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M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
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 + N^6, N^10 methylene tetrahydrofolate

Tetrahydrofolate + glycine → NAD^+ + NH₄^+ + CO₂ + NADH + N^6, N^10 methylene tetrahydrofolate
\[ \text{Gly, Ser} \]
\[ N^\text{r}, N^\text{r} \text{ methylene tetrahydrofolate} \]
\[ N^\text{r} \text{ formyl tetrahydrofolate} \]

### Biosynthesis of methionine
\[ N^\text{r} \text{ methyl tetrahydrofolate} \]
\[ \text{NAD}^+ \]
\[ \text{NADH} + \text{H} \]

### Biosynthesis of thymidylate
\[ N^\text{r}, N^\text{r} \text{ methylen tetrahydrofolate} \]
\[ \text{NADP}^+ \]
\[ \text{NADPH} + \text{H} \]

### Biosyntheses of purines
\[ N^\text{r} \text{ formyl tetrahydrofolate} \]
\[ \text{H}_2\text{O} \]
Methionine Cycle
And Biological Methyl Groups
homocysteine $\xrightarrow{\text{vitamin B}_12} \text{methionine}$
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

\[ \text{Tetrahydrofolate} \]

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

methionine

\[ \text{methionine} \]

NADH + H^+

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

NAD^+

\[ \text{NAD}^+ \]

homocysteine

\[ \text{homocysteine} \]
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.