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M1 - Renal, Fall 2007

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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 $\rightarrow$ glycine + $\text{N}^4, \text{N}^{10}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ $\text{N}^4, \text{N}^{10}$ methylene tetrahydrofolate
\[ \text{N}^4 \text{- methyl tetrahydrofolate} \quad \xrightarrow{\text{Biosynthesis of methionine}} \quad \text{Biosynthesis of thymidylate} \quad \xrightarrow{\text{Biosynthesis of purines}} \]

\[ \text{N}^4, \text{N}^6 \text{ methylene tetrahydrofolate} \quad \xrightarrow{\text{NAD}^+} \quad \xrightarrow{\text{NADH} + \text{H}^+} \]

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

Chemical structures:
- \(\text{N}^4\text{- methyl tetrahydrofolate}\)
- \(\text{N}^{14}\text{L formyl tetrahydrofolate}\)
Methionine Cycle
And Biological Methyl Groups
homocysteine $\xrightarrow{\text{vitamin B}_12} \text{methionine}$
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.