INE | INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Micronutrients: Vitamin B9 (Folate)

Dr. Ritamarie Loscalzo

Medical Disclaimer: The information in this presentation is not intended to replace a one-on-one relationship with a qualified health care professional and is not intended as medical advice. It is intended as a sharing of knowledge and information from the research and experience of Dr. Ritamarie Loscalzo, drritamarie.com, and the experts who have contributed. We encourage you to make your own health care decisions based upon your research and in partnership with a qualified health care professional.

B Vitamins At a Glance

Letter	Names	Notes/Actions
B1	Thiamin, Benfotiamine	Energy, heart, muscle, and nerve function
B2	Riboflavin, R 5'-Phosphate	Energy, red blood cells, vision
B3	Niacin, Nicotinic Acid, Niacinamide	Energy, nerve function, circulation and heart
B4	Choline, Adenine, Carnitine	Loosely considered as B vitamins - cell membranes, memory, neuromuscular
B5	Pantothenic Acid	Coenzyme A, adrenals, skin
B6	Pyridoxine, Pyridoxal 5'-Phosphate	Brain and nerve, hormones, protein synthesis
B7	Biotin	Hair, metabolism
B8	Inositol	Loosely considered a B vitamin
B9	Folate, Methylfolate, Folinic Acid	Red blood cell production, DNA repair, brain
B10	Pteroylmonoglutamic Acid (PABA – Para-aminobenzoic Acid)	Really a form of folate, skin protector
B11	Salicylic Acid	Not technically a vitamin, loosely categorized
B12	Cobalamin	Red blood cells, DNA repair, nervous system

Folate General Info

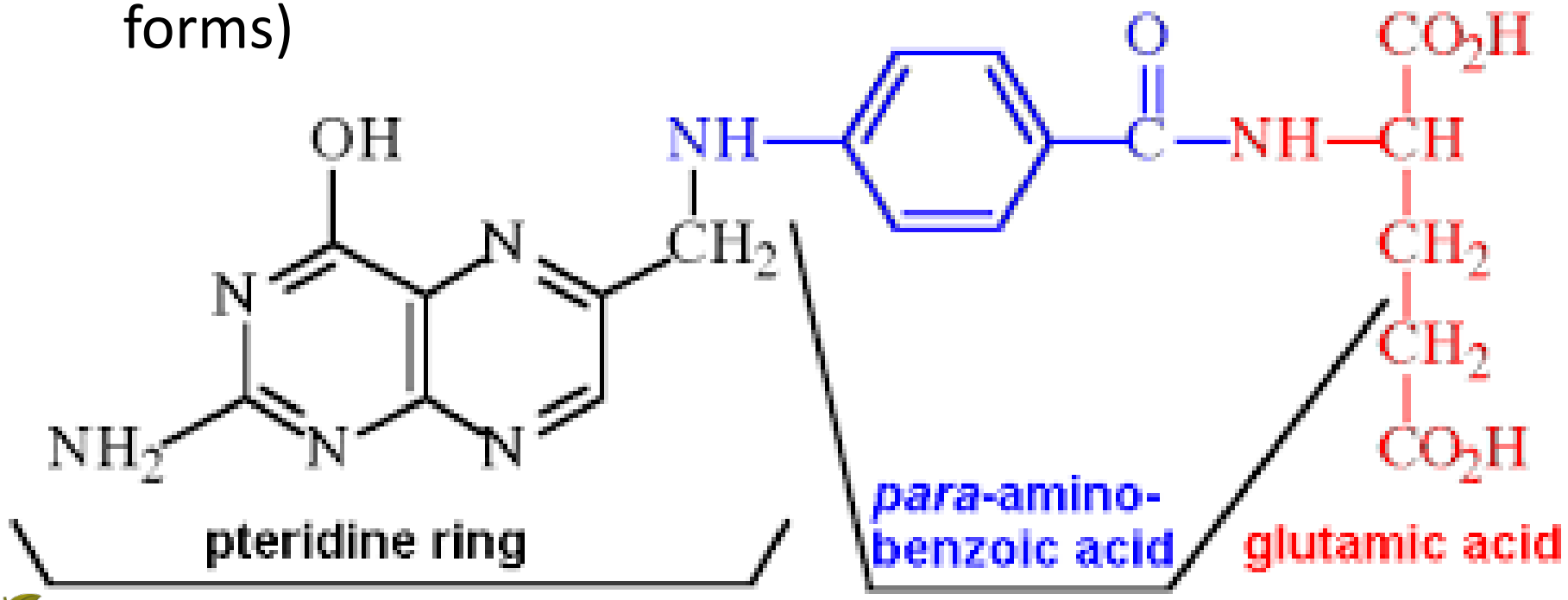
- ✓ Water-soluble vitamin B-vitamin
- ✓ Naturally present in many foods
- ✓ Also known as pteroylglutamate or pteroylmonoglutamate
- ✓ A form of folate, called folic acid, is used in dietary supplements and fortified foods

- ✓ Folate is **needed to make DNA** and other genetic material
- ✓ Folate is also **needed for the body's cells to divide** (mitosis)
- ✓ Comes from the Latin word folium, meaning "leaf"

Folate Structure

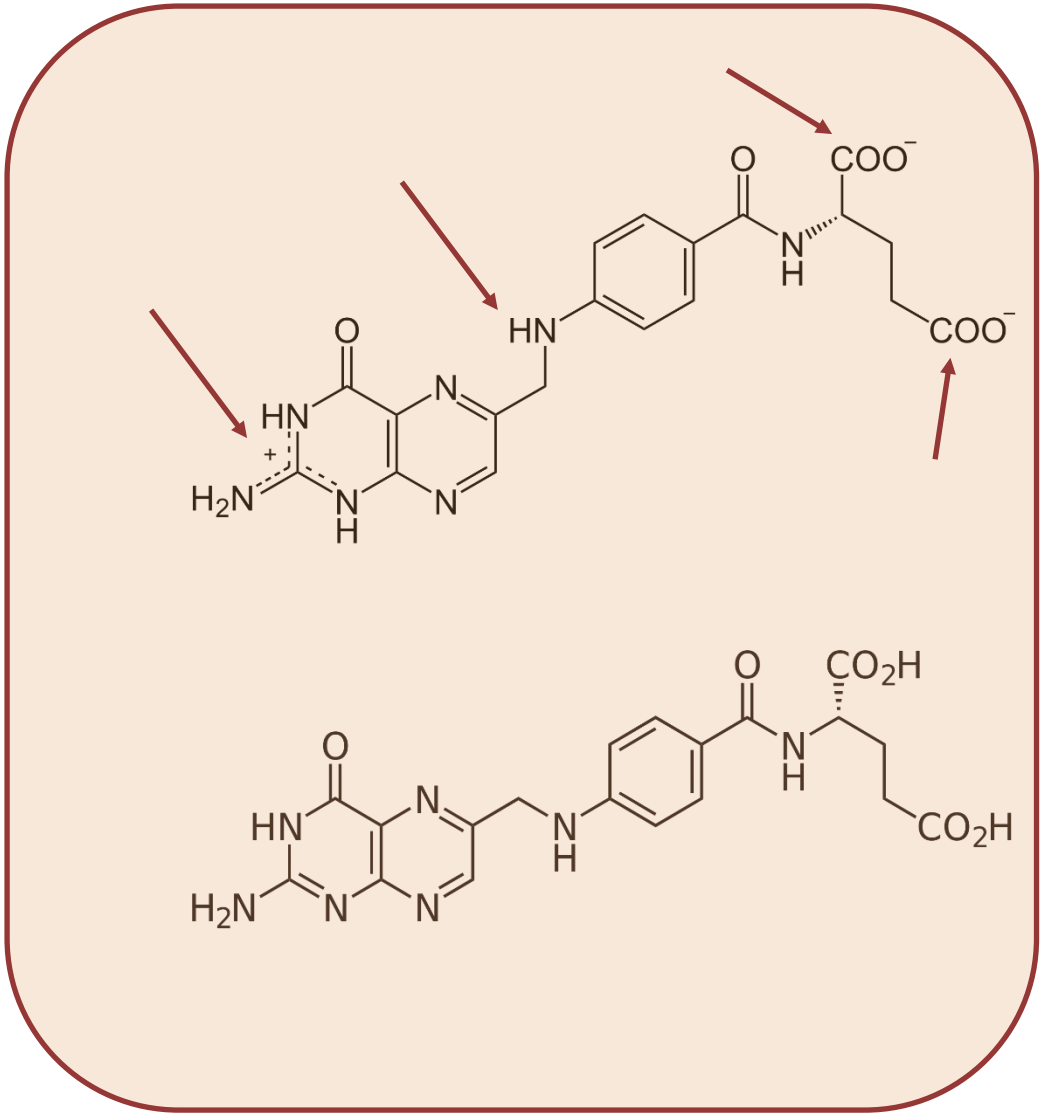
Made up of 3 distinct parts

- Pteridine
- PABA
- Glutamic acid (multiple in metabolically active forms)



Folate Structures Compared

- ✓ **Folates**
  - ➢ Metabolically active forms in the body
  - ➢ Reduced form
  - ➢ Found in foods
- ✓ **Folic acid**
  - ➢ Major synthetic form
  - ➢ Oxidized form
  - ➢ Found in fortified foods and vitamin supplements



Folate Chemistry

- ✓ Supplements are pteromonoglutamate: the most stable and oxidized form
- ✓ Food forms (reduced) generally have up to 9 glutamate residues
  - ➢ 5 methyl tetrahydrofolate (THF) - 5-MTHF
  - ➢ 10-formyl THF
- ✓ The reduced dihydro and tetrahydro forms are unstable
- ✓ Up to 150 forms identified
- ✓ Bioavailability ranges from 96% in cooked lima beans to 25% in romaine lettuce
- ✓ 50% to 95% of folate is estimated to be lost in food preparation or processing
- ✓ Sensitivity to heat varies by the form

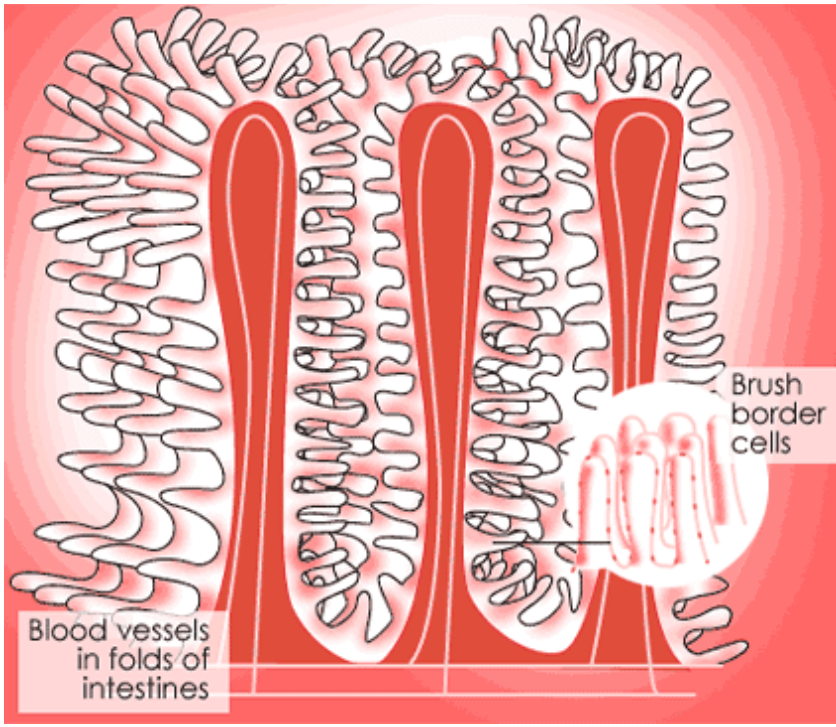
Active Co-Enzyme Folate Forms and Functions

- ✓ Co-enzyme form: Tetrahydrofolic acid – THF
  - ➢ For normal red blood cell synthesis and all other cells
  - ➢ DNA synthesis and cell division
  - ➢ Related to chemotherapeutic agent - methotrexate
  - ➢ Amino acid metabolism

- ✓ Active forms of THF accept and donate one-carbon units
  - ➢ 5 and 10 formyl THF
  - ➢ 5-formimino THF
  - ➢ 5,10 methenyl THF
  - ➢ 5,10 methylene THF
  - ➢ 5-methyl THF

Folate Absorption

- ✓ Must be hydrolyzed to monoglutamic form by conjugase enzymes
  - ➢ In jejunal brush border – zinc dependent
  - ➢ In pancreatic juice
  - ➢ In bile
- ✓ Active transport – requires transporters to cross cell membranes
  - ➢ Sodium dependent
  - ➢ pH dependent
  - ➢ Found in jejunal brush border
  - ➢ Some, i.e. in milk, absorbed more in ileum
- ✓ Some passive diffusion occurs in pharmacologic doses
- ✓ Average absorption of food folate is 50%
- ✓ Slightly higher absorption of monoglumate forms in supplements but lots of metabolic downsides



Influences on Folate Absorption

Decreases Absorption

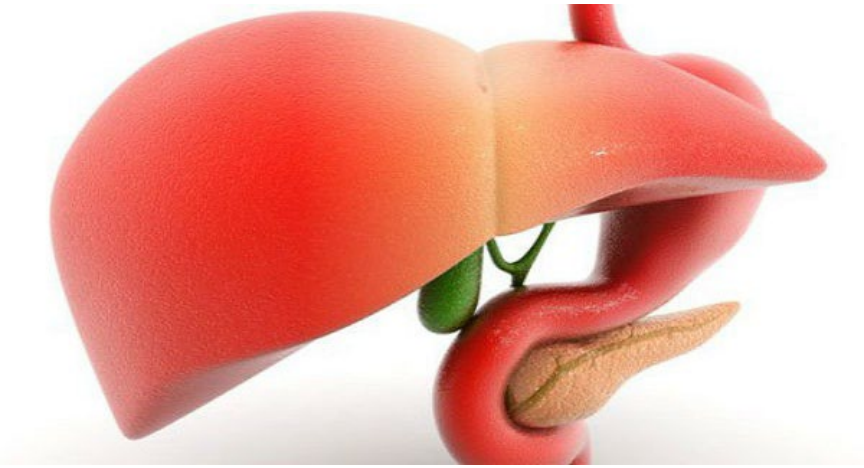
- ✓ Zinc deficiency
- ✓ Alcohol
- ✓ Legumes, especially lentils
- ✓ Cabbage
- ✓ Oranges
- ✓ Mutations in SLC46A1 gene
- ✓ Pernicious anemia
- ✓ Celiac disease
- ✓ IBD, i.e., Crohn's
- ✓ Bacterial overgrowth
- ✓ Parasites
- ✓ Reduced HCl
- ✓ Chronic pancreatitis
- ✓ Gastric surgery
- ✓ Antacids
- ✓ Green or black tea

Increases Absorption

- ✓ Empty stomach
- ✓ Drinking water
- ✓ Vitamin B12
- ✓ Vitamin C

Folate Transport and Storage

- ✓ **Liver:** Small, insignificant quantities
  - ➢ In portal circulation as 5MTHF
  - ➢ THF: 33%
  - ➢ 5-MTHF: 37%
  - ➢ 10-formyl: 23%
  - ➢ 5-formyl: 5%



- ✓ **Blood**
  - ➢ RBCs have more folate than plasma (longer term status)
  - ➢ Glutamate residues removed
  - ➢ 2/3 Protein bound
  - ➢ Some bound to albumin (about 50 percent of bound folate)
  - ➢ Forms in blood: THF, 5MTHF, 10-formyl THF and others
- ✓ **Urine**
  - ➢ Excess excreted

Folate Transporters and Receptors

✓ Receptors found in:

- Liver
- Renal tubules – for retaining what's needed
- Hematopoetic cells

✓ Types of receptors and transporters:

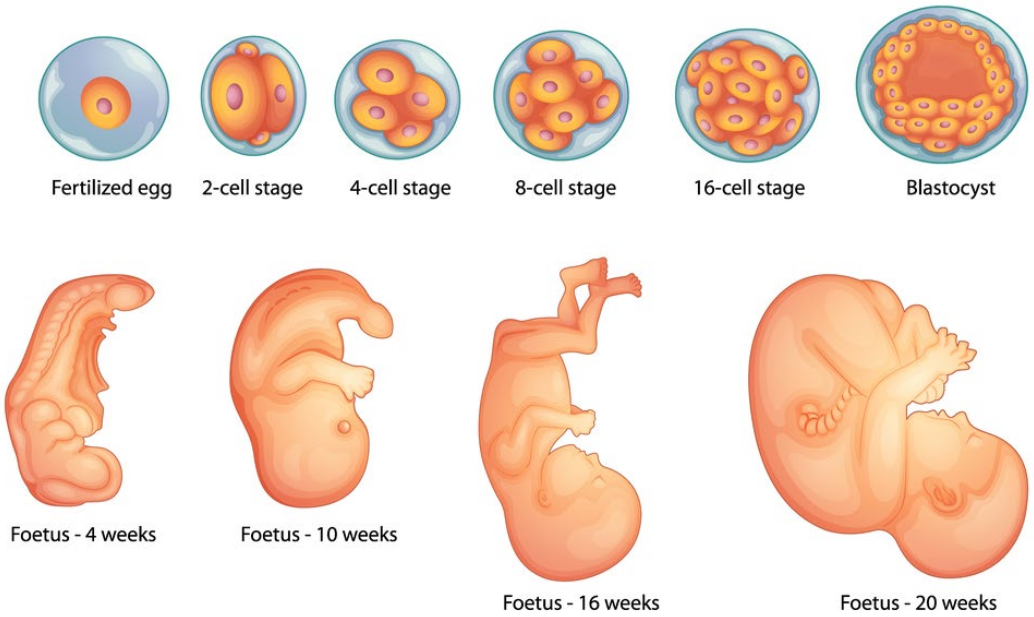
- **PCFT** (proton-coupled folate transporter): **SLC46A1 gene**
- **RFC** (reduced folate carrier): **DHFR gene**
- **FRα** (folate receptor alpha): **FOLR 1 gene**
- **FRβ** (folate receptor beta): **FOLR 2 gene**

Folate Transporters and Receptors

- ✓ **PCFT** (proton-coupled folate transporter): **SLC46A1 gene**
  - ➢ Major role in intestinal transport
  - ➢ Mutations cause hereditary folate malabsorption
  - ➢ Defects leads to impaired folate transport into the brain
- ✓ **RFC** (reduced folate carrier): **DHFR gene**
  - ➢ Transport across BBB when extracellular folate is high
  - ➢ Cytotoxic in severe folate deprivation
- ✓ **FRα** (folate receptor alpha): **FOLR 1 gene**
  - ➢ Mediates folate uptake by endocytosis
  - ➢ Facilitates transport across BBB when extracellular folate is low
- ✓ **FRβ** (folate receptor beta): **FOLR 2 gene**
  - ➢ Carries folate into cells
  - ➢ Affinity for neutral pH

Folate Absorption and Fetal Development

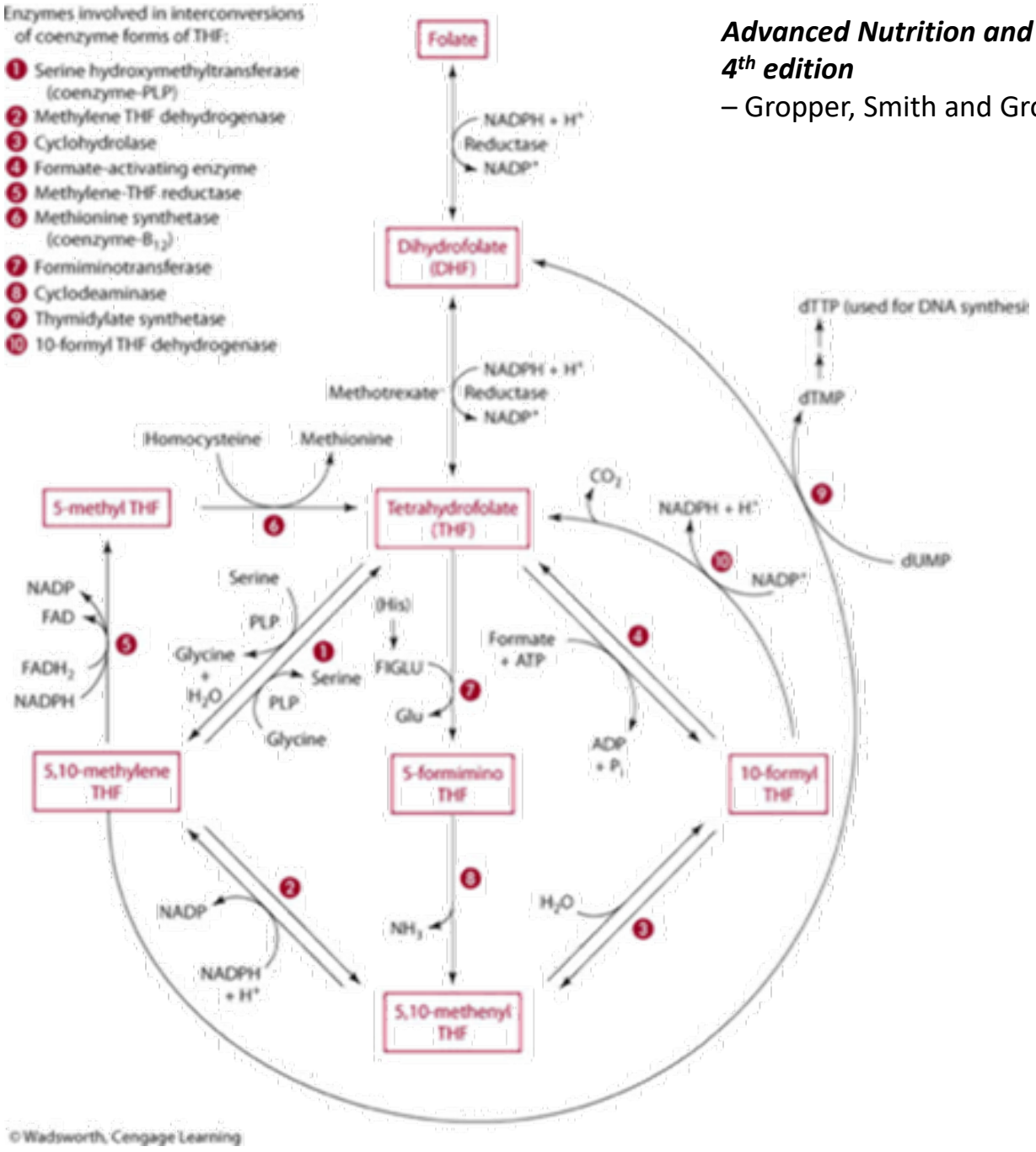
- ✓ Essential for the proper development of the embryo and the fetus
- ✓ The placenta concentrates folate to the fetal circulation, leading to higher folate in the fetus compared to mom
- ✓ All types of receptors have been associated with folate transport across the placenta during pregnancy
  - ➢ PCFT
  - ➢ RFC
  - ➢ FRα



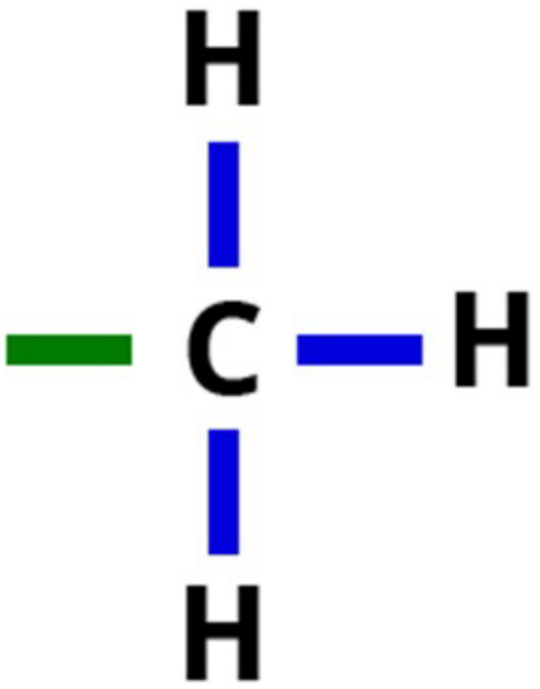
Folate Storage

- ✓ Total body levels 11 mg to 28 mg
- ✓ Liver stores half of this
- ✓ Intracellular binding proteins important
- ✓ Acts as coenzyme and 1 carbon transporter
  - ➢ Cytosol
  - ➢ Mitochondria
- ✓ Main storage forms are polyglutamate
  - ➢ THF
  - ➢ 5MTHF

Advanced Nutrition and Human Metabolism 4th edition
– Gropper, Smith and Groff. page 302



Methylation



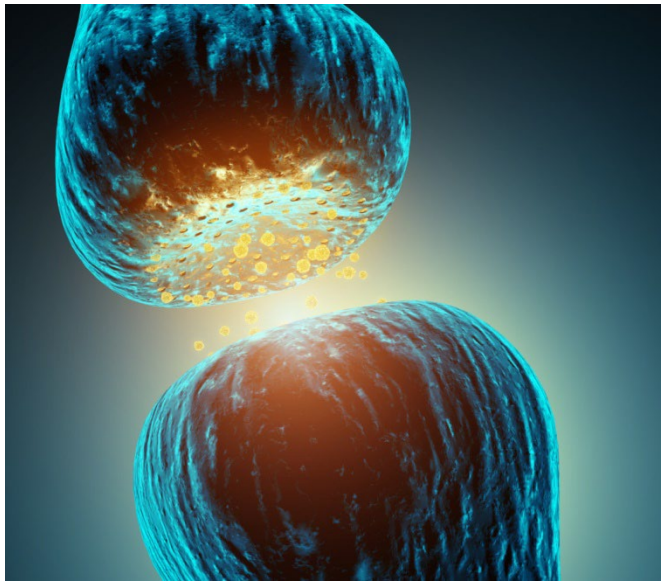
Methyl group

Methyl Donors

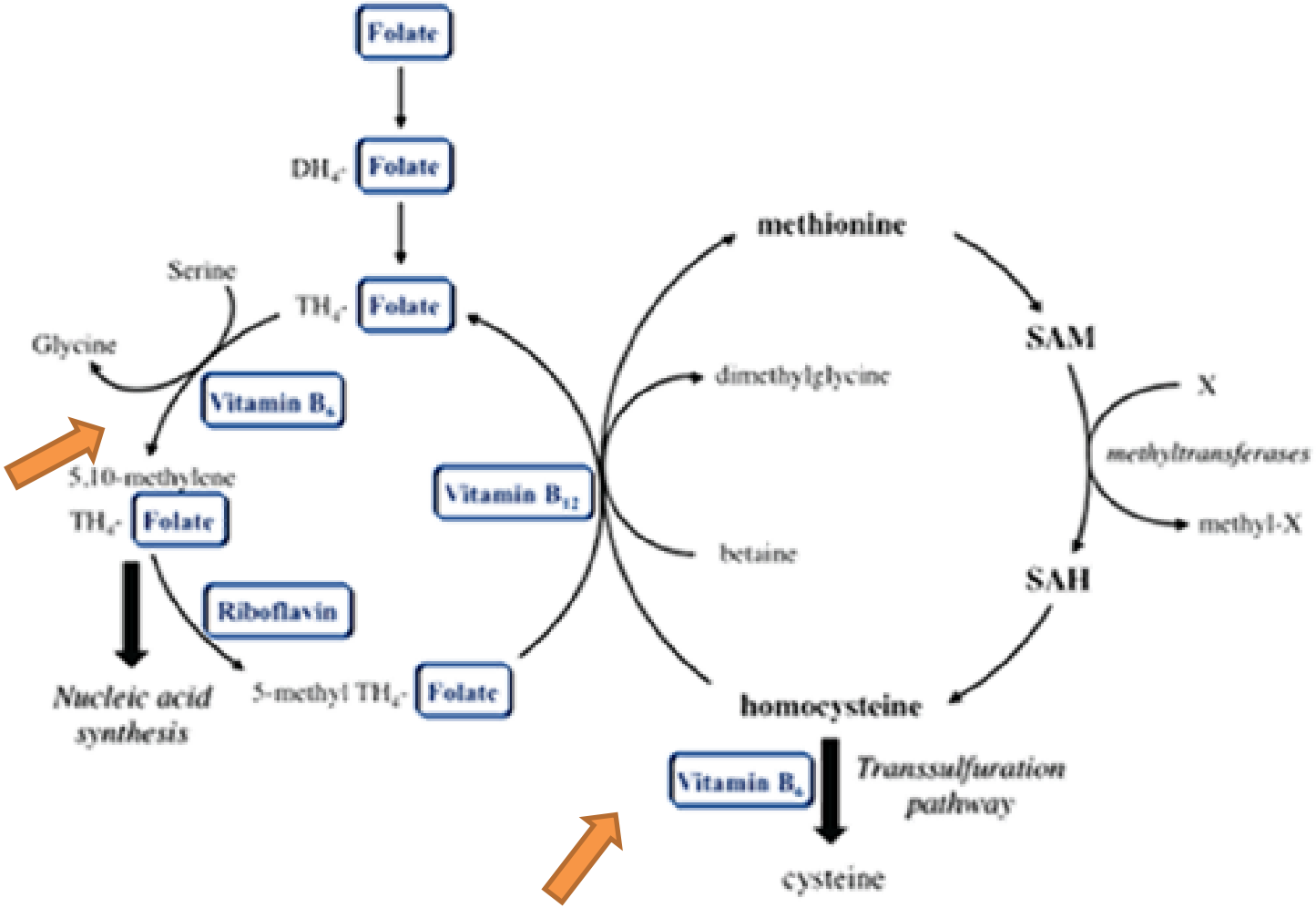
- SAM-e
- Folate
- Vitamin B12
- TMG
- DMG

Methylation Functions

- ✓ Turn on and off genes
- ✓ Process chemicals, endogenous and xenobiotic compounds
- ✓ Build neurotransmitters (norepinephrine, epinephrine, serotonin, melatonin)
- ✓ Metabolize neurotransmitters (dopamine, epinephrine)
- ✓ Process hormones (estrogen)
- ✓ Build immune cells (T cells, NK cells)
- ✓ Synthesize DNA bases
- ✓ Produce energy (CoQ10, carnitine, creatine, ATP)
- ✓ Produce protective coating on nerves (myelination)
- ✓ Build and maintain cell membranes (phosphatidylcholine)



Vitamin B9 and Methylation

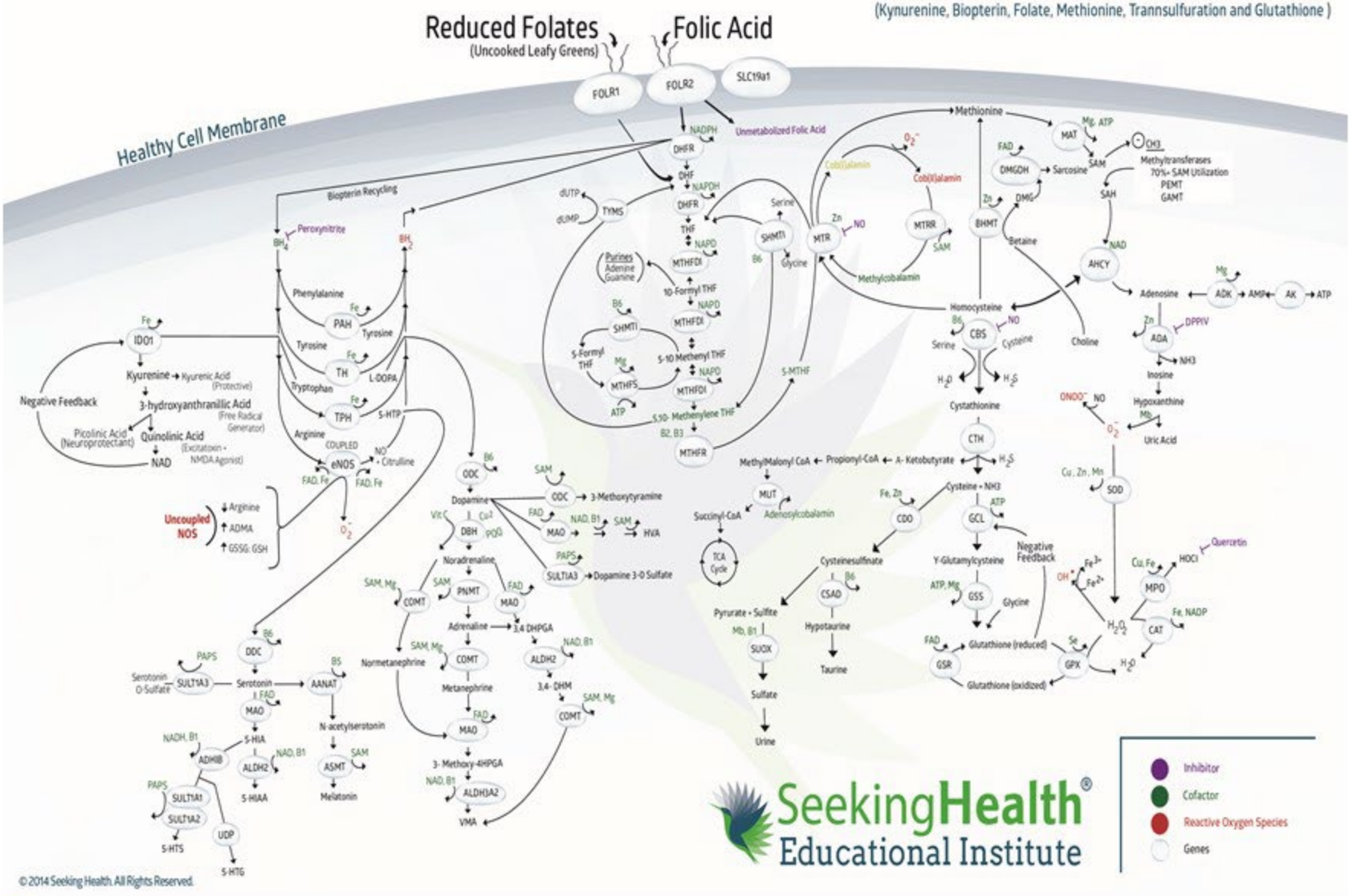


SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH4-folate, tetrahydrofolate.

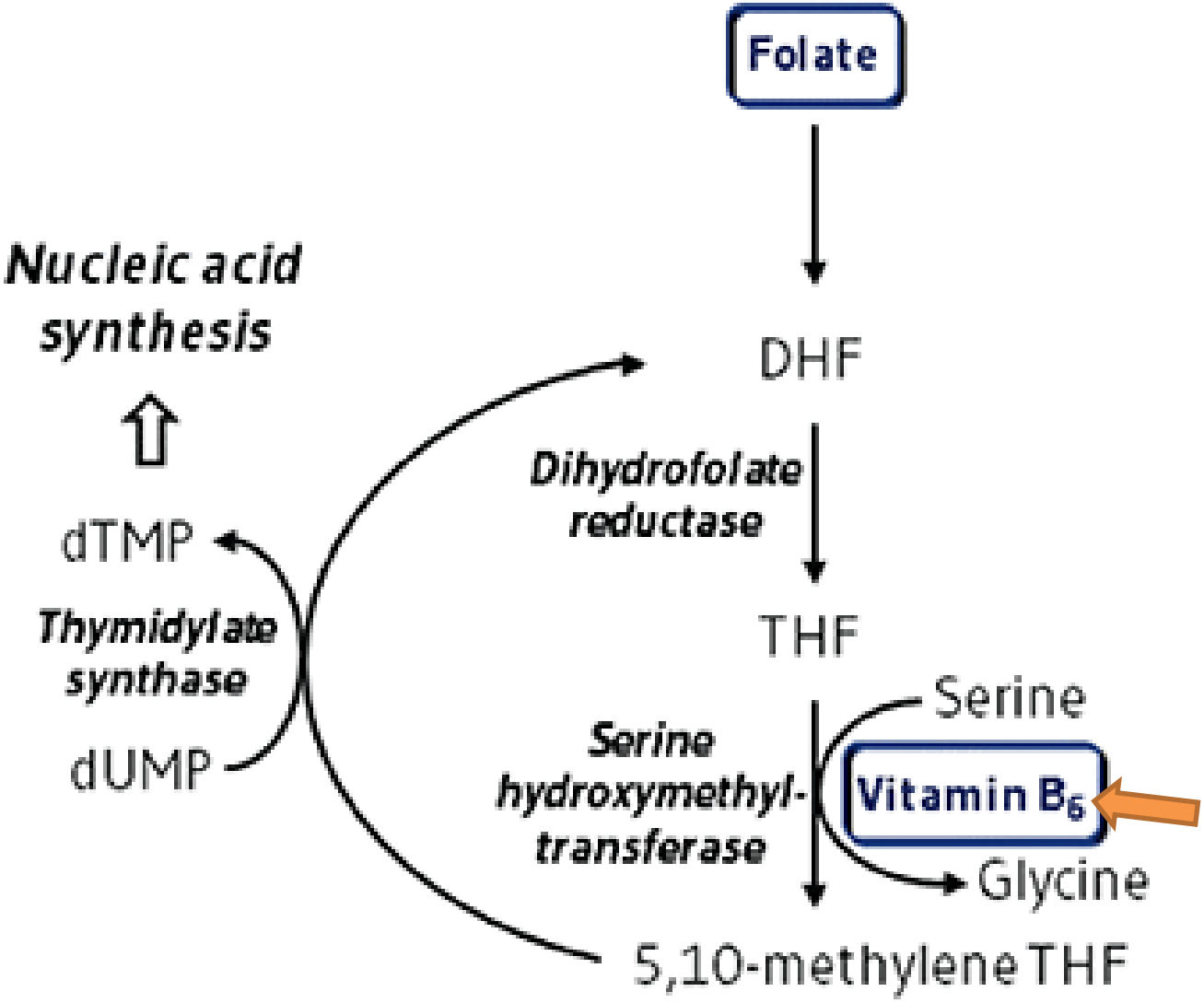
SeekingHealth.org

Pathway Planner

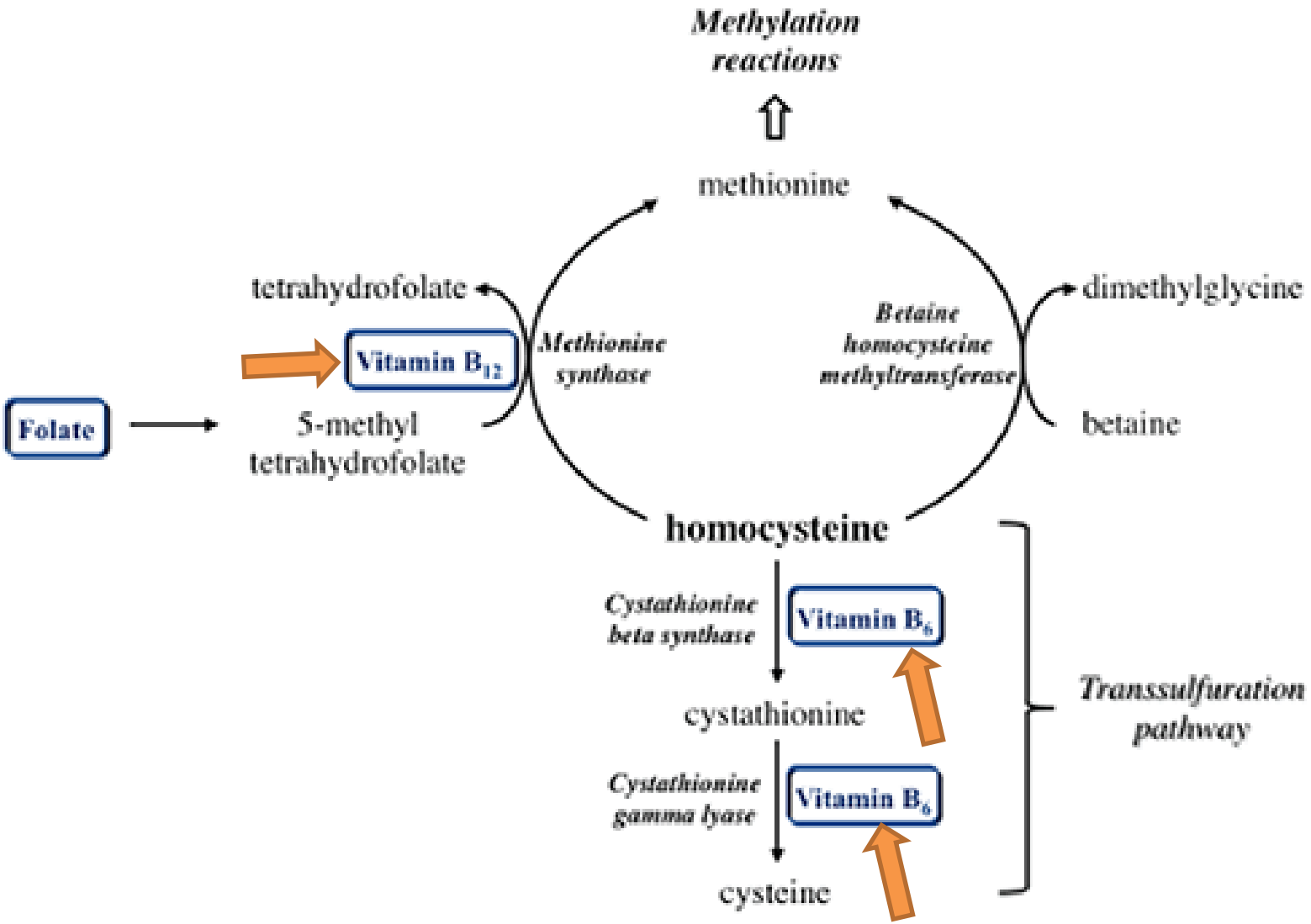
(Kynurenine, Biopterin, Folate, Methionine, Trannsulfuration and Glutathione)



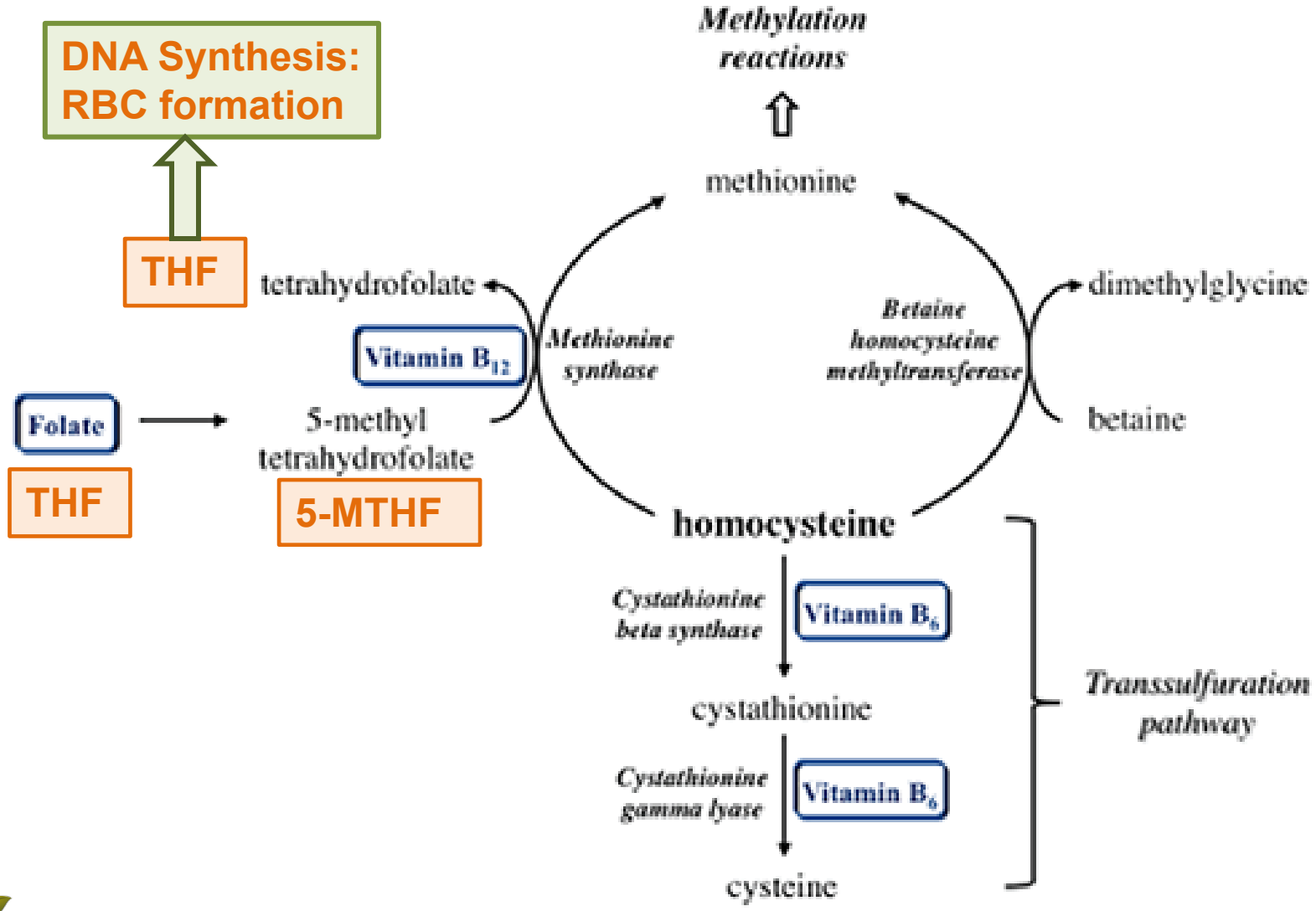
Folate and Vitamin B6 Metabolism

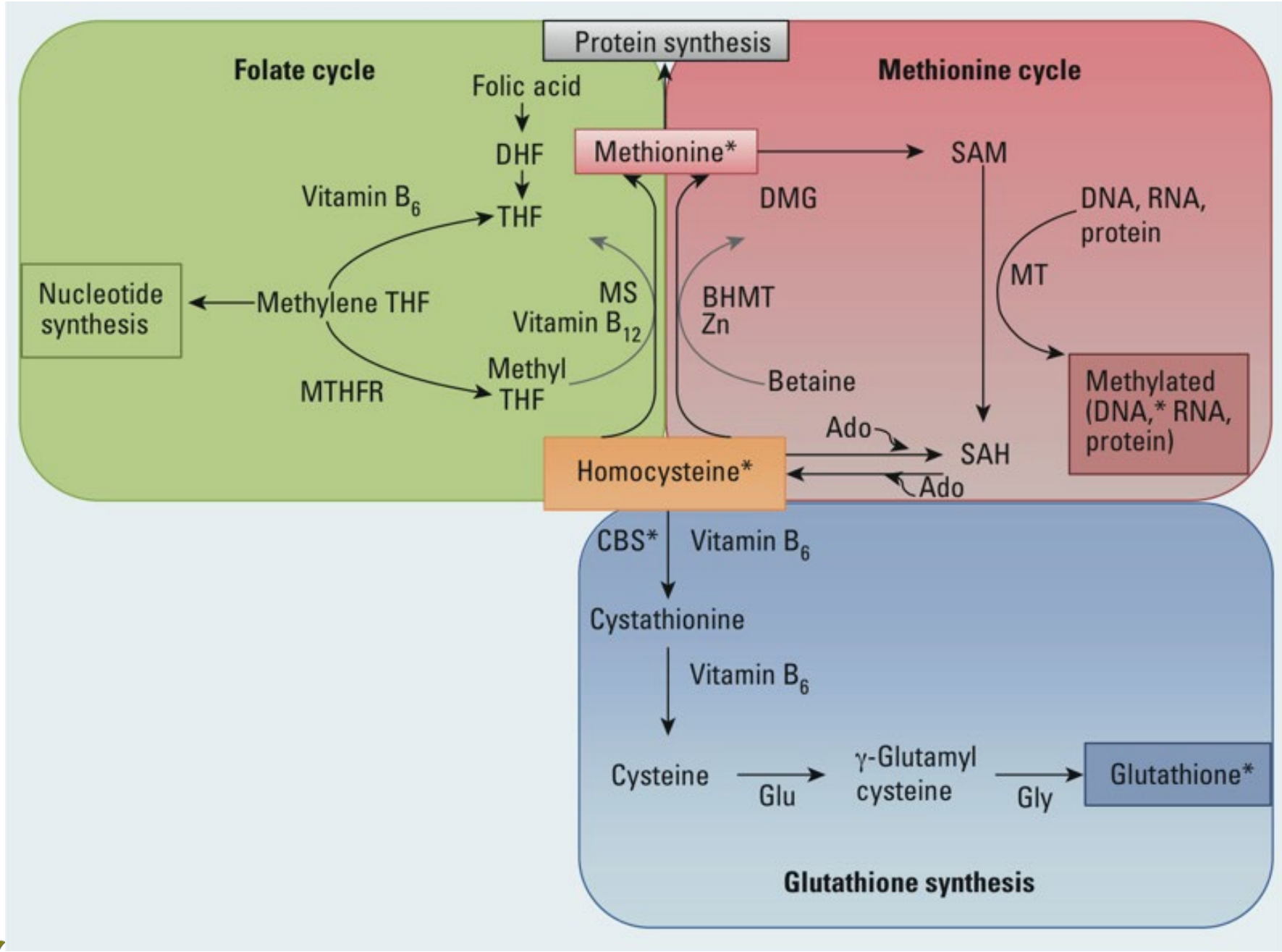


Folate and Homocysteine



Vitamin B12, Folate, and DNA





MTHFR Problems

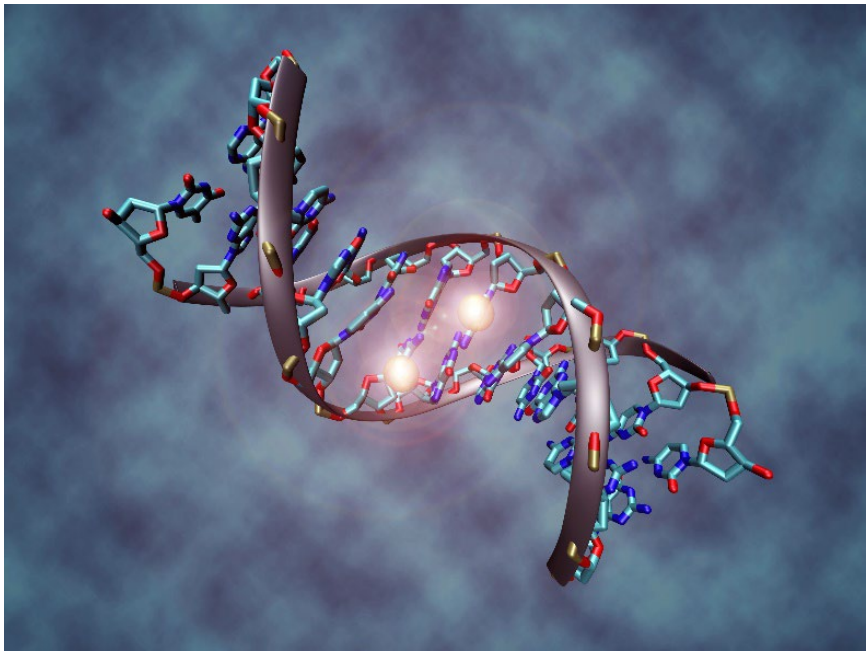
- ✓ Increased homocysteine (HCY) levels
- ✓ Increased risk of cardiovascular disease or thrombosis
- ✓ Insufficient substrate for DNA repair, synthesis, or methylation
- ✓ Increased risk of pregnancy miscarriage
- ✓ Potential methotrexate intolerance (used in treating RA and cancer) and may require dosage adjustments
- ✓ Neurotransmitter problems
- ✓ Excess ***folic acid*** may lead to problems such as cancer
- ✓ ***Folic acid*** blocks methylfolate at blood brain barrier
- ✓ Dairy can block folate receptors, especially in brain (**FOLR1, FOLR2, FOLR3**)

Genes Associated with Folate Metabolism

Gene	Support	Function
FOLR 1,2,3	Lipids, phospholipids	Bind 5-MTHF and transport into cell
SLC19A1	Lipids, phospholipids	Membrane protein which regulates IC [folate]
ALDH1L1	THF	10-FormylTHF + NADP+ → THF + NADPH + CO2
DHFR	NAD (B3)	THF + NADP+ → DHF + NADPH
MTHFS	Mg	ATP + 5-FormylTHF → ADP + P + 5,10-MTHF
MTHFD1	THF	a) 5,10-methyleneTHF + NADP + = 5,10-methenylTHF + NADPH b) 5,10-methenylTHF + H2O = 10-formylTHF c) ATP + formate + THF = ADP + P + 10-formylTHF
SHMT 1,2	P-5-P (B6)	5,10-methyleneTHF + glycine + H2O = THF + L-serine SHMT2: Primary source of IC Glycine
MTHFR	FAD (B2)	5,10-methyleyeTHF + NADPH → 5-MTHF + NADP+

Folate Related Genes

- ✓ MTHFR C677T
- ✓ MTHFR A1298C
- ✓ FOLR1
- ✓ FOLR2
- ✓ SLC
- ✓ DHFR
- ✓ MTHFD1
- ✓ MTHFD2
- ✓ MTRR
- ✓ MTR
- ✓ RFC1
- ✓ TYMS
- ✓ NOS3
- ✓ BHMT
- ✓ BHMT2
- ✓ CBS



http://www.drritamarie.com/go/118SNPsOfFolateRelatedGenes

Who Is Impacted by MTHFR?

Approximately 45% of the population has 1 copy of the MTHFR C677T.

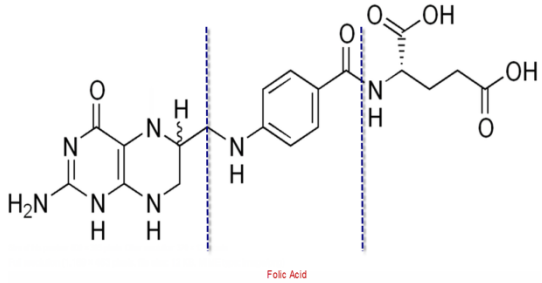
Approximately 90% of those with chronic disease have 1 copy of the MTHFR C677T.

Dr. Ben Lynch recommends that ***everyone be tested.***

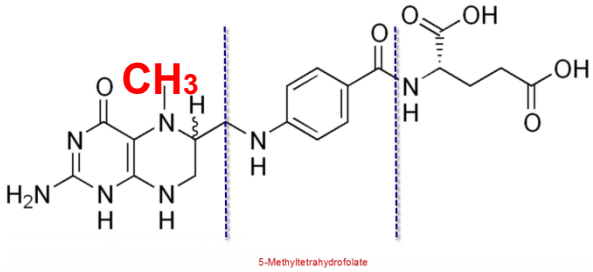
Synthetic Folic Acid vs. Folate

- ✓ ***Folic acid does NOT equal folate.***
- ✓ Folic acid is only ONE type of folate.
- ✓ Folic acid is not found in nature; it's synthetic.
- ✓ Folic acid must undergo various transformations prior to utilization.

FOLIC ACID
→



METHYLFOLATE
→



Different types

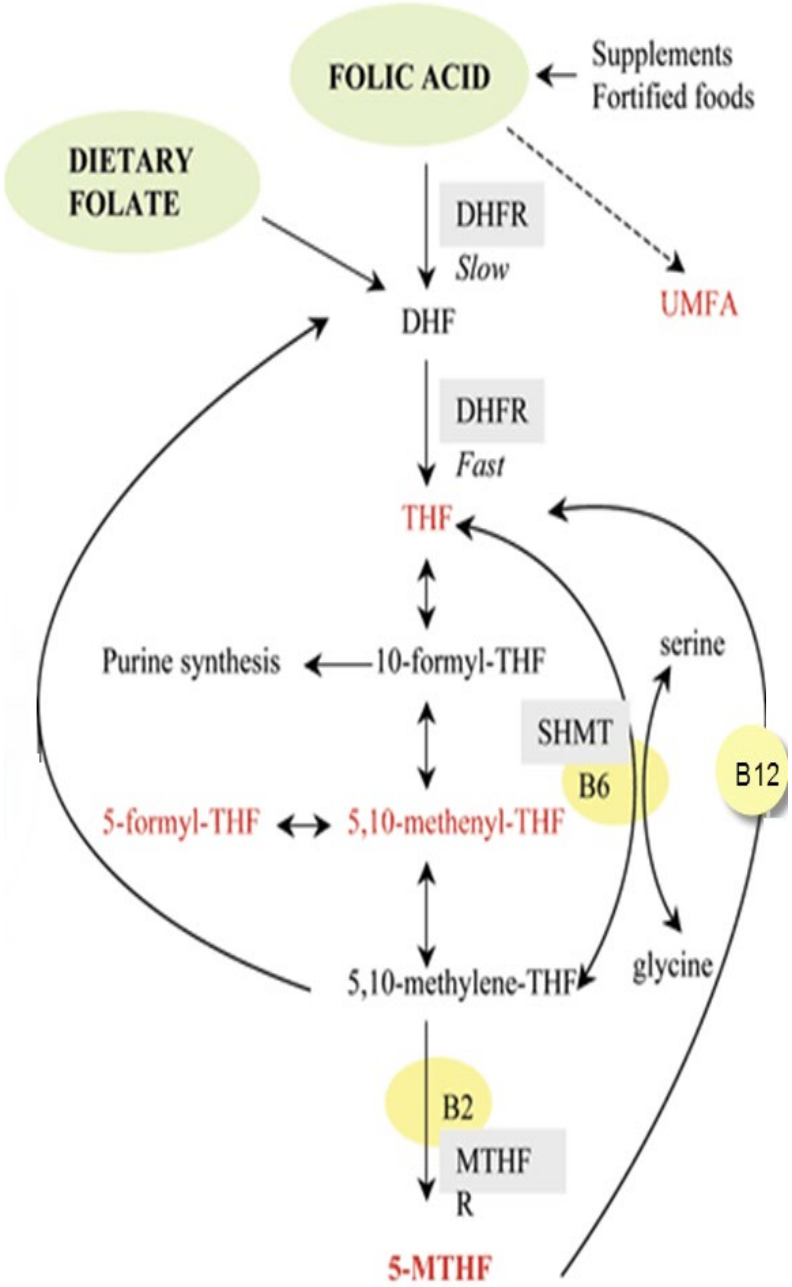
- ✓ Folic acid
- ✓ Folinic acid (5-FormylTHF)- product of SHMT enzyme within folate cycle
- ✓ Methylfolate (5-MTHF)

Folate vs Folic Acid Video

http://www.drritamarie.com/go/YTFolicAcidvsFolate

Methylation Requires:

1) Uncooked leafy greens
2) Functioning enzymes
3) Available receptors
4) Transport
5) **Vitamins, minerals, and pH:**
    - B2
    - B6
    - B12
    - Acidic environment (for absorption)

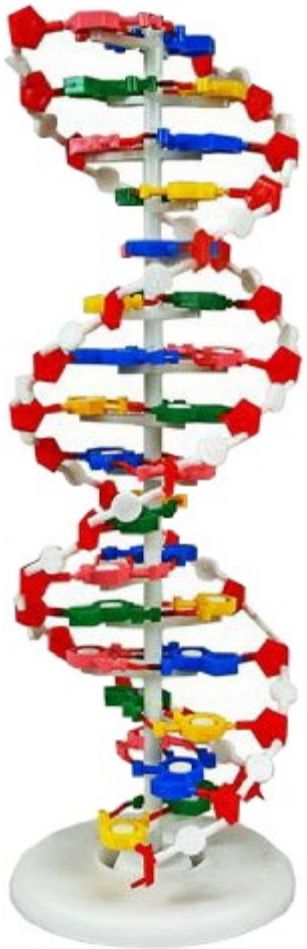


Before Addressing MTHFR:

- ✓ Foundational lifestyle/diet
- ✓ Remove all folic acid
- ✓ Improve B12 status
- ✓ Test homocysteine levels
- ✓ Reduce oxidative stress levels
- ✓ Evaluate thyroid
- ✓ Address mitochondrial dysfunction

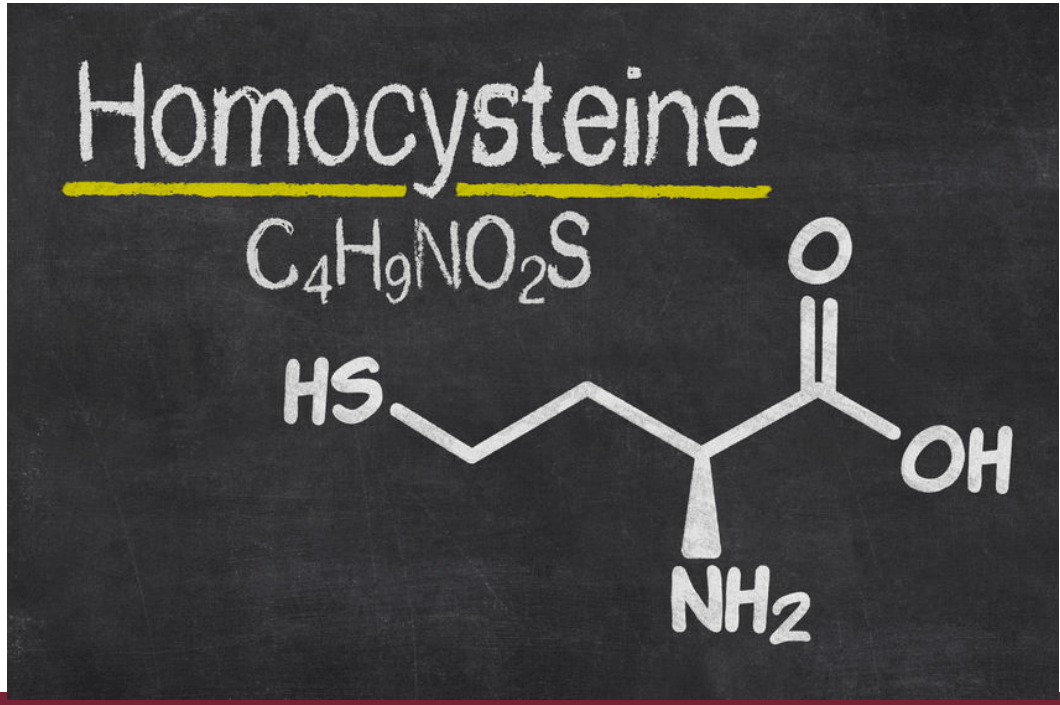
Functions of Folate

1. Methylation
2. Supports the production and repair of DNA and RNA
3. Erythropoesis
4. **Energy** production
5. Removes homocysteine from the blood
6. Important for **protein metabolism**
7. **Works with vitamin B12**
   - Maturation of red blood cells
   - Helps iron work better in the body
   - Helps produce S-adenosylmethionine (SAMe)



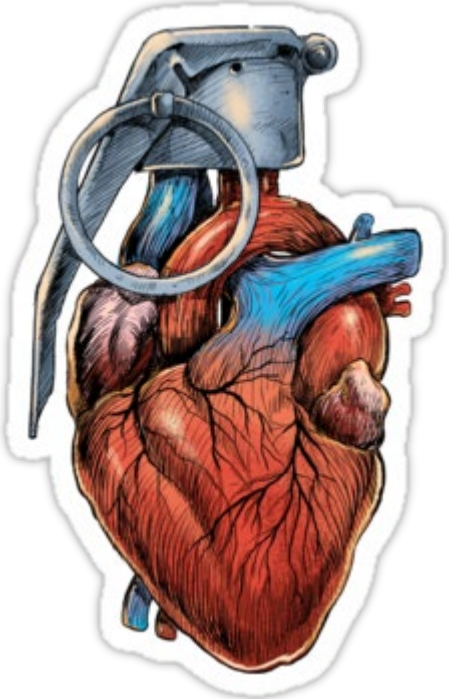
Folate and Homocysteine

- ✓ Homocysteine is a **nerve and vessel toxin**
- ✓ Methionine is an <u>essential amino acid</u>
- ✓ Some **methionine is turned into homocysteine**
- ✓ The **body normally converts homocysteine to other molecules**, one of which is back into methionine
- ✓ If this pathway is blocked, homocysteine increases

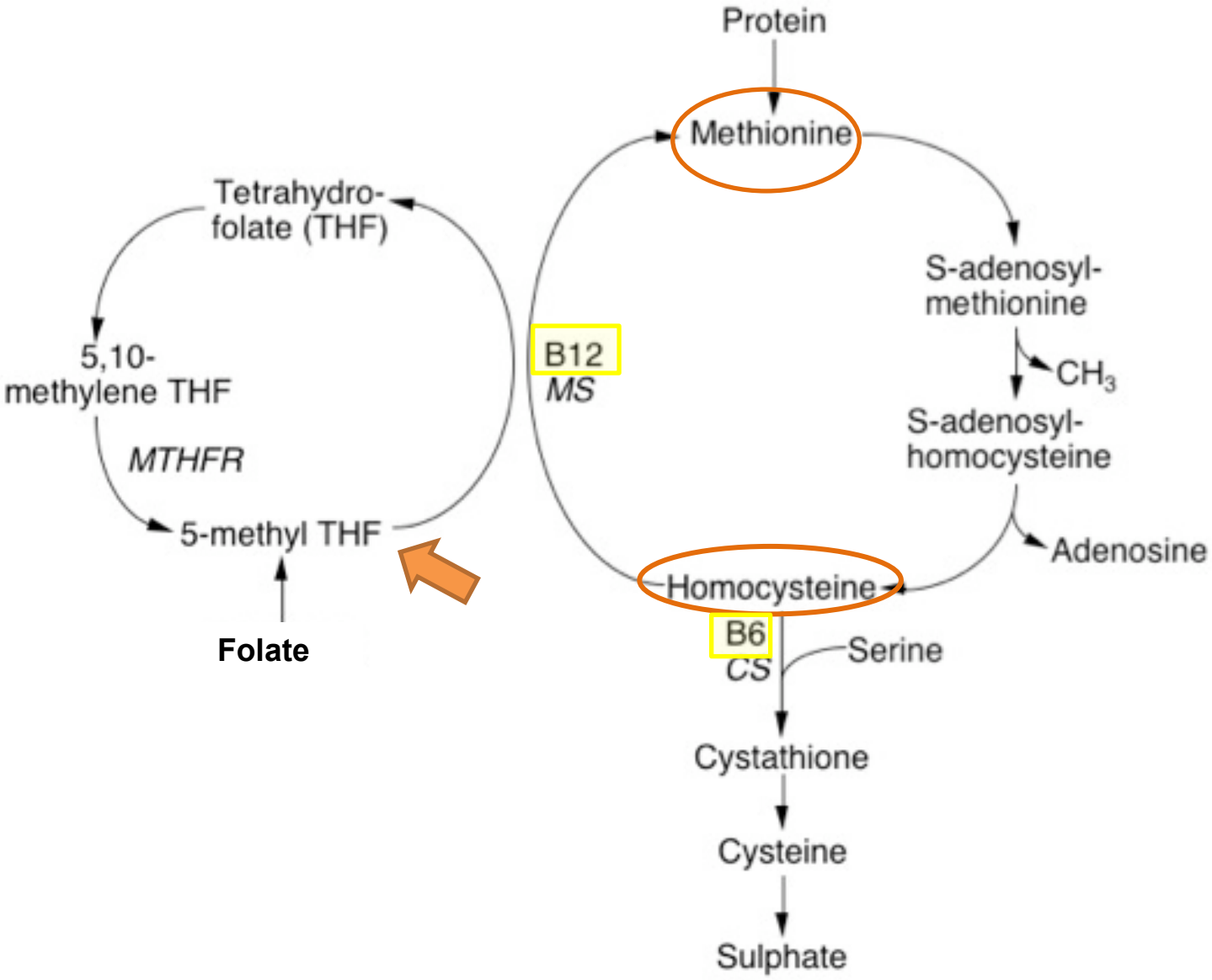


Homocysteine and Heart Disease

- ✓ Homocysteine is thought to cause cardiovascular disease by oxidative stress and vessel wall damage
- ✓ With high homocysteine, **risk of developing coronary artery disease doubles**
- ✓ 2.5 times increased risk of **stroke**
- ✓ Risk factor for cardiovascular disease, blood clotting abnormalities, atherosclerosis
- ✓ **Related to deficiencies** of **vitamin B6 and vitamin B12** in addition to folate

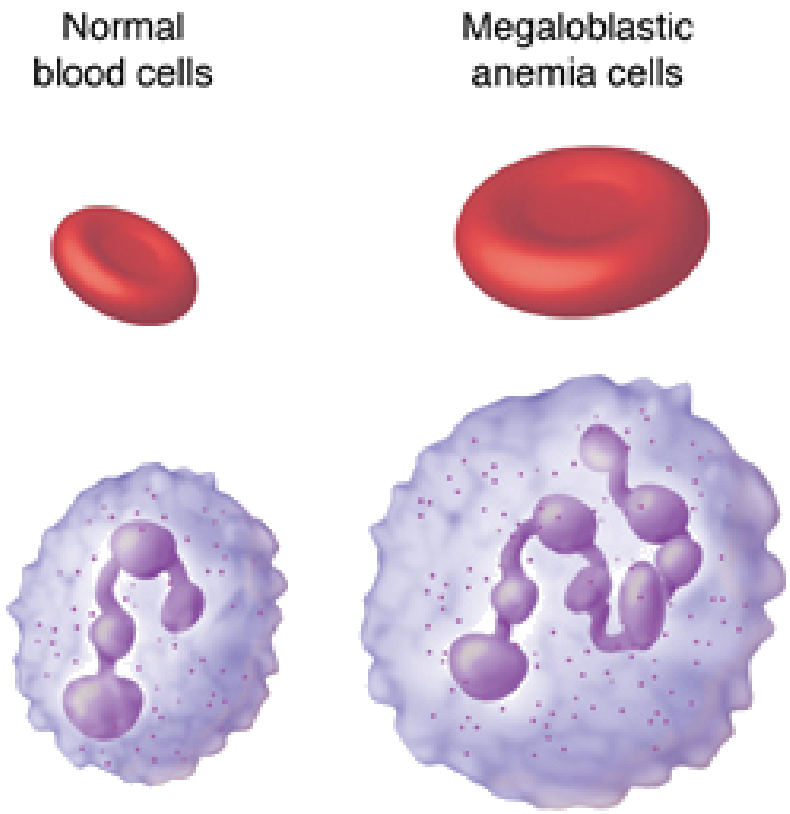


Folate Homocysteine Pathway

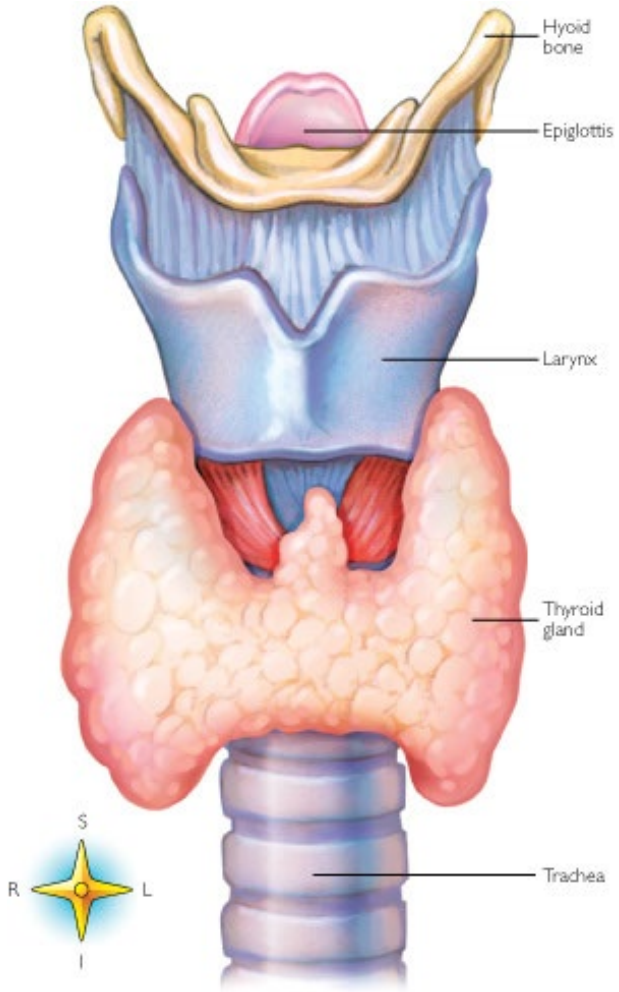


Folate and Anemia

- ✓ **Macrocytic anemia:** Mean Corpuscular Volume (MCV) increased
- ✓ **Megaloblastic anemia:** Abnormally large red blood cells are observed under a microscope



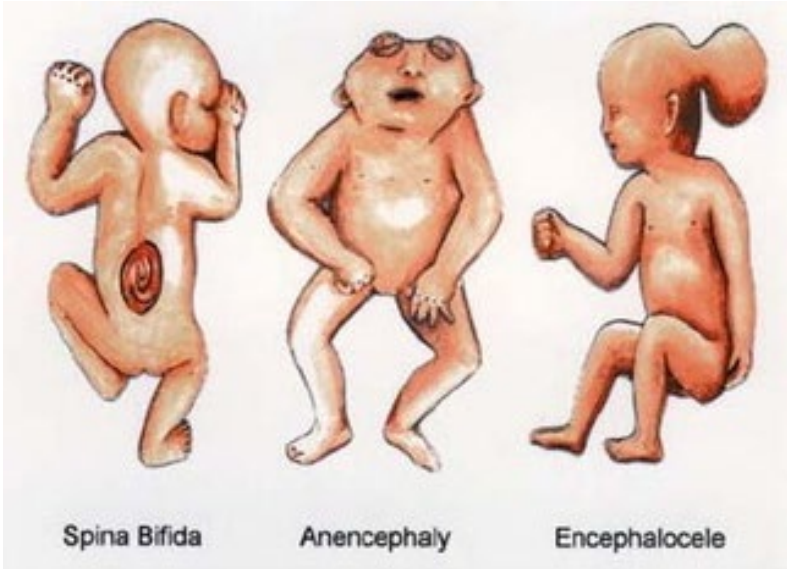
Folate and Thyroid Health



- ✓ Increased homocysteine which can result from **inadequate folate or MTHFR SNP** can contribute to thyroid receptor resistance.
- ✓ T4 is needed to convert riboflavin to the active form of B2 (FAD) which controls MTHFR function.

Folate and Birth Defects

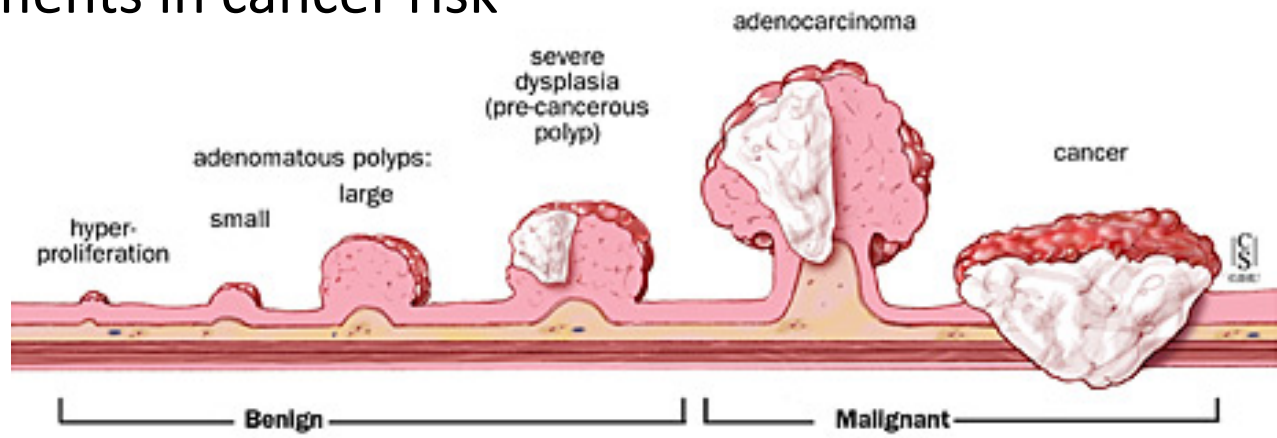
- ✓ Prevents Neural Tube Defects (NTD)
- ✓ Since 1998, the U.S. FDA has required folic acid be added to enriched bread, cereal, flour, cornmeal, pasta, rice, and other grain products



- ✓ Incidence of neural tube defects has decreased since 1998
- ✓ Might reduce risk of having a premature baby
- ✓ May prevent congenital heart problems
- ✓ Folic acid intakes have increased since 1998

Folate and Cancer

- ✓ May decrease the risk of several forms of cancer
- ✓ Before cancer develops might decrease cancer risk
- ✓ High doses taken after cancer begins (especially colorectal cancer) might speed up its progression
- ✓ Proceed with caution with doses in excess of 1,000 mcg
- ✓ People who have a history of colorectal adenomas (which sometimes turn into cancer) may be at highest risk
- ✓ More research is needed to understand the roles of dietary folate and folic acid supplements in cancer risk



Folate and the Brain and Nervous System

- ✓ Production of messaging molecules that are used by nerves to send signals throughout out body
- ✓ Critical to brain and nervous system function
  - ➢ Role in nucleic acid synthesis
  - ➢ Role in methylation reactions
- ✓ High folate diets associated with decreased incidence of Alzheimer's
- ✓ Reduces homocysteine, leading to cognitive impairment
- ✓ Deficiency related to depression due to folate's role in methylation, which is related to synthesis of neurotransmitters dopamine and serotonin
- ✓ Related to BH4 cycle:
  - ➢ Folate stabilizes production of BH4 – required for monoamine neurotransmitter synthesis (i.e. dopamine and serotonin)
  - ➢ BH4 required for conversion of phenylalanine to tyrosine
  - ➢ BH4 cross the BBB using the same transport mechanism as folate
- ✓ Possible connections to glutamic acid and GABA production

http://www.drritamarie.com/go/AMRVol13No3

Folate Medication Interactions

- ✓ Methotrexate (Rheumatrex®, Trexall®)
- ✓ Anti-epileptic medications such as phenytoin (Dilantin®), carbamazepine (Carbatrol®, Tegretol®, Equetro®, Epitol®), and valproate (Depacon®)
- ✓ Sulfasalazine (Azulfidine®) for ulcerative colitis

Folate Nutrient Interactions

- ✓Vitamin B12
- ✓Vitamin B6
- ✓Vitamin B2 (riboflavin)

The pathways that utilize folate and vitamin B12 are also dependent on vitamin B6 and riboflavin for proper functioning

Folate RDA and Adequate Intake

Life Stage	Recommended Amount
Birth to 6 months	65 mcg DFE
Infants 7–12 months	80 mcg DFE
Children 1–3 years	150 mcg DFE
Children 4–8 years	200 mcg DFE
Children 9–13 years	300 mcg DFE
Teens 14–18 years	400 mcg DFE
Adults 19–50 years	400 mcg DFE
Adults 51–70 years	400 mcg DFE
Adults 71+ years	400 mcg DFE
Pregnant teens and women	600 mcg DFE
Breastfeeding teens and women	500 mcg DFE

Food Sources of Folate

- ✓ Vegetables, especially asparagus, Brussels sprouts, and dark green leafy vegetables, such as spinach and mustard greens
- ✓ Avocado
- ✓ Fruits, especially oranges, papaya, grapefruit, and strawberries
- ✓ Nuts and seeds, such as almonds, flax seeds, and sunflower seeds
- ✓ Legumes such as lentils, kidney beans, and black-eyed peas
- ✓ Beef liver

Only small amounts of folate are found in other animal foods like meats, poultry, seafood, eggs, and dairy products

http://www.drritamarie.com/go/GHCFolicAcidFoods

Forms of Folate Found in Food

- ✓ Methylfolates
- ✓ Dihydrofolates
- ✓ Monoglutamyl folates
- ✓ Polyglutamyl folates
- ✓ Fortified and enriched foods contain folic acid

WHF: Food Sources of Folate

Food	Serving Size	Cals	Amount (mcg)	DRI/DV (%)
Lentils	1 cup	229.7	358.38	90
Asparagus	1 cup	39.6	268.20	67
Spinach	1 cup	41.4	262.80	66
Turnip Greens	1 cup	28.8	169.92	42
Broccoli	1 cup	54.6	168.48	42
Beets	1 cup	74.8	136.00	34
Romaine Lettuce	2 cups	16.0	127.84	32
Bok Choy	1 cup	20.4	69.70	17
Cauliflower	1 cup	28.5	54.56	14
Parsley	0.50 cup	10.9	46.21	12
Pinto Beans	1 cup	244.5	294.12	74
Garbanzo Beans	1 cup	269.0	282.08	71
Black Beans	1 cup	227.0	256.28	64
Navy Beans	1 cup	254.8	254.80	64
Kidney Beans	1 cup	224.8	230.10	58
Papaya	1 medium	118.7	102.12	26
Brussels Sprouts	1 cup	56.2	93.60	23
Green Peas	1 cup	115.7	86.78	22
Bell Peppers	1 cup	28.5	42.32	11
Green Beans	1 cup	43.8	41.25	10
Celery	1 cup	16.2	36.36	9
Cabbage	1 cup	43.5	36.00	9
Summer Squash	1 cup	36.0	36.00	9
Strawberries	1 cup	46.1	34.56	9

http://www.drritamarie.com/go/WHFfolate

Herbs Reported to Be High In Folate

Nettle leaf

Red clover

Oatstraw

Parsley

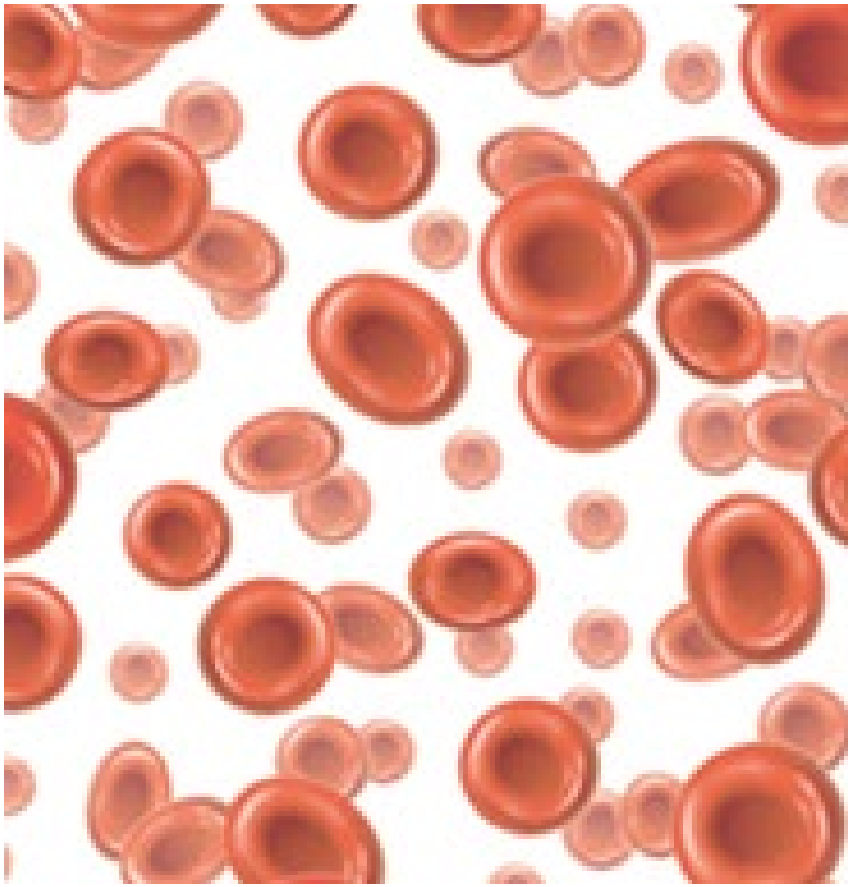
Basil

Bioavailability of Folate

- ✓ Polyglutamated folate found in vegetables and citrus fruits can be absorbed in the 60-98% range
- ✓ Methylated folate (5-methyl-tetrahydrofolate) is the major form in most plant cells
- ✓ 5-MTHF appears to be the only form that crosses the blood brain barrier
- ✓ DFEs do not tell the whole story of this vitamin with respect to health benefits
- ✓ Whole natural foods providing a variety of forms are best sources

Symptoms of Folate Deficiency

- ✓ Megaloblastic anemia
  - ➢ Weakness
  - ➢ Fatigue
  - ➢ Difficulty concentrating
  - ➢ Irritability
  - ➢ Headache
  - ➢ Heart palpitations
  - ➢ Shortness of breath
- ✓ Open sores on the tongue and inside the mouth
- ✓ Changes in the color of the skin, hair, or fingernails
- ✓ Restless leg syndrome
- ✓ Neural tube defects, such as spina bifida
- ✓ Premature or low-birth-weight baby



Folate Deficiency Risk Factors

- ✓ Pregnant – not taking folate in supplement form
- ✓ Intestinal problems that interfere with absorption
- ✓ Alcohol interferes with the absorption
- ✓ Certain prescription medications, such as some anti-seizure drugs, block absorption
- ✓ Hemodialysis for kidney failure
- ✓ People on some cancer drugs
- ✓ Diet lacking in fresh fruits and vegetables
- ✓ Consistent overcooking of vegetables

At-Risk Populations for Folate Deficiency

- ✓ Teen girls
- ✓ Women aged 18 - 30 years (especially before and during pregnancy)
- ✓ Non-Hispanic black women
- ✓ People with celiac disease
- ✓ People with inflammatory bowel disease
- ✓ Alcoholics

Impact of Folate Excess

- ✓ Large doses can mask a vitamin B12 deficiency leading nerve damage (>800 mcg)
- ✓ High doses of folic acid might also increase the risk of colorectal cancer and possibly other cancers in some people

Age	Upper Limit
Birth to 6 months	Not established
Infants 7–12 months	Not established
Children 1–3 years	300 mcg
Children 4–8 years	400 mcg
Children 9–13 years	600 mcg
Teens 14–18 years	800 mcg
Adults	1,000 mcg

http://www.drritamarie.com/go/PMID15499634

Assessing Status of Folate

- ✓ Dietary intake tracking
- ✓ Serum/plasma folate
- ✓ RBC folate
- ✓ Homocysteine (if B12 is adequate)
- ✓ Hypersegmentation of neutrophils
- ✓ CBC – Increased MCV: Increased size of RBC

Methyl Folate Supplement Types

- ✓ **Best forms:** Most biologically active: L forms, all equivalent
  - L-5-MTHF
  - L-5-Methyltetrahydrofolate
  - 6(S)-L-MTHF
  - 6(S)-L-Methyltetrahydrofolate
- ✓ **Well absorbed:**
  - L-Methylfolate Calcium
  - Metafolin
  - Levomefolic Acid
- ✓ **Caution:** May or may not be 99% pure, biologically active - L or D form not specified
  - 5-MTHF
  - 5-Methylfolate
  - 5-Methyltetrahydrofolate
- ✓ **Avoid these:**
  - D-5-MTHF
  - D-5-Methyltetrahydrofolate
  - 6(R)-L-MTHF
  - 6(R)-L-Methyltetrahydrofolate

D and L forms of methylfolate are stereoisomers in the form of diastereoisomers

Folate Administration

- ✓ Topical cream
- ✓ Liposomal
- ✓ Sublingual drops
- ✓ Sublingual lozenges
- ✓ Capsules
- ✓ Tablets
- ✓ Soft gels
- ✓ Lozenges

Take with water on an empty stomach. Doses range from 150 mcg up to 15 gm.

References

- ***Advanced Nutrition and Human Metabolism*** – Gropper, Smith and Groff.
- Guyton AC, Hall JE. ***Textbook of Medical Physiology***, 9th ed.
- Murray RK, Granner DK, Mayes PA, Rodwell VW. ***Harper's Biochemistry***, 24th ed.
- Food and Nutrition Board, Institute of Medicine. ***Folate. Dietary Reference Intakes***: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. http://www.drritamarie.com/go/NAPFolateDRI
- Choi SW, Mason JB. ***Folate and carcinogenesis: an integrated scheme***. J Nutr. http://www.drritamarie.com/go/PMID10720158
- Bailey LB, Gregory JF, 3rd. ***Folate metabolism and requirements***. J Nutr. http://www.drritamarie.com/go/PMID10203550
- ***Linus Pauling Institute:*** http://www.drritamarie.com/go/LPIFolate
- **Dr. Ben Lynch:** http://www.drritamarie.com/go/DrBenLynchMethylfolate
- Folate and Depression: http://www.drritamarie.com/go/AMRVol13No3

Folate Videos

- B12 and Folate Metabolism:
  http://www.drritamarie.com/go/YTFCB12Folate
- Folic Acid vs Folate – What is the Difference:
  http://www.drritamarie.com/go/YTFolicAcidvsFolate
- Methyl Trap of Homocysteine Cycle – Folate and B12:
  http://www.drritamarie.com/go/YTHomocysteineCycle
- All About Vitamin B9 (Folate):
  http://www.drritamarie.com/go/YTB9Tutorial
- Folate and Methylation Defects and Metabolism:
  http://www.drritamarie.com/go/YTFolateMethylationDefects