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
\[ \text{Tetrahydrofolate} + \text{serine} \rightarrow \text{glycine} + \text{N}^4, \text{N}^{10} \text{methylene tetrahydrofolate} \]

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$N^\prime$-methyl tetrahydrofolate $\rightarrow$ Biosynthesis of methionine

Gly, Ser $\rightarrow$ $N^\prime$, $N^\circ$ methylene tetrahydrofolate $\rightarrow$ Biosynthesis of thymidylate

$N^\prime$, $N^\circ$ methenyl tetrahydrofolate $\rightarrow$ $H_2O$ $\rightarrow$ $N^\prime\prime$ formyl tetrahydrofolate $\rightarrow$ Biosyntheses of purines

$N^\prime$-methyl tetrahydrofolate

$N^\prime\prime$ formyl tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
Homocysteine is converted to methionine via the addition of a methyl group to form N\textsuperscript{6}-methyl THF.
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N°, N° methylene tetrahydrofolate

methionine

NADH + H⁺

homocysteine

NAD⁺

N° 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.