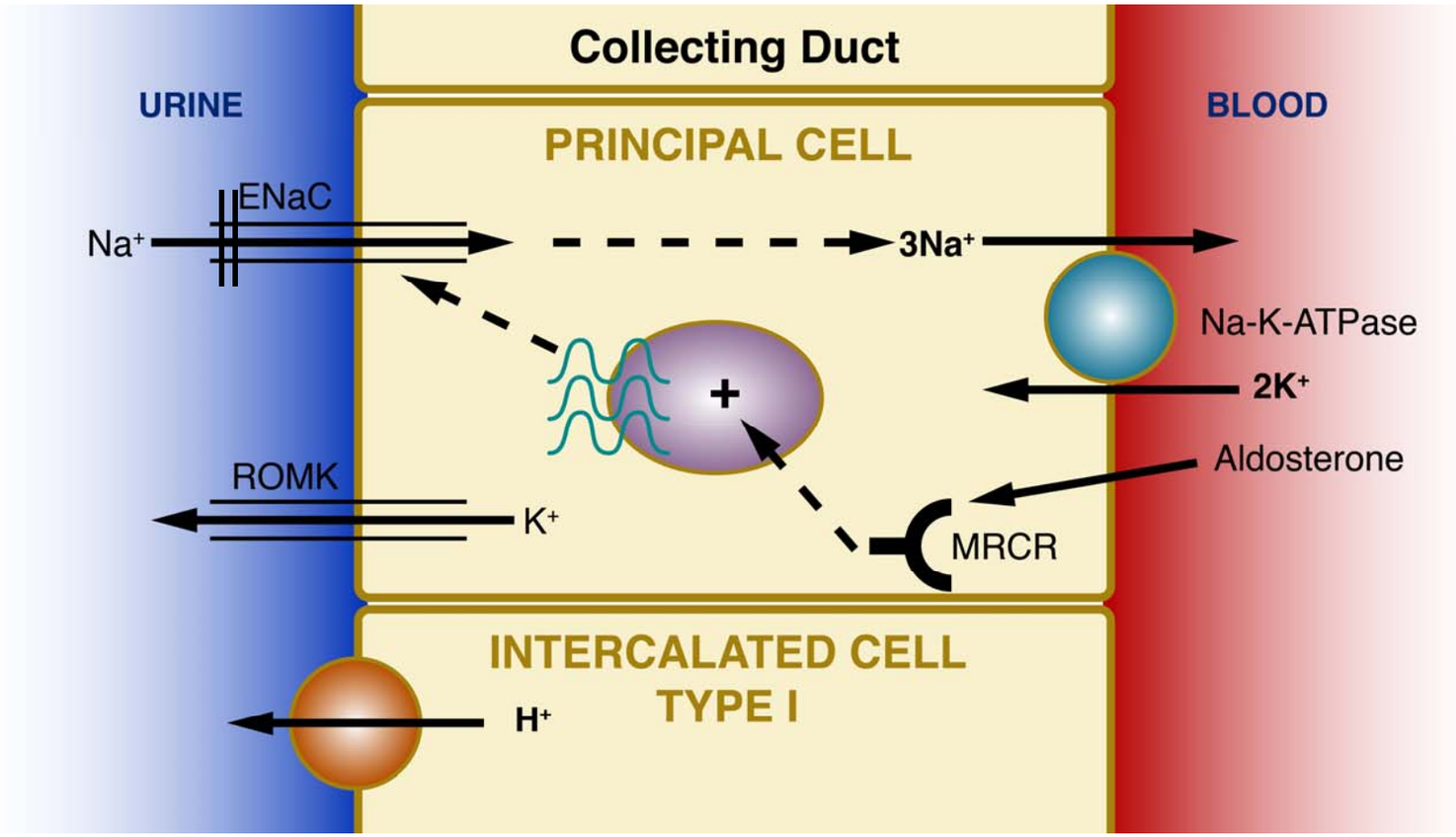
Homer said it all



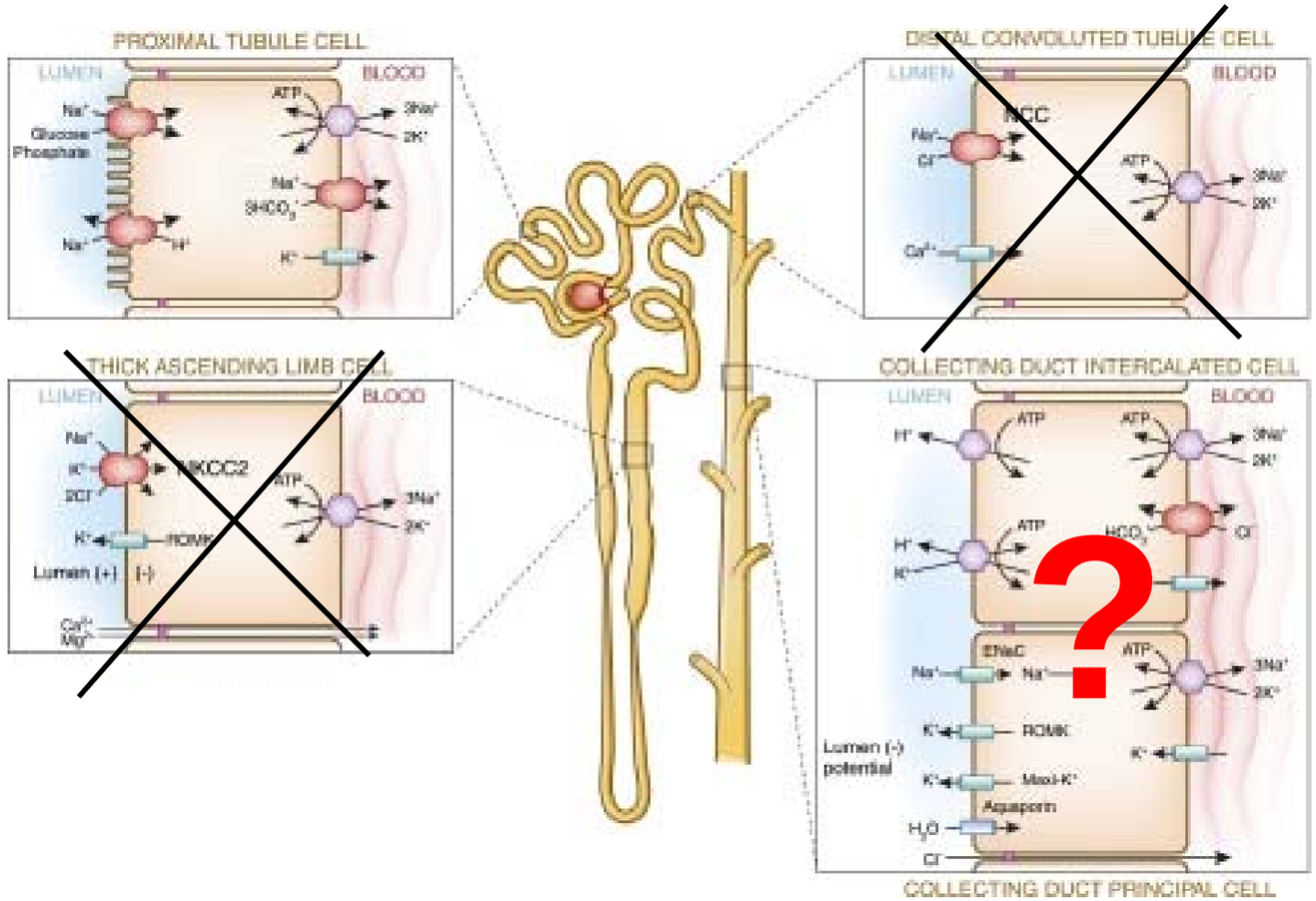
How to move forward?

- Palliative care
- Titration with HCl
- Nephrectomy(ies)
- amiloride

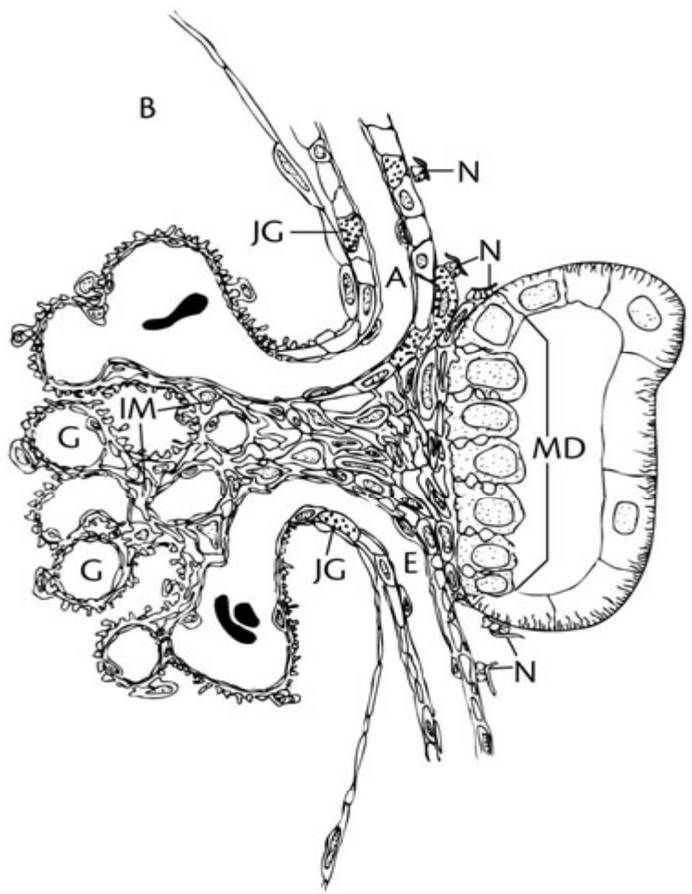
Amiloride action



Pathophysiology



Bartter syndrome affects tubuloglomerular feedback



- MD cells are TAL cells
- ↓ chloride reabsorption leads to renin/angiotensin activation **via** ↑ Prostaglandins
- COX-2 ↑

↑

Amiloride justification

- JG apparatus is “short circuited”, as no chloride reabsorption
- => prostaglandin=>renin=>aldosterone independent of volume status
- Volume homeostasis must be maintained by adequate salt supplementation

Course since

- Blood pH <7.6
- Improved mental state
- No further phosphate supplementation
- Discharged home age 12 months (2 months after starting amiloride)

- Severe developmental delay
- CKD stage 3 (eGFR 30 ml/min)

Conclusions

- Renal salt handling regulates volume homeostasis
- Renal sodium transport is molecularly linked to multiple other transport pathways
- Volume homeostasis “rules”!
- Disorders of renal sodium handling clinically manifest with altered BP and secondary electrolyte abnormalities
- They rarely affect plasma sodium concentration