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M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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Amino Acid metabolism

- Amino acids
  - Glu, Gln, Asp, NH₃
  - Urea

Folate metabolism

- Methylene THF
- Met Cycle

TCA Cycle

- oxaloacetate
- fumarate

Nucleic Acid metabolism

- Purines
  - DNA
  - RNA
  - Pyrimidines
  - Uric Acid
  - (energy)
Folate ("One-Carbon") Pathways

Click on any blue box to see details
(Start with the section with ‘Diet’ and follow the paths with red arrows)
Folic Acid is Synthesized By Bacteria

Dietary folate: folic acid (meats, green veggies) *requires* the intestinal enzyme ‘Conjugase’ for absorption.
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine → H₂O + glycine + N⁶, N⁴⁺ methylene tetrahydrofolate

Tetrahydrofolate + glycine → NAD⁺ + NADH + N⁶, N⁴⁺ methylene tetrahydrofolate
\[ \text{N}^4 \text{ methyl tetrahydrofolate} \rightarrow \text{NAD}^+ \rightarrow \text{NADH} + H^+ \rightarrow \text{NADP}^+ \rightarrow \text{NADPH} + H^+ \rightarrow \text{N}^4, \text{N}^6 \text{ methylene tetrahydrofolate} \rightarrow H_2O \rightarrow \text{N}^4 \text{ formyl tetrahydrofolate} \rightarrow \text{Biosyntheses of purines} \]

\[ \text{Gly} \quad \text{Ser} \quad \text{Biosynthesis of methionine} \quad \text{Biosynthesis of thymidylate} \]

\[ \text{N}^4 \text{- methyl tetrahydrofolate} \]

\[ \text{N}^{14} \text{ formyl tetrahydrofolate} \]
Methionine Cycle
And Biological Methyl Groups
\[
\begin{align*}
\text{homocysteine} & \xrightarrow{\text{vitamin B}_12} \text{methionine} \\
\text{N}^6\text{-methyl THF} & \xrightarrow{\text{THF}} \text{methionine}
\end{align*}
\]
Other methyl acceptors:

- DNA ("CpG Islands")
- RNA

Chemical structures:

- Methionine
- S-Adenosyl methionine
- Norepinephrine
- Epinephrine
**Folate Deficiencies:** Symptom: megaloblastic anemia

Dietary deficiency:
Common especially in developing countries, lower socioeconomic classes
Folate deficiency secondary to bowel irritation:

- Conjugase is essential for adequate absorption of dietary folates

- Conjugase production may be compromised by bowel irritation:

  ‘Tropical Sprue’ - bowel irritation probably arising from bacterial origin, causes intestinal inflammation and malabsorption.

  ‘Celiac Sprue’ - similar outcome, but the original irritation is due to an allergic response, for example to gliaden (a component in gluten)
Folate Deficiency Secondary to B12 deficiency: the ‘methyl trap’ hypothesis

B12 is also critical in other reactions, ones for which the deficiency has serious neurological consequences.