Acid-Base Balance:
The objectives of this lecture are:
1. List in sequel the body lines of defense against disturbance of ph.
2. Explain how the interaction between plasma K⁺ and H⁺ concentrations affects the tubular secretion of these ions.
3. Describe the role of the kidneys in the regulation of acid-base balance.
4. Explain how activation of the renin-angiotensin-aldosterone system results in the stimulation of aldosterone secretion.

Precise H⁺ regulation is essential because the activities of almost all enzyme systems in the body are influenced by H⁺ concentration. Therefore, changes in hydrogen concentration alter virtually all cell and body functions.

Compared with other ions, the H⁺ concentration of the body fluids normally is kept at a low level. For example, the concentration of sodium in extracellular fluid (142 mEq/L) is about 3.5 million times as great as the normal concentration of H⁺, which averages only 0.00004 mEq/L. Equally important, the normal variation in H⁺ concentration in extracellular fluid is
only about one millionth as great as the normal variation in sodium ion (Na\(^+\)) concentration. Thus, the precision with which H\(^+\) is regulated emphasizes its importance to the various cell functions.

There are three primary systems that regulate the hydrogen ion concentration in the body fluid to prevent acidosis or alkalosis:

1. The chemical acid base buffer system of the body fluids, which immediately combine with acid or base to prevent excessive change in hydrogen ion concentration.
2. The respiratory center, which regulates the removal of CO2 and therefore, H2CO3 from the extracellular fluid.
3. The kidneys.

### Renal Acid-Base Regulation

When there is a change in H\(^+\) ions conc., the buffer system of the body fluids reacts within a fraction of a second to minimize these changes; the second line of defense is the respiratory system, also acts within few minutes to eliminate CO2 and therefore H2CO3 from the body by ventilation changes. These first two lines of defense keep the H\(^+\) ion conc. from changing too much until the more slowly responding third line of defense, the kidneys that eliminate the excess acid or base from the body. Although the kidneys are relatively slow to respond, compared with the other defenses, they are over a period of hours to several days by far the most powerful of the acid base regulatory systems.

The kidneys help to regulate the blood pH by excreting H in the urine and by reabsorbing bicarbonate. The H enters the filtrate in two ways: by filtration through the glomeruli and
by secretion into the tubules. Most of the H secretion occurs across the wall of the proximal tubule in exchange for the reabsorption of Na. This exchange is performed by a transport carrier described as “counter transport” because it moves the Na and H in opposite directions actively.

Since the kidneys normally reabsorb almost all of the filtered bicarbonate and excrete H, normal urine contains little bicarbonate and is slightly acidic with a pH range between 5 and 7.

Reabsorption of Bicarbonate in the Proximal Tubule
The apical membranes of the tubule cells (facing the lumen) are impermeable to bicarbonate. The reabsorption of bicarbonate must therefore occur indirectly. When the body need alkaline, the urine is acidic, HCO₃⁻ in the urine combines with H to form carbonic acid. Carbonic acid in the filtrate is then converted to CO₂ and H₂O in a reaction catalyzed by carbonic anhydrase. This enzyme is located in the apical cell membrane of the proximal tubule in contact with the filtrate.

Notice that the reaction that occurs in the filtrate is the same one that occurs within red blood cells in pulmonary capillaries.

The tubule cell cytoplasm also contains carbonic anhydrase. As CO₂ concentrations increase in the filtrate, the CO₂ diffuses into the tubule cells. Within the tubule cell cytoplasm carbonic anhydrase catalyzes the reaction in which CO₂ and H₂O form carbonic acid. The carbonic acid then dissociates to HCO₃⁻ and H within the tubule cells.

The bicarbonate within the tubule cell can then diffuse through the basolateral membrane and enter the blood.

When conditions are normal, the same amount of HCO₃⁻ passes into the blood as was removed from the filtrate. The H, which was produced at the same time as HCO₃⁻ in the cytoplasm of the tubule cell, can either pass back into the filtrate or pass into the blood. Under acidotic conditions, almost all of the H goes back into the filtrate and is used to help reabsorb all of the filtered bicarbonate.

During alkalosis, less H is secreted into the filtrate. Since the reabsorption of filtered bicarbonate requires that HCO₃⁻ combine with H to form carbonic acid, less bicarbonate is reabsorbed.

This results in urinary excretion of bicarbonate, which helps to partially compensate for the alkalosis.

By these mechanisms, disturbances in acid-base balance caused by respiratory problems can be partially compensated for by changes in plasma bicarbonate concentrations.
Metabolic acidosis or alkalosis in which changes in bicarbonate concentrations occur as the primary disturbance similarly can be partially compensated for by changes in ventilation.

**Buffering of Hydrogen Ions in the Body Fluids**

A buffer is any substance that can reversibly bind H+. The general form of the buffering reaction is in this example, a free H+ combines with the buffer to form a weak acid (H buffer) that can either remain as an unassociated molecule or dissociate back to buffer and H+. When the H+ concentration increases, the reaction is forced to the right, and more H+ binds to the buffer, as long as buffer is available. Conversely, when the H+ concentration decreases, the reaction shifts toward the left, and H+ is released from the buffer. In this way, changes in H+ concentration are minimized.

\[
\text{Buffer} + \text{H}^+ \rightleftharpoons \text{H Buffer}
\]

**Bicarbonate Buffer System**

The bicarbonate buffer system consists of a water solution that contains two ingredients: (1) a weak acid, H2CO3, and (2) a bicarbonate salt, such as NaHCO3. H2CO3 is formed in the body by the reaction of CO2 with H2O.

\[
\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{carbonic anhydrase}} \text{H}_2\text{CO}_3
\]

This reaction is slow, and exceedingly small amounts of H2CO3 are formed unless the enzyme carbonic anhydrase is present. This enzyme is especially abundant in the walls of the lung alveoli, where CO2 is released; carbonic anhydrase is also present in the epithelial cells of the renal tubules, where CO2 reacts with H2O to form H2CO3. H2CO3 ionizes weakly to form small amounts of H+ and HCO3⁻.

\[
\text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-
\]
The second component of the system, bicarbonate salt, occurs predominantly as sodium bicarbonate (NaHCO3) in the extracellular fluid. NaHCO3 ionizes almost completely to form HCO3– and Na+, as follows:

\[
\text{NaHCO}_3 \rightleftharpoons \text{Na}^+ + \text{HCO}_3^- \]

**Phosphate Buffer System**

Although the phosphate buffer system is not important as an extracellular fluid buffer, it plays a major role in buffering renal tubular fluid and intracellular fluids. The main elements of the phosphate buffer system are H2PO4– and HPO42−. When a strong acid such as HCl is added to a mixture of these two substances, the hydrogen is accepted by the base HPO42− and converted to H2PO4–.

\[
\text{HCl} + \text{Na}_2\text{HPO}_4 \rightarrow \text{NaH}_2\text{PO}_4 + \text{NaCl} 
\]

The result of this reaction is that the strong acid, HCl, is replaced by an additional amount of a weak acid, NaH2PO4, and the decrease in pH is minimized.

**Proteins: Important Intracellular Buffers**

Proteins are among the most plentiful buffers in the body because of their high concentrations, especially within the cells. The pH of the cells, although slightly lower than in the extracellular fluid, nevertheless changes approximately in proportion to extracellular fluid pH changes. There is a slight amount of diffusion of H+ and HCO3– through the cell membrane, although these ions require several hours to come to equilibrium with the extracellular fluid, except for rapid equilibrium that occurs in the red blood cells. CO2, however, can rapidly diffuse through all the cell membranes. This diffusion of the elements of the bicarbonate buffer system causes the pH in intracellular fluid to change when there are changes in extracellular pH. For this reason, the buffer systems within the cells help prevent changes in the pH of extracellular fluid but may take several hours to become maximally effective.

In the red blood cell, hemoglobin (Hb) is an important buffer, as follows:

\[
\text{H}^+ + \text{Hb} \rightleftharpoons \text{HHb} 
\]
Approximately 60 to 70 per cent of the total chemical buffering of the body fluids is inside the cells, and most of this results from the intracellular proteins. However, except for the red blood cells, the slowness with which H\(^+\) and HCO\(_3^-\) move through the cell membranes often delays for several hours the maximum ability of the intracellular proteins to buffer extracellular acid-base abnormalities.

**Juxtaglomerular Apparatus**

**Two parts:**

1. The region in each nephron where the afferent arteriole comes into contact with the last portion of the thick ascending limb of the loop, there are **Granular cells within the afferent arteriole** secrete the enzyme renin into the blood; this enzyme catalyzes the conversion of angiotensinogen (a protein) into angiotensin I (a ten-amino-acid polypeptide).

Secretion of renin into the blood thus results in the formation of angiotensin I, which is then converted to **angiotensin II** (an eight-amino-acid polypeptide) by angiotensin-converting enzyme (ACE). This conversion occurs primarily as blood passes through the capillaries of the lungs, where most of the converting enzyme is present. Angiotensin II, in addition to its other effects, stimulates the adrenal cortex to secrete aldosterone. Thus, secretion of renin from the granular cells of the juxtaglomerular apparatus initiates the reninangiotensin-aldosterone system. Conditions that result in increased renin secretion
cause increased aldosterone secretion and, by this means, promote the reabsorption of Na+ from cortical collecting duct into the blood.

2. The region of the ascending limb in contact with the granular cells of the afferent arteriole is called the macula densa. There is evidence that this region helps to inhibit renin secretion when the blood Na+ concentration is raised. The cells of the macula densa respond to the Na+ in the filtrate delivered to the distal tubule. When the plasma Na+ concentration is raised, or when the GFR is increased, the rate of Na+ delivered to the distal tubule is also increased. Through an effect on the macula densa, this increase in filtered Na+ inhibits the granular cells from secreting renin. Aldosterone secretion thus decreases, and since less Na+ is reabsorbed in the cortical collecting duct, more Na+ is excreted in the urine.

Regulation of Renin Secretion
Renin which converted to angiotensin II is like aldosterone in dealing with plasma Na⁺.

Functions of Angiotensin II
An inadequate dietary intake of salt (NaCl) or hyponatremia of any cause is always accompanied by a fall in blood volume. The fall in blood volume and the fall in renal blood flow that result cause increased renin secretion. Increased renin secretion is believed to be due in part to the direct effect of blood pressure on the granular cells, which may function as baroreceptors in the afferent arterioles. Renin secretion is also stimulated by sympathetic nerve activity, which is increased by the baroreceptor reflex when the blood volume and pressure fall. An increased secretion of renin acts, via the increased production of angiotensin II, to stimulate aldosterone secretion. Consequently, less sodium is excreted in the urine and more is retained in the blood.