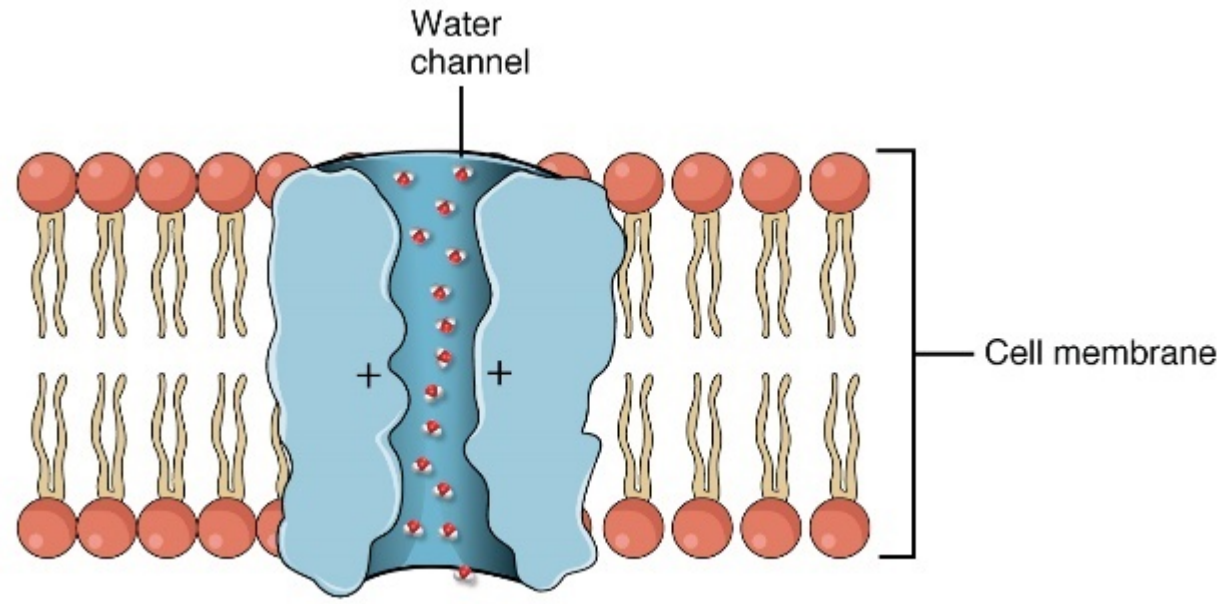
4.2.4

Urine Concentration and Dilution

The kidney can adjust its water output (urine) to compensate for high or low body water. The kidney can generate urine that is down to 30mosmol when total body water is high (i.e. when we are in taking large amounts of water), or it can produce urine that is 1200mosmol (4 times more concentrated) than the plasma when we become dehydrated. The kidney does this using the principle of osmosis to pull water from the tubule back into the blood (concentrated urine), or simply allowing the water to stay in the tubule system (diluted urine).

The loop of Henle plays a key role in the dilution or concentration of urine. In order to concentrate or dilute urine the loop of Henle has to separate the solutes from the water. To do this the loop takes advantage of special proteins that select for water or for solutes (mainly NaCl). As stated, the descending limb of the loop of Henle cells contain specialized proteins that form water channels called **aquaporins**.



Aquaporin Water Channel.

Link: https://cnx.org/resources/5b37a640e0dcf6fbea4584705019559704b26009/2625_Aquaporin_%20Water_Channel.jpg Author: OpenStax College License: Creative Commons Attribution 3.0 Unported license

The descending limb does not contain many proteins that move ions. Recall that about 15% of the filtered water is reabsorbed from the descending limb of the loop of Henle. Thus, as the filtrate moves through the descending limb it becomes more and more concentrated. In contrast, the ascending limb of the loop of Henle cells contain specialized proteins that form pumps that actively transport NaCl into the medullary interstitium. However, the cells of the ascending limb are impermeable to water so that as the filtrate moves through this section of the nephron it becomes more dilute.

Because the two limbs of the loop of Henle are next to each other, one side moves ions and the other side allows water to follow the ion gradient generated. This arrangement creates a system known as a **counter-current multiplier system**. A counter-current system is one in which there are two tubes running next to each other with the contents of the tubes moving in opposite directions. This system is a counter-current **multiplier** system because the ascending limb actively transports salts out of the lumen while preventing water from following.

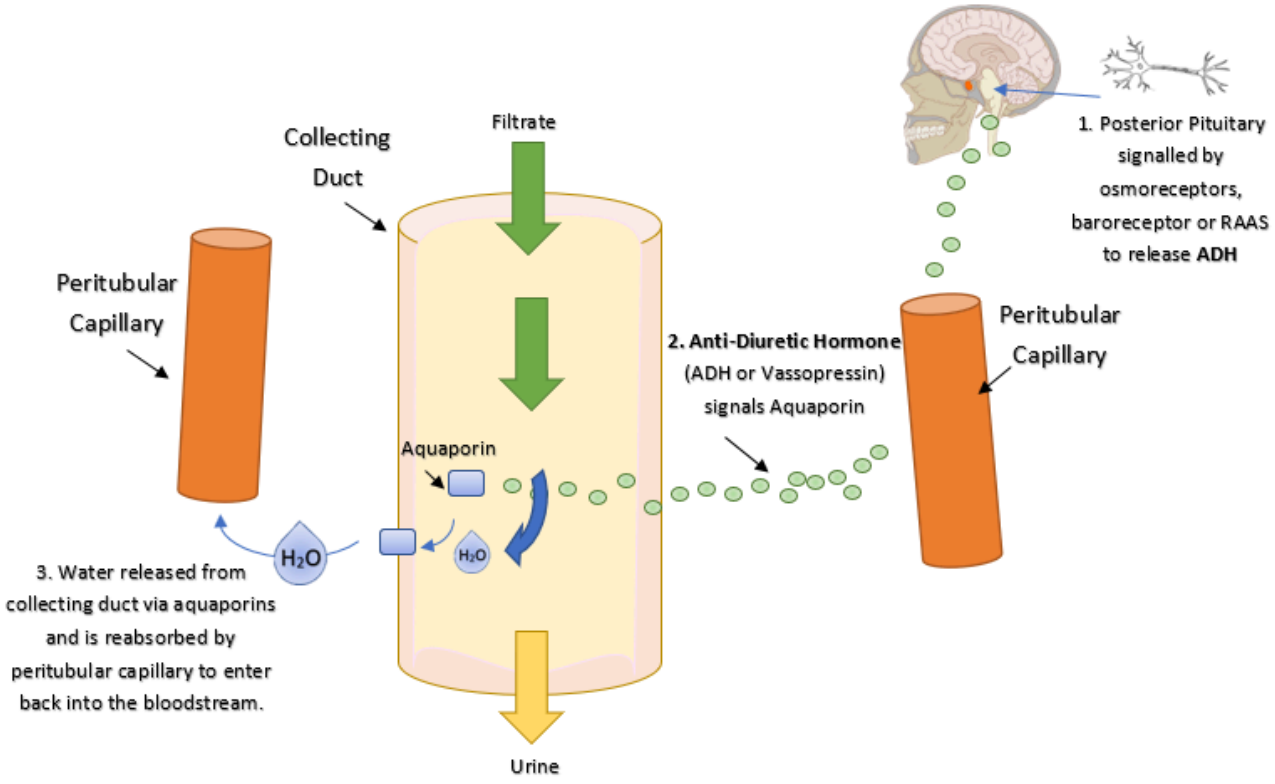
In terms of reabsorption, since the peritubular capillaries and the vasa recta are found in the medullary interstitium, the excess water and excess ions are picked up by the blood. The vasa recta form another counter-current system. Both the descending limb and the ascending limbs of the vasa recta are permeable to both water and NaCl. As the blood moves down the descending limb into the concentrated medulla, water leaves the blood by osmosis while salts enter the blood by diffusion. As the vasa recta reaches the bottom of the medulla the blood plasma's ion concentration is the same as that of the interstitial fluid, around 1200mOsm. If this capillary network were to exit the kidney at this point, it would leave the water behind and remove the salt, effectively destroying the gradient that the loop of Henle has worked so hard to create. However, instead of leaving the kidney at this point the vasa recta makes a 180 degree turn and heads back up toward the cortex. As the blood ascends water now enters the blood vessel by osmosis and NaCl leaves by diffusion. By the time the blood gets back to the cortex it is once again nearly isosmotic with the interstitial fluids. This special arrangement allows the vasa recta to remove excess salts and water while leaving the medullary concentration gradient intact.

This phenomenon can be explained using the actual concentration values. As filtrate enters the Bowman' s capsule and proximal tubule of the nephron it does so at the same concentration as that of the plasma. This concentration is around 300 mOsm. Since the filtrate moves first to the descending limb, water will begin to move from the descending limb into the interstitium/blood making the filtrate in the nephron more concentrated. Thus, the osmolarity will begin to change from 300 to 400 to 500 etc. The maximum value it will achieve is 1200 mOsm. As the filtrate moves back up the ascending limb, the ions will begin to be pumped out causing the filtrate to become more dilute, moving from 1200 to 1000 to 500 mOsm etc. until it reaches a value of about 100 mOsm. The net result is that of the 100% of the filtrate that began in the proximal tubule, only 20% remains as it enters the distal tubule. In the distal tubule another ~10% is reabsorbed. This is possible in the distal convoluted tubule because the osmolarity of the filtrate is 100 mOsm while that of the interstitial fluid is 300 mOsm. This filtrate then enters the collecting duct and travels back down through the medulla. In conditions of hydration, the kidney medulla will maintain a hyperosmotic gradient of around 500 mOsm. But in conditions of dehydration, the gradient can be maintained at 1200 mOsm, thus increasing the amount of water reabsorbed by the kidneys. To reach the hypertonic environment of 1200 mOsm, the kidneys take advantage of filtered urea to help reach those high numbers. Urea is a waste product of the breakdown of product of protein metabolism. Approximately 600 mOsm of the 1200 is contributed to NaCl concentrations and 600 mOsm are the result of urea. The gradient from NaCl has already been explained, but how urea accumulates is a bit more complex.

Urea is not made by the kidney instead it is released into the blood from the liver as a product of protein metabolism. Urea enters the kidney via filtration at the glomerulus. When urea reaches the collecting duct the cells express UT-A1 and UT-A3 urea transporters. The number and activity of these transporters can be regulated by the hormone arginine vasopressin (also called antidiuretic hormone). As the urea is reabsorbed and put into the interstitium, some of it moves back into the tubules at the loop of Henle through UT-A2 and some of it moves into the vasa recta through UT-B. Urea that is secreted back into the loop is trapped until it reaches the collecting duct again where it can do the cycle again. This “recycling” of urea will result in a build up of urea in the interstitial spaces deep in the medulla. The urea that enters the vasa recta will be used by the red blood cells. The red blood cells rapidly move in urea to increase their intracellular osmolarity and help prevent crenation as they move through the 1200 mOsmolar surrounding fluid.

Because of the shape of the nephron, the collecting duct starts in the cortex and descends through the "salty" medulla to finally dump its contents in the calyces of the kidney. Thus, the collecting duct is optimally positioned to serve as a regulatory section. In addition, the collecting duct can change its permeability to water. Inside the cells of the collecting duct are aquaporin channels housed in vesicles of cells called **principal cells** in the collecting duct. During times of dehydration, the channels are inserted into the plasma membranes of the collecting duct cells allowing water to move

out of the collecting duct. Since the concentration gradient is already established in the medulla, the water simply follows the gradient, leaving the collecting duct lumen by osmosis and being reabsorbed by the vasa recta. The osmolarity of the fluid in the collecting duct will change from 300 mOsm at the top of the collecting duct to up to 1200 mOsm by the time it enters the renal calyces. Under these conditions, the urine will be very concentrated and low volume, exactly what we would want if we are dehydrated. When we are hydrated, the aquaporin channels simply stay "concealed" and the 100 mOsm urine moves through the tubules losing only NaCl. Thus, the end product will be a very dilute urine (60 mOsm) and high volume, exactly what we would need to do if we had too much water in our system.



ADH acting on Principle cells of the Collecting Duct to Reabsorb Water

Created by BYU-Idaho instructor T. Orton Fall 2017. Image of Brain from By Patrick J. Lynch, medical illustrator
Link: https://upload.wikimedia.org/wikipedia/commons/a/a5/Hypophyse.png CC 3.0 License: CC BY-SA 3.0

Physicians can take advantage of the concepts of gradients and force the kidneys to secrete lots of dilute urine even though the physiology of the system would dictate concentrated urine. This is accomplished through the use of **diuretics**. A diuretic is any substance that promotes the production of urine. There are many different types of diuretics, but most work under the same general principle, that is they prevent the nephron from reabsorbing salt (furosemide blocks the Na+/K+/2Cl- transporter and thiazide blocks the Na+/Cl- transporter). By blocking the reabsorption of salt in different sections, the nephron loses the ability to increase the tonicity of the medulla. Thus, even though the nephron collecting duct could be avidly trying to retain water, by the insertion of aquaporin channels, without a salty gradient to drive water reabsorption, the water would remain in the tubule and eventually be excreted. Some diuretics, osmotic diuretics, work by administering a solute that is not reabsorbed and thereby acts as an osmotic particle to keep water from moving out (i.e. mannitol). Other diuretics (aquaretics) block the ADH receptors (V2). Diuretics are used to treat heart failure, liver cirrhosis, hypertension and even certain kidney diseases. Thus, diuretics help remove excess body water that has accumulated because of the failure of another system by forcing the kidneys to excrete the excess water. Unfortunately, diuretics are often abused by individuals who suffer from eating disorders, especially bulimics, to aid in weight loss.