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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
- Met Cycle
- Methylene THF

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)

- Connects to Amino Acids
- Donation of one carbon (from Ser, Gly)

THF Cycle

Methionine Cycle

- THF
- DHF
- Folate

Connects to Nucleic Acids lectures

Methyl-THF

Methylene-THF

Formyl-THF

Purine biosynthesis

Thymidylate synthetase
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 → glycine + \( \text{N}^6, \text{N}^{10} \) methylene tetrahydrofolate

Tetrahydrofolate + glycine → \( \text{N}^6, \text{N}^{10} \) methylene tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups

Methionine
\[ \text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{CO}_2^- \]

S-Adenosyl Methionine
\[ \text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{CO}_2^- \]

Homocysteine
\[ \text{HS} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{CO}_2^- \]

S-Adenosyl Homocysteine
\[ \text{HS} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{CO}_2^- \]

Serine
\[ \text{HO} - \text{CH}_2 - \text{C} - \text{CO}_2^- \]

Cysteine
\[ \text{HS} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{CO}_2^- \]

Methyl acceptor

NS methyl tetrahydrofolate

Methylated acceptor

ATP + H_2O

Biogenetic Methylation reaction

see examples
\[
\text{homocysteine} \xrightarrow{\text{vitamin } B_{12}} \text{methionine}
\]
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

N⁰, N⁰ methylene tetrahydrofolate

methionine

NADH + H⁺

homocysteine

NAD⁺

N⁰ methyl tetrahydrofolate
Other methyl acceptors:

DNA ("CpG Islands")
RNA

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.