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HY Arrows

It is to my observation that if a student ever fails the USMLE Step 1, his or her concept of arrows (i.e., should a hormone, electrolyte, etc., be ↑, ↓, or ↔) is always terrible.

I consider this one of the most important pieces of content I've created to date. It comprises 168 HY arrow questions.

I would say that >90% of the arrow questions I discuss in this document are essential to merely pass USMLE Step 1. Maybe about the other 10% are more difficult but important enough that I included them. I have only included the concepts I view as the highest yield for the exam.

I'm aware some students might go through this PDF and say, "Oh but Mike, you could have also included arrow questions on x, y, and z." And my response is, yes, we could by all means sit together in a conference room with a whiteboard and draw up, e.g., 300+ potential arrow questions. But I want to reiterate that the purpose of this document is not to be a massive agglomeration of questions just for the sake of it. The value of this document is specifically in the fact that it's highly potent and concise despite there being a broad range of testable material for USMLE.

I considered adding a table to contents to this document, as some students might prefer to jump to certain subject areas, but after starting one, I decided it was better to omit it in order to not give away some answers, essentially.

1. Patient has high aldosterone. What are the arrows (i.e., ↑ or ↓) for serum Na^+, K^+, pH, bicarb, and CO2?

- **↑ Na^+, ↓ K^+, ↑ pH, ↑ bicarb, ↑ CO2.**
- Remember that all arrows go the same direction as aldosterone, except for potassium, which is the opposite.
- Aldosterone upregulates the sodium-potassium ATPase pump on the basolateral membrane of the cortical collecting duct in the kidney. This causes Na^+ reabsorption and K^+ secretion. Water follows sodium; this will function to increase volume status and blood pressure.
- Aldosterone also upregulates an apical H^+-ATPase pump. If protons are kicked out into the urine, the patient develops metabolic alkalosis (i.e., bicarb goes up).
- CO2 is acidic. If we have a metabolic alkalosis, we want to retain acidic CO2, so we slow respiratory rate – i.e., metabolic alkalosis with respiratory compensation.

2. Patient has low aldosterone. What are the arrows (i.e., ↑ or ↓) for serum Na^+, K^+, pH, bicarb, and CO2?

- **↓ Na^+, ↑ K^+, ↓ pH, ↓ bicarb, ↓ CO2.**
- Remember that all arrows go the same direction as aldosterone, except for potassium, which is the opposite.
- Decreased aldosterone would mean metabolic acidosis (normal anion gap in this case) with respiratory compensation.
- I will go into more detail on different things as we move along. However for starters, you knowing the above arrows for high versus low aldosterone is paramount for USMLE, which is why I started this way.

3. Patient is given lisinopril. What change will this cause (i.e., ↑ or ↓) in renin, angiotensin I, angiotensin II, and aldosterone?

- **↑ Renin, ↑ angiotensin I, ↓ angiotensin II, ↓ aldosterone.**
- Lisinopril is an ACE inhibitor. This will decrease cleavage of AT I into AT II in the lungs. AT II and aldosterone will go down as a result.
- Lower aldosterone will cause reduced fluid status, which will cause renin secretion to go up to compensate. This will lead to increased angiotensin I production (renin cleaves hepatically synthesized angiotensinogen into AT I in the plasma).
- Another way to think of it is: if you block the step between AT I and AT II, substrates on the left go up; products on the right go down.

4. Patient is given valsartan. What change will this cause (i.e., ↑ or ↓) in renin, angiotensin I, angiotensin II, and aldosterone?

- **↑ Renin, ↑ angiotensin I, ↑ angiotensin II, ↓ aldosterone.**
- Valsartan is an angiotensin II receptor blocker (ARB).
- Unlike with ACE inhibitors, there is no inhibition of the synthesis of AT II.
- Since the AT II receptors are blocked, aldosterone synthase activity in the zona glomerulosa of the adrenal cortex goes down.
- Lower aldosterone causes lower fluid status, so renin goes up to compensate. This in turn leads to more angiotensinogen cleavage into angiotensin I.
- More angiotensin I is then cleaved into angiotensin II in the lungs.

5. Patient is given spironolactone. What change will this cause (i.e., ↑ or ↓) in renin, angiotensin I, angiotensin II, aldosterone, and K^+ levels?

- **↑ Renin, ↑ angiotensin I, ↑ angiotensin II, ↑ aldosterone, ↑ K^+.**
- Spironolactone is an aldosterone receptor antagonist. Blocking aldosterone receptor will cause all substrates to increase.
- Since aldosterone causes potassium secretion from the blood into the urine, blocking aldosterone receptors can cause hyperkalemia.
- High potassium can also be caused by ACE inhibitors and ARBs, since they decrease aldosterone.
- It should be noted that spironolactone is anti-androgenic and can cause gynecomastia. There is less risk of this with eplerenone.

6. If a patient is given enalapril, what will happen (i.e., ↑, ↓, or ↔) to left ventricular afterload, systemic arteriolar diameter, renal afferent arteriolar diameter, and renal efferent arteriolar diameter?

- **↓ LV afterload, ↑ systemic arteriolar diameter, ↔ afferent diameter, ↑ efferent diameter.**
- AT II is a potent vasoconstrictor. Not only does it increase aldosterone synthase activity in the zona glomerulosa of the adrenal cortex, but it also constricts peripheral arterioles.
- ACEi (e.g., enalapril) and ARBs decrease afterload on the LV by relieving the constrictive effects of AT II on peripheral arterioles.
- Some students will get pedantic about potential minor effects of AT II on the afferent arterioles. This will get you questions wrong on USMLE. Do not over-think things. The exam assesses AT II as a potent vasoconstrictor at the **efferent** arterioles. This increases filtration fraction and maintains GFR in the setting of reduced renal blood flow.
- AT II will constrict (i.e., ↓ diameter) of efferent arterioles. Therefore ACEi/ARBs ↑ diameter.

7. 32F + abdominal bruit + BP of 160/100. What are the arrows (i.e., ↑ or ↓) for Na^+, K^+, pH, bicarb, and CO2?

- **↑ Na^+, ↓ K^+, ↑ pH, ↑ bicarb, ↑ CO2.**
- Diagnosis is fibromuscular dysplasia (FMD), which is tunica media proliferation, generally in women 20s-50s. This results in decreased renal perfusion → renin secretion by JGC → RAAS activation.
- This is **not** the same as renal artery stenosis, which is due to atherosclerosis. The vignette will instead be a patient with, e.g., intermittent claudication, Hx of CABG, or many years of smoking.

8. 74M + hyperpigmentation of the forearms + eosinophils 23% + 6-month Hx of fatigue + BP 100/60. What are the arrows (i.e., ↑ or ↓) for Na^+, K^+, pH, bicarb, CO2, and ACTH?

- **↓ Na^+, ↑ K^+, ↓ pH, ↓ bicarb, ↓ CO2, ↑ ACTH.**
- Patient has Addison disease (primary hypoadrenalism). I've seen it in young and old patients on NBME. Most commonly, the etiology is autoantibodies against 21-hydroxylase in the adrenal cortex.
- Patients with Addison disease have ↓ aldosterone and ↓ cortisol.
- ↓ cortisol results in ↓ negative feedback at hypothalamus and anterior pituitary → ↑ CRH and ACTH secretion. POMC is precursor to both ACTH and α-MSH. The latter (as well as ACTH to some extent) causes hyperpigmentation.
- In Addison, the adrenal gland itself is the location of the pathology, so aldosterone *and* cortisol are low. In secondary hypoadrenalism (i.e., ↓ ACTH production by the anterior pituitary), only cortisol is low; in the latter case, there is nothing wrong with the adrenal gland, so AT II can still ↑ aldosterone synthesis without a problem.
- Eosinophilia is common in adrenal insufficiency. This is HY, especially on 2CK IM Qs. Don't go chasing stool ova and parasites. Cortisol can function to sequester eosinophils in the spleen.

9. 45M + one-year Hx of fatigue and darkening of skin of forearms + BP 100/60; exogenous ACTH is administered and shows marginal increase in cortisol levels. Prior to administration of ACTH, what are the arrows (i.e., ↑, ↓, or ↔) for this patient's serum ACTH, eosinophils, Na^+, K^+, pH, bicarbonate, and CO2?

- **↑ ACTH, ↑ eosinophils, ↓ Na^+, ↑ K^+, ↓ pH, ↓ bicarbonate, ↓ CO2.**
- This patient has Addison disease. The ACTH stimulation test is used to diagnose, which will show a very marginal increase in serum cortisol, thereby demonstrating the patient has adrenal insufficiency (i.e., unable to adequately make cortisol in response to ACTH).
- Healthy patients will demonstrate a robust increase in serum cortisol in response to exogenous ACTH.
- Patients with Addison have low serum cortisol and aldosterone. Low cortisol means less negative feedback at the hypothalamus and anterior pituitary, leading to increased CRH and ACTH levels.
- Eosinophilia is a common finding in Addison disease. This is especially prevalent in 2CK-level IM Qs. Once again, do not go chasing stool ova and parasites.
- Low aldosterone means less sodium reabsorption, as well as less potassium and proton secretion in the cortical collecting duct of the distal kidney. Retention of protons means serum bicarb is low.
- CO2 is low because the patient will have metabolic acidosis, so it is blown off as compensation.

10. 39F + 20-year-Hx of rheumatoid arthritis managed with NSAIDs, prednisone, methotrexate, and infliximab. She has Cushingoid appearance. What are the arrows (i.e., ↑, ↓, or ↔) for her ACTH and cortisol levels?

- **↓ ACTH, ↓ cortisol.**
- Students get this question wrong all of the time.
- Prednisone is **not** the same as cortisol. It is merely a cortisol (i.e., glucocorticoid) analogue.
- Prednisone will induce negative feedback at the hypothalamus and anterior pituitary, causing a reduction in CRH and ACTH.
- Because ACTH is low, the adrenal gland is under-stimulated, and endogenous cortisol production decreases.
- Students erroneously assume cortisol must be high if a patient is Cushingoid in appearance. The ↓ for ACTH and cortisol in the setting of exogenous glucocorticoids is exceedingly high-yield for USMLE.
- If the USMLE tells you the patient is on prednisone, that makes the question easy. They will sometimes say a Cushingoid patient with an autoimmune disease, e.g., SLE, IBD, RA is “managed with multiple medications,” and just assume you can infer he/she is on prednisone.
- Not hard now that we discussed it. But students fuck this up a lot.

11. 13M + three days ago treated for meningococcal septicemia + now has BP of 80/50. What are the arrows (i.e., ↑, ↓, or ↔) for serum aldosterone, cortisol, ACTH, K^+, Na^+, $HCO3^-$, pH, and CO2?

- **↓ Serum aldosterone, ↓ cortisol, ↑ ACTH, ↑ K^+, ↓ Na^+, ↓ $HCO3^-$, ↓ pH, and ↓ CO2.**
- Diagnosis is Waterhouse-Friderichsen syndrome, which is hemorrhagic necrosis of the adrenal glands secondary to meningococcal septicemia. Both the zona glomerulosa (aldosterone-producing layer) and zona fasciculata (cortisol-producing layer) are affected. The zona reticularis (androgen-producing layer) could in theory be affected, but don't worry about that here.
- Cortisol normally functions to upregulate α1-receptors on arterioles. Catecholamines (norepinephrine and epinephrine) agonize these receptors and cause vasoconstriction, thereby maintaining blood pressure. If cortisol is low, then NE and E can't do their job, so BP is low.
- If the USMLE asks which drug to give in this setting (following the administration of normal saline), the answer = hydrocortisone, which is a cortisol analogue. If you give NE, it won't significantly increase BP since α1-receptors aren't being expressed adequately due to the low cortisol.
- Low aldosterone would in theory cause low BP from less fluid retention, but in the case of W-F syndrome, the low BP is more an acute effect of ↓ cortisol, resulting in ↓ α1-receptor expression.
- Low aldosterone causes high potassium, low sodium, low bicarb, and low pH (metabolic acidosis). CO2 then goes down to compensate (we want to blow off CO2 since it's acidic).
- ACTH is high since there is less cortisol exerting negative feedback at the hypothalamus and anterior pituitary.

12. 31M + Cushingoid appearance + serum ACTH levels undetectable + serum cortisol high; if high-dose dexamethasone is administered, what will happen (i.e., ↑, ↓, or ↔) to his ACTH and cortisol levels?

- **↔ ACTH, ↔ cortisol.**
- Dexamethasone is a cortisol analogue that is capable of exerting negative feedback at the hypothalamus and anterior pituitary. Given to healthy individuals, the result is suppression of ACTH and cortisol levels.
- This patient has undetectable ACTH and high serum cortisol. Giving exogenous dexamethasone, if anything, would only further suppress ACTH by inducing negative feedback at the hypothalamus and anterior pituitary. Because levels are already undetectable, they will not go lower (on NBME).
- Low serum ACTH in the setting of high serum cortisol means the diagnosis is Cushing syndrome secondary to primary adrenal cortical secretion. This is most likely due to an adenoma, but could also be diffuse cortical hyperplasia.
- **Cushing syndrome** = how the patient looks/presents; can refer to any cause of Cushingoid presentation (i.e., exogenous glucocorticoids, ACTH-secreting tumor of anterior pituitary, cortisol-secreting tumor of adrenal cortex, small cell bronchogenic carcinoma secreting ACTH).
- **Cushing disease** = ACTH-secreting tumor of anterior pituitary.
- Low-dose dexamethasone = yes or no test only for Cushing syndrome; doesn't tell us etiology.
- If low-dose dex is administered and patient's cortisol goes down, he/she does not have Cushing syndrome. If cortisol does not go down, then yes, he/she has Cushing syndrome; we don't know the cause, but yes, he/she has Cushing syndrome.
    - Failure of cortisol suppression with low-dose dex; high-dose dex administered + patient's cortisol goes down; answer = Cushing disease (anterior pituitary tumor secreting ACTH). Only Cushing disease will suppress with high-dose dex.
    - Failure of cortisol suppression with low-dose dex; high-dose dex administered + patient's cortisol goes not go down; answer = either primary adrenal secretion (i.e., adenoma or hyperplasia), or small cell bronchogenic carcinoma secreting ACTH. We know that because cortisol did not go down with high-dose dex, the cause of our Cushing syndrome cannot be Cushing disease.
    - Patient has high ACTH; failure of cortisol suppression with low-dose dex; high-dose dex administered + patient's cortisol goes not go down; answer = small cell bronchogenic carcinoma secreting ACTH.

  - Patient has low ACTH; failure of cortisol suppression with low-dose dex; high-dose dex administered + patient's cortisol goes not go down; answer = primary adrenal (cortisol-secreting tumor or diffuse hyperplasia).

- If a patient is on exogenous glucocorticoids, we do not do dexamethasone suppression test because the Cushing syndrome is clearly due to the exogenous steroids. We use the dexamethasone suppression test to identify endogenous causes of Cushing syndrome.

13. 45F + Cushingoid in appearance + serum ACTH levels high + serum cortisol high; MRI of the brain shows a mass; if high-dose dexamethasone is administered, what will happen (i.e., ↑, ↓, or ↔) to ACTH and cortisol levels?

- **↓ ACTH, ↓, cortisol.**
- Since the patient's diagnosis is Cushing disease (i.e., ACTH-secreting tumor of the anterior pituitary), she will experience successful suppression of cortisol with high-dose dexamethasone.
- Only Cushing disease will suppress with high-dose dex.
- In contrast, if the patient had high ACTH due to small cell bronchogenic carcinoma, neither ACTH nor cortisol would suppress with high-dose dex.

14. 50M + Cushingoid appearance + proximal muscle weakness + successful ability to maintain upward gaze for 60 seconds + serum ACTH levels high + serum cortisol high; if high-dose dexamethasone is administered, what will happen (i.e., ↑, ↓, or ↔) to his ACTH and cortisol levels?

- **↔ ACTH, ↔ cortisol.**
- The patient has both Lambert-Eaton and Cushing syndromes secondary to small cell bronchogenic carcinoma.
- Since the etiology for his Cushing syndrome is not Cushing disease, ACTH and cortisol will not suppress.
- Patients with Lambert-Eaton can maintain upward gaze for 60 seconds; patients with myasthenia gravis cannot (this detail shows up a lot on NBMEs).

15. 35F + central obesity with purple striae + adrenal mass visualized on CT of the abdomen. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's serum ACTH, cortisol, and urinary potassium?

- **↓ Serum ACTH, ↑ cortisol, ↑ urinary potassium.**
- This patient has Cushing syndrome due to a cortisol-secreting adenoma of the zona fasciculata.
- Serum ACTH is suppressed due to negative-feedback in the setting of high cortisol.
- Chronically high glucocorticoid levels can cause potassium wasting at the distal kidney similar to aldosterone. Patients with Cushing syndrome can sometimes have hypokalemia.
- Do not start psychoanalyzing questions and thinking aldosterone is high just because the patient has hypokalemia. I make a point about hypokalemia in Cushing syndrome just so you're not confused if you get a K^+ of 3.0 (NR is 3.5-5.0) in a patient with Cushingoid presentation.

16. 28F + gave birth one week ago via C-section in which she lost a lot of blood + now has fatigue + difficulty breastfeeding postpartum; what are the arrows (i.e., ↑, ↓, or ↔) for serum prolactin, ACTH, TSH, and aldosterone?

- **↓ Prolactin, ↓ ACTH, ↓ TSH, ↑ aldosterone.**
- These exact arrows are from a retired Step 1 NBME exam. I agree it's weird that they assess an ↑ for aldosterone in this case, but it's not my opinion. It's on NBME.
- Diagnosis is Sheehan syndrome. The pituitary doubles in size during pregnancy in order to produce more prolactin → greater oxygen demand. If patient loses a lot of blood during parturition, she is at risk of ischemic infarction → decreased production of pituitary hormones.
- Patient's fatigue implies hypothyroidism (↓ TSH here means secondary hypothyroidism).
- The patient will not have hyperaldosteronism as a result of Sheehan syndrome. In other words, the patient is not going to have an overt Conn syndrome-type of picture (i.e., ↑ Na^+, ↓ K^+, ↑ pH, ↑ bicarb) in the vignette. It is likely the case the USMLE wants you to know that aldosterone would be ↑ relative to its theoretical baseline because ACTH is ↓. In other words:
- ACTH → increases cortisol → upregulates α1 receptors on systemic arterioles → increases blood pressure; without this effect, blood pressure is lower, thereby providing impetus for aldosterone to increase. Once again, it's on a retired Step 1 NBME. I'm not disagreeing that this seems like an unusual arrow to ask.

17. 40M + recent weight gain + pituitary mass visualized on MRI + point tenderness over a vertebra at L1 + compression fracture visualized on x-ray + slight muscle weakness. What are the arrows (i.e., ↑, ↓, or ↔) for prolactin, ACTH, and serum K^+?

- **↔ Prolactin, ↑ ACTH, ↓ K^+.**
- Point tenderness over a vertebra on USMLE = compression fracture = osteoporosis.
- Cushing disease can present as mere osteoporosis and weight gain in a patient with a pituitary adenoma. Do not confuse this with avascular necrosis of the femoral head, which can also occur in Cushing disease.
- This is not a prolactinoma, so prolactin will be unchanged. Prolactin can cause impotence in men, amenorrhea in women, and galactorrhea in both genders.
- Serum potassium is sometimes decreased in patients with Cushing syndrome due to the fractional mineralocorticoid effects (i.e., function like aldosterone) of glucocorticoids at the kidney.
- All glucocorticoids will have fractional mineralocorticoid effects, some more than others.
- Fludrocortisone (often given to treat Addison) is a glucocorticoid with high mineralocorticoid effect.
- Endogenous cortisol, as well as exogenous prednisone, hydrocortisone, and dexamethasone all have very minor mineralocorticoid effect (i.e., they do not function similarly to aldosterone). In spite of this, chronically elevated levels can lead to reduced serum potassium.

18. What are the arrows (i.e., ↑, ↓, or ↔) for serum sodium, urinary osmolality, and urinary specific gravity if vasopressin (anti-diuretic hormone; ADH) is high?

- **↓ Serum sodium, ↑ urinary osmolality, ↑ urinary specific gravity.**
- ADH causes the insertion of aquaporins in the medullary collecting duct of the distal kidney. This results in increased free water reabsorption. Think of this process as diluting out serum sodium, while simultaneously making the urine more concentrated.
- Urinary osmolality refers to your concentration of solutes within the urine. The urine is becoming more concentrated because free water is being pulled out.
- Urinary specific gravity is another way of measuring concentration/diluteness of the urine. This variable shows up a lot, particularly in 2CK Qs. If urinary specific gravity is ↑, the urine is concentrated; if it is ↓, the urine is dilute.
- Patients will have elevated ADH in the setting of dehydration and syndrome of inappropriate secretion of ADH (SIADH).

19. What are the arrows (i.e., ↑, ↓, or ↔) for serum sodium, urinary osmolality, and urinary specific gravity if vasopressin (anti-diuretic hormone; ADH) is low?

- **↑ Serum sodium, ↓ urinary osmolality, ↓ urinary specific gravity.**
- If ADH is low, there is less aquaporin insertion in the medullary collecting duct of the distal kidney, and therefore less reabsorption of free water. The serum sodium will not be diluted out by free water, so the serum tonicity is greater.
- Urine osmolality and specific gravity are reduced because the urine is more dilute.
- Central diabetes insipidus (DI) is a condition of excessive urination due to decreased production of ADH by the hypothalamus (of defective storage by the posterior pituitary).
- In nephrogenic DI, ADH levels are high due to insensitivity to ADH at the kidney. Serum sodium will remain high, resulting in continual secretion of ADH by the hypothalamus. This is different from SIADH, since in nephrogenic DI, the high levels of ADH are appropriate given the increased serum sodium.

20. 45M + long history of smoking + recent weight loss + confusion; what are the arrows (i.e., ↑, ↓, or ↔) in this patient for serum sodium, urinary osmolality, and urinary specific gravity?

- **↓ serum sodium, ↑ urinary osmolality, ↑ urinary specific gravity.**
- The patient has SIADH secondary to small cell bronchogenic carcinoma (i.e., his vasopressin is high).
- Mental status change can occur with low or high serum sodium.
- HY small cell lung cancer paraneoplastic syndromes:
    - SIADH (ADH secretion).
    - Cushing syndrome (ACTH secretion).
    - Lambert-Eaton syndrome (pre-synaptic voltage-gated Ca^{2+}-receptor antibodies).
    - Neurologic/cerebellar dysfunction (Anti-Hu/-Yo antibodies).
- HY squamous cell lung cancer paraneoplastic syndrome:
    - Hypercalcemia often presenting as urolithiasis (PTH-related peptide; i.e., PTHrp, secretion).

21. 17M + was in car accident 6 weeks ago in which he witnessed his father pass away + since incident has heard voices telling him to drink a lot "to cleanse himself of the evil spirits." What are arrows (i.e., ↑, ↓, or ↔) in this patient for serum sodium, urinary osmolality, and urinary specific gravity?

- **↓ serum sodium, ↓ urinary osmolality, ↓ urinary specific gravity.**
- The patient has psychogenic polydipsia (i.e., drinking too much) secondary to schizophreniform disorder (psychosis 1-6 months in duration).
- In patients who drink too much, ADH will be low in order to permit the micturition of free water (thereby causing dilute urine), however serum sodium will be low, not high, because the ADH is appropriately low (i.e., we want ADH to be low if our serum is too dilute from water consumption).
- USMLE could also give a bodybuilder who drinks gallon jugs of water.

22. 30M + hospitalized for the past week due to motorcycle accident in which he incurred head trauma; urinary output is 800 mL/hour. What are arrows (i.e., ↑, ↓, or ↔) in this patient for serum sodium, urinary osmolality, and urinary specific gravity?

- **↑ serum sodium, ↓ urinary osmolality, ↓ urinary specific gravity.**
- This patient has central diabetes insipidus secondary to head trauma.
- Students should be aware that USMLE Qs can give central DI ***or*** SIADH secondary to head trauma or meningitis.
- This patient has high urinary output, indicating central DI with dilute urine, rather than SIADH with concentrated urine.

23. 24F + bipolar disorder + mildly tremulous + increased urinary output. What are arrows (i.e., ↑, ↓, or ↔) in this patient for tonicity of her proximal convoluted tubule (PCT), juxtaglomerular apparatus (JGA), and medullary collecting duct (MCD) in comparison to her serum tonicity?

- **↔ PCT, ↓ JGA, ↓ MCD.**
- USMLE Step 1 loves this combo of variables.
- This patient has nephrogenic diabetes insipidus secondary to the lithium she takes for her bipolar disorder. Lithium causes tremor and nephrogenic DI, among many adverse effects.
- The USMLE will ask the arrow combination for PCT, JGA, and MCD in a variety of patient vignettes. What you need to know is this:
- The PCT is always isotonic no matter what.
- The JGA is always hypotonic no matter what.
    - The JGA, which technically bridges the early-distal convoluted tubule (early-DCT) with the afferent arterioles of the kidney, is considered to be located at the early-DCT (top of thick ascending limb of loop of Henle) for USMLE Qs. Since there is massive ion reabsorption in the thick ascending limb (i.e., notably high concentrations of $Na^+/K^+/2Cl^-$ symporters), the urine will always be dilute at the early-DCT.
- The MCD will be hypotonic in DI (both central and nephrogenic) and psychogenic polydipsia.
- The MCD will be hypertonic in SIADH and dehydration.

24. 32F + marathon runner + currently 10 miles into a run + has not had anything to drink. What are the arrows (i.e., ↑, ↓, or ↔) in this patient for tonicity of her proximal convoluted tubule (PCT), juxtaglomerular apparatus (JGA), and medullary collecting duct (MCD) in comparison to her serum tonicity?

- **↔ PCT, ↓ JGA, ↑ MCD.**
- This patient has dehydration from being on a long run.
- The PCT is always isotonic no matter what.
- The JGA is always hypotonic no matter what.
- The MCD will be hypertonic in SIADH and dehydration.
- The MCD will be hypotonic in DI (both central and nephrogenic) and psychogenic polydipsia.
- Not super hard now that we've discussed it. Very important question for USMLE Step 1.

25. 47F + has been taking large doses of ibuprofen the past 25 years. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's urine volume and urine osmolality in response to exogenous administration of ADH?

- **↔ urine volume; ↔ urine osmolality.**
- Correct, the USMLE will be this vague with the stem, and these are the arrows they want.
- Patient has analgesic nephropathy secondary to long-term NSAID use.
- Analgesic nephropathy is a broad, umbrella term that can be used to refer to any renal disease caused by NSAIDs.
- USMLE wants you to know that nephrogenic diabetes insipidus can be caused by NSAIDs.
- Insensitivity to ADH at the kidney means there will be no change in urine volume or osmolality to exogenous ADH since endogenous ADH is already maximally high.
- ADH will normally increase urine osmolality and decrease urine volume due to its upregulation of aquaporins in the medullary collecting duct that function to reabsorb free water.

26. 24M + receives intravenous infusion of mannitol. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's ADH and serum osmolality as an immediate result of this infusion?

- **↑ ADH, ↑ serum osmolality.**
- Mannitol is a sugar alcohol. Infusion will cause immediate increase in serum osmolality since we are increasing the solute concentration of the serum (i.e., there's more "stuff" now in the serum).
- An increase in serum osmolality will trigger ADH release, which in turn will reabsorb more free water in the medullary collecting duct of the kidney to help re-dilute the serum back to original osmolality.
    - ↑ serum tonicity + osmolality → ↑ ADH release → dilutes serum back to normal.
    - ↓ serum tonicity + osmolality → ↓ ADH release → concentrates serum back to normal.
- Mannitol is an osmotic diuretic that acts by exerting oncotic pressure within the PCT and thin descending limb of the loop of Henle, thereby helping to facilitate tubular water retention and diuresis. It is the answer on 2CK forms for how to reduce intracranial pressure in patients who are already being hyperventilated (low CO2 reduces cerebral perfusion).
- Avoid mannitol in patients with heart failure, since initial increases in plasma volume due to higher serum osmolality will transiently increase preload on the heart.

27. In primary vs secondary hyperthyroidism, what are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, and T4?

- Primary hyperthyroidism: ↓ **TSH,** ↑ **T3,** ↑ **T4.**
- Secondary hyperthyroidism: ↑ **TSH,** ↑ **T3,** ↑ **T4.**
- Primary hyperthyroidism traditionally refers to Graves disease, toxic adenoma, and toxic multinodular goiter. It can also refer to transient thyroiditis (deQuervain, postpartum, or drug-induced). Don't worry, I'll elaborate on what you need to know for these HY DDx as we move forward in this PDF.
- Secondary hyperthyroidism could refer to a TRH- or TSH-secreting tumor.
- There is a retired Step 1 NBME Q where they give you a two-line stem where they say TSH and T4 are elevated, then they ask for whether it's primary or secondary hypo- vs hyperthyroidism; answer is secondary hyperthyroidism. Not difficult. But I'm just making a point that the NBME has asked this point-blank without any type of substantive vignette or disease application.

28. In primary vs secondary hypothyroidism, what are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, and T4?

- Primary hypothyroidism: ↑ **TSH,** ↓ **T3,** ↓ **T4.**
- Secondary hypothyroidism: ↓ **TSH,** ↓ **T3,** ↓ **T4.**
- Primary hypothyroidism traditionally refers to Hashimoto and iodine deficiency. TSH is high because of decreased negative feedback at the hypothalamus and anterior pituitary by T3 and T4.
- Secondary hypothyroidism is typically seen in Sheehan syndrome. Yes, Sheehan is classically ↓ prolactin, but NBME has also assessed TSH as decreased as well.

29. 33F + exophthalmos + tremulousness + type I diabetes mellitus; what are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↓ TSH, ↑ T3, ↑ T4, ↑ ^{131}I uptake.**
- Diagnosis is Graves disease. Exophthalmos (proptosis) is only seen in Graves disease.
- Mechanism is autoimmune production of thyroid-stimulating immunoglobulin (TSI).
- TSI is structurally similar to TSH and will agonize the TSH receptor (type II hypersensitivity).
- Relevance of type I diabetes is that "autoimmune diseases go together" – i.e., if a patient has one autoimmune disease (i.e., SLE, RA, IBD, etc.), there is increased risk of another. HLA associations are very loose on USMLE. Do not try to overthink based on specific HLAs. This will get you Qs wrong.
- Uptake of iodine into the thyroid gland signifies that the thyroid gland is producing thyroid hormone. In Graves, the uptake is diffusely increased. If uptake is increased in one area only, the answer is toxic adenoma. If uptake demonstrates multiple areas of uptake in an elderly patient, the answer is toxic multinodular goiter.
- If a patient has hyperthyroidism but decreased uptake, the answer is thyroiditis of some kind (i.e., drug-induced, deQuervain, or postpartum). In thyroiditis, the patient can be either hypo- or hyperthyroid; in the event he/she is hyperthyroid, the mechanism is increased release of thyroid hormone due to inflammation of the gland; the gland itself is not producing (which is why uptake is low, not high).

30. 19F + menstrual periods heavier and longer past 6 months + low mood + HR 60 + ↑ hepatic AST + ↑ total cholesterol + ↑ serum creatine kinase + mom has pernicious anemia; what are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↑ TSH, ↓ T3, ↓ T4, ↓ ^{131}I uptake.**
- Diagnosis is Hashimoto thyroiditis (chronic lymphocytic thyroiditis).
- Mechanism is mixed antibody- (anti-thyroperoxidase [aka anti-microsomal], anti-thyroglobuin) and T cell-mediated destruction of the thyroid gland.
- Uptake is diffusely decreased, or will be described as “patchy uptake” in a stem where the patient clearly has Hashimoto.
- Descriptors such as brittle hair, dry skin, constipation, and cold intolerance are too easy for many USMLE Qs. Don’t rely on these as a crutch.
- Students need to be aware of menstrual irregularities, bradycardia, dysthymia/depression, hepatic transaminitis, dyslipidemia, and myopathy (increased CK) as important parts of the disease.
- 2CK IM Qs in particular will give findings such as high AST (or ALT) and CK in a patient with bradycardia and fatigue and expect you to know that is Hashimoto.
- Hashimoto is the most common cause of hypothyroidism in Western countries. Iodine deficiency is the most common cause worldwide.

31. 24M + tremulous + heat intolerance + HR 92 + tender thyroid; what are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↓ TSH, ↑ T3, ↑ T4, ↓ ^{131}I uptake.**
- This is one of the most common incorrectly answered Qs on USMLE.
- Diagnosis is deQuervain (subacute granulomatous thyroiditis; or just subacute thyroiditis).
- Mechanism is viral infection followed by a **painful/tender** thyroid. There is inflammation of the thyroid gland, which causes the spacing between the cells to increase slightly, allowing for the release of pre-formed thyroid hormone into the blood. The gland is not over-producing thyroid hormone. This is why uptake is not increased.
- Viral infections are often asymptomatic, so most deQuervain vignettes will not mention the viral infection.
- Subacute granulomatous thyroiditis can be either hypo- or hyperthyroid. The key detail you need to know is that **uptake is always decreased *even if the patient is hyper-*.**
- DeQuervain vignettes will almost always be given as hyperthyroidism because the USMLE wants to specifically assess that you know uptake is decreased. If they give you hypo-, of course you'll select decreased for uptake.
- Decreased uptake applies to all thyroiditis conditions (i.e, deQuervain, drug-induced, and postpartum).

32. 40F + palpable thyroid nodule + biopsy shows amyloid demonstrating apple-green birefringence with Congo red stain under polarized light. What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↔ TSH, ↔ T3, ↔ T4, ↔ ^{131}I uptake, OR ↑ TSH, ↓ T3, ↓ T4, ↓ ^{131}I uptake.**
- Diagnosis is medullary thyroid carcinoma. Serum calcitonin will also be elevated.
- Patients with thyroid carcinoma (i.e., papillary, follicular, medullary, anaplastic) will be either euthyroid or hypothyroid; they will not be hyperthyroid.
- If the patient has a thyroid nodule and is hyperthyroid, the diagnosis is toxic adenoma. Adenomas are non-malignant tumors (i.e., they do not have metastatic potential). Carcinomas have metastatic potential.
- It should be noted that on 2CK FM Qs, choose “palpation of thyroid gland” before “check serum TSH” if the patient requests thyroid cancer screening.
- If patient with nodule has normal or high TSH (i.e., euthyroid or hypothyroid), do ultrasound before fine-needle aspiration. This is assessed on the new 2CK Free 120, where ultrasound is correct over FNA for evaluation of thyroid nodule. It had long been pushed in resources that ultrasound is always wrong. But this is on Free 120.
- 2CK IM Q gives euthyroid patient with nodule where FNA is the answer, but ultrasound not listed.
- So my conclusion (based on NBME/Free 120 content, not my opinion) is: for eu- or hypothyroid patient with thyroid nodule, ultrasound is correct over FNA if both are listed. If ultrasound isn’t listed but FNA is, FNA is correct.
- If patient has low TSH (i.e., hyperthyroid), do radioiodine (^{131}I) uptake scan, not ultrasound.
- Since carcinomas are non-secretory of thyroid hormone, if a patient is hyperthyroid, we’re not concerned about carcinoma, which is why we don’t go the USS then FNA route. We just do uptake to better see if the patient’s etiology for hyperthyroidism is Graves (diffuse), toxic adenoma (single nodular uptake), or toxic multinodular goiter (multifocal nodular uptake).

33. Patient is injecting triiodothyronine (T3). What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↓ TSH, ↑ T3, ↓ T4, ↓ ^{131}I uptake.**
- This is a “hard” question.
- Diagnosis is factitious (or surreptitious) thyrotoxicosis.
- Remember, T4 is converted to T3, but T3 is not converted to T4.
- Triiodothyronine is T3. Thyroxine is T4.
- If we inject T3, we will suppress TSH due to negative feedback. In turn, the thyroid gland will be under-stimulated, so uptake is low. The thyroid gland will often be described as “small and non-palpable.” Since the thyroid gland will be under-stimulated (we don’t need production if we’re injecting it), **production of T4 will be reduced.**
- This arrow combo for T3 injection is on one of the retired Step 1 NBMEs.
- “But Michael, what about T4 injection then?” → Ok, go to the next question.

34. Patient is injecting levothyroxine (T4). What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↓ TSH, ↑ T3, ↑ T4, ↓ ^{131}I uptake.**
- T4 is converted to T3, so if we inject T4, we will also have high T3.
- High T3 and T4 cause suppression of TSH, which in turn leads to decreased iodine uptake into the thyroid gland.
- Remember, T3 is not converted to T4. If we inject triiodothyronine, T3 will be high, but T4 will be low because we're not able to produce it if we shut off the thyroid gland.
- It is not sufficient to merely ask, "If patient injects thyroid hormone, what will the arrows be?" We need to specify whether it's T3 or T4 we're injecting.
- Some students might say, "Wait, if TSH is low, and that's the reason our ^{131}I uptake is low, then why isn't uptake low in Graves disease for instance. Cuz isn't TSH low in Graves?" → TSH is low in Graves, but don't forget that the mechanism for that disease is TSI production, which mimics TSH, thereby stimulating the gland to make thyroid hormone.
- In the case of toxic adenoma and toxic multinodular goiter, even though TSH is low, uptake is high because those conditions are tumorous, where the gland is autonomously producing and secreting thyroid hormones without the need for TSH.

35. 50M + routine screening by family practitioner reveals subclinical hypothyroidism. What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, and T4?

- **↑ TSH, ↔ T3, ↔ T4.**
- In subclinical hypothyroidism, the patient will be asymptomatic (hence subclinical) and will have normal T3 and T4, despite an elevated TSH.
- Most patients with subclinical do not need to be treated.
- Step 3 wants you to know that you treat if TSH >10, patient is pregger, or anti-Hashimoto Abs are +.

36. 54M + recovering in hospital from ARDS secondary to pancreatitis + currently being weaned from a ventilator. This is all the Q says and they want you to pick the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and rT3.

- **↔ TSH, ↔ T4, ↓ T3, ↑ rT3.**
- This is where a lot of students say wtf? Relax.
- Diagnosis is euthyroid sick syndrome (or sick euthyroid syndrome).
- Vignette will either be patient being weaned from a ventilator, or a patient who's had recent major trauma or surgery.
- Etiologies are manifold, but one proposed mechanism is that in times of stress (usually acute), spikes in cortisol and other inflammatory mediators can inhibit peripheral conversion of T4 to T3. This causes T3 to go down.
- T4, however, rather than being detectable in excess, is converted to an inactive form of thyroid hormone called reverse T3 (rT3), so rT3 is high.
- T4 is therefore still in the normal range, as is TSH (presumably because T4 is normal).
- Call it weird all you want, but USMLE asks this. This is one of the most "underrated" thyroid diagnoses, as students will often have heard of it but then disregard it, thinking it's minutiae and probably won't show up. → Bad fucking idea. Euthyroid sick syndrome is important for USMLE.
- Do not confuse the arrows for this condition with subclinical hypothyroidism (↑ TSH, ↔ T3, ↔ T4).

37. 25F + G1P0 + 10 weeks' gestation + pregnancy progressing uneventfully. What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, free T4, total T4, and free/total T4 ratio?

- **↔ TSH, ↔ T3, ↔ free T4, ↑ total T4, ↓ free/total T4 ratio.**
- USMLE wants you to know that **estrogen** causes increased thyroid-binding globulin (TBG) production by the liver. TBG is the protein carrier molecule for thyroid hormone in the blood.
- Free T4 is the physiologically active form of thyroid hormone. T4 protein-bound to TBG (99%) has minimal effect. Free T4 + TBG-bound T4 = total T4.
- TBG will mop up free T4, causing free T4 to transiently decrease and TSH to rise (less negative feedback). This rise in TSH will stimulate more production of T4 by the thyroid gland, making total T4 go up. The absolute amount of free T4 will increase back to normal, thereby suppressing TSH back to normal. But the *total* amount of T4 is now increased – i.e., free T4 is normal again, but TBG-bound T4 is higher. This means the free/total T4 ratio has decreased.
- T3 is normal because free T4 is normal. Free T4 is peripherally converted to T3. I've never seen anything about "free T3" on NBME material and I wouldn't worry about it.
- A student might say, "Wait, but why are you giving the above bold arrows if you just gave me all sorts of transient changes in the arrows based on TBG?" → It's because the bold arrows are what the USMLE wants. Pregnant women who are euthyroid will have normal free T4 and increased total T4, and their TSH will be normal. The changes due to TBG rising are likely synchronous and slow enough that the patient's arrows stay as the bold ones.

38. 2M + recently diagnosed with thyroid-binding globulin deficiency. What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, free T4, total T4, and free/total T4 ratio?

- **↔ TSH, ↔ T3, ↔ free T4, ↓ total T4, ↑ free/total T4 ratio.**
- The USMLE does not expect you to be intimately aware of some obscure condition called thyroid-binding globulin deficiency. The reason they ask about this is because the arrows for *pregnancy* are super high-yield.
- In pregnancy, since TBG is high, this ultimately results in high total T4 despite a normal free T4. So if the student is very aware of those arrows for pregnancy, then he/she can easily infer, "Well, if our TBG merely is low, rather than high, then total T4 must be low while free is same. Sort of like pregnancy but just the opposite direction."

39. 25F + G1P1 + gave birth 8 weeks ago + no complications with pregnancy or labor; no past medical Hx; four-day Hx of tremulousness, tachycardia, and heat intolerance. What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, and radioiodine (^{131}I) uptake into the thyroid gland?

- **↓ TSH, ↑ T3, ↑ T4, ↓ ^{131}I uptake.**
- Diagnosis is postpartum thyroiditis. This patient is hyperthyroid, but the condition can present as hypo- as well.
- Same as with deQuervain (subacute granulomatous) and drug-induced thyroiditis, **uptake is low *even if the patient is hyper-*.**
- These arrows have nothing to do with the TBG-related ones seen during pregnancy.
- With thyroiditis conditions, there is merely increased spacing between the cells of the thyroid gland due to inflammation, allowing thyroid hormone to leak out into the blood. The gland itself is not excessively producing thyroid hormone. Then we have negative feedback causing low TSH, and in turn less stimulation of the thyroid gland, which is why uptake is low.

40. 40F + taking lithium for bipolar disorder + complains of increased thirst and heat intolerance. What are the arrows (i.e., ↑, ↓, or ↔) for TSH, T3, T4, radioiodine (^{131}I) uptake, tonicity of the medullary collecting duct compared to serum, and serum ADH levels? **(6 arrows)**

- **↓ TSH, ↑ T3, ↑ T4, ↓ ^{131}I uptake, ↓ tonicity of medullary collecting duct, ↑ ADH.**
- Patient has drug-induced thyroiditis and nephrogenic diabetes insipidus secondary to lithium.
- Similar to deQuervain and postpartum thyroiditis, the patient can be either hyper- or hypothyroid. Because this is thyroiditis, uptake is low, *even if the patient is hyper-.*
- In nephrogenic diabetes insipidus, sensitivity to ADH at the kidney is reduced, leading to decreased aquaporin insertion at the medullary collecting duct and urine that is dilute (hypotonic compared to serum).
- ADH is high, not low, because the hypothalamus and posterior pituitary function just fine; the hypothalamus will increase production of ADH to compensate for lack of receptor sensitivity at the kidney. In central DI, ADH is low.

41. Patient with primary hypo- vs hyperparathyroidism. What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$ and PTH?

- Primary hypoparathyroidism: ↓ **Ca^{2+}**, ↑ **$PO4^{3-}$**, ↓ **PTH.**
- Primary hyperparathyroidism: ↑ **Ca^{2+}**, ↓ **$PO4^{3-}$**, ↑ **PTH.**
- Primary hypoparathyroidism is classically due to *thyroid* surgery that leads to removal of or damage to the parathyroid glands. It is also due to DiGeorge syndrome.
- Primary hyperparathyroidism is usually due to a PTH-secreting adenoma, but can also be due to diffuse four-gland hyperplasia.
- Parathyroid hormone (PTH) functions to increase serum calcium in three main ways:
    - **1) Pulls calcium out of the bone and puts it in the blood.**
        - PTH binds to osteo**blasts,** which will then express RANK-L on their cell surface, which will bind to RANK receptor on the surface of osteoclasts. Osteoclasts then resorb (break down) bone. The calcium enters the blood, increasing serum calcium.
    - **2) PTH increases renal reabsorption of calcium.**
        - PTH causes Ca^{2+} reabsorption at the late-DCT of the kidney by increasing expression of an apical calcium channel.
    - **3) PTH upregulates 1α-hydroxylase.**
        - PTH upregulates 1α-hydroxylase in the PCT of the kidney, which converts inactive 25-OH-vitamin D3 (calcidiol) into active 1,25-$(OH)_2$-D3 (calcitriol).
        - 1,25-$(OH)_2$-D3 then goes to the small bowel, where it increases absorption of both calcium and phosphate.
- PTH decreases serum phosphate by inhibiting its reabsorption in the PCT of the kidney.
    - PTH causes the downregulation of apical PCT phosphate transporters.
    - If PTH is low, we don't get downregulation of these transporters, too much phosphate is reabsorbed, and serum $PO4^{3-}$ goes up.

42. 24M + 2-hour Hx of shooting groin pain + family Hx of thyroid cancer. What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$, PTH, and TSH?

- **↑ Ca^{2+}, ↓ $PO4^{3-}$, ↑ PTH, ↔ TSH.**
- Diagnosis is MEN 2A.
- MEN 1 = parathyroid adenoma (or hyperplasia), pituitary adenoma, pancreatic adenoma.
- MEN 2A = parathyroid adenoma (or hyperplasia), pheochromocytoma, medullary thyroid carcinoma.
- MEN 2B = Marfanoid body habitus, mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma.
- Shooting flank or groin pain suggests urolithiasis (nephro- vs ureterolithiasis, respectively) secondary to hypercalcemia.
- Family Hx of thyroid cancer in his patient suggests medullary carcinoma, considering patient also has hypercalcemia (hyperparathyroidism).
- Patients with thyroid carcinoma are usually euthyroid or hypothyroid.
- Serum calcitonin will be increased in patients with medullary thyroid carcinoma.

43. 25F + total thyroidectomy one week ago for treatment of papillary thyroid carcinoma; examination shows twitching of masseter with stimulation. What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$, and PTH?

- **↓ Ca^{2+}, ↑ $PO4^{3-}$, ↓ PTH.**
- Thyroidectomy can result in removal of or damage to the parathyroid glands, resulting in decreased PTH secretion and, in turn, hypocalcemia. Phosphate goes up because there is increased renal reabsorption (PTH normally downregulates apical PCT phosphate transporters, thereby promoting excretion).
- Twitching of the masseter with stimulation is called Chvostek sign of hypocalcemia.
- Hypocalcemia causes “up” findings – i.e., muscle tetany and hyperreflexia.
- Trousseau sign of hypocalcemia is carpopedal spasm with blood pressure cuff inflation (i.e., twitching of the hand/wrist). The USMLE can give you either Chvostek or Trousseau sign when Ca^{2+} is low.
- Hypercalcemia, in contrast, causes “down” findings – i.e., muscle flaccidity and hyporeflexia.
- Do not confuse Trousseau sign of hypocalcemia with Trousseau and Troisier signs of malignancy.
- Troisier sign of malignancy is a palpable left supraclavicular lymph node sometimes seen in visceral malignancy (aka Virchow node).
- Trousseau sign of malignancy is migratory thrombophlebitis classically seen in head of pancreas adenocarcinoma (but can be other adenocarcinomas, such as bronchogenic).

44. 44M + chronic alcoholic + serum calcium 7.8 mg/dL (NR 8.4-10.2); appropriate dose of IV calcium gluconate is administered; new serum level is measured at 7.9 mg/dL. What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$, PTH, and Mg^{2+}?

- **↓ Ca^{2+}, ↑ $PO4^{3-}$, ↓ PTH, ↓ Mg^{2+}.**
- Alcoholics are susceptible to hypomagnesemia as a result of dietary deficiency (EtOH is 7kcal/g, so they fill up on alcohol).
- Low magnesium can cause hypocalcemia and hypokalemia nonresponsive to supplementation (i.e., you give calcium or potassium for low serum levels, but the serum levels do not appreciably rise).
- Basal levels of magnesium are required for proper functioning of the parathyroid gland, so low magnesium can cause low PTH secretion.
- Patients with hypomagnesemia may indeed have completely normal serum levels for calcium, phosphate, and PTH, but if we are forced to choose arrows, we would choose a Ca^{2+}/$PO4^{3-}$/PTH combo that reflects low PTH secretion.
- The Step 2 exam will often just say an alcoholic has low calcium or potassium nonresponsive to supplementation, and then the next best step in management is “check serum magnesium levels.” This isn’t hard at all. But some students will be like “Oh wow.”

45. 47M + 5-yr Hx of recurrent duodenal ulcers + impotence + reduced tendon reflexes. What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$, PTH?

- **↑ Ca^{2+}, ↓ $PO4^{3-}$, ↑ PTH.**
- This patient has MEN 1.
- MEN 1 = parathyroid adenoma (or hyperplasia), pituitary adenoma, pancreatic adenoma.
- MEN 2A = parathyroid adenoma (or hyperplasia), pheochromocytoma, medullary thyroid carcinoma.
- MEN 2B = Marfanoid body habitus, mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma.
- Recurrent duodenal ulcers, or any mention of a jejunal or ileal ulcer, almost always = Zollinger-Ellison syndrome (gastrinoma) on USMLE. (Otherwise we're talking about *H. pylori*)
- Impotence is frequently how prolactinoma presents in men. Galactorrhea may also be seen.
- Hypercalcemia can cause reduced tendon reflexes and muscle weakness.

46. 2M + cleft lip + absent thymic shadow + recurrent viral and *Pneumocystis* infections + harsh systolic murmur auscultated at left sternal border. What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$, PTH, T cell levels, and B cell levels?

- **↓ Ca^{2+}, ↑ $PO4^{3-}$, ↓ PTH, ↓ T cell levels, ↔ B cell levels.**
- Diagnosis is DiGeorge syndrome.
- Mechanism is most frequently 22q11 deletion, resulting in agenesis of the 3rd and 4th pharyngeal pouches.
- The 3rd pouch becomes the thymus + two inferior parathyroids.
- The 4th pouch becomes the two superior parathyroids.
- Tetralogy of Fallot and truncus arteriosus are common heart defects.
- Agenesis of the parathyroid glands → primary hypoparathyroidism → low calcium + high phosphate.
- DiGeorge is characterized by T cell deficiency. Recurrent viral, fungal, and protozoal infections are characteristic.
- Absent thymic shadow = T cell deficiency → DiGeorge.
- Scanty lymph nodes/tonsils = B cell deficiency → Bruton agammaglobulinemia.
- If Q says kid has both absent thymic shadow *and* scanty lymph nodes/tonsils → answer = SCID.

47. 66F + long-standing Hx of type II diabetes + serum creatinine of 4.3 mg/dL (NR 0.7-1.2) + blood urea nitrogen 67 mg/dL (NR <20). What are the arrows (i.e., ↑, ↓, or ↔) for Ca^{2+}, $PO4^{3-}$, and PTH?

- **↓ Ca^{2+}, ↑ $PO4^{3-}$, ↑ PTH.**
- This patient has secondary hyperparathyroidism, which is almost always due to renal failure.
- There are two reasons why calcium is low:
    - 1) The kidney cannot reabsorb it in the late-DCT like it's supposed to.
    - 2) The kidney cannot synthesize activated (1,25) vitamin D3 in the PCT like it's supposed to. Since 1,25-D3 absorbs calcium in the small bowel, and 1,25-D3 levels are lower, serum calcium will also be lower.
- The low serum calcium will cause PTH to go up (deceased negative feedback at the calcium-sensing receptors on the parathyroid glands).
- Since the etiology for the increased PTH secretion is not the parathyroid glands themselves, we call this secondary hyperparathyroidism. If the etiology is due to the parathyroid glands themselves (i.e., adenoma or diffuse hyperplasia), we call that primary hyperparathyroidism.
- The calcium and phosphate arrows for secondary hyperPTH are the opposite of primary hyperPTH.
- Phosphate is high in renal failure, despite the high PTH, because the kidney is not able to downregulate the PCT phosphate transporters, so there is too much phosphate reabsorption.

48. 64M + acute tubular necrosis. What are the arrows (i.e., ↑, ↓, or ↔) for $HCO3^-$, pH, CO2, and anion gap?

- **↓ $HCO3^-$, ↓ pH, ↓ CO2, ↑ anion gap.**
- Both acute and chronic renal failure cause high-anion gap metabolic acidosis. This is due to a combination of reduced ability to reabsorb bicarbonate in the PCT and secrete protons in the cortical collecting duct.
- Anion gap is calculated as serum Na^+ - (Cl^- + $HCO3^-$). A value >12 is considered high. 8-12 is normal.
- The high anion-gap metabolic acidoses for Step are MUDPILES → Methanol toxicity, Uremia (renal failure), DKA, Phenformin (weird drug you don't need to know), Iron tablets/Isoniazid, Lactic acidosis, Ethylene glycol toxicity, Salicylates (aspirin).
- CO2 is acidic, so we blow this off to compensate in the setting of metabolic acidosis.

49. 70M + chronic renal failure. What are the arrows (i.e., ↑, ↓, or ↔) for his serum K^+, $PO4^{3-}$, and $HCO3^-$?

- **↑ Serum K^+, ↑ $PO4^{3-}$, ↓ $HCO3^-$.**
- Potassium is elevated in renal failure mostly due to impaired distal renal secretion (normally performed by aldosterone).
- Phosphate is elevated mostly due to impaired inhibition of reabsorption in the PCT. Normally, PTH will downregulate apical PCT phosphate reabsorption transporters, enabling phosphate to be micturated.
- Sodium can be variable in renal failure.

50. 50F + renal insufficiency due to granulomatosis with polyangiitis. What are the arrows (i.e., ↑, ↓, or ↔) for 24,25-$(OH)_2$-vitamin D3, fecal Ca^{2+}, and 1,25-$(OH)_2$-vitamin D3?

- **↑ 24,25-$(OH)_2$-vitamin D3, ↑ fecal Ca^{2+}, ↓ 1,25-$(OH)_2$-vitamin D3.**
- In the PCT of the kidney, we normally have inactive 25-OH-D3 → active 1,25-$(OH)_2$-D3 via 1α-hydroxylase under the action of PTH.
- In renal insufficiency, this process is disrupted, so 1,25-D3 levels decrease, and 25-D3 levels rise.
- If we are forced to choose an arrow for inactive 25-D3, it would be ↑, since it is not converted sufficiently to 1,25-D3, however, 25-D3 can be converted to another inactive storage form called 24,25-$(OH)_2$-vitamin D3.
- For all intents and purposes, on USMLE, think of 24,25-D3 and 25-D3 as the same. If 25-D3 builds up, then so does 24,25-D3.
- The caveat is: 24,25-D3 is **not** converted directly to 1,25-D3. Only 25-D3 is converted to 1,25-D3.
- Since active 1,25-$(OH)_2$-vitamin D3 causes absorption of calcium in the small bowel, if there is reduced 1,25-D3 synthesis, then less calcium is absorbed, and more ends up in the feces. Call it weird/unusual all you want, but USMLE asks this variable on some of the retired Step 1 NBMEs.

51. 35F + parathyroid adenoma. What are the arrows (i.e., ↑, ↓, or ↔) for urinary Ca^{2+}, serum Ca^{2+}, and urinary cAMP?

- **↑ Urinary Ca^{2+}, ↑ serum Ca^{2+}, ↑ urinary cAMP.**
- Some students will immediately think there's an erratum here. There's not. Relax.
- In primary hyperparathyroidism, PTH will be high. PTH functions to reabsorb calcium in the late-DCT of the kidney, so in theory, you'd think urinary calcium would be low, not high. Sounds logical.
- However, even though more Ca^{2+} is indeed reabsorbed in the late-DCT, since serum Ca^{2+} is high in primary hyperparathyroidism, *more calcium is filtered through the glomerulus to begin with*. So even though more is reabsorbed distally, the urinary calcium *is still high* because we had more to start with.
- PTH causes increased urinary cAMP. This is a weird variable that you should be aware of. PTH acts through G-α-s G-proteins, where adenylyl cyclase activity and, in turn, cAMP are increased.

52. 22M + asymptomatic + has mutation in calcium-sensing receptor at parathyroid glands that results in reduced sensitivity of the receptor. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+} and PTH?

- **↑ Serum Ca^{2+}, ↑ PTH.**
- The calcium-sensing receptors at the parathyroid glands are negative feedback receptors. That is, when calcium binds, PTH secretion is suppressed as a result.
- If the calcium-sensing receptors demonstrate attenuated sensitivity, then there is also diminished ability to adequately suppress PTH in the setting of elevated calcium levels. Therefore, PTH will demonstrate inappropriately high secretion.
- High PTH will cause serum calcium to be high.

53. 24M + asymptomatic + diagnosed with familial hypocalciuric hypercalcemia on biochemical screening. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, urinary Ca^{2+}, parathyroid calcium-sensing receptor sensitivity, and renal calcium-sensing receptor sensitivity? **(4 arrows)**

- **↑ Serum Ca^{2+}, ↓ urinary Ca^{2+}, ↓ parathyroid Ca^{2+}-sensing receptor sensitivity, ↓ renal Ca^{2+}-sensing receptor sensitivity.**
- As the name of the condition implies, for familial hypocalciuric hypercalcemia (FHH), serum calcium will be high and urinary calcium low.
- The condition is caused by slightly decreased (not absent) sensitivity of the calcium-sensing receptors at both the parathyroid glands and kidneys, resulting in a slightly higher setpoint for calcium levels in the blood, that may be variable depending on the patient.
- Most patients are asymptomatic, and PTH is often higher end of normal, or slightly elevated. Patients do not experience signs of bone resorption sometimes seen in patients with primary hyperparathyroidism.
- In primary hyperparathyroidism, despite increased distal renal reabsorption of calcium, urinary calcium is still high because serum calcium is high, so more calcium will be filtered through the glomerulus. In other words, if the urine starts off with more calcium, the amount urinated out is still higher despite increased reabsorption. The calcium-sensing receptors in the renal PCT and loop of Henle function normally and can sense the high calcium, thereby decreasing paracellular reabsorption (unrelated to PTH's effect in the DCT); this allows for greater calciuresis (urination of calcium).
- In familial hypocalciuric hypercalcemia, calcium-sensing receptors in the renal tubules (unrelated to PTH) have decreased sensitivity. Therefore, the tubules interpret urinary calcium to be low and will increase reabsorption in the PCT and loop of Henle to compensate, thereby decreasing calciuresis (less urinary calcium). In other words, in FHH, the kidney thinks, "Fuck, we must have low serum calcium since I can't sense it, so I goin' reabsorb more so we can retain our calcium."

54. 30F + parathyroid adenoma + is administered a drug called cinacalcet, which is a calcimimetic that potentiates the effects of calcium at calcium-sensing receptors at the parathyroid glands. What are the arrows (i.e., ↑, ↓, or ↔) for the expected changes in serum Ca^{2+}, serum $PO4^{3-}$, urinary Ca^{2+}, and PTH as a result of administration of this drug?

- **↓ Serum Ca^{2+}, ↑ serum $PO4^{3-}$, ↓ urinary Ca^{2+}, ↓ PTH.**
- Cinacalcet agonizes the calcium-sensing receptors at the parathyroid glands. This will cause a suppression of PTH secretion and a resultant reduction in serum calcium and elevation in phosphate.
- Urinary calcium is normally elevated in primary hyperparathyroidism. When PTH decreases and serum calcium falls, urinary calcium will also decrease.
- Although PTH increases reabsorption of calcium in the late-DCT, it must be reiterated that high serum calcium in primary hyperparathyroidism causes more calcium to be filtered through the glomerulus in the first place, meaning that, despite increased reabsorption by the distal kidney, more calcium will still be left in the urine to be micturated out.
- When PTH levels return to normal and normocalcemia is attained, urinary calcium will also decrease.

55. 22M + bony nodules on forearms + round cheeks + shortened 4^{th} and 5^{th} metacarpals. In response to the administration of exogenous PTH, what will be the change (i.e., ↑, ↓, or ↔) in serum Ca^{2+}, serum $PO4^{3-}$, and urinary cAMP?

- **↔ Serum Ca^{2+}, ↔ serum $PO4^{3-}$, ↔ urinary cAMP.**
- The diagnosis is pseudohypoparathyroidism, which is characterized by a defective PTH receptor, and therefore insensitivity to PTH.
- There are different types of pseudohypoparathyroidism. The USMLE will give you type I, which presents with what is referred to as the Albright hereditary osteodystrophy phenotype (i.e., shortened 4^{th} + 5^{th} metacarpals, round face, and bony abnormalities). Osteoma cutis (nodules of subcutaneous ossification) can be seen (on retired NBME Q).
- In pseudohypoparathyroidism type I, there is no response to exogenous PTH, so we will not see any changes in serum calcium, serum phosphate, or urinary cAMP.
- Normally, exogenous PTH would cause an increase in serum calcium, a decrease in serum phosphate, and an increase in urinary cAMP.
- Patients with pseudohypoparathyroidism will have low serum calcium, high serum phosphate, and high serum PTH levels. That is, the calcium and phosphate levels appear as though the patient has low PTH, when in reality there is just insensitivity to it. PTH goes up due to decreased negative feedback at the calcium-sensing receptors at the parathyroid glands, since serum calcium is low.

56. 16F + bony nodules on forearms + round cheeks + shortened 4th and 5th metacarpals; what are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, urinary Ca^{2+}, serum $PO4^{3-}$, and PTH?

- **↓ Serum Ca^{2+}, ↓ urinary Ca^{2+}, ↑ serum $PO4^{3-}$, ↑ PTH.**
- The diagnosis is pseudohypoparathyroidism type I, presenting with the Albright hereditary osteodystrophy phenotype.
- Insensitivity at PTH receptor causes low serum calcium, high serum phosphate, and high serum PTH (due to decreased negative feedback at the Ca^{2+}-sensing receptors since serum Ca^{2+} is low).
- Urinary calcium is low because serum calcium is low, so less is filtered through the glomerulus into the urine to begin with, even though insensitivity to PTH means less distal renal reabsorption.

57. 70F + chronic renal failure; serum electrolytes show evidence for tertiary hyperparathyroidism. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, and PTH?

- **↑ Ca^{2+}, ↑ $PO4^{3-}$, ↑ PTH.**
- In order to understand tertiary hyperparathyroidism, let's first review secondary hyperparathyroidism:
- Patients with renal failure will initially develop secondary hyperparathyroidism, where calcium is low, phosphate is high, and PTH is high. Calcium is low due to failure of reabsorption at the late-DCT of the kidney and because of decreased synthesis of activated vitamin D3 (leading to decreased small bowel absorption). Phosphate is high due to failure to downregulate PCT reabsorption pumps (i.e., more pumps reabsorb phosphate). PTH is high because calcium is low (less negative feedback).
- Tertiary hyperparathyroidism results from hyperplasia of the parathyroid glands in patients with long-standing secondary hyperparathyroidism, such that even if the renal failure is brought under control and serum calcium is brought back into the normal range, PTH continues being autonomously secreted at higher basal levels than prior to the renal disease, effectively resetting the body's setpoint for calcium homeostasis.
- This causes a rise in serum calcium in a patient with renal failure. This should immediately raise a red flag for tertiary hyperPTH, since renal failure patients will almost always have low, not high, calcium.
- Even though the parathyroid glands will be hyper-secreting PTH, this is not primary hyperparathyroidism, since the etiology for the high PTH was not idiopathic adenoma or hyperplasia.
- Phosphate is high, not low, because the patient has renal failure. Phosphate is always high in renal failure. Even though PTH is high, remember that the kidney can't downregulate the PCT reabsorption pumps the way they're supposed to.

58. 9M + alopecia + determined to have rare condition characterized by an inactivating mutation in his vitamin D receptors. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, PTH, and 24,25-$(OH)_2$-vitamin D3?

- **↓ Serum Ca^{2+}, ↑ PTH, ↓ 24,25-$(OH)_2$-vitamin D3.**
- The Step 1 NBME wants you to know the findings for vitamin D receptor insensitivity.
- Since vitamin D causes intestinal absorption of calcium, serum calcium will be low. The low calcium causes PTH to go up (due to decreased negative feedback).
- The NBME doesn't ask about phosphate levels for this condition, possibly because whilst vitamin D deficiency will ordinarily cause low phosphate (due to decreased intestinal absorption), it is possible that in patients with chronically elevated PTH in the setting of a vitamin D receptor mutation, phosphate might be variable.
- Recall that inactive 25-OH-D3 can be converted to another inactive storage form called 24,25-D3. If PTH is high, then 1α-hydroxylase activity is high, so there will be less 25-D3 available to be shunted to 24,25-D3. The NBME mentions 24,25-D3 levels as "undetectable" in the setting of vitamin D receptor mutation. This also means if USMLE asks you for merely the 25-OH-D3 levels, choose a down arrow.
- The NBME gives normal serum levels for 1,25-$(OH)_2$-D3. This might sound weird, since if there's a mutation in the vitamin D receptor, then theoretically more 1,25-D3 should be produced to compensate. This explains the low 24-25-D3, but perhaps in patients with this condition, 1,25-D3 is often normal, rather than elevated.

59. 50M + 60-pack-yr Hx of smoking + 10-kg weight loss past 2 months + recently treated for kidney stone + coin lesion visualized on chest x-ray. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, and PTH?

- **↑ Serum Ca^{2+}, ↓ serum $PO4^{3-}$, ↓ PTH.**
- The diagnosis is squamous cell carcinoma of the lung with paraneoplastic parathyroid hormone-related peptide (PTHrp) secretion. *This is not the same as endogenous PTH.*
- PTHrp exerts very similar physiologic effects as PTH, causing high serum calcium and low phosphate.
- PTH secretion by the parathyroid glands will be suppressed in this setting due to the high serum calcium.
- NBME will give you lung cancer + high serum calcium + low serum PTH, with the answer being squamous cell carcinoma of the lung. The low PTH will throw some people off. But this is not weird. PTH is not the same as PTHrp (which will be up-arrow).

60. 58F + blood in the urine + left flank pain + 10-kg weight loss past two months + occasional headaches and blurry vision + renal ultrasound shows a heterogenous mass in the left kidney. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, PTH, and hemoglobin?

- **↑ Serum Ca^{2+}, ↓ serum $PO4^{3-}$, ↓ PTH, ↑ hemoglobin.**
- Diagnosis is renal cell carcinoma (RCC).
- USMLE wants you to know that RCC, similar to squamous cell carcinoma of the lung, can secrete PTHrp → therefore high calcium and low phosphate.
- Endogenous PTH is suppressed due to the high calcium. Once again, PTHrp and PTH are different.
- RCC can also secrete erythropoietin (EPO), causing secondary polycythemia. This can lead to hyperviscosity syndrome characterized by headache, blurry vision, and Raynaud phenomenon.
- For USMLE, smoker + flank pain + red urine + high calcium + high hematocrit = RCC.

61. 6F + 10th percentile for weight and height + bowing of the tibias + family recently immigrated to the US from Ireland. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, and PTH?

- **↓ Serum Ca^{2+}, ↓ serum $PO4^{3-}$, ↑ PTH.**
- Diagnosis is rickets (vitamin D deficiency in children). In adults, the condition is called osteomalacia.
- Calcium and phosphate are both low because vitamin D is needed for intestinal absorption of both.
- PTH goes up because calcium is low (decreased negative feedback).
- It should be noted that in vitamin D deficiency caused by renal failure, phosphate is high, not low, because the effect of the renal failure on phosphate levels wins over the mere vitamin D deficiency. In renal failure, the kidney cannot downregulate the PCT phosphate reabsorption channels, thereby increasing absorption.
- **Never choose low phosphate in renal failure,** even though vitamin D3 activation is low.
- Renal failure + low vitamin D:
    - **↓ serum Ca^{2+}, ↑ serum $PO4^{3-}$, ↑ PTH.**
- No renal failure + low vitamin D (i.e., rickets/osteomalacia):
    - **↓ serum Ca^{2+}, ↓ serum $PO4^{3-}$, ↑ PTH.**

62. 77F + bone densitometry shows bone density of hips and vertebrae >2.5 standard deviations below the mean for 20-yr-old women. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, PTH, and 1,25-$(OH)_2$-vitamin D3?

- **↔ Serum Ca^{2+}, ↔ serum $PO4^{3-}$, ↔ PTH, ↔ 1,25-$(OH)_2$-vitamin D3.**
- Diagnosis is osteoporosis. All laboratory findings will be normal.
- Students often get this question wrong, assuming, e.g., calcium must be low, but serum findings are completely normal for most patients.
- USMLE question will often be in graph form, with calcium on the x-axis and PTH on the y-axis, with letters at different locations. The correct answer here is simply the letter in the normal range for both calcium and PTH.

63. 68F + bone densitometry shows bone density of hips and vertebrae >2.5 standard deviations below the mean for 20-yr-old women. What are the arrows (i.e., ↑, ↓, or ↔) for osteoblast activity, osteoclast activity, and RANK-L activity?

- **↓ osteoblast activity, ↑ osteoclast activity, ↑ RANK-L activity.**
- Cytokine activity at bone (namely IL-1 and -6) stimulates RANK-L activity → stimulates osteoclasts → decreased bone density.
- Estrogen normally functions to suppress cytokine activity → preserves bone density.
- Osteoblasts build bone; osteoclasts resorb (break down) bone.
- USMLE wants the above three arrows for osteoporosis.
- Some students have asked about ALP in this setting. ALP is reflective of osteo**blast** activity. If osteoblast activity is increased (e.g., hyperparathyroidism, Paget disease), ALP is always high on USMLE. In contrast, if osteoblast activity is low, ALP activity can be normal or low.

64. 74M + favorite hat does not fit him the way it used to + fell and hit his head in the bathroom + non-contrast CT of head shows no bleeding but reveals heterogenous mixed osteoblastic and -clastic areas in the occipital region. What are the arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, PTH, and alkaline phosphatase (ALP)?

- **↔ Serum Ca^{2+}, ↔ serum $PO4^{3-}$, ↔ PTH, ↑ ALP.**
- Diagnosis is Paget disease of bone, which is characterized by increased bone turnover and mixed areas of osteoblastic and -clastic predominance.
- USMLE wants you to know that Paget causes an isolated increase in serum ALP. Calcium, phosphate, and PTH are normal. This is how it will be for 9/10 questions.
- I've seen one 2CK-level NBME Q where ALP was normal, but the rest of the vignette was obvious for Paget.
- ALP levels reflect osteoblast activity. Since there is increased bone turnover, ALP is increased.
- Patients are often diagnosed incidentally, as with this patient, who had a non-contrast CT looking for a bleed, but it was discovered that he has mixed -blastic and -clastic areas of bone. Next best step in management on 2CK is "check serum ALP levels."
- Patients can often get high-output cardiac failure, with an S3 heart sound accompanied by a high, not low, ejection fraction. This is due to AV fistulae that develop within bone.

65. 68F + metastatic breast cancer. What are the most likely arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+} and PTH?

- **↑ Serum Ca^{2+}, ↓ PTH.**
- Once metastases seed at bony locations, cytokine activity causes lysis of the bone and release of calcium into the blood. Hypercalcemia is common in the setting of metastatic malignancy (not limited to breast).
- PTH is suppressed due to the high calcium.

66. 67M + one-month Hx of mid-back pain + serum protein electrophoresis shows an IgG M protein spike + nephrotic syndrome + renal biopsy shows apple-green birefringence with Congo red stain + S4 heart sound. What are the most likely arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, PTH, and ESR?

- **↑ Serum Ca^{2+}, ↓ PTH, ↑ ESR.**
- The diagnosis is multiple myeloma.
- Serum calcium is high due to lytic lesions of bone. This will cause suppression of PTH (negative feedback at calcium-sensing receptors).
- Elevated ESR with rouleaux formation is seen upon centrifugation of RBCs. This is because immunoglobulins produced by the malignant plasma B cells bind to RBCs and make them "sticky."
- Renal and cardiac amyloidosis are common.
- Amyloidosis refers to the deposition of protein where it shouldn't be depositing. The neoplastic plasma B cells in multiple myeloma secrete immunoglobulin light chains (proteins). These find their way into the urine (Bence-Jones proteins), but also deposit in the renal parenchyma itself, causing renal amyloidosis (a nephrotic syndrome).
- Deposition of immunoglobulin proteins in the heart causes cardiac amyloidosis. An S4 heart sound refers to a stiffened left ventricle due to diastolic dysfunction (inability to expand properly). Amyloidosis causes a restrictive cardiomyopathy.
- One could make the argument of, "Well if renal amyloidosis could lead to renal failure, wouldn't that cause secondary hyperparathyroidism, so calcium would be low, not high?" → Patients with multiple myeloma will have hypercalcemia due to lytic lesions far before renal failure ensues.

67. 32F + African-American + long history of dry cough + red shins on physical exam + chest x-ray shows bihilar lymphadenopathy. What are the most likely arrows (i.e., ↑, ↓, or ↔) for serum Ca^{2+}, serum $PO4^{3-}$, and PTH?

- **↑ Serum Ca^{2+}, ↑ serum $PO4^{3-}$, ↓ PTH.**
- Diagnosis is sarcoidosis, which classically presents in African-American women 20s-40s.
- Patients classically have hypervitaminosis D (sophisticated way of saying high vitamin D).
- Hypervitaminosis D on USMLE will not be some 15-year-old girl sitting in her room trying to commit suicide with vitamin D pills. Patients in real life with high vitamin D will almost always have granulomatous disease.
- Biopsy of the lungs will show non-caseating granulomas. Activated macrophages within the granulomas (referred to as epithelioid macrophages) secrete 1α-hydroxylase, which will convert inactive 25-D3 into active 1,25-D3.
- The active 1,25-D3 then goes to the small bowel, where it increases absorption of calcium and phosphate.
- PTH is suppressed due to the high calcium.
- Very high-yield for USMLE.

68. 35F + long history of dry cough + fever + chest x-ray shows bihilar lymphadenopathy. What are the most likely arrows (i.e., ↑, ↓, or ↔) for fecal calcium, 24,25-$(OH)_2$-vitamin D3, and 1,25-$(OH)_2$-vitamin D3?

- **↓ Fecal calcium, ↓ 24,25-$(OH)_2$-vitamin D3, ↑ 1,25-$(OH)_2$-vitamin D3.**
- Diagnosis is sarcoidosis. Fever can sometimes be seen in autoimmune flares even when there's no infection of any kind.
- The non-caseating granulomas are secreting 1α-hydroxylase, which activates vitamin D3, causing increased intestinal absorption of Ca^{2+}. Therefore, there is decreased calcium to be excreted in feces.
- 24,25-D3 is low because there is increased conversion of inactive 25-D3 into active 1,25-D3.
- 24,25-D3, similar to 25-D3, is merely an inactive storage form of vitamin D3. 25-D3 is in physiologic equilibrium with 24,25-D3. If 25-D3 goes down because it is converted over to 1,25-D3, then less is available to be converted into 24,25-D3.

69. 40M + long history of dry cough + erythema nodosum + MCV 82 + Hb 10.5 g/dL + chest x-ray shows bihilar lymphadenopathy. What are the most likely arrows (i.e., ↑, ↓, or ↔) for renal PCT 1α-hydroxylase activity, 25-OH-vitamin D3, and PTH?

- **↓ Renal PCT 1α-hydroxylase activity, ↓ 25-OH-vitamin D3, ↓ PTH.**
- Diagnosis is sarcoidosis.
- Epithelioid macrophages within the non-caseating granulomas in the lungs secrete 1α-hydroxylase, causing increased calcitriol, increased small bowel absorption of calcium, hypercalcemia, and in turn, suppression of PTH. This leads to decreased *renal* 1α-hydroxylase activity.
- PTH functions to upregulate 1α-hydroxylase in the PCT of the kidney; it has no role in relation to the non-caseating granulomas in the lungs secreting 1α-hydroxylase.
- 25-D3 is low because more of it is being converted over to active 1,25-D3.

70. 24F + parathyroid adenoma. What are the arrows (i.e., ↑, ↓, or ↔) for osteoblast activity, osteoclast activity, RANK-L expression, and fecal calcium?

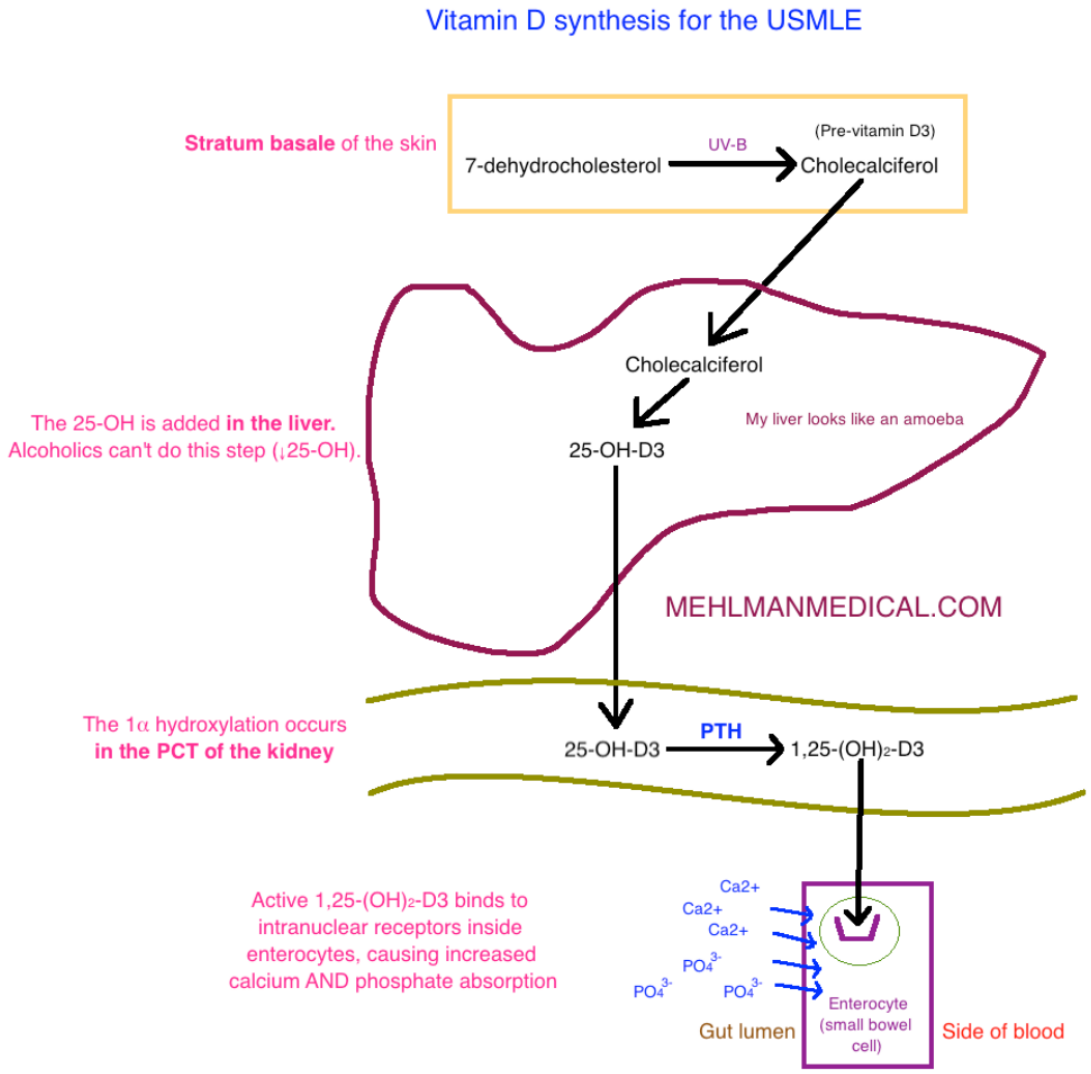
- **↑ Osteoblast activity, ↑ osteoclast activity, ↑ RANK-L expression, ↓ fecal calcium.**
- Osteoblasts build/create new bone. Osteoclasts break down/resorb bone.
- You might say, "I thought PTH causes bone resorption in order to increase serum calcium. Why would osteoblast activity be increased?" → USMLE wants you to know that PTH binds to **osteoblasts, not -clasts.** The osteoblasts then express RANK-L on their cell surface, which binds to RANK receptor on osteoclasts, and in turn activates the osteoclasts to resorb the bone.
- I've seen different answers across NBME forms the mechanisms for PTH – i.e., "increased maturation and activation of osteoclasts," or "stimulation of osteoblasts." You have to be flexible in terms of your willingness to select certain answers here. This is why understanding the mechanism of PTH on bone is important.
- Fecal calcium is decreased because PTH activates 25-D3 into 1,25-D3, which goes to the small bowel to increase absorption of calcium.

71. 6F + cystic fibrosis + steatorrhea. What are the arrows (i.e., ↑, ↓, or ↔) for bone osteoid concentration, bone hydroxyapatite concentration, serum calcium, serum phosphate, and PTH levels? **(5 arrows)**

- **↑ Bone osteoid concentration, ↓ bone hydroxyapatite concentration, ↓ serum calcium, ↓ serum phosphate, ↑ PTH levels.**
- Cystic fibrosis can cause exocrine pancreatic insufficiency due to defective secretion/delivery of enzymes to the duodenal lumen. This can cause impaired fat absorption. Vitamins A, D, E, and K are the fat-soluble vitamins (All Dogs Eat Kittens).
- Vitamin D is required to convert unmineralized osteoid into mineralized hydroxyapatite. In vitamin D deficiency, there is increased osteoid within bone and decreased hydroxyapatite.
- Serum calcium and phosphate are low due to reduced intestinal absorption.
- Low serum calcium causes PTH to go up to compensate (decreased negative feedback at calcium-sensing receptors on parathyroid glands).

72. 45M + construction worker + chronic alcoholic + consumes lots of fish and milk. What are the arrows (i.e., ↑, ↓, or ↔) for hepatic hydroxylase activity, renal hydroxylase activity, 25-(OH)-vitamin D3, and 1,25-$(OH)_2$-vitamin D3?

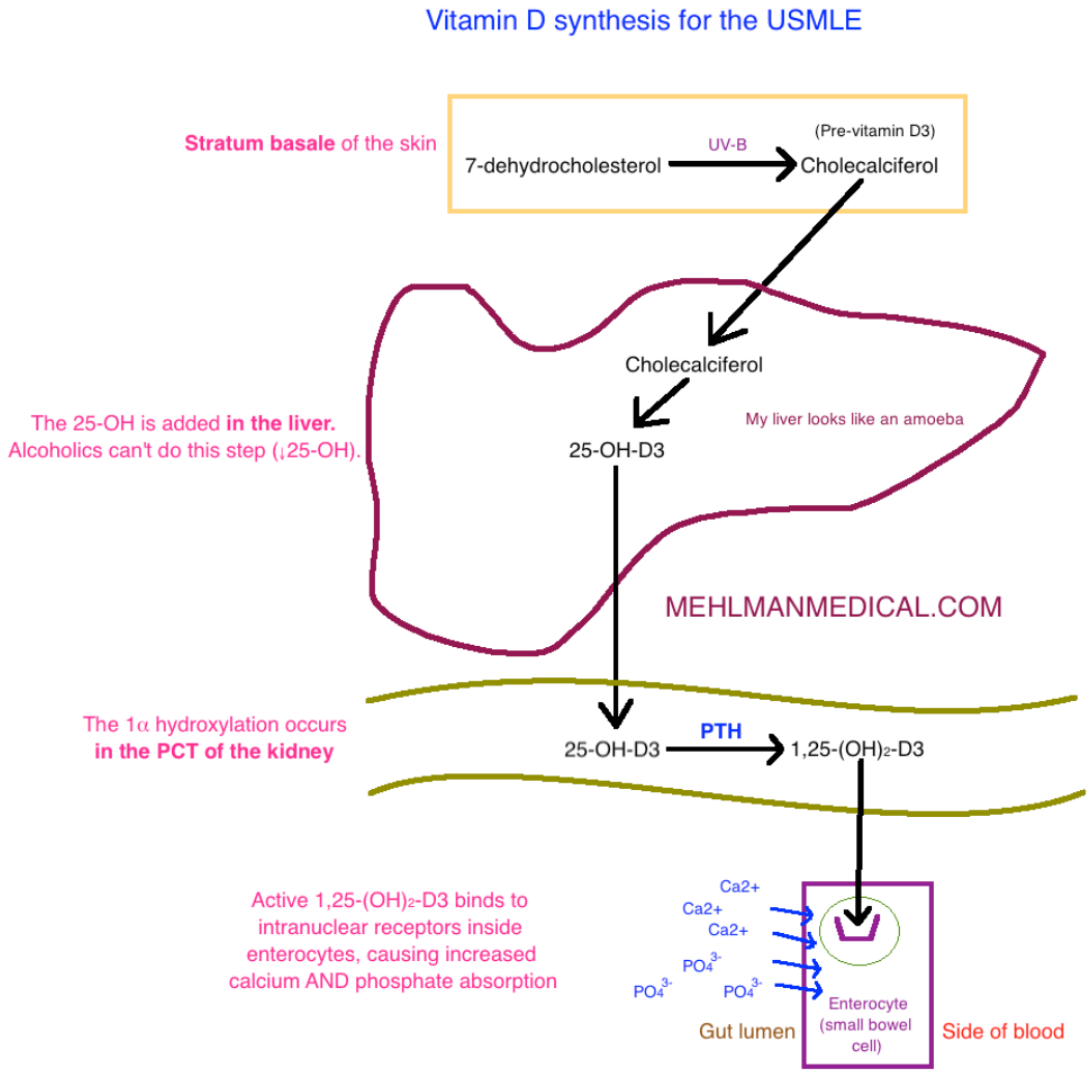
- **↓ hepatic hydroxylase activity, ↑ renal hydroxylase activity, ↓ 25-(OH)-D3, ↓ 1,25-$(OH)_2$-D3.**



- Adequate sunlight means this patient can initiate vitamin D synthesis in the skin without a problem.
- Since he is an alcoholic, he will have ↓ hepatic hydroxylase activity and ↓ synthesis of 25-OH-D3.
- Since 25-D3 is low, 1,25-D3 will also be low, since there is less substrate to be converted to product.
- Low 1,25-D3 means ↓ intestinal absorption of calcium. Even though his diet is rich in calcium, he will not be able to absorb it adequately. PTH will then go up to compensate (less negative feedback).
- High PTH will ↑ activity of renal 1α-hydroxylase in an attempt to produce more 1,25-D3. However, the latter is still low because, as we said, 25-D3 is low due to the alcoholism.
- USMLE will sometimes give a calcium/vitamin D-type Q with an alcoholic, and the answer will simply be “decreased hepatic hydroxylase activity.”

73. 40F + office worker + never gets out in the sun + consumes lots of fish. What are the arrows (i.e., ↑, ↓, or ↔) for 7-dehydrocholesterol, cholecalciferol, 25-OH-D3, and 1,25-$(OH)_2$-D3?

- **↑ 7-dehydrocholesterol, ↓ cholecalciferol, ↓ 25-OH-D3, ↓ 1,25-$(OH)_2$-D3.**
- UV-B radiation is required to convert 7-dehydrocholesterol in the stratum basale of the epidermis into cholecalciferol.
- If the USMLE mentions a patient who gets decreased sun exposure, and they ask which substrate's synthesis is decreased, the answer is cholecalciferol, not 7-dehydrocholesterol.
- Cholecalciferol is hydroxylated into 25-OH-D3 (calcidiol) at the liver. Since cholecalciferol synthesis is low, less 25-OH-D3 will be synthesized. In turn, lower 25-D3 levels will lead to lower 1,25-D3 levels.



74. 54F + hot flashes + irregular menses for the past year. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's estrogen, inhibin B, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels?

- **↓ Estrogen, ↓ inhibin B, ↑ LH, ↑ FSH.**
- Diagnosis is menopause. The ovaries will decrease production of estrogen and inhibin B. This will cause decreased negative feedback at the hypothalamus and anterior pituitary, leading to increased gonadotropin-releasing hormone (GnRH), LH, and FSH levels.
- GnRH is produced by the hypothalamus, which causes increased LH and FSH secretion by the anterior pituitary.
- LH activates theca interna cells in the ovaries to secrete androgens.
- FSH activates granulosa cells in the ovaries to secrete aromatase and inhibin B.
- Aromatase from the granulosa cells converts androgens from the theca interna cells into estrogens.
- In males, Leydig cells are the theca interna cell equivalent; Sertoli cells are the granulosa cell equivalent.
- Premature ovarian failure is when menopause occurs age 40 or younger; the arrows will also be as per above.

75. 14F + never had menstrual period + height is 4’10” + breast development is Tanner stage 1. What are the arrows (i.e., ↑, ↓, or ↔) for this patient’s estrogen, inhibin B, LH, and FSH levels?

- **↓ Estrogen, ↓ inhibin, ↑ LH, ↑ FSH.**
- Diagnosis is Turner syndrome (45XO).
- Patient will have “streak ovaries” and “menopause before menarche.”
- Turner syndrome presents with short height, webbed neck (cystic hygroma), shield chest, aortic coarctation, bicuspid aortic valve, and scattered nevi.
- The ovaries produce less estrogen and inhibin B, so LH and FSH are both elevated.

76. 18F + runs cross country + BMI 16 + no menstrual period last 4 months. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's estrogen, inhibin B, GnRH, LH, and FSH levels? (5 arrows)

- **↓ Estrogen, ↓ inhibin B, ↓ GnRH, ↓ LH, ↓ FSH.**
- Amenorrhea seen in anorexia is an important concept for USMLE.
- Leptin is a protein that causes the feeling of satiety. In low BMI state, leptin is low. However, leptin is also required for normal GnRH pulsatility and secretion. This means GnRH is low in anorexia.
- Low GnRH causes a reduction in both LH and FSH.
- The low GnRH seen in anorexia leading to amenorrhea is sometimes referred to as hypogonadotropic amenorrhea, or central amenorrhea. Sometimes the USMLE will give you a Q with anorexia and amenorrhea, and the answer is just simply, “decreased secretion of gonadotropins.”
- LH stimulates the theca interna cells in the ovaries to make androgens, which are low in anorexia.
- FSH stimulates the granulosa cells to secrete aromatase and inhibin B.
- Low FSH therefore means not only is inhibin B low, but aromatase is also low, leading to decreased estrogens in amenorrhea.
- Estrogen is also produced by aromatase from adipose tissue, which is reduced in anorexia.
- Since estrogen and inhibin B ordinarily induce negative feedback at the hypothalamus and anterior pituitary, and in anorexia they are both low, we should theoretically see an increase in GnRH, LH, and FSH. However, the problem with anorexia is central, meaning low GnRH is the source of the problem, so it will not go up in response to reduced negative feedback from estrogen and inhibin.
- Bottom line:
    - Menopause, premature ovarian failure, Turner syndrome: **↓ Estrogen, ↑ FSH.**
    - Anorexia: **↓ Estrogen, ↓ FSH.**

77. 22M + height is 6’2” + eunuchoid body shape + electron microscopy of somatic cells shows a Barr body.

    What are the arrows (i.e., ↑, ↓, or ↔) for this patient’s testosterone, estrogen, LH, and FSH levels?

- **↓ Testosterone, ↑ estrogen, ↑ LH, ↑ FSH.**
- Diagnosis is Klinefelter syndrome (47XXY).
- Dysgenesis of the seminiferous tubules leads to decreased testosterone production. This means less negative feedback at the hypothalamus and anterior pituitary. GnRH, LH, and FSH all go up to compensate.
- Estrogen is high because of overexpression of aromatase (CYP19) in the testes of men with Klinefelter, which causes increased conversion of testosterone to estrogen.

78. 24F + occasional missed periods + acne + BMI 27. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's testosterone, LH, FSH, and luteal progesterone?

- **↑ Testosterone, ↑ LH, ↓ FSH, ↓ luteal progesterone.**
- Diagnosis is polycystic ovarian syndrome (PCOS). The mechanism is linked with high BMI and insulin resistance, which precipitates abnormal GnRH pulsation with a characteristic ↑ LH/FSH ratio.
- Some students will ask if FSH is increased along with LH, but if it's just merely within the ratio that FSH is low. The answer is no. If the USMLE asks for the LH and FSH arrows separately, do not choose an up-arrow for FSH. Choose a down-arrow.
- LH stimulates theca interna cells to produce androgens, which in turn are increased.
- FSH causes the granulosa cells to produce aromatase. Although FSH is low, estrogen in patients with PCOS is usually in the normal range.
- The LH spike will normally trigger ovulation. FSH normally causes follicular development.
- Since FSH is low, this means follicular development is insufficient by the time LH is ready to trigger ovulation. Ovulation will therefore not occur because a Graafian follicle will not be ready to rupture. A corpus luteum (follicular remnant), in turn, will not form.
- The corpus luteum normally secretes progesterone, which maintains the endometrial lining. If we do not ovulate, we will not secrete progesterone during the menstrual cycle.
- The corpus luteum will naturally degrade over the 2-week luteal/secretory phase of the menstrual cycle if fertilization does not occur. This is because human chorionic gonadotropin (hCG) from a placenta serves the purpose of maintaining the corpus luteum.
- Menstruation is caused by the presence, then withdrawal of, progesterone. If progesterone isn't secreted (then withdrawn) because we don't get a corpus luteum (followed by its apoptosis in the absence of fertilization), then there can't be menstruation, which is why we get missed periods in PCOS.
- The clinical relevance of PCOS is not only does it cause subfertility in women, but it is also a risk factor for endometrial cancer. Estrogen causes growth of endometrium. Progesterone limits growth of endometrium. In patients with PCOS, their lifetime production of progesterone is lower. We call this "unopposed estrogen," where estrogen's proliferative effects on endometrium go unchecked when progesterone isn't there, so endometrial hyperplasia and atypia are more prone to occur.

79. 28F + occasional missed periods + acne + BMI 27. What are the arrows (i.e., ↑, ↓, or ↔) for serum testosterone, insulin, and FSH?

- **↑ Serum testosterone, ↑ insulin, ↓ FSH.**
- Diagnosis is PCOS.
- High BMI causes insulin resistance, resulting in hyperinsulinemia.
- Insulin resistance causes abnormal GnRH pulsation, with a high LH/FSH ratio.
- As independent variables, LH is high and FSH is low.
- Sometimes you will get a PCOS presentation, and they'll ask what you're most likely to see in this patient, and answer will simply be "hyperinsulinemia."

80. 22M + very large muscle bulk + competes in bodybuilding events + acne on face and back. What are the arrows (i.e., ↑, ↓, or ↔) for his serum LH and intra-testicular testosterone levels?

- **↓ Serum LH, ↓ intra-testicular testosterone levels.**
- Patients who take exogenous androgens will suppress their production of LH at the anterior pituitary due to negative feedback exerted by the androgens.
- Whilst serum testosterone is high, *intra-testicular* testosterone is low because production is decreased since LH is decreased.
- LH normally stimulates the Leydig cells in the testes to make testosterone.

81. 16F + not yet had a menstrual period + vagina ends in blind pouch + breasts Tanner stage 4 + scanty pubic/axillary hair. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's serum LH and serum testosterone levels?

- **↑ LH, ↑ testosterone.**
- Diagnosis is androgen insensitivity syndrome (karyotype 46XY).
- Q will usually present as a teenage girl who's never had a menstrual period and whose vagina ends in a blind pouch. Breast development is normal, although pubic/axillary hair will be scant. If you get the same vignette but pubic/axillary hair is normal/coarse, the answer is Mullerian agenesis (46XX).
- Since the patient's androgen receptors are insensitive to androgen, there is less negative feedback at the hypothalamus and anterior pituitary, so LH goes up.
- LH will stimulate production of testosterone, causing serum testosterone to go up.

82. 12F + grown 4 inches in past 4 months + new hair growth over upper lip + clitoral hood measures 3cm. Compared to healthy individuals, what are the arrows (i.e., ↑, ↓, or ↔) for testosterone, 5α-reductase activity, dihydrotestosterone (DHT), and phosphodiesterase 5 levels?

- **↑ testosterone, ↓ 5α-reductase, ↓ DHT, ↔ phosphodiesterase 5.**
- Diagnosis is 5α-reductase deficiency. This enzyme normally converts testosterone → DHT.
- One of the classic vignettes for 5α-reductase deficiency is "phallus at age 12." Phallus is the medical term for penis.
- Patients are karyotypically male, but since external male characteristics only develop if DHT is present, the patient will be phenotypically female. However, at the onset of puberty when testosterone levels rise, this can partially overcome the deficiency of 5α-reductase, whereupon sufficient DHT is present to begin inducing virilization.
- The USMLE vignette can also sometimes give 5α-reductase deficiency as a confirmed 46XY neonate with ambiguous genitalia.
- Phosphodiesterase 5 has no relation to this diagnosis. I was just being trolling by putting it here, since students sometimes confuse these enzymes. Sildenafil (Viagra) is a phosphodiesterase 5 inhibitor, which prevents the breakdown of cGMP. More cGMP promotes vasodilation and engorgement of corpus cavernosum → erection.

83. 30M + one-year Hx of impotence + milky discharge can be expressed from both nipples + difficulty seeing out of his periphery. What are the arrows (i.e., ↑ or ↓) for this patient's prolactin, GnRH, and estrogen?

- **↑ prolactin, ↓ GnRH, ↓ estrogen.**
- The patient has prolactinoma, which can cause impotence and galactorrhea. In women, amenorrhea is also common.
- Prolactin can suppress GnRH pulsation, leading to a reduction in sex hormones (testosterone + estrogen).
- **Bromocriptine** (a dopamine-2 receptor agonist) is the pharmacologic treatment for prolactinoma.
- Dopamine inhibits prolactin secretion.
- Antipsychotics and metoclopramide (D2 receptor antagonists) can cause hyperprolactinemia.
- (Completely unrelated, but also know thiazides can cause galactorrhea. This is on offline NBME 20).

84. 16M + car accident + pituitary stalk is severed. What are the arrows (i.e., ↑ or ↓) for her resultant serum levels of LH, FSH, ACTH, growth hormone, TSH, and prolactin?

- **↓ LH, ↓ FSH, ↓ ACTH, ↓ growth hormone, ↓ TSH, ↑ prolactin.**
- The pituitary stalk is what enables hormonal signaling between the hypothalamus and anterior pituitary.
- GnRH stimulates LH and FSH.
- CRH stimulates ACTH.
- GHRH stimulates growth hormone.
- TRH stimulates TSH.
- **Dopamine inhibits prolactin.**
- It's like "Oh wow holy shit, dopamine *inhibits* prolactin."
- If you sever the pituitary stalk, all of the anterior pituitary hormones decrease because they lose their stimulatory signals from the hypothalamus. But prolactin loses its *inhibitory* signal, so its levels increase.
- Some students might raise the contention that TRH can have stimulatory effects on prolactin, which is true, but recognize that the overwhelming impetus for prolactin secretion is still *lack of* dopamine.

85. 45F + 9 weeks' gestation + chorionic villus sampling (CVS) demonstrates fetal trisomy 21. If a tri-screen was performed prior to the CVS, what were the most likely arrows (i.e., ↑, ↓, or ↔) for serum levels of pregnancy-associated plasma protein A (PAPPA), β-hCG, and fetal nuchal translucency?

- **↓ PAPPA, ↑ β-hCG, ↑ fetal nuchal translucency.**
- The first trimester tri-screen (performed at 8-10 weeks) for Down syndrome will have a decreased maternal serum level of PAPPA, increased β-hCG, and increased fetal nuchal translucency.
- Nuchal translucency is the sonographic appearance of fluid under the skin and behind the fetal neck. It is thickened/widened in Down syndrome.
- It should also be noted tangentially that the nasal bone will often be hypoplastic in Down syndrome. This is observable on the first trimester ultrasound. It is not a formal part of the screening process, but if identified by the sonographer, is a suggestive feature for Down syndrome → flattened facies.

86. 45F + 17 weeks' gestation + concerned about risk for Down syndrome. If the fetus does in fact have Down syndrome, what are the most likely arrows (i.e., ↑, ↓, or ↔) for serum levels of alpha-fetoprotein (AFP), β-hCG, estriol, and inhibin A?

- **↓ AFP, ↑ β-hCG, ↓ estriol, ↑ inhibin A.**
- Second trimester quad-screen (16-18 weeks) for Down syndrome will show low AFP (Down in Down syndrome). AFP will be high in neural tube defects, anencephaly, multiple gestation pregnancies, and omphalocele/gastroschisis.
- Estriol is considered a marker of fetal well-being. You can say, "Well, having Down syndrome isn't good, so that's not well-being, so estriol is down."
- I had a student point out once, "The variables that have 'H' in them are the ones that are high." That is, β-hCG and inhibin A both have an H in them, so those are the up-arrows. AFP and estriol don't have an H, so those are the down-arrows.
- I should make note that inhibin A is what is used as part of the second trimester quad-screen. Inhibin B is what granulosa cells (in the female) and Sertoli cells (in the male) secrete in response to FSH.
- In Edward syndrome (trisomy 18), all four quad screen arrows are down. USMLE will not ask arrows for Patau (trisomy 13).

87. 26F + 8 weeks' gestation + vomiting every 3 hours for the past 48 hours. What are the arrows (i.e., ↑, ↓, or ↔) for her serum K^+, Cl^-, $HCO3^-$, pH, CO2, and urinary ketones?

- **↓ Serum K^+, ↓ Cl^-, ↑ $HCO3^-$, ↑ pH, ↑ CO2, ↑ urinary ketones.**
- Very high-yield you know that vomiting causes a hypokalemic, hypochloremic, metabolic alkalosis.
- Vomitus contains lots of potassium, chloride, and protons. In addition, volume depletion can promote distal renal losses of K^+ and H^+ secondary to RAAS upregulation.
- CO2 is acidic, so the patient will retain CO2 to compensate.
- Nausea and vomiting in pregnancy are attributed to rising hCG levels during the first 8-10 weeks. Recall that the purpose of hCG (secreted by the syncytiotrophoblastic cells of the placenta) is to maintain the corpus luteum (follicular remnant from ovulation) so that it can continue secreting progesterone, which in turn will maintain the endometrial lining and the pregnancy.
- At 8-10 weeks, the placenta will begin taking over production of progesterone, thereby obviating the need for the corpus luteum. hCG levels will decline (since we no longer need to maintain the corpus luteum). If USMLE shows you a graph with pregnancy hormones, hCG is the one that peaks at 8-10 weeks.
- However, when do we consider vomiting in pregnancy to be excessive? Hyperemesis gravidarum is what we call vomiting in pregnancy that is so severe that the patient begins producing ketone bodies, which appear in the urine. Urinary ketones are how we diagnose hyperemesis gravidarum. This is exceedingly HY for 2CK Obgyn. The treatment on 2CK is “admit to hospital and give IV antiemetic therapy.”

88. 18F + using laxatives to promote weight loss. What are the arrows (i.e., ↑, ↓, or ↔) for serum K^+, Cl^-, $HCO3^-$, pH, CO2, and anion-gap?

- **↓ Serum K^+, ↑ Cl^-, ↓ $HCO3^-$, ↓ pH, ↓ CO2, ↔ anion gap.**
- Stool is rich in potassium and bicarb. Diarrhea and laxative abuse can cause a normal anion-gap metabolic acidosis. Since CO2 is acidic, we blow this off to compensate.
- Serum chloride is high due to cellular shifts.
- The high anion-gap metabolic acidoses for Step are MUDPILES → Methanol toxicity, Uremia (renal failure), DKA, Phenformin (weird drug you don't need to know), Iron tablets/Isoniazid, Lactic acidosis, Ethylene glycol toxicity, Salicylates (aspirin).
- Diarrhea is not part of MUDPILES and is thus normal anion-gap.

89. 26F + abusing furosemide in order to lose weight. What are the arrows (i.e., ↑, ↓, or ↔) for serum K^+, Cl^-, $HCO3^-$, pH, and CO2?

- **↓ Serum K^+, ↓ Cl^-, ↑ $HCO3^-$, ↑ pH, ↑ CO2.**
- Furosemide is a loop diuretic. It will block the apical $2Cl^-/K^+/Na^+$ symporter in the thick ascending limb.
- Since water follows ions, and ion reabsorption is impaired, increased diuresis (urination) occurs.
- Volume loss causes upregulation of RAAS and distal secretion of protons under the control of aldosterone, leading to metabolic alkalosis. This is referred to as “contraction alkalosis,” where volume contraction induced by diuretics promotes metabolic alkalosis.
- CO2 is retained to compensate since it is acidic.
- Thiazide diuretics will also follow this arrow pattern.
- Additionally, make note that these arrows are the same as for vomiting.

90. 25M + works as pharmacist + abusing spironolactone. What are the arrows (i.e., ↑, ↓, or ↔) for serum K^+, $HCO3^-$, pH, CO2, and androgen receptor activity?

- **↑ Serum K^+, ↓ $HCO3^-$, ↓ pH, ↓ CO2, ↓ androgen receptor activity.**
- Spironolactone and eplerenone are aldosterone receptor antagonists.
- Since aldosterone normally increases distal renal secretion of potassium, these diuretics are called potassium-sparing, since they prevent this action.
- Normal anion-gap metabolic acidosis occurs because aldosterone's ability to activate the secretory apical H^+-ATPase is blocked.
- ENaC inhibitors (triamterene and amiloride) are also potassium-sparing diuretics and will lead to impaired aldosterone effects at the kidney. This is because if apical ENaC is inhibited, the basolateral Na^+/K^+-ATPase cannot do its job secondarily.
- Spironolactone also blocks androgen receptors and can cause gynecomastia. Eplerenone causes lesser risk of this.
- USMLE wants one of the potassium-sparing diuretics (i.e., spironolactone, eplerenone, triamterene, or amiloride) as the answer for the second diuretic that should be used in a patient who is already on a loop diuretic but who needs additional fluid-unloading – i.e., if you give a thiazide after a loop, you will drop the patient's potassium too much.

91. 44M + essential hypertension + commenced on hydrochlorothiazide. What are the arrows (i.e., ↑, ↓, or ↔) for the changes in his serum Ca^{2+}, K^{+}, $HCO3^{-}$, pH, and urinary calcium?

- **↑ Serum Ca^{2+}, ↓ K^{+}, ↑ $HCO3^{-}$, ↑ pH, ↓ urinary calcium.**
- Thiazide diuretics inhibit the Na^{+}/Cl^{-} symporter on the apical membrane of the early-DCT. This disruption of electrolytes promotes DCT reabsorption of calcium.
- Thiazides can be used to decrease risk of calcium stones in patients with recurrent urolithiasis.
- The ability of thiazides to promote distal calcium reabsorption can sometimes cause hypercalcemia.
- Volume depletion caused by thiazides leads to RAAS upregulation and distal secretion of protons and potassium in the cortical collecting duct.
- Loop diuretics have the opposite effect on calcium (i.e., ↓ serum Ca^{2+}, ↑ urinary calcium). Similar to thiazides, loops will also cause hypokalemia and metabolic alkalosis.

92. 20F + reports increased urination past one month following consumption of expired tetracyclines found in medicine cabinet at home. What are the arrows (i.e., ↑, ↓, or ↔) for PCT reabsorption of amino acids, glucose, phosphate, and bicarbonate?

- **↓ amino acids, ↓ glucose, ↓ phosphate, ↓ bicarbonate.**
- Diagnosis is Fanconi syndrome due to consumption of expired tetracyclines.
- Fanconi syndrome is characterized by impaired PCT reabsorption of amino acids, glucose, phosphate, and bicarbonate. The impairment of the latter can cause renal tubular acidosis (RTA) type II.
- A retired Step 1 NBME Q has all down arrows for the PCT reabsorption of these variables.
- Do not confuse Fanconi syndrome with Fanconi anemia. The latter is an autosomal recessive aplastic anemia where the patient has characteristic absent/hypoplastic thumbs/radii.
- RTA type I = inability of DCT to secrete protons.
- RTA type II = inability of PCT to reabsorb bicarbonate.
- RTA type IV = due to either insensitivity of aldosterone at the kidney (i.e., essentially the aldosterone equivalent of nephrogenic DI with ADH), or hyporeninemic hypoaldosteronism.
- You do not need to obsess over the RTAs for USMLE. Just know the above mechanisms, as well as that they cause normal anion-gap metabolic acidosis (i.e., they are not part of MUDPILES).

93. 22F + abusing diuretics for past year + examination shows poor skin turgor + orbits are sunken + mucous membranes are dry. Serum creatinine and BUN are elevated. If the answer choices force you to choose between high vs low numerical values, what are the most likely arrows (i.e., ↑, ↓) for BUN/Cr and FeNa (fractional excretion of sodium)?

- **↑ BUN/Cr, ↓ FeNa.**
- Diagnosis is prerenal azotemia caused by dehydration from diuretic use.
- Other notable causes of prerenal azotemia are left heart failure and NSAID use.
- Classic values are:
    - Prerenal: BUN/Cr >20; FeNa <1%.
    - Intrarenal or postrenal: BUN/Cr <20; FeNa >1%.
    - Do not worry about intra- vs postrenal being different values. NBME forms will give numbers all over the place.
    - I've seen a couple 2CK-level NBME Qs that give BUN/Cr for prerenal <20, but in these Qs either FeNa is written as <1%, or the patient obviously has dehydration.
- BUN/Cr is >20 in prenenal because low renal perfusion → kidney tries to reabsorb more water from the urine to compensate → it accomplishes this by reabsorbing more sodium and urea in the PCT → water follows sodium and urea → fluid retention.
- Since the kidney is pulling urea out of the urine → higher serum BUN → so BUN/Cr is higher.
- Since the kidney is pulling sodium out of the urine → less in urine → lower FeNa.

94. 40F + has hysterectomy performed; during surgery, she loses lots of blood and BP falls to 80/40 for 30 seconds; she is resuscitated appropriately; after surgery she develops oliguria. Serum creatinine and BUN are elevated. If the answer choices force you to choose between high vs low numerical values, what are the most likely arrows (i.e., ↑, ↓) for BUN/Cr and FeNa?

- **↓ BUN/Cr, ↑ FeNa.**
- Diagnosis is acute tubular necrosis. This is intrarenal. We expect BUN/Cr <20 and FeNa >1%.
- Students frequently mistake this scenario for prerenal.
- In situations where perfusion to the kidney is *acutely* decreased (i.e., blood loss or ventricular fibrillation), the answer is acute tubular necrosis, not prerenal. This is because the PCT has the highest oxygen demand in the kidney due to the high concentrations of ATPase pumps, so it is most susceptible to an abrupt drop in oxygenation/perfusion.
- Prerenal is the answer for more subacute or chronic etiologies of reduced renal perfusion, such as diuretic use, dehydration, left heart failure, and NSAIDs. These etiologies take days to months to cause prerenal azotemia. In contrast, exsanguination or ventricular fibrillation will cause an abrupt and fast drop in perfusion.
- This is important and tested across Steps 1 and 2. They will give you a one-liner, without mentioning BUN/Cr or FeNa, where they just say, "Dude loses blood during surgery and received 5 packs of RBCs. Now has oliguria. Is this prerenal or acute tubular necrosis?" → answer = acute tubular necrosis.
- Other important causes of acute tubular necrosis for USMLE are aminoglycosides, IV contrast, and rhabdomyolysis (myoglobin is nephrotoxic).
- Postrenal will be either an old guy with BPH, or a woman with cervical or ovarian cancer causing ureteral impingement. It could also theoretically be due to posterior urethral valves in peds.
- Compared to prerenal azotemia, for intra- and postrenal failure, BUN/Cr is lower and FeNa higher because the kidney is not trying to reabsorb urea and sodium to compensate for reduced renal perfusion. In prerenal, urea and sodium reabsorption occurs so that water can follow them, which assists in fluid retention and restoration of blood volume.

95. 30M + goes to mountains for holiday + is prescribed acetazolamide. What are the arrows (i.e., ↑, ↓, or ↔) for the resulting changes in urinary volume, urinary bicarbonate, and urine pH?

- **↑ Urinary volume, ↑ urinary bicarbonate, ↑ urine pH.**
- Acetazolamide is a carbonic anhydrase inhibitor that can act as a diuretic. By preventing the combination of and CO2 and H2O in the PCT of the kidney to make H_2CO_3, there is lesser equilibration into HCO_3^- and H^+. Normally HCO_3^- is reabsorbed by the PCT. Since acetazolamide inhibits this process, it causes a metabolic acidosis.
- Since less bicarbonate is reabsorbed, there is less Na^+ and K^+ cation reabsorption that occurs concurrently. Since water follows ions, there is less water reabsorption → diuresis.
- Bicarbonate is basic, so more bicarb in the urine means greater urine pH.
- Acetazolamide can be used for altitude sickness. At higher altitude, O2 tension is lower, so the patient will hyperventilate in an attempt to achieve adequate oxygenation. This causes CO2 to be expired, resulting in an acute respiratory alkalosis. The kidney, however, will take a minimum of 12-24 hours to increase bicarbonate excretion to appreciably compensate. In the meantime, the patient can take acetazolamide to effectively force the kidney to excrete the bicarb faster than it normally would.
- It should be noted that with acetazolamide, we also have:
    - **↓ serum volume, ↓ serum bicarbonate, ↓ serum pH.**
    - Just be careful because the USMLE will ask both serum and urine arrows.

96. 4F + ambiguous genitalia + serum 17-OH-progesterone is increased + blood pressure is normal. What are the arrows (i.e., ↑, ↓, or ↔) for serum K^+, Na^+, pH, $HCO3^-$, and glucose?

- **↑ Serum K^+, ↓ Na^+, ↓ pH, ↓ $HCO3^-$, ↓ glucose.**
- Diagnosis is 21-hydroxylase deficiency.
- Congenital adrenal hyperplasia refers to 21-, 11-, or 17-hydroxylase deficiency.
- Do not freak out about memorizing the flow chart of all of the substrates moving through the adrenal cortex. I'll tell you exactly what you need to know to answer NBME Qs without all of the **horseshit.**
- For both 21- **AND** 11-hydroxylase deficiencies:
    - **↑ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone).**
    - **↑ DHEA-S, ↑ androstenedione.**
    - If you see any of these up in the Q, you know right away answer is either 21- or 11-.
- 21-hydroxylase deficiency:
    - **↑ Serum K^+, ↓ Na^+, ↓ pH, ↓ $HCO3^-$, ↓ glucose**
    - **↓/↔ BP**
    - (Cortisol and aldosterone, as well as their precursors, are all low)
- 11-hydroxylase deficiency:
    - **↓/↔ Serum K^+, ↑/↔ Na^+, ↑/↔ pH, ↑/↔ $HCO3^-$, ↑/↔ glucose**
    - **↑ BP**
    - (Cortisol and aldosterone are low, but their precursors, which have some effect, are high)
- For 17-hydroxylase deficiency:
    - **↓ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↓ DHEA-S, ↓ androstenedione**
    - **↓ Serum K^+, ↑ Na^+, ↑ pH, ↑ $HCO3^-$** (high aldosterone)
    - **↓ glucose** (cortisol and its precursor are low)
- If you're just trying to pass USMLE, I want you to just memorize the arrows at the top of this page for 21-hydroxylase deficiency.

97. 4M + high BP + high serum DHEA-S. What are the arrows (i.e., ↑ or ↓) for serum K^+ and 17-OH progesterone?

- **↓ Serum K^+, ↑ 17-OH progesterone.**
- Diagnosis is 11-hydroxylase deficiency.
- High DHEA-S immediately means we're dealing with either 21- or 11-hydroxylase deficiency.
- Then we look at BP and potassium. If either potassium is high or BP low, we know we're dealing with 21-hydroxylase deficiency. If potassium not high (i.e., low or normal) or BP up, then answer is 11-hydroxylase deficiency.
- High BP in the setting of high DHEA-S means we have 11- deficiency. So we know potassium will be either low or normal, and that 17-OH substrates will be elevated.
- For both 21- **AND** 11-hydroxylase deficiencies:
    - **↑ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↑ DHEA-S, ↑ androstenedione**
    - If you see any of these up in the Q, you know right away answer is either 21- or 11-.
- 21-hydroxylase deficiency:
    - **↑ Serum K^+, ↓ Na^+, ↓ pH, ↓ $HCO3^-$, ↓ glucose**
    - **↓/↔ BP**
    - (Cortisol and aldosterone, as well as their precursors, are all low)
- 11-hydroxylase deficiency:
    - **↓/↔ Serum K^+, ↑/↔ Na^+, ↑/↔ pH, ↑/↔ $HCO3^-$, ↑/↔ glucose**
    - **↑ BP**
    - (Cortisol and aldosterone are low, but their precursors, which have some effect, are high)
- For 17-hydroxylase deficiency:
    - **↓ 17-OH substrates (i.e., 17-OH-progesterone oand17-OH-pregnenolone)**
    - **↓ DHEA-S, ↓ androstenedione**
    - **↓ Serum K^+, ↑ Na^+, ↑ pH, ↑ $HCO3^-$** (high aldosterone)
    - **↓ glucose** (cortisol and its precursor are low)

98. 4M + high BP + low serum DHEA-S and 17-OH-pregnenolone. What are the arrows (i.e., ↑ or ↓) for serum K^+, Na^+, pH, $HCO3^-$, and glucose?

- **↓ Serum K^+, ↑ Na^+, ↑ pH, ↑ $HCO3^-$, ↓ glucose.**
- Diagnosis is 17-hydroxylase deficiency.
- If 17-OH substrates, DHEA-S, and/or androstenedione are low, you know right away 17-hydroxylase deficiency is the answer.
- Aldosterone is increased, so we have low potassium, high sodium, and metabolic alkalosis.
- Glucose is low because 17-hydroxylase is needed to produce glucocorticoids.
- BP is elevated because aldosterone is elevated.
- For both 21- **AND** 11-hydroxylase deficiencies:
    - **↑ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↑ DHEA-S, ↑ androstenedione**
    - If you see any of these up in the Q, you know right away answer is either 21- or 11-.
- 21-hydroxylase deficiency:
    - **↑ Serum K^+, ↓ Na^+, ↓ pH, ↓ $HCO3^-$, ↓ glucose**
    - **↓/↔ BP**
    - (Cortisol and aldosterone, as well as their precursors, are all low)
- 11-hydroxylase deficiency:
    - **↓/↔ Serum K^+, ↑/↔ Na^+, ↑/↔ pH, ↑/↔ $HCO3^-$, ↑/↔ glucose**
    - **↑ BP**
    - (Cortisol and aldosterone are low, but their precursors, which have some effect, are high)
- For 17-hydroxylase deficiency:
    - **↓ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↓ DHEA-S, ↓ androstenedione**
    - **↓ Serum K^+, ↑ Na^+, ↑ pH, ↑ $HCO3^-$** (high aldosterone)
    - **↓ glucose** (cortisol and its precursor are low)

99. 4F + high serum potassium and DHEA-S; blood pressure is normal. What are the arrows (i.e., ↓ or ↔) for 17-hydroxylase, 11-hydroxylase, and 21-hydroxylase functionality?

- **↔ 17-hydroxylase, ↔ 11-hydroxylase, ↓ 21-hydroxylase.**
- Diagnosis is 21-hydroxylase deficiency.
- If DHEA-S, androstenedione, and/or 17-OH substrates are high, you know right away the answer is either 21- or 11- deficiency.
- Then, if potassium is high and/or BP low/normal, you know right away it is 21- deficiency.
- For both 21- **AND** 11-hydroxylase deficiencies:
    - **↑ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↑ DHEA-S, ↑ androstenedione**
    - If you see any of these up in the Q, you know right away answer is either 21- or 11-.
- 21-hydroxylase deficiency:
    - **↑ Serum K^+, ↓ Na^+, ↓ pH, ↓ $HCO3^-$, ↓ glucose**
    - **↓/↔ BP**
    - (Cortisol and aldosterone, as well as their precursors, are all low)
- 11-hydroxylase deficiency:
    - **↓/↔ Serum K^+, ↑/↔ Na^+, ↑/↔ pH, ↑/↔ $HCO3^-$, ↑/↔ glucose**
    - **↑ BP**
    - (Cortisol and aldosterone are low, but their precursors, which have some effect, are high)
- For 17-hydroxylase deficiency:
    - **↓ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↓ DHEA-S, ↓ androstenedione**
    - **↓ Serum K^+, ↑ Na^+, ↑ pH, ↑ $HCO3^-$** (high aldosterone)
    - **↓ glucose** (cortisol and its precursor are low)

100.6F + blood pressure high + 17-OH-progesterone high. What are the arrows (i.e., ↓ or ↔) for 17-hydroxylase, 11-hydroxylase, and 21-hydroxylase functionality?

- **↔ 17-hydroxylase, ↓ 11-hydroxylase, ↔ 21-hydroxylase.**
- Diagnosis is 11-hydroxylase deficiency.
- If 17-OH-substrates, DHEA-S, and/or androstenedione are high, you know right away you're dealing with either 21- or 11- deficiency.
- Then we look at potassium and BP. If potassium is high and/or BP normal/low, answer is 21-deficiency.
- If potassium is normal/low and/or BP is high, answer is 11-hydroxylase deficiency.
- For both 21- **AND** 11-hydroxylase deficiencies:
    - **↑ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↑ DHEA-S, ↑ androstenedione**
    - If you see any of these up in the Q, you know right away answer is either 21- or 11-.
- 21-hydroxylase deficiency:
    - **↑ Serum K^+, ↓ Na^+, ↓ pH, ↓ $HCO3^-$, ↓ glucose**
    - **↓/↔ BP**
    - (Cortisol and aldosterone, as well as their precursors, are all low)
- 11-hydroxylase deficiency:
    - **↓/↔ Serum K^+, ↑/↔ Na^+, ↑/↔ pH, ↑/↔ $HCO3^-$, ↑/↔ glucose**
    - **↑ BP**
    - (Cortisol and aldosterone are low, but their precursors, which have some effect, are high)
- For 17-hydroxylase deficiency:
    - **↓ 17-OH substrates (i.e., 17-OH-progesterone and 17-OH-pregnenolone)**
    - **↓ DHEA-S, ↓ androstenedione**
    - **↓ Serum K^+, ↑ Na^+, ↑ pH, ↑ $HCO3^-$** (high aldosterone)
    - **↓ glucose** (cortisol and its precursor are low)

101. 11F + one-day Hx of severe lethargy and feelings of unwellness; one-week Hx of drinking a lot + peeing a lot; recently recovered from an upper respiratory tract illness. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's pH, $HCO3^-$, and CO2?

- **↓ pH, ↓ $HCO3^-$, ↓ CO2.**
- Diagnosis is diabetic ketoacidosis (DKA).
- Etiology is classically recent viral infection (usually Coxsackie B) followed by polyuria and polydipsia.
- Lack of insulin production by the pancreas results in severely diminished ability of cells to pick up glucose from the blood → causes increased gluconeogenesis, lipolysis, and ketogenesis.
- Ketone bodies are acidic → causes metabolic acidosis (decreased bicarbonate).
- CO2 is acidic, so we blow that off to compensate. Kussmaul breathing is deep, labored breathing seen in DKA.

102. 12F + Hx of type I diabetes mellitus; goes to a sleepover at friend's house and doesn't take evening insulin; in the morning has severe lethargy and delirium. What are the arrows (i.e., ↑, ↓, or ↔) for this patient's serum β-hydroxybutyrate, serum osmolality, and anion gap?

- **↑ β-hydroxybutyrate, ↑ serum osmolality, ↑ anion gap.**
- Diagnosis is DKA.
- β-hydroxybutyrate is a ketone body. Since we have ketosis (ketone production), it will be increased. I have seen this specific ketone body as an arrow on an offline Step 1 NBME.
- Serum osmolality is increased because serum glucose is markedly increased (insulin isn't present to drive glucose into cells).
- DKA is one of the high anion-gap metabolic acidoses (MUDPILES) → Methanol toxicity, Uremia (renal failure), DKA, Phenformin (weird drug you don't need to know), Iron tablets/Isoniazid, Lactic acidosis, Ethylene glycol toxicity, Salicylates (aspirin).
- Anion gap is calculated as serum Na^+ - (Cl^- + $HCO3^-$). A value >12 is considered high. 8-12 is normal.

103. 8M + recent viral illness + severe lethargy + polyuria + polydipsia. What are the arrows (i.e., ↑, ↓, or ↔) for serum Na^+, serum K^+, total body K^+, and glomerular filtration rate (GFR)?

- **↓ Serum Na^+, ↑ serum K^+, ↓ total body K^+, ↑ GFR.**
- Diagnosis is DKA.
- Serum sodium is decreased mostly due to dilutional hyponatremia. As mentioned earlier, serum osmolality is high, which causes fluid retention intravascularly → dilutes out serum sodium. In addition, low insulin means less glucose enters cells → less ATP production → less cellular Na^+/K^+-ATPase activation → sodium not pumped out of cells.
- We describe the state of K^+ as: hyperkalemia (high serum K^+) despite a low total body potassium.
- Serum potassium is high for two main reasons:
    - 1) **Potassium-proton shift:** Acidosis (due to ketosis) causes protons in the blood to exchange with potassium in the cell via the H^+/K^+-antiporter (i.e., H^+ goes into cell; K^+ moves out).
    - 2) **Insulin drives potassium into cells (and we don't have insulin in DKA):** Insulin normally leads to the upregulation of a Na^+/K^+-ATPase antiporter that moves $3Na^+$ out for every $2K^+$ in. If insulin is low, then less K^+ will be moved into the cell → hyperkalemia (high potassium in blood).
- Total body potassium is low because of increased losses at the kidney. Since serum potassium is high, more potassium is filtered through the glomerulus, so more is excreted (i.e., the kidney thinks there's too much potassium in the body since more is being filtered, so it tries to get rid of more of it). However, this causes bodily depletion of K^+ because the processes that cause hyperkalemia are unmitigated, so the kidney continues to excrete potassium.
- GFR is increased because of hyperfiltration secondary to hyperglycemia. That is, since serum glucose is high, more glucose is filtered through the glomerulus, which pulls water with it → hyperfiltration.

104. 3F + consumes bottle of pills left open in medicine cabinet at home + has blood in the stool + the pills are visible on abdominal x-ray. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, CO2, and anion-gap?

- **↓ pH, ↓ $HCO3^-$, ↓ CO2, ↑ anion-gap.**
- Diagnosis is acute iron toxicity.
- Iron tablets are one of the MUDPILES high anion-gap metabolic acidoses.
- (MUDPILES) → Methanol toxicity, Uremia (renal failure), DKA, Phenformin (weird drug you don't need to know), Iron tablets/Isoniazid, Lactic acidosis, Ethylene glycol toxicity, Salicylates (aspirin).
- Iron tablets can sometimes be visualized on abdominal x-ray because of their metal content, aiding in diagnosis in the event of infant consumption.
- CO2 is acidic, so we blow it off to compensate.

105. 25M + consumed bottle of aspirin 10 minutes ago. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, and CO2?

- **↑ pH, ↔ $HCO3^-$, ↓ CO2.**
- This patient has acute respiratory alkalosis due to aspirin. Aspirin initially causes an isolated respiratory alkalosis (within the first 20 minutes) due to direct upregulation of respiratory centers in the brain.
- The pH is high because we are blowing off CO2 (which is acidic).
- Bicarbonate is normal because there's not enough time for it to change. It takes a minimum of 12-24 hours for the kidneys to significantly alter bicarbonate reabsorption and excretion in the setting of a respiratory disturbance.
- For this patient, it is his normal bicarbonate level that denotes the acid-base disturbance as an acute respiratory alkalosis. If bicarbonate is observed to be low as compensation (e.g., after 1-2 days at high altitude), then we can say there is a chronic respiratory alkalosis.
- The acid-base disturbance caused by aspirin (salicylates) occurs in two steps:
    - 1) **Acute respiratory alkalosis.** The literature will differ depending on the length of time this phase lasts, but 20 minutes is generally accepted.
    - 2) **Mixed metabolic acidosis-respiratory alkalosis** (i.e., a metabolic acidosis and respiratory alkalosis at the same time).
- Aspirin itself is an acid (salicylic acid), so it will ultimately cause a metabolic acidosis (low bicarb) that wins over the respiratory alkalosis (i.e., pH will ultimately go low).
- In other words, for aspirin we have:
    - First 20 minutes: acute respiratory alkalosis (**↑ pH, ↔ $HCO3^-$, ↓ CO2).**
    - After 20 minutes: mixed metabolic acidosis-respiratory alkalosis (**↓ pH, ↓ $HCO3^-$, ↓ CO2).**
- The low bicarbonate we see after 20 minutes **is not compensation.** It coincidentally goes low (as we'd expect for renal compensation in the setting of respiratory alkalosis). But remember that the kidney cannot induce this change until a minimum of 12-24 hours later. The reason bicarb is low after 20 minutes is because aspirin itself is an acid that is causing a metabolic acidosis and driving the bicarb low.

106. 20F + consumed bottle of pills one hour ago + has lethargy and ear-ringing. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, CO2, anion-gap, Na^+, and K^+?

- **↓ pH, ↓ $HCO3^-$, ↓ CO2, ↑ anion-gap, ↔ Na^+, ↔ K^+.**
- Diagnosis is salicylate (aspirin) toxicity. Tinnitus (ear-ringing) is the most common first symptom.
- This patient has mixed metabolic acidosis-respiratory alkalosis (i.e., both a metabolic acidosis and respiratory alkalosis at the same time).
- Aspirin initially causes an isolated respiratory alkalosis (within the first 20 minutes) due to direct upregulation of respiratory centers in the brain.
- However, aspirin itself is an acid (salicylic acid), so it will ultimately cause a metabolic acidosis that wins over the respiratory alkalosis (i.e., pH will ultimately go low).
- Anion gap is high. Salicylates are the S in MUDPILES.
- Sodium and potassium are normal in salicylate toxicity. I have seen these arrows listed before, which causes students confusion, but they are unchanged. Sometimes the Q will give you numerical values where you need to calculate anion gap – i.e., Na^+ - ($HCO3^-$ + Cl^-). The value must be 13 or greater since it is one of the MUDPILES. Normal range is 8-12.
- In summary, once again, for aspirin:
    - First 20 minutes: acute respiratory alkalosis (**↑ pH, ↔ $HCO3^-$, ↓ CO2).**
    - After 20 minutes: mixed metabolic acidosis-respiratory alkalosis (**↓ pH, ↓ $HCO3^-$, ↓ CO2).**
- The low bicarbonate we see after 20 minutes **is not compensation.** It coincidentally goes low (as we'd expect for renal compensation in the setting of respiratory alkalosis). But remember that the kidney cannot induce this change until a minimum of 12-24 hours later. The reason bicarb is low after 20 minutes is because aspirin itself is an acid that is causing a metabolic acidosis and driving the bicarb low.

107. 38F + in hospital recovering from C-section 48 hours ago + sore left leg + acute-onset shortness of breath and tachycardia. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, and CO2?

- **↑ pH, ↔ $HCO3^-$, ↓ CO2.**
- Diagnosis is pulmonary embolism.
- Patients have respiratory alkalosis because respiratory rate is increased (tachypnea).
- CO2 diffuses quickly. O2 diffuses slowly. This means that even if lung pathology is present where adequate oxygenation cannot occur, insofar as the patient is hyperventilating, CO2 will be low. This is the case for 14/15 Qs on USMLE. I will discuss the exception in a bit. Keep your pants on.
- Bicarbonate is normal because there is not enough time for it to change in the acute setting. It takes a minimum of 12-24 hours for the kidney to significantly change bicarb levels. If bicarb were to change here, it would go down (because bicarb is basic, so we'd want to get rid of it in the setting of respiratory alkalosis), but once again, it will be normal in acute respiratory disturbances.

108. 12M + wheezing and difficulty breathing on the soccer field past 10 minutes; family Hx of eczema and seasonal allergies. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, and CO2?

- **↑ pH, ↔ $HCO3^-$, ↓ CO2.**
- Diagnosis is acute asthma attack.
- Similar to pulmonary embolism, CO2 is low because the patient is hyperventilating, so we have an acute respiratory alkalosis.
- Bicarbonate is unchanged because it takes 12-24 hours for the kidney to significantly alter reabsorption and excretion.
- Remember that CO2 diffuses quickly, whereas O2 diffuses slowly. This means that even in a setting where your lungs are fucked up and O2 can't get in properly, insofar as you're hyperventilating, CO2 can still get out without a problem because it diffuses quickly. This is why O2 and CO2 are both low → O2 diffuses slowly so can't get in, but CO2 diffuses quickly so can get out no issues.

109. 12M + wheezing on soccer field and in respiratory distress + given nebulized albuterol. After 40 minutes, O2 remains low. Respiratory rate is 6 per minute. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, and CO2?

- **↓ pH, ↔ HCO_3^-, ↑ CO_2.**
- The patient has respiratory acidosis due to respiratory fatigue.
- Initially in an asthma attack, we have **respiratory alkalosis, not acidosis,** because respiratory rate is high in order to try to get oxygen in. However, the patient can become tired and begin to slow his or her respiratory rate *in spite of* low oxygen status.
- Normal respiratory rate is 12-16 per minute. This patient has low respiratory rate and will have respiratory acidosis.
- The acid-base disturbance in an asthma attack goes through three stages:
    - Initially: **↑ pH, ↔ HCO_3^-, ↓ CO_2 (acute respiratory alkalosis),** caused by high respiratory rate. The combination of a low O2 and low CO2 is referred to as type I respiratory failure (O2 and CO2 go the same direction).
    - Second: **↔ pH, ↔ HCO_3^-, ↔ CO_2.** The patient is getting tired so has slowed his/her respiratory rate. CO2 goes back up to normal; pH comes back down to normal. This is *despite* O2 still being low. This signifies impending type II respiratory failure, where CO2 is high and O2 low (O2 and CO2 go the opposite direction).
    - Finally: **↓ pH, ↔ HCO_3^-, ↑ CO_2.** The patient's respiratory rate has slowed because he/she is tired, and we now have a respiratory acidosis. If the patient transitions from type I to type II respiratory failure in an asthma attack, intubation may be required.

110. 16F + called to principal's office + hyperventilates. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, CO2, cerebral perfusion?

- **↑ pH, ↔ $HCO3^-$, ↓ CO2.**
- This patient has a panic attack. Hyperventilation causes a respiratory alkalosis.
- Bicarbonate is unchanged because it takes 12-24 hours for the kidney to significantly alter reabsorption/excretion.
- **Decreased CO2 causes decreased cerebral perfusion.** → This is exceedingly HY for USMLE.
- Patient faints in panic attack due to decreased cerebral perfusion in the setting of hyperventilation.
- There is an NBME Q somewhere that asks how an anesthesiologist could increase cerebral perfusion, and the answer is "decrease the respiratory rate" → increases CO2 retention → increases cerebral perfusion. Might sound weird, but if you know decreased CO2 causes decreased cerebral perfusion as the HY point, then this opposite scenario is easily inferable.
- Hyperventilation is also the first step in management in patients who have increased intracranial pressure.

111. 72M + long history of COPD + fever 100 F + presents in acute distress with labored breathing. Respiratory rate is 32/minute. What are the arrows (i.e., ↑, ↓, or ↔) for pH, $HCO3^-$, and CO2?

- **↓ pH, ↑ HCO_3^-, ↑ CO_2.**
- Diagnosis is acute exacerbation of COPD (usually due to viral infection).
- This CO_2 pattern is the exception to the high respiratory rate rule for USMLE.
- Normally, we said that when patients hyperventilate, their CO_2 is low. This is the case for probably 14/15 USMLE Qs. The exception is acute exacerbation of COPD, where patients will have "chronic respiratory acidosis and acute respiratory acidosis," (aka "acute on chronic," but I've seen it written the long way on a 2CK NBME Q).
- Patients with COPD (chronic bronchitis + emphysema) will have decreased alveolar surface area available for gas exchange and are therefore chronic CO_2 retainers. This means they have chronic respiratory acidosis **(↑ CO_2, ↑ HCO_3^-, ↓ pH).** Bicarbonate goes up because the patient's respiratory acidosis is chronic, so the kidney has more than enough time to compensate. Since CO_2 is acidic, we want to retain alkaline bicarb to compensate.
- When a viral illness precipitates an acute exacerbation of COPD, the decrease in alveolar surface area available for gas exchange means that *even if the patient hyperventilates, CO_2 will still be high*. In other words, in patients with severe COPD, even though CO_2 diffuses quickly, it still can't get out because the decreased alveolar surface area precludes CO_2 from effectively leaving the capillaries.
- There is a 2CK NBME Q floating around where they give a respiratory rate of 32 in a guy with severe COPD, and they show CO_2 as 80 mmHg (NR 33-44). The answer is "chronic respiratory acidosis and acute respiratory acidosis." That is, the patient has an acute increase in CO_2 that his/her chronic elevation in HCO_3^- does not compensate for.

112. 68M + long history of COPD + not in acute distress. What are the arrows (i.e., ↑ or ↓) for pH, $HCO3^-$, and CO2?

- **↓ pH, ↑ HCO3, ↑ CO2.**
- Patients with COPD are chronic CO2 retainers and will have chronic respiratory acidosis.
- Since this is a chronic process, bicarbonate is elevated as compensation. Patients may have blood pH that is normal or low depending on the severity of the hypercarbia.
- Obstructive sleep apnea, obesity, severe ankylosing spondylitis, and severe kyphoscoliosis can cause restrictive lung pathologies that lead to chronic CO2 retention, even though gas exchange is not impaired. These patients will have the same biochemistry of: **↓ pH, ↑ $HCO3^-$, ↑ CO2** (chronic respiratory acidosis), but *will* be able to decrease CO2 by hyperventilating.

113. 60F + recovering in hospital following hip surgery + on morphine for pain; physical examination shows mild crackles at the lung bases bilaterally. Respiratory rate is 8 per minute. What are the arrows (i.e., ↑ or ↔) for CO2 and A-a (Alveolar-arteriolar) O2 gradient?

- **↑ CO2, ↔ A-a gradient.**
- Opioids (such as morphine), barbiturates, and benzodiazepines can all cause respiratory depression and respiratory acidosis. CO2 is increased since respiratory rate is low (NR 12-16/minute).
- A-a gradient is the difference between the oxygen levels in the alveoli and the arterioles.
- A-a gradient is normal because alveolar and arteriolar oxygen are both low.
- Most students assume that any lung issue automatically = high A-a gradient. But think about what this means for a second: in hypoventilation (e.g., from opioids), the only reason the patient's arteriolar oxygen is low *is because he or she is hypoventilating*. So of course alveolar oxygen is also low.
- In contrast, if we have, e.g., pulmonary fibrosis, A-a gradient would be high because the patient can get O2 into the alveoli just fine. It is merely the case that the oxygen can't get into the arteries, so the difference between the alveoli and arterioles is high.
- The USMLE does not expect you to know normal A-a numerical ranges. They will merely give you answer choices where some answer choices are, e.g., 40, and the others are, e.g., 8, and you can easily infer that you'd pick the one that says 8 for opioids, barbiturates, or benzos.

114. 65M + long history of hypertension and smoking + S3 heart sound + sleeps on 4 pillows at night to facilitate breathing. What are the arrows (i.e., ↑ or ↔) for this patient's A-a gradient and pulmonary capillary wedge pressure (PCWP)?

- **↑ A-a gradient, ↑ PCWP.**
- Diagnosis is dilated cardiomyopathy with left heart failure. An S3 heart sound means a dilated left ventricle with systolic dysfunction.
- Needing to sleep on pillows in order to breathe properly is called orthopnea. This is common in patients with left heart failure. When the patient lies flat, there is increased venous return to the right heart → increased preload arriving at left heart → left heart can't handle it → blood backs up to lungs → pulmonary edema + difficulty breathing. So if the patient sleeps on pillows → slightly less venous return to right heart → left heart can tolerate lower preload slightly better → less pulmonary edema.
- Fluid in the lungs impairs gas exchange across the alveolar capillaries. The patient can oxygenate his alveoli just fine, but merely can't get the oxygen into the capillaries because fluid is sitting there. This means A-a is high (alveolar oxygen is high/good, but arteriolar is low).
- Pulmonary capillary wedge pressure is the pressure sensed by a catheter tip if it is inserted through the right heart and into a distal pulmonary capillary. The pressure waves it senses come from the left atrium. Therefore, left atrial pressure (LAP) = PCWP.
- For USMLE, you need to know that any left heart pathology increases PCWP.
- Left heart pathology → LAP goes up → PCWP is up since LAP = PCWP → increased pulmonary capillary hydrostatic pressure → transudation of fluid into alveolar spaces (pulmonary edema).
- There is a 2CK IM NBME Q that gives a vignette of pulmonary edema and then asks the mechanism for the patient's dyspnea; answer = "increased alveolar-arteriolar oxygen gradient."

115. 8M + Hx of recurrent lung infections + failure to pass meconium at birth + increased pulmonary vascular markings seen on chest x-ray + loud P2 heart sound + right bundle branch block + JVD. What are the arrows (i.e., ↑, ↓, or ↔) for PCWP and 24,25-$(OH)_2$-vitamin D3?

- **↔ PCWP, ↓ 24,25-$(OH)_2$-vitamin D3.**
- Diagnosis is cor pulmonale due to cystic fibrosis (CF).
- Cor pulmonale is defined as right heart failure due to a pulmonary cause (i.e., COPD, CF, pulmonary fibrosis, etc.).
- Recall that PCWP = LAP. PCWP is normal in cor pulmonale because the left heart is unaffected. Cor pulmonale is specifically when we have a problem starting with the lungs and backing up to the right heart; the left heart is normal so PCWP (LAP) should be normal.
- Loud P2 (pulmonic component of S2) = pulmonary hypertension on USMLE. The pulmonic valve slams shut because of the increased distal pressure in the pulmonary circulation.
- Right bundle branch block usually = right ventricular hypertrophy on USMLE. (Likewise, LBBB often = LVH).
- Patients with CF have exocrine pancreatic insufficiency, with decreased ability to absorb fat-soluble vitamins. Although the patient could theoretically produce vitamin D from the skin, dietary consumption is still important for normal vitamin D levels. Cholecalciferol is the type of vitamin D3 found in most foods and supplements.
- Cholecalciferol will go to the liver and be hydroxylated into 25-OH-D3 (calcidiol).
- Since 25-OH-D3 is in equilibrium with 24,25-$(OH)_2$-D3, if 25-OH is low, then 24,25-D3 is also low.
- If you weren't sure which vitamin D form is absorbed from food, another way to think about it is: if patients with CF are prone to vitamin D deficiency, that can cause low Ca^{2+} absorption from the bowel, which in turn would increase PTH, which in turn would upregulate 1α-hydroxylase, which would convert more 25-OH-D3 into 1,25-$(OH)_2$-D3, thereby decreasing 24,25-$(OH)_2$-D3 anyway.

116. 47M + occasional color change of fingers with cold + Hx of gastroesophageal reflux + one-year Hx of worsening shortness of breath. What are the arrows (i.e., ↑ or ↓) for ventilation/perfusion (V/Q) ratio, anti-centromere antibodies, and anti-mitochondrial antibodies?

- **↓ V/Q, ↑ anti-centromere antibodies, ↓ anti-mitochondrial antibodies.**
- Diagnosis is pulmonary fibrosis secondary to limited systemic sclerosis (CREST syndrome).
- Patients can develop pulmonary fibrosis in both limited and diffuse types of systemic sclerosis.
- In pulmonary fibrosis, perfusion (Q) is unaffected (i.e., there's no problem with blood flow to the lungs).
- However, the fibrosis means some parts of the alveoli will be under-ventilated because inhaled oxygen won't be able to reach them, so ventilation (V) is reduced. This means V/Q is low.
- In contrast, V/Q is high in pulmonary embolism, since blood flow (perfusion; Q) is reduced.
- **Low V/Q = shunt** → applies to most lung pathologies.
- **High V/Q = dead space** → refers to pulmonary embolism.
- Shunt and dead space can apply physiologically (i.e., no pathology) to the lungs notably when the patient is upright. Both ventilation and perfusion increase from apex to base, but fluid sinks more than air due to gravity, so perfusion increases *more* than ventilation from apex to base.
- This means at the bases, Q has increased a lot, so V/Q is lower (natural shunt) at the bases. V/Q is around 0.6 at the bases.
- At the apices, there's a lot less perfusion because gravity pulls it down, so Q is a lot lower at the apices and V/Q is high (natural dead space at apices). V/Q is around 3.0 at the apices.
- Anti-centromere antibodies are classic for CREST syndrome. Anti-topoisomerase (anti-Scl-70) are seen in diffuse systemic sclerosis.
- Anti-mitochondrial antibodies having nothing to do with CREST. They are seen in primary biliary cirrhosis. I just decided to be an asshole and throw a random variable in there for kicks because that's literally what the USMLE does. You'll handle it.

117. 40F + heavy smoker past 20 years + taking combined oral contraceptive pills + develops acute-onset shortness of breath and tachycardia. What are the arrows (i.e., ↑, ↓, or ↔) for pH, CO2, bicarb, and V/Q?

- **↑ pH, ↓ CO2, ↔ $HCO3^-$, ↑ V/Q.**
- Diagnosis is pulmonary embolism. Combined oral contraceptive pills are contraindicated in women over 35 who are smokers because of increased risk for thromboembolic events.
- As discussed earlier, in PE, we have an acute respiratory alkalosis because we are hyperventilating. CO2 is down and pH is up. Bicarb is normal because there isn't enough time for it to change.
- V/Q is up because we have impaired perfusion (Q) to the lungs.
- Recall that shunt is low V/Q; dead space is high V/Q. So in PE, we have pathologic dead space.
- Alveolar dead space refers to natural V/Q shifts in the lungs from apices to bases (as discussed earlier).
- Anatomic dead space refers to areas of the respiratory tree that are naturally ventilated but not perfused (e.g., the bronchi).
- Physiologic dead space = alveolar dead space + anatomic dead space.
- There is one retired Step 1 NBME Q where they list alveolar dead space, anatomic dead space, physiologic dead space, and shunt all as answers.

118. 46M + chronic alcoholic + abdominal pain + serum calcium 7.5 mg/dL (NR 8.4-10.2) + glucose 200 mg/dL + severe hypoxemia + chest x-ray shows bilateral infiltrates. What are the arrows (i.e., ↑, ↓, or ↔) for PCWP, V/Q ratio, and pulmonary surfactant protein D concentration?

- **↔ PCWP, ↓ V/Q ratio, ↑ surfactant protein D.**
- Diagnosis is acute respiratory distress syndrome (ARDS) secondary to pancreatitis.
- Low calcium and high glucose are poor prognostic variables for pancreatitis. Of the Ranson criteria for 2CK Surg Qs, the most important ones to know are low calcium and high glucose. You should also know that amylase and lipase levels don't correlate with prognosis.
- Low calcium occurs due to saponification (soap formation). Enzymatic fat necrosis within the pancreas causes chelation of calcium.
- ARDS is an inflammatory lung condition in which proteinaceous exudate floods the alveolar spaces. ARDS is always bilateral. Since the left heart is not the cause of the pulmonary edema (i.e., non-cardiogenic), PCWP is normal.
- If the Q gives you high PCWP and bilateral infiltrates, they're telling you the pulmonary edema is due to left heart pathology.
- V/Q ratio is down because this is a shunt, where low oxygen in the blood is due to impaired ventilation of the alveoli. Perfusion (Q) to the lungs is unaffected. V/Q is up in pulmonary embolism.
- Surfactant protein D is a marker of lung injury and is increased in ARDS (on retired Step 1 NBME).

119. 55M + non-smoker + 6-month Hx of progressive shortness of breath and dry cough + CT of the chest shows reticulonodular pattern (“honeycombing”). What are the arrows (i.e., ↑ or ↓) for forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC?

- **↓ FEV1, ↓ FVC, ↑ FEV1/FVC.**
- Diagnosis is idiopathic pulmonary fibrosis, a type of restrictive lung disease.
- **FEV1/FVC can be normal or increased** in restrictive lung disease. Sometimes Qs will only give one arrow direction and force you to choose.
- In contrast, FEV1/FVC is decreased in obstructive lung conditions like COPD, CF, and asthma.
- USMLE wants you to know idiopathic pulmonary fibrosis is also known as **usual interstitial pneumonitis (UIP)** → shows up a few times as the answer on Step 1 NBMEs. In other words, memorize that UIP = pulmonary fibrosis.
- FEV1 (as much air expired as possible in one second) and FVC (total amount of air patient is capable of maximally inspiring followed by maximally expiring) are both decreased in both restrictive and obstructive lung diseases, however the FEV1/FVC ratio is normal or high in restrictive conditions.
- This is because of **radial traction,** or "stickiness" of fibrosis on the outside of the airways, which keeps them open longer, thereby allowing FEV1 to not decrease as much in comparison to obstructive conditions, where radial traction is not a salient feature.

120. 70F + healthy + has pulmonary function tests performed as part of a study. In comparison to a healthy woman age 20, what are her arrows (i.e., ↑ or ↓) for FEV1, FVC, and FEV1/FVC?

- **↓ FEV1, ↓ FVC, ↓ FEV1/FVC.**
- USMLE wants you to know that people naturally develop obstructive lung disease throughout the course of their lives, likely as a result of lifetime inhalation of particulates.
- These arrows are the same for COPD due to smoking, asthma, and α1-antitrypsin deficiency (emphysema).
- Knowing the FEV1, FVC, and FEV1/FVC arrows for obstructive vs restrictive lung diseases is mandatory to pass Step 1.

121. 25M + non-smoker + progressively worsening shortness of breath + chest x-ray shows bullous changes; dad died of alcoholic liver disease at age 45. What are the arrows (i.e., ↑, ↓, or ↔) for residual volume, arterial pO2, and A-a gradient?

- **↑ residual volume, ↓ arterial pO2, ↑ A-a gradient.**
- Diagnosis is α1-antitrypsin deficiency.
- Classically causes pan-acinar emphysema and cirrhosis of the liver.
- α1-antitrypsin is a protease produced in the liver that breaks down elastase in the lungs. Elastase destroys lung tissue. So if α1-antitrypsin is present, there's less elastase, and less destruction of lung tissue. In this disease (deficiency), we get emphysema due to lung destruction.
- "Bullous changes on chest x-ray" = emphysema on USMLE. Emphysema = obstructive lung disease.
- Codominant inheritance pattern. Vignettes might give sibling or parent also with lung or liver disease.
- Student says, "But dad died of *alcoholic* liver disease it says, so why is that genetic?" → implication is the father had one or more of the disease alleles, which caused greater susceptibility to accelerated liver disease in the setting of alcohol consumption. (I've seen this in NBME vignettes)
- Residual volume is increased in obstructive lung diseases and decreased in restrictive.
- Arterial pO2 is decreased in both obstructive and restrictive lung diseases.
- A-a gradient is increased in both obstructive and restrictive lung diseases, as well as in pulmonary edema.
- The key point to remember about A-a gradient is that it is normal (i.e., not elevated) in hypoventilation / ventilatory insufficiency → benzos, barbiturates, opioids → all cause respiratory depression.

122. Neonate born at 26 weeks' gestation + respiratory distress. What are the arrows (i.e., ↑, ↓, or ↔) for pulmonary compliance, pulmonary elastic recoil, pulmonary sphingomyelin, and lamellar body activity?

- **↓ pulmonary compliance, ↑ elastic recoil, ↑ sphingomyelin, ↓ lamellar body activity.**
- Diagnosis is neonatal respiratory distress syndrome (NRDS), caused by surfactant deficiency.
- Compliance = ability to expand.
- Elastic recoil = ability to collapse.
- Surfactant prevents alveolar collapse by providing a lipophilic lining to the alveolar sacs that decreases hydrostatic collapsing forces.
- If surfactant is low, then collapsing forces are greater. Therefore, elastic recoil is up.
- If collapsing forces are greater, then ability to expand is less. Therefore, compliance is down.
- The lecithin (dipalmitoyl phosphatidylcholine) : sphingomyelin ratio is high (i.e., >2.0-2.4) when fetal lungs have matured >36 weeks' gestation. In other words, a high ratio is good; a low ratio is bad.
- In NRDS, we expect lecithin (dipalmitoyl phosphatidylcholine) to be low and sphingomyelin to be up.
- Lamellar bodies are specialized organelles within type II pneumocytes that produce surfactant. Activity is reduced when the lungs have not yet matured. (I've seen this asked on retired Step 1 NBME)

123. 50M + long history of smoking + COPD. What are the arrows (i.e., ↑, ↓, or ↔) for mucous production, activity of airway cilia, and alveolar macrophage function?

- **↑ mucous production, ↓ activity of airway cilia, ↓ alveolar macrophage function.**
- In COPD, bronchiolar mucous production is increased (increased Reid index ratio).
- Cilia function of pseudostratified columnar epithelial cells of the airway is decreased. This is exceedingly HY for USMLE. Students might say, “Wait, but if there are more particulates in the lungs from smoking, wouldn’t cilia function be up to compensate cuz we’re clearing stuff out more?” → apparently particulates/smoking actually impair the cilia function. I’ve also seen NBME ask which cell in a smoker is most impaired, and the answer is “pseudostratified columnar epithelial cell” → implying the ciliated cell of the airways.
- Particulates/smoking impair alveolar macrophage function. Similar to the cilia scenario, a student might think there’s increased activity to compensate, but the macrophage function is damaged in the setting of ongoing particulate exposure.

124. 25F + goes for a 10-mile run + has not yet had anything to drink. What are the arrows (i.e., ↑, ↓, or ↔) for carotid sinus baroreceptor firing rate, vagus nerve firing rate, and sinoatrial sympathetic activity?

- **↓ Carotid sinus baroreceptor firing rate, ↓ vagus nerve firing rate, ↑ sinoatrial sympathetic activity.**
- The feedback loop for autoregulation is:
- Carotid sinus baroreceptors (sense blood pressure/volume) → afferent cranial nerve IX (glossopharyngeal) to solitary nucleus of the medulla → efferent CN X (vagus; parasympathetic) to cardiac nodal tissue → change in heart rate accordingly.
- Patient is dehydrated. The carotid sinus baroreceptor firing rate is *stretch-dependent*, meaning that if blood volume (or BP) is low, firing rate is *low, not high*. Students frequently get this wrong because they think that any change in pressure – high or low – "wakes up" the baroreceptors and they always fire more, but this is not the case. High BP = high firing rate; low BP or dehydration = low firing rate.
- If BP low → carotid sinus stretch low → CN IX activity low → CN X activity low → HR goes up.
- If BP high → carotid sinus stretch high → CN IX activity high → CN X activity high → HR goes down.
- If you have trouble with this, just remember that BP, CN IX, and CN X activity go the same direction.
- Sympathetic activity goes the opposite direction.
- If BP low → low CN IX firing rate → high sympathetic firing rate → HR goes up.
- The afferent CN IX / carotid sinus baroreceptor activity arrow being down, not up, in the setting of low BP, is exceedingly HY for USMLE. As I said, many students fuck that up.

125. 65M + orthopnea + paroxysmal nocturnal dyspnea. What are the arrows (i.e., ↑, ↓, or ↔) for pulmonary capillary hydrostatic pressure, alveolar interstitial hydrostatic pressure, and alveolar interstitial oncotic pressure?

- **↑ pulmonary capillary hydrostatic pressure, ↑ alveolar interstitial hydrostatic pressure, ↓ alveolar interstitial oncotic pressure.**
- The patient has left heart failure. The backup of pressure from the left heart causes increased pressure in the pulmonary circulation.
- Since left atrial pressure (LAP) is up, PCWP must be up. High PCWP means pulmonary capillary hydrostatic pressure is up.
- Hydrostatic pressure = fluid pressure (i.e., lots of fluid/volume in a compartment = higher pressure).
- Oncotic pressure = solute pressure (i.e., lots of solutes/proteins in a compartment = higher pressure).
- Hydrostatic pressure is an outward pressure (i.e., high hydrostatic pressure in a vessel → more fluid leaves vessel).
- Oncotic pressure is a retention pressure (i.e., high oncotic pressure in a vessel → fluid less likely to leave vessel).
- High PCWP = high pulmonary capillary hydrostatic pressure → fluid leaves pulmonary microvasculature for the alveolar spaces → pulmonary edema.
- Since we now have fluid in the alveolar spaces, alveolar interstitial hydrostatic pressure must now be higher (i.e., the mere presence of fluid there means there must be a greater hydrostatic pressure).
- This fluid that enters the alveolar spaces is transudate, not exudate. Transudate is relatively devoid of proteins, cells, and LDH, and is a result of differences in hydrostatic and oncotic pressures between fluid compartments. Exudate is high in proteins, cells, and LDH, and is the result of an inflammatory process.
- Since the fluid in the alveolar spaces is transudate, it is low in protein. So the oncotic pressure it exerts is low.
- This combination of arrows for this Q seems a bit unusual but is asked on the Step 1.

126. 28F + non-smoker + 6-month Hx of progressive shortness of breath + chest x-ray shows increased pulmonary vascular markings + dilated pulmonary artery; there is loud P2 on physical exam. What are the arrows (i.e., ↑, ↓, or ↔) for PCWP, endothelin-1, pulmonary vascular resistance, and systemic vascular resistance?

- **↔ PCWP, ↑ endothelin-1, ↑ pulmonary vascular resistance, ↔ systemic vascular resistance.**
- Diagnosis is primary pulmonary hypertension, usually caused by mutations in BMPR2.
- Vignette will usually be a female in her 20s-30s who's a non-smoker.
- Loud P2 means pulmonary hypertension on USMLE. The pulmonary valve is slamming shut because of increased pressure distal to it.
- PCWP is normal because the left heart is completely normal. PCWP = LAP. This question 100% tests whether you understand PCWP. PCWP is only high in left heart problems.
- Endothelin-1 is a potent vasoconstrictor. In pulmonary hypertension, endothelin-1 activity is increased and nitric oxide synthase activity is decreased. Bosentan is an endothelin-1 receptor antagonist used for pulmonary hypertension.
- Pulmonary vascular resistance is up because we have constriction of the pulmonary vessels due to increased endothelin-1.
- Systemic vascular resistance (i.e., of the peripheral arterioles) is unchanged because this condition only affects the lungs.

127. 55M + long history of systemic hypertension + chest x-ray shows pleural effusion and diffuse pulmonary infiltrates; ECG shows left bundle-branch block. If we are forced to pick high or low values, what are the arrows (i.e., ↑ or ↓) for pleural fluid LDH, pleural fluid protein, and pleural fluid glucose?

- **↓ Pleural fluid LDH, ↓ pleural fluid protein, ↑ glucose.**
- Patient has fluid in his lungs due to increased pressures in his left heart secondary to systemic hypertension.
- LBBB = left ventricular hypertrophy on USMLE.
- The fluid would be transudate because the cause is increased pulmonary capillary hydrostatic pressure.
- Pleural fluid:serum LDH ratio of <0.6 is consistent with transudate; >0.6 is exudate.
- Pleural fluid:serum protein ratio <0.5 is transudate; >0.5 is exudate.
- In other words, there's low LDH and protein in transudate.
- Low glucose in the pleural fluid signifies bacterial or fungal infection (i.e., glucose is being consumed by the organisms). In this case, we don't overtly suspect an infection, so if we are forced to choose between an up or down arrow, up makes more sense.
- On the USMLE, you will sometimes get columns of numbers in the answer choices, where you're forced to choose between, e.g., a 20 or 80 mg/dL for glucose. The 20 would be for exudative pleural effusion in the setting of pneumonia. 80 would be for transudate. The concept is: glucose of pleural fluid that "isn't too far away from" serum glucose is consistent with transudate.

128. 45F + type II diabetes mellitus + commenced on enalapril. As a result of this medication, what are the arrows (i.e., ↑, ↓, or ↔) for change in systemic vascular resistance, renal efferent arteriolar diameter, heart rate, and ejection fraction?

- **↓ Systemic vascular resistance, ↑ renal efferent arteriolar diameter, ↑ heart rate, ↑ ejection fraction.**
- Enalapril is an ACE inhibitor. Angiotensin II is a potent vasoconstrictor. ACEi will cause decreased vasoconstriction of peripheral arterioles, thereby decreasing blood pressure.
- AT II constricts the efferent arterioles. Therefore, giving an ACEi decreases this constrictive effect and increases diameter.
- Since systemic vascular resistance decreases, heart rate goes up to compensate via the baroreceptor reflex.
    - If we dilate arterioles → BP goes down → HR goes up to compensate.
    - If we constrict arterioles → BP goes up → HR goes down to compensate.
- Drugs like ACEi, ARBs (e.g., valsartan), dihydropyridine calcium channel blockers (e.g., nifedipine), $\alpha 1$ antagonists (e.g., prazosin), and hydralazine will increase arteriolar diameter → BP goes down → HR goes up to compensate.
- Drugs like $\alpha 1$ agonists (phenylephrine, oxymetazoline, midodrine) constrict arterioles → BP goes up → HR goes down to compensate.
- Ejection fraction goes up when arteriolar diameter increases because there's less afterload on the heart → easier for heart to pump. ACEi/ARBs are first-line for heart failure and increase ejection fraction.

129. 15M + jumps into cold lake. What are the arrows (i.e., ↑, ↓, or ↔) for change in central blood volume, atrial natriuretic peptide (ANP) secretion, and ADH release?

- **↑ Central blood volume, ↑ ANP secretion, ↓ ADH release.**
- If the kid jumps into cold water, he will experience increased peripheral vasoconstriction in order to conserve heat. This will increase central blood volume (i.e., blood returning to the heart).
- ANP is secreted by atrial myocytes in response to increased stretch. Since central blood volume is up, ANP is also up. ANP is an endogenous/natural diuretic, essentially.
- USMLE wants you to know ANP inhibits renin release and decreases renal retention of sodium.
- ANP is also responsible for "aldosterone escape," where high aldosterone levels ultimately result in higher blood volume, which in turn results in higher ANP levels, which in turn results in a blunted effect of aldosterone at the kidney by preventing sodium reabsorption (i.e., ANP is one of the negative feedback mechanisms keeping any type of runaway aldosterone effect in check).

130. Neonate + ventricular septal defect (VSD) + has VSD repaired with a prosthetic patch. What are the arrows (i.e., ↑, ↓, or ↔) for the change in left ventricular pressure, right ventricular pressure, and left atrial pressure as a result of this repair?

- **↑ Left ventricular pressure, ↓ right ventricular pressure, ↓ left atrial pressure.**
- When a VSD is repaired, less blood is leaving the left ventricle for the right ventricle, so left ventricular pressure increases and right ventricular pressure decreases.
- Since less blood enters the right ventricle, less blood will be returned through the lungs back to the left atrium, thereby decreasing left atrial preload and pressure.
- This combo of arrows is on the NBME for Step 1, both on offline and online forms (i.e., the Q is repeated).

131. 15F + asymptomatic + cardiac auscultation reveals fixed splitting of the S2 heart sound. Compared to normal values, what are the arrows (i.e., ↑, ↓, or ↔) for superior vena cava pO2, right atrial pO2, right ventricular pO2, and pulmonary artery pO2?

- **↔ Superior vena cava pO2, ↑ right atrial pO2, ↑ right ventricular pO2, ↑ pulmonary artery pO2.**
- Diagnosis is atrial septal defect (ASD).
- Since the defect is between the atria, and pressures are greater on the left side of the heart than the right, oxygenated blood from the LA will move into the RA, thereby increasing the RA chamber pO2 compared to normal. This higher pO2 will carry through to the RV and then to the pulmonary arteries.
- Vena cava pO2 is unchanged because the SVC and IVC are prior to the defect.
- The USMLE usually gives this type of Q in the reverse direction – i.e., they'll list a bunch of chamber oxygen values and expect you to be able to infer the type of defect (i.e., ASD or VSD).

132. 4M + holosystolic murmur at the lower left sternal border. A ventricular septal defect (VSD) and left atrial dilatation are seen on echo. Compared to normal values, what are the arrows (i.e., ↑, ↓, or ↔) for superior vena cava pO2, right atrial pO2, right ventricular pO2, left ventricular pO2, and pulmonary artery pO2?

- **↔ Superior vena cava pO2, ↔ right atrial pO2, ↑ right ventricular pO2, ↔ left ventricular pO2, ↑ pulmonary artery pO2.**
- The diagnosis is VSD. It is classically described as a holosystolic murmur at the lower left sternal border.
- The left-to-right shunt causes increased preload in the right ventricle, leading to increased circulation back through the lungs to the left atrium, causing left atrial dilatation in some patients. I have seen this on NBME.
- The vena cava and RA pO2 are normal because they are proximal to the defect.
- Left ventricular pO2 is normal because blood is only moving left to right from high → low pressure.

133. 24M + healthy + changes position from supine to standing up. What are the arrows (i.e., ↑, ↓, or ↔) for the change in venous return, carotid sinus baroreceptor activity, and cerebral blood flow?

- **↓ Venous return, ↓ carotid sinus baroreceptor activity, ↓ cerebral blood flow.**
- Moving from supine to standing / sitting up decreases venous return (due to increased venous pooling).
- This means less central blood volume and less cardiac output.
- Less cardiac output means less carotid sinus baroreceptor firing rate (i.e., less CN IX afferent firing).
- Remember that the carotid sinus baroreceptor firing rate is *stretch-dependent*. If volume/BP is low, firing rate is low, not high. Likewise, if volume/BP is high, firing rate is high.
- Cerebral blood flow is lower because cardiac output is lower.

134. 50M + commenced on propranolol. What are the arrows (i.e., ↑, ↓, or ↔) for change in left ventricular end-diastolic volume, cardiac output, and systemic vascular resistance?

- ↑ **Left ventricular end-diastolic volume,** ↓ **cardiac output,** ↑ **systemic vascular resistance.**
- Propranolol is a non-specific beta-blocker at both β1 and β2 receptors.
- β1 blockade results in lower heart rate (chronotropy) and contractility (inotropy).
- The slower the heart rate, the greater the fraction of the cardiac cycle is spent in diastole relative to systole. Since the heart fills during diastole, if the heart rate is slower, end-ventricular diastolic volume is greater.
- A student might say, "Wait, but if beta-blockers increase preload, then how could they possibly decrease oxygen demand, cuz doesn't higher preload mean higher oxygen demand on myocardium?" → we have a net decrease in oxygen demand because the effect of the reduced chronotropy and inotropy outweigh the increase in preload.
- Cardiac output is lower because heart rate and contractility are lower.
- β2 agonism causes peripheral arteriolar dilation (i.e., reduces systemic vascular resistance). Therefore, β2 antagonism causes less peripheral vasodilation and greater resistance.
- Even if you didn't know the above point about β2, another way to think of it is: if cardiac output decreases due to beta-blockade, then we would theoretically want increased peripheral vasoconstriction to compensate (i.e., if we have lower cardiac output, then we want more resistance to maintain BP).

135. 55M + commenced on nitrates for his ischemic heart disease. Following administration, what are the arrows (i.e., ↑, ↓, or ↔) for change in venous return, heart rate, and cardiac output?

- **↓ Venous return, ↑ heart rate, ↓ cardiac output.**
- Nitrates cause venodilation, leading to venous pooling and decreased venous return.
- This causes decreased cardiac output.
- Lower cardiac output → decreased stretch of carotid sinus baroreceptors → decreased afferent CN IX firing rate → decreased efferent CN X firing rate → increase in heart rate.
- Remember that CN X (Vagus nerve) is parasympathetic. If we decrease parasympathetic activity on the heart, then heart rate goes up. In addition, sympathetic firing would increase to the heart as a result of lower cardiac output.
- Even though heart rate increases (which should theoretically increase oxygen demand on myocardium), the reduction in preload outweighs this.

136. 42F + commenced on nifedipine. What are the arrows (i.e., ↑, ↓, or ↔) for change in systemic vascular resistance, heart rate, and left ventricular ejection fraction?

- **↓ Systemic vascular resistance, ↑ heart rate, ↑ left ventricular ejection fraction.**
- In contrast to nitrates, which dilate veins, nifedipine, a dihydropyridine calcium channel blocker, dilates peripheral arterioles.
- Dilation of arterioles will decrease systemic vascular resistance.
- This leads to decreased blood pressure proximally in the aorta, thereby causing less carotid sinus baroreceptor stretch, less CN IX afferent firing, less CN X efferent firing → heart rate goes up.
- Ejection fraction goes up because afterload is decreased (i.e., the heart can pump more easily if there's less resistance in the arterioles to pump against).
- ACE inhibitors (e.g., enalapril), ARBs (e.g., valsartan), $\alpha 1$ blockers (e.g., prazosin), and hydralazine will have the same arrows.

137. 67M + shortness of breath on exertion + dilated cardiac silhouette on chest x-ray + S3 heart sound. What are the arrows (i.e., ↑, ↓, or ↔) for left ventricular ejection fraction, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume?

- **↓ LV ejection fraction, ↑ LV end-diastolic pressure, ↑ LV end-diastolic volume.**
- The patient has dilated cardiomyopathy and systolic dysfunction.
- S3 = dilated left ventricle = volume overload (preload) = systolic dysfunction (i.e., the heart cannot pump/contract properly).
- S3 can rarely be seen physiologically in high-endurance athletes and pregnancy.
- Volume overload causes an increase in LV pressure.
- USMLE wants you to memorize above arrows as “systolic dysfunction.”

138. 65F + Hx of hypertension + JVD + peripheral edema + S4 heart sound. What are the arrows (i.e., ↑, ↓, or ↔) for left ventricular ejection fraction, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume?

- **↔ LV ejection fraction, ↑ LV end-diastolic pressure, ↔ LV end-diastolic volume.**
- The patient has hypertrophic cardiomyopathy and diastolic dysfunction.
- S4 = stiff left ventricle = pressure overload (afterload) = diastolic dysfunction (i.e., the heart cannot expand properly).
- Student might immediately say, "Wait, if the heart can't expand, why is LV volume normal then? Shouldn't volume be low?" → in diastolic dysfunction, the LV can achieve normal volume; *it just merely requires more pressure to get there.*
- Highest yield point is that ejection fraction is not reduced. This is really important.
- In summary (comparing systolic vs diastolic dysfunction):
    - S3 = dilated LV = volume overload (preload) = systolic dysfunction = dilated cardiomyopathy.
        - **↓ LV ejection fraction, ↑ LV end-diastolic pressure, ↑ LV end-diastolic volume.**
    - S4 = stiff LV = pressure overload (afterload) = diastolic dysfunction = restrictive + hypertrophic cardiomyopathies.
        - **↔ LV ejection fraction, ↑ LV end-diastolic pressure, ↔ LV end-diastolic volume.**
- I should make note that I've seen right-sided S4s in 2CK IM Qs due to either pulmonary hypertension or severe mitral stenosis that backs up all the way to the right heart. So just be aware S4 isn't always left ventricular.

139. 67M + crushing central chest pain + ST-segment elevations in anterior leads + BP 85/50. What are the arrows (i.e., ↑ or ↓) for CO2, pH, $HCO3^-$, systemic vascular resistance, PCWP, and cardiac output?

- **↓ CO2, ↓ pH, ↓ $HCO3^-$, ↑ systemic vascular resistance, ↑ PCWP, ↓ cardiac output.**
- The question here forces you to choose an acid-base disturbance in the setting of an acute myocardial infarction where BP is low (cardiogenic shock).
- USMLE wants you to know that in any type of shock (i.e., cardiogenic, septic, hypovolemic), lactic acidosis can occur secondary to increased peripheral anaerobic glycolysis.
- If tissues aren't being perfused as well as they should be, then they are not being oxygenated as well as they should be → increased anaerobic respiration + lactate production → lactic acidosis + reduced serum bicarbonate.
- CO2 is blown off to compensate.
- I have also seen Qs where bicarb is low in severe pulmonary embolism and dehydration.
- I talked about earlier how PE should be acute respiratory alkalosis. However, I have seen one 2CK-level Q where they gave low pH in PE + a low CO2 → only way that's possible is if bicarb is low due to lactic acidosis. In theory, this would be a mixed metabolic acidosis-respiratory alkalosis.
- This concept of lactic acidosis in the setting of shock is exceedingly HY for USMLE.
- Since cardiac output is because the heart can't pump, we expect systemic vascular resistance to go up to compensate.
- PCWP is high in pretty much any MI because the left heart would be involved. Although not impossible, it is very rare to have isolated right heart MIs.

140. 15F + stung by a bee + BP 80/40 + RR 30 + HR 120. What are the arrows (i.e., ↑ or ↓) for cardiac output, systemic vascular resistance, and pulmonary capillary wedge pressure?

- **↑ cardiac output, ↓ systemic vascular resistance, ↓ PCWP.**
- Diagnosis is anaphylactic shock, a type I hypersensitivity response.
- What I've seen in NBME Qs is: they want IgE crosslinking on surface of mast cells and basophils → causes release of histamine + prostaglandin → causes the recruitment of eosinophils secondarily.
- Histamine + prostaglandin are vasodilators → decrease SVR → low BP.
- Cardiac output is increased because venous return is high. Even though there may be some swelling in patients with anaphylaxis, fluid for the most part has not left the vessels. Blood pressure is low because SVR is low, but the blood is still being returned venously to the heart. This, combined with high heart rate, contributes to overall high cardiac output. The literature/Google will frequently mention how cardiac output is decreased in anaphylaxis, but this is wrong on USMLE.
- PCWP = left atrial pressure. **This may be low or normal,** but often the USMLE will force you to choose an up or down arrow for shock questions. The important point to know is that PCWP will simply just not be high. Whether it's low or normal doesn't really matter because it can vary depending on the question. PCWP is only high in cardiogenic shock (e.g., from an MI) or left heart pathologies.
- **Important point:**
- If the USMLE Q gives you the CO, SVR, PCWP variables in the vignette and then wants you to pick the diagnosis, pretty much the first thing I always look at is PCWP. If it's high, you know right away they want cardiogenic shock (i.e, the heart can't pump). If it's not high (doesn't matter whether it's low or normal), you can say, "Ok, cool, not cardiogenic shock." (But you have to look at other variables still in order to diagnose)
- It is to my observation with students over years of tutoring that not understanding PCWP is the most common reason people get shock Qs wrong. That's why I'm really reinforcing PCWP in this PDF.

141. 34F + worsening skin infection + fever 103 F + BP 80/40 + HR 120. What are the arrows (i.e., ↑ or ↓) for cardiac output, systemic vascular resistance, and pulmonary capillary wedge pressure?

- **↑ cardiac output, ↓ systemic vascular resistance, ↓ PCWP.**
- Diagnosis is septic shock.
- Systemic vascular resistance is decreased due to TNFα-mediated peripheral vasodilation.
- Fever is due to interleukin-1.
- PCWP can be low or normal. The point to know is simply that it's not high because we don't have cardiogenic shock (i.e., the left heart can pump fine).
- Cardiac output is high because venous return is high. What goes in is what comes out.
- The arrows for septic shock and anaphylactic shock are the same.
- Some pedantic students will say, "Well what about early vs late septic shock, etc." My advice is to relax. USMLE just wants above arrows for septic shock.

142. 22M + bleeding from gunshot wound + drowsy. What are the arrows (i.e., ↑ or ↓) for cardiac output, systemic vascular resistance, and pulmonary capillary wedge pressure?

- **↓ cardiac output, ↑ systemic vascular resistance, ↓ PCWP.**
- Diagnosis is hypovolemic shock.
- Loss of blood volume → low cardiac output → decreased stretch of carotid sinus baroreceptors → decreased CN IX (glossopharyngeal) firing → decreased efferent CN X (vagus; parasympathetic) firing + increased sympathetic nerve firing → increased heart rate to compensate.
- Systemic vascular resistance is high because of norepinephrine + epinephrine binding to $\alpha 1$ receptors on peripheral arterioles → vasoconstriction → higher systemic resistance as compensation for low cardiac output.
- PCWP is low because blood volume is low. I have seen an NBME Q where PCWP is in the normal range for hypovolemic shock. The point is simply just that it's not high.

143. 9M + viral infection + low blood pressure + HR 120 + chest x-ray shows enlarged heart and hazy lung fields + red urine. What are the arrows (i.e., ↑ or ↓) for cardiac output, systemic vascular resistance, and pulmonary capillary wedge pressure?

- **↓ cardiac output, ↑ systemic vascular resistance, ↑ PCWP.**
- Diagnosis is cardiogenic shock secondary to dilated cardiomyopathy due to coxsackie B virus.
- I'm being an asshole by really reinforcing PCWP in relation to shock here.
- Patient also has IgA nephropathy (red urine 1-2 days post viral infection), but this is unrelated to the cardiogenic shock. There's an offline NBME Q with both of these combined in the presentation.
- In cardiogenic shock, heart rate can be low, normal, or high. I've seen Qs with it all over the place. HR in and of itself doesn't mean jack shit in terms of pump function. You can have a patient who's just had an MI who has a HR of 120, but the ejection fraction is through the floor.
- Cardiac output is low because the heart is not able to pump properly.
- Systemic vascular resistance is high in order to compensate for the low cardiac output. This will help maintain pressure proximally.
- PCWP is high because the left heart cannot pump, so left atrial afterload is increased.
- **Increased PCWP is the hallmark of cardiogenic shock. You must know this detail.**
- JVD and increased central venous pressure are also seen in cardiogenic shock (i.e., decreased right heart filling).

144. 12M + viral infection one week ago + now has nosebleeds. What are the arrows (i.e., ↑, ↓, or ↔) for bleeding time, prothrombin time (PT), and activated partial thromboplastin time (aPTT)?

- **↑ bleeding time, ↔ PT, ↔ aPTT.**
- Diagnosis is idiopathic (immune) thrombocytopenic purpura (ITP).
- Mechanism is viral infection causing autoantibodies against glycoproteins IIb/IIIa on platelets, thereby disrupting platelet aggregation (i.e., platelets binding to each other). Do not confuse this with Gp Ib, which mediates platelet adhesion to endothelium.
- Bleeding time = platelet function.
- PT and aPTT = clotting factor function.
- PT = extrinsic pathway (starts with factors III and VII); aPTT = intrinsic pathway (starts with factor XII).
- Bleeding time is high because platelets get fucked up here.
- PT and aPTT are completely normal because clotting factors have no relation here.
- ITP will present as either a school age kid with viral infection or as random bruising in a woman 30s-40s with an increased bleeding time and low platelet count.
- 2CK Family Med Qs like to mix ITP Qs with domestic abuse:
    - 34F + random bruising + high bleeding time = ITP.
    - 34F + random bruising + normal bleeding time = domestic abuse.
- If you are forced to choose between high bleeding time and low platelet count for diagnostic purposes, choose low platelet count.
- Treat with steroids, then IVIG, then splenectomy, in that order.
- Some Qbank Qs floating around with “no Tx necessary” for mild cutaneous findings in peds, or straight to IVIG over steroids for ultra-low platelet count, are wrong fucking answers on USMLE.

145. 10M + blood in his knee joint after playing soccer at recess + has maternal uncle who died early in life after mild head trauma. What are the arrows (i.e., ↑, ↓, or ↔) for bleeding time, PT, and aPTT?

- **↔ bleeding time, ↔ PT, ↑ aPTT.**
- Diagnosis is hemophilia A or B. Both are X-linked recessive.
- Hemarthrosis in school-age boy = textbook vignette for hemophilia.
- Hemophilia A (factor VIII deficiency) is more common than B (factor IX deficiency).
- aPTT is elevated because factors VIII and IX are only in the intrinsic pathway.
- PT and bleeding time are always normal in hemophilia.
- IV desmopressin (DDAVP) can be used as Tx for hemophilia A only (increases production of factor VIII).
- If Q tells you a patient with hemophilia A or B becomes gradually non-responsive to factor replacement, the mechanism is production of antibodies against factor VIII or IX, respectively. That is, factor replacements can gradually induce the production of antibodies that make the treatments less effective with time.

146. 17F + history of nosebleeds + routinely has heavy menses with clots + normal aPTT; dad also has history of nosebleeds. What are the arrows (i.e., ↑, ↓, or ↔) for bleeding time, PT, and platelet count.

- **↑ Bleeding time, ↔ PT, ↔ platelet count.**
- Before you freak out about aPTT, relax, I'll explain.
- Diagnosis is von Willebrand disease (vWD), an autosomal dominant condition.
- vWF normally bridges glycoprotein Ib on platelets to vascular endothelium / underlying collagen (i.e., it acts as a bridging agent that enables platelet adhesion).
- Vignettes will almost always give a presentation that entails a mix of one clotting factor problem (i.e., heavy menses, excessive bleeding after tooth extraction) and one platelet problem (i.e., usually mild, cutaneous findings such as petechiae, or epistaxis).
- Because platelet function is fucked up, we know bleeding time is high.
- vWF has a secondary role where it helps stabilize factor VIII in plasma. Therefore, we sometimes get elevated aPTT in the condition. But it need not be elevated.
- **It is to my observation that ~50% of vWD Qs on NBME will have normal aPTT; the other ~50% will have elevated aPTT.**
- The stabilization of factor VIII by vWF is not its primary role; it's a mere secondary/auxiliary role. So it makes sense that aPTT is not always elevated.
- Where students run into problems is when they get a vWD Q that shows aPTT is normal, and then they say, "Ok, well it can't be vWD because we'd have high aPTT also." → No. aPTT is normal in about half of vWD Qs. You need to know that.
- Platelet count is normal in vWD.
- IV desmopressin (DDAVP) can be used as Tx.

147. 29F + recently treated for leukemia; cytogenic studies show a t(15;17) translocation; patient has bleeding/oozing from IV and catheter sites. What are the arrows (i.e., ↑, ↓, or ↔) for bleeding time, PT, and aPTT?

- **↑ bleeding time, ↑ PT, ↑ aPTT.**
- Diagnosis is disseminated intravascular coagulation (DIC) caused by treatment of acute promyelocytic leukemia (APL; aka AML type M3). Release of Auer rods (composed of myeloperoxidase) into circulation can precipitate DIC.
- Etiologies for DIC are multifarious, but common causes are sepsis, trauma, treatment of APL, and amniotic fluid embolism. Condition is characterized by runaway consumption of platelets and clotting factors.
- Bleeding time is increased because platelets are consumed.
- PT and aPTT are high because clotting factors are consumed.
- Schistocytes are frequently seen on blood smear in DIC.
- I should make a point that students will memorize “bleeding from IV/catheter sites” as automatically = DIC no matter what. However, on one of the 2CK surgery forms, they give a Q where a guy receives 20-odd packs of RBCs during a surgery in which he lost a lot of blood, then had bleeding from IV/catheter sites. They ask for diagnosis, but DIC isn’t listed. Answer = thrombocytopenia. So you should be peripherally aware that packed RBCs don’t contain platelets, and patients receiving many transfusions can get dilutional thrombocytopenia.

148. 30F + just delivered newborn baby at term; 30 seconds after delivery of the placenta, she has shortness of breath and tachycardia. There is bleeding observed from IV sites. What are the arrows (i.e., ↑, ↓, or ↔) for platelet count, serum fibrinogen, serum plasmin activity, and serum D-dimer?

- **↓ Platelet count, ↓ serum fibrinogen, ↑ serum plasmin activity, ↑ serum D-dimer.**
- Diagnosis is DIC secondary to amniotic fluid embolism.
- Platelets and clotting factors are consumed and are low.
- The clotting cascade ultimately results in the synthesis of fibrin from fibrinogen. Since more fibrinogen is converted to fibrin, fibrinogen is down.
- Since there is more fibrin being produced, more fibrin is also being broken down. D-dimer is just another way of saying “fibrin degradation products.”
- Fibrin is broken down by an enzyme called plasmin. Therefore, plasmin activity is increased.
- In summary for DIC:
- **↑ bleeding time, ↑ PT, ↑ aPTT.**
- **↓ Platelet count, ↓ serum fibrinogen, ↑ serum plasmin activity, ↑ serum D-dimer.**

149. Neonate + born at home + bleeding from umbilical stump. What are the arrows (i.e., ↑, ↓, or ↔) for bleeding time, PT, and aPTT?

- **↔ Bleeding time, ↑ PT, ↑ aPTT.**
- Diagnosis is vitamin K deficiency. Bleeding from the umbilical stump in a neonate is the most common presentation for it on Step.
- Vignette can also be patient on broad-spectrum antibiotics for many weeks (kills off gut flora that synthesize vitamin K).
- Vitamin K activates clotting factors II, VII, IX, and X (and anti-clotting proteins C and S).
- Since many clotting factors are fucked up, we have high PT and aPTT.
- Since platelets are completely normal / are unaffected, bleeding time is normal. Clotting factors have nothing to do with bleeding time.

150. 40M with chronic renal failure + high BUN + high creatinine + 2-week history of nosebleeds. What are the arrows (i.e., ↑, ↓, or ↔) for platelet count, bleeding time, PT, and aPTT?

- **↔ Platelet count, ↑ bleeding time, ↔ PT, ↔ aPTT.**
- Diagnosis is uremic platelet dysfunction. USMLE may also write it as “acquired platelet dysfunction.”
- For whatever reason, high BUN causes platelets to not work, leading to a **qualitative, not quantitative,** platelet problem.
- Students are always like, “Oh wow platelets are normal holy shit.” I know. Incredible.
- Bleeding time is high because we have a platelet problem.
- PT and aPTT are normal because this condition has nothing to do with clotting factors.
- Patients with uremia need hemodialysis prior to any type of surgery to prevent excessive bleeding.

151. 33F + G1P0 + 30 weeks' gestation + BP 150/95 + protein in urine + schistocytes seen on blood smear.

What are the arrows (i.e., ↑, ↓, or ↔) for platelet count, hematocrit, and liver enzymes?

- **↓ platelet count, ↓ hematocrit, ↑ liver enzymes.**
- Diagnosis is preeclampsia that has progressed to HELLP syndrome.
- On USMLE, preeclampsia = proteinuria and hypertension after 20 weeks of pregnancy. I say “on USMLE,” because in real life, the definition is a bit expanded.
- If we add seizures, we call it eclampsia.
- HELLP syndrome = Hemolysis, Elevated Liver enzymes, Low Platelet count.
- **Schistocytes** are seen on blood smear.
- Hemolysis means our hematocrit drops.
- Liver enzymes (i.e., ALT, AST) are elevated because of fibrin deposits in the hepatic sinusoids that obstruct hepatic blood flow.

152. 30F + normal menstrual periods without excessive bleeding + smear shows pale RBCs. What are the arrows (i.e., ↑, ↓, or ↔) for mean corpuscular volume (MCV), hematocrit, serum iron, serum ferritin, transferrin saturation, and red cell distribution width (RDW)?

- **↓ MCV, ↓ hematocrit, ↓ serum iron, ↓ serum ferritin, ↓ transferrin saturation, ↑ RDW.**
- Diagnosis is iron deficiency anemia (IDA). IDA is common in young women due to their menses, even if they're not heavy. I've seen 2CK FM Qs where they specifically say a woman's menses are normal/not heavy + pale RBCs on smear, then the answer is IDA.
- MCV, hematocrit, serum iron, and serum ferritin are all low simply because iron availability is low.
- Ferritin is a storage form of iron that is the most sensitive indicator of iron status. For instance, if serum iron is low but ferritin is normal, the patient does not have iron deficiency (this pattern is consistent with anemia of chronic disease).
- Transferrin is the carrier molecule for iron. Saturation of transferrin is low in IDA since transferrin levels are high (the body is trying hard to transport more iron when levels are low). In addition, the binding sites for iron on the transferrin are sparsely occupied.
- Red cell distribution width (RDW) refers to the spectrum/range of RBC sizes. If we have a wide range of sizes, RDW is up. If we have a narrow range of sizes, RDW is down.
- **RDW is high in IDA.** Low iron in the bone marrow results in a non-uniformity of production of some microcytic RBCs as well as normocytic ones.
- RDW is low or low-normal in thalassemia, since defective hemoglobin chain production results in RBCs that are more uniformly small.
- RDW is one of the most underrated parameters on USMLE Qs for heme. That is, it shows up a lot, but students don't normally think of it, nor have they often heard of it.

153. 8F + recurrent episodes of joint pains + high ESR + salmon pink body rash. What are the arrows (i.e., ↑, ↓, or ↔) for MCV, hematocrit, serum iron, serum ferritin, and serum transferrin?

- **↔ MCV, ↓ hematocrit, ↓ serum iron, ↔ serum ferritin, ↓ serum transferrin.**
- Diagnosis is juvenile rheumatoid arthritis (JRA). This condition is hugely HY for 2CK peds in particular.
- Anemia of chronic disease (AoCD) shows up a lot in JRA Qs.
- It is very important I explicate that whilst AoCD is classically described as being normal MCV, I have seen at least two 2CK peds NBME Qs where MCV is down. The biggest piece of value I can provide you regarding AoCD is that MCV can absolutely be down. Do not exclude the diagnosis because the MCV is low.
- Patients do not have iron deficiency. This is why ferritin is normal. Recall that we said ferritin is the most sensitive indicator of iron status. Inflammation merely results in lesser ability to incorporate iron into heme, so there's less iron that ends up in the blood, essentially.
- Serum transferrin is low because it is suppressed by the inflammatory process. Transferrin saturation can be low-normal, normal, or high. This is why I didn't make transferrin *saturation* an arrow. I have seen NBME Qs where the diagnosis is AoCD and the transferrin saturation is on the lower end of normal.
- The key point for USMLE is that you're able to look at a vignette where a patient has an autoimmune disease (e.g., SLE, RA, IBD, etc.), chronic infection (i.e., hepatitis B or C), or chronic renal failure, and then have AoCD as a DDx in your mind if hemoglobin/hematocrit is low.
- Erythropoietin (EPO) is the Tx for AoCD if chronic renal failure is the etiology. If the etiology is not renal failure, do not pick EPO. Any other etiology of AoCD, the answer is treat the underlying cause.

154. 22F + G1P0 + 8 weeks' gestation + α-thalassemia confirmed by hemoglobin electrophoresis. What are the arrows (i.e., $\uparrow$, $\downarrow$, or $\leftrightarrow$) for MCV, hematocrit, serum iron, serum ferritin, and RDW?

- **↓ MCV, ↓ hematocrit, ↔ serum iron, ↔ serum ferritin, ↔ RDW.**
- Thalassemia is when one of the hemoglobin chains (i.e., α or β) isn't synthesized properly, so your hemoglobin is structurally abnormal.
- Thalassemia is the answer on USMLE (α- or β-; it doesn't matter) when the patient has low MCV and low hematocrit **but a normal serum iron and ferritin** (i.e., a microcytic anemia despite normal iron studies).
- 2CK obgyn Qs in particular obsess over this. They will tell you a woman in early pregnancy had initial bloods done that showed microcytic anemia (i.e., low MVC and low Hb). Then after three weeks on iron supplementation, her MCV and hemoglobin are still low ***despite*** normal iron and ferritin levels. The answer is then "hemoglobin electrophoresis" to diagnose thalassemia.
- RDW can be normal or low. I've seen both. The key point is that it's simply just not high. Because if it's high, then that's IDA.

155. 30F + constantly feels restless in bed at night and moves legs before falling to sleep. What are the arrows (i.e., ↑ or ↓) for MCV, hematocrit, and CNS dopamine transmission?

- **↓ MCV, ↓ hematocrit, ↓ CNS dopamine transmission.**
- Diagnosis is restless leg syndrome. USMLE wants you to know the most common cause is iron deficiency anemia.
- Check the patient's iron and ferritin. If the patient does not have IDA, the mechanism is classically related to impaired dopamine transmission.
- Treatment is iron if IDA is the cause. If IDA not the cause, give a D2 receptor agonist such as pramipexole or ropinirole.
- Bromocriptine could in theory be used, but I've seen this one more for prolactinoma Qs, whereas pramipexole and ropinirole show up for restless leg syndrome Tx.
- USMLE also wants you to know that patients have increased risk of developing Parkinson disease, even if low iron is the etiology. This makes sense, since D2 agonists are treatment, and Parkinson disease is characterized by loss of dopamine-secreting neurons.

156. 22F + iron deficiency anemia. Compared to individuals without IDA, what are the arrows (i.e., ↑, ↓, or ↔) for arterial pO2, hemoglobin saturation, and arterial O2 content?

- **↔ Arterial pO2, ↔ hemoglobin saturation, ↓ arterial O2 content.**
- NBME loves this Q. It's repeated across forms.
- Arterial O2 content = oxygen dissolved in the blood (pO2) + oxygen bound to hemoglobin (Hb-O2).
- The pathway for oxygen entering the body is: Inhaled into lungs → moves through capillary walls of alveoli → dissolves in blood as pO2 → hops onto hemoglobin as Hb-O2.
- In iron deficiency anemia, there is simply low hemoglobin. There is absolutely nothing wrong with the ability of the lungs to conduct gas exchange, so arterial pO2 is normal.
- Since pO2 is normal, the dissolved oxygen hops onto the available hemoglobin, so hemoglobin saturation is normal. Just because hemoglobin is low due to anemia doesn't mean there is any impairment in the ability of hemoglobin to bind oxygen.
- Since we have less hemoglobin, even though hemoglobin saturation is normal, the total quantity of oxygen bound to hemoglobin is therefore decreased. This is why arterial oxygen content is low.
- Some students might say, "Well if we have the same oxygen making its way into the blood but we have less hemoglobin, wouldn't the available hemoglobin have increased saturation then?" → hemoglobin saturation is not increased because Hb is already maximally saturated in the absence of anemia in healthy patients, so it won't go up anymore.

157. 21F + stressed studying for med school exams + two-day history of yellow eyes + no other symptoms + has had a few episodes like this before. What are the arrows (i.e., ↑, ↓, or ↔) for hematocrit, indirect bilirubin, direct bilirubin, and total bilirubin?

- **↔ Hematocrit, ↑ indirect bilirubin, ↔ direct bilirubin, ↑ total bilirubin.**
- Diagnosis is Gilbert syndrome (pronounced Jeel-BEAR).
- Mechanism is decreased uptake enzyme at the liver for bilirubin (UDP-glucuronosyltransferase).
- Benign condition. No treatment necessary.
- Indirect (unconjugated) bilirubin = not water-soluble; type of bilirubin that exists after RBCs are broken down in the spleen, but before the bilirubin arrives at the liver.
- Direct (conjugated) bilirubin = water-soluble; the type of bilirubin that exists after it is taken up by the liver and secreted into bile.
- Indirect bilirubin is high in hemolysis (i.e., hemolytic anemia, spherocytosis, G6PD deficiency), sickle cell, and Gilbert syndrome.
- Direct bilirubin is high if we have post-hepatic obstruction (i.e., choledocholithiasis, head of pancreas cancer impinging on common bile duct, biliary atresia), autoimmune disease (primary sclerosing cholangitis, primary biliary cirrhosis).
- Some conditions can present with either conjugated or unconjugated (i.e., cirrhosis, hepatitis).
- In Gilbert, hematocrit is normal because this condition has nothing to do with hemolysis or RBC turnover.
- Indirect bilirubin is high because the liver cannot take up the bilirubin.
- Direct bilirubin is normal because there is no post- or intra-hepatic obstruction.
- Total bilirubin is increased because indirect bilirubin is high. Total bilirubin, in and of itself, does not tell us anything about etiology. We want to know whether a patient has high direct or indirect bilirubin.

158. 57F + jaundiced + pale stools + dark urine + had cholecystectomy performed one week ago + intraoperative cholangiography was not performed. What are the arrows (i.e., ↑, ↓, or ↔) for hematocrit, indirect bilirubin, direct bilirubin, and total bilirubin?

- **↔ Hematocrit, ↔ indirect bilirubin, ↑ direct bilirubin, ↑ total bilirubin.**
- Diagnosis is choledocholithiasis (stone in the biliary tree).
- Do not confuse this with cholelithiasis, which is a stone in the gall bladder.
- One of the vignettes USMLE will give is someone with recent cholecystectomy. The implication is there may have been a retained stone in the cystic duct that descended into the common bile duct post-operatively. The question need not mention intraoperative cholangiography was not performed.
- Because we have a post-hepatic biliary obstruction, direct bilirubin is high.
- Since less bilirubin can make its way into the small bowel, and then ultimately into the stool, stools can be pale or whiteish in appearance (known as acholic stools).
- The direct bilirubin, since it is water-soluble, can make its way into the urine (dark urine).
- Indirect bilirubin is normal because we have no problem with uptake, nor do we have increased breakdown of RBCs. A blockage after the liver can sometimes lead to increases in indirect bilirubin, but the classic USMLE picture for obstruction is high direct with normal indirect.
- Total bilirubin is high because the direct bilirubin is elevated.

159. 10M + recently took dapsone + yellow eyes. What are the arrows (i.e., ↑, ↓, or ↔) for hematocrit, indirect bilirubin, direct bilirubin, and total bilirubin?

- **↓ Hematocrit, ↑ indirect bilirubin, ↔ direct bilirubin, ↑ total bilirubin.**
- Diagnosis is G6PD deficiency. Hemolysis can be precipitated by drugs such as dapsone and primaquine, as well as by fava beans.
- In G6PD deficiency, there is less NADPH production, so RBCs are more prone to oxidative stress.
- Since we have increased RBC breakdown and turnover, more indirect bilirubin will be produced, thereby also increasing total bilirubin.
- Direct bilirubin may be normal or slightly increased. The liver has a high capacity to handle increased indirect bilirubin arriving for uptake. If you get a Q where the focus is hemolysis, you will see that the increase in bilirubin is predominantly indirect, with no change, or a very marginal increase, in direct bilirubin.

160. 20M + eats large turkey dinner. What are the arrows (i.e., ↑ or ↓) for activity of glycogen phosphorylase, glucokinase, phosphoenolpyruvate (PEP) carboxykinase, and pyruvate carboxylase?

- **↓ Glycogen phosphorylase, ↑ glucokinase, ↓ PEP carboxykinase, ↓ pyruvate carboxylase.**
- If you immediately are freaking out about biochemistry stuff, don't. I don't want you to obsess over the pathways, etc. As long as you memorize the arrows I write out, you're good. You can know jack shit otherwise. Just know the arrows. → "Michael, that sounds fucking great." "I know."
- The first thing we have to ask is: is he in the fed or fasting state → he's in the fed state.
- Then we ask, "Ok, well do we expect each enzyme to be active or inactive in the fed state?"
- Glycogen phosphorylase *breaks down* glycogen. Glycogen synthase builds it up. In the fed state, we'd have glycogenesis, not glycogenolysis, so glycogen phosphorylase would be decreased in activity.
- Glucokinase is the hexokinase variant in the liver. This is the first enzyme of glycolysis. In the fed state, we have increased glycolysis, so glucokinase is up.
- PEP carboxykinase is a gluconeogenic enzyme that converts oxaloacetate to PEP, so that PEP can make its way back up to glucose. Don't worry about the pathway stuff here. All I want you to know is: PEP carboxykinase activity is down if we're fed, and it's up if we're fasting and want to make glucose.
- Pyruvate carboxylase is a gluconeogenic enzyme that converts pyruvate into oxaloacetate, so that oxaloacetate, via PEP carboxykinase, can go back to PEP, and ultimately up to glucose. Once again, don't worry about the pathway stuff. Just know the pyruvate carboxylase is down in the fed state and up in the fasting state.

161. 20M + eats turkey dinner. What are the arrows (i.e., ↑ or ↓) for activity of glycogen synthase, phosphofructokinase-2 (PFK-2), glucose-6-phosphatase, and pyruvate dehydrogenase?

- **↑ Glycogen synthase, ↑ PFK-2, ↓ glucose-6-phosphatase, ↑ pyruvate dehydrogenase.**
- Glycogen synthase is up because we have glycogenesis in the fed state (so far not hard).
- Normally in glycolysis, fructose-6-phosphate (F6P) is converted to fructose-1,6-bisphosphate (F-1,6-BP) via PFK-1, the rate-limiting enzyme of glycolysis. However, some F6P can be shunted into a side pathway, via PFK-2, into F-2,6-BP. The latter is a positive allosteric regulator of PFK-1, thereby driving glycolysis forward. Once again, don't freak out. What I want you to know is simply this:
    - Are we fed? Yes. Okay, F-2,6-BP production and PFK2 activity are up.
    - No, we're fasting. Okay, F-2,6-BP production and PFK2 activity are down.
- Glucose-6-phosphatase is a gluconeogenic enzyme that converts glucose-6-phosphate in the liver back into glucose (deficient in von Gierke disease). We would expect gluconeogenesis to be decreased in the fed state.
- Pyruvate dehydrogenase converts pyruvate (last molecule in glycolysis) into acetyl-CoA for entrance into the TCA cycle. Activity is increased in the fed state. Do not confuse this with pyruvate carboxylase, which is a gluconeogenic enzyme that converts pyruvate into oxaloacetate, so that oxaloacetate can be ultimately sent back to glucose.

162. 10F + viral infection + polyuria + polydipsia. What are the arrows (i.e., ↑ or ↓) for GLUT-4 expression, lipolysis, glucokinase activity, serine-threonine kinase activity, and ubiquitin-mediated proteolysis?

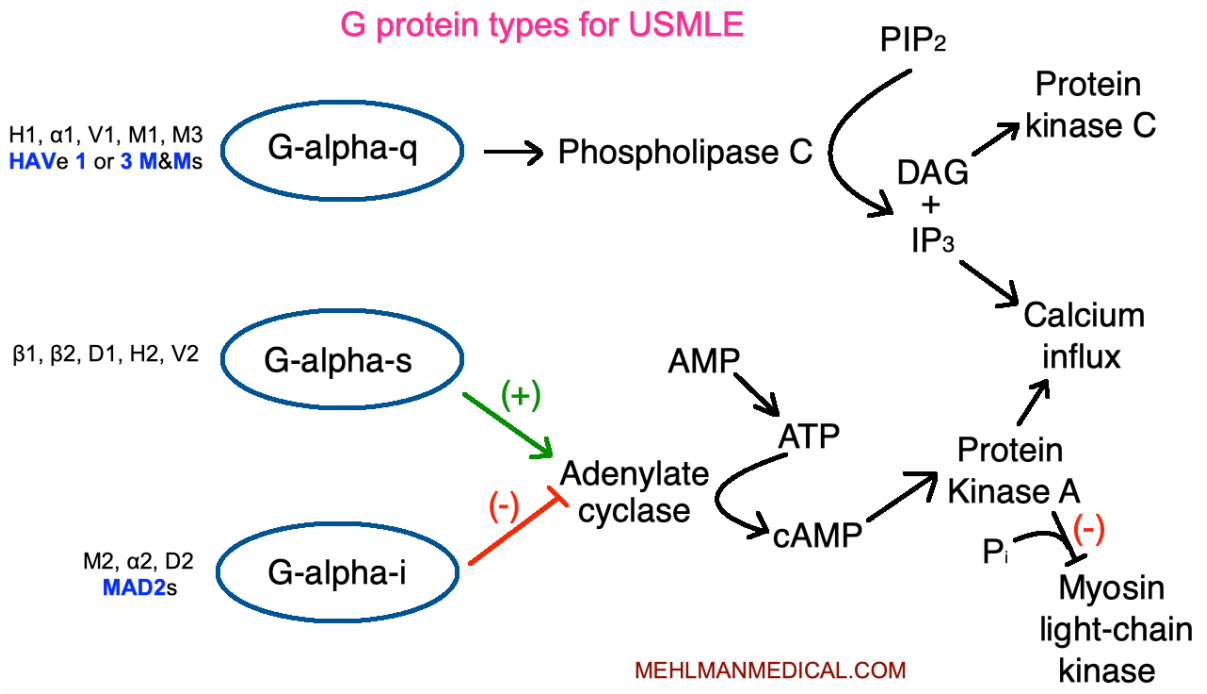
- **↓ GLUT-4 expression, ↑ lipolysis, ↓ glucokinase activity, ↓ serine-threonine kinase activity, ↑ ubiquitin-mediated proteolysis.**
- The patient has DKA. Insulin is deficient.
- Insulin normally upregulates GLUT-4, which allows glucose to enter cells. If insulin is low, GLUT-4 expression is low.
- Since insulin is low and cells are unable to uptake glucose as efficiently, energy must be produced in other ways. Lipolysis, glycogenolysis, and gluconeogenesis are all increased.
- Insulin upregulates glucokinase in the liver. Since insulin is low in DKA, glucokinase activity is also low.
- USMLE wants you to know insulin increases activity of MAP tyrosine kinases and serine-threonine kinases. If insulin is deficient, activity is reduced for both of these.
- When proteins are broken down within the cell, they can be tagged with ubiquitin in order to be sent to the proteasome. Insulin is anabolic and increases protein synthesis, not breakdown. If insulin is low, we'd get more protein breakdown in order to liberate free amino acids for energy. Therefore, low insulin means more ubiquitin-mediated proteolysis.

163. A researcher is comparing glucokinase from a liver cell with hexokinase from a skeletal muscle cell. In terms of glucose processing, what is the Km and Vmax (i.e., ↑ or ↓) of glucokinase compared to hexokinase?

- **Glucokinase has ↑ Km and ↑ Vmax compared to hexokinase.**
- ↑ Km = lower affinity; ↓ Km = higher affinity.
- ↑ Vmax = higher capacity; ↓ Vmax = lower capacity.
- In other words, glucokinase has both lower affinity and greater capacity for glucose than hexokinase.
- Hexokinase is expressed by cells throughout the body. Glucokinase is predominantly just the liver.
- The reason glucokinase has lower affinity for glucose is because we don't want the liver taking up glucose when blood levels are low. We'd want cells throughout the body to preferentially get that glucose for energy utilization. If the liver takes it up, it will store it as glycogen. We don't want that unless levels are high, so it's good that glucokinase doesn't bind glucose as easily as hexokinase.
- But when glucose is high (meaning insulin goes up), we now want the liver to buffer out some of that glucose and convert it to glycogen for storage, so glucokinase gets activated by insulin. The liver converts glucose into glucose-6-phosphate (G6P), via glucokinase. G6P can then be converted to G1P in order to be polymerized into glycogen via glycogen synthase.
- In addition, we need glucokinase to be able to process large amounts of glucose because it's specifically activated when blood levels are high. So the capacity of glucokinase for glucose is greater than hexokinase.

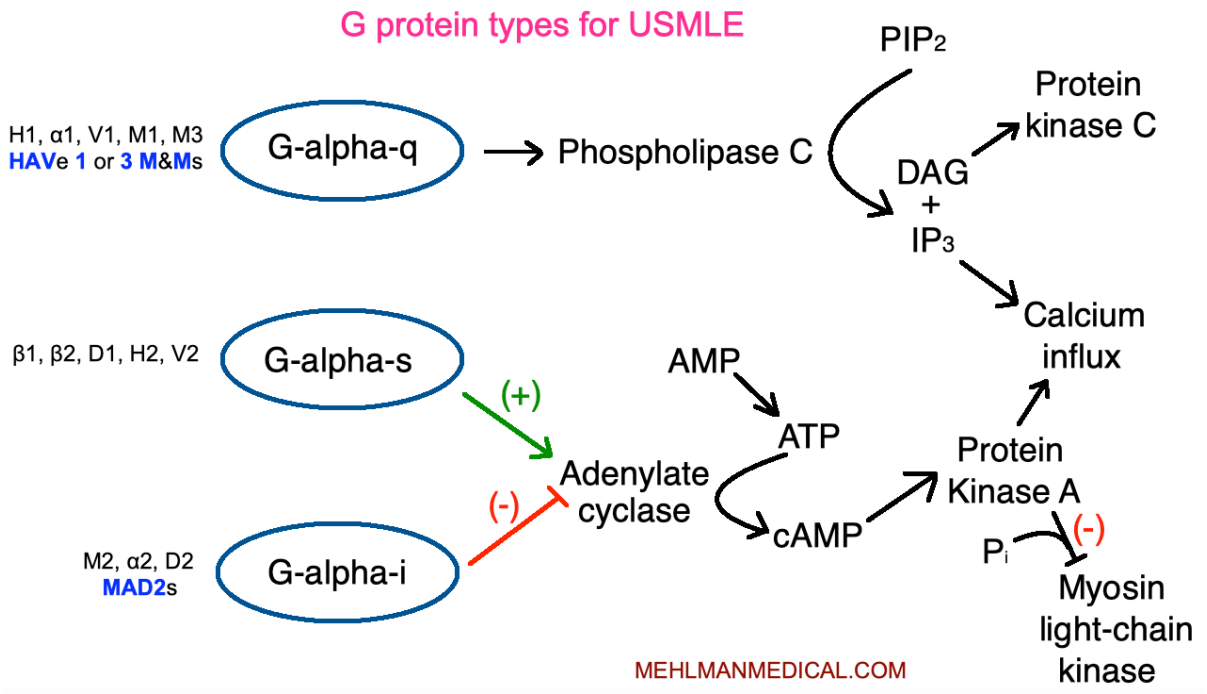
164. 25F + G1P0 + 40 weeks' gestation + oxytocin administered to augment uterine contractions. What are the arrows (i.e., ↑, ↓, or ↔) for intracellular inositol triphosphate (IP3), diacylglycerol (DAG), and cAMP?

- **↑ IP3, ↑ DAG, ↔ cAMP.**
- For some magical reason, the NBME asks about oxytocin receptor binding across multiple forms.
- Oxytocin activates G-α-q G-proteins, which causes increased IP3 and DAG. cAMP is unchanged.
- You do not need to obsess over the G-protein cascades for Step 1. The following image I put in here only to appease some pedantic students.



165. 43M + treated with cimetidine for gastric ulcers. As a result of this medication, what are the arrows (i.e., ↑, ↓, or ↔) for intracellular inositol triphosphate (IP3), diacylglycerol (DAG), and cAMP?

- **↔ IP3, ↔ DAG, ↓ cAMP.**
- Cimetidine is a histamine-2 receptor blocker (H2 blocker).
- The H2 receptor is a G-α-s G-protein. Agonism increases cAMP. However, since cimetidine is an H2 antagonist, cAMP will decrease.
- Cimetidine can cause gynecomastia (HY for USMLE).



- Once again, don't stress about the above diagram. I only put it in here because some students will flip out if I don't. If you don't remember any of this stuff, just know oxytocin and cimetidine, as I discussed above.

166. 24M + lost in the woods for 3 weeks + only consumed water and occasional berries; BMI is 27; he is found by family who gives him a big meal. Following the consumption of food, what are the arrows (i.e., ↑, ↓, or ↔) for expected acute changes in his serum K^+ and serum $PO4^{3-}$?

- **↓ K^+, ↓ $PO4^{3-}$.**
- Refeeding syndrome can occur when a patient consumes food following days to weeks of starvation.
- BMI can be *low, normal, or high* in refeeding syndrome. Do not be confused if BMI is not low.
- **Hypophosphatemia** is the primary disturbance the USMLE wants you to know about. Rapid synthesis of glycolytic intermediates will trap phosphate and deplete serum levels.
- Hypokalemia can also occur due to a spike in insulin, which will drive potassium into cells.
- Patients must be monitored for electrolyte disturbances closely during refeeding in order to prevent arrhythmia.

167. 30M + bacterial meningitis + what are the arrows (up, down, no change) for CSF glucose, protein, polymorphonuclear (PMN) cells, and lymphocytes?

- ↓ Glucose, ↑ protein, ↑ PMNs, ↔ lymphocytes.

- Bacterial meningitis: low glucose, high protein, high PMNs (neutrophils), no change lymphocytes.

- Fungal meningitis: low glucose, high protein, no change PMNs (neutrophils), high lymphocytes.

- Viral (aseptic) meningitis: no change glucose, no change (or ever so slightly elevated) protein, no change PMNs (neutrophils), high lymphocytes.

- In herpes encephalitis, CSF RBCs will also be high in 6 out of 7 questions due to temporal lobe hemorrhage.

- Meningitis usually presents as fever + stiff neck (meningism) and photophobia.

- Encephalitis usually presents as fever + confusion.

168.30M + fever + stiff neck + HIV + CSF staining with India ink confirms diagnosis. What are the arrows (up, down, no change) for CSF glucose, protein, polymorphonuclear (PMN) cells, and lymphocytes?

- **↓ Glucose, ↑ protein, ↔ PMNs, ↑ lymphocytes.**

- Diagnosis is *Cryptococcus neoformans* meningitis in HIV patient. India ink staining is HY for CSF analysis.

- Fungal meningitis: low glucose, high protein, no change PMNs (neutrophils), high lymphocytes.

- Bacterial meningitis: low glucose, high protein, high PMNs (neutrophils), no change lymphocytes.

- Viral (aseptic) meningitis: no change glucose, no change (or ever so slightly elevated) protein, no change PMNs (neutrophils), high lymphocytes.

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