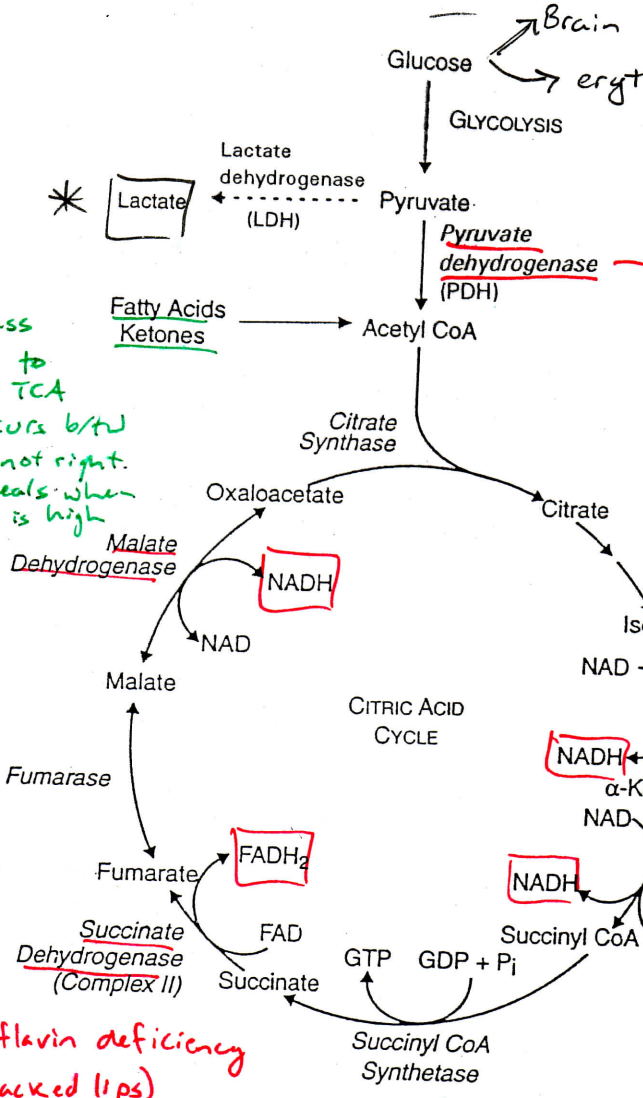
AEROBIC OXIDATION OF FUELS FOR ENERGY
PYRUVATE DEHYDROGENASE & THE CITRIC ACID (KREBS) CYCLE



Brain must always have — goes through Krebs etc.

erythrocyte has no Krebs or PDH
They use Lactate Dehydrogenase b/c no Mitochondria (or other anaerobic tissues)

Bypass PDH to enter TCA
This occurs b/tw meals, not right after meals when glucose is high

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

Vitamins
1. Thiamine * B1
2. None
3. Pantothenate B5
4. Riboflavin B2
5. Niacin B3

W/water soluble vitamin deficiency will have low PDH activity
Mostly see CNS problems by blocking progression into TCA cycle

Dehydrogenases produce energy in the form of NADH (or $FADH_2$)
3 NADH, 1 $FADH_2$

α-Ketoglutarate Dehydrogenase → same cofactors as PDH

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

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

In riboflavin deficiency (rash, cracked lips) impairs Succinate DH b/c it produces $FADH_2$

Krebs Intermediates
Citrate Can
Is I
Krebs Keep
Starting Selling
Substrate Sex
For For
Making Money
Oxaloacetate officer

THIAMINE DEFICIENCY — cannot degrade glucose b/c ↓ PDH activity

Wernicke-Korsakoff Syndrome ← Alcoholic

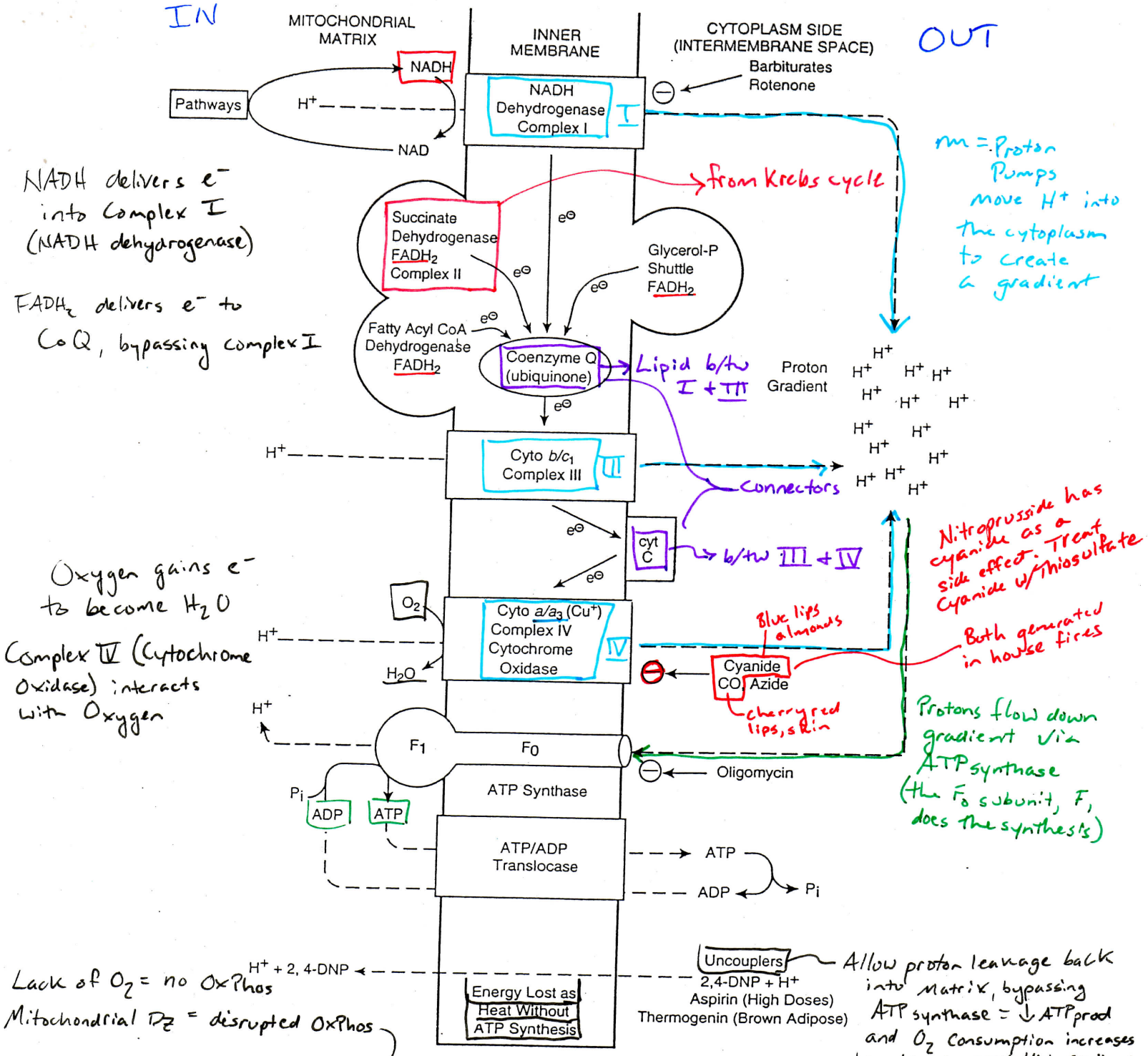
Wernicke's
- peripheral neuropathy, ataxia
- nystagmus, ophthalmoplegia → paralysis of eyes

Korsakoff's
- amnesia, confabulation
- disorientation, psychosis

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

Mitochondrial Dz's
During Ischemic event → everything becomes Anaerobic (LDH)

OXIDATIVE PHOSPHORYLATION — uses NADH from Krebs



NADH delivers e⁻ into Complex I (NADH dehydrogenase)

FADH₂ delivers e⁻ to CoQ, bypassing complex I

Oxygen gains e⁻ to become H_2O

Complex IV (Cytochrome Oxidase) interacts with Oxygen

= Proton Pumps move H+ into the cytoplasm to create a gradient

Nitroprusside has cyanide as a side effect. Treat cyanide w/ thiosulfate

Both generated in house fires

Protons flow down gradient via ATP synthase (the F_0 subunit, F_1 does the synthesis)

Lack of O_2 = no OxPhos

Mitochondrial Dz = disrupted OxPhos

Allow proton leakage back into matrix, bypassing ATP synthase = ↓ ATP prod and O_2 consumption increases b/c try to reestablish gradient

Mitochondrial Diseases – mitochondrial gene mutations – esp Complexes I III IV ATP synthase

Maternal Inheritance
└ mother always passes on

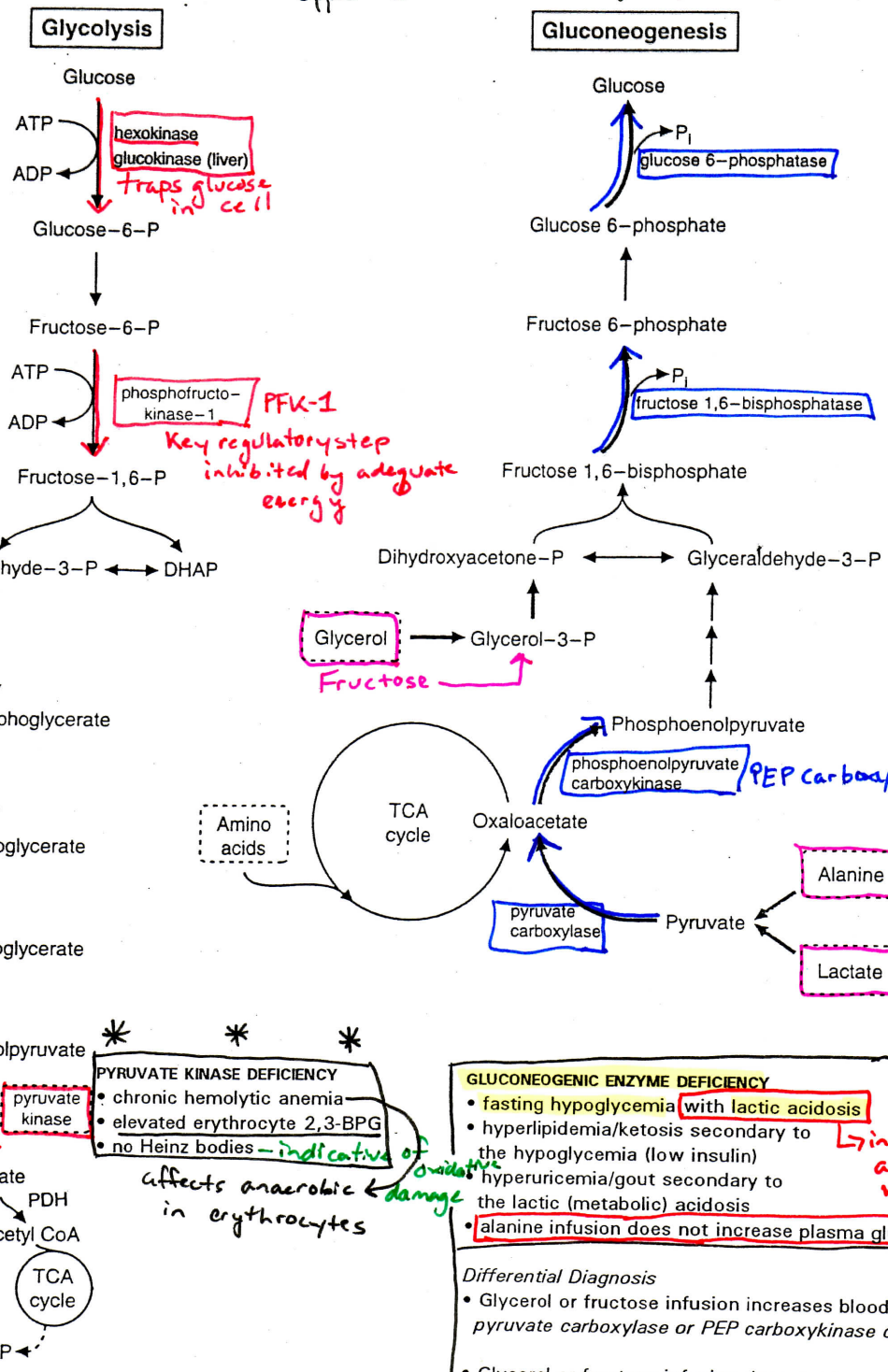
- Leber hereditary optic neuropathy = LHON
- MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
- Myoclonic epilepsy with ragged red muscle fibers

GLYCOLYSIS & GLUCONEOGENESIS

opposites

↳ strictly liver during fasting – esp overnight fast

Irreversible —



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

↳ interferes w/uric acid excretion in kidney

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

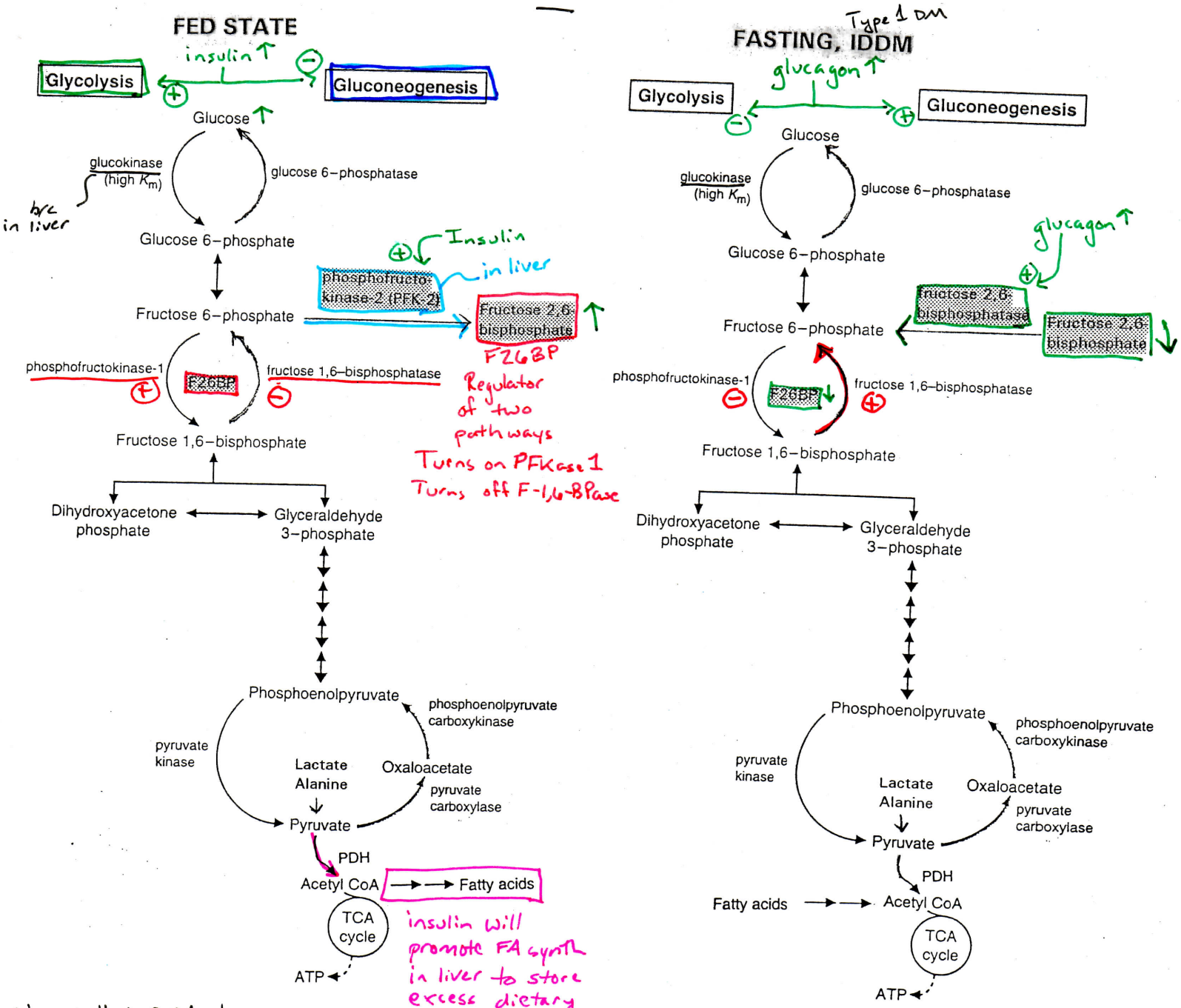
Liver glycogen only lasts for 24 hrs of fasting. After that use gluconeogenesis.

Glucogenic and Ketogenic Amino Acids

Ketogenic *	Ketogenic and Glucogenic	Glucogenic
Leucine Lysine	Phenylalanine Tyrosine Tryptophan Isoleucine Threonine	All others esp. Ala

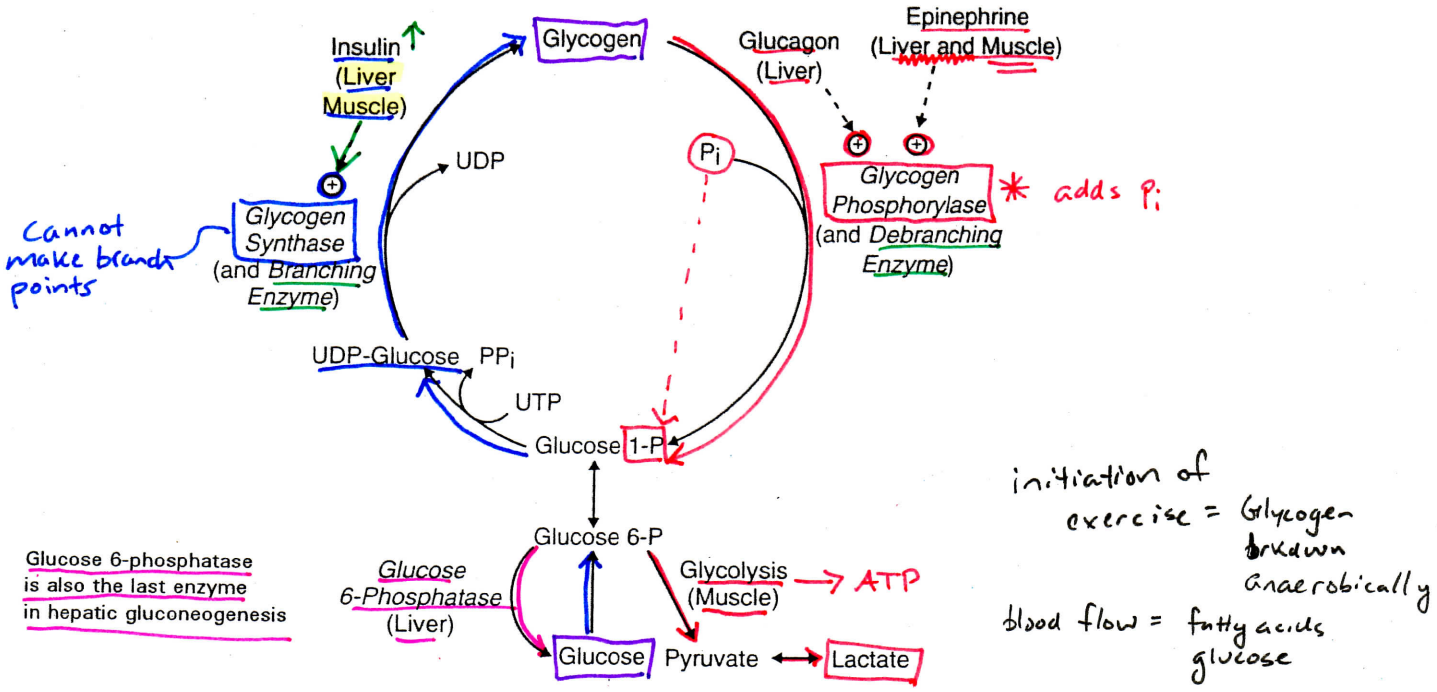
Cannot be converted to Glucose in Liver

RECIPROCAL REGULATION OF HEPATIC GLYCOLYSIS & GLUCONEOGENESIS



F26BP levels follow insulin levels

GLYCOGENESIS & GLYCOGENOLYSIS

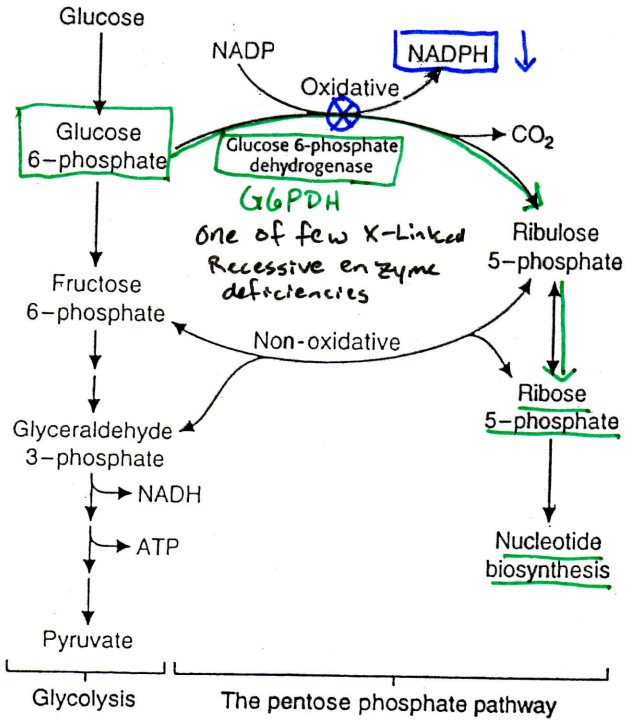


Glycogen Storage Diseases

Type	Deficient Enzyme	Cardinal Clinical Features	Glycogen Structure
I: von Gierke	Glucose-6-phosphatase	Severe hypoglycemia, lactic acidosis, hepatomegaly, hyperlipidemia, hyperuricemia, short stature	Normal
II: Pompe	Lysosomal α-1,4-glucosidase	Cardiomegaly, muscle weakness, death by 2 years	Glycogen-like material in inclusion bodies
III: Cori	Glycogen debranching enzyme	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	Muscle cramps and weakness on exercise	Normal
VI: Hers	Hepatic glycogen phosphorylase	Mild fasting hypoglycemia, hepatomegaly, cirrhosis	Normal

Type I: von Gierke — Skinny arms/legs, Doll like facial features
Deficient Enzyme: Liver ↳ glycogenolysis, ↳ gluconeogen
Cardinal Clinical Features: when fasting; 2° to lactic acidosis; 2° to hypoglycemia
Glycogen Structure: fasting hypoglycemia + Lactic acidosis = problem in gluconeogenesis
Type II: Pompe — glycogen/Lysosomal
Type V: McArdle — "myophosphorylase"
Cardinal Clinical Features: myoglobinuria
Glycogen Structure: Normal — Child w/exercise intolerance

THE PENTOSE PHOSPHATE PATHWAY & DISACCHARIDE METABOLISM



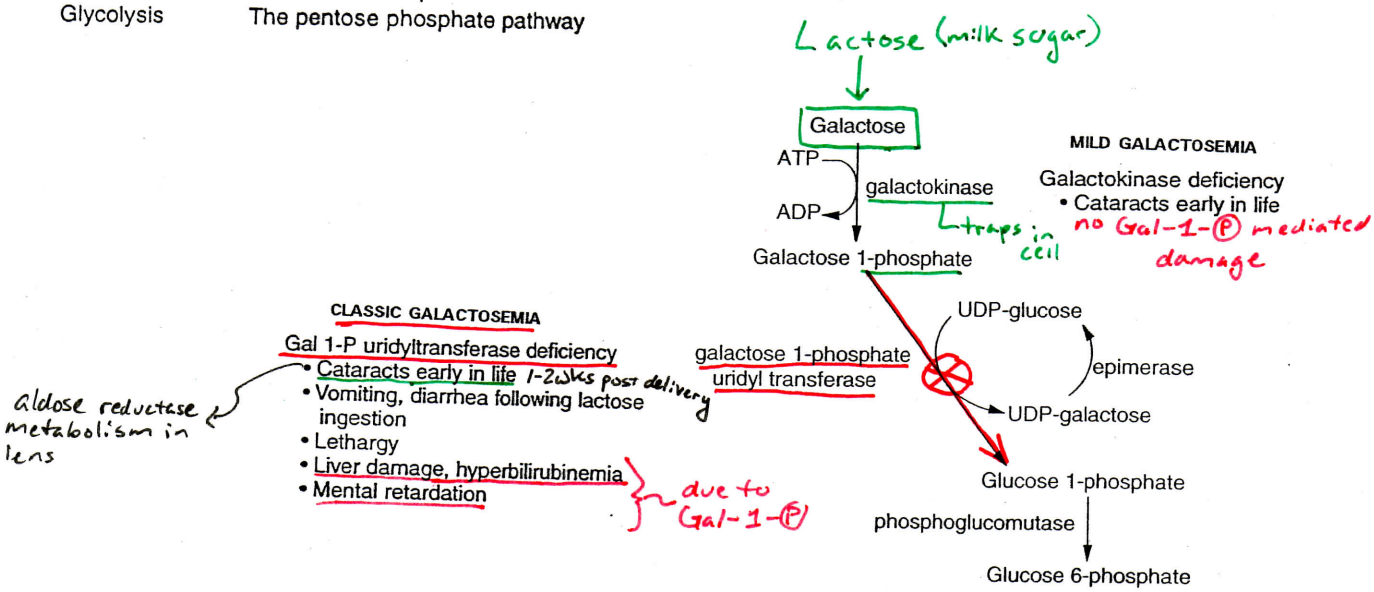
NADPH IS CONSUMED (AND NADP RECYCLED) IN ANABOLIC PATHWAYS

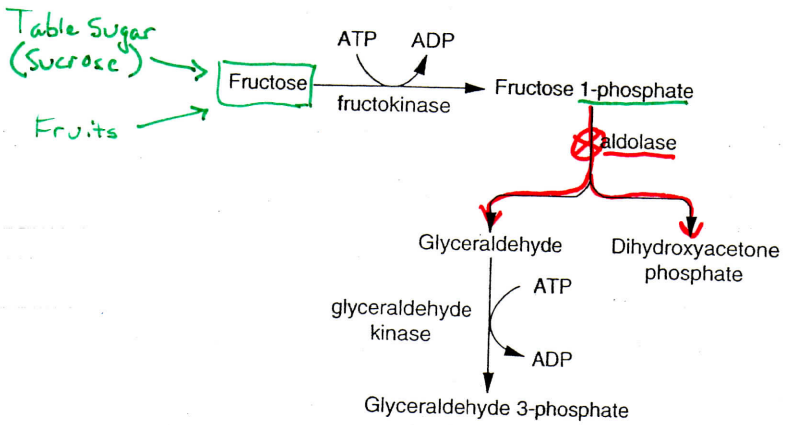
ERYTHROCYTE - synthesis of reduced glutathione — Critical oxidative stress protection
PHAGOCYTE - synthesis of superoxide anion
LIVER - synthesis of fatty acids and cholesterol
ADRENAL CORTEX, OVARY, TESTIS - synthesis of steroid hormones

GLUCOSE 6-P DEHYDROGENASE DEFICIENCY – Most Common Worldwide

Partial
- acute episodes of oxidant-induced hemolytic anemia (infections, drugs or fava beans) → in acute episodes → antimalarials & sulfa drugs
- jaundice, hemoglobinuria
- Heinz bodies – oxidative
- normal erythrocyte 2,3-BPG
- bite cells

Severe
- chronic hemolytic anemia + immunodeficiency
- CGD-like symptoms (which is an NADPH oxidase deficiency)



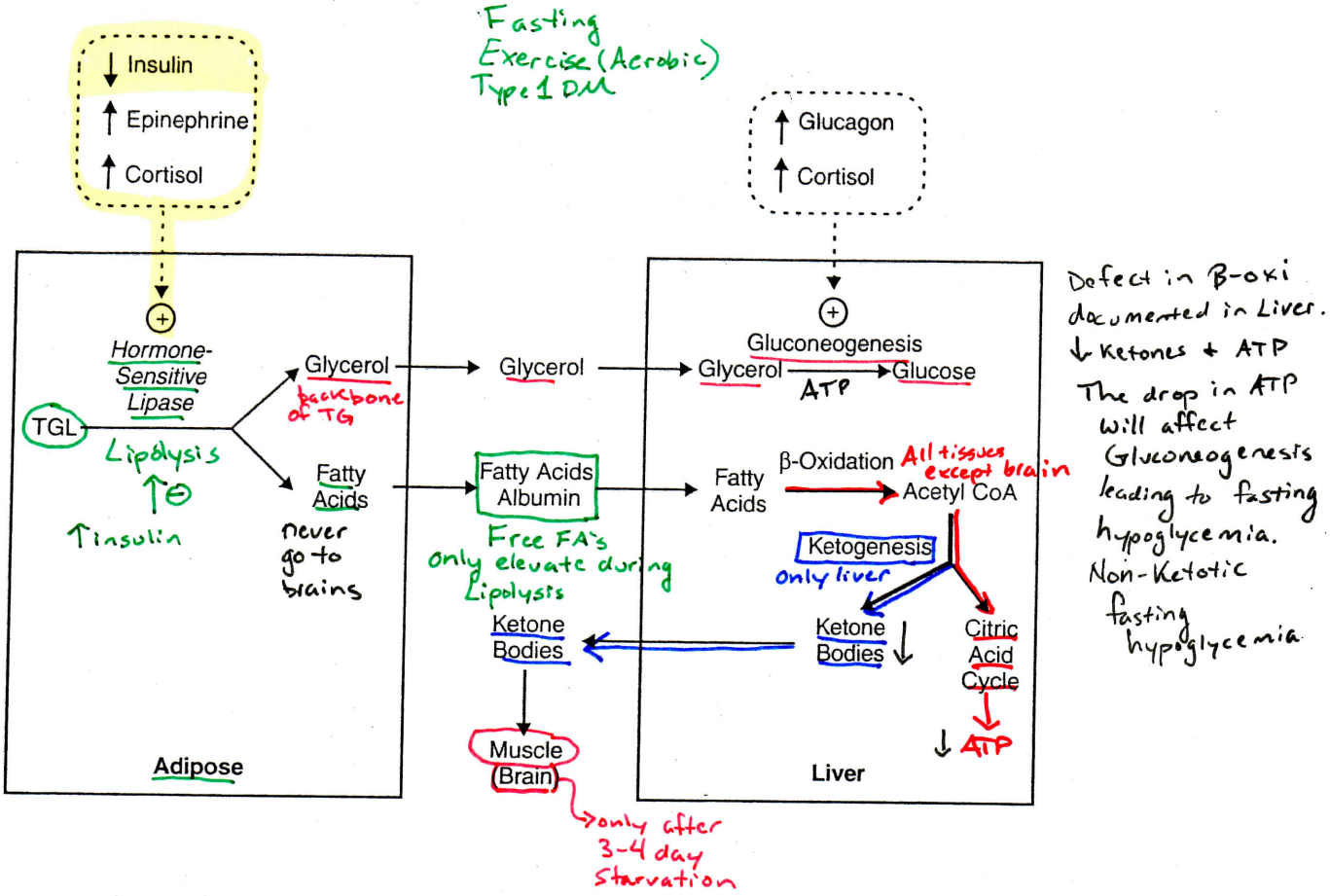


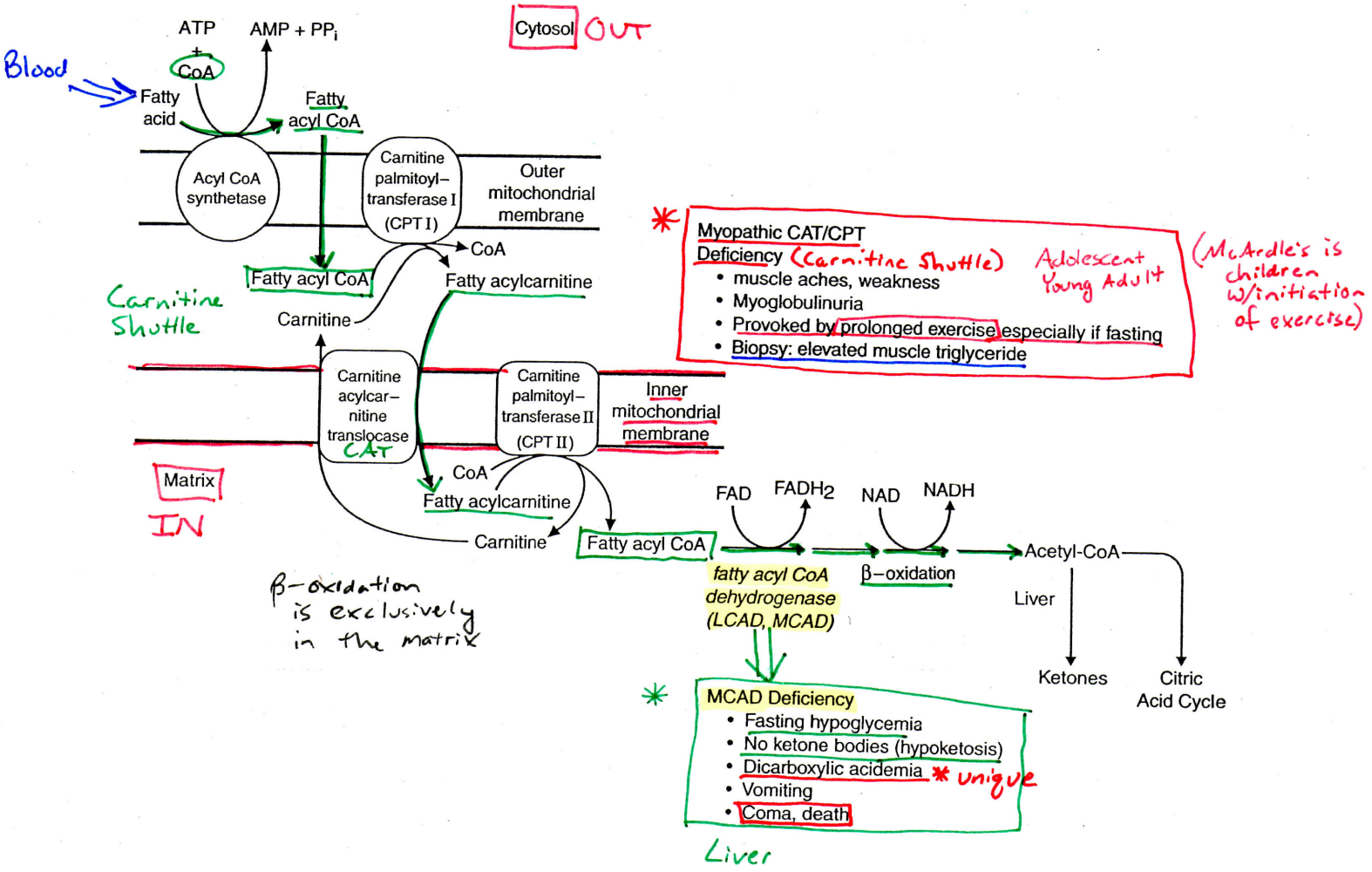
FRUCTOSE INTOLERANCE

Aldolase B (fructose 1-P aldolase activity) deficiency: NO CATARACTS
- Lethargy, vomiting
- Liver damage, hyperbilirubinemia
- Hypoglycemia
- Hyperuricemia → No neuroproblems b/c not metabolized by brain

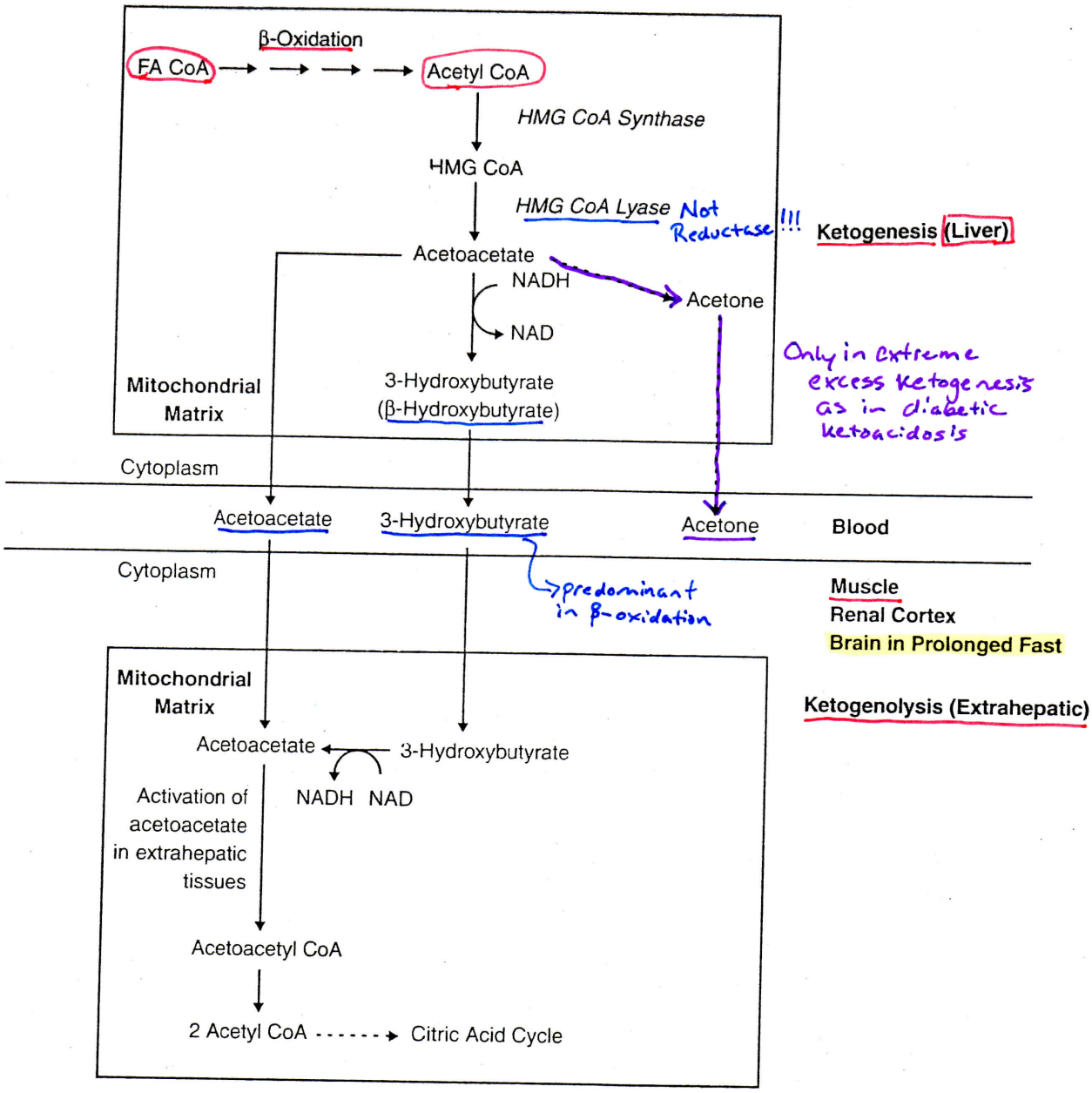
Classically seen in child being weaned from milk

TRIGLYCERIDE DEGRADATION & FATTY ACID OXIDATION

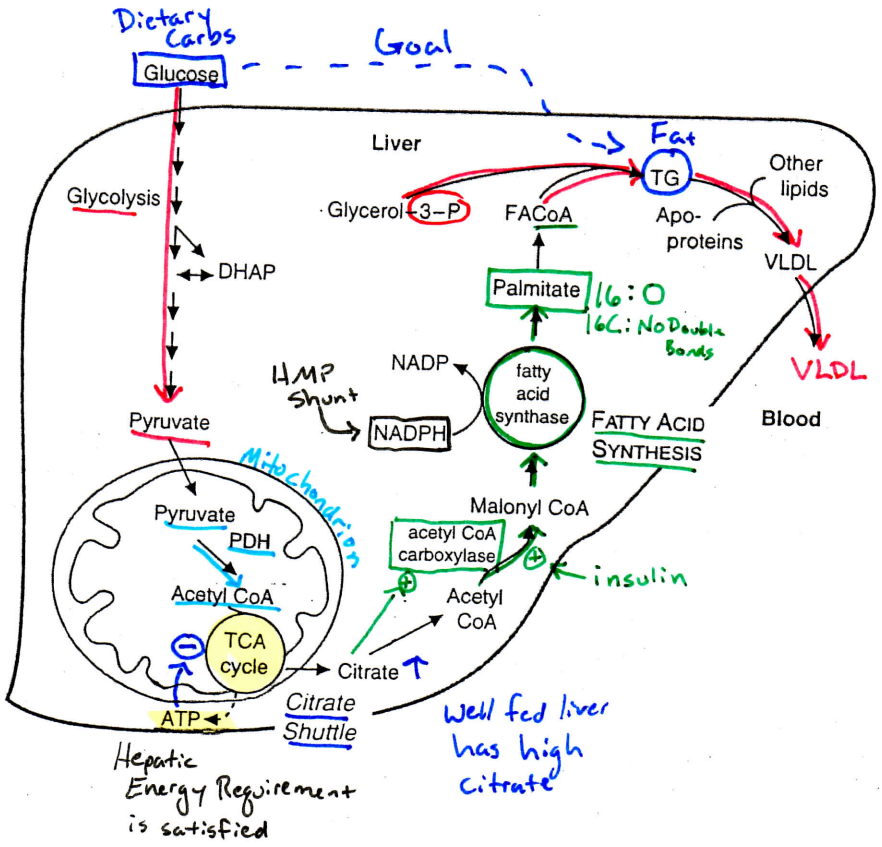


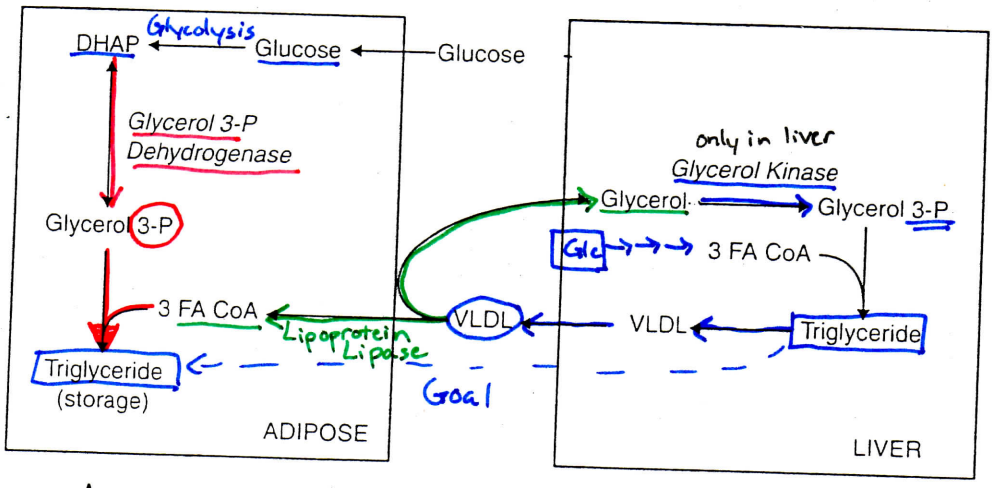


KETONE BODY SYNTHESIS & DEGRADATION



POSTPRANDIAL SYNTHESIS AND STORAGE OF FAT





Adipose cannot use VLDL Glycerol — it returns to liver

LIPOPROTEIN METABOLISM

Classes of Lipoproteins and Important Apoproteins

Lipoprotein	Functions	Apoproteins	Functions
Chylomicrons	Transport dietary triglyceride and cholesterol from intestine to tissues	apoB-48 apoC-II apoE – remnants	Secreted by epithelial cells – gets out of gut Activates lipoprotein lipase – get out of blood Uptake by liver of remnants
VLDL	Transports triglyceride from liver to tissues (adipose)	apoB-100 apoC-II apoE – remnants	Secreted by liver – get out of liver Activates lipoprotein lipase Uptake of remnants by liver ~ IDL
LDL	Delivers cholesterol into cells – Liver	apoB-100	Uptake by liver and other tissues via LDL receptor (apoB-100 receptor) → e.g. blood vessels
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-receptor Shuttles apoC-II and apoE in blood	apoA-1	Activates lecithin cholesterol acyltransferase (LCAT) to produce cholesterol esters

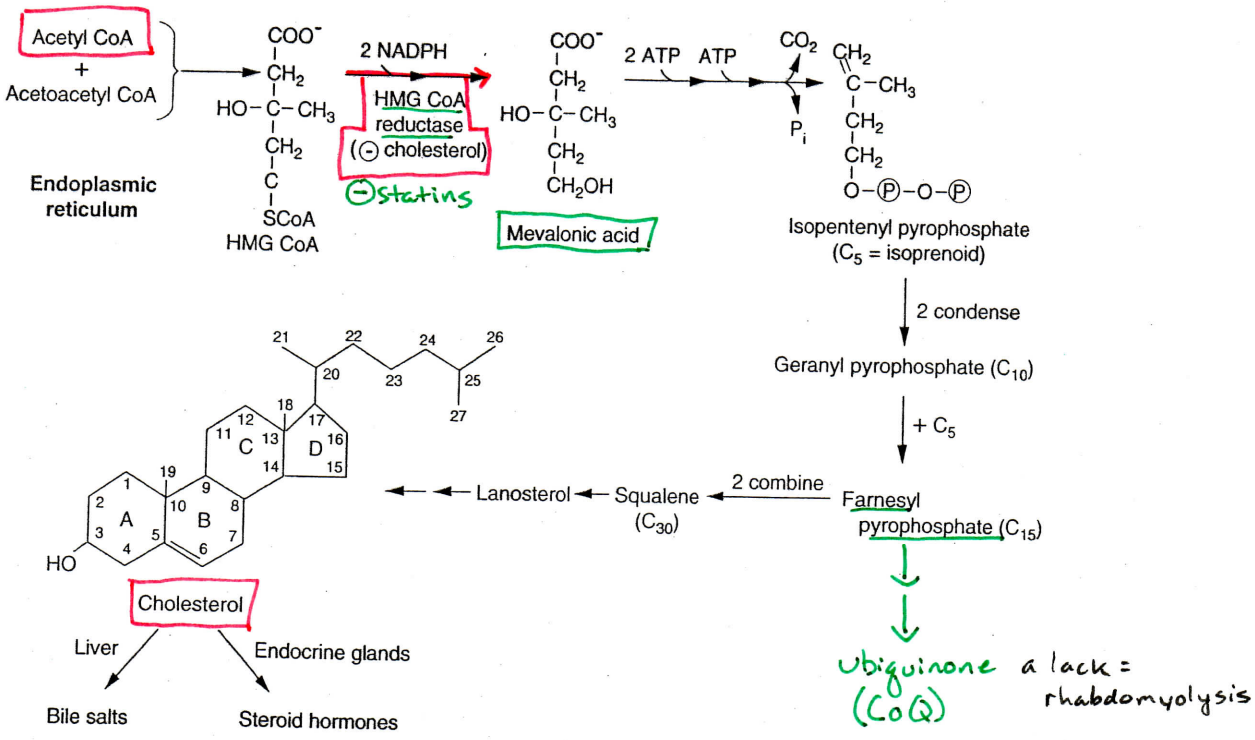
A-1 – defect = hypo HDL
B-48 – defect = fat malabs
B-100 – defect = fatty liver
C-II – defect = hyperTG
E – defect = hyperTG hypercholesterol

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 **	Familial hypercholesterolemia Autosomal dominant (Aa 1/500, AA 1/10^6) LDL (Apo B-100) Receptor Def. can't get LDL out of blood	Cholesterol	LDL	High risk of atherosclerosis and coronary artery disease Homozygous condition usually death <20 years Xanthomas of the Achilles tendon Tuberous xanthomas on elbows Xanthelasmas Corneal arcus – blue ring around cornea

Middle Age Onset

CHOLESTEROL SYNTHESIS & SPHINGOLIPID STORAGE DISEASES



Cholesterol biosynthesis. *HMG CoA* = hydroxymethylglutaryl CoA

membrane lipids

Genetic Deficiencies of Sphingolipid Catabolism

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 tired, bruising Characteristic macrophages (crumpled paper inclusions)
Niemann-Pick	Sphingomyelinase	Sphingomyelin	Hepatosplenomegaly Microcephaly, severe mental retardation Zebra bodies in inclusions Characteristic foamy macrophages Early death

Cherry Red Spots on Macula (40%)

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 → Tyr
Val
Trp

Thr
Ile
Met

His
Arg *
Leu
Lys

never Tires (Tyr)

Nitrogen Balance $N_{in} = N_{out}$ (i.e. protein$_{in}$ ≠ urea$_{out}$)

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

$N_{in} < N_{out}$

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

- Protein malnutrition (kwashiorkor) → ascites + edema
- * A dietary deficiency of even one essential amino acid
- Starvation marasmus (protein calorie malnutrition)
- Uncontrolled diabetes
- Infection

$N_{in} > N_{out}$

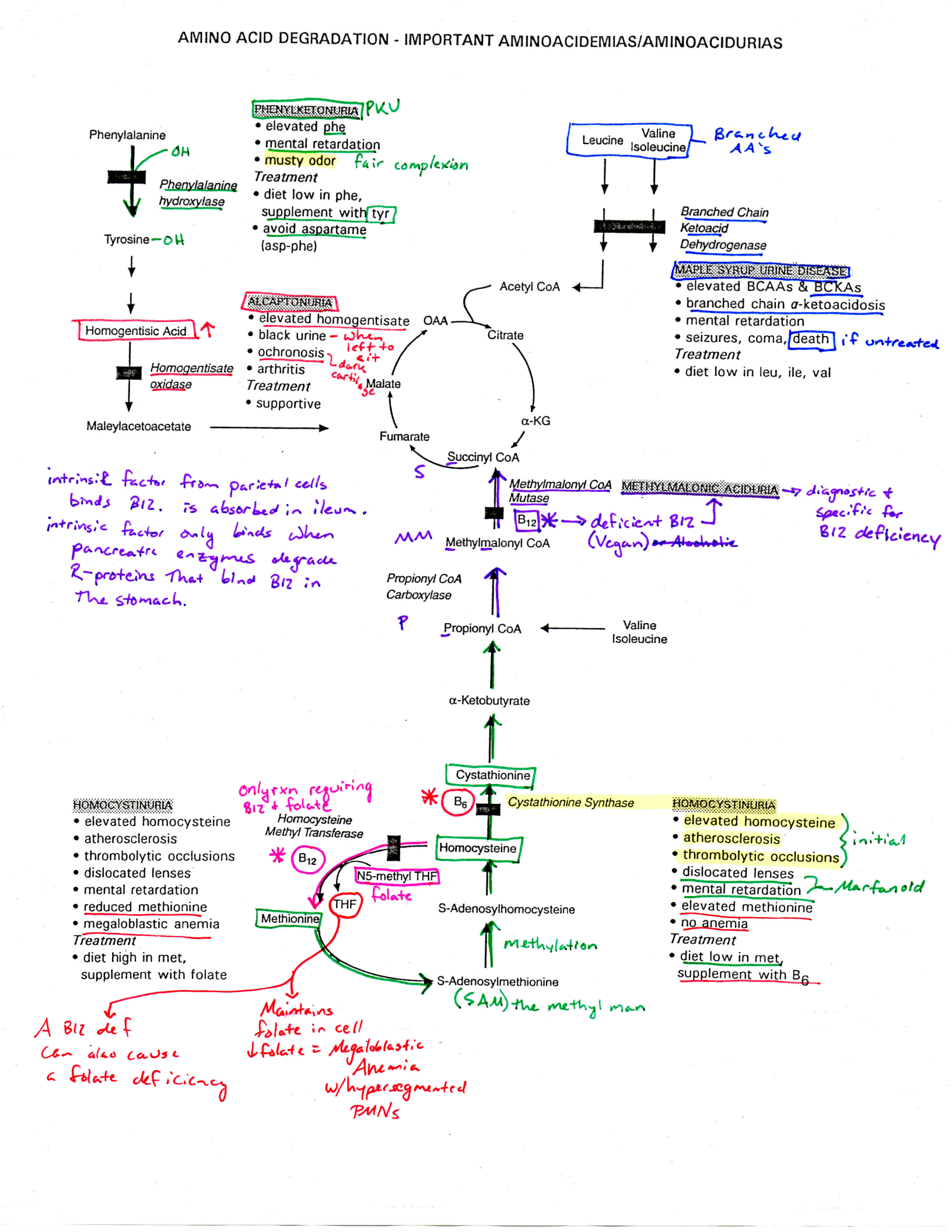
Positive nitrogen balance occurs when the amount of nitrogen incorporated exceeds the amount excreted and is associated with:

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

Products of Amino Acids

Amino Acid	Products
Tyrosine	Thyroid hormones T_3 and T_4 Melanin Catecholamines D → NE → E
Tryptophan	Serotonin NAD, NADP
Arginine	Nitric oxide (NO)
Glutamate	γ-Aminobutyric acid (GABA)
Histidine	Histamine

AMINO ACID DEGRADATION - IMPORTANT AMINOACIDEMIAS/AMINOACIDURIAS



GENETIC DISORDERS OF THE UREA CYCLE

A. General Features

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

Lab Results
- hyperammonemia → compensatory for excess ammonia
- elevated plasma and urinary glutamine
- abnormally-low blood urea nitrogen (BUN)

B. Differential Diagnosis

ENZYME DEFECT

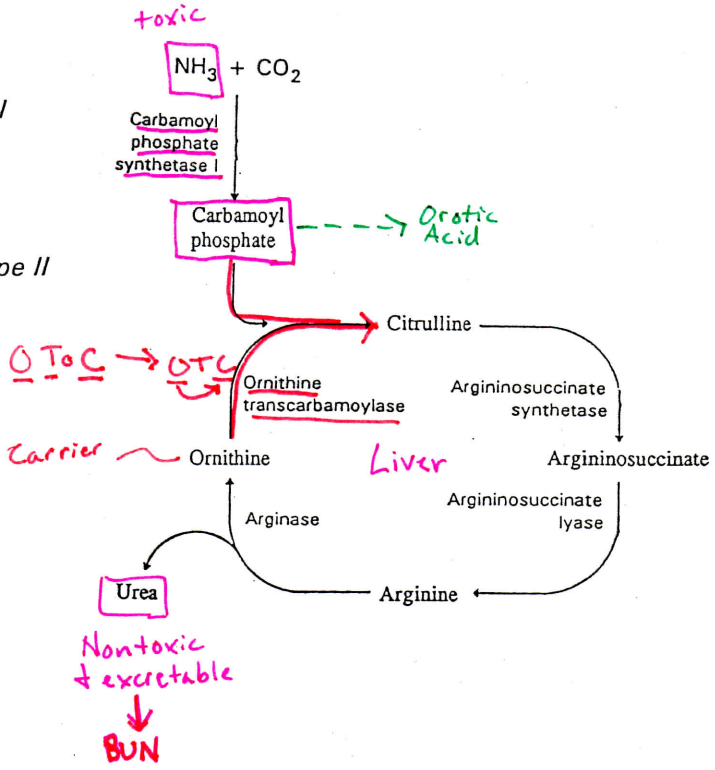
1. *Carbamoyl-P synthetase I - hyperammonemia Type I*
   - low citrulline
   - no orotic aciduria
   - autosomal recessive

2. *Ornithine transcarbamoylase - hyperammonemia Type II* (Most common)
   - low citrulline
   - orotic aciduria (diagnostic)
   - X-linked recessive → only XLR in urea cycle

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

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

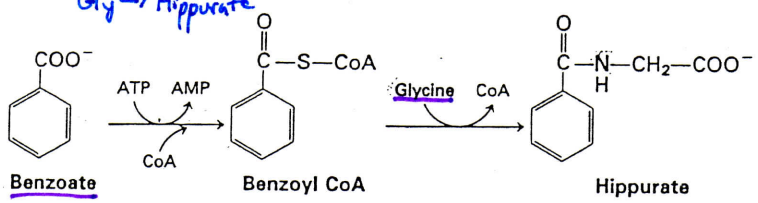
5. *Arginase - argininemia*
   - high arginine

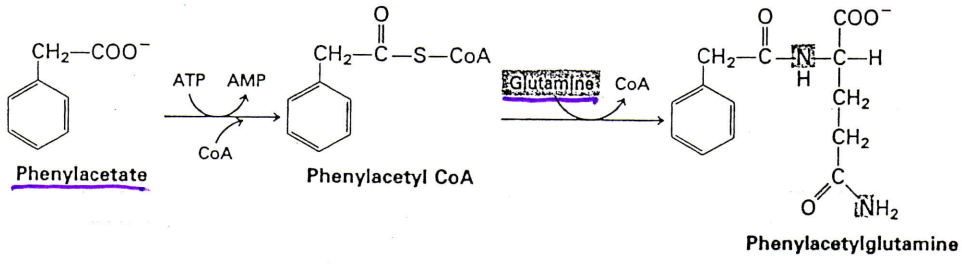


C. Treatment

Severe Hyperammonemia
- exchange transfusion
- IV benzoate + phenylacetate ~ deplete Gly + Gln

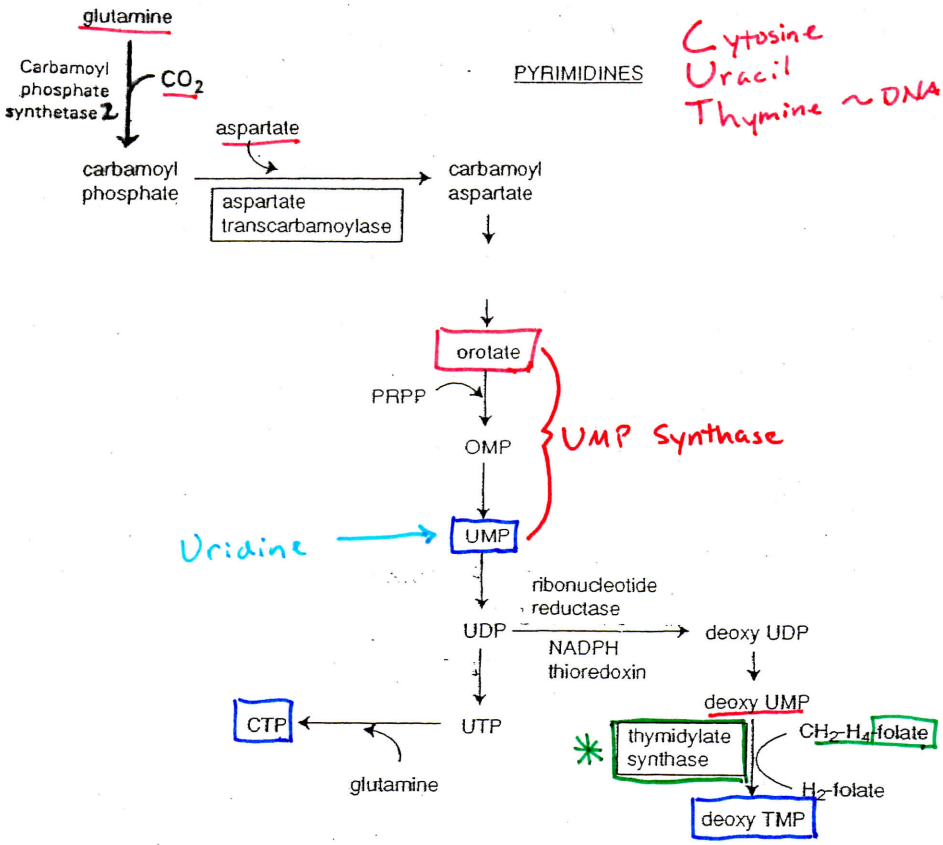
Gly → Hippurate





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

PYRIMIDINE NUCLEOTIDE BIOSYNTHESIS



Two Orotic Aciduria

1. Hyperammonemia

   No megaloblastic anemia

   - Pathway: Urea cycle
   - Enzyme deficient: OTC ~ Ornithine Transcarbamylase

2. Megaloblastic anemia

   No hyperammonemia

   - Pathway: Pyrimidine synthesis ~ UMP Synthase Def. Treat w/Uridine → UMP
   - Enzyme deficient: UMP synthase

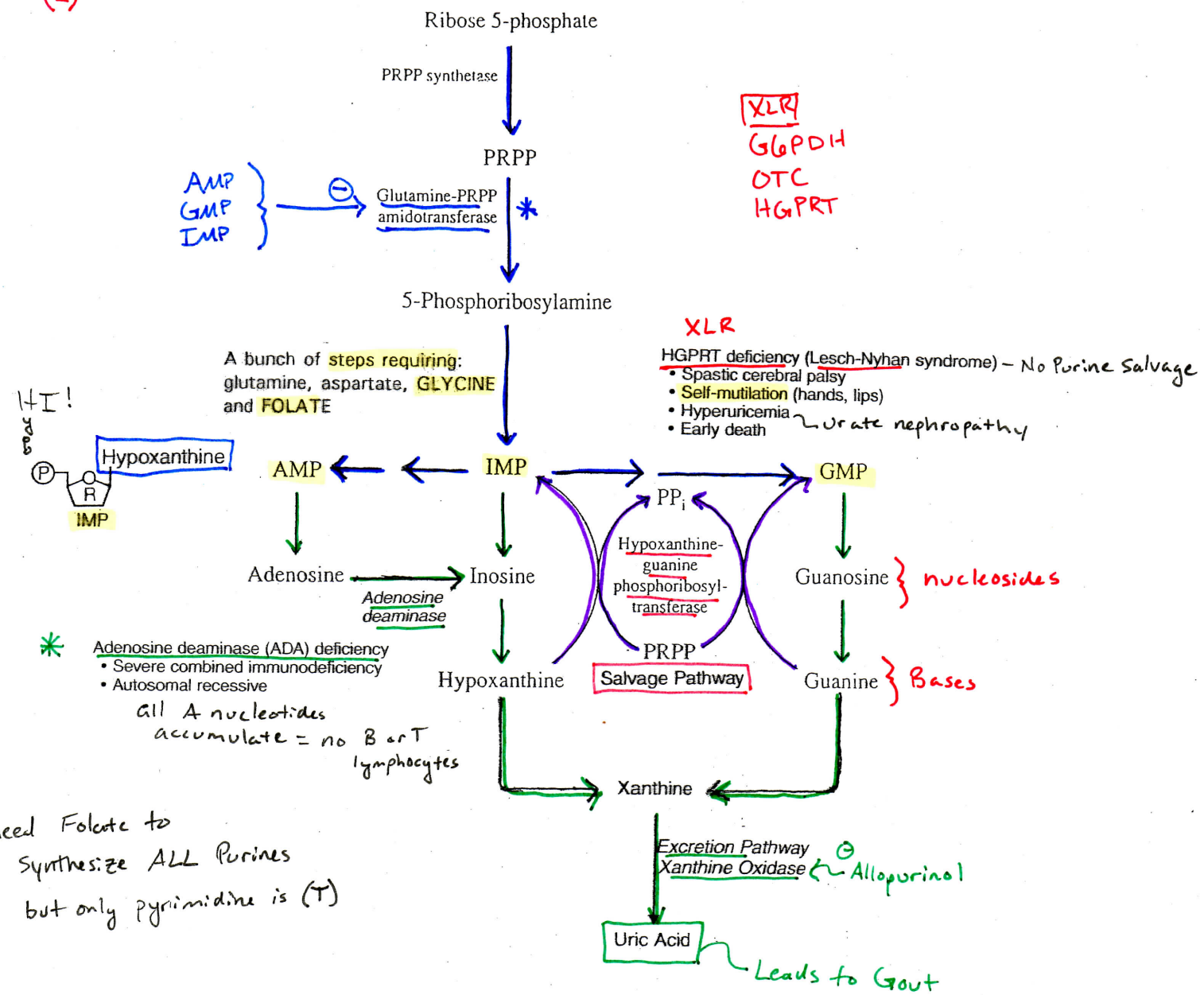
Folate deficiency: = ↓ Thimidylate Synthase megaloblastic anemia

But no orotic aciduria

PURINE NUCLEOTIDE SYNTHESIS, DEGRADATION & SALVAGE

10% 90%

A G (I)



XLR
G6PDH
OTC
HGPRT

XLR

HGPRT deficiency (Lesch-Nyhan syndrome) – No Purine Salvage
- Spastic cerebral palsy
- Self-mutilation (hands, lips)
- Hyperuricemia → urate nephropathy
- Early death

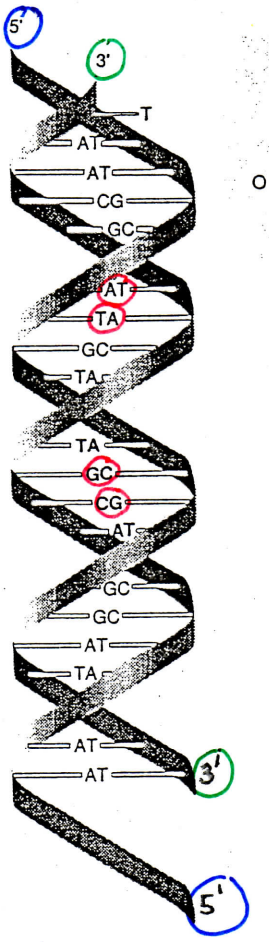
* Adenosine deaminase (ADA) deficiency
- Severe combined immunodeficiency
- Autosomal recessive

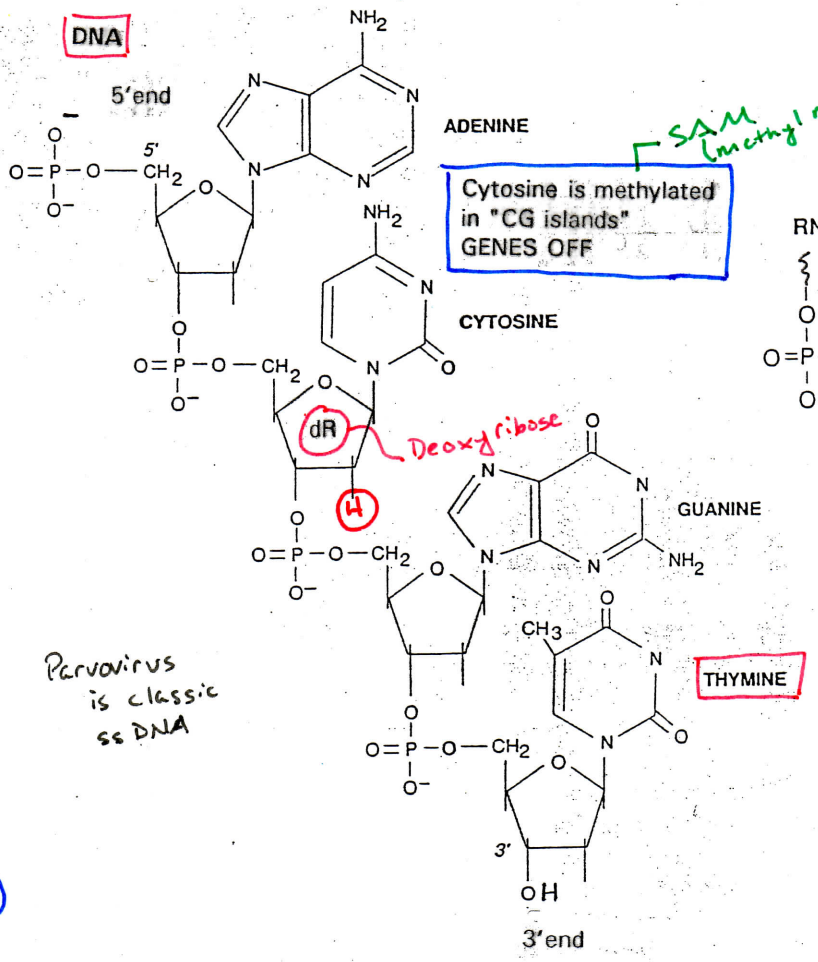
all A nucleotides accumulate = no B or T lymphocytes

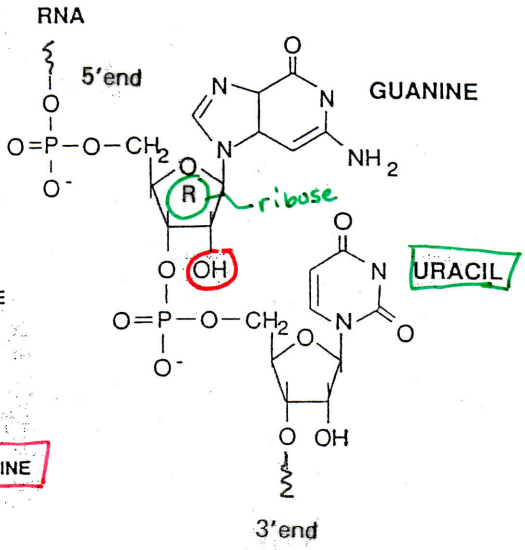
Need Folate to synthesize ALL Purines but only Pyrimidine is (T)

Needle shaped, Bifringent Crystals

Pick indomethacin for pain







Strand Sequence

5′ T C G A 3′
or
T C G A

Always 5′ → 3′ (L → R)

must assume 5′ → 3′ (L → R)

3′ A G C T 5′

If written backwards, end must be clearly designated.

5′ p T p C p G p A 3′

Sometimes the PDE bond is indicated.

* 5′ T C G A 3′
3′ A G C T 5′

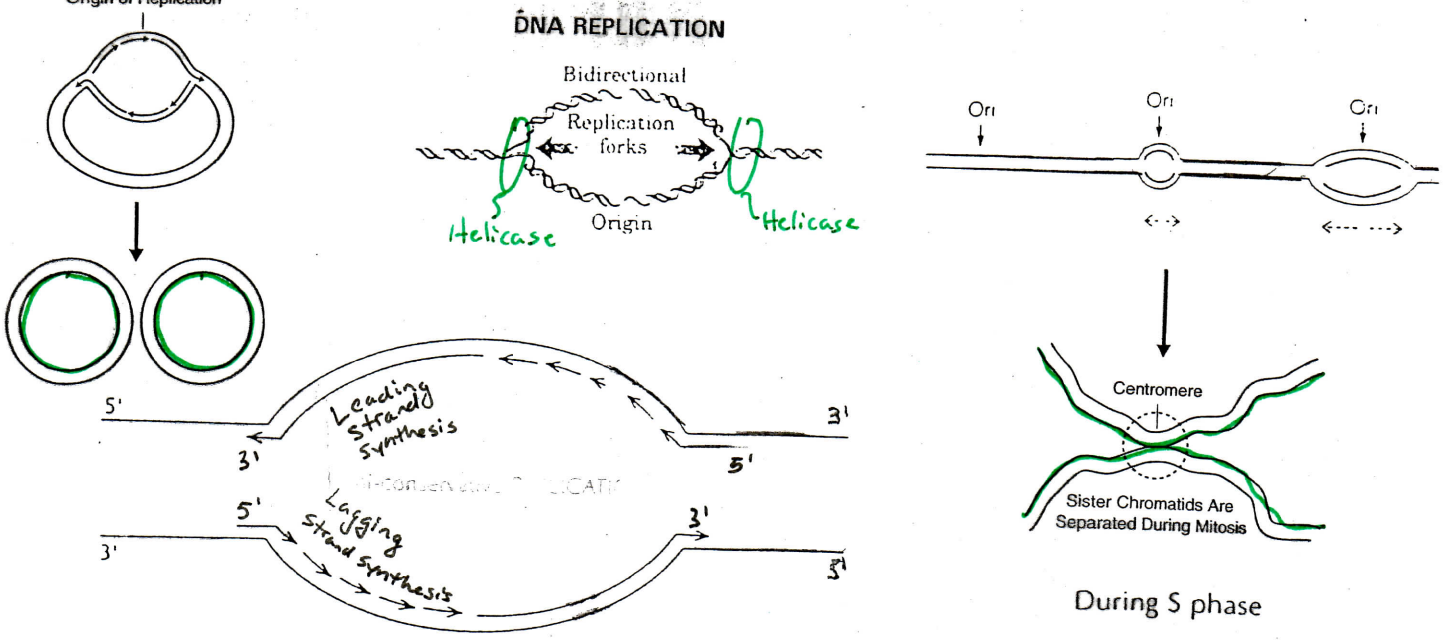
Strands must be anti-parallel to base pair. If complementary then also anti-parallel.

2H Bonds = weaker

3H bonds = stronger

* in DNA % T = % A
% C = % G

purines = pyrimidines

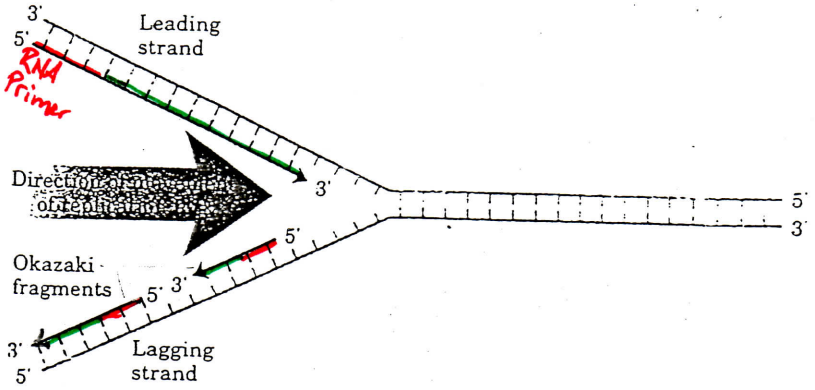


Copied Strand = Template

Helicase separates strands at ORI

ORI's are rich in AT

Synthesis is always 5'→3'



Comparison of DNA and RNA Polymerases

	DNA Polymerase	RNA Polymerase
Nucleic acid synthesized (5′→3′)	DNA	RNA
Required template (copied 3′→5′)	DNA*	DNA*
Required substrates	dATP, dGTP, dCTP, dTTP	ATP, GTP, CTP, UTP
Required primer (5'end)	RNA (or DNA) ← for PCR	None
Proofreading activity (3′→5′ exonuclease)	Yes	No

*Certain DNA and RNA polymerases require RNA templates. These enzymes are most commonly associated with viruses.

The Steps and Proteins Involved in DNA Replication

	Prokaryotic cells	Eukaryotic cell nuclei
1. Unwinding of DNA double-helix at replication origin(s)	Helicase (requires ATP)	Helicase (requires ATP)
2. Stabilization of unwound template strands	Single-strand binding protein (SSB)	Single-strand binding protein (SSB)
3. Synthesis of RNA primers	Primase	Primase
4. Synthesis of DNA • leading strand • lagging strand (Okazaki fragments)	DNA polymerase III DNA polymerase III	DNA polymerase δ + α DNA polymerase α + δ α β γ δ γ repair in mitochondria
5. Removal of RNA primers	DNA polymerase I (5′ - exonuclease)	Unknown
6. Replacement of RNA with DNA	DNA polymerase I	Unknown
7. Joining of Okazaki fragments	DNA ligase (requires NAD)	DNA ligase (requires ATP)
8. Removal of + supercoils ahead of advancing replication forks	Topoisomerase II (DNA gyrase) • inhibited by nalidixic acid, norfloxacin	Topoisomerase II • inhibited by etoposide, teniposide
9. Synthesis of telomeres	Not required	Telomerase ~ contains strand of RNA to act as primer internally Loss = T cell aging hyperactivity = CA

Other Eukaryotic DNA Polymerases

DNA polymerase γ replicates mitochondrial DNA in eukaryotes.

DNA polymerases β and ε (in eukaryotic cell nuclei) are thought to participate primarily in DNA repair. DNA pol ε may substitute for DNA pol δ in certain cases

Reverse Transcriptase

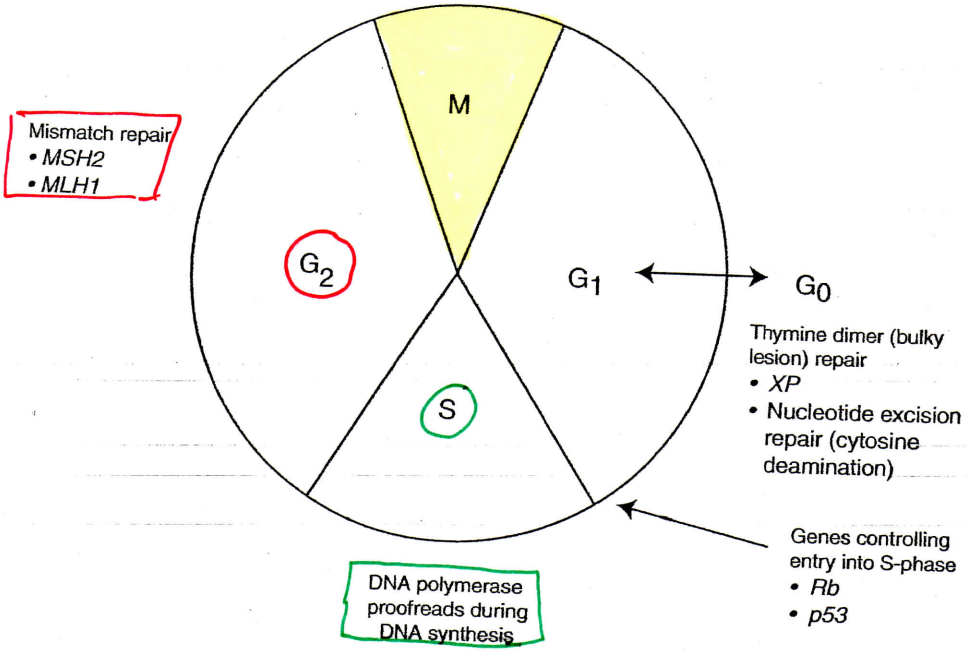
RNA → (RT) → cDNA

Reverse transcriptase, an enzyme found in some viruses, is an RNA-dependent DNA polymerase. This enzyme requires an RNA template to direct the synthesis of new DNA. Retroviruses, most notably HIV, utilize this enzyme to replicate their RNA genomes.

Requires primer
No exonuclease activity

DNA Repair

Damage	Cause	Recognition/ Excision Enzyme	Repair Enzymes
Thymine dimers (G_1)	UV radiation	Excision endonuclease (deficient in Xeroderma pigmentosum)	DNA polymerase DNA ligase
Cytosine deamination (G_1) C→U	Spontaneous/ chemicals	Uracil glycosylase AP endonuclease	DNA polymerase DNA ligase
Apurination or apyrimidination (G_1)	Spontaneous/ heat	AP endonuclease	DNA polymerase DNA ligase
Mismatched base (G_2)	DNA replication errors	A mutation on one of two genes, hMSH2 or hMLH1, initiates defective repair of DNA mismatches, resulting in a condition known as hereditary nonpolyposis colorectal cancer—HNPCC. Lynch Syndrome	DNA polymerase DNA ligase

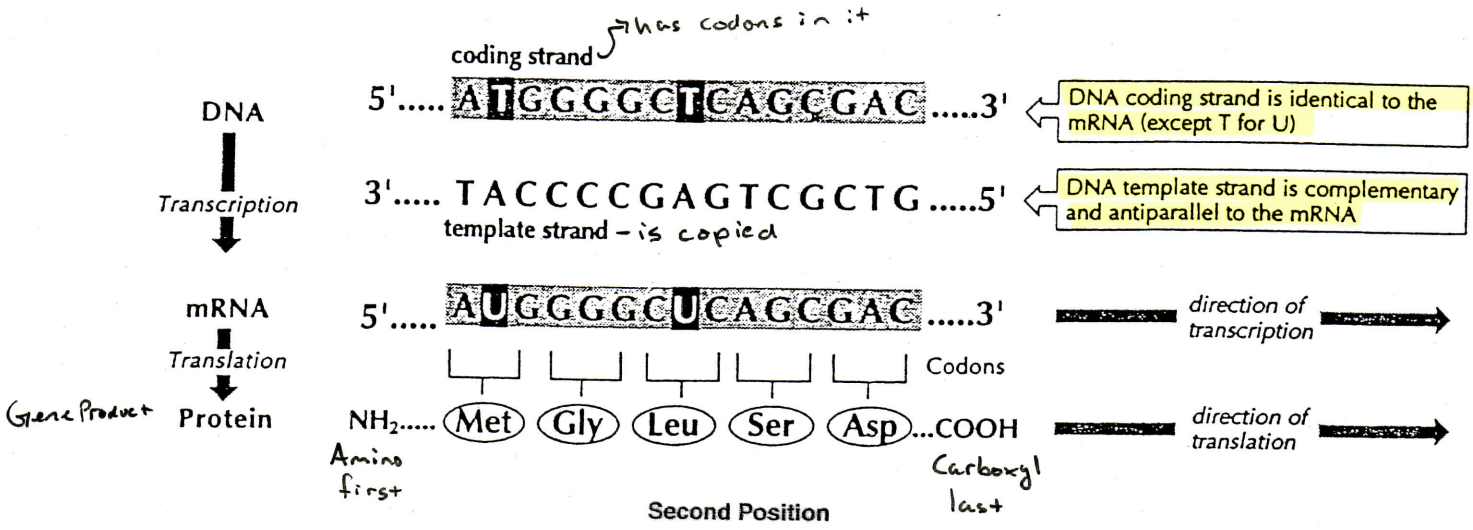


Tumor Suppressor Genes and DNA Repair

DNA repair may not occur properly when certain tumor suppressor genes have been inactivated through mutation or deletion:

- The *p53* gene encodes a protein that prevents a cell with damaged DNA from entering the S phase. Inactivation or deletion associated with Li Fraumeni syndrome and many solid tumors.
- *ATM* gene encodes a kinase essential for p53 activity. *ATM* is inactivated in ataxia telangiectasia, characterized by hypersensitivity to x-rays and predisposition to lymphomas.
- *BRCA-1* (breast, prostate, and ovarian cancer) and *BRCA-2* (breast cancer) required for p53 activity.
- *Rb* The retinoblastoma gene was the first tumor suppressor gene cloned, and is a negative regulator of the cell cycle through its ability to bind the transcription factor E2F and repress transcription of genes required for S phase.

Flow of Genetic Information from DNA to Protein



Second Position

First Position (5' End)	U	C	A	G	Third Position (3' End)
U	UUU, UUC Phe; UUA, UUG Leu	UCU, UCC, UCA, UCG Ser	UAU, UAC Tyr; UAA, UAG Stop	UGU, UGC Cys; UGA Stop; UGG Trp	U C A G
C	CUU, CUC, CUA, CUG Leu	CCU, CCC, CCA, CCG Pro	CAU, CAC His; CAA, CAG Gln	CGU, CGC, CGA, CGG Arg	U C A G
A	AUU, AUC, AUA Ile; AUG Met Start	ACU, ACC, ACA, ACG Thr	AAU, AAC Asn; AAA, AAG Lys	AGU, AGC Ser; AGA, AGG Arg	U C A G
G	GUU, GUC, GUA, GUG Val	GCU, GCC, GCA, GCG Ala	GAU, GAC Asp; GAA, GAG Glu	GGU, GGC, GGA, GGG Gly	U C A G

Wobble

CC_ = Pro, always

1 2 3
5'–ACG–3'
Codon

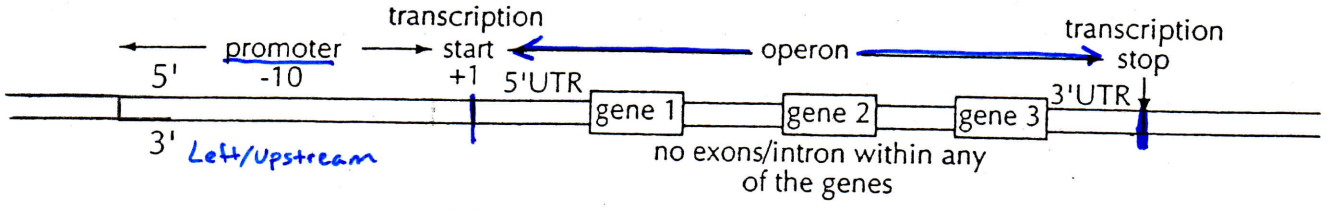
Stop is not an AA

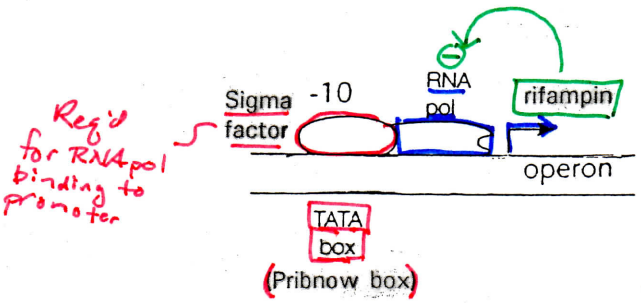
U Are Alien
U Are Gone
U Go Away

Effect of Some Common Types of Mutations on Protein Structure

Type of Mutation	Effect on Protein
Silent: new codon specifies same amino acid	None (wobble position substitution)
Point: Missense: new codon specifies different amino acid (HbA–glu, HbS–Val)	Possible decrease in function; variable effects
Nonsense: new codon is stop codon (TAA TGA TAG)	Shorter than normal; usually nonfunctional Premature Termination
Frameshift: deletion or addition of a base (~~TAA TGA TAG~~)	Usually nonfunctional; often shorter than normal
Large segment deletion (unequal crossover in meiosis)	Loss of function; shorter than normal or entirely missing
Splice donor or acceptor site mutations	Variable effects ranging from addition or deletion of a few amino acids to deletion of an entire exon
Triplet repeat expansion (Huntingtons, Fragile X)	Expansions in coding regions cause protein product to be longer than normal and unstable. Disease often shows anticipation in pedigree.

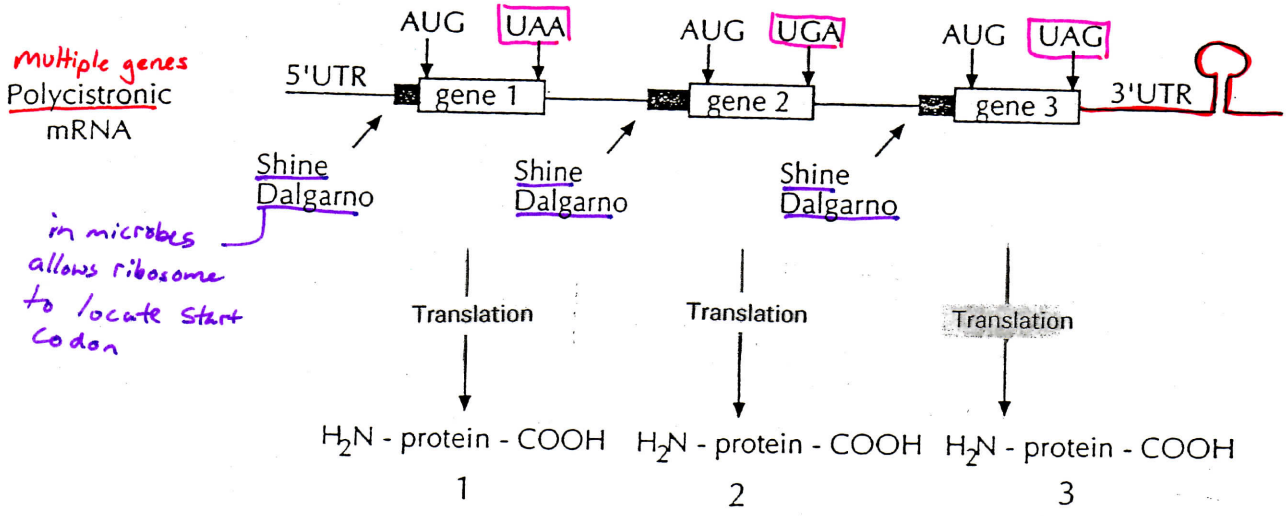
CYTOPLASMIC EXPRESSION OF A BACTERIAL OPERON





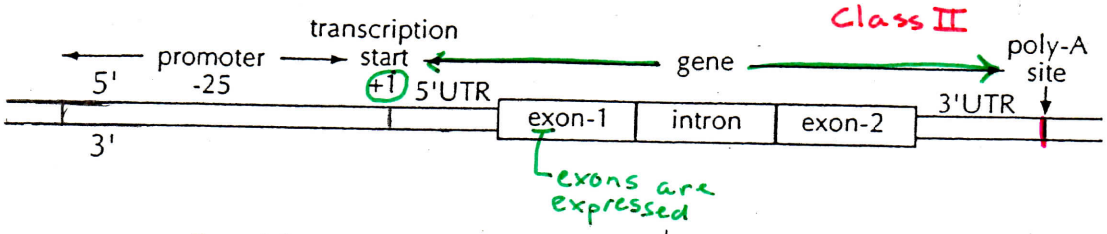
Transcription

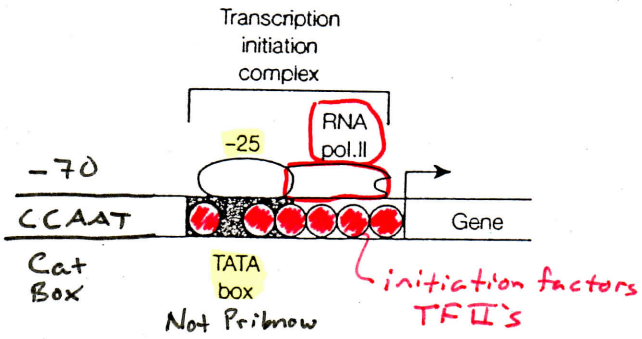
stem/loop in mRNA stops transcription



EXPRESSION OF A NUCLEAR PROTEIN-CODING GENE

Class II

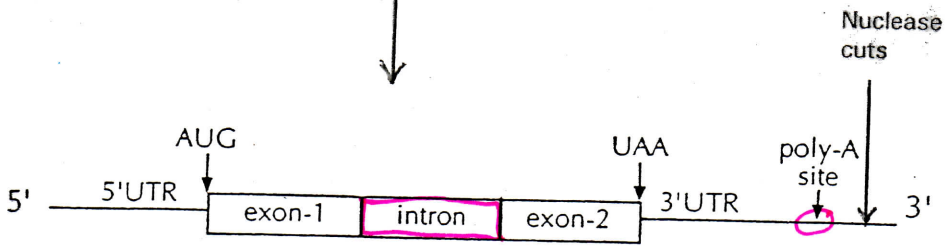


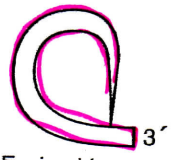


Transcription (nucleus)

pre-mRNA (hnRNA) *

has introns



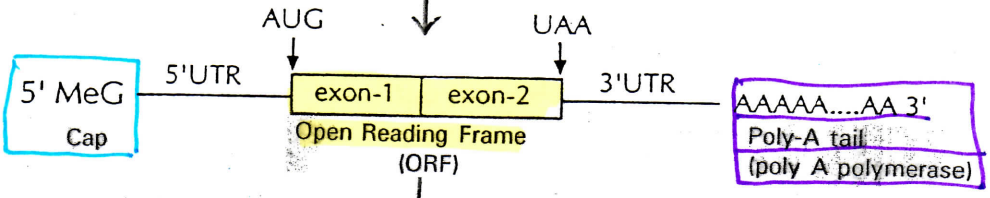


Excised Intron (Lariat) Degraded in Nucleus

RNA Processing (nucleus)
1. Capping (to initiate translation) — 5' end - Methyl G
2. Tailing (to prevent RNA degradation) — 3' end
3. Splicing (to generate an ORF) — remove introns
   - spliceosome with U-rich snRNA

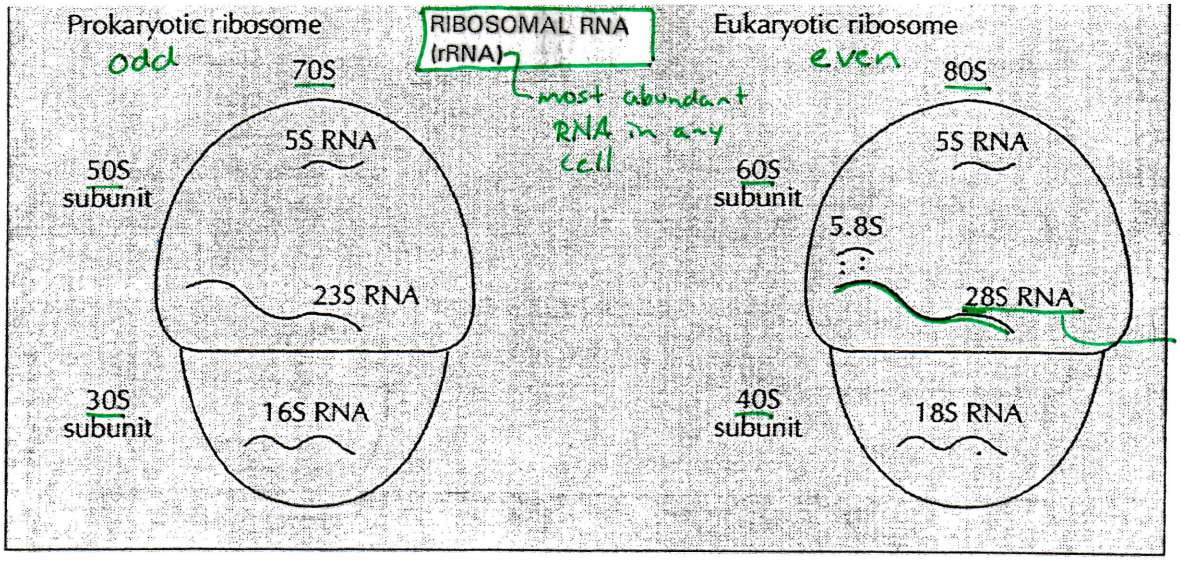
mRNA

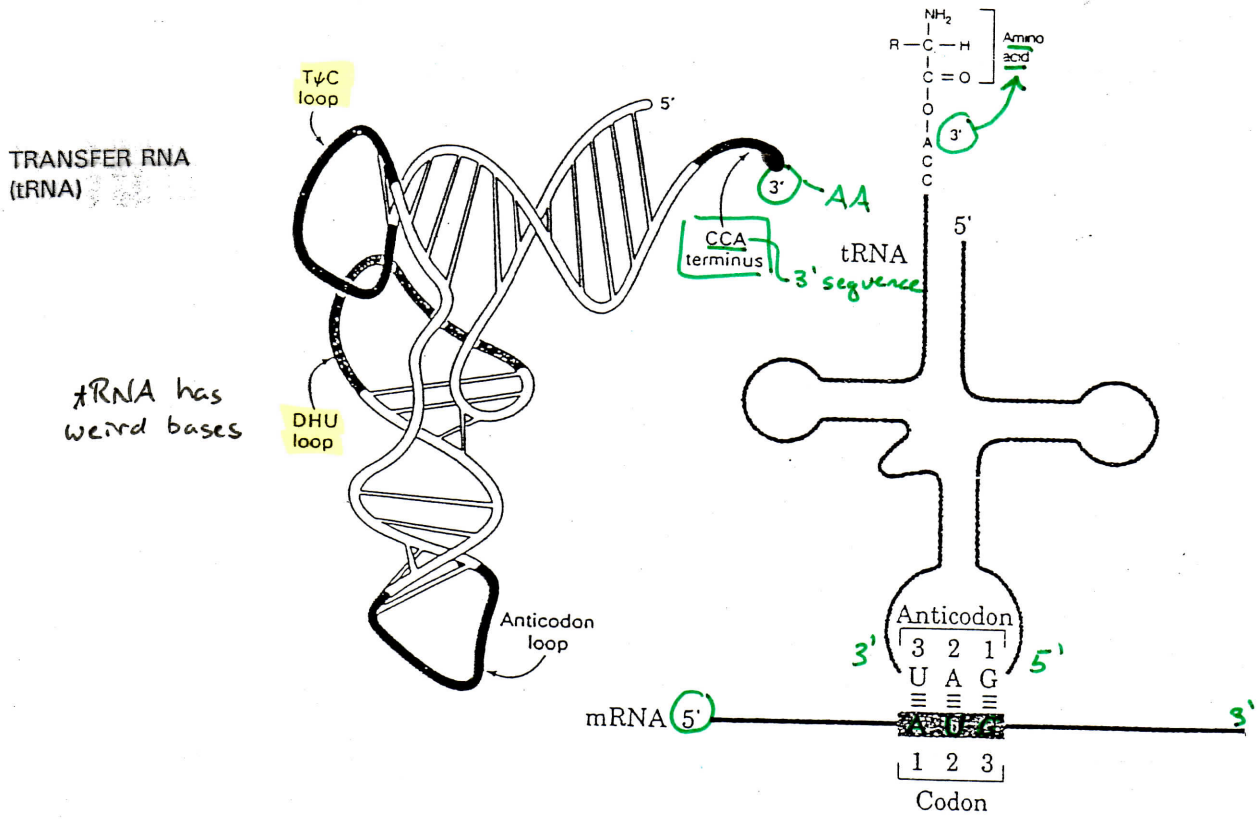
No Introns!!



Translation (cytosol)

H_2N - protein - COOH





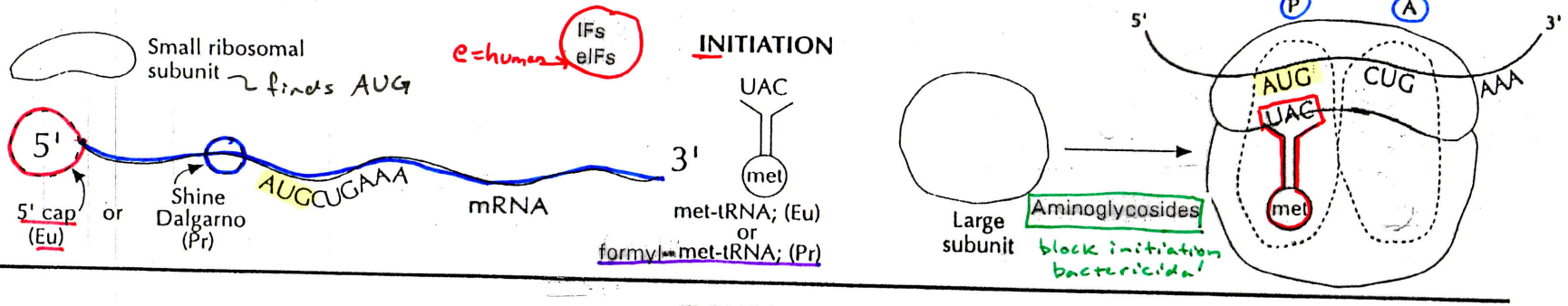
Mushrooms

Eukaryotic Nuclear RNA Polymerases

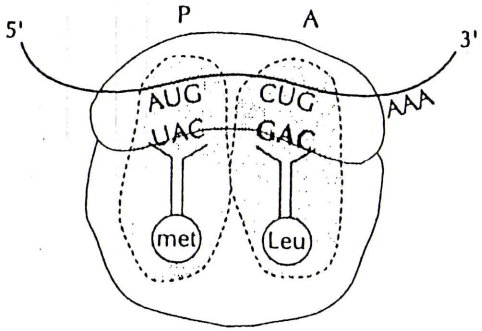
Type	α-Amanitin Sensitivity	Subcellular Localization	RNA Product
I	Insensitive	Nucleolus	45S rRNA
II	Very sensitive to low levels	Nucleoplasm	hnRNA (mRNA) and some snRNAs
III	Sensitive to high levels	Nucleoplasm	tRNA, 5S rRNA

hnRNA = heterogeneous nuclear RNA; mRNA = messenger RNA; rRNA = ribosomal RNA; snRNAs = small nuclear RNAs; tRNA = transfer RNA.

Steps in Translation



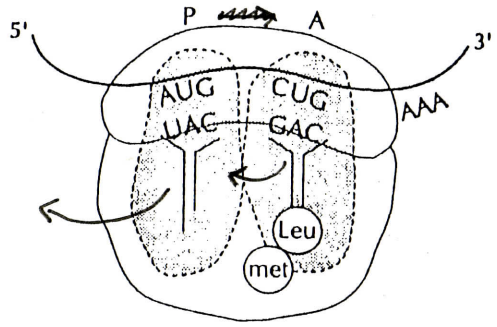
ELONGATION



1. Aminoacyl-tRNA binds to A site

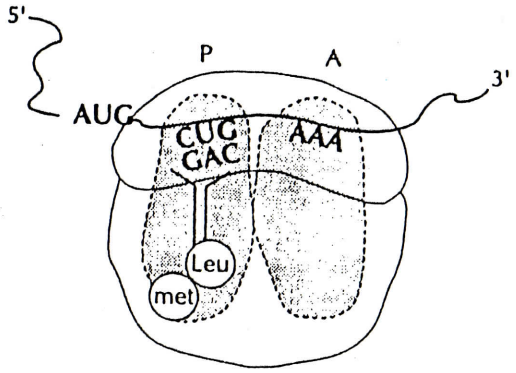
   GTP
   EF_{TU} and EF_{TS} (Pr)
   eEF-1 (Eu)

   Tetracyclines → blocks A site
   bacteriostatic



2. Peptide bond forms. Peptidyl transferase in large subunit

   Chloramphenicol → gray baby syndrome w/ ↑ dose
   bacteriostatic/cidal



3. Translocation of ribosome 3 nucleotides along mRNA

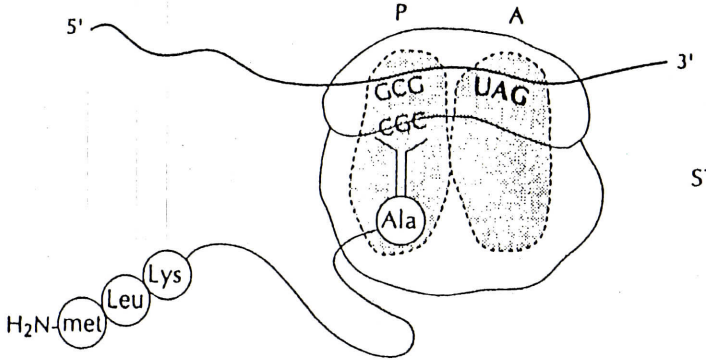
   GTP
   EF-G(Pr)
   eEF-2(Eu) ← TOXINS → Diptheria, Pseudomonas
   → moves ribosome

   Macrolides, Clindamycin
   bacteriostatic

Elongation cycle repeats for each amino acid added.

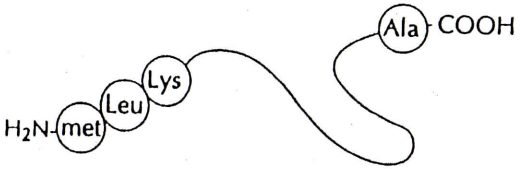
TERMINATION

RFs → release
eRFs



STOP CODON in A site

Completed protein released from ribosome Ribosomal subunits separate mRNA released



↳ i.e. rotavirus

A double-stranded RNA genome isolated from a virus in the stool of a child with gastroenteritis was found to contain 15% uracil. What is the percentage of guanine in this genome?

so
15% A

70% C + G

A. 15
B. 25
✓C. 35 —
D. 75
E. 85

A medical student working in a molecular biology laboratory is asked by her mentor to determine the base composition of an unlabeled nucleic acid sample left behind by a former research technologist. The results of her analysis show 10% adenine, 40% cytosine, 30% thymine and 20% guanine. What is the most likely source of the nucleic acid in this sample?

A. Bacterial chromosome
B. Bacterial plasmid
C. Mitochondrial chromosome
D. Nuclear chromosome
✓E. Viral genome —

It is now believed that a substantial proportion of the single nucleotide substitutions causing human genetic disease are due to misincorporation of bases during DNA replication. Which proofreading activity is critical in determining the accuracy of nuclear DNA replication and thus the base substitution mutation rate in human chromosomes?

A. 3′ to 5′ polymerase activity of DNA polymerase δ
B. 3′ to 5′ exonuclease activity of DNA polymerase γ
C. Primase activity of DNA polymerase α
D. 5′ to 3′ polymerase activity of DNA polymerase III
✓E. 3′ to 5′ exonuclease activity of DNA polymerase δ —

The proliferation of cytotoxic T-cells is markedly impaired upon infection with a newly discovered human immunodeficiency virus, designated HIV-V. The defect has been traced to the expression of a viral-encoded enzyme that inactivates a host-cell nuclear protein required for DNA replication. Which protein is a potential substrate for the viral enzyme?

A. TATA-box binding protein (TBP)
B. Cap binding protein (CBP)
C. Catabolite activator protein (CAP)
D. Acyl-carrier protein (ACP)
✓ E. Single-strand binding protein (SBP) —

The deficiency of an excision endonuclease may produce an exquisite sensitivity to ultraviolet radiation in Xeroderma pigmentosum. Which of the following functions would be absent in a patient deficient in this endonuclease?

A. Removal of introns
✓ B. Removal of pyrimidine dimers —
C. Protection against DNA viruses
D. Repair of mismatched bases during DNA replication
E. Repair of mismatched bases during transcription

The anti-*Pseudomonas* action of norfloxacin is related to its ability to inhibit chromosome duplication in rapidly dividing cells. Which of the following enzymes participates in bacterial DNA replication and is directly inhibited by this antibiotic?

A. DNA polymerase I
B. DNA polymerase II
C. Topoisomerase I
✓ D. Topoisomerase II — (DNA Gyrase)
E. DNA ligase

Cytosine arabinoside (araC) is used as an effective chemotherapeutic agent for cancer, although resistance to this drug may eventually develop. In certain cases, resistance is related to an increase in the enzyme cytidine deaminase in the tumor cells. This enzyme would inactivate araC to form

A. cytosine
B. cytidylic acid
C. thymidine arabinoside
✓ D. uracil arabinoside —
E. cytidine

Dyskeratosis congenital (DKC) is a genetically inherited disease in which the proliferative capacity of stem cells is markedly impaired. The defect has been traced to inadequate production of an enzyme needed for chromosome duplication in the nuclei of rapidly dividing cells. Structural analysis has shown that the active site of this protein contains a single-stranded RNA that is required for normal catalytic function. Which step in DNA replication is most likely deficient in DKC patients?

A. Synthesis of centromeres
B. Synthesis of Okasaki fragments
C. Synthesis of RNA primers
✓ D. Synthesis of telomeres —
E. Removal of RNA primers

5' 3'

During RNA synthesis, the DNA template sequence TAGC would be transcribed to produce which of the following sequences?

5' 3'

A. ATCG
B. GCTA
C. CGTA
D. AUCG
✓E. GCUA —

The base sequence of codons 57-58 in the cytochrome β5 reductase gene is CAGCGC. The mRNA produced upon transcription of this gene will contain the sequence:

A. GCGCTG
B. CUGCGC
C. GCGCUG
✓D. CAGCGC —
E. GUCGCG

A gene encodes a protein with 150 amino acids. There is one intron of 1,000 bps, a 5′-untranslated region of 100 bp, and a 3′-untranslated region of 200 bp. In the final processed mRNA, how many bases lie between the start AUG codon and the final termination codon?

A. 1,750
B. 750
C. 650
✓D. 450 —
E. 150

In the genetic code of human nuclear DNA, one of the codons specifying the amino acid tyrosine is UAC. Another codon specifying this same amino acid is

A. AAC
B. UAG
C. UCC
D. AUG
✓E. UAU —

Items 2 and 3

A. ATGCAA...→ ATG**T**AA
B. ATGAAA...→ **G**TGAAA
C. TATAAG...→ T**C**TAAG
D. CTTAAG...→ **G**TTAAG
E. ATGAAT ...→ ATG**C**AT

The options above represent mutations in the DNA with base changes indicated in boldface type. For each mutation described in the questions below, choose the most closely related sequence change in the options above.

✓Nonsense mutation A

✓Mutation decreasing the initiation of transcription C

Accumulation of heme in reticulocytes can regulate globin synthesis by indirectly inactivating eIF-2. Which of the following steps is most directly affected by this mechanism?

A. Attachment of spliceosomes to pre-mRNA
B. Attachment of the ribosome to the endoplasmic reticulum
C. Met-tRNAmet binding to the P-site
D. Translocation of mRNA on the ribosome
E. Attachment of RNA polymerase II to the promoter

A nasopharyngeal swab obtained from a 4-month-old infant with rhinitis and paroxysmal coughing tested positive upon culture for *Bordetella pertussis*. He was admitted to the hospital for therapy with an antibiotic that inhibits the translocation of peptidyl-tRNA on 70S ribosomes. This patient was most likely treated with

A. erythromycin
B. tetracycline
C. chloramphenicol
D. rifamycin
E. levofloxacin