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M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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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

![Folic Acid Molecular Structure]

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 + N^6, N^10 methylene tetrahydrofolate

Tetrahydrofolate + glycine → N^6, N^10 methylene tetrahydrofolate
Methionine Cycle And Biological Methyl Groups

\[
\text{CH}_3 - S - \text{CH} - \text{CH} - \text{CH} - \text{COO}^(-) \quad \text{Methionine}
\]

\[
\text{CH}_3 - S - \text{CH} - \text{CH} - \text{CH} - \text{COO}^(-) \quad \text{S-Adenosyl Methionine}
\]

\[
\text{CH}_3 - S - \text{CH} - \text{CH} - \text{CH} - \text{COO}^(-) \quad \text{S-Adenosyl Homocysteine}
\]

\[
\text{CH}_3 - S - \text{CH} - \text{CH} - \text{CH} - \text{COO}^(-) \quad \text{Homocysteine}
\]

\[
\text{CH}_3 - S - \text{CH} - \text{CH} - \text{CH} - \text{COO}^(-) \quad \text{Serine}
\]

\[
\text{CH}_3 - S - \text{CH} - \text{CH} - \text{CH} - \text{COO}^(-) \quad \text{Cysteine}
\]

(remainder of homocysteine degraded for energy)
\[
\text{homocysteine} \xrightarrow{\text{vitamin B}_12} \text{methionine}
\]
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

$N^\delta, N^\epsilon$ methylene tetrahydrofolate

methionine

$N^\delta$ methyl tetrahydrofolate

NADH + $H^+$

NAD$^+$

homocysteine
Other methyl acceptors:
DNA ("CpG Islands")
RNA
**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.