

# Understanding the Serum Vitamin B<sub>12</sub> Level and its Implications for Treating Neuropsychiatric Conditions: An Orthomolecular Perspective

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**Abstract:** *Vitamin B<sub>12</sub> (cobalamin) ranks among the most useful, safe and effective orthomolecules when treating a diverse array of neuropsychiatric conditions. However, most clinicians do not consider vitamin B<sub>12</sub> important unless the serum level is below laboratory reference ranges. Ten research reports, summarized here, indicate metabolic consequences from low-normal (but not deficient) serum B<sub>12</sub> levels, and/or clinical improvements following therapy that markedly increased serum B<sub>12</sub> levels. My clinical experience, along with the summarized reports, suggests that (1) serum levels of vitamin B<sub>12</sub> not “classically” deficient by current laboratory standards are associated with neuropsychiatric signs and symptoms, and (2) clinical improvement results when serum vitamin B<sub>12</sub> levels are optimized or markedly increased following vitamin B<sub>12</sub> treatment. Vitamin B<sub>12</sub>’s mechanisms of action are believed to include increased S-adenosylmethionine production, improved methylation, decreased plasma and brain homocysteine, compensation for inborn errors of metabolism, normalized gene expression, correction of long-latency vitamin B<sub>12</sub> debt, and anti-inflammatory activity. Clinicians may wish to re-evaluate the importance of lower-than-optimal serum vitamin B<sub>12</sub> levels, pursue additional testing such as urinary methylmalonic acid, and consider the potential benefits of vitamin B<sub>12</sub> treatment.*

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## Introduction

For approximately twelve years I have been using pharmacological doses of nutrients to mitigate a variety of neuropsychiatric signs and symptoms, such as anxiety, aphasia (i.e., both expressive and receptive types), ataxia, cognitive impairment, depression, delusions, developmental delays, fatigue, hallucinations, insomnia, irritability, memory problems, mood swings, muscle weakness, neuralgias, neuropathy, obsessions, paranoid ideations, paresthesias, psy-

choses, and/or seizures. When treating such a diverse array of neuropsychiatric presentations, vitamin B<sub>12</sub> (cobalamin) ranks among the most useful, versatile, safe, and effective orthomolecules at my disposal. Despite my success in observing improvements among my patients prescribed vitamin B<sub>12</sub>, recognition of vitamin B<sub>12</sub> insufficiency remains neglected. Most clinicians do not consider vitamin B<sub>12</sub> important unless the serum level is deficient when indicated by laboratory reference ranges. Vitamin B<sub>12</sub> therapy con-

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tinues to be viewed by many mainstream-minded clinicians as unexpected or unwarranted. The purpose of this paper is therefore to show the rationality of using vitamin B<sub>12</sub> therapeutically, even in the absence of “classical” deficiency.

### **What Serum Vitamin B<sub>12</sub> Level Defines “Classical” Deficiency?**

A number of publications discuss the serum levels of vitamin B<sub>12</sub> that reflect “classical” deficiency. According to one author, a patient is considered to be deficient in vitamin B<sub>12</sub> when the serum vitamin B<sub>12</sub> level is < 100 pg/mL (74 pmol/L).<sup>1</sup> In another article, deficiency was defined as having a serum vitamin B<sub>12</sub> level < 203 pg/mL (150 pmol/L) on two separate occasions, or when the serum vitamin B<sub>12</sub> level is < 203 pg/mL (150 pmol/L) and total serum homocysteine level is > 13 μmol/L or serum methylmalonic acid > 0.4 μmol/L.<sup>2</sup> In the province where I reside, most laboratories consider a patient to be deficient in vitamin B<sub>12</sub> if the serum level is less than 149 pg/mL (110 pmol/L). When vitamin B<sub>12</sub> reaches a level that would reflect “classical” deficiency, it is important to determine and rule-out underlying causes (e.g., alcoholism, pernicious anemia, and vegetarian diet) and prescribe appropriate vitamin B<sub>12</sub> replacement therapy.

### **Review of Ten Neuropsychiatric Research Reports about Vitamin B<sub>12</sub>**

While vitamin B<sub>12</sub> deficiency has been associated with problems in cognition, mood and psychosis, and less commonly, anxiety, three patients with serum vitamin B<sub>12</sub> levels outside of the “classical” deficient range also suffer from various neuropsychiatric signs and symptoms reflective of vitamin B<sub>12</sub> “insufficiency.” When these patients are given therapeutic doses of vitamin B<sub>12</sub>, their serum levels further increase and their clinical picture usually improves. I summarized 10 research reports that suggest metabolic consequences from lower-normal (but not deficient) serum vitamin B<sub>12</sub> levels, and/or noted clinical improvements following marked increases in serum vitamin B<sub>12</sub> levels.

### **Report #1: 29 Subjects with Fatigue**

Twenty-nine subjects (7 male and 22 female; mean age 41.5 years) complaining of idiopathic fatigue or tiredness completed a double-blind cross-over trial.<sup>4</sup> The subjects were provided with intramuscular (IM) injections of hydroxocobalamin (5 mg twice weekly for two weeks) or identical-looking placebo injections, followed by a rest period of two weeks, and then a similar course of hydroxocobalamin or identical-looking placebo injections depending on treatments given during the initial two week trial period. Symptoms were evaluated by a daily self-rating card that assessed appetite, general feeling of well-being, fatigue, mood (i.e., level of happiness), injection response (i.e., how the injection made the subject feel), and sleep. Those subjects who received the placebo in the first two week period showed a favourable response to hydroxocobalamin in the second period on all measurements made. The results showed statistical significance with respect to general well-being (p=0.006) and happiness (p=0.032). The initial mean serum vitamin B<sub>12</sub> level was 358.4 pg/mL (264.4 pmol/L). By the end of treatment serum concentrations had risen to more than 2000 pg/mL (1476 pmol/L) in all but three of the total 29 subjects. The three subjects that did not have serum vitamin B<sub>12</sub> values above 2000 pg/mL, had concentrations at or above 450 pg/mL (332 pmol/L).

The authors of this study concluded that vitamin B<sub>12</sub> has a “tonic” effect. They reasoned that the response to vitamin B<sub>12</sub> was related to pharmacological factors such as the ability of the vitamin to penetrate into the brain or neurons, or to an influence of vitamin B<sub>12</sub> on neural metabolism. While none of the patients had serum levels of vitamin B<sub>12</sub> that would be considered deficient, they did respond favourably to vitamin B<sub>12</sub> administration after their serum levels were dramatically increased by intramuscular injections.

### **Report #2: 61 Patients - Serum vs. Brain Status of Vitamin B<sub>12</sub>**

This study sought to determine to what extent vitamin B<sub>12</sub> in the serum is a real reflection of vitamin B<sub>12</sub> status of brain tis-

sue.<sup>5</sup> It was comprised of three groups of patients and one control group. Group 1 involved 23 patients aged 60-85 with dementia, group 2 involved 16 patients aged 30-60 with organic affective syndrome, group 3 involved 10 female patients aged 25-40 with postnatal depression (and complaints of neurasthenia), and the control group of 12 patients aged 25-50. All patients were normal haematologically, had normal liver function and kidney function tests, but did have evidence of "soft" neurologic symptoms (i.e., some combination of encephalopathy and/or polyneuropathy or neuropathy). When the serum levels of vitamin B<sub>12</sub> were tested, normal values (200-800 pg/mL; 148-590 pmol/L) were found in 45 of the 49 patients from groups 1-3. All 12 patients in the control group had serum B<sub>12</sub> levels in the normal range. Deficient cerebrospinal fluid levels (CSF) of vitamin B<sub>12</sub> (<5 pg/mL; <3.7 pmol/L) were found in 30 of the total 49 patients (or in 26 of the 45 patients with normal serum levels). All 12 patients in the control group had CSF levels in the normal range (>10 pg/mL; >7.4 pmol/L). Because there was a marked difference between both compartments when measured, these results indicate that a potentially treatable vitamin B<sub>12</sub> deficiency will be overlooked in a significant portion of patients if CSF B<sub>12</sub> levels are not included in the assessment. Ten patients were given six weeks of twice weekly IM treatment of hydroxocobalamin (1,000 mcg) plus daily treatment

with an oral supplement containing 50 mg zinc-DL-aspartate and 250 mg of taurine. Two patients were given 6 weeks of a daily supplement containing cyanocobalamin (0.1 mg) plus 50 mg zinc-DL-aspartate and 250 mg of taurine. **Table 1** (below) highlights the changes in both serum and CSF that resulted from vitamin B<sub>12</sub> treatment. Treatment with IM hydroxocobalamin produced more significant increases than oral cyanocobalamin in the patients' CSF levels of vitamin B<sub>12</sub>.

In group 1 (patients with dementia), the authors speculate that zinc deficiency and its corresponding high levels of copper block the transport of B<sub>12</sub> in the choroid plexus (and therefore, the CSF), similar to the effects of free radical chain reaction inducers like mercury, cadmium and other neurotoxins. Group 2 (patients with organic affective syndrome), all had exposures to toxic chemicals (i.e., alcohol, industrial solvents or halogenated hydrocarbons), which were considered causative in their neurasthenic-depressive clinical presentation. The authors speculate that these neurotoxins may block the entry of vitamin B<sub>12</sub> into the brain, leading to CSF deficiency of the vitamin. In group 3 (patients with postnatal depression), the authors suggest that estrogens or estrogen-receptor binding chemicals (e.g., halogenated hydrocarbons) have an effect on B<sub>12</sub> transport through the blood-brain barrier and choroid plexus, thus causing deficiency of the vitamin with the CSF.

**Table 1.** Changes in serum and CSF vitamin B<sub>12</sub> concentrations following treatment

Group	Pre-treatment serum B <sub>12</sub> (pg/ml)	Pre-treatment CSF B <sub>12</sub> (pg/ml) serum	Post-treatment serum B <sub>12</sub> (pg/ml)	Post-treatment CSF B <sub>12</sub> (pg/ml)
IM injection (n=10)	310 (229 pmol/L) (average)	<5 (<3.7 pmol/L) (average)	>2400 (>1771 pmol/L) (average)	70 (52 pmol/L) (average)
Oral (Patient #1)	430 (317 pmol/L)	14 (10 pmol/L)	2400 (1771 pmol/L)	21 (15.5 pmol/L)
Oral (Patient #2)	450 (332 pmol/L)	<5 (<3.7 pmol/L)	>2400 (>1771 pmol/L)	9.6 (7.1 pmol/L)

### Report #3: 16 Patients with Dementia and 13 Patients with Neurasthenia

In another publication by the authors of report #2, 16 geriatric patients aged 60-85 years with dementia or organic affective syndrome with co-existing dementia were assessed.<sup>6</sup> All patients had normal liver function and no gross haematological abnormalities. These patients did have signs and symptoms of polyneuropathy. Three patients had low levels of serum B<sub>12</sub>, and low levels of CSF B<sub>12</sub>. The remaining 13 patients had normal serum B<sub>12</sub> levels (220-540 pg/mL; 162-398 pmol/L), with nine of them also having deficient CSF B<sub>12</sub> levels. Five patients that had normal serum levels and deficient CSF levels were given three months of treatment with parenteral hydroxocobalamin (unstated dose). After three months, they experienced clinical improvement and had a marked rise in their CSF B<sub>12</sub> levels (50-90 pg/mL; 37-66 pmol/L).

In a second group of 13 patients (29-50 years of age) with neurasthenic symptoms, the vitamin B<sub>12</sub> levels were assessed in both the serum and CSF. All patients had normal liver function and no gross haematological abnormalities. These patients did have 'soft' neurological signs of encephalopathy and neuropathy. All 13 patients had normal serum levels of vitamin B<sub>12</sub> (range, 280-750 pg/mL; 207-553 pmol/L), but 11 of them had deficient CSF levels (<5 pg/mL; <3.7 pmol/L). By not performing routine CSF analysis, the majority of these patients would not have been found to have a vitamin B<sub>12</sub> deficiency.

The authors concluded that all patients displaying organic mental symptoms should have their CSF levels of vitamin B<sub>12</sub> assessed. I am of the opinion that routine CSF measurements of vitamin B<sub>12</sub> are impractical, expensive, and invasive. Perhaps another way of interpreting these results is to know that serum vitamin B<sub>12</sub> levels within normal ranges might not reflect what is happening within the brain. To encourage normal or even optimal CSF levels of vitamin B<sub>12</sub>, marked increases in serum levels of the vitamin might be achieved through IM administration.

### Report #4: 14 Patients with Dementia, Degenerative Types

Vitamin B<sub>12</sub> levels in the serum and the CSF were assessed in 14 patients with dementia.<sup>7</sup> Eleven of these patients had degenerative types of dementia, such as Alzheimer's disease, senile dementia, and Pick's disease. The serum vitamin B<sub>12</sub> levels in all patients were normal (500-1,300 pg/mL; 369-959 pmol/L). CSF levels of vitamin B<sub>12</sub> did not correlate with severity of the dementia. After oral methylcobalamin (2,000 mcg per day), neither serum or CSF levels of vitamin B<sub>12</sub> were significantly elevated. On the other hand, when the patients were given the same oral dose plus daily IM injections of methylcobalamin (500 mcg), marked elevations occurred in both the serum and CSF compartments. This study is compelling on two fronts. First, the serum vitamin B<sub>12</sub> ranges used in this study are much higher than those reported in other publications.<sup>1-5</sup> Perhaps in Japan they are aware that a higher serum vitamin B<sub>12</sub> level correlates with better health; thus, the need for a reference range that "captures" more deficient patients. Second, IM methylcobalamin was the only way to markedly increase both serum and CSF levels of vitamin B<sub>12</sub> among the patients with dementia. Oral methylcobalamin did not appreciably increase serum and CSF levels of vitamin B<sub>12</sub>.

### Report #5: 8 Patients with Personality Symptoms

Eight patients were administered IM hydroxocobalamin to treat their personality symptoms, as assessed by the Minnesota Multiphasic Personality Inventory (MMPI).<sup>8</sup> The patients in this trial had the following diagnoses: paranoid schizophrenia (one patient), angioneurotic edema (one patient), cancer prevention (one patient), depression (two patients), recurrent duodenal ulcer (one patient), insomnia (one patient), and cocaine addiction (one patient). All of the patients were 16 years of age and older and not on any medication. They were taking a variety of supplements such as vitamins, minerals, and unsaturated fats. Their serum

vitamin B<sub>12</sub> levels were within the laboratory's normal range (115-800 pg/mL; 85-590 pmol/L). All patients, through trial and error, were given injections of hydroxocobalamin to establish ideal doses of the vitamin (doses ranged from 3,000 mcg four times each week to 9,000 mcg per day). Serum vitamin B<sub>12</sub> levels were drawn when patients felt the greatest sense of well-being and were also drawn after the injections were discontinued for 5-7 days. Patients also completed the MMPI numerous times during the trial period. The highest serum vitamin B<sub>12</sub> levels (average: 465,173 pg/mL; 343,205 pmol/L) were associated with MMPI patterns at or closer to normal (profile elevation average: 56.1). With lower serum vitamin B<sub>12</sub> levels (average: 110,611 pg/mL; 81,609 pmol/L), the MMPI patterns showed much more emotional distress (profile elevation average: 67.5).

The author concluded that vitamin B<sub>12</sub> dependency disorders are common and neglected by the medical profession because: (1) the body level of vitamin B<sub>12</sub> needed for full biological efficiency is unknown; (2) patients might have a deficiency in transporting vitamin B<sub>12</sub> into their tissues (low levels of transcobalamin II); and (3) a large increase in a vitamin level might be needed to "force" one or more abnormal chemical reactions to proceed normally.

#### **Report #6: Two patients with Sleep-wake Disorders**

Two adolescent patients with persistent sleep-wake schedule disorders responded to treatment with oral methylcobalamin.<sup>9</sup> A 17-year-old male had hypernycthemeral syndrome (non-24-hour circadian rhythm disorder) and was unable to attend school despite trying various medications. A 15-year-old girl had delayed sleep phase syndrome (DSPS) and was similarly unable to attend school despite numerous medication trials. Both patients did not have any laboratory or clinical evidence of vitamin B<sub>12</sub> deficiency or hypothyroidism. Improvement of their sleep-wake schedule disorders appeared immediately after the administration of high doses (3,000 micrograms per day) of

oral methylcobalamin. Serum concentrations of vitamin B<sub>12</sub> during the treatment period were in the high range of normal or above normal. The female patient's serum level of B<sub>12</sub> was 1,078 pg/mL (795 pmol/L) after two weeks of treatment. Her baseline serum B<sub>12</sub> level was not provided in the report. The male patient's baseline serum vitamin B<sub>12</sub> level was 589.5 pg/mL (434.9 pmol/L) and was measured three more times during treatment. His last serum vitamin B<sub>12</sub> measurement during treatment was 1,161.6 pg/mL (857.03 pmol/L). For the male patient, treatment reduced the sleep-wake cycle from 24.6 hours to 24.0 hours, which was significant since his sleep-wake rhythm became entrained to the environmental 24-hour rhythm. For the female patient with DSPS, treatment decreased sleep from 10 hours to seven hours, and the time of sleep onset normalized from 2 a.m. to midnight.

It appears that these patients responded when their serum levels increased to the high range of normal, or to levels exceeding normal. It was concluded that vitamin B<sub>12</sub> benefited these patients either by enhancing the phase-setting effects of light through some action on the eye or retinohypothalamic tract, or by a direct phase-setting effect.

#### **Report #7: Patient with Hypersomnia**

This communication describes the successful use of oral methylcobalamin in a 32 year-old-male patient with recurrent hypersomnia of 12 years duration.<sup>10</sup> He would have episodes lasting a few times each year, but when the episodes increased to once every month, he was referred to a psychiatrist for further evaluation and treatment. He was prescribed 1500 mcg of oral methylcobalamin from May 1993 until October 1993. Episodes of hypersomnia stopped during this treatment period and did not recur during the 17 months of follow-up. The baseline serum B<sub>12</sub> level was 420 pg/mL (310 pmol/L), and increased to 980 pg/mL (723 pmol/L) one month after B<sub>12</sub> administration.

This patient's response to vitamin B<sub>12</sub> therapy suggests that it was effective at preventing his recurrent hypersomnia, although a spontaneous remission was possible. Vitamin B<sub>12</sub> was pre-

sumed to increase sensitivity to environmental conditions including light stimulation, thereby increasing the patient's level of consciousness and preventing episodes of hypersomnia.

### Report #8: Patients with Depression

This study determined if there was an association between vitamin B<sub>12</sub> and folate levels and the six-month treatment outcome in patients with major depressive disorder.<sup>11</sup> Haematological indices, erythrocyte folate and serum vitamin B<sub>12</sub> levels were determined in 115 outpatients with major depressive disorder at baseline and again six months later. The 17-item Hamilton Depression Rating Scale (HDRS) was also assessed at baseline and again six months later. None of the patients in this study had deficient vitamin B<sub>12</sub> levels. In the non-response group (n=40), the average baseline vitamin B<sub>12</sub> measurement was 470.5 pg/mL (347.2 pmol/L). In the partial response group (n=34), the average baseline vitamin B<sub>12</sub> measurement was 536.6 pg/mL (396.0 pmol/L). The full response group (n=41) had an average baseline vitamin B<sub>12</sub> measurement of 594.9 pg/mL (439.1 pmol/L). Higher baseline vitamin B<sub>12</sub> levels were associated with a better outcome. There was no relationship between the haematological indices and the six month outcome. A positive correlation was found between both the vitamin B<sub>12</sub> level at baseline ( $r = 0.39, p < 0.001$ ) and on follow-up ( $r = 0.26, p = 0.006$ ), and the decline (i.e., improvement) in the HDRS score during six months of treatment.

The authors concluded that the serum level of vitamin B<sub>12</sub> may correlate with recovery from major depression. They speculated that patients might need more vitamin B<sub>12</sub> because of lower intakes of vitamins from food or impaired assimilation from the gastrointestinal tract, higher metabolic rates, issues in monoamine synthesis, and/or the elevations of homocysteine leading to excitotoxic reactions within the brain.

### Report #9: Survey of 1,000 patients for B<sub>12</sub> levels

This study involved a total of 1,000 individuals, aged 75 years or older living in their homes and registered with three gen-

eral practitioners in Banbury, Oxfordshire, England.<sup>12</sup> Deficient serum vitamin B<sub>12</sub> concentrations were identified in approximately 13% (125) of study subjects and were associated with memory impairment and depression. These subjects had serum vitamin B<sub>12</sub> levels <180 pg/mL (133 pmol/L). After adjusting for various parameters (age, sex and smoking), subjects with serum vitamin B<sub>12</sub> or holotranscobalamin (holoTC) in the bottom compared with top quartiles had a 2-fold risk (OR = 2.17; 95% CI 1.11-4.27) and a 3-fold risk (OR = 3.02; 95% CI 1.31-6.98) of cognitive impairment, respectively. The mean vitamin B<sub>12</sub> levels in the bottom two quartiles were 169.4 pg/mL (125 pmol/L) and 251 pg/mL (185 pmol/L) respectively. Absence of ankle tendon jerks was also associated with low vitamin B<sub>12</sub> status.

Treatment with vitamin B<sub>12</sub> (1,000 mcg hydroxocobalamin IM) once each month for 3 consecutive months corrected the biochemical abnormalities, but had no effect on any of the clinical measurements. In older individuals without anaemia, low vitamin B<sub>12</sub> concentrations were associated with cognitive impairment and missing ankle tendon jerks.

### Report #10: 107 Patients without Cognitive Impairment

This study involved 107 community-dwelling subjects aged 61-87 years without cognitive impairment at enrollment.<sup>13</sup> It was a prospective study that assessed the relationship between markers of vitamin B<sub>12</sub> status and brain volume loss over a 5-year period. All subjects were assessed annually by clinical examination, magnetic resonance imaging scans, and cognitive tests. Blood was drawn at baseline for measurement of serum vitamin B<sub>12</sub>, transcobalamin (TC), holotranscobalamin (holoTC), methylmalonic acid (MMA), total homocysteine (tHcy), and serum folate. Brain volume loss was greater among those with lower serum vitamin B<sub>12</sub> and holoTC levels and higher plasma tHcy and MMA levels at baseline. Linear regression analysis showed that associations with vitamin B<sub>12</sub> and holoTC remained significant after adjustment for various parameters

(i.e., age, sex, creatinine, education, initial brain volume, cognitive test scores, systolic blood pressure, ApoE epsilon4 status, tHcy, and folate). Increased rate of brain volume loss (odds ratio 6.17, 95% CI 1.25-30.47) was associated with vitamin B<sub>12</sub> in the bottom tertile (< 417.3 pg/mL; <308 pmol/L).

The authors concluded that low vitamin B<sub>12</sub> status should be investigated as a treatable cause of brain atrophy and of apparent subsequent cognitive impairment in the elderly.

### **Purported Mechanisms of Action for Vitamin B<sub>12</sub>**

My clinical experience and the above-noted reports suggest the following: first, serum levels of vitamin B<sub>12</sub> that are not “classically” deficient by current laboratory standards are associated with neuropsychiatric signs and symptoms not limited to declines in cognitive functioning (i.e., neurological deficits), tiredness, affective disorders, psychosis, insomnia/sleep-wake disturbances, and even brain volume loss; and second, a variety of neuropsychiatric signs and symptoms improve when serum vitamin B<sub>12</sub> levels are optimized or markedly increased following vitamin B<sub>12</sub> treatment.

Vitamin B<sub>12</sub> participates in the production of S-adenosylmethionine (SAM), a donor of methyl groups, and therefore it plays a decisive role in the functioning of the neuropsychiatric system. An adequate production of SAM facilitates the formation of phospholipids that comprise neuronal myelin sheaths and cell receptors,<sup>14</sup> and the synthesis of monoamine neurotransmitters.<sup>14,15</sup> Insufficient vitamin B<sub>12</sub> would decrease the production of SAM, which would impair methylation and, consequently, impair the metabolism of neurotransmitters, phospholipids, myelin and receptors.

Therapeutic vitamin B<sub>12</sub> supplementation might also lower plasma and brain levels of homocysteine, which might mitigate, reverse, and potentially normalize damaged brain neurons. Elevations of homocysteine can cause neuronal injury by augmenting neuronal calcium influx, contributing to oxidative stress,<sup>16</sup> activating N-methyl-D-as-

partic acid channels that stimulate glutamate excitotoxicity,<sup>17</sup> lowering cerebral concentrations of N-acetyl-aspartate,<sup>18</sup> and inducing cerebral mitochondrial dysfunction.<sup>19</sup>

Four interrelated mechanisms for vitamin B<sub>12</sub>'s therapeutic benefits were highlighted by Kaplan et al<sup>20</sup> when delineating the potential reasons by which vitamins and minerals influence mood. Supplemental vitamin B<sub>12</sub> might correct for inborn errors of metabolism. Pauling,<sup>21</sup> Newbold,<sup>8</sup> and Ames<sup>22</sup> reasoned that micronutrients, which would include vitamin B<sub>12</sub>, are required to increase coenzyme concentrations and therefore correct defective enzymatic activity by enabling abnormal chemical reactions to proceed normally. Another mechanism involves the correction of deficient methylation. Methylation deficiency has been described in the literature to be responsive to IM injections of vitamin B<sub>12</sub> (as cyanocobalamin) in a patient with schizophrenia,<sup>23</sup> and has been identified as being part of the pathogenesis of schizophrenia.<sup>24</sup> A further mechanism involves the correction of altered gene expression. It is well established that nutrients influence genetic expression. Genotyping identified transcobalamin II (TCNII) gene variants among community-dwelling older women.<sup>25</sup> These gene variants lead to decreased vitamin B<sub>12</sub> availability (i.e., tissue vitamin B<sub>12</sub> deficiency), leading to reduced energy metabolism, and contribute to frailty pathology. It is possible that TCNII gene variants exist among individuals presenting with various neuropsychiatric signs and symptoms. Vitamin B<sub>12</sub> supplementation might modify the TCNII genes (and possibly other vitamin B<sub>12</sub> dependent genes) that depend on sufficient vitamin B<sub>12</sub> levels and therefore modify the phenotypic expression of the implicated genes.

An additional mechanism reasons that micronutrients might resolve long-latency deficiency diseases. It has been argued that many chronic diseases (e.g., cancer, cardiovascular disease, and central nervous system degeneration) are long-latency effects.<sup>26</sup> Kaplan et al<sup>20</sup> cite the development of depression and bone density loss as an example of a long-latency

disease since it occurs many years following inadequate calcium absorption. With respect to vitamin B<sub>12</sub>, perhaps some patients who present with neuropsychiatric signs and symptoms do so after years of vitamin B<sub>12</sub> debt. This might explain why a disproportionate amount of patients with clinical features of vitamin B<sub>12</sub> debt tend to be older as opposed to younger. However, I have seen young patients with clinical features of vitamin B<sub>12</sub> debt as well. This mechanism is questionable since early childhood neuropsychiatric symptoms can result from suboptimal vitamin B<sub>12</sub> status (e.g., due to dietary factors, gastrointestinal factors, and/or some other reasons), and would therefore be a short- and not long-latency effect.

One more mechanism that might account for some of vitamin B<sub>12</sub>'s benefits has to do with its purported anti-inflammatory effects. It is known that vitamin B<sub>12</sub> debt might lead to neurologic damage since deficiency in rats has been associated with increased tumour necrosis-alpha (TNF-alpha) and decreased epidermal growth factor (EGF), an important neurotrophic agent.<sup>27</sup> Supplemental vitamin B<sub>12</sub> (in the form of methylcobalamin) has been shown *in vitro* to blunt inflammatory cytokine production in patients with rheumatoid arthritis.<sup>28</sup> While preliminary, vitamin B<sub>12</sub> might reduce inflammation by modifying the levels of TNF-alpha and EGF within the body and perhaps within the brain as well.

**Table 2** (p.85) highlights the biochemical reasons (underlying mechanisms) for vitamin B<sub>12</sub>'s therapeutic effectiveness.

### Evaluating Patients with Neuropsychiatric Signs and Symptoms

In addition to hypothesis-driven physical examination, all patients presenting with neuropsychiatric signs and symptoms should have their fasting serum vitamin B<sub>12</sub> levels tested. I created/adapted an evaluation scheme by drawing from my clinical experience and combining a published guideline<sup>1</sup> with vitamin B<sub>12</sub> laboratory reference ranges from several medical laboratories in Ontario. **Table 3**, (p.85) presents a diagnostic process to consider when reviewing serum vitamin B<sub>12</sub> levels.

With respect to **Table 3**, urinary methyl-

malonic acid (uMMA) testing can identify tissue vitamin B<sub>12</sub> deficiency when serum levels are considered normal by conventional laboratory standards.<sup>29-31</sup> While I have not found a large percentage of patients to have elevated uMMA levels (reflecting tissue vitamin B<sub>12</sub> deficiency), I routinely requisitioned this test to investigate this possibility.

### Treatment Options

Prior research does support a clinical trial of vitamin B<sub>12</sub> in patients with neuropsychiatric signs and symptoms.<sup>32</sup> Hydroxocobalamin and methylcobalamin are the forms of vitamin B<sub>12</sub> that I administer for therapeutic purposes. I tend to rely exclusively on methylcobalamin when a patient presents with neurologic abnormalities, and use a combination of methyl and hydroxo forms when neurologic and psychiatric abnormalities are present. There is evidence supporting the use of methylcobalamin for a variety of neurological diseases, such as Alzheimer's disease,<sup>33,34</sup> Bell's palsy,<sup>35</sup> and multiple sclerosis.<sup>36</sup> While there is proof that an oral dose of cyanocobalamin (1,000 mcg daily for 3 years) can effectively treat patients with pernicious anemia,<sup>37</sup> my clinical experience has shown it to be inferior to the other forms of vitamin B<sub>12</sub>. A report did demonstrate a greater rise in the baseline serum vitamin B<sub>12</sub> level following parenteral hydroxocobalamin (106% increase) compared to parenteral cyanocobalamin administration (78% increase).<sup>38</sup> Parenteral forms of vitamin B<sub>12</sub> outperformed oral (43% increase) and sublingual (34% increase) cyanocobalamin in the same study. Methylcobalamin is believed to be effective whether it is administered parenterally or orally because positive clinical results have been reported irrespective of the method of administration.<sup>35</sup>

I have not observed any side effects or toxicity from methylcobalamin. The only rare side effect from hydroxocobalamin is an acneiform exanthema, particularly in women.<sup>39</sup> The lesions consist of loosely disseminated small papules or papulopustules on the face, the upper parts of the back and chest, and can spread to the upper arm. They go away

within a week after discontinuing regular injections and/or oral supplementation.

Although IM injections are clinically more efficacious than oral forms of vitamin B<sub>12</sub>, the frequency, dose, and method of administration must be individualized to each patient. Some patients respond clinically to 1,000 mcg IM of either form each month, while other patients require 5,000 mcg twice each week of IM methylcobalamin to control their symptoms. A trial-and-error approach based on patient response, willingness to comply with regular IM injections, and/or the capacity to self-administer injections is needed

when using vitamin B<sub>12</sub> therapeutically.

Here, I present two cases from my clinical practice showing the benefits of maintaining high serum levels of vitamin B<sub>12</sub>. Written consent was obtained from these patients for publication of this report.

### Case #1

A 47-year-old male presented to my private practice several years ago. He first started having anxiety symptoms 20 years ago coupled with obsessive compulsive behaviours. He would often drive to and from locations worrying about hitting someone,

**Table 2.** Purported mechanisms of action for vitamin B<sub>12</sub>

1. Increases S-adenosylmethionine, which participates in the formation of phospholipids that comprise neuronal myelin sheaths and cell receptors, and the formation of monoamine neurotransmitters
2. Lowers plasma and brain levels of homocysteine, which might mitigate, reverse, and potentially normalize damaged brain neurons
3. Corrects inborn errors of metabolism
4. Corrects deficient methylation processes
5. Corrects altered gene expression
6. Resolves long-latency vitamin B<sub>12</sub> debt (?)
7. Anti-inflammatory properties

**Table 3.** Evaluating serum vitamin B<sub>12</sub> results in patients with neuropsychiatric signs and symptoms

Serum Vitamin B <sub>12</sub> Result	Further Testing	Intervention
< 149 pg/ml (110 pmol/L)	Search for underlying causes which might include anti-parietal, anti-intrinsic factor antibody testing, gastroscopy, and rule-out malabsorption	Treat with vitamin B <sub>12</sub>
149-400 pg/ml (110-295 pmol/L)	Urinary methylmalonic acid to identify tissue vitamin B <sub>12</sub> deficiency	Empiric trial with vitamin B <sub>12</sub>
> 400 pg/ml (> 295 pmol/L)	Not required	Empiric trial with vitamin B <sub>12</sub>

or that he had in fact hit someone with his car. He would also worry excessively about having cancer and other diseases. His symptoms became so bad that at 34 years of age he had a nervous breakdown. The patient was on zoloft® (sertraline hydrochloride) at a dose of 75 mg daily and had used antidepressants for 13 years. The Zoloft®, according to his report, improved his symptoms by about 80%. He had an initial Beck Anxiety Inventory (BAI) score of 28, placing him in the “severe anxiety” category. All laboratory tests were normal (red blood cell magnesium and folate, ferritin, fasting plasma glucose, and complete blood count). His serum vitamin B<sub>12</sub> result was above normal at 343 pg/mL (253 pmol/L), but not optimal by my standards.

On December 11th, he was given an intramuscular injection of 5,000 mcg of vitamin B<sub>12</sub> (methylcobalamin). He was also prescribed 5 mg of oral methylcobalamin to take daily. On January 22nd, he had his second follow-up appointment. He could not believe the improvement. He was able to reduce the Zoloft® to 50 mg, and noted that his anxiety seemed to be well controlled. His BAI score decreased to 11 (mild anxiety). The patient’s plan was to wean off the zoloft® over the next few months.

On March 28th, another serum vitamin B<sub>12</sub> test was done. His level increased to greater than 1,762 pg/mL (1,300 pmol/L). He returned for another follow-up on September 17th and reported having had a stressful summer. Even though he had plenty of worries (selling his home, moving to a new home, and trying to have a baby), he was able to wean himself off his medication during the month of May. This was the first time in 13 years that he was able to discontinue mainstream antidepressant medication and feel relatively normal and symptom free.

## Case #2

This 49-year-old female patient presented to my clinical practice. She described herself as being “Type A” while working in a high-pressure advertising position for the past 23 years. Two years prior to my con-

sultation, she had an episode where words became blurry on her computer screen, she could not grab things with her hands, and she could not speak. She recalled that during the episode, stop signs appeared backwards and she could not even remember her dog’s name. A neurologist diagnosed the patient as having had a transient ischemic attack (TIA), even though the episode lasted for a couple of days. She recounted similar, albeit smaller episodes, a few months prior to my consultation. A computed tomography scan revealed no space-occupying lesion or focal abnormalities and the electroencephalogram result was normal. Physical examination revealed no abnormalities or neurologic deficits. She had difficulty remembering three words that I asked her to repeat five minutes later. I explained to the patient that I wasn’t sure about her diagnosis. I mentioned that her vitamin B<sub>12</sub> status might be implicated in the genesis of her neurologic symptoms.

The patient’s serum vitamin B<sub>12</sub> result was 290 pg/mL (214 pmol/L) and not optimal according to my standards. I administered an IM injection of 1,000 mcg hydroxocobalamin and told the patient to return in 10 days for another injection. A second injection was given, but this time the dose was increased to 1,500 mcg. About one month after the initial consultation (end of February), the patient returned for a third injection. She felt about 80% better, and noticed that she could remember events and articulate her thoughts better. Other symptoms remitted as well, which included numbness, tingling, and dizziness. She was given another injection of 1,500 mcg during the visit. She returned in early March for a follow-up visit. She maintained her 80% improvement level and was given another injection at 1,000 mcg of hydroxocobalamin. She also brought serum vitamin B<sub>12</sub> results from another clinician, and her level increased to greater than 2,000 pg/mL (1,476 pmol/L) since commencing treatment.

About one month later, in early April, the patient returned for another visit. She noticed a regression of her symptoms by about 20%, as her speech issues were return-

ing. I gave the patient an injection of 1,500 mcg (1,000 mcg hydroxocobalamin and 500 mcg methylcobalamin). Two weeks later, she came in for another injection and felt back to her original improvement level. Since that time, the patient comes every two weeks and feels that her symptoms are kept at bay from receiving IM injections of vitamin B<sub>12</sub>. It should also be noted that the patient had symptoms of mild anxiety when she first presented. She scored a 14 on the BAI, placing her in the "mild anxiety" category. About 5 weeks after vitamin B<sub>12</sub> therapy commenced, her BAI score decreased to a 6, which is essentially normal.

## Conclusion

Clinicians may wish to re-evaluate the importance of lower-than-optimal serum vitamin B<sub>12</sub> levels, pursue additional testing such as uMMA, and consider the potential benefits of vitamin B<sub>12</sub> treatment.

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