Divine Intervention Episode 50 Comprehensive Step 1 Biochemistry Review (Session 1)

...

Some PGY1

Introduction

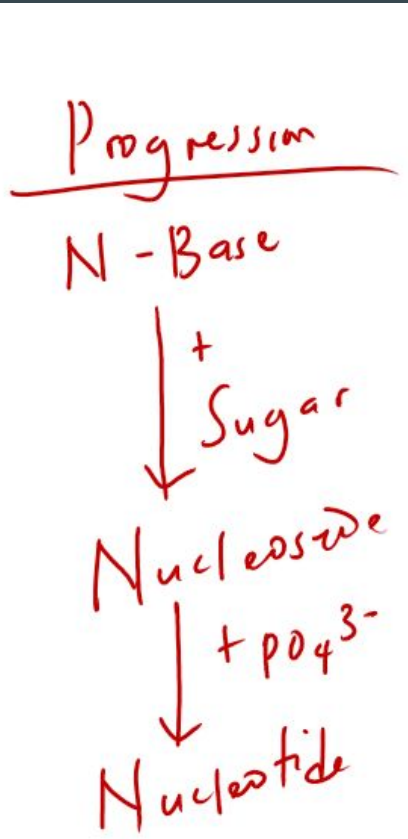
-Primary goal is to review metabolism as relevant to Step 1.

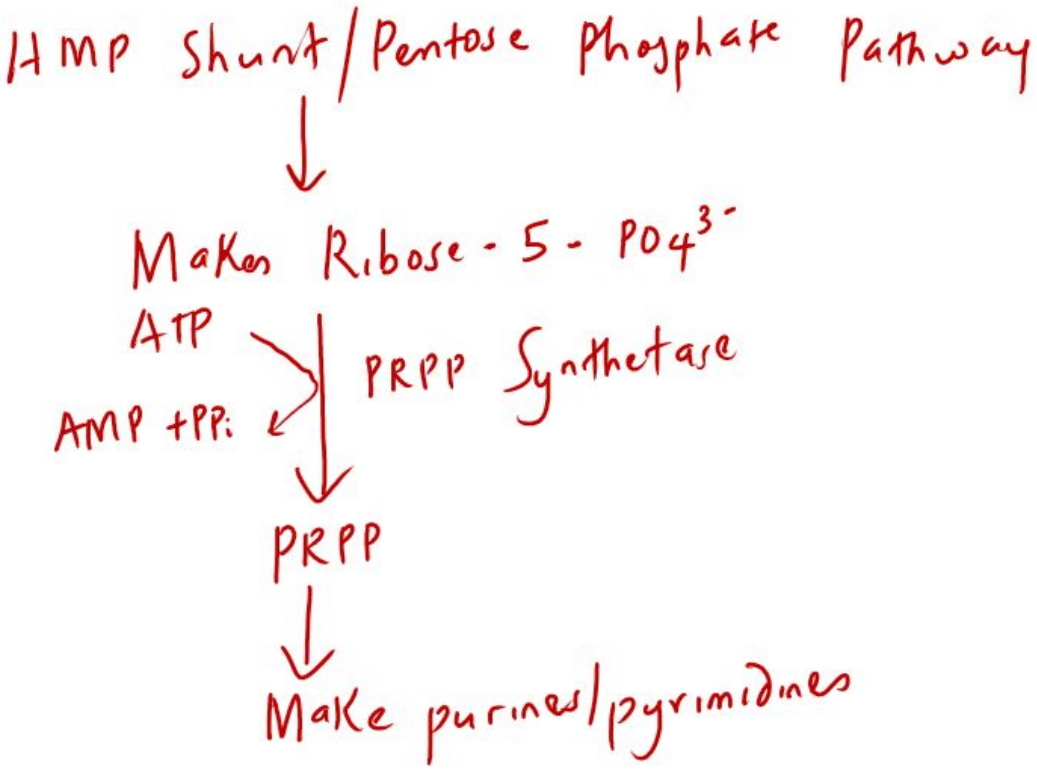
-My approach today will be to use a combo of questions AND mechanistic explanations of stuff to make you feel very comfortable with Step 1 metabolism.

-Where appropriate, I'll integrate Pharm, Pathology, and Physiology.

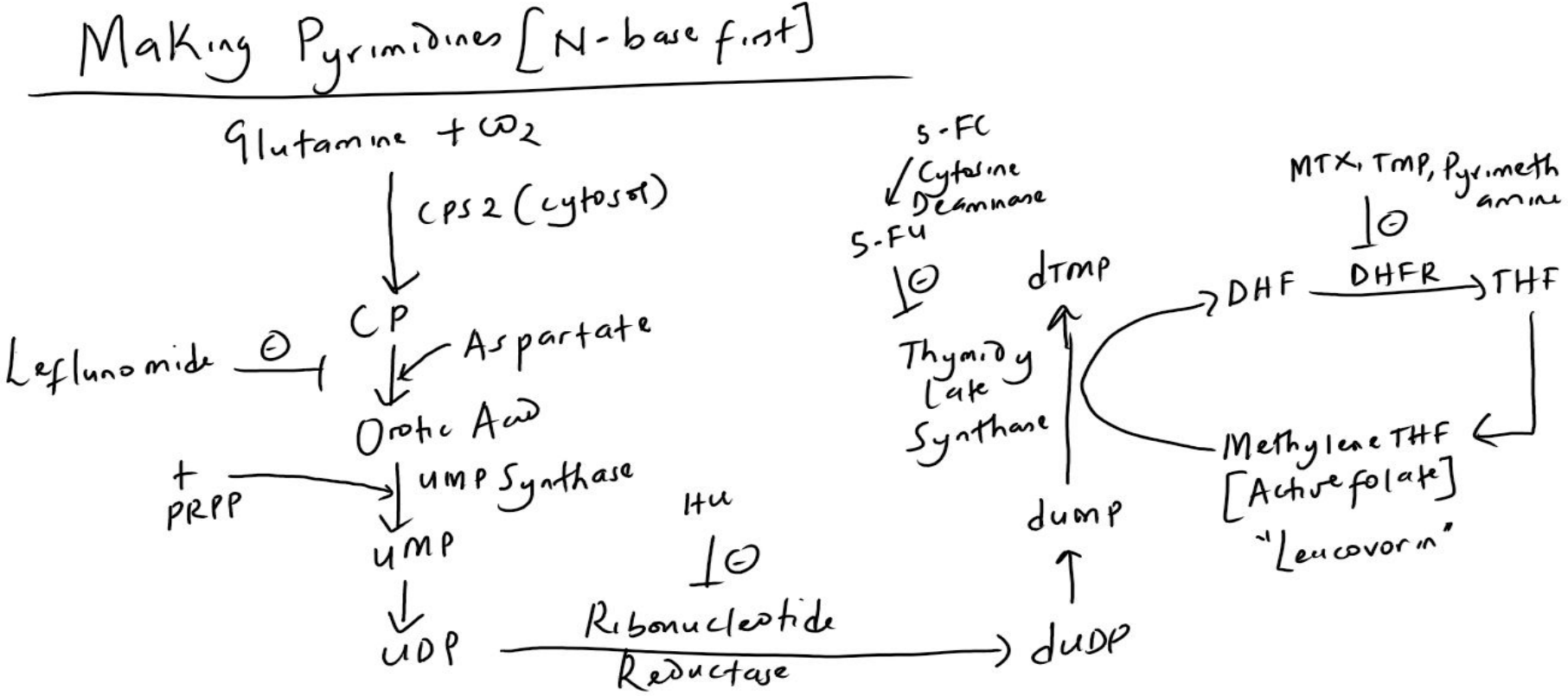
-I am going to spend a lot of time going over how the material WILL be tested.

Intro To Nucleotide Synthesis





Pyrimidine and Purine Synthesis (+ The 2 Orotic Acidurias)



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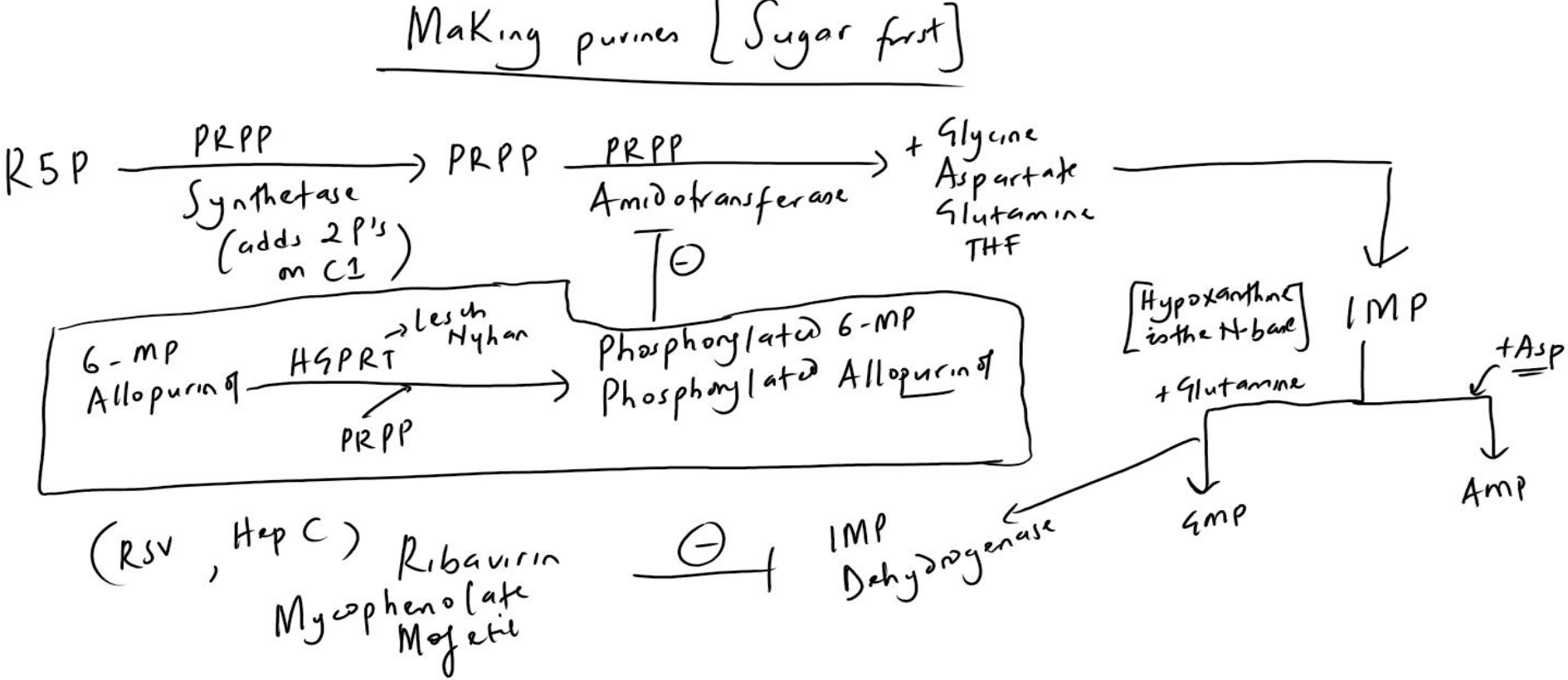
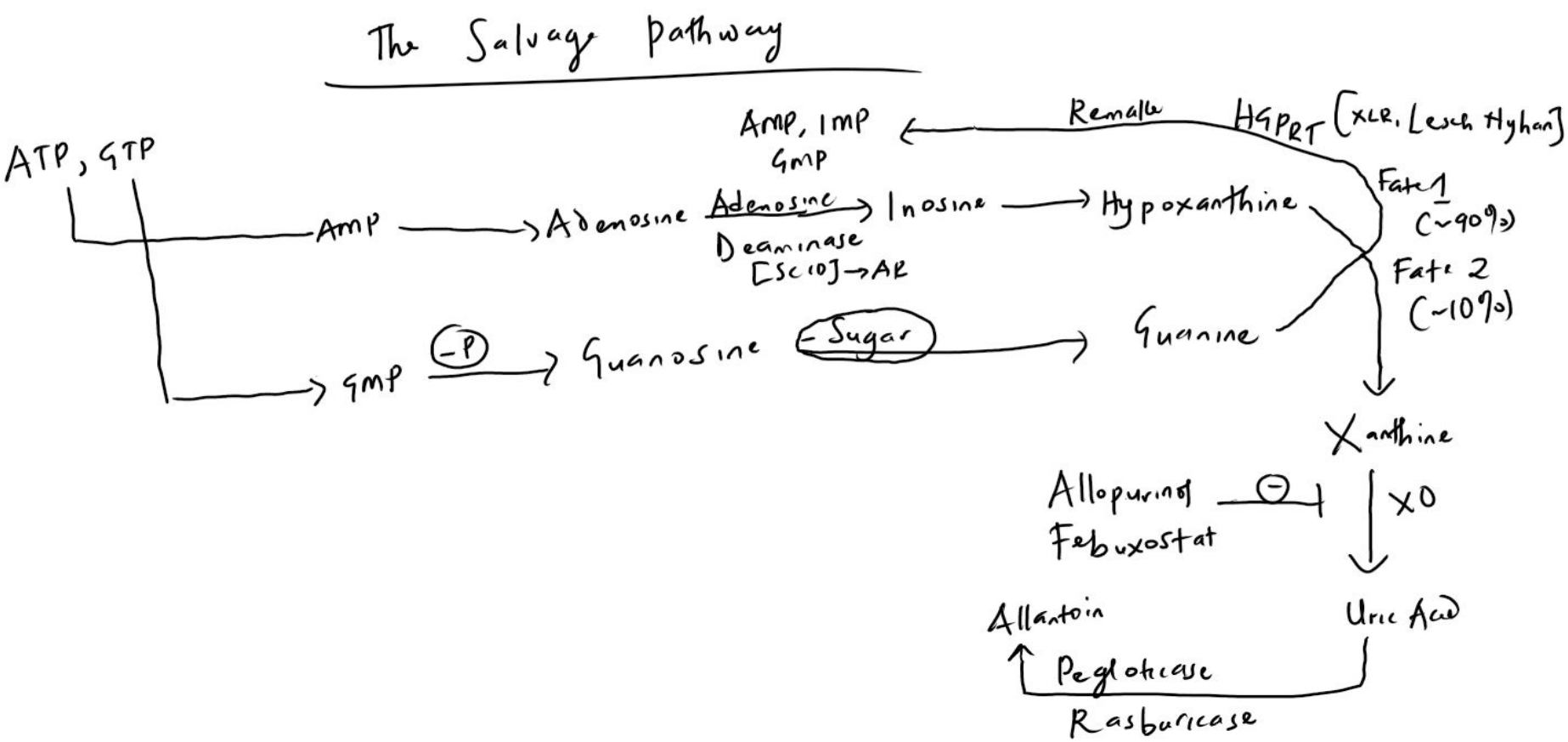


The Purine Salvage Pathway (+dATP and RR and SCID), Gout, Tumor Lysis Syndrome, 6-MP toxicity



Protein Digestion

-Starts with the **low pH** environment of the stomach (denaturing) and the action of **pepsin** from chief cells.

-Pancreas releases t**rypsin, chymotrypsin, carboxypeptidase**, etc (to digest protein). The initial kickstarter for this process is **enterokinase** (working on trypsinogen).

-AAs are reabsorbed in single **AAs (and also as di/tripeptides**, vs glucose). This requires Na symport.

-HY disorders to know here include **Hartnup disease** (gut + renal neutral AA transport like tryptophan) AND **Cystinuria** (gut + renal basic AA transport like cysteine, can cause renal stones with a specific shape?? And can be treated with a drug??)

Dealing With Our Protein Problem

-We love protein as humans. However, they have a problem that we have to deal with on a daily basis **(ammonia)**. We deal with this problem through the **urea cycle** and partially with **ammonium** excretion.

-To make your life easy, think of the body having **only 2 NH3 carriers (glutamine and alanine)**. The only source of **alanine is muscle (why does this make sense?)**.

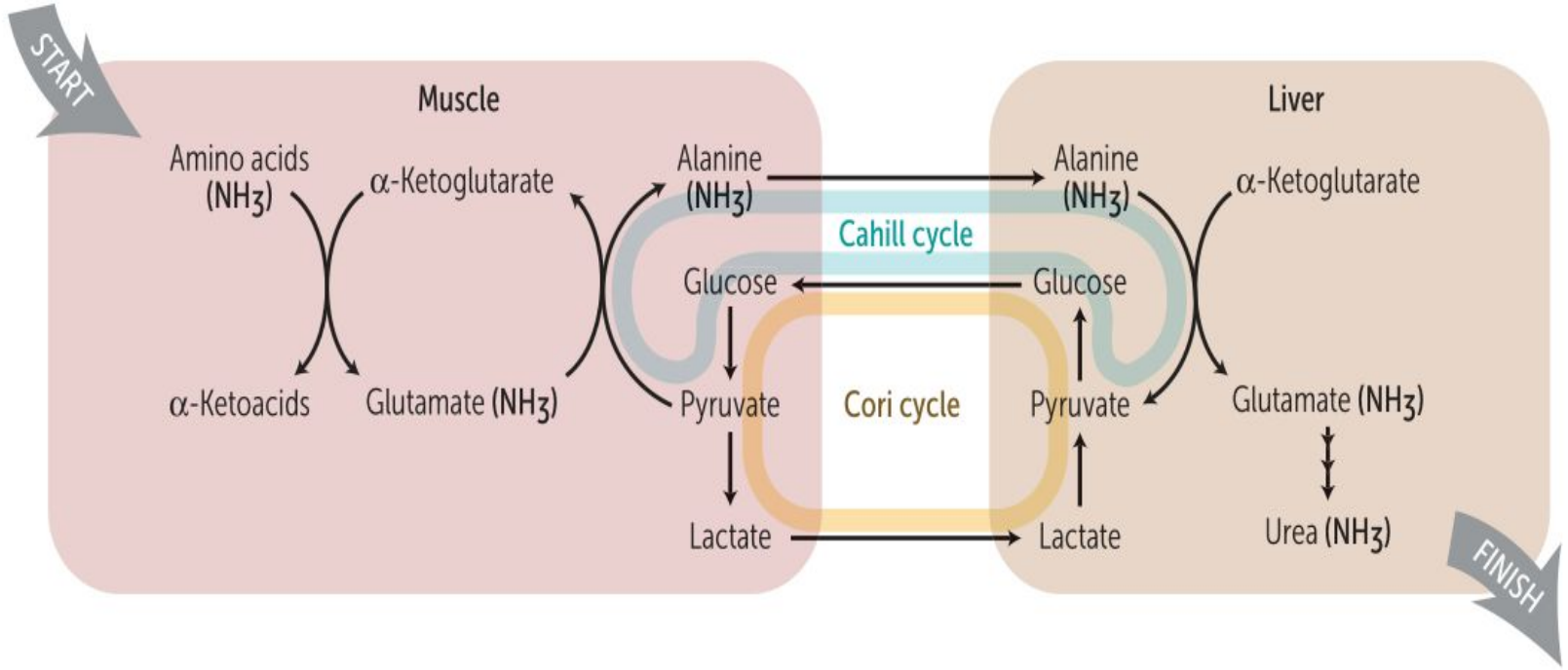
-The **kidney** has an enzyme **(glutaminase)** to strip the NH3 off glutamine, add a H+, and then excrete the NH3 as NH4+.

-The **liver** primarily forms **urea** (which can travel safely in the blood w/o trouble). Urea has **2 amino** groups. These 2 amino groups come from **2 sources-> glutamate and aspartate**.

-If you understand these basics, the urea cycle becomes very doable. Go over it again!

Relax, we'll talk through this logically. Just summarizes what was on the previous slide.

Transport of ammonia by alanine



The Urea Cycle Key Takeaways

-There are only **2 enzymes** you need to know in the urea cycle-**CPS 1 and Ornithine Transcarbamylase**.

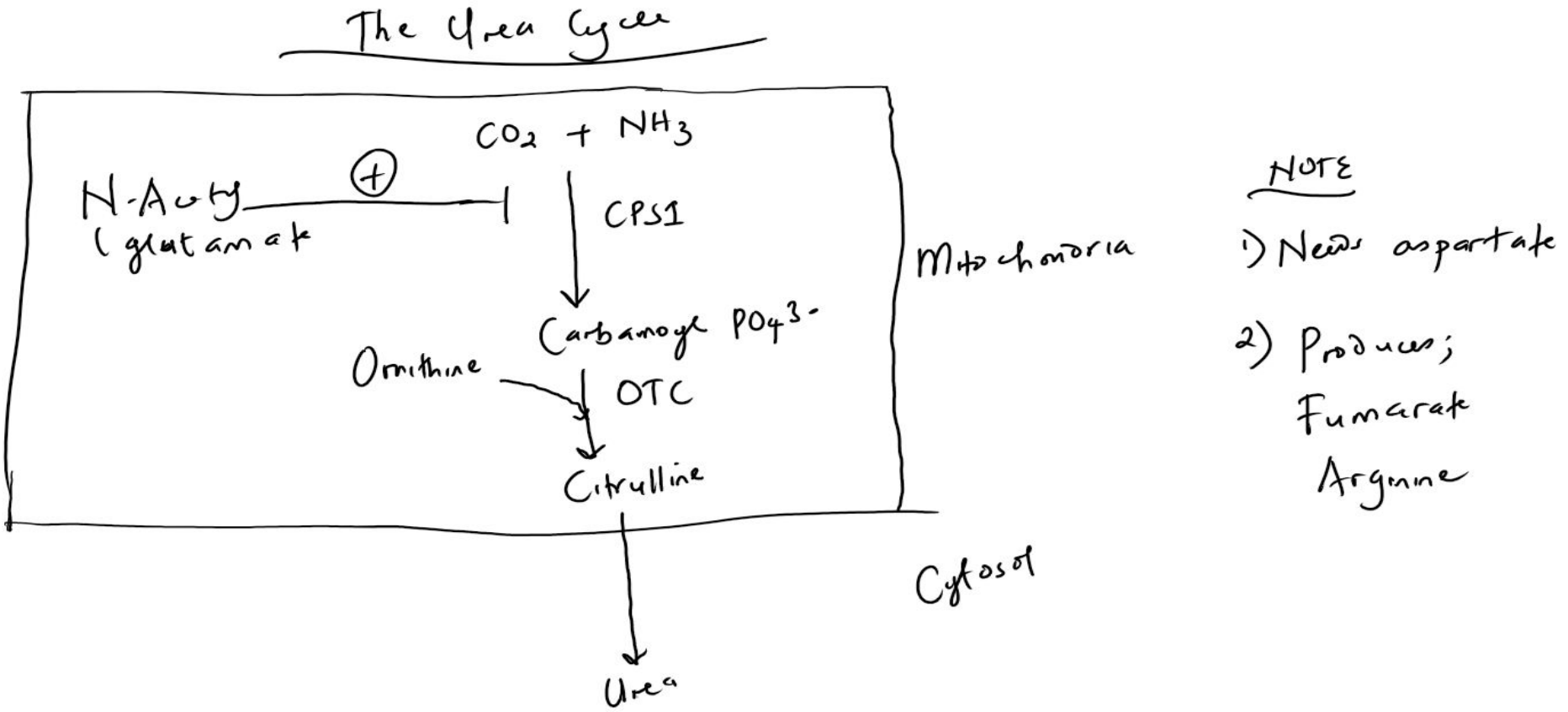
-Location matters here. **First 2** steps are in the **mitochondria**. Final steps are in the **cytosol**. These **"double location"** details are HY for Step 1!

-Primary regulation here is with **N-Acetylglutamate** being an obligate CPS1 activator (makes sense, NAG is something you'd potentially get from a **"high protein meal"**, taking in proteins should logically make you upregulate the pathway that deals with ammonia problems).

-NH2 group #1 comes from Step 1. NH2 group #2 comes from Step 3 (aspartate).

-Don't forget your pesky **arginine details (histones, NO synthesis)**. How would you manage **hepatic encephalopathy??**

The Urea Cycle



NOTE

1) Needs aspartate

2) Produces; Fumarate Arginine

A Nice Step 1 Worthy Question.

How would you differentiate between a UMP Synthase deficiency, a CPS1 deficiency, and an Ornithine Transcarbamylase deficiency?

As an aside, what is the cofactor used quite extensively by transaminases? Carboxylases? Can you recall the enzymes used in the PDH complex? What are your B vitamins (and their other names)?

Protein Breakdown Diseases (super HY!) + VOMIT pathway

-Remember your **PKU** and a **mousy/musty** odor (and **PAH or THB reductase** deficiency). **Tyrosine** becomes an essential AA.

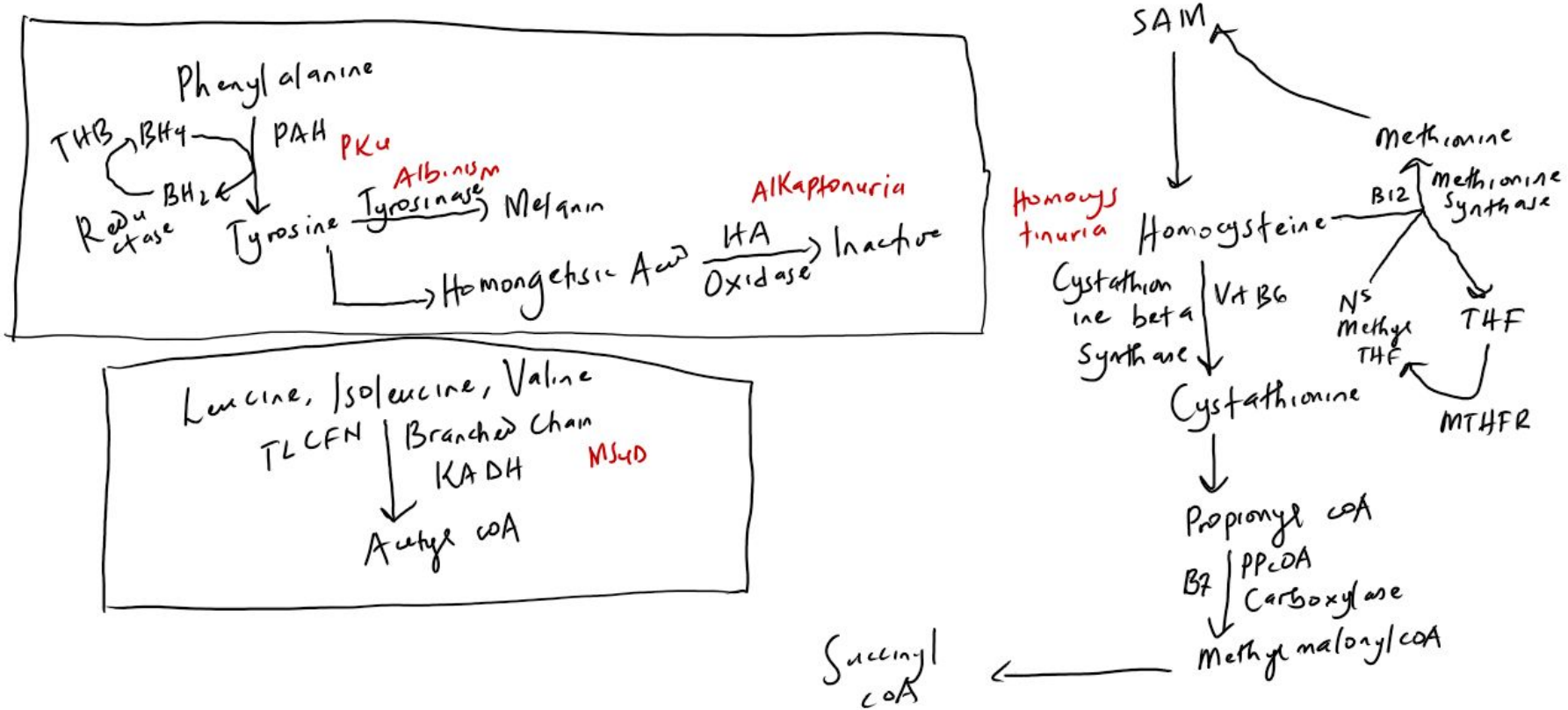
-**Albinism** is associated with a **tyrosinase** deficiency (tyrosine to melanin).

-**Alkaptonuria** is associated with a **homogentisic acid oxidase** deficiency. Homogentisate makes **urine blue black** and causes **joint disease** (from deposition).

-**Branched chain ketoacid DH** breaks down branched chain AAs (LIV). A deficiency in this enzyme causes **MSUD**. This enzyme is also HY from the standpoint of some **eerie relationship to the PDH complex and alpha ketoglutarate DH**.

-**Homocystinuria (SH groups)** can be caused by a **CBS (B6)** deficiency or a **homocysteine methyltransferase (methionine synthase, B12)** deficiency. What are 2 key details that differentiate this disorder from **Marfan's** (think IQ and eye findings)?

Protein Breakdown Disease Summary



Some Other HY AA Details

Remember;

GABA is made from glutamate by GAD (needs B6, autoantibodies in T1DM)

Tryptophan is a 5-HT (serotonin) and niacin precursor.

Histamine is made from histidine (by histidine decarboxylase, scombroid association??)

Vitamins and Minerals

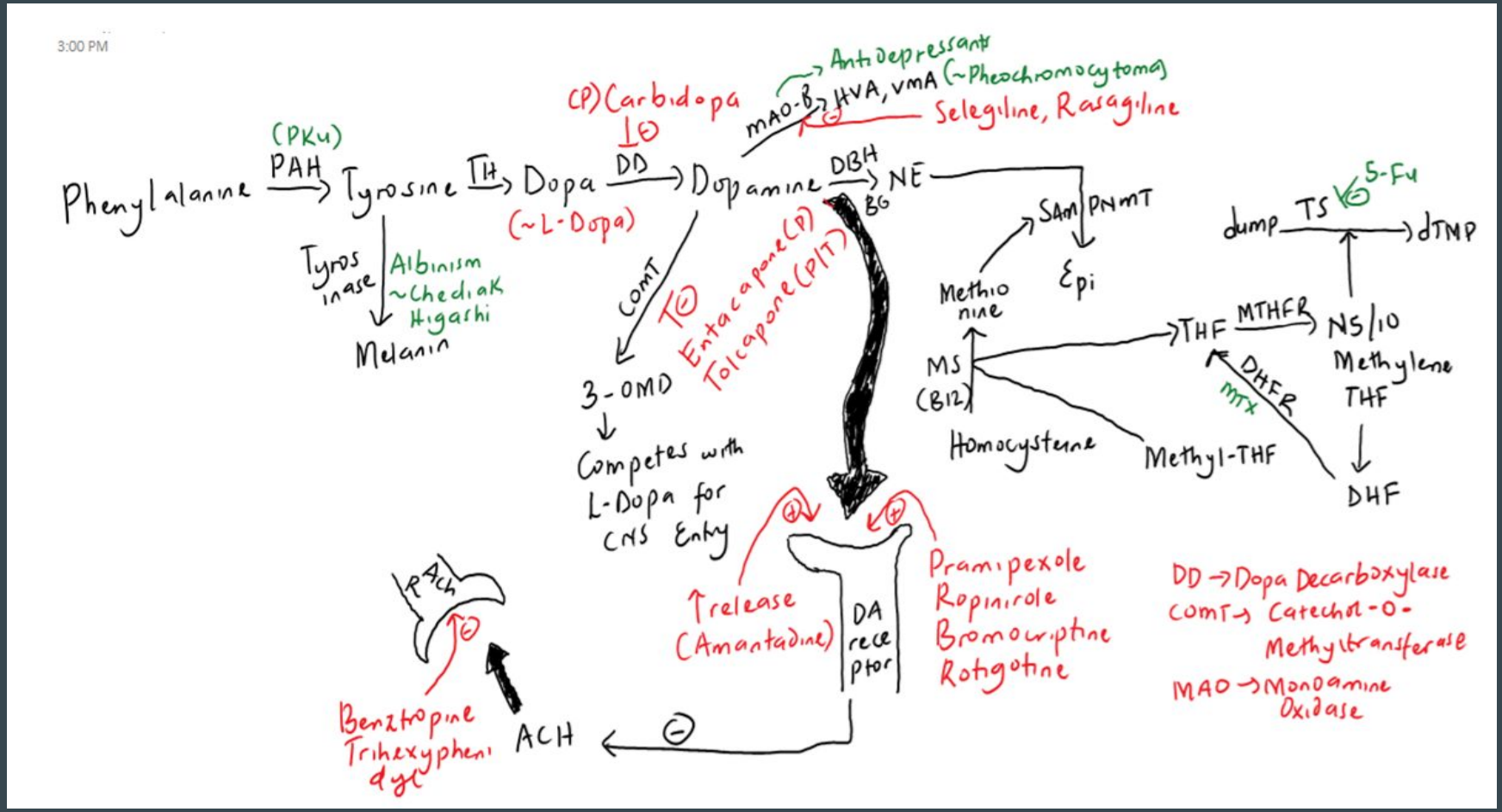
-Learn your vitamins and minerals in the **context of folate metabolism and phenylalanine metabolism** (contain most of the vitamin info you need for Step 1).

-For **phenylalanine** metabolism, remember our stories with **PKU, Albinism, Parkinson's treatment, Vitamin C (and its role in collagen synthesis), PNMT** and its special role in the adrenal medulla, and the **HVA/VMA** role in diagnosing a pheochromocytoma.

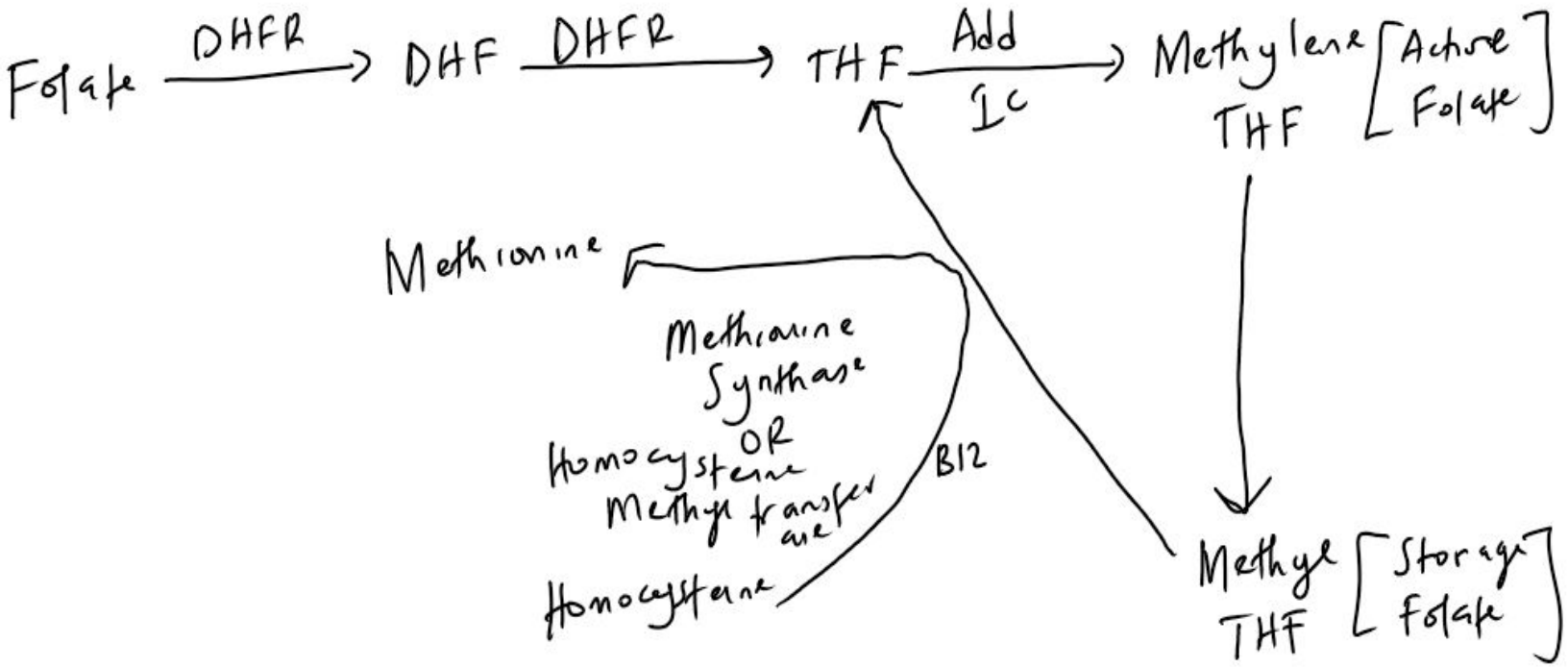
-There are **2 KINDS of folate** in the body -> **active folate** (AF, with a charged C) and **storage folate** (SF, with a methyl which is largely unreactive). All the **fancy** stuff folate does in the body is with its **AF form**. **SF** seems to be largely useless until you recognize one key fact -> It is a **precursor to AF** (with this **irreversible interconversion** carried out by **homocysteine methyltransferase/methionine synthase, requires B12**).

-Folate is needed for **pyrimidine synthesis** (remember thymidylate synthase?). W/o DNA from folate, cells **increase in size w/o "nuclear doubling" -> megaloblastic anemia**.

Tyrosine Metabolism and Parkinson's Disease and PNMT



Folate and B12 Metabolism (Can you slot in the thymidylate synthase and DHFR inhibitors here???)



Another Step 1 Worthy Question (+ B12 depleting bug)

B6 (Pyridoxal phosphate), B9 (Folate), and B12 (Cyanocobalamin) deficiencies can all cause homocystinuria. How would you differentiate b/w a B6 vs B9/12 deficiency as a cause of homocystinuria (think of the other elevated stuff)? After doing this, how would you differentiate b/w B9 and B12 deficiency as a cause of homocystinuria? What are the 2 classic NBME folate deficient patients?

The Heme Synthesis Pathway (+ avoiding barbiturates)

-You need to know **5 enzymes** in this pathway and some associated stories.

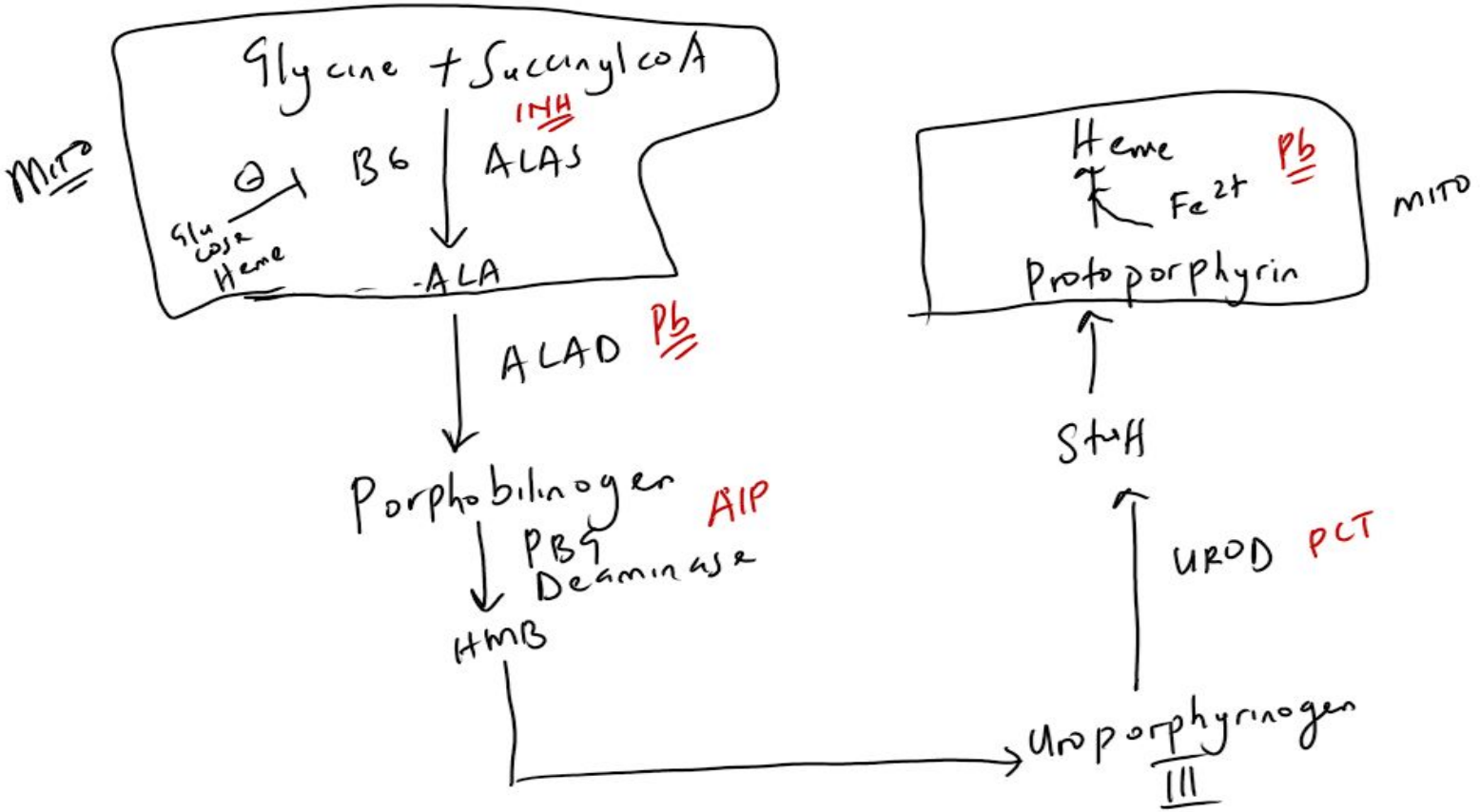
-**ALAS** is the r**ate limiting enzyme (B6 cofactor, re-Isoniazid)**. It is inhibited by **heme**.

-**Pb** poisoning **(moonshine, old house)** can cause a sideroblastic anemia with an increase in **free erythrocyte protoporphyrin from ALAD and Ferrochelatase** inhibition. Note your classic **blood smear** findings (+ neuro, + wrist drop, + abdominal pain).

-A **porphobilinogen deaminase** deficiency is associated with **AIP (no photosensitivity but neuro problems, port wine stained urine)**. So happens that Uroporphyrinogen 3 is the **first porphyrin** in this pathway and since it comes after PBGD, we don't have a "photoactive" substance building up.

-A **UROD** deficiency is associated with Porphyria Cutanea Tarda which does have photosensitivity (+ hirsutism, + Hep C association, + intense "hand" sweating).

Heme Synthesis Pathway (Note the double location business going on here)



Another Step 1 Worthy Question

How would you differentiate b/w Fe deficiency, Pb poisoning (just think of ferrochelatase), and B6 deficiency wrt FEP levels, ALA levels, ferritin levels, etc.

Absorbing Fe/Breaking Down Heme

-Fe is **absorbed (also only carries O2) in the 2+** form only. **Vit C** encourages this process (what are 2 other HY functions of Vit C that have been discussed?).

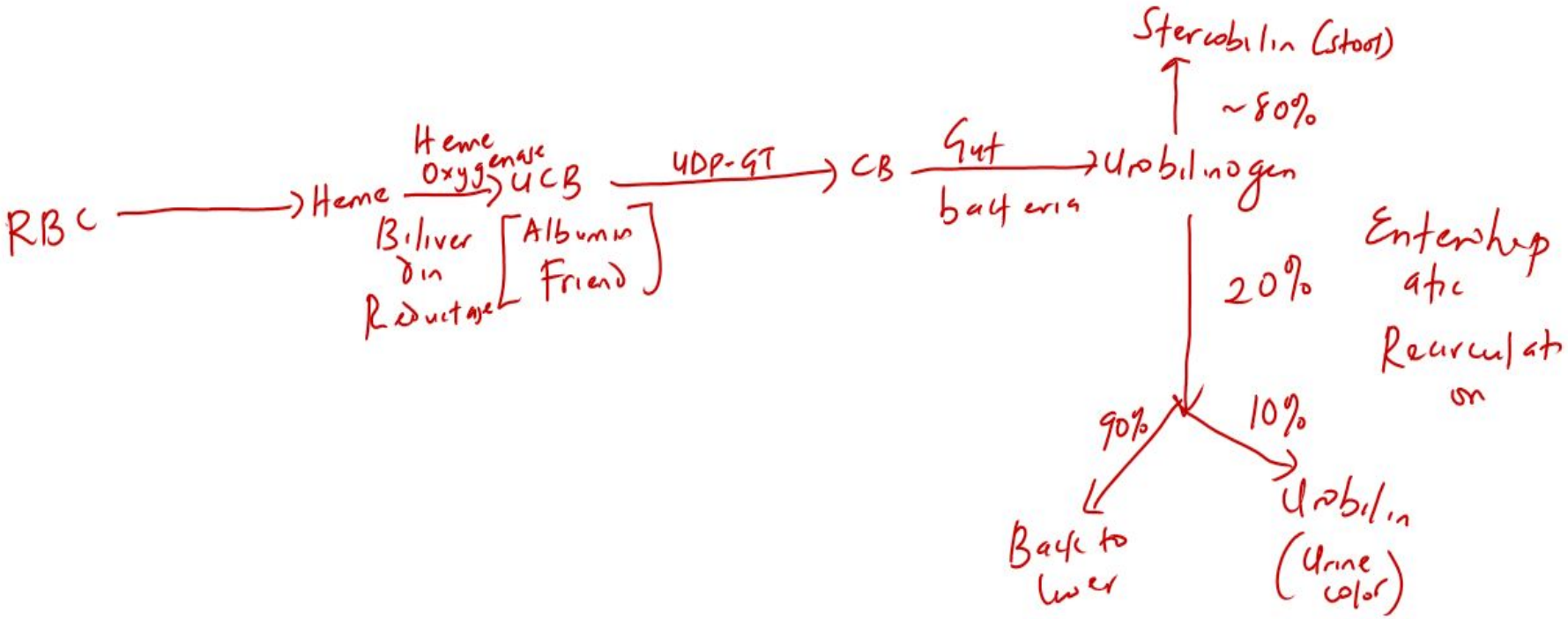
-HFE regulates this process. A **HFE mutation** can cause too much Fe reabsorption (**hemochromatosis, tx w/phlebotomy**). What should your **first step** in diagnosis be?

-I'd encourage you to also try recalling the relationship b/w **Fe2+/Fe3+ w/pathologies**.

-It is HY to know the breakdown pathway for heme and the different diseases that could arise from issues along that pathway (as well as the associated kind of hyperbilirubinemia)-> **Hemolytic anemia, Newborn jaundice, TMP-SMX toxicity, Crigler Najjar (T1 and 2), Gilbert's, Dubin Johnson, Rotor, Obstructive process**, etc.

-Remember that **Fe** is absorbed in the **duodenum**, **folate** is absorbed in **duodenum/jejunum**, **B12** is absorbed in the **terminal ileum** (re-Crohn's association).

Heme Breakdown



Another Step 1 Worthy Question/Thought

Can you explain these lesions?

Option A-Increased urine bilirubin, decreased urine urobilinogen, increased direct bilirubin, dark/tea colored urine, acholic stools.

Option B-Increased urine urobilinogen, no urine bilirubin, increased indirect bilirubin, normal colored urine, dark colored stools.

Some General Principles (make thy life super easy!)

-Insulin works through **tyrosine kinase** receptors. Insulin is a **dephosphorylator**.

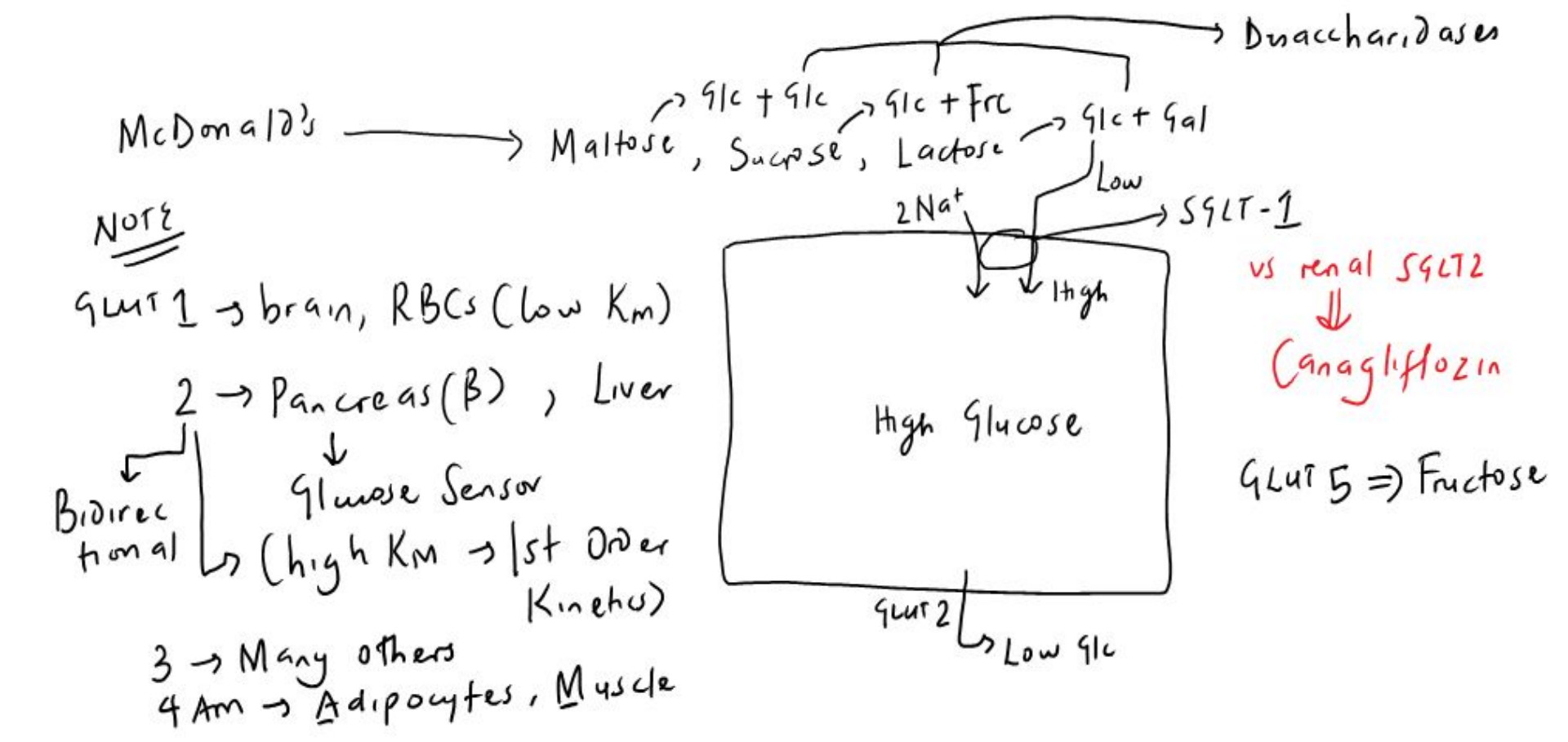
-Glucagon works through **G protein coupled receptors** which activate PKA. Glucagon is a **phosphorylator**.

-If you know this, you can easily reason that **if an enzyme is activated by insulin, the activated form must be a "dephosphorylated form" of the enzyme** (and vice versa for glucagon).

-**Carboxylase enzymes are ABC enzymes** (they use ATP and Biotin, hence the AB). C stands for carboxylase (and CO_2).

-Kinase enzymes as a rule add phosphate groups to stuff.

GLUT Transporters



Other Important Stuff

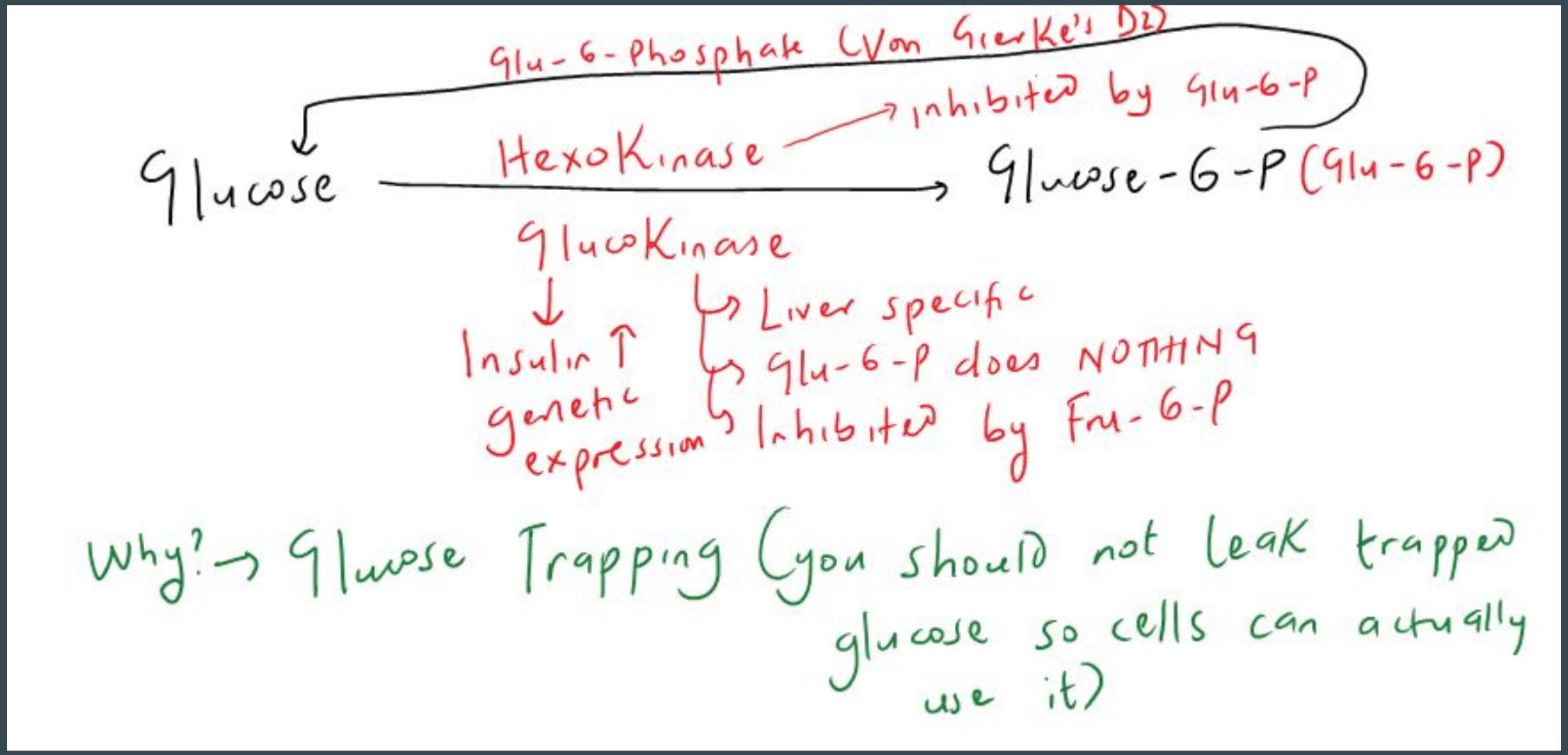
-As a correlation from prior blocks, remember that GLUT1 transporters operate under **zero order kinetics** by virtue of their low KM (approx. 5 mM) which tracks along with normal blood glucose levels.

-GLUT 2 transporters have a **KM that is much higher** than normal blood glucose levels. If you consider the Michaelis Menten curve, this is ideal b/c the transporters will operate on the "straight line" portion which essentially guarantees **"proportional" glucose uptake that tracks along with blood glucose levels**.

-Why are **GLUT2 transporters bidirectional**?

-GLUT4 transporters are **insulin dependent**. Muscle has the unique ability to express GLUT4 transporters in an **"insulin independent" fashion in the setting of exercise**.

Glycolysis Broken Down Part 1



Glucokinase vs. Hexokinase

-Hexokinase has a low KM and VMAX.

-Glucokinase has a high KM and VMAX. Glucokinase is also induced by insulin. Glucokinase is regulated by a regulatory protein under the auspices of F-6-P and glucose.

Glucokinase Regulatory Protein

-Is an inhibitor of glucokinase (GK).

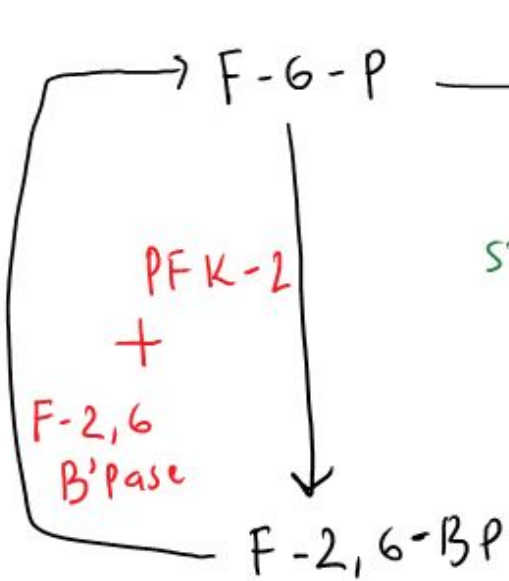
-Binds GK and sends it to the nucleus (where it is inactive).

-GKRP has the ability to bind both F6P and glucose.

-When bound by F6P, GKRP has a higher affinity for GK (which sequesters GK by taking it to the nucleus).

-When bound by glucose, GKRP has a much lower affinity for GK (which brings it back to the cytoplasm for reaction).

Glycolysis Broken Down Part 2



PFK-1 (+) AMP
(-) Citrate, ATP

F-1,6-BP

↳ future "feed forward" P-Kinase activator

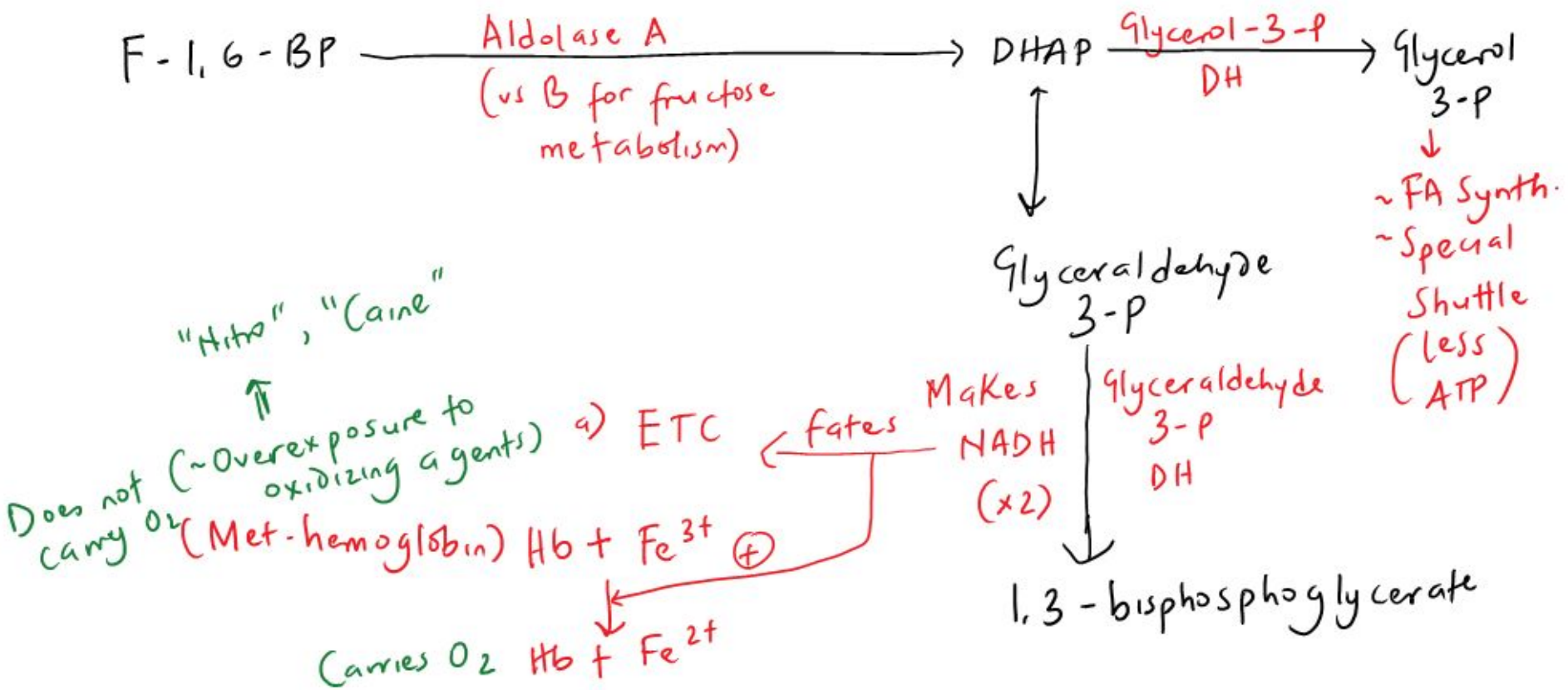
START! ~ Special Case

a) F-2,6-BP turns on PFK-1 (pro-glycolysis)
b) Insulin is pro-glycolysis
c) Insulin is a dephosphorylator
d) So PFK-2 must be active when dephosphorylated ↳ FINISH!

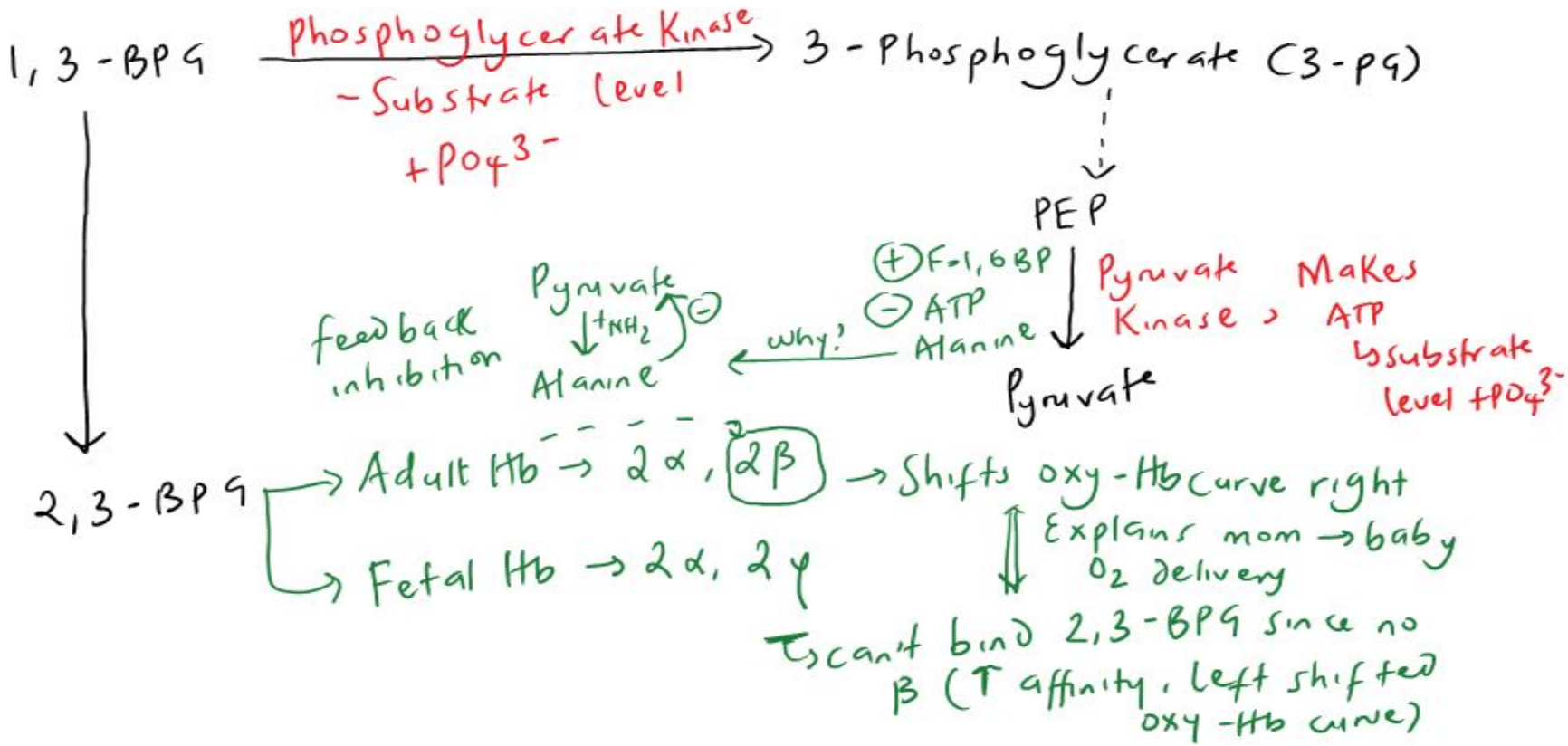
Low Energy Indicators → Should activate glycolysis → AMP

High Energy Indic. → Should Kill glycolysis → ATP Citrate

Glycolysis Broken Down Part 3



Glycolysis Broken Down Part 4



Some Other Important Stuff

-Overall, glycolysis gives rise to the **rule of 2s (2 ATPs, 2 NADH, and 2 Pyruvates)**.

Pyruvate has multiple fates;

-It can form **lactate under the action of lactate DH**. This step **regenerates NAD** to keep the Glyceraldehyde-3-P DH step working.

-Pyruvate can go into **mitochondria** to receive special attention from the **PDH complex ultimately leading to Acetyl-coA** formation.

-Pyruvate can receive special attention from **Pyruvate carboxylase (what is a HY cofactor utilized by this enzyme???)** to form **OAA that can reverse course in gluconeogenesis** (through subsequent PEPCK action).

References

-First Aid for The USMLE Step 1 2018