A Case for Chronotherapy

A Case Presentation

- Norman O. Moser, DO, Pharm.D., R.Ph, PGY 35
- Nephrology Lima, Ohio

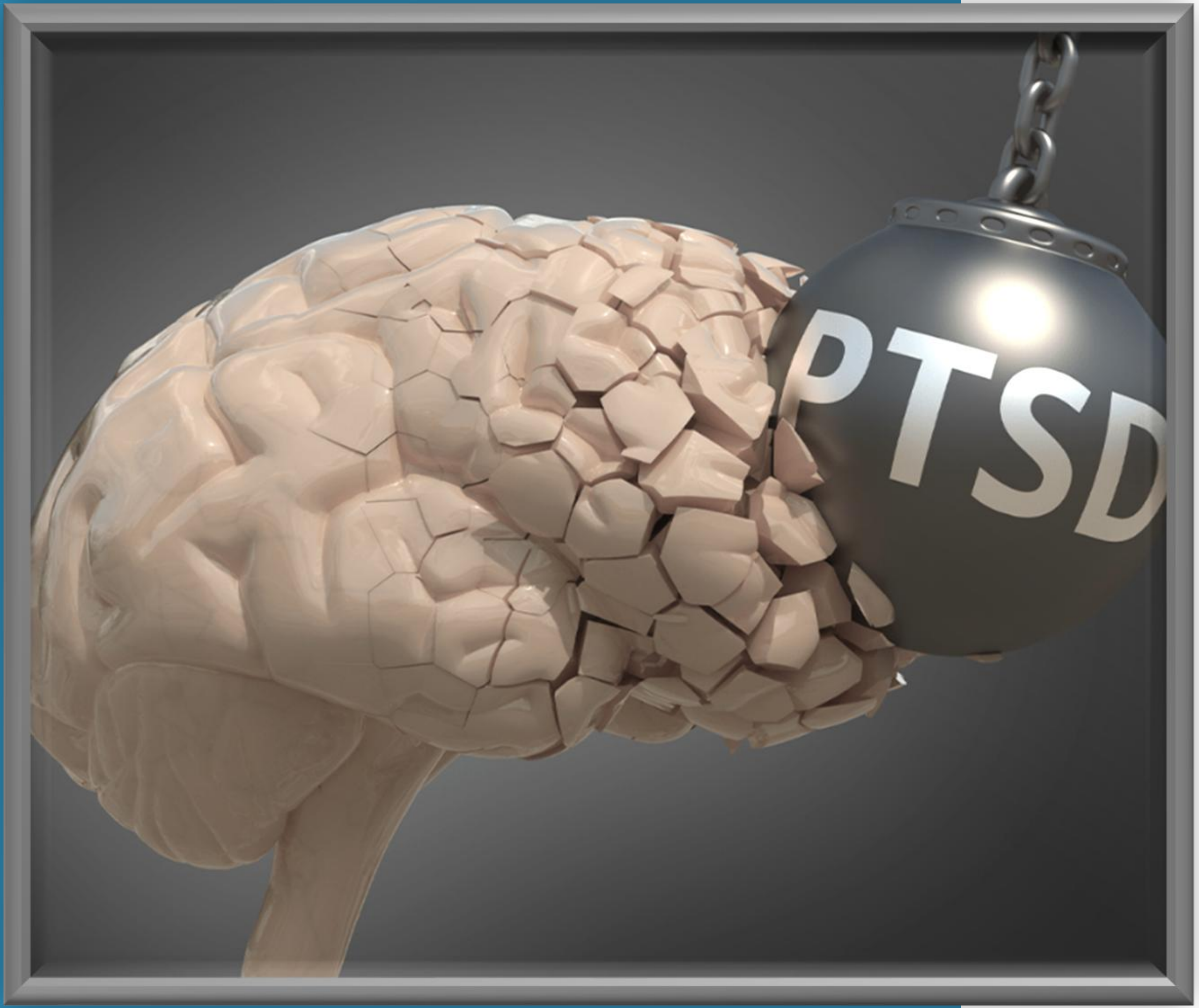
- Last updated 11/03/2025

There will be a 10 question Kahoot quiz at the end of the lecture.

Have your cell phones ready.

The Patient

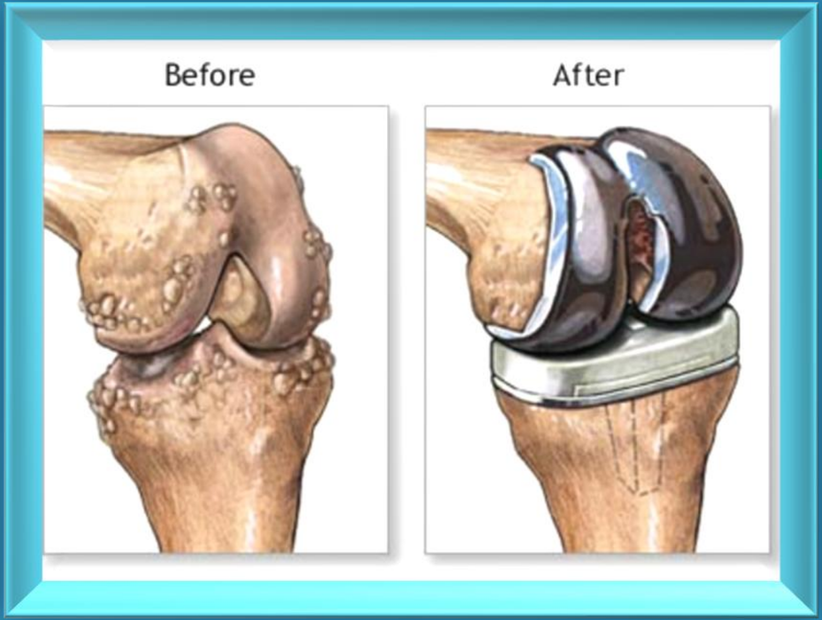
- TS is a 57 YOWM who presented to ER 12/28/23 for left upper back and chest pain.
- Presenting blood pressure was 225/125.
  - Abdominal pain.
  - Extreme anxiety.
- Was diagnosed with HTN in 2015 but has not been treating it.
- CTA chest W/WO contrast showed 70% proximal renal artery stenosis (performed due to complaint of abdominal pain).
- 50% stenosis of proximal superior mesenteric artery.
- Was sent to our clinic for follow up treatment.

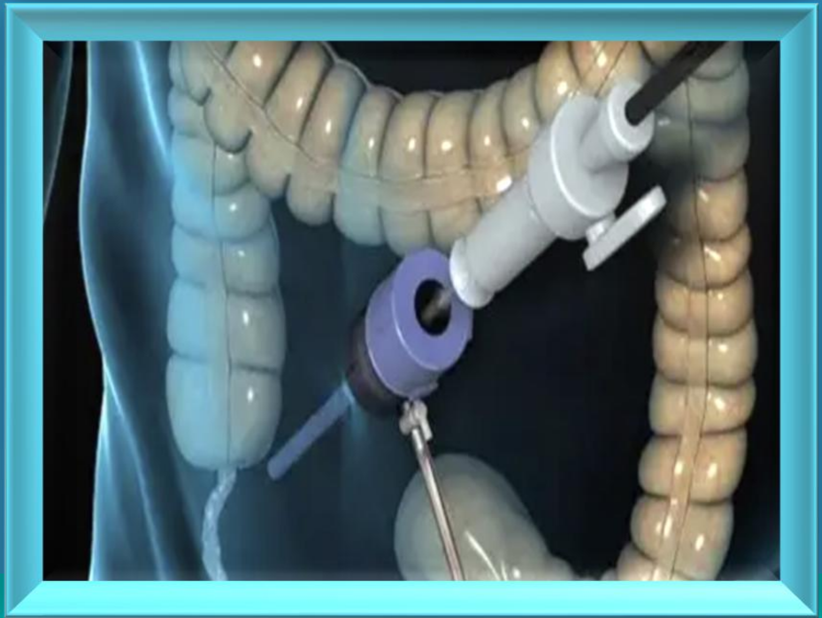


The Patient

- Past medical history.
  - HTN since 2015-untreated.
    - He did not believe in pills.
  - Depression
  - PTSD-significant.
  - Insomnia.
  - Indigestion.
  - Renal artery stenosis.
  - Chronic Kidney disease G-IIIA-A2.
  - Mesenteric artery stenosis.
  - Anger management disorder.

The Patient





- Past Surgical History.
  - Ankle surgery.
  - Appendectomy.
  - Knee surgery.
  - Laparoscopic Cholecystectomy.

The Patient

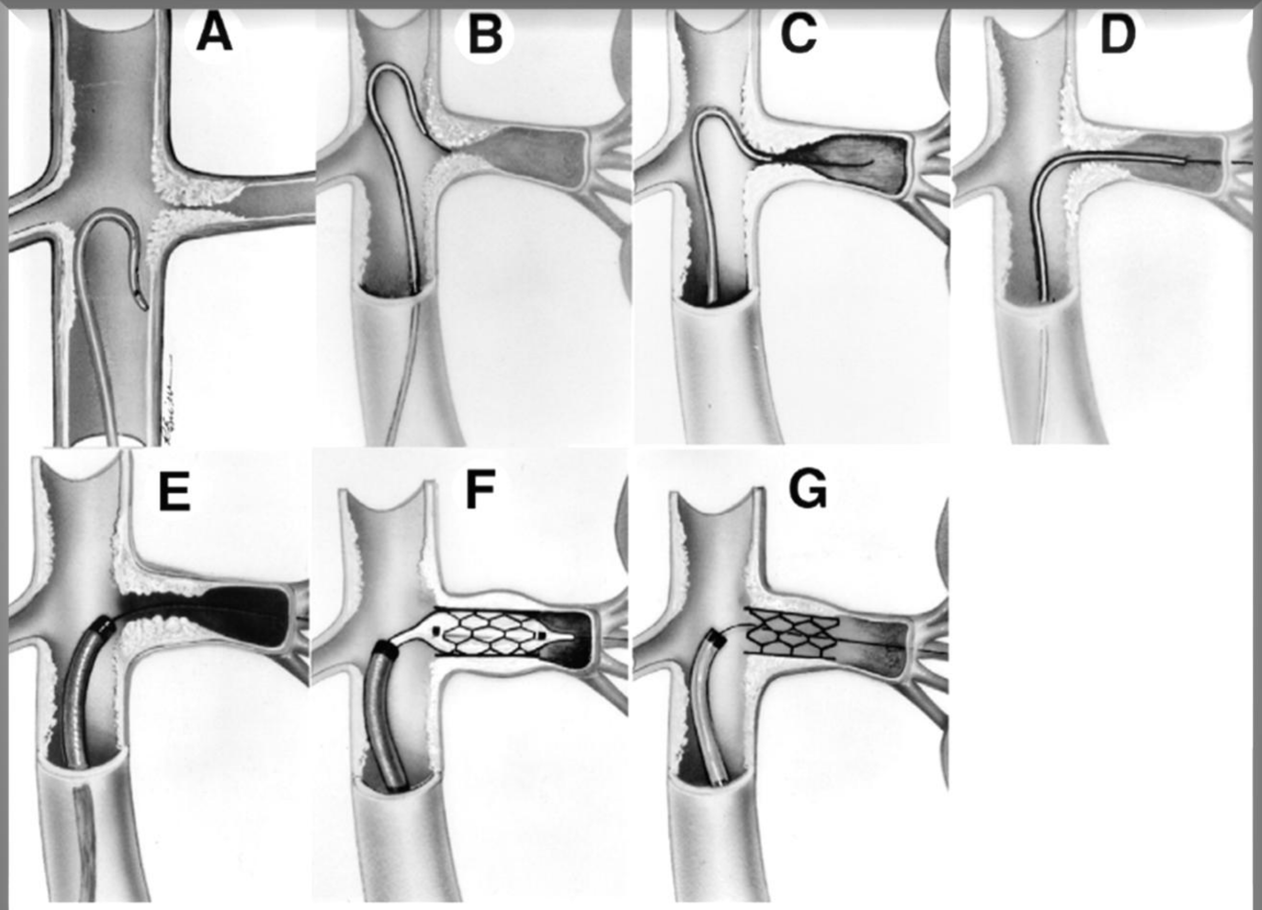
- Past Family History
  - Mother had cancer.

The Patient

- Substance use.
  - Smoker 58.5 pack years.
  - 1.5 PPD since 11/06/1987.
- Smokeless: none.
- Alcohol: Minimal.
- Marijuana: daily.
- Caffeine: 3-4 cups per day.
- E-cigarettes: none.
- Vaping: none.
- Heavy NSAID use.

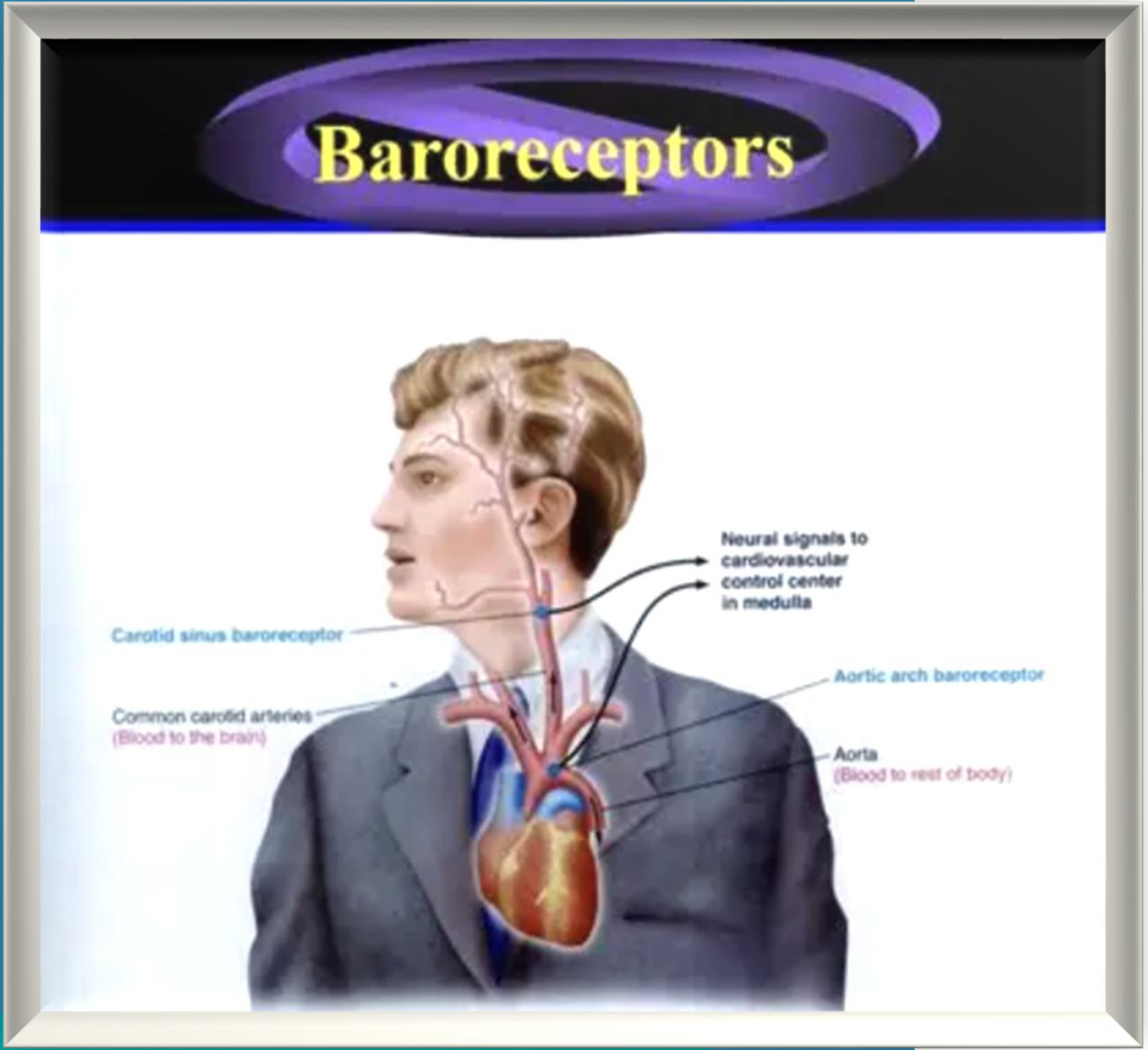
The Patient

- Physical examination.
  - HEENT: WNL.
  - Neck: Supple. No JVD. No Bruits.
  - Lungs: decreased breath sounds. No rales. No rhonchi.
  - Heart: RRR. No Murmur. No rub.
  - Abd: soft. NT. ND. Soft bruit over renal artery.
  - Ext: Minimal clubbing. No ischemia.



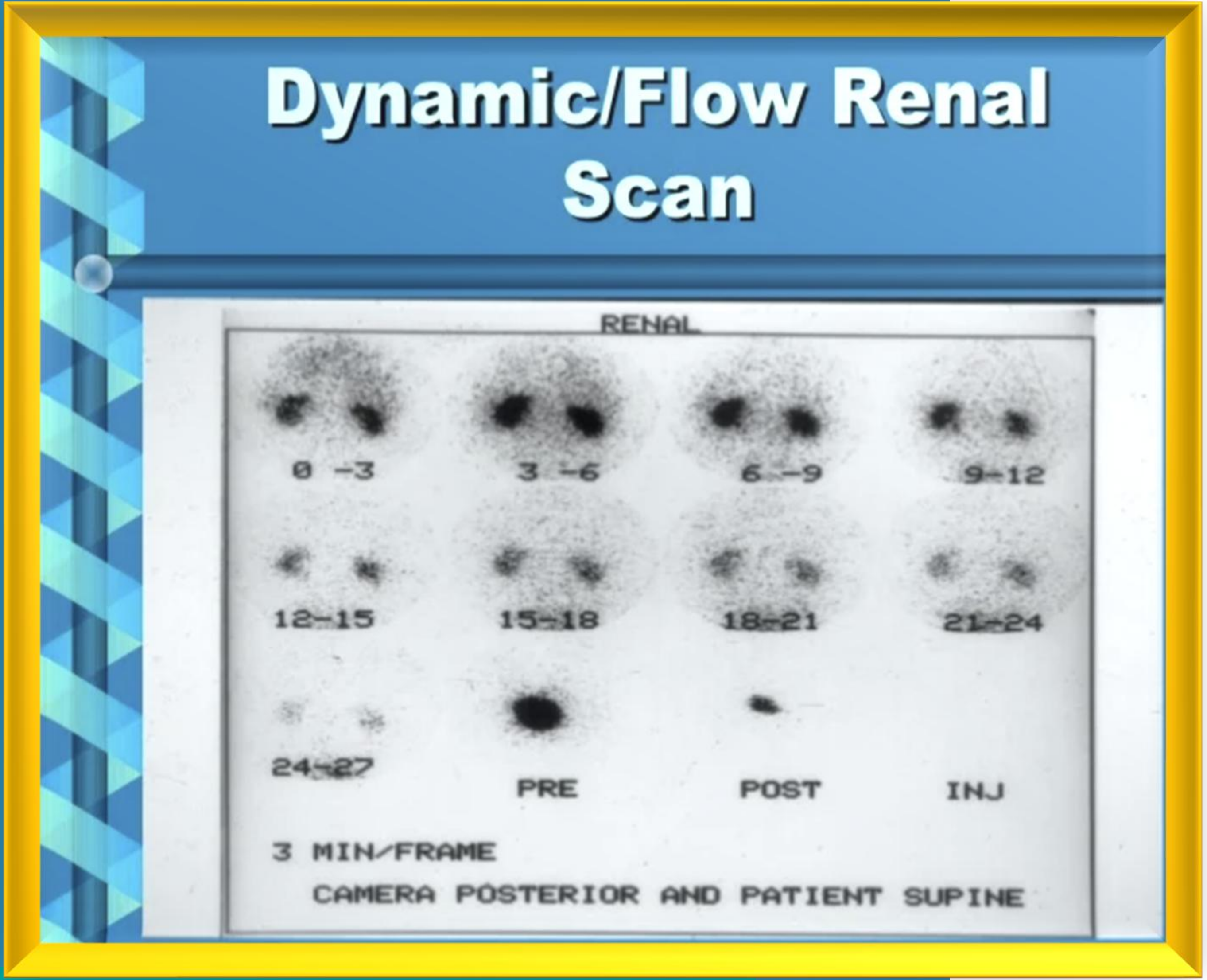
The Patient

- Procedures performed while in our care.
- Renal artery stenting.
    - No influence on blood pressure.
- Screening for pheochromocytoma twice.
    - Data was normal.
- Thyroid function tests.
    - Data was normal.
- Adrenal gland tests.
    - Data was normal.



The Patient

- **Procedures performed while in our care.**
- EKG.
  - NRS.
  - Incomplete RBBB.
- Echocardiogram
  - LVEF-55-60%.
  - LV wall motion was normal.
  - LV wall thickness was normal.
  - Normal diastolic function.
- Tilt table test (looking for baroreceptor dysfunction)
  - Normal.

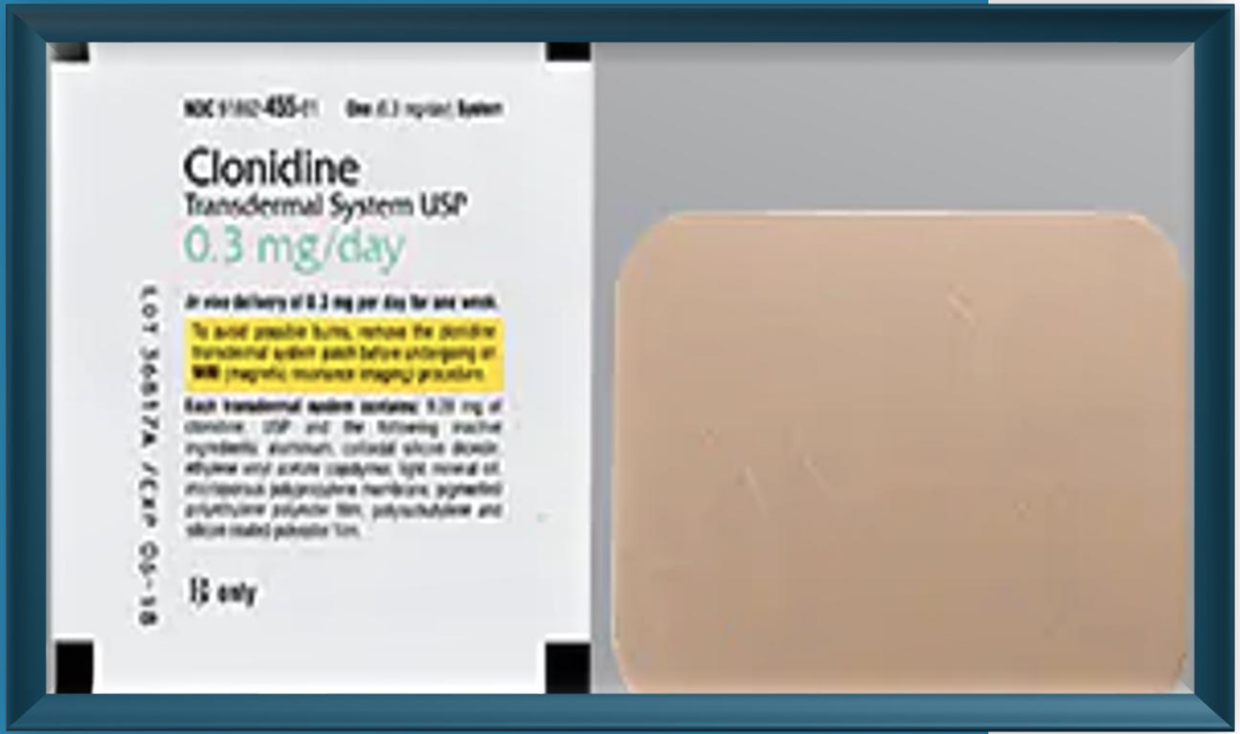


The Patient

- **Procedures performed while in our care.**

- Nuclear Renal Scan
  - Slightly decreased perfusion of the left kidney.
  - 33% renal function in left kidney.
  - 67% renal function in the right kidney.
  - After Lasix, prompt excretion of radio nuclide from both kidneys.

- Chest X-ray
  - Hyperinflation of the lungs.
  - Otherwise, unremarkable.



Clinical Course

- Started on Catapres TTS 1
    - Made him drowsy.
    - Dry mouth
    - Dropped daytime blood pressure too low.

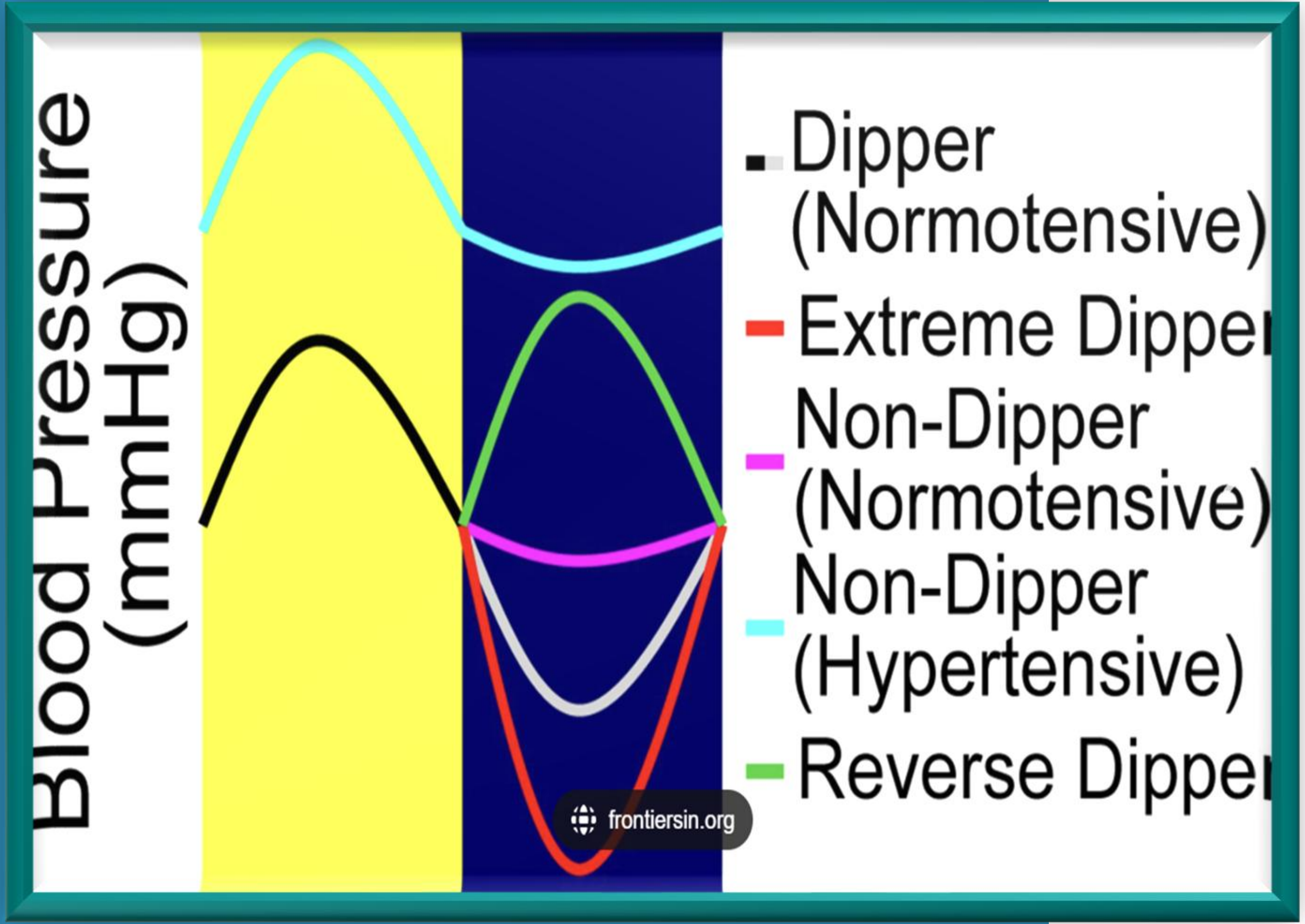
    - Switched to long acting calcium channel blocker.
        - Poor influence on nighttime blood pressure.

    - Underwent right renal artery stenting.
        - No influence on blood pressure.
            - This procedure will, however, protect the kidney function.

Clinical Course

- Tilt table test was normal.
  - Less likely that he has baroreceptor dysfunction.
- We noticed that his weight is quite variable and that it responded to sodium consumption. High sodium intake resulted in fluid retention and weight gain with a resultant rise in blood pressure.
- We also noticed a widended pulse pressure suggesting hardening of the arteries.

Clinical Course

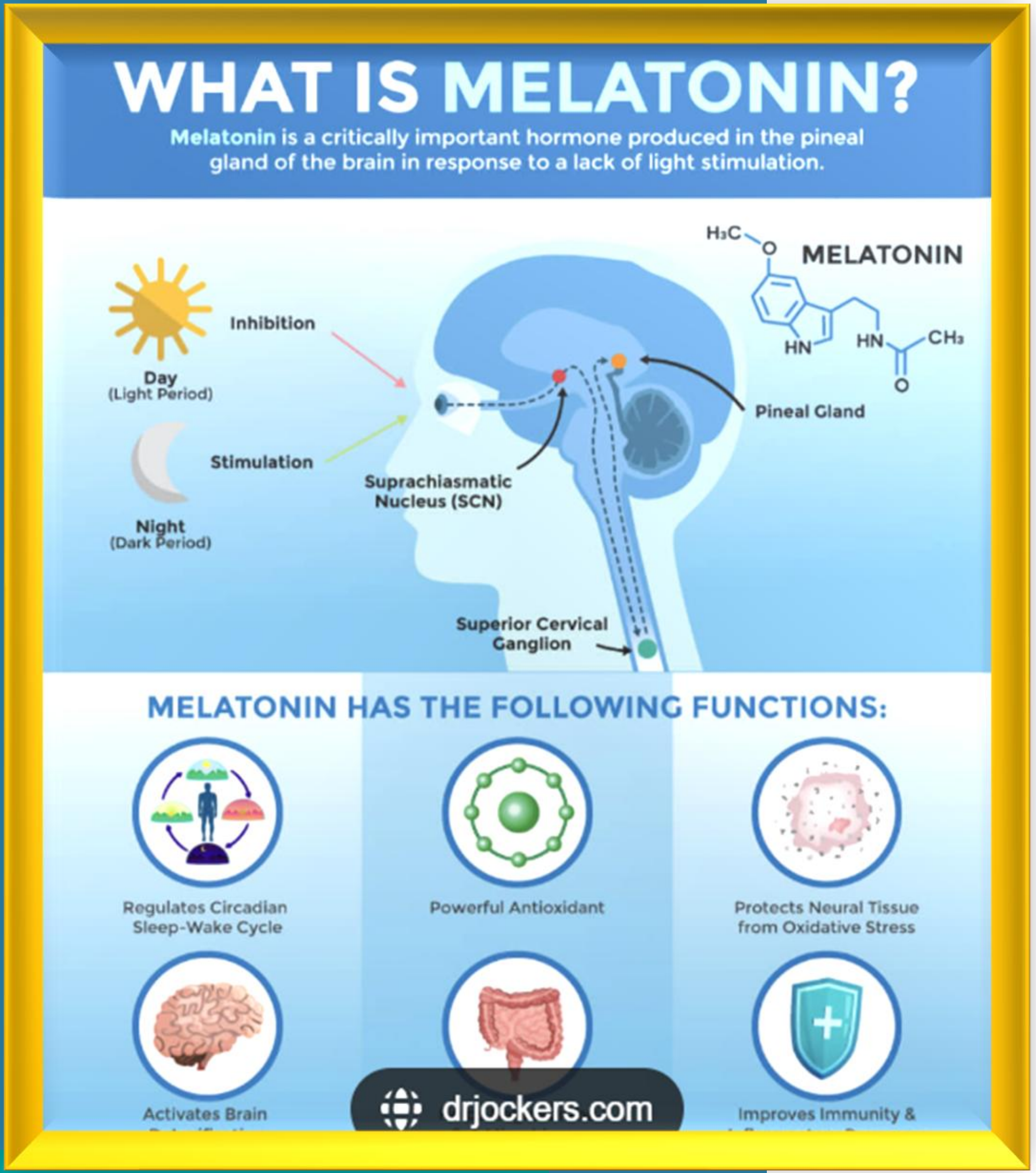


- The medical literature suggested that he has reverse dipping hypertension.
- He also is very sodium sensitive.
- Therefore, his final diagnosis is.
- SODIUM SENSITIVE, REVERSE DIPPING, NOCTURNAL HYPERTENSION.
- NOW, how do we treat this.

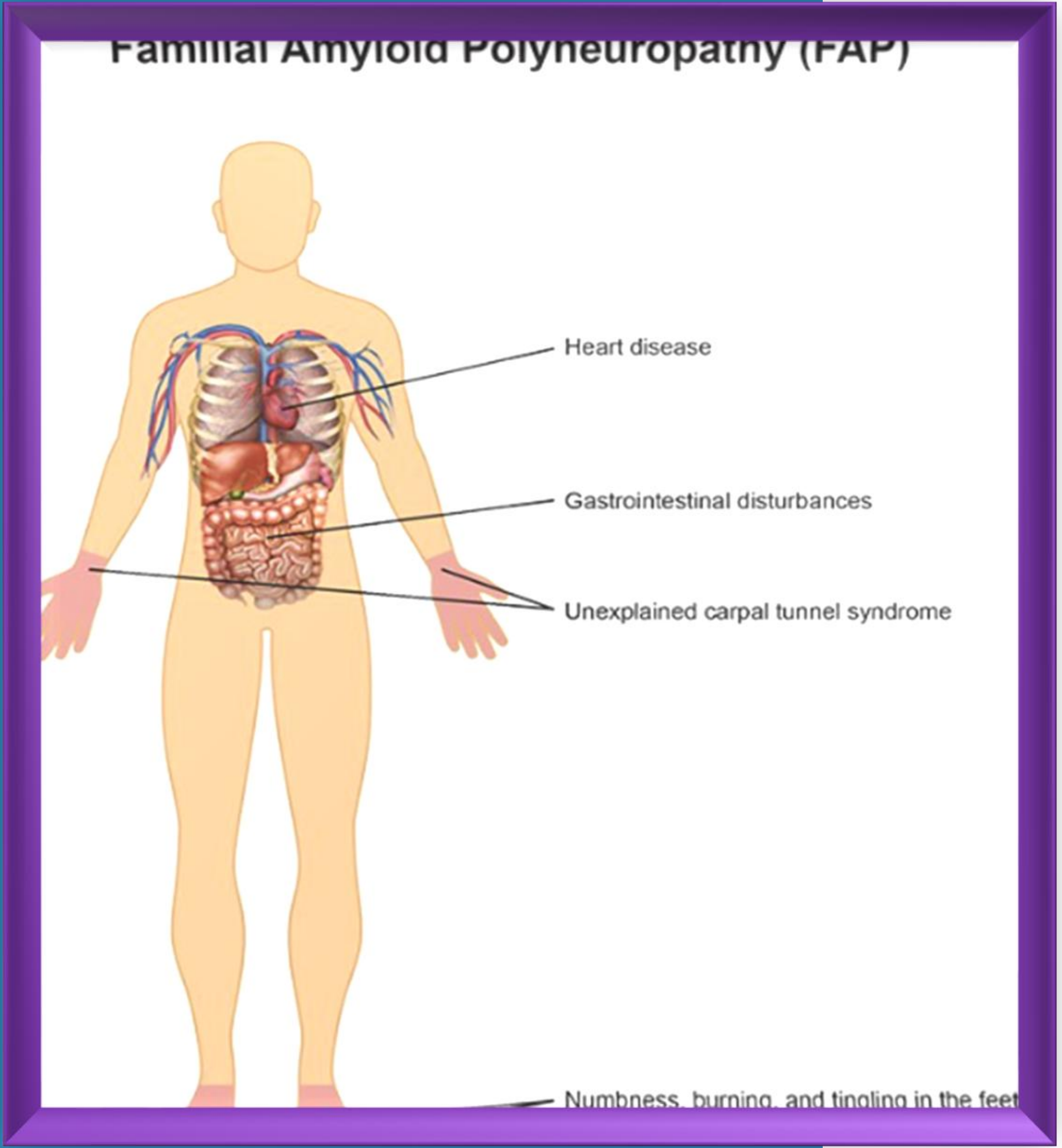
Conditions associated with reverse and non dippers

- Hyperthyroidism.
- Primary hyperaldosteronism.
- Hyperparathyroidism.
- Hypercortisolism.
- Pheochromocytoma.
- Acromegaly.
- Chronic kidney disease.
- Renal transplant.
- Unilateral nephrectomy.

Conditions associated with reverse and non dippers



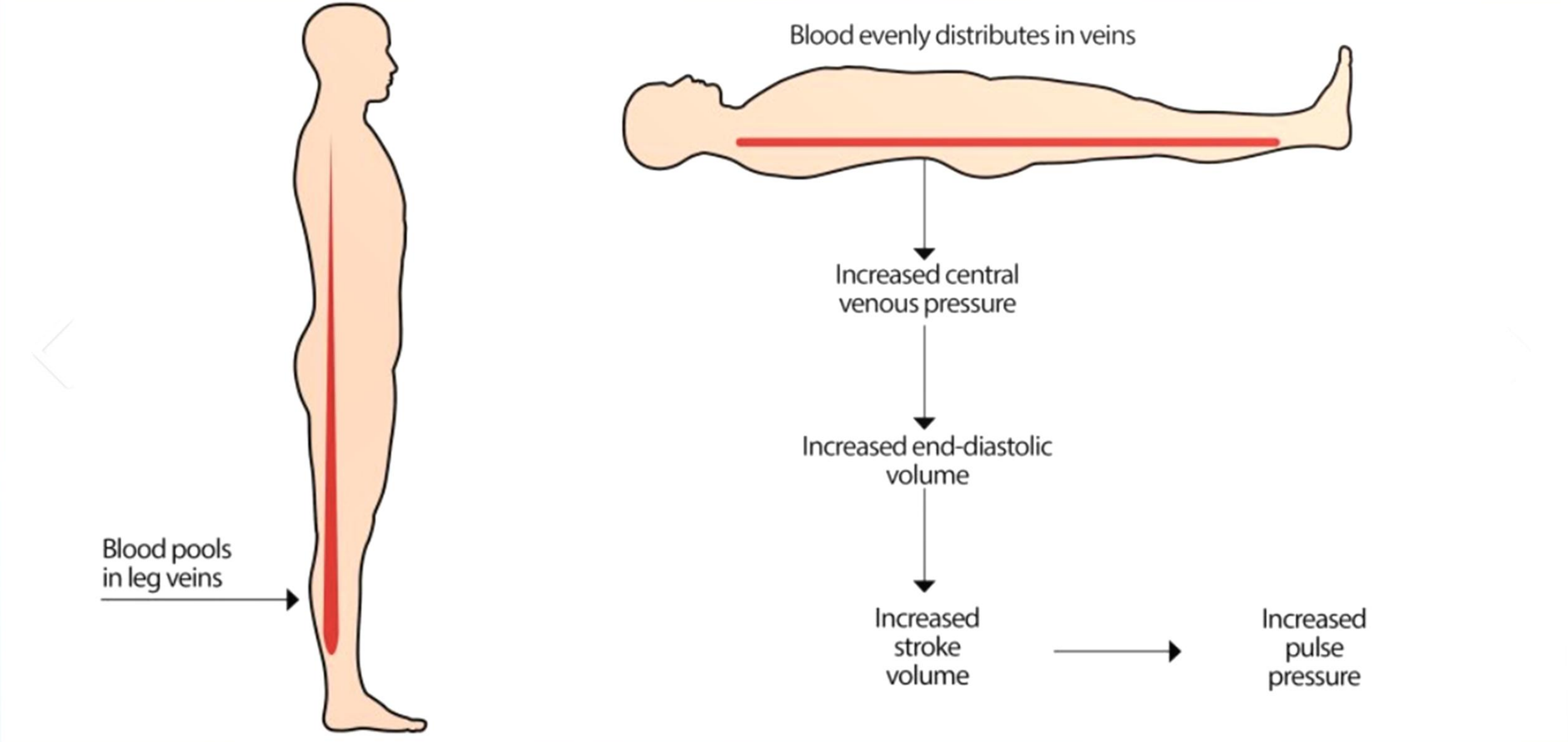
- Immunosuppressive therapy.
- Disturbances in circadian plasma melatonin levels.
- Genetic factors.



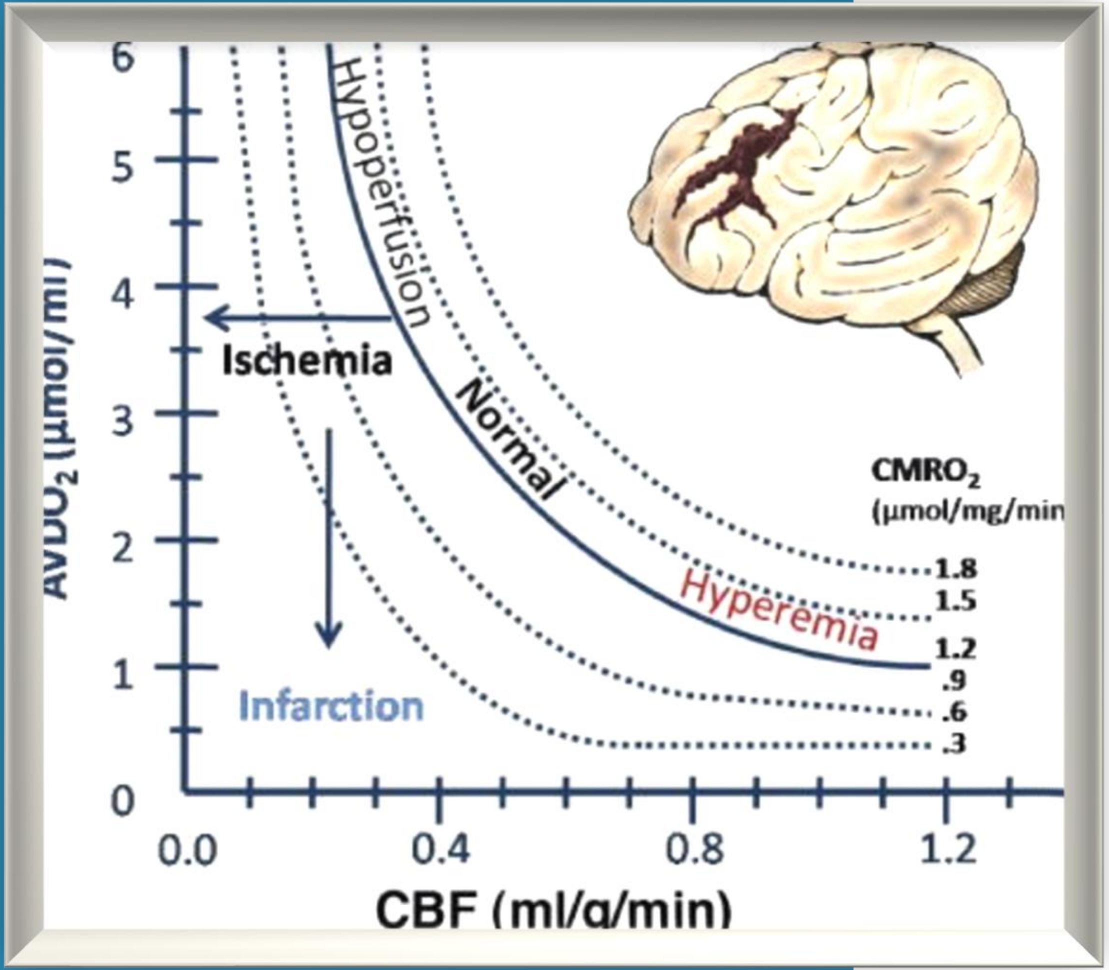
Conditions associated with reverse and non dippers

- Renovascular hypertension.
- Disturbances of the autonomic nervous system.
- Orthostatic hypotension.
- Diabetic neuropathy.
- Parkinson’s disease.
- Pure autonomic failure.
- Multiple system atrophy.
- Uremic neuropathy.
- Familial amyloidotic polyneuropathy.

Fig 3. Gravity and the vascular system



Cerebral Autoregulation



- CEREBRAL AUTOREGULATION OF BLOOD PRESSURE.

- Cerebral autoregulation is the brains ability to maintain stable blood flow despite changes in blood pressure in the rest of the body.
- It involves a complex mechanism where the brain microcirculation can contract and dilate in response to variations in blood pressure, ensuring a constant cerebral blood flow.
- This process is crucial for maintaining cerebral perfusion pressure, which is maintained relatively constant between 50 and 150 mm/hg mean arterial pressure.
- The cerebral perfusion pressure can be reset at lower or higher values.

Clinical Course

- Due to the fact that his blood pressure has been very high for a long time, we considered that his cerebral perfusion pressure was set at a higher point.
- For that reason, we elected to lower his blood pressure slowly to prevent under perfusing the brain.
- I drop their blood pressure goal range by 20-25 mm/hg.
    - Eg. If the patients average blood pressure was 180/100; I would make their goal 160/80.
- EVERY PATIENT OF YOURS SHOULD HAVE A TREATMENT GOAL WHEN THEY LEAVE YOUR OFFICE, EVERY TIME.

Clinical Course

- Chronotherapy for hypertension.
  - Using short duration of effect medications to treat the elevated blood pressure while asleep.
  - We chose hydralazine to start.
    - Typical duration of effect is 8-10 hours.
    - Started at 100 mg every bedtime.
    - This helped, but we needed to do better.
    - Increased Hydralazine to 200 mg every bedtime.

Clinical Course

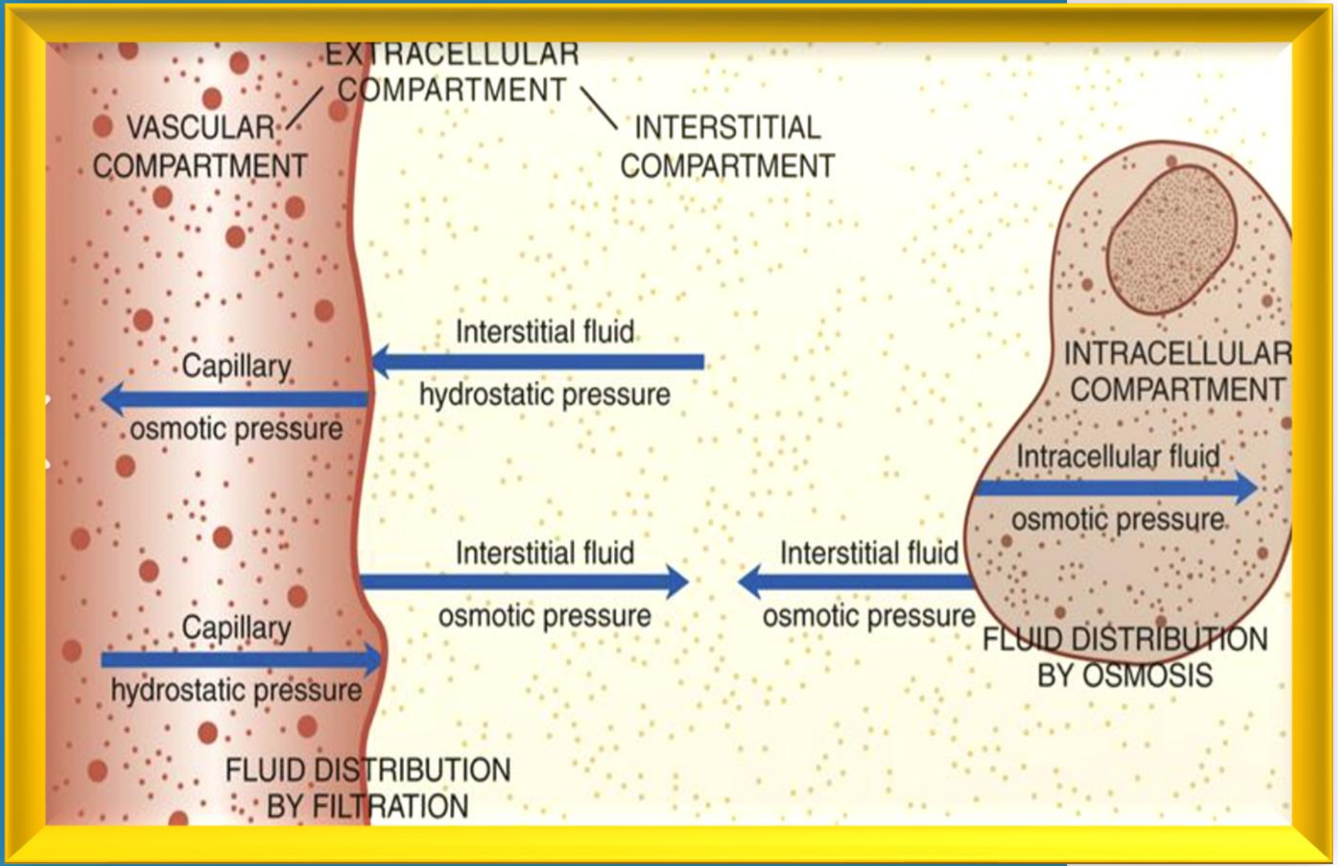
- Chronotherapy for hypertension.
  - Aspirin at bedtime.
    - Reduces blood pressure raising hormones that are more active overnight (angiotensin II).
    - Improves the bodies circadian rhythm.
    - Reduces oxidative stress and restores the blood vessels ability to relax.
    - Reduces morning platelet activity protecting against cardiovascular events.

Clinical Course

- Chronotherapy for hypertension.
  - Added Clonidine.
    - Clonidine helps with insomnia as well.
    - He took his pills at 9:30 PM.
    - He went to the rest room at midnight and passed out from low blood pressure.
    - It also made him very thirsty and he drank way too much fluid. And gained weight.
    - Stopped Clonidine
    - Increased Hydralazine to 250 mg at bedtime.

Drugs used for Chronotherapy

- Short acting Beta-blockers (especially those that are negative inotrope).
- Mineralocorticoid receptor blockers and the new mineralocorticoid synthase inhibitors when on the market.
- Short acting calcium channel blockers.
- Short acting vasodilators.



Aldosterone

- aldosterone

Lasix only lasts 6 hours.

During diuresis, the patient volume contracts.

The diuretic can remove fluid from the vascular space faster than interstitial fluid can migrate back into the vascular space.

The adrenal glands via the RAAS will increase aldosterone secretion.

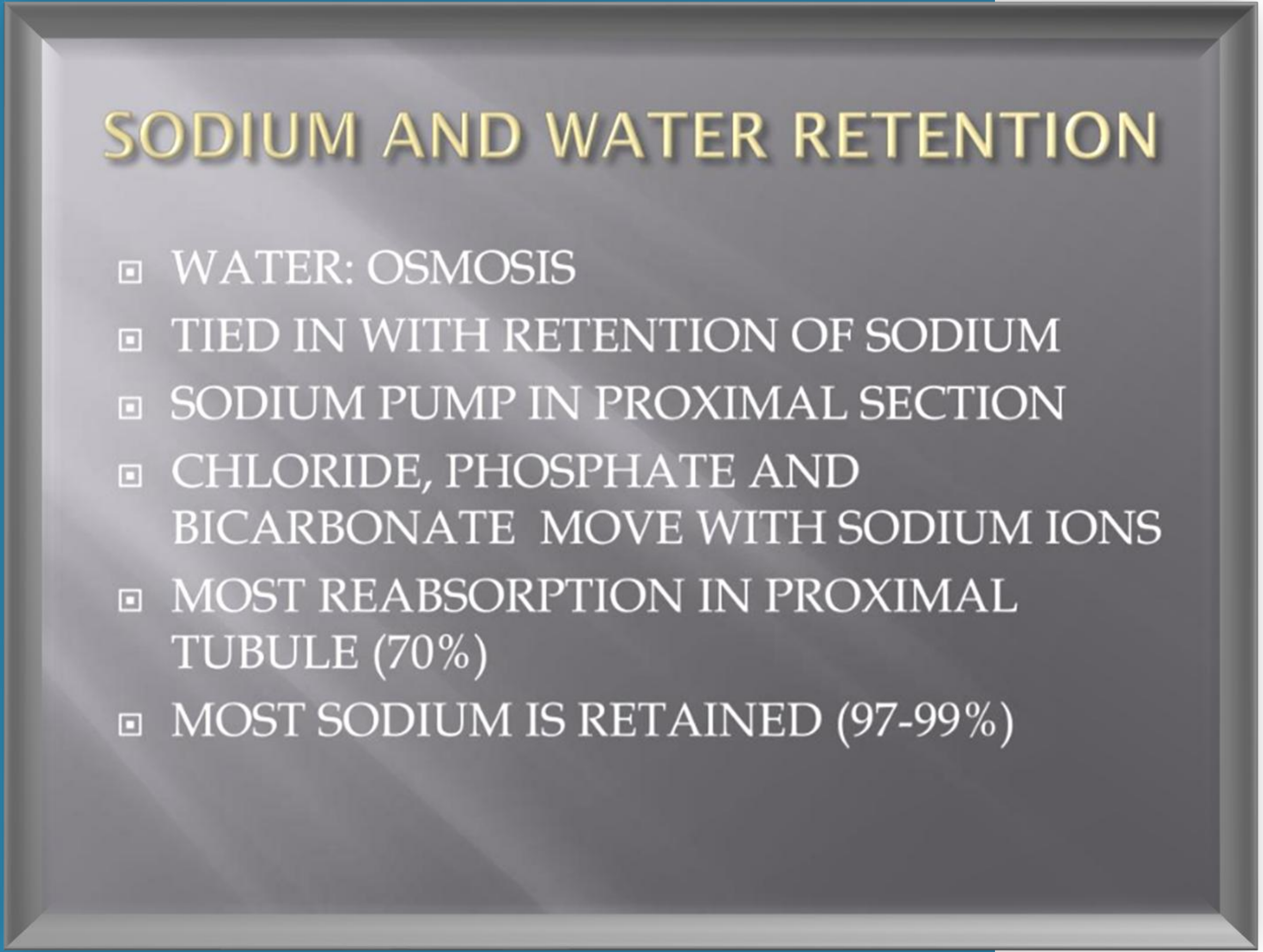
Therefore, the diuresis that Lasix just caused is reversed by sodium retention from aldosterone.

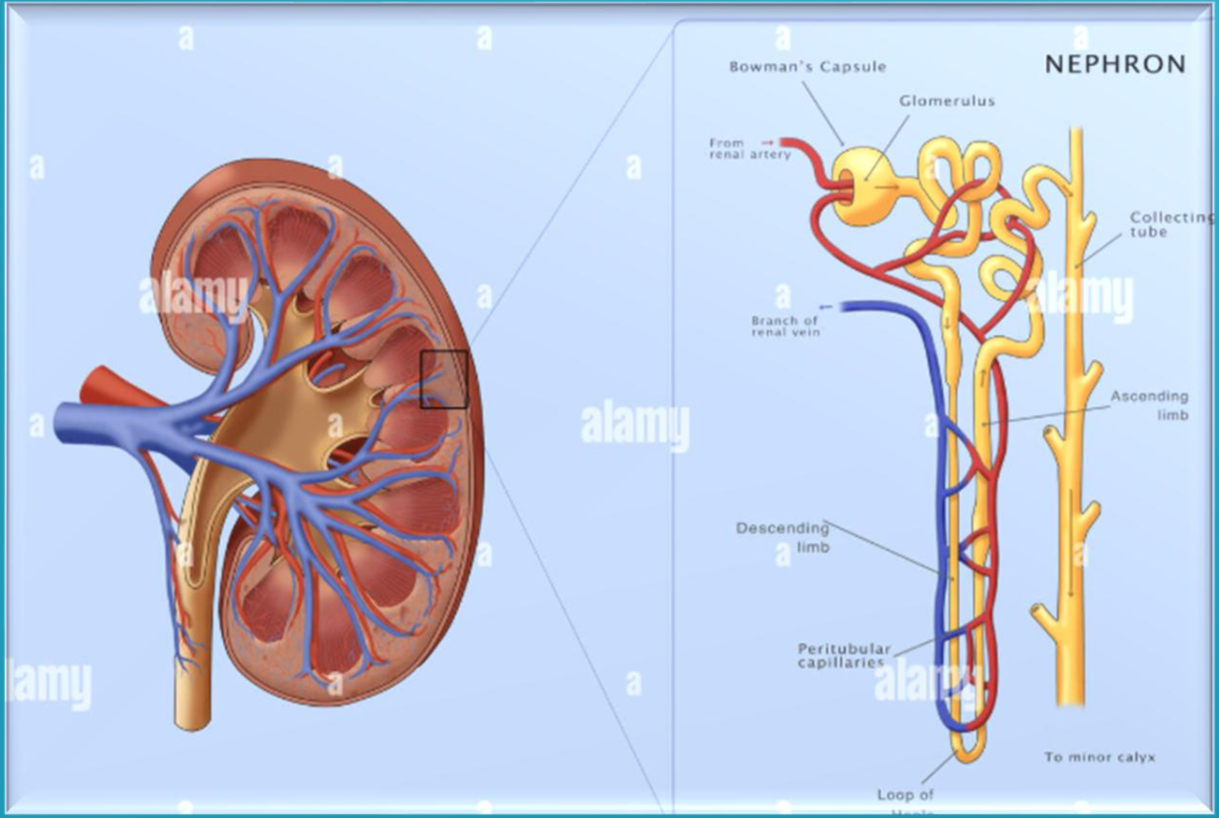
African Americans respond more aggressively to aldosterone.

By culture, African Americans consume higher amounts of sodium.

Aldosterone

- Physiologic functions of Aldosterone
  - Causes sodium retention which promotes water retention increasing blood volume and blood pressure.
  - Increase potassium excretion in the urine maintaining electrolyte balance.
  - Contributes to acid-base balance by stimulating the kidneys to secrete hydrogen ions into the urine.
  - The increased fluid balance can lead to ventricular remodeling and scarring.
  - May also play a role in modulating the immune response and inflammation.





The normal throughput of sodium filtered by the kidneys in young people is ~2300 mg of sodium per day.

The typical western diet has 5000-7000 mg sodium consumption per day.

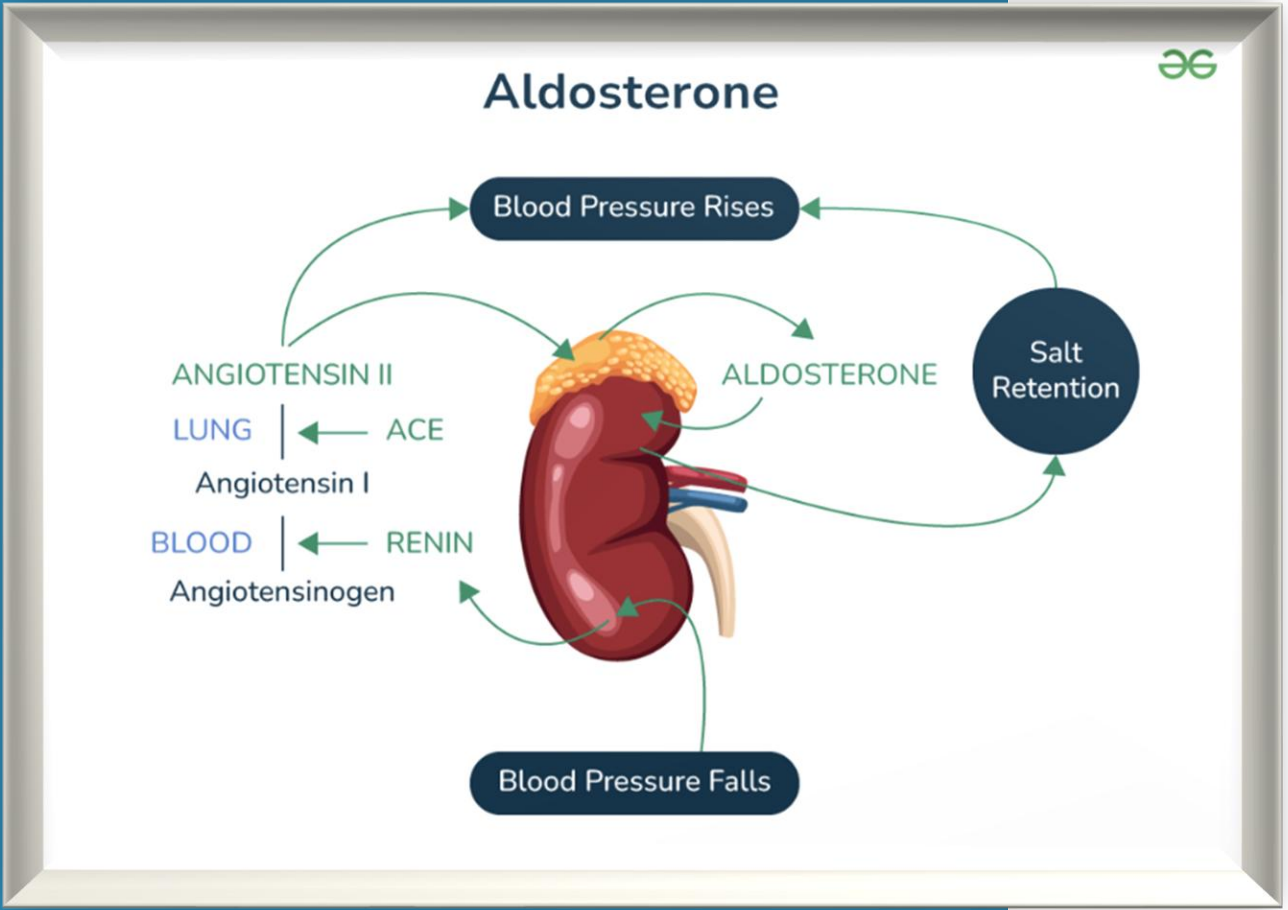
African Americans consume 10,000-12,000 mg sodium per day.

Humans have 750,000-1,000,000 nephrons per kidney when young.

After the age of 35, you start losing nephrons at the rate of about 100 per kidney per week or about 10,500 nephrons lost per year due to natural cell senescence.

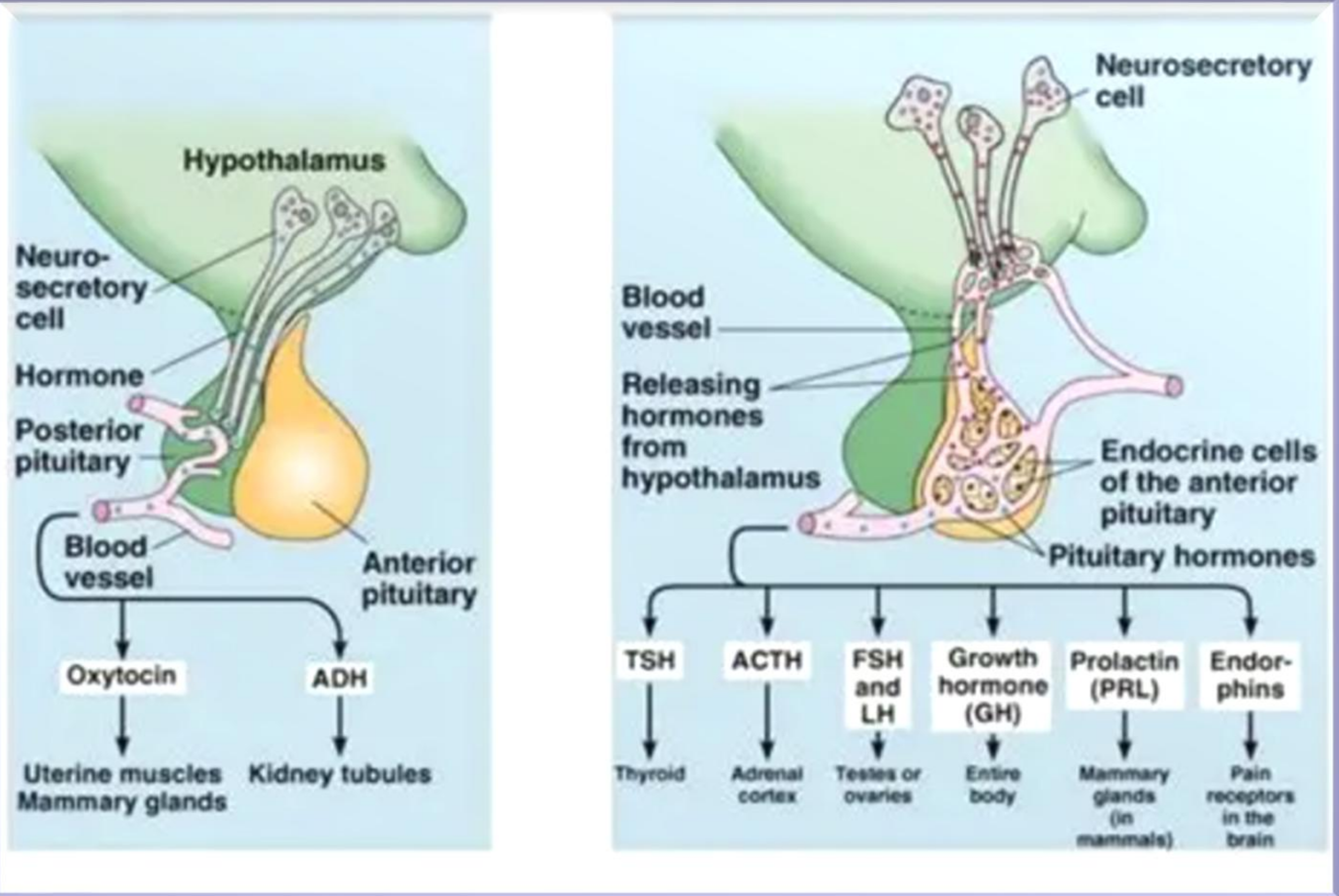
This will reduce nephron mass and reduce renal clearance of sodium.

Aldosterone-Characteristics



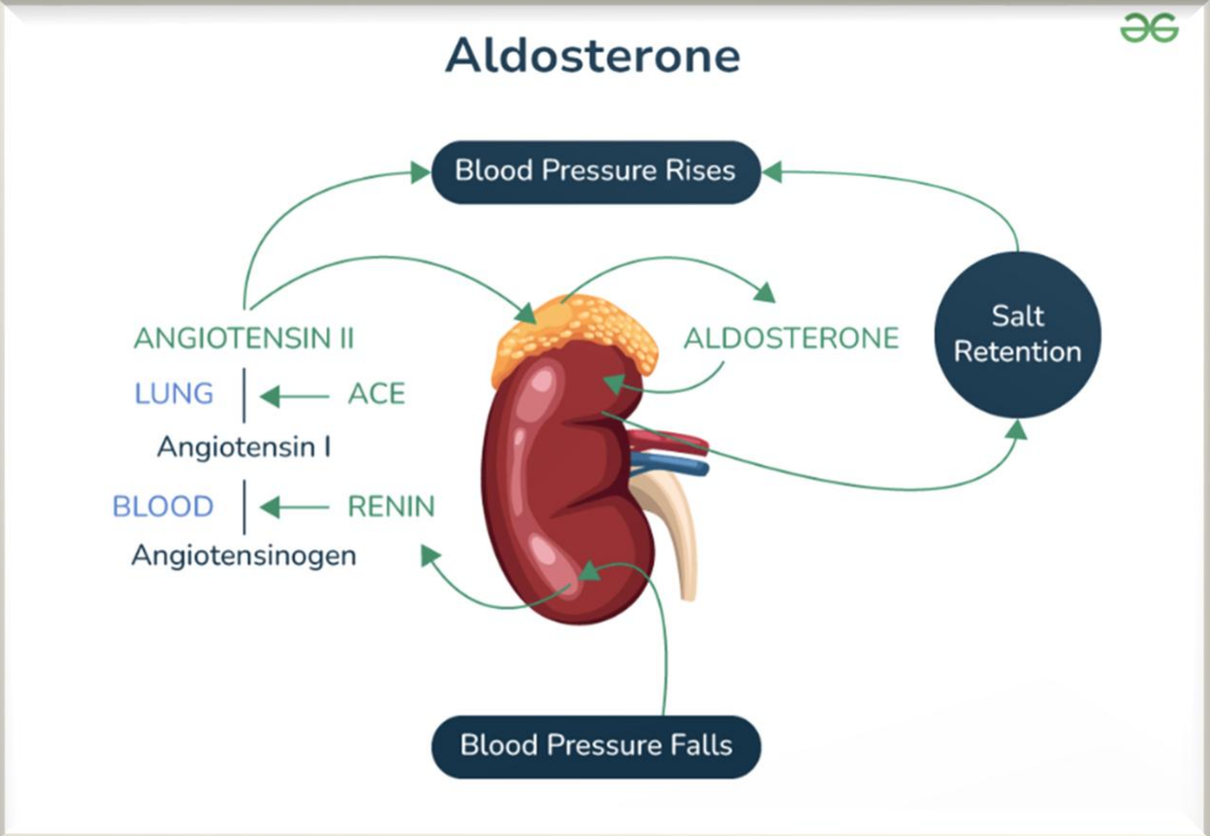
- Aldosterone will rise in response to volume contraction and dehydration to promote sodium and water retention by both the kidneys and the colon.
- It also increases urinary excretion of potassium.

- Aldosterone will fall in response to fluid or sodium overload allowing more sodium to be eliminated by the kidneys and colon followed by water.
- Potassium will be retained.
- THIS IS WHY GIVING SALT TABLETS FOR HYPONATREMIA CAN NOT WORK!!



Reset Osmostat Syndrome

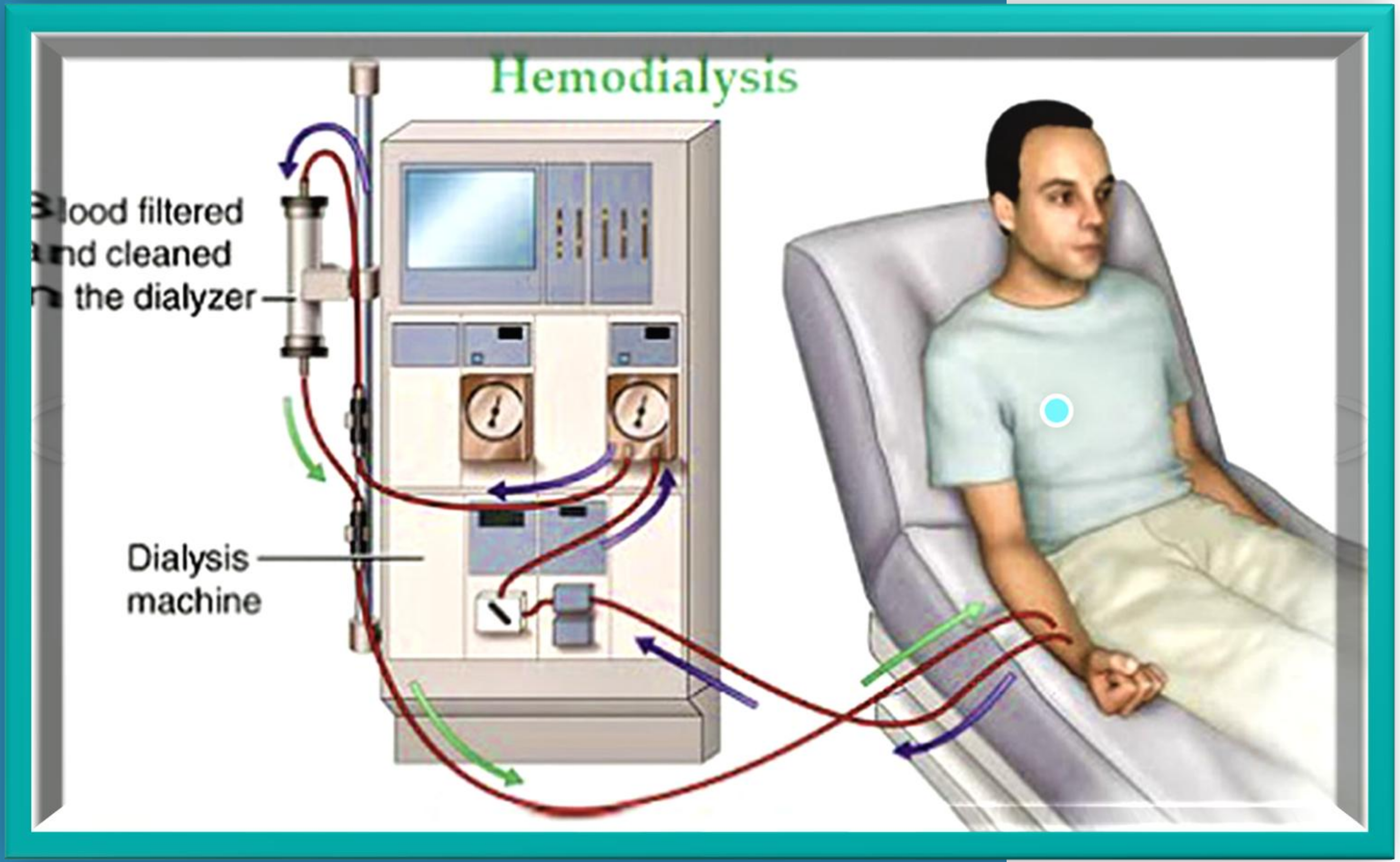
- The osmostat is located in the hypothalamus and senses serum osmolality.
- Sodium is the strongest osmol in circulation.
- The osmostat can reset itself to a higher or lower value over time.
- If the osmostat is set at a lower value (eg 132 mEq/L), then giving sodium tablets will not work.
- As the salt tablet dissolves, the osmolality will rise to a value higher than the osmostat is set at.
- ADH will rise causing fluid retention.
- Aldosterone will fall allowing the sodium to escape into the urine.
- Since sodium attracts water, you will observe a saline diuresis and will lose water.



Aldosterone- Characteristics

- In reverse dipping hypertension, the normal circadian rhythm of aldosterone is disrupted, with nocturnal aldosterone levels remaining high or even rising instead of the normal falling.

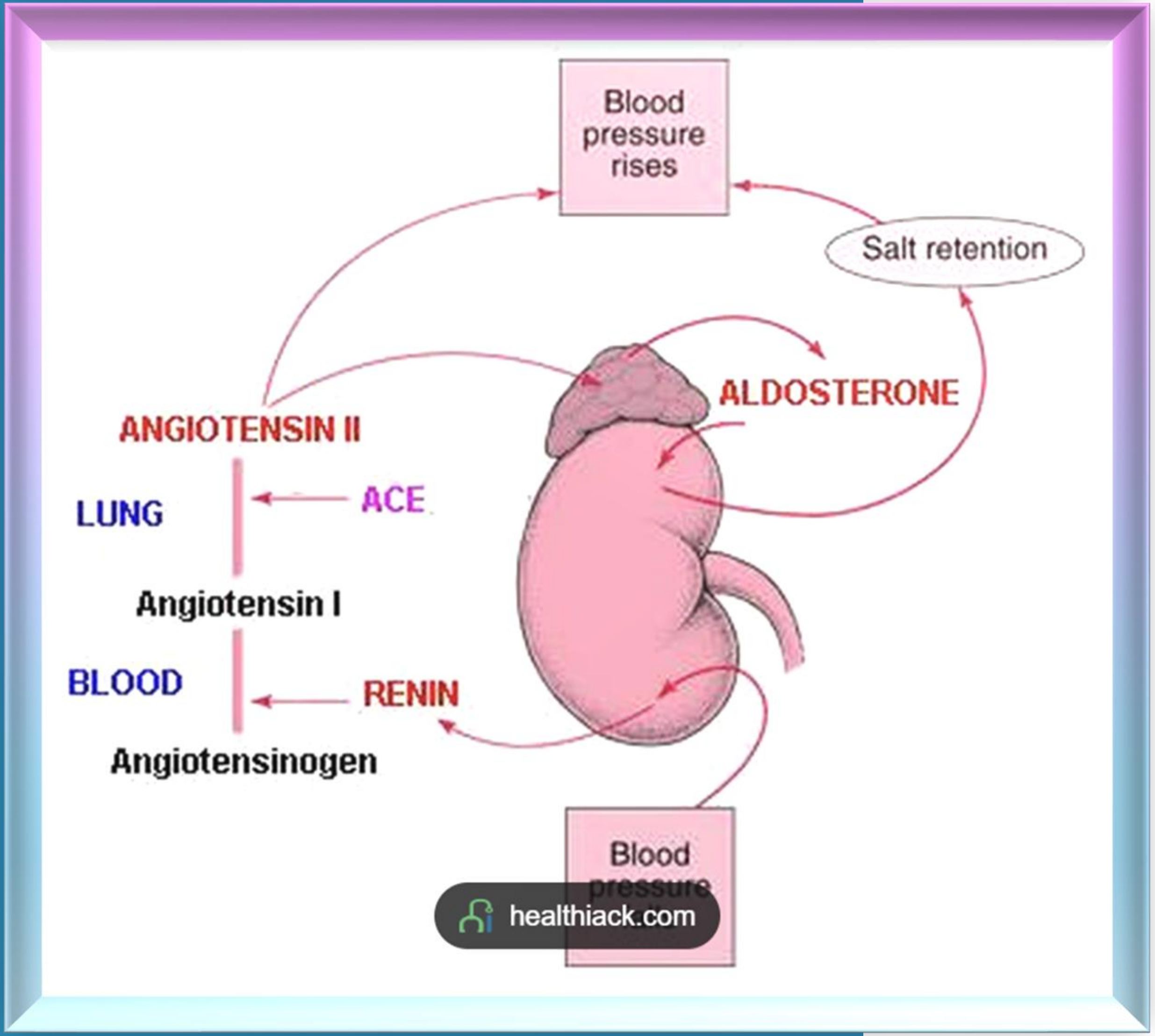
- Key behaviours.
  - Sustained or increased RAAS activity.
  - "Relative" aldosterone excess.
  - Volume expansion.
  - Early morning hypertension.
  - The sustained high nocturnal BP, causes further overactivation of the RAAS causing even more increase in aldosterone.
  - Causes oxidative stress, inflammation, and vascular stiffness, promoting cardiovascular damage independent of its BP elevating effects.



Human Fluid Balance

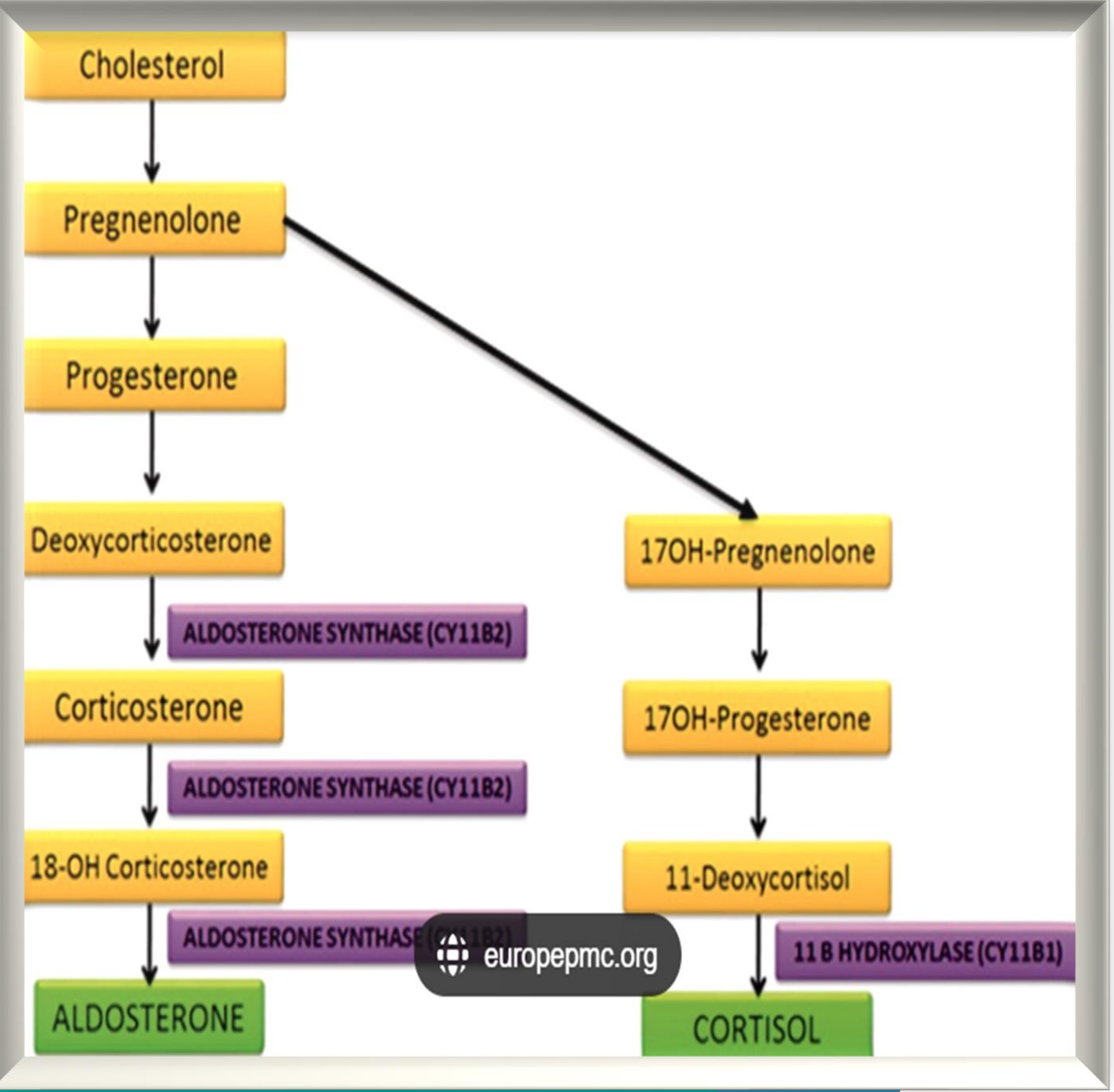
- Lasix only lasts 6 hours (Lasix=lasts six).
- During diuresis, volume contraction occurs.
- You can remove water faster from the vascular space than it can move from interstitial space back into vascular space.

- Dialysis patients that make no urine will accumulate a lot of water in between treatments.
- When you give a patient a diuretic, the intent is to volume contract them.
- This volume contraction causes aldosterone to rise.



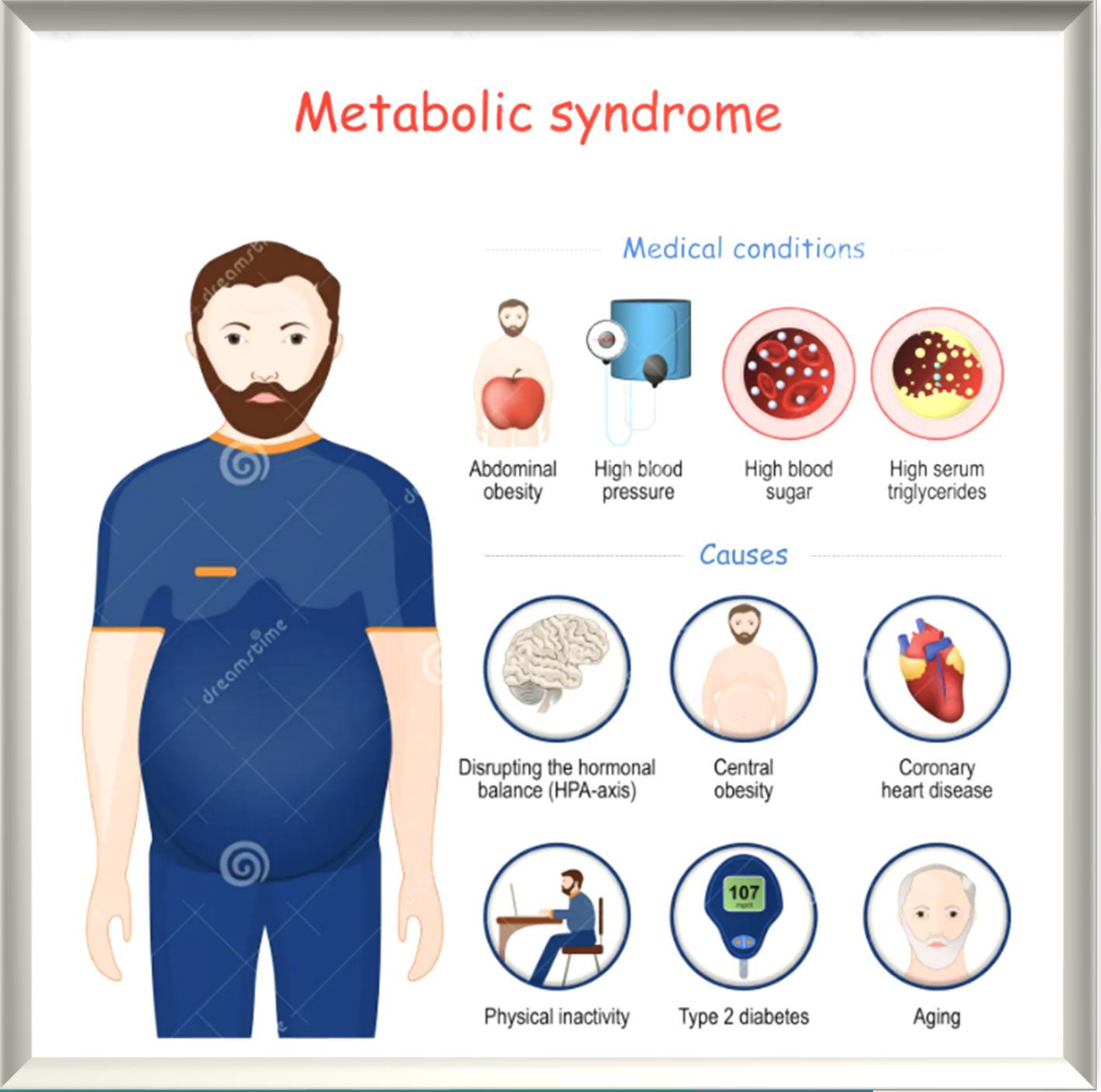
Aldosterone- Effects of Volume Contraction on Aldosterone

- Aldosterone is the most powerful sodium retainer known to man.
- During diuresis, you are unaware of what aldosterone is doing.
- With volume contraction, aldosterone level will rise causing powerful sodium retention.
    - Fludrocortisone is the most powerful drug at retaining sodium.
    - Other steroids also retain sodium.
    - So do NSAIDS.
    - And many other drugs.



Aldosterone- Effects of High Aldosterone on Humans

- Sustained and difficult to control blood pressure.
- Myocardial fibrosis, hypertrophy, and impaired heart function.
- Atrial fibrillation due to scarring and fibrosis causing conduction disturbances.
- Insulin resistance.
- Impaired pancreatic beta cell function.
- Promotes inflammation in adipose tissue.



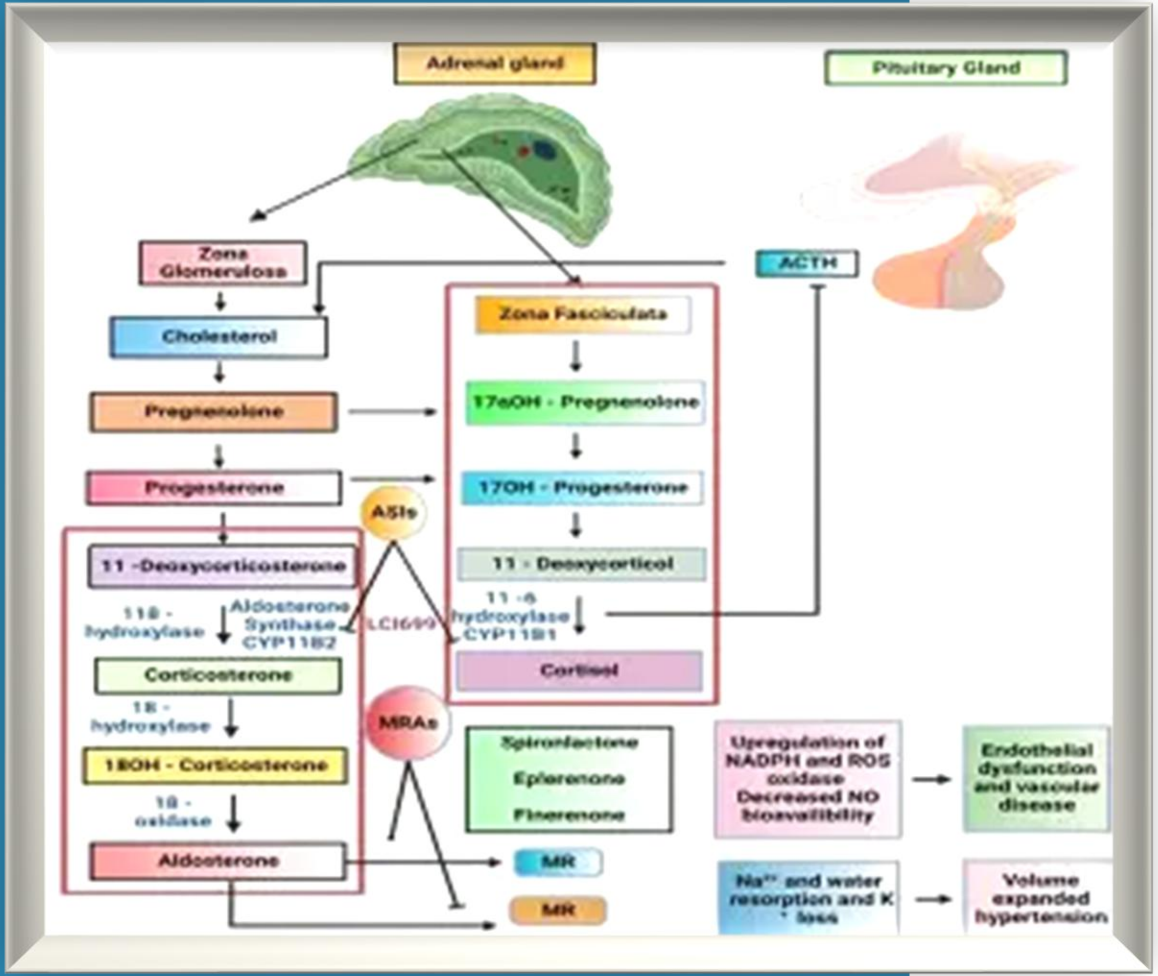
Aldosterone- Potential Causes of Aldosterone Overactivity

- Obstructive sleep apnea.
  - Causes sympathetic nervous overactivity that activates the RAAS.
- CKD can lead to dysregulation of salt and water balance.
- Metabolic syndrome and obesity.
  - Adipose tissue can secrete substances that directly stimulate aldosterone secretion.
- Primary hyperaldosteronism.
- Medication timing. Taking diuretics or RAAS blockers only during the day may exacerbate reverse dipping.

Q=N/D=Sodium/Fluid=Aldosterone/ADH

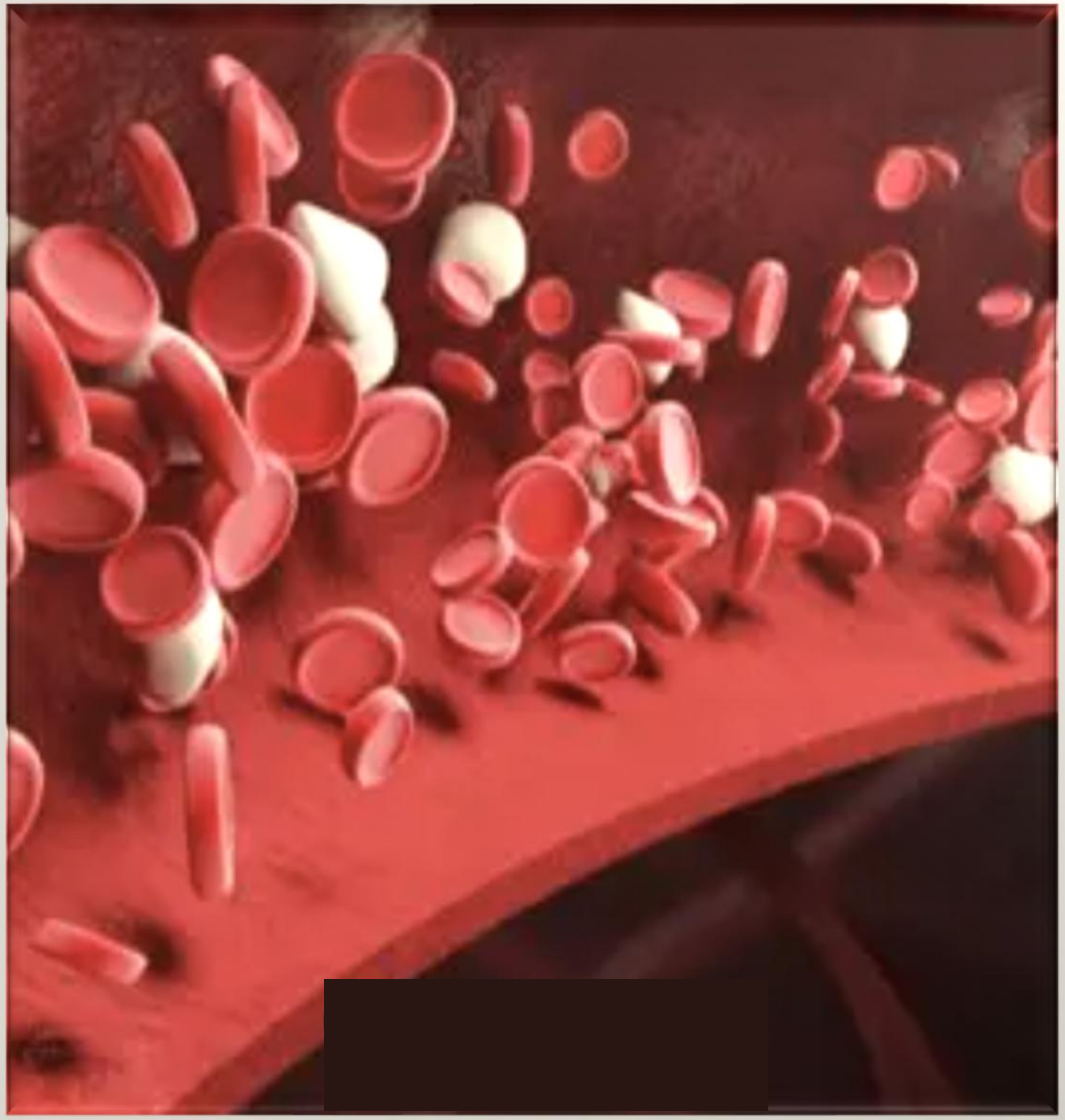
Sodium Management

- The sodium level on the lab report is a concentration measured as milliequivalents per liter (mEq/L).
- This is a ratio between the amount of sodium dissolved in a known fluid volume of 1 liter.
- It is a fraction with your value as the quotient, sodium amount as the numerator and fluid volume as the denominator.



Upcoming Aldosterone Synthase Inhibitors

- Baxdrostat
- Lorundrostat
- Vicadrostat
- Dexfadrostat
- Osilodrostat (Isturisa) marketed for Cushing’s disease



- Baxdrostat and Lorundrostat.

Mineralcorticoid synthase inhibitor (New research drugs).

Blocks cytochrome P450 11B2.

Aldosterone level increases during the night and peaks in the early morning hours rising with cortisol levels.

Aldosterone causes powerful sodium retention.

Causes potassium loss.

Causes coronary inflammation, fibrosis and thickening of the heart muscle.

High aldosterone levels can cause kidney damage.

Can increase insulin resistance and promote fat accumulation.

Can modulate the immune system and increase inflammation.

Upcoming Aldosterone Synthase Inhibitors

- Why is development of aldosterone synthase inhibitors beneficial? Why are they better than mineralcorticoid receptor blockers?
    - When you give a drug that blocks a receptor, the cell will, over time, upregulate the production of the receptors being blocked.
    - If you abruptly stop the drug or miss a dose, a normal circulating level of the hormone will now show a more aggressive response as it binds more receptors.
        - Eg. Reflex tachycardia after abrupt beta blocker withdrawal.

Remember. An apple a day keeps the doctor away.

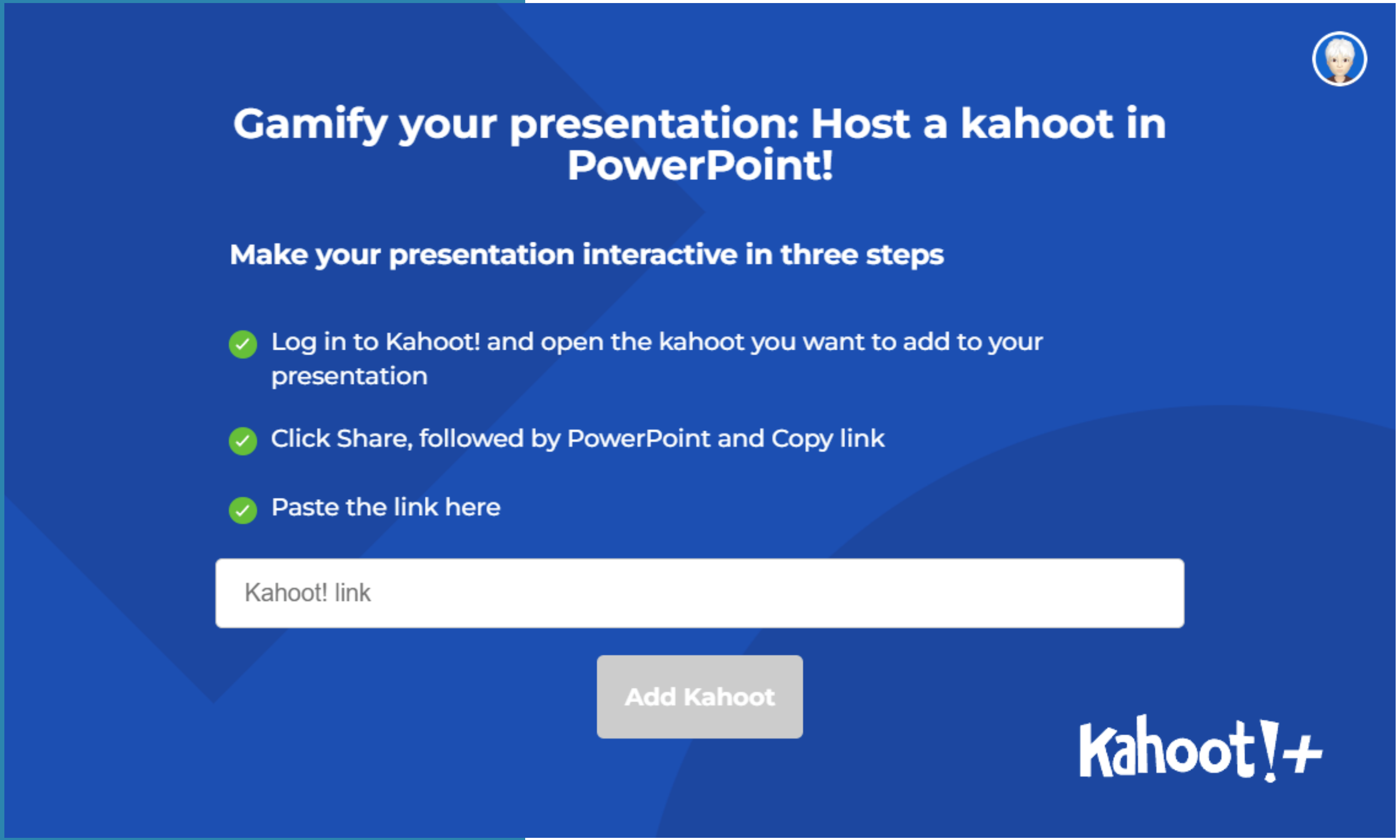
You just have to aim it real well.

The best way to treat disease

is to prevent disease.

KAHOOT TIME

Get your cellphone ready


Gamify your presentation: Host a kahoot in PowerPoint!
Make your presentation interactive in three steps
Log in to Kahoot! and open the kahoot you want to add to your presentation
Click Share, followed by PowerPoint and Copy link
Paste the link here
Kahoot! link
Add Kahoot
Kahoot!+