بسم الله الرحمن الرحيم

Bartter and Related Syndromes

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Mohamed Alaa Thabet

Professor of Pediatrics

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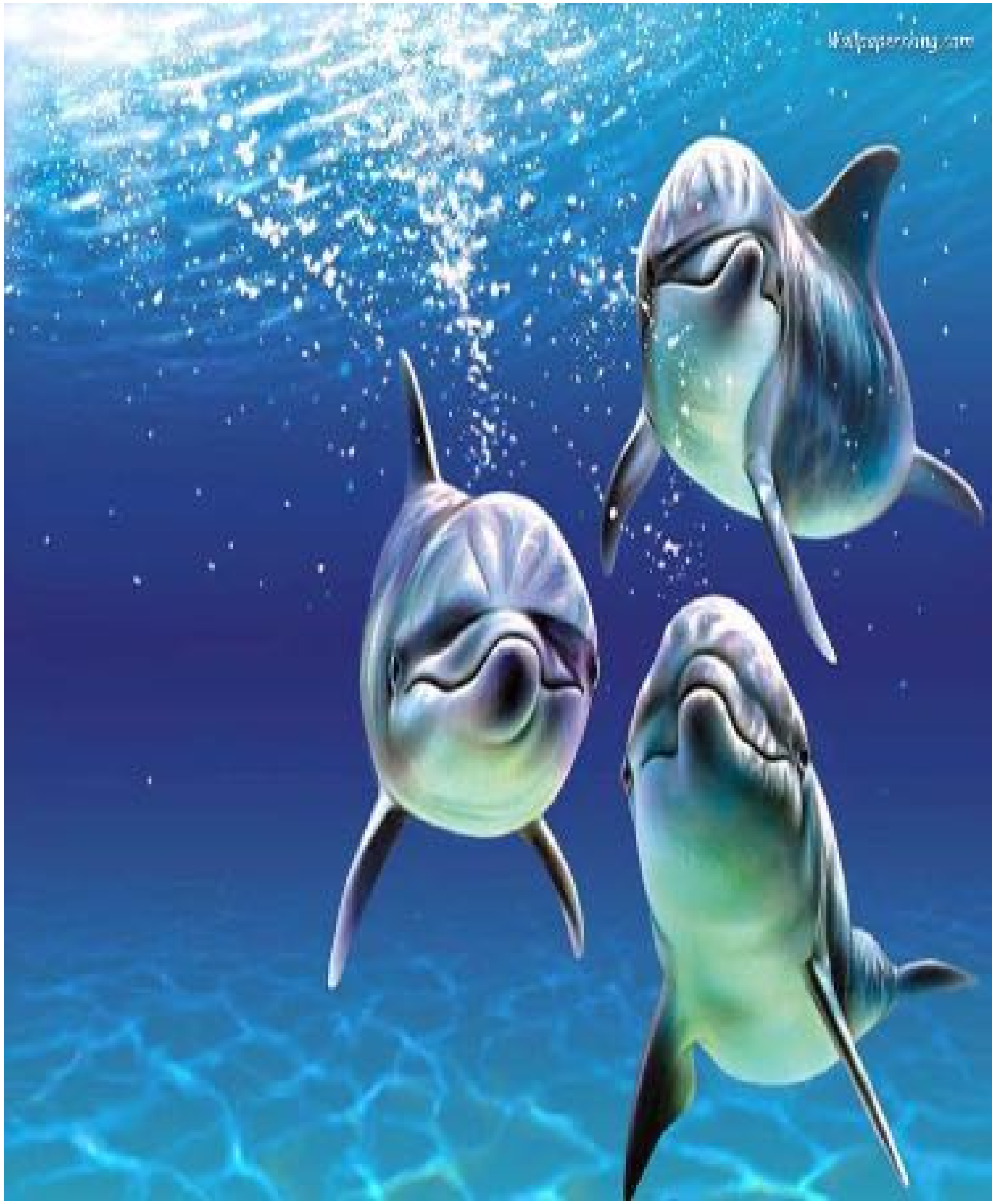

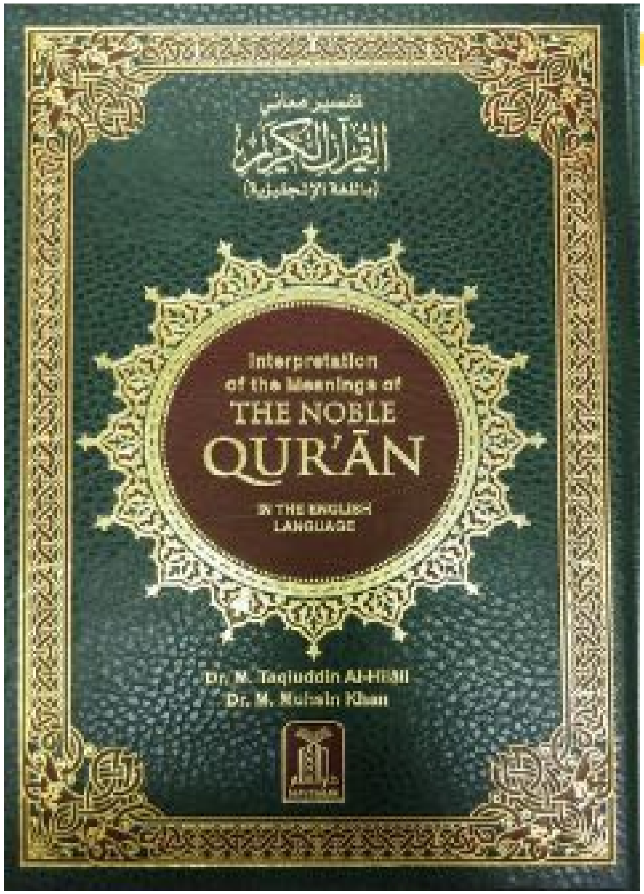

وَجَعَلْنَا مِنَ الْمَاءِ كُلَّ
شَيْءٍ حَيٍّ ۖ

God made from water
every living thing

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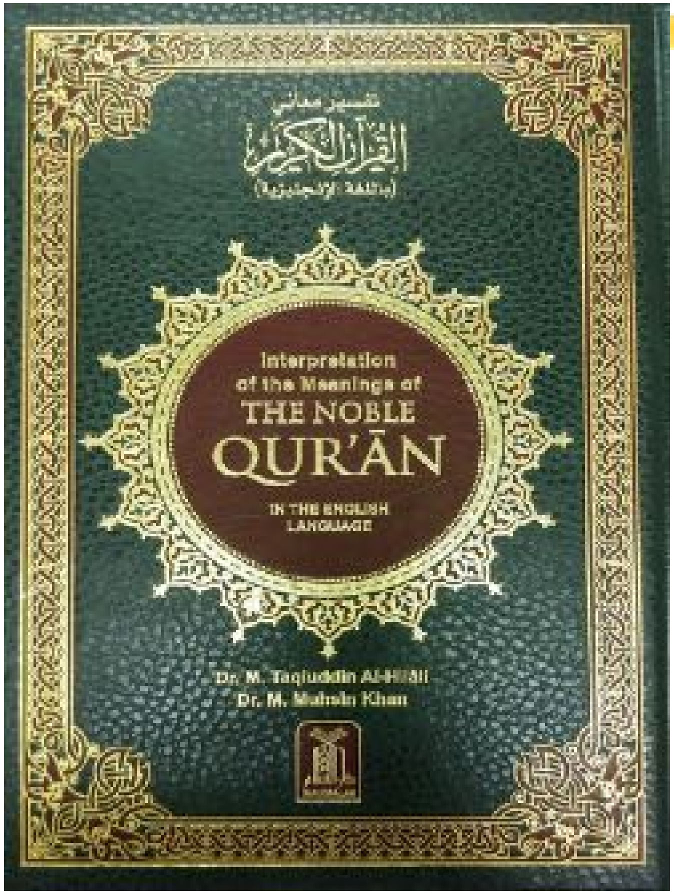
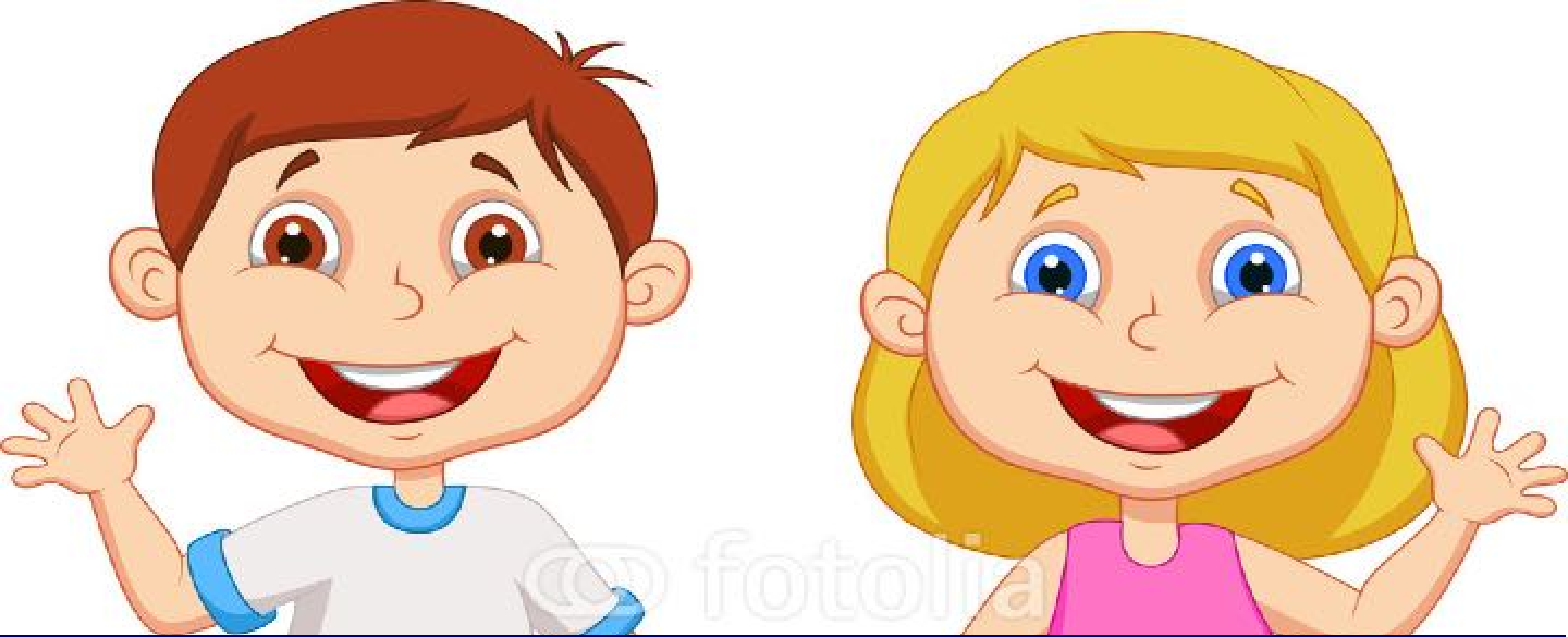


وَهُوَ الَّذِي خَلَقَ مِنَ الْمَاءِ بَشَرًا
فَجَعَلَهُ نَسَبًا وَصِهْرًا ۗ

God has created from water human being



2/3 water

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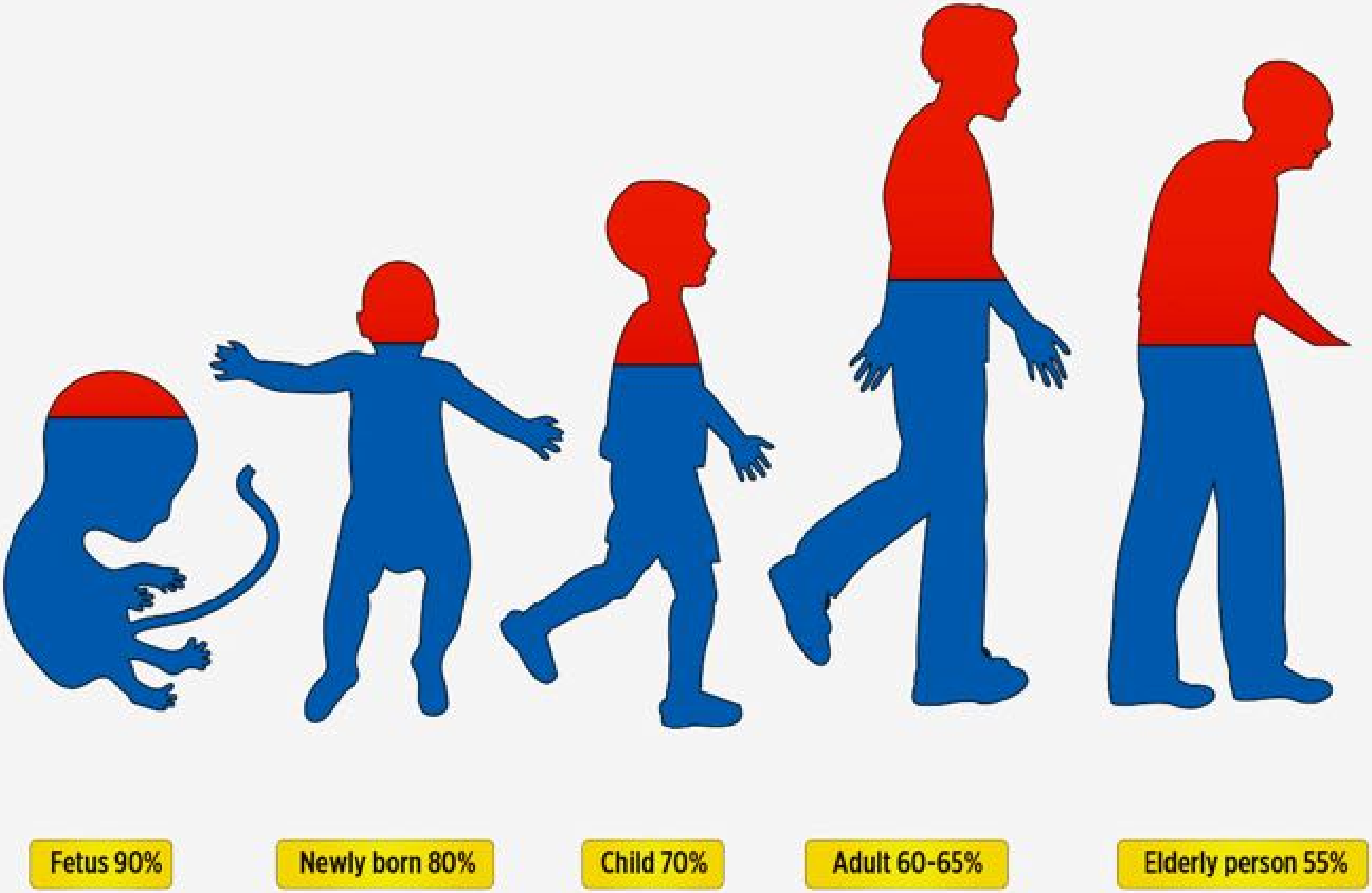
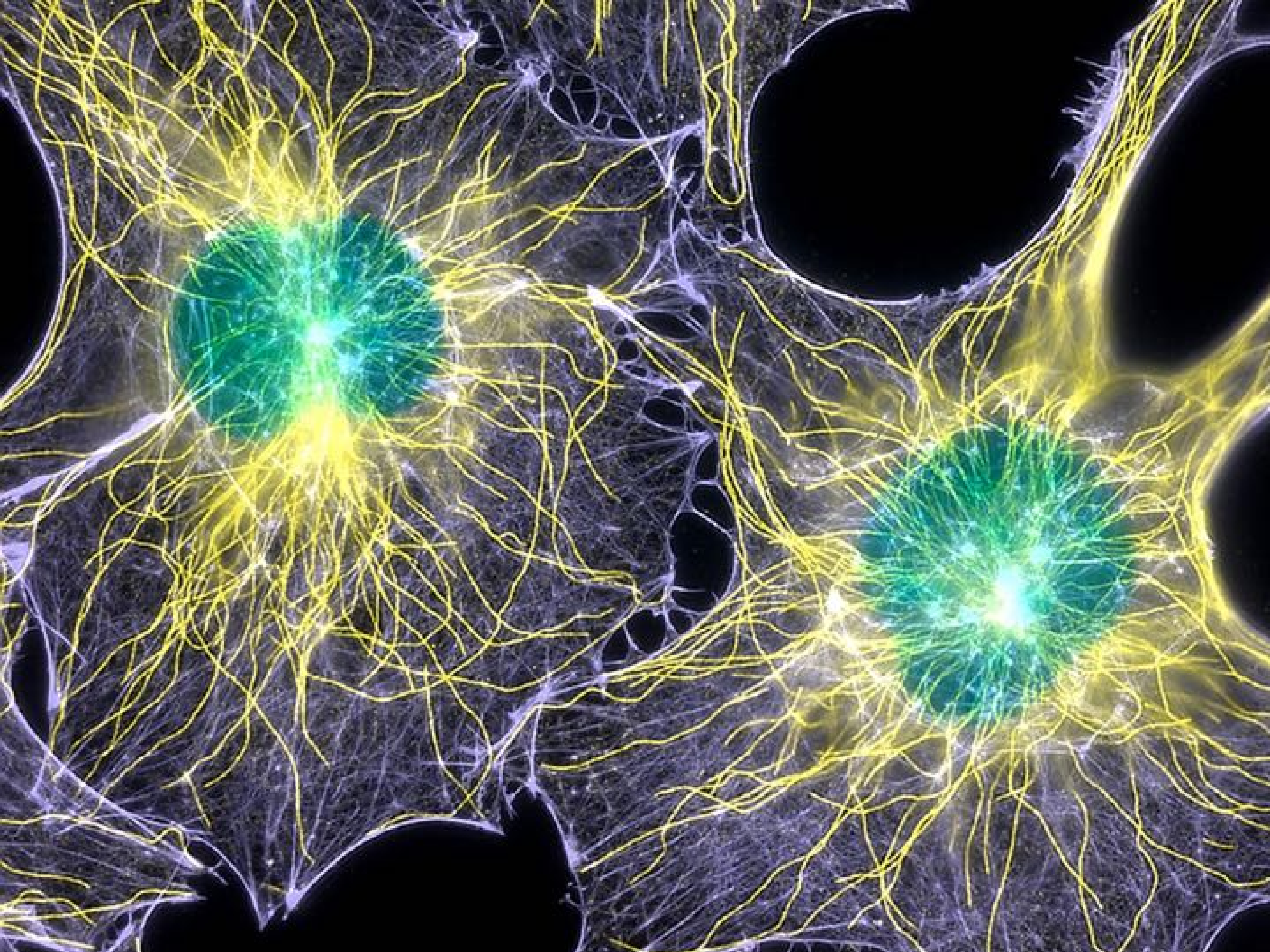
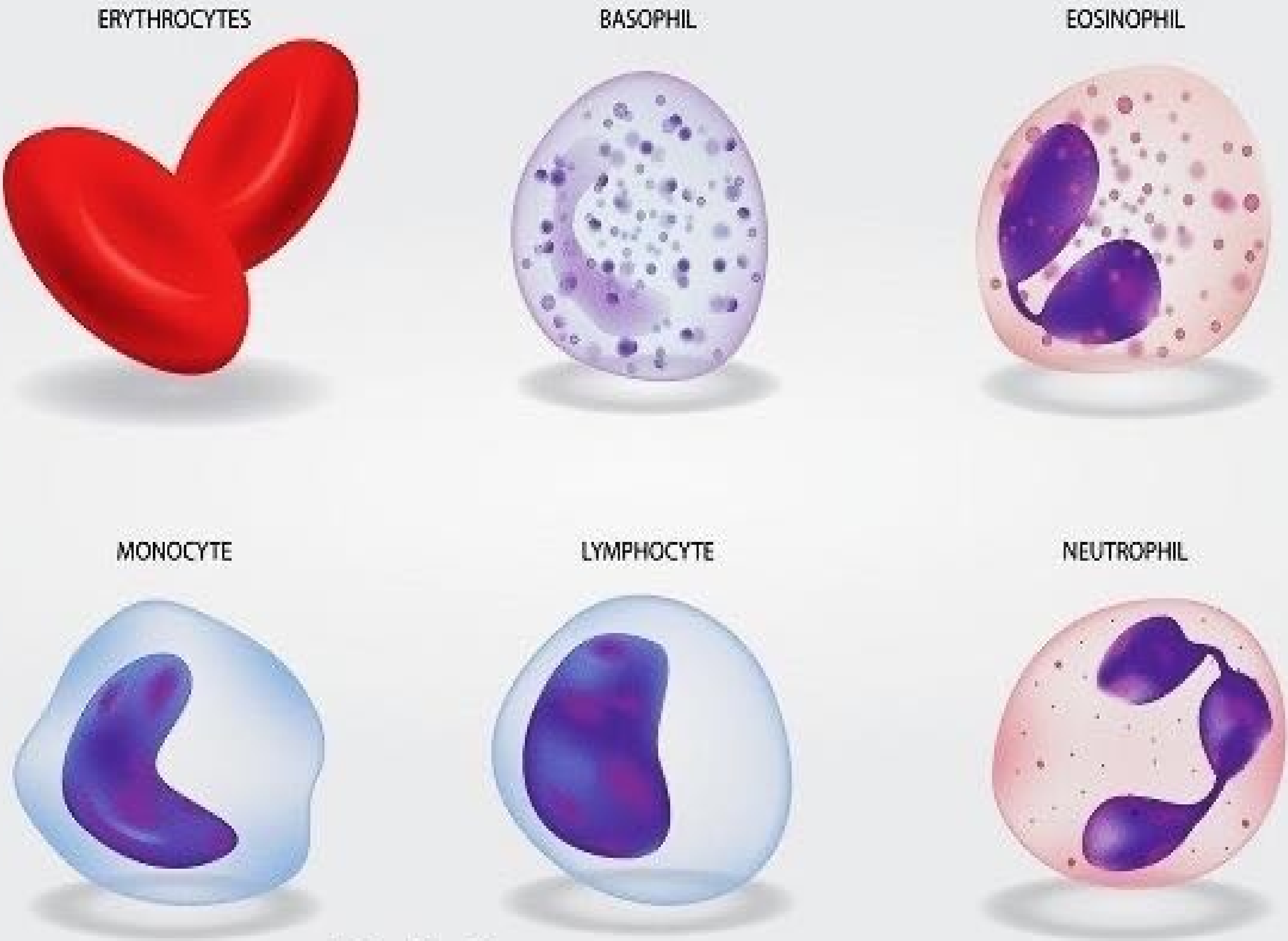
Water is the secret of life




ERYTHROCYTES
BASOPHIL
EOSINOPHIL
MONOCYTE
LYMPHOCYTE
NEUTROPHIL

Blood cells

Healthy kidneys

reabsorb > 99% of the filtered Na load

- **60%** Proximal tubule
- **30%** TAL
- **5%** DCT1
- **4%** ASDN (aldosterone-sensitive distal nephron)

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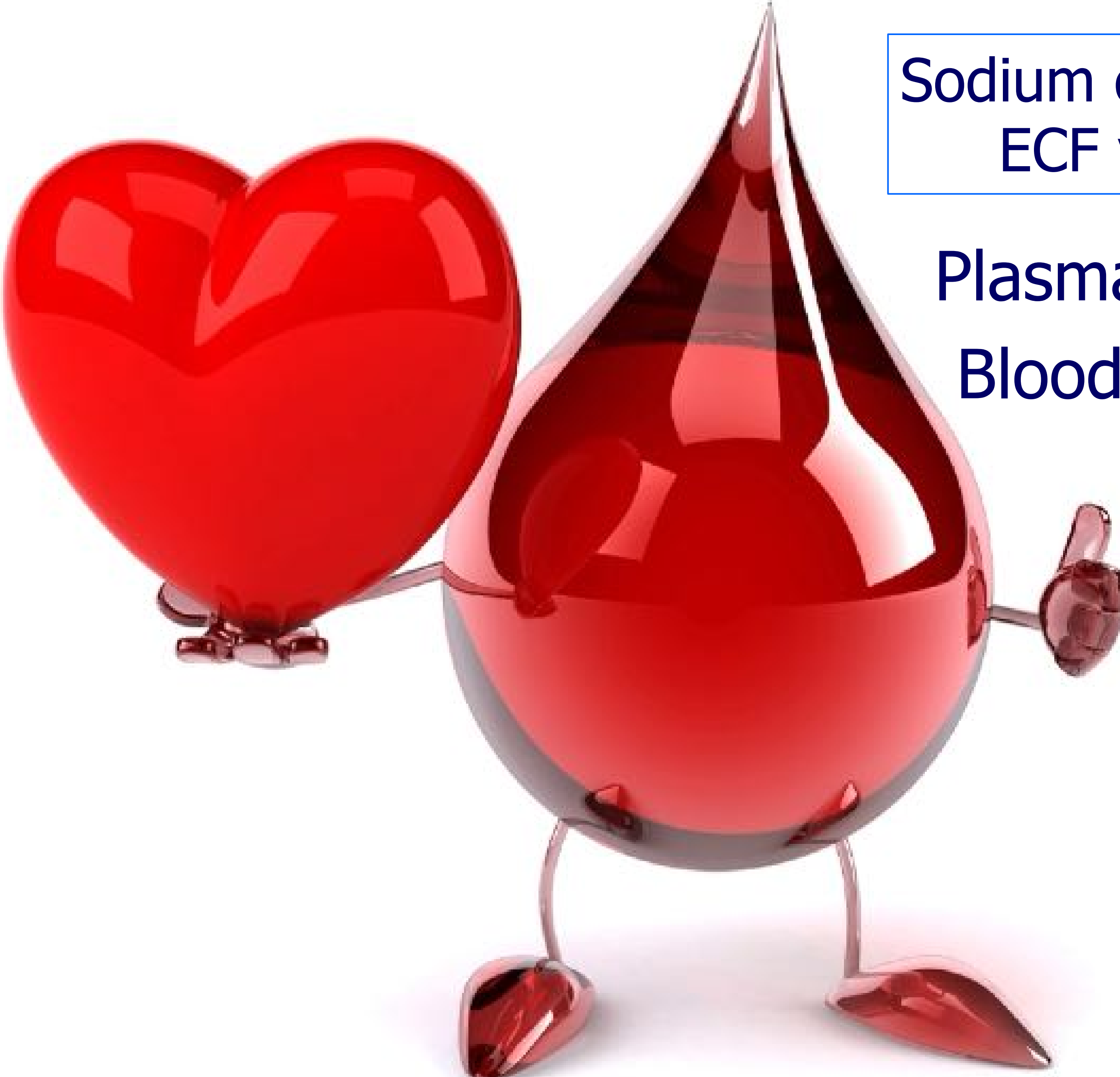
WHY ?

Healthy kidneys reabsorb

> 99%

of the filtered

Na load

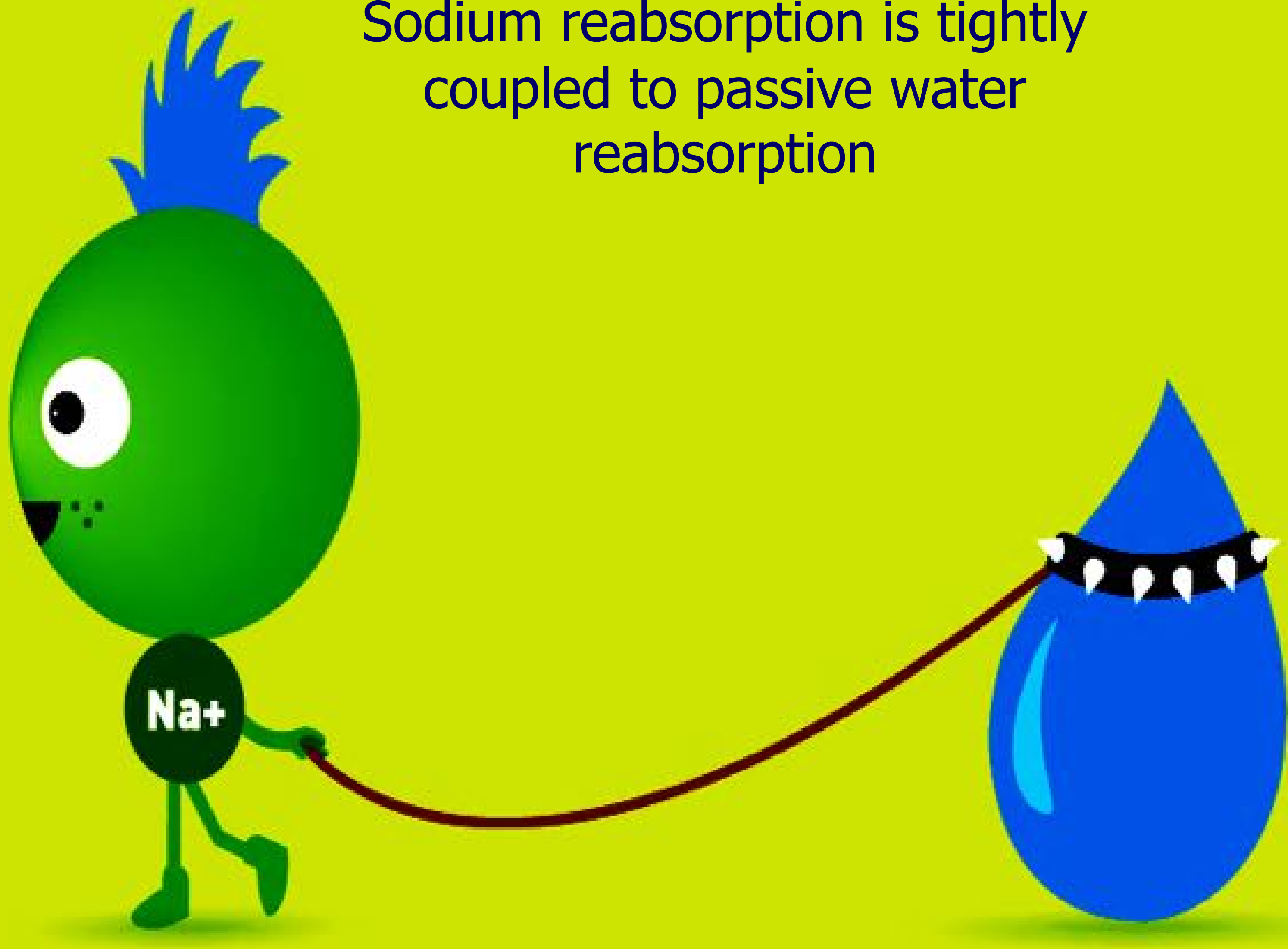


Sodium determines ECF volume

Plasma volume,
Blood volume,
BP.


SALT
Na
WATER
Net Weight 40 lbs

Sodium reabsorption is tightly coupled to passive water reabsorption



"Water follows salt"

BEST FRIEND OF ELECTROLYTES

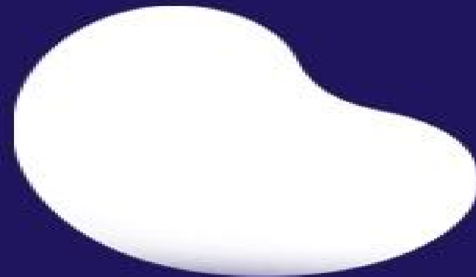
GFR= 100ml/min/1.73m^2

GFR= 100ml/60min/24hr

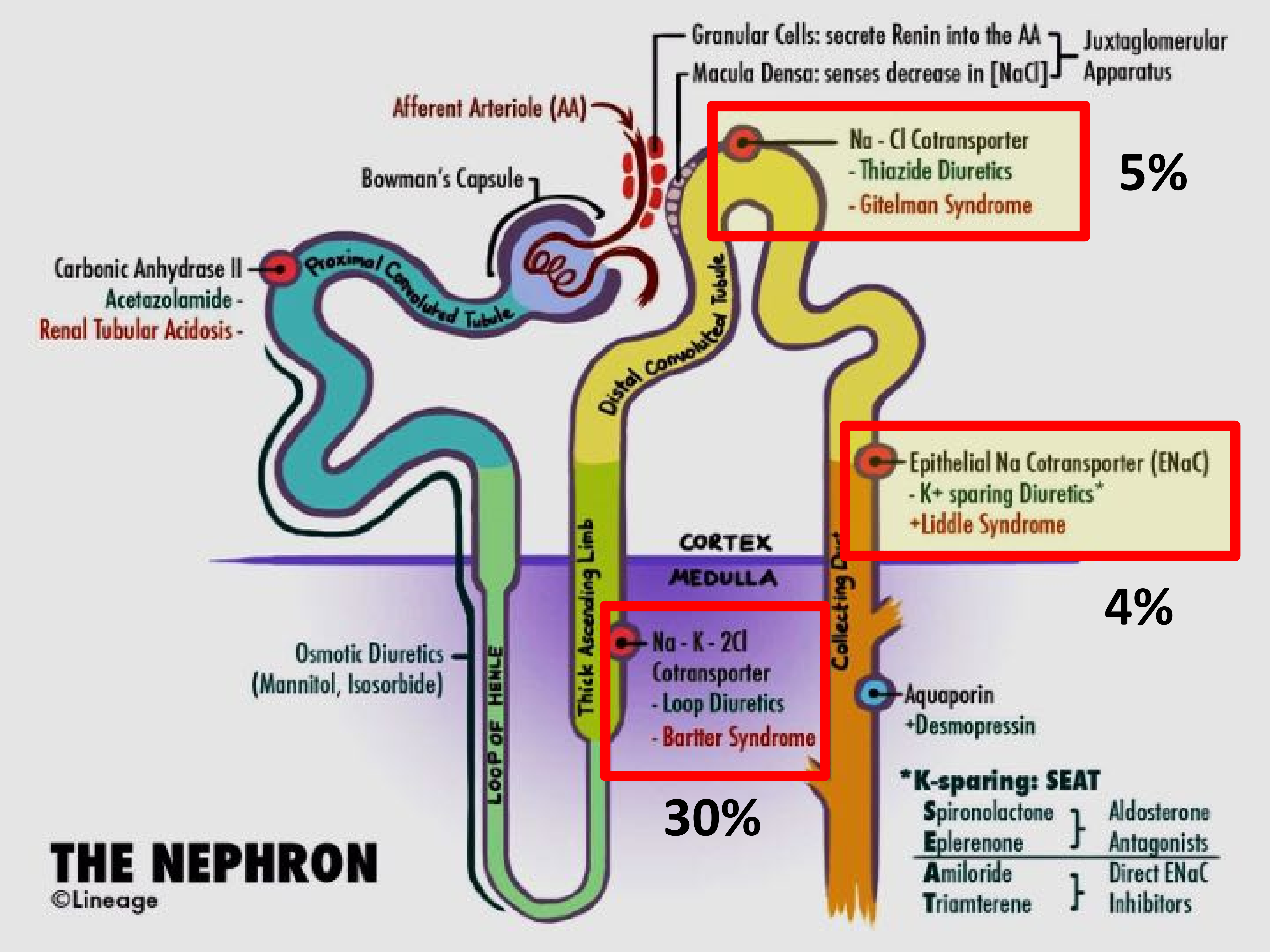
144 L / daily

You can not drink this amount

Your kidney can do it



KEEP
CALM
AND
LOVE
YOUR
KIDNEYS



Granular Cells: secrete Renin into the AA
Macula Densa: senses decrease in [NaCl]
Juxtaglomerular Apparatus
Afferent Arteriole (AA)
Bowman's Capsule
Na - Cl Cotransporter
- Thiazide Diuretics
- Gitelman Syndrome
5%
Carbonic Anhydrase II
Acetazolamide -
Renal Tubular Acidosis -
Proximal Convoluted Tubule
Distal Convoluted Tubule
Epithelial Na Cotransporter (ENaC)
- K+ sparing Diuretics*
+Liddle Syndrome
CORTEX
MEDULLA
4%
Thick Ascending Limb
Collecting Duct
Na - K - 2Cl Cotransporter
- Loop Diuretics
- Bartter Syndrome
Osmotic Diuretics
(Mannitol, Isosorbide)
LOOP OF HENLE
Aquaporin
+Desmopressin
30%
*K-sparing: SEAT
Spironolactone
Eplerenone
Aldosterone Antagonists
Amiloride
Triamterene
Direct ENaC Inhibitors
THE NEPHRON
©Lineage

Bartter Syndrome

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Barter

History

1962, Bartter et al

a new syndrome

characterized by

hypokalemia , metabolic alkalosis ,

hyperaldosteronism

&

hyperplasia of the juxtaglomerular apparatus (JGA).

History

1962, Bartter et al

These patients were different

from

the typical patients with

hyperaldosteronism

because they were

younger,

had normal BP & growth retardation.

BARTTER SYNDROME

Hypokalemic

Hypochloremic

Metabolic alkalosis

Normotensive

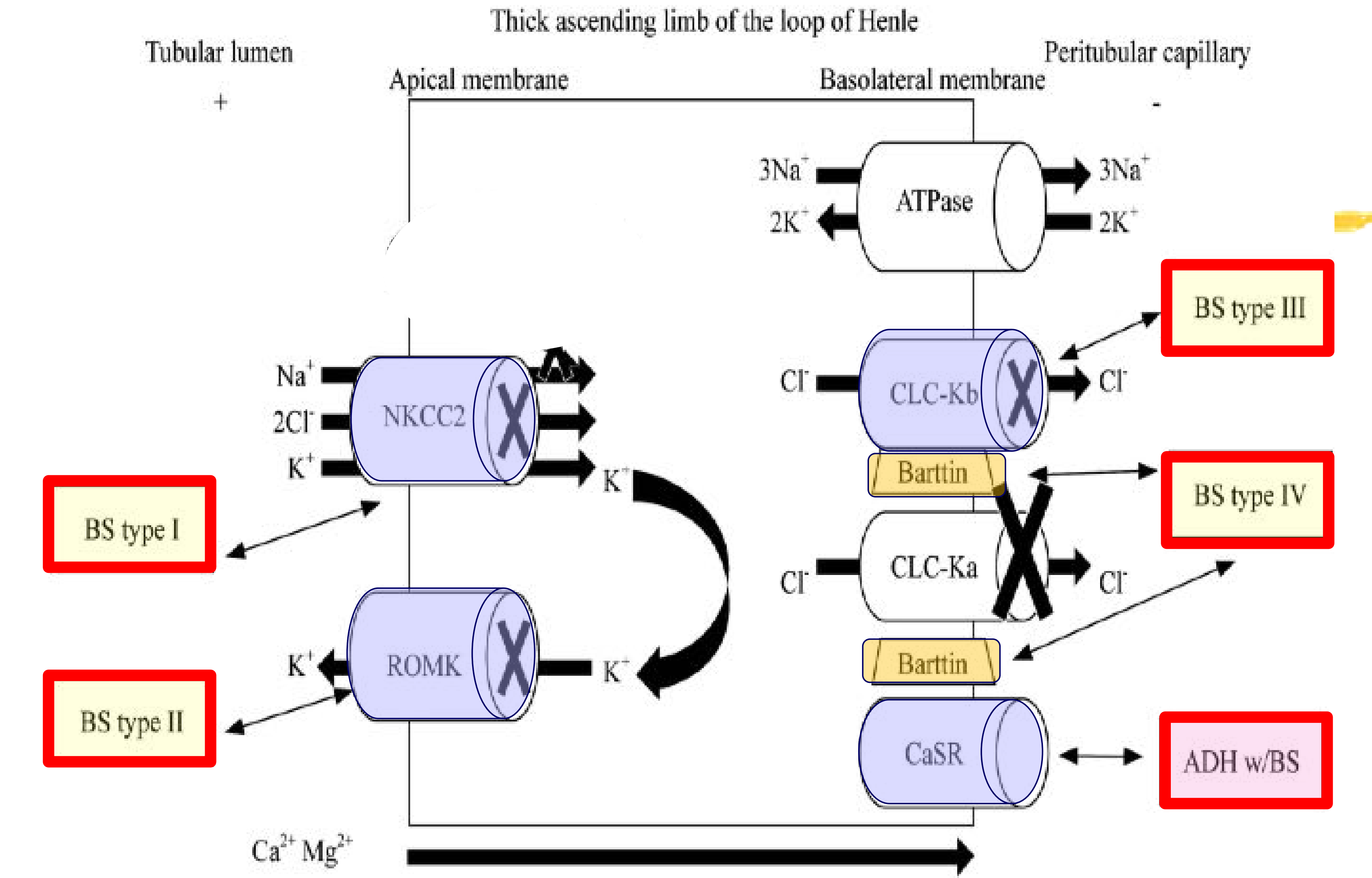
Elevated plasma renin level

BARTTER SYNDROME

- Autosomal recessive
- Renal salt wasting
- Dysfunction of **5** ion-transporting proteins

Defective proteins in TAL ➡ BS

1	**NKCC2**	Furosemide sensitive Na- K- Cl co-transporter
2	**ROMK**	Renal Outer Medullary K channel
3	**CLC-Kb**	Chlorid channel Kb
4	**Barttin**	(β subunit of CLC-Ka & CLC-Kb)
5	**CaSR**	Calcium sensing receptor



Bartter's syndrome: clinical findings, genetic causes and therapeutic approach

Flavia Cristina Carvalho Mrad, Sílvia Bouissou Morais Soares, Luiz Alberto Wanderley de Menezes Silva, Pedro Versiani dos Anjos Menezes, Ana Cristina Simões-e-Silva

World Journal of Pediatrics **volume 17**, pages 31–39 (2021)

TAL is involved in 3 key functions:

1. Salt reabsorption 30%

Hypokalemia **Alkalosis**

2. Generation of the interstitial conc. gradient needed for urinary conc. in CD.

Polyuria **Poldipsia**

Dehydration

Fever

3. Calcium & magnesium reabsorption

Hypercalciuria

BARTTER SYNDROME

TAL
30 %

Inhereted tubular defect

Decreased Na Cl transport

Na Cl WASTING

ECF contraction

RAAS

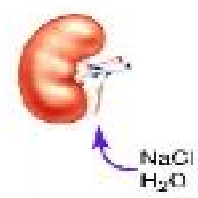
PGE2

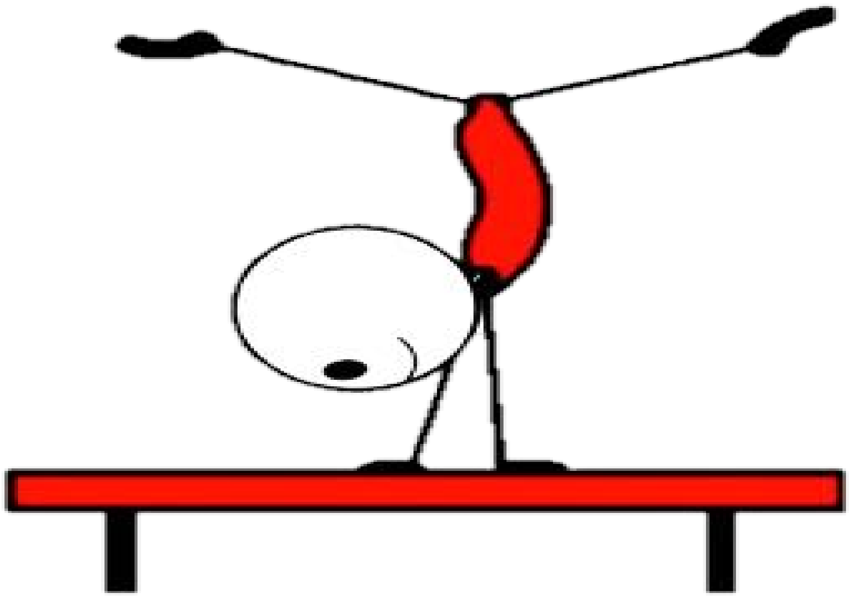
Increased urinary K^+ H^+ excretion

Decreased urinary concentrating ability

Polyuria

Hypokalemic Metabolic Alkalosis





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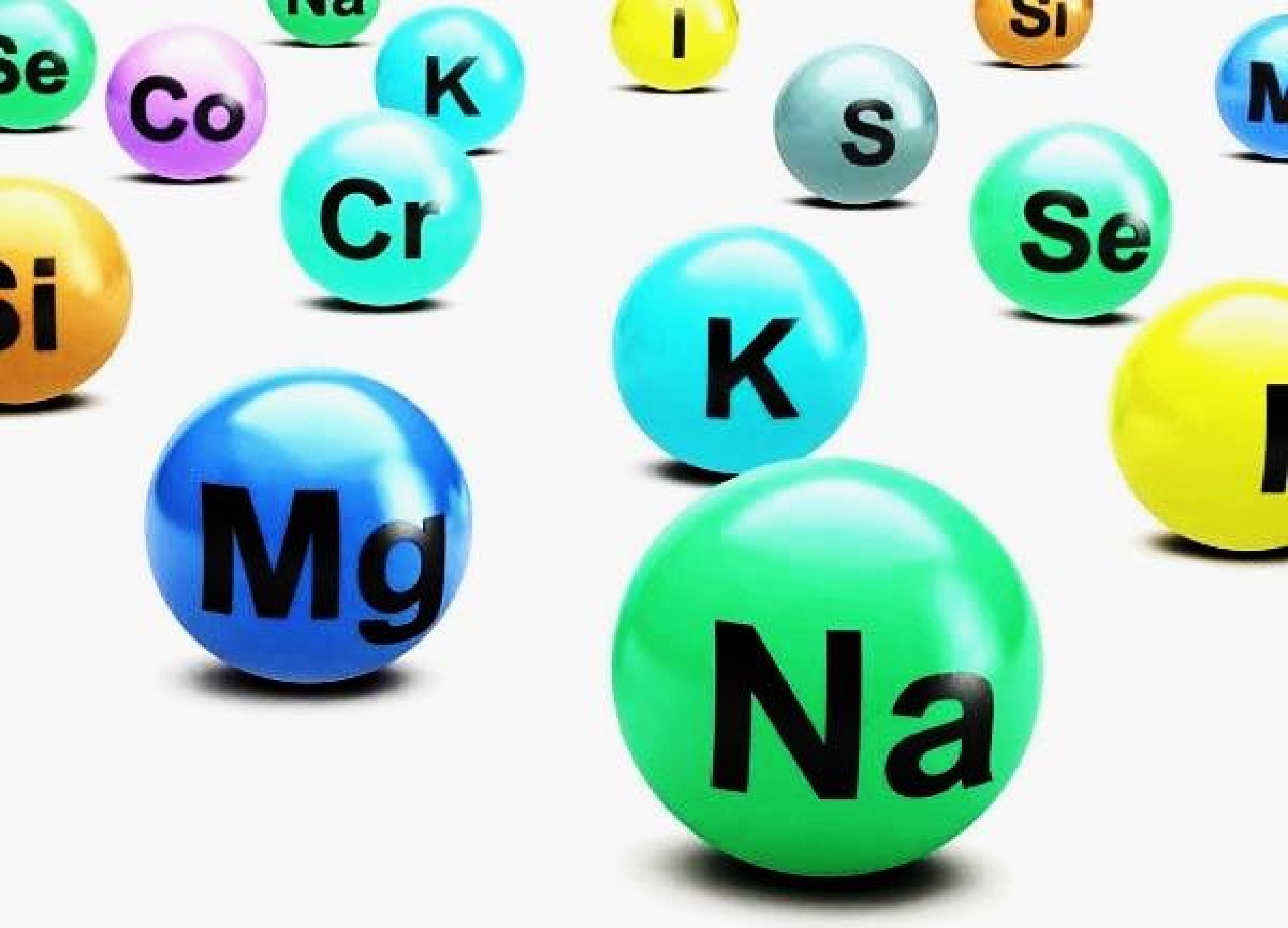
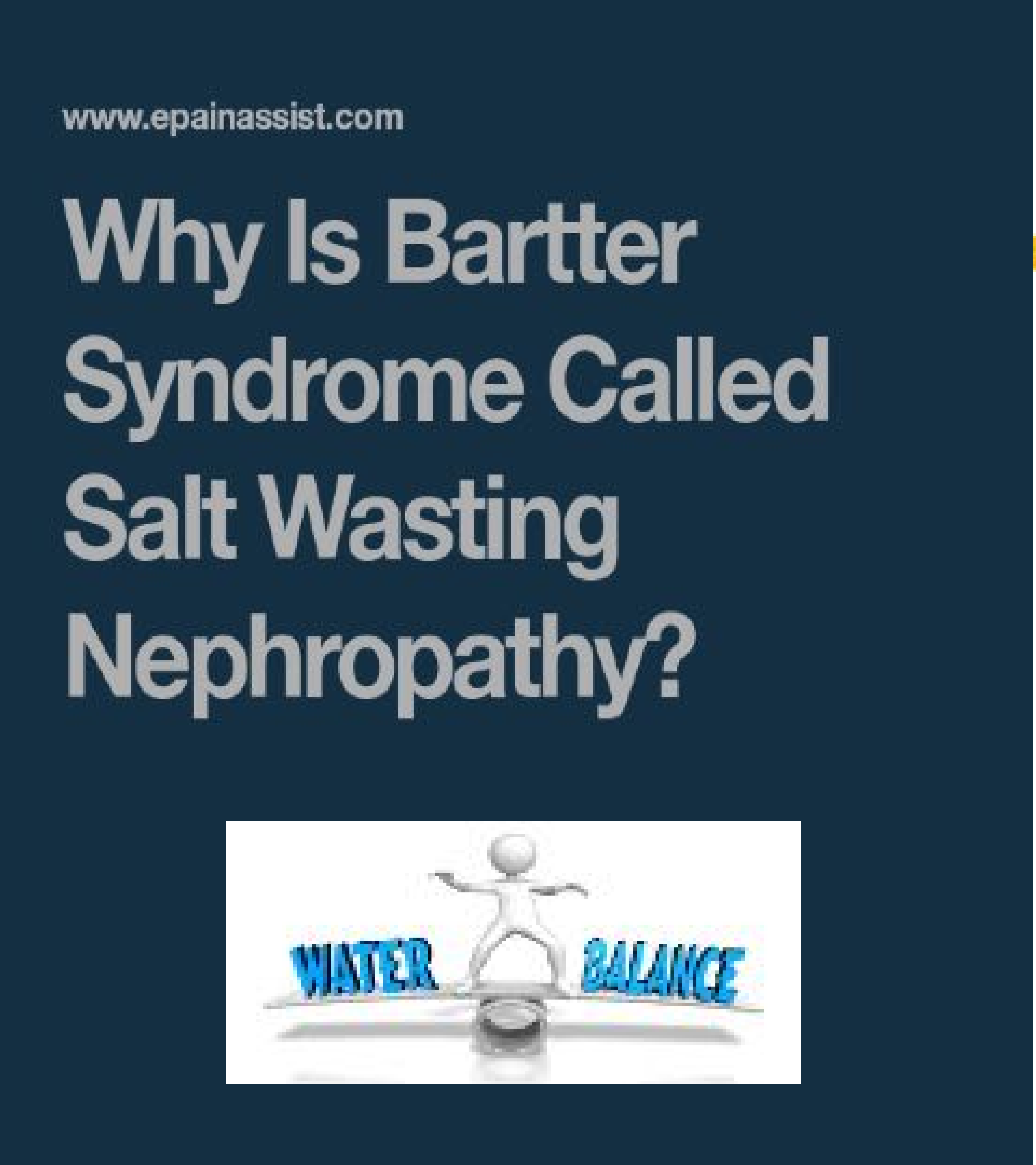

Co
K
Cr
I
S
Se
K
Mg
Na


ELECTROLYT


WATER
BALANCE



The primary defect in Bartter syndrome is

impaired Na reabsorption,

&

K wasting reflects the renal response

to

maintain volume homeostasis.

If Bartter is salt wasting

What about Na intake ?

Na supplementation is key in the treatment of

Bartter syndrome.

Adequate salt intake may help in management of hypokalemia.

If Bartter is salt wasting
What about Na intake ?

Consequently,

generous salt supplementation

(up to 10 mmol / kg)

can help ameliorate the hypokalemia.

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TYPES of BS

1. **Type I** **“Antenatal Bartter ”**
2. **Type II** **“Antenatal Bartter ”**
3. **Type III** **“ Classical Bartter ”**
4. **Type IV** **“Sensorineural deafness ”**
5. **Type V** **“ Hypocalcemic tetay”**

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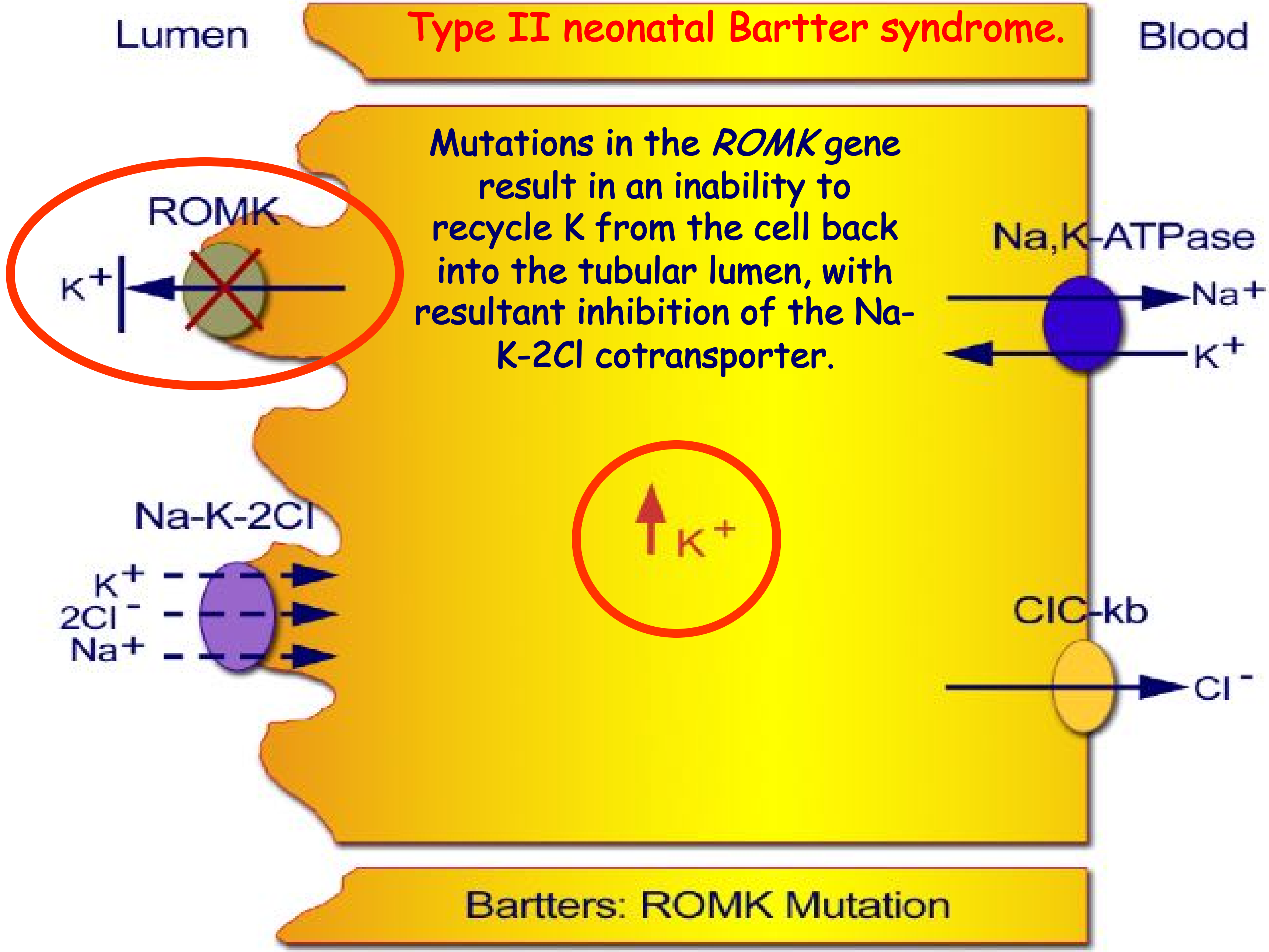
TYPES of BS

- 1, 2, and 4 have antenatal or neonatal presentation.

- Type 2 may be characterized by *hyperkalemia*, rather than hypokalemia, in the neonatal period.

- Bartter type 3 is the "classic Bartter syndrome."

- Bartter 4 has associated sensorineural deafness.


Type II neonatal Bartter syndrome.
Lumen
Blood
Mutations in the *ROMK* gene result in an inability to recycle K from the cell back into the tubular lumen, with resultant inhibition of the Na-K-2Cl cotransporter.
ROMK
K+
Na,K-ATPase
Na+
K+
K+
Na-K-2Cl
K+
2Cl−
Na+
ClC-kb
Cl−
Bartters: ROMK Mutation

Pseudohypoaldosteronism type 1

- AR or AD
- Severe urinary salt wasting,
- Metabolic acidosis, hyponatraemia, hyperkalaemia
- Raised plasma renin & aldosterone.
- Presenting in the neonatal period
    1. weight loss,
    2. vomiting, dehydration,
    3. sometimes respiratory distress.

Classification
according clinical picture

1. Neonatal / Severe

2. Classic / Mild

Clinical features
Antenatal

1. Fetal polyuria → Polyhydramnios
2. IUGR
3. Preterm birth

Clinical features
Postnatal

1. Polyuria
2. Failure to thrive
3. Nephrocalcinosis
4. Growth retardation
5. Recurrent vomiting
6. Severe dehydration episodes

Clinical features
Postnatal

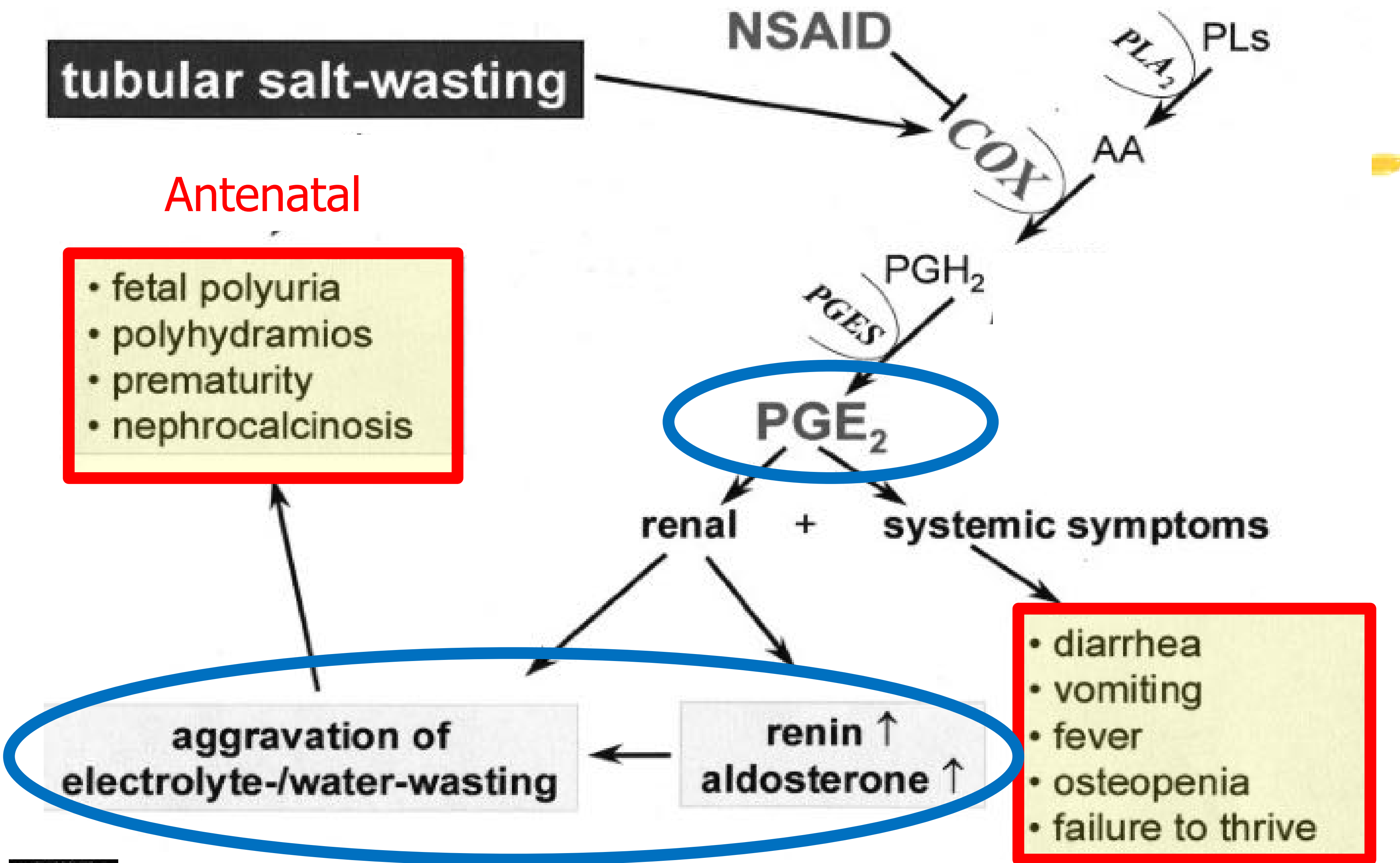
1. The polyuria can be massive (>20 mL/kg/h)
2. Life-threatening episodes of dehydration

Clinical features
Postnatal

Systemic manifestations including

1. fever of unknown origin
2. diarrhea
3. vomiting
4. convulsions

Hyperprostaglandin E syndrome / antenatal Bartter syndrome



Postnatal

Kidney International 2002 62253-260DOI: (10.1046/j.1523-1755.2002.00435.x)

Clinical features
Classical form

- Milder phenotype
- Variable age of onset
- Diagnosis is frequently delayed from infancy to adolescence

Clinical features
Classical form

- Enuresis
- Polydipsia
- Weakness
- Salt craving
- Occasional polyuria
- Episodes of dehydration
- Growth retardation
- Mild mental retardation

DIAGNOSIS OF BARTTER SYNDROME

- *CLINICAL PICTURE*
- *BIOCHEMICAL PROFILE*
- *GENETIC STUDIES*


INVISIBLE

Bartter syndrome:

Differential diagnosis

From early infancy to childhood, BS must be considered in the D.D. of these conditions

1. *FTT*
2. *FUO*
3. *Vomiting*
4. *Dehydration*
5. *Muscle weakness*

BARTTER SYNDROME

Spot U_K

U_K **> 20** mEq/L

NOT DIAGNOSTIC

RENAL K WASTING

BARTTER SYNDROME

Spot U_{Cl} ↑

U_{Cl} > 20 mEq/L

Crucial for diagnosis

U_{Cl} > 35 mEq/L

Mechanism of hypokamemia is renal

Renal NaCl loss

Skin NaCl Loss

GIT NaCl Loss

ECF contraction

RAAS

Increased urinary K^+ H^+ excretion

Hypokalemic Metabolic Alkalosis

$U_K > 20$ mEq/L

Pseudo-Bartter Syndrome

D.D.

1. Diuretic abuse
2. Laxative abuse
3. Cystic fibrosis
4. Cyclic vomiting
5. Pyloric stenosis
6. Gitelman syndrome
7. Mineralocorticoid excess
8. Congenital chloride diarrhea

Pseudo-Bartter Syndrome

Hypokalemic Metabolic Alkalosis

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D.D. Pseudo-Bartter Syndrome

A large group of disorders with overproduction or defect of a mineralocorticoid hormone may present with hypokalemic alkalosis but,

unlike BS,

they have high blood pressure.

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D.D. Pseudo-Bartter Syndrome

HTN	THE LACK OF HTN RULES OUT MINERALOCORTICOID OR MINERALOCORTICOID-LIKE EXCESS

↓U_{Cl}	CYSTIC FIBROSIS	1. VOMITING 2. NG SUCTION 3. CHLORIDE D.
	Skin NaCl Losses	**GIT NaCl Losses**

BARTTER SYNDROME

D.D.

↑ U_{Cl}

1. BARTTER
2. GITELMAN
3. DIURETIC USE

BARTTER SYNDROME

D.D.

U_{Cl} < 20 mEq/L	U_{Cl} > 20 mEq/L
VOMITING	BARTTER
NG SUCTION	GITELMAN
CONG CHLORIDE D	RECENT DIURETIC
CYSTIC FIBROSIS	LIDDLE
REMOTE DIURETIC	EXCESS M.

Mg

HTN

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Pseudo-Bartter Syndrome

NO HTN
NO Polyuria
NO Calcinosis

$U_{Cl} < 20$ mEq/L

Skin Losses

GIT Losses

ECF contraction

RAAS

Increased urinary K^+ H^+ excretion

Hypokalemic Metabolic Alkalosis


Trust me
I'm a Doctor

Aim of management

BS cannot be cured

Tubular defects

can not be corrected

but can be controlled

AIM
OF
MANAGEMENT


A
B
C


Co
K
I
S
Cr
Se
K
Mg
Na


WATER
BALANCE

Aim of management

Replacement therapy
of
fluids & electrolytes is the rule

First line of management

Not enough

Aim of management

1. Block PGE2 (Indomethacin)
2. Block aldosterone (Spironolactone)
3. Block angiotensin II (ACE i)

Bartter Syndrome

Treatment

Indomethacin
0.5-2.5 mg/kg/d

Spironolactone
1-1.5 mg/kg/d

Na
10 mmol/kg/d

K
1-4 mmol/kg/d

Mg

Urinary losses must be monitored & replaced

Amounts of fluids & lytes, exceed conventional limits
500 ml/kg/day

Management of fluid volume depletion/hydration states

Treatment of Neonatal Bartter syndrome

Maintenance of euvolemia in the immediate postnatal period by meticulous replacement of renal fluid and salt loss is of

central importance before starting NSAID therapy, which

might precipitate acute renal failure if ECF volume

is depleted.

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Treatment of Neonatal Bartter syndrome

- Indomethacin starting 6 weeks after birth
- 0.5 to 2.5 mg/kg/day
- 3 mg/kg/day is nephrotoxic

Treatment of Neonatal Bartter syndrome

- Potential benefit of indomethacin in premature babies & neonates should be weighted against risks of severe GIT complications, such as
  - ✓ulcers
  - ✓perforation
  - ✓ necrotizing enterocolitis

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Treatment of Neonatal Bartter syndrome

- **ROMK-deficient newborn**

Indomethacin (doses below 1 mg/kg/day) .

- ✓oliguric renal failure
- ✓severe hyperkalemia.

Treatment of Classical Bartter syndrome

1. Sodium & Potassium supplementation
2. Indomethacin
3. Spironolactone
4. ACEi
5. Magnesium supplementation
6. Gastrostomy tube
7. Growth hormone therapy

Treatment of Classical Bartter syndrome

(ACE) inhibitors
should be used with caution
as these drugs could
block the distal compensatory Na
reabsorption.

Treatment of Classical Bartter syndrome

Thiazides should not be used to reduce hypercalciuria,

they interfere with compensatory mechanisms in DCT
and further aggravate dehydration.

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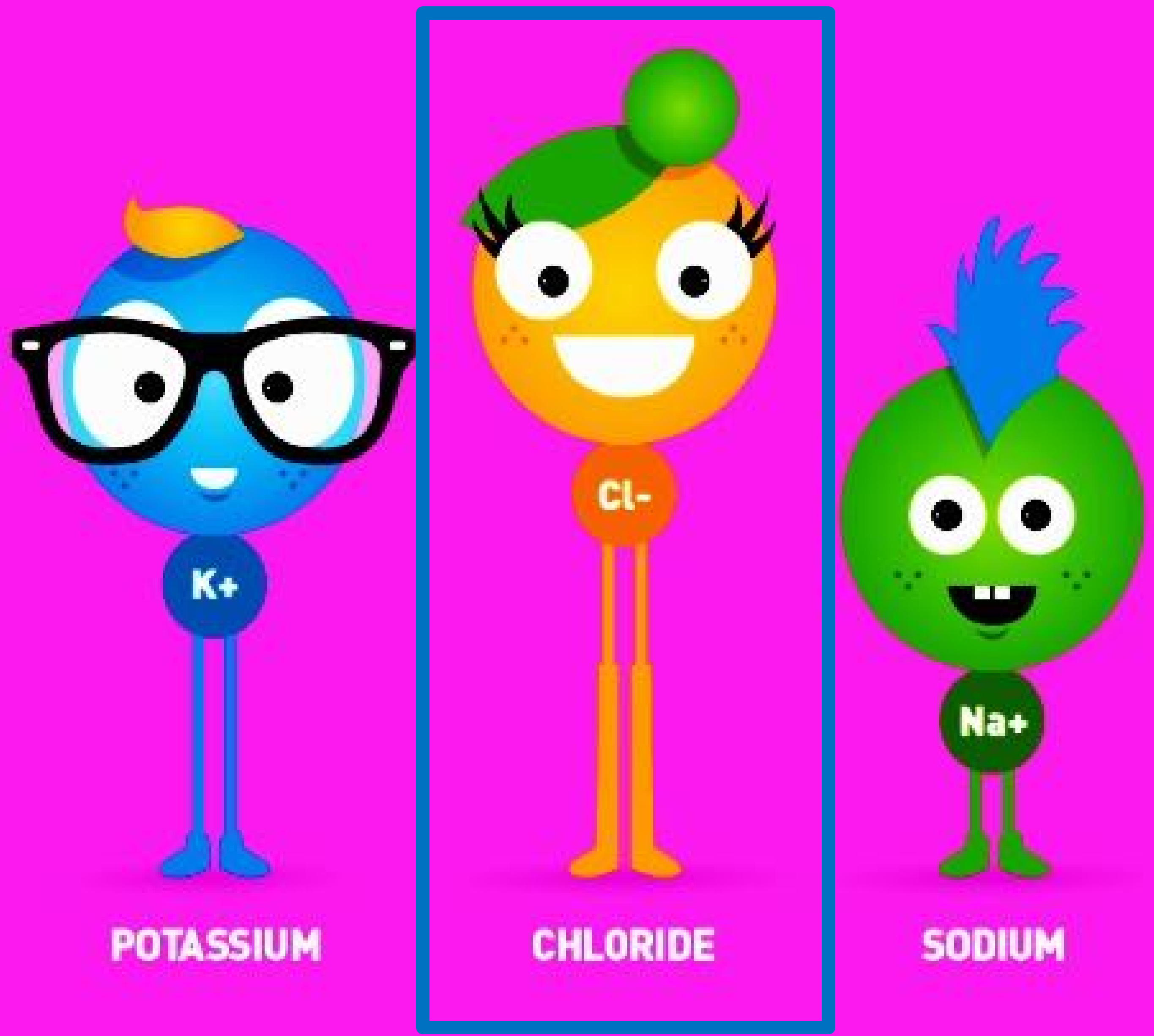
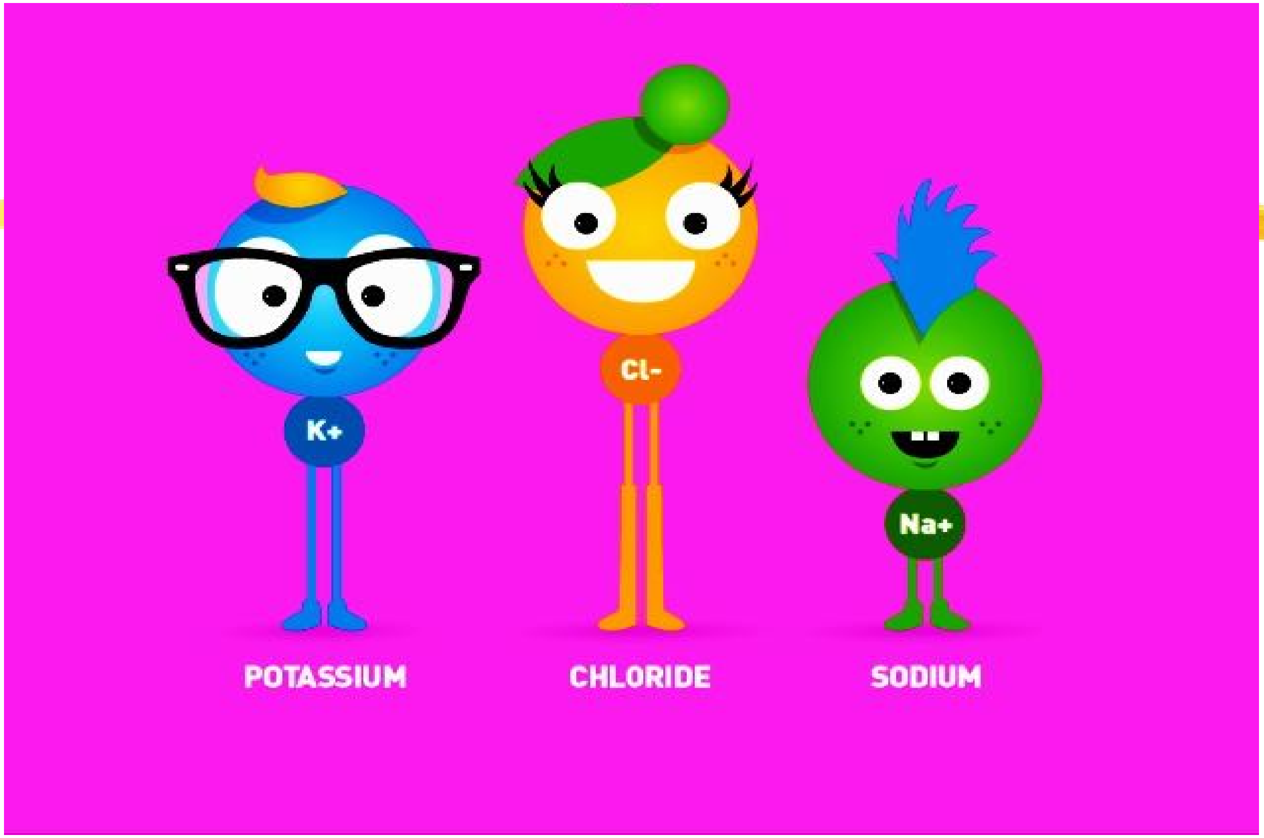

K+
Cl-
Na+
POTASSIUM
CHLORIDE
SODIUM



VERY HIGH DOSES
ARE
USUALLY REQUIRED

The magnesium level

K level cannot be corrected until hypomagnesemia

has been corrected.

Treatment of Classical Bartter syndrome

Under stressful situations,
including acute illness,
surgical procedures & trauma
blood electrolytes may rapidly change,
requiring immediate & vigorous
intravenous treatment.

Gitelman, Syndrome

Gitelman syndrome

Gentle Variant of BS

Gitelman syndrome

Hypocalciuric
Hypomagnesemic

variant of

BS

Gitelman syndrome

Gentle Variant

Milder

Presents later

No nephrocalcinosis

No dehydration.

Gitelman syndrome

Benign Variant of BS

GITELMAN

Inhereted tubular defect

Decreased Na Cl transport

Increased urinary Na Cl excretion

ECF contraction

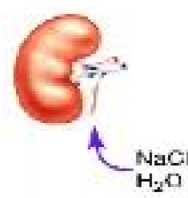
RAAS

Increased urinary K^+ H^+ excretion

Hypokalemic Metabolic Alkalosis

DCT

5%



Normal urinary PGE2 levels

Normal urinary conc. ability

Gitelman syndrome

- Salt craving
- Fatigue, low BP
- Thirst, polydipsia
- Muscle weakness, cramps.

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Gitelman syndrome

Gitelman syndrome

Pediatric patients are often

ASYMPTOMATIC,

but may be diagnosed coincidentally during

a diagnostic workup for

GROWTH RETARDATION

CONSTIPATION

MUSCLE WEAKNESS

HYPOTENSION

ENURESIS.

Gitelman's syndrome: treatment

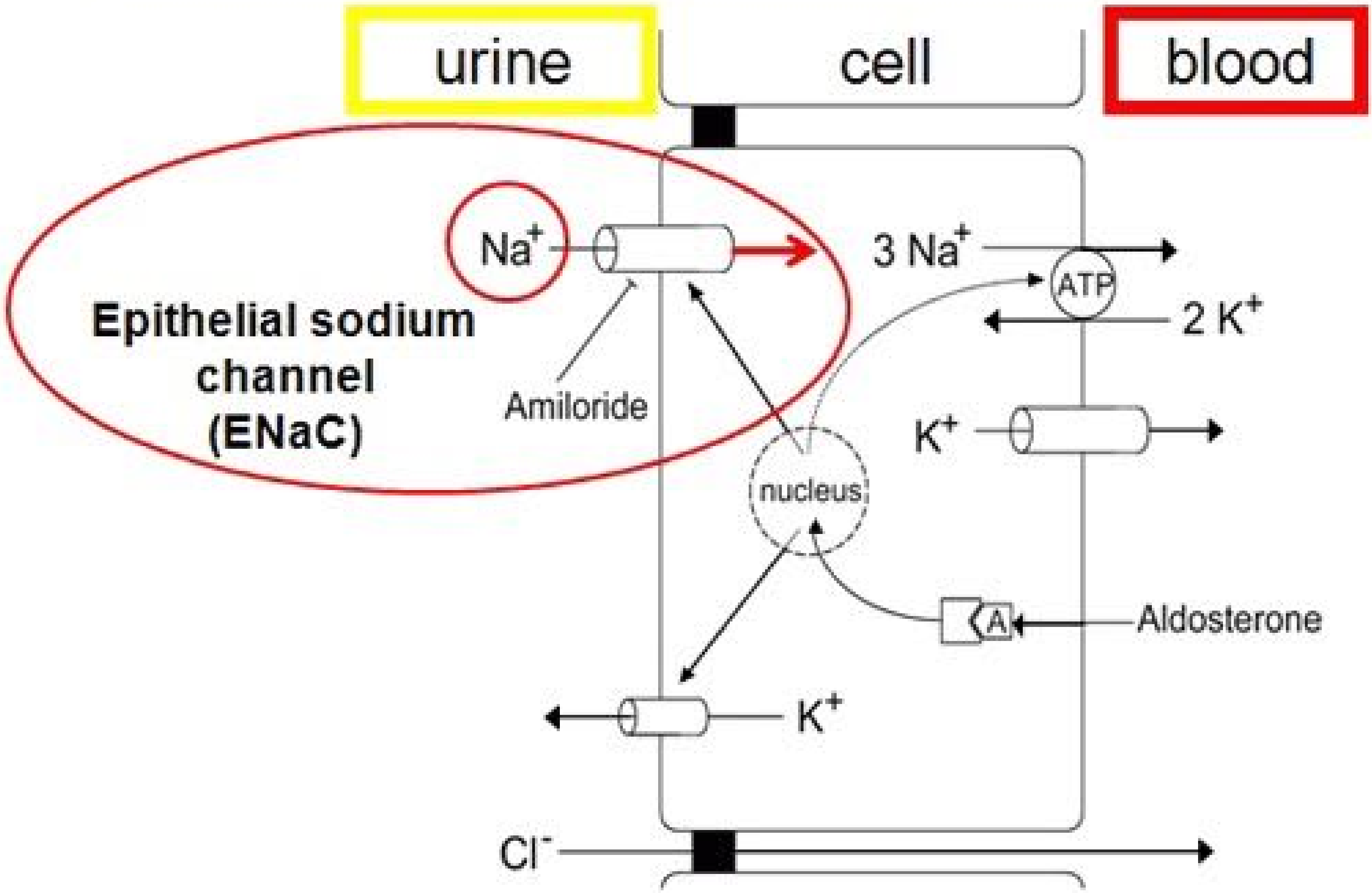
The mainstay of treatment of Gitelman syndrome is electrolyte supplementation.

Gitelman's syndrome: treatment

- Na , K & Mg supplementation.
- Spironolactone or amiloride
- ACEI's
- **NSAIDS of no benefit**

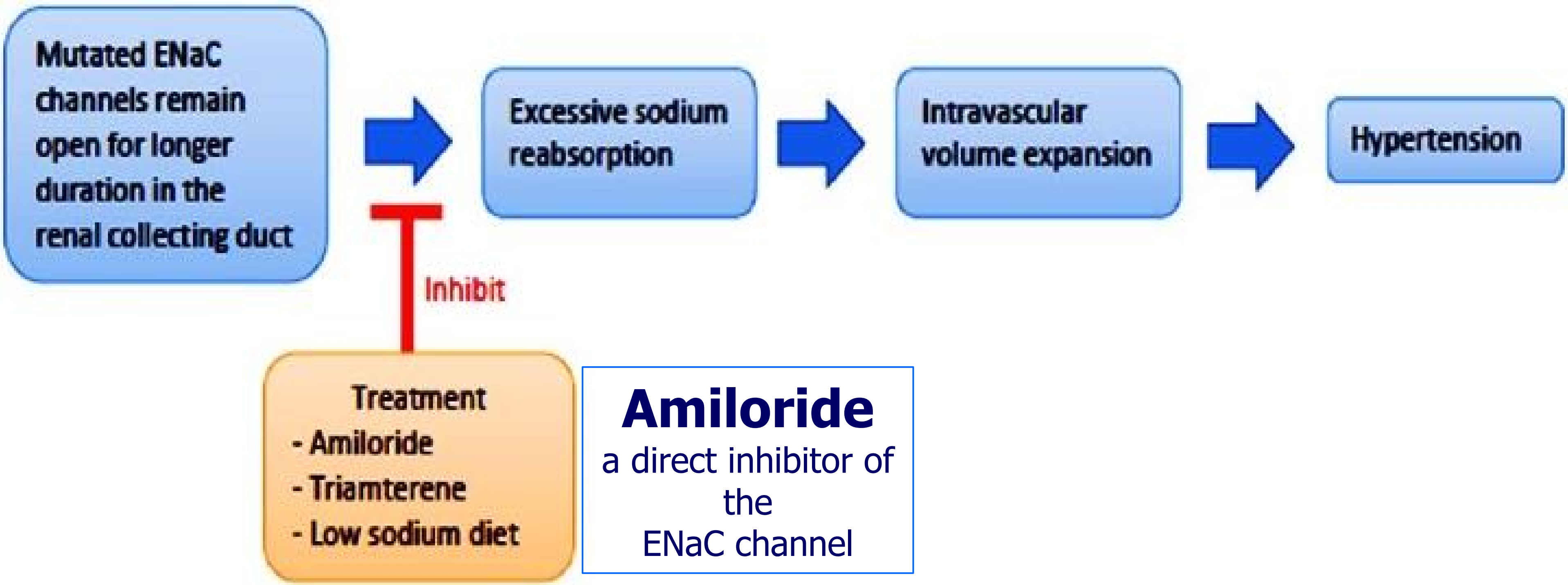
Liddle Syndrome

Aldosterone-sensitive distal nephron



Liddle syndrome

Not Salt Losing

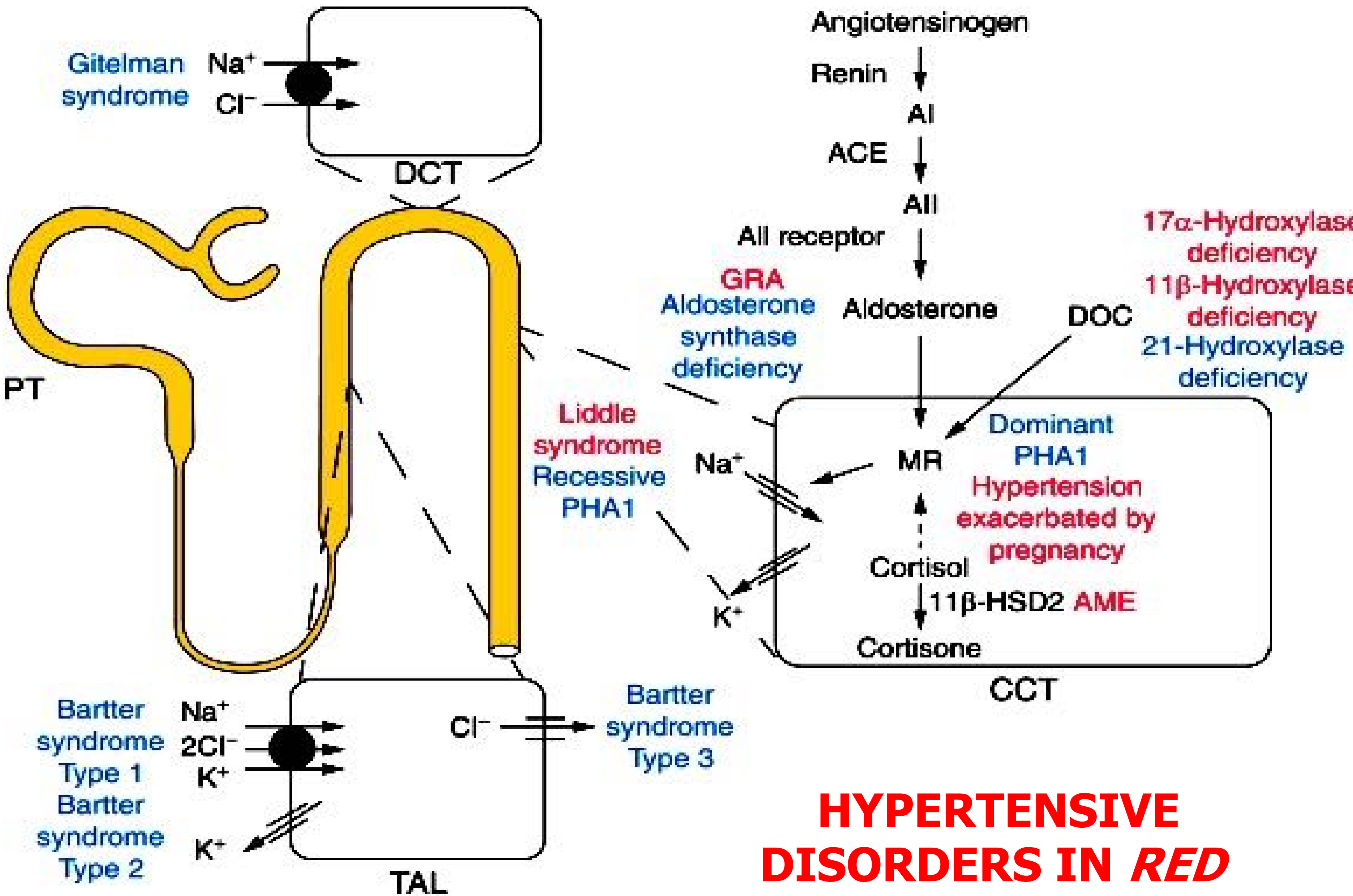


Amiloride
a direct inhibitor of the
ENaC channel

Spironolactone is not effective.

Liddle syndrome

- **AD.**
- **Low** renin & aldosterone.
- Severe early onset **hypertension**.
- Hypokalemic metabolic alkalosis.



HYPERTENSIVE DISORDERS IN *RED*

Lifton, R.P., Gharavi, A.G. & Geller, D.S. (2001). Molecular mechanisms of human hypertension. *Cell* 104, 545–56.

METABOLIC ALKALOSIS AND HYPOKALEMIA

HTN

1ry Hyper-Aldosteronism	Pseudo Hyper-Aldosteronism	2ry Hyper-Aldosteronism
Low Renin High Aldosterone	Low Renin Low Aldosterone	High Renin High Aldosterone

METABOLIC ALKALOSIS AND HYPOKALEMIA

HTN

High renin	Low renin	
High Aldosterone	High Aldosterone	Low Aldosterone
2ry hyperaldosteronism Malignant HTN Reno-vascular HTN Renin secreting tumors Diuretic therapy for HTN	**1ry hyperaldosteronism** GRA Adrenal adenoma Adrenal hyperplasia	CAH Cushing Exogenous Steroids Licorice, Liddle's AME

METABOLIC ALKALOSIS AND HYPOKALEMIA

Low Renin HTN
Low Aldosterone

Plasma Cortisol

High

Ectopic ACTH
Cushing syndrome

Normal

Liddle's
Licorice
AME

Low

CAH
11 β hydorxylase D
17 α hydorxylase D

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"اللهم انفعنا بما علمتنا,
وعلمنا ماينفعنا,
وزدنا علما"

MCQ

- **A 12 YEARS OLD BOY COMPLAINS OF FATIGABILITY AND WEAKNESS**

- **PHYSICAL EXAM:** BP 122/68, HR 72/MIN, NO ORTHOSTATIC CHANGES, NO EDEMA

- **LABS (mEg/L): Na**:**135**, **K**: **2.1**, **Cl**: **85**, **HCO3**:**45**, $\mathbf{U_{Na}}$=**80**, $\mathbf{U_{K}}$=**70**

MCQ1:

WHY IS HIS POTASSIUM LOW?

A. CYCLIC VOMITING
B. DIURETIC USE
C. BARTTER/GITELMAN
D. None of the above
E. All of the above

MCQ2:

WHAT TEST(S) WILL HELP YOU MAKE THE DIAGNOSIS?

A. Spot Urine K
B. Spot Urine Cl
C. Spot Urine K/Cr
D. None of the above
E. Any of the above

MCQ3:

WHICH SALT YOU ARE GOING TO USE TO TREAT THIS PATIENT?

A. k acetate
B. K citrate
C. K chloride
D. None of the above
E. Any of the above


Thank you