OUTLINE:

BB 422/622

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic
Fermentations

Exam-1 material

Pyruvate
Krebs' Cycle
Oxidative Phosphorylation
- Electron transport
- Chemiosmotic theory: Phosphorylation

Exam-2 material

Fat Catabolism
Fatty acid Catabolism
- Mobilization from tissues (mostly adipose)
- Activation of fatty acids
- Transport; carnitine
- Oxidation: β-oxidation, 4 steps:

Protein Catabolism
Amino-Acid Degradation
- Dealing with the nitrogen; Urea Cycle
- Dealing with the carbon; Seven Families

Nucleic Acid & Nucleotide Degradation

Exam-3 material

ANABOLISM I: PHOTOSYNTHESIS:

Overview and Key experiments:
Light Reactions
- energy in a photon/pigments
- Reaction center &Photosystems (PSII & PSI)

Proton Motive Force – ATP
Carbon Assimilation – Calvin Cycle
- **Rubisco/**Oxygenase (Glycolate cycle)
- remaking Ru 1,5P_2

Overview and regulation
C4 versus C3 plants
Kornberg cycle – glyoxylate
Carbohydrate Biosynthesis in Animals
- precursors/Cori cycle

Gluconeogenesis
- reversible steps
- irreversible steps – four

Glycogen Synthesis
- UDP-Glc/Glycogen synthase/branching

Pentose-Phosphate Pathway
- oxidative-NADPH
- non-oxidative-Ribose 5-P

Regulation of Carbohydrate Metabolism
Anaplerotic reactions
Biosynthesis of Fatty Acids
- contrasts
- location & transport
- synthesis
  - ACC
  - FAS; ACP priming; 4 steps
  - Control

Diversification of fatty acids
- elongation
- desaturation
- Eicosanoids
  - Prostaglandins and Thromboxane

Exam-4 material

ANABOLISM II:

Biosynthesis of Fatty Acids and Lipids
- Fatty Acids
- Triacylglycerides
- Membrane lipids
  - Glycerophospholipids
  - Sphingolipids
  - Isoprene lipids: **Cholesterol**
    - Ketone body synthesis
    - Mevalonate
    - **Cholesterol**
      - bile acids
      - steroids
      - metabolism
      - control of cholesterol biosynthesis

ANABOLISM III:

Biosynthesis of Amino Acids and Nucleotides
- Nitrogen fixation
  - nitrogenase
- Nitrogen assimilation
- Amino-acid Biosynthesis
- Nucleotide Biosynthesis
- Control of nitrogen metabolism
- Biosynthesis of secondary products of amino acids

Exam-5 material

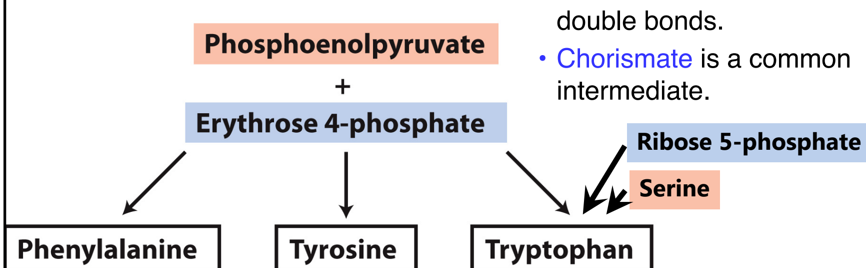
Biosynthesis Amino Acids & Nucleotides

Aromatic Family: Phe, Trp

Aromatic Amino Acids Derive from PEP and Erythrose 4-Phosphate

(and Rib5P and Ser)

- Very complicated and amazing chemistry!
- Rings must be synthesized and closed and then oxidized to create double bonds.
- Chorismate is a common intermediate.



Biosynthesis Amino Acids & Nucleotides

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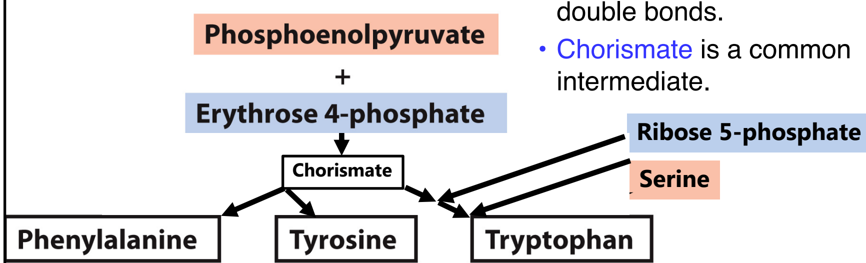
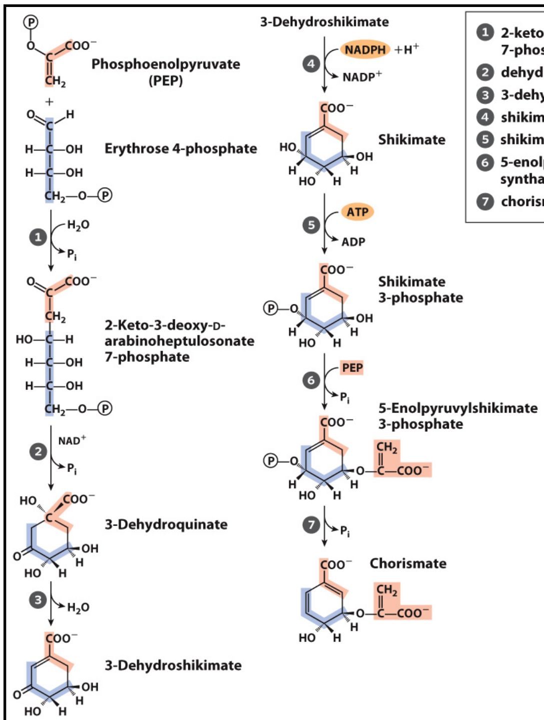
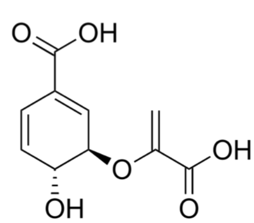




1. 2-keto-3-deoxy-D-arabinoheptulosonate 7-phosphate synthase
2. dehydroquinate synthase
3. 3-dehydroquinate dehydratase
4. shikimate dehydrogenase
5. shikimate kinase
6. 5-enolpyruvylshikimate 3-phosphate synthase
7. chorismate synthase

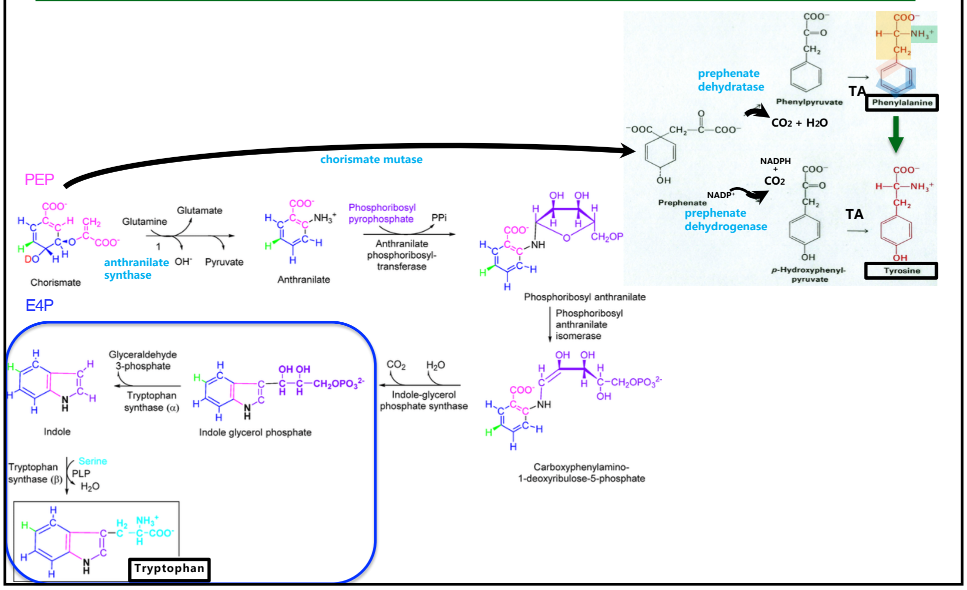
Biosynthesis of Chorismate, a Key Intermediate in Aromatic Amino Acid Biosynthesis



Chroismate

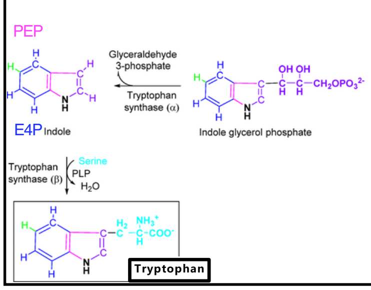
Biosynthesis Amino Acids & Nucleotides

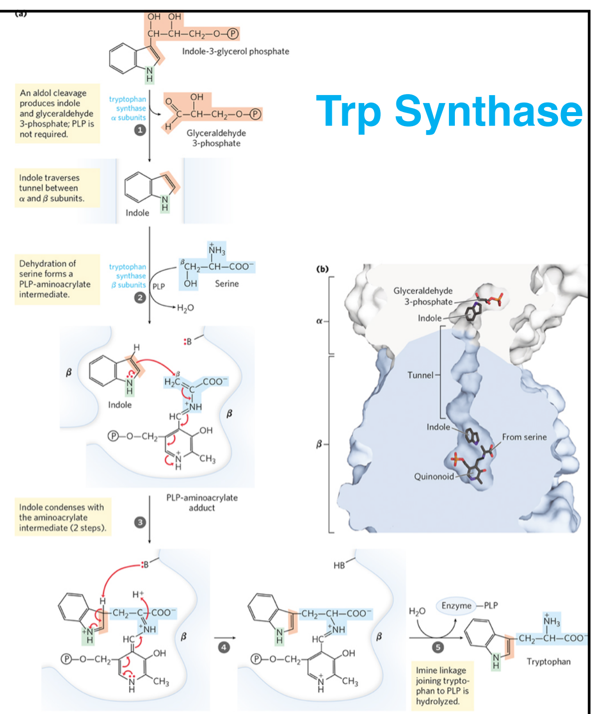
Aromatic Family: Phe, Trp

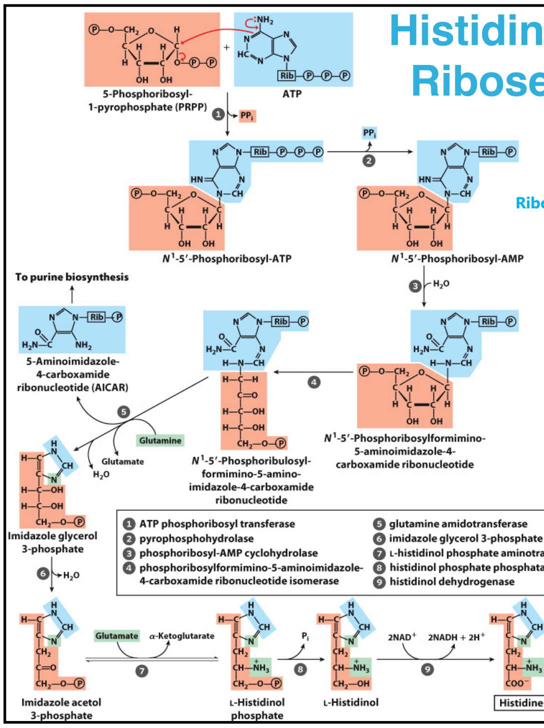


Biosynthesis Amino Acids & Nucleotides

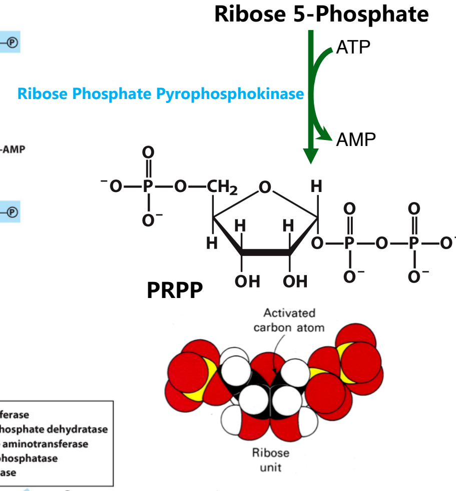
Trp Synthase







Histidine Derives from Ribose 5-Phosphate



- Synthesized from ribose 5-phosphate via *ribose phosphate pyrophosphokinase*
  – a highly regulated allosteric enzyme

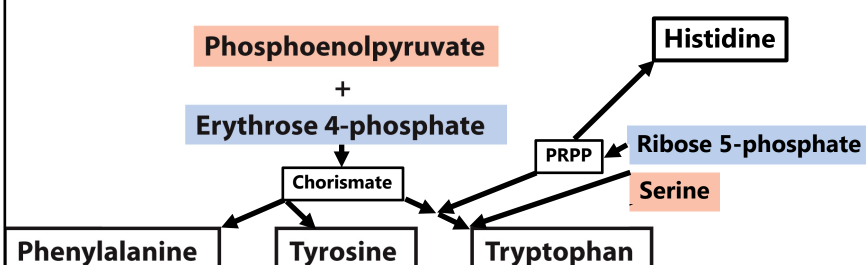
Biosynthesis Amino Acids & Nucleotides

Aromatic Family: Phe, Trp

Aromatic Amino Acids Derive from PEP and Erythrose 4-Phosphate

(and Rib5P and Ser)

…..and HIS



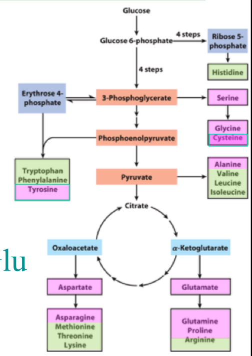
Biosynthesis Amino Acids & Nucleotides

Asp	1	*	OAA
Glu	1	*	α-KG
Ala	1	*	Pyr
Asn	1	–	Asp
Gln	1	–	Glu
Pro	3(1)	(*)	Glu/Arg
Ser	3	–	3PGA
Gly	1	*	Ser
Cys	2	*	Ser/Met
Tyr	1	*	Phe

Red=biosynthesis specific *reverse of degradation

Essential Amino acids:

These require many steps and unique to those used for degradation.



Family	AA	Steps	Precursors
Asp/Pyruvate Family	Met	7	–Asp/Cys/THF/Glu
	Thr	5	–Asp/Glu
	Lys	9	–Asp/Pyr/Glu
	Ile	10	–Asp(Thr)/Pyr/Glu
	Val	4	–Pyr/Glu
	Leu	7	–Pyr/AcCoA/Glu
Aromatic Family	Phe	10	–E4P/PEP/Glu
	Trp	12	–E4P/PEP/Gln/R5P/Ser
Histidine	His	10	–R5P/ATP/Gln/Glu

Biosynthesis Amino Acids & Nucleotides

Asp	1	*	OAA
Glu	1	*	α-KG
Ala	1	*	Pyr
Asn	1	–	Asp
Gln	1	–	Glu
Pro	3(1)	(*)	Glu/Arg
Ser	3	–	3PGA
Gly	1	*	Ser
Cys	2	*	Ser/Met
Tyr	1	*	Phe

Red=biosynthesis specific *reverse of degradation

Essential vs. Nonessential and Conditionally Essential Amino Acids

- Essential amino acids must be obtained as dietary protein.
- Nonessential amino acids are easily made from central metabolites.
- Consumption of a variety of foods supplies all the essential amino acids.

TABLE 18-1 Nonessential and Essential Amino Acids for Humans and the Albino Rat

Nonessential	Conditionally essential[a]	Essential
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

[a]Required to some degree in young, growing animals and/or sometimes during illness.

- Conditionally Essential amino acids are made from essential, or become essential in certain physiological conditions.

Conditionally Essential Amino Acids

TABLE 18-1	Nonessential and Essential Amino Acids for Humans and the Albino Rat	
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Adapted from:
The Low-Down on Conditionally Essential Amino Acids
By: by Amino Science
Posted on: February 9, 2018

The 7 Conditionally Essential Amino Acids
There are seven nonessential amino acids that sometimes become conditionally essential. These are:
Arginine, Cysteine, Glutamine, Glycine, Proline, Serine, Tyrosine

Arginine
Arginine is perhaps best known for its ability to increase production of the important vasodilator nitric oxide, which improves blood flow and reduces blood pressure. Because of its role in boosting nitric oxide production, arginine is a key player in heart health and can be useful in treating hypertension, angina, circulatory diseases, and erectile dysfunction.
Arginine also helps prevent the formation of ammonia in the liver, enhances immune function, and aids in glucose metabolism, making it potentially useful for people suffering from diabetes.
However, certain catabolic conditions—those that lead to the breakdown of protein—may necessitate dietary supplementation of arginine.
Preterm infants, for example, can't make arginine on their own. The aging process also results in less efficient production of arginine. And people with serious wounds and burns may need the added support of dietary arginine to assist with the healing process.
Good dietary protein sources of arginine include: Meat, Poultry, Dairy products, Soybeans, Chickpeas, Spirulina, Nuts, Seeds

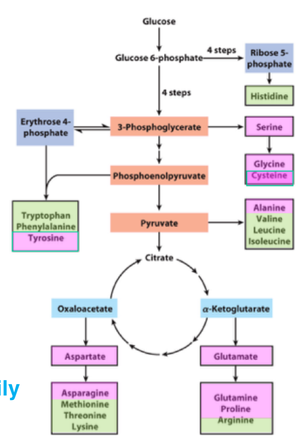
Biosynthesis Amino Acids & Nucleotides

Non-essential Amino acids:
These are very few steps and often the same enzyme(s) used for degradation.

Arg-Val-His-Ile-Leu-Lys-Met-Phe Thr-Trp
Professor A.V.HILL M.P. was a Tea Totaller

AA	#steps	same as degradation	From?	
Asp	1	✓	OAA	Transaminase route
Glu	1	✓	α-KG	Transaminase route
Ala	1	✓	Pyr	Transaminase route
Asn	1	–	Asp	Amidation route
Gln	1	–	Glu	Amidation route
Pro	3(1)	(✓)	Glu/Arg	Glu Family
[Arg	3(1)	(✓)	Pro]	Glu Family
Ser	3	–	3PGA	3-PGA Family
Gly	1	✓	Ser	3-PGA Family
Cys	2	✓	Ser/Met	3-PGA Family / From Essential Family
Tyr	1	✓	Phe	From Essential Family

Red=biosynthesis specific Green=essential



ANABOLISM III: Biosynthesis Amino Acids & Nucleotides

1) Nitrogen fixation: $N_2 \rightarrow NH_4$

2) Nitrogen assimilation: incorporation of ammonia into biomolecules

3) Biosynthesis of amino acids
   a) non-essential
   b) essential

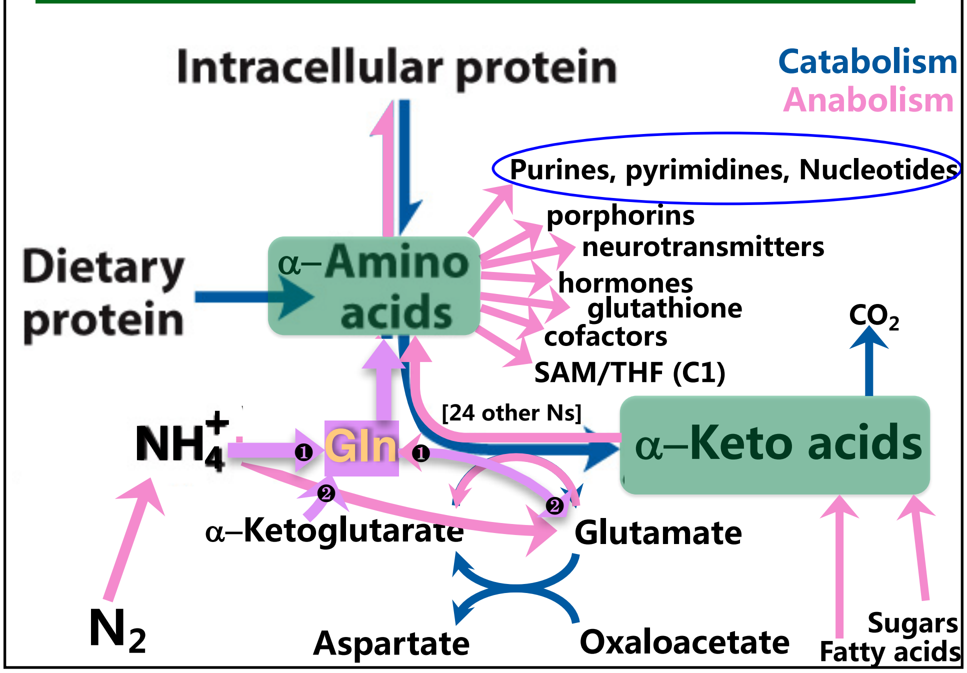
4) Biosynthesis of nucleotides
   a) sources
   b) *de novo* purines (R)(as nucleotides*); salvage; regulation
   c) *de novo* pyrimidines (Y)(as bases); making nucleotide; regulation
   d) deoxy-ribonucleotides, dTMP, and phosphorylation to NTP & dNTP
   e) regulating levels for DNA synthesis

5) Control of nitrogen metabolism

6) Biosynthesis and degradation of heme; other 2° products of amino acids

*Bases synthesized *while* attached to ribose-5-P; products are RMP (R is one-letter code for purine, Y is one letter code for pyrimidine)

Biosynthesis Amino Acids & Nucleotides

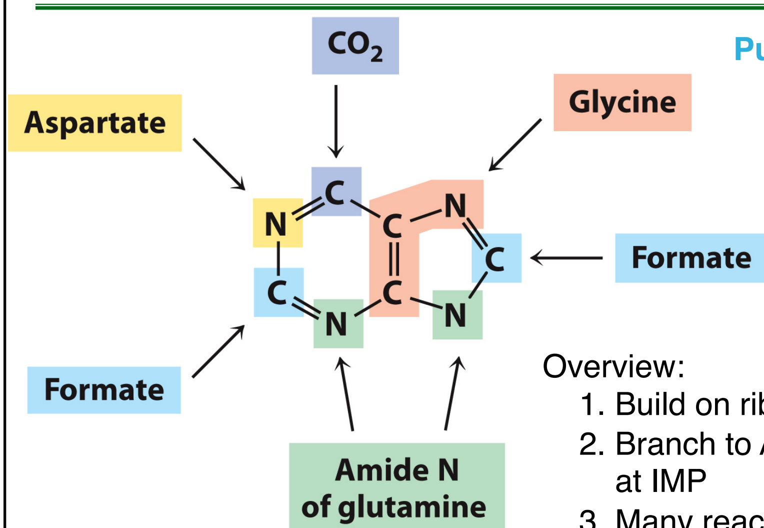


Biosynthesis Amino Acids & Nucleotides

Two major sources of Nucleotides:

1. They can be synthesized *de novo* ("from the beginning")
   - Purine nucleotides: from Gly, Gln(NH_3), Asp(NH_3), THF, and CO_2, and ribose-5-phosphate (PRPP)
   - Pyrimidine nucleotides: from Asp, carbamoyl-phosphate, and ribose-5-phosphate (PRPP)
2. Nucleotides can be salvaged from RNA, DNA, and cofactor degradation and diet.
   - Recall purines are degraded to uric acid (no energy) but pyrimidines can be oxidized to acetyl-CoA and succinyl-CoA
   - Purine salvage is a significant contribution (80-90%)
   - Interesting: Many parasites (e.g., malaria) lack *de novo* biosynthesis and rely exclusively on salvage. Therefore, compounds that inhibit salvage pathways are promising anti-parasite drugs.
3. Because ATP/ADP are involved in so many reactions and regulation mechanisms, the absolute [nucleotide] are kept low; so cells must continually synthesize them.
   - This synthesis may actually limit rates of transcription and replication.
4. Unlike amino-acid biosynthesis, pathways are conserved in ALL organisms.

Biosynthesis Amino Acids & Nucleotides



Overview:

1. Build on ribose (PRPP)
2. Branch to AMP & GMP at IMP
3. Many reactions like those seen before

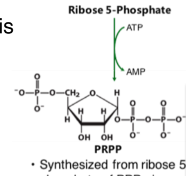
Biosynthesis Amino Acids & Nucleotides

De Novo Biosynthesis of Purin

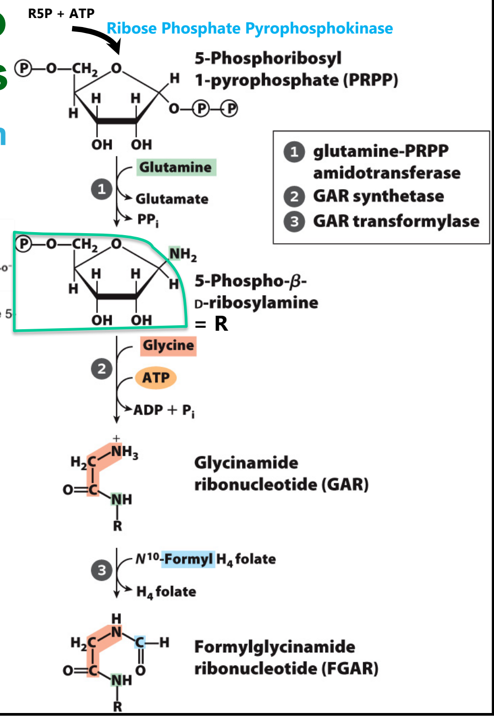
0. Begins with PRPP synthesis
1. PRPP reacts with Gln (like Glu synthase; ammonia channel).

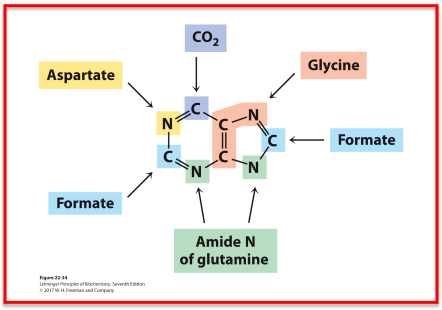
Committal Step

2. Addition of three carbons from glycine by making amide
3. Add C1 from THF



• Synthesized from ribose 5-phosphate of PPP via *ribose phosphate pyrophosphokinase*
– a highly regulated allosteric enzyme

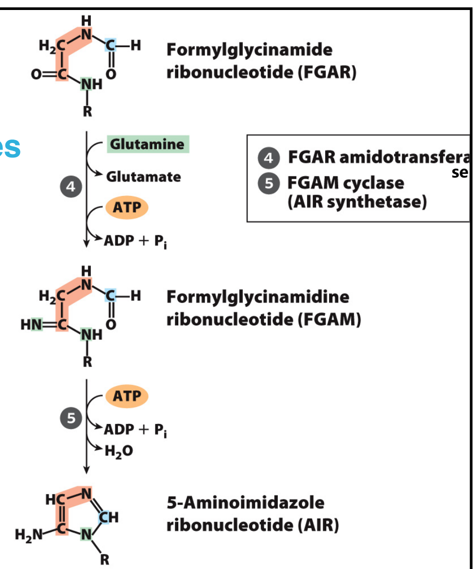


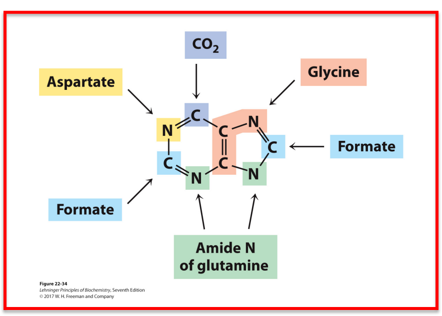


Biosynthesis Amino Acids & Nucleotides

De Novo Biosynthesis of Purines

4. FGAR reacts with Gln (like Glu synthase; ammonia channel).
5. Looks like Schiff base, but its an elimination after phosphorylation.

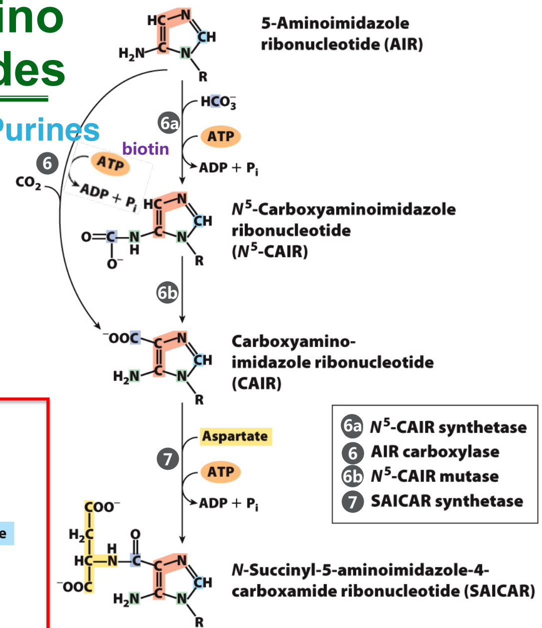


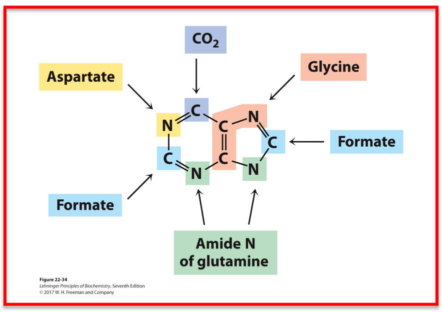


Biosynthesis Amino Acids & Nucleotides

De Novo Biosynthesis of Purines

6. Typical carboxylase (6a/b in microorganisms)
7. Add Nitrogen of Asp (recall Urea Cycle).



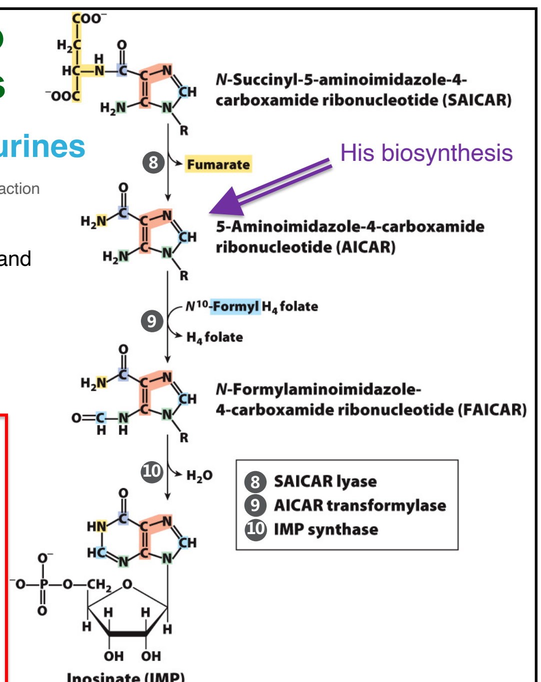


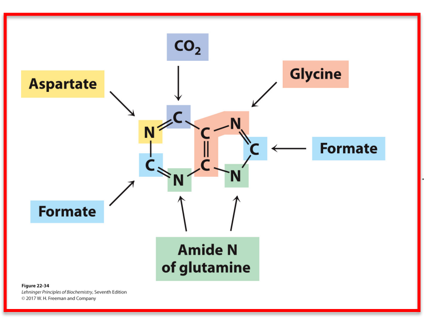
Biosynthesis Amino Acids & Nucleotides

De Novo Biosynthesis of Purines

8. Removal of fumarate (can act as anaplerotic reaction to keep ATP synthesis)
9. Add C1 from THF
10. Schiff base formation gets ring closure and **IMP**

Total ATP=10 (2 for N^{10}-formylTHF)

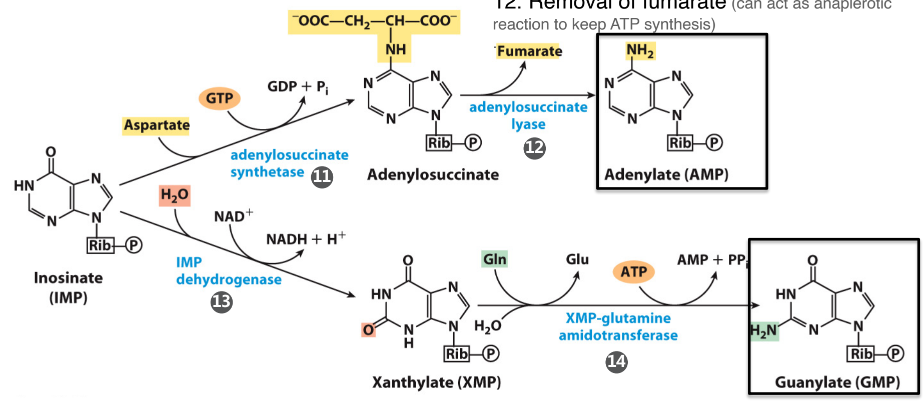




Biosynthesis Amino Acids & Nucleotides

Synthesis of AMP and GMP from IMP

11. Add Nitrogen of Asp (recall Urea Cycle)
12. Removal of fumarate (can act as anaplerotic reaction to keep ATP synthesis)



13. Add water cross imine and oxidize to keto (recall fatty acid oxidation, except at imine not alkene)
14. Add nitrogen from Gln (recall Glu synthase (ammonia channel), and 3rd time we saw use of Gln for this)

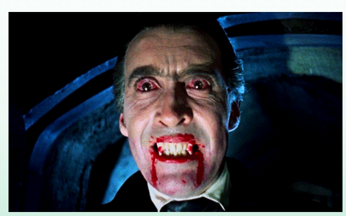
Note that ATP is used to synthesize GMP precursor, while GTP is used to synthesize AMP precursor.

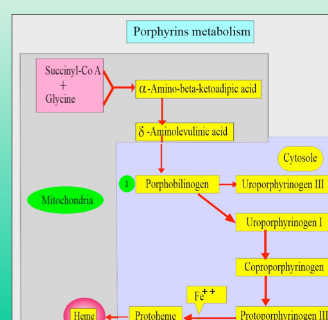
Clinical Correlations

Difficulties making Heme: anemias

Defects in Heme Biosynthesis

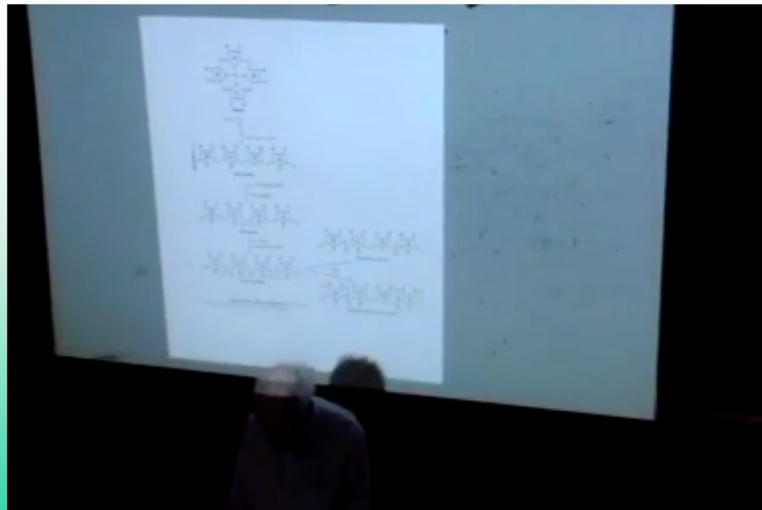
- Most animals synthesize their own heme.
- Mutations or mis-regulaton of enzymes in the heme biosynthesis pathway lead to **porphyrias** (pour-fear-ia).
  - Precursors accumulate in red blood cells, body fluids, and liver.
- Accumulation of precursor uroporphyrinogen I
  - Urine becomes discolored (pink to dark purplish depending on light, heat exposure).
  - Teeth may show red fluorescence under UV light.
  - Skin is sensitive to UV light.
  - There is a craving for heme.
- Explored as possible biochemical basis for vampire myths





Clinical Correlations

Color me: Bruises to Bowels



Porphyrin Degradation