APPENDIX 2

Body Water Compartments

The most abundant compound in the human body is water, accounting for 40% to 80% of the body weight depending upon the amount of adipose tissue present. The body contains the highest proportion of water at infancy, up to 80%, and then the water content decreases as old age is approached. The average water content of an adult male is 60% of the body weight whereas the average water content of an adult female is 50% of the body weight. This difference is due to the content of subcutaneous fat.

The total body water can be categorized as existing in two main compartments: intracellular water and extracellular water. The intracellular water consists of all the water within the cells and constitutes over half of the total body water. Since red blood cells are surrounded by plasma, and all other cells are surrounded by interstitial fluid, the intracellular compartment has been sub-divided to represent these two cell types in figure 1. The extracellular water, which includes all of the fluid outside of the cells, can be further sub-divided into compartments which represent interstitial fluid, circulating blood plasma, lymph, and transcellular water. The interstitial fluid surrounds cells outside of the vascular system whereas plasma is contained within the blood vessels. Avascular tissues such as dense connective tissue and cartilage contain interstitial water which slowly equilibrates with tracers used to determine extracellular fluid volume. For this reason, additional compartments are sometimes used to represent these avascular tissues. Lymph is interstitial fluid which has flowed into the lymphatic vessels and is eventually returned to the vascular system. A small fraction of the extracellular fluid is separated from other extracellular compartments by a layer of epithelium. This compartment, which includes cerebrospinal fluid, aqueous and vitreous humor, synovial fluid, and fluid secretions of glands, makes up the transcellular compartment. These body water compartments, and the interactions between them, are shown in figure 1. The average size of each compartment, in terms of percent body weight, has been determined for adult males and females (West, 1985) and is included in this figure. The lymph compartment, which is often included in the interstitial compartment, has been determined to be approximately 2.0% of the body weight (Pitts, 1974). The size of the lymph compartment for females was determined by multiplying 2.0% by 5/6 (recall that the average female body is 50% water and the average male body is 60% water).

Cerebrospinal fluid and aqueous humor, which make up a part of the transcellular compartment, are formed by epithelial cells secreting sodium ions into the associated chamber (Guyton, Taylor, & Granger, 1975). The secretion of positively charged sodium ions creates a potential difference, with respect to the blood, thereby causing negatively charged ions to flow from the plasma, into the epithelial cells, and eventually into the chambers. The excess ions then cause water to flow across the epithelial membranes by osmosis. Therefore, water flows from the intracellular fluid of the epithelial cells into the chambers by osmosis. Since osmosis is also the primary force for the flow of water between the cellular compartment and the interstitial compartment, and since

the transcellular compartment accounts for less than 2% of the body weight, this compartment has been lumped together with the interstitial compartment in figure 1.

Osmosis

Osmosis refers to the movement of solvent across a semipermeable membrane which is permeable to solvent but not to solutes. A cell membrane, which is freely permeable to water but not to most solutes, is an example of such a semipermeable membrane. Osmosis is similar to diffusion in that a concentration gradient is the driving force behind the movement of molecules, however, diffusion refers to the movement of solute molecules whereas osmosis refers to the movement of solvent molecules. Additionally, osmosis and diffusion occur in opposite directions since when the concentration of solute molecules is high, the concentration of water must be low. The process of osmosis is illustrated in figure 2, where the small spheres represent water molecules and the large spheres represent solute molecules. The two solutions on each side of the semipermeable membrane initially have different solute concentrations (step 1). The solvent molecules, in this case water, begin crossing the membrane from the side with the lower solute concentration to the side with the higher solute concentration. This process continues until the concentration solute is the same on both sides (step 2a). The larger the solute concentration difference on each side, the stronger the driving force, or osmotic force, for water movement. This osmotic force is sometimes called the osmotic pressure. If a downward pressure is applied to side b (step 2b), the movement of water across the membrane can be eliminated and this downward pressure is equal to the osmotic pressure.

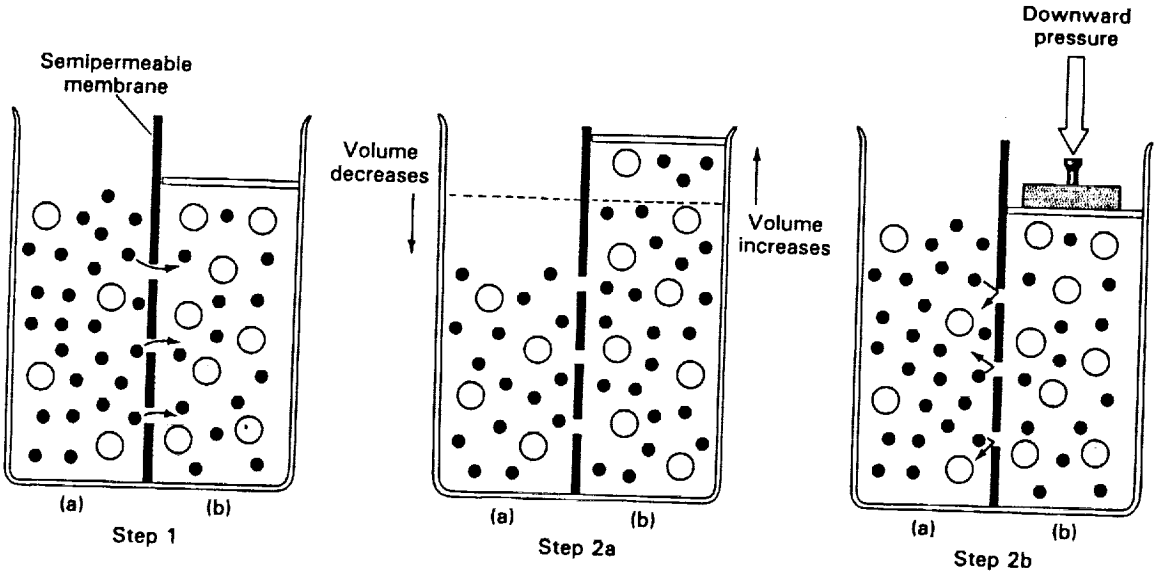

Figure 2: An example of osmosis where the small spheres represent water molecules and the large spheres represent solute molecules. (taken from Martini, 1989)

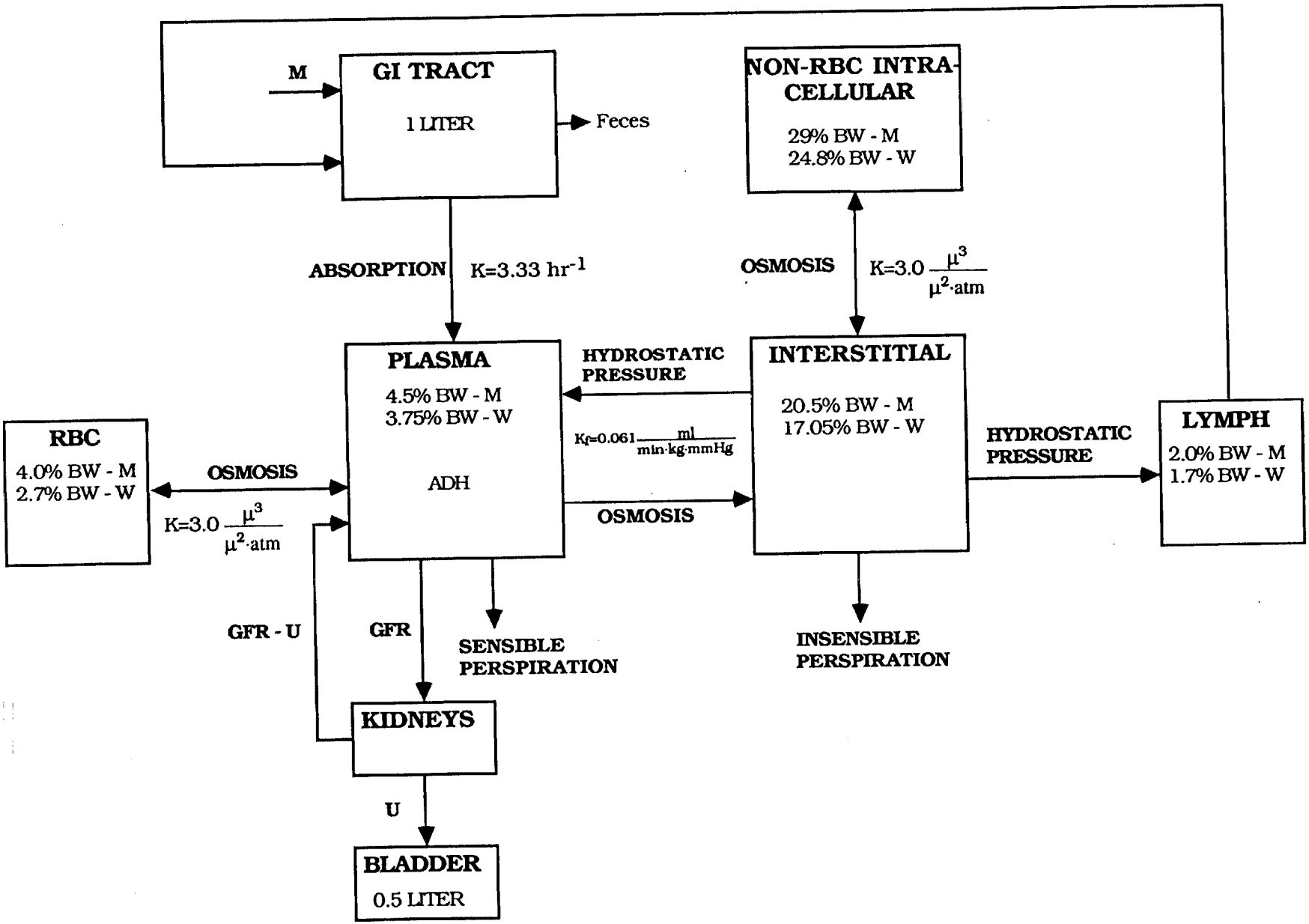

Figure 1: Body water compartments and the forces which cause flow between them. Mass transfer coefficients are represented by K. The size of each compartment is shown for both males and females where BW = body weight, M = male, & F = female.

Interactions between Body Water Compartments

Water enters the body through the digestive tract and moves across the mucosa of the small and large intestines in response to osmotic gradients (Ganong, 1991). Previous studies have estimated that water is absorbed from the gastrointestinal tract (GI tract) at a constant rate with a zeroth order rate constant of 3.3 hr^{-1} (Reeve & Guyton, 1967). The volume of the stomach, which is given in figure 1, is about one liter (Hole, 1987). Water is also produced by the intracellular metabolism of nutrients. The movement of water between the fluid compartments is controlled by hydrostatic pressure, osmotic pressure, or both.

Fluid movement between the extracellular and intracellular compartments is built on three main points: (1) that water can easily move between the two compartments; (2) that most of the solutes on each side of the cell membrane will not penetrate the membrane easily; and (3) that hydrostatic pressure differences do not play a major role in the final fluid distribution (Coleman, Norman, & Manning *in* Guyton, Taylor, & Granger, 1975). In other words, water will cross the cell membrane until osmotic equilibrium has been attained between the two compartments. Hydrostatic pressures are not a major factor in this osmotic equilibrium since the cell wall is extremely flexible and marked volume changes do not produce significant intracellular hydrostatic pressure (Coleman, Norman, & Manning *in* Guyton, Taylor, & Granger, 1975).

To determine the rate at which water penetrates the cells, the cell membrane permeability and surface area must be known. The hydraulic permeability of the human cell membrane to water is approximately 3.0 μ^3 water/μ^2·atm (West, 1985). The surface area of the red blood cell compartment, which is in osmotic equilibrium with the plasma compartment, can be calculated from the blood volume, hematocrit (Hct), red blood cell volume, and red blood cell surface area. The blood volume can be calculated with the following equation.

$$\text{Blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hct}} \qquad (1)$$

The average normal hematocrit is 0.47 for men and 0.42 for women (Ganong, 1991). The volume and surface area of a normal red blood cell are 9.7×10^{-8} µl and 135 μm^2, respectively (West, 1985). The surface area of the non-red blood cell compartment, which is in osmotic equilibrium with the interstitial fluid, can be calculated from the average cell size and the volume of the non-red blood cell compartment. The average cell is roughly cubic with dimensions of 10µm x 10µm x 10µm (Martini, 1989).

The exchange of fluid between the plasma and interstitial compartments can be described by what are called Starling forces. This exchange occurs

across the capillary walls and is responsible for supplying cells with oxygen and nutrients while removing cellular wastes. Capillary hydrostatic pressure and interstitial osmotic pressure forces fluid out of the capillaries and into the interstitial spaces. Conversely, the interstitial hydrostatic pressure and the plasma osmotic pressure force fluid back into the capillaries. The composition of the plasma is almost identical to that of the interstitial fluid with the exception of the protein content. Most of the relatively large protein molecules cannot penetrate the capillary wall, therefore, the protein content is substantially higher in the plasma and causes the osmotic effects. The protein osmotic pressure is sometimes referred to as the oncotic pressure. Typically the plasma hydrostatic pressure declines from about 37 mm Hg to 17 mm Hg along the length of the capillary whereas the oncotic pressure and interstitial hydrostatic pressure remain relatively constant at 25 mm Hg and 1 mm Hg, respectively. Consequently, fluid is forced out of the arteriole end of the capillary and fluid is forced into the venous end of the capillary. This situation is shown in figure 3.

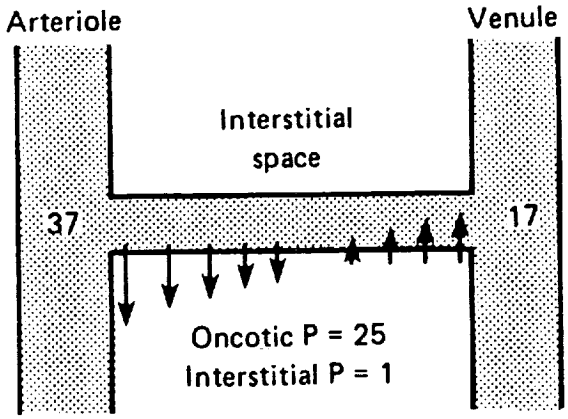

Figure 3: Representation of pressure gradients across the wall of a muscle capillary. The arrows indicate the approximate magnitude and direction of fluid movement. (taken from Ganong, 1991)

Fluid movement is related to the Starling forces through the following expression.

$$\text{Fluid movement} = K_f[(P_C+\pi_i) - (P_i+\pi_C)] \quad (2)$$

where K_f = capillary filtration coefficient
P_C = capillary hydrostatic pressure
P_i = interstitial hydrostatic pressure
π_C = capillary oncotic pressure
π_i = interstitial oncotic pressure

For the entire body, K_f has been found to be approximately 0.061 ml fluid/min·kg body weight·mm Hg (Landis & Pappenheiner, 1963).

During a 24 hour period, about 2 liters more fluid is filtered across the capillary walls than is reabsorbed (Little, 1989). This fluid then flows into the lymphatic system due to a hydrostatic pressure difference. However, since the flow rate of this interstitial fluid and the distance to a lymphatic capillary is extremely small, the pressure gradient between the interstitial spaces and lymphatic capillary is too slight to be measurable (Guyton, Taylor, & Granger, 1975). A primary characteristic of the lymphatic system is that under normal conditions any excess fluid that collects in the tissues is returned back to the circulation (Guyton, 1984). Previous studies have found that the rate of lymph flow can increase up to 20 times the resting level (Guyton, Taylor, & Granger, 1975). This phenomena is mainly due to the structure of the lymphatic capillaries. Endothelial cells of the lymphatic vessels overlap to form pores (see figure 4). As the interstitial space fills with liquid, the tissue swells and the endothelial cells are pulled apart causing the pores to open wider. Therefore, the greater the tissue pressure, the greater the lymph formation rate. The overlapping edges of the endothelial cells also prevent fluid from flowing out of the lymphatic capillary so any compressive force will cause lymph to flow forward through the vessel (Guyton, 1984).

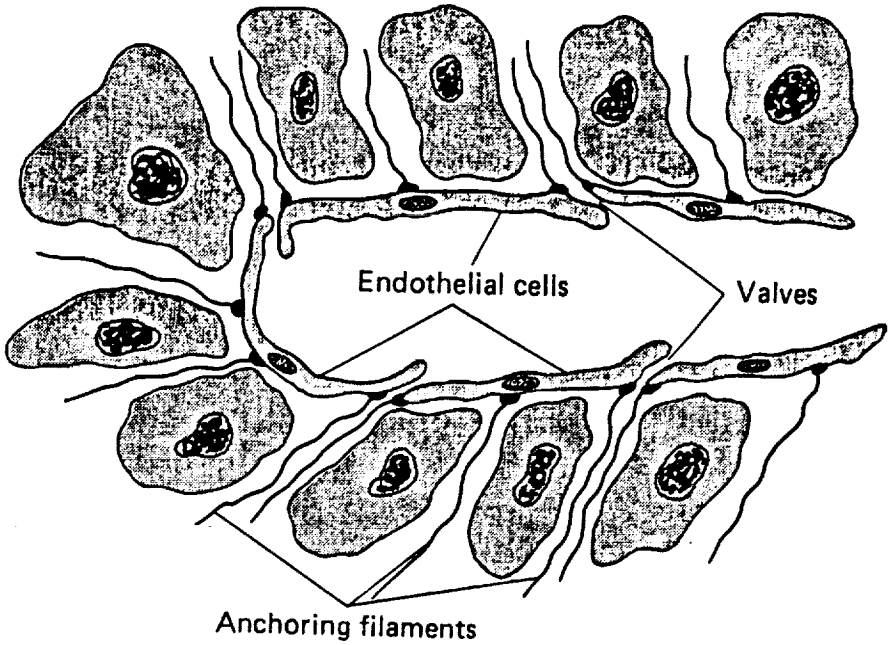

Figure 4: Structure of the lymphatic capillaries which allows for the variable, one directional flow of lymph. (taken from Guyton, 1984)

For the above stated reasons, it is assumed that the lymph flow rate is equal to the net formation of interstitial fluid in figure 1. Figure 5 illustrates the effect of capillary pressure on interstitial fluid pressure, interstitial fluid volume, and lymph flow. From figure 5, it can be seen that the interstitial fluid volume remains relatively constant as the capillary pressure and interstitial pressure are increased until edema, which is an accumulation of fluid in the tissue spaces, occurs. Over this range of capillary pressures, the lymph flow

increases 15 to 20 times normal. Therefore, the lymphatic regulatory system which prevents the buildup of interstitial fluid performs close to its maximum level before edema occurs. Once edema results, the lymphatic system continues to operate at the maximum level thereby alleviating the swelling as quickly as possible.

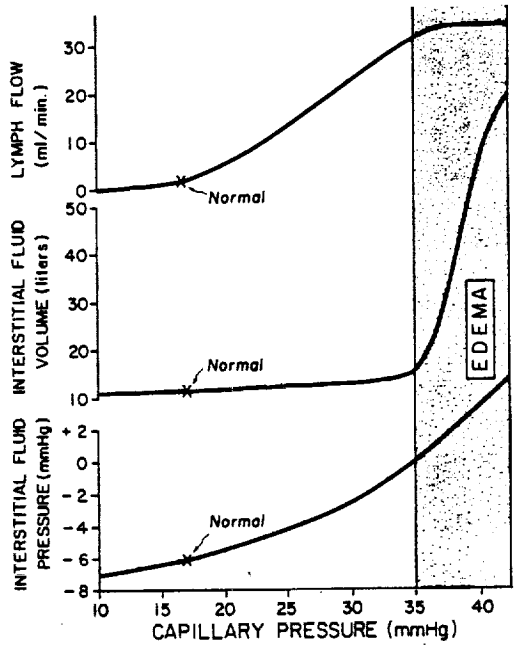

Figure 5: Computed effects of progressive increase in capillary pressure on interstitial fluid pressure, interstitial fluid volume, and lymph flow. (taken from Guyton, Taylor, and Granger, 1975)

Regulation of Body Water

Water can enter the body as a liquid, with moist food, and as the result of intracellular oxidative metabolism of various nutrients. The primary regulator of water intake is thirst, and although the thirst mechanism is poorly understood, it seems to involve the osmotic pressure of extracellular fluid and a thirst center in the hypothalamus (Hole, 1987).

Water is lost from the body through four routes: sensible perspiration, insensible perspiration, urine, and feces. Water lost by sensible perspiration, or sweating, is a necessary part of the body's temperature control mechanism; water loss in feces accompanies the elimination of undigested food materials; and water losses through diffusion and evaporation (i.e. insensible perspiration) are largely unavoidable (Hole, 1987). Consequently, the only significant route of water loss which can be regulated is the formation of urine. The urine volume, which can vary from less than 1 liter/day to more than 20 liters/day, is determined primarily by the blood pressure and the plasma level of antidiuretic hormone (ADH) (West, 1985). ADH is secreted from the posterior pituitary

gland and the secretion rate is controlled by a center located in the hypothalamus.

The osmolality of the body fluids is regulated by thirst and the renal excretion rate of electolytes. Ingesting hypotonic liquids will dilute the extracellular water compartment and therefore reduce plasma osmolality. ADH and another hormone, aldosterone, regulate the urinary loss of sodium and potassium.

The thirst center and the ADH secretion rate are stimulated mainly by two physiological conditions, increases in plasma osmolality and decreases in plasma volume (West, 1985). Changes in plasma osmolality are sensed by nerve cells called osmoreceptors located in the hypothalamus. It is believed that the osmoreceptors become reduced in volume by osmotic dehydration when plasma osmolality is elevated, which triggers thirst and ADH release (Cowley *in* Guyton, Taylor, & Grange, 1975). Changes in plasma volume are sensed by stretch receptors located in the heart and blood vessels and by the juxtaglomerular apparatus of the kidney. The stretch receptors are stimulated by distention and their afferent nerve fibers pass via the glossopharyngeal and vagus nerves to the medulla (Ganong, 1991). The juxtaglomerular apparatus secretes an enzyme, renin, in response to a decreased blood volume or decreased blood pressure. Renin converts a circulating blood protein which is produced by the liver, angiotensinogen, to angiotensin I. Angiotensin I is then converted in the lungs to angiotensin II. The actions of angiotensin II include vasoconstriction, which elevates the blood pressure, increased secretion rates of aldosterone and ADH, and stimulation of the thirst center. A change in plasma osmolality of 1% doubles the plasma level of ADH, and the thirst center is stimulated when the plasma osmolality changes 1 to 2%, whereas the change in blood volume necessary to cause these responses is on the order of 10 to 15% (Cowley *in* Guyton, Taylor, and Granger, 1975). However, if the osmoreceptors and volume receptors provide conflicting information, for example a low blood volume with a low osmolality, the volume regulating mechanism will be the only observed mechanism. In other words, volume overrides tonicity. Since the stretch receptors adapt to abnormal blood volumes over a period of several days, and the osmoreceptors do not adapt to abnormal plasma osmolalities (Cowley *in* Guyton, Taylor, and Granger, 1975), the volume regulating mechanism is valid only when considering short term regulation. The osmolality mechanism will be valid for both short term and long term body water regulation. The effect of plasma osmolality and volume on the circulating levels of ADH are shown in figure 6. The relationship between the intensity of thirst and the plasma osmolality is shown in figure 7.

An increase in arterial pressure increases the amount of fluid the kidneys withdraw from the vascular compartment and hence increases the urine flow rate. The relationship between renal arterial pressure and urine production is shown in figure 14 and will be discussed in the following section.

Description of the kidney

The urinary system includes the kidneys, ureters, bladder, and urethra. The function of this system is to maintain homeostasis of the body fluids by adjusting the composition of circulating blood. The kidneys receive about 25%

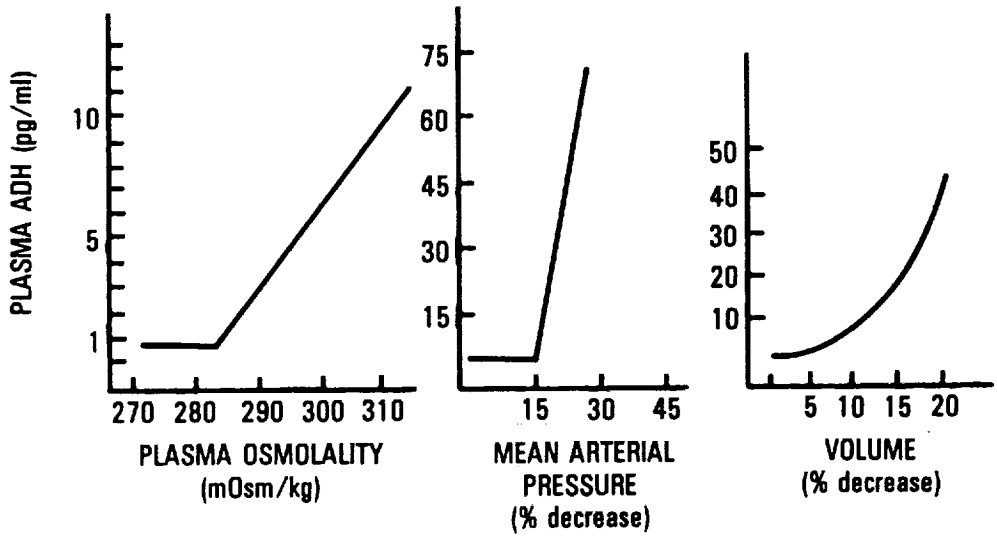

Figure 6: Control of plasma ADH concentration by osmolality, mean arterial pressure, and circulatory volume. (taken from West, 1985)

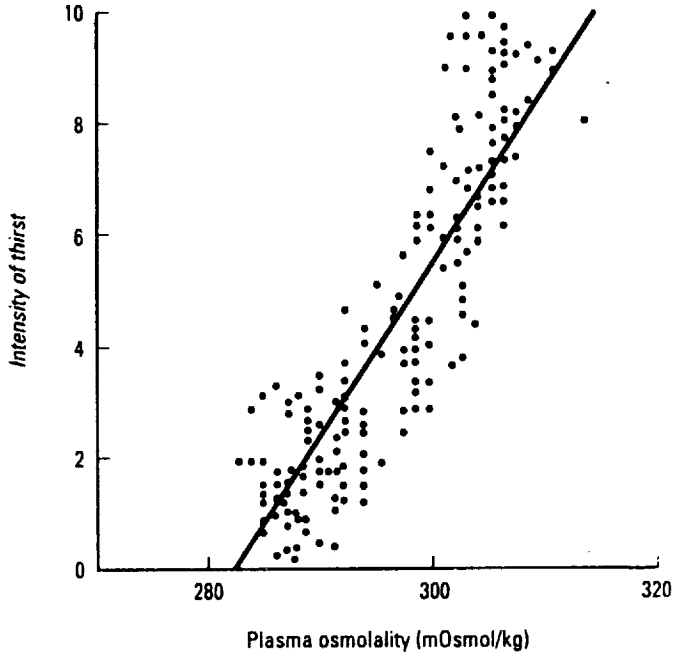

Figure 7: Relation of plasma osmolality to thirst in healthy adult humans during infusion of hypertonic saline. The intensity of thirst is measured on a special analog scale. (taken from Ganong, 1991)

of the cardiac output and filters out a fluid similar to plasma. The composition of this filtered fluid changes as it flows through the kidney tubules since compounds are continually being secreted and reabsorbed. Ultimately, the plasma-like fluid becomes urine. Through this mechanism, the kidneys eliminate wastes while conserving body water, electrolytes, and metabolites.

The kidneys are shaped similar to lima beans and weigh about 300 grams apiece. The internal structure of the kidney can be divided into two parts, an outer portion called the cortex and an inner portion called the medulla (see figure 8). The medulla of each kidney contains 6-18 conical renal pyramids, whose tips, or papillae, are each surrounded by a minor calyx (Martini, 1989). Several minor calyces combine to form a major calyx and the major calyces join within the renal pelvis which is connected to a ureter.

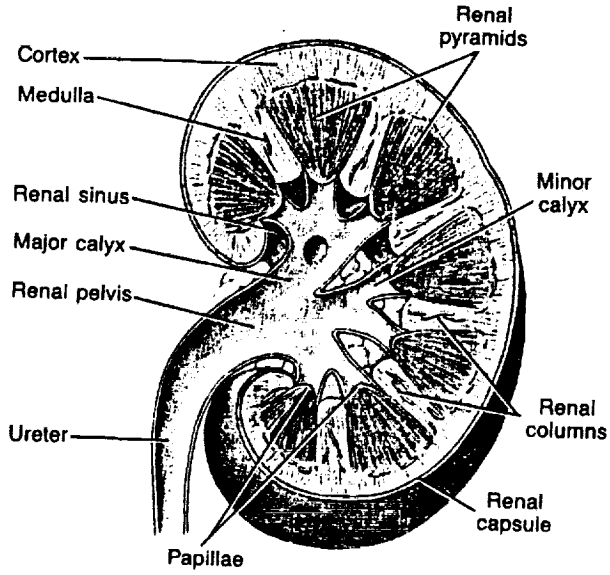

Figure 8: Gross anatomy of the right kidney, in sectional view. (taken from Martini, 1989)

The nephron is the functional unit of the kidney and consists of a renal tubule and an expanded end or Bowman's capsule (see figure 9). Each human kidney contains about 1.3 million nephrons. The Bowman's capsule surrounds a capillary bed, the glomerulus, which receives blood through an afferent arteriole and discharges blood, less some filtrate, through an efferent arteriole. Fluid must penetrate three layers, the fenestrated capillary endothelium, the basement membrane which surrounds the capillary wall, and the glomeular epithelium, before it can enter the capsular space (see figure 10). The structure of these membranes allow water and other small molecules to cross easily but restricts the passage of larger molecules such as plasma proteins. The forces which control the filtration of plasma fluid into the Bowman's capsule include the capillary hydrostatic pressure and capsular oncotic pressure, which force

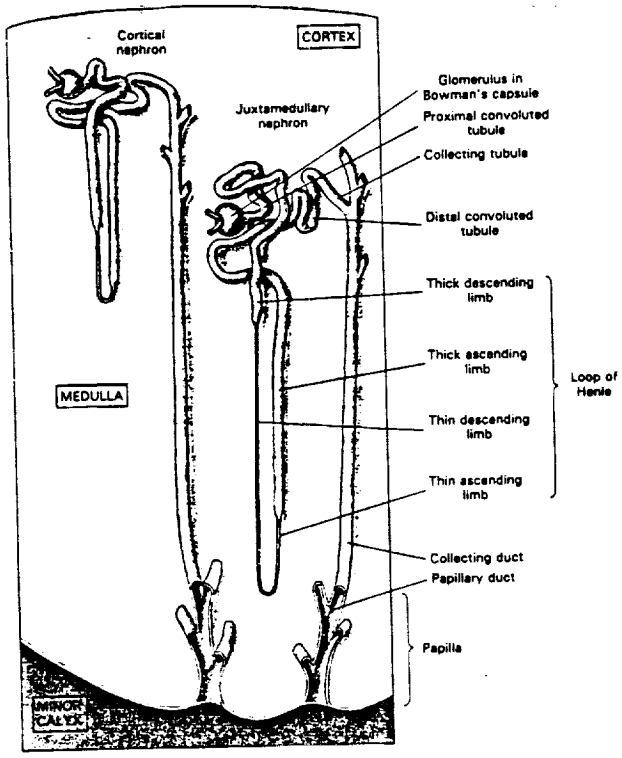

Figure 9: The functional nephron. (taken from Martini, 1989)

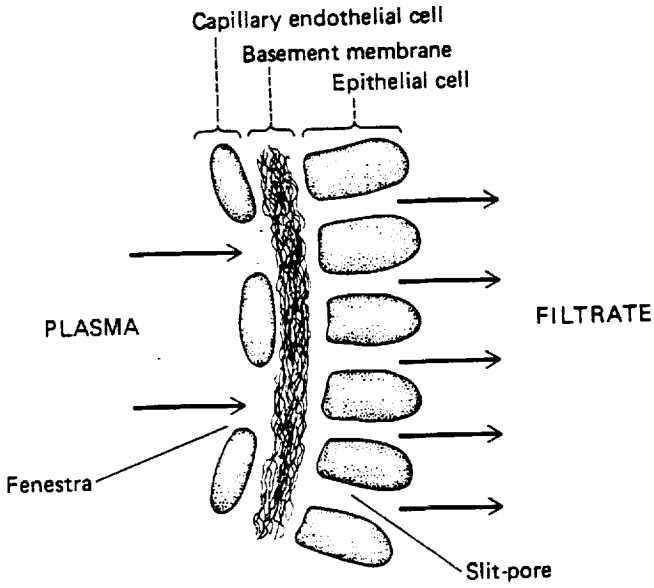

Figure 10: Functional structure of the glomerular membrane. (taken from Guyton, 1984)

fluid into the capsular space, and the plasma oncotic pressure and capsular hydrostatic pressure, which force fluid into the capillaries. The renal capillary pressure is normally 60 mm Hg, whereas the colloid pressure in the glomerulus is normally 32 mm Hg (Guyton, 1984). The pressure in Bowman's capsule is about 18 mm Hg, and the colliod osmotic pressure is in the capsule is essentially zero (Guyton, 1984). The capillary hydrostatic pressure may be varied considerable by the constriction of the afferent or efferent arterioles. The rate at which filtrate enters the capsule is called the glomerular filtration rate (GFR). Typically, 180 liters of fluid enter the renal tubules each day although only about one liter of urine is produced due to the secretion and reabsorption processes which occur along the length of the nephron.

The glomerular filtrate passes from the capsular space into the proximal convoluted tubule due to a hydrostatic pressure gradient. Simple cuboidal epithelial cells with microvilli line this portion of the nephron. The function of the proximal tubule is to actively reabsorb electrolytes and nutrients from the filtered fluid. As these solutes are absorbed, water flows into the epithelial cells and eventually into the interstitial fluid by osmosis. Consequently, the tubular fluid remains isotonic with respect to plasma as it travels through the proximal tubule. By the time the tubular fluid reaches the next segment of the nephron, the loop of Henle, 60 - 70% of the filtered solute and water have been removed (Ganong, 1991).

From figure 9, it can be seen that the loop of Henle consists of a descending limb and an ascending limb, each of which have thin and thick segments. The length of the loop Henle depends upon the location of the nephron within the kidney. Nephrons in the outer portions of the kidney, or cortical nephrons, have short loops whereas nephrons closer to the medulla, or juxtamedullary nephrons, have longer loops. For the juxtamedullary nephrons, a concentration gradient exists within the interstitial fluid along the length of the loop of Henle. The variation of osmolality within the medulla is shown in figure 11.

The descending limb of Henle, which is composed mainly of the thin segment, is freely permeable to water and relatively impermeable to ions (Martini, 1989). Since the osmolality of the interstitial fluid increases with depth into the medulla, water is reabsorbed from this segment by osmosis. The ascending thin limb of Henle is impermeable to water and permeable to sodium. The ascending thick limb is also impermeable to water and actively reabsorbs sodium. Since the rate of active transport is proportional to the concentration, more sodium is reabsorbed in the deeper portion of the ascending limb than in the superficial portion of the ascending limb. This active transport aids in maintaining the osmotic gradient within the medullary interstitial fluid. By the time the tubular fluid reaches the next portion of the nephron, the distal convoluted tubule, the osmolality has fallen to 100 mosm.

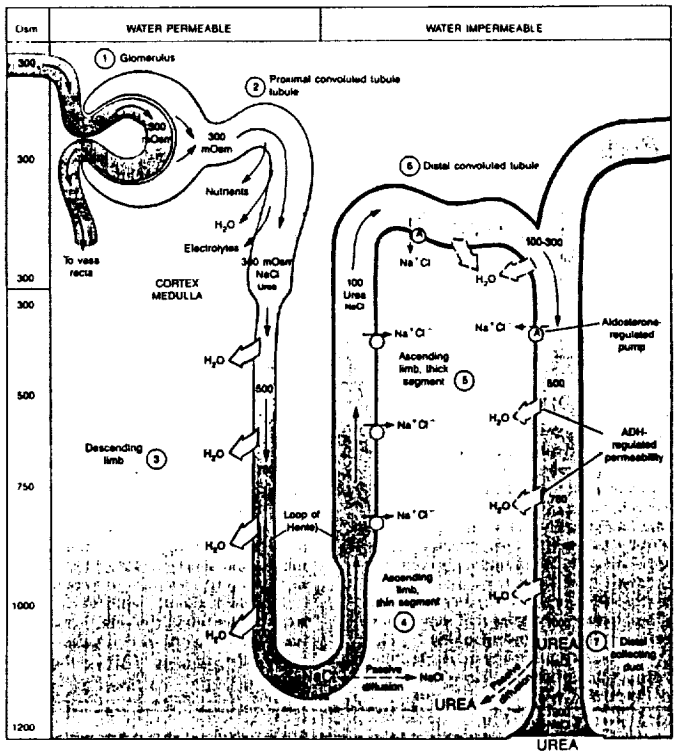

Figure 11: An overview of kidney function. (taken from Martini, 1989)

Near the portion of the nephron where the afferent and efferent arterioles permeate the Bowman's capsule, the ascending limb of Henle ends and forms a tight bend that places a portion of the distal tubule in direct contact with the arterioles (see figure 12). The cells of the distal tubule which contact the arterioles are known as the macula densa, and the associated smooth muscle cells in the wall of the afferent arteriole are called the juxtaglomerular cells. Together, the macula densa and the juxtaglomerular cells make up the juxtaglomerular apparatus, a secretory complex which releases renin and erythropoietin in response to a lowered blood pressure. Renin converts circulating angiotensinogen to angiotensin I which is converted to angiotensin II, a powerful vasoconstrictor, in the lung capillaries. Angiotension II also increases the secretion rates of ADH and aldosterone. The renin-angiotensin system is shown in figure 13. Erythropoietin stimulates the formation of red blood cells in the bone marrow and therefore maintains or in some cases increases the oxygen carrying capacity of the blood.

The distal convoluted tubule, collecting tubule, and collecting duct are essentially impermeable to water unless ADH is present in the body fluids. ADH in the interstitial kidney fluid binds to receptors located in the basal membranes of cells in these portions of the nephron (see figure 14). This coupling of receptor and ADH activates adenyl cyclase, an enzyme associated with the cell membrane, which catalyzes the production of cyclic adenosine monophosphate (cyclic AMP) (Sullivan, 1982). It is the increased cyclic AMP concentration within the cell that increases the permeability of the apical membrane, however, the mechanism by which the permeability changes is not well established. In high concentrations, ADH increases the amount of water absorbed in these nephron segments, thereby causing the formation of a

concentrated urine. Conversely, in the absence of ADH, large amounts of a dilute urine will be formed.

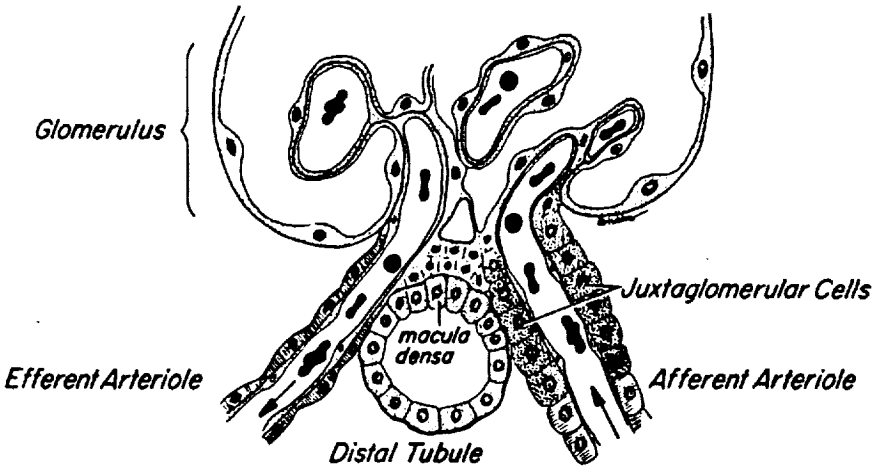

Figure 12: The juxtaglomerular apparatus. (taken from Brown & Stubbs, 1983)

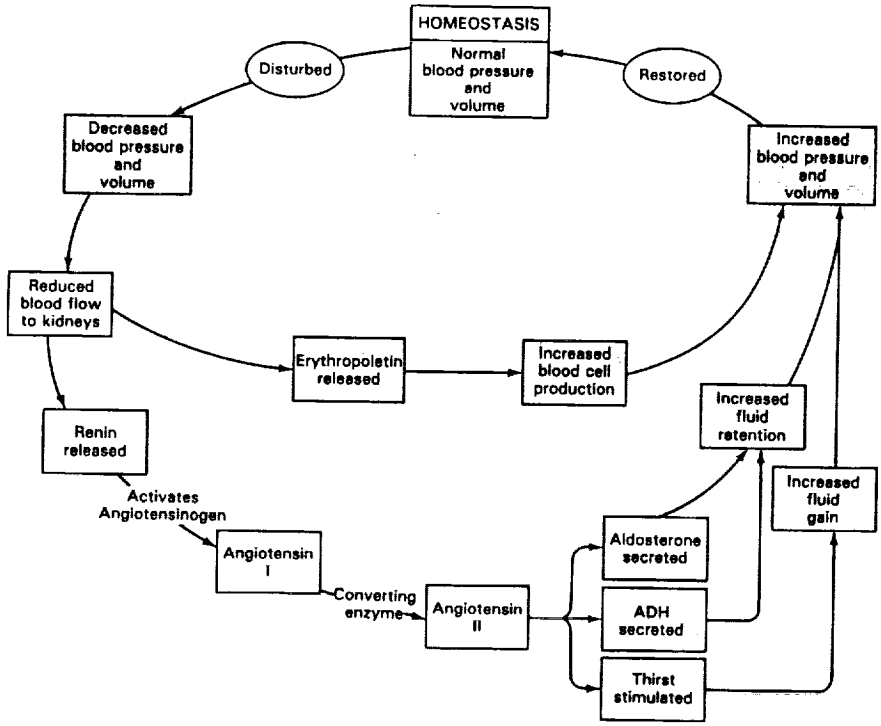

Figure 13: The renin-angiotensin system. (taken from Martini, 1989)

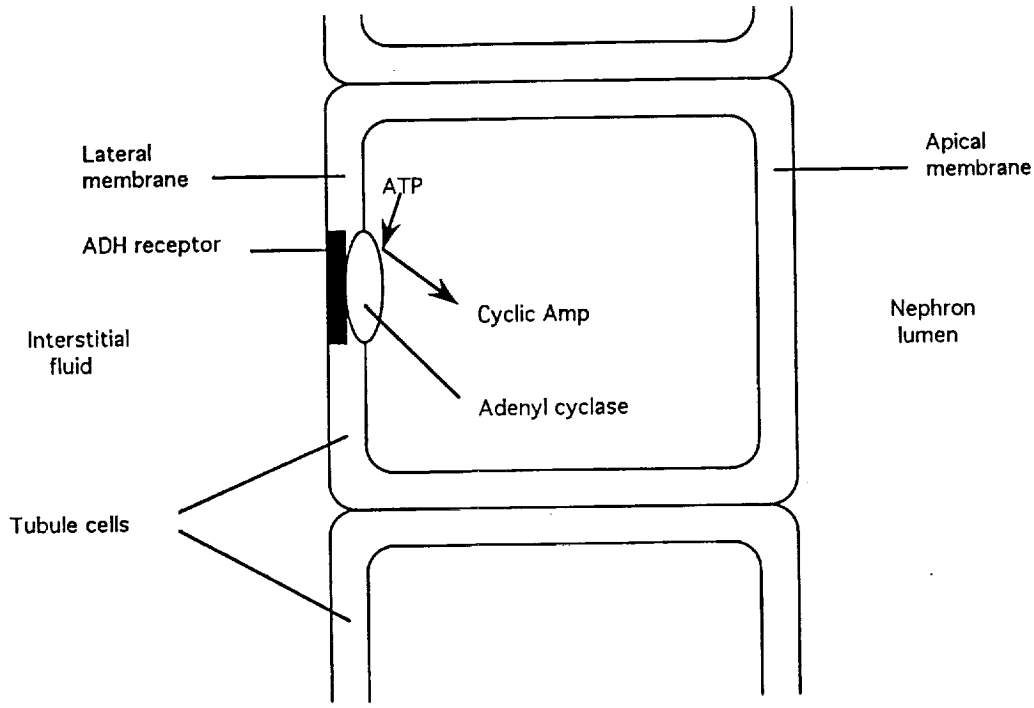

Figure 14: The binding of ADH to cells of the distal tubule and collecting duct.

The reabsorption of sodium from the tubular fluid within the distal convoluted tubule, collecting tubule, and collecting duct is controlled by the hormone aldosterone, which is secreted from the adrenal gland when plasma levels of angiotensin II or potassium are elevated. Aldosterone stimulates ion pumps in these portions of the nephron, which then exchange sodium ions for potassium ions. Therefore, aldosterone increases the urinary loss of potassium while reducing this loss of sodium.

Sodium accounts for over 90% of the cations in the extracellular fluid (Guyton, 1984). Due to electroneutrality of the extracellular fluid, the amount of cations automatically controls the number of anions present, so by regulating the concentration of sodium, over 90% of the ions are also controlled. Since the ions account for most of the dissolved species in the bodily fluids, the concentration of sodium is directly related to the fluid osmolality. Therefore, in terms of regulating the body fluid compartments, the renal handling of water and sodium will be the most important factors to consider when modeling kidney function.

In regulating the body fluid compartments, volume is controlled primarily by the arterial pressure, sodium concentration primarily by anti-diuretic hormone, and potassium levels primarily by aldosterone (Guyton & Young *in* Guyton, Taylor, and Granger, 1975). Increasing the arterial pressure slightly increases renal blood flow and the glomerular filtration rate, however, the urine flow rate can be greatly increased. Furthermore, urine production may cease altogether if the arterial pressure falls below 60 mm Hg. The variation of renal

blood flow, GFR, and urine flow is shown as a function of arterial pressure in figure 15. Therefore, a depleted blood volume, which causes a drop in blood pressure, will decrease urine flow and tend to alleviate the problem. Alternatively, an expanded blood volume, which causes an elevated blood pressure, will increase the urine flow rate thereby decreasing the blood volume.

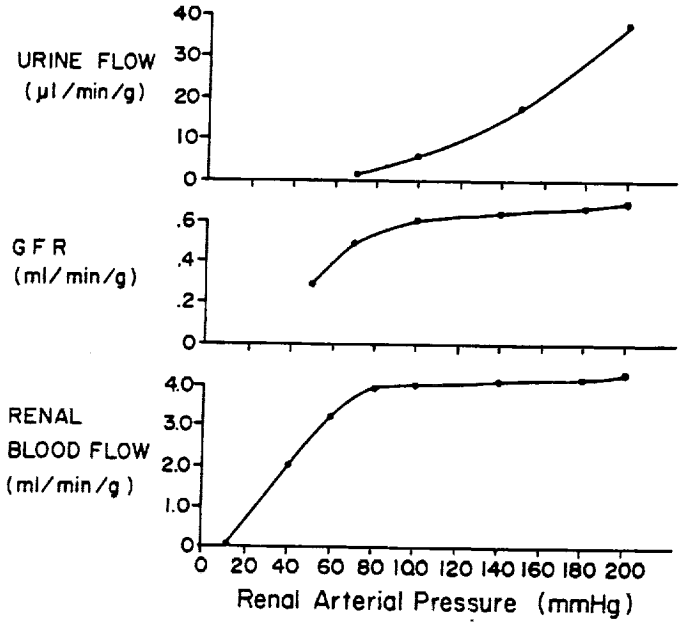

Figure 15: Effect of acute changes in arterial pressure on the important hemodynamic variables of renal function that relate to renal volume excretion. (taken from Navar & Guyton *in* Guyton, Taylor, & Granger, 1975)

The secretion rate of ADH and the thirst center response are strongly related to the plasma osmolality. A change in plasma osmolality of 1% doubles the plasma level of ADH and the thirst center is stimulated when the plasma osmolality changes 1 to 2% (Cowley *in* Guyton, Taylor, and Granger, 1975). An elevated plasma level of ADH is usually believed to increase the blood volume by reducing the urinary water loss and increasing the amount of water ingested. Increasing the plasma ADH level initially will increase in the blood volume but only to a small extent because of the associated increase in arterial pressure and urine flow rate (see figure 15) and the urine which is formed, will have a high solute to water ratio. Consequently, persistently high levels of ADH will cause a slight increase in the blood volume but will also decrease the plasma osmolality due to a high flow rate of concentrated urine. Since sodium is responsible for about 95% of the plasma osmolality, ADH primarily affects the sodium concentration of the extracellular fluid.

Aldosterone causes cells in the later portion of the nephron to absorb sodium from the tubular fluid with the simultaneous secretion of potassium. It would therefore be expected that aldosterone would control the sodium and

potassium levels in the extracellular fluid. However, previous studies have found that aldosterone plays about ten times as much role in the control of potassium concentration as in the control of sodium ion concentration (Guyton & Young *in* Guyton, Taylor, and Granger, 1975). The reason for this is that the ADH-thirst mechanism is a very potent mechanism for control of sodium ion concentration, so potent that the aldosterone mechanism, in competing with this more potent mechanism, is indeed a very poor competitor (Guyton & Young *in* Guyton, Taylor, and Granger, 1975).

Modeling Kidney Function

Since sodium accounts for over 90% of the cations in the extracellular fluid, and the number of cations is balanced by the number of anions, considering the renal handling sodium and water only should sufficiently describe the relationship between the plasma compartment and kidneys. The following model has been adapted from a previous model of normal renal function in man (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

Cardiovascular system

The cardiovascular system consists of a pump, the heart, an assortment of conducting channels, the vessels, and a flowing fluid, the blood. These components are illustrated in figure 16. Arteries carry blood away from the heart and veins return blood to the heart. The blood vessels, which make up the circulatory system, can be sub-divided into to parts. Pulmonary vessels bring blood to and from the lungs whereas systemic vessels service the rest of the body.

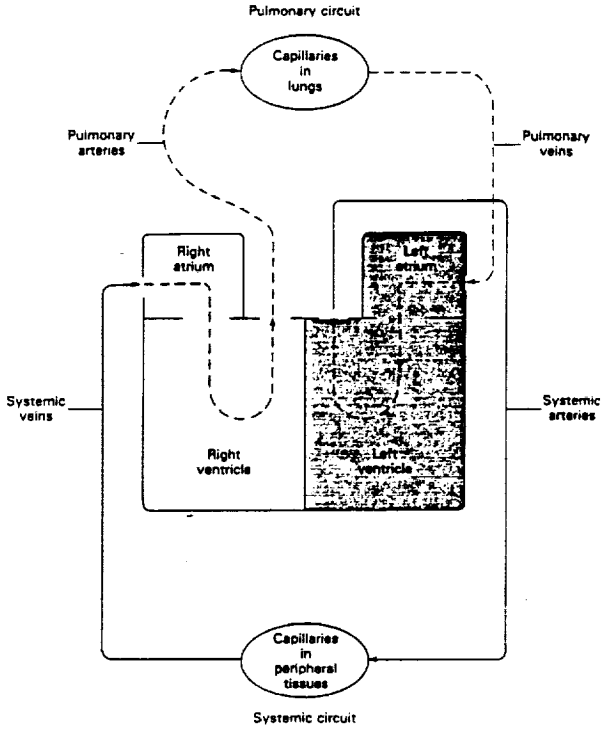

Figure 16: The cardiovasular system. (taken from Martini, 1989)

Blood pressure, which affects the glomerular filtration rate, is directly related to the blood volume. An increased blood volume increases the cardiac output and consequently the blood pressure. Additionally, an increased blood volume stretches elastic fibers located in the vessel walls which causes the fibers to contract more powerfully and elevate the blood pressure. A decreased blood volume causes the opposite effects. The experimental relationship between the blood volume, BV, and the mean systemic pressure, MSP, can be described by

$$MSP = 3.5(BV - 3) \tag{3}$$

where the mean systemic pressure is the average pressure within the blood vessels from the root of the aorta to the end of the great veins (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

Since angiotensin II is a powerful vasoconstrictor, it will influence the peripheral resistance which is the resistance to blood flow caused by friction with the vessel walls. Short term, neural control of vascular tone is neglected in this model. The relationship between the resistance of the entire circulatory system, or total peripheral resistance (TPR), and the plasma level of angiotensin II (A) can be approximated for humans by the following equations (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$TPR = 19 + 0.037A \qquad \text{for } A \leq 27 \frac{ng}{l} \tag{4}$$

$$TPR = 12.2 + 5.44 \log(A) \qquad \text{for } A > 27 \frac{ng}{l} \tag{5}$$

Cardiac output, CO, increases with oxygen consumption which is primarily determined by the metabolic rate. The relationship between cardiac output and oxygen consumption is approximately linear (McArdle, Katch, & Katch, 1986) and is shown in figure 17. This will be described more in detail when increased levels of activity are included in the model. At rest the cardiac output is about 5 liters/min.

Blood flow through vessels can be described by the following relationship.

$$\text{Blood flow} = \frac{[\text{Pressure (upstream)} - \text{Pressure (downstream)}]}{\text{Resistance}} \tag{6}$$

The arterial pressure (AP) can be solved for from equation 6.

$$AP = CO(TPR) \tag{7}$$

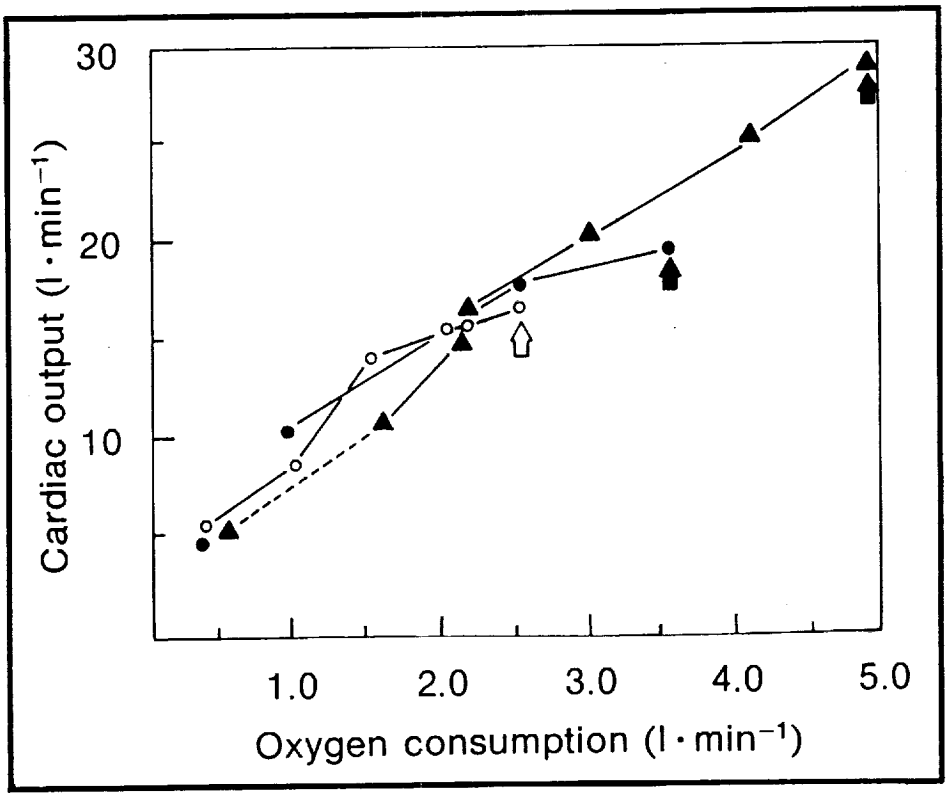

Figure 17: Cardiac output in relation to oxygen consumption diuring upright exercise in endurance athletes (solid triangles) and sedentary college students prior to (hollow circles) and following (solid circles) 55 days of aerobic training. Arrows represent maximum oxygen consumption for each catagory. (taken from McArdle, Katch, & Katch, 1986)

Renal function

Glomerular function The forces which control the filtration of plasma fluid into the Bowman's capsule include the capillary hydrostatic pressure and capsular oncotic pressure, which force fluid into the capsular space, and the plasma oncotic pressure and capsular hydrostatic pressure, which force fluid into the arterioles. These latter three pressures remain relatively constant under normal physiological conditions, therefore, the glomerular filtration rate will depend mainly upon the pressure within the arterioles. The following relationship between the arterial pressure and glomerular filtration rate has been previously determined (Goldstein & Rypins, 1992).

$$GFR = 4.50 - 1.62AP + 0.100(AP)^2 - 1.2\times10^{-3}(AP)^3 + 5.73\times10^{-6}(AP)^4 - 9.89\times10^{-9}(AP)^5 \quad (8)$$

Chemical analysis of glomerular filtrate has found that it has approximately the same sodium concentration as plasma (Lote, 1987) so the rate of filtration of sodium into the proximal tubule (FNa) is given by

$$FNa = GFR(PNa) \tag{9}$$

Proximal tubule Electrolytes are actively reabsorbed in this portion of the nephron therefore the rate of sodium reabsorption (SPTR) can be described by a mass transfer coefficient multiplied by the sodium concentration of the tubular fluid.

$$SPTR = GTB(FNa) \tag{10}$$

where GTB is the glomerular tubular balance or mass transfer coefficient. This coefficient is known to be a function of the sodium concentration of the tubular fluid. Since the concentration of sodium in the proximal tubule is nearly equal to the concentration of sodium in the plasma (PNa), the following linear relationship has been previously derived as a first-order approximation (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$GTB = 5.815 - 0.0357PNa \tag{11}$$

As electrolytes are pumped out of this portion of the tubule, water follows by osmosis. Since sodium makes up the majority of the cations in the filtered fluid, and as sodium is removed from tubule negatively charged ions follow due to an electrical gradient, the fraction of water reabsorbed in the proximal tubule will be nearly equal to the fraction of sodium reabsorbed.

$$EPTR = GTB(GFR) \tag{12}$$

where EPTR is the rate of water reabsorption in the proximal tubule. From equations 10 and 12, the flow rates of sodium (SFLH) and water (EFLH) into the loop of Henle can be determined.

$$SFLH = FNa - SPTR \tag{13}$$

$$EFLH = GFR - EPTR \tag{14}$$

Loop of Henle Examinations of the reabsorptive characteristics of sodium and water for the entire loop have demonstrated that the fraction of water reabsorbed (EBLH) is a function of transit time, or an inverse function of flow rate, whereas the fraction of sodium reabsorbed remains fairly constant with flow rate. The following relationships for the rate of reabsorption of sodium (SLHR) and water (ELHR) have been derived for this portion of the nephron (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$EBLH = -0.01EFLH + 0.65 \tag{15}$$

$$ELHR = EBLH(EFLH) \quad (16)$$

$$SLHR = 0.8SFLH \quad (17)$$

The flow rate of water (EFDT) and sodium (SFDT) into the distal tubules is given by

$$EFDT = EFLH - ELHR \quad (18)$$

$$SFDT = SFLH - SLHR \quad (19)$$

Distal and collecting tubules In these portions of the nephron, the amount of water reabsorbed is controlled by antidiuretic hormone (ADH) and the amount of sodium reabsorbed by aldosterone (ALD). Using data from previous experiments, relationships for the rate of water reabsorbed (EDTR) and the rate of sodium reabsorbed (SDTR) have been derived (Goldstein & Rypins, 1992).

$$EDTR = EFDT[0.0417 - 0.400ADH + 0.637(ADH)^2 - 0.222(ADH)^3 + 0.0345(ADH)^4 - 0.00254(ADH)^5 + 7.25\times10^{-5}(ADH)^6] \quad (20)$$

$$SDTR = SFDT [\ 0.572 + 0.00195(ALD) + 5.15\times10^{-5}(ALD)^2 - 7.98\times10^{-7}(ALD)^3 + 4.93\times10^{-9}(ALD)^4 - 1.69\times10^{-11}(ALD)^5 + 3.52\times10^{-14}(ALD)^6 - 4.56\times10^{-17}(ALD)^7 + 3.61\times10^{-20}(ALD)^8 - 1.59\times10^{-23}(ALD)^9 + 3.02\times10^{-27}(ALD)^{10}\ ] \quad (21)$$

Urine flow (UFL) is then given by

$$UFL = EFDT - EDTR \quad (22)$$

and the urinary excretion rate of sodium (UNa) is given by

$$UNa = SFDT - SDTR \quad (23)$$

Note that these equation predict that ADH can produce large percentage changes in fluid reabsorption whereas aldosterone has only a small modulating effect on sodium reabsorption. This agrees with the discussion at the end of the previous section (Description of the kidney) which stated that ADH is the primary controller of sodium in the extracellular fluid and the urinary sodium excretion rate. However, a full analysis requires the inclusion of aldosterone.

Hormonal systems

Having derived equations for the reabsorption of sodium and water in the latter portions of the nephron, which depend upon ADH and aldosterone, the levels of these hormones must now be estimated.

Control of ADH concentration Plasma ADH concentration is determined by three factors: the rate of ADH release from the posterior pituitary gland which depends upon signals from osmoreceptors and stretch receptors, the rate of clearance of ADH from the body by the liver and kidneys, and the volume in which the ADH is dispersed. As seen in figure 6, plasma ADH levels, and consequently the ADH release rate, increase as plasma osmolality increases and blood volume decreases. Equations for ADH release as a function of plasma osmolality (ADHSP) (DeHaven & Shapiro, 1970) and extracellular compartment volume (ADHSV) (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985) have been derived from experimental data.

$$ADHSP = 0.833PNa - 117.45 \quad \text{for } PNa \geq 141.9 \text{ mosm/l} \tag{24}$$

$$ADHSP = 0.06PNa - 7.83 \quad \text{for } PNa < 141.9 \text{ mosm/l} \tag{25}$$

$$ADHSV = 0.0 \quad \text{for } DWV \geq 1.8 \tag{26}$$

$$ADHSV = 0.15 - 0.083DWV \quad \text{for } 1.8 > DWV \geq 1.0 \tag{27}$$

$$ADHSV = 0.813 - 0.75DWV \quad \text{for } 1.0 > DWV \geq -1.2 \tag{28}$$

$$ADHSV = 1.71 \quad \text{for } -1.2 > DWV \tag{29}$$

where DWV is the deviation of the extracellular compartment volume (E) from the normal value (E_N).

$$DWV = E - E_N \tag{30}$$

The signals for ADH release in response to variations in plasma osmolality and blood volume are additive if both signals tend to increase the ADH release rate (ie. increased plasma osmolality with decreased blood volume). However, if both the plasma osmolality and blood volume are above normal, the signal for blood volume will be the primary signal. Recall that volume overrides tonicity. For this case the net rate of ADH (ADHS) release is given by the following equations (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$ADHS = \frac{17.0(DWV)(ADHSV) + ADHSP}{17.0(DWV) + 1.0} \quad \text{for POS} > 299.6 \text{ mosm/l and DWV} > 2.0 \tag{31}$$

$$ADHS = \frac{[33.0(DWV) - 32.0]ADHSV + ADHSP}{33.0(DWV) - 31.0} \quad \text{for POS} > 299.6 \text{ mosm/l and } 1.0 \leq DWV \leq 2.0 \tag{32}$$

For all other cases

$$ADHS = \frac{ADHSV + ADHSP}{2.0} \quad (33)$$

The rate of clearance of ADH from the plasma (DADH) has been found to be related to the plasma concentration of ADH (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$DADH = 0.206 \quad \text{for ADH} > 4.0 \text{ munits/l} \quad (34)$$

$$DADH = 0.374 - 0.042\,ADH \quad \text{for ADH} \leq 4.0 \text{ munits/l} \quad (35)$$

where the clearance rate of a substance is defined as the amount of blood completely cleared of the substance per unit time. For example, a clearance rate for ADH of 0.206 l/min means that ADH is completely removed from 0.206 liters of blood every minute.

Previous studies have found that ADH is confined mainly to the plasma compartment, therefore, the volume that ADH is distributed into is equal to the plasma volume (PV) (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985). A material balance on ADH yields

$$(PV)\frac{d(ADH)}{dt} = ADHS - DADH(ADH) \quad (36)$$

Control of aldosterone concentration Aldosterone release is one of the final consequences of the renin/angiotensin system, the function of which is to provide feedback control on the rates of sodium and potassium excretion, and thereby influence the volume of the extracellular and intracellular compartments (see figure 13). In absence of more explicit data, a linear relationship has been postulated for the rate of renin release (RS) as a function of the amount of sodium entering the distal tubule (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$RS = 0.0163 - 0.0093SFDT \quad (37)$$

This equation in consistant with the fact that the macula densa, which secretes renin into the plasma compartment, monitors fluid within the distal tubule. Renin is removed from the circulation on passage through the liver with a clearance rate of approximately 0.135 l/min (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985). A material balance on renin yields

$$(PV)\frac{dR}{dt} = RS - 0.135R \quad (38)$$

where R is the plasma concentration of renin.

Renin catalyses the reaction which converts circulating angiotensinogen to angiotensin I. Angiotensin I is rapidly converted to angiotensin II by enzymes

in the lungs. The following equation has been derived for the rate of formation of angiotensin II (AS) (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$AS = 583.3R(PV) \tag{39}$$

The rate of clearance of angiotensin II from the plasma has been found to be approximately 4.04 l/min (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985). A material balance on angiotensin II yields

$$(PV)\frac{dA}{dt} = AS - 4.04A \tag{40}$$

The major factor which regulates the release of aldosterone from the adrenal gland is the plasma concentration of angiotensin II. From previous animal studies, the following relationships for the rate of aldosterone release (ALS) as a function of plasma angiotensin II concentration have been derived (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985).

$$ALS = 0.75A + 7.76 \qquad \text{for } A < 18 \text{ ng/l} \tag{41}$$

$$ALS = 3.32A - 38.5 \qquad \text{for } 18 \leq A < 34.0 \tag{42}$$

$$ALS = 0.585A + 54.6 \qquad \text{for } A \geq 34.0 \tag{43}$$

The clearance rate of aldosterone from the plasma has been found to be approximately 0.62 l/min (Uttamsingh, Leaning, Bushman, Carson, & Finkelstein, 1985) which leads to the following material balance.

$$(PV)\frac{dALD}{dt} = ALS - 0.62ALD \tag{44}$$

Sodium and potassium balance Since the overall model of the body water compartments is concerned mainly with water and sodium, recall that sodium ions account for almost 95% of the cations in the extracellular fluid, the present model will assume that the extracellular potassium concentration remains constant at a typical value of 4 meq/l. The timed average daily ingestion rate of sodium (SODMIN) and the urinary excretion rate of sodium (UNa) will determine the amount of sodium in the extracellular fluid (TENa).

$$\frac{d(TENA)}{dt} = SODMIN - UNa \tag{45}$$

Since cellular membranes are relatively impermeable to electrolytes when compared to water, the amount of sodium in the intracelluar fluid will remain constant.

$$\frac{d(TINA)}{dt} = 0 \qquad (46)$$

The concentration of sodium in the extracellular compartment (PNa) and the intracellular compartment (INa) will then be given by

$$PNa = \frac{TENA}{E} \qquad (47)$$

$$INa = \frac{TINA}{I} \qquad (48)$$

where E is the extracellular fluid volume and I is the intracellular fluid volume.

Total body water balance A mass balance on total body water (W) gives

$$dW/dt = FLUMIN - UFL \qquad (48)$$

where FLUMIN is the flow rate of water into the body. Assuming instantaneous osmotic equilibration between the intracellular (I) and extracellular (E) compartments

$$(TENA + TEC)/E = (TINA + TIC)/I \qquad (50)$$

where TEC and TIC are constants which represent the other dissolved species within the extracellular and intracellular compartments, respectively. Instantaneous osmotic equilibrium between the extracellular and intracellular compartments will be assumed only when testing the kidney model. Since the mass transfer coefficient for the transfer of water across cellular membranes is known (see figure 1), the overall model of the body water compartments will not assume instantaneous equilibrium.

Since W = E + I, the size of the intracellular and extracellular compartments can be derived from equation (50).

$$E = W/[1 + (TINA + TIC)/(TENA + TEC)] \qquad (51)$$

$$I = W/[1 + (TENA + TEC)/(TINA + TIC)] \qquad (52)$$

Testing the kidney model

To test the validity of the proposed kidney model, results predicted by the model will be compared to actual data involving injected or ingested fluids and subsequent urine flow rates. Under these conditions, water enters the body through the plasma compartment and leaves the body through the formation of urine. Intravenously injected fluids enter the plasma compartment immediately whereas ingested fluid must first be absorbed by the intestines. The rate constant for water absorption from the gastrointestinal tract has been estimated

to be 3.33hr^{-1} (see figure 1). Amounts of water produced by cellular metabolism and excreted through sensible and insensible perspiration will be relatively small and consequently neglected for this case. Comparison of the model simulation to actual data following the ingestion of 1 liter of water is shown in figure 18. In figure 19, the model simulation is shown with actual data following the intravenous infusion of hypertonic saline.

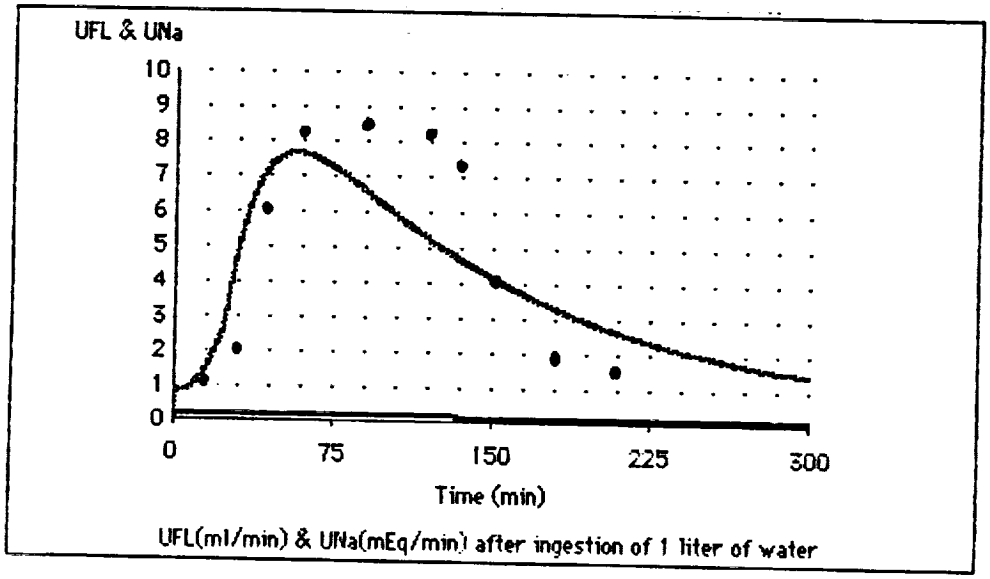

Figure 18: Results from the model simulation (solid line) and experimental data (solid circles) following ingestion of 1 liter of water. (actual data taken from Baldes & Smirk, 1934)

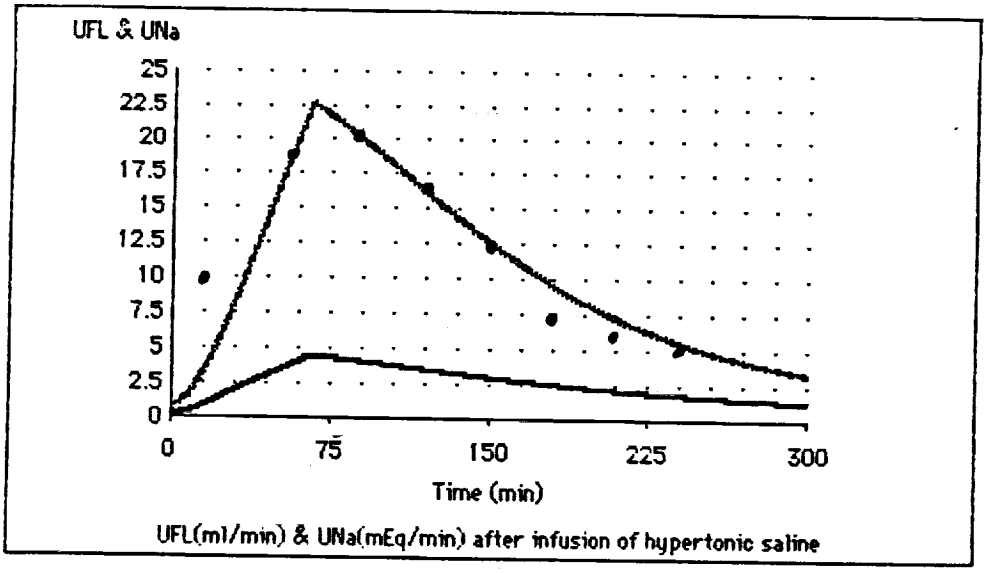

Figure 19: Results from the model simulation (solid line) and experimental data (solid circles) following infusion of 9.8 g/min of a 10% NaCl solution for 65 minutes. (actual data taken from Dean & McCance, 1949)

Nomenclature

Symbol	Description	Typical value
A	concentration of angiotensin II in plasma (ng/l)	27.0
ADH	concentration of ADH in plasma (munits/l)	4.0
ADHS	net release rate of ADH (munits/min)	0.825
ADHSP	release rate of ADH due to plasma osmolality (munits/min)	0.84
ADHSV	release rate of ADH due to diminished fluid volume (munits/min)	0.81
ALD	concentration of aldosterone in the plasma (ng/l)	85.0
ALS	net rate of secretion of aldosterone (ng/min)	52.7
AP	arterial pressure (torr)	100.0
AS	rate of formation of angiotensin II (ng/min)	105.0
BV	blood volume (l)	5.0
CO	cardiac output (l/min)	5.0
DADH	clearance rate of ADH (l/min)	0.206
DWV	excess fluid in extracellular compartment (l)	0.0
E	extracellular fluid volume (l)	15.0
E_N	normal extracellular fluid volume (l)	15.0
EBLH	fraction of water reabsorbed in the loop of Henle	0.33
EDTR	rate of reabsorption of water in the distal nephron segments (ml/min)	19.7
EFDT	rate of flow of water into the distal tubule (ml/min)	
EFLH	rate of flow of water into the loop of Henle (ml/min)	31.25
ELHR	rate of reabsorption of water in the loop of Henle (ml/min)	10.55
EPTR	rate of water reabsorption in the proximal tubule (ml/min)	93.75
FLUMIN	rate of ingestion of water (ml/min)	*
FNa	filtered load of sodium (mEq/min)	17.75
GFR	glomerular filtration rate (ml/min)	125.0
GTB	fraction of filtered load of sodium reabsorbed in the proximal tubule	0.75
Hct	hematocrit (unitless)	0.47 males 0.42 females
I	intracellular fluid volume (l)	25.0
INa	intracellular concentration of sodium (mEq/l)	10.0
Kf	capillary filtration coefficient (ml/min·kg·torr)	0.061
MSP	mean systemic pressure (torr)	7.0
Pc	capillary hydrostatic pressure (torr)	27.0
Pi	interstitial hydrostatic pressure (torr)	1.0
PK	extracellular concentration of potassium (mEq/l)	5.0
PNa	extracellular concentration of sodium (mEq/l)	142.0
POS	plasma osmolality (mEq/l)	299.6
PV	plasma volume (l)	3.0
R	concentration of renin in plasma (GU/l)	0.06

RS	rate of release of renin (GU/min)	0.008
RVR	resistance to venous return (torr/l·min)	1.4
SDTR	rate of reabsorption of sodium from the distal nephron segments (mEq/min)	0.757
SFDT	rate of flow of sodium into the distal tubule (mEq/min)	0.89
SFLH	rate of flow of sodium into the loop of Henle (mEq/min)	4.44
SLHR	rate of reabsorption of sodium from the loop of Henle (mEq/min)	3.55
SODMIN	rate of ingestion of sodium (mEq/min)	*
SPTR	rate of reabsorption of sodium from the proximal tubule (mEq/min)	13.3
TEC	total extracellular osmotic components other than sodium (mEq)	2418.0
TENa	total extracellular sodium (mEq)	2130.0
TIC	total intracellular osmotic components other than sodium	7555.0
TINa	total intracellular sodium (mEq)	250.0
TPR	total peripheral resistance (torr/l·min)	20.0
UFL	urine flow rate (ml/min)	1.0
UNa	rate of excretion of sodium (mEq/min)	0.128
VR	venous return (l/min)	5.0
W	total body water (l)	40.0
πc	capillary oncotic pressure (torr)	25.0
πi	interstitial oncotic pressure (torr)	0.0

(* subject dependent variable)