Learning Objectives:
- Differentiate the following processes: filtration, reabsorption, secretion, excretion
- Explain how the structure of the glomerulus promotes and limits filtration
- Describe the factors that influence GFR and the processes involved in its regulation
- Explain how creatinine clearance is determined and describe its clinical significance

INTRO AND BASICS

URINE: Fluid waste produced by the kidneys
KIDNEYS (primary function): Homeostatic regulation of water and ion content of the blood; also called salt and water balance or fluid and electrolyte balance

Six general areas of kidney function:
1) Regulation of extracellular fluid volume and blood pressure
2) Regulation of osmolarity
3) Maintenance of ion balance
4) Homeostatic regulation of pH
5) Excretion of wastes
6) Production of hormones

I. Anatomy of Urinary System

a. Urinary system is composed of the kidneys and accessory structures
b. Study of kidney function is called renal physiology
c. Urinary system consists of Kidneys, Bladder, and Urethra
   i. First step of urine production, water and solutes move from plasma into nephrons (hollow tubes) that make up the bulk of the kidneys
      1. Tubules modify composition of the fluid as it passes through
      2. Modified fluid leaves the kidney and passes into another hollow tube called a ureter
         I. Two ureters
         II. One leading from each kidney to the urinary bladder
   ii. The bladder expands and fills with urine until it contracts and expels (by reflex action) urine through a single tube, the urethra
      1. Micturition: More commonly known as urination, is the process by which urine is excreted
d. The Nephron is the Functional Unit of the Kidney
   i. Contains two layers that are formed by the arrangement of nephrons
      1. Outer Cortex
      2. Inner Medulla
         i. Nephrons
            - 80% contained within cortex (cortical nephrons)
            - 20% contained within medulla (juxtamedullary nephrons)
            - Is the functional unit of the kidney

   e. Kidney Vascular Elements
      i. Blood enters the kidney through the renal artery, then into smaller arteries and then arterioles in the cortex
      ii. Kidney arrangement of blood vessels is a portal system, one of the three in the body!!!
          1. Blood flows from the afferent arteriole into the glomerulus (Ball-like network of capillaries)
          2. Blood flowing out from glomerulus enters into efferent arteriole
          3. Blood flowing out of efferent arteriole then enters into peritubular capillaries that surround the tubule
          4. Peritubular capillaries (in juxtamedullary nephrons) that dip into the medulla are called vasa recta
             FUNCTION OF RENAL PORTAL SYSTEM:
             1. Filter fluid out of blood and into lumen of the Nephron at the glomerular capillaries
             2. Reabsorb fluid from tubule back into the blood at the peritubular capillaries

[Extra Knowledge]Three Portal System Locations
1. Kidneys
2. Brain (Hypothalamic-hypophyseal; connects hypothalamus and anterior pituitary)
3. Digestive System (combination of two capillary beds from digestive tract and liver, joined by the hepatic portal vein)
RUNING PROBLEM: GOUT is a metabolic disease characterized by high blood concentrations of uric acid (hyperuricemia). If uric acid concentration reaches a critical level of 7.5mg/dL, crystals of monosodium urate form in peripheral joints, particularly in feet, ankles, and knees. The crystals trigger an inflammatory reaction and cause period attacks of excruciating pain.

f. Kidney Tubular Elements
   i. Bowman’s Capsule: Beginning of the nephron; hollow ball-like structure that surrounds the glomerulus
      1. Combination of glomerulus and Bowman’s capsule is called the renal corpuscle
         [MORE INFORMATION ON THIS TOPIC AT FILTRATION SECTION]
   ii. Proximal Tubule
      1. Receives filtered fluid from Bowman’s capsule
   iii. Loop of Henle
      1. Following the proximal tubule
      2. Divided into two limbs
         I. Descending Limb (thin)
         II. Ascending limb (thin and thick segments)
   iv. Distal Tubule
      1. Distal tubules of up to eight nephrons drain into a single larger tube called the...
   v. Collecting Duct
      1. Combination of Distal tubule and Collecting duct form the Distal Nephron
      2. Collecting Ducts pass from cortex through the medulla and drain into the...
   vi. Renal Pelvis
      1. From the Renal pelvis, the filtered fluid is now called Urine and flows into the ureter on its way for secretion
II. OVERVIEW OF KIDNEY FUNCTION

a. In a twenty four hour period of time the kidneys (nephrons) moves 180 liters of plasma

b. Kidneys excrete only about 1.5 L a day so more than 99% of fluid that enters the nephrons is entered back into the blood

c. The Three Processes of the Nephron are Filtration, Reabsorption, and Secretion
   i. Filtration: movement of fluid from blood into the lumen of the nephron
      1. Only takes place in renal corpuscle
         I. Walls of glomerular capillaries and bowman’s capsule are modified to allow bulk flow of fluid
      2. Once fluid passes into the lumen of the nephron, it becomes part of the body’s external environment just as substances passing in the intestinal tract are part of the external environment
      3. Non-selective process
   ii. Reabsorption: process of moving substances in the filtrate from the lumen of the tubule back into the blood flowing through peritubular capillaries
   iii. Secretion: Removes selected molecules from the blood and adds them to the filtrate in the tubule lumen
      1. Specific membrane transporters

NOTE: The body has receptors, not for what is good to keep in, but for what is bad and needs to be secreted out into the collecting ducts for excretion

d. Volume and Osmolarity Change as Fluid Flows Through the Nephron
   i. 180 L of fluid filter into Bowman’s capsule each day
   ii. Filtrate entering the proximal tubule, about 70% of its volume is reabsorbed in the peritubular capillaries, leaving 54 L in the lumen
      1. Primary function of proximal tubule: \textit{bulk reabsorption of isosmotic fluid}
      2. Reabsorption occurs when proximal tubule cells transport solutes out of lumen, and water follows by osmosis
      3. Filtrate leaving has same osmolarity as filtrate that entered
   iii. Loop of Henle
      1. Primary site for creating dilute urine
      2. By this step 90% of the original volume in the nephron tubule system has been reabsorbed into the capillaries
   iv. Collecting Duct
      1. Filtrate has a volume of 1.5 L/day
      2. Final volume and osmolarity of urine depend on body’s need to conserve or excrete water and solute

NOTE: Secretion: Separate something from its source  
Excretion: Move out of or away from the body
III. (DETAILS) FILTRATION

a. First step of Urine formation

b. Under normal conditions blood cells remain in the capillary so that filtrate is composed only of water and dissolved solutes

c. The Renal Corpuscle Contains THREE Filtration Barriers
   i. Renal Corpuscle = Glomerular capillaries (surrounded by) + Bowman’s Capsule
   ii. Contains Afferent and Efferent arterioles
   iii. Substances leaving the plasma must pass through THREE filtration barriers (before entering tubule lumen)
      1. Glomerular Capillary Endothelium
         i. Fenestrated Capillaries [large pores that allow most components of plasma to filter through endothelium]
            a. Pores are small enough to prevent blood cells from leaving capillary
         ii. NEGATIVE charged proteins on pore surface help to repel NEGATE charged plasma proteins
            [Negative – Negative = Repel]
            [Negative – Positive = Attract]
      III. Mesangial Cells
         a. Lie between and around glomerular capillaries
         b. Contain actin-like filaments that enable them to contract and alter blood flow through capillaries
         c. Secrete cytokines associated with immune and inflammatory processes
      2. Basil Lamina (basement membrane)
         i. Contains NEGATIVELY charged Glycoprotein’s to repel away most plasma proteins from the fluid that filters through it
      3. Epithelium of Bowman’s Capsule
         i. Podocytes
            a. Surround each glomerular capillary
            b. Contain Food Processes that warp around glomerular capillaries and interlace with one another, leaving narrow filtration slits
            c. Similar to Mesangial cells in that they contain contractile fibers

Amount of any substances excreted in the urine reflects how the substance was handled during its passage through the nephron

Amount excreted is equal to the amount filtered into the tubule, minus the amount reabsorbed into the blood, plus the amount secreted into the tubule lumen

NOTE: Only 20% of the plasma that passes through the glomerulus is filtered; less then 1% (.05) of filtered fluid is eventually excreted [turn to back page for more percentages]
IV. Filtration Occurs Because of Hydrostatic Pressure in the Capillaries [Driving force of Filtration]

a. Hydrostatic Pressure
   i. \( P_h \)
   ii. Blood Pressure (MAP)
   iii. Hydrostatic pressure of blood flowing through glomerular capillaries forces fluid through the leaky endothelium
   iv. \( P_h \) decline along the length of the capillaries but remains higher than opposing pressures, so filtration takes place along nearly the entire length of the glomerular capillaries
   v. Capillary blood pressure averages 55 mm Hg favoring filtration into Bowman's capsule

b. Colloid Osmotic Pressure
   i. \( \pi \)
   ii. Is higher inside glomerular capillaries then that of the fluid in Bowman's capsule
   iii. Pressure gradient due to presence of proteins in the plasma but not in Bowman’s capsule
   iv. Averages 30 mm Hg favoring movement back into the capillaries

c. Hydrostatic Fluid Pressure (Hydrostatic pressure of Filtrate)
   i. \( P_{fluid} \)
   ii. Bowman’s capsule is an enclosed space (unlike interstitial fluid) so it creates hydrostatic pressure that opposes fluid movement into the capsule
   iii. Fluid pressure created by fluid in Bowman’s capsule
   iv. Averages 15 mm Hg opposing filtration
Hypostatic pressure (blood pressure): **INCREASES** efflux

Colloid osmotic pressure: **DECREASES** efflux

Hydrostatic Fluid (filtrate) pressure: **DECREASES** efflux

<table>
<thead>
<tr>
<th>DECREASE FILTRATION</th>
<th>INCREASE FILTRATION</th>
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<tbody>
<tr>
<td>Hypotension</td>
<td>Hypertension</td>
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<tr>
<td>Kidney Stone</td>
<td>Liver Failure</td>
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Liver Failure Explained: Liver produces proteins which help blood bind with water; with less proteins being produced, more fluid will be leaking out because water will have a harder time attaching to blood/plasma without the help of proteins.

d. **Net Driving Force**
   i. Net driving force is **10 mm Hg** in the direction favoring filtration
   ii. Equation:
      \[
      P_H - \pi - P_{fluid} = \text{net filtration pressure}
      \]
      \[
      (55 \text{ mm Hg}) - (30 \text{ mm Hg}) - (15 \text{ mm Hg}) = (10 \text{ mm Hg})
      \]

V. **GFR [Glomerular Filtration Rate]**
a. Volume of fluid that filters into Bowman’s capsule per unit time
b. Average GFR: 125 mL/min or 180 L/day
   i. Kidney filters all 3 liters of blood volume 60 times a day; 2.5 times every hour
c. GFR influenced by TWO factors
   i. Net filtration pressure
   ii. Filtration Coefficient [Two Components]
      1. Surface area of glomerular capillaries available for filtration
      2. Permeability of capillary-Bowman’s capsule interface
d. **Blood Pressure (bp) and Renal Blood Flow (renal arteries) Influence GFR**
   i. Blood pressure provides the \( P_H \) (hydrostatic pressure) that drives glomerular filtration
   ii. Therefore most would assume that if blood pressure goes up so does GFR, but this is not true (blood pressure is NOT DIRECTLY PROPORTIONAL to GFR)
   iii. GFR is remarkably constant over a wide range of blood pressures
      1. Long as blood pressure is between 80-180 mm Hg then GFR averages 180 L/day
   iv. **GFR is controlled primary by regulation of blood flow through the Renal Arteries**
      1. Effect of increased resistance on GFR depends on where the resistance change takes place
      2. **Afferent Arteriole Increase**
         ➢ Hydrostatic pressure decreases → GFR decreases
      3. **Efferent Arteriole Increase**
         ➢ Hydrostatic pressure increases → GFR increases
e. **Autoregulation**
   i. Local control process in which the kidney maintains a relatively constant GFR in the face of normal fluctuations in blood pressure
ii. Two main responses

1. Myogenic Response [intrinsic ability of vascular smooth muscle response to pressure change]
2. Tubuloglomerular Feedback [Paracrine signaling mechanism through which changes in fluid flow through the loop of Henle influence GFR]

**Myogenic Response controls what goes on at the beginning of filtration; beginning of Nephron**

**Tubuloglomerular Feedback, feedbacks from distal tubule to the start at the Nephron**

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**Myogenic Response of Autoregulation**
- Elevated MAP stretches the afferent arteriole wall, that causes stretch-sensitive ion channels to open causing depolarization of muscle cells → leading to arteriole constriction
- Vasconstriction increases resistance to flow, so blood flow through the arteriole diminishes
- A decrease in GFR helps the body conserve blood volume

**Tubuloglomerular Feedback of Autoregulation**
- Local control pathway in which fluid flow through the tubule influences GFR
- Portion of the ascending limb of the Loop of Henle passes between the afferent and efferent arterioles
- This region of the tubular and arteriolar walls are modified in the regions where they contact each other, juxtaglomerular apparatus
  - Macula Densa Cells = sense distal tubule flow and release Paracines that affect afferent arteriole diameter
  - Granular Cells = Juxtaglomerular cells; release renin (enzyme) that is involved with salt and water balance
- When NaCl delivery past macula densa increases as a result of increased GFR, the macula densa cells send a Paracrine message to the neighboring afferent arteriole which then constricts → increasing resistance and decreasing GFR
f. **Hormones and Autonomic Neurons Also Influence GFR (with Sympathetic neurons override Autoregulation)**
   i. Neural control of GFR is mediated by sympathetic neurons that innervate both afferent and efferent arterioles
   ii. Sympathetic innervation of α-receptors causes → vasoconstriction
      1. Normal sympathetic activity has little effect on GFR
      2. During a systemic blood pressure drop (because of hemorrhage/dehydration), sympathetically induced vasoconstriction of the Arterioles occurs to decrease GFR and renal blood flow → conserving blood, fluid volume, and allowing nutrients to travel to vital organs

VI. **FILTRATION IS ESTIMTED BY MESURING CLEARANCE**
   a. Clearance can only estimate filtration if the substance is freely filtered, not reabsorbed and not secreted
      i. Clearance is defined as:
         - The volume of blood per minute from which the solute has been totally (100%) removed
         - The rate at which a solute disappears from the body by excretion or metabolism
      ii. Clearance Rate is an approximation of Filtration Rate
   b. **Creatinine**
      i. Serum Creatinine is a breakdown product of phosphocreatine (energy-storing compound found primary in muscles)
      ii. Used in clinical settings to help estimated GFR
      iii. Constantly produced by the body at a constant rate
      iv. Amount of Serum Creatinine in the Urine/time is equal to the amount Filtered/time
         1. Low Serum Creatinine
            i. Muscular Dystrophy (late stage)
            ii. Myasthenia Gravis (muscles atrophy)
   c. Serum Creatinine (Cr) is inversely proportion to renal creatinine clearance (CrCL)

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<thead>
<tr>
<th></th>
<th>Cr (Serum Creatinine)</th>
<th>CrCL (Serum Creatinine Clearance)</th>
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<tbody>
<tr>
<td><strong>NORMAL</strong></td>
<td>1 mg/dL</td>
<td>120 ml/min</td>
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<tr>
<td><strong>HIGH</strong></td>
<td>2 mg/dL</td>
<td>60 ml/min</td>
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Normal Functioning:

- Serum Cr = 0.8-1.4 mg/dl
- CrCL = 88-137 ml/min

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<thead>
<tr>
<th>CrCL</th>
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<tbody>
<tr>
<td>120 ml/min</td>
<td>NORMAL</td>
</tr>
<tr>
<td>50 ml/min</td>
<td>ADJUST DRUG DOSAGE</td>
</tr>
<tr>
<td>10 ml/min</td>
<td>SYMPTOMS OF RENAL FAILURE</td>
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</tbody>
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i. Low CrCL
   1. Glomerulonephritis (U.T.I) → Affecting Glomerular
   2. Pyelonephritis (U.T.I) → Affecting Pelvis and Ureters
   3. Reduced renal blood flow (Cause of shock, CHF)

d. Creatinine Clearance is directly proportional to GFR
   i. Low CrCL = Low GFR
   ii. High CrCL = High GFR