Chapter 26: The Urinary System

Kidney

--Overview of Kidney Function
  a. Regulation of blood ionic composition
  b. Regulation of blood pH and osmolarity
  c. Regulate blood glucose level (gluconeogenesis)
  d. Regulation of blood volume (conserving or eliminating water)
  e. Regulation of blood pressure (secreting the enzyme rennin, adjusting renal resistance)
  f. Release of erythropoietin and calcitriol (endocrine function)
  g. Excretion of wastes and foreign substances

--External Anatomy of Kidney
  * kidney, adrenal glands, and ureters are retroperitoneal
  * right kidney is lower than left kidney
  * Renal capsule: surrounds each kidney, transparent membrane maintains organ shape
  * Perirenal fat/adipose capsule: engulfs renal capsule and acts as a cushion, helps protect from trauma (nephroptosis)
  * Renal fascia: anchors kidneys to abdominal wall, dense, irregular CT that holds against back body wall
  * Hilum: renal artery, nerve enter and renal vein and ureter exit kidneys

--Internal Anatomy of Kidneys
  * Parenchyma of kidney (functional part):
    a. Renal cortex: superficial layer of kidney (outer area, renal columns)
    b. Renal medulla: inner portion consisting of 8-18 cone-shaped renal pyramids separated by renal columns (cortex), renal papilla point toward center of kidney
    c. Nephron: functional unit of kidney, juxtamedullary and cortical
  * Drainage system fills renal sinus cavity: cuplike structure (minor calyces) collect urine from the papillary ducts of the papilla, minor and major calyces empty into the renal pelvis which empties into the ureter
    a. Major calyces: converge to form pelvis
    b. Minor calyces: papillae extend
  * Renal corpuscle
    a. Bowman’s capsule: outer/parietal and inner/visceral layer
      * Podocytes: cover capillaries to form visceral layer
      * simple squamous cells form parietal layer of capsule
    b. Glomerulus: network of capillaries
  * Arterioles
    a. Afferent: blood to glomerulus
    b. Efferent: drains glomerulus
**Tubules**

- Proximal convoluted tubule
- Loops of Henle (descending limb and ascending limb)
- Distal convoluted tubules

**Collecting ducts**

**Blood and Nerve Supply of Kidney**

- Abundantly supplied with blood vessels: receive 25% of resting cardiac output via renal arteries
- Functions of 2 different capillary beds
  - *Glomerular capillaries*: where filtration of blood occurs (vasoconstriction and vasodilation of afferent and efferent arterioles produce large changes in renal filtration)
  - *Peritubular capillaries*: carry away reabsorbed substances from filtrate
  - *Vasa recta*: supplies nutrients to medulla without disrupting its osmolarity
- Sympathetic vasomotor nerves: regulate blood flow and renal resistance by altering arterioles (vasoconstriction)

**Branches of Renal Arteries**

- Renal artery ➔ segmental arteries ➔ interlobar arteries ➔ arcuate arteries ➔ interlobular arteries ➔ *afferent arterioles* ➔ *glomerular capillaries*
- *Efferent arterioles* ➔ *Peritubular capillaries/vasa recta* ➔ interlobular vein ➔ arcuate vein ➔ *Interlobar vein* ➔ *Segmental vein* ➔ *Renal vein*

**The Nephron**

- Over 1 million nephrons composed of a corpuscle and tubule
- Number of nephrons remains constant from birth (any increase in size of kidney is size increase of individual nephrons)
- Dysfunction is not evident until function declines by 25% of normal
- Removal of one kidney can cause enlargement of remaining until it can filter at 80% of normal rate of 2 kidneys
- Renal corpuscle: site of plasma filtration
  - Glomerulus: capillaries where filtration occurs
  - Glomerular (Bowman’s) capsule: double walled epithelial cup that collects filtrate
- Renal tubule
  - Proximal convoluted tubule
  - Loop of Henle dips down into medulla (descending and ascending)
  - Distal convoluted tubule
collecting ducts and papillary ducts drain urine to the renal pelvis and ureter (drain into minor calyx)

2 types of nephrons
  a. Cortical nephrons: mostly in renal cortex, have short loop of Henle that lie mostly in cortex and dip only into outer portion of renal medulla, loop of Henle receives blood supply from peritubular capillaries
     --80-85% of nephrons are cortical, renal corpuscles are in outer cortex and loops of Henle lie mainly in cortex
  b. Juxtamedullar nephrons: ability to concentrate urine, lie deep in cortex, close to medulla, have long loop of Henle, unlike cortical nephrons, the ascending limb of loop of Henle has thin and thick portions, blood supply from peritubular capillaries and vasa recta
     --15-20% of nephrons, renal corpuscles close to medulla and long loops of Henle extend into deepest medulla enabling excretion of dilute or concentrated urine

Histology of Nephron and Collecting Duct
  *single layer of epithelial cells form walls of entire tube
  *distinctive features due to function of each region (microvilli, cuboidal versus simple, hormone receptors)

History of Each Region
  a. Proximal convoluted tubule
     *simple cuboidal with brush border of microvilli that increase surface area
  b. Descending limb of loop of Henle and thin portion of the ascending limb
     *simple squamous that facilitate diffusion
  c. Ascending limb of loop of Henle
     *simple cuboidal to low columnar that regulate transport
     *forms juxtaglomerular apparatus where it makes contact with afferent arterioles (macula densa is a special part of ascending limb, together with modified smooth muscle cells (juxtaglomerular cells) in afferent arteriole forms juxtaglomerular apparatus (JGA) which plays role in controlling renal BP
  d. Juxtaglomerular Apparatus
     *structure where afferent arteriole makes contact with ascending limb of loop of Henle
     *macula densa is thickened part of ascending limb
*juxtaglomerular cells are modified smooth muscle cells in arterioles

- Distal convoluted and collecting ducts
  *simple cuboidal composed of: Prinicipal cells (have receptors for ADH and aldosterone) and Intercalated cells (have microvilli to control blood pH)

--Types of Capillaries in Kidney
  *the filtration barrier separating blood from space in Bowman’s capsule consists of: fenestrated endothelium, basal lamina, and slit membranes that cover the filtration slits

--Overview of 3 Types of Capillaries
  a. continuous capillaries
    *few intercellular clefts b/w neighboring cells
    *Found in: skeletal m, smooth m, CT, and lungs
  b. Fenestrated capillaries
    *many pores between endothelial cells
    *Found in: kidneys, small intestine, choroid plexuses, ciliary process and endocrine glands
  c. Sinusoids
    *very large fenestrations, incomplete basement membrane
    *Found in: liver, bone marrow, spleen, anterior pituitary, and parathyroid glands

**Ureters and Urinary Bladder**

--Ureters
  *tubes through which urine flows from kidneys to urinary bladder
  *Flow of urine due to:
    a. peristaltic contractions (1-5/min)
    b. gravity and hydrostatic pressure
  *Physiological valve prevents backflow of urine from bladder into ureters: bladder wall compresses opening as it expands during filling
  *Histology of Ureters: 3 layers in wall
    a. Mucosa: transitional epithelium and underlying lamina propria (has collagen, elastic fibers, lymphatic tissue)
      --Elasticity: needed since ureters must inflate and deflate
      --Mucus: secreted by goblet cells, prevents the cells from being contracted by urine
    b. Muscularis: inner longitudinal and outer circular smooth muscle layer (opposite of GI), distal 1/3 has additional longitudinal layer, peristalsis contributes to urine flow
    c. Adventitia: layer of loose CT anchors in place (contains lymphatics and blood vessels to supply ureter)

--Urinary bladder
stores urine
hollow, distensible muscular organ w/ capacity 700-800 mL, changes shape (collapsed, spherical, to pear shape) depending on volume of urine present
rugae
trigone: smooth flat area, not a muscle, bordered by 2 ureteral openings and one urethral opening

Histology of Urinary Bladder (3 layers)
  a. Mucosa: transitional epithelium and lamina propria (since organ must inflate and deflate, mucus prevents the cells from being contracted by urine)
  b. Muscularis (known as detrusor muscle): 3 layers of smooth muscle (longitudinal, circular, longitudinal)
--circular smooth m. fibers form internal urethral sphincter
--circular skeletal m. forms external urethral sphincter
  c. Adventitia: layer of loss CT anchors in place (superior surface has serosal layer/visceral peritoneum)

Urethra
  transports urine from bladder to outside of body
difference in length between males and females
  internal and external urinary sphincters
  Anatomy of Female Urethra
  a. transitional changing to nonkeratinized stratified squamous epithelium, lamina propria with elastic fibers and circular smooth m.
  Anatomy of Male Urethra
  a. passes through prostate, UG diaphragm, and penis
  b. 3 regions of urethra: prostatic, membranous, and spongy
  c. circular smooth m. form sinternal urethral sphincter and UG diaphragm forms external urethral sphincter

Micturition Reflex
  Urine flow: hydrostatic pressure forces urine through nephron, peristalsis moves urine through ureters
  Micturition reflex: stretch of urinary bladder stimulates reflex causing bladder to contract, inhibiting urinary sphincters, higher brain centers can stimulate or inhibit reflex
  a. Stretch receptors signal spinal cord and brain (when volume exceeds 200-400mL)
  b. Impulses sent to micturition center in sacral spinal cord (S2, S3) and reflex is triggered
  --parasympathetic fibers cause detrusor muscle to contract and internal sphincter muscles to relax
  --inhibition of somatic motor neurons innervating skeletal
muscles in the external sphincter

c. Filling causes a sensation of fullness that initiates a desire to urinate before the reflex actually occurs
   --conscious control of external sphincter
   --cerebral cortex can initiate micturition or delay its occurrence for a limited period of time

--Urinary Incontinence
   *Lack of voluntary control over micturition: normal in 2-3 year olds b/c neurons to sphincter muscle are not developed
   *Stress incontinence in adults:
      a. caused by increases in abdominal pressure that result in leaking of urine from the bladder (coughing, sneezing, laughing, exercising, walking)
      b. injury to the nerves loss of bladder flexibility, or damage to the sphincter
      c. smokers have 2x the risk of developing incontinence

--Waste management in Other Body Systems
   *Body buffers bind excess H⁺
   *Blood transports wastes
   *Liver is site for metabolic recycling (conversion of AA into glucose, glucose into fatty acids or toxic into less toxic substances)
   *Lungs excrete CO₂ and liberate heat
   *Sweat glands eliminate heat, water, salt, and urea
   *GI tract eliminates solid wastes, CO₂, water, salts

**Overview of Renal Physiology**

--Nephrons and collecting ducts perform 3 basic processes
   a. Glomerular Filtration
      *a portion of the blood plasma is filtered into the kidney; some waste such as urea, creatine, uric acid, and urates are poorly reabsorbed (clearing in filtrate is important)
   b. Tubular Reabsorption (quantitatively more important)
      *water and useful substances (electrolytes/Na⁺, Cl⁻, HCO₃⁻, aa, glu) are reabsorbed into the blood
   c. Tubular Secretion (usually lowest rate relative to filtration and reabsorption)
      *wastes are removed from the blood and secreted into urine
      *Important in K⁺ and H⁺ excretion

--Urine excretion = filtration rate – reabsorption rate + secretion rate

**Glomerular Filtration**
--blood pressure produces glomerular filtrate
--filtration fraction is 20% of plasma
--48 gallons/day filtrate reabsorbed to leave 1-2 qt. urine
--Filtering capacity enhanced by:
  a. thinness of membrane and large surface area of glomerular capillaries
  b. glomerular capillary BP is high due to small size of efferent arteriole
--Filter membrane
  a. endothelial fenestration of glomerulus: prevents filtration of blood cells
     and platelets but allows all components of blood plasma to pass through
     — coarsest
  b. Basal lamina of glomerulus: prevents filtration of large plasma proteins
  c. Silt membrane between pedicles: prevents filtration of medium-sized
     proteins, not small ones
--Glomerular filterability depends on:
  a. size: filterability of solutes is inversely related to their size
  b. shape
  c. electrical charge: negatively charged large molecules are filtered less easily
     than positively charged molecules of equal molecular size b/c intracellular
     mem. proteins w/ negative charge (phospholipids)
--Glomerular Filtration Rate
  a. Amount of filtrate formed in all renal corpuscles of both kidneys per
     minute (adult male is 125mL/min)
  b. Homeostasis requires GFR that is constant (too high and useful substances
     are lost due to the speed of fluid passage through nephron, too low and
     sufficient waste products may not be removed from the body)
  c. Changes in net filtration pressure affects GFR (filtration stops if GBHP
     drops to 45mmHg, functions normally with mean arterial pressures 80-
     180)
--Determinants of glomerular filtration rate (GFR)
  *GFR = K_f x NFP where:
      K_f is capillary filtration coefficient /permeability (constant),
      this is the highest of any capillary bed (glomerulus)
      NFP is net filtration pressure is sum of hydrostatic and colloid
      osmotic pressures
--Net Filtration Pressure depends on:
  a. Glomerular (capillary) hydrostatic pressure: promotes filtration
  b. Capsular/Bowman’s hydrostatic pressure: oppose filtration (reabsorption)
  c. Blood capillary colloid osmotic pressure: opposes filtration (reabsorption)
  d. Capsular colloidal osmotic pressure: promotes filtration
     **NFP = (a + d) – (b + c) or a - b – c because d is usually 0
     **NFP = total pressure that promotes filtration
     **NFP = GBHP – (CHP + BCOP) = 10mmHg
--GFR = K_f x (filtration forces – opposing forces)
Factors that affect GFR:

a. Increased capillary filtration coefficient \((K_f)\) increases GFR. Under normal conditions \(K_f\) does not change and thus is not used for regulation of GFR (some diseases may reduce it—hypertension, diabetes mellitus increases thickness of basement membrane)

b. Increased Bowman’s capsule hydrostatic pressure: decreases GFR (obstruction of urinary tract)

c. Increased glomerular capillary colloid osmotic pressure: decreases GFR (dehydration)

d. Increased glomerular capillary hydrostatic pressure: increases GFR (systemic hypertension)

Factors that determine glomerular hydrostatic pressure:

a. arterial pressure: increase in arterial pressure increases hydrostatic pressure (However, blood pressure is maintained within limits)

b. Afferent arteriolar resistance: reduces hydrostatic pressure

c. Efferent arteriolar resistance: increases hydrostatic pressure

Renal Blood Flow (RBF)

\[
RBF = \frac{\text{pressure of renal a.} - \text{pressure of renal v.}}{\text{renal vascular resistance}}
\]

*Renal a. and v. pressures are similar to systemic arterial and venous pressures

*The total renal resistance is due mostly to resistance in:

a. interlobular artery

b. afferent arterioles

c. efferent arterioles

*all three are controlled by sympathetic NS, hormonal control, and various renal mechanisms

Filtration Fraction: the fraction of blood plasma that is filtered by the glomerular capillaries

*Filtration fraction = GFR/renal plasma flow

*Filtration fraction can be increased by:

a. increasing GFR

b. Decreasing renal blood flow

*Under normal conditions, about 20% of blood plasma is filtered with each passing through the glomerular capillaries

*Increasing the filtration fraction will lead to increase of blood colloid pressure and vice versa (more filtered \(\rightarrow\) more conc. protein in blood therefore inc. colloid pressure therefore inc. reabsorption)

Control of Glomerular Filtration and Renal Blood Flow

a. Autoregulation

*myogenic mechanism: detects changes in arterial pressures (systemic increases in BP, stretch the afferent arteriole,
smooth muscle contraction reduces the diameter of the arteriole
returning the GFR to its previous level in seconds)

*Tubuloglomerular feedback: detects changes in HaCl in tubular fluid
a. elevated system BP raises the GFR, so that fluid flows too
rapidly through the renal tubule and Na, Cl, and water
are not reabsorbed
b. macula densa detects that difference (the increase in NaCl)
and inhibits the release of NO (a vasodilator/inc.
filtration rate) from the juxtaglomerular
apparatus c. afferent arterioles constriction and
reduce GFR

b. Neuronal
*BLOOD vessels of the kidney are supplied by sympathetic fibers that
cause vasoconstricticton of afferent arterioles
*at rest renal BV are maximally dilated b/c sympathetic activity is
minimal (renal autoregulation prevails)
*With moderate sympathetic stimulation, both afferent and efferent
arterioles constrict equally (decreasing GFR only slightly)
*With extreme sympathetic stimulation (exercise/hemorrhage),
vasoconstriction of afferent arterioles reduces GFR (lowers urine
output and permits blood flow to other tissues)

c. Hormonal
*Atrial natrioretic peptide (ANP): increases GFR (stretching of the
atria that occurs with an increase in blood volume causes
hormonal release—decreases blood volume//relaxes glomerular
mesangial cells increasing capillary surface area and increasing
GFR)

*Angiotensin II: reduces GFR (RAA system) (potent vasoconstrictor
that constricts both afferent and efferent arterioles reducing GFR
due to inc. BP)
*Renin: release is stimulated by a decrease in BP (decreases GFR, inc.
BP)
*Epi/Norepi: cause vasoconstricticton
*NO: decreases renal vascular resistance (increases GFR)—most
potent vasodilator
*Prostaglandins and bradykinins: increases GFR
*Endothelin: a powerful vasoconstrictor

Tubular Reabsorption

--Reabsorption
a. passive transport
b. active transport
c. cotransport
--Specialization of tubule segments
--Substances transported
  a. active transport: moves Na\(^+\) across nephron wall
  b. Other ions molecules moved by cotransport
  c. passive transport moves water, urea, lipid-soluble, nonpolar cmpds
--normal GFR is so high that volume of filtrate in capsular space in 30 min is greater than the total plasma volume
--Nephron must reabsorb 99% of the filtrate
  *PCT with their microvilli do most of the work with rest of nephron doing just the fine-tuning (solute reabsorbed by active and passive processes, water follows by osmosis, small proteins by pinocytosis)
--Important function of nephron is tubular secretion
  *transfer of material from blood into tubular fluid (helps control blood pH because of secretion of H\(^+\), helps eliminate certain substances (ammonia, creatinine, K\(^+\))
--Reabsorption Routes
  a. Paracellular reabsorption: 50% of reabsorbed material moves b/w cells by diffusion in some parts of tubule
  b. Transcellular reabsorption: material moves through both the apical and basal membranes of the tubule cell by active transport
--Transport Mechanisms
  a. Apical and basolateral membranes of tubule cells have different types of transport proteins
  b. Reabsorption of Na\(^+\) is important
    * several transport systems exist to reabsorb Na\(^+\)
    * Na\(^+\)/K\(^+\) ATPase pumps sodium from tubule cell cytosol through the basolateral membrane only
  c. Water is only reabsorbed by osmosis
    * Obligatory water reabsorption occurs when water is obliged to follow the solutes being reabsorbed
    * facultative water reabsorption occurs in collecting duct under the control of ADH
--Glucosuria
  * renal symporters cannot reabsorb glucose fast enough if blood glucose level is above 200mg/mL (some glucose remains in the urine)
  * Common cause is diabetes mellitus because insulin activity is deficient and blood sugar is too high
  * Rare genetic disorder produces defect in symporter that reduces its effectiveness
--Reabsorption in the PCT (1st half)
*Na\(^+\) symporters help reabsorb materials from the tubular filtrate
*glucose, aa, lactate, citrate, phosphate, water-soluble vitamins and other nutrients are COMPLETELY reabsorbed in 1st half of PCT
*Intracellular sodium levels are kept low due to Na\(^+\)/K\(^+\) pump
*Na\(^+\) transporters:
  a. Na/K ATPase
  b. Na/H antiporters
  c. Na/various substances symporters

--Reabsorption of HCO\(_3^-\), Na\(^+\), and secretion of H\(^+\)
  a. Na antiporters reabsorb Na and secrete H\(^+\)
  *PCT cells produce the H\(^+\) and release bicarbonate ion to the peritubular capillaries, important buffering system
  b. Reabsorption of filtered HCO\(_3^-\)
  *for every H\(^+\) secreted into the tubular fluid, one filtered bicarbonate eventually returns to the blood
  c. angiotensin II stimulates the Na/H pump resulting in HCO\(_3^-\) reabsorption

--Passive Reabsorption in the 2nd Half of PCT
  a. Electrochemical gradients produced by symporters and antiporters cause passive reabsorption of other solutes
  b. Cl, K, Ca\(^++\), Mg\(^++\) and urea passively diffuse into the peritubular capillaries
  c. Promotes osmosis in PCT (especially permeable due to aquaporin 1 channels)

--Secretion of NH\(_3\) and NH\(_4\) in PCT
  a. Ammonia is a poisonous waste product of protein deamination in the liver (most is converted to urea which is less toxic)
  b. Both ammonia and urea are filtered at the glomerus and secreted in the PCT
  c. PCT cells deaminate glutamine in a process that generates both NH\(_3\) and new HCO\(_3^-\)
  d. Bicarbonate diffuses into the bloodstream (during acidosis more bicarbonate is generated)
  e. Isomotic reabsorption is a hallmark of PCT → high oncotic osmotic pressure in peritubular capillaries drive the reabsorption of isosmotic fluid

--Reabsorption in the Loop of Henle
*tubular fluid leaving the PCT has similar osmolarity to plasma but very different composition
  a. PCT reabsorbed 67% of the filtered water
  b. chemical composition of tubular fluid in the loop of Henle is quite different form plasma
  c. since many nutrients were reabsorbed as well, osmolarity of tubular fluid is close to that of plasma
*Sets the stage for independent regulation of both volume and osmolarity of body fluids
*Thin descending and thin ascending limbs of loop of Henle are permeable to small solutes
  ~the thin descending (but not the thick, ascending) limb is permeable to water
*Permeability and movement of solutes (in/out) in the thin limbs are passive processes, as opposed to the PCT

--Symporters in the Loop of Henle (THICK portion of ascending limb)
  *not permeable to water
  *thick limb of loop of Henle has Na/K/2Cl symporters that reabsorb these ions (about 25% of filtered Na is reabsorbed here)
  *K leaks through K channels back into the tubular fluid leaving the interstitial fluid and blood with a negative charge
  *Cations passively move to the vasa recta

--Reabsorption in the DCT
  *removal of Na and Cl continues in the DCT by means of Na/Cl symporter
  *Na and Cl are reabsorbed into peritubular capillaries
  *DCT is the major site where PTH stimulates reabsorption of Ca++
  *DCT and thick ascending limb of loop of Henle are not permeable to water

--Reabsorption and Secretion in the Collecting Duct
  *By end of DCT, 95% of solutes and water have been reabsorbed and returned to the bloodstream
  *Cells in the collecting duct make the final adjustments
    a. Principal cells: reabsorb Na and secrete K, regulated by ADH and aldosterone, fluid volume
    b. Intercalated cells: reabsorb K and HCO\(_3^-\) and secrete H\(^+\), pH reg..

--Actions of Principal Cells
  a. Na enters principal cells through leakage channels
  b. Na pumps keep the conc. of Na in the cytosol low
  c. Cells secrete variable amounts of K to adjust for dietary changes in K intake (down conc. gradient due to Na/K pump)
  d. Aldosterone increases Na and water reabsorption and K secretion by principal cells by stimulating the synthesis of new pumps and channels

--Secretion of H and Absorption of HCO\(_3^-\) by Intercalated Cells
  a. Proton pumps (H\(^+\) ATPases) secrete H into tubular fluid: can secrete against a conc. gradient so urine can be 1000 times more acidic than blood (3 pH units)
  b. Cl/HCO\(_3^-\) antiporters move bicarbonate ions into the blood (intercalated cells help regulate pH of body fluids)
  c. Urine is buffered by HPO\(_4^{2-}\) and ammonia, both of which combine irreversibly with H and are excreted
Urine Production

--In proximal tubules:
   a. Na and other substances removed
   b. water follows passively
   c. filtrate volume reduced

--In descending limb of loop of Henle
   a. water exits passively, solutes enter (making filtrate hyperosmotic)
   b. filtrate volume reduced 15%

--In ascending limb of loop of Henle
   a. Na, Cl, K transported out of filtrate
   b. water remains (making filtrate hypoosmotic)

--In distal tubules and collecting ducts
   a. water movement out is regulated by ADH
      *if absent: water is not reabsorbed and dilute urine produced
      *if present: water moves out, concentrated urine is produced

--Urine Concentration Mechanism
   a. When large volume of water consumed:
      *eliminate excess without losing large amounts of electrolytes
      *response in kidneys produce large volume of dilute urine
   b. When water is not available:
      *kidneys produce small volume of conc. urine
      *removes waste and prevents rapid dehydration
      *obligatory urine volume (0.5 liters/day); the maximal concentrating
         ability of kidney (min. volume need to lose to get rid of waste)

--Production of Dilute or Concentrated Urine
   *homeostasis of body fluids despite variable fluid intake
   *kidneys regulate water loss in urine
   *ADH controls whether dilute or conc. urine is formed (if ADH is lacking,
      urine contains high ratio of water to solutes)
   *Requirements for excreting Concentrated Urine:
      a. High level of ADH: increases water permeability in the DCT and
         collecting ducts (water reabsorption)
      b. High osmolarity in the renal medulla (interstitial spaces) to provide
         osmotic ‘pull’ for water out of tubules
      *Renal medulla becomes hyperosmotic via:
         1. anatomical arrangements and differential secretion
            ability of loops of Henle, vasa recta, and
            peritubular capillaries
         2. Coutercurrent mechanisms
         3. urea recycling

*Major Factors contributing to Solute Buildup in the Renal medulla:
a. Active transport of Na out of thick portion of ascending loop of Henle into medullar interstitium
b. Active transport of ions out of collecting ducts into renal medulla
c. Passive diffusion of large amounts of urea form collecting ducts into medullary interstitium
d. Little or no diffusion of water out of DCT and collecting ducts (ADH)

--Countercurrent Mechanism
*Descending limb is very permeable to water: higher osmolarity of interstitial fluid outside the descending limb causes water to move out of the tubule by osmosis (1200 mOsm/liter at bottom of turn)
*Ascending limb is impermeable to water, but symporters remove Na and Cl so osmolarity drops to 100 mOsm/liter
*vasa recta blood flowing in opposite directions that the loop of Henle provides nutrients and O2 without affecting osmolarity of interstitial fluid

--Formation of Concentrated Urine
*compensation for low water intake or heavy perspiration
*urine can have up to 4x greater osmolarity than plasma
*it is possible for principal cells and ADH to remove water form urine to that extent, if interstitial fluid surrounding the loop of Henle has high osmolarity (long loop of juxtamedullary nephrons make that possible via countercurrent mechanism//Na/K/2Cl symporters reabsorb Na and Cl from tubular fluid to create osmotic gradient in the renal medulla
*cells in the collecting ducts reabsorb more water and urea when ADH is increased
*Urea recycling: causes a buildup of urea in the renal medulla

--Formation of Dilute Urine
*Dilute: having fewer solutes than plasma (200 mOsm/liter)—diabetes insipidus due to lack of ADH
*Filtrate and blood have equal osmolarity in PCT
*Water reabsorbed in thin limb, but ions reabsorbed in thick limb of loop of Henle create a filtrate more dilute than plasma (can be 4x as dilute as plasma, as low as 65 mOsm/liter)
*Principal cells d/n reabsorb water if ADH is LOW

**Hormones**

--Hormonal Mechanisms
a. ADH
   *secreted by posterior pituitary
   *increases water permeability in distal tubules and collecting ducts
b. Aldosterone
   *produced in adrenal cortex
*affects Na and Cl transport in nephron and collecting ducts

c. Renin
*produced by kidneys, causes production of angiotensin II
d. Atrial natriuretic hormone (ANP)
*produced by heart when blood pressure increases (inhibits ADH, reduces ability of kidney to conc. urine, dec. blood pressure)

--Hormonal Regulation
*Hormones that affect Na, Cl, and water reabsorption and K secretion in the tubules

a. Angiotensin II and Aldosterone: decreases GFR by vasoconstricting afferent arteriole, enhances absorption of Na by activating Na/H antiporters in PCT, promotes aldosterone production which causes principal cells to reabsorb more Na and Cl, increases blood volume by increasing water reabsorption

b. Atrial Natriuretic Peptide: inhibits reabsorption of Na and water in PCT, suppresses secretion of aldosterone and ADH, increase excretion of Na which increases urine output and dec. blood volume

c. ADH: increases water permeability of principal cells so regulates facultative water reabsorption, stimulates the insertion of aquaporin-2 channels into the membrane (water molecules move more rapidly), and when osmolarity of plasma and interstitial fluid increases more ADH is secreted and facultative water reabsorption increases

Diuretics

--Substances that slow renal reabsorption of water and cause diuresis (increased urine flow rate)

a. caffeine: inhibits Na reabsorption
b. alcohol: inhibits secretion of ADH
c. prescription medicines can act on the PCT, loop of Henle, or DCT

Evaluation of Kidney Function

--Urinalysis
a. analysis of the volume and properties of urine
b. normal urine is protein free, but includes filtered and secreted electrolytes (urea, creatinine, uric acid, urobilinogen, fatty acids, enzymes, and hormones)

--Blood Tests
a. Blood urea nitrogen Test (BUN): measures urea in blood (rises steeply if GFR decreases severely)
b. plasma creatinine: from skeletal muscle breakdown
c. renal plasma clearance of substance form the blood in ml/min (drug dosage)

--Dialysis Therapy

* Kidney function is severely impaired and blood must be cleansed artificially (separation of large solutes form smaller ones by a selectively permeable membrane)

* Artificial kidney machine performs hemodialysis (directly filters blood b/c blood flows through dialysis tubing surrounded by solution, cleansed blood flows back into the body)

**Clearance and Tubular Load**

--Plasma Clearance

* volume of plasma cleared of a specific substance each minute

* \( C = \frac{UV}{P} \)

\( U = \) [substance] in urine (mg/mL)

\( V = \) urine flow—urine volume/unit time (mL/min)

\( P = \) [substance] in plasma (mg/mL)

* URINARY EXCRETION RATE = \( UV \) mg/min

* used to estimate GFR

* used to calculate RPF (renal plasma flow)

* used to determine which drugs or other substances are excreted by kidney

--Tubular Load

* total amount of substance that passes through filtration membrane into nephrons each minute

* normally glucose is almost completely reabsorbed

--Plasma clearance rate can be used to determine glomerular filtration rate:

* Inulin is the ‘gold standard’ because:

  a. it is freely filterable by the glomeruli
  b. it is not reabsorbed
  c. it is not secreted by the kidney
  d. it is not synthesized, destroyed, or stored (the filtered load equals the rate of inulin excretion)
  e. it is nontoxic
  f. its conc. in urine and plasma can be determined easily

* Drawbacks of Inulin:

  a. must be infused intravenously
  b. bladder is catheterized b/c urine collection is over short time

* Alternative to Inulin:

  a. Creatinine: continuously produced by the body and is excreted in
urine and its levels are relatively constant over long periods

*Note that:
  a. if GFR is reduced by 50%, creatinine plasma conc. doubles
  b. At low GFR, small absolute changes in GFR result in much greater changes in plasma creatinine conc.
  c. high plasma creatinine conc. indicates low GFR (diagnostic tool)

--Determination of reabsorption
  a. glucose is completely reabsorbed substance
  b. at normal glu levels, all of filtered glucose is reabsorbed
  c. at elevated glu (200 and above), glu appears in urine (glu threshold)
  d. as plasma glu inc. further, more is filtered // reabsorption reaches max due to saturation fo glu transporters // transport maximum is the maximum rate at which glucose can be reabsorbed from the tubules

--Determination of secretory function of kidneys
  a. for a substance to be completely cleared (in addition to glomerular filtration) it must be secreted
  b. there is no known substance that is 100% cleared by the kidneys
     * PAH is almost (90%) cleared by glomerular filtration and tubular secretion; used for determination of renal plasma flow
  c. Extraction Ratio (E) – difference b/w renal arterial (P_a) and venous (P_v) concentration, divided by arterial concentration (P_a)
  d. Total renal plasma flow (RPF) = C/extraction rate
  e. Renal blood flow (RBF) = RPF/(1-hemocrit)
  f. Filtration fraction (FF)) = fraction of plasma that filters through the glomerulus, need to know RPF and GFR
     \[ FF = \frac{GFR}{RPF} \]

--Measuring reabsorption or secretion:
  * if filtration rate is higher than excretion rate, then the substance must be reabsorbed
  * if filtration rate is lower than excretion rate, then the substance must be secreted