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Biochemical Context and Clinical Use of Vitamin B12

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For years I have prescribed vitamin B12, administered orally, sublingually, or by injection. I have used it for a number of disorders, none of which were autism until 1999. In the past I referred to "B12" in a generic sense, assuming that there was no difference clinically between using any of its three easily available forms: cyanocobalamin, hydroxycobalamin, and methylcobalamin. Now, four years after beginning to treat autism with "B12" I hold a very different view, that view being *the methylcobalamin form of B12 holds the greatest promise for treating children on the autistic spectrum.*

Though methylcobalamin has never been studied for its effects on autism, this presentation will demonstrate that the literature cites many studies performed on humans, animals, or in laboratory settings that indicate positive results from several disorders that share similar symptoms or pathophysiology. The results of my study using injectable methylcobalamin for 85 children who carry the diagnosis of Autism, PDD, or Asperger's syndrome will be presented. A literature review will discuss the profound effects methylcobalamin has on the central and peripheral nervous systems, the cellular and humoral immune systems, on sleep-wake cycles, and on detoxification biochemistry. Methylcobalamin's biochemistry and its key role in methylation will be discussed as it applies to the formation of purines, pyrimidines, and nucleic acids. An attempt will be made to present a plausible hypothesis why "methylcobalamin loading" spares tetrahydrofolate and methyl reserves, thereby resulting in increased DNA and purine synthesis and their secondary biochemical reactions, total body transmethylation reactions, and detoxification biochemistry.

The DAN movement continues to gain momentum among the scientific and lay communities validating that autism does have a strong biological component that can be manipulated for the benefit of those afflicted. The DAN Manual is replete with references documenting reasons why DAN Practitioners who treat children from this biological/biochemical paradigm often obtain results. Unfortunately the results reveal varying degrees of mixed successes and failures. It is possible that our failures and/or limited degrees of success are at least partially due from the fact that we are just now beginning to understand some of the key biochemical pathways involved in our children's bodies. So much more research needs to be done to predict which children may respond to which therapies. Unfortunately none of the children's bodies have read the literature or the biochemical textbooks!

Methylcobalamin therapy is one such avenue that needs to be explored. The biochemistry of B12 (also known as "cobalamin") with its scientific conclusions shares a consensus opinion among scientists as to its mechanism of action. B12/cobalamin has a complex ring structure with an ion of cobalt found at its core. It can only be synthesized

by microorganisms and would pose a problem for vegans to avoid a deficiency condition except for food contamination that is ubiquitous and cannot be avoided. Dietary sources are richest in liver and yeast. A substance known as intrinsic factor, derived from the parietal cells in a healthy stomach, are required for absorption to take place in the distal portion of the small intestine, the terminal ileum. Once absorbed, Transcobalamin II carries cobalamin to the liver and tissues. In the liver, cobalamin is stored by attaching to Transcobalamin I. Cobalamin is unique in its ability as a water-soluble vitamin to be stored in the liver rather than being quickly lost from the body.

Three forms of cobalamin exist: cyanocobalamin, hydroxycobalamin, and methylcobalamin. The cyano form is the most common form, the least expensive commercially available form, but it is not natural to the body. Hydroxcobalamin is primarily found in the cytoplasm where it is converted into its active coenzyme forms: adenosylcobalamin coenzyme (desoxyadenosylcobalamin coenzyme) and methylcobalamin coenzyme. Adenosylcobalamin coenzyme moves into the mitochondria and remains fairly stationary in that location while methylcobalamin coenzyme is the cobalamin coenzyme form that either remains in the cytosol or is returned to the plasma for transport to other tissues.

In the mitochondria, adenosylcobalamin coenzyme acts in concert with the enzyme methylmalonyl-CoA mutase on the substrate methylmalonic acid to form succinic acid. Succinic acid is an important component of the Krebs cycle and gluconeogenesis. It is plausible, though not proven, that the frequent reports of "increased energy" clinicians hear from patients receiving B12 injections may partially be the result of this biochemical pathway. Another possible reason could be the role of adenosylcobalamin coenzyme in the mitochondria and the mitochondria's primary role in energy metabolism that begins with glucose and ends in the formation of ATP. From my study, it is possible that this glucose-inducing function supplying increased fuel to the brain was one of the reasons parents frequently reported higher cognitive abilities in their children.

The hydroxycobalamin/methylcobalamin coenzyme reactions are more complicated. First, in the presence of adequate hydroxycobalamin and the enzyme methyl-tetrahydrofolate reductase, the methyl group from methyl-tetrahydrofolate is transferred to hydroxycobalamin to become methylcobalamin coenzyme. Notice that two things are happening at once. First, methylcobalamin coenzyme, in the presence of the enzyme methionine mutase, immediately passes its newly acquired one-carbon methyl group to homocysteine to regenerate the essential amino acid methionine. Methionine is then quickly converted to S-adenosylmethione (SAM), a key player in the body's overall methylation biochemistry. Second, methyl-tetrahydrofolate, by losing its one carbon methyl group to methylcobalamin, now becomes tetrahydrofolate. It is this end product, tetrahydrofolate that is vital to the formation of purines, pyrimidines, and nucleic acids.

Cobalamin/"B12" deficiency leads to three problems. First, when adenosylcobalamin coenzyme is deficient, the substrate methylmalonic acid cannot be converted into succinic acid. Therefore levels of methylmalonic acid with continue to increase and spill over into the urine, a phenomenon known as methylmalonic aciduria. Second, when the methylcobalamin coenzyme is deficient, the substrate homocysteine cannot be converted to methionine. Therefore levels of homocysteine will continue to increase and may be seen in the blood or urine resulting in homocystinemia and homocystinuria respectively.

phenomenon known as "folate trapping" occurs when hydroxycobalamin is deficient in the presence of adequate methyl-tetrahydrofolate. When this situation occurs, the methyl group on methyl-tetrahydrofolate is trapped because "it wants to leave (to become tetrahydrofolate) but can't get away".

Between May 2002 and March 2003 I obtained data on 85 children with the diagnosis of Autism, PDD, or Asperger's syndrome. The study was an open trial using injectable methylcobalamin. Children ranged in age from 2 to 19 with the majority between ages 3 and 6. The injections were started when the children were stable and not making other significant changes to their therapies, either biological or non-biological. Follow-up was done every 6 weeks with me, either in person or by telephone. Parents were instructed to write a letter describing what they saw happening with their children. These letters from parents were to be *spontaneous* and written "*in their own words*". Therefore the parent's *responses were not "directed" by a questionnaire.* The parents were instructed that conclusions or summary statements were all right to give but only if they gave as many specific examples as possible describing why they arrived at the conclusions that they did.

Of the 85 children included in the study, 71 were males and 14 were females. Fifty-one males (72%) and 12 (86%) females responded. (The number of females was probably too small for the percentage of responders to be meaningful.) Approximately 50% of the parents reported 15 or more symptoms improved. Sixty-seven urinary MMA's were performed of which 81% were negative in the total group of 67 and 80% were negative in the responders group. Forty-nine homocysteine levels were performed of which 90% were negative in the total group of 49 and 92% were negative in the group of responders. Therefore, it was my conclusion that the current "gold standard" lab tests documenting B12 deficiency as we presently define it has no predictive value as to which children may or may not respond to methylcobalamin therapy.

The "Top Ten" symptoms parents reported had improved are as follow: a) Language and Communication 71%; b) Awareness 65%; c) Cognition and Higher Levels of Cognition and Reasoning 52%; d) Engagement 43%; e) Eye Contact 37%; f) Better Behavior 35%; g) More Focused 35%; h) Greater Understanding 35%; i) Vocalization 35%; j) Trying New Things 33%. Other significant and surprising symptom improvements included many parents stating that their child: "Was much happier, much more affectionate (even if her or she already was affectionate), much more interactive, calmer, more resilient to changes in routines; had more spontaneous speech, began to use pretend play or fantasy, was able to finally sit at the table with the family and/or sit and attend to a task", etc. There were over 100 different symptom improvements parents reported (for a complete list, see the slide presentation in this syllabus). Side effects were few; the primary one of hyperactivity was reported in 10%. The second most common problem was sleep disturbance, this being reported in 6% of the children. Often giving the injections in the morning instead of at bedtime alleviated this problem. With only one exception, parents stated that the positives so far outweighed the negatives that they would deal with the negatives, e.g. hyperactivity. The one exception was a child who responded positively to over 20 symptoms but developed a severe sleep problem over a period of 6 weeks.

colleagues. My final decision, for several reasons, was to perform the original study using an injectable form. The literature admits that *the absorption of B12 is a "complex process" involving numerous physiological and biochemical steps.* These steps include binding to saliva, formation of intrinsic factor from healthy gastric parietal cells, proper stomach acid release, proper pancreatic protease release, a healthy terminal ileum, the appropriate mix of intestinal microorganisms, enterocytes properly functioning, etc. As I contemplated our children, it was my conclusion that most of them chew poorly and therefore would have minimal salivary binding of cobalamin. Hundreds of nutritional analyses gathered from this population have repeatedly demonstrated poor nutritional status with inadequate amounts of protein, carbohydrate, and essential fatty acids, the required precursor building blocks of healthy cells. Therefore there was no guarantee that the children would be able to meet the requirements necessary for "functional release" of gastric acid or intrinsic factor. Also, due to the belief shared by DAN practitioners that inappropriate functional release of pancreatic enzymes often exists (consider the Repligen study and the positive benefit of secretin in some children), there was no way to insure adequate digestive enzyme function. As previously demonstrated and/or continues to be documented by the work of Wakefield, Krigsman, and Buie, the terminal ileum is frequently inflamed and demonstrates varying degrees of ileitis. This finding alone was enough to exclude the oral route of administration as a valid "initial step" in determining the potential effectiveness of methylcobalamin therapy for my study. Other factors I had to consider included dysbiosis and the mix of microorganisms in the terminal ileum that may interfere with my ability to know the "dose absorbed" by the child relative to the "dose produced" by microorganisms and/or the "dose administered" by me. Therefore, it was my strong opinion then (and even stronger now) that until I answered the first question definitively – does methylcobalamin play a vital role in the autistic population? – that these multiple variables inherent to the gastrointestinal tract, variables that were impossible to predict who suffered from them and variables that were impossible to consistently control due to many factors, must be bypassed by injections. It was also my strong conviction that unless the dose and route of administration were fairly free of variables, there would be no way to interpret the data to predict optimum dosing or to evaluate a child's response, either positive or negative.

Once I decided to use injectable methylcobalamin, the next dilemma that needed to be addressed was *whether to use the intramuscular, intravenous, or subcutaneous route of administration.* Initially I used both the intramuscular and/or subcutaneous routes. However, within 6 to 8 weeks it was my "impression" that I was getting a higher response rate in the group of children that were using the subcutaneous route of administration. Hypothetically, *subcutaneous injections may produce a "slow time-release" process, allowing a "leaching effect"* of the methylcobalamin. This theoretically could allow a "relatively higher dose" of the substance to remain in the body for longer periods of time if this was compared to the in intramuscular or intravenous routes of administration. One reason for this is that the kidneys are known to quickly clear any excess cobalamin. Because cobalamin is a red substance, I have occasionally been called by panicking parents reporting "red urine" in their child's urine who were worried the child was bleeding. I have never seen red urine with the subcutaneous route of administration but I have seen it infrequently with intravenous and intramuscular administration. Formal research will need to be conducted to determine whether or not my theory is valid.

seen in detail on the slides that follow. It should be noted that *this protocol is in a dynamic state of change* as I continue to search for "the optimum dose and the ideal frequency of injections". When I advised parents to give doses lower than 75 mcg per kilogram, there was a lower percentage of responders and there was a different "mix" of symptoms improved. Parents no longer seemed to report improvements from the "top 10" symptom response list that accompanies my higher dose protocol. Instead, there were only minor symptom improvements, e.g. "he seems to have more energy". Most parents that stopped the injections because they did not see what they believed to be significant degrees of improvement usually were on the phone within 2-4 weeks begging to restart the injections because their children regressed. The most common "regressions" reported were language, awareness, and cognition – these were also my "Big Three" -- the symptoms most commonly reported to improve!

The question arises: "Is there any research to support any of my findings or hypotheses?" Fortunately the answer is a resounding "yes" as shown from the references cited. It should be noted that hundreds more references are available but only those necessary to complete this presentation are listed. A few pertinent articles with key points are important to draw your attention to and discuss. Ikeda[10] demonstrated that **communication, cognition and intellectual functions, and emotion** in Alzheimer patients were improved in the group that achieved the highest levels of methylcobalamin and that maintained these high levels for the longest period of time. Hall[8] discussed **methylcobalamin deficiency found in early infancy shows developmental delay, hypotonia, lethargy, poor responsiveness, and frequent seizures.** Two types of treatment responses were noted: a) the first type showed slow steady psychomotor improvement over a long period of time suggesting improvement in myelination; b) the second type showed rapid improvement within 24-48 hours of hypotonia, responsiveness, and lethargy. Yamamoto[41] suggests that transmethylation by methylcobalamin may induce functional recovery from **ischemia**. It should be noted that much conjecture has occurred regarding flow-function discrepancies in the brains of autistic children. Four articles[14, 21, 22, 37] were chosen to illustrate the possible role methylcobalamin plays in protection from **toxic agents**, e.g. from heavy metals, chemicals, and biological agents, possibly as they work through detoxification pathways involving glutathione and sulfation. Ikeuchi[11] concluded that methyl groups, induced only by the methylcobalamin form of B12, are required for **"long-lasting" postsynaptic field potential amplification.** Four references[16, 21, 38, 42] are presented to illustrate that **ultra-high doses of methylcobalamin, either oral or injectable, may result in nerve regeneration.** Akaike[1] describes chronic use of methylcobalamin's **role in the protection of cortical neurons** from cytotoxicity. Three references[8, 16, 36] are cited to present the possibility of methylcobalamin's direct and/or indirect role in **protection from demyelination and/or its potential role in remyelination.** Goto's study[7] is reviewed indicating methylcobalamin's role in the **prevention of encephalopathy.** Four references[5, 30 34, 35] are cited that definitively show methylcobalamin's role in immune enhancement. These studies document that **both the cellular and the humoral arms of the immune system are positively affected.** Funada's study[6] is reviewed indicating methylcolbalamin **may downregulate allergic responses.** Sandberg[31] discusses that **methylcobalamin is the major form of B12 present in breast milk.** Lindenbaum's study[18] discusses the **vital role of methylcobalamin in rapidly dividing tissues of the body, specifically the**

brain. The reference also addresses inherited errors of cobalamin metabolism and their management. Kira[16] and Ohta[27] report that **patients who respond to therapy may have been shown to have normal lab values prior to treatment.** Three references[11, 20, 2] have been selected to show that **the methyl form of B12 is the form most likely to result in positive responses.** Two references[8, 27] show that the **response to methylcobalamin therapy may be immediate.** Five references[10, 16, 21, 27, 38] are cited indicating that **high to ultra-high doses of methylcobalamin may be required** and/or needed to produce positive results. Three references are cited[1, 10, 16] **to illustrate that long-term chronic use may be necessary to achieve or maintain positive clinical results.** Two references[3, 10] were cited showing there were **no toxic effects or side effects, even with high dose long-term use.**

In conclusion, methylcobalamin appears to play a vital role in autistic biochemistry. I hypothesize that loading with high dose methylcobalamin spares the body's need to convert hydroxcobalamin into methylcobalamin by using methyl-tetrahydrofolate to regenerate tetrahydrofolate. Therefore the "additional" tetrahydrofolate is now available to be shunted to methiene-tetrahydrofolate to produce DNA; and directly or indirectly through methenyl-tetrahydrofolate to form purines. These "additional" purines are now available to participate in DNA formation, G-regulatory protein reactions, protein kinase reactions, and to enter into detoxification pathways. I further hypothesize that loading with high dose methylcobalamin spares the body's limited methyl reserves that are necessary to convert homocysteine into SAM and necessary to participate in general body transmethylation reactions. Loading doses also result in more regeneration of homocysteine, a prerequisite for cysteine and detoxification reactions.

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Vitamins B12, Folate, and Ascorbic Acid in Mercury Detoxification

For many years physicians have used large doses of intramuscular vitamin B12, in the form of cyanocobalamin, for treatment of chronic fatigue and fibromyalgia, a majority of patients showing at least some degree of improvement. One author wrote that, in treating thousands of patients over a period of 10 years, he had seen no serious side effects.[i]

Largely based on research from Sweden, it now appears that one of the major mechanisms of vitamin B12, when used along with other vitamin cofactors, is in bringing about a reduction in mercury levels in body tissues.

According to recently received information, elemental mercury vapor derived from dental amalgams is largely converted to methyl mercury by mouth bacteria, in which form up to 70% is absorbed into the system. Once inside body cells, including those of the nervous system, the mercury is reconverted into the inorganic form which, according to World Health Organization, is far more toxic to the nervous system than other forms of mercury.

While mercury vapor and methyl mercury readily pass through cell membranes, including the blood/brain barrier, the inorganic mercury does not readily pass through these barriers. Consequently it tends to accumulate in the tissues. Thus, inorganic mercury in the brain has a very long half life of over 20 years. (References available on request).

The rationale for use of a combination of vitamin B12 and folate is that as methylators, they reconvert the inorganic mercury to methylated form, which is more readily removed from the body. Guinea pig studies have shown that combinations of vitamin B12, folic acid, and ascorbic acid, added to guinea pig food, brought about substantial reductions in both methyl mercury and inorganic mercury concentrations in brain and liver. However, all three vitamins in combination were required for best results.[ii]

Three forms of vitamin B12 are available:

1. Cyanocobalamin, given by intramuscular injection. This requires frequent administrations at home, self-administered by the patient or some family member. It is relatively inexpensive.

2. Injectable methyl cobalamin: This is the form of vitamin B12 being administered by some physicians in Sweden, based on the fact that the "methyl" form of cobalamin is the form naturally found in the human brain. Methyl cobalamin is legally available from at least one compounding pharmacy in the U.S.A. It is expensive and requires addition of preservatives, which some patients may not tolerate.

3. Sublingual methyl cobalamin: this form appears to be well absorbed and has the obvious advantage that it can be taken orally.

Along with the vitamin B12, a relatively large dose (20 mgs) of **folic acid** is recommended. This is taken as a capsule, which requires as prescription.

For **Vitamin C**, we recommend 1,000 mgs of either buffered C or ascorbic acid, depending on the recommendation of your Woodland's physician, taken 3 times daily.

Doses may vary, according to individual needs.

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[i] Charles W Lapp, *The CFIDS Chronicle*, November/December, 1999:14-16.
[ii] NE Zorn, JT Smith, *Life Sciences*, Volume 47, 1990:167-173.