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M1 - Renal, Fall 2007

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Amino Acid metabolism
- 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 $\rightarrow$ H$_2$O + glycine

Tetrahydrofolate + glycine $\rightarrow$ N$^\delta$, N$^{\delta\prime}$ methylene tetrahydrofolate
The diagram illustrates the biosynthesis of methionine, thymidylate, and purines from tetrahydrofolate derivatives.

- **N^1-methyl tetrahydrofolate**
  - Reaction with NADH + H^+ yields NAD^+.
  - Reduction to NADPH + H^+.

- **N^1, N^6-methylene tetrahydrofolate**
  - Fusion with Gly and Ser.
  - Reaction with NADPH + H^+ yields NADP^+.

- **N^1, N^6-methenyl tetrahydrofolate**
  - Fusion with water (H_2O).
  - Resulting in N^1-formyl tetrahydrofolate.

- **Biosynthesis of methionine**
  - Involves N^1-methyl tetrahydrofolate.

- **Biosynthesis of thymidylate**
  - Involves N^1, N^6-methylene tetrahydrofolate.

- **Biosynthesis of purines**
  - Involves N^1, N^6-methenyl tetrahydrofolate.

Chemical structures of N^1-methyl tetrahydrofolate and N^1-formyl tetrahydrofolate are also shown.
Methionine Cycle
And Biological Methyl Groups
homocysteine $\xrightarrow{\text{vitamin } B_12} \text{methionine}$
Carbon donor (e.g., serine or glycine)

Tetrahydrofolate

\[ \text{N}^\circ, \text{N}^\circ \text{ methyl methylene tetrahydrofolate} \]

methionine

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

homocysteine

\[ \text{NAD}^+ \]
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.