III. FORMATION OF URINE

- Urine formation consists of 3 steps, which occur at different regions of the renal tubule.

- Overview:

  1. We will move almost everything from the bloodstream into the tubule during filtration.

  2. However, we will leave large substances … mostly blood cells and proteins …. in the capillary (think of what is left over as a “sludge”). That way, when we reabsorb later, water will move via osmosis back into the “sludge” found in the vessels, and will not be lost to the surrounding tissues.

  3. We will reabsorb 99% at the tubules. Most of this will be active transport of sodium, and let other substances follow.

  4. Water will rush back into the “sludge” present in the peritubular capillaries. The movement of water will carry a lot of dissolved solutes (nutrients and electrolytes) back to the vessel for conservation!

  5. The tubules will secrete certain substances into the filtrate.

- URINE - anything non-resorbed (water + waste). Contains:

  1. Non-lipid soluble items (low resorption rates).
  2. Molecules too large to pass through pores of tubular cells.
  3. Anything that lacks active carriers.

    * Most important = NITROGENOUS WASTES (product of protein metabolism) = HOH soluble (= UREA = NH3+).

    URIC ACID - crystallized form = kidney stones.

A) FILTRATION AT THE RENAL CORPUSCLE

1. Overview

- Corpuscle does FILTRATION (or GLOMERULAR FILTRATION) - formation of FILTRATE (water + dissolved electrolytes & wastes).

  Filtration is a passive process. No hormone control. BP is the only determinate, and size of the solutes

  * No metabolic energy (ATP) needed! Filtration is done using HYDROSTATIC PRESSURE.

- The corpuscle does this using the FILTRATION MEMBRANE, a thin, porous surface through which blood plasma is filtered. Membrane is part vascular & part tubular.

  * This filtration membrane is 1000 x more permeable to HOH & solutes than normal capillary.
Glomerulus = capillary bed, composed of FENESTRATED CAPILLARIES = allow liquid under high pressure to pass out of the vessel.

Enters the Glomerular capsule like a fist in a balloon.

* This gives the Glomerular Capsule 2 layers:

  PARIETAL ("against the wall") and VISCERAL ("against the viscera"; in this case, the blood vessel).

  The VISCERAL LAYER composed of special squamosal epithelial cells called PODOCYTES with "foot projections".

The “foot projections” of the podocytes are interwoven, forming FILTRATION SLITS. These are fused with the capillary endothelium, forming the FILTRATION MEMBRANE.

There is a thick basement membrane adhering them. This membrane has a negative charge.
- This forms an effective barrier against large, charge substances such as proteins and blood cells. They will stay in the bloodstream, forming the “sludge” mentioned earlier.

**The size of the slits, the size of the fenestrations, and the charge of the basement membrane keep large blood elements, like cells and albumin, in the vessel.**

**Remember:** We do not want everything to move into the capsule. Instead, we want to form a “sludge” in the capillaries, assuring that water + dissolved elements will return to the bloodstream.

- What gets filtered through his membrane? EVERYTHING smaller than a medium-sized protein.

The filtrate consists of:
- Water
- Glucose
- Amino acids and small proteins
- Ions (K+, Cl-, H+, HC03-, Na+)
- Urea and other nitrogenous wastes

- Glomerular filtration rates are so high that the entire blood volume enters the renal tubules in less than a half hour.

**See later section of Glomerular Filtration Rate. But first, let’s continue forming urine!**
B) TUBULAR RESORPTION

- REABSORB from the filtrate back into blood.

- 99% of the filtrate must be reabsorbed, or the body would soon dehydrate.

- This occurs at the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule and the beginning of the collecting duct.

- What do we reabsorb? Kidneys restore plasma concentrations of water, electrolytes, amino acids, glucose, vitamins, and other nutrients.
  * All these linked to Na+ pumping – see later
  * 99% of the filtrate is reabsorbed!
  * Kidneys have important role in ion homeostasis, and pH through the reabsorption of bicarbonate and H+.

- Reabsorption can be active, or passive.

  1. Active Tubular Resorption – In general, actively pump Na+, and let HOH and anions follow!

    * Convoluted tubules have a lot of mitochondria and protein carriers. Same mechanisms we saw in the Digestion Chapter

    * In primary active transport, ATP provides the energy needed.

    * During cotransport, a solute is moved down its electromagnetic gradient, which pulls another solute of opposite charge along with it, against its electromagnetic gradient.

      * symporters and antiporters.

    * Also recall solvent drag: moving dissolved substances with water. This helps move everything back into the bloodstream.

  2. Passive Tubular Resorption – most water and anions follow the cations.
- This reabsorption can be mandatory, or it can be optional (controlled by hormones):

1. **Obligatory Reabsorption** = not controlled, just happens at a regular pace.
   * 80-90% in PCT & LOH (see later)

2. **Non-obligatory Reabsorption** – changes due to body’s needs. Controlled by hormones.
   * DCT and Collecting Duct are involved if we want to change water concentration, or the concentration of some electrolytes in the bloodstream

C) **TUBULAR SECRETION** - reabsorption in reverse.

- Certain substances must be secreted back into the tubular fluid, in order to fine tune the solute concentrations of the blood and maintain homeostasis.

- Some substances, especially H+, K+, ammonium ion, and organic acids are resorbed, then secreted back into tubule. Mostly occurs at the collecting duct. Important process for:
  1. Eliminating substances that either were not filtered or were reabsorbed by passive means, such as urea.
  2. Eliminating substances that were reabsorbed by passive means, such as urea.
  3. Putting excess potassium into the urine
  4. Controlling blood pH via the secretion of H+ and bicarb.

Since they are secreted in this manner, these drugs must be taken several times per day in order to maintain a sufficiently high concentration in the blood.

D) **Location and Manner of Reabsorption and Secretion of Specific Substances**

1) The PCT: Majority of reabsorption. PCT reabsorbs 65% of filtrate. Majority of solute and water reabsorption happens here … most involve active transport with sodium. PCTs account for 6% of your resting ATP usage!

**This IS NOT a complete list:**

1. **Solute** - In general: sodium is pumped, water and anions follow passively. How sodium affects these other substances:
Reabsorption of Glucose, amino acids and vitamins are reabsorbed using cotransport with sodium. Most is obligatory reabsorption in the PCT.

* Glucose is COMPLETELY reabsorbed, unless there is too much present for the mechanisms to work correctly. Diabetics have “sweet” urine, and dehydrate as excessive glucose draws water into the urine.

* Syports with sodium using SGLT proteins (Sodium-dependent glucose cotransporters)

  ** Amino acids and vitamins are transported in the same manner.

* Glucose, amino acids, and vitamins are then carried into the bloodstream via solvent drag.

Reabsorption of Cl- and other anions

* Cl- is absorbed over the apical membrane by cotransport with sodium.

  Most is obligatory reabsorption in the PCT.

  As sodium moves in, the negatively-charged Cl- follows.

Nitrogenous wastes, especially urea

Urea is water soluble and small, so it is filtered at the glomerulus. However, due to its small size, Urea is reabsorbed, following water, into the bloodstream

* At the PCT, the nephron reabsorbs about 50% of filtered urea as it follows water.

* We will secrete the urea back into the renal tubule farther down the PCT. However, a significant amount is returned to the bloodstream.

* The kidneys do not remove all nitrogenous wastes from the blood. Rather, it maintains a low enough concentration in the bloodstream to prevent reaching toxic levels.

Bicarbonate Reabsorption

Important in homeostasis of pH. In general (not an absolute but a rule of thumb): We will control blood pH using bicarb, not H+. If the blood is too low in pH, more bicarb is reabsorbed. If the blood is too high in pH, less bicarb is reabsorbed.

Notice that Bicarbonate is not directly reabsorbed from the filtrate. Instead, CO2 diffuses into the epithelial cell, and is converted to bicarb. More detail in the Homeostasis of pH section in the “Electrolyte Balance” section!

Lipid soluble molecules passively move across epithelial membranes.

Secretion of Drugs, such as antibiotics, occurs here.

This is why you must take these drugs more than once during the day in order to maintain blood plasma levels
2. Water

- At the PCT, water is reabsorbed at a constant rate; no matter what the body’s water needs are at the time. About 65% of water is reabsorbed here.

- Recall: never “pump” HOH; instead, move ions & water follows. Water will move via osmosis. This is termed “Obligatory Water Reabsorption”.

- The osmolarity of the bloodstream, maintained by the presence of RBCs and blood proteins that were not filtered, keeps water moving into the Peritubular capillaries.

* Sometimes water will follow pumped electrolytes.

* Occasionally, as water moves, it carries dissolved substances in a process called “solute drag”.

### Summary of Reabsorption and Secretion at the PCT
(only use this if it helps you!)

![Diagram of urinary system](image-url)
2) Loop of Henle: Filtrate enters the LOH. Water is removed (another 15-20%), using sodium and chloride ion.

Notice this is obligatory.

This will be used to draw water out of the Collecting Duct, if we want to conserve more water later. See later section entitled "REGULATION OF URINE CONCENTRATION - WATER BALANCE".

What to know:

Descending limb is permeable to water but not solutes

The thick ascending loop is not permeable to water but solutes are pumped out

Therefore, osmolarity of medullary tissue is elevated, which keeps water being drawn water out of the descending limb...prohibiting it from ever going to equilibrium.

This is termed the "Medullary Osmotic Gradient", formed by a "countercurrent exchange system"

So this is still obligatory reabsorption

3) Fluid now enters the Distal Convoluted Tubule (DCT) and Collecting Duct (CD)

- 80-90% of the water has been reabsorbed from the fluid entering the DCT. If the body is happy with the following variables (see below), nothing else happens, and we are done.

  However, these 3 variables can be regulated at the DCT and CD through NON-OBLIGATORY REABSORPTION & SECRETION :

  1. water balance
  2. some solute levels (especially Na+, K+ an Ca++)
  3. blood pH (via bicarbonate)

  * Non-obligatory = "hormonally controlled"

- The following can happen:

  1. We can increase reabsorption of Ca++ and Na+.

     Ca++ is increased using PTH

     Na+ is increased using aldosterone

  2. We can get rid of (secrete) K+, which is particularly dangerous at high levels.

  3. We can either reabsorb or secrete bicarbonate depending on pH needs.

     Secrete more bicarb if pH is too high

     Secrete less bicarb if pH too low

  4. We can reabsorb up to 10% more water
- We can do this in more than 1 way:

  (i) reabsorb water by itself by making the CD tubules more leaky.

  ADH forms aquaporins in the CD

  Recall...we made the medullary osmotic gradient with the LOH. So if we make the CD more leaky, water will come out!

  (ii) We can couple water reabsorption to an increase in solute pumping, conserving much more water.

  Water follows charged ions! This greatly increases how much water we reabsorb!

  We can also do THIS in main ways:

  a. Also increase aldosterone, so water follows sodium

  b. Urea might be resorbed to help draw out more water, but if so, it is immediately secreted again!

Here, however, water is not automatically coupled to solute reabsorption.

Left alone, these cells are mostly impermeable to water.

IV. Glomerular Filtration Rate: Regulating the rate (speed) of urine formation

- Once the filtrate is formed it moves down the tubule. Pressure of the fluid determines how fast the filtrate moves through the tubule.

  1) GFR and NFP

- The glomerular filtration rate (GFR) is the amount of filtrate formed per minute within the renal corpuscle. If it is too slow, wastes build up in bloodstream. If it is too high, the filtrate is moved too quickly through the tubule for reabsorption to occur properly.

* If GFR is too slow, filtrate stops moving through the renal tubules, and urine production stops. Wastes build up in the blood.
* If GFR is too fast, filtrate passes too quickly through the renal tubule for reabsorption. Important substances are lost from the body into the urine.

- The production and movement of filtrate depends on three pressures:
  
i. Glomerular blood hydrostatic pressure (GBHP) is pressure within the capillaries. GBHP is dependent on blood pressure. GBHP is around 55 mmHg and increases GFR.
  
ii. Capsular hydrostatic Pressure (CHP) is back pressure from the fluid already in the Bowman's capsule; CHP is around 15 mmHg and decreases GFR.
  
iii. Blood colloidal osmotic pressure (BCOP) is the tendency of blood proteins to draw water back into blood. BCOP is 30 mm Hg and decreases GFR.

The net filtration pressure (NFP) is the sum of all three pressures, and is the pressure of the filtrate as it enters the PCT:

\[ \text{NFP} = \text{GBHP} - \text{CHP} - \text{BCOP} \]

*As blood pressure increases or decreases, so does NFP and GFR.

*A normal NFP insures a normal amount of glomerular filtration.

Normal NFP = 10 mmHg.

* A normal GFR must be maintained to regulate the composition of body fluids.

Normal GFR = 105-125 mL /min

- GFR can be regulated by adjusting:
  
2. Surface area of glomerular capillaries.

- There are three main ways to make these adjustments:
  
1. Renal autoregulation - Renal autoregulation is where the kidneys themselves regulate blood flow.
   
   * Afferent arteriole and Macular densa

   
   * Sympathetic neurons

3. Hormonal regulation.
   
   * Juxtaglomerular cells and Mesangial cells
### Summary Table of Regulation of GFR and NFP

<table>
<thead>
<tr>
<th></th>
<th>BP Threatens to increase the filtration pressure and rate. But that doesn’t happen</th>
<th>BP Threatens to decrease the filtration pressure and rate. But that doesn’t happen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoregulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myogenic (characteristic: smooth muscle)</td>
<td>Smooth muscle of afferent arteriole causes vasoconstriction</td>
<td>Smooth muscle of afferent arteriole causes vasodilation</td>
</tr>
<tr>
<td></td>
<td>Less GBIIP, lower GFR</td>
<td>Higher GBIIP, higher GFR</td>
</tr>
<tr>
<td>Tubuloglomerular (local chemicals released by Nacula Densa)</td>
<td>Vasoconstriction of afferent arteriole</td>
<td>Vasodilation of afferent arteriole</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>Nervous Regulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic only</td>
<td>Vasoconstriction of afferent arteriole</td>
<td>Vasodilation of afferent arteriole</td>
</tr>
<tr>
<td>Fast response</td>
<td>Less GBIIP, lower GFR</td>
<td>Higher GBIIP, higher GFR</td>
</tr>
<tr>
<td><strong>Hormonal Regulation- part 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(JCA and Mesangial cells begin hormone loops)</td>
<td>Increased angiotensinII promotes vasoconstriction of efferent arterioles</td>
<td>- At rest, sympathetic stimulation is weak and renal autoregulation is the dominant mechanism for controlling GFR. Sympathetic stimulation is most important during extreme rises or falls in blood pressure.</td>
</tr>
<tr>
<td>Renin-Angiotensin</td>
<td>Higher GBHP, higher GFR</td>
<td>This cause juxtaglomerular cells to produce renin.</td>
</tr>
<tr>
<td><strong>Hormonal Regulation- part 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Atrial cells stretch)</td>
<td>Higher BF causes.... ANP causes the mesangial cells of the glomerulus to relax, lowering of systemic BP while maintaining GFR and increasing the surface area of the capillaries.</td>
<td>A sudden large increase in blood pressure will cause the atria of the heart to stretch.</td>
</tr>
</tbody>
</table>