GENERAL SYSTEMIC STATES
These are states which common to so many diseases and they are considered the base which contribute to the effects of many diseases.

1. Toxemia
It means circulation of toxins in the blood stream, bacteria or parasites or produced by body cells. This state does not include the diseases caused by plants or insects or ingested organic or inorganic poisons.

Causes:
(A) Antigenic toxins:
Produced by bacteria and to less extent by helminthes parasites. Antigenic toxins are divided into:-
- Exotoxins: Which are diffused in the surrounding media this toxin may be ingested or may be produced by heavy growth in the bowel e.g. enterotoxaemia, or from growth in tissues as in black leg, black disease.
- Endotoxins: They are lipopolysaccharides and are found within the cell as a part of cell wall. They find their way into the medium and into the systemic circulation only when the bacterial walls break down and liberate them.

(B) Metabolic Toxins:
These toxins produced by body metabolism, or by abnormal metabolism. When the normal mechanisms of detoxification are disrupted, mainly in hepatic dysfunction, the toxins accumulate beyond the critical point and resulted in a state of toxemia, e.g. ketone bodies and histamine.

Pathogenesis:
1- Effect on carbohydrate metabolism:
* Fall in blood sugar level.
* Sever drop of liver glycogen.
* Rise in the level of blood pyruvate, and lactate as a result of poor tissue perfusion and the anaerobic nature of tissue metabolism.

2- Effect on protein metabolism:
* Increase in tissue break down.
* Rise in blood-non-protein nitrogen levels.
* Increase in total serum protein as a result of the increase in antibody production.
* Alteration in relative proportion of amino acid in blood.

3- Mineral Metabolism:
* Hypo ferremia.
* Hypo zincemia.
* Hypo cupraemia due to increased blood ceruloplasmin.

4- Damage to liver, and kidney parenchyma.
5- Weakness of myocardium with decreased response to cardiac stimuli.
6- Damage to renal tubules and glomeruli - Albuminuria.
7- General depression as in cl. tetani.
8- Loss of tone of muscle fibers.
9- Depression of hemapoiesis with increase of leukocytes.
10- Hypersensitivity reactions.
Clinical Findings:
* Depression and lethargy.
* Failure to grow or produce, anorexia and emaciation.
* Constipation, weak pulse, rapid but regular.
* Heart rate is increased, but the sounds reduced.
* Albuminuria.
* Fever may be present usually in infections.
* Muscular weakness, collapse, coma or convulsions, death.

Treatment:
- Intensive fluid and electrolyte therapy by continuous I/V infusion.
- Parental nutrition.
- The use of glucose corticoids 1 mg/kg body weight i/v every 24 hours.
- Non-steroidal anti-inflammatory as acetylsalicylic acid, phenyl butazone (15 mg/kg B.U initially and 10 mg/kg B.W at 6-12 hrs).
- Course of broad spectrum Antibiotic.

2. Septicemia / Viremia
Septicemia is the Disease State compounded of toxemia, hyperthermia and the presence of large numbers of infectious microorganisms including viruses, bacteria and protozoa in the blood stream.

- **Bacteremia:** Bacteria are present in the blood stream for only transitory periods and do not produce clinical signs.
- **Septicemia:** the causative agent is present throughout the course of the disease and is directly responsible for the appeared clinical signs.

Causes:
***In all species:***
- Anthrax, pasteurellosis, salmonellosis.
- Pseudomonas pseudomonas.
- Rift valley fever.
- Leptosporidia, sarcosporidia.

***Cattle, sheep, pig:***
- *Pasteurella multocida, Pasteurella haemolytica.*
- *Pasteurella (yersinia) pseudotuberculosis.*

***Sheep:***
- *Histophilus ovis.*
- *Hoemophilus agni.*

***Horse:***
*Pasteurella haemolytica.*

***Pig:***
- Hog cholera, African swine fever.
  - *Streptococcus zoeoepidemicus.*
  - *Erysipelothrix insidiosa.*
**Special septicemia:**

The principal cause of death in subacute radiation injury is septicemia resulting from loss of leukocyte production because of injury to bone marrow. Congenital defect in the immune system or when immuno-suppression occurs in older animals as a result of corticosteroid therapy or toxin or infection such as virus in Bovine viral diarrhea.

**Pathogenesis:**

Two mechanisms operate in septicemia: 1) The Exotoxins or Endotoxins produced by infectious agents produce a profound toxemia and high fever: This is due the rapidity by which they multiply and the rapid spread to all body tissues
2) Also localization occurs in many organs and may produce serious in animals, which survive the toxemia. 3) They also cause direct endothelial damage and hemorrhages into tissues.

In Viremia, the same general principles also present to except that toxins are not by virus, the general signs, which occur, caused by the products of tissue cells killed by the multiplying virus.

* Disseminated intravascular coagulation occurs in septicemia diseases especially that terminates fatally. Circulation of foreign materials such as bacterial cell walls, antigen-antibody complexes and endotoxins vascular injury with partial disruption of the intimate with subsequent platelets adherence and formation of platelet thrombi.

**Clinical findings:**

* Are those of toxemia and Hypertherthemia?
* Submucosal and subepidermal hemorrhages, which is usually petecial, or ecchymotic. The hemorrhages are best seen under the conjunctiva, mucosa of mouth and vulva.
* Localizing signs in heart, joints valve, eyes, and meninges.

**Diagnosis:**

(1) Clinical signs, P.M. findings and clinical laboratory findings.
(2) Isolation of the causative agent from the blood stream.

**Treatment:**

(1) The same general recommendations for treatment of fever.
(2) Intravenous treatment with antibacterial drugs or sera and antitoxins is so urgent as soon as possible.
(3) Hygienic precautions and prophylactic measures to prevent spread of the disease.

**3. Pain**

Pain is one of the more difficult manifestations of the disease to conceptualize because it is necessary to describe, quantify, and characterize outward physical responses that have an sensitive, as well as physiologic basis.

Except for some behavioral abnormalities, pain is one of the few manifestation of disease that require the clinician to identify and immediately interpret the clinical signs exhibited by the anatomic and physiologic consequences of a particular stimulus. We must also consider the animal’s perception of the problem.
It is generally stated that free nerve endings of small-diameter serve the function of perception and production of pain. These nerve endings have been identified or found in the superficial layers of the skin, joint surfaces, periosteum, muscle, tooth pulp, and viscera.

- Stimulation of these receptors results in transmission of pain impulses to the spinal cord, hypothalamus, brainstem and cerebral cortex.
- These signals are processed in the manner that resembles the processing of information from other types of receptors. When the stimulus is of sufficient intensity to exceed the pain detection threshold, these impulses is centrally processed which permits characterization of the intensity and location of the stimulus.
- The end result of pain perception is elicitation of either or multiple motor responses generally indicative of arousal and avoidance.

Classification of pain:
According to its origin, pain may be classified into superficial, deep, or visceral one.
- Superficial pain refers to painful responses that initiated by stimuli applied to the skin or subcutaneous tissues.
- Deep pain originates from muscles, joints, bones and connective tissues.
- Visceral pain that originates from stimulation of nerve endings in the viscera due to localized damage to the viscous.

Motor Response to pain:
The motor responses of painful stimuli include changes in the animals pasture and demand, causing restlessness, guarding, reluctance or difficulty in moving, prolonged recumbency, vocalization and self-mutilation.

1. Visceral pain:
Although the viscera are well supplied with nociceptors, generally these receptors do not impart impulses to the central nervous system in response to local stimulation.
- A localized damage to the viscous, as occurs with ischemia or infection, stimulates the nerve endings and may cause unrelenting (sever = unmerciful) pain.
- The most common causes of visceral pain include stretching of the wall of the viscous secondary to obstruction, increased tension on the mesenteric or supporting ligaments, and spasms of the visceral smooth muscles. It is characterized by rhythmic cramps.
- Although visceral pain may be severe, it is generally considered to be poorly localized. Because pain impulses originating in either the abdominal or thoracic cavities are transmitted through the autonomic nervous system, the sensation is either corresponds to general region or may be referred to distant sites.

Therefore it is difficult if not impossible to more accurately localize the underlying region just on the basis of clinical manifestation in an animal with abdominal pain.

11. Parietal pain:
Stimulation of nociceptors in the parietal pleura, peritoneum or pericardium result in the propagation of the impulses that travel to the CNS via the spinal nerves. The resulting sensation is one of stabbing pain that is extremely well localized. Parietal is usually evident directly over the affected site, which is directly contrast to visceral pain.

11I. Referred pain:
Referred pain is that type which is perceived to originate at a site distant from the actual lesion. The origin of the pain impulses is visceral in nature, and the pain is felt either on the surface of the skin or at another deep visceral site.

The referred pain occurs because the visceral afferent fibers synapse on neurons in the spinal cord that receive similar input nerve fibers from the skin. Consequently, impulses from the skin, and the patient feels a sharp pain on the surface of the body and a dull, aching pain within the body cavity.

Pathophysiologic effects of pain:
From the clinical point of view, there are several adverse effects of pain that must be considered. Because the autonomic control centers in the brainstem are under the influence of the hypothalamus, the central processing of impulses associated with pain increases the activity of the sympathetic portion of the autonomic nervous system and inhibits the activity of parasympathetic.

Causes of Abdominal pain:

<table>
<thead>
<tr>
<th>Causes</th>
<th>Ruminants</th>
<th>Horses</th>
</tr>
</thead>
</table>

TRP = Traumatic reticulo peritonitis.

Causes of chest pain:

<table>
<thead>
<tr>
<th>Causes</th>
<th>Ruminants</th>
<th>Horses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Pleuropneumonia, TRP-Pericarditis, thrombosis of caudal vena cava.</td>
<td>Lung abscess, pleurisy, pleuropneumonia, Pneumonia.</td>
</tr>
<tr>
<td>Less common</td>
<td>Atypical interstitial pneumonia, Choke, fractured ribs, pleuritis Mediastinal masses.</td>
<td>Choke, fractured ribs, ruptured esophagus, Mediastinal masses.</td>
</tr>
</tbody>
</table>

2. Disturbances of body fluids, Electrolytes and
**Acid-Base balance**

*Dehydration:*

It is a disturbance of body water balance in which more fluid is lost from the body than that absorbed which result in reduced circulating volume of blood and dryness of tissues to that degree of impairment of body function.

**Etiologies:**

There are two major causes of dehydration: 1) Failure of water intake, such as in esophageal obstruction and lack of thirst in toxemia. 2) Excessive fluid loss which is more common in the following: Diarrhea, vomiting, polyuria, loss of fluid from extensive skin wounds, copious sweating, acute carbohydrate engorgement in ruminants, acute intestinal obstruction, and diffuse peritonitis, torsion of and dilatation of abomasum.

However, some animals have the ability to survive for long periods without water in hot climates e.g. camels and Merino sheep because of the followings:

1. Good insulation.
2. The ability to carry water in the rumen and extracellular fluid spaces.
3. The ability to adjust electrolyte concentrations in several fluid locations.
4. The ability of the kidneys to conserve water and the ability to maintain circulation with the lower plasma volume.

**Pathophysiology:**

(1) **Fluid loss:**

- The initial response to negative water balance is (A) withdrawal of fluid from the tissues and the maintenance of normal blood volume.
- The fluid is drained primarily from the intravascular compartment and the interstitial fluid space. The loss of fluid from these spaces results in loss of skin elasticity, dryness of skin and mucous membranes and enophthalmia (Reduction and retraction of eyeball) due to reduction in the volume of postorbital fat deposits.
- The secondary response of fluid loss is (B) loss of fluid leads to reduced circulating blood volume and an increase in the concentration of blood (hemocencentration) which result in peripheral circulatory failure.

(2) **In case of water deprivation:**

Deprivation of water and electrolyte or inability to consume water usually results in dehydration; but in minimal degree because:

- The kidneys compensate the defect by decreasing output and increasing concent.
- Reduced fecal output and increased absorption preserve water, which result in dehydration of gastrointestinal contents.
- In calves with diarrhea, total fluid losses are not significantly than the normal calves. In this condition, kidneys compensate for fecal water loss and plasma volume could be maintained if there is an adequate oral fluid intake. Therefore oral fluid intake is very important in such cases.
- Dehydration in horses is hypotonic, which may account for the lack of thirst in some cases of dehydrated horses with exhaustion syndrome.

(3) **Effects of dehydration on tissues:**
There is an increased breakdown of fat, carbohydrates and protein to produce water of metabolism.

Anaerobic oxidation results in formation and production of lactic acid with eventual acidosis.

Reduced urine output together with endogenous metabolic products result in accumulation of NPN (Non protein nitrogen).

Increased body temperature may cause dehydration hyperthermia.

Dehydration may cause death, especially in acute intestinal obstruction, vomiting, and diarrhea.

Clinical findings:
- Dryness and wrinkling of the skin, giving the body and face a shrunken appearance.
- Enophthalmia.
- Picking up the skin leads to folding of the skin, which subsides slowly depending on the degree of dehydration.
- Loss of body weight.
- Muscular weakness.
- Lack of appetite.
- Animals are very thirsty.
- Decreased urine output.
- Reduced milk yield.

*Electrolyte Imbalance:*
Most electrolyte imbalance are due to loss of electrolytes caused by many disease conditions including:
- Diseases of the alimentary tract.
- Exudation from burns.
- Excessive salivation.
- Excessive sweating.

(1) Sodium
Serum sodium concentration is a function of the exchangeable cation content = the exchangeable sodium in the extracellular fluid volume plus the exchangeable potassium in the intracellular fluid volume, relative to the total body water. The following equation indicated this balance & relationship.

Changes in water balance are primarily responsible for changes in serum sodium concentration. Hyponatremia is an indication of relative water excess, whereas hypernatremia is an indication of a relative water deficit. Serum sodium concentration provides a mean of categorizing dehydration into hypertonic, isotonic and hypotonic types.
- Hypertonic dehydration occurs when water losses exceed the losses of sodium and potassium and is indicated by hypernatremia.
- Isotonic dehydration occurs with a balanced loss of water and electrolytes. In this condition the concentration on sodium remains unchanged. e.g. early stage of acute diarrhoea and dehydration due to excessive sweating.
• Hypotonic dehydration occurs when the losses of exchangeable cations exceed the net change of water balance. Hyponatremia indicates this. E.g. subacute and chronic diarrhea.

**Hyponatremia:**

Hyponatremia is often associated with conditions that causes sodium depletion such as:

- Vomiting.
- Diarrhoea.
- Excessive sweating.
- Blood loss.
- Fluid drainage (pleural drainage, gastric reflux).

Accumulation of sodium-containing fluid in the body cavities or gut lumen as a result of:

- Ascitis.
- Ruptures ob urinary bladder.
- Peritonitis.
- Torsion volvulus of the gut.

The conditions which referred as third-space problems. The plasma volume is reduced, and serum sodium concentration decreased due to water retention caused by compensating response of the kidneys.

Rupture of the urinary bladder in the neonatal foals is associated with a marked Hyponatremia and hypochloremia. As water intake continues and dilute urine accumulates in the abdomen, sodium, chloride and other ions are drawn from the extra cellular fluid into this cavities. These conditions are usually associated with hypotonic dehydration, which is indicated by Hyponatremia.

**Pathophysiology of Hyponatremia:**

Hyponatramia causes an increase in renal excretion of water in order to maintain normal osmotic pressure this result in a decrease in the extracellular fluid space leading to a decreased circulating blood volume and development of the following signs:

- Hypotension.
- Renal failure.
- Peripheral circulatory failure.
- Muscular weakness.
- Hypothermia.
- Marked dehydration.
- Mental depression.
- Polyuria and polydipsia occure in cattle with dietary sodium chloride deficieny

**Hypernatremia:**

Hypernatremia may occur in the initial stafes of vomiting, diarrhoea or renal disease when the water loss exceeds the loss of electrolytes. Food and water deprivation in normal animals is associated with reduced urine and fecal output; but continued cutaneous and respiratory water loss may result in hypernatremia due to only water loss.
Hypernatremia also occurs in case of administration of hypertonic saline or sodium bicarbonate when water intake is restricted. Also hypernatremia can result in case of salt poisoning in cattle.

(2) Chloride

Alteration in chloride concentration usually are associated with proportional changes in sodium concentration as the result of changes in relative water balance. Meanwhile, chloride concentration tends to vary inversely with bicarbonate concentration.

Hypochloremia is associated with acute gastric dilatation, torsion of the abomasum, acute high intestinal obstruction, failure of reabsorption of H+ and Cl- by the intestine. Therefore, hypochloremia alkalosis is a common feature in these digestive troubles and is caused by loss of chloride-rich fluids or sequestration of such fluids in the abomasum and forestomach. Clinical findings include, anorexia, weight loss, lethargy, mild polydipsia and polyuria.

(3) Potassium

There are many factors that may alter either the internal or external balance of potassium. Changes in postossium concentration in serum is associated with a variety of clinical problems and have a profound muscular effect that may cause changes in the cell membrane potential.

Hypokalemia:

Hypokalemia may result from depletion of the body’s potassium stores, from redistribution of potassium from the extracellular fluid space into the intacellular fluid space, or from dietary deficiency. It is most common with altered intake and absorption and with excessive potassium losses as in:-

- Vomiting.
- Diarrhoea.
- Vagal indigestion with internal vomiting.
- Third-space problems.
- Excessive sweat.
- Prolonged anorexia.
- Metabolic alkalosis.

Administration of insulin or glucose, and rapid administration of sodium bicarbonate in large doses, can result in alkalosis and hypokalaemia.

Pathophysiology of Hypochloremia:

- The metabolic alkalosis and hypokalemia are accompanied by muscular weakness and paradoxic aciduria. Hypokalemia causes lowering potential of cell membranes which resulting in decreased excitability of neuromuscular tissues which cause muscular weakness.
- Hypokalemia and alkalosis: Hypokalemia due to true potassium deficit causes reduced intracellular concentration of K. The reduced K+ and excess H+,causes excretion of hydrogen ions in the urine when sodium reabsorption is required.
- The distal rephron avidity for sodium reabsorption is increased to protect the extracellular fluid volume. This reabsorption of sodium is at the expense of
hydrogen secretion. Which is contrary to the need of acid retention in the presence of alkalosis.

Consequently, the most prominent signs associated with hypokalemia include, muscular weakness, tremors, depression, recumbency, coma and cardiac abnormalities.

**Hyperkalemia:**

It is more serious than hypokalemia. It usually results from renal potassium as in Addison’s disease, renal failure and renal shutdown. Hyperkalemia often is associated with a metabolic acidosis, particularly when the acidosis results from volume depletion and is complicated by renal shutdown.

It is usually associated with muscular necrosis, short-term exercise of horse at high intensity results in marked, but transient hyperkalemia (9-10 mEq/L).

*Acid-base Homeostasis:*

Acid-base physiology is inherently a slightly confusing subject, but clinical acid-base terminology makes it very confusing. The body’s defenses against blood pH changes operate at different time rates. Chemical buffering is almost instantaneous; Pulmonary responses occur in minutes; renal responses in hours to days.

**Hydrogen ions and pH:**

*Clinical significance of free hydrogen ions:*

The free hydrogen ion concentration (H+) in the blood must be maintained within very narrow limits to maintain life. Consequently, slight alteration in the free (H+) may have profound, life threatening effects on the chemistry of the body.

**Definition of pH:**

The actual (H+) in the blood is very low, approximately 0.00000004 Eq/L. Obviously monitoring clinical changes using these units would be a very difficult process. Therefore, it has become customary to express (H+) as pH. The definition of pH is the negative log of the free (H+). The normal range for pH in arterial blood is 7.35 to 7.45.

**Relationship between pH and (H+):**

It is important to understand the relationship between (H+) and pH, because it is not a simple direct one. Because the pH is the negative log of the free hydrogenation concentration, the relationship between pH and (H+) is inverse. An increase in the pH reflects a decrease in (H+), whereas a drop in pH is associated with a buildup of hydrogen ions. Also, because the relationship is logarithmic, relatively large change in hydrogen ion concentration only slightly alters the numeric value of pH.

**Acid-Base Balance**

*Acids:*

Free hydrogen ions enter the blood on their release from other chemical substances. Any chemical substance capable of releasing a H+ into solution is defined as acids. Therefore, the greater the number and quantity of acids present in solution, the higher the (H+) and the lower the pH will be. Variety of acids is normally present in the blood, and serves as the source of free hydrogen ions.
**Bases:**
All hydrogen ions released in solution do remain free. Many hydrogen ions are attracted to and combined with other chemical substances that are present in the blood. Any substance capable of combining with or accepting a hydrogen ion in solution is called a base. Thus, from the chemical standpoint, the blood pH is a result of the balance of acids and bases at any given time.

**pH Homeostasis:**
Body cells and organs function very well under constant internal conditions including normal pH. Maintenance of a constant internal environment is called homeostasis. Both acids and bases must be regulated closely to ensure stable levels and a normal pH. Maintenance of a constant pH is called pH homeostasis.

The dynamic regulation of blood pH is accomplished through the interaction of the lungs, the kidneys, and the blood buffers. The lungs and the kidneys maintain levels of acids and bases present in the blood. The blood buffers serve a protecting role, preventing large changes in pH when abnormal conditions expose the blood to acid-base abnormalities.

**Acid Homeostasis:**
Normal body metabolism tends to result in an accumulation of excess acids. Thus, it is important that the body excrete acid at a rate equivalent to its production to maintain pH homeostasis.

*Acid excretion:
Two major organ systems are responsible for the excretion of acids: the kidneys and the lungs. Although the kidneys are often the first organs thought of when considering acid excretion, the lungs are actually the major organs of acid excretion.

**Acid Group:**
The kidneys and the lungs each excrete a different general chemical group of acids. The lungs excrete volatile acids. For all practical purposes, carbonic acid \( \text{H}_2\text{Co}_3 \) is the only volatile acid excreted by the lungs under ordinary conditions.

**Base Homeostasis:**
Like acids, the bases in the blood stream must also be maintained in a constant balance. The organ responsible for the regulation of blood bases is the kidney. The plasma bicarbonate level is the major blood base, which has clinical significance. The \( \text{HCO}_3^- \) is carefully controlled in the nephron.

*The lungs and regulation of volatile acid:
The role of the lungs in acid-base balance and pH homeostasis is to maintain the concentration of carbonic acid \( \text{H}_2\text{Co}_3 \) at constant levels in the arterial blood.

**Hydrolysis Reaction:**
\( \text{CO}_2 \) is produced continuously in the cells as end-product of aerobic metabolism. This \( \text{CO}_2 \) then diffuses to the systemic circulation where some of it reacts with water to form carbonic acid; this reaction is called hydrolysis reaction because water is broken down as it reacts with \( \text{CO}_2 \) to form carbonic acid.
**Direct relationship between [CO\(_2\)] and [H\(_2\)CO\(_3\)]**

There is a direct, linear relationship between dissolved Co\(_2\) and the concentration of carbonic acid in the blood at normal body temperature. When blood PCO\(_2\) level increase, blood levels of H\(_2\)CO\(_3\) increase; thus Pco\(_2\) can be used as a marked of blood volatile acid level.

**Co\(_2\) Homeostasis:**

Dissolved Co\(_2\) is maintained at constant internal levels due to its direct on pH and other Physiologic reasons.

**Co\(_2\) Production:**

Production of Co\(_2\) depends on both quantity and the nature of metabolism. The dquantity of metabolism varies directly with body temperature. Metabolism increases as an individuale body temperature rises. The nature of metabolism depends on the type of foodstuff. For example, carbohydrate metabolism produces more Co\(_2\) than dose fat metabolism.

Large increases in metabolism and Co\(_2\) production sufficient to result in PaCo\(_2\) elevation. Such elevations may occur in patients with sepsis or massive burns. Also, rise in blood PaCo\(_2\) can occur after intravenous administration of sodium bicarbonate.

The individual with a normal respiratory system responds to the increased Co\(_2\) with a parallel rise in alveolar ventilation and Co\(_2\) excretion. The inability to increase alveolar ventilation may be seen when the central nervous system ventilatory control mechanisms are not intact or when the respiratory muscles are paralyzed.

**Co\(_2\) Excretion:**

In the clinical setting, increased Co\(_2\) production is usually balanced by increasing alveolar ventilation. An increase in alveolar ventilation results in a decreased PaCo\(_2\). Conversely, a decrease in alveolar ventilation causes an increased PaCo\(_2\).

**Co\(_2\) Transport:**

Co\(_2\) is transported in the blood in both plasma and within the erythrocytes. Co\(_2\) is carried in the blood in four basic forms: dissolved Co\(_2\), carbonic acid, bicarbonate, and carbamino compounds.

**Plasma Bicarbonate formation:**

The amount of HCo\(_3\) formed in the plasma, however, tends to be very small for two reasons. First, the accumulation of the products of the hydrolysis reaction tends to halt the reaction. Second, the hydrolysis reaction itself occurs at a very slow rate in the plasma because there is no enzyme to catalyze the reaction.

Based on these limitations, the amount of Co\(_2\) to be transported to HCo\(_3\) would be expected to be very small. But, surprisingly, HCo\(_3\) is actually the major mechanism of Co\(_2\) transport from tissues to lungs. This is because of an interesting phenomenon known as the chloride shift.
**Chloride shift:**

As CO₂ enters the blood from the tissues, it accumulates in the blood plasma. Because CO₂ diffuses through cell membranes, CO₂ level also increases within the erythrocytes therefore, the hydrolysis reaction also takes place within the erythrocytes.

Inside the erythrocytes, the hydrolysis reaction can occur at a much faster rate than in the plasma for two reasons. First, the presence of carbonic anhydrase enzyme speeds up the reaction. Second, the products of hydrolysis reaction (H⁺, HCO₃⁻) are not permitted to accumulate within the red blood cell. Consequently, hydrogen ions combine with desaturated Hb to prevent their accumulation and changes in intracellular pH. Simultaneously, bicarbonate ions are transported through cell membrane into the plasma of HCO₃⁻ from the erythrocyte to the plasma, and in turn the movement of chloride anions into the erythrocyte is known as chloride shift = hamburger phenomenon.

*Chloride shift at the tissues:*

At the tissues, chloride enters the RBCs as bicarbonate enters the blood plasma. Thus, the most majority of CO₂ transport is in the form of HCO₃⁻. This HCO₃⁻ is produced in RBCs but is transported from the tissues to the lungs in the plasma.

*Chloride shift in the lungs:*

As CO₂ diffuses from the blood to the alveolar the chloride shift occurs in the opposite direction. i-e, Chloride returns to the plasma in exchange for the return of bicarbonate ions to the erythrocytes. Inside the cells, HCO₃⁻ is converted back to dissolved CO₂ and can be excreted from the plasma into the alveoli.

**Carbamino Compounds:**

1- **Plasma Carbamino Compounds:**

A small amount of CO₂ is transported in the plasma in combination with protein. In this case CO₂ reacts with amino acid groups present on the protein molecule and forms what is called carbamino compounds in the plasma. This form account for only 2% of CO₂ transport.

2- **Carbamino – Hemoglobin:**

CO₂ can react or combine with hemoglobin because of the presence of globin. The combined form of hemoglobin with CO₂ is called carbamino-hemoglobin. The percentage of CO₂ transport in the form of carbamino-hemoglobin is about 10%. Thus, the total amount of CO₂ transported as carbamino compounds is 12%.

**Percentages of CO₂ transport from tissues To lungs:**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate</td>
<td>80%</td>
</tr>
<tr>
<td>Carbamino-compounds</td>
<td>12%</td>
</tr>
<tr>
<td>Dissolved Co₂</td>
<td>8%</td>
</tr>
</tbody>
</table>
**The kidneys and acid-Base balance:**

The renal system acts only second to the lungs in their role of controlling blood pH. The kidney serves two major functions in acid-Base homeostasis: fixed acid excretion and normal regulation of bicarbonate in the blood.

**Regulation of fixed acids in the blood:**

Fixed acid is produced through normal body metabolism. These fixed acids cannot be converted into gases to be excreted via the lungs. Therefore, the kidneys are responsible for maintaining normal fixed acid homeostasis.

In addition several disease conditions can result in an abnormal increase in fixed acid concentration. In this case, the kidney accelerates acid excretion and attempts to maintain homeostasis.

**Origin of fixed acids:**

(A) **Metabolism:** Non-volatile acids are a common product of metabolism. The types of fixed acids accumulating in the blood depend mainly on nature of substance being metabolized and the conditions surrounding metabolism (Presence or absence of O₂, disease condition).

<table>
<thead>
<tr>
<th>Substances</th>
<th>Fixed acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Sulfuric acid</td>
</tr>
<tr>
<td>Incomplete lipid metabolism</td>
<td>Phosphoric acid</td>
</tr>
<tr>
<td>Carbohydrate metabolism (Anaerobic)</td>
<td>Keto acids</td>
</tr>
<tr>
<td></td>
<td>Lactic acid</td>
</tr>
</tbody>
</table>

(B) **Non-metabolic origin:** An increase in fixed acids in the blood may originate from a cause other than metabolism. This finding occurs typically when ammonium chloride is administered intravenously to a patient with severe metabolic alkalosis. Ammonium chloride is metabolized by the liver and results in the production of hydrochloric acid.

**Excretion of fixed acids:**

The amount of fixed acids excreted through the kidneys is normally small, therefore, usually no problem in maintaining fixed acid homeostasis. The problem usually originates when there is over production of fixed acids due to incomplete metabolism or when chloride salt is administered. Also there is a problem in maintaining homeostasis in case of renal diseases. However, the end result is accumulation of fixed acids that leads to an excess of hydrogen ions in the blood. This non respiratory (or metabolic) acid-base disturbance results in a fall in blood pH. (metabolic acidosis).
Buffer systems:
Another important aspect of acid-base homeostasis is the blood buffer system. This important system tends to stabilize the body’s pH despite substantial alterations in the concentrations of acids or bases.

Types of buffer or conjugate acid-base pairs:
The buffer may be formed from weak acids and their salts with strong base or from weak bases and their salts with strong acids. The buffer and its salt called buffer pair.

- CH₃COOH  Acetic Acid (weak acid).
- CH₃COON  Salt of acetic acid and strong base (NaOH).
- H₂CO₃  Carbonic acid (weak A).
- NaHCO₃  Sodium bicarbonate.
- NaH₂PO₄  Sod. Dihydrogen phosphate (monobasic acid phosphate).
- Na₂HPO₄  Disodium monohydrogen phosphor (Sodium salt dibasic..).
- NH₄OH  Ammonium hydroxide (alkaline).
- NH₄CL  Ammonium chloride.

The principal blood Buffers:
The blood consists of many buffer systems including the bicarbonate buffer. These buffer systems constitute the first line of defense against abrupt changes in the blood pH. The blood buffers work very quickly and effectively to minimize alterations in pH. The blood buffers exist both within the cells (Intracellular) and within the plasma (extracellular fluid).

<table>
<thead>
<tr>
<th>Extracellular fluid Buffers</th>
<th>Intracellular fluid Buffers</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Plasma proteins.</td>
<td>* Hemoglobin.</td>
</tr>
<tr>
<td></td>
<td>* Inorganic phosphates.</td>
</tr>
<tr>
<td></td>
<td>* Organic phosphates.</td>
</tr>
</tbody>
</table>

ACID-BASE IMBALANCE
Using the traditional approach to acid-base balances, the four primary acid-base imbalances and their compensating responses are presented in Table 22-5, Acidosis is associated with an increase in hydrogen ion concentration (decreasing pH), whereas alkalosis is caused by a decrease in hydrogen ion concentration (increasing pH). When the primary imbalance is associated with a change in bicarbonate concentration, the acid-base imbalance is called a metabolic disorder. The compensating response for a metabolic acid-base imbalance is mediated by the respiratory tract, which alters the PCO₂ to counterbalance the primary imbalance and to partially restore the pH toward normal. Primary respiratory imbalances are related to alterations in alveolar ventilation, which results in an increased PCO₂ in