Midterm 2 Results

High: 97.5%
Low: 16%
Mean: 58%
Standard Deviation: 16.3
Lecture 17

Amino Acid Metabolism

• Urea Cycle

• N and S assimilation

• Last cofactors: THF and SAM
**Dietary (Exogenous) Proteins**

- Hydrolyzed in **digestive system** (~100 g/day)
- Replenish **endogenous** amino acids (muscle **protein**)
- Replenish **glycogen stores** (glucogenic amino acids)
- Excess intake for **ATP** production and **lipid** synthesis
- Excess nitrogen is excreted (urea, ammonia)
- “Nitrogen” balance is **typically zero**
Dietary Protein $\xrightarrow{\text{Proteases, Peptidases}}$ Amino Acids

(e.g., Trypsin, Pepsin)

Amino Acids $\xrightarrow{\text{Blood}}$ Liver

Hepatocytes (Cytosol)

Aminotransferases (PLP-dependent)

$\text{Amino Acid}_x + \alpha$-KGA $\rightleftharpoons \alpha$-Keto Acid$_x + \text{Glu}$

From and To Mitochondria
GluGlu + NAD⁺ + H₂O $\rightleftharpoons$ α-KGA + NADH + NH₃

Glu Dehydrogenase

GluGlu + OAA $\rightleftharpoons$ α-KGA + Asp

Asp Aminotransferase

Mitochondria

From cytosol

Hepatocytes

To cytosol
Synthesis of Urea from Ammonia and Aspartate

The Urea Cycle

Freiedrich Wöhler (1828)

Urea

James Sumner (1926)

Urease

Sir Hans Krebs

Urea Cycle (1932)

TCA Cycle (1937)
Detoxification of ammonia

\[
\text{GLU} + \text{NAD}^+ + \text{H}_2\text{O} \xrightleftharpoons[1]{\gamma} \alpha\text{KGA} + \text{NADH} + \text{H}^+ + \text{NH}_3
\]

\[
\text{NH}_3 + \text{HCO}_3^- + 2 \text{ATP} \xrightleftharpoons[2]{\gamma} 2 \text{ADP} + \text{HPO}_4^{3-} + \overset{2-}{\overset{\text{O}}{\overset{\text{O}}{\overset{\text{P}}{\overset{\text{O}}{\overset{\text{C}}{\text{NH}_2}}}}}}\text{Carbamoyl-P}
\]
The Urea Cycle

1. Ornithine
   \[ \text{Ornithine} \rightarrow \text{Citrulline} \]

2. Citrulline
   \[ \text{Citrulline} \rightarrow \text{Argininosuccinate} \]

3. Argininosuccinate
   \[ \text{Argininosuccinate} \rightarrow \text{Fumarate} \]

4. Fumarate
   \[ \text{Fumarate} \rightarrow \text{Aspartate} \]

5. Aspartate
   \[ \text{Aspartate} \rightarrow \text{Urea} \]

6. Urea
   \[ \text{Urea} \rightarrow \text{Water} \]

The Urea Cycle

\[ \text{Ornithine} \rightarrow \text{Citrulline} \rightarrow \text{Argininosuccinate} \rightarrow \text{Fumarate} \rightarrow \text{Aspartate} \rightarrow \text{Urea} \]

\[ \text{ ATP } + \text{ Aspartate } \rightarrow \text{ AMP } + \text{ PPI } \]

\[ \text{Water} + \text{ ATP } \rightarrow \text{ AMP } + \text{ PPI } \]
The urea cycle involves the conversion of ammonia ($\text{NH}_3$), bicarbonate ($\text{HCO}_3^-$), and ATP into carbamoyl phosphate ($\text{Carbamoyl-P}$) with the subsequent reactions:

$$\text{NH}_3 + \text{HCO}_3^- + 2\text{ATP} \rightarrow \text{Carbamoyl-P} + 2\text{ADP} + \text{Pi}$$

Key intermediates include ornithine, aspartate, and fumarate, with the cycle occurring in both the mitochondria and the cytosol.

**Carbamoyl-P Synthetase**

- **Input:** $\text{NH}_3 + \text{HCO}_3^- + 2\text{ATP}$
- **Output:** $\text{Carbamoyl-P} + 2\text{ADP} + \text{Pi}$
**Urea Cycle Net Reaction**

**ATP Requirement**

\[
\text{NH}_3 + \text{HCO}_3^- + \text{Asp} + 3\text{ATP} \rightarrow \\
\text{Urea} + \text{Fumarate} + 2\text{ADP} + \text{AMP} + 4\text{Pi} \\
(4 \text{ P\textendash}bonds cleaved = “4 ATP”)
\]

**But… NADH Generation**

\[
\text{Glu} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \alpha\text{-KGA} + \text{NADH} + \text{NH}_3 \\
\rightarrow 6 \text{ ATP (ETC)}
\]

\[
\text{Malate} + \text{NAD}^+ \rightarrow \text{OAA} + \text{NADH}
\]

**Net Gain of 2ATP/Urea**
Endogenous Proteins

A. Normal Protein Turnover (50-200 g/day)

- Digestive enzymes (pancreas: >30 g/day)
- Plasma proteins
- Cell death (e.g., intestinal mucosa, immune system)
- Intracellular turnover (damaged proteins, enzyme regulation)

B. Mobilization of Skeletal Muscle Protein

- Fasting, exercise, trauma, injury
- Gluconeogenesis
- Malnutrition (diets deficient in essential amino acids)
Death by Veganism

By Nina Planck

WHEN Crown Shukur died of starvation, he was 6 weeks old and weighed 3.5 pounds. His vegan parents, who fed him mainly soy milk and apple juice, were convicted in Atlanta recently of murder, involuntary manslaughter and cruelty.

This particular calamity — at least the third such conviction of vegan parents in four years — may be largely due to ignorance. But it should prompt frank discussion about nutrition.

I was once a vegan. But well before I became pregnant, I concluded that a vegan pregnancy was irresponsible.

Why babies can't live on vegetables alone.

You cannot create and nourish a robust baby merely on foods from plants.

Indigenous cuisines offer clues about what humans, naturally omnivorous, need to survive, reproduce and grow: traditional vegetarian diets, as in India, invariably include dairy and eggs for complete protein, essential fats and vitamins. There are no vegan societies for a simple reason: a vegan diet is not adequate in the long run.

Protein deficiency is one danger of a vegan diet for babies. Nutritionists used to speak of proteins as "first class" (from meat, fish, eggs and milk) and "second class" (from plants), but today this is considered denigrating to vegetarians.

The fact remains, though, that humans require animal proteins and fats to cereals and tubers, because they contain all the essential amino acids needed for life in the right ratio. This is not true of plant proteins, which are inferior in quantity and quality — even soy.

A vegan diet may lack vitamin B12, found only in animal foods; usable vitamins A and D, found in meat, fish, eggs and butter; and necessary minerals like calcium and zinc. When babies are deprived of all these nutrients, they will suffer from retarded growth, rickets and nerve damage.

Responsible vegan parents know that breast milk is ideal. It contains many necessary components, including cholesterol (which babies use to make nerve cells) and countless immune and growth factors. When breastfeeding isn't possible, soy milk and fruit juice, even in seemingly sufficient quantities, are not safe substitutes for a quality infant formula.

Yet even a breastfed baby is at risk. Studies show that vegan breast milk lacks enough docosahexaenoic acid, or DHA, the omega-3 fat found in fatty fish. It is difficult to overstate the importance of DHA, vital as it is for eye and brain development.

A vegan diet is equally dangerous for weaned babies and toddlers, who need plenty of protein and calcium. Too often, vegetans turn to soy, which actually inhibits growth and reduces absorption of protein and minerals.

That's why health officials in Britain, Canada and other countries express caution about soy for babies. (Not here, though — perhaps because our farm policy is so soy-friendly.)

Historically, diet-honored tradition: we ate the foods that our mothers, and their mothers, ate. Now, your neighbor or sibling may be a meat-eater or vegetarian, may ferment his foods or eat them raw. This fragmentation of the American menu reflects admirable diversity and tolerance, but food is more important than fashion. Though it's not politically correct to say so, all diets are not created equal.

An adult who was well-nourished in utero and in infancy may choose to get by on a vegan diet, but babies are built from protein, calcium, cholesterol and fish oil. Children fed only plants will not get the precious things they need to live and grow.
**Skeletal Muscle** → **Intracellular Proteolysis** → **Amino Acids**

**Aminotransferases**

\[
\text{Amino Acid}_x + \alpha\text{-KGA} \rightarrow \alpha\text{-Keto Acid}_x + \text{Glu}
\]

**Ala Aminotransferase**

\[
\text{Glu} + \text{Pyr} \rightarrow \alpha\text{-KGA} + \text{Ala}
\]

**To Liver**
Intracellular Proteolysis

Skeletal Muscle → Amino Acids

Aminotransferases

\[ \text{Amino Acid}_x + \alpha\text{-KGA} \rightarrow \alpha\text{-Keto Acid}_x + \text{Glu} \]

Glu Dehydrogenase

\[ \text{Glu} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \alpha\text{-KGA} + \text{NADH} + \text{NH}_3 \]

Glutamine Synthetase

\[ \text{NH}_3 + \text{Glu} + \text{ATP} \rightarrow \text{ADP} + \text{Pi} + \text{Gln} \]

To Liver → To Kidneys
Urea
Liver

\[ \text{Ala} + \alpha\text{-KGA} \rightarrow \text{Glu} + \text{Pyr} \rightarrow \text{Glucose} \]

NH\textsubscript{3} or Asp

Glutaminase

\[ \text{Gln} + \text{H}_2\text{O} \rightarrow \text{Glu} + \text{NH}_3 \]

Urea
Kidneys

Glutaminase

\[ \text{Gln} + \text{H}_2\text{O} \rightarrow \text{Glu} + \text{NH}_3 \rightarrow \text{Urine} \]
Muscles (other extrahepatic organs)
The Cori and Alanine Cycle

Glycogen ↔ Glucose → Pyruvate

Proteins

Muscle

Blood

Liver

Glycogen ↔ Glucose ← Pyruvate

Lactate ↔ Alanine

Lactate ↔ Alanine

Urea

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Degradation of Amino Acids: Fate of C-Skeletons

**Glucogenic** Amino Acids: C-skeletons are converted to
- Pyruvate
- $\alpha$-Ketoglutarate
- Succinyl-CoA
- Fumarate
- Oxaloacetate (OAA)

**Ketogenic** Amino Acids: C-skeletons are converted to
- Acetyl-CoA
- Acetoacetate
Glucose

Pyruvate → Acetyl-CoA

Omega-oxidation

Succinyl-CoA

Isocitrate

Malate

Fumarate

Oxaloacetate

Citrate

α-Ketoglutarate

TCA Cycle

Glucogenic

Ketogenic

- Lipids
- Ketone Bodies
<table>
<thead>
<tr>
<th>Amino Acids</th>
<th>Common Degradation Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Only glucogenic</strong></td>
<td></td>
</tr>
<tr>
<td>Ala, Cys, Gly, Ser, Thr</td>
<td>Pyruvate</td>
</tr>
<tr>
<td>Asp, Asn</td>
<td>OAA</td>
</tr>
<tr>
<td>Met, Thr (humans), Val</td>
<td>Succinyl-CoA</td>
</tr>
<tr>
<td>Arg, Glu, Gln, His, Pro</td>
<td>α-Ketoglutarate</td>
</tr>
<tr>
<td><strong>Only ketogenic</strong></td>
<td></td>
</tr>
<tr>
<td>Leu, Lys</td>
<td>Acetoacetate</td>
</tr>
<tr>
<td><strong>Ketogenic and glucogenic</strong></td>
<td></td>
</tr>
<tr>
<td>Phe, Tyr</td>
<td>Fumarate, Acetoacetate</td>
</tr>
<tr>
<td>Trp</td>
<td>Pyruvate, Acetyl-CoA</td>
</tr>
<tr>
<td>Ile</td>
<td>Succinyl-CoA, Acetyl-CoA</td>
</tr>
</tbody>
</table>
Nitrogen and Sulfur Assimilation

(Amino Acid Synthesis)
Nitrogen and Sulfur Assimilation (Amino Acid Biosynthesis)
"Bioenergetics" of Macronutrient Assimilation

**Electronegativity**

<table>
<thead>
<tr>
<th>Element</th>
<th>Electronegativity</th>
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<tbody>
<tr>
<td>O</td>
<td>3.4</td>
</tr>
<tr>
<td>N</td>
<td>3.0</td>
</tr>
<tr>
<td>S</td>
<td>2.6</td>
</tr>
<tr>
<td>C</td>
<td>2.6</td>
</tr>
<tr>
<td>H</td>
<td>2.2</td>
</tr>
<tr>
<td>P</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Assimilation**

1. **N** (3.0) → \( \text{NO}_3^- \) → \( \text{NH}_3 \) via NAD(P)H
2. **S** (2.6) → \( \text{SO}_4^{2-} \) → \( \text{H}_2\text{S} \) via NAD(P)H + ATP
3. **C** (2.6) → \( \text{CO}_2 \) → \( \text{CHO} \) via NAD(P)H + ATP
4. **H** (2.2) → \( \text{H}_2\text{O} \) → \( \text{H}_2 \) via Photosynthesis
5. **P** (2.1) → \( \text{PO}_4^{3-} \) → \( \text{PH}_3 \)
Nitrate Assimilation and Nitrogen Fixation

A. Most Microorganisms, Fungi, and Plants

**Nitrate Reductase**

\[ \text{NO}_3^- + \text{NADH} + \text{H}^+ \rightarrow \text{NO}_2^- + \text{NAD}^+ + \text{H}_2\text{O} \]

**Nitrite Reductase**

\[ \text{NO}_2^- + 6 \text{Fd}_{\text{red}} + 8 \text{H}^+ \rightarrow \text{NH}_4^+ + 2 \text{H}_2\text{O} + 6 \text{Fd}_{\text{ox}} \]

B. Biological Nitrogen Fixation (Microorganisms)

**Nitrogenase**

\[ \text{N}_2 + 8\text{e}^- + 10\text{H}^+ + 16 \text{ATP} + 16 \text{H}_2\text{O} \rightarrow 2 \text{NH}_3 + 16 \text{ADP} + 16 \text{Pi} + \text{H}_2 \]
Assimilation of Ammonia

Major Pathway for Ammonia Net Assimilation (MO, Fungi, Plants)

**Glutamine Synthetase (GS)**

\[
\text{NH}_3 + \text{Glu} + \text{ATP} \rightarrow \text{Gln} + \text{ADP} + \text{Pi}
\]

**Glutamate Synthase**

\[
\text{Gln} + \alpha\text{-KGA} + \text{NAD(P)H} + \text{H}^+ \rightarrow 2 \text{Glu} + \text{NAD(P)}^+
\]

**Glutamate Aminotransferase (also present in animals)**

\[
\text{Glu} + \alpha\text{-Keto Acid} \leftrightarrow \alpha\text{-KGA} + \text{L-}\alpha\text{-Amino Acid}
\]

**Glutamine Amidotransferase (also present in animals)**

\[
\text{Gln} + \text{R-OH or R}_{1}(\text{C}=\text{O})\text{-R}_{2} \rightarrow \text{Glu} + \text{R-NH}_{2} \text{or R}_{1}(\text{C}=\text{NH})\text{-R}_{2}
\]
Sulfur Assimilation

SO₄²⁻ ↔ Adenosine monophosphate sulfate (APS)

Adenine

carrier-S-SO₃⁻

6 Reduced Ferredoxin

6 Oxidized Ferredoxin

Acetate

O-acetyl serine

carrier-S-S⁻

Cysteine

AMP

2Fdox

2Fdred

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**Sulfur Assimilation**

\[
\text{O-pi} \text{CH}_2 \text{C} \text{C} \text{OH} \quad \text{3-Phosphoglycerate (3PGA)}
\]

\[
\text{NAD}^+ \quad \text{NADH + H}^+ 
\]

\[
\text{O-pi} \text{CH}_2 \text{C} \text{C} \text{OH} \quad \text{Hydroxy-P-pyruvate}
\]

\[
\text{Glu} \quad \alpha \text{KG}
\]

\[
\text{O-pi} \text{CH}_2 \text{CH} \text{C} \text{OH} \quad \text{O-phospho-serine}
\]

\[
\text{H}_2\text{O} \quad \text{Pi} \quad \text{Serine}
\]

\[
\text{H}_3\text{C} \text{C} \text{O} \text{CH}_2 \text{CH} \text{C} \text{OH} \quad \text{O-acetyl serine}
\]