Kidney Function

- Is to regulate plasma and interstitial fluid by formation of urine
- In process of urine formation, kidneys regulate:
  - Volume of blood plasma, which contributes to BP
  - Waste products in plasma
  - Concentration of electrolytes
    - Including Na⁺, K⁺, HCO₃⁻, and others
  - Plasma pH
Gross Structure of the Urinary System

Structure of Urinary System

- Paired kidneys are on either side of vertebral column below diaphragm
  - About size of fist
- Urine flows from kidneys into ureters which empty into bladder
- Urethra drains urine from bladder

Structure of Kidney

- Cortex contains many capillaries and outer parts of nephrons
- Medulla consists of renal pyramids separated by renal columns
- Pyramid contains minor calyces which unite to form a major calyx
Structure of Kidney

- Major calyces join to form the renal pelvis which collects urine
- Conducts urine to ureters which empty into bladder

Microscopic Structure of the Kidney

Renal Blood Vessels

- Blood enters kidney through renal artery
  - Which divides into interlobar arteries
    - That divide into arcuate arteries that give rise to interlobular arteries
  - Interlobular arteries give rise to afferent arterioles which supply glomeruli
  - Glomeruli are mass of capillaries inside glomerular capsule that gives rise to filtrate that enters nephron tubule
  - Efferent arteriole drains glomerulus and delivers that blood to peritubular capillaries (vasa recta)
  - Blood from peritubular capillaries enters interlobular veins
Nephron

- Is functional unit of kidney; responsible for forming urine
- >1 million nephrons/kidney
- Consists of small tubes and associated small blood vessels
Type of Nephrons

- **Cortical nephrons** originate in outer 2/3 of cortex
- **Juxtamedullary nephrons** originate in inner 1/3 cortex
- Have long LHs
- Important in producing concentrated urine

Formation of Urine

Glomerular Filtration
Glomerular Filtration

- Glomerular capillaries and Bowman's capsule form a filter for blood
- Glomerular Caps are fenestrated—have large pores between its endothelial cells
  - Big enough to allow any plasma molecule to pass
  - 100-400 times more permeable than other Caps

Glomerular Filtration continued

- To enter tubule filtrate must pass through narrow slit diaphragms formed between pedicels (foot processes) of podocytes of glomerular capsule

Glomerular Filtration continued

- Plasma proteins are mostly excluded from the filtrate because of large size and negative charge
  - The slit diaphragms are lined with negative charges which repel negatively-charged proteins
  - Some protein (especially albumin) normally enters the filtrate but most is reabsorbed by receptor-mediated endocytosis
  - Proteinuria = Defects in the slit diaphragm results in massive leakage of protein in the filtrate and thus appears in the urine
The Formation of Glomerular Ultrafiltrate

- Only a fraction of plasma proteins (green) are filtered.
- Smaller plasma solutes (purple) easily enter the glomerular ultrafiltrate.
Glomerular Filtration Rate (GFR)

- Is volume of filtrate produced by both kidneys/min
  - Averages 115 ml/min in women; 125 ml/min in men
  - Totals about 180L/day (45 gallons)
    - So most filtered water must be reabsorbed or death would ensue from water lost through urination

Regulation of GFR

- Is controlled by
  - extrinsic (sympathetic nervous system)
  - intrinsic (renal autoregulation) mechanisms
  - Vasoconstriction or dilation of afferent arterioles affects rate of blood flow to glomeruli and thus GFR

Sympathetic Effects

- Sympathetic activity constricts afferent arteriole
- Helps maintain BP and shunts blood to heart and muscles
Renal Autoregulation

- Defined as the ability of kidneys to maintain relatively constant GFR in the face of fluctuating B.P.
- 2 mechanisms responsible:
  - Myogenic constriction of afferent arteriole due to smooth muscle responding to an increase in arterial pressure
  - Achieved via effects of locally produced chemicals on afferent arterioles part of tubuloglomerular feedback

Juxtaglomerular Apparatus (JGA)

- Renal Autoregulation is also maintained by negative feedback between afferent arteriole and volume of filtrate (tubuloglomerular feedback)
- Increased flow of filtrate sensed by macula densa (part of juxtaglomerular apparatus) in thick ascending LH
- Signals afferent arterioles to constrict
Reabsorption of Salt and Water

- In PCT returns most molecules and H₂O from filtrate back to peritubular capillaries
- About 180 L/day (45 gallons) of ultrafiltrate produced; only 1–2 L of urine excreted/24 hours
- Urine volume varies according to needs of body
- Minimum of 400 ml/day urine necessary to excrete metabolic wastes (obligatory water loss)

Table 17.1 Regulation of the Glomerular Filtration Rate (GFR)

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Stimulus</th>
<th>Afferent Arteriole</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic nerves</td>
<td>Activation by baroreceptor reflex or by higher brain centers</td>
<td>Constricts</td>
<td>Decreases</td>
</tr>
<tr>
<td>Autoregulation</td>
<td>Decreased blood pressure</td>
<td>Dilates</td>
<td>No change</td>
</tr>
<tr>
<td>Autoregulation</td>
<td>Increased blood pressure</td>
<td>Constricts</td>
<td>No change</td>
</tr>
</tbody>
</table>

Minimum of 400 ml/day urine necessary to excrete metabolic wastes (obligatory water loss)
Reabsorption of Salt and H₂O

- The transport of molecules out of the tubular filtrated back into the blood = **reabsorption**
- Water is never transported
- Other molecules are transported and water follows by osmosis

**The Mech. of Reabsorption in the proximal tubule**

- There is coupled transport of glucose and Na⁺ into the cytoplasm &
- Primary active transport of Na⁺ across basolateral membrane by Na⁺/K⁺ pump
- Glucose is then transported out of cell by facilitated diffusion and is reabsorbed into the blood

**Salt and water reabsorption in the proximal tubules:**

- Cl⁻ transport (passive)
- Na⁺ transport (active)
- H₂O follows salt by osmosis
- Fluid reduced to 1/3 original volume, but still isosmotic
Significance of PCT Reabsorption

- ~65% Na⁺, Cl⁻, and H₂O is reabsorbed in PCT and returned to bloodstream
- An additional 20% is reabsorbed in descending loop of Henle
- Thus 85% of filtered H₂O and salt are reabsorbed early in tubule
- This is constant and independent of hydration levels
- Energy cost is 6% of calories consumed at rest
- The remaining 15% is reabsorbed variably, depending on level of hydration

Concentration Gradient in Kidney

- In order for H₂O to be reabsorbed, interstitial fluid must be hypertonic
- Osmolality of medulla interstitial fluid (1200-1400 mOsm) is 4X that of cortex and plasma (300 mOsm)
- This concentration gradient results largely from loop of Henle which allows interaction between descending and ascending limbs

The Countercurrent Multiplier System

- Extrusion of NaCl from ascending limb makes surrounding interstitial fluid more concentrated
- Multiplication of concentration due to descend. limb passively permeable to water—causing fluid to inc. in concen. as the surrounding interstitial fluid more concen.
- Deepest region of medulla at 1,400mOsm
Ascending Limb Loop of Henle

- Has a thin segment in depths of medulla and thick part toward cortex
- Impermeable to H₂O; permeable to salt; thick part actively transports salt out of filtrate
- Active transport of salt causes filtrate to become dilute (100 mOsm) by end of Loop of Henle

The Transport of Ions in the Ascending Limb

- In thick segment, Na⁺ and K⁺ together with 2 Cl⁻ enter tubule cells
- Na⁺ then actively transported out into interstitial space and Cl⁻ follows passively
- K⁺ diffuses back into filtrate; some also enters interstitial space

AT in Ascending Limb LH

- Na⁺ is actively transported across basolateral membrane by Na⁺/K⁺ pump
- Cl⁻ passively follows Na⁺ down electrical gradient
- K⁺ passively diffuses back into filtrate
Countercurrent Multiplier System

- Countercurrent flow and proximity allow descending and ascending limbs of Loop of Henle to interact in a way that causes osmolality to build in medulla.
- Salt pumping in thick ascending part raises osmolality around descending limb, causing more H₂O to diffuse out of filtrate.
- This raises osmolality of filtrate in descending limb which causes more concentrated filtrate to be delivered to ascending limb.
- As this concentrated filtrate is subjected to Active Transport of salts, it causes even higher osmolality around descending limb (positive feedback).
- Process repeats until equilibrium is reached when osmolality of medulla is 1400.

The Role of Urea in Urine Concentration

- Urea diffuses out of inner collect. duct into interstitial fluid in medulla.
- Urea then passes into ascend. limb so it recirculates in interstitial fluid in medulla.
- Water is reabsorbed by osmosis from collect. duct.

Collecting Duct (CD)

- Plays important role in water conservation.
- Is impermeable to salt in medulla.
- Permeability to H₂O depends on levels of ADH.

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Renogran</th>
<th>Secretion of ADH</th>
<th>Effects on Urine Volume</th>
<th>Effects on Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased water pressure, decreased blood osmolality</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased blood volume</td>
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<td>Increased blood volume</td>
</tr>
</tbody>
</table>
Homeostasis of Plasma Concentration Maintained by ADH

- Is secreted by post pituitary in response to dehydration
- Stimulates insertion of aquaporins (water channels) into plasma membrane of Collect. Duct
- When ADH is high, H$_2$O is drawn out of CD by high osmolality of interstitial fluid
- And reabsorbed by vasa recta

Osmolality of Different Regions of the Kidney

Renal Plasma Clearance
Secretion is the Opposite of Reabsorption

- The active transport of substances from the peritubular capillaries into the tubular fluid = secretion
- Secretion is opposite in direction to that which occurs in reabsorption
- Reabsorption decreases renal clearance; secretion increases renal clearance

Renal Clearance

- Excretion rate = (filtration rate + secretion rate) - reabsorption rate

Measurement of Renal Blood Flow

- Not all blood delivered to glomerulus is filtered into glomerular capsule
  - 20% is filtered; rest passes into efferent arteriole and back into circulation
  - Substances that aren't filtered can still be cleared by active transport (secretion) into tubules
Glucose and Amino Acid Reabsorption

- Filtered glucose and amino acids are normally 100% reabsorbed from filtrate
- Occurs in Proximal Tubule by carrier-mediated cotransport with Na+
  - Transporter displays saturation if ligand concentration in filtrate is too high
  - Level needed to saturate carriers and achieve maximum transport rate is transport maximum ($T_m$)
- Glucose and amino acid transporters don't saturate under normal conditions

Role of Aldosterone in Na$^+$/K$^+$ Balance

- 90% filtered Na$^+$ and K$^+$ reabsorbed before Distal Tub.
- Remaining is variably reabsorbed in Distal Tub. and cortical Collect. Duct according to bodily needs
  - Regulated by aldosterone (controls K$^+$ secretion and Na$^+$ reabsorption)
  - In the absence of aldosterone, 80% of remaining Na$^+$ is reabsorbed in Distal Tub. and cortical Collect. Duct
  - When aldosterone is high all remaining Na$^+$ is reabsorbed

K$^+$ is Reabsorbed and Secretion

- K$^+$ almost completely reabsorbed in prox. tubule
- Under aldosterone stim. secreted into cortical collect. Ducts
- All K$^+$ in urine from secretion rather than filtration
Juxtaglomerular Apparatus (JGA)

- Is specialized region in each nephron where afferent arteriole comes in contact with thick ascending limb LH

Renin-Angiotensin-Aldosterone System

- Is activated by release of renin from granular cells within afferent arteriole
  - Renin converts angiotensinogen to angiotensin I
  - Which is converted to Angio II by angiotensin-converting enzyme (ACE) in lungs
  - Angio II stimulates release of aldosterone
Macula Densa

- Located where tubule cells make contact with granular cells
- Acts as sensor for tubuloglomerular feedback; needed for autoreg. of GFR
  - Signals afferent arteriole to constrict
  - Signals granular cells to dec. secretion of renin when blood Na+ is inc.

Atrial Natriuretic Peptide (ANP)

- Is produced by atria due to stretching of walls
- An aldosterone antagonist
- Stimulates salt and H₂O excretion
- Acts as an endogenous diuretic