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HST 151
March 10, 2005

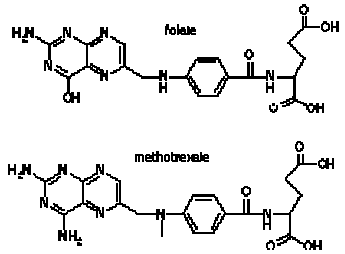
# Dietary Folate

- Folate is heat labile and therefore destroyed by cooking
- RDA: 200 ug for males, 180 ug for females, 100 ug for children, 35 ug for infants.
- Food sources: liver, kidney, spinach, broccoli, bran, peanuts, cabbage, lettuce, avocados, bananas, oranges, wholemeal breads, eggs, some fish, meat, poultry.

# Clinical Consequences of Folate Deficiency

- Elevated serum bilirubin and LDH from ineffective erythropoiesis
- Atrophic glossitis and diffuse chronic gastritis
- **Megaloblastic anemia**
  - Megaloblasts result from inadequate conversion of deoxyuridate to thymidylate, which decreases DNA synthesis identical to that caused by vitamin $B_{12}$ deficiency; only serum folate levels or other specialized testing can conclusively demonstrate source of anemia
  - Unlike folate deficiency, vitamin $B_{12}$ deficiency also causes neurologic manifestations
  - Vitamin $B_{12}$ deficiency develops much more slowly due to higher levels stored in body
  - Also need to assess chronic alcoholics for thiamine deficiency

# Pharmacology of Folate: Folate Analogues




- Folate analogues which inhibit DHFR:
  - Methotrexate (MTX) – chemotherapeutic agent
  - Trimethoprim – antibacterial agent (specific for bacterial DHFR)
  - Pyrimethamine – antimalarial agent (specific for parasitic DHFR)

- Drugs which inhibit DHFR prevent regeneration of THF from DHF; therefore they both:
  - Prevent synthesis of purine nucleotides
  - Prevent methylation of dUMP to dTMP

- **Use of MTX in chemotherapy**
  - MTX is highly potent, producing reversible DHFR inhibition at subnanomolar concentrations
  - MTX causes growth arrest in S phase of mammalian cells
  - High-dose MTX chemotherapy is combined with leucovorin rescue
  - Used for carcinomas of breast, lung, head and neck; ALL; and choriocarcinoma
  - Leucovorin (folinic acid) is administered several hours after an MTX dose that would otherwise be lethal to the patient; this selectively kills malignant cells. This is known as “leucovorin rescue”

# Pharmacology of Folate: PABA Analogues

Bacterial cells must synthesize folic acid de novo from para-aminobenzoic acid (PABA)

Sulfa drugs are PABA analogues which selectively inhibit dihydropteroate synthase and thereby halt bacterial synthesis of purines & pyrimidines

These drugs are bacteriostatic, not bactericidal
Two classes of drugs:

**Sulfonamides**: sulfanilamide, sulfadiazine, sulfamethoxazole
**Sulfones**: dapsone