The symptoms of vitamin B12 deficiency range from mild to severe, and in many cases are not specific enough to confirm a diagnosis. Symptoms can include diarrhea or constipation, fatigue, light headedness on standing, poor appetite, pallor, difficulty concentrating, shortness of breath on exertion, glossitis. Neurologic symptoms can appear after chronic deficiency and involve changes in mental status, depression, peripheral neuropathy, loss of balance. [Anemia – B12 deficiency. http://www.nlm.nih.gov/medlineplus/ency/article/000574.htm]

Some of the symptoms of folate deficiency overlap with B12, including fatigue and glossitis, but others such as accelerated graying of hair, oral ulcers, and poor growth rates do not. [Folate deficiency. http://www.nlm.nih.gov/medlineplus/ency/article/000354.htm]

The indicated blood tests for B12 deficiency are complete blood count (CBC), reticulocyte count, serum LDH and vitamin B12, while those for folate deficiency are CBC, serum and RBC folate. Other useful tests are serum homocysteine and methylmalonic acid (MMA). Serum homocysteine will be high with both deficiencies, while only MMA will be increased in B12 deficiency. [Vitamin B12 and Folate. http://labtestsonline.org/understanding/analytes/vitamin-b12/tab/test]

As genetic testing has become more widely available, specific analysis of known single nucleotide polymorphisms (SNP) is increasingly accepted as an aid to diagnosis. In the case of folate metabolism several SNP have been identified as significant; the first SNP to gain widespread attention affected the MTHFR gene. The MTHFR gene supplies instructions for making the enzyme methylenetetrahydrofolate reductase. MTHFR is essential in metabolizing amino acids, and is central in the chemical reaction involving the various forms of folate, or folic acid. The enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF), the active form of the vitamin. This reaction leads to the multistep process that converts homocysteine to methionine. [MTHFR. http://ghr.nlm.nih.gov/gene/MTHFR] It was about the same time that genetic testing became available that the term methylation defects appeared in the literature. There is an introductory presentation well worth watching at http://mthfr.net/methylation-and-mthfr-defects-presentation/2012/04/25/. This website, http://mthfr.net/, is an excellent resource for learning about MTHFR gene mutations.

The principle health conditions associated with genetic mutations affecting the MTHFR gene include homocystinuria (40 associated mutations), anencephaly (a common neural tube defect [NTD] specifically caused by the 677C>T SNP), spina bifida (another NTD that led to a better understanding of the need to provide sufficient folate during pregnancy). Polymorphisms in the MTHFR gene have been suggested as risk factors for other common conditions: heart disease, stroke, hypertension, preeclampsia,
glaucoma, psychiatric disorders. [ibid.] Certain types of cancer are associated with these SNP, in fact a large body of epidemiologic evidence suggests that the MTHFR 677C>T is associated with cancer risk in a site-specific manner, and its presence can aid the selection of beneficial chemotherapeutic drugs. [Kim YI. Role of the MTHFR polymorphism in cancer risk modification and treatment. Future Oncol. 2009 May;5(4):523-42. PMID 19450180] Another cancer related study concluded that “the MTHFR SNP, C677T and A1298C, were associated with breast cancer survival. The variant alleles had opposite effects on disease outcome in the study population. Race/ethnicity modified the association between the two SNPs and breast cancer survival.” [Damalai NM, et al. Association of MTHFR gene polymorphisms with breast cancer survival. BMC Cancer 2006, 6:257. http://www.biomedcentral.com/1471-2407/6/257]

What SNP are associated with folate metabolism defects? C677T and A1298C are the most commonly studied, others are less common and are beyond the scope of this discussion.

Methionine biosynthesis – The essential contributions of folate, vitamin B12 and B6

The vitamins 5-MTHF, B12 and B6 and B2 are the source of coenzymes which participate in one carbon metabolism. In this metabolism, a carbon unit from serine or
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glycine is transferred to tetrahydrofolate (THF) to form methylene-THF [Selhub J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. J Nutr Health Aging. 2002;6(1):39-42. PMID 11813080]

The biologically active form of folate, N5-methyltetrahydrofolate, donates its methyl
group to a vitamin B12-dependent enzyme, methionine synthase, which recycles
homocysteine back to methionine. [Scott, JM, et al. Folic acid metabolism and

What types of folate are available?
Folic acid - Folic acid is not biologically active until its conversion to dihydrofolic acid in
the liver. [Bailey SW, Ayling JE. The extremely slow and variable activity of
dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc
Natl Acad Sci USA. 2009 Sep 8;106(36):15424-9. PMID 19706381] Folic acid is a
synthetic vitamin found in many vitamin supplements and fortified foods. Due to the
prevalence of MTHFR gene mutations in the human population, folic acid is not an
effective vitamin in patients with these SNP; it is recommended that folic acid be
avoided, and either 5-methyltetrahydrofolate (oral dosing) or folinic acid (parenteral
dosing) be utilized.

Clarification of terminology: “In the case of folate: Folic acid (pteroylglutamic acid) is
now used to denote the fully oxidized chemical compound not present in natural foods.
The term ‘folate’ is [mis]used to denote the large group of compounds possessing the
same vitamin activity and includes natural folates and folic acid.” [Hoffbrand AV, Weir DG.
The History of Folic Acid, British Journal of Haematology 2001(113):579. Thanks to Jonathan Wright, MD,
for emphasizing the point that the term ‘folate’ is misused, leading to possible misunderstanding in the
use of this important nutrient (private communication) In the cited reference the original quote stated “The
term folate is used…”

L-Folinic acid is a biologically active form of folic acid, and is available as a parenteral
drug - Folinic acid is a 5-formyl derivative of tetrahydrofolic acid. It is readily converted
to other reduced folic acid derivatives (e.g., tetrahydrofolate), so, has vitamin activity
that is equivalent to that of folic acid. Unlike folic acid, it does not require the action of
dihydrofolate reductase (DFR) for its conversion to an active form, its function is
unaffected by inhibition of DFR by drugs such as methotrexate. L-Folinic acid or
Levoleucovorin (aka Leucovorin calcium) was approved by the FDA in 2008.
5-methyltetrahydrofolate (aka Levomefolic acid) is the biologically active form of folic acid required for DNA synthesis, the cysteine cycle and the metabolism of homocysteine. This form needs to be prescribed for all patients with a homozygous C677T polymorphism (prevalence 11%) and is recommended but not essential for heterozygous patients (prevalence 47%) [Mischoulon D, et al. Prevalence of MTHFR C677T and MS A2756G polymorphisms in major depressive disorder, and their impact on response to fluoxetine treatment. CNS Spectr. 2012 Jun;17(2):76-86. PMID 22789065] An earlier study found the prevalence of C677T and A1298C to vary between ethnic groups:

“The prevalence of the two MTHFR SNPs was determined by polymerase chain reaction (PCR) mediated restriction fragment length polymorphism analysis. In the Caucasian population, homozygosity for the MTHFR A1298C SNP was detected in 4% (2/50) of the individuals tested, while 42% (21/50) were heterozygous for this SNP. Among Hispanics, 4% (2/50) were homozygous and 38% (19/50) heterozygous for the A1298C SNP. Homozygosity for the C677T MTHFR SNP was detected in 16% (8/50) and 10% (5/50) of Caucasians and Hispanics, respectively.” [Peng F, et al. Single nucleotide polymorphisms in the methylenetetrahydrofolate reductase gene are common in US Caucasian and Hispanic American populations. Int J Mod Med. 2001 Nov;8(5):509-11. PMID 11605019]

Food sources of folates - http://ods.od.nih.gov/factsheets/Folate-HealthProfessional/

The cobalamins
Vitamin B12 has the largest and most complex chemical structure of all the vitamins, and it is exclusive among vitamins in that it contains the metal ion cobalt. Consequently cobalamin is the term used to refer to compounds containing vitamin B12 activity. Methylcobalamin and 5-deoxyadenosyl cobalamin are the biologically active forms of

The figure below shows where the mutations affect Vitamin B12 activity.


Discussion & recommendations
A person who is diseased, especially chronically, has decreased energy reserves to address the needs of healing plus the activities of daily living. It is more efficacious to supply them with the active forms of nutrients they are deficient in, so that additional energy expenditures are not required to convert inactive precursors to biologically active metabolites. An example of this would be using flax oil (containing the essential fatty
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acids Alpha-linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid) to increase body levels of the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). With current knowledge regarding genetic SNP it is important to use the biologically active nutrients especially if genetic testing is not performed.

Sidebar: Humans can synthesize longer omega-6 and omega-3 fatty acids from the essential fatty acids LA and ALA, respectively, through a series of desaturation (addition of a double bond) and elongation (addition of two carbon atoms) reactions. LA and ALA compete for the same elongase and desaturase enzymes in the synthesis of longer polyunsaturated fatty acids, such as AA and EPA. Although ALA is the preferred substrate of the delta-6 desaturase enzyme, the excess of dietary LA compared to ALA results in greater net formation of AA (20:4n-6) than EPA (20:5n-3).


Recommendations

**Folates**
Folic acid – physicians are advised to avoid prescribing to patients, as ingestion by those with methylation defects caused by SNP effecting MTHFR can lead to adverse effects.
5-MTHF – This form should be used for routine oral supplementation.
Deplin (generic name L-methylfolate) – This is the prescription drug form of active folate.
Folinic acid – When parenteral nutrition is required, folinic acid is preferred over folic acid.

**Cobalamins**
Cyanocobalamin – This is the least expensive form of vitamin B12, both orally and parenterally. Commonly found in “cheap” brand name multivitamins, for example One A Day [http://labeling.bayercare.com/omr/online/oad-men-health-formula.pdf].
Cyanocobalamin is also the most common form of parenteral vitamin B12, is the least expensive, and the most shelf-stable; best used intramuscular, not intravenous due to rapid renal excretion. It is acceptable for treatment of patients with B12 deficiency who do not have methylation defects. It is not the best choice for patients with neurological disease (see methylcobalamin below)
Hydroxocobalamin – This is a good choice for intravenous infusion, as it binds to carrier proteins better than other cobalamins; also known as long-acting B12
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Methylcobalamin – The active form of vitamin B12 should be used preferentially for any patient with neurological disease, and is now found in most “physician brand” quality oral supplements. It is also available as a compounded parenteral drug, that may be administered intramuscularly (best) or intravenously.

Biochemical individuality
Biochemical Individuality was a term first introduced by Dr. Roger J. Williams in 1956, when he published his book of the same name. Dr. Williams was one of the first to appreciate that humans differ biochemically from each other. Dr. Williams was also one of the first to recognize that nutritional status influences the expression of genetic characteristics. Time and scientific advancements have allowed us to better understand biochemical individuality. Genetic research lead to more affordable genetic testing, and in the case of the MTHFR gene, has allowed us to determine why some patients respond favorably to folic acid, whereas others only respond when administered 5-MTHF. Even though patients may have similar genetic testing results, they may react differently to the same nutrient – enter the concept of epigenetics – currently represented by two “camps.” Bruce Lipton has emphasized the importance of environmental factors and mental states [http://www.brucelipton.com/], whereas others in the area of scientific inquiry see it a little differently. [http://www.sciencemag.org/content/330/6004/611.short] Perhaps the aphorism “The more we know, the more we know we don’t know” is apropos at this point.

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