Needless to say, all living organisms require at least a minimal amount of water/fluid to remain viable. For health, fluid balance is regulated and it is critical for it to be maintained within a fairly narrow range. An 8-10% loss of total body fluid, amounting to about 1+ gallon in a 200 pound individual, can be critical and lead to neurological symptoms and death. It should be remembered that fluid volume and distribution in the body are integrally related to hydrostatic and osmotic forces. Movement of water is often passive and follows osmotic gradients in the different fluid compartments (see following paragraph). Redistribution of fluid between the various compartments can also be associated with disease.

The purpose of this lecture is to cover normal fluid volume, the various fluid compartments in the body, regulation of fluid balance, and how disturbed fluid balance can be associated with disease.

NORMAL FLUID VOLUME, BALANCE, AND REGULATION (slides 2 – 7)

In late term fetuses and neonates, water represents approximately 80% of the weight of the body. Adults are composed of about 65% water on a total body weight or lean mass basis. Fat contains very little water so obese individuals would have proportionally less water relative to body weight and size. Fluids in the body are divided between four separate compartments (slide 4). In health, there is a constant and dynamic turnover of water in these compartments but the volume of fluid in each compartment remains relatively stable. The largest compartment is the intracellular fluid (41%), the fluid within cells. Extracellular fluid, the water outside of the cells, can be divided into three compartments. The largest of these is the interstitial compartment (15%); the fluid that bathes and surrounds cells. The transcellular compartment (5%) is composed of the fluids in the body cavities and eyes. The intravascular compartment, the smallest (4%), consists of the fluid component within the vasculature, blood and lymphatic vessels.

Body water content is controlled by hormones that in turn are regulated by pressure and osmoreceptors located in various tissues. The functions of these hormones are inter-related. Renin is a hormone produced by the juxtaglomerular apparatus in the kidney. The stimulus for renin release is decreased blood flow (perfusion) to the kidney as might occur when there is a reduction in cardiac output or decreased fluid volume in the intravascular compartment. Renin then converts a plasma protein synthesized by the liver, angiotensinogen, to an intermediate angiotensin I. Angiotensin I is then metabolized to an active form of the hormone angiotensin II by an enzyme, angiotensin converting enzyme, found in endothelial cells lining blood
vessels of the lung and kidney. Angiotensin II has multiple functions (Table 1) including actions on two other hormones aldosterone (mineralocorticoid) and vasopressin (antidiuretic hormone; ADH). The net effect of angiotensin II is to increase fluid volume and blood pressure, ultimately restoring renal blood flow which serves as negative feedback for renin secretion (slide 6). These effects are explained in a little more detail below:

- **Nervous system:** increased activity of the sympathetic nervous system. One effect of this is positive *inotropic* (the force of muscle contraction) and *chronotropic* (the rate of muscle contraction) stimulation of the heart in an effort to improve blood flow and blood pressure.
- **Kidney:** stimulates absorption of sodium from the renal tubules along with water. The net effect is to increase fluid volume.
- **Adrenal gland:** increases aldosterone secretion. Aldosterone is a mineralocorticoid hormone secreted by the zona glomerulosa of the adrenal cortex. The effect is to increase absorption of sodium and water from the renal tubules increasing blood volume. Another effect that balances the resorption of sodium is the extrusion of potassium into the tubule which is lost in the urine. **Addison’s disease** is a deficiency of aldosterone secretion.
- **Pituitary gland:** Angiotensin II stimulates the release of antidiuretic hormone (vasopressin, ADH). ADH increases the passive resorption of water from the collecting ducts of the kidney, increasing fluid volume. Microtubules and microfilaments are required for this effect. What affect would *colchicine* (lecture 3) have on the function of ADH? **Diabetes insipidus** is due to either an absolute deficiency of ADH or to non-responsiveness of the kidney to the action of this hormone.
- **Blood vessels:** Angiotensin II is a potent vasoconstrictor. It is approximately 40 times more potent than norepinephrine in elevating blood pressure. This is a direct effect on the smooth muscle of arterioles, independent of the effects of angiotensin II in increasing sympathetic nervous system activity.

<table>
<thead>
<tr>
<th>Organ or tissue</th>
<th>Function</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>↑ sympathetic activity</td>
<td>↑ inotropic &amp; chronotropic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(heart)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Na⁺ &amp; H₂O resorption</td>
<td>↑ fluid volume</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>aldosterone secretion</td>
<td>renal Na⁺ &amp; H₂O resorption</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>vasopressin release</td>
<td>renal H₂O resorption</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>arteriolar constriction</td>
<td>↑ blood pressure</td>
</tr>
</tbody>
</table>
Water intake is a necessary component of the equation. Basal urine output (volume of urine produced even with water restriction) in horses is approximately 0.5/L/100 kg bodyweight/day. Normal adult humans produce about 1.5 L of urine/day. These urinary losses along with loss of water from the respiratory system, through sweating, or via other routes must be replenished. The sensation of thirst is controlled by osmoreceptors in the hypothalamus, separate from the neurons in the supraoptic nucleus that secrete vasopressin. A brain structure that seems to stimulate thirst is the subfornical organ via a further action of angiotensin II. The final hormone controlling fluid volume is atrial natriuretic factor (peptide) synthesized and stored in granules within myocytes of the atrial myocardium (slide 7). These cells respond to distension of the atria by release of natriuretic factor (ATF). The action of ATF is antagonistic to the hormones mentioned previously. It acts on renal tubules to prevent the resorption of Na⁺ and water stimulating diuresis, decreases blood pressure, and inhibits the secretion of renin, aldosterone, and antidiuretic hormone (vasopressin).

ABNORMAL FLUID ACCUMULATIONS (slides 8 – 21)

Accumulation of fluid in this sense is a poor choice of words. There is often not a true net increase in total water content in tissues, organs, or the body; rather there is a redistribution of fluids between compartments. One compartment gains fluid at the expense of another.

*Intracellular fluid accumulation.* When the fluid is redistributed from the interstitial to the intracellular compartment, it is called hydropic change (also hydropic degeneration or intracellular edema) and the cells appear swollen with clear, nonstaining cytoplasm. “Change” is preferred because this process is not irreversible and not all cells will die and sometimes the increase in intracellular water represents a normal physiological response. During normal neuronal activity in the brain, the extracellular space may be reduced by as much as 30%. In this case, there is a normal redistribution of water as astrocytes take up potassium released into the interstitium from depolarized neurons. Hydropic change can, however, indicate damage to the cell, either directly to the cell membrane or due to energy failure (hypoxia, ischemia). Cell damage from hypoxia and ischemia is due to failure of the energy driven sodium-potassium pump (Na-K-ATPase); Na⁺ moves into the cell along with water from the interstitium and K⁺ moves out of the cell along ionic gradients. The influx of water results in cell swelling and vacuolation (slides 10 and 11). At some point, the injury becomes irreversible and the cell will die. A prime example would be the generalized brain swelling (cerebral edema) that occurs from hypoxia and ischemia. Hydropic change can also result from altered osmotic gradients. As you will remember from lecture 10, the hepatocellular cloudy swelling that occurs in Cushing’s disease can be in part due to accumulation of glycogen resulting in an osmotic burden and water redistribution into the cytoplasm of hepatocytes.

*Extracellular fluid accumulation.* Accumulation of fluid in the extracellular compartments can represent some of the most dramatic examples of fluid redistribution. Here we are most concerned with the interstitial and transcellular compartments. Edema is accumulation of fluid, due to redistribution from blood to the interstitium that surrounds cells. The nomenclature for accumulation of fluid in transcellular compartments is only a little more complicated. Here, the fluid accumulation is termed hydro- + body cavity:
• **Hydrothorax** = fluid accumulation in the chest
• **Hydroperitoneum** = fluid accumulation in the abdomen. Another name for accumulation of fluid in the abdomen is **ascites**.
• **Hydropericardium** = accumulation of fluid in the membranous sac that surrounds the heart
• **Hydrocephalus** = hydrocephalus is somewhat of a stretch here but accumulation of excess fluid in the cerebral ventricular system can develop by at least one mechanism similar to those in other body cavities, i.e. increased hydrostatic pressure due to blockage of cerebrospinal fluid outflow.

### Mechanisms of Abnormal Fluid Accumulation

**Forces Governing Normal Fluid Distribution.** Fluid redistribution occurs due to events at the level of the microcirculation: arterioles, capillaries, venules, and lymphatics. The principal forces are **hydrostatic pressure** and **colloidal osmotic pressure**. At the arterial end, hydrostatic or blood pressure, drives fluid from the blood out of the vasculature into the interstitial or, to a limited extent, transcellular compartments. This outward driving force is balanced by osmolytes, mainly proteins, within the blood that tend to return fluids to the blood vessels from the interstitial spaces at the venous end (slide 14) of the circulation. From this we can see that normal fluid distribution is a dynamic process; fluid moves into the interstitium at the arterial end and returns to the blood from the venous side of the circulation. This dynamic ensures that cells and tissues are constantly bathed by nutrient-rich fluid. When all forces are in balance between blood and the interstitium, there remains a slight net positive force favoring the movement of fluid into the interstitium; this fluid is then drained away via lymphatic vessels in the interstitium and returned to the general circulation. Slide 15 summarizes these forces. Now that we understand the forces that maintain normal fluid distribution, we can begin a discussion of the main mechanisms underlying abnormal redistribution of water.

**Mechanisms Underlying Abnormal Fluid Distribution:** The major mechanisms underlying abnormal fluid distribution are fairly simple:

- Increased vascular permeability
- Increased intravascular hydrostatic pressure
- Decreased intravascular colloidal osmotic pressure
- Increased tissue colloidal osmotic pressure
- Decreased lymphatic drainage

Although these mechanisms are simple, disease can be due to a combined interplay of more than one mechanism.

**Increased intravascular permeability.** This is the one mechanism that occurs independent of the forces mentioned previously but these forces contribute to the severity of the fluid redistribution. The integrity of blood vessels can be compromised by a variety of injuries. Inflammation, either localized or systemic, and no matter what the cause (microorganisms, immune-mediated) leads to increased permeability. Other causes include toxins, metabolic abnormalities and **anaphylaxis**. Increased permeability means that the blood vessels become
leaky; fluid leaks out of the blood vessels along with other substances commonly excluded such as plasma proteins.

**Increased hydrostatic pressure.** Increased intravascular hydrostatic pressure (hypertension) upsets the balance in favor of fluid redistribution to interstitial and transcellular compartments. On the arterial end, generalized (systemic) hypertension (high blood pressure) does not typically cause florid fluid redistribution and edema. Localized increases in blood pressure do occur, as in inflammation (slide 17). Here, increased pressure from the arterial end along with increased permeability of blood vessels accounts for two of the four cardinal signs of inflammation, redness and swelling. Increases in hydrostatic pressure on the venous side of the circulation (slide 18), on the other hand, can cause dramatic fluid redistribution. Take for instance the complex events in congestive heart failure. Here, the heart is not an effective pump and there is a back up or sludging of blood flow in the venous circulation. In right-sided congestive heart failure, these effects are generalized. Common manifestations include ascites, less commonly hydrothorax, and dependent edema of the limbs. In mainly left-sided heart failure, pulmonary edema and some degree of hydrothorax dominate the picture. There is also another complicating issue. In congestive heart failure there is commonly decreased renal perfusion that stimulates renin production and, hence, sodium retention. The sodium retention increases the interstitial colloidal osmotic pressure favoring further redistribution of fluid from the blood. Increased hydrostatic pressure with edema can also be localized. Obstruction of veins by thrombi and tourniquets are examples.

**Decreased intravascular colloidal osmotic pressure.** Decreased intravascular colloidal osmotic pressure is due exclusively to hypoproteinemia. A drop in the intravascular colloidal osmotic pressure alters the fluid dynamic in favor of fluid redistribution, often dramatic, to the interstitial or transcellular compartments (slide 19). Albumin (produced by the liver) is the plasma protein primarily responsible for maintaining intravascular colloidal osmotic pressure. Hypoproteinemia (hypalbuminemia) can be due to maldigestion/malnutrition/starvation, gastrointestinal parasitism, severe liver disease, or to loss of protein from the body in disease states. The primary portals of protein loss are from the intestinal tract in the form of chronic diarrhea and from the kidney (proteinuria). In Johnes disease, caused by Mycobacterium avium, subspecies paratuberculosis, there is inability to absorb protein from the intestine due to severe chronic inflammation of the bowel wall. Proteinuria is observed with diseases that result in leaky renal glomeruli (amyloidosis, lecture 10).

**Increased interstitial colloidal osmotic pressure** is neither a primary nor a dramatic cause of fluid redistribution but can contribute in some instances. As noted previously, at sites of inflammation there is increased vascular permeability with leakage of proteins into interstitial spaces that can increase the colloidal osmotic pressure within the tissue. Also as previously noted, the sodium retention that occurs in congestive heart failure can increase interstitial colloidal osmotic pressure.

**Decreased lymphatic drainage.** Blockage of lymphatic drainage contributes to edema by failing to drain away the slight excess of fluid that potentially would accumulate when all other forces remain in balance (slide 21). The flow of lymph can be blocked at the level of lymphatic vessels or can occur from total obliteration of lymph nodes that are situated along the
course of these vessels. Fluid accumulation in the interstitium because of lymphatic obstruction is sometimes referred to as **lymphedema**. Lymph vessels are very thin-walled and can be compressed at sites of inflammation and space occupying masses such as **abscesses** or cancerous lesions. Some cancers spread or **metastasize** via lymphatics and can occlude these vessels. Certain infectious agents or microorganisms have a tendency to reside within or spread along lymphatic vessels, inciting inflammation that can obstruct lymphatic drainage. Examples here include the mosquito-transmitted filarid nematodes *Wuchereria bancrofti* and *Brugia malayi* that reside in lymphatics; the causes of **elephantiasis** in some tropical areas of the world. Other examples include **sporotrichosis** (*Sporothrix schenckii*) in some species (horses, humans) and **epizootic lymphangitis** (*Histoplasma farciminosum*) in horses. Lymphedema can also be **congenital** due to failure of lymph vessels to develop properly and can be **iatrogenic** following extensive surgical removal of lymph nodes during radical mastectomy in women.

### Images of Fluid Accumulation (Slides 22 – 28)

- **Slide 22** – Ascites is the accumulation of fluid in the abdominal cavity. Another name given to this condition that you might hear is **hydroperitoneum**, the term peritoneum referring to the serosal lining of the abdomen. Redistribution of fluid into the abdomen causing ascites is a manifestation of right-sided congestive heart failure and can be seen with severe hypoproteinemia.
- **Slides 23** is a section of intestine. Here the submucosa (the layer between the outer smooth muscle and the inner mucosa) is greatly expanded and has a gelatinous appearance indicating edema.
- **Slide 24** is a pig with edema disease. In this disease, a toxin produced by certain strains of *Escherichia coli* causes vascular damage, increased vascular permeability, and fluid redistribution into the interstitial compartment. In this photo, there is edematous swelling of the snout and palpebrae (eyelids).
- **Slide 25** shows edema of the mesentery of the coiled or spiral colon. This can be seen with edema disease of pigs, *Clostridium difficile* infection in young pigs, and is a lesion that can be seen in some cases of coccidiosis (a protozoal parasite) in calves.
- **Slide 26** depicts pulmonary edema. Edematous lungs are heavy, wet, and frothy fluid may exude from the bronchi and trachea. Causes of pulmonary edema include left-sided heart failure.
- **Slide 27** shows edema of the rear limb in a cat. In this case, lymphatic vessels are obstructed by a basal cell carcinoma (a cancer arising from basal epithelial cells of the epidermis). The primary site of the carcinoma was the paw pad.
- **Slide 28** is a case of congenital lymphedema in a dog due to failure of lymphatic vessels to develop properly.

### Consequences of Edema (slides 29 and 30)

The greatest significance of abnormal fluid redistribution is not the accumulation of fluid itself but the underlying cause. There are two primary and significant exceptions, edema of the lungs (slide 29) and edema of the brain (slide 30). The primary function of the lung is to deliver oxygen-rich air to the alveoli where oxygen is exchanged for carbon dioxide by diffusion through the alveolar septae to the capillaries. In slide 29, normal well aerated lung is at the top.
At the bottom of the photo, alveoli are flooded with pink-staining proteinaceous edema fluid preventing exchange of gases. Edema of the brain with brain swelling is a very serious outcome following a variety of injuries. The brain is encased in a bony vault, the skull or calvarium, leaving very little room for brain swelling. When the brain swells (slide 30), pressures inside the calvarium increase, at times to the point where there is no further room for expansion and brain displacement may occur. The right photo in slide 30 illustrates brain displacement with herniation of the cerebellum through the foramen magnum.

HYPERVOLEMIA / OVERHYDRATION (Slide 31)

For the most part, overhydration (too much body water) is not a common problem and develops in only a few situations.

- The **syndrome of inappropriate antidiuretic hormone (ADH) hypersecretion (SIADH)** is a complex condition that can potentially result in **hypervolemia**. Previously in these notes, the function of ADH is to promote water resorption from the more distal component of the renal tubules (distal convoluted tubules and collecting ducts). ADH accomplishes this by stimulating the insertion of transmembrane water channels including aquaporins-2 & 3 into the cell membrane of tubular epithelial cells. As mentioned before, this process requires microtubules and also cyclic AMP and protein kinase A. The effect is to increase the absorption of water from the tubules but not solutes such as ions; the result being the excretion of hypertonic urine. Characteristic of this syndrome is **hyponatremia** (sodium blood levels < 135 mEq/L) due to expansion of the intravascular fluid compartment. Blood sodium levels < 105 mEq/L can be life threatening. Edema, redistribution of water to other compartments, is not a typical feature of SIADH. If fact, clinical signs and **morbidity** are related to the hyponatremia, not hypervolemia or fluid redistribution. In humans, there are a variety of causes but most cases are **idiopathic**. Recognized causes include brain injury, various conditions in the lung, a variety of drug interactions, and many others. In veterinary medicine, cases are rare and have occurred in dogs; most have been idiopathic but cases have been reported in dogs with concurrent **meningitis** and heartworm disease.
- **Iatrogenic** – Administration of fluids intravenously can result in hypervolemia if done too rapidly, when too much is administered, and/or when the kidneys are comprised and urine production is poor. A common manifestation of this is rapidly developing pulmonary edema.
- **Idiopathic / idiosyncratic water drinkers**. Some humans as well as animals for unknown reasons drink too much water (**polydipsia**). Some cases may be due to faulty regulation of thirst; the first case was described in a schizophrenic patient and much of the literature is devoted to polydipsia in psychiatric patients. Hyponatremia can be a complication.

HYPOVOLEMIA / DEHYDRATION (slides 32 – 36)

Hypovolemia and dehydration reflect too little total body water. The causes are varied. No matter what the cause, in dehydration there is inadequate fluid intake to match fluid loss. As long as the mechanisms stimulating thirst in the brain and other homeostatic
mechanisms to maintain fluid balance remain intact, the body is typically able to maintain total fluid volume but there are many instances in which dehydration can and does occur.

Causes of Hypovolemia

- **Insufficient water intake.** As mentioned previously, the basal urine output in adult horses is approximately 0.5/L/100kg/day. This is the minimum amount of water that must be ingested or dehydration can occur. The ambient temperature, physiological states such as pregnancy, and physical exertion all modify the daily needs for water. Diets high in salt (NaCl) can also increase the needs for water. Salt poisoning (Na⁺ toxicosis) is a neurological disorder (also term eosinophilic meningoencephalitis in pigs) in animals that is in reality due to water deprivation; animals on a high salt diet are at increased risk.

- **Increased loss due to kidney disease.** As we have seen so far, the kidney is one of the primary organs involved in fluid balance. Specific gravity of urine, the level of solutes in the urine, is a measure of the kidney’s ability to function properly and to conserve water through production of concentrated urine. Persistently low urine specific gravity can be one sign of kidney disease. One response to dehydration is increased water consumption (polydipsia). If the kidney, however, cannot concentrate urine to compensate for dehydration, a persistent cycle of polydipsia-polyuria occurs.

- **Vomiting and diarrhea.** Severe protracted vomiting and/or diarrhea can also result in significant water loss. Here there are additional concerns beside the loss of fluid. With vomiting, there are also losses of H⁺ that can result in alkalosis (covered in lecture 20); with diarrhea there are losses of ions such as Na⁺ and Cl⁻ that can complicate the situation.

- **Hyperhidrosis and hyperpnea.** Profuse sweating and rapid respiration can also increase loss of water from the body; if not replenished, dehydration will occur.

- **Drugs.** Here we are mainly dealing with diuretics, drugs that increase urine production.

- **Diabetes insipidus.** This disease can either be due to a deficiency of antidiuretic hormone (ADH) (pituitary dependent diabetes insipidus) or due to failure of the kidney to respond to ADH (nephrogenic diabetes insipidus). ADH is synthesize by neurons in the hypothalamus and stored in the pituitary gland for release when needed. Causes of pituitary dependent diabetes insipidus include diseases of the brain (space occupying masses, inflammation) that prevent the storage and release of ADH from the pituitary gland. There are multiple underlying causes of nephrogenic diabetes insipidus including polycystic kidney disease, renal amyloidosis, some medications especially lithium, and hereditary causes are recognized. One hereditary form is X-linked and due to a defective membrane receptor for ADH. The other rare form has simple autosomal recessive inheritance and is associated with a mutation in the aquaporin-2 gene. No matter the cause, the kidneys of patients with diabetes insipidus are unable to concentrate urine. One sees urine of persistently low specific gravity, polyuria-polydipsia, and dehydration if water consumption is inadequate.

- **Hypoadrenocorticism (Addison’s disease).** Addison’s disease is typically due to destruction of the adrenal cortex. The adrenal cortex produces two hormones,
cortisone (glucocorticoids) and aldosterone (mineralocorticoid). Addison’s disease is due primarily to a deficiency of aldosterone. Due to this deficiency, the renal tubules are unable to absorb and conserve sodium and water. Dehydration is a potential consequence due to production of dilute urine. Of even greater significance, however, is potentially life-threatening hyponatremia (low blood sodium).

Sequence of Events in Dehydration

1. There is initially a loss of interstitial fluid with redistribution to blood in order to maintain blood volume.
2. With further dehydration; there is a loss of intracellular fluid in a further attempt to maintain blood volume.
3. Eventually, these mechanisms fail if total body water is not replenished resulting in hyperviscosity of blood and a generalized hyperosmolar state.

The systemic effects are seen mainly on the cardiovascular system and brain. Due to hyperviscosity, the heart has difficulty pumping blood that sludges in blood vessels leading to decreased perfusion of vital organs. Along with decreased perfusion, the hyperosmolar state has direct consequences for the brain.

The Brain During Dehydration

The brain has mechanisms for protection against osmotic imbalances that are created during dehydration. Although other osmolytes contribute, hyperosmolarity is generally measured in the context of blood Na⁺. During hyperosmolarity that occurs with dehydration, there is hyponatremia.

- **Acute phase** of dehydration (1-2 days): During this acute phase, the brain attempts to correct the imbalance by elimination of ions. Since water flows passively along ionic gradients, fluid is also lost from the brain and the brain shrinks. Death may occur at this stage and the principal lesion that may be seen is hemorrhage due to tearing of blood vessels in the meninges.
- **Chronic phase** of dehydration (3+ days). Ionic balance in the brain is critical for normal neuronal activity. The brain attempts to restore a more normal ionic balance by production of organic osmolytes such as glutamine, glycine, phosphoinositol and others. These organic compounds offset the osmotic dysequilibrium allowing a more normal ionic balance to be restored in the brain. Death may also occur at this stage if the dehydration worsens.
- **The dangers of rehydration.** Once a chronic phase has been established, rehydration should be done with care. Rehydration, with either oral or especially with intravenous fluids, should be done carefully. With rehydration, the fluid volume in the intravascular compartment is rapidly replenished and blood osmolarity begins to return to normal. It takes time, however, for the brain to eliminate the organic osmolytes. If rehydration occurs too fast, a gradient is established between the hyperosmolar state of the brain and the falling osmolarity of the blood. As a result, fluid moves from the blood into the brain.
along the ionic gradient resulting in brain swelling that can result in serious brain damage and death.