Autism References: Autism Research Directory

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Methyl-B12: Doing It Right!
Methylcobalamin Update

Disclaimer: The following manuscript regarding methyl-B12 and related subjects is the work product from my practice. The majority of the concepts and conclusions are based on my cumulative clinical experiences since first using methyl-B12 in March, 2002. Much of the methylation, transsulfuration, and methyl-B12 biochemistry described is conventional wisdom. Much of the research mentioned is universally accepted. However, some of the biochemistry and research discussed represents newer thinking, one specific example being methionine synthase’s activity in the body vs. the brain. Many of the research ideas will be proven in time. Others will need to be updated and modified. So it is with my hypotheses and conclusions. Many will stand the test of time. Others I will modify as more data are accumulated. Many are shared by my colleagues; some are not. Nonetheless, there is fairly universal agreement among those of us who are using methyl-B12 that it is a powerful treatment for children on the autistic spectrum.

OVERVIEW:
In our practice we continue to see that methyl-B12, when used correctly, is still the single most predictable treatment we have to treat children on the autistic spectrum that gives numerous global benefits at the same time. At follow-up our average number of responses during the initial 1st six week methyl-B12 Initiation Phase is 30 to 45 or more. We have now monitored well over . million doses of methyl-B12 using numerous protocols. From these data we can document that over 90% of our patients are able to demonstrate undeniable changes as a result of the shots. Of this Responder Group, approximately 20% have remarkable gains, 20% moderate gains, and the remaining 60% show only mild improvements.

We have also learned that if methyl-B12 therapy is continued for several years, its benefits are cumulative and synergistic with all the other therapies parents are using. As a general rule, we have observed that the majority of methyl-B12 responders will regress or fail to progress at the same rate if they stop their methyl-B12 shots too soon. However if their shots were given for 3 to 4 years, we have then seen many of these children be able to reduce the frequency of the shots or stop them altogether. From patients who ultimately ended up in our practice after having been treated by other biomedically-oriented clinicians, we have observed that most families had stopped their shots far too soon because they never knew how to correctly define a methyl-B12 responder by our criteria, James A. Neubrander, MD had expected too much too soon, or their child had “plateaued”. Once the shots
were restarted according to our protocol and after the child's progress wasfollowed using the evaluation forms we use, the parents once again had positiveresponses that could be documented as an undeniable effect secondary only tomethyl-B12 therapy.

**KEY SCIENTIFIC DISCOVERY:**
Dr. Richard Deth's work from Northeastern University is seminal in helping usunderstand why the methyl form of B12 produces the greatest number of globalbenefits with the strongest intensity of clinical responses, especially whencompared to patient outcomes using any other form of B12. From his work welearn that methionine synthase in the cortex of the brain has a uniqueconfiguration that makes it dependent upon the methyl group from methyl-B12such that in the cortex of the brain methionine synthase does not work as wellwith any of the other forms of B12 (cyano, hydroxy, adenosyl, glutathionyl). UntilDr. Deth’s discovery, B12 (cobalamin) was viewed as being incorporated into themethionine synthase enzyme superstructure that would undergo oxidation/reductionreactions at the B12-cobalt binding site. The B12-cobalt site is only oneof 5 functional sites (domains) on the long and convoluted methionine synthaseenzyme. The other 4 functional sites are the methyl-tetrahydrofolic acid domain,the SAM domain, the CAP domain, and the homocysteine domain.

The purpose of the methionine synthase enzyme is to transfer methyl groups.
This process begins when the B12-cobalt domain receives a methyl group frommethyl-tetrahydrofolic acid domain and subsequently hands it off tohomocysteine. When it is empty, the B12-cobalt site requires “protection” by theCAP domain so that excessive oxidation does not occur. When the cobalt atomdoes get oxidized, the SAM domain can repair it by donating its methyl group.

Dr. Deth discovered that the superstructure of methionine synthase is differentin the brain than it is in the body and that brain methionine synthase can bemissing critical “domains” or functional sites (i.e. the SAM and CAP domains).When these sites are absent, the oxidized brain B12 is actually able to dissociateand come off the methionine synthase enzyme and be replaced by a methyl-B12.

Because of this unique characteristic where the methionine synthase enzymecontinually loses its oxidized B12 in the cortex of the brain, methyl-B12 mustcontinually be replenished in order for the methionine synthase/methyl-B12complex to reach its maximum clinical potential for children on the autisticspectrum. At least in autism it is because of this phenomenon that we findourselves dealing with a relative methyl-B12 dependency more than we findourselves dealing with an actual methyl-B12 deficiency.

Because oxidative stress is present in the majority of children on the spectrum,there arises the continual need for the methionine-homocysteine-glutathionebiochemical pathway to recycle enough homocysteine back to methionine to drivemethylation reactions (in the brain this accounts for focus, attention,synchronization of brain waves, speech, language, socialization, emotion) aswell as to shunt enough homocysteine onward to become glutathione to satisfyJames A. Nebrander, MDthe body’s transsulfuration needs (quenching free radicals, decreasinginflammation, removing toxic chemicals and heavy metals from the body). In
the body this can process can be accomplished using the methionine synthase enzyme and various nutritional B12 forms and/or the betaine homocysteine methyl transferase enzyme (BHMT) and the nutrient betaine (TMG, not DMG). However, BHMT is not present in the brain. It is only found in the liver and kidney. By contrast, methionine synthase is present throughout the body and is rich in the brain. Therefore the process of methylation and transsulfuration in the brain is dependent upon methionine synthase which in turn is dependent upon the methyl form of B12. To convert other forms of B12 (cyano, hydroxy, adenosyl, glutathionyl) into methyl-B12 requires that these other forms of B12 always be available, that some “free form” for immediate use always be present by not being bound to receptors or enzymes, and that there be a uniform distribution of these other B12 forms between the body and the cortex of the brain. Only by adding the methyl form of B12 directly into the body will one be able to bypass the amount of time and kinetic energy it takes for these other forms of B12 to be converted into the required methyl form quickly enough and in adequate enough amounts to meet the demands that are continually being placed on the body by oxidative stressors.

Understanding the difference between the deficiency vs. dependency concept of methyl-B12 allows us to understand that when methyl-B12 is used at the doses needed to positively affect children on the autistic spectrum, it is being used as a pharmacologic agent, not as a vitamin to treat a nutritional deficiency. This is no different than when lithium – a nutritional mineral -- is used at pharmacologic doses to treat bipolar disorders. Patients with bipolar disorders are not deficient of lithium but they definitely are dependent upon lithium for its pharmacological, not nutritional effects. So it appears to be with methyl-B12 and autism wherein no true nutritional deficit is present but rather the children are dependent upon its pharmacological effects.

When one treats the body for “a deficiency” of B12 by giving adequate or even large amounts of any B12 form (cyano, hydroxy, adenosyl, glutathionyl, and methyl) by any delivery system other than the slow delivery subcutaneous route, very quickly the B12 leaves the plasma and attaches to B12 receptors, is transported across the cell membranes into the cells, and is ultimately incorporated into the methionine synthase enzyme. All of this is a “relatively slow” process. Any excess B12 not bound by receptors (which is the majority of B12 in any pulse therapy – IM, oral, nasal, sublingual) will quickly pass through the kidneys into the urine and be lost. In the brain B12 forms will require incorporation into the methionine synthase enzyme, a process which takes time and energy, and which subsequently must receive the addition of a methyl group from methyl-tetrahydrofolic acid (5-MTHF), a process that depends on adequate MTHFR enzyme activity and adequate dietary or supplementation of methylated folic acid precursors. Children on the spectrum frequently have mutations of the MTHFR enzyme and diets extremely limited in folic acid containing foods. Therefore, with this combination of problems that is commonly present in James A. Neubrand, MD children on the autistic spectrum, the continual need for methyl-B12 by the methionine synthase enzyme in the brain due to methyl-B12 dissociation from the
methionine synthase enzyme will not be satisfied, at least not very quickly by other forms of B12. The process of converting other forms of B12 into methyl-B12 will also require a great amount of kinetic energy all done at the body’s expense. In addition, even methyl-B12, when given in a pulse-therapy fashion, will be unable to meet the “dependency demands” of the body that requires the constant availability of methyl-B12.

By contrast, when one treats for “a dependency” of methyl-B12 by providing the slow, steady, continuous leeching of methyl-B12 from the subcutaneous tissue of the buttocks into the bloodstream, the blood is never saturated. Therefore the receptors are never overwhelmed, and the transport of methyl-B12 from the plasma to B12 receptors across cell membranes into the cells and subsequently into the methionine synthase enzyme is always operative and readily available. This slow steady process ensures that a continual supply of “just a little bit” of methyl-B12 will always be present to re-supply the methyl-B12 that has dissociated and come off the methionine synthase enzyme. The addition of the methyl form of B12 is both time and energy efficient and does not depend on the proper function of the MTHFR enzyme or adequate dietary or supplement contributions by folic acid family members.

Non-methyl-B12 forms of B12 work well to correct a true B12 deficiency. However, their actions are limited because their primary function is to be incorporated into the B12 binding site on the methionine synthase molecule. Once they are attached to this binding site, it is essentially the same as if they were “locked up in prison cell”. Once imprisoned in this manner, they are now dependent on the classical interactions of B12 with methionine synthase and methyl-tetrahydrofolic acid (MTHF), those actions being to accept the methyl group from MTHF and pass this methyl group onward to homocysteine while continually altering the cobalt-B12 oxidation/reduction state and repeating the process. “Only methyl-B12 has a key to the prison” and therefore is not bound to the prison-B12 rules. Only methyl-B12 has the freedom to bypass the need to receive its methyl group from MTHF. Only methyl-B12 has its own methyl group to pass onward to homocysteine. Therefore only methyl-B12 has the ability to act more quickly and more efficiently than other forms of B12.

THE CONTROVERSIES AND THE CONFUSION:
Overview
The most common controversies center around being told one is an overmethylator or that the child should use hydroxy-B12 instead of methyl-B12 or that the child should use “the shortcut” to recycle homocysteine back to methionine by using TMG, methionine, and SAM instead of methyl-B12. Much of this controversy is due to the results of genomic testing or not understanding that methionine-homocysteine-glutathione pathways act differently in the body than they do in the brain and that in the body they compete for dominance.

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The use of TMG
As previously discussed, methionine synthase in the brain has a different configuration than the configuration methionine synthase has in the body. Also discussed above is the fact that the enzyme TMG upregulates BHMT which is not
present in the brain but is primarily found in the liver (and kidney but to a lesser extent). This is in contrast to the enzyme that methyl-B12 upregulates, methionine synthase, which is present throughout the body but is critically important in the brain for its methylation products. **Brain methylation products result in cognition, focus, attention, brain wave synchronization, speech, language, emotion, and socialization.** Because the brain is only one part of the total body, it is important to understand that when the body as a whole perceives the need to create more methionine by adding a methyl group to homocysteine, it can do so by accepting a methyl group from methyl-B12 or by accepting one of the methyl groups from trimethylglycine (TMG). [Homocysteine + one methyl group (either from methyl-B12 or TMG) D methionine D SAM D homocysteine D repeat the cycle] Remember, it is the body’s purpose is to always create equilibrium. Therefore, when BHMT enzyme activity is upregulated by TMG stimulation to produce more methionine, the counterbalancing effect to maintain equilibrium by not overproducing too much methionine is for methionine synthase enzyme activity to be downregulated. Because the cortex of the brain at least for children on the autistic spectrum, needs large amounts of methionine synthase enzyme activity to produce cognition, language, socialization, etc., anything that decreases its activity in the body also decreases its activity in the brain. Our clinic has repeatedly documented (with rare exception) that the use of TMG blocks the desired effects of methyl-B12: cognition, language, socialization, etc., and it is not until TMG is discontinued that the child’s potential for cognition, language, socialization, etc., is able to realized to a significant degree. The before and after changes we have seen have been documented as “undeniable” improvements when compared to all other methyl-B12 protocols and when the reporting has been evaluated using the Parent Designed Report Form. **The use of SAM and methionine**

We have also documented that when on methyl-B12 according to our protocol further loading of the methionine-homocysteine pathway with SAM or high doses of methionine (greater than its nutritional requirement) frequently causes side effects or only minimal improvements. Children on the autistic spectrum have low levels of homocysteine, partially due to a poor diet but also due to increased utilization of homocysteine to form glutathione that is required to offset chronic inflammatory conditions, autoimmunity, and toxic chemical and heavy metal burdens (“oxidative stressors”). Therefore when more brain methylation products are desired (cognition, focus, attention, synchronization of brain waves, language, socialization, emotion), the addition of more substrate (excess methionine, SAM) will increase the amount of homocysteine in the body if the dose of methyl-B12 has reached its maximum capacity to transfer methyl groups. This “relative excess” of homocysteine will continue to rise if the “relative speed” James A. Neubrander, MD by which it can be metabolized and subsequently recycled back to methionine or onward to cysteine, metallothionein, glutathione, and taurine is exceeded. The biochemical result is what I call a “metabolic mess” but what parents perceive clinically as side effects. If one thinks of the methylation cycle as a pinwheel
whose arms are molecules with methionine at the top of the pinwheel and homocysteine at the bottom of the pinwheel [methionine (top) D SAM (right side) D homocysteine (bottom) D methyl-B12 (left side) D methionine (top again)], what needs to be done is to “spin” the pinwheel by “blowing” on it with methyl-B12 from the left side rather than to “load the pinwheel down” and have it become “bottom heavy” by adding extra methionine and SAM. This blowing action of methyl-B12 upregulates the methionine synthase activity, not only in the body but also in the brain to produce the clinical benefits parents want to see. It is far more important to recycle whatever amount of homocysteine is already present in the body by pushing methyl-B12 and methionine synthase activity to its limit than it is to add more substrate (i.e. excess methionine, SAM) that just clogs up the system. This maximum recycling process can occur when adequate amounts of methyl-B12 are present to treat the “dependency” condition. It should be noted that excess amounts of methyl-B12 will not increase the clinical benefits once the methyl-B12 dependency needs have reached maximum capacity. This dependency phenomenon is not to be confused with a true B12 deficiency which will not be present after the few first methyl-B12 injections! Though I hesitate to use SAM at all anymore, I do recommend that nutritional amounts of methionine be achieved by every child from diet and supplements because methionine is an essential amino acid. Methionine is found at the headwaters of the detoxification system and critical to life. Therefore I approve the judicious use of methionine at nutritional levels that will aid the production of adequate amounts of homocysteine (not “relative excesses” of homocysteine that exceed methyl-B12’s and methionine synthase’s ability to process it). This proper balance allows the methylation cycle to proceed at maximum capacity and create adequate amounts of SAM whose methyl groups are needed by the brain.

The use of folinic acid

In our practice we always start with methyl-B12. Therefore our side effect rate from the addition of folinic acid at a later time is approximately 25% to 30%. We find that we when a child is on methyl-B12, the child does not need the high doses of folinic that were used in the original study by Jill James (James SJ, et. al., Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am. J. Clinical Nutrition, Dec 2004; 80: 1611–1617.) Based on the weight of the child our current dosing requirements for the majority of the children usually ranges between 200 mcg to 800 mcg. The use of folinic acid, unlike the use of TMG, SAM, or excessive methionine does not interfere with the effectiveness of methyl-B12.

The use of 5-MTHF, BH4, DMG, and other methylators

Each of these products has value and does not seem to block the benefits seen with methyl-B12 therapy as does TMG. In general, with methyl-B12 in place, 5-MTHF is probably not necessary or only minimally so. There is some evidence James A. Nebrannder, MD that 5-MTHF may be able to reverse itself and go back through the MTHFR enzyme though only to a very small degree. BH4 (tetrahydrobiopterin) has been said to possibly have value with A1298C MTHFR mutations but too little evidence exists for anyone to make strong statements about this possibility. It is important
to note that DMG does not affect the BHMT enzyme as does TMG because DMG is not a substrate for the BHMT enzyme. It is important to understand that once TMG gives away one of its methyl groups to homocysteine, what is left is DMG (Tri-methyl-glycine D Di-methyl-glycine). We have not seen DMG block methyl-B12’s clinical responsiveness as we continually see happen with TMG. Many parents have heard the DMG has been shown to help speech and language. This is true but one must consider the history of this discovery as it relates to methyl-B12 therapy and the biochemical pathways involved. DMG enters the one carbon biochemistry pathway (the folic acid pathway), and as it is metabolized and changed it eventually presents itself to the MTHFR enzyme, is reduced, becomes methyltetrahydrofolic acid (5-MTHF), donates this methyl group to methyl-B12 to become methyl-B12. It is this methyl-B12 that is famous for working with methionine synthase to “spin the pinwheel” to form SAM. One of the things the methyl groups do that SAM donates is to create language. Therefore the most likely reason that DMG was found to help language was because it eventually was metabolized to methyl-B12! Too many other methylation products exist to discuss in detail at this time though none of them seems to interfere with methyl-B12. Genomics, over-methylators, the use of hydroxy-B12 or cyano-B12, and the antelope herd

Due to the results of genomics testing, parents are often told several things they should give to their child and several things they should avoid. The reason that parents and clinicians should still use great caution with interpretations and subsequent treatments based on genomics testing is because the results of the tests do not necessarily prove that a child will do better avoiding or taking certain things or that a child will do worse avoiding or taking other things. The purpose of genomics testing is to document genetic polymorphisms to help a person understand his/her risk of developing or expressing certain diseases. To understand this process, it is important to review a few of the basic terms that are used when discussing genomics. A polymorphism is the presence of two or more distinct phenotypes in a population due to the expression of different alleles of a given gene, as human blood groups A, B, AB, and O. A phenotype is the expression of a specific trait, such as stature or blood type, based on genetic and environmental influences. An allele is any of several forms of a gene, usually arising through mutation that are responsible for hereditary variation. A gene is the basic physical unit of heredity composed of a linear sequence of nucleotides along a segment of DNA that provides the coded instructions for synthesis of RNA, which, when translated into protein, leads to the expression of hereditary character. A nucleotide is any of a group of molecules that, when linked together, form the building blocks of DNA or RNA. Nucleotides are composed of a phosphate group, the bases adenine, cytosine, guanine, and thymine (or uracil in RNA), and a pentose sugar. The bases have specific partners with whom they James A. Neubrander, MD

pair with under normal conditions. In DNA the base pairs are cytosine:guanine and adenine:thymine. In RNA the base pairs are cytosine:guanine and adenine:uracil. A single nucleotide polymorphism (commonly known as a “SNP”) is the substitution of one base by another base due to a mutation. When
this occurs, abnormal proteins with reduced ("slowed") enzyme activity are formed. Common examples talked about in the autism community include mutations in the enzyme methylenetetrahydrofolic acid reductase (MTHFR) where cytosine is substituted at position 677 (chromosomal locus) on the DNA molecule by thymine (C677DT) or adenine is substituted at position 1298 (chromosomal locus) on DNA by cytosine (A1298DC). Because DNA is doublestranded, each position (chromosomal locus) consists of a base pair (dinucleotide, i.e. C-G on one strand and G-C on the other strand). When only one base pair at a specific chromosomal locus has a base pair substitution, the mutation is reported as heterozygous (SNP x 1; e.g. the normal C677 on one DNA strand and the abnormal C677 DT mutation on the other DNA strand). When both base pairs at that same specific chromosomal locus each have a base pair substitution, the mutation is said to be homozygous (SNP x 2; e.g. an abnormal C677DT mutation on one DNA strand and another abnormal C677DT mutation on the other DNA strand).

A mutation on only one DNA strand at the same chromosomal locus (heterozygous: +, -) indicates mild to moderate weakness or slowing of the enzyme while a mutation on both DNA strands at the same chromosomal locus (homozygous: +, +) indicates a moderate to strong weakness or slowing of the enzyme. What is not being stated clearly from many of the laboratories performing the tests or from many of the clinicians interpreting the tests and subsequently advising patients is that a significant percentage of the normal population already has these same mutant SNPs with minimal to no clinical significance attached to their presence. For example, C677T is present in the heterozygous form in approximately 45% of Caucasians and 20% of African Americans and not thought to be clinically significant. The homozygous form is present in approximately 12% of Caucasians and 1.2% of African Americans. (Stevenson et al., Am J Hum Genet 60:229, 1997). False positives or false negative results may occur for reasons that are multifactorial including, but not limited to genetic variants or somatic heterogeneity of the tissue sample, i.e. blood being only one type of tissue tested.

Unfortunately a “slowing” does not mean that a child cannot use a product, e.g. methyl-B12, nor does it mean that by using methyl-B12 the child will get worse. The opposite scenario is also true whereby genomics testing may say that certain products are necessary to normalize biochemical pathways because the child tested has significant single nucleotide polymorphism (SNP) abnormalities. Let me give examples of why parents and clinicians must be cautious in both their interpretation and subsequent application of genomics test results.

Recently I saw a child with multiple homozygous and heterozygous SNPs indicating that the child would have tremendous difficulty making glutathione.

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Surprisingly, by direct testing of the blood, the child had one of the highest glutathione levels I had seen in over a year! Laboratory error was not the explanation for this huge discrepancy because multiple SNPs showed problems in the glutathione production and because the child presented as a child who was not glutathione depleted.
Unfortunately the next example I will share with you arises very commonly in my practice. Very frequently parents come to me having been told their child is an over-methylator and that they should use hydroxy-B12 or cyano-B12 instead of methyl-B12. Regrettably we have seen an incredible number of children who stopped using methyl-B12 or who never started using it in the first place because of such advice by their clinician. Because a clinical trial of an agent, in this case methyl-B12, is the only way to really see how the body will handle a substance, it is our practice to initiate such a trial. It has been our observation after working with these children using various methyl-B12 protocols common to our practice, the majority of the children do show positive results with minimal to no side effects! Side effects have not been noted to be more common with the SNP positive group of children than with children who have never been tested for SNPs. Our rate of responders has also been essentially the same in the SNP positive group as it has been in the SNP-untested group. Our side effect pattern, when present, has also followed our typical diminution or resolution sequence (as stated in the Autism One 2005 handout) when the children who did not have intolerable side effects (as given by our definition in the same handout) were treated for at least 4 to 6 months.

I will end this section by describing a herd of antelope. Ninety-nine members are healthy while one member has a gimp leg. When the pride of lions begins its attack, should the ninety nine healthy antelope hang around because one of their members can’t run or should they hightail it out of there and save the herd? Here the answer is obvious. Though sad to lose one of its members, the herd must be saved! So it is with SNPs and the concept of over-methylation. Just because a SNP shows that it will have a problem with methylation does not mean that there are not hundreds of other reactions in the body that need to be methylated more, not less! This is where God and Mother Nature come in to upregulate certain pathways while down-regulating others, all the while directing the body’s biochemistry down alternative pathways here and around detours there! This will happen over time for the majority of SNP problems that are not life-threatening like PKU!

Caution

It is very unfortunate that many children who come to us have been on methyl-B12 by other clinicians, had side effects, switched to other forms of B12, lost the side effects and at the same time began to see some positive benefits. What we have found to be the case with these children is 100% of the time is that when they stopped using methyl-B12 and switched to hydroxyl-B12 and/or cyano-B12, they also started using new vitamin or herbal products at the same time. Because parents never like to see side effects in their children and because the switch from James A. Neubrand, MD methyl-B12 to hydroxyl-B12 and/or cyano-B12 caused the side effects to go away, parents attributed the benefits they were seeing to the other form(s) of B12 and not due to the simultaneous use of supplements and herbal agents which undoubtedly can lead to positive benefits. Therefore the important message to remember is that it is always possible to remove or lessen a side effect by giving a less effective or non-effective form of B12. However, this does not mean that the
other form of B12 was the reason for the benefit when other treatments were added simultaneously. Neither does it mean that greater benefits would not have been seen if the parents worked through the side effects as indicated in this paper and more completely in the Autism One 2005 document.

**THE PITFALLS:**

**Pulse therapies vs. a continuous delivery system for methyl-B12**

All pulse-therapy applications of methyl-B12 (IM, oral, nasal, sublingual) will very quickly clear any excess methyl-B12 from the body through the urine once the B12 receptors have become saturated. Because the rate of renal clearance is fairly constant in a patient, the limiting factor to how effective the clinical response will be is not due to the total dose administered but rather how quickly the B12 receptors can deliver their methyl-B12 payload from the plasma into the cells before reloading and doing it again, and how many times this can occur before the excess methyl-B12 has been cleared from the body through the urine. It is very important to understand that methyl-B12 deficiencies are very easily corrected and are DOSE DEPENDENT whereas methyl-B12 dependencies are not easily corrected and are FREQUENCY DEPENDENT and require that methyl-B12 be continually present. The only way to accomplish this using any pulse therapy delivery system is to increase the frequency, something that is impractical in the real world in which we live. Therefore, a DELIVERY SYSTEM that assures slow, steady, continuous availability of the medication, similar to an insulin pump for a diabetic, is what is required for optimum clinical effectiveness. Possibilities for this type of a delivery system include methyl-B12 pumps, methyl-B12 implants, methyl-B12 subcutaneous injections, or transdermal methyl-B12. To date pumps and implants are not available and will not become available until the research documents the effectiveness of methyl-B12 for children with autism so that insurance will pay. Unfortunately this type of research is years from completion and will require better clinical outcome studies than presently designed. Once available these treatments will not only be invasive but extremely expensive as well. Therefore there is little likelihood that most parents will use them. With that being the case, there is little financial incentive for any company to create such products. That leaves us with injectable and transdermal methyl-B12. The most attractive and logical alternative is transdermal methyl-B12 rather than the injectable form. However, our clinical research has shown this delivery system to be much less effective than subcutaneous injections. Regrettably there are vendors now making claims that their transdermal methyl-B12 is just as effective as the subcutaneous injections and they give testimonials from parents and clinicians saying how pleased they are with the transdermal form. Unfortunately this is deceptive and is just not the case at all! It appeals to a large subset of parents whose children are on the spectrum because the idea of shots is something they are afraid of. For the group of parents who will never give their child a shot, transdermal methyl-B12 is one option I believe in (though from our clinical experience the nasal pulsatile form works much better than the transdermal form even though it’s pulsatile). It is extremely disturbing that such marketing techniques divert many parents away from providing their children
with the most effective method of methyl-B12 therapy that will produce the
greatest number of global responses with the greatest intensity. We have
continued to compare all of our now more than . million methyl-B12 doses by
the same evaluation instrument, and we can say a certainty that some forms of
transdermal methyl-B12 may be better than other forms of transdermal methyl-
B12 but that no transdermal form of methyl -B12 gives the same number of global
responses, nor do the responses achieve the same intensity as can be attained
using subcutaneous injections in the adipose tissue of the buttocks.
Using higher doses of methyl B12
Using higher doses of methyl B12 than our standard dose protocol or even going
higher than our high dose protocol has been described above in the section above
entitled Key Scientific Discovery. As stated, B12 receptors have a limited capacity
for the amount of B12 they can receive, that the transport mechanism out of the
plasma into the cells has a maximum speed at which it can proceed, that the
methionine synthase enzyme has a maximum capacity for the amount of methyl-
B12 it can hold, and that methionine synthase has a limited speed at which it can
proceed. Higher doses delivered by any pulsatile form of administration (IM,
oral, sublingual, nasal) will result in any excess methyl-B12 not bound by the
receptors or incorporated into the enzyme immediately start to be eliminated
from the body with each pass of the blood through the kidneys. The process that
eliminates the excess takes only a few hours. As previously stated, though
transdermal methyl-B12 is an option, our clinical research does not indicate it to
be a viable option when maximum effectiveness for both global benefits and
intensity of response is the goal. Higher doses even with the subcutaneous route
of administration, though the preferable route for the reasons stated throughout
this paper, has the same limitations. Though methyl-B12 receptors should never
reach a saturation point with subcutaneous injections, methionine synthase may
not need more methyl-B12 than is already being provided by our protocol doses.
In our practice we have learned that somewhere between 40% to 50% of children
seem to do better when the shots are given more frequently than once every 3
days, e.g. once daily or once every 2 days. However, with few exceptions we have
been disappointed by not observing significantly increased gains when we have
used doses much higher than the protocol doses we describe with our standard
dosing pattern, whether or not the frequency was every 3 days, every 2 days, or
daily.
Combinations of methyl-B12 with other agents, e.g. NAC, folic acid, or
adenosyl-B12
As stated in previous papers I have written, the more concentrated the stock
solution, the less its surface area and therefore the slower and more consistent
the release of methyl-B12 will be into the subcutaneous tissue. This medication
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delivery system uses one of the important pharmacological principles employed
when a medication is given by implants or when a medication uses a “depot form”.
Both of these delivery systems use concentrated forms of the medication. When a
pharmacy uses my protocol stock solution of methyl-B12 at 25 mg/mL but then
combines it with anything else, unless that stock solution is also at least 25
mg/mL or stronger, due to the excess carrier solution (diluent) the total volume will be greater than necessary and will yield a final concentration much more dilute. Therefore this will negate one of the important principles for methyl-B12 effectiveness, that being to use the most concentrated stock solution in order to yield the least surface area possible. To inject NAC or folic acid mixed together into one syringe does not present a problem because we are not concerned about their final concentration. However, methyl-B12 must be injected separately! Should a child have an abnormal MMA value, weigh more than 68 pounds, the clinician can use adenosyl-B12 created from an adenosyl-B12 stock solution concentrated to 25 mg/mL. The methyl-B12 and adenosyl-B12 can then be combined into one shot because neither solution will dilute the other solution. However, this is not the case for children less than 68 pounds. For details on the use of adenosyl-B12, see the protocol section below.

**Using the same dose of methyl-B12 but from a more dilute stock solution (concentration)**

I have previously stated in this paper and in many other documents that the more concentrated the stock solution, the slower will be methyl-B12’s dissolution into the surrounding tissues. Therefore the shots will last longer and the frequency of the shots can be much less often. Also, the more concentrated the shots, the less variable the dissolution will be into the surrounding tissues. Therefore the PRINCIPLE IS MINIMAL SURFACE AREA as much as or MORE THAN TOTAL DOSE! From our clinical trials we have documented that equivalent doses of methyl-B12 made from either a 25 mg/mL stock solution vs. a 12.5 mg/mL stock solution do not yield equal clinical benefits. Logically one would think that 0.04 mL of a 25 mg/mL stock solution and 0.08 mL of a 12.5 mg/mL stock solution (both 1000 mcg of methyl-B12) would give the same results and that the results would last just as long. This is not the case. The weaker solutions consistently yielded significantly fewer results that would only last about 66% as long. Therefore more shots were required to get fewer benefits!

**Laboratory testing, serum B12 levels, interpretation of MMA and homocysteine levels, and the use of adenosyl-B12**

Frequently serum B12 levels are high-normal or high in untreated children later found to be methyl-B12 responders. The reason this occurs is most likely due to the fact that when B12 is presented to the transcobalamin receptor, the receptor is epigenetically compromised and unable to deliver B12 from the plasma into the cell fast enough or at full capacity. Therefore B12 builds up in the plasma to high levels. This phenomenon is analogous to glucose building up in a diabetic’s plasma because the glucose is unable to cross the cell membrane and get into the cell where it is needed due to an insulin problem.

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**Much confusion exists between nutritional B12 principles in general and the specific way B12 is handled in a child on the autistic spectrum.** The two most glaring examples of this misunderstanding is with homocysteine and methylmalonic acid (MMA).

Consider first homocysteine and children with autism. Classically physicians and nutritionists test homocysteine levels in the blood. Because of the methionine—
homocysteine recycling biochemical pathway, the nutritional principle states that if there is a B12 (or folic acid or B6) deficiency, homocysteine will accumulate. The reason that this is classically true in non-autistic children is because B12 from food (hydroxy-B12) or vitamins (cyano-B12) is required to exchange its hydroxyl group or cyano group for a methyl group from methylated folic acid in order to then become methyl-B12. It is this methyl group on methyl-B12, in the presence of methionine synthase, that is accepted by the homocysteine molecule to become "methylated homocysteine", more commonly known as methionine. Next it becomes SAM, then SAH, and eventually completes the cycle to once again become homocysteine, ready to repeat the cycle. If nutritionally there is not enough methylated folic acid or hydroxy-B12 or cyano-B12 to form new methyl-B12, when homocysteine needs to find a methyl group from methyl-B12 to repeat the cycle and "spin again", the homocysteine will just sit there and accumulate in the blood. Therefore one of the classic nutritional tests for B12 (and folic acid) deficiency is elevated homocysteine, not low homocysteine. However, children with autism frequently have low homocysteine levels, partly because of concurrent gastrointestinal issues with secondary malabsorption, partly because of extremely limited diets, and partly because of the significantly increased consumption of homocysteine due to oxidative stressors. The first two reasons result in low homocysteine because inadequate methionine (an essential amino acid only present from protein-containing foods), the precursor of homocysteine, is presented to the body. The latter reason homocysteine is low in these children is because 80+% of children on the autistic spectrum have been found to have significant oxidative stress. Whenever there is oxidative stress, their bodies need to quench the fire inside the cells by making glutathione. Glutathione is made from homocysteine, a process that essentially consumes itself in the process rendering homocysteine low by lab tests. Therefore when a child with autism tests low for homocysteine, it in no way indicates that they have enough folic acid, hydroxy-B12, cyano-B12, or methyl-B12. To the contrary, it usually means they do not have enough of the B12 and folic acid family and methionine from which to make an adequate supply of homocysteine and glutathione.

Now consider methylmalonic acid (MMA) and autism. Because of the classic nutritional principle, clinicians test for MMA and if elevated conclude that B12 is deficient. For individuals without autism this is often the case. However, in an autistic child the same conclusion cannot be automatically made. The reason this is so is because “food B12 (hydroxy-B12)” comes to a crossroads where approximately 50% of it is supposed to be converted to make methyl-B12 coenzyme and the other 50% is supposed to be converted to make adenosyl-B12 coenzyme. Only methyl-B12 and adenosyl-B12 become active coenzyme forms James A. Neubrander, MD and only coenzyme forms of B12 have the ability to interact with their respective enzymes to do what the body needs. One must understand that hydroxycobalamin, cyanocobalamin, and glutathionylcobalamin (not discussed in this paper) are all inactive intermediate forms of the B12 family (the cobalamin family). Therefore when an individual eats a food or takes a vitamin, the B12 from the food
(hydroxy-B12) or the B12 from the vitamin (usually cyano-B12) enters the body through the distal ileum. It then becomes methyl-B12 coenzyme by exchanging a methyl group from methylated folic acid for the hydroxyl group on hydroxy-B12 or alternatively by exchanging a methyl group from methylated folic acid for the cyano group on cyano-B12. Now focusing only on the adenosyl-B12 coenzyme, adenosyl-B12 interacts with the enzyme methylmalonic acid mutase to transform methylmalonic acid (MMA) into succinic acid. If this reaction does not occur, then MMA will build up in the plasma. Therefore the assumption from the classic nutritional point of view is that an elevated MMA means that B12 is deficient in the diet. As previously stated above, this is often the case in children with autism because gastrointestinal and dietary issues are common. However, from this line of thinking two serious errors can easily occur when considering which children need treatment with methyl-B12 and/or adenosyl-B12.

\textit{The first error} is when the MMA level is normal in an autistic child. When normal, clinicians and nutritionists assume that the child has enough B12. This may be true for adenosyl-B12 coenzyme but it is not necessarily true for methyl-B12 coenzyme. From the work of Dr. Richard Deth and Dr. Jill James, children on the spectrum have increased needs for methyl-B12 in the cortex of the brain, and increased needs for glutathione, a downstream product of methyl-B12, in both the brain \textit{and} in the body. In addition, children on the spectrum have an increased frequency for an MTHFR enzyme mutation. When present an MTHFR defect slows the body’s ability to form methylated folic acid at optimal rates. Therefore without adequate amounts of methylated folic acid to form methyl-B12, methyl-B12 will be inadequate to meet the methylation demands of the brain and body. Even if these children could make enough of their own methylated folic acid, it does not automatically mean that they can meet the increased methyl-B12 requirements in the cortex of the brain due to the unique form of methionine synthase that is present in the brain, nor does it automatically mean that they can meet the requirements for the increased glutathione demands secondary to the significant oxidative stress they are known to have.

\textit{The second error} is more commonly made by clinicians who are familiar with the biomedical approach to autism, who use methyl-B12 in their practices, and who test methylmalonic acid (MMA). When they find MMA elevated they treat with methyl-B12, their assumption being that MMA proves that there is a “B12” deficiency in general and that treatment with methyl-B12 will normalize the MMA on repeat testing. This does not necessarily happen because adenosyl-B12 coenzyme is found in the mitochondria, not in the plasma whereas methyl-B12 coenzyme is found in the plasma and not in the mitochondria. \textit{Methyl-B12 coenzyme does not become adenosyl-B12 coenzyme.} Because methylmalonic acid James A. Neubrander, MD resides in the mitochondria and requires adenosyl-B12 to work with its specific and unique enzyme, methylmalonic acid mutase, the addition of methyl-B12 will in no way affect methylmalonic acid (MMA), at least not directly. Therefore the treatment for elevated MMAs for a child with autism is adenosyl-B12, not methyl-B12. \textit{However,} when a non-autistic patient is found to have elevated MMA, vitamin B12 in the vitamin form of cyano-B12 or the dietary or vitamin form of
hydroxy-B12 is usually adequate to correct the situation because approximately equal amounts of methyl-B12 coenzyme and adenosyl-B12 coenzyme will be made from these two forms of vitamin B12.  

In summary for children with autism: a) a normal MMA does not indicate that the child has enough methyl-B12 and a clinical trial of methyl-B12 treatment should always be tried; b) an elevated MMA will not respond directly to methyl-B12 treatment because the treatment requires adenosyl-B12, not methyl-B12.  

REGARDING CONCERNS ABOUT SIDE EFFECTS AND HOW TO TREAT THEM WHEN THEY ARE PRESENT:  
Please be aware that it is not the message of my practice to have parents put up with intolerable or severe side effects. However, it is my message that parents know how I define side effects and how I treat them so that they may obtain the benefits methyl-B12 very likely could provide for their child. Therefore I refer the readers to the Autism One 2005 document found on our website at www.drneubrander.com. In addition, let me update that document with a few concepts that clinicians and parents should be aware of. As stated in this paper, side effects are usually only temporary while the body readjusts its equilibrium point. Parents whose child exhibits tolerable and/or positive-negative side effects and continues treatment for 4 to 6 months will typically see the side effects lessen or resolve while the “brain methylation benefits” (focus, attention, synchronization of brain waves, speech, language, socialization, emotion) are maintained or increase. Side effects occur in about 30% of children. The most common side effects are hyperactivity and mouthing objects. The next most common side effect is stimming. Less commonly we see sleep disturbances. Loose stools are rare. I do not believe this side effect to be the result of increased yeast or dysbiosis as has been popularized on the Internet. Instead I see them to be a temporary healing response or detoxification reaction while the body readjusts towards biochemical baseline. Enuresis is very rare and usually occurs in pre-pubertal or pubertal children. Because it happens so infrequently I do not have sufficient data from which to form a reasonable hypothesis. The reason why our clinic addresses side effects as it does is still poorly understood by the majority of clinicians and parents. Unfortunately the power of methyl-B12 is often not appreciated because parents decrease or stop methyl-B12 due to hyperactivity or other nuisance side effects. As stated in my Autism One 2005 article, though all side effects are a nuisance they may also be tolerable in nature and if allowed to continue for 4 to 6 months the child’s body will reestablish a new equilibrium. This is no different than the well established biochemical mechanism of “gaining tolerance” as seen with many medications or James A. Neubrander, MD drugs. Throughout the ages God and Mother Nature have been up-regulating, down-regulating, and establishing alternative pathways and biochemical detours for children and adults who have polymorphisms of one type or another. However, these biochemical detours and alternative pathways take time to become established. Until established, “side effects” may be what parents see and children experience. I will repeat again the important concept that these side effects will typically diminish or resolve when given enough time for the body to
reestablish equilibrium. This usually occurs within 4 months but may take as long as 6 months to happen. It has been my experience that approximately 6% of children do not respond to methyl-B12 or whose side effects are serious enough to have to stop the shots, at least for a while. Approximately 3% of children have side effects that make it impossible to take methyl-B12 using any of my standard protocols. Whenever I have an intolerable or severe side effect I stop methyl-B12 treatments. I look for other problems that may be the real reason for the side effect and later, once the child is re-stabilized, I may restart methyl-B12 shots at a 50% dose/volume reduction. If the initial side effects were extreme, I may restart at a 75% dose/volume reduction instead. The most important point I can make when this occurs is to once again allow no other additions or deletions to the child’s therapy while trying to reestablish whether or not the child will be able to use methyl-B12 and benefit from it. Additionally, and just as important, the Parent Designed Report Form must once again be the evaluation tool by which to compare the child who has experienced severe side effects with all the other children we have evaluated who have had mild, moderate, or no side effects at all.

**MY TREATMENT PROTOCOLS:**

1) Methyl-B12 Initiation Phase – 1st 6 weeks.
   a) *At the very first appointment the parents begin the methyl-B12 Initiation Phase!* My protocol does not require that parents start or complete any other type of therapies before commencing the methyl-B12 Initiation Phase. It has been my experience that methyl-B12 is the most predictable, reproducible, consistent, immediately obvious, and powerful treatment I can offer. I have documented no reason that requires a person to start diets, clean up the gut, add supplements, etc. in order to see methyl-B12 benefits. Therefore I allow the child to continue doing whatever s/he is doing while immediately adding methyl-B12. We see benefits in 94% of our children within the first 5-6 weeks. Because the parents do only one thing, they are able to document “undeniable benefits”. Therefore it becomes infinitely easier to subsequently recommend more difficult things for them to try, e.g. a restrictive diet, giving supplements to a child who has food or tactile defense issues, etc.
   b) Treatment starts with methyl-B12 made from a 25 mg/mL stock solution.
   c) A dose as close to 64.5 mcg/kg is injected into the subcutaneous tissue of the buttocks shallowly enough to assure subcutaneous delivery once every 3 days. At times the shots will need to be extremely shallow in order for the medication to actually get into the subcutaneous tissue. When extreme James A. Neubrand, MD angles are used (almost at the horizontal plane) the red medication will be observed by the parents and a methyl-B12 tattoo may be seen for several weeks at the injection site. This is normal and this is safe!
   d) Because a child’s weight will vary, the shot volume will often need to be rounded up or rounded down. In our practice we usually round up to the next higher volume, e.g. a 38 pound child’s dose at 64.5 mg/kg is 1114 mcg which is a volume that cannot be made from a 25 mg/mL stock solution.
Therefore the prescription can either be 0.04 mL (10% under dosing) or 0.05 mL (12% over-dosing). Our clinic’s routine is to round up to the next higher dose/volume.
e) *** The only needle we allow to be used is a Becton Dickson 3/10 cc ultrafine insulin syringe. *(BD 3/10 cc; item number 328438 only – no substitutions!)*
f) **CRITICAL:** *Allow no other treatments to be added for 5 weeks!* Followup during the 6th week.
g) **CRITICAL:** *Allow* no other treatments to be deleted for 5 weeks! Followup during the 6th week.
h) The follow-up procedure is to use the *Parent Designed Report Form* using its 3 part process.
i) Section A: the parents indicate the dose and frequency of the shots; therapies being used prior to the shots; changes made during the evaluation period; overall global impression.
j) Section B: the parents indicate the intensity they have observed from the 135 common responses with methyl-B12 therapy.
k) *** Section C: the parents document in letter or paragraph form the reasons why they believe what they say to be true is true. They are to indicate what their child was like before methyl-B12 therapy and how it changed. They are to give as many specific examples as possible.

i) Because the parents are “doing nothing else”, if there are lab tests I want to obtain, this is the time I order them so they will be available at our 6 week follow-up. Frequently I will order an MTHFR and MMA test from a commercial lab. *(Insurance companies usually pay for these tests)*

2) Addition of supplements and diet – 2nd 6 weeks.
a) If the parents do not have their child on supplements, or if the doses of supplements are lower than protocols I have established for my patients, this is the next step I have the parents take.
b) If the parents already have their child on my recommended doses of supplements or are close, I “tweak” their supplement program.
c) I review any lab tests previously ordered and/or order any additional lab tests indicated by the child’s present history.
d) I continue the same dose/volume of methyl-B12 for another 6 weeks before making any changes to the methyl-B12 protocol. The reason I do not move yet to the clinical trial of daily shots is because the rate of change seen *(“the Y-Axis” as described in the Parent Designed Report Form and all my patients understand and document)* may not have plateaued yet. Until the rate of change has stabilized to a new slope, to change the methyl-B12 protocol would make it impossible to know whether any future changes have been beneficial.

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improvements were due to increasing methyl-B12 or were nothing more than a continuation of the previous methyl-B12 every 3 day protocol.

3) Increase methyl-B12 frequency from every 3 days to daily.
a) In our practice between 40% to 50% of children once again show “undeniable” benefits when keeping the dose/volume of the shots the
same but increasing the frequency from once every 3 days to daily. In the past I used to increase the shot frequency from every 3 days to every 2 days before progressing to daily shots. However, this slowed down my overall ability to add other important biomedical treatments because each time I made a dosage or frequency adjustment I allowed nothing to be added to or deleted from a child’s program for at least 4 weeks. After evaluating thousands of Parent Designed Report Forms, the majority of children who did better on the daily shots did not do as well on the every 2 day protocol (exceptions occur) so knowing that, there is now no reason for me to delay and not to go from every 3 days to daily shots.
b) If the parents can document “undeniable” changes, I keep the child on the daily shot protocol.
c) If the parents cannot document “undeniable” changes or if the changes are “only soft at best”, I return to the once every 3 day protocol.
4) Addition of adenosyl-B12 when MMA is positive
a) My initiation protocol for adenosyl-B12 is to start at 25% of my standard methyl-B12 dose which is roughly 16 mg/kg once every 3 days.
b) If I see good clinical results or if I see that the MMA value is not returning to normal, I will incrementally increase the adenosyl-B12 dose by 25% increments upwards until I have a 1 to 1 adenosyl-B12 to methyl-B12 value. I cannot remember needing to go this high with adenosyl-B12 but I would try it as long as the basics were followed every time I attempted this protocol change, that being to allow no other changes and to evaluate response by using the Parent Designed Report Form.
c) Because the smallest dose able to be accurately drawn up into the syringe is 0.02 mL, most of the doses of adenosyl-B12 will need to be made from a stock solution weaker than 25 mg/mL. For example, a 25% dose of adenosyl-B12 made from a 25 mg/mL stock solution with a 0.02 volume is 500 mcg. For my standard initiation protocols this could not be used in a child less than 68 pounds. [2000 mcg methyl-B12 and 500 mcg adenosyl-B12 (25% of the methyl-B12 dose) every three days.]
d) For a child less than 68 pounds the adenosyl-B12 and methyl-B12 shots cannot be combined and will have to be given separately. For a child greater than 68 pounds you can request that the pharmacy make the adenosyl-B12 shots from a 25 mg/mL stock solution. You can then have the pharmacy add the adenosyl B12 shot volume to the methyl-B12 shot volume so you only have to administer one shot instead of two shots.
e) If the child is already receiving methyl B12 shots every day when you start the adenosyl-B12 shots, even if the child is greater than 68 pounds you will need to start the adenosyl-B12 shots on an every 3 day protocol while keeping the methyl-B12 on the daily protocol.
5) Methyl-B12 nasal spray with folic acid
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a) If I have a very high functioning child with ADD or ADHD, a child whose parents are afraid of the shots, or when methyl-B12 hasn’t seemed to work well, I will try the nasal spray.
b) I use 1250 mcg of methyl B12 combined with 300 mcg of folinic acid. For smaller children I have the parents give one spray daily. For larger children I have them use two sprays daily. c) Until the studies are completed and replicated, the responses that have been reported may just as well be the result of the folinic acid as the methyl-B12. The reason I say this is because there are studies showing that the CSF is low in folic acid and one of the reasons that this nasal route of administration may be good is because the nasal spray has the potential of presenting itself to the cribriform plate, a semi-permeable membrane that separates the sinus cavity from the brain. d) I recommend that all my parents give also the shots intramuscularly daily whenever their child has the “kiddy crud” – mucoid material in the nasal cavity from colds, sinus infections, or allergies. The reason I say this is because methyl-B12 has been shown to positively affect the immune system. Therefore when methyl-B12 is needed the most is when a child is sick and when the child is sick s/he is less likely to let the parent squirt something up his/her nose and even if s/he did, the medication would have little chance of getting into body through all the “gunk”. The reason I request IM shots at this time instead of SQ shots is because this is one time I want to overwhelm all the receptors as quickly as possible to get as much methyl-B12 into the body at once to jumpstart the immune system. I am not looking for a slow release in this situation. e) If I believe the child cannot tolerate folinic acid, I leave this out of my prescription.

M.I.N.D. INSTITUTE STUDY UPDATE:
It has now been more than three years since the scientists and clinicians met in July 2004 to design the first clinical study for methyl-B12. At that time it was determined that more than 40 subjects would be needed to complete a 12 week double blind cross over study in order to show true statistical significance. By July 2007, 3 years later, the study is just half way there! Only 22 subjects have completed the 12 week course and there has been no significant difference on any of the measures that were used to evaluate their responses. However, in a personal communication from Dr. Robert Hendren, the director of the study, two did very well and five did well. Over half of the parents felt it was helpful enough that when the blind was broken, they chose to continue in the 3 and 6 month extension phase. As I have written in the past in other documents regarding this study, only the best responders to methyl-B12 will be able to be identified and of that small group, even they may not show “statistical significance” though clinically the parents can document “undeniable changes”. From this small study group of 22, the percentage of children responding is essentially the same as what I saw in my initial study group of 16 children and reported at a special meeting in San Diego, July 2002. Two out of the sixteen did incredibly well. One who previously had no spontaneous speech started talking to everyone within ten days and one who was sick with a new cold every three to six weeks no longer got sick. My initial report stated that approximately 20% would do very well and another
30% would respond strongly enough for the parents to take note. This is exactly what the M.I.N.D. study is showing “clinically”. The M.I.N.D. study is also showing that the wheels of science turn very slowly, and that we do not yet have an evaluation tool that is able to include more than exclude what parents know to be real. Statistical significance is something that can only identify the best responders for any type of study. Many excellent treatments of all types are being tossed away because they do not meet the criteria for statistical significance and therefore remain unpublished or if published they deliver the wrong message. What needs to happen in the future for the next methyl-B12 study is to redesign the evaluation tools that we are using so these new tools will be able to validate what parents know to be real even though what they see is infrequent, sporadic, and inconsistent but things they know to be undeniably so, things that are new and things that can only be explained from the use of methyl-B12

THE SYNERGY BETWEEN METHYL-B12 AND HBOT:
At this time our clinic has monitored over 25,000 hours of hyperbaric oxygen therapy using both low pressure low oxygen concentrations and high pressure high oxygen concentrations. For a detailed discussion of what I have observed using hyperbaric oxygen therapy for children on the spectrum I refer you to the article I have written entitled Hyperbaric Oxygen Therapy for Children with Autistic Spectrum Disorders also found in the proceedings of this conference: USAAA, Denver, August 2007. It is my strong bias that the use of methyl-B12 with hyperbaric oxygen produces a strong synergistic effect. It has been proposed for several years that hyperbaric oxygen wakes up sleeping or idling neurons which I say secondarily results in more “total neuronal work product”. Therefore at least one plausible hypothesis why the use of methyl-B12 appears to act synergistically with HBOT would be because methyl-B12, along with methionine synthase, will now have more neurons upon which to produce more total neuronal methylation work products (focus, attention, synchronization of brain waves, speech, language, socialization, emotion).

FINAL WORDS:
Methyl-B12 works and it works well when used as a pharmacological agent, not as a vitamin and when it is used for years instead of months. Methionine synthase can use any form of B12 when it works in the body. However methionine synthase functions much better in the brain with methyl-B12 and because brain methylation products are what parents want to see in their children (focus, attention, synchronization of brain waves, speech, language, socialization, emotion), methyl-B12 is the only form of B12 that should be used to achieve these goals. Certain items block methyl-B12 effectiveness and should not be used concurrently when parents are trying to regain normal brain function in their child. The need for methyl-B12 in autism should be thought of as being a dependency, not a deficiency problem. Most side effects will diminish or resolve over time as the body re-establishes a new equilibrium while it keeps the good and eliminates the bad. Caution must be used when interpreting tests of any kind James A. Nebrander, MD with methylation/transsulfuration biochemistry because only a clinical trial is able to utilize the ultimate laboratory, one’s own body. Whenever starting or
changing a methyl-B12 protocol, no other additions to or deletions from the child’s current treatment plan should occur for at least 4 to 6 weeks and the evaluation process should use the methyl-B12 Parent Designed Report Form so that the child’s response can be accurately compared to the thousands of other children’s responses to methyl-B12 therapy.

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