Heriditäre Salzverlust-Tubulopathien

mit sekundären Hyperaldosteronismus :

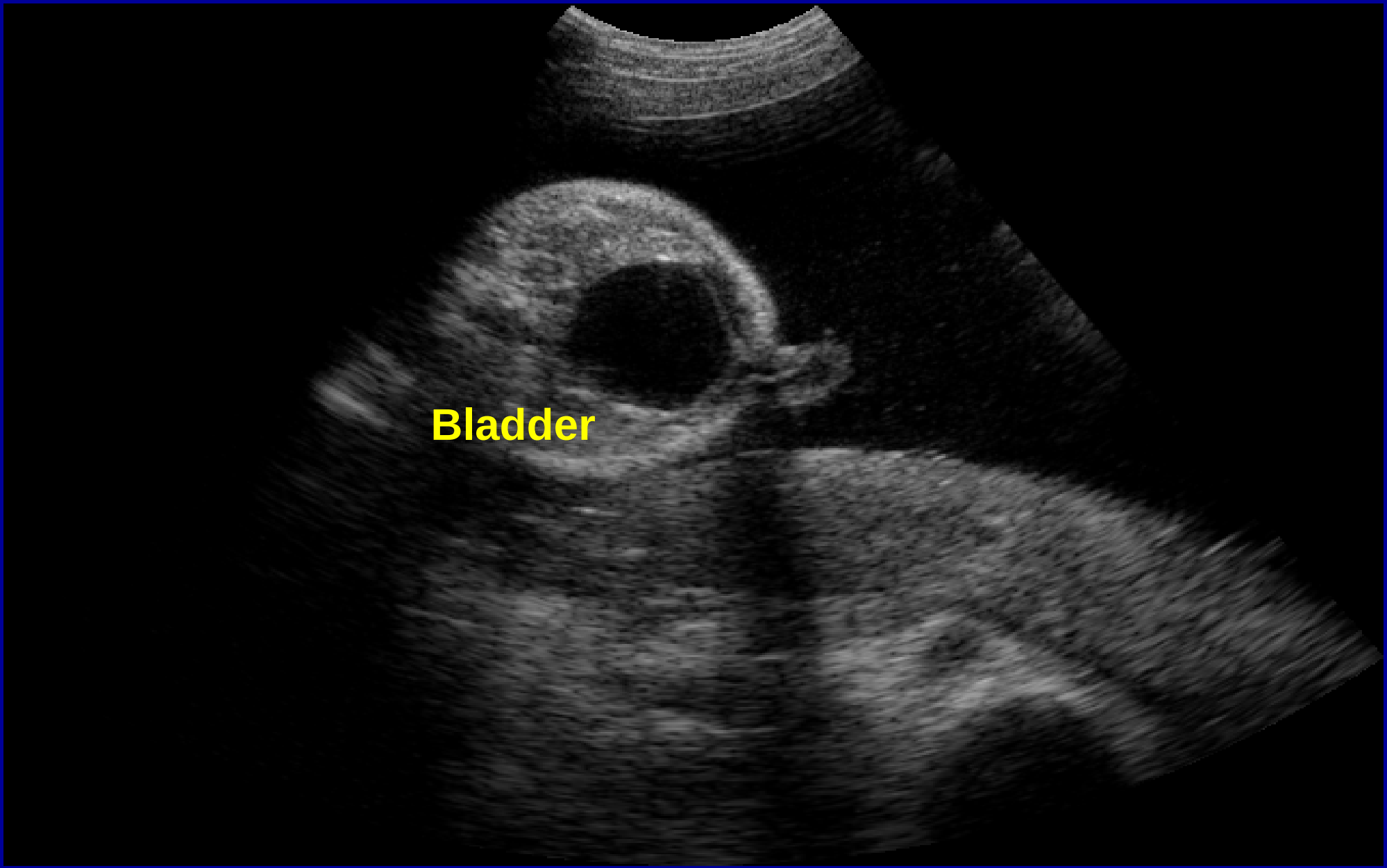
Seltene Nierenerkrankungen bei Kinder und Erwachsenen

H.W. **Seyberth**, Zentrum für Kinder- und Jugendmedizin,
Philipps Universität Marburg
und
Kommission für Arzneimittelsicherheit im Kindesalter (KASK) der **DGKJ**

PMS-Workshop:
Arzneimittel seltener Krakheiten – Herausforderungen und Chancen
25. Januar 2007 Berlin-Brandenburgische Akademie der Wissenschaften

GIII/PII; current gestational age: 32 + 0 weeks, amniotic fluid volume about 15 l
Polyhydramnios started to develop in the 22nd week of gestation

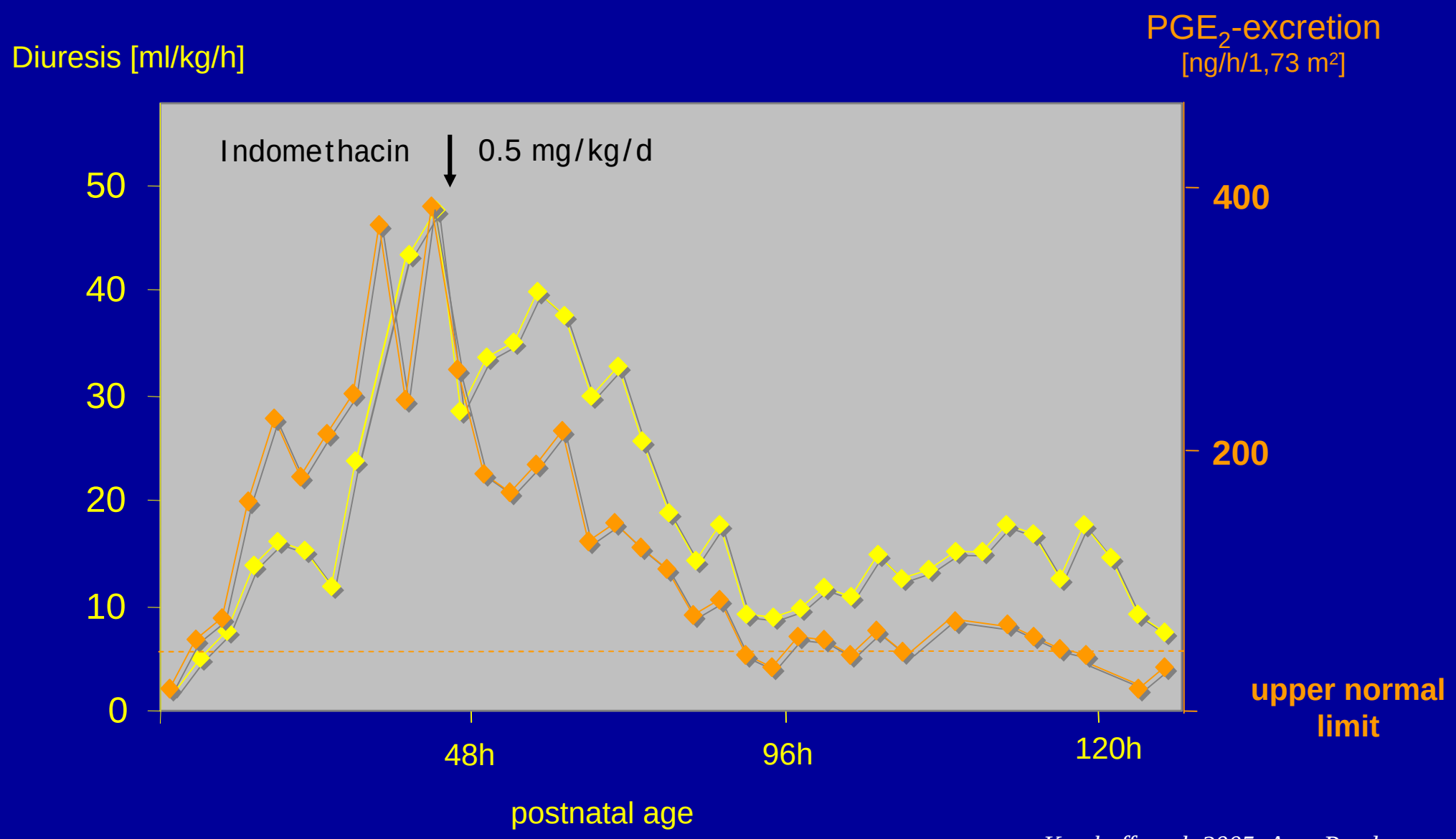

ATL
03/06/12:105305
C5-2 40R OB/GEBH
12 Jun 03
10:54:58
TIk 0.1 MI 1.0
B. 91 23.0cm


Bladder

after amniocentesis with drainage of 3 L fluid
Chloride concentration 116 mM (normal up to 112 mM)

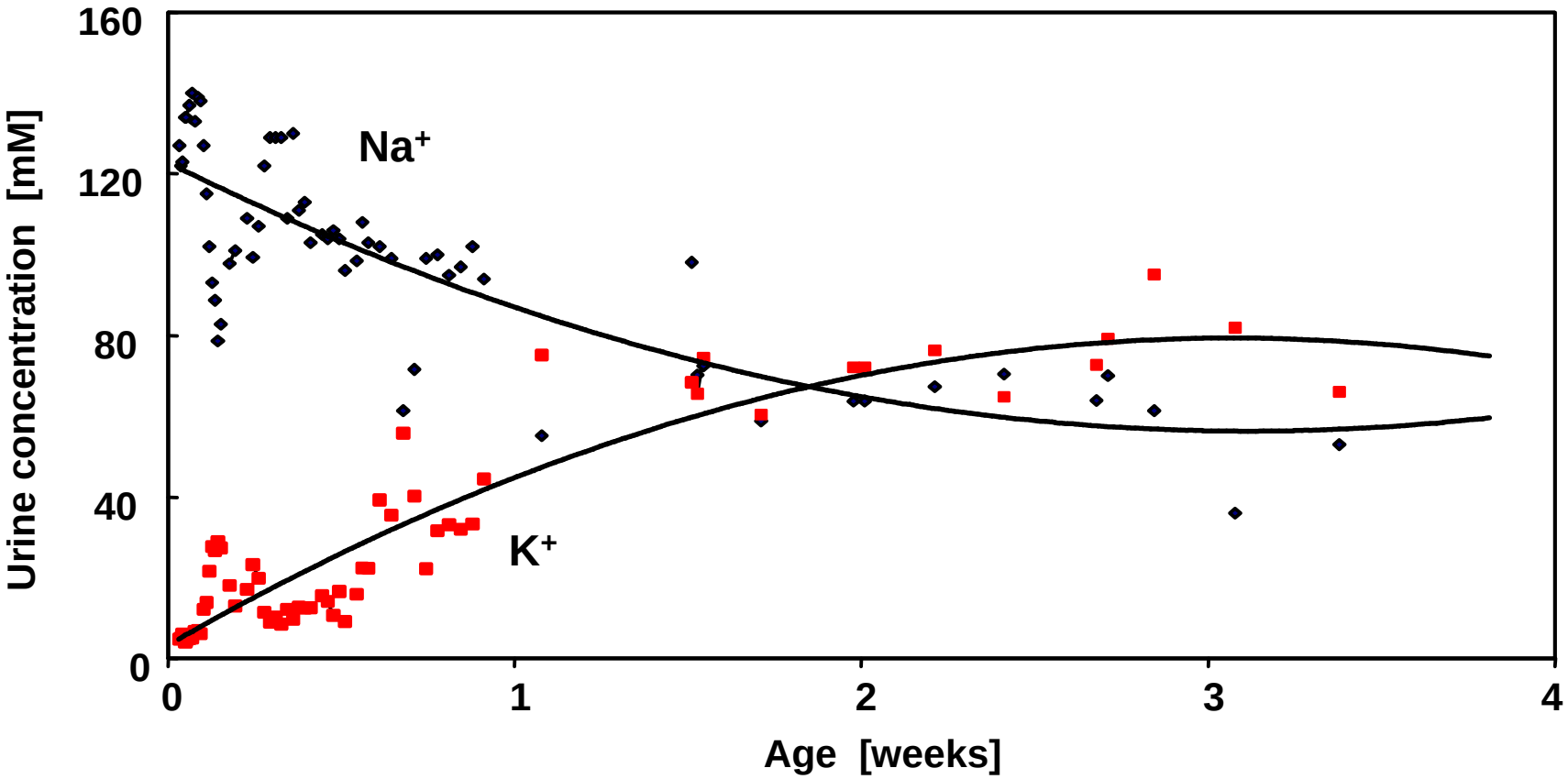

ARJO
ARJO

Indomethacin reduces polyuria in Hyperprostaglandin E Syndrome



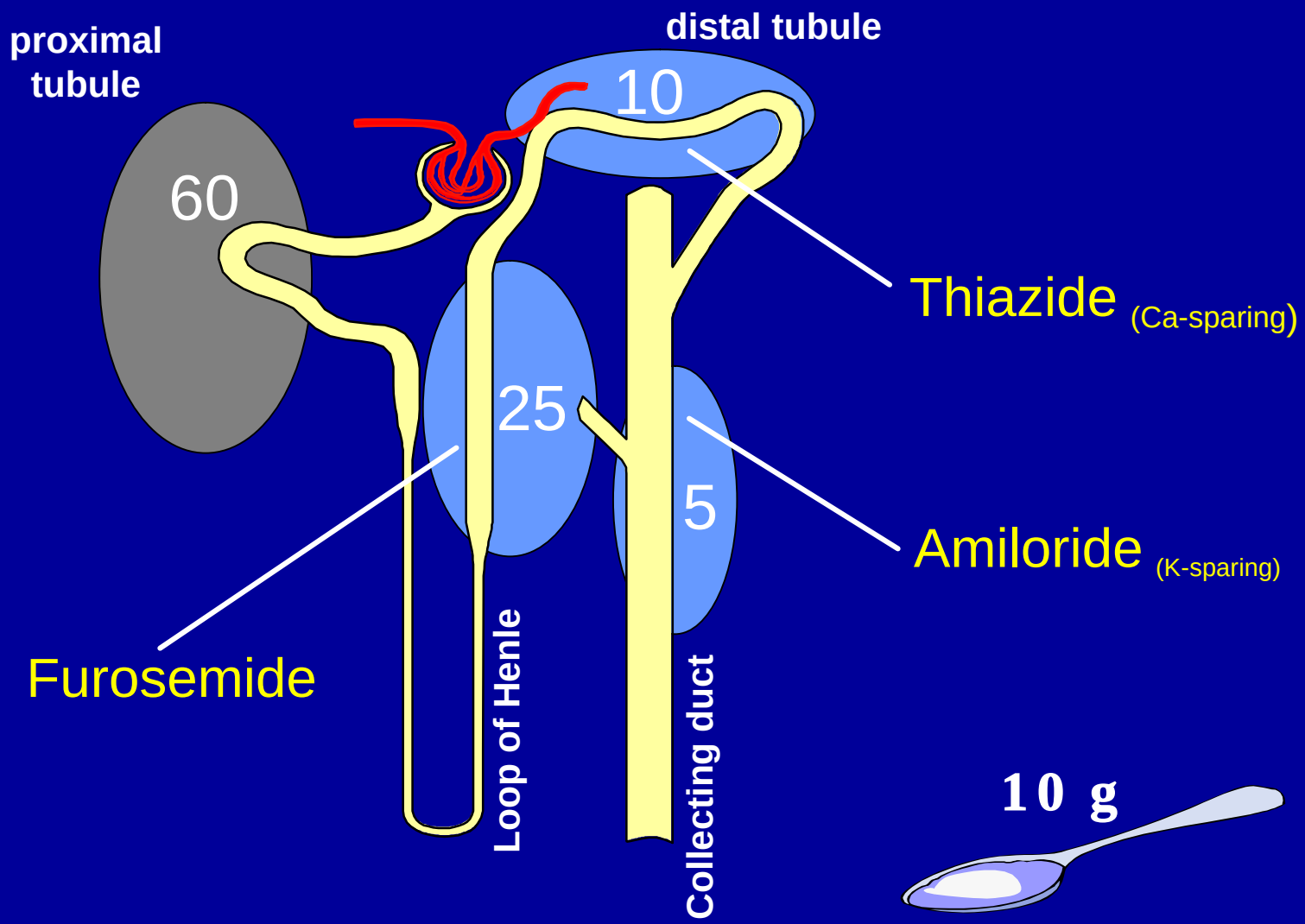
Komhoff et al, 2005, Acta Paed

Sodium-Potassium-Switch in HPS

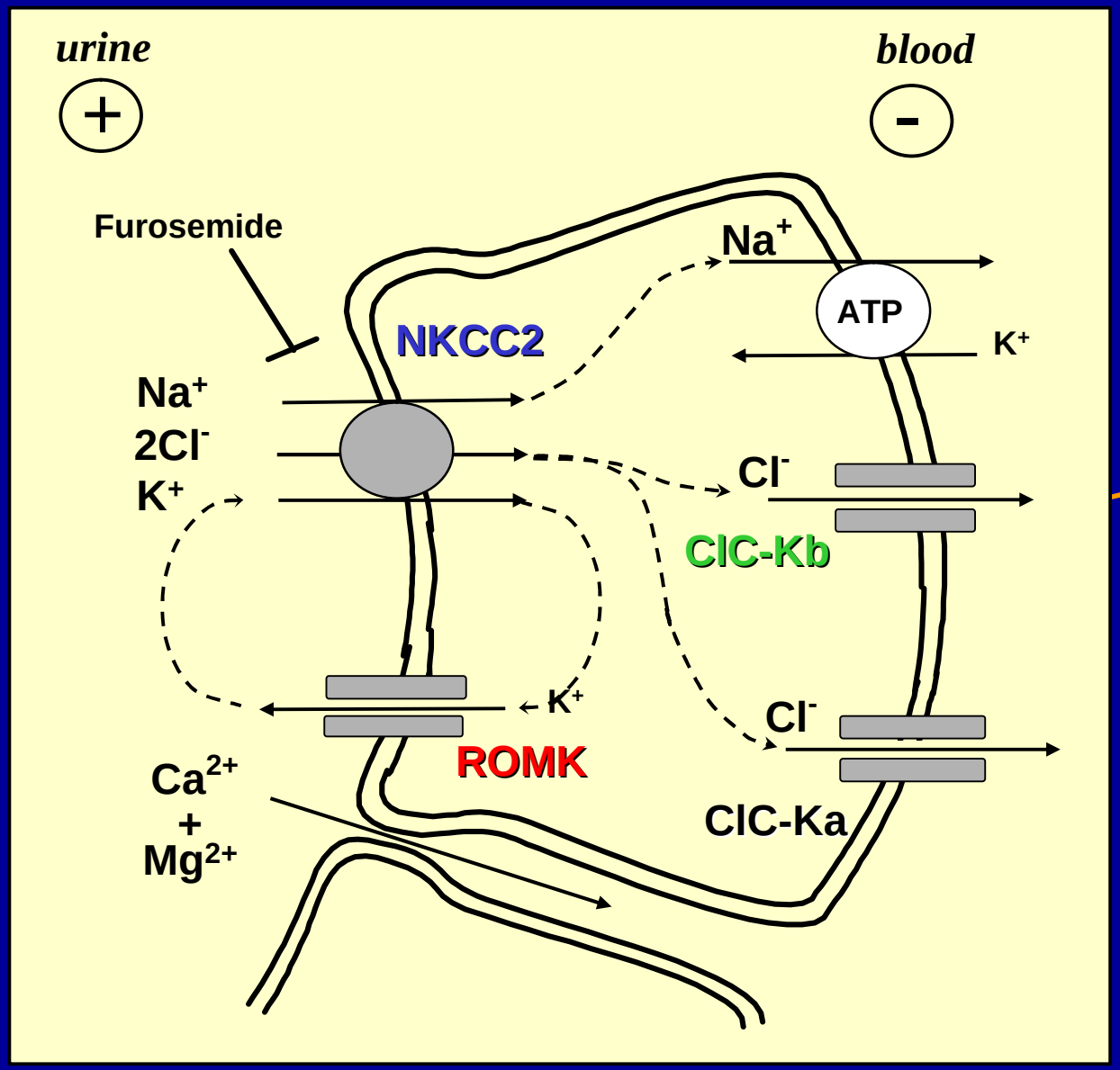


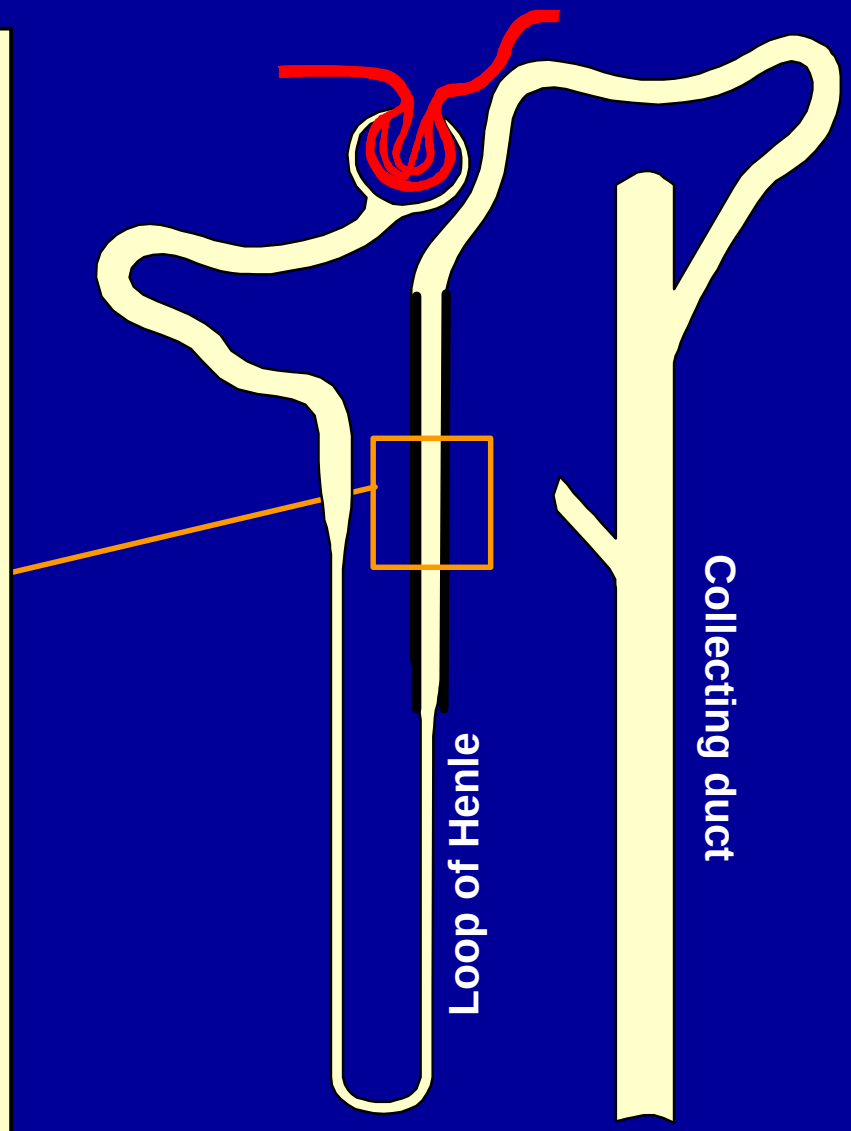
Reinalter et al. 1998, Pediatr Nephrol

Renal sodium reabsorption along the distal tubule

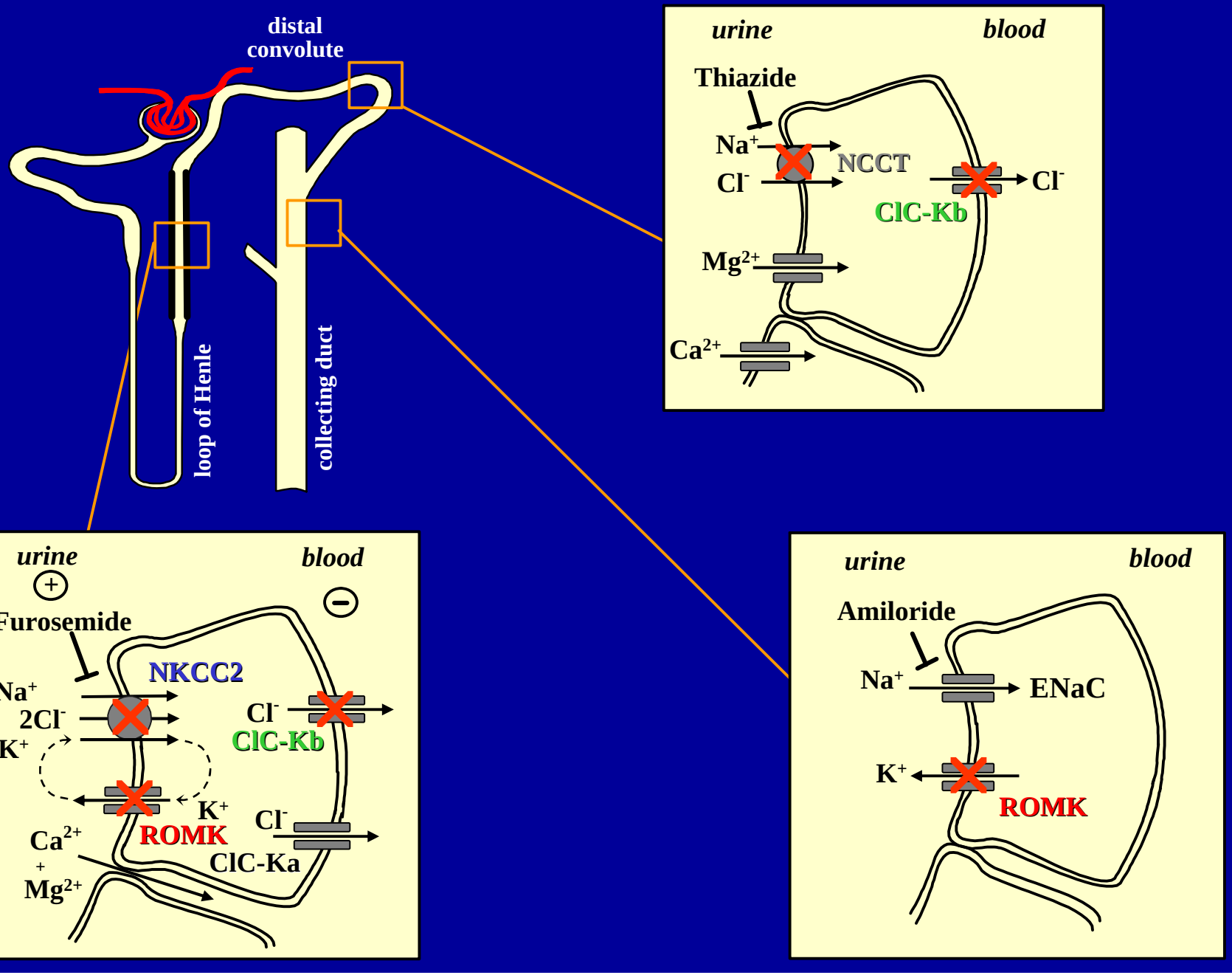


Modules of transepithelial electrolyte transport in the distal tubule



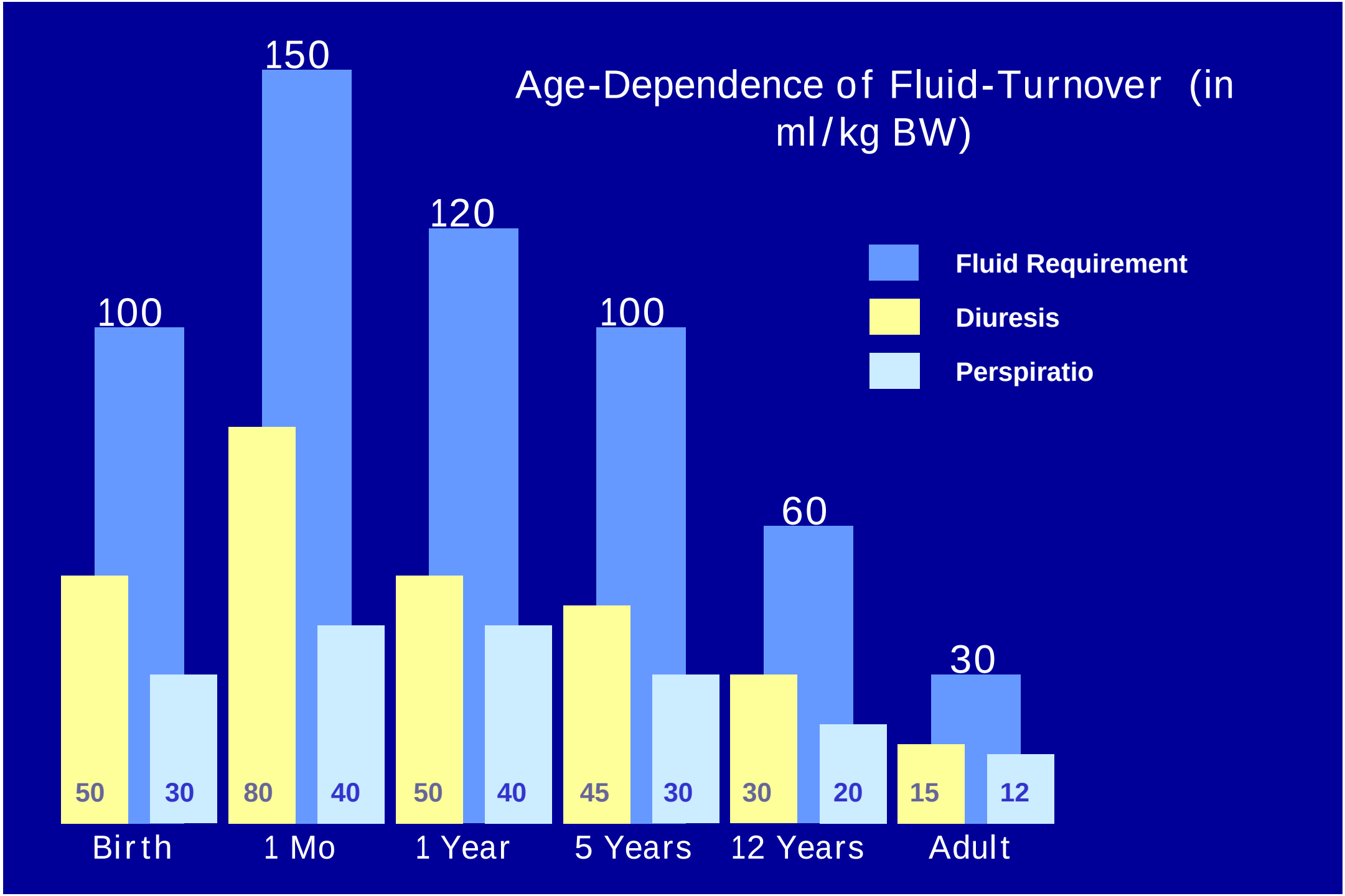


Modules of transepithelial electrolyte transport in the distal tubule



Fazit: Der Ausfall eines Moduls wird zwangsläufig auch Auswirkungen auf andere Module entlang des Nierentubulus haben.

Frage: Warum ist diese genetische Salzverlust-Erkrankung besonders im frühen Kindesalter so lebensbedrohlich?


Age-Dependence of Fluid-Turnover (in ml/kg BW)
Fluid Requirement
Diuresis
Perspiratio
100
150
120
100
60
30
50
30
80
40
50
40
45
30
30
20
15
12
Birth
1 Mo
1 Year
5 Years
12 Years
Adult

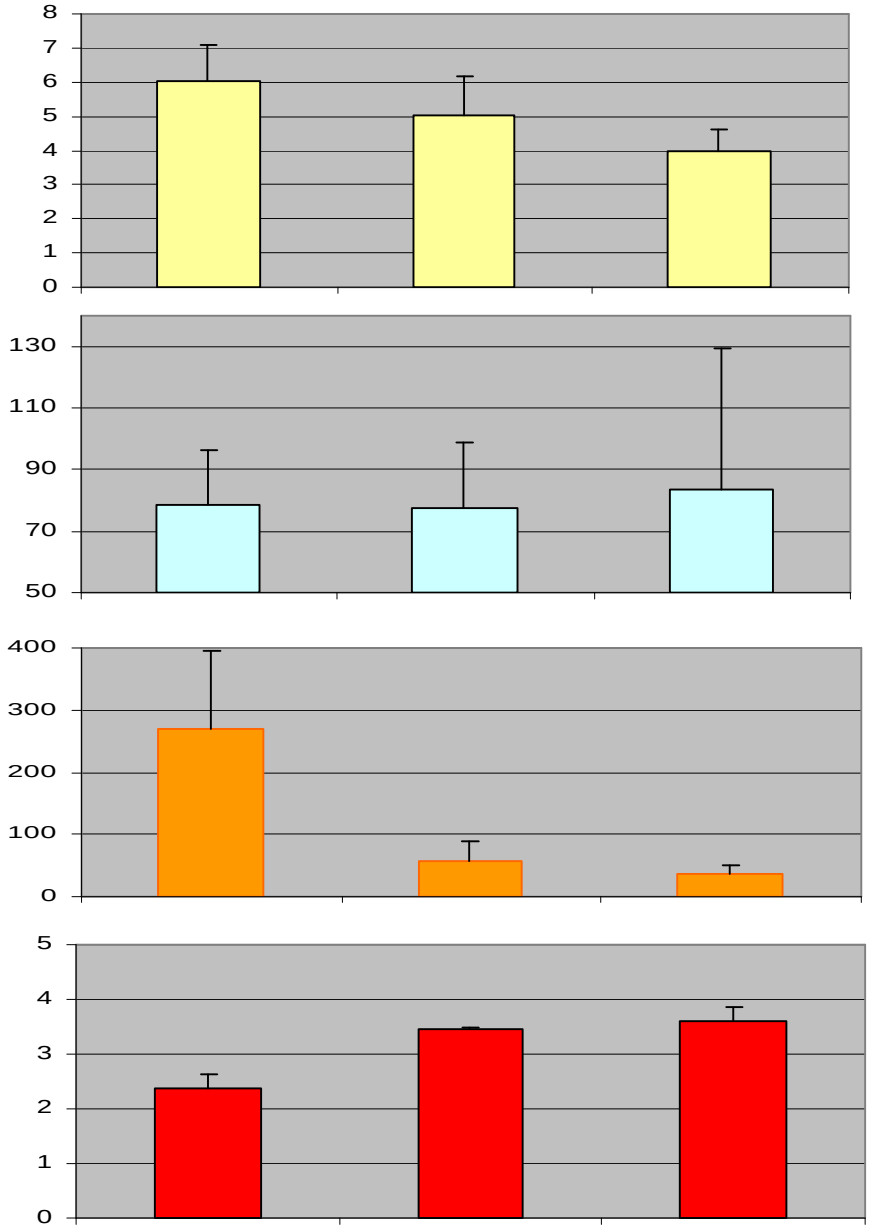
M. Michael geb.04.05.1986

T. Maria geb.22.10.1982

R. Ranjit geb.11.09.1984

Foto März 1994

4 HPS-Patienten im 10 J. Follow-up



Diurese [ml/kg/h]

PGE2-Exkretion [ng/min/1,73m²]

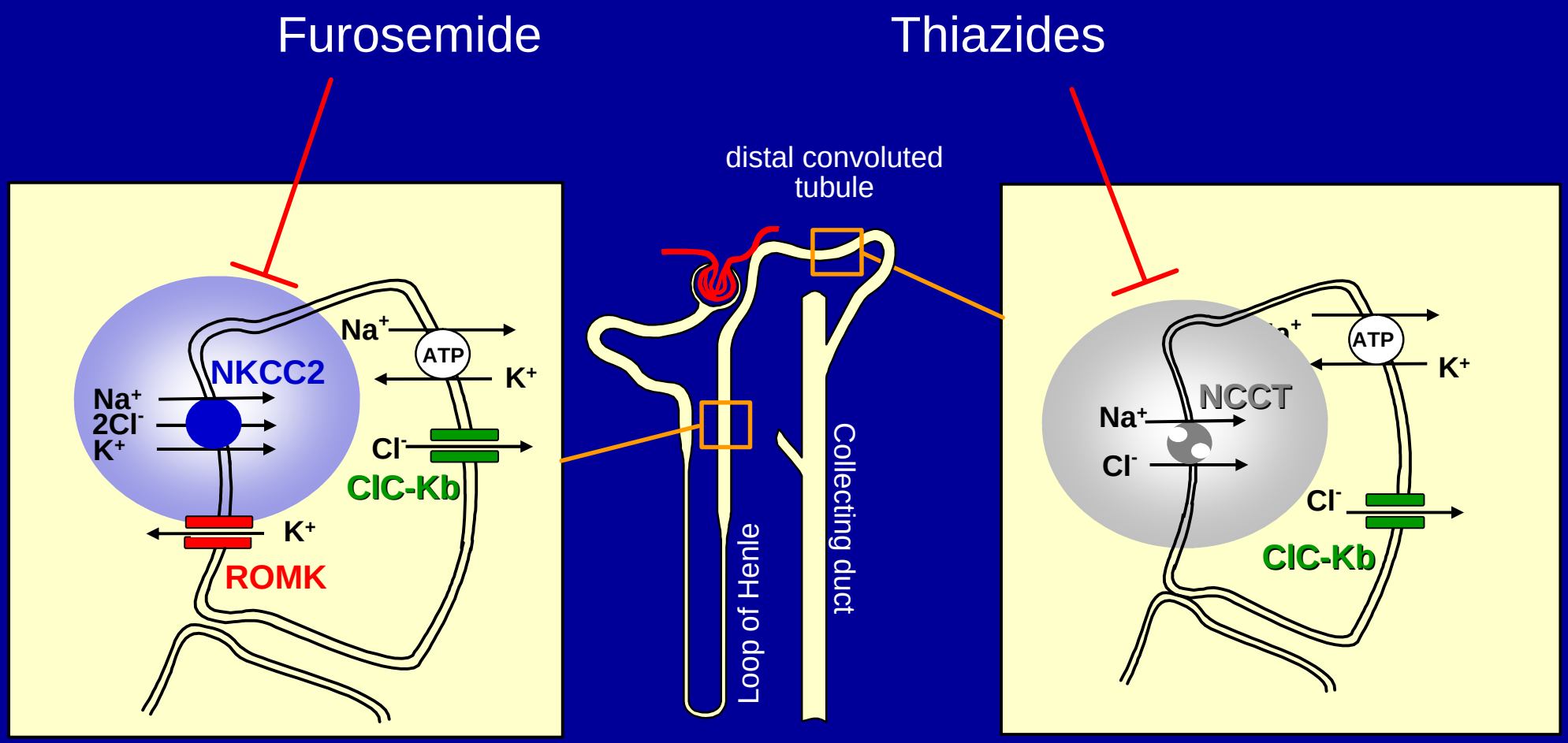
Renin [ng/ml/h]

Serum-Kalium [mmol/L]

Alter [Jahren]

BMI [SDS]

Na-(K)-Cl transporters along the distal tubule



Hypothese: Beim heriditären Salzverlust mit Schleifen-Defekt entwickelt sich im weiteren Verlauf der Erkrankung eine distale Convolut(DC)-Kompensation bzw. der Furosemid-Resistenz vergleichbarer Zustand.

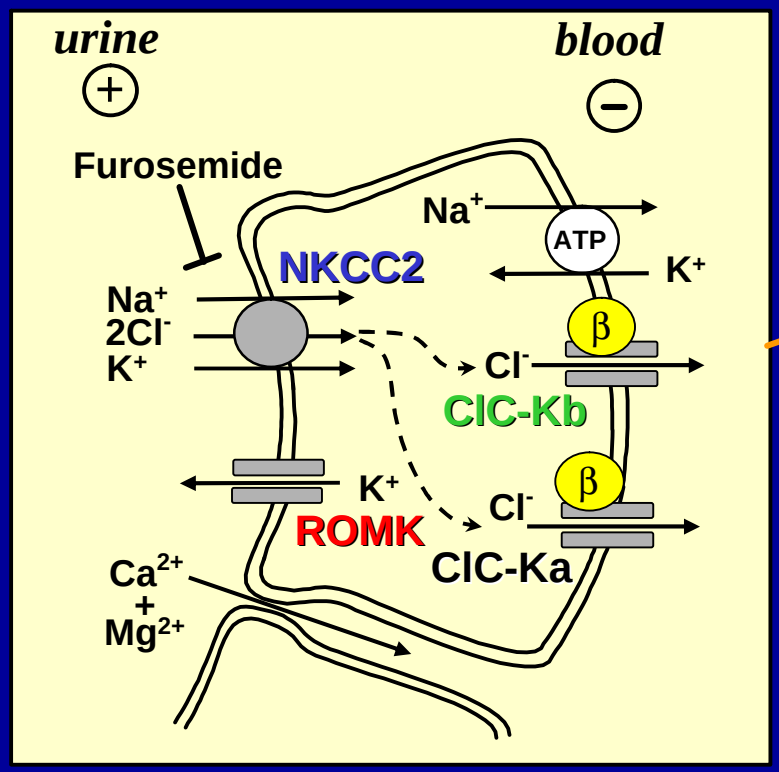
Proof of Concept:

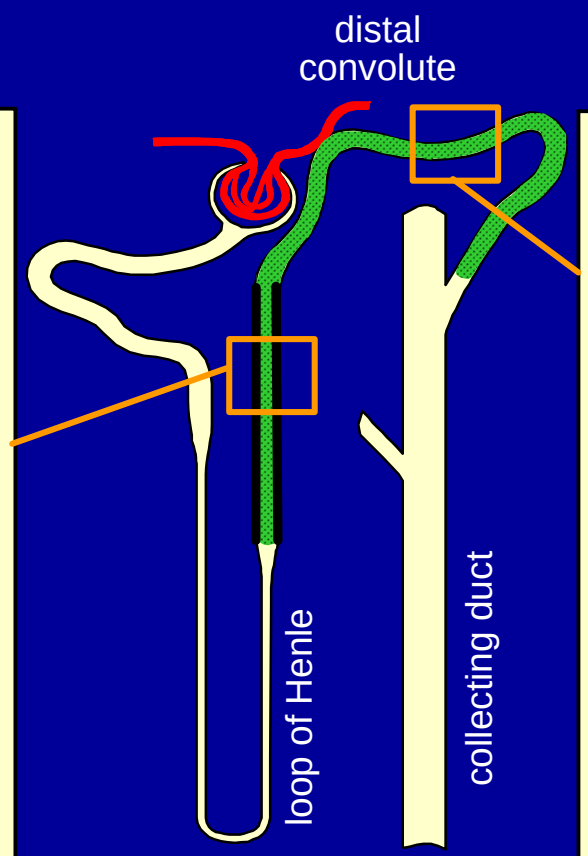
There is a special furosemide-like SLT (HPS)

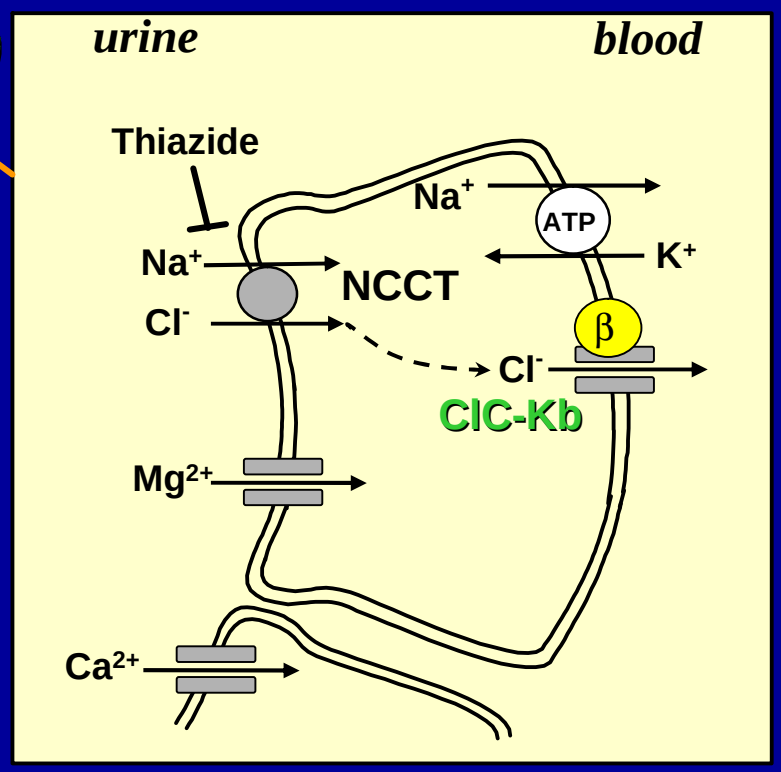
without DC-compensation over time and

without hypercalciurea and nephrocalcinosis

Furosemide-like SLT without hypercalciurea and DC-compensation is a combined loop- and distal convolute-defect.



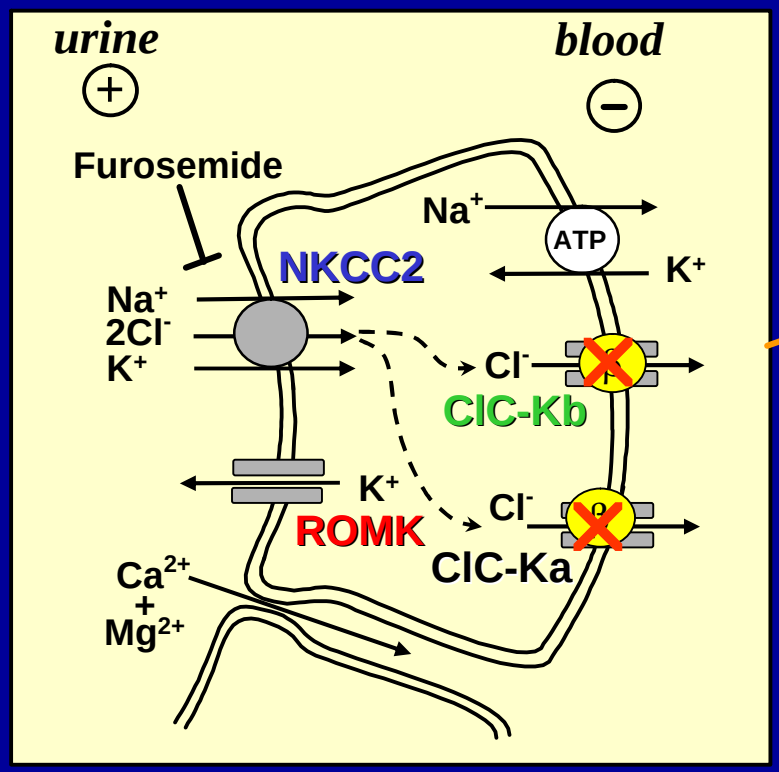


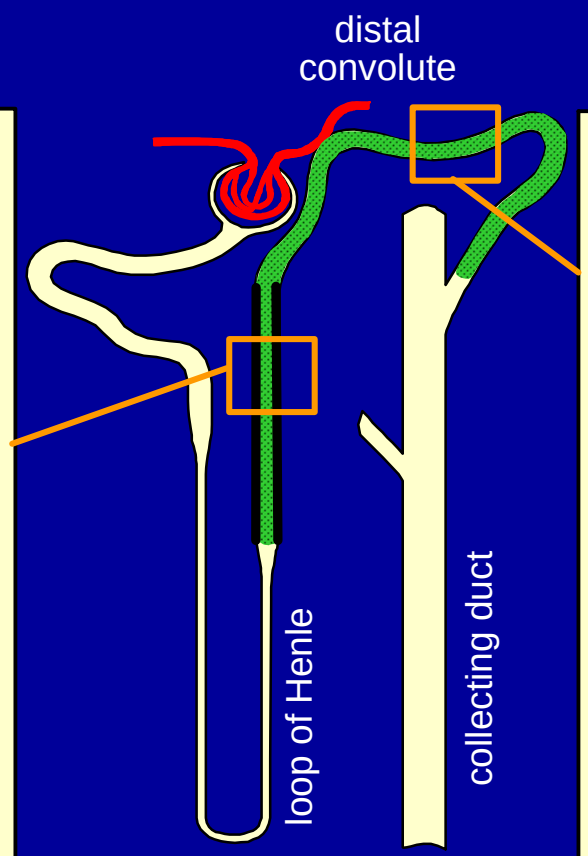


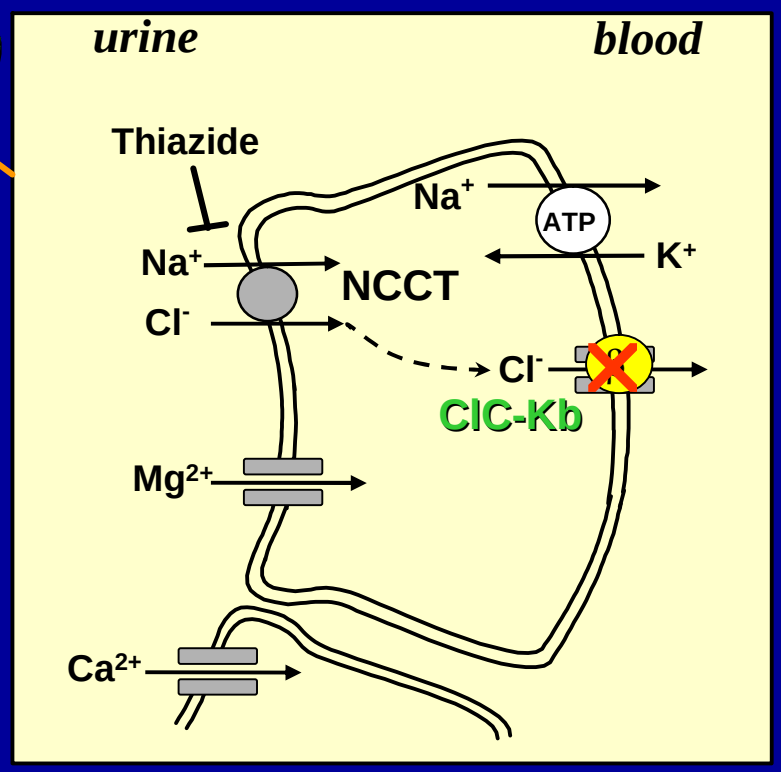
Loop of Henle

Distal Convolute

Furosemide-like SLT without hypercalciurea and DC-compensation is a combined loop- and distal convolute-defect.







Loop of Henle

Distal Convolute

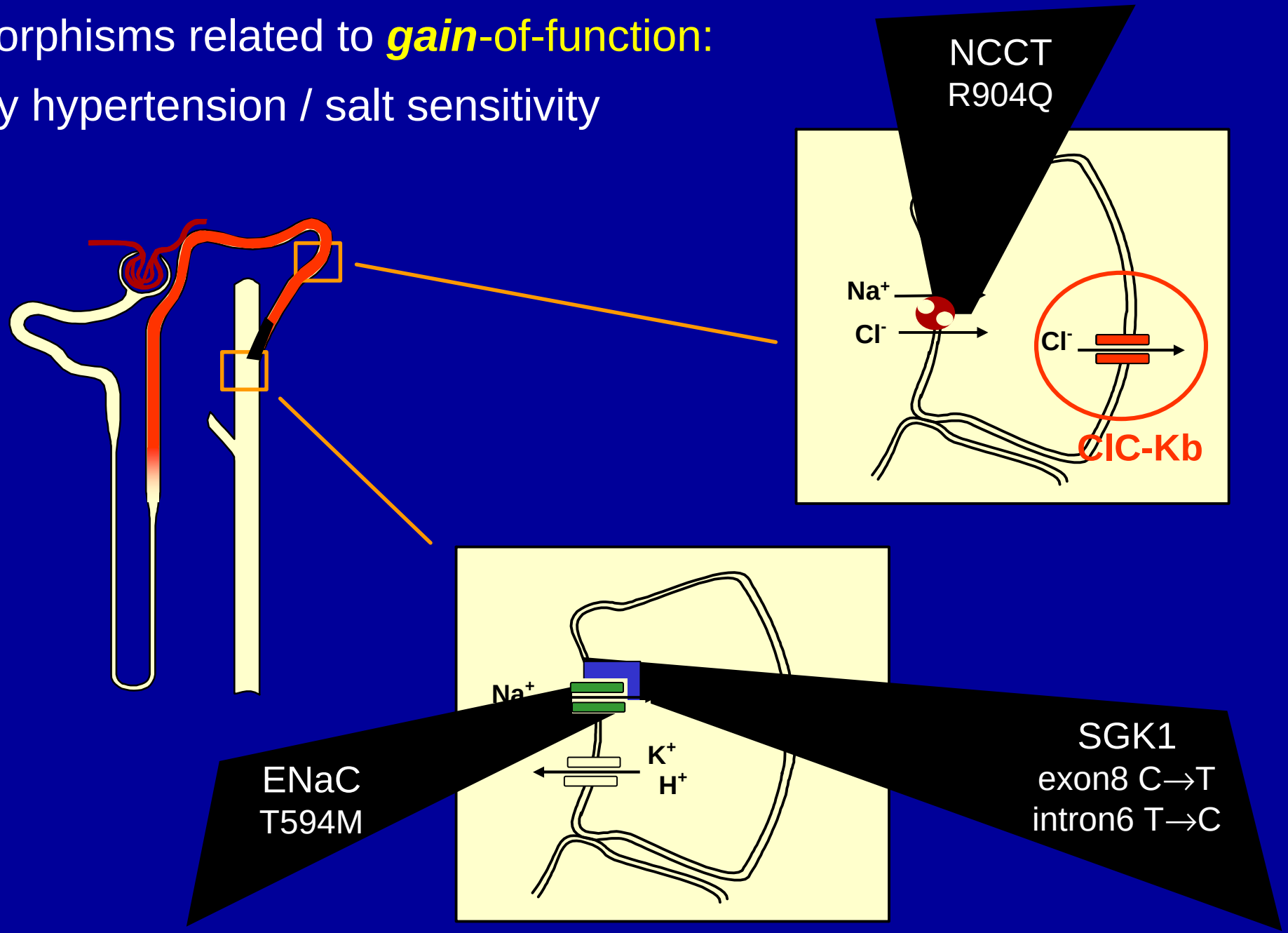
Letzter therapeutischer Ausweg bei dem kombinierten Schleifen- und distaler Konvolut-Defekt ist die unilaterale Nephrektomie bzw. Nierentransplantation.

Möglicher Nutzen von einer seltenen Krankheit:

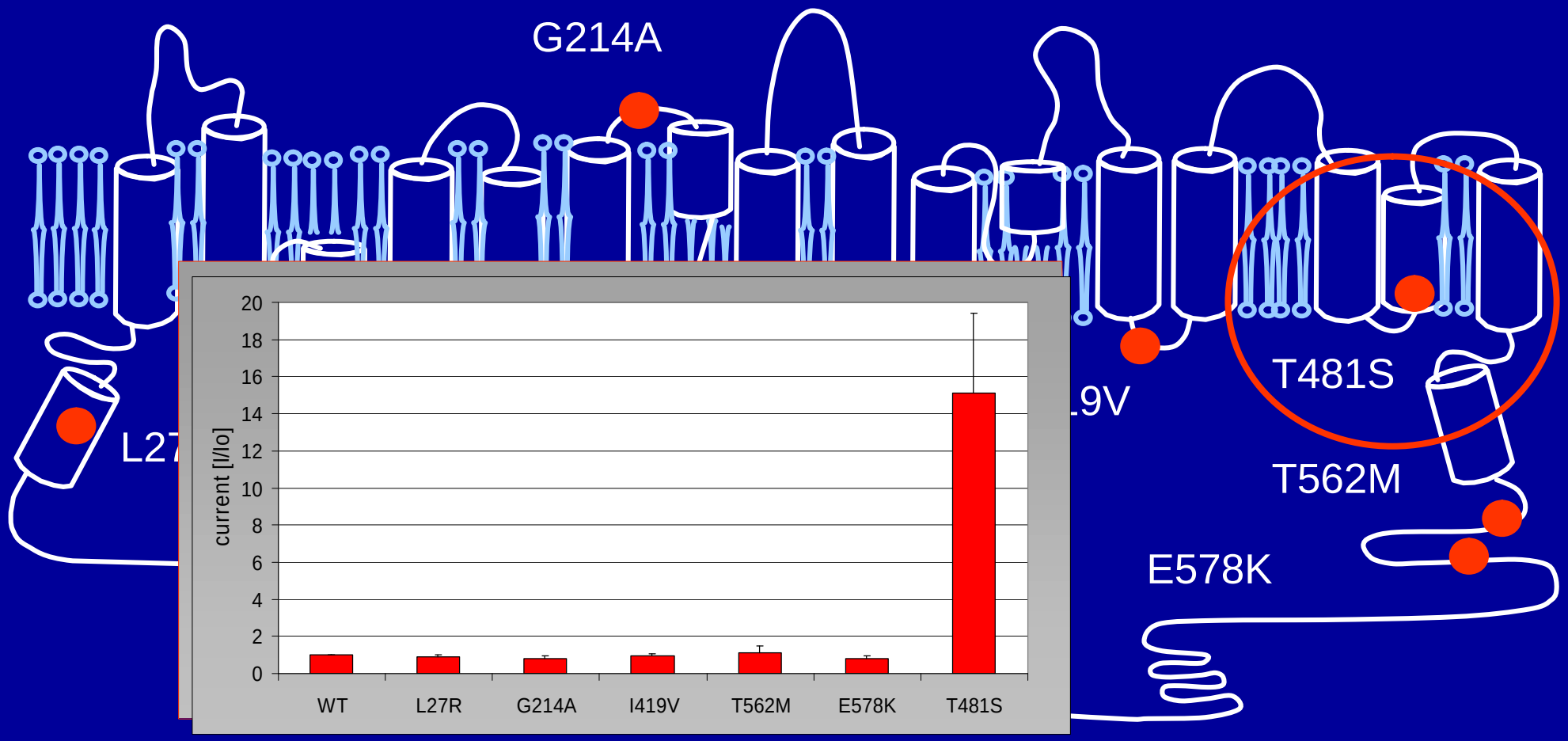
Von einer extrem seltenen Salzverlust-Krankheit (<1:100 000) zu einer weit verbreiteten Volkskrankheit (~30%) :
der Salz-sensitiven arteriellen Hypertonie ?

Polymorphisms related to ***gain***-of-function:

primary hypertension / salt sensitivity



ClC-Kb polymorphisms



This ClC-Kb T481S mutation with gain-of-function is associated with an elevated blood pressure in healthy volunteers

	T481S/WT	WT/WT	significance
n	35 (f/m~1/1)	156 (f/m~1/1)	
age (years)	33.0 ± 2.3	30.5 ± 0.9	ns
hight (cm)	173.3 ± 1.8	173.7 ± 0.8	ns
weight (kg)	67.8 ± 2.2	69.4 ± 1.1	ns
RR sys (mmHg)	138.1 ± 3.1	128.1 ± 1.2	p=0.0011
RR dias	84.1 ± 1.6	78.1 ± 0.8	p=0.0012
n(%) RR>140/90	51.4%	24.4%	p=0.012

The T481S polymorphism of CLC-Kb is almost twice as often in an African population from Ghana

Genotype	Tübingen (n=220)	Accra (n=131)
A allel	88.0 %	77.8 %
T allel	12.0 %	22.1 %

Jeck et al. 2004

The T481S polymorphism of CLC-Kb is almost twice as often in an African population from Ghana

Genotype	Tübingen (n=220)	Accra (n=131)
A allel	88.0 %	77.8 %
T allel	12.0 %	**22.1 %** Jeck et al. 2004

Schußfolgerungen

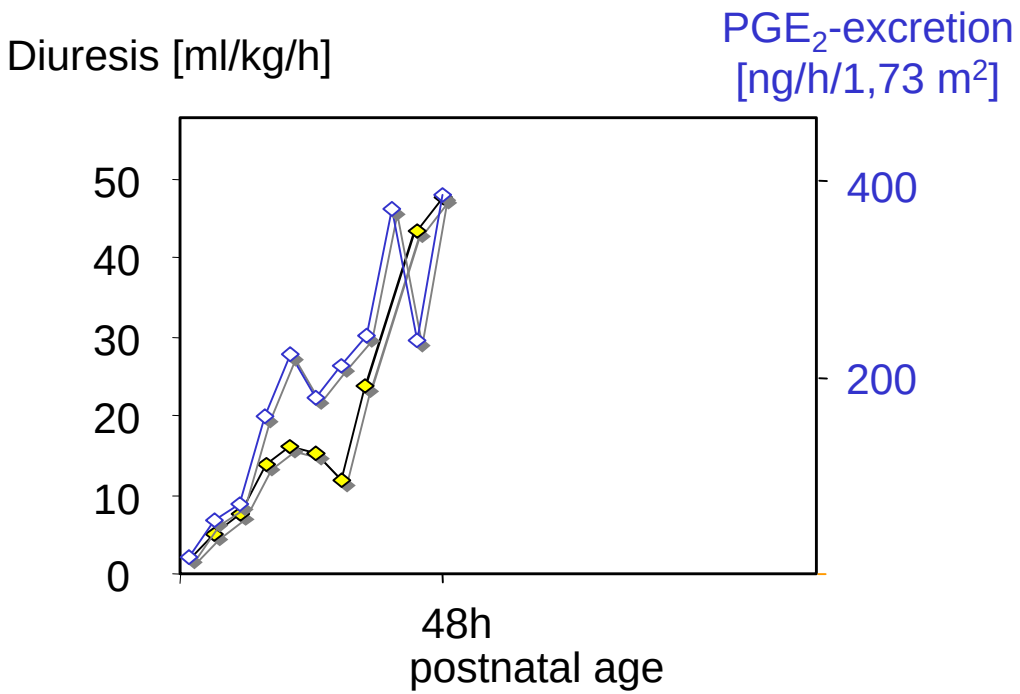
- Für die Volkskrankheit: Dem ClCK b-Kanal kommt bei dem transepithelialen Salztransport eine zentrale Stellung zu und bieten sich als „Target“ für die Entwicklung neuartiger Diuretica, z.B. für die Behandlung der Kochsalz-senitiven Hypertonie an.

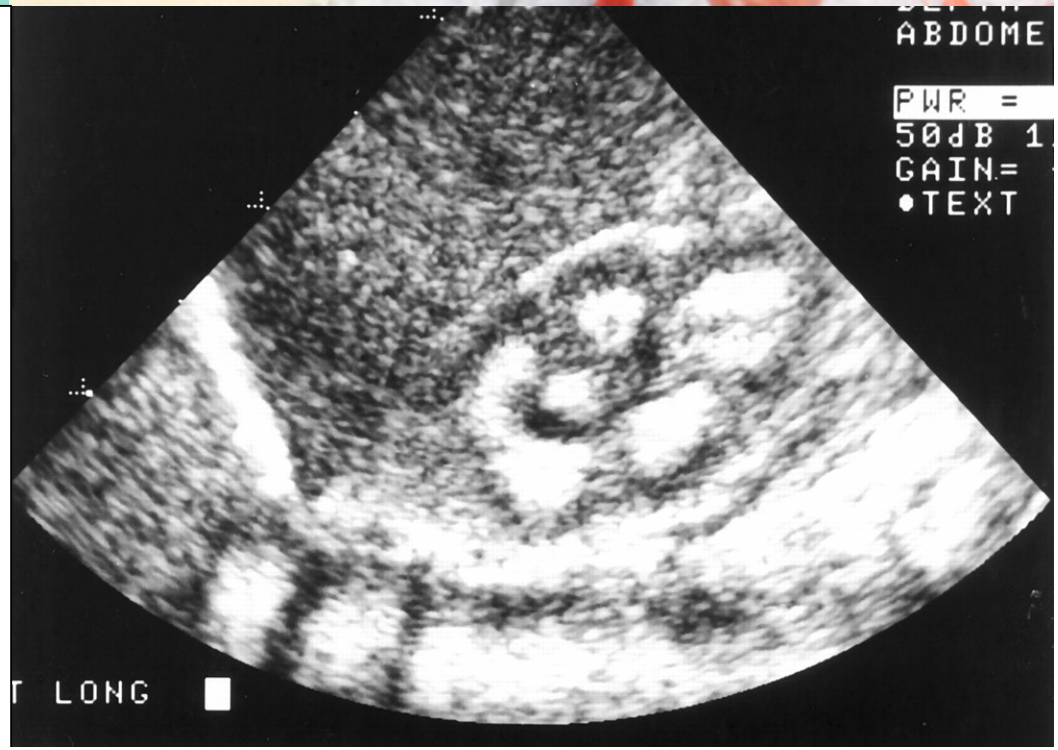
Schußfolgerungen

- Für die Volkskrankheit: Dem ClCK b-Kanal kommt bei dem transepithelialen Salztransport eine zentrale Stellung zu und bieten sich als „Target“ für die Entwicklung neuartiger Diuretica, z.B. für die Behandlung der Kochsalz-senitiven Hypertonie an;

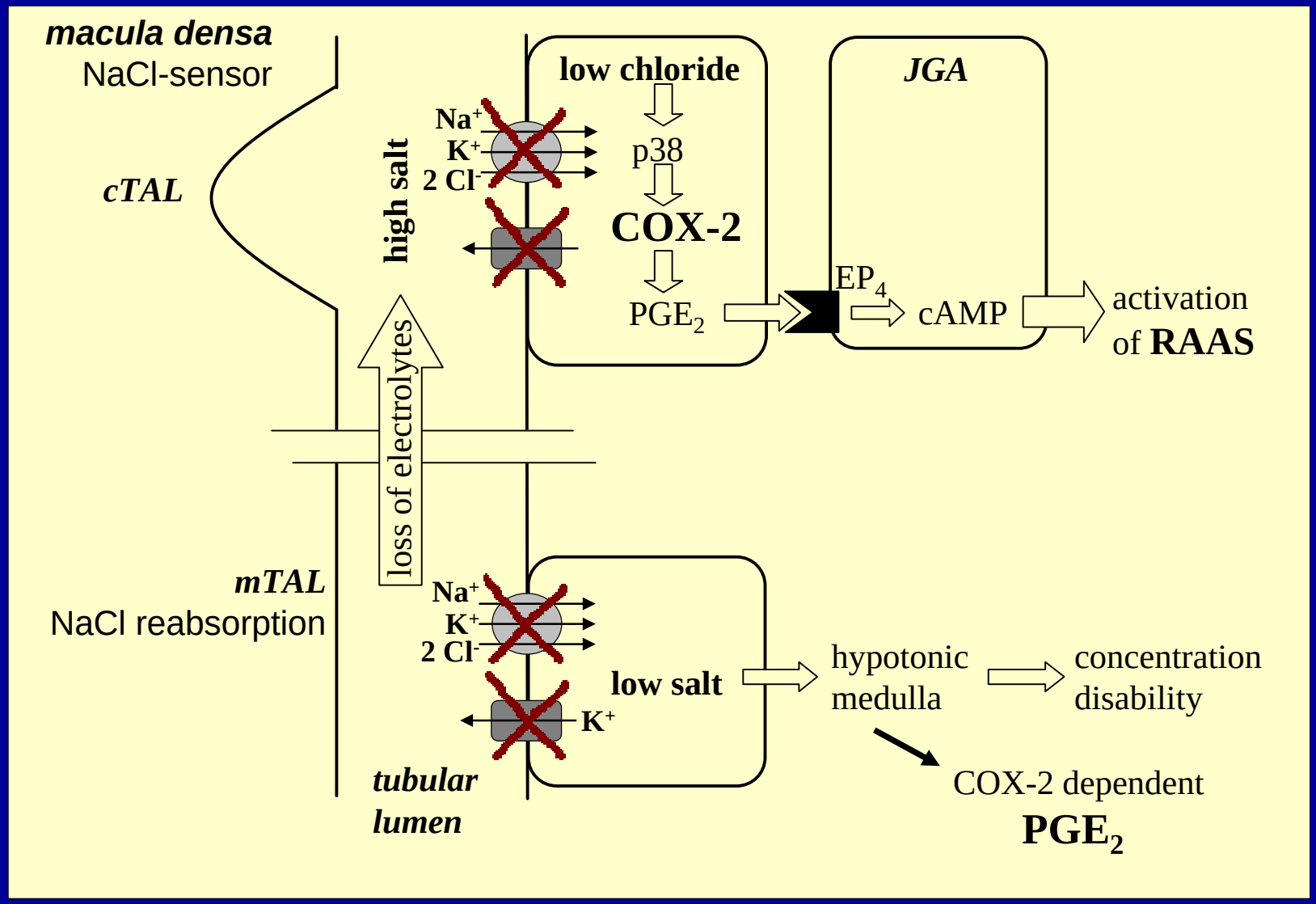
  weniger für den seltenen renalen Salzverlust,

  wie dem Hyperprostaglandin E-Syndrom (HPS)

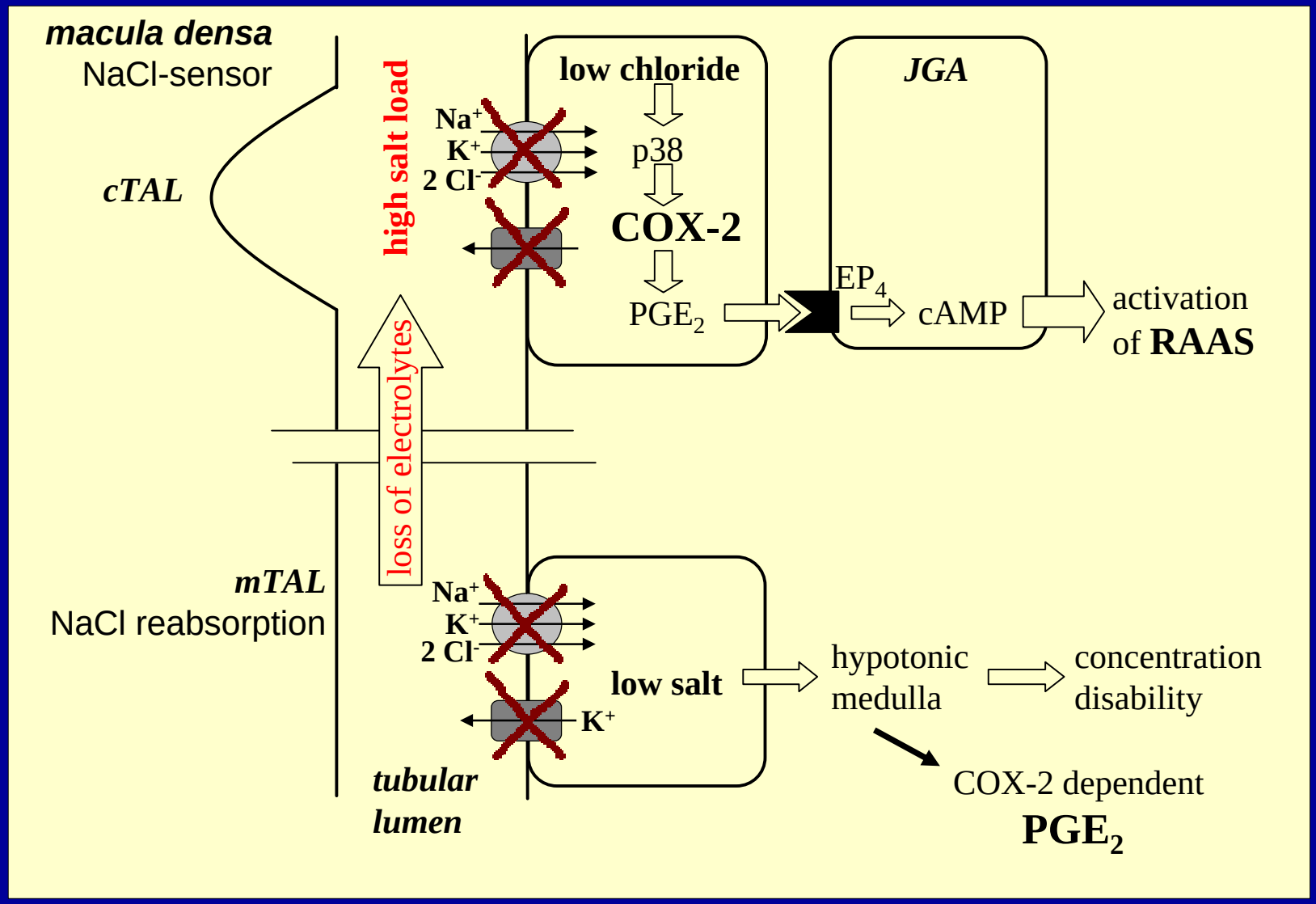

Diuresis [ml/kg/h]
PGE2-excretion
[ng/h/1,73 m2]
50
40
30
20
10
0
400
200
48h
postnatal age


ABDOME
PWR =
50dB 1
GAIN=
•TEXT
T LONG

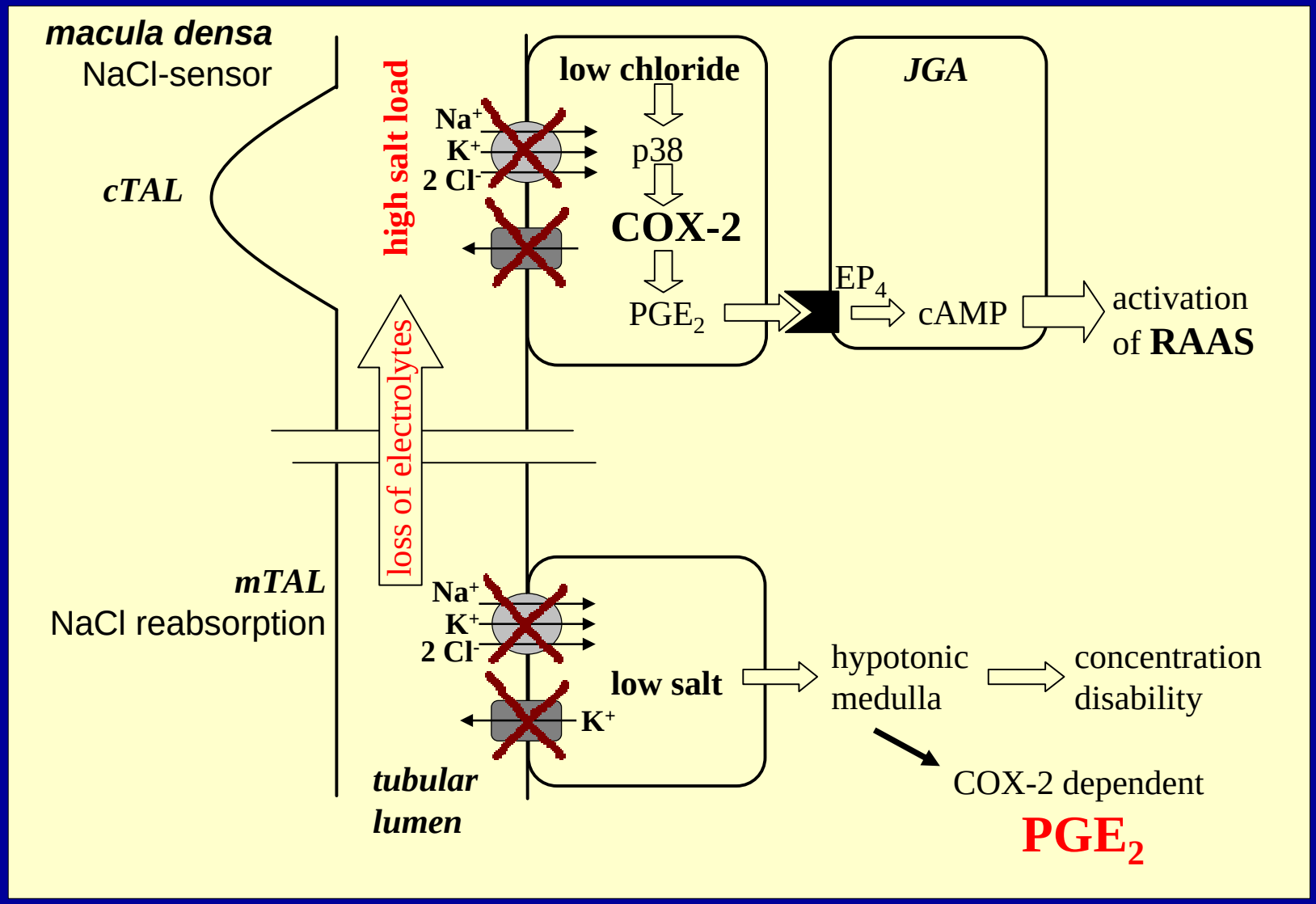
Present hypothesis of the relation between renal salt-wasting, RAAS-activation, and PGE-2-stimulation in the distal tubule



Present hypothesis of the relation between renal salt-wasting, RAAS-activation, and PGE-2-stimulation in the distal tubule



Present hypothesis of the relation between renal salt-wasting, RAAS-activation, and PGE-2-stimulation in the distal tubule



Schußfolgerungen

- Für die Volkskrankheit: Dem ClCK b-Kanal kommt bei dem transepithelialen Salztransport eine zentrale Stellung zu und bieten sich als „Target“ für die Entwicklung neuartiger Diuretica, z.B. für die Behandlung der Kochsalz-senitiven Hypertonie an.
- Für die seltene Erkrankung (HPS): Cox 2 und PGE2 sind integraler Teil der Signalverarbeitung im transepithelialen Salz-Transport in der Henle`schen Schleife und bieten sich als neues therapeutisches „Target“ an.

The Pediatric Research Team at our Department in Marburg, Germany

Neonatology/Nephrology

Andreas Leonhardt
Günther Klaus

Genetics

Nicola Jeck
Piet Schlingmann

Physiology

Petra Waldegger
Siegfried Waldegger

Pharmacology

Martin Kömhoff
Stephan Reinalter

Mass-Spectrometry

Horst Schweer
Bernhard Watzer

Reservedias

Conclusions

- ClC-K chloride channels participate in a critical way in chloride reabsorption along the distal nephron.
- Loss-of-function mutations in ClC-Ka and ClC-Kb cause a combined loop- and distal convolute-defect associated with severe renal salt wasting
- Gain-of-function mutations of ClC-Kb predisposes to renal salt retention and elevated blood pressure.

Conclusions

- ClC-K chloride channels participate in a critical way in chloride reabsorption along the distal nephron.
- Loss-of-function mutations in ClC-Ka and ClC-Kb cause a combined loop- and distal convolute-defect associated with severe renal salt wasting
- Gain-of-function mutations of ClC-Kb predisposes to renal salt retention and elevated blood pressure.
- A thiazide ought be the ideal antihypertensive target drug for this subpopulation, which is about 20% of the total caucasian population.

The second *General Conclusion* :

Orphan diseases, which are some kind of human knock-out models and can teach us general principles in normal and pathological physiology, are best studied in ealy life - even prenatally.

Modules of transepithelial electrolyte transport in the distal nephron