Carbohydrate Metabolism
Overview

• Glucose is key blood sugar and normally circulates at levels of 65-100 mg/dL – highly regulated – hyperglycemia and hypoglycemia can be serious pathologic circumstances

• Glucose has three metabolic fates
  • Metabolism to pyruvate by glycolytic pathway
  • Conversion to pentose phosphates by the hexose monophosphate shunt
  • Storage as glycogen
Important Features of the Glycolytic Pathway

- Glycolysis is an anaerobic process. Takes place in the absence of oxygen.
- Glycolysis is carried out by all cells.
- Glycolytic pathway occurs in the cytosol.
Important Features of the Glycolytic Pathway

• Aerobic conditions, glucose is oxidized through pyruvate to \( \text{CO}_2 \) and \( \text{H}_2\text{O} \) in the mitochondria

• Anaerobic conditions - pyruvate is converted to L-lactate (contracting muscle)
Glycolytic Reactions

- 10 Enzymatic Steps
- 1st part of pathway, there is an expenditure of two ATP molecules
- 2nd stage of pathway, four ATP molecules are produced
- Results in net gain of two ATP molecules
Liver has an additional enzyme called glucokinase, which catalyzes the same reaction as hexokinase. Glucokinase is a low affinity, high capacity enzyme. Under low glucose conditions, hexokinase has first call on glucose. Under high glucose conditions, liver stores glucose as glycogen.
Phosphofructokinase

Fructose-6-phosphate + ATP → Fructose-1,6-bisphosphate + ADP

- Key regulatory step in glycolysis. Inhibited by ATP and citrate, activated by AMP and fructose 2,6-bisphosphate
- Committed step in glycolysis
Pyruvate Kinase Deficiency

- Inherited Metabolic Disorder
- Autosomal dominant and recessive inheritance
- Hemolytic anemia
- No treatment for mild anemia
- Blood transfusion or splenectomy
Metabolic fates of glycolytic endproducts

Glucose + 2 NAD$^+$ + 2 ADP + 2 P$_i$ $\rightarrow$

2 pyruvate + 2 NADH + 2 H$^+$ + 2 ATP + 2 H$_2$O
Metabolic fates of pyruvate and NADH

Pyruvate + NADH → lactate + NAD^+

- Pyruvate and NADH are converted to lactate, and NAD^+, respectively, under anaerobic conditions by LDH.
Regulation of Phosphofructokinase

PFK allosterically inhibited by ATP and citrate. Both lower affinity of PFK for fructose-6-phosphate substrate. Why?

PFK allosterically activated by AMP. Why?

PFK is also activated by fructose-2,6-bisphosphate, the most important regulator of PFK activity.

![Diagram of PFK regulation](image-url)
Metabolism of other hexoses

Galactose, fructose, and mannose are all present in the diet in varying amounts.
Galactose metabolism

Galactose

Galactokinase

ATP

ADP

Galactose-1-P

Galactose-1-P

Uridylyltransferase

UDP-Glucose

UDP-Galactose

UDP-Galactose-4-epimerase

Glucose-1-P

Phosphoglucomutase

Glucose-6-P
Galactosemia

- Failure to thrive
- Vomiting in infants upon lactose ingestion
- Liver deterioration
- Mental retardation
- Galactose-1-phosphate accumulation
Disaccharides

Maltose → 2 Glucose

Lactose → Galactose + Glucose

Sucrose → Fructose + Glucose

Disaccharides present in diet in large amounts
Converted to monosaccharides extracellularly (gut)
Lactase deficiency causes diarrhea, discomfort
Pentose Phosphate Pathway - AKA Hexose Monophosphate Shunt or Phosphogluconate Pathway

Two major general functions

1. Generate NADPH (not NADH)
   
   Fatty acids and cholesterol

2. Generate ribose-5-phosphate
   
   Nucleotides

PPP occurs in Cytosol

Two components

1. Oxidative phase

2. Nonoxidative phase
Glucose 6-phosphate dehydrogenase deficiency is the most common disease-causing enzyme deficiency in the world and causes a drug-induced hemolytic anemia. Anemia caused by diminished level of erythrocytic glutathione, which maintains redox potential in red blood cells.
Drugs or food that cause the hemolytic anemia observed in G6PDH deficiency are those that induce oxidative stress, e.g., produce oxygen species, e.g., peroxide. Examples include fava beans, aspirin, some NSAIDs, quinine, penicillin, primaquine, sulfonilamides, chloramphenicol.
Glucose 6-phosphate dehydrogenase deficiency is an X-linked disorder that is very prevalent in the black population. Trait thought to be a selective advantage against malaria.

Why?
Nonoxidative portion of the HMP shunt
Oxidative Metabolism

Pyruvate Dehydrogenase (PDH) Complex
TCA (Krebs) Cycle
Pyruvate Dehydrogenase (PDH) Complex

TCA (Krebs) Cycle
The diagram illustrates the cycle of the citric acid cycle (also known as the Krebs cycle). Starting with Acetyl-CoA, it reacts with oxaloacetate to form citrate, which undergoes a series of reactions to produce NADH, FADH₂, and ATP (in the form of GTP). The cycle is completed with the regeneration of oxaloacetate. Each step in the cycle is catalyzed by specific enzymes, and the reactions involve the transfer of carbon atoms and electrons between molecules.
Vitamin $B_1$ deficiency

Beriberi

Early manifestations: Fatigue, drowsiness, depression, poor mental concentration, nausea, vomiting, abdominal pain

Later manifestations: Peripheral neuritis, paresthesias, decreased reflexes, loss of vibration sense, cramping, heart failure, death

Treat with thiamine hydrochloride
Wernicke’s Syndrome *
- Loss of motor control
- Ataxia (staggering gait)
- Ophthalmoplegia (paralysis of eye movements)
- Confusion
- Vitamin B1 reversible

Korsakoff’s Patients *
- Severe memory loss
- Vitamin B1 irreversible

* Observed in chronic alcoholism and among drug addicts
Pyruvate Dehydrogenase Deficiency

- Common neurodegenerative disorder associated with abnormal mitochondrial metabolism
- Most often X-linked E1 alpha gene
- Lactic acidosis
- Neurodegenerative, retardation, blindness
- Leigh syndrome
- Treatment with ????
TCA cycle

Key features
- It’s a cycle
- 2 carbons go in.
- 2 carbons go out
α-Ketoglutarate dehydrogenase requires 5 cofactors

- Thiamine
- Riboflavin
- Lipoic acid
- Niacin
- Pantothenate
- Thiamine pyrophosphate
- FAD
- Lipoic acid
- NAD⁺
- Coenzyme A
TCA cycle intermediates provide carbon backbones for other metabolites.

Intermediates for amino acids, porphyrins, purines, pyrimidines, fatty acids, sterols, ketone bodies
Gluconeogenesis

Definition: Gluconeogenesis is the process by which noncarbohydrate precursors are converted to glucose.
Gluconeogenesis is not a reversal of glycolysis
Glucose 6-phosphatase

\[ \text{Glucose 6-phosphate} + \text{H}_2\text{O} \rightarrow \text{Glucose} + \text{P}_i \]

Bypasses hexokinase

Found in liver and kidney. Not found in brain or skeletal muscle

Enables glucose release into the bloodstream
Glycogen

Storage form of glucose

Needed because blood only contains about 3.3-7.0 grams of glucose
Glycogen storage diseases

- Von Gierke’s disease
  - Glucose 6-phosphatase deficiency
  - Liver cannot provide glucose to brain/muscle
  - Deadly

- McArdle’s syndrome
  - Muscle glycogen phosphorylase deficiency
  - Cramping/tetany upon moderate exercise
Amino Acid Metabolism

Great clinical relevance. Genetic, pharmacologic, and dietary aberrations of amino acid and purine metabolism common.
Examples of Inborn Errors or Inherited Disorders of Amino Acid Metabolism

• Argininosuccinicaciduria
• Carbamoylphosphate synthetase deficiency
• Citrullinemia
• Homocystinuria
• Hyperammonemia
• Hypermethionemia
• Maple Syrup Urine Disease
• Phenylketonuria
• Alkaptonuria
• Tyrosinemia
• Hyperglycemia
• Proprionic acidemia
Major functions of amino acids

- Building blocks for protein
- Energy substrates
- Precursors for nitrogen-containing compounds
Key nitrogenous derivatives that are amino acid derivatives

1. Purines and pyrimidines
2. Porphyrins and hemes
3. Neurotransmitters
4. Hormones
5. Pigments
6. Creatine
7. Polyamines
8. Glutathione
9. Antibiotics (not made in humans)
10. Aminosugars
11. Nitric Oxide
<table>
<thead>
<tr>
<th>Essential</th>
<th>Nonessential</th>
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</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>Alanine</td>
</tr>
<tr>
<td>Histidine</td>
<td>Aspartic acid</td>
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<tr>
<td>Isoleucine</td>
<td>Asparagine</td>
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<tr>
<td>Leucine</td>
<td>Cysteine</td>
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<tr>
<td>Lysine</td>
<td>Glutamic acid</td>
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<tr>
<td>Methionine</td>
<td>Glutamine</td>
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<tr>
<td>Phenylalanine</td>
<td>Glycine</td>
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<tr>
<td>Threonine</td>
<td>Proline</td>
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<tr>
<td>Tryptophan</td>
<td>Serine</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Valine</td>
<td></td>
</tr>
</tbody>
</table>
Digestion of dietary protein is profoundly affected by genetic, pharmacological, or dietary perturbation.
Trypsinogen deficiency

```
STOMACH

pepsin ————
(attacks Phe, Tyr, Glu, Asp)

smaller polypeptides

typesin ————
(attacks Lys-X, Arg-X)

chymotrypsin ————
(attack hydrophobic)

elastase ————
(attacks Ala, Gly, Ser)

oligopeptides

carboxypeptidases ————
(A attacks neutral, hydrophobic)
(b attacks Arg-COO-, Lys-COO-)

amino acids

SMALL BOWEL

from pancreas
```
Protein Malnutrition Diseases

**Kwashiorkor**
- Protein insufficiency
- Caloric sufficiency
- Characterized by edema, anemia, learning deficits

**Marasmus**
- Protein insufficiency
- Caloric insufficiency
- Characterized by anemia, extreme wasting, weakness, growth retardation, death
Na\textsuperscript{+}-ATP-dependent amino acid transporters

1. Basic amino acid transporter
2. Neutral amino acid transporter
3. Acidic amino acid transporter
4. Imino amino acid transporter
5. Other transporters
Genetic disorders of amino acid transport

- Cystinuria - defect in basic amino acid transporter - cystine stones
- Hartnup’s disease - a benign defect in the neutral amino acid transporter activity
Drug-Nutrient Interactions, a Physician’s Dilemma

Many naturally occurring compounds and drugs are amino acid analogs. The entry of amino acids into cells can be effectively competed by drugs, and the entry of drugs into cells can be effectively competed by amino acids at the transport level.

L-DOPA is classic example
ALT

**Alanine Aminotransferase (ALT)**

**Aspartate Aminotransferase (AST)**

- **t-alanine**
  - Alanine Aminotransferase
  - **t-aspartate**
    - Aspartate Aminotransferase

- **pyruvate**
  - **t-glutamate**
    - **oxaloacetate**
Serum ALT and AST are assessment markers for liver and other (cardiac, renal, muscular, pancreatic, RBC) pathologies

- AST - aspartate transaminase
- GOT - glutamate oxaloacetate transaminase
- SGOT - serum glutamate oxaloacetate transaminase
- ALT - alanine transaminase
- GPT - glutamate pyruvate transaminase
- SGPT - serum glutamate pyruvate transaminase

ALT more liver-specific than AST. Most other tissues express high AST.
Synthesis of nonessential amino acids

Nonessential amino acids are synthesized from glycolytic and TCA cycle intermediates. Glycolysis and TCA cycle provide carbon backbones, which are transaminated to form amino acids.
Glycolytic

3-phosphoglycerate → Serine → Cysteine
Pyruvate → Alanine → Glycine

TCA Cycle

Oxaloacetate → Aspartate → Asparagine
α-ketoglutarate → Glutamate → Glutamine → Proline
Synthesis of Glycine

- Serine transhydroxymethylase
Folate synthesis pathway in microbes is site of action for sulfanilamides

- Broad spectrum antibiotics (component of Bactrim)
- Urinary tract infections
- Chlamydia infections
- Limitations to clinical utility
Dihydrofolate reductase
Dihydrofolate reductase (DHFR) target for chemotherapeutica

- Methotrexate
- Trimethoprim
- Pyrimethamine
Methotrexate

- Cancers - many varieties
- Psoriasis
- Arthritis - lupus, rheumatoid
Trimethoprim

- UTIs
- Sinusitis
- Prostatitis
- Typhoid
- Dysentery
Trimethoprim - Sulfamethoxazole

- *Pneumocystis jiroveci*
- Bactrim
Pyrimethamine
Pyrimethamine-Trisulfapyrimidinedine
Homocystinuria

Methionine

S-Adenosylmethionine (SAM)

biosynthetic methylation

methyl acceptor

methylated acceptor

Homocysteine

S-Adenosylhomocysteine

Cystathionine biosynthesis

alpha-Ketobutyrate

Cysteine
Homocysteinuria treatment

- Vitamin $B_6$
- Folate
- Vitamin $B_{12}$
Cystathioninuria

\[
\begin{align*}
\text{Methionine} & \quad \text{S-Adenosylmethionine (SAM)} \\
\text{Homocysteine} & \quad \text{S-Adenosylhomocysteine} \\
\text{Cystathionine} & \quad \text{alpha-Ketobutyrate} \\
\end{align*}
\]
Arginine

Arginine is an intermediate in the urea cycle and its synthesis will be addressed later.
Phenylketonuria

- 1 in every 10,000 live births
- Tyrosine auxotrophy
- Elevated phenylalanine
- Neurotoxicity
PKU treatment

- Low protein diet
- Low and carefully monitored Phe
- Tyr supplementation because tyrosine is now an essential amino acid
Amino acid breakdown

• Amino acid excess - amino acids, unlike carbohydrates and fats, are not stored
• Fasting and starvation - maintenance of blood glucose requires catabolism of muscle protein
• Diabetes
End products of amino acid catabolism

- **Ammonotelic animals:** most aquatic vertebrates, especially bony fishes, and amphibia larvae
- **Ureotelic animals:** most terrestrial vertebrates, also sharks
- **Uricotelic animals:** birds, snakes, lizards
Mitochondrion

$2\text{ATP} + \text{HCO}_2^- + \text{NH}_3 \rightarrow \text{H}_2\text{N}^-\text{C}--\text{OPO}_4^{2-} + 2\text{ADP} + \text{P}_i$

Carbamoyl phosphate

\[ \text{O} = \text{C} - \text{NH}_2 \]
\[ \text{NH} \]
\[ (\text{CH}_2)_3 \]
\[ \text{H} - \text{C} - \text{NH}_3^+ \]
\[ \text{COO}^- \]

Ornithine

\[ \text{N}^+ \text{H}_3 \]
\[ (\text{CH}_2)_3 \]
\[ \text{H} - \text{C} - \text{NH}_3^+ \]
\[ \text{COO}^- \]

Citrulline

\[ \text{O} = \text{C} - \text{NH}_2 \]
\[ \text{NH} \]
\[ (\text{CH}_2)_3 \]
\[ \text{H} - \text{C} - \text{NH}_3^+ \]
\[ \text{COO}^- \]

Citrulline

\[ \text{O} = \text{C} - \text{NH}_2 \]
\[ \text{NH} \]
\[ (\text{CH}_2)_3 \]
\[ \text{H} - \text{C} - \text{NH}_3^+ \]
\[ \text{COO}^- \]

Aspartate

\[ \text{C} \]

Urea cycle

\[ \text{O} \]
\[ \text{H}_2\text{N}^-\text{C}--\text{NH}_2 \]
\[ \text{H}_2\text{O} \]

Urea

\[ \text{H}_2\text{N}^-\text{C}--\text{NH}_2 \]
\[ \text{H}_2\text{O} \]

Arginine

\[ \text{H}_2\text{N}^-\text{C}--\text{NH}_2 \]
\[ (\text{CH}_2)_3 \]
\[ \text{H} - \text{C} - \text{NH}_3^+ \]
\[ \text{COO}^- \]

Cytosol

\[ \text{O} \]
\[ \text{H}_2\text{N}^-\text{C}--\text{NH}_2 \]
\[ (\text{CH}_2)_3 \]
\[ \text{H} - \text{C} - \text{NH}_3^+ \]
\[ \text{COO}^- \]

Fumarate

\[ \text{C} \]
Inborn errors

- Genetic defects in each enzyme of the urea cycle.
- Hyperammonemia
- Severe mental retardation
- Lethargy, coma, and death
- Nutritionally managed through low protein diets
Mechanism of NH$_4^+$ neurotoxicity

\[ \text{NH}_4^+ + \alpha\text{-ketoglutarate} + \text{NADPH} + \text{H}^+ \rightarrow \text{glutamate} + \text{NADP}^+ + \text{H}_2\text{O} \]

\[ \text{(NADH}^+) \rightarrow \text{(NAD}^+) \]
Pharmacologic treatment for hyperammonemia
Conversion of carbon skeletons of amino acids to fuel molecules
Ketogenic versus Glucogenic Amino Acids

- Amino acids that are converted to glycolytic or TCA cycle intermediates are considered to be glucogenic, i.e., net glucose synthesis can occur.

- Amino acids that are degraded to acetyl CoA or acetoacetyl CoA are considered to be ketogenic. No net synthesis of glucose occurs.
Carbon skeletons of all amino acids are funneled into seven metabolites.
Glucogenic versus ketogenic amino acids
Alkaptonuria
Maple syrup urine disease
Amino acid derivatives
Purines, pyrimidines, porphyrins, heme

[Diagram of molecular structures]
Collagen metabolites

4-Hydroxyproline

5-Hydroxylysine
GABA - Inhibitory neurotransmitter

GABA increases passage of chloride ion through postsynaptic membrane. Hyperpolarizes
Histamine - Powerful vasodilator

- Histamine acts locally in inflammation
- Histamine acts systemically in shock
Tryptophan is a precursor for serotonin.

Serotonin is a neurotransmitter that affects appetite, aggression, sleep, and sexual activity.
Hey. I thought niacin was a vitamin, and, therefore required in the diet.
Tyrosine is a precursor for catecholamines
Arginine, glycine, and methionine are precursors for creatine synthesis.
Creatinine

- Creatinine is synthesized nonenzymatically from phosphocreatine
- Creatinine in the urine is in direct proportion to muscle mass
- Diagnostic for certain muscular dystrophies and for measuring glomerular filtration rates
Ornithine is a precursor for polyamines

DFMO

DFMO

PLP

S-Adenosylmethionine

decarboxylated S-adenosylmethionine

Methylthioadenine

Putrescine (1,4 diaminobutane)

Spermidine

Spermine

H₂N-CH₂-CH₂-CH₂-CH₂-NH₂
Arginine is a precursor for nitric oxide

Nitric oxide is a short-lived chemical signal
Purine and Pyrimidine Metabolism
IMP branchpoint pathway

1. Inosine monophosphate (IMP) is converted to Adenylosuccinate (AMPS) by Adenylosuccinate Synthetase.
2. GTP and Mg$^{2+}$ are required for this reaction.
3. Adenylosuccinase catalyzes the conversion of Adenylosuccinate (AMPS) to Adenosine monophosphate (AMP).
4. IMP Dehydrogenase converts IMP to Xanthosine monophosphate (XMP) using NAD$^+$.
5. Xanthosine monophosphate (XMP) is converted to Guanosine monophosphate (GMP) using ATP and Glutamine.
6. Glutamate is used as a co-factor in the conversion of Xanthosine monophosphate (XMP) to Guanosine monophosphate (GMP).

The pathway involves several enzymes and co-factors, highlighting the interconversion of nucleotides in the IMP pathway.
Adenine phosphoribosyltransferase (APRT)

APRT deficiency causes production of 2,8-dihydroxadenine stones
Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)

HGPRT deficiency causes hyperuricemia and neurologic abnormalities.

6-mercaptopurine and 6-thioguanine are suicide substrates of HGPRT.

HGPRT deficiency causes hyperuricemia and neurologic abnormalities.
• ADA deficiency causes SCID
• PNP deficiency causes T cell deficiency
Purine catabolism
Gout

- Hyperuricemia (elevated serum urate)
- Deposition of sodium urate crystals in periphery
- Gouty arthritis
- Uric acid or urate stones
Causes of Gout

- Purine overproduction
- Renal disorders
Treatment of hyperuricemia and gout

• **Allopurinol** is a suicide inhibitor of xanthine oxidase and very effective hypouricemic agent

• NSAIDs – Prednisone

• Colchicine blocks inflammation - many adverse side effects, however
Inborn errors of purine metabolism

<table>
<thead>
<tr>
<th>Clinical Disorder</th>
<th>Defective Enzyme</th>
<th>Nature of the Defect</th>
<th>Characteristics of Clinical Disorder</th>
<th>Inheritance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td>PRPP synthetase</td>
<td>Superactive (increased $V_{max}$)</td>
<td>Purine overproduction and overexcretion</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Gout</td>
<td>PRPP synthetase</td>
<td>Resistance to feedback inhibition</td>
<td>Purine overproduction and overexcretion</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Gout</td>
<td>PRPP synthetase</td>
<td>Low $K_m$ for ribose 5-phosphate</td>
<td>Purine overproduction and overexcretion</td>
<td>Probably x-linked recessive</td>
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<tr>
<td>Gout</td>
<td>HGPRTase¹</td>
<td>Partial deficiency</td>
<td>Purine overproduction and overexcretion</td>
<td>X-linked recessive</td>
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<tr>
<td>Lesch-Nyhan syndrome</td>
<td>HGPRTase¹</td>
<td>Complete deficiency</td>
<td>Purine overproduction and overexcretion; self-mutilation.</td>
<td>X-linked recessive</td>
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<tr>
<td>Immunodeficiency</td>
<td>Adenosine deaminase</td>
<td>Severe deficiency</td>
<td>Combined (T cell and B cell) immunodeficiency, deoxyadenosinuria</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Purine nucleoside phosphorylase</td>
<td>Severe deficiency</td>
<td>T cell deficiency, inosinuria, deoxyxynosinuria, guanosinuria, deoxyguanosinuria, hypouricemia</td>
<td>Autosomal recessive</td>
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<tr>
<td>Renal lithiasis</td>
<td>Adenine phosphoribosyltransferase</td>
<td>Complete deficiency</td>
<td>2,8-Dihydroxyadenine renal lithiasis</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Xanthinuria</td>
<td>Xanthine oxidase</td>
<td>Complete deficiency</td>
<td>Xanthine renal lithiasis, hypouricemia</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

¹HGPRTase = hypoxanthine-guanine phosphoribosyltransferase
Lesch-Nyhan syndrome - complete HGPRT deficiency

- X-linked
- Hyperuricemia
- Gout
- Kidney stones
- Mental retardation (?)
Thymidylate synthase

\[
\text{dUMP} + N^5, N^10\text{-Methylenetetrahydrofolate} \xrightarrow{\text{Thymidylate synthase}} \text{dTMP}
\]

Fluorouracil

Fluorodeoxyuridylicate
(Suicide inhibitor)

\[
\text{dUMP} \xrightarrow{\text{Thymidylate synthase}} \text{dTMP}
\]

\[
N^5, N^10\text{-Methylene tetrahydrofolate} \rightarrow \text{Dihydrofolate}
\]

Dihydrofolate reductase

\[
\text{Inhibited by aminopterin and amethopterin (methotrexate)}
\]
Pyrimidine salvage

- Azidothymidine
- Acyclovir
- Arabinosylcytosine
- Dideoxynucleosides
- Gemcitabine
- 2-Chlorodeoxyadenosine
- Fludarabine

Diagram:

1. Uridine → UMP
   - Uridine Cytidine Kinase
2. Cytidine → CMP
3. Thymidine → TMP
   - Thymidine Kinase
4. Deoxycytidine → dCMP
   - Deoxycytidine Kinase
Inborn error of pyrimidine metabolism - orotic aciduria

Defect in the orotate phosphoribosyltransferase - OMP decarboxylase tandem protein

Symptoms include a megaloblastic anemia unresponsive to the usual forms of therapy (iron, folic acid and $B_{12}$) and sometimes leucopenia. Failure to thrive, developmental retardation, cardiac malformations

Cure - Lots of oral uridine daily
Water Soluble Vitamins - Nutrition
All water soluble vitamins are B vitamins except Vitamin C.
TPP is needed for 3 important cellular reactions
Beriberi

1. Peripheral Neuropathy
2. Muscle Weakness and Tenderness
3. Atrophy
4. Paralysis
5. Fatigue
6. Congestive Heart Failure
7. Edema
**Wernicke’s Syndrome** *

- Loss of motor control
- Ataxia (staggering gait)
- Ophthalmoplegia (paralysis of eye movements)
- Confusion
  - Vitamin B1 reversible

**Korsakoff’s Patients** *

- Severe memory loss and psychosis
  - Vitamin B1 irreversible
Niacin or Vitamin $B_3$
Niacin can also be synthesized!!!!

• Approximately 1.6% of the amino acid tryptophan is converted to niacin via the kynurenine pathway
Tryptophan → Tryptophan 3.2 dioxygenase → Kynurenine → kynurenic acid → 3-OH kynurenine → xanthurenic acid → 3-OH anthranilic acid → Nicotinic acid
Niacin Deficiency
Pellagra

- Dietary deficiency of niacin, tryptophan, or both
- Causes dermatitis, dementia, diarrhea, and death
- Treat with nicotinamide (nicotinic acid causes peripheral vasodilatation/flushing)
Biotin (vitamin B\textsubscript{7}, vitamin H, coenzyme R)

Plays key role in cellular carboxylation reactions
Acetyl CoA Carboxylase
Propionyl CoA Carboxylase
Pyruvate Carboxylase
Vitamin $B_6$ is a group of related compounds that serve as precursors for pyridoxal phosphate (PLP).

Pyridoxal phosphate is a coenzyme for $>60$ reactions, many of which are involved with amino acid metabolism.
Vitamin B₆ Deficiencies
• **Nutritional deficiencies are rare**
  – Infants on $B_6$-deficient formula are subject to seizures

• **Pharmacologically induced deficiencies not uncommon**
  – Isonicotinic acid used to treat TB
  – Hydralazine used to treat hypertension
Vitamin $B_{12}$ or Cobalamin

Complex tetrapyrroline structure that contains cobalt ion – similar to heme – called a corrin

Vitamin $B_{12}$ is found exclusively in animal products
Cobalamin has only two known cellular functions in humans
Vitamin $\text{B}_{12}$ Deficiencies
Pernicious anemia


Cause – genetic deficiency in intrinsic factor, a gastric glycoprotein required for cobalamin absorption. Autoimmune, destruction of parietal cells of gastric mucosa

Cure – by B\textsubscript{12} injection
Folic acid or folate

Folate converted to tetrahydrofolate, the active derivative of folate
• Folate abundant in plant food sources, e.g., green leafy vegetables, also found in meat, nuts, grains, and legumes
• Dietary deficiencies are rare

• Causes megoblastic anemia – similar to pernicious anemia

• $B_{12}$ and folate metabolism are intertwined
Folate megadoses

• Folate supplementation before and during pregnancy to prevent neural tube defects
Vitamin C

L-Ascorbic acid $\leftrightarrow$ L-Dehydroascorbic acid
- Ascorbic Acid is a Simple Sugar
- Powerful Reducing Agent
- Antioxidant
- Source of Reducing Equivalents
Vitamin C Deficiency
Scurvy

Lack of access to fresh fruits and vegetables

Symptoms: Decaying teeth and gums, bleeding, fatigue, depression, and death
Vitamin C Megadoses

Advocated for colds, heart disease, cancer, etc."

Linus Pauling – most famous advocate

Best doubled blind studies have failed to provide a definitive correlation between vitamin C and therapeutic efficacy
The End