

# Diuretics: More than a Guessing Game

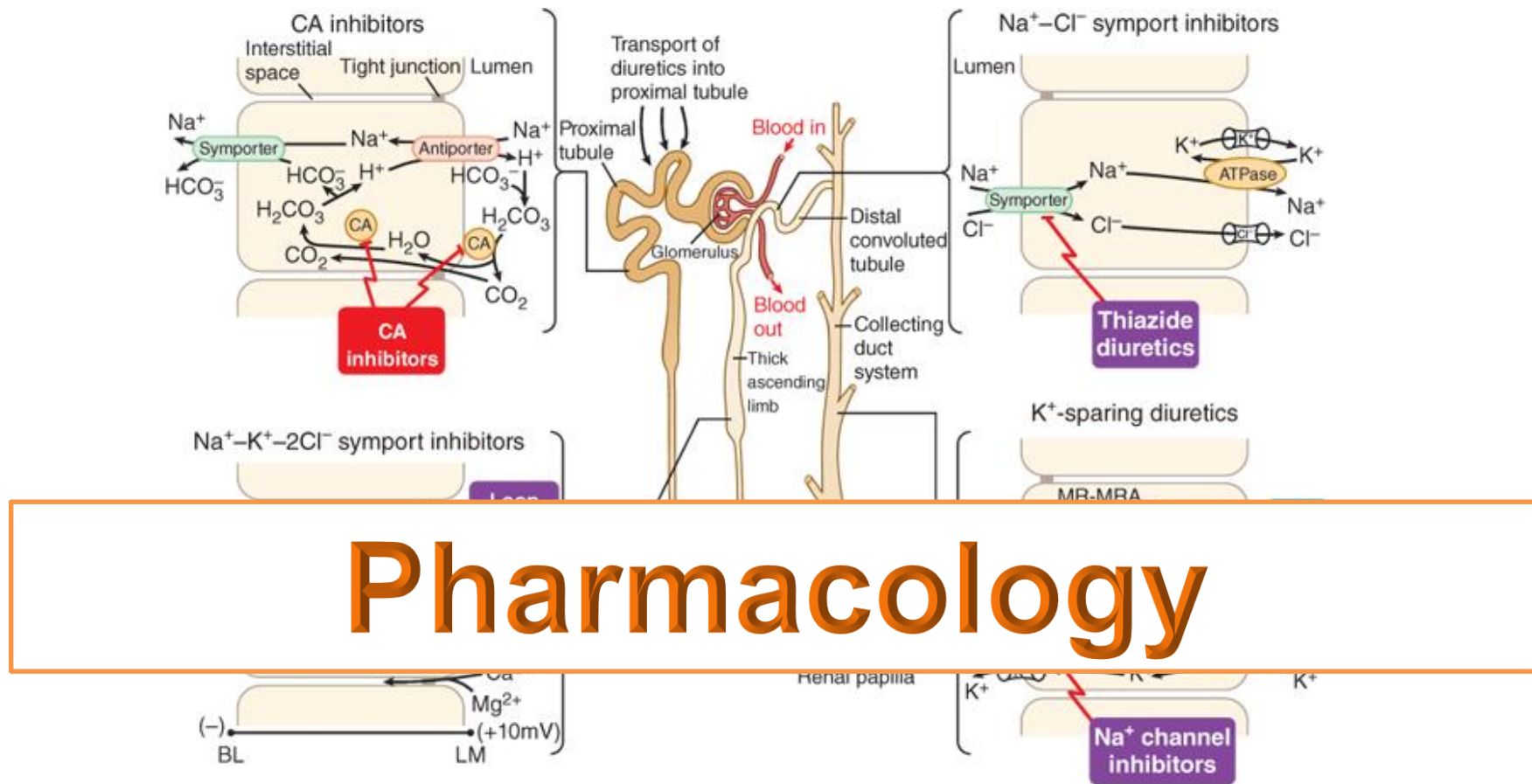
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# Objectives

- Describe pharmacology
- Compare potencies
- Special strategies for special circumstances



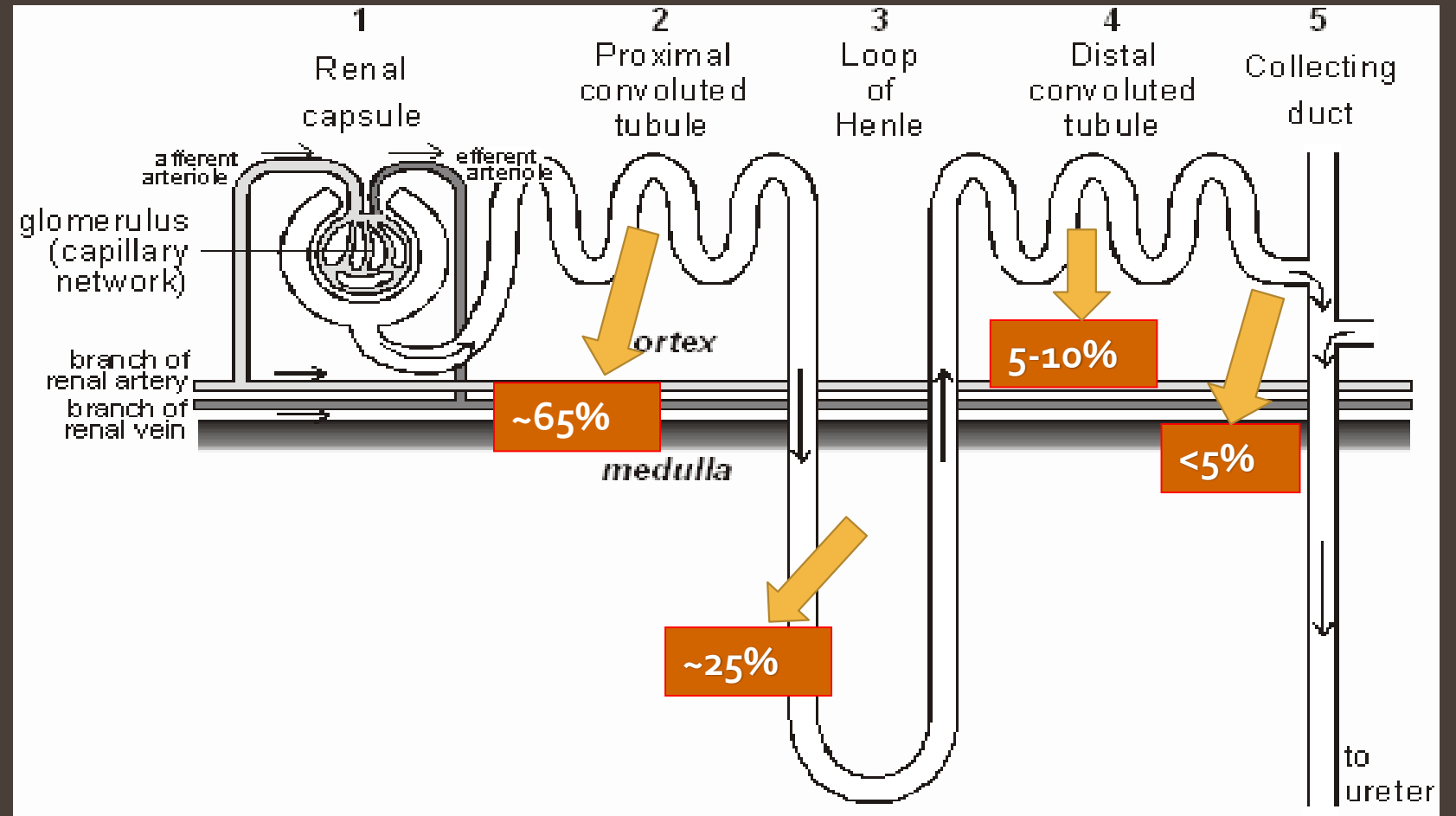
# Pharmacology

Source: Laurence L. Brunton, Björn C. Knollmann, Randa Hilal-Dandan:  
 Goodman & Gilman's: The Pharmacological Basis of Therapeutics,  
 Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Sites and mechanisms of action of diuretics. Three important features are noteworthy: 1. Transport of solute across epithelial cells in all nephron segments involves highly specialized proteins, which for the most part are apical and basolateral membrane integral proteins. 2. Diuretics target and block the action of epithelial proteins involved in solute transport. 3. The site and mechanism of action of a given class of diuretics are determined by the specific protein inhibited by the diuretic.

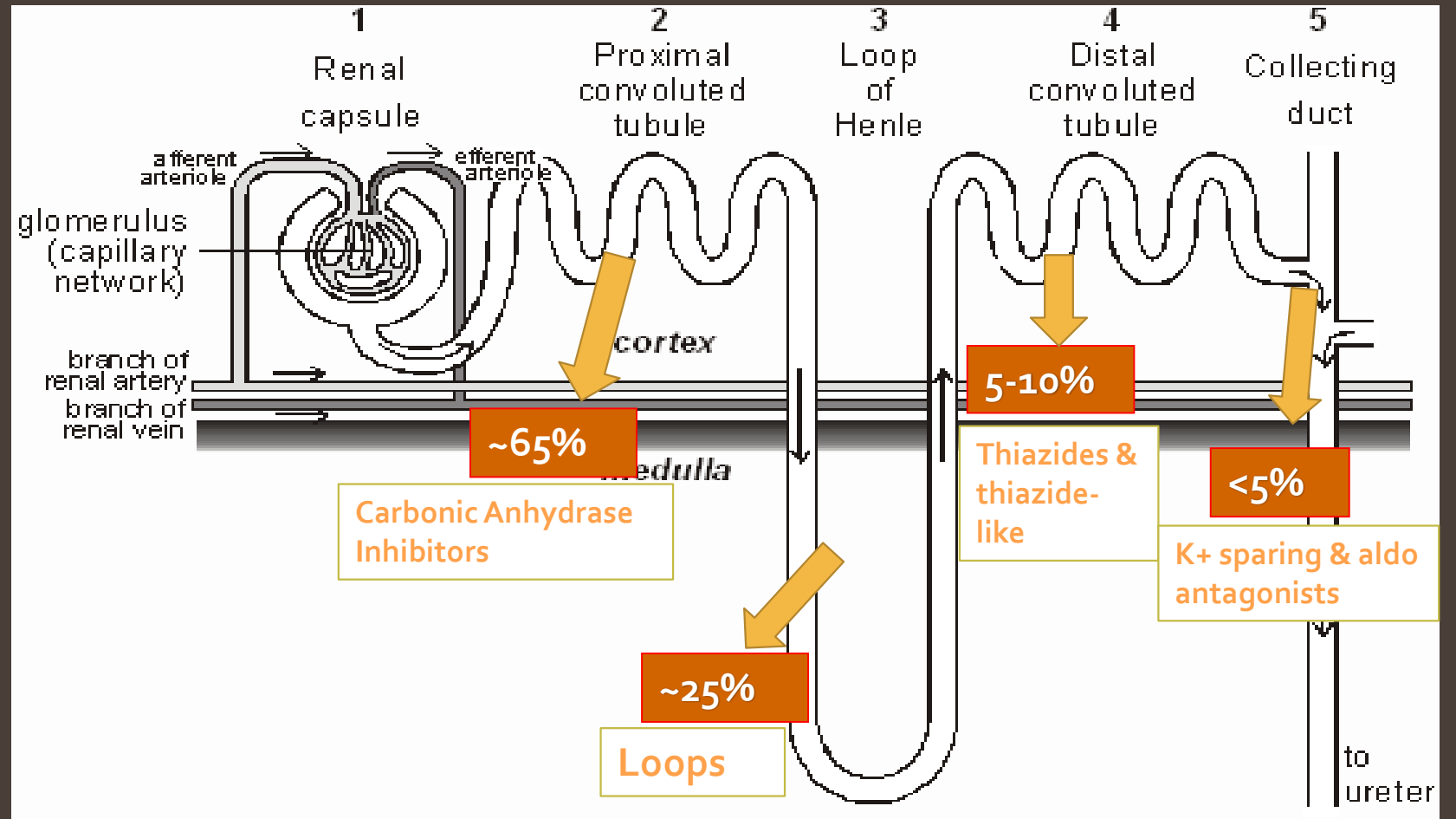
# Mechanism & Site of Action

## Na<sup>+</sup> Reabsorption



# Mechanism & Site of Action

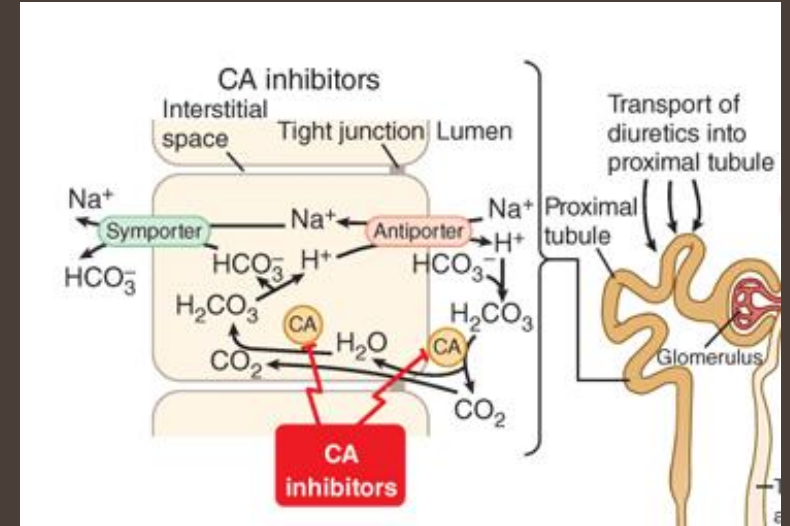
## Classes



# More Pharmacology

## Carbonic Anhydrase Inhibitors

- Acetazolamide
- Efficacy: Limited
  - High levels of CA in proximal tubule
  - Self-limited due to effect of decreased filtered  $\text{HCO}_3^-$
- Major ADE: metabolic acidosis



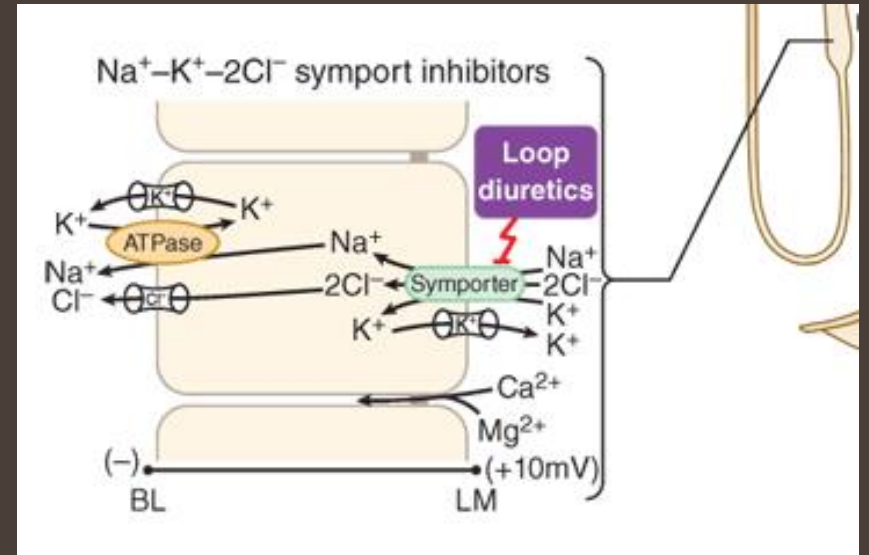
# More Pharmacology

## Loops

- Furosemide, Torsemide, Bumetanide, Ethacrynic Acid

- Efficacy: most effective

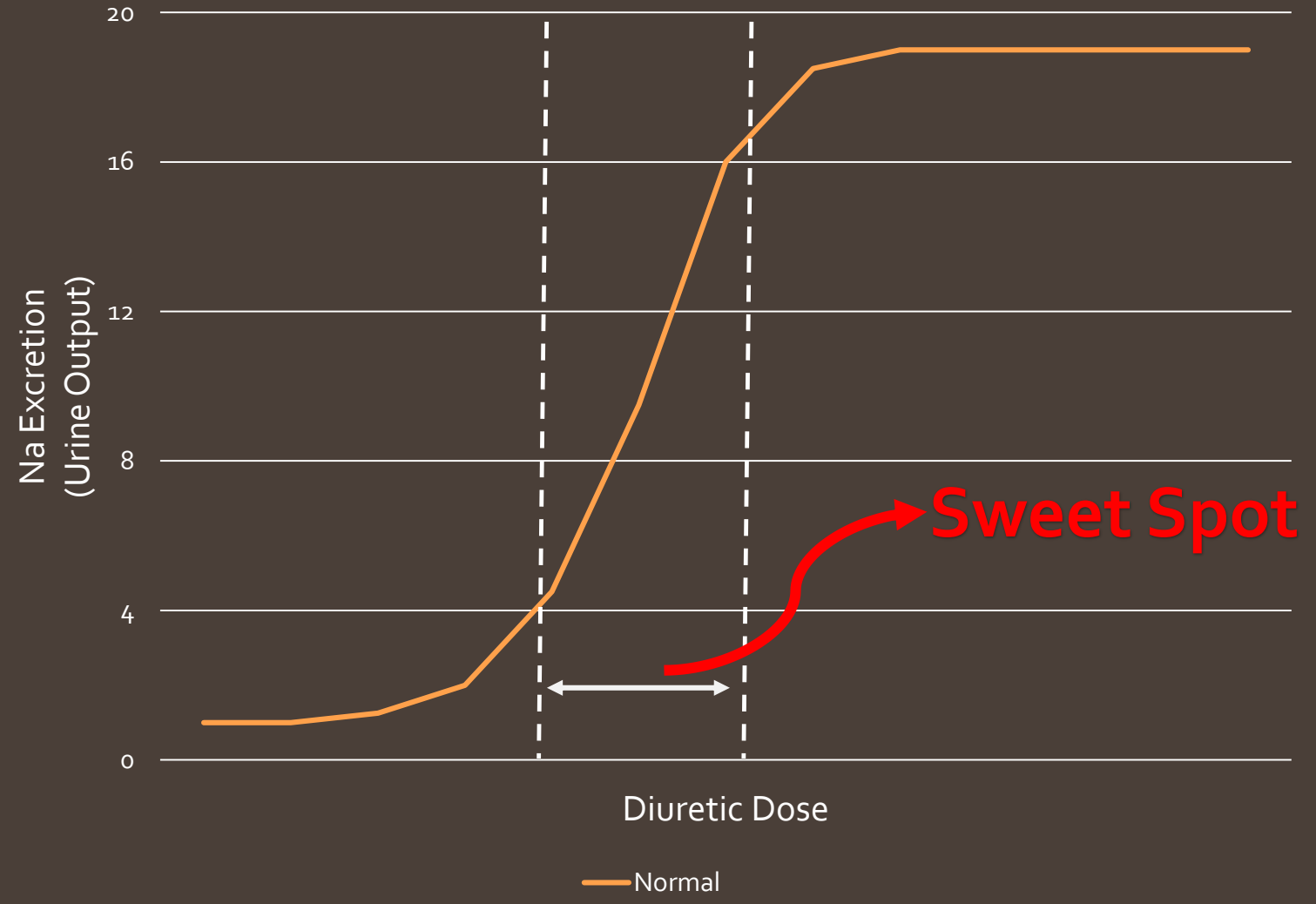
- Major ADE: hypo  $K^+$ , alkalosis
  - High doses cause ototoxicity



# More Pharmacology

## Loops

### The DIURETIC WINDOW





# The Diuretic Window

## How to get there

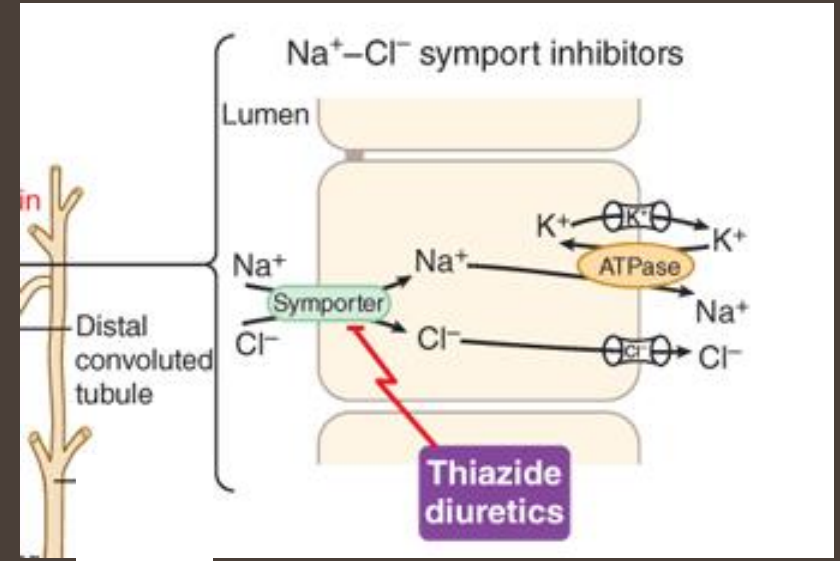
- **Rules of Thumb**

- The diuretic effect is defined by the output that a single dose achieves (i.e. dose-response)
  - Watch urine output
  - Double the dose until desired response is seen
  - If you've titrated to an EFFECTIVE dose, lower doses will not work...if 40mg doesn't work, 20mg won't work
- 
- Example: A patient on Lasix 40mg has consistent edema that has worsened over the past few weeks. She takes her dose once daily, but she's noticed her urine output has declined. So, she started taking a 2<sup>nd</sup> dose later in the day: 40mg BID.
    - Is this appropriate? Will it be effective?

## More Pharmacology

### Thiazides & the like

- HCTZ, Chlorthalidone
- Likes -Metolazone

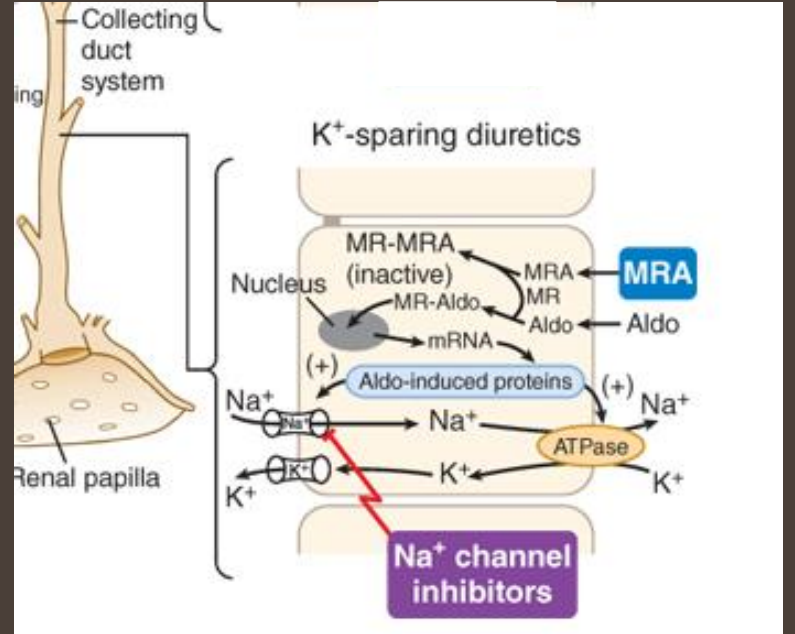


- Efficacy: limited for diuresis
  - Metolazone is exception
- Major ADE: Hypo  $\text{k}^+$ , hyper  $\text{Ca}^{2+}$

# More Pharmacology

## K<sup>+</sup> Sparing

- Triamterene, Amiloride
- Spironolactone



- Efficacy: Less effective than loops
- Major ADE: hyper K<sup>+</sup>, gynecomastia (spir)

# Comparative Efficacy

In other words...



or



Who wore it BETTER?

## Empiric Efficacy

- Based on site of action (interclass)
- IV or PO ???
- Intraclass differences

# Efficacy

## IV or PO

- Which is more effective?
- What is bioavailability?
  - Used to determine the *oral* dose needed to BE JUST AS EFFECTIVE as an *intravenous* dose
- Advantages of IV
  - Faster onset
  - Predictable onset & duration



## Efficacy

## Intraclass Differences

|            | PO | IV      | Bioavailability | Duration            |
|------------|----|---------|-----------------|---------------------|
| Furosemide | 40 | 20      | ~50%            | Po:6-8h,<br>IV:2h   |
| Torsemide  | 20 | 20 (na) | ~80%            | 6-8h                |
| Bumetanide | 1  | 1       | ~80%            | Po:4-6h,<br>IV:2-3h |



## Efficacy

## Intraclass Differences

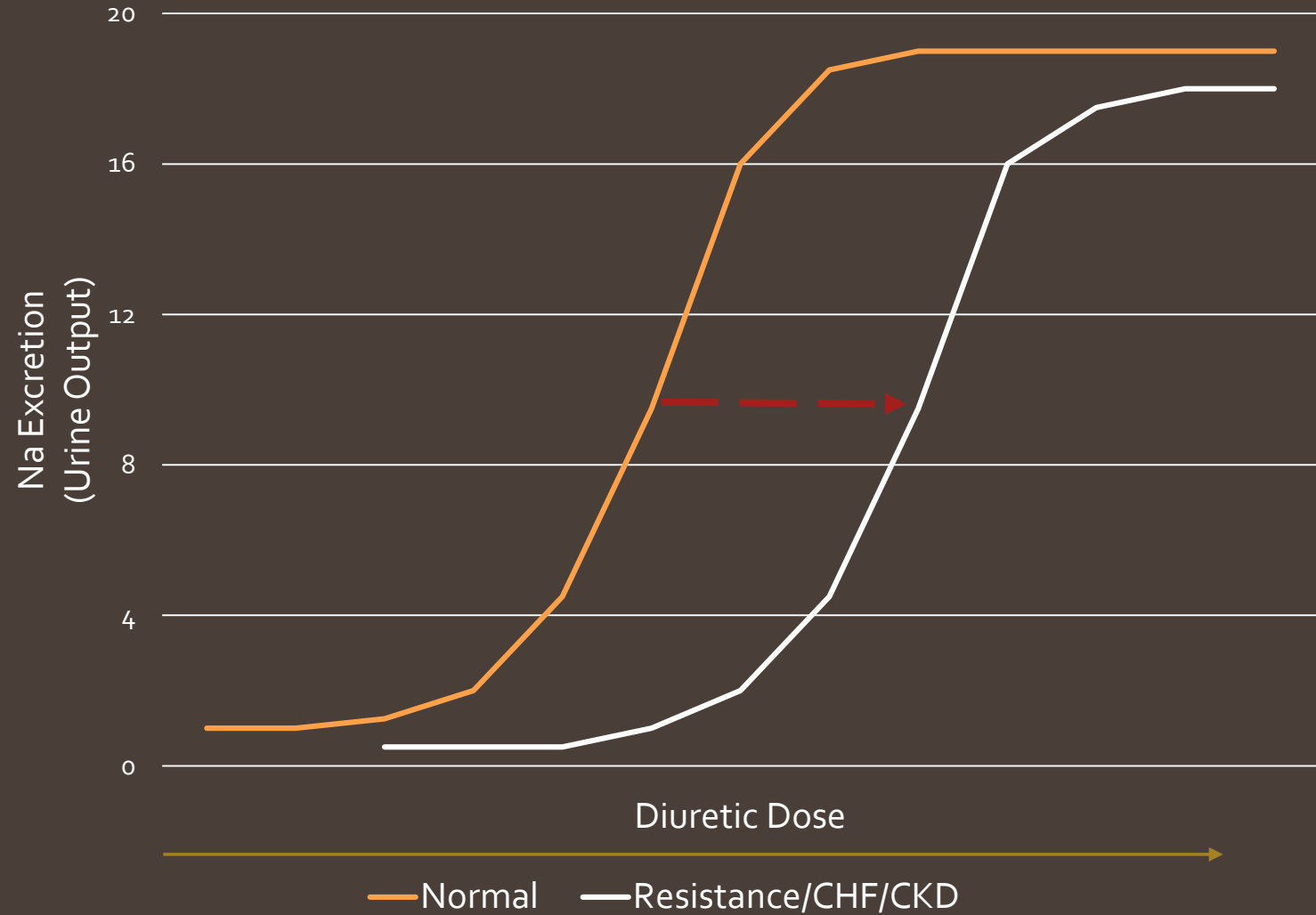
- Thiazides
  - ~30 days of diuretic effect
  - Higher doses than for HTN
- Metolazone
  - Potent, long half-life
  - Doesn't lose diuretic efficacy



# Special Strategies for Special Circumstances

# Diuretic Resistance

Diuretic therapy and resistance in congestive heart failure.  
*Cordiology* 2001;96:132-143. S. Karger AG.



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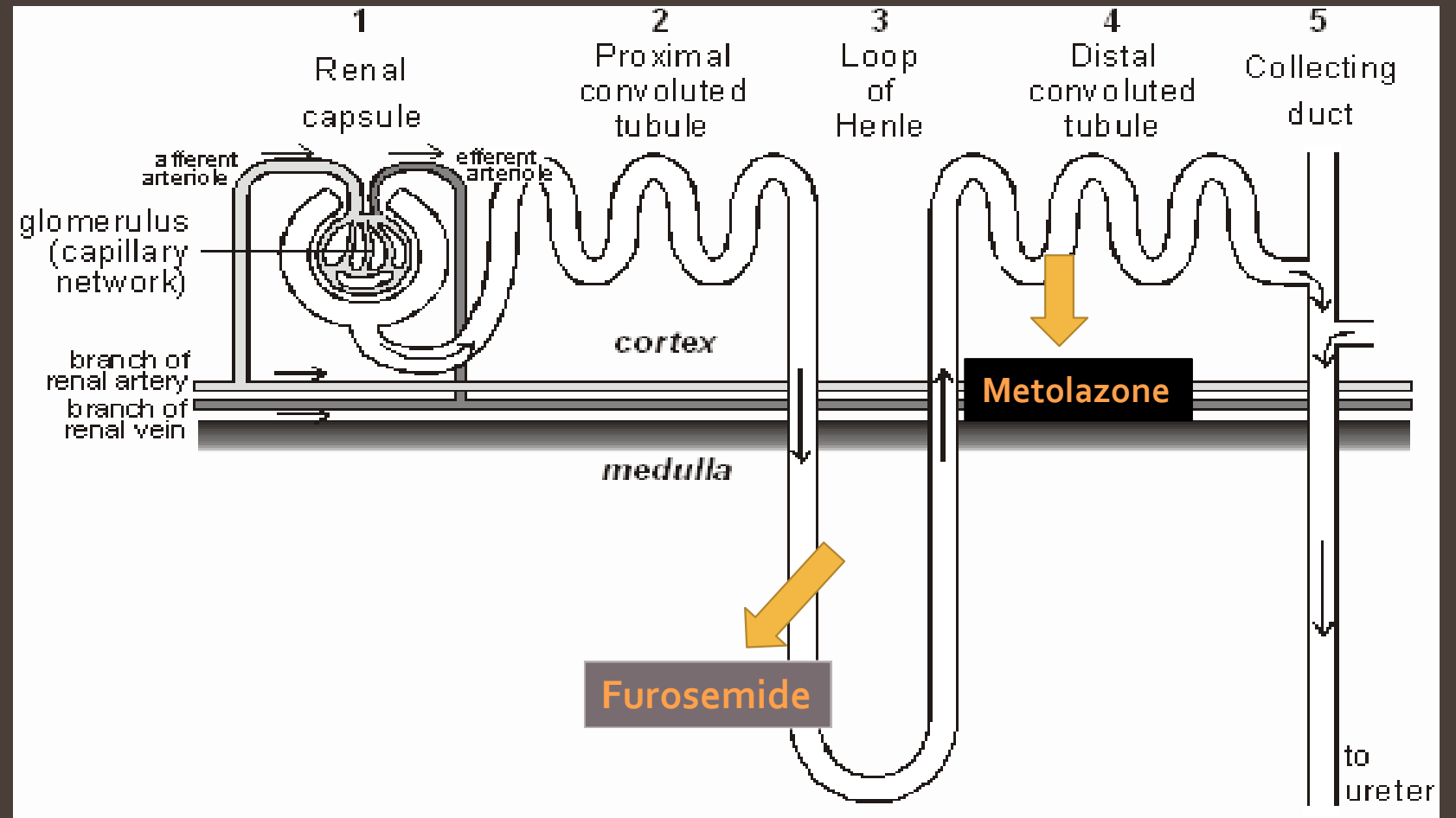
- Reduced GFR = less drug delivered
- Counter-regulatory mechanisms due to reduced glomerular perfusion
  - RAAS
  - SNS
  - Hypertrophied cells in distal tubule → enhanced Na<sup>+</sup> reabsorption

**Breaking Phenomenon**



\*All of the above may be induced by repeated loop diuretic administration

# Diuretic Synergy



## Now, for a very special case...

- (Could become a) ***NIGHTMARE CASE:***
- 57 yom with HFrEF admitted for AKI secondary to volume depletion/dehydration
- Trace LE edema with a BUN:Cr 44:1.7
- NS started at 110 cc/hr
- 12 hours later, develops crackles and LE edema is 1+
- What would you do?

## Diuresis for ADHF

Felker GM, et al. N Engl J Med 2011;364:797-805.

### Diuretic Strategies in Patients with Acute Decompensated Heart Failure

- 4 arms: Comparison of low dose with high dose AND IV bolus with continuous infusion
  - Low dose = equivalent to home dose
  - High dose = 2.5x home dose

| Outcomes                     | Bolus vs Clnf  | Low vs High Dose                                   |
|------------------------------|--|--|
| Symptoms                     | NS   | NS, p=0.06   |
| Fluid loss (mL)              | 4237 vs 4249, p=0.89                                 | 3575 vs 4899, p=0.001                              |
| Death, readmit, ED           | With Clnf: <b>HR 1.15</b> (95% CI 0.83-1.60), p=0.41 | With HD: <b>HR 0.83</b> (95% CI 0.60-1.16), p=0.28 |
| Dose Increase required @ 48h | 21 vs 11%, p=0.01                                    | 24 vs 9%, p=0.003                                  |
| Cumulative dose @ 72h        | 592 vs 480mg, p=0.06                                 | 358 Vs 773mg, p<0.001                              |
| Creatinine Δ                 | NS   | NS   |

# Torsemide vs Furosemide in heart failure


Am J Cardiol.  
2020;125:92-99.

|  |   | Torsemide    | Furosemide   | P-value          |
|--|---|--------------|--------------|------------------|
| Meta-analysis, 19 studies (10 observational) |   |              |              |                  |
| Baseline characteristics                     | Age   | 64.8 yo      | 67 yo        | <u>&lt;0.001</u> |
|  | HFrEF   | 63.3%        | 69.6%        | <u>&lt;0.001</u> |
|  | NYHA III/IV   | 50.8%        | 49.7%        | 0.688            |
|  | CKD   | 42.4%        | 32.6%        | <u>&lt;0.001</u> |
|  | <b>ACEI/ARB</b>   | <b>67.7%</b> | <b>77.3%</b> | <u>&lt;0.001</u> |
|  | <b>Beta-blockers</b>  | <b>66.5%</b> | <b>74.6%</b> | <u>&lt;0.001</u> |
|  | <b>Spirolacatone</b>  | <b>46.9%</b> | <b>36.5%</b> | <u>&lt;0.001</u> |
|  | LVEF %  | 33.1         | 31           | <u>&lt;0.001</u> |
|  | BNP pg/mL   | 290          | 286          | 0.870            |
| Results                                      | <b>Hospitalization due to HF</b>  | 10.6%        | 18.4%        | <b>0.07</b>      |
|  | NYHA improvement  | 72.5%        | 58%          | 0.004            |
|  | All cause mortality   |              |              | 0.65             |
|  | <b>Cardiac mortality</b>  | 1.5%         | 4.4%         | <b>&lt;0.001</b> |
|  | Med side effects  |              |              | 0.48             |
| Comments                                     | Results in <b>RED</b> were different when reanalyzed by separating RCTs from observational studies or by including only where diuretics were started outpatient. Found to have less numerical difference and non-significant differences. There are multiple baseline differences that could benefit torsemide. |              |              |                  |
| Author conclusions                           | Torsemide is associated with better outcomes. May be due to longer t <sub>1/2</sub> , although authors also state bioavailability could be a reason. They also say to interpret findings with caution due to heterogeneity and re-analysis contradictions.  |              |              |                  |



## Diuretics in CKD/ESRD

KDIGO Clinical Practice  
Guideline for the  
Management of Blood  
Pressure in Chronic Kidney  
Disease, 2012

- Diuretic window shifted to the right 
  - Higher doses required
- Making urine?
  - May use in conjunction with dialysis if making urine
- Thiazide or Loop diuretic indicated for treatment of HTN
  - Increased hydrostatic pressure
  - Also useful for hyperK<sup>+</sup>
- Avoid K<sup>+</sup> sparing diuretics
- Synergy may be used
  - Metolazone is useful at low GFRs

## Diuretics in Ascites

AASLD Practice  
Guideline: Management  
of Adult Patients with  
Ascites due to Cirrhosis,  
2012

- Spironolactone 100mg ± furosemide 40mg once daily
  - Consider starting at lower dose
  - Ratio maintains eukalemia and is used initially
    - Adjust ratio if K<sup>+</sup> is abnormal
  - Combination faster diuresis than spironolactone alone
- Plus Na<sup>+</sup> restriction (NTE 2000mg/day)
- Midodrine added to improve diuresis and mitigate HoTN
- Monitor urine Na<sup>+</sup>/K<sup>+</sup> ratios (desired: >1)

## Diuretics in Hyponatremia

- Mostly studied in patients with heart failure
- Use limited to patients with hypervolemic states and/or low urine solute
- In combination with 3% saline ~25 cc/hr
  - + IV furosemide 40mg

Happy Diuresing!