Concepts related to fluid balance in the body.

Membrane Transport

To understand fluid balance in the body, one must fully understand the terminology of the systems. Initially we need to consider the fluid compartments of the body. Basically we can break this down into the fluid that is inside the cells (intercellular fluid) and the fluid that is outside the cells (extracellular fluid). The intracellular fluid is the cytosol inside the cell. The extracellular fluid is divided into the interstitial fluid (the fluid surrounding the body cells) and the blood plasma. We will learn more key terms later in this lecture. When learning the key terms related to fluid imbalance in the body ask yourself how they may relate to the fluid balance of the body.

The composition of the two components of the extracellular fluid, that is the plasma and the interstitial fluid, are more similar to each other than either is to the intracellular fluid. Blood plasma has high concentrations of sodium, chloride, bicarbonate, and protein. The interstitial fluid has high concentrations of sodium, chloride, and bicarbonate, but a relatively low concentration of protein. In contrast, the intracellular fluid has elevated amounts of potassium, phosphate, magnesium, and protein.

In order for fluids to move from one fluid compartment to another they must cross the barrier between the compartments. The barrier consists of plasma membranes. Movement of substances through the plasma membrane happens in essentially two ways: 1. passively and 2. actively.

In Passive processes substances penetrate the membrane without any energy input from the cell.

In active processes the cell provides the metabolic energy (ATP) that drives the transport process to move the substance across the membrane.

Passive Processes: Diffusion

Diffusion is the tendency of molecules or ions to scatter evenly throughout the environment. Molecules are said to diffuse along or down their concentration gradient.

Because the driving force is the kinetic energy of the molecules themselves, the speed of diffusion is influenced by the size of the molecules and the temperature.

Because a plasma membrane has a hydrophobic lipid interior, it acts as a barrier to free diffusion. Molecules will diffuse passively through the plasma membrane if they are 1. lipid soluble, 2. small enough to pass through membrane pores, or 3. assisted by carrier molecules.

The unassisted diffusion of lipid soluble or very small particles is called <u>simple diffusion</u>. Simple diffusion of water is known as <u>osmosis</u>.

Substance that commonly undergo simple diffusion include; oxygen, carbon dioxide, fats, and alcohol.

<u>Osmosis</u> is the diffusion of a solvent, such as water, through a selectively permeable membrane. Since water is highly polar, it cannot pass through the lipid bilayer, but it is small enough to pass through the pores of most plasma membranes.

<u>Facilitated diffusion</u>. Certain molecules, notably glucose and other simple sugars, are both lipid insoluble and too large to pass through the plasma membrane pores. Facilitated diffusion is the process in which these molecules are transported across the plasma membrane by carrier molecules. It is believed that these carrier molecules engulf the substance and then change their shape to release the molecule into the cytosol. Unlike osmosis, which is a very non-selective process relying only on particle size, facilitated diffusion is very specific. The carrier molecule for glucose will only recognize glucose, etc.

Passive Processes: Filtration

Filtration is the process by which water and solutes are forced through a membrane or capillary wall by fluid, or hydrostatic, pressure. In filtration the gradient is a pressure gradient rather than a concentration gradient. Filtration is not selective: only blood cells and protein molecules too large to pass through the membrane are held back.

Active Processes

Whenever a cell used its energy from ATP to move substances across the membrane, the process is referred to as active.

What are some instance when active transport would be necessary? Whenever a substance is unable to cross the membrane because it may be too large to pass through the pores, unable to dissolve in the bilipid membrane core, or required to move against rather than with a concentration gradient.

As mentioned in your textbook most body fluids are neutral in charge. This happens because the cations, the positively charged ions, and the anions, the negatively charged ions, are balanced in most body fluids. In general sodium ions, which are positive ions, and chloride ions, which are negative ions are concentrated in the extracellular fluid whereas potassium, positively charged ions, are concentrated inside cells. Although sodium and potassium ions can leak through membranes at membrane pores, the high levels of potassium on the inside of the cell and low levels of sodium on the outside of the cell are maintained by a sodium potassium pump located in the cell membrane. These pumps use energy supplied by ATP to pump sodium out of the cell and potassium into the cell.

Other key terms include:

Dehydration: insufficient water in the blood and other body tissues.
Diuresis: excessive production of urine.
Hydrostatic pressure: the pressure exerted by a fluid against the wall.
Homeostasis: the maintenance of constant conditions within the body.

We will find that ions (charged particles) play a very large role in fluid balance, therefore we should be familiar with the terms related to ion levels.

The first prefix to be aware of is "**hyper**". Hyper denotes an increase.
The second prefix to be aware of is "**hypo**". Hypo denotes a decrease.
Using these prefixes in front of the names of our various ions will give you a much better understanding of the clinical terms related to fluid balance/imbalance in the body.

Root words denoting various ionic substances that you will need to know to understand fluid balance include:

Calcemia: calcium
Capnia: carbon dioxide
Chloremia: chloride
Kalemia: potassium
Natremia: sodium
Phosphatemia: phosphate

Putting the prefix with the root word will give you a name for a clinical or physiological condition. For example hyperkalemia is increased levels of potassium in the blood and hypokalemia is low levels of potassium in the blood.

To fully understand the fluid balance in the body we must understand plasma osmolality and be able to identify ways in which plasma osmolality is maintained. Plasma osmolality is the ratio of solutes to a volume of solvent in the plasma. Plasma osmolality reflects a person's state of hydration. So more simply stated it is the concentration of a substance in the blood stream. If water is removed from the bloodstream the relative concentrations of the substances in the blood become higher.

If you recall your basic biochemistry, chemical reactions that occur inside the human body occur in aqueous solutions. The dissolved substances are called solutes. In the human body solutes may be proteins, lipids, and carbohydrates, but for the purposes of this lecture, most importantly, electrolytes.

Because chemical reactions occur in aqueous solutions it is important to understand the body water content from one tissue to another. It is also important to understand that water will move through semipermeable membranes from one compartment to another compartment via a process called osmosis. Recall that osmosis is basically the diffusion of water from regions of higher concentration to regions of lower concentration along an osmotic gradient.

Body water content

Human beings are mostly water ranging from about 75% of body mass in infants, to about 50 to 60% of body mass in adults, to as low as 45 percent in the elderly. It is not uncommon to see that an 80-year-old could have 20% less body water that a 20-year-old. This leads to several conditions that are related to aging.

When considering fluid balance within the body we must understand fluid movement between the various body compartments. Movement from one body compartment into another body compartment, generally sets up some form of osmotic imbalance which will influence the surrounding body compartments.

For purposes of our discussion we will start by moving from the blood into the interstitial fluid. At the proximal end of a capillary hydrostatic pressure within the capillaries forces solutes through the capillary wall into the interstitial fluid. This is because the capillary hydrostatic pressure is greater than the blood colloid osmotic pressure. Midway through the capillary there is no net movement of fluid into or out of the capillary since capillary hydrostatic pressure and blood colloid osmotic pressure are essentially equal. At the distal end of the capillary we will see reabsorption back into the capillary because the capillary hydrostatic pressure is now less than the blood colloid osmotic pressure. If you put this into nonbiochemical and non-anatomical terms it may be simpler to understand. At the proximal end of the capillary the nutrients and other substances that are needed by the tissue are at a higher concentration within the capillary than in the interstitial fluid outside of the capillary. Those substances will leave the capillary pushed by the capillary hydrostatic pressure and essentially follow a concentration gradient into the interstitial fluid. Midway along the capillary the nutrients have left the capillary into the interstitial fluid. This means that essentially the concentration inside the capillary and outside the capillary are equal so there should be no net movement. At the distal end of the capillary waste products that have been created by the cells and placed in the interstitial fluid are in a higher concentration in the interstitial fluid than their concentrations within the capillary, therefore these substances will diffuse along their concentration gradient into the blood to be carried away by the bloodstream.

It is important to note that the movement of some solutes between compartments is a passive process along a concentration gradient. However the movement of some solutes between compartments is an active process which requires energy expenditure. An example of this would be the facilitated diffusion of glucose molecules moving down a concentration gradient through a carrier protein in the membrane.

What are the sources of water in the body?

Water can enter the body as liquids that you have been drinking. Water also enters the body as a component of food that you consume. A small percent of body water is actually a result of metabolic processes such as aerobic respiration.

Since the majority of water in your body enters the body through your drinking of liquids we should consider what it is that drives your thirst sensation. As your body becomes dehydrated there is a net loss of water that results in insufficient water in the blood and other tissues. Water that leaves the body may leave as exhaled air, sweat, or urine, and this water ultimately came from blood plasma. As the blood becomes more concentrated a thirst response, which is a sequence of physiological processes, is triggered. Basically there are a series of pathways which will lead to an individual drinking water. The first is that there will be a decrease in the volume in the extracellular fluid. This stimulates osmoreceptors in the hypothalamic thirst center. Stimulation of these osmoreceptors results in the sensation of thirst which of course causes the person to take a drink. The water in the liquid that was consumed will be absorbed into the extracellular fluid surrounding the gut tube. This decreases the osmolality of the extracellular fluid. Another pathway would be to increase the osmolality of the extracellular fluid. This will result in decreased saliva production which will cause dry mouth, which causes the person to have a sensation of thirst and therefore take a drink. In either case taking a drink increases the volume of the extracellular fluid which is sensed by the osmoreceptors in the hypothalamic thirst center to work as an inhibition feedback.

Let's consider what would happen in a dehydrated person. Consider that in dehydration you have lost water from the plasma volume of the blood. This would result in higher sodium concentrations in the plasma. Osmoreceptors in the hypothalamus will sense this increased sodium concentration and cause the posterior pituitary to release antidiuretic hormone (ADH). Recall that a diuretic is something that causes your body to produce urine. So an anti-diuretic would be something that causes your body to produce less urine. Why would that be important in this case? Antidiuretic hormone acts on the collecting ducks in the kidney tubules in such a way that the kidney tubules will increase their water reabsorption thus adding water back into the plasma thus decreasing the sodium concentration or the osmolality of the sodium. This will result in a decrease in the volume of urine production. At the same time, the hypothalamus of a dehydrated person also sends signals to the salivary glands in the mouth. These signals cause a decrease in the watery type of saliva and an increase in a thick pasty type of saliva. This results in a condition commonly referred to as dry mouth and a sensation of thirst.

There are two additional affects one would see when they have a decrease in blood volume resulting from water loss. First blood pressure receptors in the arch of the aorta and in the carotid arteries of the neck detect a drop in blood pressure resulting from the decrease blood volume. This signals the heart to increase its heart rate or strength of contractions to compensate for the lower blood pressure. Second the kidneys activate a renin-angiotensin hormone system to increase the production of the active form of a hormone known as angiotensin II. Angiotensin II helps stimulate thirst but it also stimulates the release of the hormone aldosterone from the adrenal glands. Aldosterone increases the reabsorption of sodium in the kidney tubules. Recall that increase sodium will result in obligatory water reabsorption, basically your body's attempt to dilute the sodium. If water is reabsorbed into the bloodstream from the kidney tubules that means blood volume increases, which in turn causes an increase in blood pressure.

Electrolytes in the body

Electrolytes are important in our body because they aid in nerve excitability, membrane permeability, buffering of body fluids, endocrine secretion, and control of movement of fluids between fluid compartments. Ions enter the body through the digestive tract. More than 90% of calcium and phosphate that enter the body is incorporated into your bones and teeth. Ions are lost from the body mainly through the kidneys with some loss through sweat and fecal matter. Some conditions that cause excessive loss of ions are excessive sweating, in which case you will lose mainly sodium and chloride, severe vomiting or diarrhea cause a loss of chloride and bicarbonate ions. As we learned in the respiratory and renal lectures this may lead to alkalosis and acidosis in the bloodstream.

Let us now look at the various roles the electrolytes play in maintaining body homeostasis.

Bicarbonate

As discussed in the respiratory and renal lectures bicarbonate is the second most abundant anion in the blood. In our previous discussion the main function of bicarbonate was maintaining the acid-base balance of the blood. Because we spent extensive time discussing the bicarbonate ion buffer system we will not repeat that discussion here.

Calcium

Calcium ions in the body are necessary for muscle contraction, blood coagulation and some enzyme activities. In addition calcium helps to stabilize cell membranes and is essential for the release of neurotransmitters from neurons and the release of hormones from some endocrine glands. The majority of calcium in our body is found in bone and teeth, with the bones acting as a calcium reserve. Calcium is absorbed in our intestines, but only under the influence of vitamin D. Recall that milk is a good source of calcium. However recall that most milk is vitamin D fortified. This ensures that you have the proper amounts of vitamin D so that you can absorb the calcium from the milk. Calcium deposition in the bone is regulated by the hormone calcitonin which is secreted by the thyroid gland. Calcium removal from bone is regulated by parathyroid hormone, secreted by the parathyroid glands. Removal of the thyroid gland, and thus the removal of the parathyroid glands since they are embedded in the thyroid gland, can lead to abnormally low blood calcium levels, referred to as **hypocalcemia**. **Hypercalcemia**, abnormally high calcium blood levels may be seen and hyperparathyroidism, where excessive levels of parathyroid hormone stimulate the release of calcium from the bone and promote calcium reabsorption in the kidney tubules.

Chloride

Chloride is the major and ion found in extracellular fluids. Chloride is the major contributor to the osmotic pressure gradient between the intracellular fluid and the extracellular fluid. It plays in important role in maintaining proper hydration. Recall that chloride is an anion, and as such chloride functions to balance the cations in the extracellular fluid, thereby maintaining an electrical neutrality of these fluids. In general we are all familiar with the compound known as sodium chloride, commonly referred to as table salt. Because sodium ions and chloride ions are so closely related the secretion and absorption pathways of chloride ions in the renal system generally follow those of the sodium ions. **Hypochloremia** is a lower than normal blood chloride level. This can occur because of defective tubular reabsorption in the kidneys. Vomiting, diarrhea, and metabolic acidosis can also lead to hypochloremia. **Hyperchloremia** is a higher than normal blood chloride level. It can be due to dehydration, excessive intake of salt, or swallowing of seawater. Hyperchloremia can also be due to aspirin intoxication, congestive heart failure and the chronic lung disease that we learned during our coverage of the respiratory system, cystic fibrosis. High chloride levels in sweat are often used to diagnose cystic fibrosis.

Phosphate

The majority of phosphate found in the human body is found in bone and in the teeth where it is used as a component of the calcium phosphate salts which make up bone and teeth. Phosphate is also found in phospholipids, the molecules adenosine triphosphate and adenosine diphosphate, and in many of the buffers found throughout the body. **Hypophosphatemia** is abnormally low blood phosphate levels. **Hypophosphatemia** generally occurs with the heavy use of antacids or during malnourishment. Normally the kidneys are involved in reabsorbing phosphate from the filtrate but during starvation the reabsorption of phosphate by the kidneys is greatly impaired. Hyperphosphatemia is an abnormally increased level of phosphates in the blood. This can occur if there is renal failure or in cases of lymphocytic leukemia. Because phosphate is a major constituent of the intracellular fluid any significant distruction of cells may result in the dumping of phosphate into the extracellular fluid.

Potassium

Potassium is a cation, a positively charged ion. Potassium is the major cation found in the intracellular fluid. It is essential in establishing the resting membrane potential in neurons and in muscle fibers. **Hypokalemia** is an abnormally low potassium blood level. Hypokalemia can occur because there is either a total reduction of potassium in the body or there could be a relative reduction of potassium in the blood due to a redistribution of potassium out of the bloodstream. An absolute loss of potassium could arise from decreased intake of potassium which is often related to starvation. Excess vomiting, alkalosis, or diarrhea may also cause hypokalemia. Because potassium is so vital in neuron activity and muscular contraction, patients suffering from hypokalemia may suffer from severe muscle cramping. **Hyperkalemia** is an elevated blood potassium level. Hyperkalemia can impair the function of skeletal muscles in the nervous system and the heart. Elevated potassium blood levels may be the result of increased dietary intake of potassium. Excessive intake of potassium into the blood results in increased potassium levels in the extracellular fluids. This can result in partial depolarization of the plasma membrane of skeletal muscle fibers, neurons, and the cardiac cells of the heart. This can also lead to an inability of these cells to repolarize. In the case of the heart this means that it will not relax after contraction which will effectively stop the heart from pumping blood, which of course would be fatal within minutes. Some symptoms of hyperkalemia maybe mental confusion, numbness, and weakened respiratory muscles.

Sodium

Sodium, is a positively charge ion, which means it is a cation. Sodium is the major cation of the extracellular fluid and it is responsible for roughly 1/2 of the osmotic pressure gradient that exists between the interior of cells and their surrounding environment, in other words the osmotic gradient between the interstitial fluid and the intracellular fluid. Sodium play is a very large in whether or not the kidneys reabsorb water in the proximal convoluted tubules or allow the water to pass in the urine. This was covered in the urinary lectures. Excess sodium in the blood stream will lead to tubular reabsorption of water in the kidney tubules which in turn leads to increased blood volume which leads to increased blood pressure. Excess sodium consumption can lead to hypertension (high blood pressure). **Hypernatremia** is an abnormal increase of blood sodium. It can result from water loss from the blood which results in a higher concentration of plasma constituents. Hormonal imbalances involving anti-diuretic hormone and aldosterone also result in higher than normal sodium values in the blood. **Hyponatremia** is a lower than normal concentration of sodium in the blood. This usually occurs due to excess water in the blood which dilutes the sodium. Low sodium in the blood may be due to decreased intake of sodium ion or excess of excretion of sodium in urine, or a combination of the two. Excessive loss of sodium can be caused by several factors including excessive sweating, vomiting, diarrhea, the use of diuretics, excessive production of urine (which is commonly seen in diabetics and in acidosis, either metabolic acidosis or diabetic ketoacidosis). Diabetic ketoacidosis is a very serious complication of diabetes. In this condition the body does not produce enough insulin. Insulin is a hormone that signals cells to take glucose (blood sugar) into the cell where the cell can the use the glucose for energy. If you do not have enough insulin you body starts to break down fats as its source of energy. The breakdown of fats results in ketones (a type of acid) building up in the bloodstream. Ketones are filtered by the kidneys, so the major diagnosis for this condition is high levels of ketones in the urine. Another sign of possible diabetic ketoacidosis would be high blood sugar levels (hyperglycemia). Can you provide a rationale for this?

Recall from lectures on the renal system that your average human being produces 1.5 L of urine per day. Although overall urine production is tied to the amount of liquids consumed by the individual, there is a minimum amount of urine that must be produced each day to rid the body of certain metabolic wastes that must be removed from the bloodstream. The minimum level of urine production necessary to maintain normal body functions is approximately 1/2 quart per day.

Acid/Base balance of the blood

Recall from previous lectures that metabolic acidosis is a condition where there is a deficiency of bicarbonate ions in the blood causing it to be overly acidic. Metabolic alkalosis is a condition where there is an excess of bicarbonate ions causing blood to be overly alkaline.

Respiratory acidosis is a condition where you have an excess of carbon dioxide in the blood causing it to be overly acidic. Respiratory alkalosis is a condition where you have low levels of carbon dioxide in the blood causing it to be overly basic.

Regulation of sodium ions and potassium ions is generally controlled by the collecting tubules of the kidneys. Since this was discussed in the lectures over the urinary system it will not be discussed in this lecture.