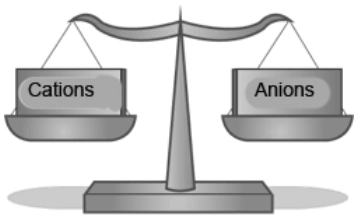
Acid-Base Balance and the Anion Gap

1. The body strives for electrical neutrality.



   a. Cations = Anions

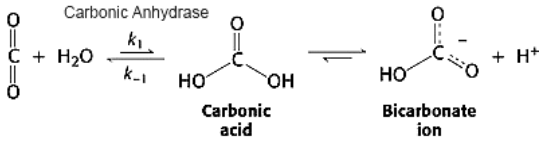
   b. One of the cations is very special, H^+, and its concentration is monitored and regulated very closely.

   c. Volatile acid (CO_2) and non-volatile acids, lactate, H_2PO4^-, H_2CO_3

2. Blood pH is described by the Henderson-Hasselbalch equation

$$pH = 6.1 + \log \frac{HCO_3^-}{Pa_{CO_2} \times 0.0301}$$

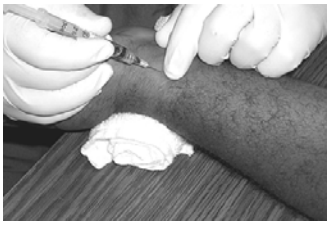
3. Note the importance of



   a. Arterial CO_2, indicated as Pa_{CO_2},
   b. Bicarbonate, HCO_3^-
   c. Carbonic anhydrase

4. We measure the pH of **arterial** blood.

   a. Arterial blood has been through the lungs and should be at optimal pH.



   b. This is not the case for venous blood.

   c. 7.35-7.45

   d. Central nervous system control of respirations and therefore Pa_{CO_2}

   e. The control of bicarbonate, HCO_3^-, by the kidneys
      i. Retention or
      ii. Excretion

5. So how does it all work under normal circumstances to keep our pH about 7.4?

   a. Normally, CO_2 production and loss are matched

   b. Pa_{CO_2} is maintained at about 40 mmHg

   c. Pa_{CO_2} is regulated by **respiration rate**, either slowing down or speeding up respirations, to either **blow off or retain CO_2**.
      a. Control comes from the CNS by regulating respiration rate.

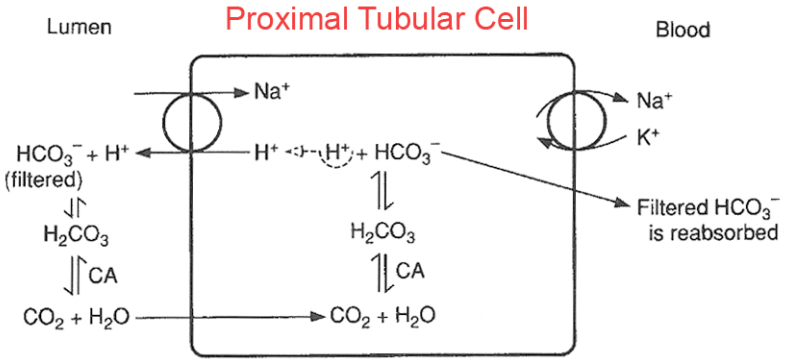
      b. Production rate of CO_2 is not subject to regulation,

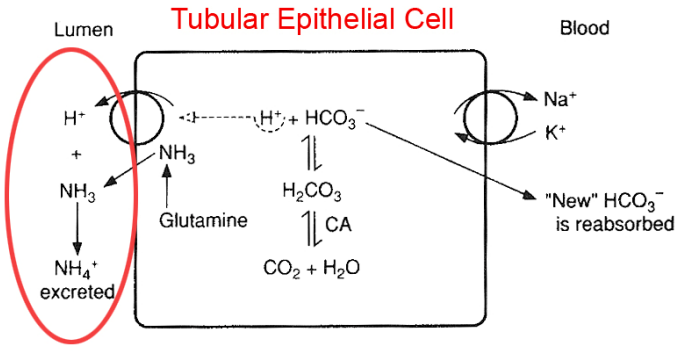
   d. The kidney regulates plasma [HCO_3^-] (by extension [H^+] and pH) by three mechanisms

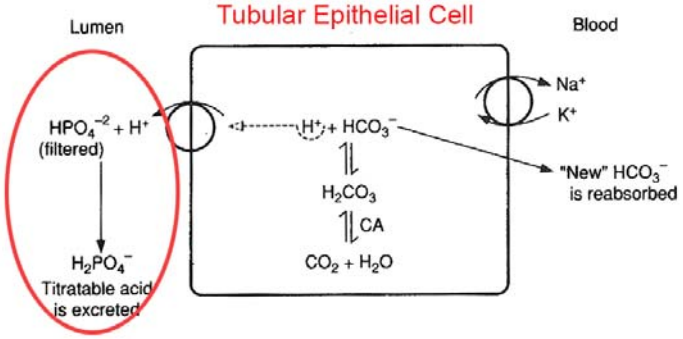
      a. **Reabsorption** of filtered HCO_3^-, this is a recovery operation

      b. Formation of titratable acid, H_2PO4^- distal tubule

      c. Excretion of NH_4^+ distal tubule







Get this. The kidney glomerulus passively filters on the order of 4000 mmol of HCO_3^- each day. This has to be reabsorbed. To lose it would be a disaster. In order to reabsorb this filtered load of HCO_3^-, the tubular cells must therefore secret 4000 mmol of hydrogen ions. This allows the conversion of carbonic acid to CO_2 and water, which will passively come back into the proximal tubular cell. The secretion of titratable acid by the kidney, used to actually modify the blood pH, goes on in the distal tubule.

6. Basically, the regulation of arterial pH includes

    a. Regulation of Pa_{CO2} by the respiratory system.

    b. Regulation of HCO_3^- by the kidneys

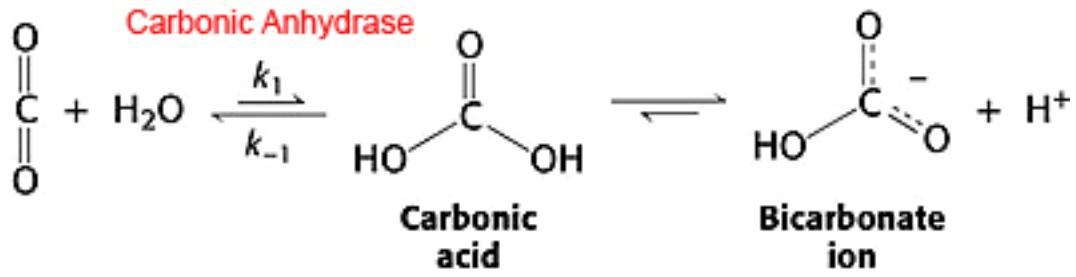
    c. Chemical buffering in the form of NH_4^+ and $H_2PO_4^-$ secretion by the distal convoluted tubule cells.

7. Simple acid/base disorders, adjustments and compensation for running a road race.

    a. Primary respiratory and/or metabolic disturbances invoke predictable compensatory changes to restore the Pa_{CO2} and pH to normal.

        If uncomplicated by other factors, a high Pa_{CO2} means a lowered pH. Respiration picks up because of the elevated Pa_{CO2}. The increased respiration rate results in the blowing off CO_2, which pulls the pH back up into the healthy range.

        Buffering capacity comes thanks to the miracle of carbonic anhydrase.



Metabolic acidosis means extra H^+ ions are coming from a metabolic derangement, such as lactic acidosis in a diabetic, which will result in excessive respiration rate, lowering the Pa_{CO2}, while at the same time raising the Pa_{O2}.

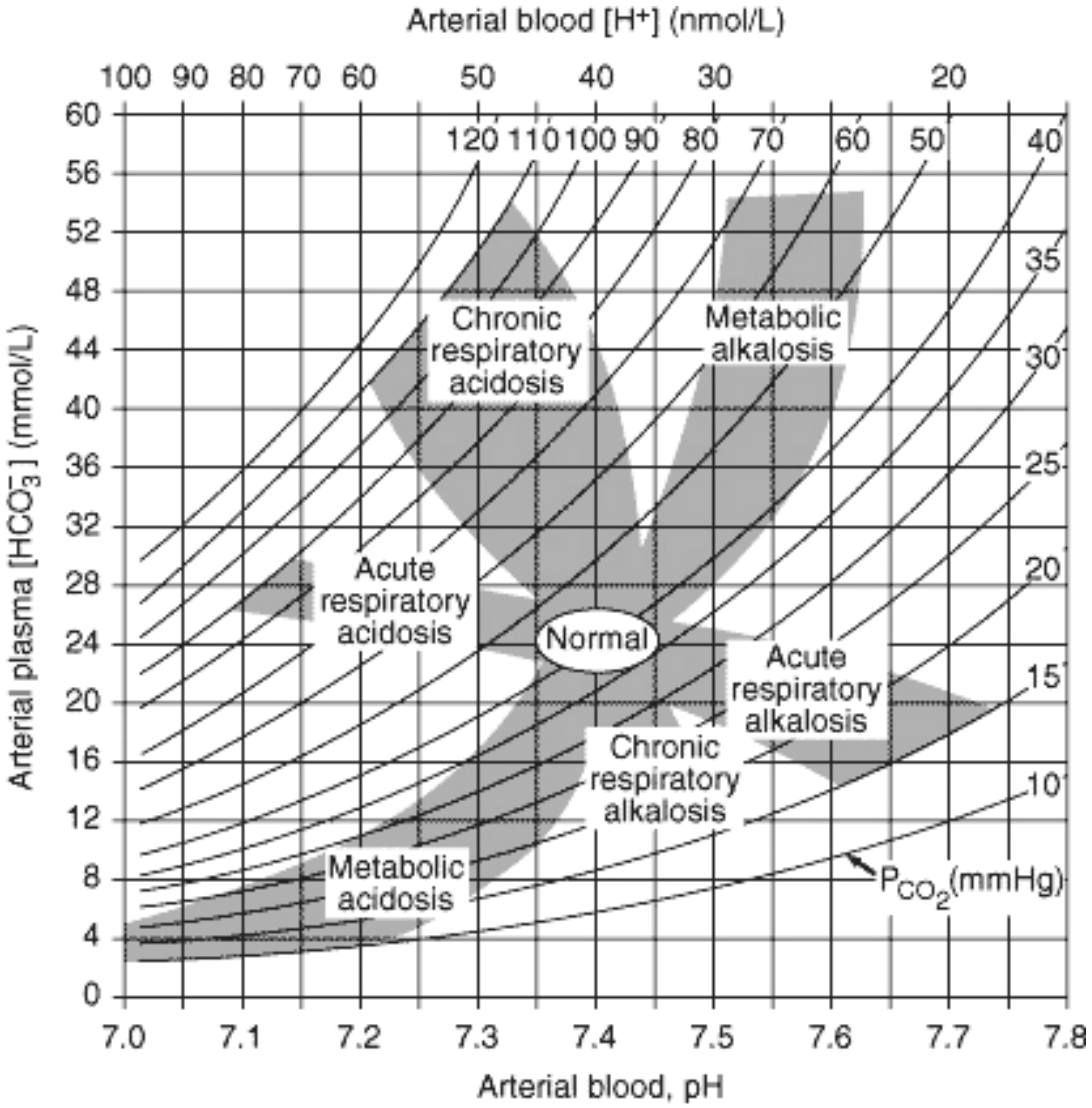
Predict the degree of respiratory compensation with a **metabolic acidosis**.

$Pa_{CO2} = (1.5 \text{ X } [HCO_3^-]) + 8$

Pa_{CO2} decreases 12 mmol/L for each mmol/L of HCO_3^-

Thus a patient with a metabolic acidosis and 12 mmol/L of HCO_3^- would be expected to have a Pa_{CO2} between 24 and 28. If it's higher or lower, there is something else going on, in other words a **mixed acid/base disorder.**

For simple acid/base disturbances, the diagram below can be quite helpful.



8. Mixed acid-base disorders. Here **several problems of acid-base management** are colliding at the same time. It's definitely not just a matter of the body trying to compensate for one such disorder.

   a. An example would be a diabetic with ketoacidosis, who also happens to have emphysema, or develops a bad pneumonia (which is not all that unusual), and as a result develops a respiratory acidosis.

   b. You can even have a mixed condition consisting of an acidosis and alkalosis. Here the pH might even be in the reference range. How would know there is a actually a serious problem underlying things?

      i. Look at the **anion gap.**
      ii. **Bicarb gap**

9. Diagnosis of acid-base disorders.

   a. Get arterial blood gases and electrolytes at the same time.

   b. Compare the HCO_3^- value from the blood gases and lytes to verify accuracy.

   c. Calculate the anion gap (AG)

   d. Review the four common causes of high AG acidosis

      i. ketoacidosis
      ii. lactic acidosis
      iii. renal failure
      iv. toxin

   e. Review the two major causes of hyperchloremic, or non-gap, acidosis

      i. HCO_3^- loss from the GI tact
      ii. renal tubular acidosis

   f. Estimate compensatory response.

   g. Compare ΔAG and ΔHCO_3^-

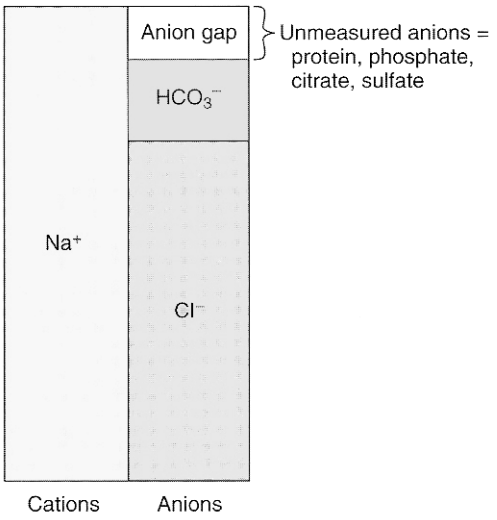
   h. Compare change in $[Cl^-]$ with change in $[Na^+]$

   i. **A good history and physical**

      - Renal failure, chronic vomiting, sepsis, heart failure, pneumonia, COPD, drug use, especially sedatives and loop type diuretics (thiazidess) and carbonic anhydrase inhibitors (acetazolamide)
      - Better watch serum $[K^+]$, remember shifts with high $[H^+]$.

10. The **anion gap**, is really not a gap at all, it just represents the anions we don't usually measure.

a. AG = Na^+ - (Cl^- + HCO_3^-), typically about 10 to 12 mmol



b. The AG represents anions such as proteins, phosphates, sulfates and organic anions.

c. **Increase in the AG**

i. Is most often due to increased serum lactate or acetoacetate.

ii. Rarely, an increased AG may be due to a decrease in cations such as Ca^{+2}, magnesium and/or K^+

d. **Decrease in the AG**

i. Increase in unmeasured cations
ii. Addition of something new to the blood such as Li^+
iii. Reduction in a major plasma protein such as albumin (renal loss).
iv. Hyperlipidemias and other less common causes.

11. Basic rules to keep in mind for simple, one cause, problems.

a. Is a pH disturbance metabolic or respiratory in origin?

- Respiratory acidosis, $PaCO_2$ is > 44
- Metabolic acidosis, HCO_3^- is < 22
- Respiratory alkalosis, $PaCO_2$ is < 36
- Metabolic alkalosis, HCO_3^- is > 26

b. If the primary change is

- HCO_3^-, then the underlying cause is most likely metabolic
- CO_2, the underlying cause is most likely respiratory

c. Metabolic acidosis with calculated ion gap

- increased endogenous acid production
  - lactate
  - ketoacidosis

- accumulation of endogenous acids with renal failure
- loss of HCO_3^-, diahrea
- Toxic stuff like methanol and antifreeze

d. metabolic acidosis with no ion gap

- loss of HCO_3^-, diahrea
- renal loss of HCO_3^-, renal tubular acidosis
- Carbonic anhydrase inhibition

e. metabolic alkalosis

- vomiting
- milk-alkali syndrome
- K^+ wasting as with Conn's syndrome
- Loss of H^+
- Compensate is respiratory, retain CO_2

f. Respiratory acidosis

- CNS
- Airway obstruction
- Neuromuscular and faulty respiration
- CO_2 is high and the reason is poor ventilation
- Compensation must be to increase HCO_3^-

g. Respiratory alkalosis

- CO_2 is low
- Pregnancy
- Sepsis
- Anxiety and physical pain leading to increased resp rate
- Salicylates
- Liver disease

12. If only life could be this simple all the time. But, a person may have more than one disease at a time that can cause an acid-base disturbance. So, how do you know?

    a. With the coexistence of two metabolic acid-base disorders may be made apparent by calculating the difference between the change in the anion gap (*delta AG*), and the change in the serum CO_2 (*delta* CO_2).

    b. This value goes by several names, either the delta or bicarbonate gap.

Delta (bicarbonate) gap = *delta AG* - *delta* HCO_3^-

Where

Delta AG = patient's AG - 12 mEq/L

Delta HCO_3^- = 27 mEq/L - patient's HCO_3^-

If there is just one acid-base abnormality, there should be a 1:1 correlation between the rise in the anion gap and a corresponding drop in the bicarbonate.

Example: if the AG goes up by 10, then the HCO_3^- should drop by 10.

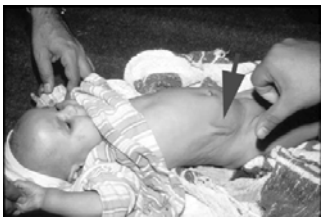
Delta AG - *delta* HCO_3^- = 10 – 10 = 0

Just one acid-base problem here.

Variation of the bicarbonate gap from zero, either + or – means there is a mixed acid-base problem. However, it certainly doesn't tell you the type.

13. Let's see how this operates with two different mixed acid-base conditions.

Case : This 22 year-old man presents with several days of vomiting, nausea and abdominal pain. His blood pressure is low and he has tenting of the skin. His electrolytes are Na^+ = 144, Cl^- = 95, K^+ = 4.2, HCO_3^- =14.



AG = 35
Delta AG = 23 (35 – 12)

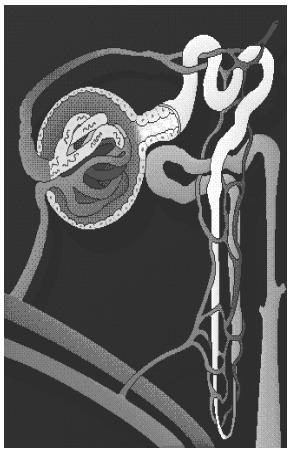
Delta HCO_3^- = 13 (27 – 14)

Delta (HCO_3^-) gap = +10

The high HCO_3^- gap indicates there are **two conditions** at work.

- **Metabolic acidosis** from dehydration and poor tissue perfusion (lactatic acid accumulation).

- **Metabolic alkalosis** from vomiting and loss of stomach acid.



14. Renal acidosis is in a league of its own.

    a. The renal tubules reabsorb HCO_3^- and secretes acid

    b. Failure of either leads to renal tubular acidosis

    c. All forms of renal tubular acidosis are characterized by

    - minimally elevated to normal ion gap
    - hyperchlormia
    - net retention of HCl^- , generally
    - Three basic patterns
        - Distal type (type 1 RTA)
        - Proximal type (type 2 RTA)
        - Type 3 RTA is absence of carbonic anhydrase.
        - Hypoalderstonism (type 4 RTA)

	Type 1 RTA	**Type 2 RTA**	**Type 4 RTA**
Primary defect	Impaired distal acidification	Reduced proximal bicarbonate reabsorption	Decreased aldosterone secretion or effect
Plasma bicarbonate	Variable, may be below 10 meq/L	Usually 12 to 20 meq/L	Greater than 17 meq/L
Urine pH	Greater than 5.3	Variable, greater than 5.3 if above bicarbonate reabsorptive threshold	Usually less than 5.3
Plasma potassium	Usually reduced but hyperkalemic forms exist; hypokalemia largely corrects with alkali therapy	Reduced, made worse by bicarbonaturia induced by alkali therapy	Increased

A case of renal related acidosis: Amy is a 24 year-old mother of one who develops acute renal failure after a perforated ulcer gave her peritonitis and shock. Her labs are Na^+ 140 mEq/L, K^+ 4 mEq/L, Cl^- 115 mEq/L, CO_2 5 mEq/L, pH = 7.12, $PaCO_2$ 13 mmHg, and HCO_3^- 4 mEq/L.

$AG = 20 = (140 – (Cl^- + HCO_3^-))$

Delta AG = 9 = (21-12)

Delta HCO_3^- = 23 = (27-4)

Delta (HCO_3^-) gap = -14 = *delta AG – delta* HCO_3^-

Her anion gap is up, but not off the chart. The bicarbonate gap is off.

So, her *Delta* (HCO_3^-) is significantly off at -14 mEq/L; that is 14 mEq/L **lower** than would be expected given her excess anion gap of 9 (above normal). Were this a simple 'one cause' acidosis, the acid causing her drop in pH should have lowered her CO_2 to only about 19 mEq/L. The fact that her CO_2 is actually 5 mEq/L means there must an additional reason for her acidosis.

- In this case a hyperchloremic metabolic acidosis, which is commonly seen with renal failure. Below are her two renal related problems.
  - Uremia from kidney failure causing the elevated AG.
  - The tubular related problem of HCO_3^- recovery and acid secretion, which leads to a non-ion gap acidosis with hyperchloremia.

Summing it up

Respiratory, metabolic and mixed problems
Compensation
Anion and bicarb gap
Renal contribution to normal pH and problems of renal acidosis
Hyperchoremia