Normal Renal Function

Functions of the Kidney:

- balances solute and water transport
- excretes metabolic waste products
- conserves nutrient
- regulates acid-base balance
- secretes hormones that help regulate blood pressure, erythrocyte production, and calcium metabolism.
- forms urine
**Formation of Urine in the Kidney**

A kidney contains around one million nephrons. In general, the kidneys can adequately function with only one third of the normal number of nephrons. Less than that, the body will retain waste products, especially urea and creatinine.

Nephrons process the blood to make urine. A tuft of capillaries called the glomerulus is contained in each nephron. The glomerulus is surrounded by Bowman's capsule. The capillaries are extremely porous, allowing large amounts of solute-rich fluids to pass from the capillaries into the capsule. This fluid is the raw material of urine.
This fluid leaves the capsule and is channeled into the proximal convoluted tubule (PCT) of the nephron. This is where the primary active transport of the sodium ion accounts for about 80% of sodium reabsorption. During the primary active transport of sodium, chloride is simultaneously reabsorbed as are all amino acids and glucose. Primary active transport also occurs to some extent in the other tubules except in the descending loop of Henle.

The secondary active secretion of H⁺ during Na⁺ reabsorption is called countertransport since the ions move in opposite directions. Normally, only 20% of total Na⁺ reabsorption occurs during active secretion of H⁺ and K⁺. When H⁺ ions are not available for exchange as in alkalemia, K⁺ ions are secreted. This is why alkalemia may lead to hypokalemia. In H⁺ and K⁺ secretion, HCO₃⁻ ions are reabsorbed in place of Cl⁻. When chloride ions are in short supply, there is an increased demand for H⁺ and K⁺ secretion to reabsorb sodium.

The proximal tubules are responsible for the iso-osmotic reabsorption of water, electrolytes, non-electrolytes. As much as 80% of the filtrate is reabsorbed into the capillaries that line the tubules.

1. All glucose and amino acids filtered are completely reabsorbed.
2. Almost all potassium is reabsorbed.
3. Almost all uric acid is reabsorbed.
4. 90% of bicarbonate is reabsorbed.
5. Two-thirds of filtered sodium is reabsorbed.
6. H₂O, chloride, and urea are reabsorbed by passive transport.
7. Hydrogen ion is secreted, creatinine is secreted.
8. Most of the calcium and phosphate is reabsorbed.
Past the PCT is the loop of Henle which consists of both ascending and descending limbs. The descending limb is freely permeable to water, while the ascending is less permeable. In the Loop of Henle there is continued reabsorption of water, sodium, chloride.

The distal convoluted tubule receives fluid from the loop of Henle. The distal tubules are important in the final regulation of water balance and acid-base balance since hydrogen ion is excreted with ammonia as ammonium and with phosphate buffers. Bicarbonate is regenerated in this process and retained in the body.

The collecting tubule then receives the newly formed urine from the nephrons. In the collecting duct water reabsorption is completed. The final concentration of urine takes place here under the control of anti-diuretic hormone (ADH). In the presence of ADH, more water is reabsorbed.

The urine flows through the minor and major calyces of the renal pelvis into the ureter. From the ureter, urine makes its way to bladder.
COUNTERCURRENT SYSTEM and the LOOP OF HENLE

1. The Loop of Henle establishes medullary hyperosmolarity

The ascending limb of the loop of Henle transports solutes (NaCl) out of the tubule lumen with little or no water, generating an hyperosmotic medullary interstitium and delivering an hyposmotic tubule fluid to the distal tubule. This is called the "single effect".

The osmolarity of the interstitium rises progressively from cortex to medulla and papilla through multiplication of the "single effect" by countercurrent flow in the branches of the loop: The single effect in fluid processed by loop segments located near the tip of the papilla occurs in fluid already subject to the single effect when the fluid was in loop segments located closer to the cortex.

Countercurrent exchange of solutes between ascending and descending vasa recta (the renal medullary capillaries) minimizes solute washout from the medullary interstitium.

2. The countercurrent system permits forming a concentrated urine

In the presence of ADH, which increases water permeability, the hyposmotic fluid that enters the distal tubule (DT) from the thick ascending limb (TAL) looses most of its water by osmotic equilibration with the surrounding cortical interstitium along the CNT and cortical collecting duct (CCD). It also continues loosing NaCl through reabsorptive transport along DT, CNT and CCD, until the tubule fluid becomes isoosmotic with plasma, by the end of the CCD.

The relatively small amount of isoosmotic fluid that flows into the medullary collecting ducts losses progressively more and more water to the hyperosmotic medullary and papillary interstitia and is finally excreted as hyperosmotic, highly concentrated urine.

3. The countercurrent system permits forming a dilute urine

In the absence of ADH, the hyposmotic fluid that enters the DT from the loop of Henle, continues to be diluted by transport of NaCl via NaCl (thiazide sensitive) cotransporters into DT cells and via Na channels (amiloride sensitive) along the CD. Water reabsorption is limited so that the tubule fluid becomes more and more dilute along DT, CNT and collecting ducts (CCD, OMCD and IMCD), until it is excreted as a large volume of hyposmotic urine.

4. Mechanism of hyperosmotic reabsorption in the TAL

There is apical Na-K-2Cl reabsorptive cotransport with K recycling through apical K-channels, and basolateral transport of Na via the Na-K-ATPase and of Cl via Cl-channels, in the water impermeable epithelium of the TAL.
A lumen positive electrical potential difference is generated by the luminal Na-K-2Cl cotransporter operating in parallel with channels that allow K to recycle into the lumen. The lumen positive potential drives passive paracellular reabsorption of more Na+ and of other cations (Mg++, Ca++)

The higher the delivery of Cl (Km=50 mM), the higher the activity of the luminal Na-K-2Cl cotransporters and the higher the rate of hyperosmotic Na reabsorption at the TAL.

5. Mechanism for hyperosmotic reabsorption in the tAL (thin ascending limb)

Water abstraction along the early part of the thin descending limb (tDL) is driven by the high osmolarity (at least half due to urea) present in the medullary interstitium. In the deep nephrons, water reabsorption increases the tubule fluid osmolarity (up to 1200 mOsm/L) and the Na concentration (up to 300 mEq/L) by the bend of the loop.

Along the water impermeable tAL, Na diffuses from the tubule lumen into the medullary interstitium driven by its concentration gradient and some urea enters from the interstitium into the lumen; the osmolarity decreases as the fluid ascends along the tAL.

Operation of this passive mechanisms of Na reabsorption along the tAL is critically dependent on efficient medullary recirculation of urea from IMCD to interstitium, to tAL.

5. Other functions of the Loop of Henle

Bicarbonate reabsorption through Na-H exchange

Reabsorption of cations such as Ca^{2+} and Mg^{2+}

Generation of cortical to medullary gradients of gaseous NH_{3} and O_{2} and of medullary to cortical gradients of CO_{2} and lactic acid

Production of Tamm-Horsfall mucoprotein (casts)

Cells survive in the hyperosmotic medullary environment through slow accumulation of osmolytes (75 mM sorbitol and 25 mM glycerophosphocholine (GPC) by synthesis, and 25 mM betaine and 10 mM inositol by Na^{+} driven cotransport), which can be rapidly released from the cells through channels that open when the osmolarity decreases.
The Loop of Henle: Concentration.

The proximal tubule reabsorbs about 70 percent of the fluid filtered from the blood by the glomerular capillaries. As there is no such thing as active transport for water (no water pump), it accomplishes this by reabsorbing electrolytes by active transport and thus dragging water across from the urine and into the blood by osmosis. This is essentially the same mechanism used by water absorbing (gut) and water secreting (salivary glands) epithelia throughout the body. The proximal tubule even gets a helping hand in this process because the blood that circulates in the capillaries near the proximal tubule is the very same blood that was filtered in the glomerular capillaries and is thus slightly hyperosmotic to begin with. Anyway, there is a limitation to this mechanism for water reabsorption. Not volume, it is possible to reabsorb vast quantities of fluid using this sort of mechanism, but rather concentration. The problem with this sort of mechanism for fluid absorption is that it works on a very small osmotic gradient and consequently, water absorption is practically isotonic. This means that the urine will also be isotonic. It won't contain the same substances as plasma (e.g. no glucose or bicarbonate etc. and more PAH or DDT etc) but the overall osmolarity will be the same. Suppose the body has taken on an excess sodium chloride load and is desperate to get rid of it because it is disturbing the osmolarity of the body. If the urine is isotonic, the salt can't be got rid of. Think about it. If the urine is always isotonic with the plasma you can adjust the amount of salt and water in the body but not the concentration. To get rid of excess salt, you would have to drink sufficient water to restore normal osmolarity and then excrete the excess salt with the excess water.

To dispose of an excess salt load, you must be able to generate a concentrated urine. Enter the renal medulla and the loop of Henle. The medulla is very poorly drained (more on that later) and so it is possible to set up a large osmotic gradient in the medulla and keep it there (anywhere else and the blood would wash the gradient away). The other part of the problem is how to create a large osmotic gradient. Active transport is the key, but even the mighty sodium pump can't shift enough sodium to create a worthwhile gradient by itself. The other part of the solution, and the reason that the loop of Henle is in fact a loop lies in the principle of countercurrent multiplication. In a countercurrent multiplier, the combined action of active pumping and circulation and re-circulation of solutes around the loop of Henle create an osmotic gradient with the following properties.
1) A huge concentration gradient between the solution in the middle of the loop and that at the beginning (or the end) of the loop.

2) Little concentration difference between solution entering the loop and that leaving the loop. In fact, the fluid leaving the loop may be hypotonic.

3) Little concentration difference between any two adjacent segments in the loop.

Ok. Now we have a huge concentration gradient extending into the medulla, The osmolarity of the medulla may be as high as 1400 mOsm/l, compared to the normal plasma osmolarity of 300 mOsm/l, but it isn't doing much good in concentrating the urine. True the urine gets very concentrated as it descends the loop of Henle into the medulla but it gets progressively weaker again as it ascends back out into the cortex. The latter part of the loop of Henle and the distal tubule are sometimes known as the 'diluting segment' of the nephron because the urine can in fact be more dilute as it enters the distal tubule than it was leaving the proximal tubule. This used to drive renal physiologists nuts. They knew that the loop of Henle was involved in concentrating the urine somehow but so far as they could tell, all it did was dilute it. The answer is in the collecting ducts. After going through the distal tubule, the urine passes into the collecting ducts. The collecting ducts travel through the medulla on their way out of the kidney. Right past the high osmolarity part of the medulla in fact. If the collecting ducts are water permeable then the huge concentration gradient between the medulla and the collecting ducts will drag water out of the urine into the medulla. Finally we have a concentrated urine. Next stop after the collecting ducts is the bladder. The extent to which the urine is concentrated depends mainly on how water permeable the collecting ducts are. The water permeability of the collecting ducts is controlled by anti-diuretic hormone (ADH). In the absence of ADH, the collecting ducts are water impermeable, no water is reabsorbed and a large volume of dilute urine is produced. In the presence of a high concentration of ADH the collecting ducts are highly water permeable, a lot of water is reabsorbed and a small volume of very concentrated urine is produced. ADH, working via cAMP as a second messenger stimulates insertion of water channels into the plasma membrane.
The V2 receptors for ADH is yet another example of a 7-membrane-spanning-domain-G-protein-coupled receptor. All intermediate stages of water absorption are possible so that the volume and the concentration of urine can respond to the changing needs of the body in regulating fluid and electrolyte homeostasis.

Before I forget. One of the requirements to build a countercurrent multiplier is to keep it away from the blood supply, otherwise the blood will wash it away before it gets started. The capillaries that accompany the long loops of Henle on their trip to the medulla and back are called the vasa recta. These capillaries also form long loops and run in parallel to the loop of Henle, most importantly, the arterial and venous ends of the capillaries run in parallel with each other (in other words a hairpin loop). This allows a process called countercurrent exchange to occur. In short, countercurrent exchange allows exchange of solute between the ascending and descending limbs of the capillaries and prevents them from dissipating the medullary concentration gradient. Among the solutes exchanged in this process are oxygen and carbon dioxide (e.g. oxygen moves from the descending limb of the vasa recta to the ascending limb without travelling around the loop, carbon dioxide moves in the opposite direction). All of which makes the vasa recta a terrible blood supply by all normal criteria. It has been suggested that the cells at the base of the loop of Henle have make ATP anaerobically (by glycolysis) to survive.