

**Methyl-B<sub>12</sub>: Making It Work For You!**  
**Autism One Presentation**  
**Chicago, Illinois**  
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*Sometimes things are just meant to be!* So it was with the *accidental discovery* I made in May 2002 showing methyl-B<sub>12</sub>'s profound effect on autism and other neurodevelopmental disorders. So it was with the Jill James study validating what I observed. Dr. Paul Cutler, the physician supplying her the patient samples, heard my initial methyl-B<sub>12</sub> lecture and had Dr. James *extend the study* they were doing several more weeks with the addition of methyl-B<sub>12</sub>. The rest is history!

B<sub>12</sub> (cobalamin) is a vitamin “family” with five unique family members that each do different things: a) cyanocobalamin; b) hydroxycobalamin; c) adenosylcobalamin; d) glutathionylcobalamin; e) methylcobalamin. Out of the B<sub>12</sub> family, only methyl-B<sub>12</sub> has the ability to activate the methionine/homocysteine biochemical pathway directly. It is this pathway that is responsible for the body's entire sulfur-based detoxification system. It is this pathway that is responsible for the formation of S-adenosylmethionine (SAME), the universal methyl donor. It is this pathway that is responsible for the formation of homocysteine, the “crossroads” molecule that is responsible either to reform methionine and SAME or create cysteine, taurine, and glutathione. Glutathione is the body's primary intracellular antioxidant and is responsible for many detoxification reactions, most notably those that involve the binding and removal of mercury, lead, cadmium, arsenic, nickel, tin, antimony, and many other lesser-known heavy metals that also bind to glutathione's sulfur group.

Methyl-B<sub>12</sub> is closely allied with the folic acid biochemical pathway. A precursor folic acid molecule must interact with the enzyme MTHFR (methylenetetrahydrofolic acid) to become 5-methyltetrahydrofolic acid, the molecule that donates its methyl group to B<sub>12</sub> so it can become methyl-B<sub>12</sub>. Unfortunately, many children have a defect in this enzyme.

In my practice, 94% of children have been found to respond to methyl-B<sub>12</sub> therapy. Executive function is improved in 90% of children – things like awareness, cognition, appropriateness, eye contact when called, and “just being more like a normal kid”. Speech and language is improved in 80% of children – all phases including spontaneous language, more complex sentences, increased vocabulary, etc. Socialization and emotion is improved in 70% of the children – initiation and interactive play, understanding and feeling emotions, possibly for the first time or to a much more normal degree, etc. When parents evaluate the responses of their child by using the Parent Designed Report Form and the Parents Specifics Documentation Letter, approximately 50% of the *Responders* have greater than 28 out of 136 responses. This group has an excellent prognosis as long as the therapy is maintained for 2 to 3 years. *Many* of the other 50% from the *Responder Group* who have fewer than 28 responses *will still respond very well* if the treatment is also continued for the same period of time. You can go online to my website at

www.drneubrand.com and watch over 6 hours of video where parents tell you the good and the bad about methyl-B<sub>12</sub> therapy. In addition, you can watch parents demonstrating on their children how to give the shots. You will hear them tell about how fearful they were to think about giving their child a shot and then you will hear them tell you how giving the shots became the easiest thing they do. You will hear children who could not talk before the shots now talk. You will get a clear sense of the *entire* methyl-B<sub>12</sub> story: some children progress within a year or two and officially lose their diagnosis; some children, though responsive, make only mild to moderate improvement but enough that the parents do not want to discontinue the shots. In addition, from the website you can download the Parent Designed Report Form and see what are the common things that methyl-B<sub>12</sub> is famous for. Also, you will be able to use this valuable form whether or not your clinician includes it in his or her follow-up requirements.

Side effects are not uncommon and of two types: tolerable (“nuisance” – ranging from mild to severe) vs. intolerable. It is extremely important to understand how to approach side effects when they occur in order to treat with the most effective dose of methyl-B<sub>12</sub> and obtain the maximum clinical benefits while waiting for the side effects to diminish or disappear over the next 2 to 6 months, or to know when treatment must be discontinued.

The most common side effects are increased activity levels with or without stimming, sleep disturbances, and increased mouthing of objects. Just as pain is a necessary accompaniment of a successful operation, so side effects may be necessary while “getting your child back”. *The tricky part is to know when you are dealing with a tolerable though undesirable side effect or a side effect that is truly intolerable.* One of my greatest surprises came when I first learned that my *highest dropout rate* occurred in children who were definitely responders, who had side effects, and whose *dose we therefore lowered enough to take the side effects away*; in contrast to children who were responders with side effects who continued their dose unchanged. It is now obvious to me that *“enough time at the right dose” is necessary to reap the greatest rewards.* Therefore, my current protocol determines whether a side effect is tolerable vs. intolerable. If tolerable, I continue the dose unchanged while the parents state, “We’re getting our child back and though we don’t like the side effects, we’re not about to quit!” However, *if the side effect is truly intolerable, I will stop the shots until the side effect goes away and then try to restart the shots at a 10 to 15% dose.* Unfortunately, most children with true intolerable side effects cannot handle even the smallest amount of methyl-B<sub>12</sub>.

**Hyperactivity and/or stimming:** The most common side effect is an increase in hyperactivity and/or stimming. As a general rule when at home 90% of your time as a parent is spent making your child feel loved, wanted, and important to the family unit as you create the child’s “safe haven”. Only 10% of your time is spent educating and disciplining. At school the opposite occurs; 90% of the time is spent educating and disciplining whereas only 10% of the time is *actively* spent making the child feel loved and important to the class and society. Therefore, if a child can focus, learn and stay on task in the controlled school environment, but is hyper and stimmy at home, this is defined as a tolerable side effect. This is

analogous to you going to work and putting on your best face, but when getting home just “letting loose” in your safe haven – sometimes how you let loose is desirable; sometimes it is not! So it is with your child. Because the most common initial positive effect seen in children taking methyl-B<sub>12</sub> is increased executive function, especially awareness, after the addition of methyl-B<sub>12</sub>, many children are suddenly bombarded with a *tremendous amount of new stimuli* that now must be processed. These new stimuli must also be processed faster and within the same period of time that it used to take to process far less data prior to methyl-B<sub>12</sub>. The cumulative result is *sensory overload* where the child just needs to “let it all out” once back in his or her safe haven. For them to stim in this type of circumstance is no different than what an adult does by squeezing a squishy ball or rubbing a smooth stone between his fingers to take away tension and relax. In contrast to this “tolerable” side effect, if a child cannot stay on task and learn at school or in other types of controlled environments, then the side effect is defined as intolerable. In my experience the tolerable side effect of hyperactivity and stimming usually diminishes significantly or resolves completely by the 6<sup>th</sup> month as the body up-regulates and down-regulates the appropriate metabolic sequences and enzymatic processes.

Sleep disturbance: The good news is that more children begin sleeping better rather than sleeping worse. This is most likely due to the fact that methyl-B<sub>12</sub> improves the body’s supply of melatonin. However, for children that sleep more poorly the following discussion applies. The entire B<sub>12</sub> family is something that has been given to the elderly, the tired, and the chronically fatigued for years “to wake them up”. As you know, children are already full of energy and awake more than we want them to be when we are already tired and exhausted. However, if a child is more active at night but does not “fall asleep in his soup” during the day, needs more naps, or is lethargic during the day, I define the side effect as tolerable. If however the child does sleep during the day, needs more naps, and is lethargic and all washed out, then I consider the side effect intolerable, stop the shots, and proceed in the same manner I described in the section about hyperactivity and stimming. In my experience, the tolerable side effect of sleep disturbance usually diminishes significantly or resolves completely by the 2<sup>nd</sup> to 6<sup>th</sup> month for the same reasons stated above.

Increased mouthing of objects: This is different than true PICA, which is putting anything and everything in the mouth, a phenomenon that only rarely occurs with methyl-B<sub>12</sub>. However, what one does see frequently with methyl-B<sub>12</sub> is younger children touching or playing with their mouths, lips, tongue, and starting to bite on their shirts or shirtsleeves. They may bite on furniture, sometimes to a marked degree. Older children who are verbal state that their tongue tickles or that their tongue is buzzing. What is happening is that the children are showing a “positive negative” because the nerves in their mouth are starting to come back alive, receive signals, and tingle – a healing process. It is important to remember that treatment with the B<sub>12</sub> family has been used for years to heal diabetic peripheral neuropathy with its “stocking glove” distribution. The long nerves to the hands

usually take 6 to 9 months before starting to come back while the even longer nerves to the legs typically take 9 to 15 months before they start to regenerate. It is at this point in time when patients first observe sensations returning to their hands or feet (a process medically called paresthesia or dysesthesia). Their descriptions of what they are experiencing are similar to what children on the spectrum are observed to have or state they feel. Because the nerves to the mouth are the shortest peripheral nerves, this side effect can appear within weeks after initiating therapy, not months. As with diabetic peripheral neuropathy, this process indicates that there was a problem that has now entered the healing phase. In my experience, the tolerable side effect of mouthing objects usually diminishes significantly or resolves completely by the 2<sup>nd</sup> to 4<sup>th</sup> month but can occasionally last as long as 6 months.

It is important to understand how to interpret a “true negative” side effect from what I call a “positive negative” side effect. For example, all aggression, biting, hitting, kicking, and tantruming are not bad though it is always undesirable. The reason I say this goes back to one of the main benefits of methyl-B<sub>12</sub> therapy, increased awareness. Soon after initiating methyl-B<sub>12</sub> therapy, most children are suddenly more aware of their wants and needs. They are more aware of what they can and cannot do. They have lived in a state of social void for several years not being able to get what they needed, nor possibly even knowing what they needed. Now the world and all it has to offer is suddenly presented to them and they are overwhelmed, they cannot speak or make their wants and needs known, so therefore they act out inappropriately. The same line of reasoning applies when children may be found crying, moody, or sullen. Suddenly they are more aware of their social needs as well as their social inadequacies. Because methylation affects all parts of the brain including the hippocampus and limbic system, for the first time in their lives, or at least to a stronger degree than ever before, they not only feel their emotions but act appropriately upon them and cry. As a general rule, “positive negative” side effects also diminish or disappear within 2 to 6 months.

It is important for parents and clinicians to understand that the positive effects of methyl-B<sub>12</sub> are predictable, reproducible, consistent, and undeniably obvious within the first five weeks of therapy as long as no other biomedical variables are introduced or eliminated from a child’s program during this five-week period. To underscore the importance of this point I tell my patients that if they are giving their child heroin or cocaine they cannot stop and if they are not feeding their child they cannot start until after the five week methyl-B<sub>12</sub> Initiation Phase has been completed and evaluated with the Parent Designed Report Form. The Parent Designed Report Form is the most sensitive and specific tool available to determine whether or not a child is a methyl-B<sub>12</sub> responder. The accurate completion of this form is so important to the overall success of a child that I fondly call it my “Little Green Hairs – Red Freckles” form. The reason I call it this is because parents are only interested in “the biggies” – executive function, speech and language, socialization and emotion. Therefore, unless parents know “all the other little things” methyl-B<sub>12</sub> does as I illustrate from my silly analogy, “Methyl-B<sub>12</sub> makes little green hairs grow out of children’s ears and changes their brown freckles to red ones”, they will never report these findings, never know that their child is a responder, and will

therefore stop the shots, never realizing for their child the benefits methyl-B<sub>12</sub> would have produced!

Methyl-B<sub>12</sub> is a treatment, not a cure. However, many children using methyl-B<sub>12</sub> combined with other biomedical and non-biomedical therapies have lost their diagnosis! It is important that all parents and clinicians understand that the maximum results from methyl-B<sub>12</sub> therapy occur over years, not months, not weeks. Though the initial results will be obvious within the first five-week period of time, methyl-B<sub>12</sub>'s power is in long-term use. I tell my parents that they are growing trees, not bamboo. Though there are occasional responders that lose their diagnosis within a year, the majority of children never lose their diagnosis. However, over time they make tremendous strides in that direction.

Clinicians need to teach parents that after the first three to four six-week evaluation cycles, the undeniable obvious changes directly attributable to methyl-B<sub>12</sub> will be lost in a child's overall progress due to his or her combined therapies. It is at that time that the only way to compare the effects methyl-B<sub>12</sub> has is by comparing children in a classroom setting who are taking methyl-B<sub>12</sub> with children who are not taking methyl-B<sub>12</sub>, but who are doing everything else the same. My clinical observation has seen it numerous times where children prior to methyl-B<sub>12</sub> therapy were at the bottom of their classes but within one to two years climbed to the top of their classes or were moved to new more challenging classrooms. In fact, I have several children who are now in mainstream classrooms without a shadow or an aide and who cannot be differentiated from their classmates by anyone except a highly trained professional!

Methyl-B<sub>12</sub>, in the presence of methionine synthase, *spins* the methionine/homocysteine *biochemical pinwheel* sending methyl groups and glutathione to the brain and body. I will not review the biochemistry at this time; if you are interested you can see it on my website. However, as parents and clinicians you are most interested in my clinical observations. It is important to understand that the effects of methyl-B<sub>12</sub> are due to what methyl-B<sub>12</sub> allows to happen in the brain and not because it "makes speech", "makes awareness", or "makes socialization". If I put earmuffs and a blindfold on you and drop you by parachute deep into the heart of Africa, once you land and are found by the natives, you will not understand the language. If you continue to wear the earmuffs and blindfold, because you cannot lip-read or hear the language being spoken, you will remain in the dark. However, once you remove the earmuffs and blindfold, though you still do not know the language, you will now have the same advantage every other baby born into their society has. You will have the *opportunity* to begin to lip-read. You will have the *opportunity* to hear the language spoken. You will have the *opportunity* to first understand receptive language. And eventually your tribesmen will have the *opportunity* to hear you express yourself to them! Removing the earmuffs and blindfold did not increase your intelligence nor did it add any new brain cells. What it did was now allow your brain to begin to absorb information, store information, utilize information, process information, and respond appropriately to the situations at hand.

So it is with children taking methyl-B<sub>12</sub>; they seem to blossom over time. Everything kicks in and starts working; therapists are amazed! IEP's continually have to be updated and changed, sometimes at unbelievable speeds! Children surpass their teacher's wildest expectations. What has happened is methyl-B<sub>12</sub> has taken off the earmuffs and blindfold that have been blocking the children's brains from utilizing the neurons and brain cells that were already in place but that were just waiting for the right circumstances to occur. The addition of methyl-B<sub>12</sub> allows the conditions to be right! However, methyl-B<sub>12</sub> is not what does it, is not what makes the child learn, is not what brings the child back. Instead, it is ABA, OT, PT, speech therapy, and all the other forms of therapy that finalizes the deal and gives the child back to his parents and to the world. However, without methyl-B<sub>12</sub> leveling the playing field, children on the spectrum would never be able to realize the advantage that unaffected children enjoy in a learning environment! And so it is – methyl-B<sub>12</sub> the gloves, therapies the hands!

Methyl-B<sub>12</sub> works for children of all ages. I have used it in children as young as 6 months of age and in children 18 years old. My success rate is the same: 90%+. However, different ages show different positive responses, which is a subject beyond the scope of this text.

The medical literature does not indicate that B<sub>12</sub>, more specifically methyl-B<sub>12</sub>, is toxic. Doses equal and higher than I use in my standard protocol of 64.5 mcg/kg/every 3 days (150 mcg/kg/week) have been used for years with patients with pernicious anemia, Lymes disease, and others.

Currently there is no test that can accurately predict clinically which children will and which children will not respond to methyl-B<sub>12</sub> shots. Curiously, 85% of children who respond to methyl-B<sub>12</sub> therapy are shown to have high-normal or high levels of methyl-B<sub>12</sub> in their blood. The explanation for this is thought to be due to the fact that B<sub>12</sub>'s oxidative state cannot be "recycled" once it delivers its initial methyl group to homocysteine. Therefore it just "sits there, all dressed up but no place to go", unable to change from its "now used up" oxidative methyl-less state into its "recycled" oxidative state that is now able to re-capture a new methyl group to spin the pinwheel again. Only methyl-B<sub>12</sub> that gets into the cell does work. The B<sub>12</sub> that is sitting outside the cell as described above is functionless but shows up on blood tests falsely indicating that the child has too much B<sub>12</sub> and should therefore not be treated. This scenario is analogous to blood sugar being high in the blood but low in the cells where it is needed! Research is underway at this time to evaluate genomics and single nucleotide polymorphisms ("SNPs") as ways to predict which children need methyl-B<sub>12</sub>. However, though theoretically promising, at this time only the child's own body – his or her true laboratory -- is able to produce conclusive results whether the child is a methyl-B<sub>12</sub> responder or not.

The major obstacle for parents duplicating my success with their children is the fear of giving an injection. They argue; they negotiate; they manipulate; they find someone or some group who will agree with them and say what they want to hear. So be it. However, after personally evaluating over 60,000 shots with 500 children, I cannot make the statement too strongly, "Only the subcutaneous injectable route of administration into

the adipose tissue of the buttocks will produce the remarkable results parents want to see!” Without a doubt, all forms of administration work to some degree, and some better than others. However, nothing comes close to the subcutaneous route. My research has shown that all the “pulsatile” forms of methyl-B<sub>12</sub> therapy are inferior to the subcutaneous injectable route. This is because the goal is to have a continuous leaching slow steady delivery of methyl-B<sub>12</sub> to the system “24/7”. Oral dosing is one of the pulsatile forms of administration. All cobalamins are absorbed in the distal portion of the small intestine, the terminal ileum. From the work of doctors Wakefield, Kringsman, and Buie, an extremely high percentage of children on the autistic spectrum have an inflammatory bowel condition that affects this region of the intestinal tract. Therefore, oral absorption of all forms of B<sub>12</sub> is limited at best. Sublingual administration is a curiosity. It is only theoretical for children on the spectrum because the majority cannot hold a pill under their tongues. Consequently, the methyl-B<sub>12</sub> is swallowed and becomes a “delayed oral” administration technique. Even for the rare older child that can do this, the dosing is still pulsatile in nature offering minimal effects when compared to the subcutaneous route. Intramuscular injections are also pulsatile in nature because the medication begins to be eliminated from the body within an hour after it is injected. Though intramuscular administration shows clinical benefit, the subcutaneous route produces the most benefits with the highest intensity that last for the longest period of time. Transdermal administration theoretically should work because the medication is being delivered into the subcutaneous tissue and therefore its release from the application site to the rest of the body should be slow and continuous. Nevertheless, in clinical practice the subcutaneous route eclipses the results of transdermal administration.

Over the last 3 years I have personally monitored all my children closely. I have tweaked and re-tweaked my protocols. I have basked in my successes and cried from my failures. What I have learned is that “the whole recipe in the correct sequence” is necessary in order to obtain maximum clinical results in the shortest period of time with the fewest confounding variables. It is my strong opinion that if parents and clinicians follow each item listed exactly as described, then and only then will they be able to reproduce my results. I recommend that everyone read the paper from my website [www.drneubrand.com](http://www.drneubrand.com) entitled, “Methyl-B<sub>12</sub>: Myth, Masterpiece, or Miracle?” Here I discuss in detail my research and the reasons for each of my conclusions. It is here you can read the article by Dr. Jill James. It is here you can watch the videos of parents telling their methyl-B<sub>12</sub> stories – not only the good, but also the bad. Should you decide to use methyl-B<sub>12</sub> with your child, you can download the Parent Designed Report Form to help you decide if your child is a methyl-B<sub>12</sub> responder or not. The majority of children’s parents initially report scores of mild or mild-to-moderate (reported as “ones” and “twos”), not moderate, moderate-to-significant, or significant (reported as “threes”, “fours” or “fives”). From 136 possible responses, approximately 50% of parents report more than 28 positive or positive-negative responses while the remaining 50% of parents report fewer than 28 responses. Children scoring greater than 28 responses have an excellent long-term prognosis, while children scoring fewer than 28 responses may have a good prognosis, though the prognosis is guarded and only accurately evaluated after adequate time has elapsed to compare those children’s progress to their peers.

To summarize, methyl-B<sub>12</sub> injections into the buttocks have the power to change lives, not only for the children, but also for the family. No treatment to date has demonstrated the predictable and reproducible results that injectable methyl-B<sub>12</sub> has shown. Though many parents believe “chelation will cure”, it is undoubtedly true that “methyl-B<sub>12</sub> will treat”. Though diets and supplements and treating the gut and dozens of other treatments are all proven therapies that help many children on the spectrum, methyl-B<sub>12</sub> is definitely the power hitter on the team. It is methyl-B<sub>12</sub> who is able to step up to the plate and start swinging. It is methyl-B<sub>12</sub> whose batting average is unequalled and who will usually get a hit in every game. And though not every hit is a home run, methyl-B<sub>12</sub> does have the power to hit home runs -- not tomorrow, not next week, not next month but rather the *possibility* to hit a home run today!

### **PROVEN PROTOCOL** *(Concepts; Basic Protocol; and Resources)*

1. Total dose [for approximately 85% of children 64.5 mcg/kg/every 3 days works well].
2. Methyl-B<sub>12</sub> concentration [25 mg/ml provides the least surface area resulting in a slower and more uniform rate of release]. [Note: 95% of my clinical results are from methyl-B<sub>12</sub> injections prepared by Hopewell Pharmacy. At this time I am investigating several possible reasons why response rates appear to be different from “equivalent” concentrated preparations made by various pharmacies. Currently I have no answer why at times this phenomenon seems to exist so please continue to check with my website as information becomes available regarding this issue.]
3. Require each compounding pharmacy to provide a recent Certificate of Analysis documenting the potency of their methyl-B<sub>12</sub> substrate concentration to assure that what the pharmacy says the child is receiving is actually what is being given. Potencies have been off by as much as 25% to 33% and unfortunately this is not an uncommon problem! There is “an art” to get the 25% concentration into solution and then to stay in solution. Though all compounding pharmacies can do it, most of the leading pharmacies have had “to play with it” over time in order to get their formulations to deliver accurate results. Do not take this comment lightly no matter what your pharmacy says! I spot check various pharmacies and know that this is a problem. Hopewell Pharmacy provides one to me once every 3 months or sooner. This is now what I consider to be my standard of excellence.
4. Injection into the adipose tissue of the buttocks [less vascular; slower rate of release].
5. Injections that are “shallow/closer to the horizontal than vertical plane” in the subcutaneous tissue far away from the SQ:IM junction or the muscle itself and without “pinching the fat” [see Injection Instructions for Methyl-B<sub>12</sub> Shots from my website].
6. The first 5-weeks of methyl-B<sub>12</sub> use must allow absolutely no additions and allow absolutely no deletions to the child’s current program. This 5-week period can be started early in the child’s program or later on depending on the clinician’s preference. However, whenever methyl-B<sub>12</sub> is initiated, it is then that the 5-week “no change time clock” begins ticking. Of course if the child becomes ill and needs standard medical treatment, this must be done.
7. The Parent Designed Report Form, the most sensitive and specific tool available to evaluate the effects of methyl-B<sub>12</sub> must be used to evaluate the clinical

responsiveness. There can be no exceptions to this for at least for the first 5-week clinical trial. After that, completing the Parent Designed Report Form should still be required for at least the next two reviewing cycles because from the letter portion of the exercise, parents will be able to observe the subtle changes that will continue to occur that they would have otherwise missed.

8. Parents must understand and continually be reminded that it is not the intensity of the responses they see in their child that is the most important prognostic indicator but rather it is the number of responses they see that predicts whether or not a child will be a mild, moderate, or significant responder over the next 1.5 to 2.5 year period of time.
9. Parents need to thoroughly understand how to differentiate tolerable vs. intolerable side effects. If their child's side effects are tolerable, even though severe at times, parents should continue the shots without altering doses and understand that these side effects will usually diminish or disappear within 2 to 6 months. Parents must be thoroughly trained in differentiating tolerable vs. intolerable side effects so that methyl-B<sub>12</sub> therapy can be discontinued when a true intolerable side effect is present. Otherwise therapy should be continued unchanged.
10. If a child is found to be a responder, the parents need to be taught and frequently reminded that the process is a slow steady one that needs to be continued long-term. Parents need to be taught not judge whether or not their child no longer needs methyl-B<sub>12</sub> therapy because they no longer see obvious changes as those noted during the first 5-15 weeks. Currently I am recommending no less than 18 to 24 months of treatment.
11. Parents should be advised that my research indicates many, if not most children will have some form of regression and/or will lack the same degree or rate of progression they would have had if the shots had not been stopped.
12. Folinic acid should be added after the first 5-week clinical trial but not at the same time as methyl-B<sub>12</sub>. It should be added alone and its dose should start low and then be incrementally increased to see how it is tolerated. From my research, approximately 20% of children become hyper and/or cannot sleep when folinic acid is added.
13. Liposomal glutathione may be tried in an effort to enhance the glutathione portion of methyl-B<sub>12</sub>'s effects. As with all members that participate in the homocysteine recycling biochemical pathway, each addition should be made singly and observed over a period of time when no other changes are being made to the child's treatment program.
14. TMG should not be part of the initial protocol and should only be added after escalating doses of methyl-B<sub>12</sub> fail, if methyl-B<sub>12</sub> produces "intolerable" side effects according to the definitions given above, or if methyl-B<sub>12</sub> produces no significant benefits.
15. SAMe and methionine should not be added until the maximum benefit or failure of methyl-B<sub>12</sub> is determined. If these amino acids are then added, they should be initiated at low doses, added incrementally, and no other concurrent changes should be allowed to the child's treatment program while the parent's closely monitor the results of this clinical trial.

### **THE BASICS:**

- a) **During the methyl-B<sub>12</sub> Initiation Phase, absolutely no other changes to the child's treatment program can be introduced or eliminated – NO EXCEPTIONS!**

- b) **Current dosing and delivery schedule: 64.5 mcg/kg once every 3 days to the adipose tissue of the buttocks at an angle severe and horizontal enough to guarantee a “shallow” subcutaneous delivery. The only syringes allowed are Becton Dickson 3/10 cc insulin syringes with an 8 mm, 31-gauge needle, item #328438. \*\*\* Be sure to understand each part of the injection instructions and follow them *exactly!* \*\*\***
- c) **The only solution allowed is a 25 mg/mL methyl-B<sub>12</sub> stock solution. A recent Certificate of Analysis documenting potency should be requested by the clinician and/or parent and provided frequently by all participating pharmacies [I receive reports once every 3 months or less from Hopewell Pharmacy and consider this my personal standard.]**
- d) **A six-week set of prefilled syringes is prescribed with a mandatory follow-up at the beginning of the 5<sup>th</sup> week (by phone or in person).**
- e) **The evaluation tool *must be* the Parent Designed Report Form with a *detailed* Parent Specifics Documentation Letter. The instructions for these two items must be followed *exactly*. The clinician must not accept any shortcuts by parents, and when necessary the clinician must require the parents resubmit the Parent Designed Report Form and Parent Specifics Documentation Letter correctly before represcribing the next set of shots.**
  - i. **Every change the parents note must be documented by giving as many specific examples as possible. The examples must validate in detail why the parent believes the changes noted are real and not placebo effects.**
  - ii. **Grouping similar responses prior to describing the changes observed for each group is the preferred way to arrange the letter, e.g. language-related items, awareness-related items, etc.**
  - iii. **Y-axis vs. X-axis changes must be understood and accounted for by the parents and reviewed by the clinician.**

**ADVANCED PROGRAMS AND PROTOCOLS: Available to be discussed only with clinicians and on a limited basis. Contact our office at (732) 985-6600.**

Available for you from our website at [www.drneubrand.com](http://www.drneubrand.com)

1. **Over 6 hours and 65 video examples of parents discussing the positives, negatives, frustrations, and failures of methyl-B<sub>12</sub> shots.**
2. **Video examples of parents administering the shots to their children.**
3. **The Parent Designed Report Form.**
4. **Injection Instructions for Methyl-B<sub>12</sub> Shots.**
5. **The Methyl-B<sub>12</sub> Dosing Chart, Program, And Protocol. [Clinicians and Pharmacists may call to request the password. Leave both your phone and fax number as well as your office address and email address. Be sure to periodically obtain the latest updates. Last updated October 2004. Estimated overdue update to be available in June 2005.]**
6. **List of references regarding methylcobalamin and related articles. [Estimated to be available in June 2005.]**