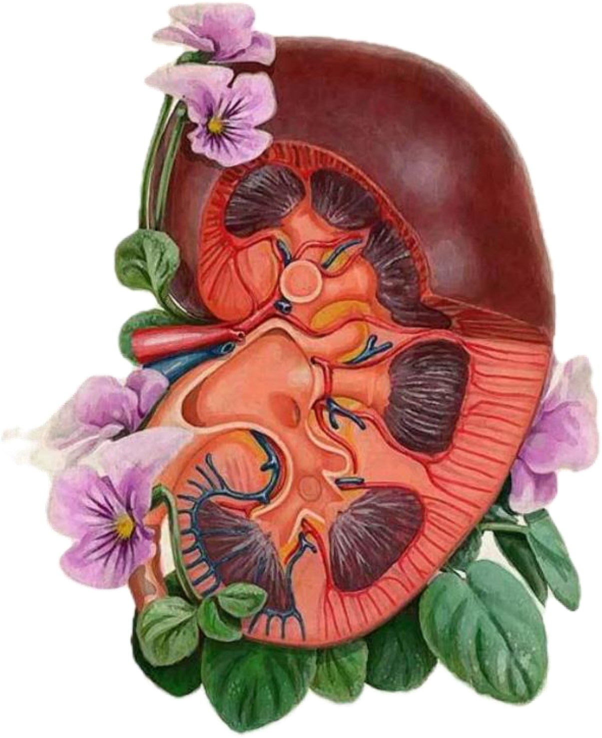
UGS Physiology Sheet 7



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Acute Kidney Injury (AKI) Recovery:

- Following AKI, the kidneys can eventually return to normal function (up to 85%), but this can take time.
- The **very last function to return to normal** is the kidney's ability to concentrate on urine. So if this is back to normal, then all other functions will also have returned to normal.

Obligatory Urine Output & Solute Excretion:

- A normal individual on a standard diet and exercise regimen generates around 1000 mOsm/day of waste (including urea, creatinine, sodium, potassium, and chloride) that must be excreted. If he exercises more, the solute load will increase. If he is bedridden and not eating, the obligatory solute load decreases to a minimum of approximately 600–700 mOsm/day even in the absence of oral intake.

The baseline plasma osmolarity is 300 mOsm/L. Normal urine is usually hypertonic (more concentrated) compared to plasma, typically yielding a daily output of about 1.5 liters.

Minimum Obligatory Urine Output: Minimum Obligatory Urine Output = Total daily waste (mOsm) / Maximum concentrating ability of the kidney (mOsm/L).

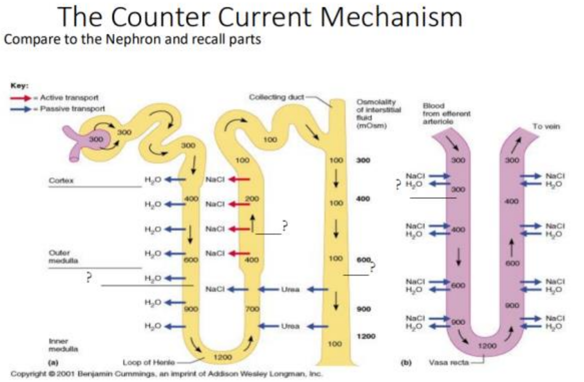
  - The maximal concentrating ability of the kidney dictates how much urine volume must be excreted each day to rid the body of metabolic waste products and ions that are ingested. A normal 70-kilogram human must excrete about 700 milliosmoles of solute each day. If maximal urine concentrating ability is 1400 mOsm/L, the minimal volume of urine that must be excreted — called the obligatory urine volume — can be calculated as: 700 mOsm/day ÷ 1400 mOsm/L = **0.5 L/day.**

- **Oliguria:** Defined as a urine output of **less than 500 mL/day.** In clinical settings, this is measured hourly; an output of less than 20 mL/hour (e.g., observing only 10 mL in half an hour) alerts the physician to kidney impairment.
- **Anuria:** Defined as a urine output of **less than 100 mL/day (not strictly zero).**

Countercurrent Mechanism

- The kidneys create concentrated urine by establishing an osmotic gradient from the cortex down into the medulla.

The osmolarity of interstitial fluid in almost all parts of the body is about 300 mOsm/L, which is like the plasma osmolarity. The interstitial fluid in the medulla of the kidney is much higher and may increase progressively to about 1200 to 1400 mOsm/L in the pelvic tip of the medulla. This means that the renal medullary interstitium has accumulated solutes in great excess of water. Once the high solute concentration in the medulla is achieved, it is maintained by a balanced inflow and outflow of solutes and water in the medulla.


The Counter Current Mechanism

Compare to the Nephron and recall parts

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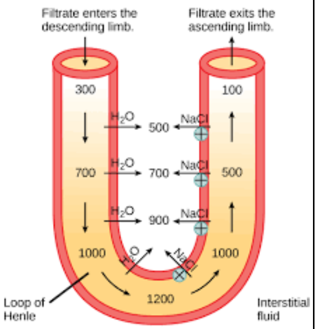
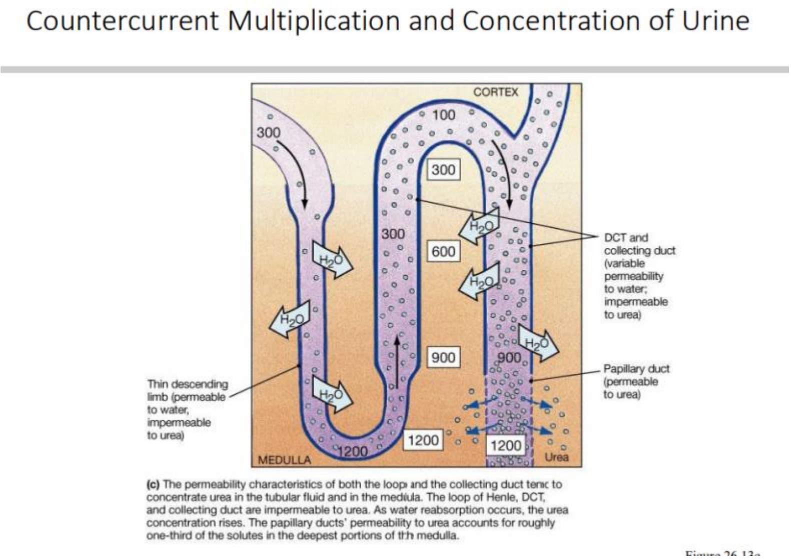
- **Proximal Tubule:** The osmolarity of the filtrate remains isotonic at 300 mOsm/L because two-thirds of the water and two-thirds of the solutes are reabsorbed equally.
- **Descending Limb of the Loop of Henle:** This segment is highly permeable to water but impermeable to solutes. Because the surrounding medullary interstitium is hyperosmolar, water moves out passively via osmosis (reabsorbing 15% of $H2 O$). As water leaves, the tubular fluid concentrates, reaching a peak osmolarity of up to 1200 mOsm/L at the tip of the loop.

- **Ascending Limb of the Loop of Henle:** This segment is completely **impermeable to water** but actively transports solutes (Na+, K+, Cl-) out of the tubule into the interstitium using the **Na-K-2Cl cotransporter**. This active separation of salt from water (the "single effect") creates the hyperosmolarinterstitium while diluting the tubular fluid down to 100 mOsm/L by the time it reaches the distal tubule.



- **Collecting Duct:** In the presence of open water channels (regulated by ADH), water moves out of the collecting duct into the hyperosmolar medulla, **allowing the final urine to be concentrated up to 1200 mOsm/L.** Ultimately, only about 1% of the filtered water remains as excreted urine.

- The Single Effect: The thick ascending limb **actively reabsorbs NaCl while remaining impermeable to water**, thereby diluting the tubular fluid (to ~100–150 mOsm/L) and **increasing the osmolarity of the medullary interstitium**, forming the basis of the **countercurrent multiplication mechanism**.



Countercurrent Multiplication and Concentration of Urine

(c) The permeability characteristics of both the loop and the collecting duct tend to concentrate urea in the tubular fluid and in the medulla. The loop of Henle, DCT, and collecting duct are impermeable to urea. As water reabsorption occurs, the urea concentration rises. The papillary ducts' permeability to urea accounts for roughly one-third of the solutes in the deepest portions of the medulla.

Maintaining the Medullary Gradient

<u>To successfully concentrate urine, the kidney relies on two major factors in the medulla:</u>

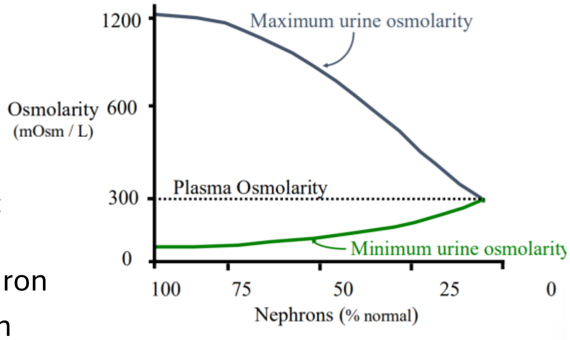
- **The Role of Urea:** The active reabsorption of NaCl only accounts for about 700 mOsm/L of the 1200 mOsm/L medullary gradient. The remaining 500 mOsm/L comes from high concentrations of **Urea**. Water reabsorption concentrates urea in the tubule, which is then reabsorbed into the inner medulla to boost interstitial osmolarity.

  Clinical note: Vegetarians may have a **reduced ability** to maximally concentrate urine (up to 1200 mOsm/L) because lower protein breakdown means less urea.

- **Vasa Recta & Blood Flow:** The cortex receives high blood flow (~500 mL/min), but the medullary blood vessels (Vasa Recta) only receive 2-3% of the total plasma flow. The vasa recta operates as a passive countercurrent exchanger. If blood flow to the medulla were high, it would "wash out" the actively transported NaCl, destroying the hyperosmolar gradient and limiting the kidney's concentration ability to around 800 mOsm/L instead of 1200 mOsm/L.

- **Diuretics** acting on the kidney often target the Na-K-2Cl transporters in the ascending limb, **preventing** active NaCl reabsorption, which consequently ruins the medullary gradient and prevents water reabsorption.

Isosthenuria & Chronic Renal Failure



A normal human has around 2 million nephrons.

What happens when nephron number decreases?

If 75% of nephrons are lost (from **2,000,000 → 500,000**):

- Total GFR = number of nephrons × GFR per nephron
- Normally: 2,000,000 × 62.5 nL/min = 125 mL/min

After nephron loss: Total GFR drops to **~40 mL/min (not proportionally),** because remaining nephrons **hyperfiltrate** (increase single nephron GFR to ~80 nL/min)

Each nephron now handles **much more fluid (↑ workload)** → this leads to a **maladaptive vicious cycle (positive feedback) that progressively damages remaining nephrons**.

As nephron loss continues: Urine can no longer be concentrated or diluted, urine osmolarity becomes **fixed at ~300 mOsm/L (isotonic to plasma).**

Leads to **Isosthenuria = loss of concentrating and diluting ability**
→ Urine volume may be normal (e.g., ~2 L/day), but osmolarity stays **constant ~300 mOsm/L**. In terms of specific gravity, isosthenuria gives a fixed SG of ~1.010.

Urine specific gravity normally ranges from 1.002 to 1.028 g/mL in humans, rising by 0.001 for every 35–40 mOsm/L increase in osmolarity.

Fluid Handling & Segmental Reabsorption

Recall that out of the 180 Liters of fluid filtered daily, the nephron segments reabsorb water progressively:

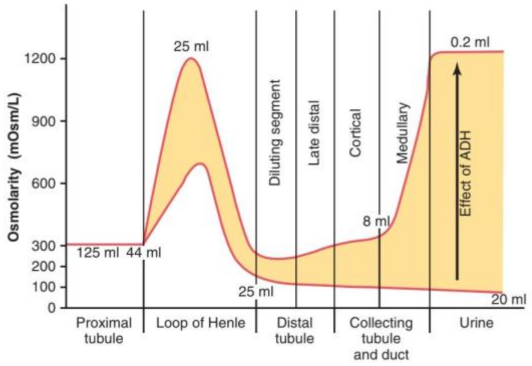
- **Proximal Tubule:** Reabsorbs **65%** of filtered water and solutes (isotonic).
- **Descending Limb:** Reabsorbs **15%** of water (permeable to water, impermeable to solutes).

- **Distal Tubule:** Reabsorbs approximately **10%**.
- **Collecting Duct:** Potentially reabsorbs **9.3%**, depending on ADH.
- This leaves about **0.7%** (roughly 1.5 L) to be excreted as normal urine output.

The ADH Mechanism and Aquaporins

<u>To concentrate urine in the collecting duct, Antidiuretic Hormone (ADH) is required:</u>

- ADH (a small peptide from the posterior pituitary) binds to basolateral receptors on the collecting duct cells.



- This triggers cAMP production, which causes the insertion of **Aquaporin-2 (AQP-2)** water channels onto the apical (luminal) membrane.

<u>Note:</u> Aquaporin-1 is in the proximal tubule and is not controlled by ADH. Aquaporins 3 and 4 are permanently located on the basolateral membrane of the collecting duct.

- **Diabetes Insipidus:** A failure of this system (either central lack of ADH or nephrogenic receptor failure) means the 9.3% of water isn't reabsorbed, leading to massive urine output (up to 18 liters/day) of highly diluted urine (50 mOsm/L).

Kidney Function Tests (KFT) & Specific Gravity

Highlights the ability to concentrate urine is a **key indicator of tubular function** (rather than glomerular function).

Specific gravity (SG) is used as a proxy to assess whether the kidney can **concentrate (high SG) or dilute (low SG) urine**.

Following acute renal failure, **tubular concentrating ability is one of the last functions to recover**.

Specific Gravity (SG) to Osmolality Conversion:

- Estimated osmolality ≈ **(last two decimal digits of SG) × 40**

Example: If a patient's urine specific gravity is **1.025**, the estimated osmolality is:
25 × 40 = 1000 mOsm/L

- This estimation is based on the **number of dissolved particles** and is only accurate when urine does not contain **large or heavy solutes** such as glucose, proteins, red or white blood cells (e.g., hematuria or UTI), or contrast agents, since **specific gravity is influenced by both particle number and molecular weight**.

Importance of Urine Concentration and Dilution

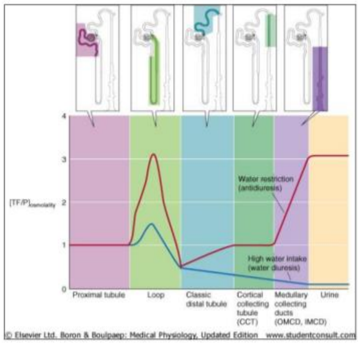
- Shows the immense adaptive range of the kidney: it can dilute urine down to **30-50 mOsm/L** (one-sixth of plasma osmolarity) to excrete excess water without losing solutes, or concentrate it up to **1200-1400 mOsm/L** to conserve water during dehydration.
- **Clinical scenario (Drinking Sea Water):** Sea water has an osmolarity of 2200-2800 mOsm/L. Because the human kidney maxes out at 1400 mOsm/L, drinking 1 liter of sea water requires the body to sacrifice extra fluid from its own stores just to excrete the massive salt load, causing severe dehydration.

Osmolality of fluid along the nephron

- Regardless of hydration status, the fluid always becomes highly concentrated at the bottom of the loop of Henle and gets diluted down in the classic distal tubule.

  The paths diverge at the collecting duct: the red line spikes to 1200 mOsm/L (ADH present), while the blue line drops further down (ADH absent).

- Red = water restriction
- Blue = high water intake
- Initial concentration of tubular fluid at loop of Henle, then finally at collecting ducts.



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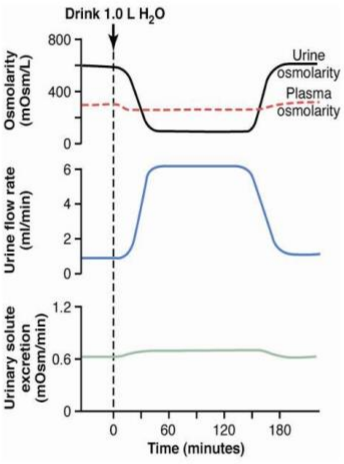
Changes in osmolarity of the tubular fluid (Volume vs. Osmolarity)

A combined look at fluid volume and osmolarity: Starts with 125 ml at 300 mOsm/L. At the tip of the loop of Henle, volume drops to 25 ml while osmolarity peaks at 1200 mOsm/L.

By the early distal tubule (diluting segment), volume is still 25 ml, but active salt pumping drops osmolarity to 100 mOsm/L. With the effect of ADH, the final urine becomes highly concentrated (1200mOsm/L) with a very small volume (0.2 mUmin).

Water diuresis in a human after ingestion of 1 liter of water.



Shows the physiological response to drinking 1.0 L of water. After a short delay (about 30-45 mins), urine flow rate spikes dramatically (from 1 ml/min to 6 ml/min) while urine osmolarity Plummets from 600 down to less than 100 mOsm/L. Importantly, **total urinary solute excretion remains perfectly flat (constant)**, proving the kidney selectively dumps water without losing valuable body salts. It takes about two hours to normalize.