ACID-BASE EMERGENCIES

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For every complex problem, there is a solution that is simple, neat, and **wrong**

HL Mencken (1880-1956)

Life-Threatening Acidosis in an Alcoholic

- 52 yr old alcoholic admitted to hospital with abdominal pains, visual disturbance, dyspnea.
- He admitted drinking a large quantity of alcohol in the previous 24h, but insisted he had only drunk vodka. He stopped drinking because of repeated vomiting.
- Fully conscious and orientated, Kussmaul respiration (40/min), BP 120/58, pulse 150/min.
- Fundus: normal.

Life-Threatening Acidosis in an Alcoholic

Glucose	50	pH	6.78 ([H^+] 167nmol/l)
Urea	40	pCO_2	23
Creatinine	1.33	HCO_3^-	3.3
Na	132	Anion Gap	44
K	5.4	ΔAG	32
Cl	85	URINE: Ketones ++++	
Hb	15.1 (next morning 11.4)		
Hct	46% (next morning 33%)		

Lactate: not yet received

EFFECTS OF METABOLIC ACIDOSIS

A. SYMPTOMS AND SIGNS

1. Rapidity of onset and severity are key determinants
2. Symptoms:
   - Fatigue
   - Abdominal pain
   - S.O.B.
   - Body ache
3. Signs
   - Vomiting
   - Kussmaul respiration
   - Cardiac; Negative Intropy
   - Venous: Periph. constrict
   - Arteriole: Periph. Dilation pulmonary constriction

B. LABORATORY FINDINGS

1. ↑ WBC
2. ↑ K^+
3. ↑ PO_4^{3-}
4. ↑ BLOOD SUGAR
5. ↑ URIC ACID
6. Ca^{2+}, PTH, Vitamin D

Life-Threatening Acidosis in an Alcoholic

pH	6.78
pCO_2	23
HCO_3^-	3.3
Anion Gap	44
ΔAG	32

Questions:

1. What is main acid-base disturbance? Severe anion gap metabolic acidosis.
2. Is there respiratory compensation?
3. Is there a tertiary abnormality?

Life-Threatening Acidosis in an Alcoholic

Henderson Equation:

$$[H^+] = \frac{pCO_2 \times 24}{[HCO_3^-]}$$

Life-Threatening Acidosis in an Alcoholic

Henderson Equation:

$$[H^+] = \frac{pCO_2 \downarrow \times 24}{[HCO_3^-] \downarrow}$$

Respiratory Compensation:

$$\text{Expected } pCO_2 = 1.5\ HCO_3^- + 8$$
$$= 13.$$

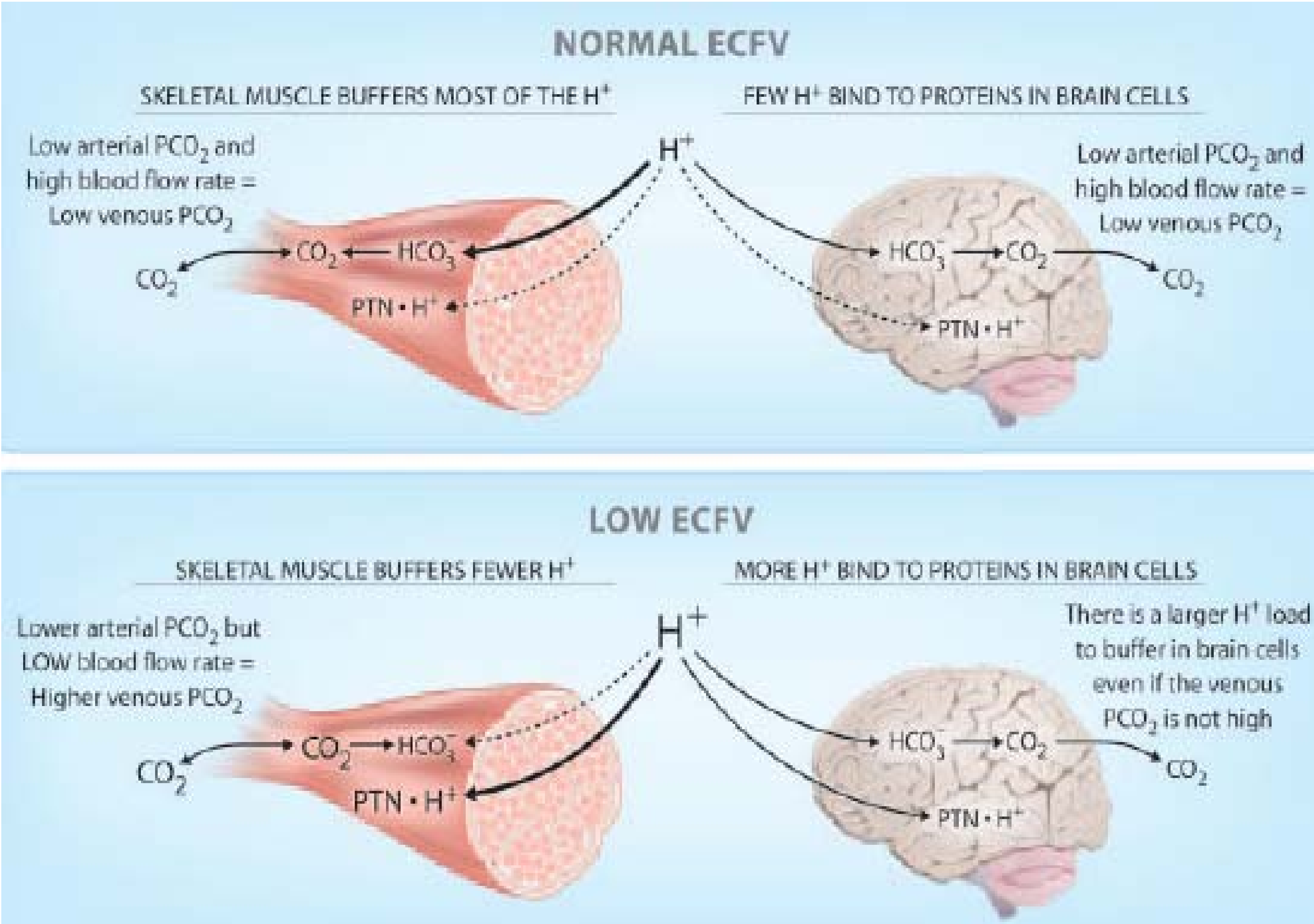
But pCO_2 = 23. Thus: ? Respiratory acidosis

Life-Threatening Acidosis in an Alcoholic

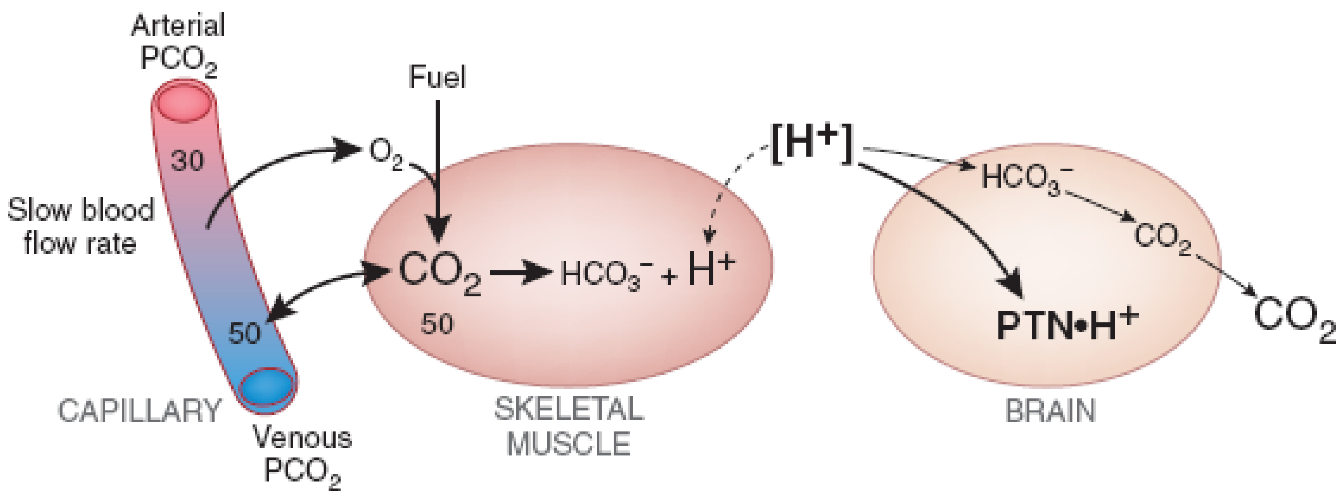
But: pt is hyperventilating, and is volume depleted (Hct on admission 46%, the following morning 33% following IV fluids, i.e. 1.26L reduction in plasma volume, given BW of 65kg)

(Change in Hct is best indicator of volume status [Halperin]).

Increased pCO_2 is not due to hypoventilation, but reduced muscle blood flow and thus reduced clearance of pCO_2.


NORMAL ECFV
SKELETAL MUSCLE BUFFERS MOST OF THE H+
FEW H+ BIND TO PROTEINS IN BRAIN CELLS
Low arterial PCO2 and high blood flow rate = Low venous PCO2
H+
CO2
CO2
HCO3-
PTN • H+
Low arterial PCO2 and high blood flow rate = Low venous PCO2
HCO3-
CO2
CO2
PTN • H+
LOW ECFV
SKELETAL MUSCLE BUFFERS FEWER H+
MORE H+ BIND TO PROTEINS IN BRAIN CELLS
Lower arterial PCO2 but LOW blood flow rate = Higher venous PCO2
H+
CO2
CO2
HCO3-
PTN • H+
There is a larger H+ load to buffer in brain cells even if the venous PCO2 is not high
HCO3-
CO2
CO2
PTN • H+

$$H^+ + HCO_3^- = H_2CO_3 = CO_2 + H_2O$$



Life-Threatening Acidosis in an Alcoholic

Is there a tertiary abnormality?

ΔHCO_3^- = 24 - 3.3 = 21

ΔAG = 42-12

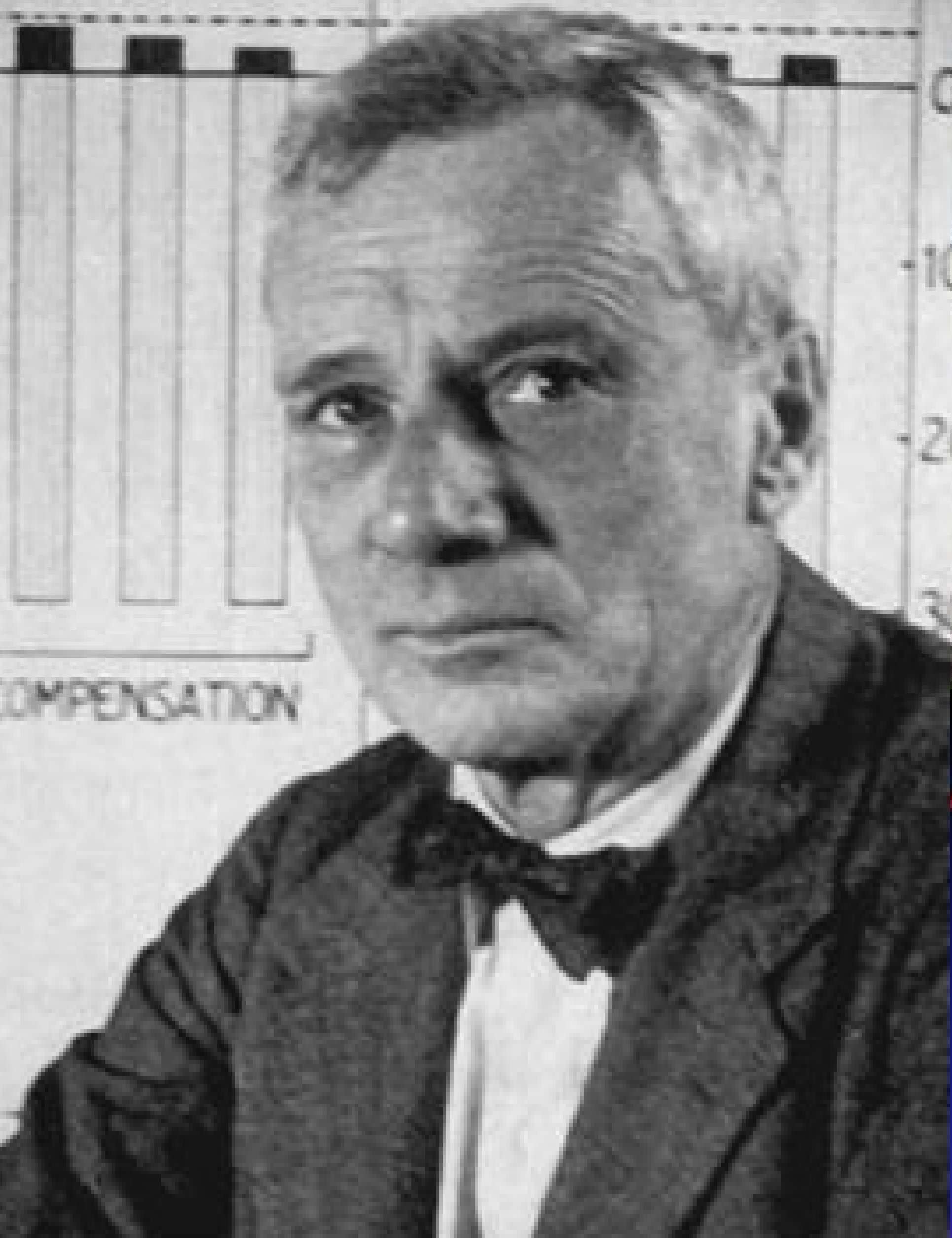
= 32

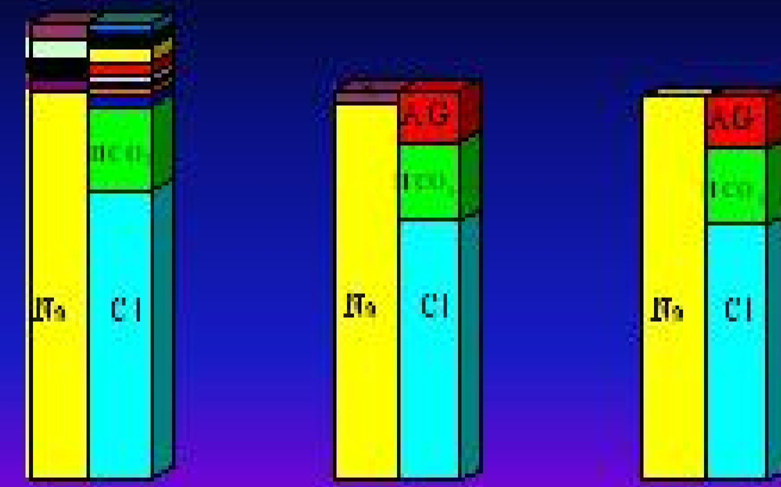
Thus $\Delta AG / \Delta HCO_3^- > 1$.

Normal $[HCO_3^-]$ is 24. Thus, if $[HCO_3^-]$ is 3.3 after buffering 32mmol/l of acid, then it must have been much higher at onset of acidosis, ? due to vomiting.

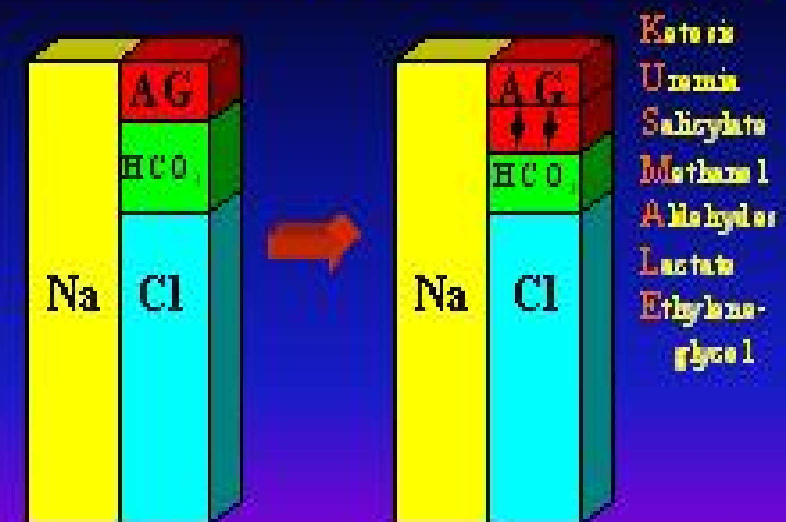
This may indicate presence of metabolic alkalosis (but inaccurate in presence of volume depletion, because this affects HCO_3^-).

Low $[Cl^-]$ supports likelihood of vomiting.



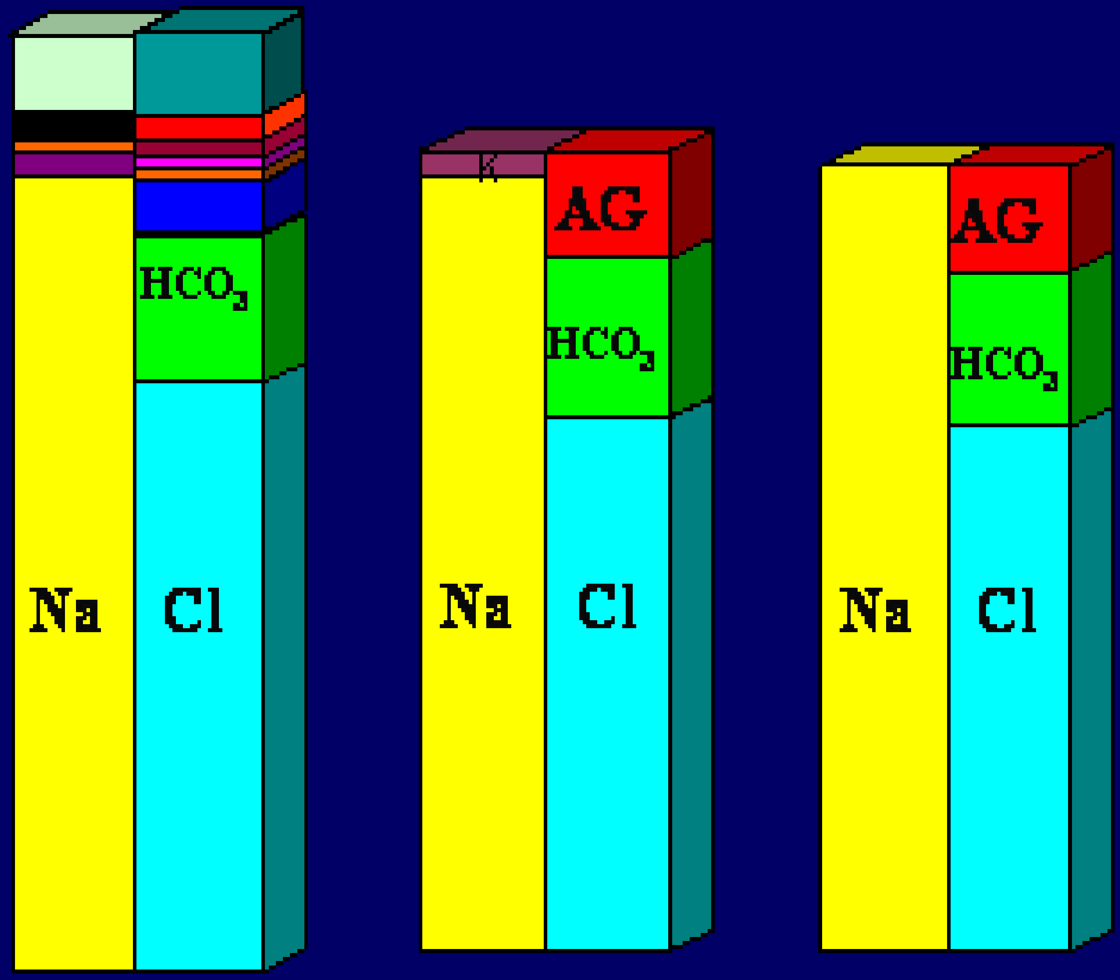


ANION GAP METABOLIC ACIDOSIS



James L. Gamble &
his "Gamblegrams"

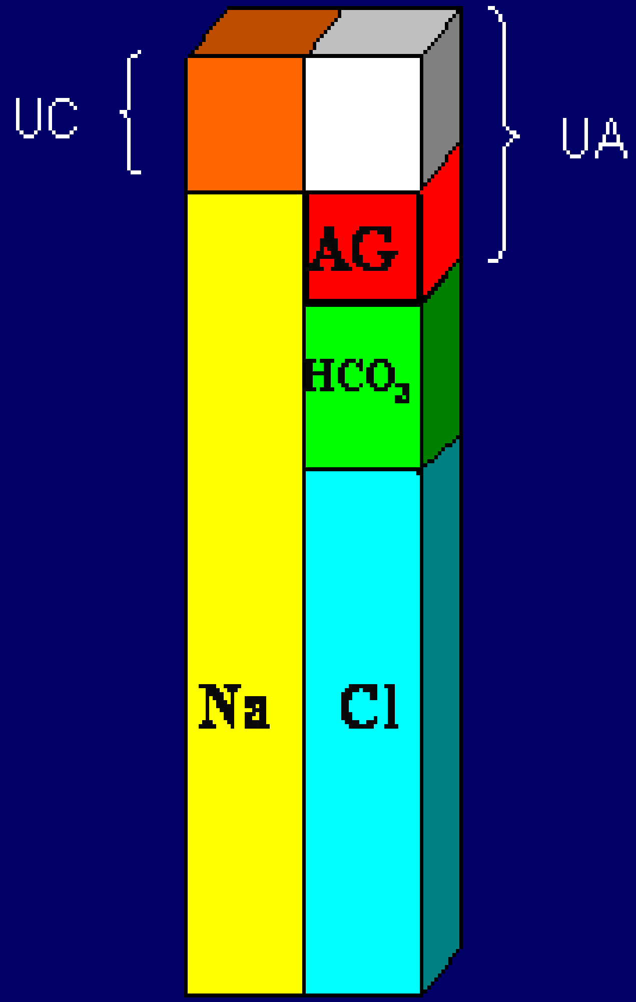
ANIONS - CATIONS AND THE ANION GAP



$AG = [(Na + K) - (Cl + HCO_3)]$

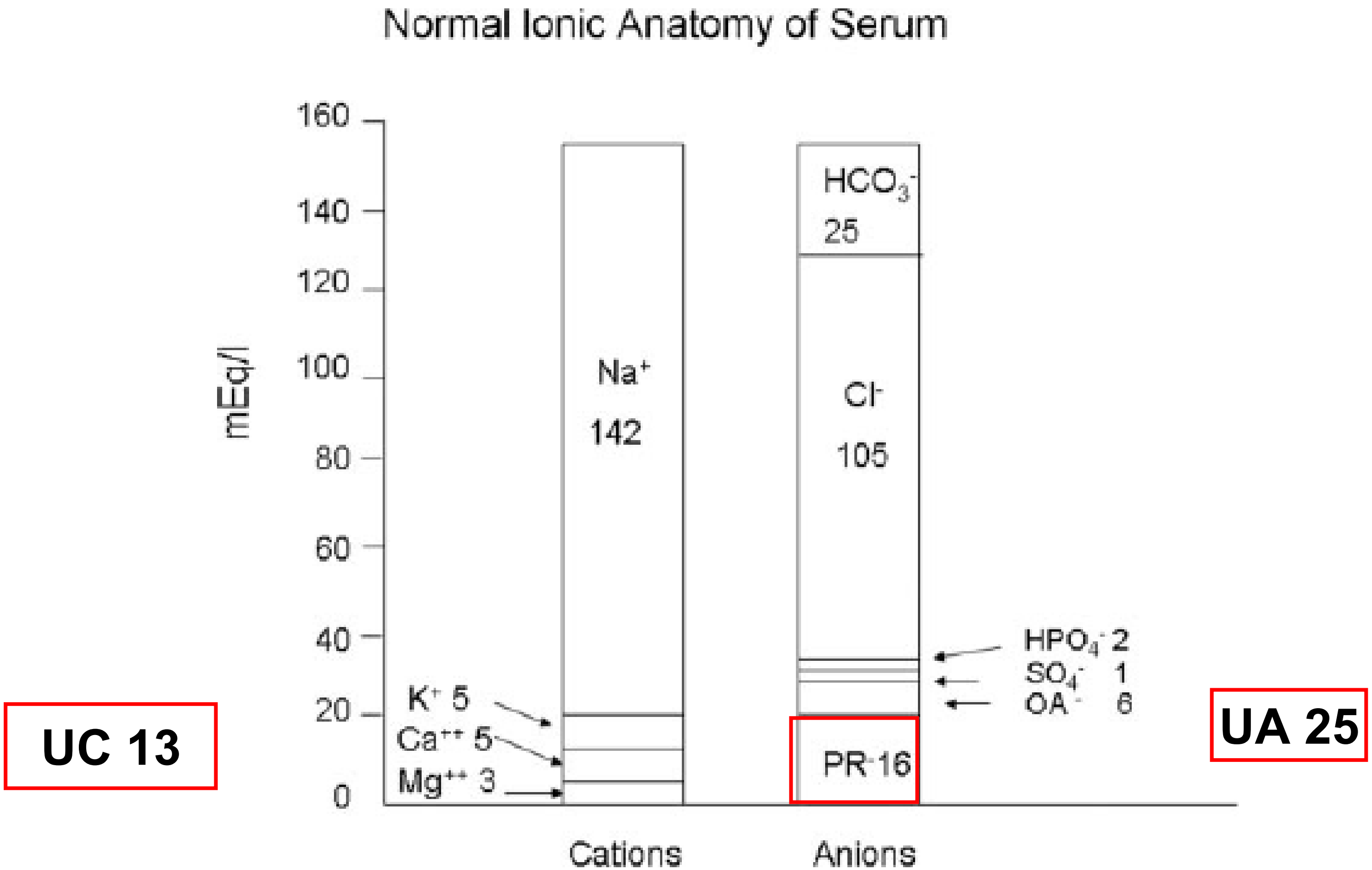
$AG = [Na - (Cl + HCO_3)]$

8-12 mEq/l



AG = UA - UC

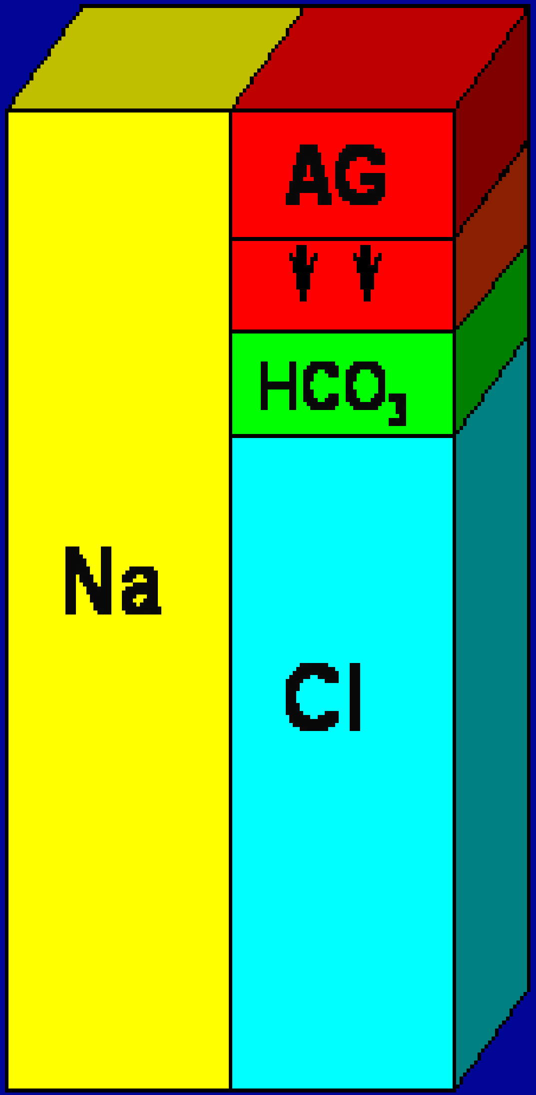
Therefore a low AG may be
Due to ↓U Anions or ↑U Cations



Most important anion is Pr^-. For every 1g reduction in serum albumin, AG falls by 2.3mmol/l.

IgG cationic, IgA anionic

ANION GAP METABOLIC ACIDOSIS



Ketosis
Uremia
Salicylate
Methanol
Aldehydes
Lactate
Ethylene-glycol

MUDPILES

Life-Threatening Acidosis in an Alcoholic

pH	6.78
pCO_2	23
HCO_3^-	3.3
Anion Gap	44
ΔAG	32

Lactate not yet received.

What is next step?

Life-Threatening Acidosis in an Alcoholic

PLASMA OSMOLAL GAP

Posm (measured):	328 mosm/kg
Posm (calc.):	286 mosm/kg
Osmolar gap	42 mosm/kg

(Normal < 10 mosm/kg)

Osmolar gap in toxic alcohol ingestion

- Measure plasma osmolality by freezing point depression (FPD)
- Calculate Posm as:

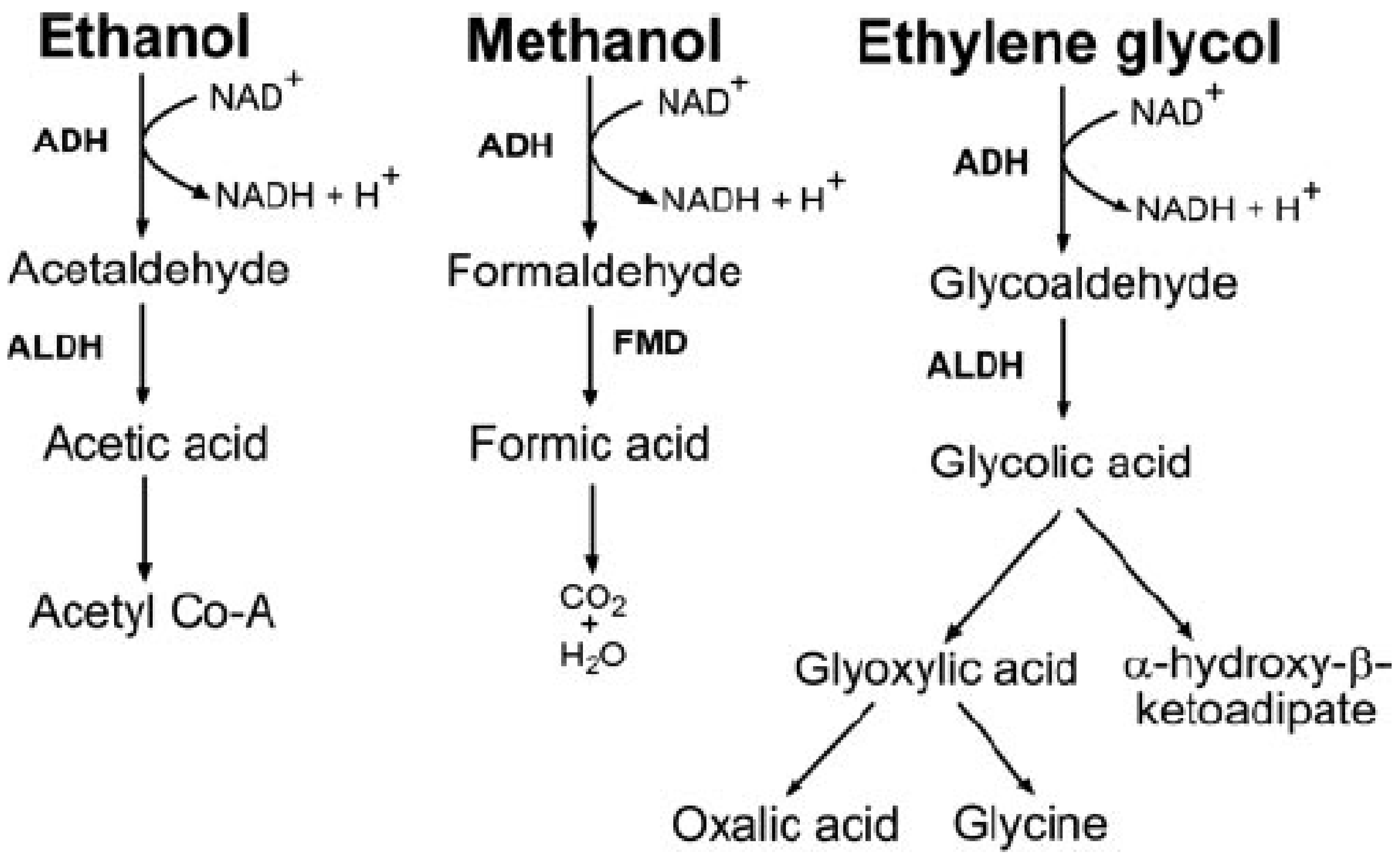
  2 Na + glu / 18 + BUN / 2.8

- Osmolar gap = FPDosm – calculated Posm
- Elevated with methanol, ethylene glycol, isopropyl alcohol, other alcohols, etc.

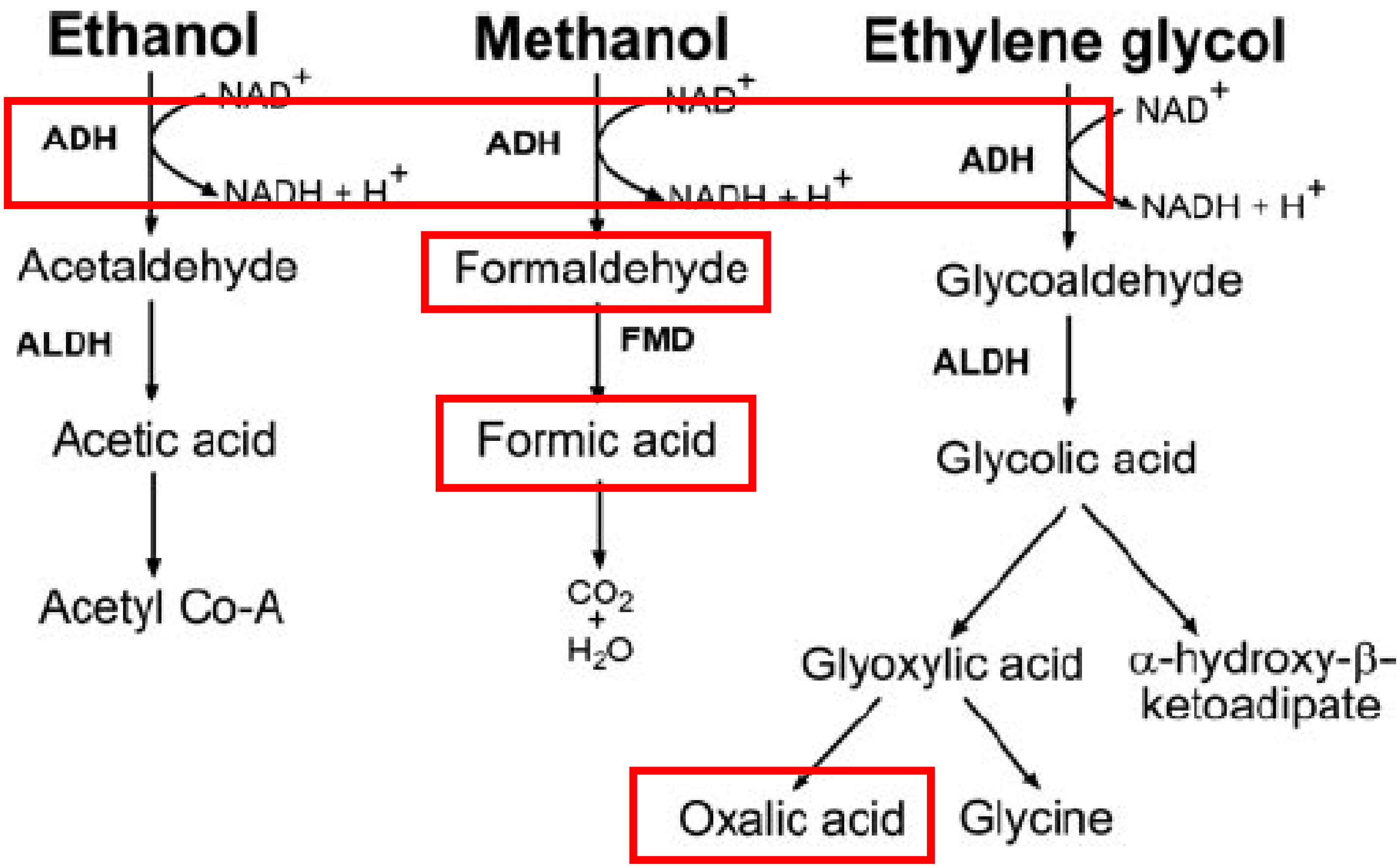
Effect of Alcohols/Glycols on Osmolar Gap

	Molecular Weight mg/mmol	Osmolar Gap Produced by 100 mg%
Ethanol	46	22 (Texas Legal Limit 80 mg% or gap of 18)
Methanol	32	31
Ethylene Glycol	62	16
Isopropanol	60	17
Acetone	58	17
Propylene Glycol	73	13

TOXIC ALCOHOLS

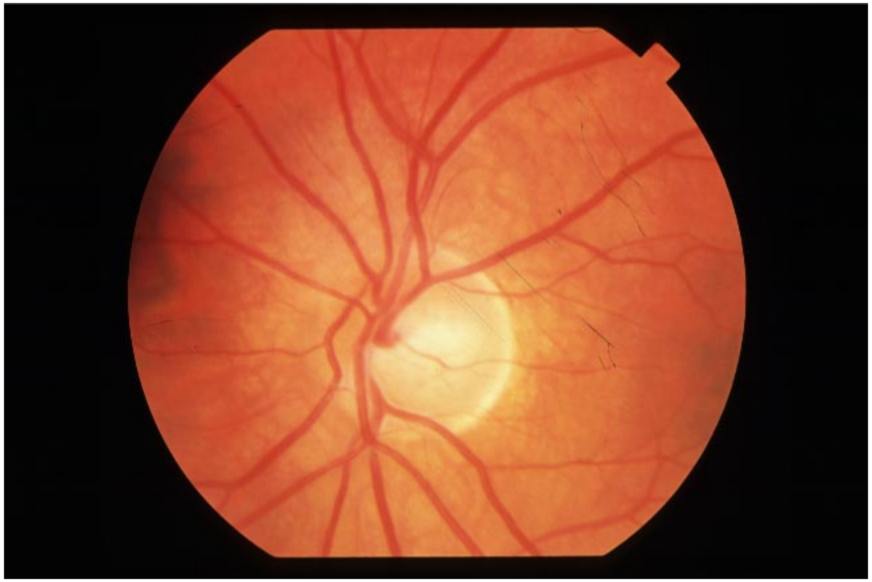
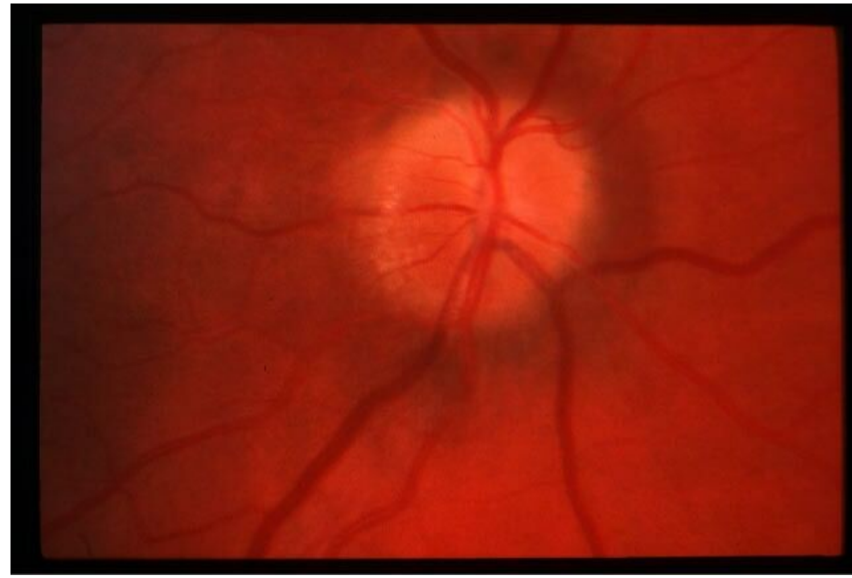


TOXIC ALCOHOLS

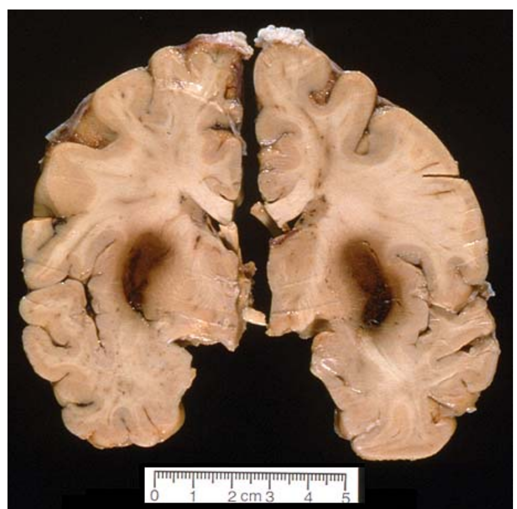


Methanol intoxication: neurological effects

Normal retina (left); optic neuritis (right)

Putamen infarcts



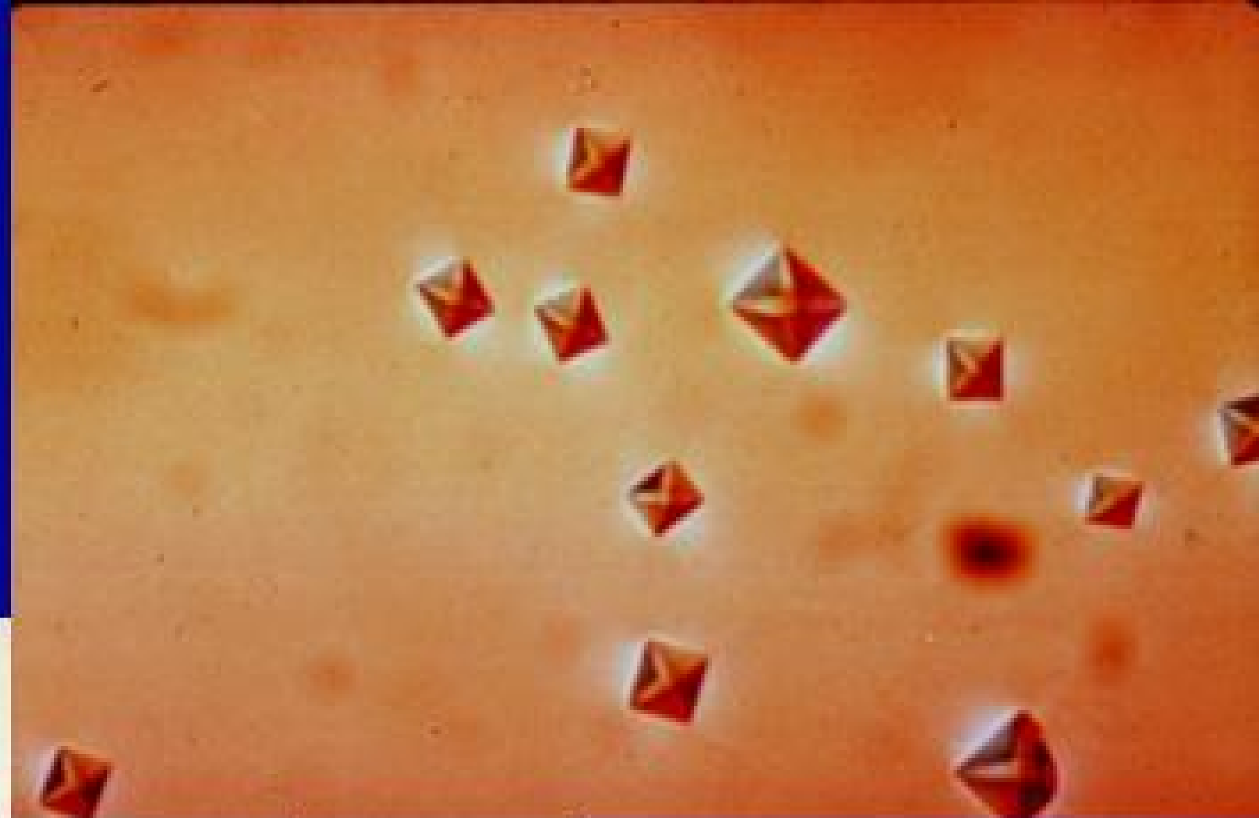
Ethylene glycol - presents with
± CNS disturbances,
cardiovascular collapse,
respiratory failure,
renal failure

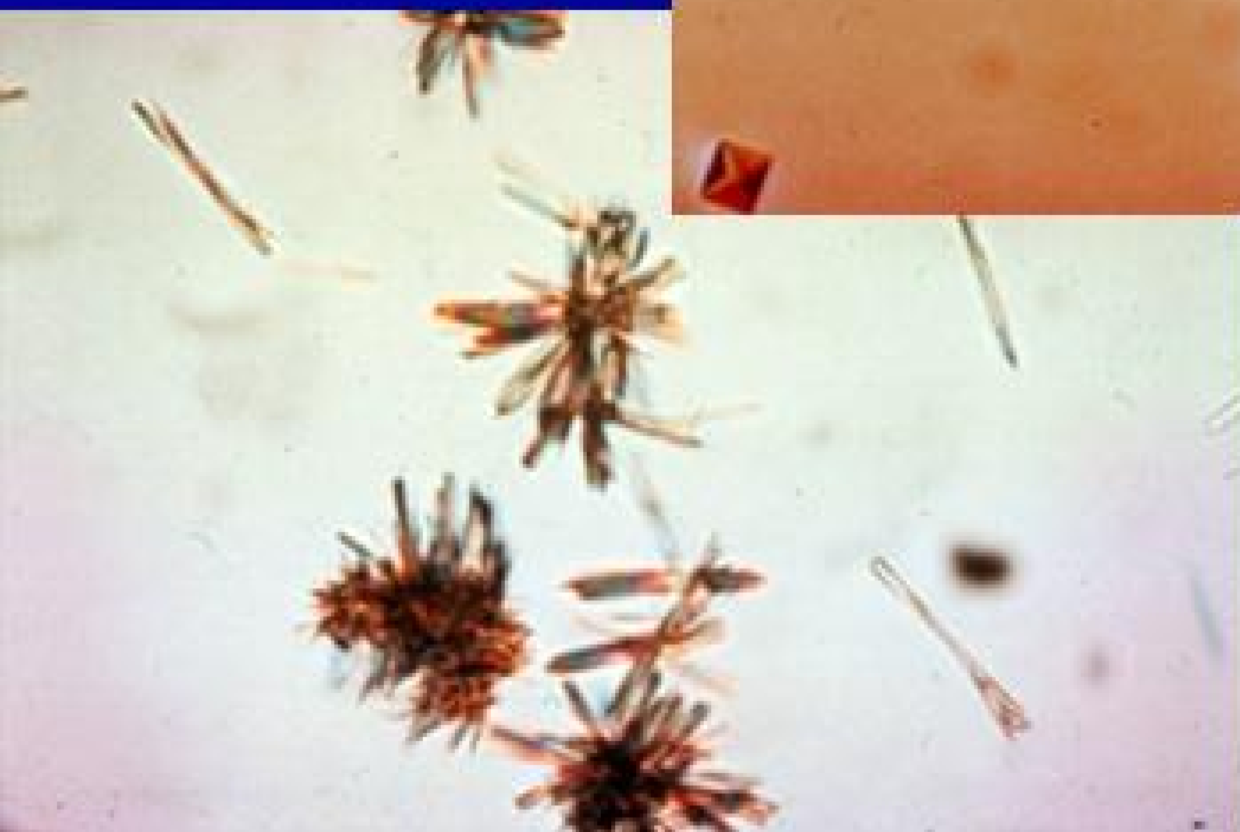
Oxalate crystals
(octahedral or dumbell)
in urine are diagnostic

Anion gap may be > 50

Osmolal gap > 10 mOsm

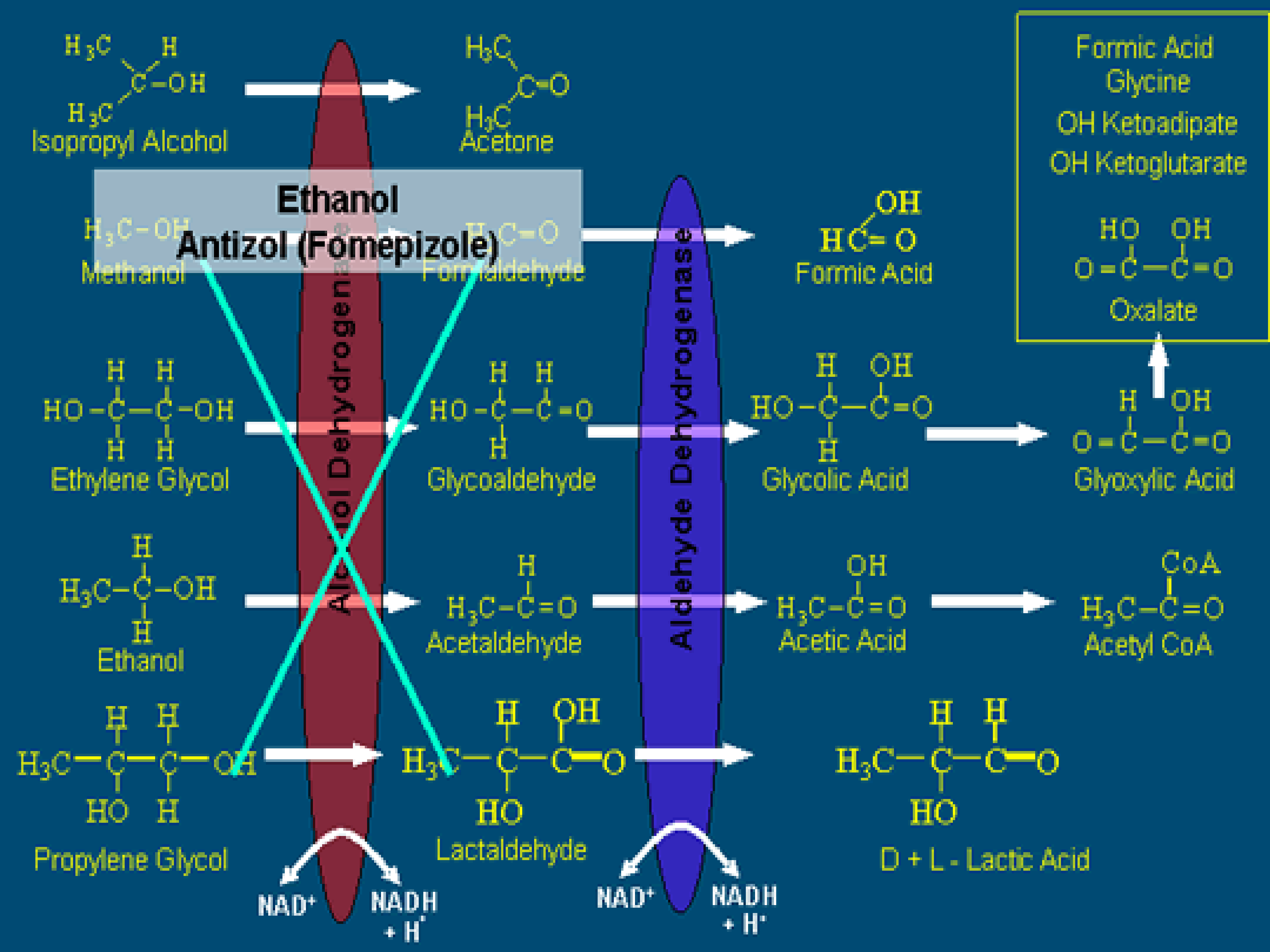
Calcium Oxalate Crystals





Blocking alcohol dehydrogenase

- Rate limiting step in initial metabolism of ethylene glycol to glycoaldehyde
- Inhibit using ethanol (~100 mg/dL)
  - Preferentially metabolized
  - But: Difficult to use
  - But: Ethanol level decreases during dialysis
- Fomepizol (Antizol®)
  - Relatively non-toxic, but $$$ expensive



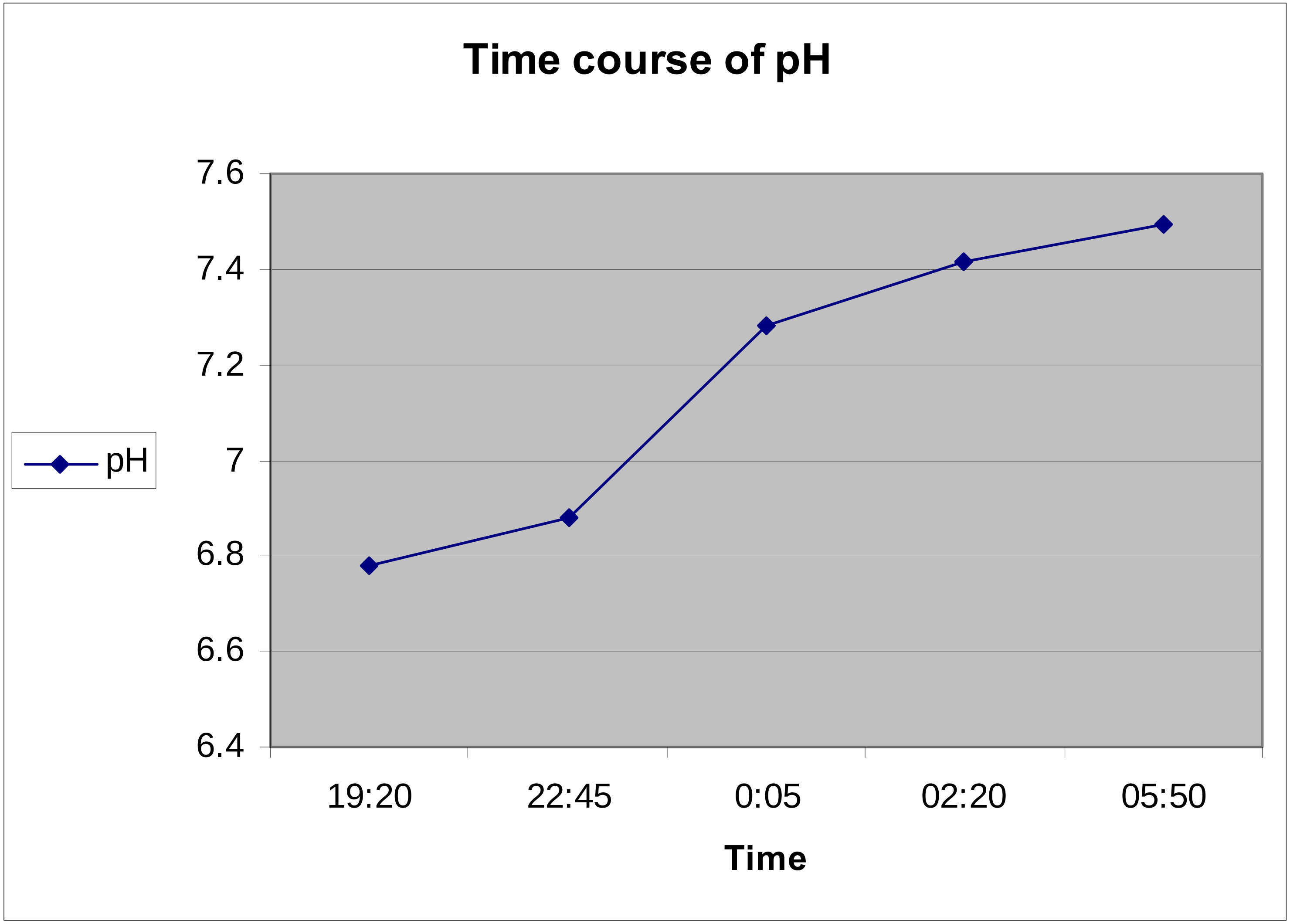
Isopropyl Alcohol
Acetone
Ethanol
Antizol (Fomepizole)
Methanol
Formaldehyde
Formic Acid
Formic Acid
Glycine
OH Ketoadipate
OH Ketoglutarate
Oxalate
Ethylene Glycol
Glycoaldehyde
Glycolic Acid
Glyoxylic Acid
Ethanol
Acetaldehyde
Acetic Acid
Acetyl CoA
Propylene Glycol
Lactaldehyde
D + L - Lactic Acid
Alcohol Dehydrogenase
Aldehyde Dehydrogenase
NAD+
NADH + H+
NAD+
NADH + H+

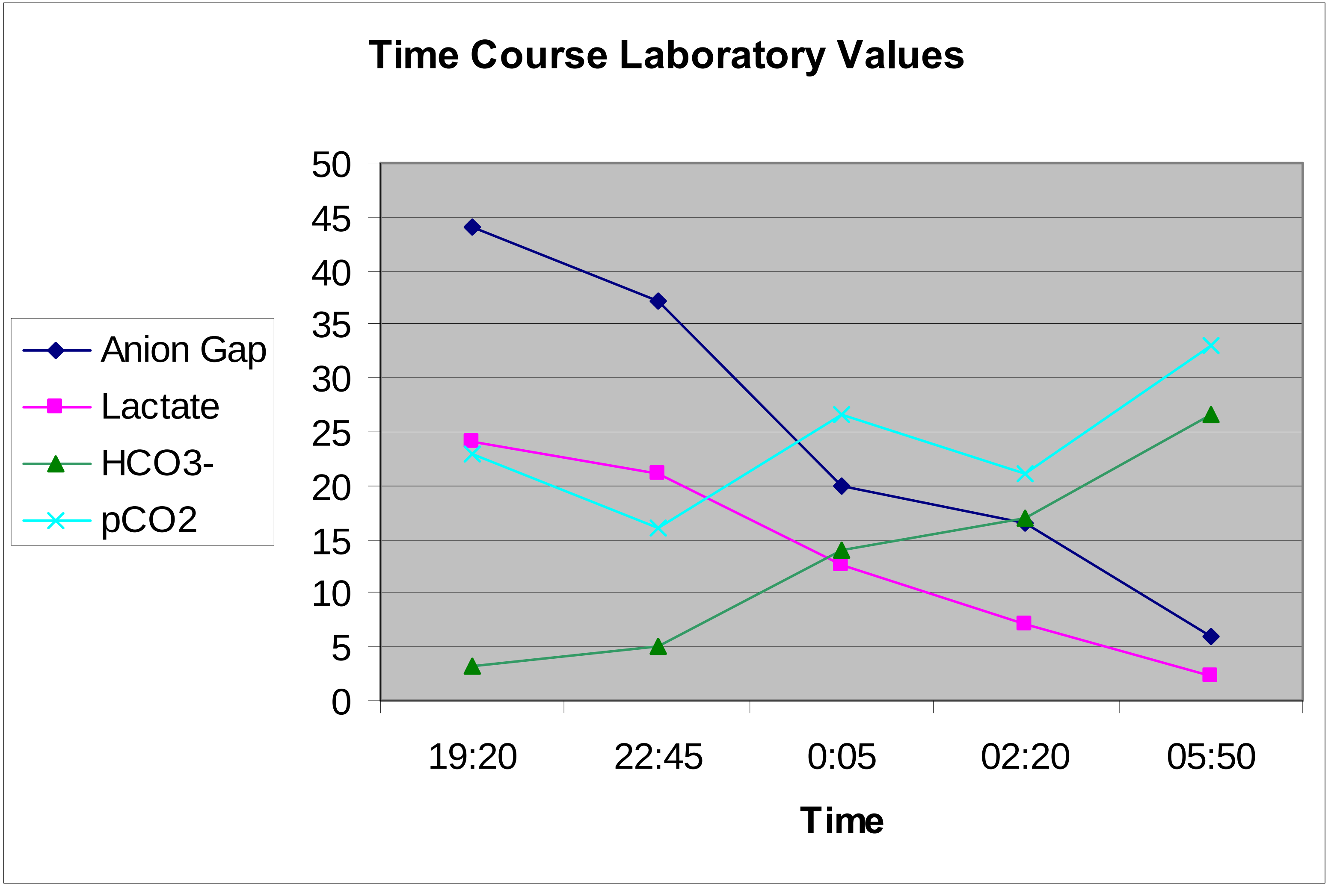
Life-Threatening Acidosis in an Alcoholic

- Since we thought that methanol poisoning was likely, even though the patient did not admit drinking methanol, IV Fomepizole (900mg) was administered, together with IV $NaHCO_3$ and Thiamine 100mg.
- Blood was taken for a toxic alcohol screen.
- He was admitted to ITU, and we prepared hemodialysis treatment.
- Serum lactate was 24mmol/L.

Life-Threatening Acidosis in an Alcoholic

Hour	16.00	19.19	21.45	22.56	04.24
pH	6.78	6.882	7.283	7.414	7.494
pCO_2	23	16	26.5	21.2	33
HCO_3^-	3.3	5.1	14	17	26.7
Lac^-	24	21	12.6	7.1	2.3
AG	44	37.2	20	16.4	6


Time course of pH
7.6
7.4
7.2
7
6.8
6.6
6.4
pH
19:20
22:45
0:05
02:20
05:50
Time


Time Course Laboratory Values
Anion Gap
Lactate
HCO3-
pCO2
50
45
40
35
30
25
20
15
10
5
0
19:20
22:45
0:05
02:20
05:50
Time

METABOLIC ACIDOSIS IN THE ALCOHOLIC

(Halperin et al: Metabolism 1983; 32: 308.)

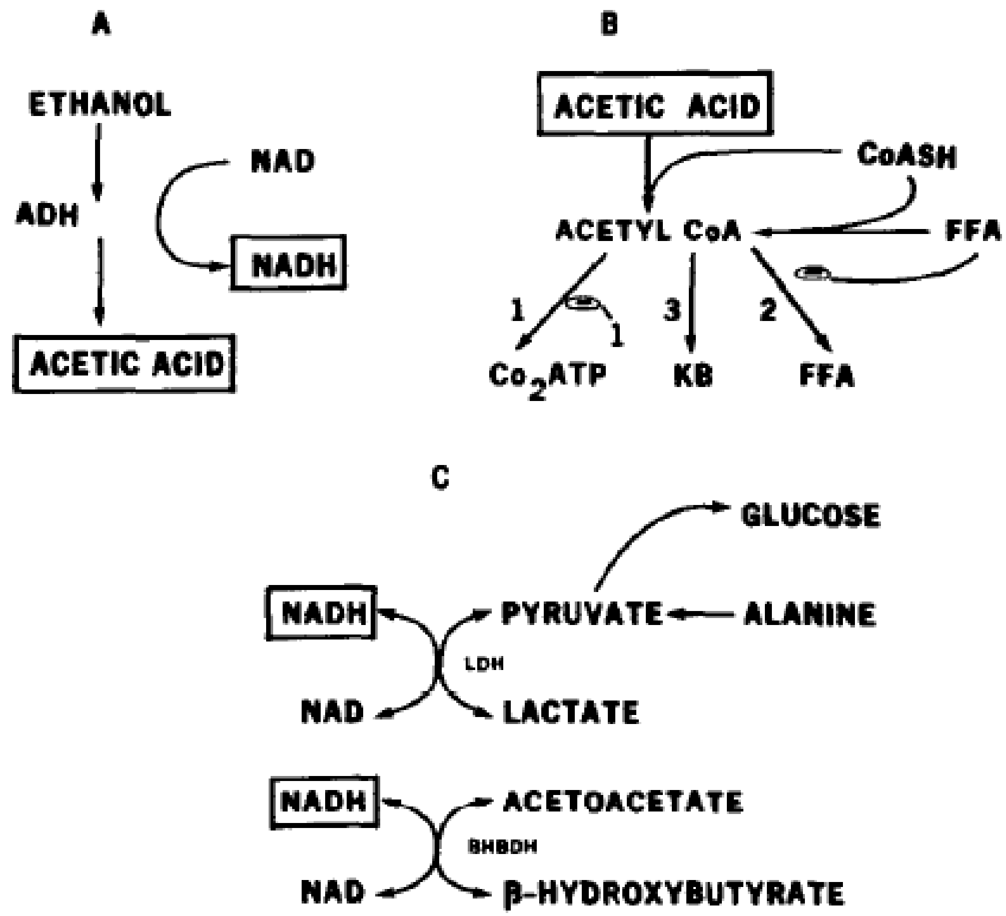
13 episodes in 10 pts:

pH	7.29$\pm$0.05
HCO_3	13$\pm$2
AG	34$\pm$3
Lactate:	7.3$\pm$1.6

β-OH-Butyrate: Normal (often raised in literature)

Thus, mild acidosis which is usually combination of lactic and ketoacidosis. Frequent concomitant metabolic alkalosis due to vomiting

ETHANOL, LACTIC ACIDOSIS & KETOSIS

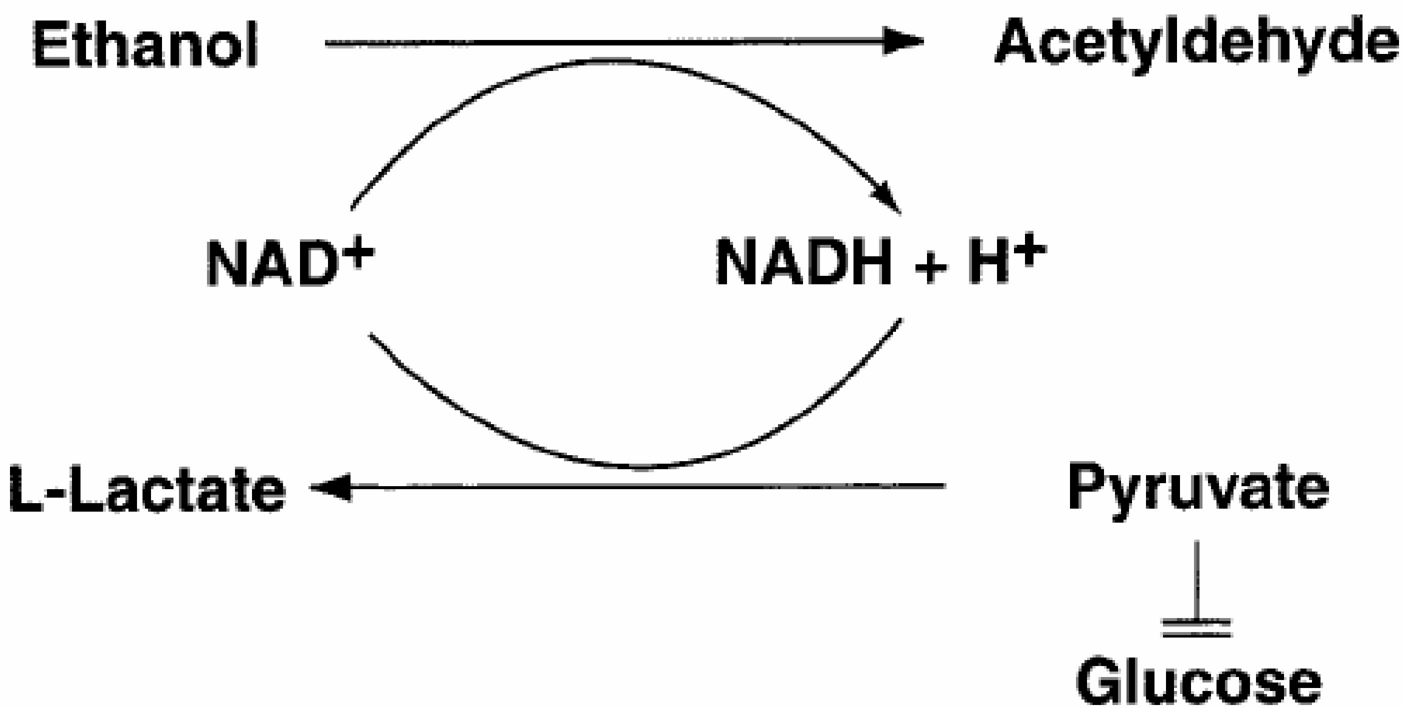


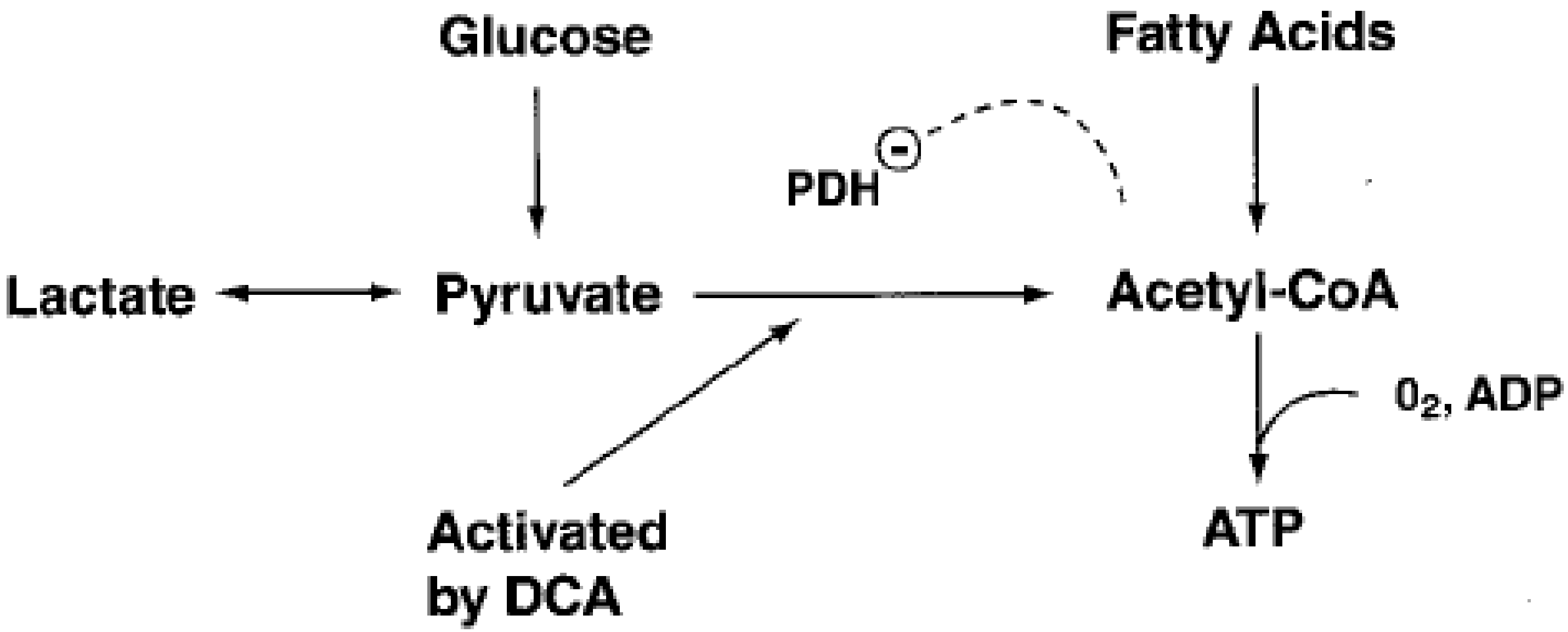
Life-Threatening Acidosis in an Alcoholic

Since acidosis improved so rapidly, without need for dialysis, and lactate was very high (with high ketones in urine), it was probably due to combined lactic & ketoacidosis of alcoholism.

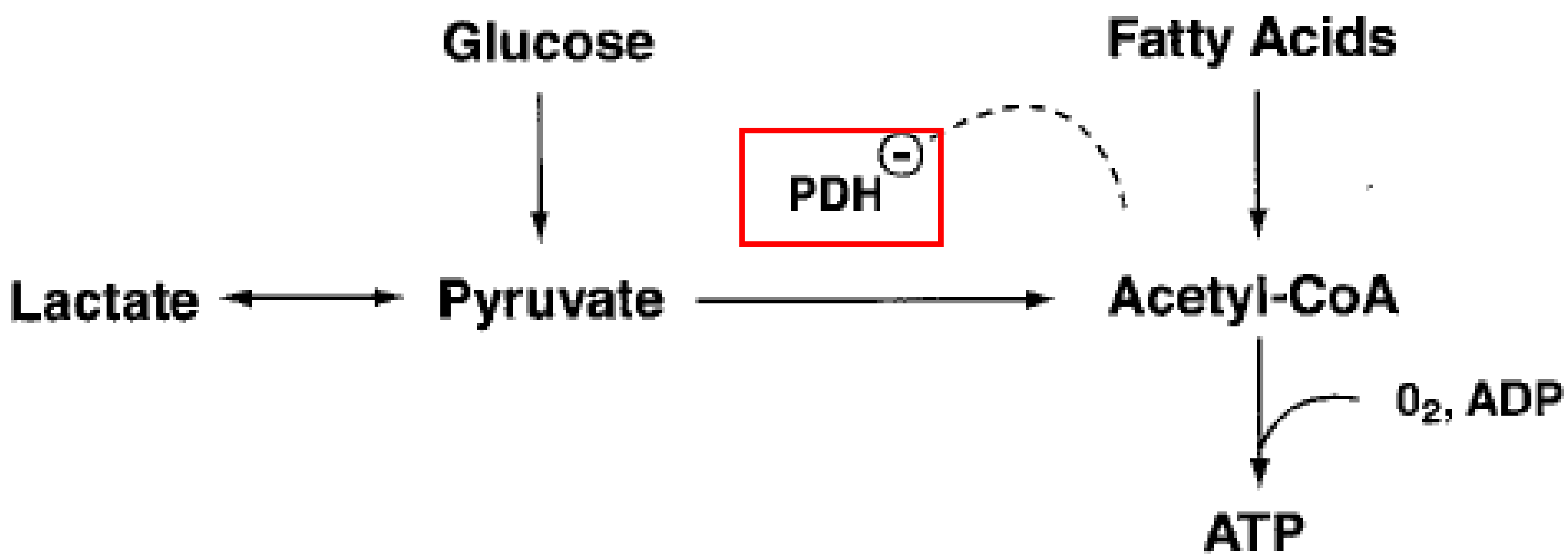
However, severity of acidosis very unusual in alcoholics.

ETHANOL & LACTIC ACIDOSIS





LACTIC ACID IS A METABOLIC DEAD END; IT CAN ONLY BE METABOLIZED VIA PYRUVATE



PDH: Pyruvate dehydrogenase
(Thiamine is coenzyme for PDH).

ETHANOL & LACTIC ACIDOSIS

- Life-threatening acidosis following alcoholic binge due to alcoholic lactic and ketoacidosis
- Lactic acidosis of alcoholism probably rendered much more severe by co-existing

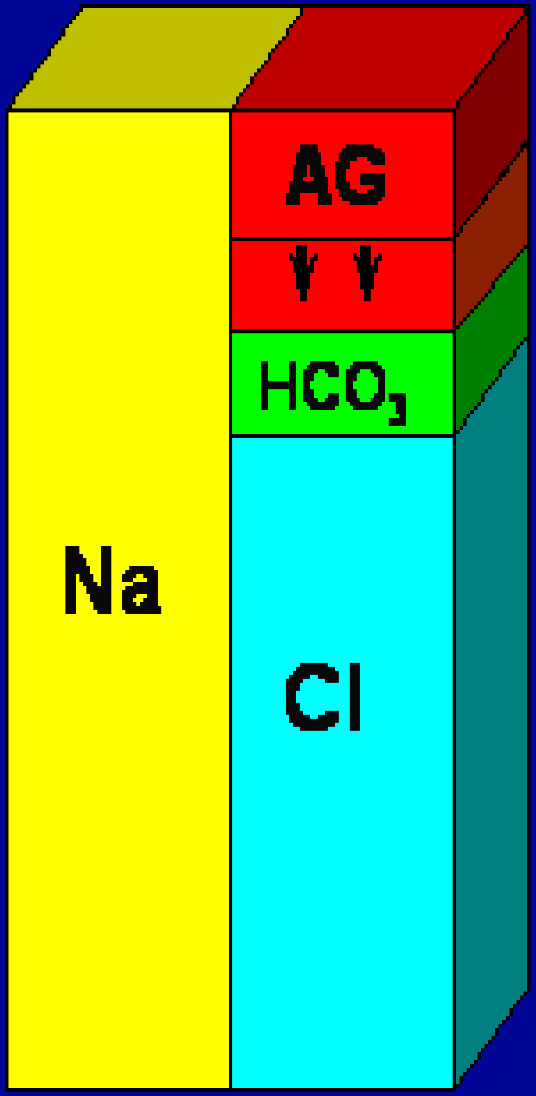
  Thiamine deficiency.
- This reduces activity of PDH, thus inhibiting metabolism of lactate.
- This patient probably had severe thiamine deficiency.

ETHANOL, LACTIC ACIDOSIS & KETOSIS

Dietary analysis several months later:

• Diet was relatively constant.
• Weight was 65kg, height 1.64m, **BMI of 24.17**.
• Caloric intake was **1525 Kcal/d** (expected intake 2262).
• Of the calories ingested, 22% were from protein, 53% from fat, and 25% from carbohydrates.
• Estimated vitamin intakes were as follows: Vitamin C: 8.4mg/d (**9%** of RDA); Thiamine 0.47mg/d (**39%** of RDA); Riboflavin 1.77mg/d (136% of RDA); Niacin **11.9mg/d** (74% of RDA); Folic acid 132mg/d (**33%** of RDA); **B6** 0.83mg/d (49% of RDA); B12 5.8mg/d (240% of RDA); Vitamin A **605mg/d** (67% of RDA); Vitamin E 6mg/d (**40%** of RDA).
•**Thus the patient, even in a stable, non-drinking state had an inadequate intake of a number of vitamins, including vitamin C, thiamine, niacin, folic acid, B6, vitamin A and vitamin E.**

ANION GAP METABOLIC ACIDOSIS



Ketosis
Uremia
Salicylate
Methanol
Aldehydes
Lactate
Ethylene-
glycol

MUDPILES

TYPES OF ACID LOADS

- **Volatile**
  - $H_2CO_3 \longrightarrow CO_2 + H_2O$ (~15,000 mmol/day)
- **Non-Volatile**
  - **Metabolizable**
    Lactic Acid, Ketoacids, Citric Acid
  - **Non-Metabolizable (~70-100 mmol/day)**
    H_2SO_4, HCl, H_2PO_4

METABOLIZABLE ACIDS – BASE GENERATION POTENTIAL BICARBONATE

$$\text{HLactate} \longrightarrow CO_2 + H_2O \text{ or Glucose}$$

$$\text{NaLactate}$$

$$Na^+ + HCO_3^- \longrightarrow NaHCO_3$$

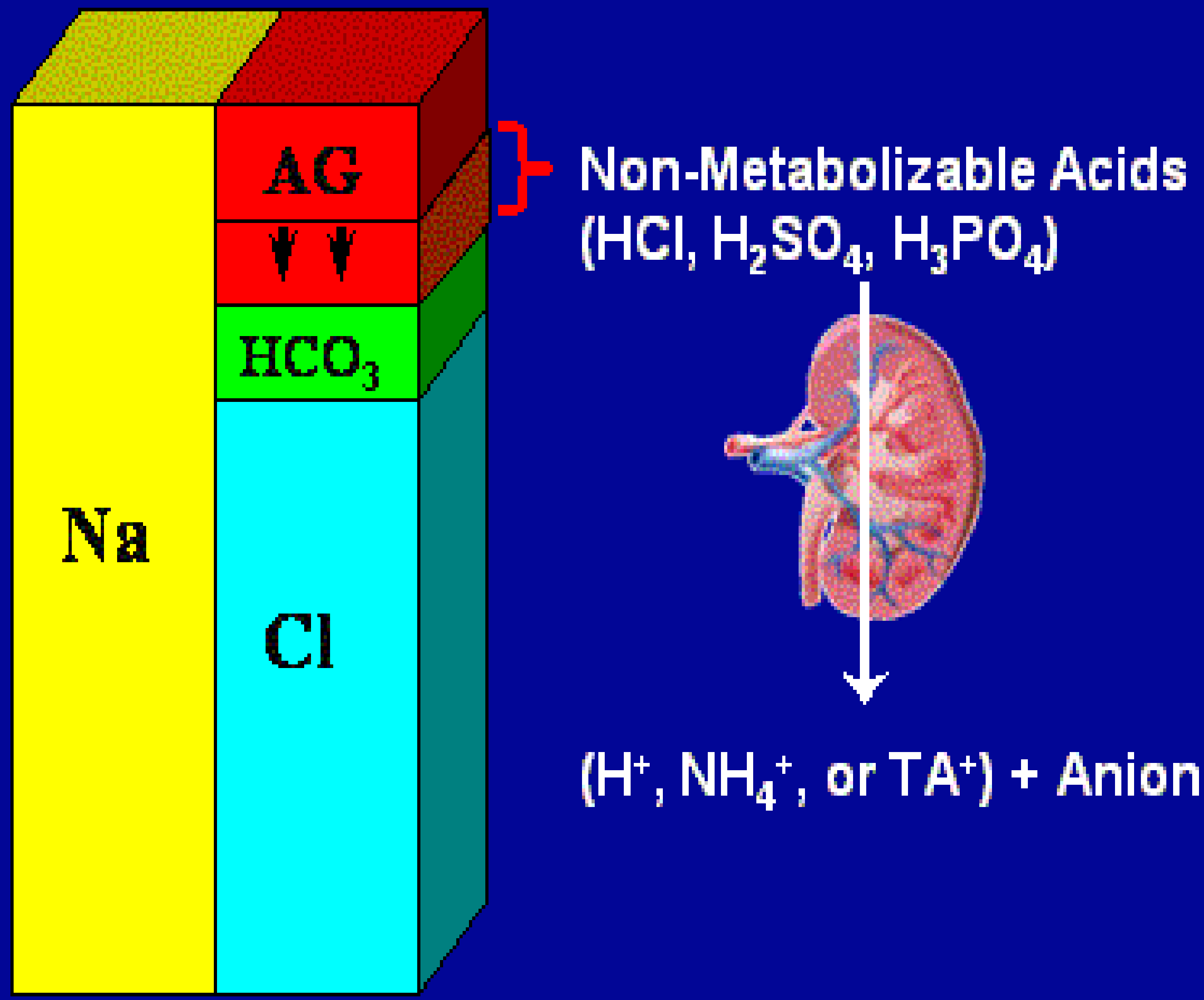
$$H_2CO_3 \longrightarrow HCO_3^-$$

$$H_2CO_3 \longrightarrow H^+$$

$$\text{Lactate}^- + H^+ \longrightarrow \text{HLactate}$$

$$\text{HLactate} \longrightarrow CO_2 + H_2O \text{ or Glucose}$$

ANION GAP ACIDOSES REVERSIBLE ONLY VIA RENAL EXCRETION



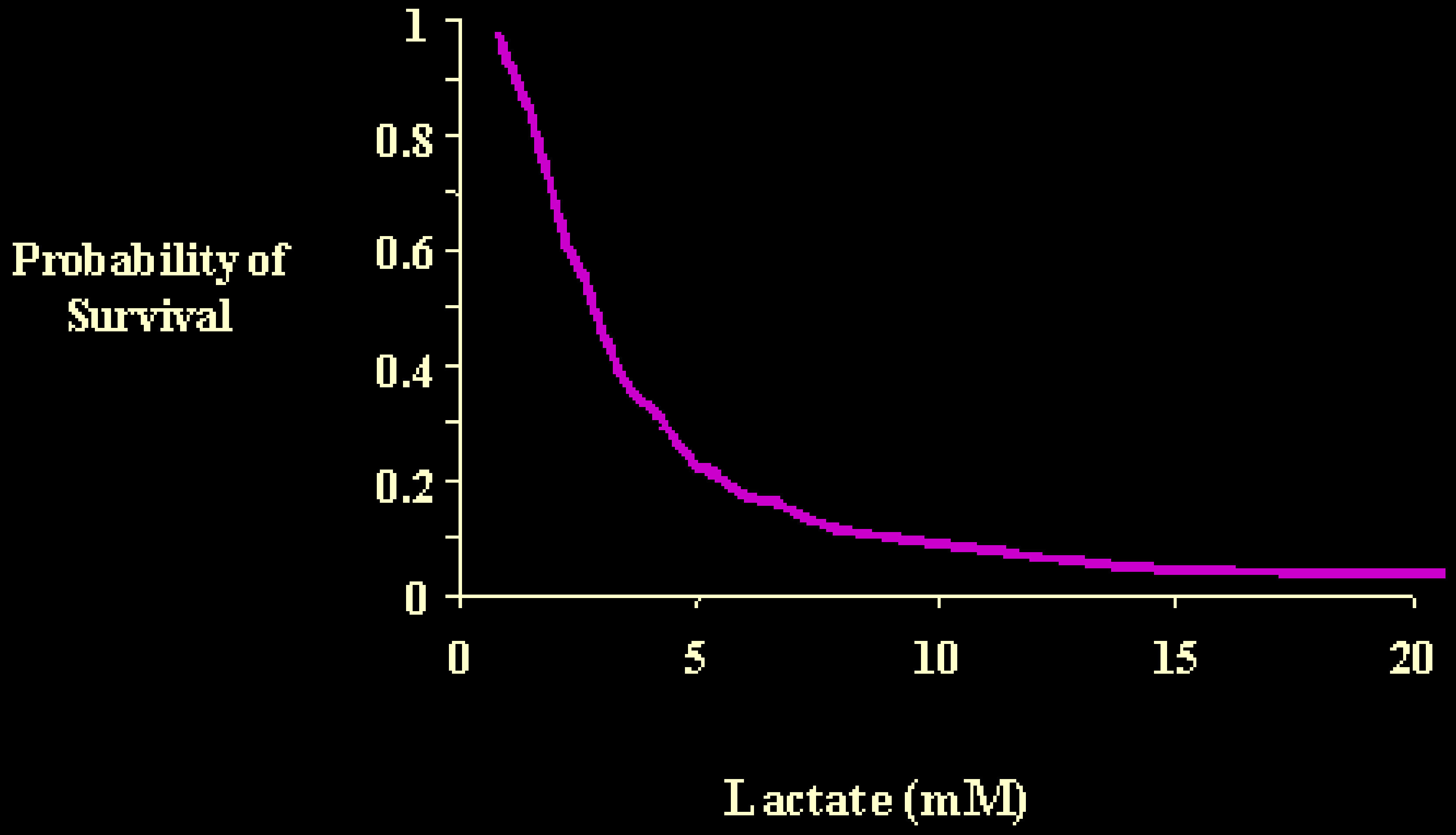
LACTIC ACIDOSIS

- Approximately 1400 mmol lactate produced/day, which are buffered by 1400 mmol HCO_3^- to form sodium lactate. This is very efficient, since $P_{lactate}$ <2mmol/L.
- Liver oxidizes lactate to restore HCO_3^-, and has major role in lactate homeostasis.
- Kidneys metabolize 10-20% of total lactate metabolized, by excretion, gluconeogenesis and oxidation. Urinary excretion is minor, since renal threshold is 6-10 mmol.

LACTIC ACIDOSIS

- **TYPE A**
  - Shock
  - Acute severe hypoxia
  - Acute severe anemia
- **TYPE B**
  - Cyanide
  - Metformin (causes shift to anerobic metabolism, esp. in GI tract cells; decreased pH_i, which decreases liver uptake and metabolism of lactate).
  - Reverse Transcriptase Inhibitors
  - Ethanol

Lactic Acidosis



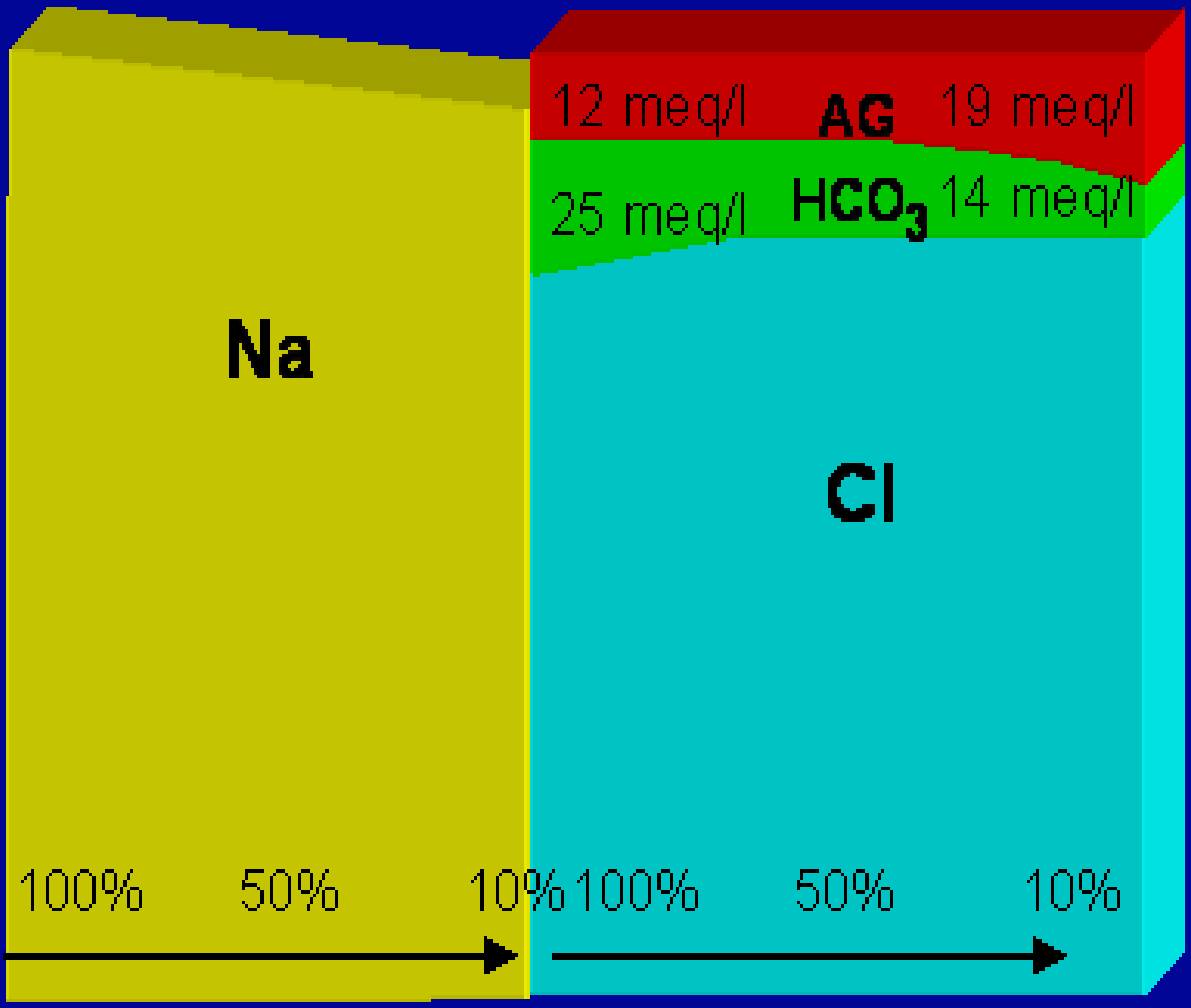
Lactic Acidosis

Prognosis

- Lactate 5 mmol/L → 80% mortality
- Mortality approaches 100% at levels >10 mmol/L

Mortality relates to underlying cause

Progression of Chronic Kidney Failure

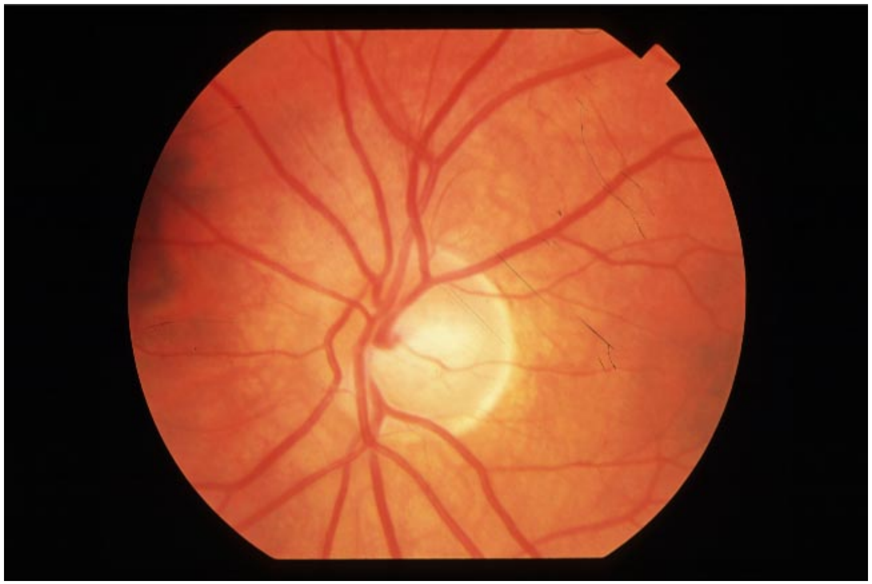


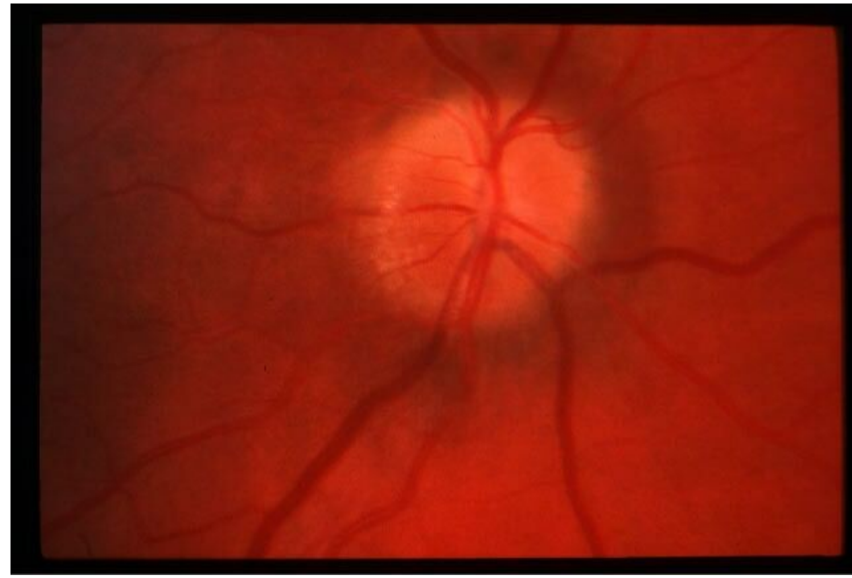
Widmer B. et al Arch Intern Med 1979

GFR

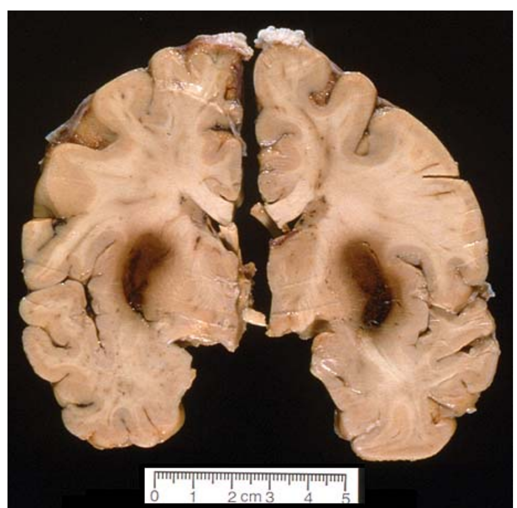
Methanol intoxication: neurological effects

Normal retina (left); optic neuritis (right)





Putamen infarcts



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Oxalate crystals
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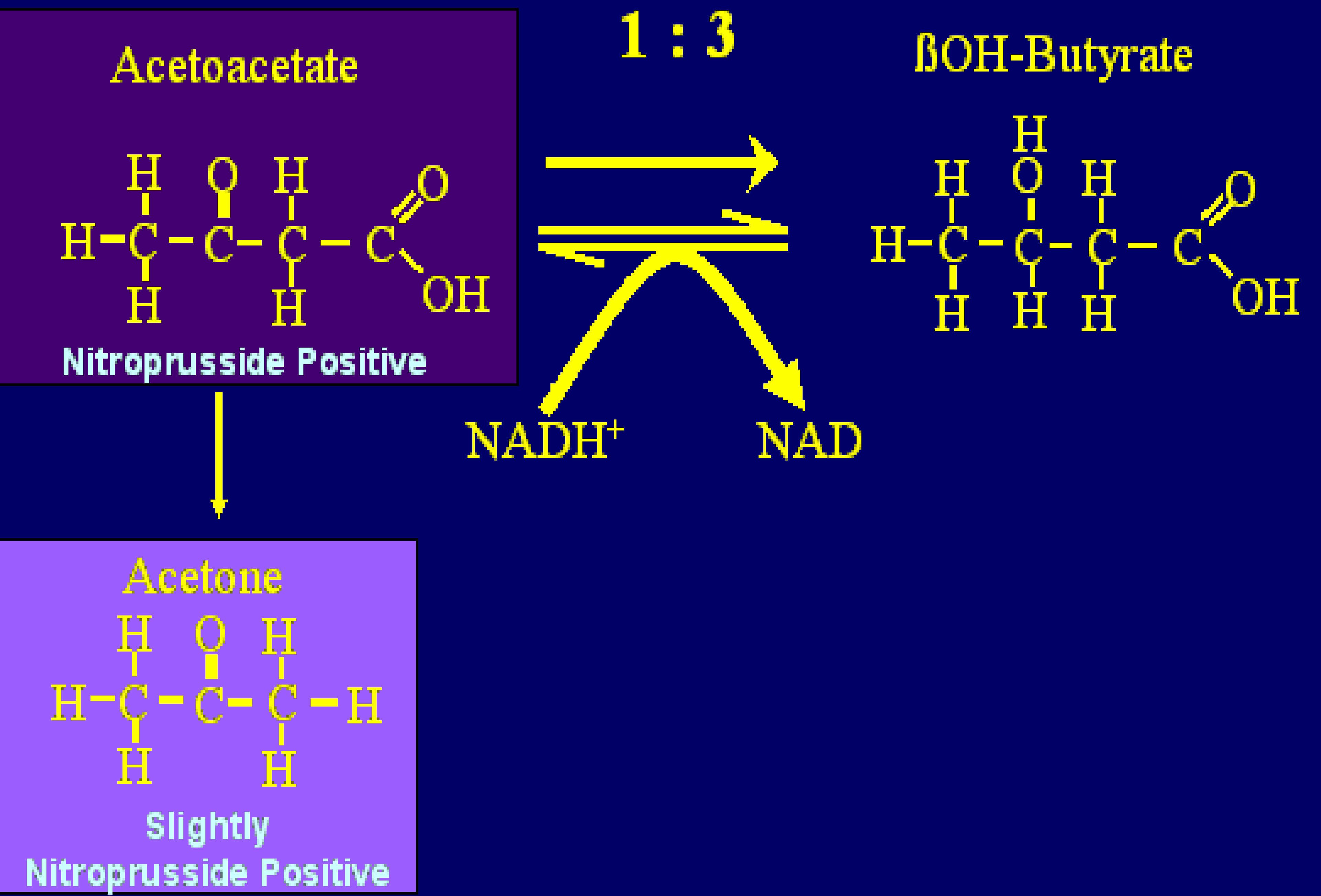
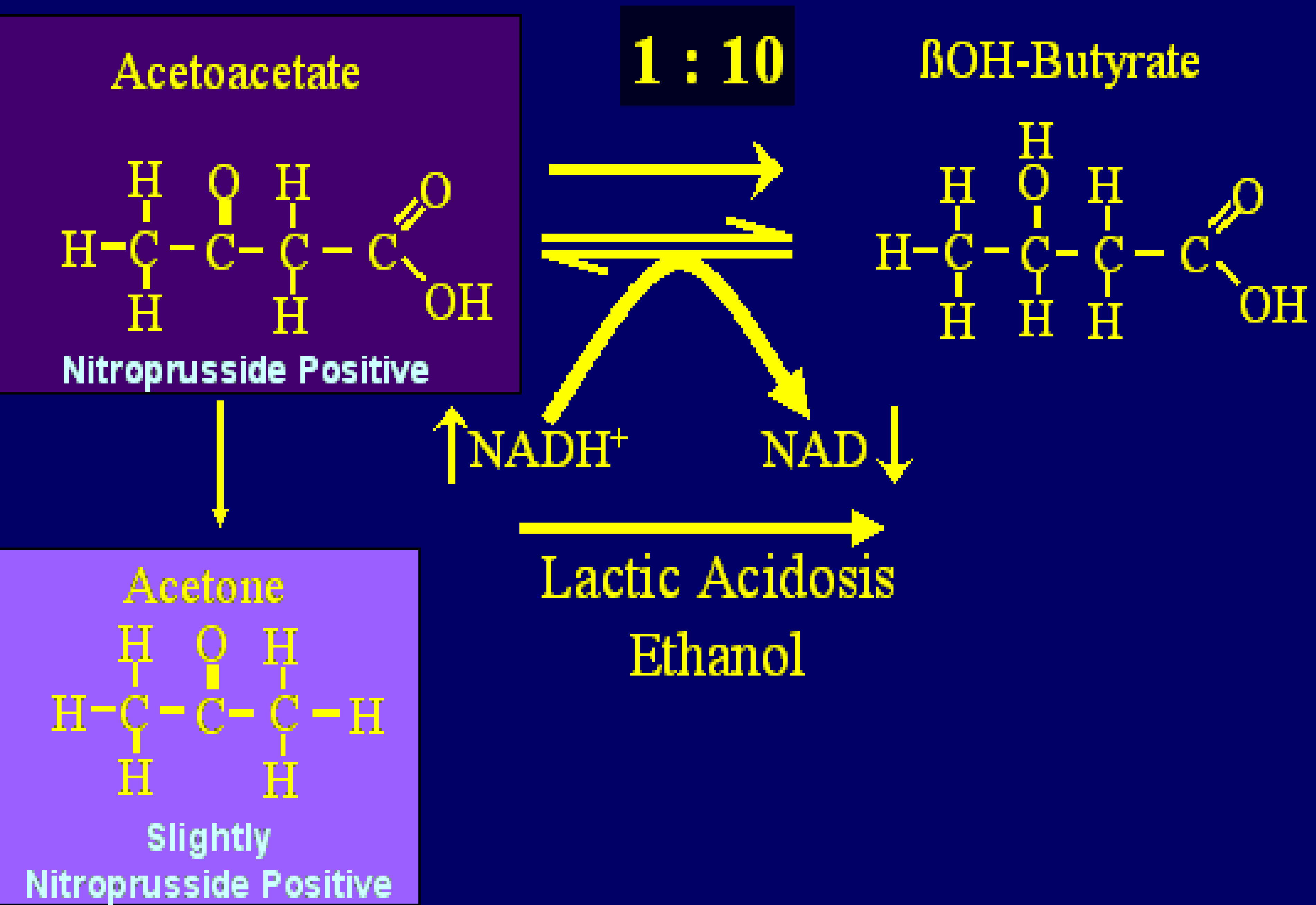
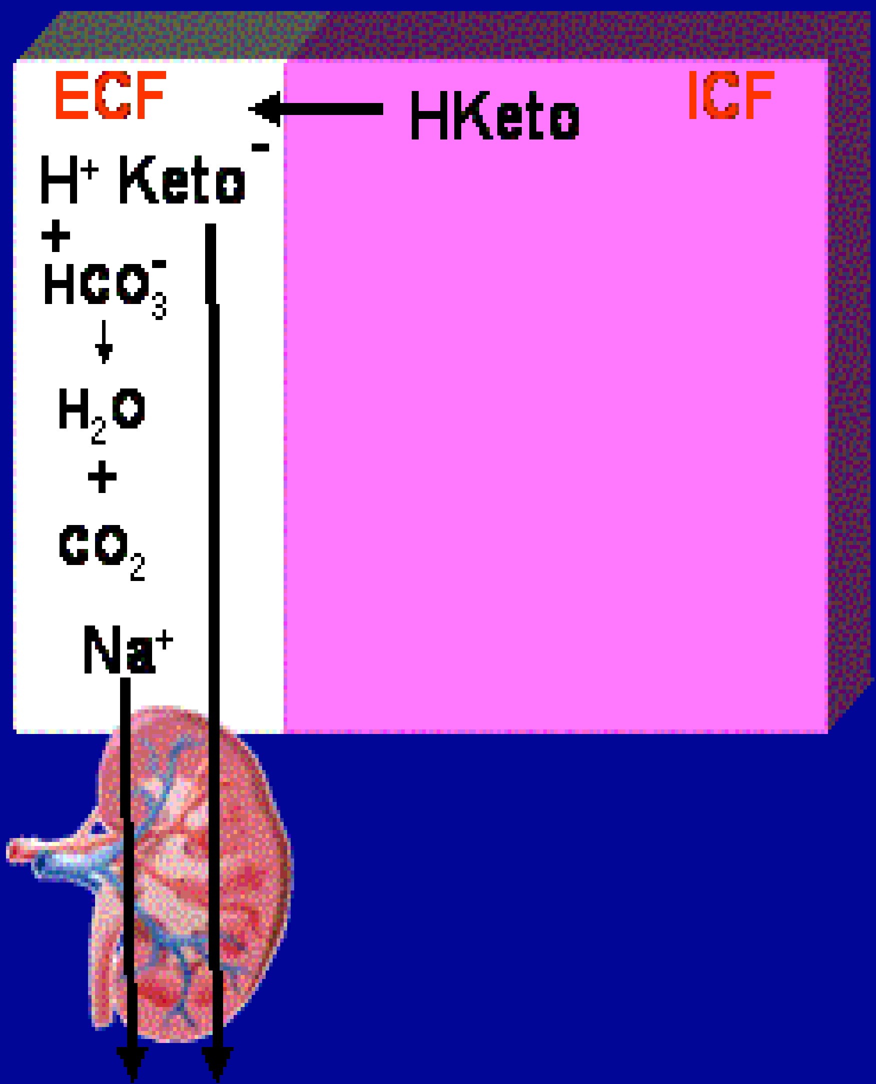
Osmolal gap > 10 mOsm

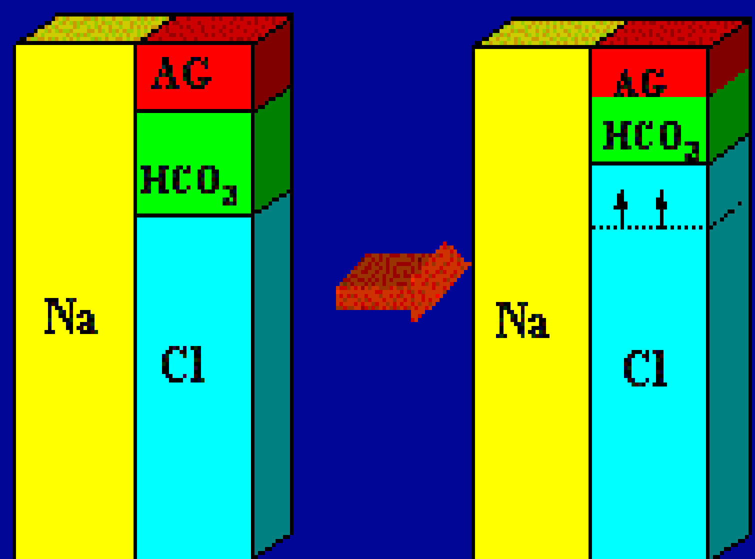

1 : 3
Acetoacetate
Nitroprusside Positive
ßOH-Butyrate
NADH+
NAD
Acetone
Slightly
Nitroprusside Positive


Acetoacetate
Nitroprusside Positive
1 : 10
ßOH-Butyrate
↑NADH+
NAD↓
Lactic Acidosis
Ethanol
Acetone
Slightly
Nitroprusside Positive

DEVELOPMENT OF DKA WITH EXCELLENT KIDNEY FUNCTION THE βOH-BUTYRATE & ACETOACETATE ARE EXCRETED AS Na SALTS



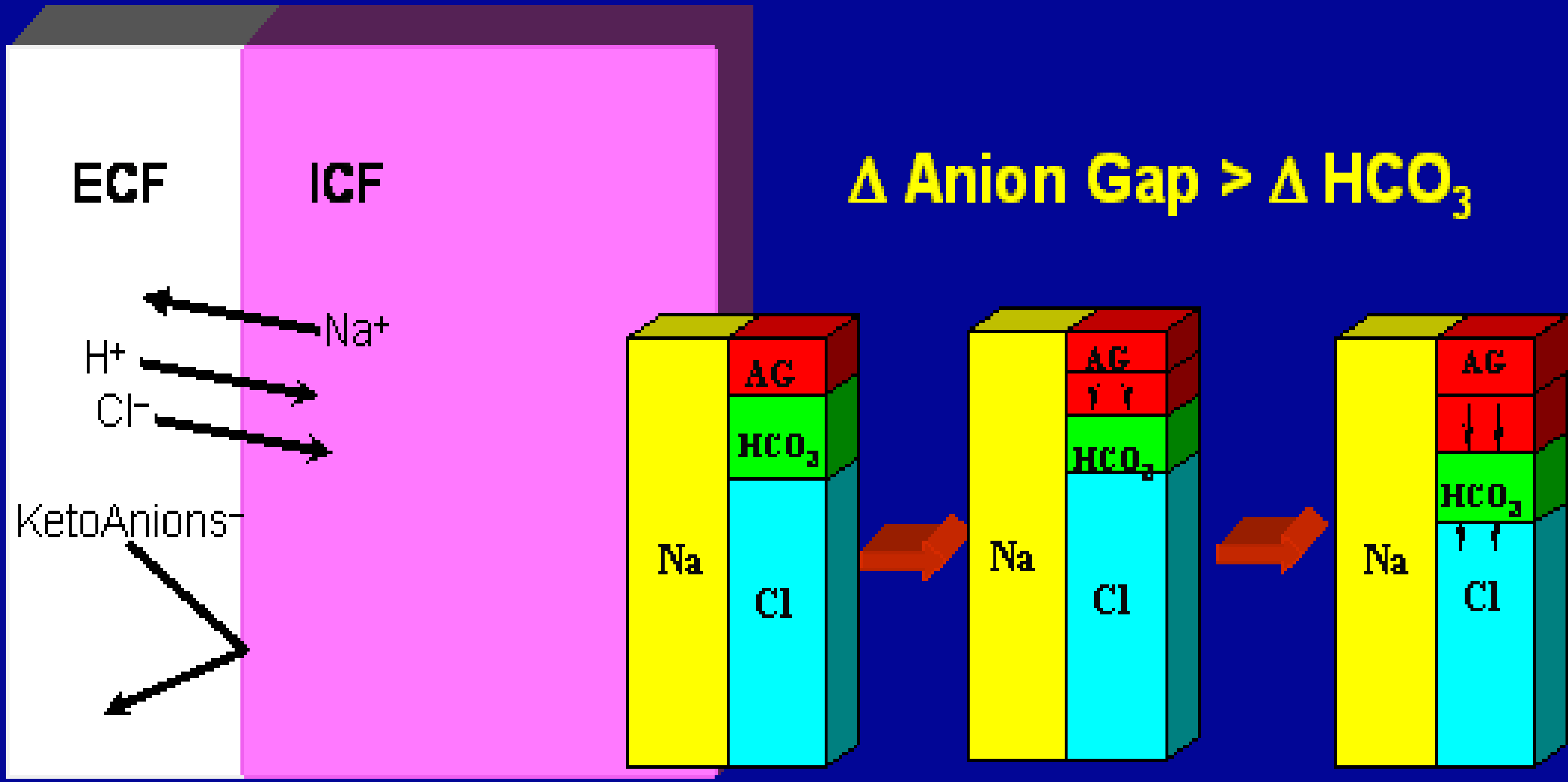
This Coverts the AG Acidosis to a Hyperchloremic Acidosis



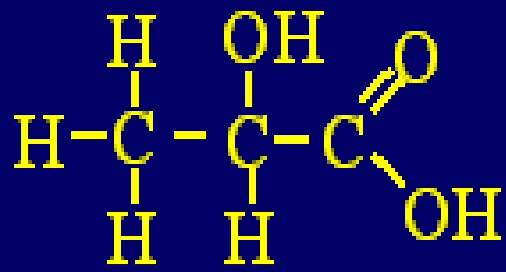
DEVELOPMENT OF DKA IN ABSENCE OF KIDNEY FUNCTION

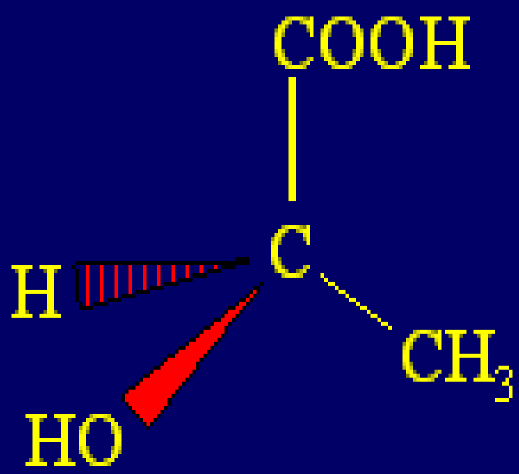
Ketoacids Are All Retained

Δ Anion Gap > Δ HCO_3

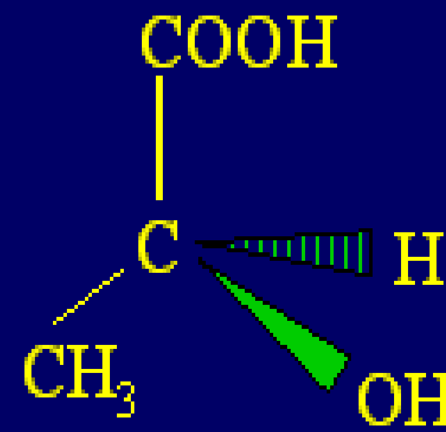


d - LACTIC ACID
Optical Isomers (Chiral Molecules)

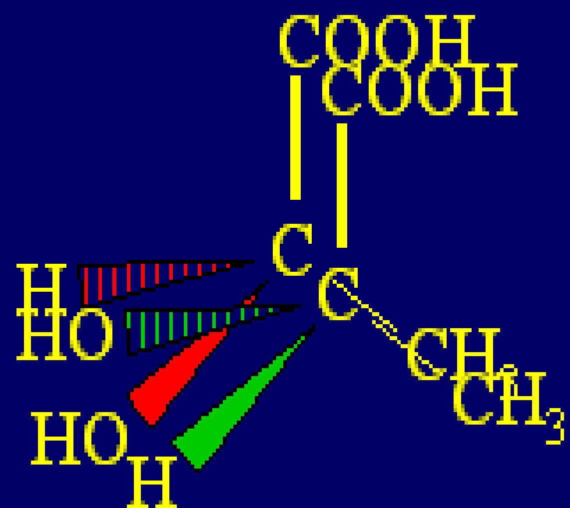




D-Lactic Acid



L-Lactic Acid



D-Lactic Acidosis

- L-isomer is found in the body
- Metabolized using L-lactic dehydrogenase
- D-Lactate made by bacteria
  - Short bowel syndrome
  - Worse with CHO loading
- Causes anion gap acidosis
  - Measure D-lactate with D-LDH enzyme
  - Gas chromatography

Management of Life-Threatening Acidosis

- Intravenous bicarbonate. Not Na lactate, citrate, acetate
- Goal: Raise bicarbonate to 8-10 mmol/L
  - 8 - 4 X 70 X 0.5 = 140 mmol
- Monitor closely and watch for mixed acidosis
- Risks of $NaHCO_3$
  - 1 N vs 2- 50 mM amps to 0.25 N NaCl
- THAM (0.3 M tromethamine) causes hypoglycemia, ventilatory depression, hyperkalemia.
- Carbicarb (sodium carbonate/bicarbonate)
  - Studies do not support claims

Guidelines for Bicarbonate Therapy in DKA

- Use only if:
  - Acidemia is very severe: pH < 7.0 in young patient and < 7.15 in older patient
- Do not correct deficit or pH to normal
  - Give initially to increase pH to 7.2 - 7.24
    - 1 or 2 amps (50-100 mEq in 250 mL 0.45% NaCl) slowly in first hr. usually sufficient unless superimposed lactic acidosis or combined respiratory acidosis, or another problem

Cause-Specific Therapy in Lactic Acidosis

- I.V. Fluids, afterload -reduction, dopamine, dobutamine, avoid Ep and NE if possible.
- Antibiotics for sepsis, dialysis of toxins, discontinue metformin, nitroprusside
- Treatment of underlying diseases (cancer, intestinal ischemia).

Complications of Bicarbonate Therapy

- Overshoot alkalosis:
  - **pH_a of 7.20 is a reasonable goal; HCO_3^- = 8-10 mEq/L**
- Increase in lactate generation
- Volume expansion
- Increased CO_2 production
- Hypocalcemia
- Cardiac depression

NEXT CASE

האם יש לכם עדיין כוח?

תזכרו את היפוקרטיס:

"ARS LONGA, VITA BREVIS"

(המקצוע ארוך, החיים קצרים)

Case 2

A 54 year old man with established chronic renal insufficiency (baseline BUN = 29, baseline creatinine =1.9) and nephrocalcinosis is admitted with flaccid paralysis and the following laboratory data:

Case 2 laboratory data

Na^+ 155, K^+ 1.9, Cl^- 129, HCO_3^- 16, BUN 84, Cr 2.7, Albumin 3.7, P_{osm} 320

Arterial Blood gases: pH 7.30, PCO_2 31, PaO_2 74, HCO_3^- 17

Urine: Specific Gravity 1.011, pH 6.5; protein and glucose (-)

Urinary calcium – 400 mg/day, urinary citrate 100 mg/day

Urine Na^+ = 38, Urine K^+ 41, Urine Cl^- 49, Urine osmolality 460

Case 2 laboratory data

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$\boxed{\text{Urine } Na^+ = 38\text{, Urine } K^+ \ 41\text{, Urine } Cl^- \ 49\text{, Urine osmolality } 460}$

URINARY AG

$(Na^+ + K^+) – Cl^-$:

- If negative: then anion ($NH4^+$) is present in urine.
- If positive, then no NH_4^+ is present in urine.
- In this case: urinary AG is (38+41-49) = 30
- Thus no NH_4^+ in urine: i.e. absent H^+ in urine (= distal RTA or Type 4 RTA)

DIFFERENTIAL DIAGNOSIS OF HYPERCHLOREMIC ACIDOSIS

Urine Net Charge is Negative = High Urine Ammonia

CAUSES

GI loss of HCO_3

Gain of HCl

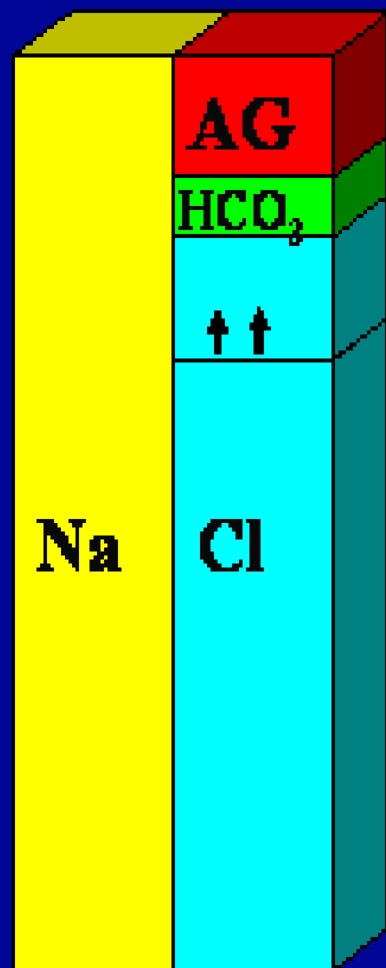
NH_4^+ Cl

PRTA when urine pH is low

CASE 2

- Non-anion gap acidosis
- Hypokalemia due to renal loss
- High urine pH
- Nephrocalcinosis
- Positive urinary AG (thus no urinary NH_4^+)
- Hypercalciuria:
- Diagnosis: DISTAL RTA

HYPERCHLOREMIC METABOLIC ACIDOSIS



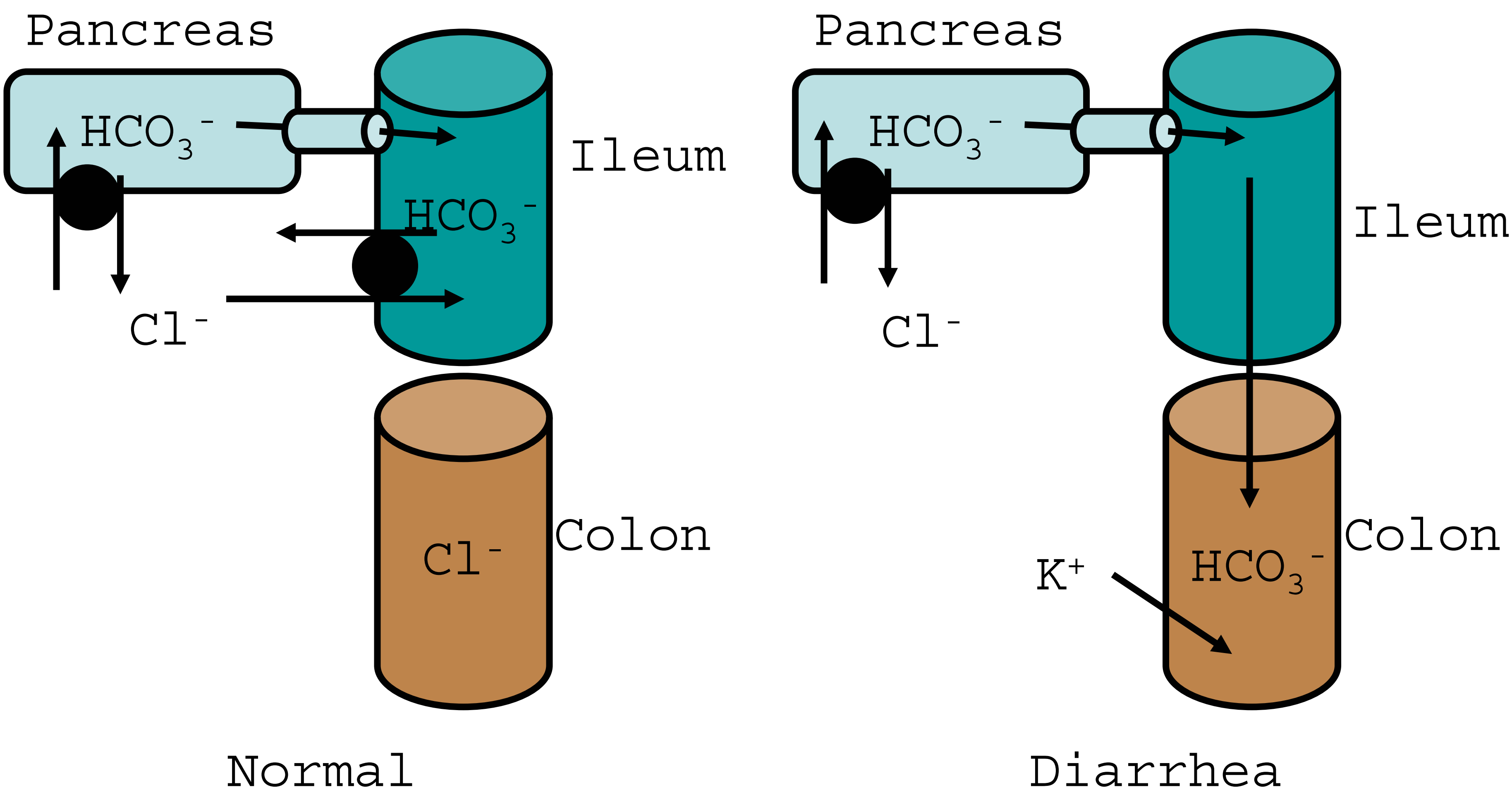
CAUSES:

1. Add HCl, or Potential HCl, to ECF

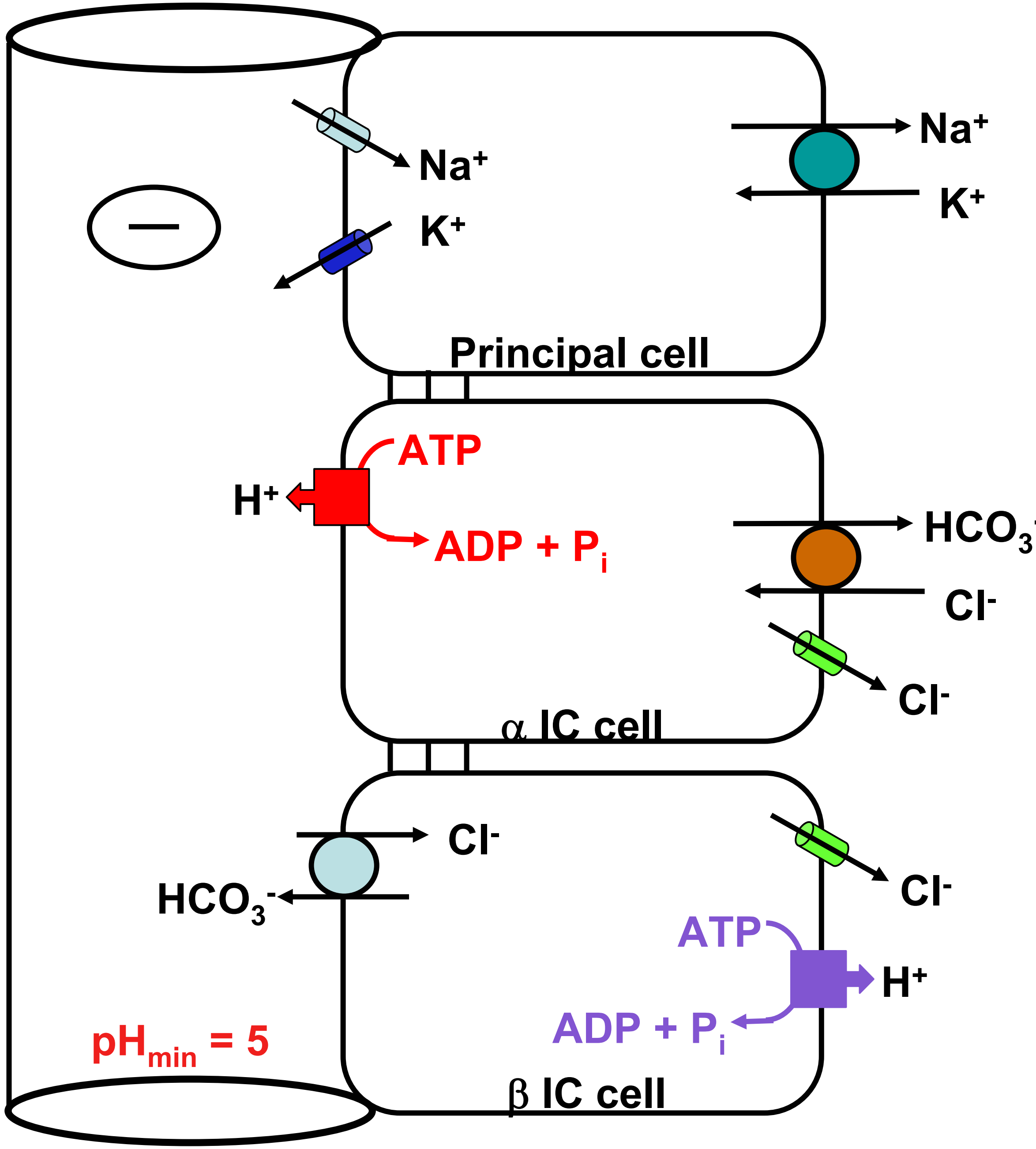
$$HCl + HCO_3^- \rightarrow Cl^- + H_2CO_3$$

2. Lose $NaHCO_3$, or Potential HCO_3, from ECF

Diarrhea Causes Loss of HCO_3^- And a Normal Anion Gap Acidosis And Hypokalemia

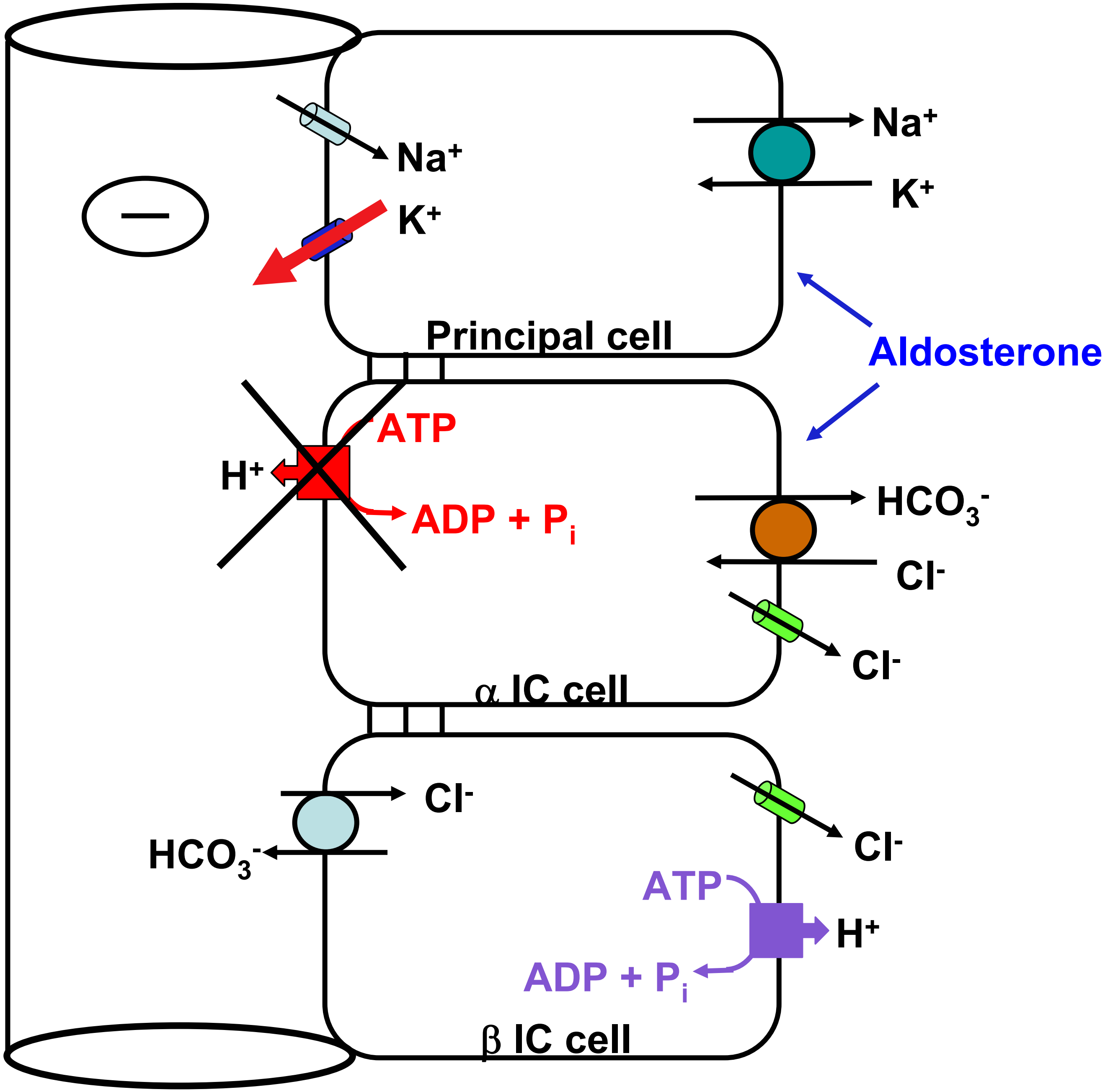


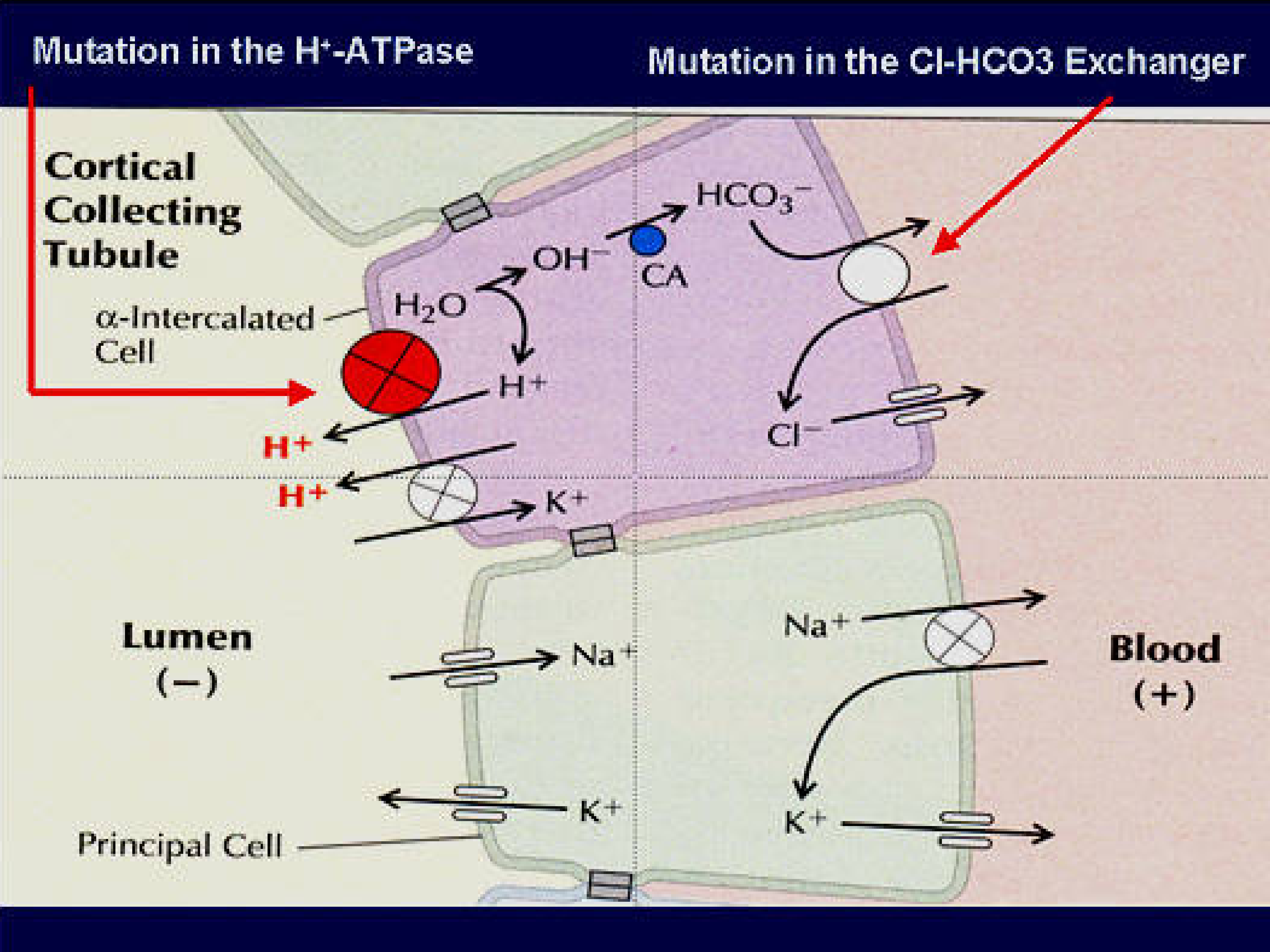
Collecting Duct Acidification



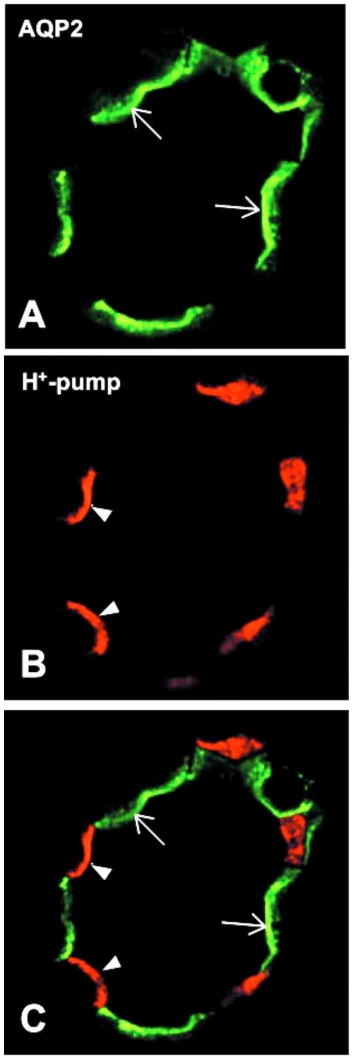
Hypo-kalemia in distal RTA:

H $^+$ no longer shunts Na $^+$ current so K$^+$ must do so

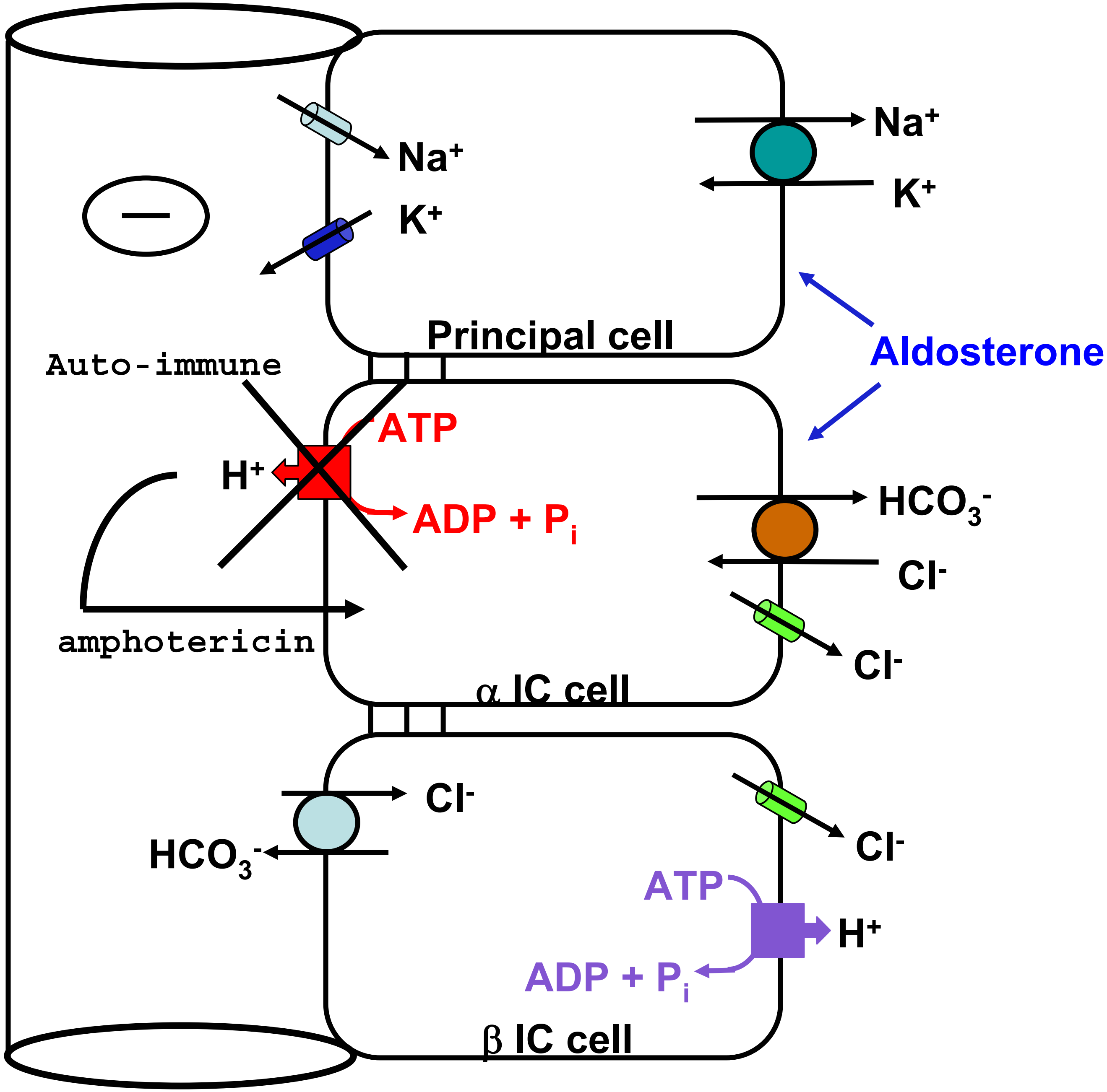



Mutation in the H+-ATPase
Mutation in the Cl-HCO3 Exchanger
Cortical Collecting Tubule
α-Intercalated Cell
H_2O
OH^-
CA
HCO_3^-
H^+
H^+
H^+
Cl^-
K^+
Lumen (−)
Blood (+)
Na^+
Na^+
K^+
K^+
Principal Cell

Distal RTA



AQP2
A
H+-pump
B
C



Na+
K+
Na+
K+
Principal cell
Aldosterone
Auto-immune
ATP
H+
ADP + Pi
HCO3-
Cl-
Cl-
amphotericin
α IC cell
Cl-
HCO3-
Cl-
ATP
H+
ADP + Pi
β IC cell

CLINICAL MANIFESTATIONS OF DISTAL RTA (continued)

Caruana and Buckalew, 58 patients

Medicine 67:84-99, 1988.

Group A: Children (24%)

Failure to thrive, vomitus, diarrhea, growth retardation.

Group B: Adults (17%)

Abnormal laboratory tests

Group C: Adults (59%)

Nephrolithiasis

Nephrocalcinosis

PATHOGENESIS OF KIDNEY STONES IN DISTAL RTA

PATHOPHYSIOLOGY

- Hypercalciuria (30%)
- ↓ Citrate excretion (30%)
- ↑ Urine pH - ↑ precipitation of calcium phosphate
- ↑ Urate excretion (23%)

DISTAL RTA - STONES - NEPHROCALCINOSIS

- Distal RTA causes nephrocalcinosis
- Nephrocalcinosis causes distal RTA
- Hypercalciuria may be the consequence or the cause of distal RTA

Citrate deficency

- Low citrate excretion is due to acidosis
- As Bicarb and repair acidosis [citrate] increases
- Bicarb therapy can lead to expanded volume

Therapy of RTA: Alkali Replacement

- Shohl's Solution (Na^+ citrate)
- $NaHCO_3$ tablets
- Baking soda (60 mEq/tsp.)
- K-Lyte (25 or 50 mEq/tablet)
- Poly citra (K^+ Shohl's)

"Those are my principles, and if you don't like them - well, I have others"

Groucho Marx