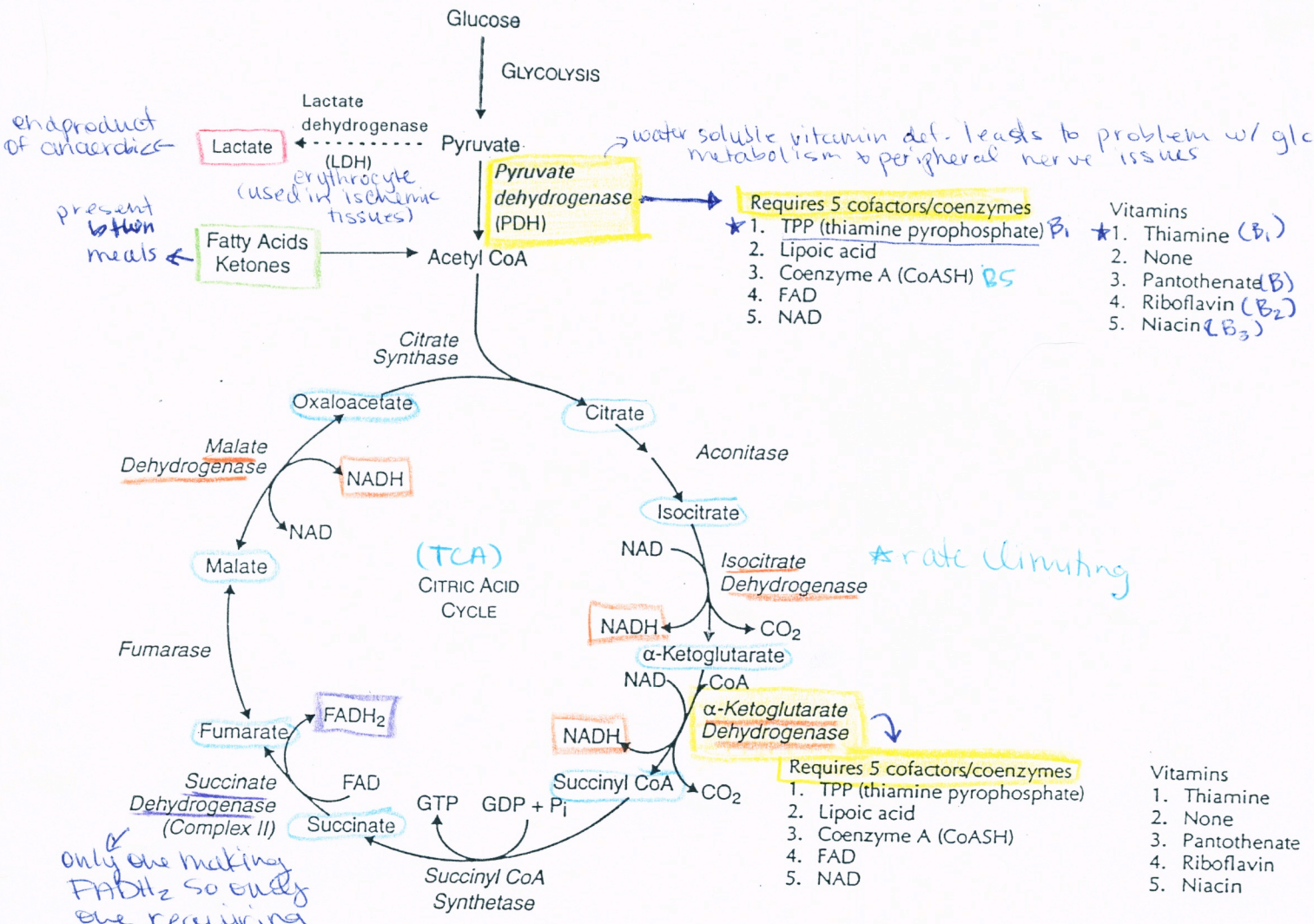
AEROBIC OXIDATION OF FUELS FOR ENERGY
PYRUVATE DEHYDROGENASE & THE CITRIC ACID (KREBS) CYCLE

brain uses glucose → CO_2; erythrocyte has no mitochondria so degrades glucose to lactate
mitochondrial diseases mess up this cycle → heart attack / stroke shoots things to anaerobic



endproduct of anaerobics

erythrocyte (used in ischemic tissues)

present between meals

water soluble vitamin def. leads to problem w/ glc metabolism & peripheral nerve issues

Requires 5 cofactors/coenzymes
1. ★ TPP (thiamine pyrophosphate) B_1
2. Lipoic acid
3. Coenzyme A (CoASH) B_5
4. FAD
5. NAD

Vitamins
1. ★ Thiamine (B_1)
2. None
3. Pantothenate (B_5)
4. Riboflavin (B_2)
5. Niacin (B_3)

★ rate limiting

Requires 5 cofactors/coenzymes
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2. Lipoic acid
3. Coenzyme A (CoASH)
4. FAD
5. NAD

Vitamins
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2. None
3. Pantothenate
4. Riboflavin
5. Niacin

only one making $FADH_2$ so only one requiring riboflavin

Citrate Can I Keep
Is Selling Sex For
Krebs Money Officer
Starting ↓
Substrate products in
For cycle
Making
Oxaloacetate

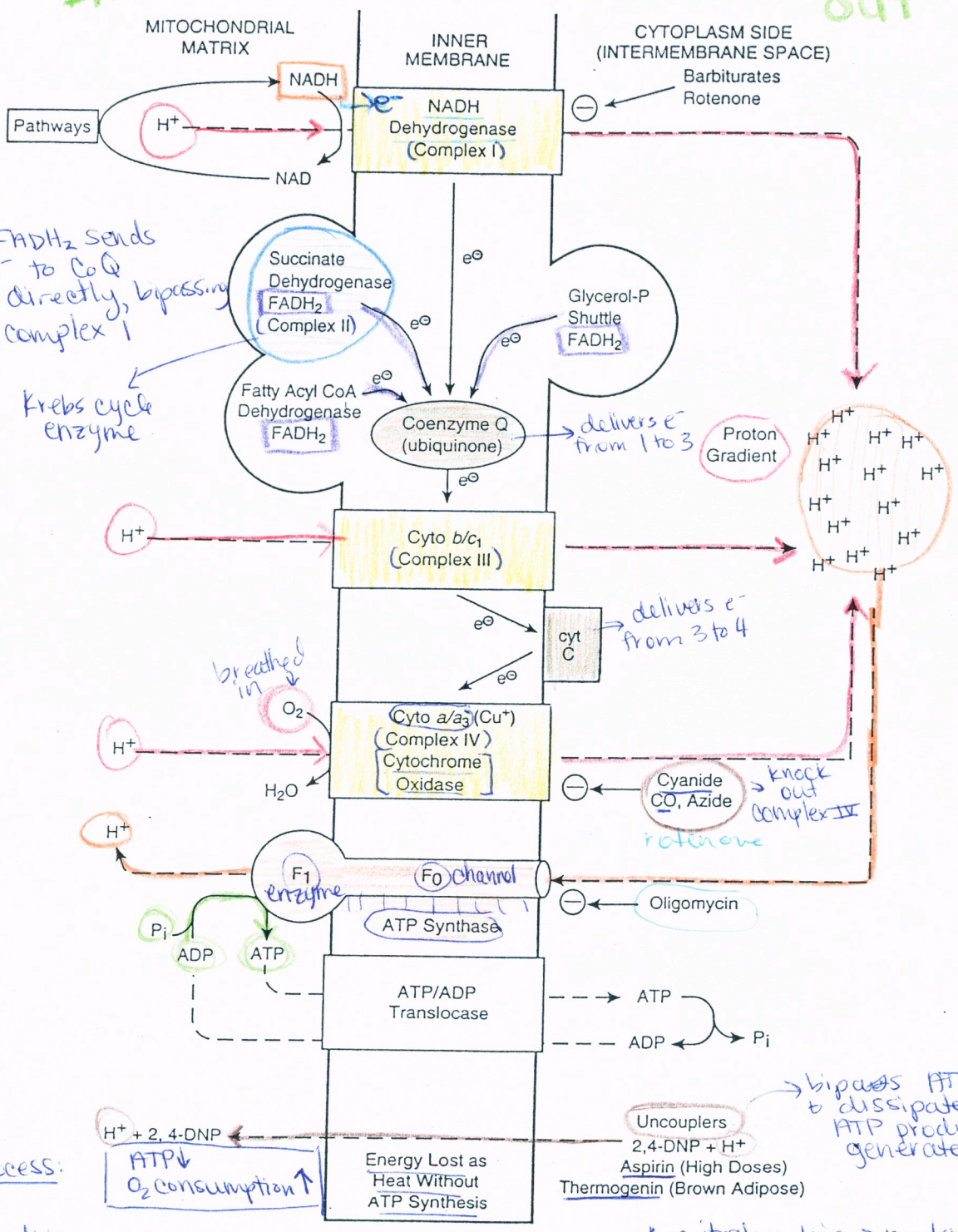
THIAMINE DEFICIENCY – alcoholism

Wernicke-Korsakoff Syndrome
- peripheral neuropathy, ataxia
- nystagmus, ophthalmoplegia
- amnesia, confabulation
- disorientation, psychosis

Wet Beri-Beri
- WKS + congestive heart failure (edema)

cells want to convert NADH/$FADH_2$ → ATP via ox/phos

OXIDATIVE PHOSPHORYLATION - aerobic tissues



Shut down process:
1. lack of O_2
2. bad mitochondria
3. uncouplers
4. cyanide / CO

Mitochondrial Diseases

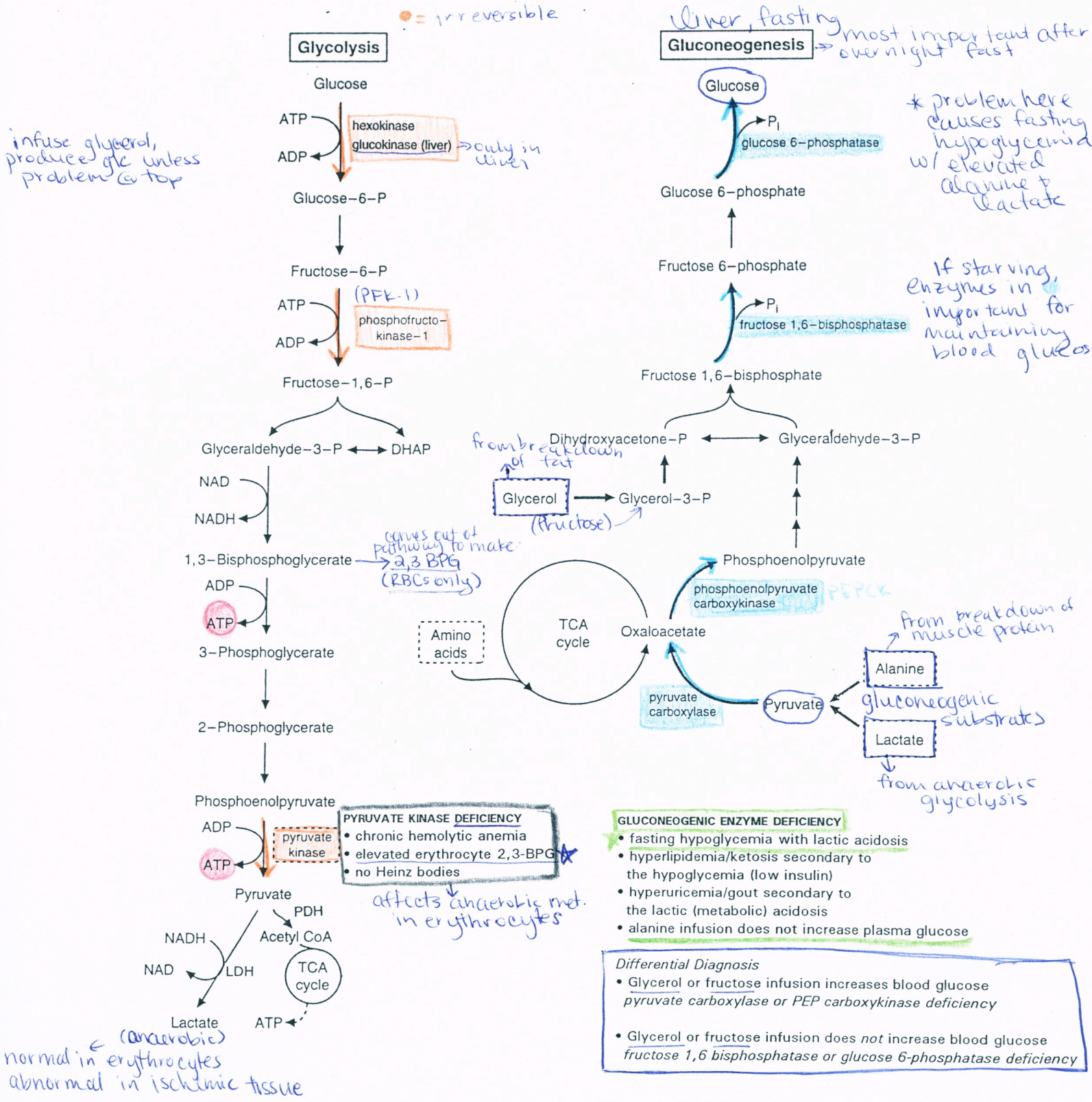
- Leber hereditary optic neuropathy
- MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
- Myoclonic epilepsy with ragged red muscle fibers [MERRF]

★ mitochondria → maternal inheritence: all from mother

Cyanide & CO generated by house fires
cyanide → lips are blue, breath smells like bitter almonds
CO → cherry red mucous membranes

nitroprusside → cyanide is toxic biproduct
thiosulfate is antidote to cyanide

GLYCOLYSIS & GLUCONEOGENESIS



infuse glycerol, produces glc unless problem @ top

liver, fasting
most important after overnight fast

* problem here causes fasting hypoglycemia w/ elevated alanine & lactate

If starving, enzymes in important for maintaining blood glucose

carves out of pathway to make 2,3 BPG (RBCs only)

PYRUVATE KINASE DEFICIENCY
- chronic hemolytic anemia
- elevated erythrocyte 2,3-BPG ★
- no Heinz bodies

affects anaerobic met. in erythrocytes

GLUCONEOGENIC ENZYME DEFICIENCY
- fasting hypoglycemia with lactic acidosis
- hyperlipidemia/ketosis secondary to the hypoglycemia (low insulin)
- hyperuricemia/gout secondary to the lactic (metabolic) acidosis
- alanine infusion does not increase plasma glucose

Differential Diagnosis
- Glycerol or fructose infusion increases blood glucose
  pyruvate carboxylase or PEP carboxykinase deficiency
- Glycerol or fructose infusion does *not* increase blood glucose
  fructose 1,6 bisphosphatase or glucose 6-phosphatase deficiency

(anaerobic)
normal in erythrocytes
abnormal in ischemic tissue

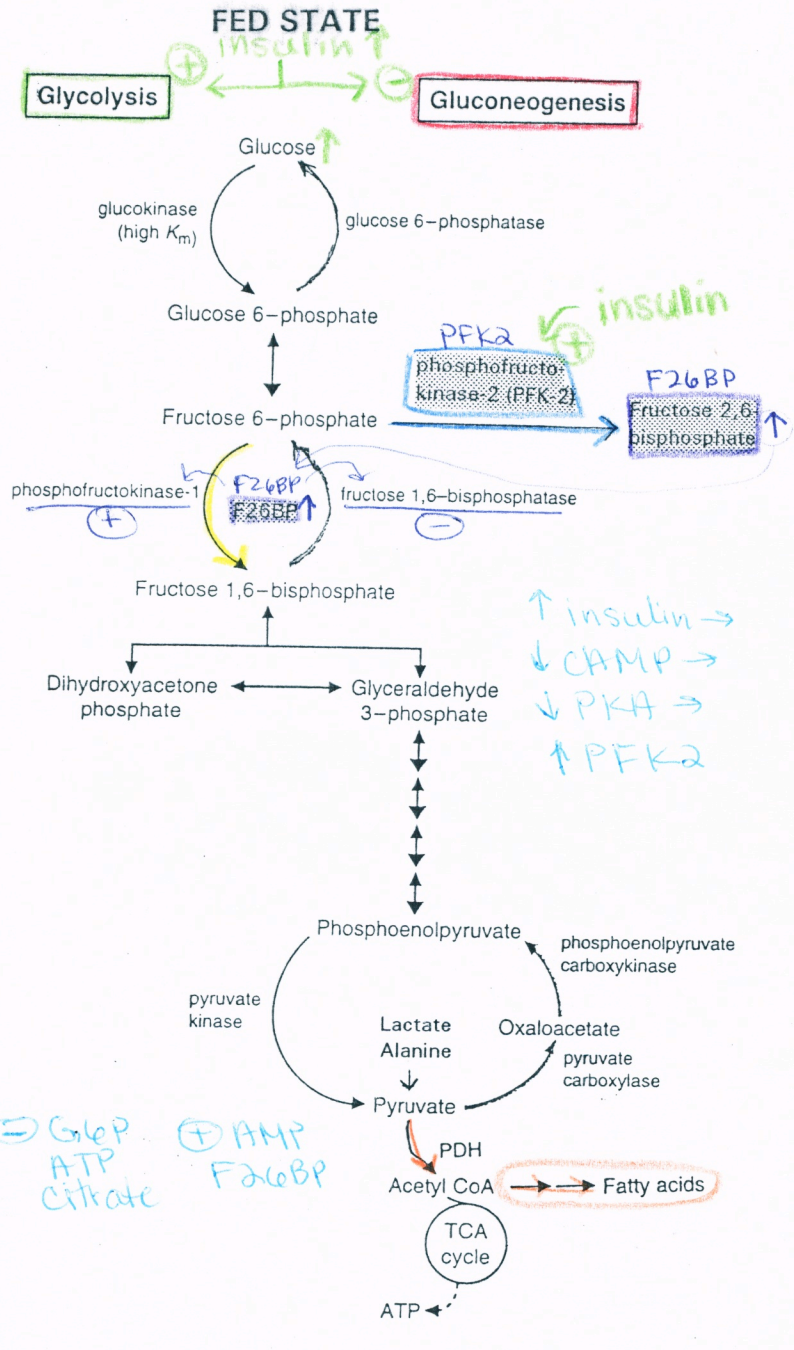
★ right shift O_2 curve w/ elevated 2,3 BPG ★

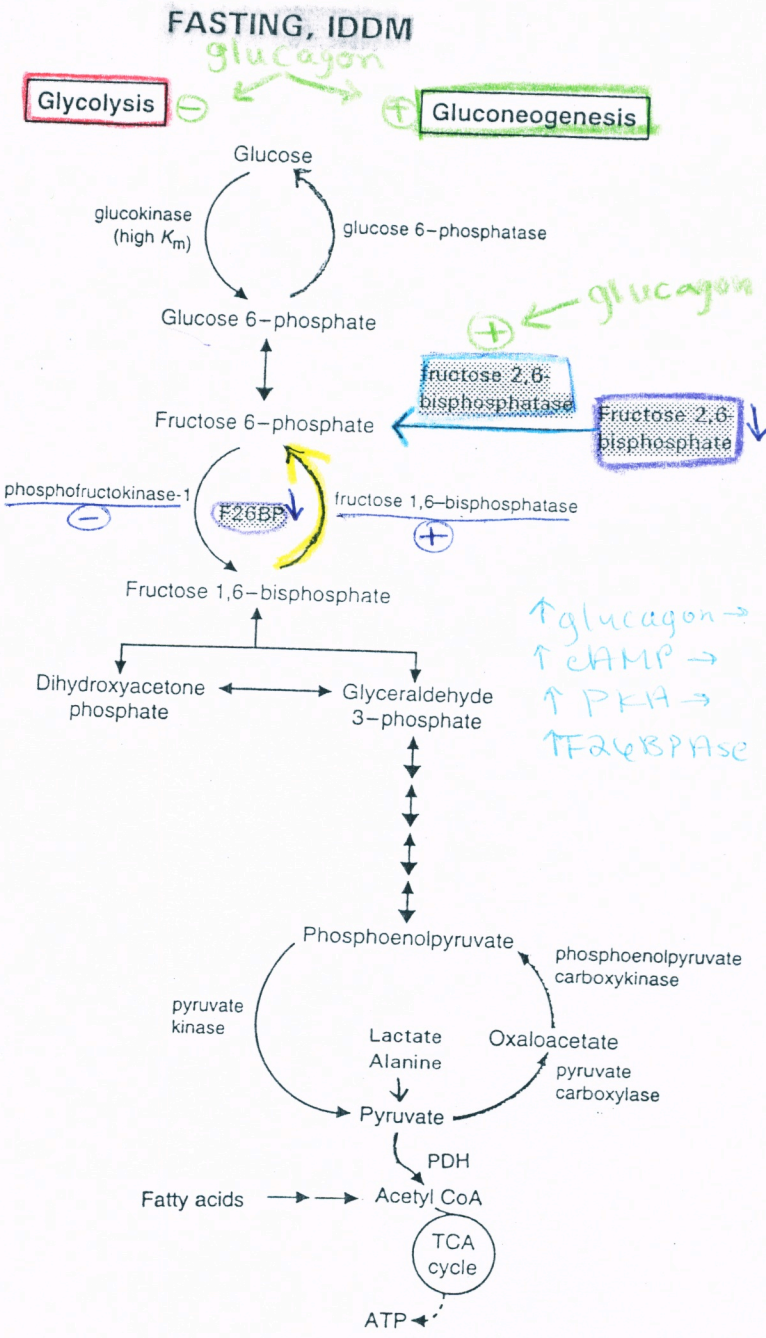
• lactic acidosis interferes w/ excretion of uric acid from kidney causing gout

Glucogenic and Ketogenic Amino Acids

Ketogenic	Ketogenic and Glucogenic	Glucogenic
Leucine Lysine CANNOT be converted to glucose in the liver	Phenylalanine Tyrosine Tryptophan Isoleucine Threonine	All others especially alanine

RECIPROCAL REGULATION OF HEPATIC GLYCOLYSIS & GLUCONEOGENESIS





* insulin ↑ in blood, F26BP ↑ in liver
- insulin stimulates glycolysis in liver to convert glucose to FA
- PFK2 is used to convert excess carb to fat

⊖ ATP alanine ⊕ F16BP

pyruvate → acetyl CoA
PDH

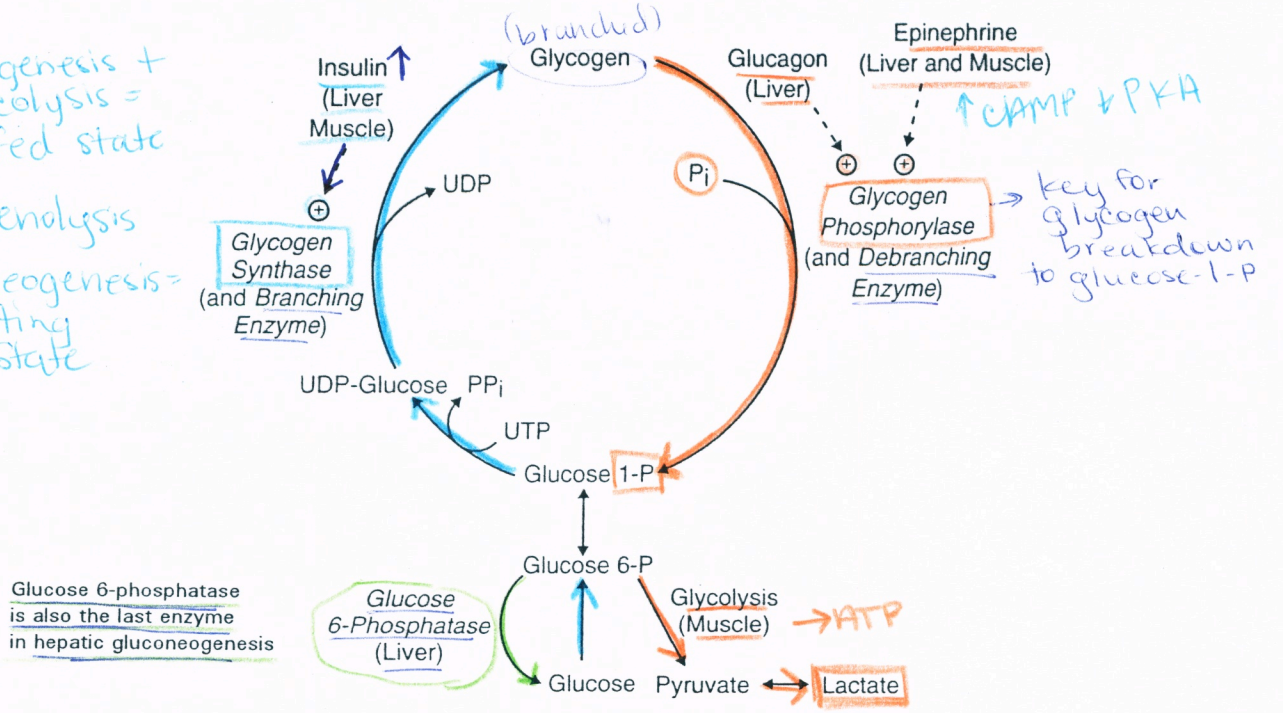
⊖ ATP, NADH acetyl CoA

GLYCOGENESIS & GLYCOGENOLYSIS

synthesis — degraded

glycogenesis + glycolysis = fed state

glycogenolysis + gluconeogenesis = fasting state



liver only glucose producer btwn meals
- initiation of exercise fueled by glycogen breakdown

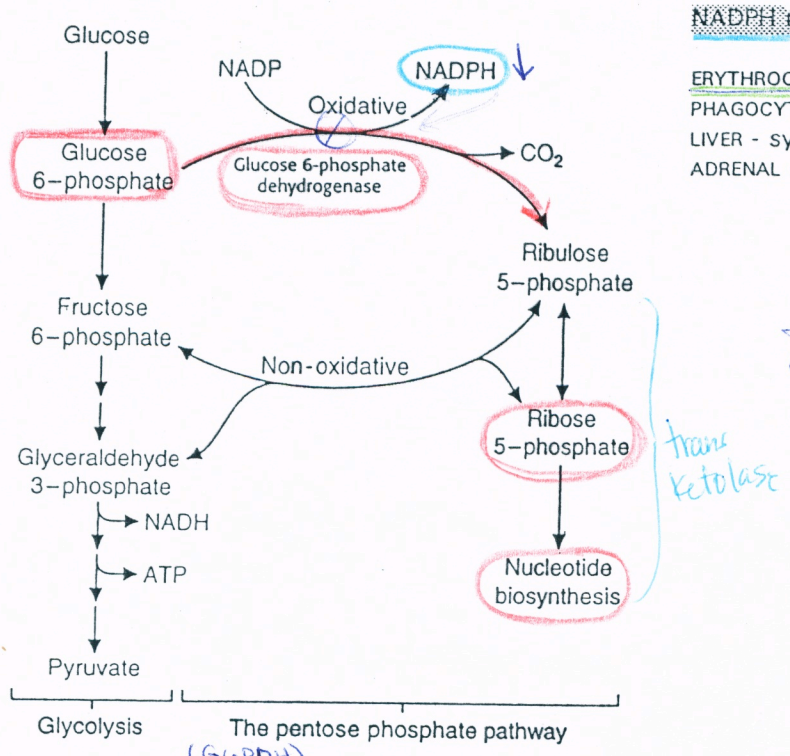
Glycogen Storage Diseases

Type	Deficient Enzyme	Cardinal Clinical Features	Glycogen Structure
I: von Gierke	Glucose-6-phosphatase (liver only: glycogen storage disease)	Severe hypoglycemia (fasting), lactic acidosis, hepatomegaly, hyperlipidemia, hyperuricemia, short stature (doll-like facies)	Normal (gluconeogenesis out + glycogenolysis; lactic acidosis w/ hypoglycemia diagnostic for tissue)
II: Pompe	Lysosomal (lysosomes) α-1,4-glucosidase	Cardiomegaly, muscle (heart) weakness, death by 2 years	Glycogen-like material in inclusion bodies
III: Cori	Glycogen debranching enzyme (glycogen phosphorylase)	Mild hypoglycemia, liver enlargement	Short outer branches Single glucose residue at outer branch
IV: Andersen (amylopectinosis)	Branching enzyme	Infantile hypotonia, cirrhosis, death by 2 years	Very few branches, especially toward periphery
V: McArdle	Muscle glycogen phosphorylase (skeletal muscle only)	Muscle cramps and weakness on exercise, myoglobinuria	Normal
VI: Hers	Hepatic glycogen phosphorylase	Mild fasting hypoglycemia, hepatomegaly, cirrhosis	Normal

THE PENTOSE PHOSPHATE PATHWAY & DISACCHARIDE METABOLISM

HMP Shunt

CGD = ↓ NADPH oxidase



transketolase

NADPH IS CONSUMED (AND NADP RECYCLED) IN ANABOLIC PATHWAYS

oxidant stress protection

ERYTHROCYTE - synthesis of reduced glutathione
PHAGOCYTE - synthesis of superoxide anion
LIVER - synthesis of fatty acids and cholesterol
ADRENAL CORTEX, OVARY, TESTIS - synthesis of steroid hormones

GLUCOSE 6-P DEHYDROGENASE DEFICIENCY → X linked recessive

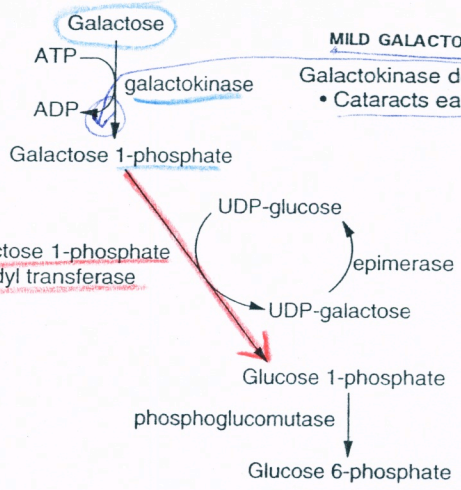
Partial
- acute episodes of oxidant-induced hemolytic anemia (infections, drugs or fava beans) → causes
- jaundice, hemoglobinuria
- Heinz bodies → from oxidative damage
- normal erythrocyte 2,3-BPG

drugs: antimalarials + sulfa drugs

Severe
- chronic hemolytic anemia + immunodeficiency
- CGD-like symptoms

*NADPH ↓ when G6PDH (G6PDase) goes out
normally generated in anabolic pathways to protect from oxidative stress

lactose (milk sugar) [FED STATE]



MILD GALACTOSEMIA (defect)
Galactokinase deficiency
- Cataracts early in life only

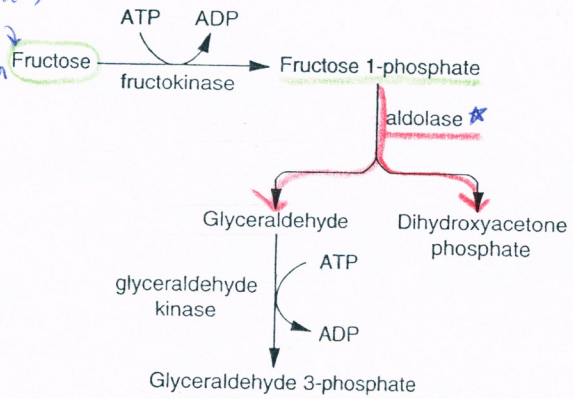
CLASSIC GALACTOSEMIA
Gal 1-P uridyltransferase deficiency
- Cataracts early in life
- Vomiting, diarrhea following lactose ingestion
- Lethargy
- Liver damage, hyperbilirubinemia
- Mental retardation

1-2 weeks after birth

galactose 1-phosphate uridyl transferase

*aldose reductase in lens breaks down excess galactose, leads to cataracts
*galactose-1-P accumulates most in liver & brain
- remove milk from diet to correct

(table sugar) sucrose → fruit



FRUCTOSE INTOLERANCE
Aldolase B (fructose 1-P aldolase activity) deficiency:
- Lethargy, vomiting
- Liver damage, hyperbilirubinemia
- Hypoglycemia
- Hyperuricemia

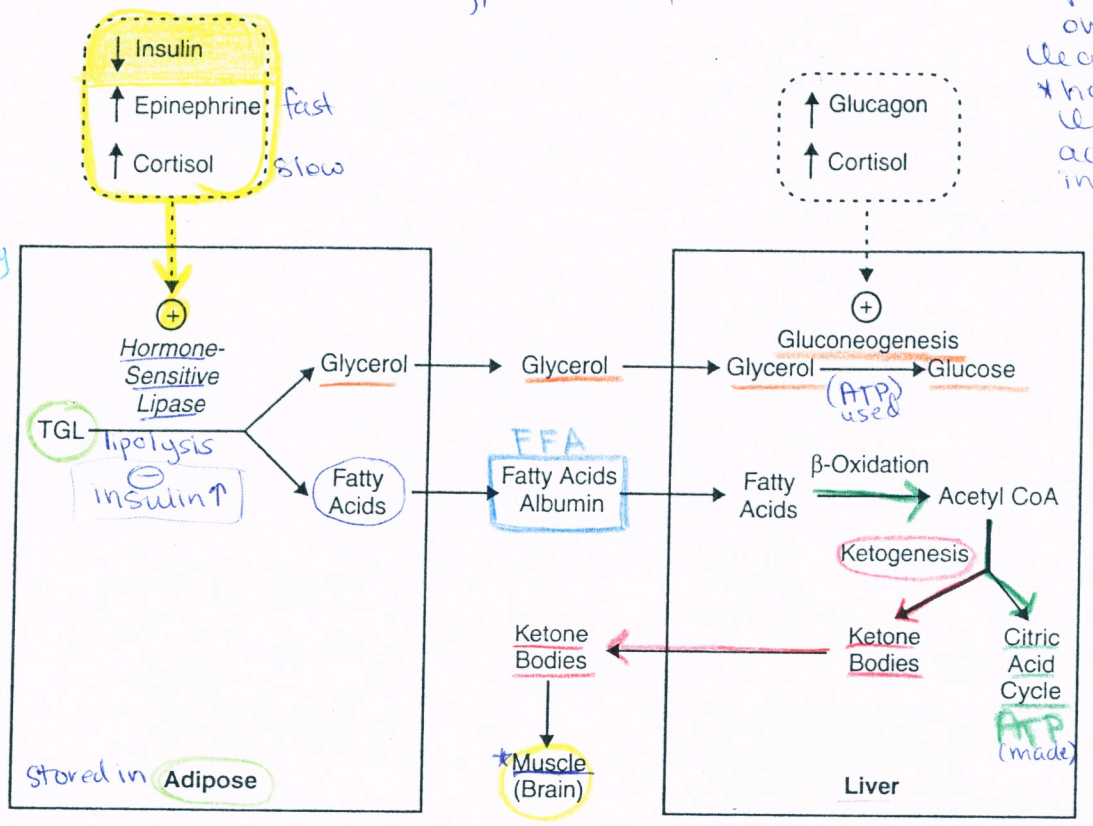
*see this problem when baby comes OFF milk and starts eating sugar / fruit

Fructose elevates in blood but does NOT cause cataracts only tissue degrading this is liver so this is a liver damage issue. won't see brain damage

TRIGLYCERIDE DEGRADATION & FATTY ACID OXIDATION

fasting, exercise, IDDM

- uncontrolled diabetic, lipolysis & ketogenesis overactivated leading to DKA
- hormone sensitive lipase is the big activated one in this case

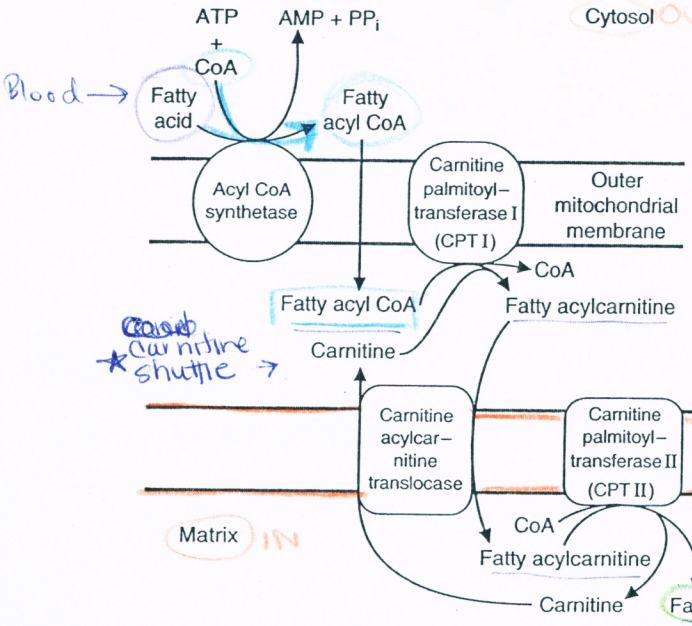


- doesn't usually happen in type 2 b/c insulin is present

- FFA accumulate in blood ONLY after lipolysis
- insulin inhibits lipolysis

- muscle is major tissue using ketones
- brain only uses after 3-4 days of fasting

- defect in β-oxidation enzyme; liver; ketones & ATP ↓, resulting problem in gluconeogenesis so fasting hypoglycemia w/ low ketones



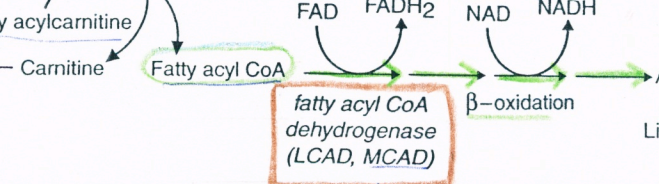
Myopathic CAT/CPT Deficiency (liver enzymes ok)
- muscle aches, weakness
- Myoglobulinuria
- Provoked by prolonged exercise especially if fasting
- Biopsy: elevated muscle triglyceride

- older kids (college) & late in exercise

vs McArdles which is kid who cramps at initiation of exercise

→ definitive diagnosis

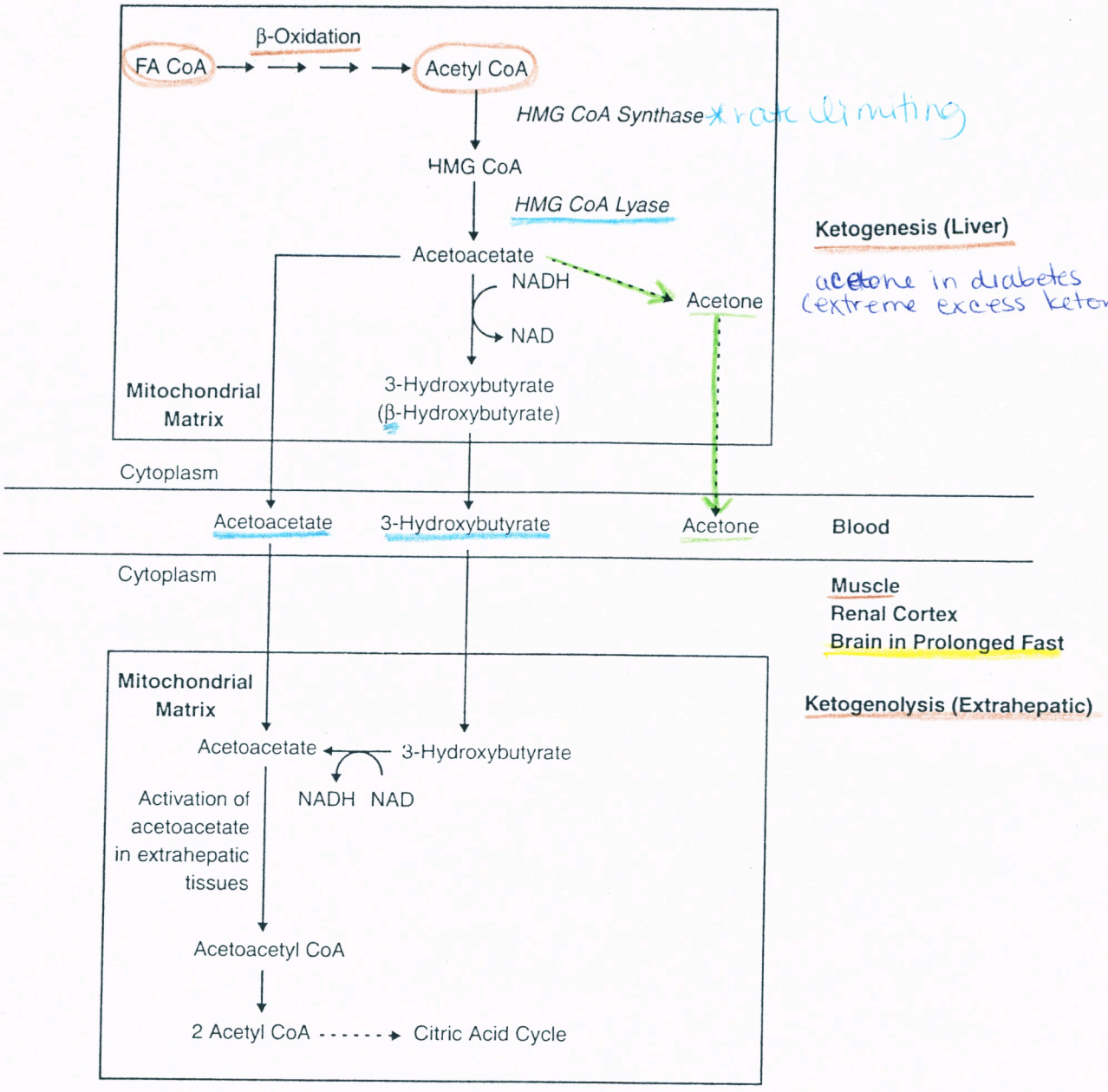
- Carnitine shuttle def. is myopathic



MCAD Deficiency
- Fasting hypoglycemia
- No ketone bodies (hypoketosis)
- Dicarboxylic acidemia
- Vomiting
- Coma, death

liver ox. defect (pox problem)

KETONE BODY SYNTHESIS & DEGRADATION



rate limiting

Ketogenesis (Liver)

acetone in diabetes (extreme excess ketones)

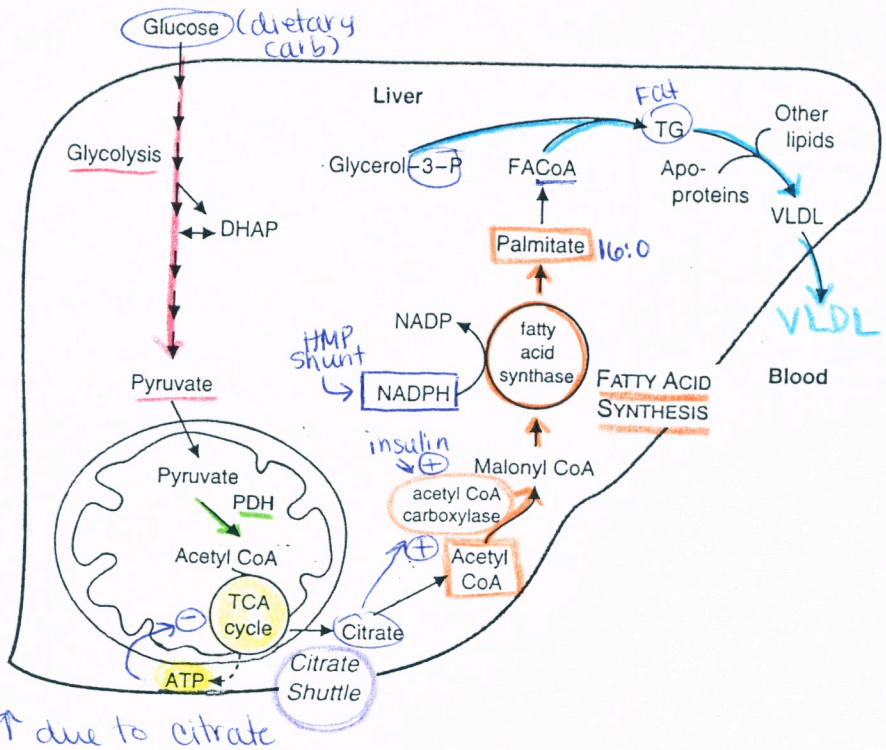
Muscle
Renal Cortex
Brain in Prolonged Fast

Ketogenolysis (Extrahepatic)

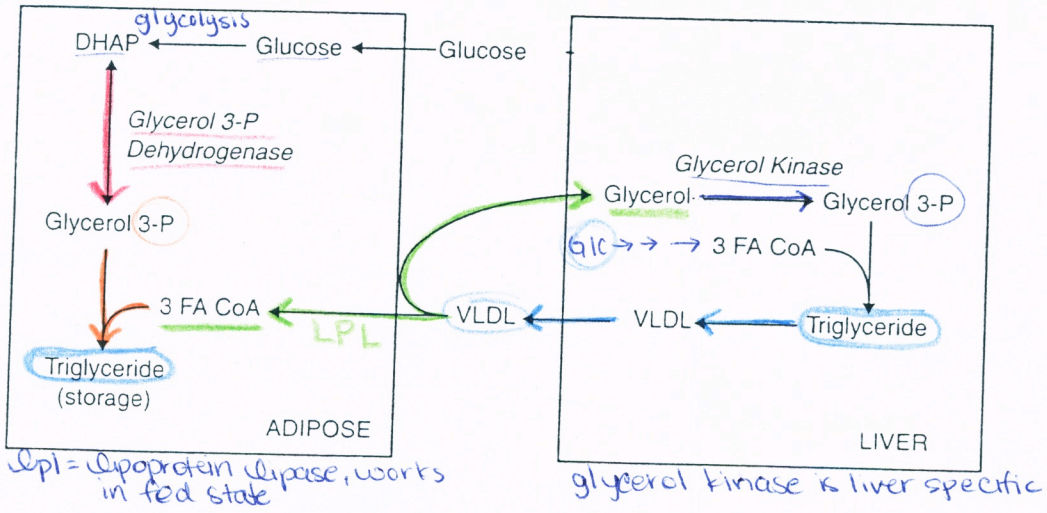
POSTPRANDIAL SYNTHESIS AND STORAGE OF FAT

* insulin ↑ = F26BP ↑

excess incoming carb → fat



* well fed liver, citrate ↑ due to citrate shuttle to make FA



lpl = lipoprotein lipase, works in fed state

glycerol kinase is liver specific

⊗ adipocyte testing for glycerol kinase gene is positive but expression negative

LIPOPROTEIN METABOLISM

Classes of Lipoproteins and Important Apoproteins

Lipoprotein	Functions	Apoproteins	Functions
Chylomicrons	Transport dietary triglyceride and cholesterol from intestine to tissues	apoB-48 (fat out of gut) apoC-II apoE	Secreted by epithelial cells Activates lipoprotein lipase Uptake by liver of remnants
VLDL	Transports triglyceride from liver to tissues	apoB-100 (out of liver) apoC-II apoE	Secreted by liver Activates lipoprotein lipase Uptake of remnants by liver (IDL)
LDL	Delivers cholesterol into cells	apoB-100	Uptake by liver and other tissues via LDL receptor (apoB-100 receptor)
IDL (VLDL remnants)	Picks up cholesterol from HDL to become LDL Picked up by liver	apoE	Uptake by liver
HDL	Picks up cholesterol accumulating in blood vessels Delivers cholesterol to liver and steroidogenic tissues via scavenger receptor (SR-B1) → HDL receptors Shuttles apoC-II and apoE in blood	apoA-1	Activates lecithin cholesterol acyltransferase (LCAT) to produce cholesterol esters → facilitates continuous removal of cholesterol from blood vessels

reproductive & adrenal

A-1
B-48
B-100
C-II
E

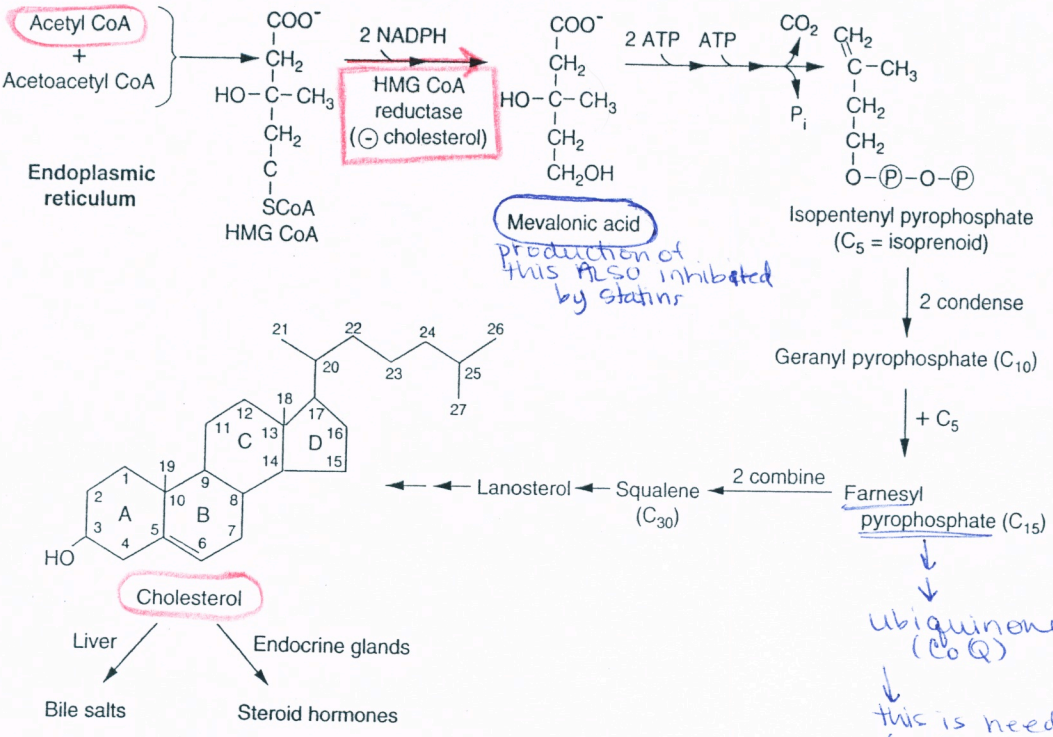
* B48 - fat malabsorption → steatorhea & ↓ fat soluble vitmins
* B100 - TG in blood ↓, TG in liver ↑ (fatty liver)
* CII - hyperTG w/o major cholesterol problems
* E - remnants accumulate in blood → hyperTG & hypercholesterol
* AI - HDL ↓, cholesterol buildup in b.v.

Primary Hyperlipidemias

Type	Deficiency	Lipid Elevated in Blood	Lipoprotein Elevated in Blood	Comments
I	Familial lipoprotein lipase (rare) apoC-II (rare) Autosomal recessive	Triglyceride	Chylomicrons	Red-orange eruptive xanthomas Fatty liver Acute pancreatitis Abdominal pain after fatty meal
IIa (late onset)	Familial hypercholesterolemia Autosomal dominant (Aa 1/500, AA 1/10^6) * LDL (apoB100) rec. deficiency	Cholesterol	LDL	High risk of atherosclerosis and coronary artery disease (autosomal dominant) Homozygous condition usually death <20 years Xanthomas of the Achilles tendon (bumps on back of feet) Tuberous xanthomas on elbows Xanthelasmas (bumps around eyes) Corneal arcus (bright blue ring around cornea)

↓ vit. E: peripheral neuropathy, pigmented retina, acanthocytes, ataxia
↓ vit. A: night blindness

CHOLESTEROL SYNTHESIS & SPHINGOLIPID STORAGE DISEASES



production of this ALSO inhibited by statins

Ubiquinone (CoQ) → [statins inhibit this too]

this is needed for oxphos (make energy) can be part of rhabdomyolysis

Cholesterol biosynthesis. *HMG CoA* = hydroxymethylglutaryl CoA

*HMG CoA reductase inhibited by ↑ cholesterol & statins

Genetic Deficiencies of Sphingolipid Catabolism: Ashkenazi Jews

Disease	Lysosomal Enzyme Missing	Substrate Accumulating in Inclusion Body	Symptoms
Tay-Sachs	Hexosaminidase A *	Ganglioside GM_2	Cherry red spots in macula Blindness, startle reflex Psychomotor retardation Death usually <2 years
Gaucher	Glucocerebrosidase	Glucocerebroside	Type 1: Adult Hepatosplenomegaly Erosion of bones, fractures Pancytopenia or thrombocytopenia Characteristic macrophages (crumpled paper inclusions)
Niemann-Pick	Sphingomyelinase	Sphingomyelin	Hepatosplenomegaly Microcephaly, severe mental retardation Zebra bodies in inclusions Characteristic foamy macrophages Early death

higher prevalence

accumulation in nerve cells

doesn't involve nervous system, just bones & marrow

tired from general marrow suppression

40% show cherry red spots on macula

ESSENTIAL AMINO ACIDS & NITROGEN BALANCE

Essential Amino Acids

Arginine*	Methionine
Histidine	Phenylalanine
Isoleucine	Threonine
Leucine	Tryptophan
Lysine	Valine

*Essential only during periods of positive nitrogen balance.

Phe → Tyrosine
Val
Trp

Thr
Ile
Met

His
Arg
Leu
Lys

Nin = Nout

Nitrogen Balance

Nitrogen balance is the (normal) condition in which the amount of nitrogen incorporated into the body each day exactly equals the amount excreted.

Nin < Nout

Negative nitrogen balance occurs when nitrogen loss exceeds incorporation and is associated with:

- Protein malnutrition (kwashiorkor) → children, not caloric def. just no protein, pot bellies + generalized edema (albumin↓)
- * A dietary deficiency of even one essential amino acid
- Starvation (marasmus, skeleton look)
- Uncontrolled diabetes
- Infection

Vegetable proteins w/o substituting (only rice or corn diet)

Nin > Nout

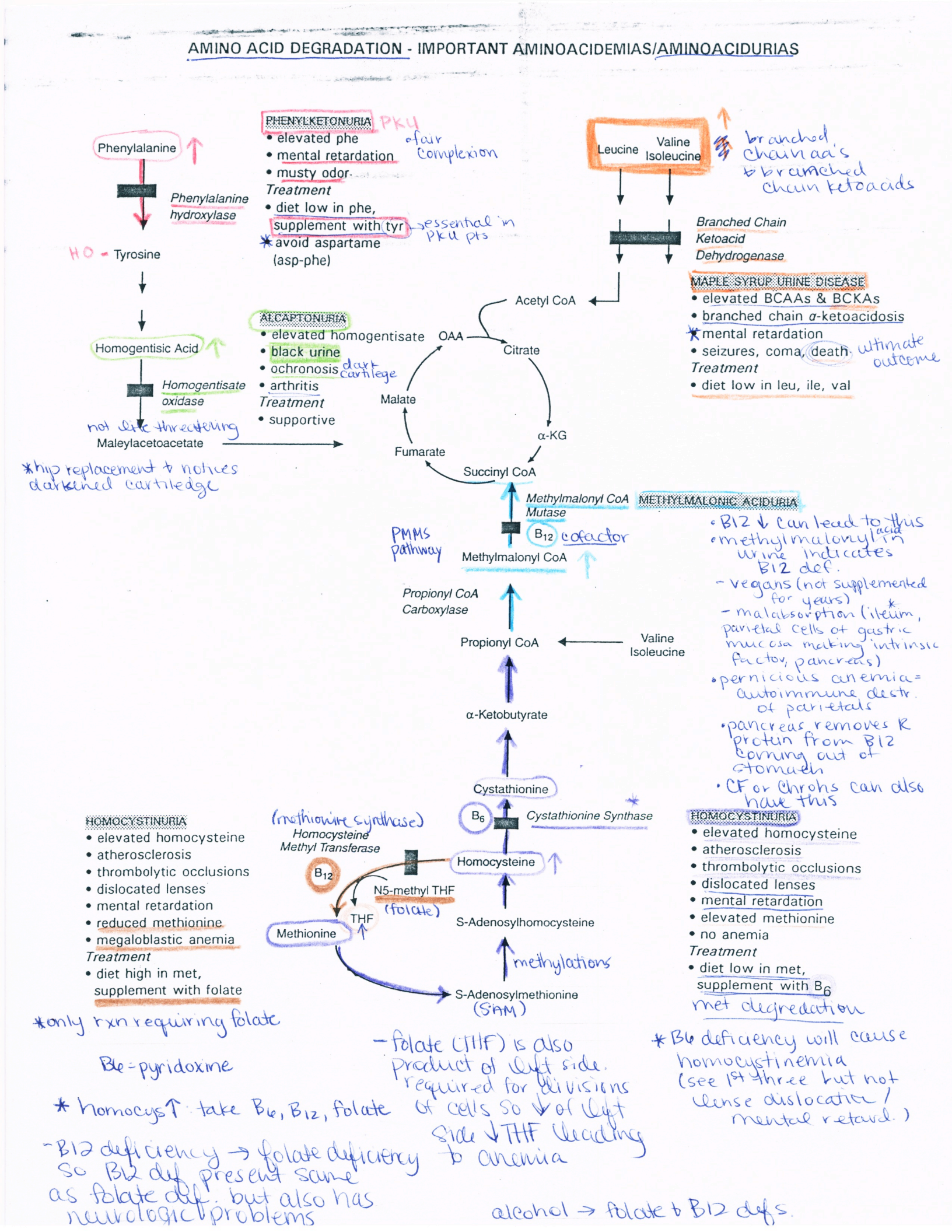
Positive nitrogen balance occurs when the amount of nitrogen incorporated exceeds the amount excreted and is associated with:

- Growth
- Pregnancy
- Recovery phase of injury or surgery
- Recovery from condition associated with negative nitrogen balance

Products of Amino Acids

Amino Acid	Products
* Tyrosine (hi yield!)	Thyroid hormones T_3 and T_4 Melanin Catecholamines (dopa → norE → epi)
Tryptophan	Serotonin NAD, NADP
Arginine	Nitric oxide (NO)
Glutamate	γ-Aminobutyric acid (GABA)
Histidine	Histamine

AMINO ACID DEGRADATION - IMPORTANT AMINOACIDEMIAS/AMINOACIDURIAS



PHENYLKETONURIA PKU
- elevated phe
- mental retardation
- musty odor

Treatment
- diet low in phe, supplement with tyr
- ✱avoid aspartame (asp-phe)

fair complexion

essential in PKU pts

branched chain aa's & branched chain ketoacids

MAPLE SYRUP URINE DISEASE
- elevated BCAAs & BCKAs
- branched chain α-ketoacidosis
- ✱mental retardation
- seizures, coma, death

ultimate outcome

Treatment
- diet low in leu, ile, val

ALCAPTONURIA
- elevated homogentisate
- black urine
- ochronosis dark cartilege
- arthritis

Treatment
- supportive

not life threatening

✱hip replacement & notices darkened cartilage

METHYLMALONIC ACIDURIA
- B12 ↓ can lead to this
- methylmalonyl acid in urine indicates B12 def.
- vegans (not supplemented for years)
- malabsorption (ileum✱, parietal cells of gastric mucosa making intrinsic factor, pancreas)
- pernicious anemia = autoimmune destr. of parietals
- pancreas removes R protein from B12 coming out of stomach
- CF or Chrohs can also have this

PMMS pathway

HOMOCYSTINURIA
- elevated homocysteine
- atherosclerosis
- thrombolytic occlusions
- dislocated lenses
- mental retardation
- reduced methionine
- megaloblastic anemia

Treatment
- diet high in met, supplement with folate

✱only rxn requiring folate

B6 = pyridoxine

HOMOCYSTINURIA
- elevated homocysteine
- atherosclerosis
- thrombolytic occlusions
- dislocated lenses
- mental retardation
- elevated methionine
- no anemia

Treatment
- diet low in met, supplement with B_6

met degredation

✱ B6 deficiency will cause homocystinemia (see 1st three but not lense dislocation / mental retard.)

✱ homocys↑ take B_6, B_{12}, folate

- folate (THF) is also product of left side. required for divisions of cells so ↓ of left side ↓ THF leading to anemia

- B12 deficiency → folate deficiency so B12 def present same as folate def. but also has neurologic problems

alcohol → folate & B12 defs.

GENETIC DISORDERS OF THE UREA CYCLE (in liver)

A. General Features

Clinical Symptoms
- lethargy, vomiting, irritability
- hyperventilation, respiratory alkalosis
- convulsions, cerebral edema, coma

panting to blow off acid

Lab Results defect in urea cycle
- hyperammonemia
- elevated plasma and urinary glutamine
- abnormally-low blood urea nitrogen (BUN)

B. Differential Diagnosis

ENZYME DEFECT

1. *Carbamoyl-P synthetase I* - *hyperammonemia Type I*
   - low citrulline
   - no orotic aciduria
   - autosomal recessive

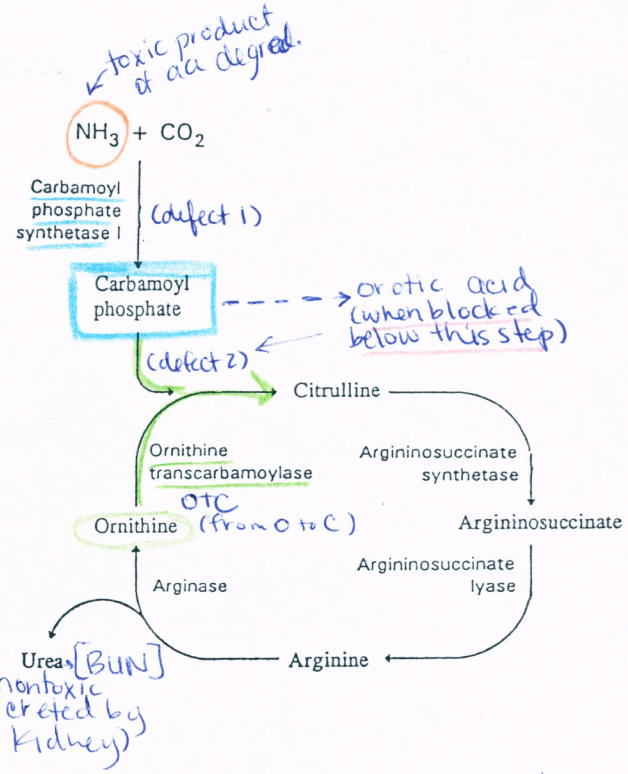
2. *Ornithine transcarbamoylase* - *hyperammonemia Type II*
   - low citrulline
   - orotic aciduria
   - X-linked recessive

megaloblastic anemia not correctable w/ B12

3. *Argininosuccinate synthetase - citrullinemia*
   - very high citrulline
   - low argininosuccinate

4. *Argininosuccinate lyase - argininosuccinic acidemia*
   - moderately high citrulline
   - high argininosuccinate

5. *Arginase - argininemia*
   - high arginine

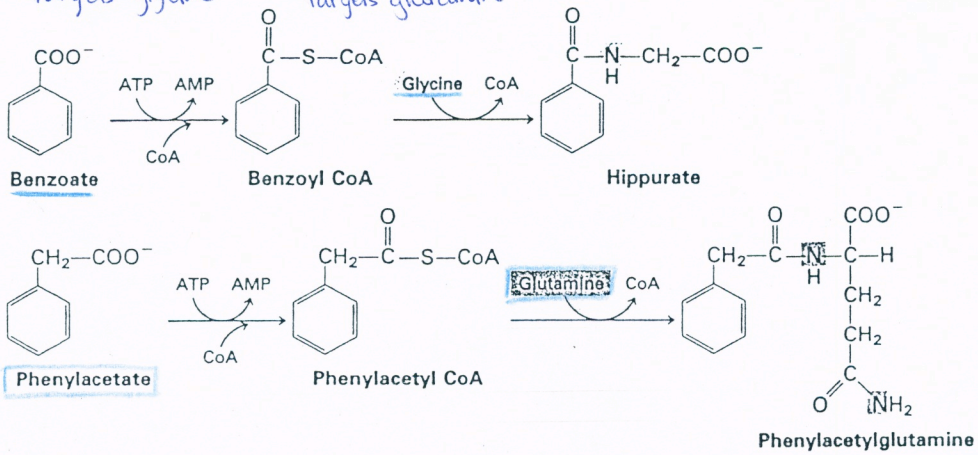


*glutamine synthetase tries to break down elevated NH_3 when issue w/ urea cycle → ↑ glutamine

C. Treatment

Severe Hyperammonemia
- exchange transfusion
- IV benzoate + phenylacetate

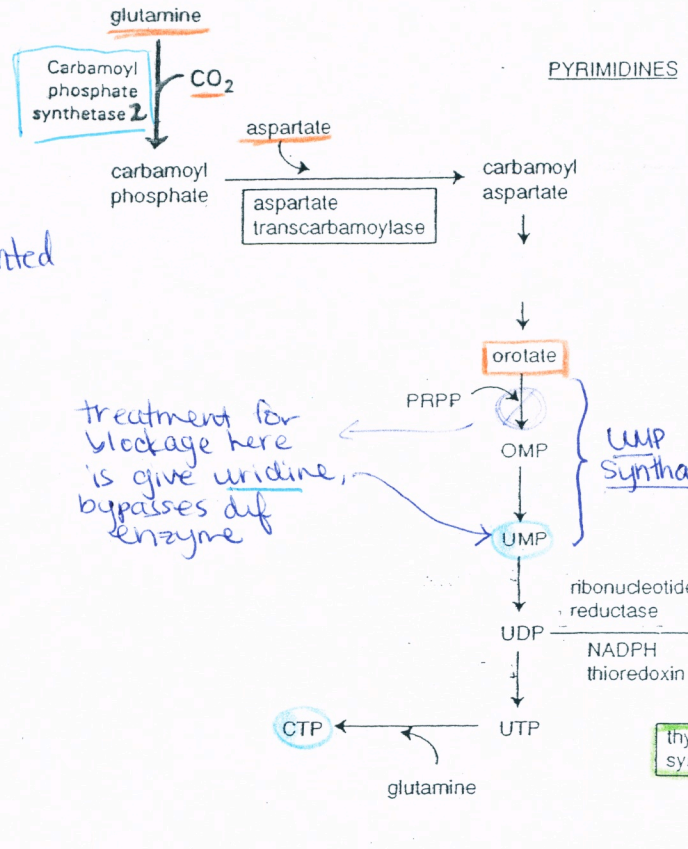
targets glycine — targets glutamine



Disease Management
- low protein, high carb diet supplemented with arginine (except argininemia)
- oral phenylbutyrate, a pro-drug which is converted to phenylacetate

Cytosine
Uracil
Thymine the py

PYRIMIDINE NUCLEOTIDE BIOSYNTHESIS



• problem w/ this pwy leads to megaloblastic anemia & hypersegmented neutrophils

treatment for blockage here is give uridine, bypasses def enzyme

• folate needed for production of thymine
• thymidylate synthase activity ↓ in folate def.

Two Orotic Aciduria

1. Hyperammonemia
   No megaloblastic anemia
   - Pathway: Urea cycle
   - Enzyme deficient: OTC
2. Megaloblastic anemia
   No hyperammonemia
   - Pathway: Pyrimidine synthesis
   - Enzyme deficient: UMP synthase

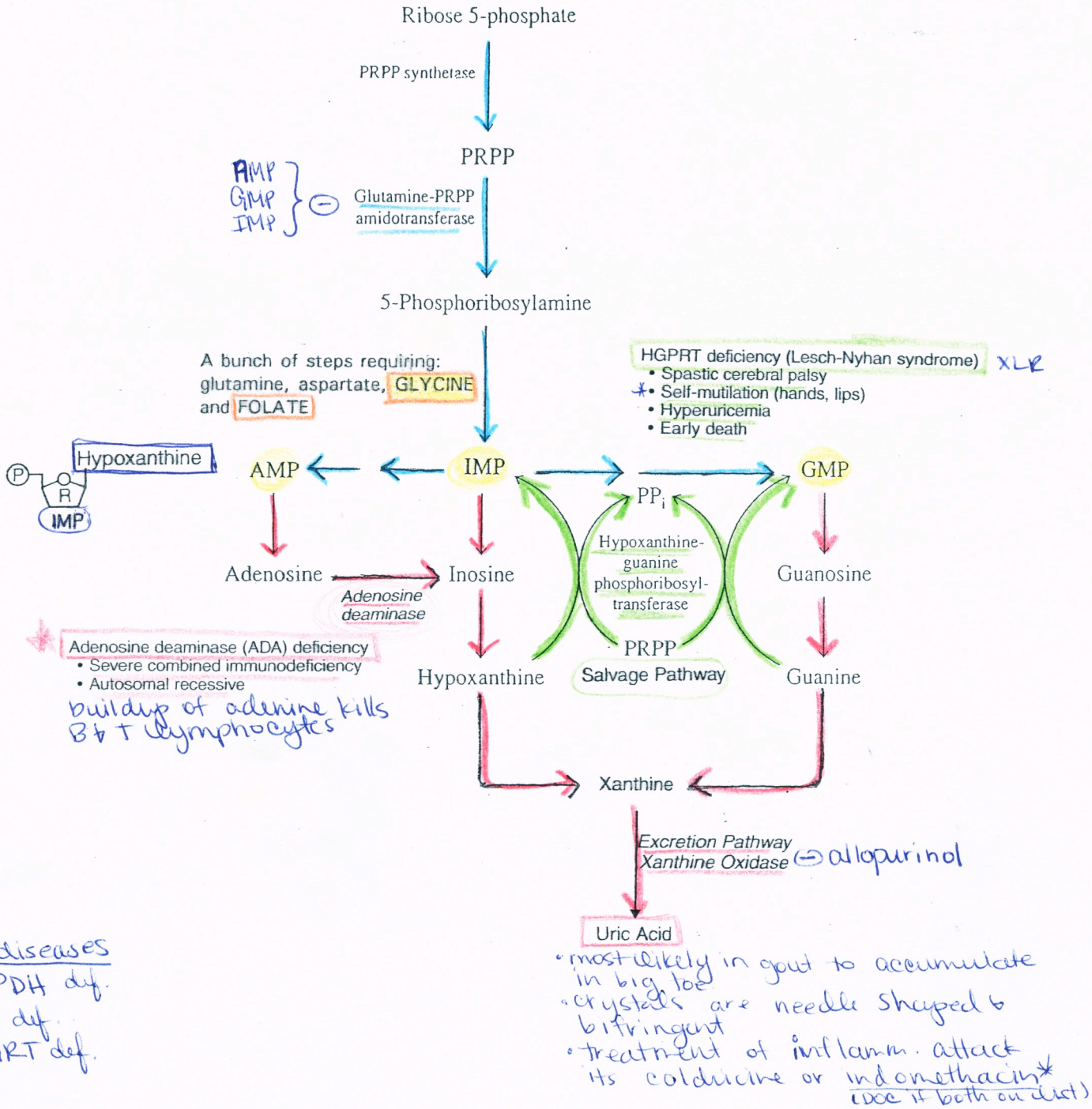
Folate deficiency: megaloblastic anemia

But no orotic aciduria (blockage ↓ this step)

PURINE NUCLEOTIDE SYNTHESIS, DEGRADATION & SALVAGE

Pure As Gold (Inosine also part of purines)

adenine guanine



XLR diseases
- G6PDH def.
- OTC def.
- HPGRT def.

- most likely in gout to accumulate in big toe
- crystals are needle shaped & bifringent
- treatment of inflamm. attack is colchicine or indomethacin* (DOC if both on list)