C. ACID-BASE BALANCE

C.a. IMPORTANCE OF pH note: page numbers are corrected to 3rd ed in 399, not here yet.

proper pH is required for 1) membrane excitability, 2) enzyme function, 3) chemical reactions, 4) electrolyte concentrations
wrong pH → ? denatured protein which ones? Na+/ K+/Ca++/Cl-/HCO3-,

C.b. MECHANISMS OF ACID-BASE BALANCE we will spend almost 2 pages doing normal

C.b.A. CONCEPTS

acids dissociate into H^+ and some anion what does dissociate mean? Profound bases accept or remove H^+ from solution
strong acids dissociate readily into H^+ and the anion –> /// H^+ in solution strong bases readily remove H^+ –> /// H^+ in solution
weak acids dissociate only slightly into H^+ and the anion –> / H^+ in solution weak bases minimally remove H^+ –> / H^+ in solution

pH = negative log of H^+ concentration
range is from 0 to 14
a pH of 0 = 1g H^+/ℓ solution = 6.023×10^{23} H^+/ℓ soln; if the soln were H_20, this is equivalent to 1 out of 55 H_20 molecules being dissociated
a pH of 7 = 6.023×10^{16} H^+/ℓ soln ($10^{23} \times 10^{-7}$); if the soln is H_20, this means 1 out of 550,000,000 H_20 molecules is dissociated.
Since pH of extracellular body fluids is normally 7.35-7.45, the H^+ concentration is *very, very* small. (Na^+ 40,000 X & K^+ is 1000 X more abundant)
(I have calculations if you are interested)

C.b.B. METABOLIC ACID PRODUCTION note to me: this is per 1000g H20, not 1000g H, thus 55 not 1000

cellular respiration using complete oxidation/catabolism w glucose and other carbohydrates as high-energy electron source
–> $C0_2$ and the volatile acid, H_2C0_3, both of which are removed by the lungs

cellular respiration using oxidation/catabolism w proteins and fats or incomplete oxidation of carbohydrates as high-energy electron source
–> fixed/nonvolatile acids which are metabolized by the liver and removed by the kidneys normally volatile H+ conc 100X fixed, ∴ look at volatile 1st

C.b.B.a. VOLATILE ACID PRODUCTION

carbonic anhydrase
lots of H_20 available dissociates bicarbonate

$$C0_2 + H_20 \xleftrightarrow{\text{carbonic anhydrase}} H_2C0_3 \longleftrightarrow H^+ + HC0_3^- \quad (E1)$$

if ↑ $C0_2$: ↑ $C0_2 + H_2O$ –> / H_2C0_3 –> / H^+ + / $HC0_3^-$ (E2)

if ↓ $C0_2$: ↓ $C0_2 + H_2O$ –> / H_2C0_3 –> / H^+ + / $HC0_3^-$ (E3)

C.b.B.b. FIXED ACID PRODUCTION one of two, non-respiratory sources of H^+

lipid oxidation –> ketoacids and phosphoric acid ⎫ starvation, diabetes gluconeogenesis
protein oxidation –> sulfuric acid ⎬ (normal total = 50-100 mmol/day; immediately buffered to sodium salt of acid)
incomplete oxidation of carbohydrates –(1)–> lactic acid ⎭ anaerobic (Key: 1: CF III.A.-2: cellular respiration)

C.b.B.b.(A.) COMPENSATION

If ↑ H^+ is from ↑ fixed acid production, –>
See this page in 3XX for additional info

$$\uparrow(H^+ + HC0_3^- \rightarrow H_2C0_3) \rightarrow \begin{cases} \rightarrow \downarrow HC0_3^- \\ \rightarrow (/\ H^+) \\ \rightarrow \uparrow H_2C0_3 \end{cases} \quad (E4)$$

compensation, which is another name for ??? homeostasis

If ↓ H^+ is from ↓ in fixed acid production, –> ∴ between E1, E4 &/or E5 & buffering (below), pH normally not a problem, because of its importance to body. (C.a.)

$$\uparrow(H_2C0_3 \rightarrow H^+ + HC0_3^-) \rightarrow \begin{cases} \rightarrow \uparrow HC0_3^- \\ \rightarrow (/\ H^+) \\ \rightarrow \downarrow H_2C0_3 \end{cases} \quad (E5)$$

C.b.C. CALCULATION OF PLASMA pH

extracellular fluid pH = f(extent of H_2C0_3 dissociation and ratio $HC0_3^-$:$C0_2$ where both are expressed in mMol/ℓ)
Altered by renal mechanisms/altered by respiration
pH = pK (H_2C0_3 buffer = 6.1 at normal body temps) + log $\frac{HC0_3^-}{CO_2}$ (modified Henderson-Hasselbach equation) (E6) K/L or B/C
(example: normal ratio of $HC0_3^-/C0_2$ = 20/1 = 20; log 20 = 1.3 ∴ normal pH = 6.1 + 1.3 = 7.4)
e.g., 19/1
ratio < 20:1 –> / plasma pH; reverse when ratio > 20:1 ie more HCO3- to pick up H+ → ↓ H+ → ↑ pH
normal range in bicarbonate is 17-29 mEq/ℓ depending upon sex & age. PCO_2 = 40 mmHg = ? mMol/ℓ
not quite correct, but close enough for our purpose.

C.b.D. REGULATION OF pH

buffer picks up H+ when H+ in excess and releases H+ when H+ is low, ∴ maintains a constant H+ concentration

1) intracellular and extracellular acid-base buffering systems: rapid response (moment by moment), but very crude
2) respiratory elimination of $C0_2$: fairly rapid response (minutes) but loses its ability to regulate pH as pH nears normal } very important!
3) renal elimination of H^+ or $HC0_3^-$: slow (hours - days) but continues until pH is returned to normal or near normal

C.b.D.a. MAJOR ACID-BASE BUFFERING SYSTEMS (the other, non-respiratory source of H+)

C.b.D.a.(A.) $HC0_3^-$ BUFFERING SYSTEM

strong acid + weak base –> weak acid + salt e.g.:
HCl + $NaHC0_3$ –> H_2C0_3 + NaCl

strong base + weak acid –> weak base + H_20 e.g.:
Na0H + H_2C0_3 –> $NaHC0_3$ + H_20

(plasma buffer & interstitial fluid buffer) (F 16.17, p 420) (TP IVC-1, red only) "Na not shown" refers to pink color

C.b.D.a.(B.) PHOSPHATE BUFFERING SYSTEM

strong acid + weak base –> weak acid + salt e.g.:
HCl + Na_2HP0_4 –> NaH_2P0_4 + NaCl
Na bi (dibasic) Na di H (monobasic) (H is bound to the single-bonded O's in each case , leaving other(s) charged.
TP IVC-2, phosphate only

strong base + weak acid –> weak base + H_20 e.g.:
Na0H + NaH_2P0_4 –> Na_2HP0_4 + H_20
TP IVC-1, purple only

(especially important as a filtrate buffer in renal tubules, e.g. see T IVB-2, footnote b & F 16.19, p 421), but also as intracellular buffer (F 16.17, p 420)

C.b.D.a.(C.) PROTEIN BUFFERING SYSTEM

TP IVC-3 do I need carbamino Hb in this one? NO I do it in TP 6

aa-H <–> aa + H^+ (F 12.8, p 312)
TP IVC-1, green only

(especially important as an intracellular buffer) (Fig 16.17, p 420) but also works as plasma buffer (pp's)

C.b.D.b. RESPIRATORY CONTROL MECHANISMS

$C0_2$ readily crosses blood-CSF barrier to CSF where it reacts w H_20 –> H_2C0_3 –> H^+ + $HC0_3^-$ (for me - must be CA in CSF as well?)
H^+ immediately stimulates respiratory center receptors in the 4th ventricle

C.b.D.c. RENAL CONTROL MECHANISMS

(for me – how does b work to elevate H^+?)

C.b.D.c.(A.) HYDROGEN ION AND BICARBONATE ION COUNTERBALANCE (F 16.18, p 420, as modified) TP IVC-4

∴ (a) needed to: 1) excrete increased H^+ from fixed acids and 2) replenish HCO_3^- lost to respiration

C.b.D.c.(B.) INTRATUBULAR BUFFERING SYSTEMS

phosphate buffering system (see C.b.D.a.(B.), above)
ammonia buffering system (F 16.19, p 421) TP IVC-2, ammonia only

C.b.E. ION EXCHANGE MECHANISMS AND THEIR EFFECT ON pH

C.b.E.a. K^+-H^+ ION EXCHANGE (F 16.20, p 421 & 16.21, p 440) (16.21 combined into 16.20; TP IVC-5)

C.b.E.b. Cl^--$HC0_3^-$ ION EXCHANGE (chloride shift, F 12.7, p 312) TP IVC-6 give % of 3 forms of $C0_2$ - globin in RBS, notice on p 293, reverse process occurs at lungs (no Cl^- shift, yet) 7% CO_2 gas, 23% carbamino Hb, 70% HCO_3^-

in plasma at tissue: ↑ $C0_2$ –(E2)–> ↑ $HC0_3^-$ –> ↑ Cl^- into RBC; (at alveolus) ↓ $C0_2$ –(E3)–> ↓ $HC0_3^-$ –> ↑ Cl^- into plasma
NB: body Na^+ levels can influence this exchange by combining w $HC0_3^-$

C.c. ALTERATIONS IN ACID-BASE BALANCE

C.c.A. GENERAL

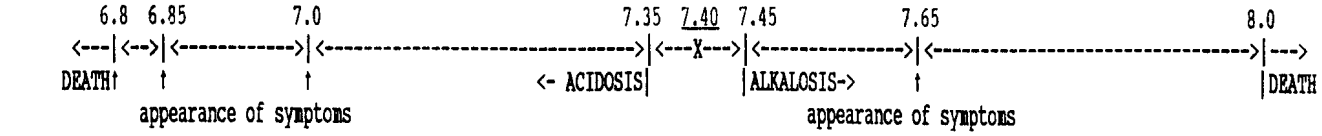

Figure IVC-1. Conditions Ascribed to Variations in Fluid pH TP IVC-7 drawn to scale

acidosis/acidemia = ↓ alkali [biological bases involving an alkali metal such as Na^+ or K^+] or ↑ acids
alkalosis/alkalemia = ↑ alkali or ↓ acids

∴ Henderson/Hasselbach

Since $NaHC0_3$ is the main extracellular alkali, & since its concentration is determined by $C0_2$ and $HC0_3^-$ levels, these two compounds are normally the ones that are tracked in acidosis/alkalosis.

C.c.A.a. METABOLIC VERSUS RESPIRATORY ACID-BASE DISORDERS

metabolic a-b disorders ↑ or ↓ in H^+ –(E4 & E5)–> ↓ or ↑ in $HC0_3^-$ –(E6)–> ↓ or ↑ in pH and metabolic acidosis or alkalosis, resp.
note: arrows not reversed
respiratory a-b disorders ↑ or ↓ in $C0_2$ –(E2 & E3) –>↑ or ↓ in H_2CO_3 –(E6)–> ↓ or ↑ in pH and respiratory acidosis or alkalosis, resp.
note: arrows reversed. Do you see why?

C.c.A.b. PRIMARY VERSUS COMPENSATORY MECHANISMS

primary mechanism (event that initiates alkalosis or acidosis)
compensatory mechanism (mechanism that attempts to maintain a homeostatic pH) i.e., E4 & E5 work both ways
primary and compensatory *cannot* involve the same systems, ∴ lungs can correct for renal induced changes and *vice versa*
volatile fixed hence, Henderson Hasselbach
compensatory mechanisms become more effective with time, thus there are differences between the levels of pH changes that occur in acute acid-base disorders versus those that occur in chronic acid-base disorders

C.c.A.c. GENERAL MANIFESTATIONS OF ACID-BASE DISORDERS 3 categories: 1), 2) & 3) below

1) those associated with the primary disorder

2) those related to the altered pH:

↥ H^+ => / H^+/K^+ exchange =(1)=> / extracellular K^+ =(2)=> <2° hyperkalemia>
=(1)=> / intracellular K^+ =(3)=> lower resting potential: (hyperpolarization) (remember, intracellular H^+ readily binds with the anionic proteins there) / distance => to threshold –> potential / NERVE/MUSCLE EXCITABILITY/ IRRITABILITY

↧ H^+ =(4)=> < calcemia> =(5)=> / NERVE/MUSCLE EXCITABILITY/ IRRITABILITY

Key: 1: F 16.20: 1° acidosis –> 2° hyperkalemia
2: CF IVB-1: similarity in electrolyte concentration of interstitium & plasma
3: P IVB-4: discussion of resting potential & action potential
4: P IVB-9: w ↓ H^+, there is ↑ Ca^{++} binding to protein, instead of H^+
5: P IVB-10: ↓ Ca^{++} –> open Na^+ channels

Path IVC-1. Pathophysiological Consequences of Acidemia and Alkalemia on Nerve/Muscle Excitability TP IVC-8

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3) those related to the homeostatic, compensatory mechanism

C.c.B. METABOLIC ACIDOSIS [=(E4)=> primary deficit in plasma bicarbonate] serious problem

C.c.B.a. ETIOLOGIC FACTORS

1) increased metabolic acid gain by increased production of nonvolatile acids OR decreased renal secretion of acids (S IV.C.b.B.b.) i.e., careful, phosphates and sulfates not mentioned here.

↥ production of non-volatile acids
↧ renal secretion of acids
=> / metabolic acid gain

2) elevated (excessive) $HC0_3^-$ loss

C.c.B.b. INCREASED METABOLIC ACID GAIN

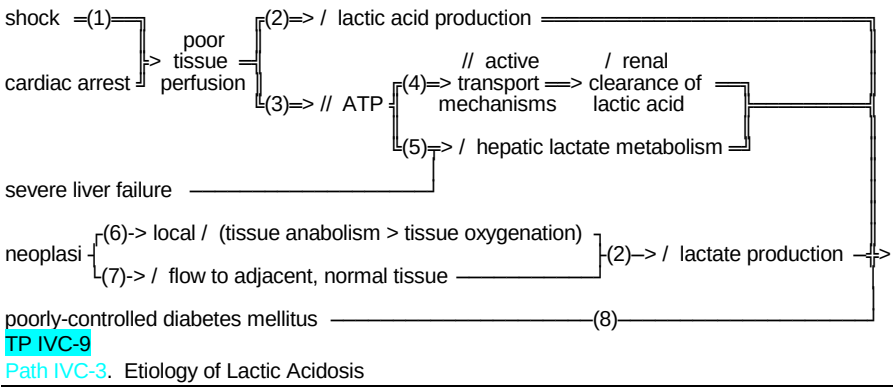
1) ↑ lactic acid, 2) ↑ ketoacids, 3) inability of kidneys to excrete metabolic acids (or conserve bicarbonate), 4) drug/chemical anion ingestion (verify)

1,2,3 => / H^+
$HC0_3^-$
=(1)=> / H_2C0_3
=> / $HC0_3^-$

Key: 1: E_4

Path IVC-2. General Relationship of Decreased pH to Decreased Bicarbonate Concentration

C.c.B.b.(A.) LACTIC ACIDOSIS



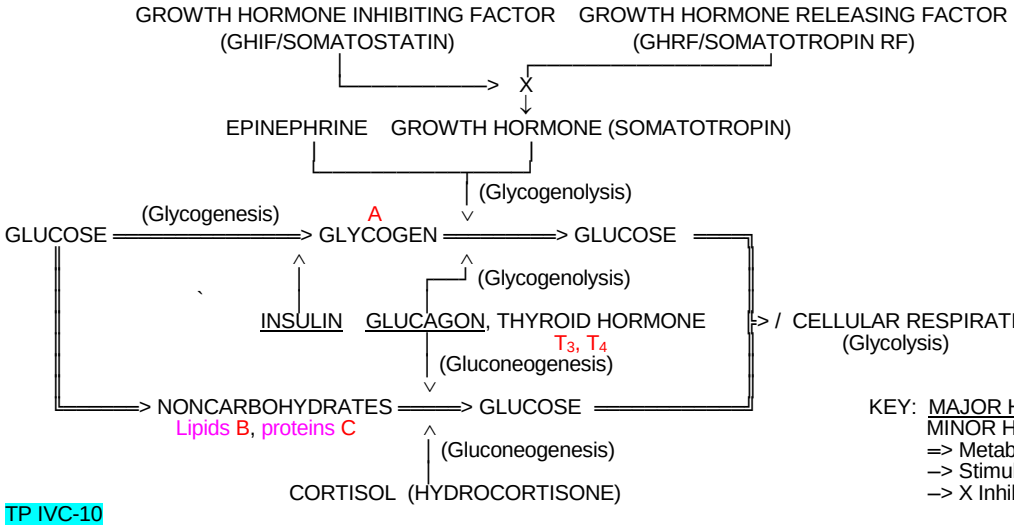
TP IVC-9

Path IVC-3. Etiology of Lactic Acidosis

Key: 1: S VI.E: circulatory shock
2: CF IIIA-2: cell resp & lactic acid production
3: CP IIIA-9: severe hypoxia –> / ATP –> cell swell –> / mito –> // ATP
4: CF IIIA-3 ATP function c)
5: CF IIIA-3 ATP function b)
6: S III.C.c.D.c.: angiogenesis & lack of bv's in center of tumor
7: CT IIIC-2: tumor diverts/ blocks blood flow from/to parenchyma
8: S VII.D: diabetes mellitus

C.c.B.b.(B.) KETOACIDOSIS 2nd example of increased metabolic acid gain

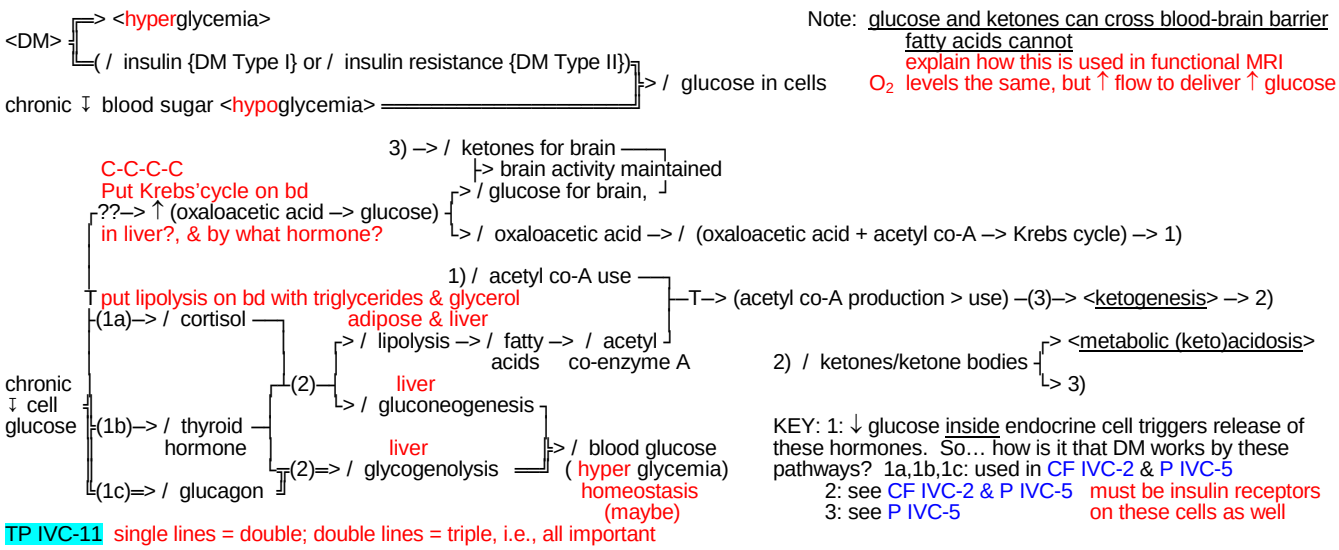
C.c.B.b.(B.a.) KETOGENESIS



KEY: MAJOR HORMONES
MINOR HORMONES
=> Metabolic Pathway
–> Stimulatory effect on metabolic pathway
–> X Inhibitory effect on metabolic pathway

TP IVC-10

Critical Figure IVC-2. Hormones Responsible for the Four, "Big-G" Metabolic Processes



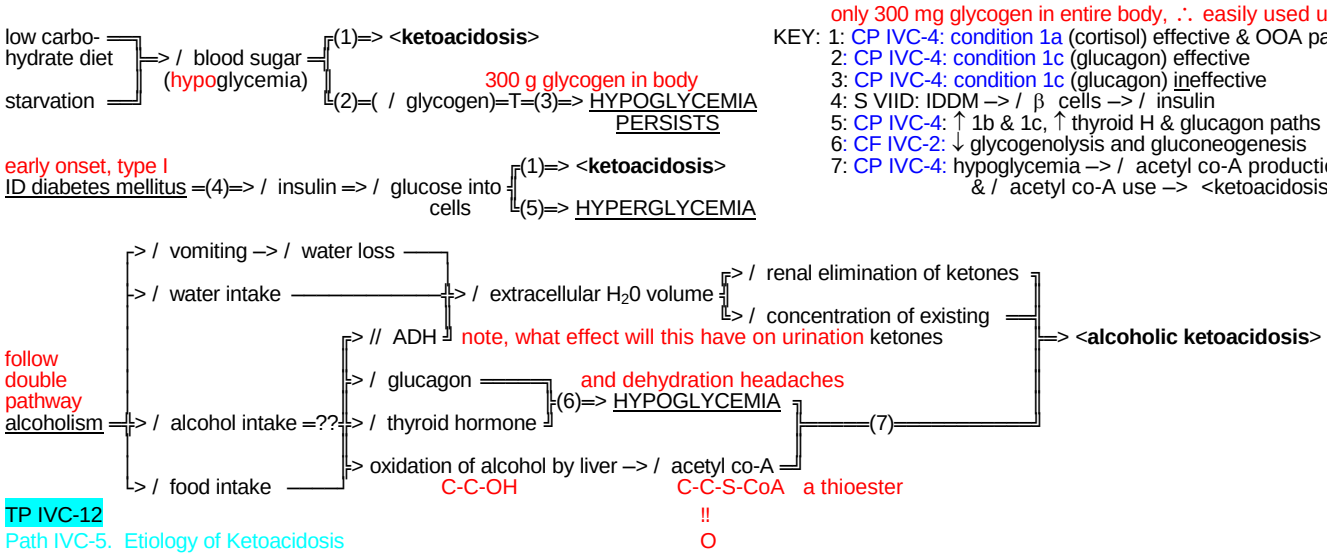
Note: glucose and ketones can cross blood-brain barrier
fatty acids cannot
explain how this is used in functional MRI
O_2 levels the same, but ↑ flow to deliver ↑ glucose

KEY: 1: ↓ glucose inside endocrine cell triggers release of these hormones. So… how is it that DM works by these pathways? 1a,1b,1c: used in CF IVC-2 & P IVC-5
2: see CF IVC-2 & P IVC-5
3: see P IVC-5
must be insulin receptors on these cells as well

TP IVC-11 single lines = double; double lines = triple, i.e., all important

Critical Path IVC-4. Metabolic Pathways Triggered by Low Cellular Glucose Levels (14, pp 552 & 831) (SN 164, p376)

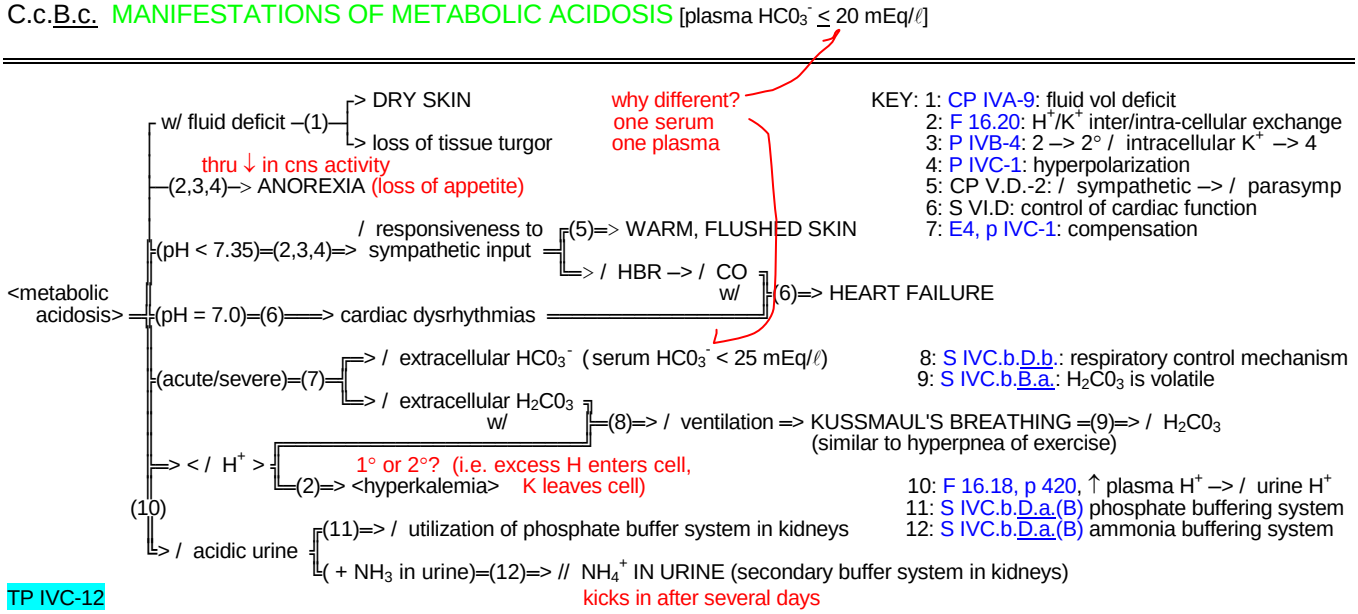
C.c.B.b.(B.b.) ETIOLOGY OF KETOACIDOSIS



TP IVC-12

Path IVC-5. Etiology of Ketoacidosis

C.c.B.c. MANIFESTATIONS OF METABOLIC ACIDOSIS [plasma $HC0_3^-$ ≤ 20 mEq/ℓ]

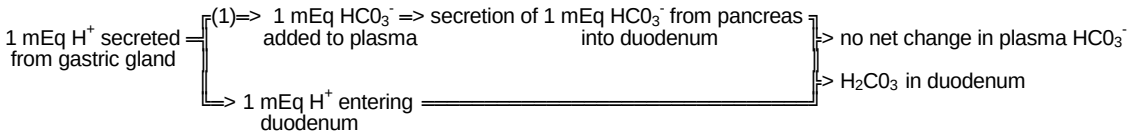


TP IVC-12

Path IVC-6. Manifestations of Metabolic Acidosis

C.c.C. METABOLIC ALKALOSIS [primary ↑ in plasma $HC0_3^-$]

C.c.C.a. LOSS OF HYDROGEN IONS



KEY: 1: F IVC-3: next page

Path IVC-7. Normal Course of Events Relative to H^+, Cl , and $HC0_3^-$ in the Stomach and Duodenum

Ie not normally a problem, but path IVC-8:

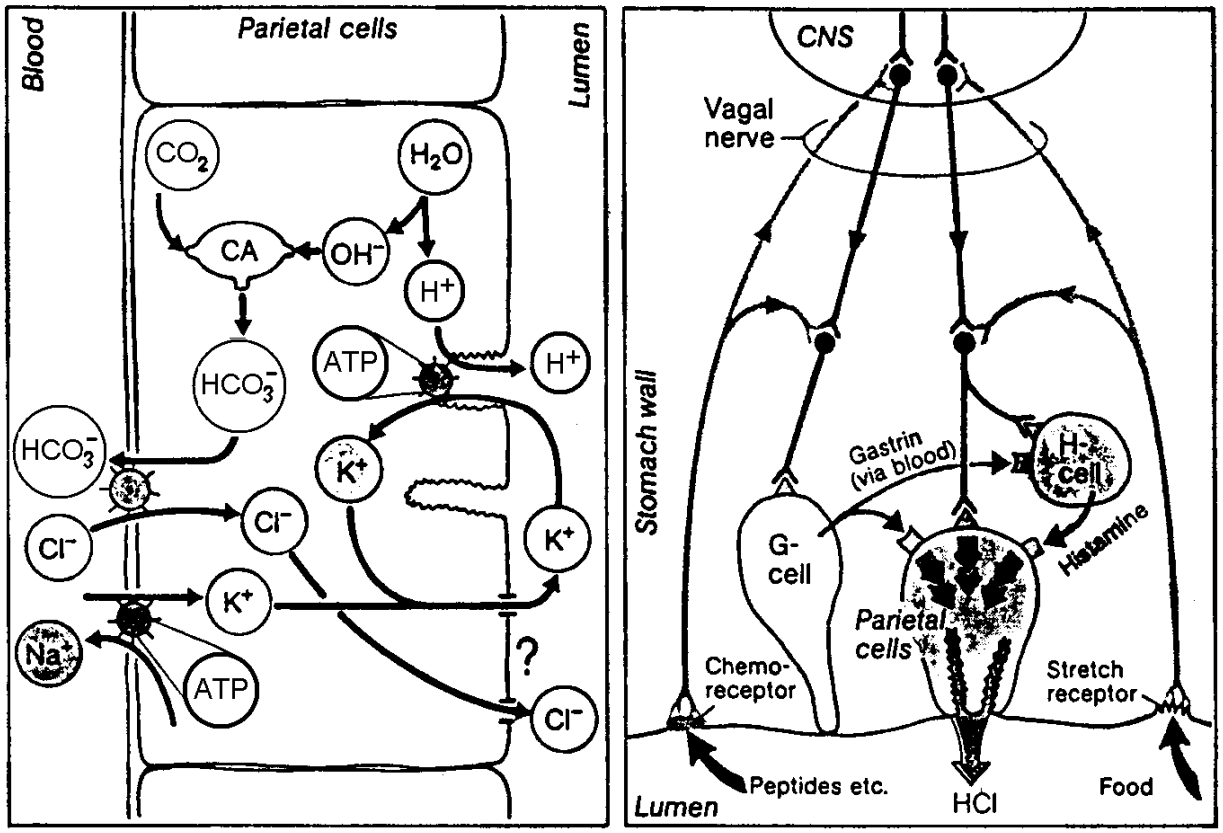
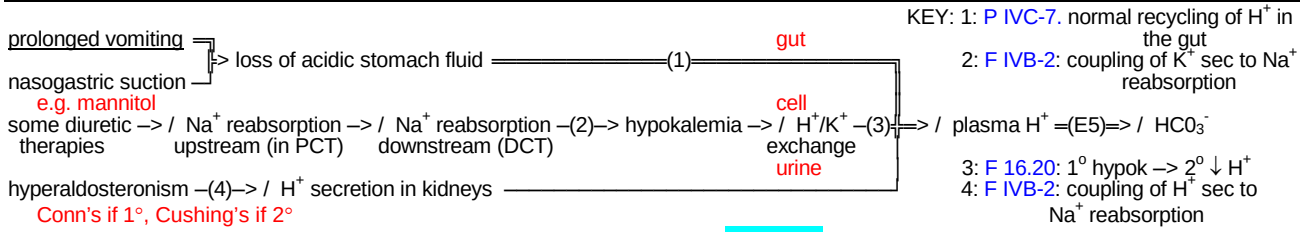


Figure IVC-3. Mechanism of HCl Secretion from Parietal Cell of Gastric Gland B. = conditions that lead to A. TP IVC-13

Skip single

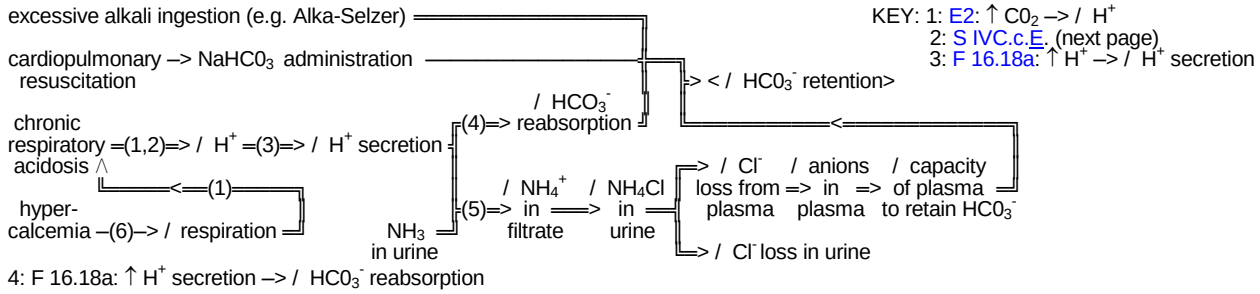


Path IVC-8. Etiology of Hydrogen Ion Loss (diuretic therapies from 36, p 497) TP IVC-14

C.c.C.b. ELEVATED $HC0_3^-$ RETENTION

two sources of $HC0_3^-$: $C0_2$ from cellular respiration [–(E1)–> $HC0_3^-$] or $HC0_3^-$ recycling by kidneys (F 16.18, p 420)

these two mechanisms normally work inversely to maintain a homeostatic $HC0_3^-$ level



TP IVC-15

Path IVC-9. Etiology of Increased Bicarbonate Retention in Metabolic Alkalosis

C.c.D. RESPIRATORY ACIDOSIS [primary ↑ in plasma carbonic acid] serious i.e. BOTH metabolic & respiratory acidosis are serious.

go back to F IVC-1 to see if you can figure out why
(less time between appearance of symptoms & death)

1) primary ↑ in $C0_2$ –(E2)–> / H_2C0_3 –> / H^+

note how this relates to hypercalcemia in Key 5 on bottom of prior page

C.c.D.a. ACUTE RESPIRATORY ACIDOSIS

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hypoventilation
(see below)
defective respiratory movements
↑ $C0_2$ inhalation
=> / P_{C02} (hypercapnea) => delayed signs ($C0_2$ diffuses across respiratory membrane 20X faster than 0_2) ∴ it is blown off, ← but O_2 is another story
=> / P_{02} (hypoxemia) => SIGNS & SYMPTOMS (S VII.A) (hypoxia) (below)

Path IVC-10. Etiology of Conditions Leading to Acute Respiratory Acidosis

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C.c.D.b. CHRONIC RESPIRATORY ACIDOSIS

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blue bloaters
pink puffers –> ↑ 0_2
COPD => / P_{CO_2} => <chronic respiratory acidosis> => / H^+

=> in brain => vasodilation => / CSF =(1)=> HEADACHE, ETC. Occurs in 30% - not known why
(2)=> / renal H^+ secretion
(2)=> / renal $HC0_3^-$ reabsorption
=> near normal pH => / H^+ no longer drives medullary => 1) respiratory center

w

<intercurrent respiratory infection> =(3)=> / hypoxemia => treat w / 0_2)

1) => shift to dependence upon 0_2 receptors in carotid bodies
occurs at PA_{O2} of 60 mm Hg

worsening of
(4)=> ventilation/perfusion ratio
2) => / RATE OF RESPIRATION
=> / DEPTH OF RESPIRATION
=> // P_{02}
=> rapid // arterial P_{CO_2} =(5)=> // H_2CO_3 => <acute respiratory acidosis>
=> abolished ventilatory drive => // ventilation => 2)
=> LIFE-TREATENING SITUATION

OK to administer 0_2, but watch patient closely

skip

KEY: 1: CP VA-4: from stress to pain
2: F16.18a: ↑ H^+ secretion → / $HC0_3^-$ reabsorption
3: S VI.G: Respiratory Function; retained secretions & bronchopasm
4: S.VI.G: Respiratory Function
5: S. IV: Respiratory Function

portions used 60, p 128-9 TP IVC-16 compare w P IVC-6
Path IVC-11. Manifestations of Chronic and Acute Respiratory Acidosis

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C.c.E. RESPIRATORY ALKALOSIS [primary ↓ in plasma carbonic acid] (F '03 Do this in detail for Nursing)

Skip 1

1) primary ↓ in $C0_2$ –(E3)–> / H_2C0_3 –> / H^+

not through hyperventilation, which is immediately below

NaHC0₃ buffer in plasma offsets this somewhat

2) hyperventilation => / removal of $C0_2$ => / $HC0_3^-$ / // $C0_2$ =(E6)=> <respiratory alkalosis>

kidneys over lungs (Henderson-Hasselbach) K/L

C.d. SUMMARY

ROME Respiratory-opposite, Metabolic-equal

ACIDOSIS (/ pH)

Metabolic (changes in $HC0_3^-$)
mnbc – metabolic bicarbonate nephron

↕ H^+ => / ($H^+ + HC0_3^-$ => H_2C0_3) => / H^+ + / $\underline{HC0_3^-}$ E4

these begin with H

↧ H^+ => / (H_2C0_3 => $H^+ + HC0_3^-$) => / H^+ + / $\underline{HC0_3^-}$ E5

ALKALOSIS (/ pH)

These are arranged as in pH: K/L

ACIDOSIS (/ pH)

Respiratory (changes in H_2C0_3)
rca - resp carbonic acid

↕ $C0_2$ => / $\underline{H_2C0_3}$ => / H^+ E2

these end with H

↧ $C0_2$ => / $\underline{H_2C0_3}$ => / H^+ E3

ALKALOSIS (/ pH)