Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities: Consensus Position Paper

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This monograph is not intended as medical advice. Its intention is solely informational and educational. Please consult a qualified medical or health professional if you wish to pursue the ideas presented.

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—The Consensus Position Paper—

This consensus position paper represents the current views of the undersigned clinicians and researchers. The consensus process was initiated at a conference convened for this purpose by the Autism Research Institute on September 29-30, 2004 in Los Angeles, California. The participants continued their discussions by telephone, fax, e-mail and, in some cases, in-person discussions. Following is the January 30, 2005 version of the Autism Research Institute's Consensus Report on Mercury Detoxification in Autism.

As of February 14, 2005, we have received 28 endorsements from reviewers who attended the Autism Research Institute's September 2004 Think-Tank on mercury detoxification in autism. We are awaiting endorsements from six reviewers who have not yet responded.

No one is more aware than the undersigned that this document represents merely a beginning step in our long-term efforts to solve an exceedingly difficult problem. We have much to learn.

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(in preparation)

THE AUTISM RESEARCH INSTITUTE
"Research That Makes a Difference"

The Autism Research Institute (ARI) has been in the forefront of research on the causes and treatment of autism since its founding in 1967. In that era, autism was considered to be a psychological disorder caused by the mother's emotional rejection of the child. Bernard Rimland, Ph.D., the founder of the ARI (as well as the founder of the Autism Society of America), is credited with destroying the "blame the mother" theory and setting autism research on its present course of seeking answers in the biomedical domain.

The ARI's Defeat Autism Now! (DAN!) project, initiated in 1995, is ARI's response to the abysmally slow rate of progress in autism research. ARI has enlisted a consortium of cutting-edge scientists and physicians from around the world to seek answers at an accelerated pace. The Mercury Detoxification Position Paper is one of many ARI/DAN! initiatives directed toward defeating autism as quickly as possible.

ARI depends upon the generosity of concerned individuals and organizations. Your help will speed the day when the horror of autism fades into history.

All donations are tax-deductible and are acknowledged.

ARI is a 501(c)(3) organization. Federal ID No. 95-2548452.

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February 8, 2005

INTRODUCTION TO THE 2005 UPDATE OF THE MERCURY DETOXIFICATION CONSENSUS REPORT

In recent years there has been a great deal of controversy regarding the possible role of mercury as a causal agent in the current worldwide epidemic of autism. While the scientific and legal issues will not be settled for some time, there are many autistic children who need help **now.**

The Autism Research Institute has been evaluating various biomedical treatments of autism since 1967. One approach has been simply to have parents rate the effectiveness of each of the biomedical treatments they have tried. Over 23,000 parents have responded to our questionnaires. Of the 77 biomedical interventions rated for efficacy by parents (see www.AutismResearchInstitute.com, select Parent Ratings of Treatments), mercury detoxification received a far higher rating than any drug, supplement, or special diet. Mercury detoxification was rated helpful by 73% of parents, with the gluten/casein-free diet coming in second with 63%. A remarkable and encouraging finding that must not be ignored!

The Autism Research Institute convened our first mercury detoxification Think-Tank in February 2001, in Dallas Texas, in response to the need for information on how best to treat mercury toxicity. The resulting Consensus Report published in May, 2001, has been widely distributed in hard copy and on the Autism Research Institute website.

A second mercury detoxification Think-Tank was held in Los Angeles in September 2004 to consider recent advances in detoxification technology. This report presents the findings of that Think-Tank.

I wish to extend my sincere thanks to the participants in our Los Angeles Defeat Autism Now! (DAN!) "Think-Tank" on mercury detoxification, whose experience and expertise are expressed in this report. Special thanks to Professor Jim Adams, Ph.D. for his superb work compiling and coordinating this 2005 Consensus Report on Mercury Detoxification for Autistic Children.

Bernard Rimland, Ph.D., Director
Autism Research Institute

Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities: Consensus Position Paper

Purpose

During the last several years, there has been growing clinical and scientific evidence that most children with autism suffer from mercury/metal toxicity. Furthermore, there have been many reports from physicians and parents that removal of mercury and other toxic metals can be very beneficial to children with autism, sometimes resulting in a major decrease in autistic symptoms. A wide variety of detoxifying agents and protocols have been used, and the purpose of this paper is to discuss the pros and cons of the different treatments available. **Overall, our consensus position is that removal of mercury and other toxic metals is one of the most beneficial treatments for autism and related disorders.** More research is needed, but effective treatments are available now. Each child is an individual, so this report presents general guidelines rather than specific recommendations.

Evidence of Mercury Toxicity in Children with Autism

There is extensive evidence that many children with autism suffer from mercury toxicity. Briefly, the evidence shows that children with autism have low levels of glutathione and cysteine (the pre-cursor to glutathione), which is the major pathway for removal of toxic metals like mercury. The children also often had excessive use of oral antibiotics, which greatly inhibits excretion of mercury. Due to their limited ability to excrete mercury, they have low levels in baby hair (an excretory tissue), high levels in baby teeth, and higher excretion when given DMSA compared to controls. The symptoms of autism are consistent with that of mercury toxicity. The epidemiology studies are mixed, but several published studies show a strong link between autism and thimerosal in vaccines. Overall, it appears that most children with autism suffer from mercury toxicity, and may potentially benefit from detoxification therapy. (See Appendix A for more details on mercury toxicity, and see Appendix B for more details on the strong evidence of mercury toxicity in children with autism).

Testing for Mercury/Metal Toxicity

There are several tests that can be considered for testing for mercury toxicity. We think that provocation testing and possibly antibody testing are the best methods, but sometimes repeated detoxification therapy is needed before significant excretion occurs. Blood, hair, and unprovoked urine are generally NOT good ways to test for infantile exposure to mercury, which is when we believe the primary exposure occurred. Other possible ways to test for mercury toxicity are described in Appendix C.

Blood: Most physicians are used to testing for the presence of lead in the blood. Most lead exposures involve a chronic ongoing exposure, so this is a reasonable method for testing for lead, even though lead has only a short half-life in the blood. However, it is

NOT a good method for testing for past exposures, since mercury and other metals have only a short half-life (weeks) in the blood.

Hair and Urine: Hair and urine are measures of the body's excretion of toxic metals, which is affected by both the body burden and the body's glutathione level (which controls excretion). Hair grows at a rate of 1 inch per 1-2 months, so the length of hair determines what time period it is averaging over. Urine is a measure of recent exposure, usually during the last few days. Glutathione levels are often low in autism, resulting in lower excretion ability, so a decreased glutathione level can mask a high body burden. In practice, hair and unprovoked urine are usually NOT good methods to test for mercury/metal toxicity in autism.

Provocation Test: The most conclusive method to test for mercury/metal toxicity is the use of detoxification agents, followed by a collection of urine or stool depending on the mode of excretion. This test tells you two important facts: 1) the metal was present in the body, and 2) it demonstrates that the detoxification agent can remove it.

One major limitation of these tests is that the reference range for the urine or stool generally involves a comparison to people who are NOT taking a detoxification agent, so that even a normal person would tend to have a high result. Thus, an experienced clinician needs to interpret the results carefully. (One exception is a DMSA test for children, for which limited data exists – see below).

Another limitation is that low doses of the detoxification agents may fail to increase excretion significantly. It is not fully understood, but it appears that the first part of the dose may be neutralized by the body, so higher doses may be needed for provocation testing vs. long-term treatment.

One complexity of provocation tests is that the detoxification agent may preferentially bind to one metal first, so excretion of that metal may hide the presence of other metals. Mercury can be tightly bound to body tissue, and it may not be removed until significant amounts of other toxic metals have been removed.

It is suggested that a baseline urine sample be collected, followed by the provoked sample the next day at the same time of day. This allows one to directly compare the effects of the provocation with the unprovoked urine. Comparing with the unprovoked urine also helps if the person has abnormal creatinine levels, as the test is usually reported as a ratio of toxics to creatinine. Creatinine is often found to be marginal in the urine of autistics, and low creatinine can skew urine analyte results to high levels. So, also take note of creatinine levels if the laboratory results include ratioing to creatinine.

Some typical provocation tests include:

- Oral DMSA (9-dose): Dosage of 10 mg/kg-dose, 3x/day, for 3 days. Just before administering the last dose, void the bladder, and then collect all urine for the next 8-10 hours. This test has the advantage that Bradstreet et al.[1] have established a reference range for typical children, based on a study of 18 typical children vs. 221 children with autism. Using Doctor's Data Laboratory, they reported levels of 1.29 +/- 1.54 mcg Hg/g-creatinine, 15.0 +/- 9 mcg Pb/g-creatinine, and 0.46 mcg Cd/g-creatinine in typical children given DMSA. Children with autism had, on average, 3x higher levels of Hg excretion.

- Oral DMSA (single dose): Dosage of 20-25 mg/kg-dose, 1x. Void bladder and then administer DMSA, and collect all urine for 6-10 hours. (Do not use only 10 mg/kg, as a study by Adams et al. found no major difference between 15 children with autism vs. 15 controls). Some physicians do not recommend this higher single dose due to concerns about adverse reactions, and prefer the series of lower doses mentioned previously.
- Rectal DMSA (single dose): 25mg / kg of body weight as a single bolus dose with urine collection beginning the next morning in potty trained children and through the night with pediatric urine collection bags in those children who aren't. Collection time varies between 12-24 hours depending on the physician's preference and family logistics

DMPS Challenges: Several DAN! physicians have experience with DMPS provocation challenges and find them to be useful, whereas other DAN! physicians do not use them. For those who support the use of DMPS, the following are the suggested dosages for single dose challenges:

- Oral DMPS (single dose): 5-10 mg/kg, single dose, followed by a 6-12 hour urine collection. Children may be at the lower dosage range, and adults may be at the higher dosage range, depending on their physician's recommendation.
- IV DMPS (single dose): Dosage of 3-5 mg/kg, followed by a 6-8 hour urine collection.
- Transdermal DMPS (single dose): Dosage of 3 mg/kg, followed by a 12-24 hour urine collection.
- Rectal DMPS (single dose): 10 mg/kg, with the suppository retained at least 30-45 minutes, followed by a 8-12 hour urine collection.

There are informal reports that co-administration of glutathione with DMPS may increase urinary excretion of toxic metals, although this is not certain yet.

One of the most common laboratories for testing urinary levels of toxic and essential minerals is Doctor's Data Laboratory, 170 W Roosevelt Rd, West Chicago, IL 60185 Phone (800) 323-2784; 708 231-3649.

Testing for Antibodies Against Metals and Their Binding Proteins

In the field of immunology it is well-known that metals can bind to different amino acids and become antigenic. Metals either oxidize proteins or form stable protein-metal chelate complexes by undergoing multi-point binding to several amino acid chains. Based on these chemical reactions, metals can persist for years in the body and continuously activate T-cells through specific alteration of self-protein. [2] [3]

These alterations of self-proteins by metals or other chemicals may result in antibody (IgG, IgM, IgA) production against the haptenic chemicals; for example, mercury, cobalt and nickel, and self-proteins such as hemoglobin and human serum albumin. Detection of IgG, IgM or IgA antibodies against these haptenic chemicals indicates chronic exposure to low levels of environmental metals and possible autoimmune response. [4]

In addition, it is documented that two different nucleoproteins, fibrillarin and chromatin, are targets for metals which induce production of autoantibodies in human. [5]

Based on these findings it is possible to measure and document antibodies against mercury and the mercury-binding proteins fibrillarin and chromatin in individuals with chemical exposure to metals.

Antibodies against mercury, fibrillarin and chromatin occur in 5-10% of controls, but in 30-50% of children with autism.[6] 0.5 mL of serum is typically needed for performing assays of mercury, fibrillarin and chromatin antibodies. One lab that offers these tests is Immunosciences (www.immuno-sci-lab.com).

Pre-Detoxification Treatment

Prior to beginning detoxification therapy, it is important to first address several issues, including reduction of toxic exposure, improvement of nutritional status, normalization of glutathione levels, treatment of intestinal dysbiosis, and baseline kidney/liver function and Complete Blood Count (CBC).

1) Reduction of Toxic Exposure: Since the goal of detoxification is to lower toxic body burden, it is important to first reduce exposure to toxic metals as much as possible. This includes:

- Avoidance of mercury-silver dental amalgams, which are the major source of mercury in most Americans. If a child has mercury amalgams, they may need to be carefully removed prior to beginning detoxification therapy. Removal should only be done by an expert dentist trained in safe removal of amalgams, using high-vacuum suction and other safety measures, and even those measures can result in a temporary increase in mercury exposure.
- Avoidance of fish and some shellfish, especially the largest fish (shark, swordfish, tuna), which are highest in mercury. (Purified fish oil is allowed, as that contains important essential fatty acids and does not contain significant amounts of mercury. The safest oils are those that have also been tested for PCB's and other fat-soluble toxins).
- Purified water: have it tested by your local water company, or use reverse osmosis to remove all the toxic (and sadly the essential) minerals
- Organic foods (preferred) or extensive washing of the surfaces of fruits and vegetables.
- Use only thimerosal-free vaccines.

2) Nutritional Status: Most children with autism have a need for increased amounts of vitamins, minerals, and some amino acids. Zinc is of especial concern, as it is usually low in autism. Some detoxification agents can remove essential minerals, so additional minerals will be needed. Anti-oxidant therapy is important to reduce oxidative stress and to raise glutathione levels. Vitamin C, Vitamin E, Vitamin B6, zinc, and selenium are especially needed, in addition to a broad-spectrum vitamin/mineral supplement. Copper

should be avoided in most cases, since that is usually high. Nutrient supplementation is discussed in more detail later in this report, and also in Biomedical Assessment Options for Children with Autism by Pangborn J and Baker SM.

3) Glutathione: Glutathione plays many important roles in the body, including binding to and eliminating toxic metals. Plasma glutathione levels are typically 50% lower in children with autism, so it is important to normalize them prior to beginning detoxification. Otherwise, it is like bailing a leaky ship; you can bail out water (toxins), but they will leak back in if the "leaks" (lack of glutathione) are not fixed. Normally, glutathione concentrations are much higher inside cells, so it is best to measure levels inside erythrocytes (red blood cells). Glutathione levels can be increased in several ways, including:

a) transdermal, subcutaneous or IV glutathione. A new lipoceutical form looks promising. It is unclear if oral administration is effective in raising plasma glutathione levels.

b) a study by James et al.[7] found that 800 mcg of folinic acid and 1000 mg of TMG partially raised levels of glutathione in children with autism, and the addition of subcutaneous injections of methyl-B12 (75 mcg/kg, 2x/week) normalized glutathione levels. Note that the dosage of methyl-B12 was suggested by Dr. J. Neubrander, based on injecting it into the adipose tissue of the buttocks. (Note that Dr. Neubrander now recommends a dosage of 64.5 mcg/kg every three days)[8] The addition of vitamin B6 (a necessary co-factor) is likely to raise levels further. The addition of methionine may be helpful, but it should be done with extreme caution after methyl-B12 has been given to prevent negative reactions.[8]

c) Vitamin C: a study by C. Johnston[9] of college students found that the addition of 500 mg/day of vitamin C raised glutathione levels 50%. Raising the vitamin C to 1000 mg had no additional benefit.

4) Gut Dysbiosis: At least 50% of children with autism suffer from constipation and/or diarrhea, and a study by Rosseneu[10] found that 95% of those children had extremely high levels of E. Coli and often other bacteria that produce high levels of endotoxins. Yeast dysbiosis may also be a concern. Some detoxification treatments can cause or exacerbate bacteria/yeast dysbiosis, either directly by providing food to them, or by causing excretion of toxic metals into the gut. This appears to especially be a problem for oral alpha lipoic acid and NAC, sometimes is a problem for oral DMSA, somewhat less of a problem for oral DMPS, and perhaps rarely a problem for transdermal DMPS. See Appendix D for a more detailed discussion.

5) Monitoring Liver/Kidney/CBC before and during Detoxification

It is important to check kidney function (BUN, creatinine) and liver function (SGOT, SGPT, GGT, ALT, AST) prior to using some detoxifiers, and it is important to continue to monitor liver and kidney function. Similarly, it is important to check Complete Blood Count (CBC) including platelet count prior detoxification, as some detoxifiers can adversely affect liver/kidney function, platelet count, and lymphocytes. This is discussed in more detail below.

Detoxification Options

Detoxification should only be considered after the issues discussed above in the Pre-Detoxification section have been addressed to the degree possible. (More information is available in Biomedical Assessment Options for Children with Autism and Related Problems, by Pangborn, J and Baker, SM, published by the Autism Research Institute.)

There are many different agents for detoxification of metals, and some agents can be administered in different ways (IV, oral, rectal suppository, transdermal). The three major ones we will discuss include DMSA, DMPS, and TTFD. In determining which agent(s) to consider, one needs to consider its efficacy, toxicity, possible removal of essential minerals, effect on gut dysbiosis, legal status, and clinical experience.

Option 1: DMSA:
Legal Status: DMSA in the oral form is approved by the FDA for treating lead poisoning in children (as young as one year of age) who have lead levels ≥ 45µg/1OOml blood. Like any approved drug, physicians can prescribe it for "off-label" uses such as treating other types of metal toxicity. It is also available as an "over-the-counter" supplement, but we strongly recommend only taking it under the supervision of a knowledgeable physician.

Efficacy: DMSA has been demonstrated to be able to bind and remove a wide range of toxic metals, including lead, mercury, arsenic, tin, nickel, and antimony. Animal studies have demonstrated that DMSA can effectively lower the level of mercury in the kidney and many other tissues, but does not seem to be able to go intracellularly or to penetrate the blood-brain barrier. Several studies have shown it does not lower the level in the brain of animals.

Absorption/Excretion: When DMSA is taken orally, about 20% is absorbed, and blood levels peak in 2-4 hours.[11] Excretion is much slower, with a half-life of approximately 2 days.[12] DMSA is primarily excreted in the urine, mostly as DMSA-cysteine disulfide.[11]

Testing Prior to and During Use of DMSA:

- Since DMSA is primarily excreted in the urine, it is important to monitor kidney function every 2-3 months.
- Long-term use of DMSA can cause bone-marrow suppression, so it is important to monitor the Complete Blood Count (CBC) and platelet count.
- DMSA can cause liver damage, it is important to monitor liver transaminases (ALT, AST, GGT).
- DMSA is known to approximately double excretion of zinc, so zinc levels should be monitored before and during treatment, since zinc is often low in autism, and zinc should be supplemented if necessary to maintain normal levels. If levels remain low after initial supplementation, unusually high levels of zinc (50-100 mg) may be needed.

- DMSA increases excretion of Cu.[12] Cu is normally high in autism, so this is usually beneficial, but Cu levels should be monitored prior to and during treatment.
- DMSA does not affect excretion of iron, calcium or magnesium.[12]

Forms of DMSA:

Oral: The oral form is most commonly used. It appears that oral absorption is approximately 22%.[11] The limitation of this form is that it causes a worsening of GI symptoms in about 10-20% of autistic children, probably because the unabsorbed DMSA can be consumed by intestinal yeast/bacteria.

Intravenous: The FDA has not approved IV DMSA, and there is no peer-reviewed scientific study of the IV form of DMSA.

Rectal: There is only limited experience with the use of rectal suppositories. They seem to offer the advantage of the oral form (slower absorption), but with less chance of aggravating intestinal dysbiosis. This form is not approved by the FDA, but may be compounded by a pharmacist upon authorization by a physician.

If used as a rectal suppository, the same administration schedule can be used; however due to bowel frequency thrice daily dosing can present problems as the suppositories should be retained for 30-45 minutes. It is possible to dose rectal DMSA once the child has fallen asleep in some children.

Dosing for detoxification between challenges is also influenced by patient specifics. Many parents dose 10 mg/kg per suppository three times daily following the 3 /11 cycle; however, single daily dosing is anecdotally well tolerated and may be a better balance for the child that moves his or her bowels more than once daily.

Additionally, rectal suppositories can not contain much more than 500 mg of DMSA and thus for larger children the dosing regime may need to be adjusted. As with any rectally administered medication, there exists the possibility of a rash. Resolution has been seen using “Bag balm”.

Recommended Administration:

DMSA should be given in oral doses of no more than 10 mg/kg/dose, and no more than 30 mg/kg/day with a maximum dose of 500 mg/dose (1500 mg/day maximum). Exceeding these limits has been associated with a significantly higher incidence of side effects and toxicity. Most physicians recommend dosing every 8 hours, but a few prefer more frequent dosing (but the same daily dose).

Typical treatment periods are 3 days, followed by 11 days off, which makes for a convenient 2-week cycle with dosing typically from Friday afternoon to Monday morning. These cycles can be continued for several months until urinary excretion is decreased to near the reference range.

If used as a rectal suppository, the dosage should be 25 mg/kg, 1x/day, for 3 days on, 11 days off.

Safety Issues:
DMSA slightly increases the excretion of zinc and copper, so those levels should be monitored, and zinc should be supplemented during therapy.
The Physicians Desk Reference reports the following side-effects when using DMSA for 19 days continuously: gastrointestinal upset in about 12% of patients, body aches (5%), increases in serum transaminases (4%), sore throat/cough (4%), rashes (3%), drowsiness (1%), eye/ear irritation (1%). Prolonged use can cause elevations in liver enzymes and bone marrow suppression in less than 1% of cases.

However, when using DMSA on a 3 day on, 11 day off schedule, the chance of these side effects is usually less. If these symptoms become serious enough, reducing the dose will usually make the symptoms tolerable. Occasionally, patients develop a maculopapular rash during treatment; this should not to be confused with an allergic reaction[13]. Some autistic children are reported to experience a transient regression in language and behavior during and shortly after treatment. Reducing the dose may also make these symptoms less bothersome. Clinical experience suggests that most children who experience regression at the start of therapy will have less regression with each subsequent cycle of treatment.

Serious side effects of DMSA are extremely rare and include allergic reaction, toxic epidermal necrolysis (TEN) and erythema multiforme (Stevens-Johnson syndrome)[1]. Potentially dangerous neutropenia and thrombocytopenia may also occur[14]. While reducing the dose may reduce the severity of the neutropenia and thrombocytopenia, truly dangerous reductions in cell count are a

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[1] No cross-sensitivity between DMSA and the sulfa antibiotics has been reported. If the patient has a history of sensitivity or allergy to other dithiol chelating agents (*e.g.* DMPS, DMPA, dimercaprol/BAL), they may not be a candidate for DMSA therapy, depending on the severity of the reaction. If the reaction was mild or ambiguous, a small test dose can help resolve the issue.

Toxic epidermal necrolysis and erythema multiforme occur without predictable pattern and their etiologies are poorly understood. Both may occur with the initial treatment or may appear after several months of therapy. Both have been reported only a few times in connection with DMSA even though tens of thousands of children have received the drug. Erythema multiforme (Stevens-Johnson syndrome) is a self-limited inflammatory disorder of the skin and mucous membranes. It is thought to be induced by immune complexes and mediated by lymphocytes. It is characterized by distinctive target-shaped skin lesions, sore throat, mucous ulcers and fever. It usually begins a week or more after therapy starts and will usually resolve spontaneously if the inciting medication is stopped. However, it can cause severe mucocutaneous complications and take weeks to resolve with supportive care.

Toxic epidermal necrolysis (TEN) is the most serious cutaneous drug reaction and may be fatal if not recognized. Its onset is generally very acute and characterized by epidermal necrosis without significant dermal inflammation. Its pathology is poorly understood but it also usually resolves when the inciting agent is stopped. There are no other specific treatments other than supportive therapy and symptom relief.

contraindication to continued therapy without a compelling reason to do so. Obviously, allergic reaction, TEN and Stevens-Johnson syndrome are absolute contraindications to continued therapy.

Benefits: Many DAN! physicians have reported good improvements with DMSA, although the improvements are sometimes accompanied by gut problems. Reported benefits include rapid progression of language ability, improved social interaction, improved eye contact, and decreased self-stimulatory behaviors ("stimming"). Children with motor problems have experienced significant improvement in both strength and coordination.

There was an open-label study of the use of DMSA on 152 autistic patients by A. Holmes.[15] It involved the same dosage proposed in this study (10 mg/kg for 3 days, then 11 days off) for at least 6 months. Alpha lipoic acid was added in month 3 onward to enhance excretion. In the youngest group (age 1-5, n=66), they found:

No improvement: 10%
Slight improvement: 15%
Moderate improvement: 39%
Marked improvement: 36%

Definitions:

- **None**
- **Slight**: now speaking in 1-2 word phrases, able to express wants and needs verbally, not conversational.
- **Moderate**: improved but not normal; obvious language delay but using sentences, answers questions.
- **Marked**: Mainstreamed into regular education; minimal or no language delay, normal social interaction and eye contact.

The benefits were generally less for the older children and teens. Several other physicians (Cave, Bradstreet, El-Dahr, others????) have reported similar results.

Anti-Oxidant Benefit: DMSA is also a potent anti-oxidant, and it could be that part of the benefit of DMSA is due to its anti-oxidant function. A recent study by James et al.[7] found that children with autism had a much higher ratio of oxidized:reduced glutathione, a study by Chauan et al[16] found increased lipid peroxidation, and a paper by McGinnis[17] discusses oxidative stress in autism in more detail. Overall, it appears that oxidative stress is an important issue in autism, so the anti-oxidant effect of DMSA may be important.

Option 2: DMPS:

Legal Status: DMPS is not an FDA-approved medication. Physicians may have it individually compounded for their patients by a pharmacist, but should inform their patients of its experimental status in the US, and have a full disclosure/informed consent document in the medical chart of each patient using DMPS. It is widely available in Europe as a prescription medication, and in Germany it is available over-the-counter. In the US, physicians can ask a pharmacist to compound it for an individual patient.

Efficacy: DMPS is an effective chelator, especially for mercury, and also for lead, cadmium, silver, tin, and arsenic. Many animal studies have demonstrated that it can lower the level of mercury in the kidneys and most other organs. A recent animal study by Pinegree et al. [18] demonstrated that repeated use of it could slowly lower the level of methylmercury in the brain, but had little effect on inorganic mercury. (Pinegree's study found that DMPS can initially increase the level of mercury in the brain if the body burden is high, presumably by transporting it from the body into the brain, and that could be related to transitory side effects before repeated use eventually decreases the level in the brain.)

Metabolism/Excretion: DMPS is rapidly metabolized in the body into an altered (disulfide) form. DMPS is primarily excreted in the urine (84% of an IV dose was excreted in the urine after 96 hours).[19] When given IV, of the DMPS that was excreted, 12% was excreted as the parent drug (DMPS), and 88% was excreted as the disulfide. The parent drug was excreted rapidly (half-life of 1.8 hours), but the disulfide was excreted much slower, so that the elimination of total DMPS had a half-life of 20 hours. Mercury excretion correlated well with urinary excretion of both the parent drug and the total DMPS.

If taken orally, the half-life for excretion is 4.4 hours for the unaltered DMPS, and 9.6 hours for the altered DMPS.[20] (The half-life is shorter for the oral form presumably because oral ingestion requires passage through the liver where it is metabolized). Mercury excretion correlated very strongly (0.92) with excretion of the unaltered DMPS, and peaked at about 2 hours after ingestion.

The half-life for transdermal applications is unknown, but it is probably somewhat longer than for the IV form.

Testing Prior to Use:
The following testing is recommended prior to use of DMPS:

- Complete Blood Count (CBC) including platelets
- Full blood chemistry panel including liver transaminases

Some physicians also suggest the following tests:

- Red Blood Cell (RBC) minerals
- Serum copper and plasma zinc levels (DMPS can decrease those)
- Iron test

Patients need to continue monitoring CBC, liver function and mineral depletion every 2-3 months during treatment.

Forms of DMPS:
Oral: It appears that oral absorption is approximately 39%, much higher than for DMSA.[19] The oral form seems to be less likely to cause gastrointestinal problems than DMSA, presumably because much lower dosages are used and more is absorbed, leaving very little DMPS available to gut bacteria/yeast. It can be compounded into a suspension for children who do not swallow capsules. Children on DMPS sometimes complain of abdominal discomfort and/or cramping, especially with the oral form.

Intravenous: The IV form is less likely to result in exacerbation of gastrointestinal dysbiosis. Several DAN! physicians have found IV DMPS safe and effective for treating children with autism. However, most DAN! physicians are not experienced with the use of IV DMPS, so more experience and research is needed before it can be recommended for general use.

Transdermal: There have been recent reports by Buttar [21] and other physicians regarding the benefit of transdermal use of DMPS. This is claimed to be an easy, non-invasive form of detoxification that appears to have a lower incidence of gastrointestinal side-effects (such as pathogen overgrowth) than the oral form. Some physicians have stated that roughly one-third of children with this treatment will temporarily have worsening behaviors after the first month of treatment, usually lasting a month or so before improving. There are several compounded formulations available, and the relative merits of the different formulations are unclear at the present time.

Recommended Administration:

Oral: Typical dosages are 1-2 mg/kg, 3x/day, for a total dose of 3-5 mg/kg-day. Typical treatment periods are 3 days, followed by 11 days off, which makes for a convenient 2-week cycle with dosing typically from Friday afternoon to Monday morning. These cycles can be continued for several months until urinary excretion is decreased to near the reference range.

Transdermal: Typical dosages are 1.5 mg/kg, every other day. If adverse effects occur, the dosage can be lowered to 1 mg/kg, or discontinued if the adverse effects are serious. Some physicians recommend only giving mineral supplements (at twice the normal dose) on the days when no DMPS is administered, to optimize the efficacy of the DMPS and to reduce loss of essential minerals.
Typical treatment duration may last from several months up to a year.

Rectal: Typical dosages are 10 mg/kg, 1x/day, for 3 days on, 11 days off.

Safety Issues:

The following excerpt is taken from the package insert of Heyl's Dimaval (DMPS):

"Occasionally, patients may develop chills, fever, or cutaneous reactions, presumably of an allergic nature such as itching or rashes (exanthema), which usually are reversible once the treatment is stopped. Severe allergic dermatological reactions (e.g. erythema exudativum multiforme, Stevens-Johnson's syndrome) have been described in a few isolated cases.

Particularly when used over a long period of time, DMPS may influence the body's mineral balance, especially that of the elements zinc and copper.

The administration of DMPS mobilizes the ingested mercury in the body. In a few cases this may trigger the clinical symptoms of mercury poisoning.

Sickness or vomiting rarely appear after ingestion of Dimaval (DMPS).

In some cases an increase in the level of transaminases may occur."

So, it is important to monitor zinc and copper levels, and to supplement zinc and possibly copper if they are low.

Benefits:
Several DAN! physicians and others have reported on the benefits of DMPS in both oral and transdermal forms. Most notable benefits of the transdermal form are reported for social and language areas. It appears to be more effective at excreting mercury than DMSA. Buttar has reported (in an unpublished study) [21] that 19 of 31 patients using transdermal DMPS with glutathione for over a year, in addition to other therapies such as restrictive diet, nutrients, mineral supplements, and anti-pathogen treatments, had a complete loss of autistic symptoms.

Option 3: TTFD (Thiamine Tetrahydrofurfuryl Disulfide)

Legal Status: TTFD is not approved by the FDA. Physicians may have it compounded for individual patients by a compounding pharmacist. The FDA has granted D. Lonsdale Investigational New Drug (IND) approval for the investigational use of oral TTFD.

Efficacy: TTFD is an open thiazolium ring disulfide derivative of thiamin. At the cell membrane it is reduced and the thiazolium ring closes within the cell to provide free thiamin. The prosthetic mercaptan is left outside the cell, becomes bound to albumin and may have a weak chelating action on SH-reactive metals (SHRM). The main action of TTFD is due to the phosphorylation of the intracellular free thiamin to form thiamin pyrophosphate (TPP) and thiamin triphosphate (TTP), thus catalyzing energy metabolism. Animal studies have shown that TTFD causes excretion of SHRM via the bile and urine. When administered in conjunction with thiol chelators the urinary concentration of these metals is greater than with either agent given alone.

In a pilot study, [22] 8 of 10 ASD children improved clinically when treated with TTFD suppositories and some of them had a significant increase in urinary SHRMs.

Testing prior to use: TPP deficiency is revealed by testing erythrocyte transketolase activity (TKA) and the effect of adding TPP to the reaction (TPPE). The test is not a necessity to using TTFD as therapy. In a pilot study, only two of ten ASD children were TPP deficient at outset, and it did not predict response.[22] This test gives no information on TTP deficiency, a presently unknown contributing factor. Call 1-888-WSTLAKE for laboratory information on TKA.

Forms of TTFD:

Oral forms of TTFD should preferably be enteric-coated tablets, presently unavailable in the U.S. It can be compounded and given by mouth in capsules, by rectal suppository or transdermally. The extremely bad taste of powdered TTFD prevents oral administration to young children should the capsule be opened for this purpose.

Recommended Administration:

Fifty milligrams (50 mg) given one or two times a day can be administered indefinitely since it represents an efficient method of providing vitamin B1. There is no set time for determination of treatment.

TTFD with Glutathione: There have been recent reports that the benefits of TTFD are increased with the simultaneous administration of transdermal glutathione. This also tends to significantly increase the odor of the TTFD.

Safety:

TTFD has an exceptional safety record. No toxicity has been reported, even at much higher doses than used therapeutically in human subjects. Studies have shown that it does not harm the embryo when given in high doses to a pregnant animal. Rectal suppositories may give rise to perianal irritation, relieved quickly by discontinuation of use. Transdermal application may cause a rash or irritation at the site. This can be obviated usually by rotating the site of application. It is thought that this is due to the excipients in the preparation rather than a direct effect of TTFD. A "skunklike" odor arises in some patients treated with either the rectal or transdermal forms of TTFD. No odor is associated with oral administration. This odor often gradually diminishes as treatment continues and is thought to be related to metabolism associated with the prosthetic mercaptan and possibly excretion of toxic metals. This prosthetic group has been well studied and is not associated with any toxicity.

Benefits:

Many DAN! physicians have reported clinically observed improvement in their ASD patients using TTFD, mainly in the transdermal form. Initial worsening of symptoms sometimes occurs, as it does with other nutrients given to ASD children, and may be followed by improvement with persistence. The only published study is that of Lonsdale et al (1). Urine studies before and after TTFD treatment showed increased concentration of SHRM in some of the subjects and this has been confirmed in unpublished observations by others.

Mineral supplements

Because of poor nutrition (often due to idiosyncratic food preferences), poor absorption, and other, poorly understood factors, autistic children usually have numerous mineral deficiencies. Chief among these deficiencies is zinc. Zinc supplements should be given prior to, during and after detoxification therapy. Zinc given with DMSA will complex with it and will be more readily absorbed as a consequence [23,24]. Supplementation with 1 – 2 mg/kg/day of elemental zinc is recommended (maximum of 50 mg/day unless guided by laboratory evidence of marked deficiency); more may be needed and plasma, erythrocyte or platelet zinc levels can be used to guide doses higher than this.

Autistic children are also often deficient in selenium. Since this mineral is one of the few that can cause a significant toxicity if it is present in excess, caution should be exercised. In the absence of laboratory evidence of a profound deficiency, selenium supplementation should be limited to 1 – 4 mcg/kg/day.

Magnesium, molybdenum, manganese, vanadium and chromium are all among the minerals that are often deficient in autistic children; these can be supplied by a multi-mineral supplement. Be

sure that this supplement does not contain copper. Copper is the one mineral that autistic children often have in excess and additional supplements will only worsen the excess.

Vitamin supplements

Although the conventional wisdom is that the "average American" receives all the vitamins and nutrients they require in a balanced diet, there are several reasons why this is not true in autistic children. First, autistic children rarely eat a balanced diet. They often have an extremely limited number of foods they will accept and these rarely encompass all of the major food groups. They may have decreased absorption of needed vitamins and minerals due to poor digestion and gastrointestinal inflammation. One study by Audhya of 180 children with autism vs. over 80 controls found that many children with autism had unusually low levels of most vitamins and several minerals.[60] They are often under significant oxidative stress,[7] so a high dosage of antioxidants is often needed. So, a broad-spectrum multi-vitamin/mineral supplement with high amounts of vitamin C is recommended.

Vitamin C: An important anti-oxidant, vitamin C can be a great benefit to autistic children. One double-blind, placebo-controlled study (n=18) of high dose vitamin C (110 mg/kg for 10 weeks) found it to be beneficial.[25] Since it is a water-soluble vitamin, it is rare to see true toxicity, although ascorbic acid crystals in the urine (and the potential for renal stones) will result from sustained use of extremely high doses. More commonly (and usually at doses over 2000 mg/day), gastrointestinal distress and diarrhea are the only side effects from vitamin C. Using the buffered preparation or vitamin C esters can significantly reduce the incidence of gastrointestinal side effects, as will dividing the dose. Vitamin C supplementation should start at 5 –10 mg/kg/day and gradually increase to tolerance. Some may tolerate and, in fact, need more than 50 mg/kg/day.

Vitamin E: Another of the anti-oxidant vitamins, vitamin E has received more press lately than vitamin C. Since it is fat soluble, it can accumulate if given to excess. Dosing in the range of 2 – 4 mg/kg/day (3 – 6 IU/kg/day) is within safe limits. Mixed tocopherols are the preferred preparation. Many vitamin E supplements are prepared from soybeans and may be a problem in children who are sensitive to soy products. Since vitamin E is important in preventing fatty acid oxidation and peroxidation, more may be needed if the child is also receiving essential fatty acid supplements.

Vitamin B_6: B6 is needed for many enzymatic reactions, including the production of cysteine, a precursor for glutathione. Vitamin B_6 can be found as B_6 (pyridoxal, pyridoxine), pyridoxal-5-phosphate (P5P). Doses of around 17 mg/kg/day of pyridoxal HCl (up to 500-1000 mg) appear to be beneficial to 50% of children and adults with autism, and sometimes even higher doses can be beneficial. For the P5P form, typically only 1/5 that dosage is used. Be aware that many of the pyridoxal-5-phosphate preparations contain supplemental copper to prevent pyridoxal retinopathy in copper-deficient people. Since autistic children are typically *high* in copper, be sure to use a copper-free preparation.

Other supplements

Melatonin: The pineal hormone that helps to regulate the sleep/wake cycle, melatonin is also an anti-oxidant. It is relatively unique among natural anti-oxidants in that it is a *terminal* anti-oxidant: once oxidized, it cannot be reduced[26]. This characteristic means that melatonin cannot participate in destructive redox cycling, where an oxidized compound is reduced by oxidizing

another compound. One study has found that neurons are protected from mercury damage by hormonal levels of melatonin[27]. Melatonin is also concentrated in the mitochondria and protects them from oxidative damage.[28]

Aside from its anti-oxidant properties, melatonin helps to regulate the sleep/wake cycle, which is often seriously deranged in autistic children. Its long-term use in institutionalized children has established its safety[29]. Doses of up to 0.1 mg/kg at bedtime should be adequate to help with sleep disturbances. Some clinicians have noted that smaller doses of melatonin (0.3 mg in adults) are just as effective for sleep and may cause fewer problems with nightmares and/or night terrors. A sustained release form of melatonin is currently under development and should help with those children who awaken four to six hours after the dose of melatonin.

Taurine: Taurine is a sulfur-containing amino acid which is important in the production of bile salts and, therefore, in the native excretion of toxins and absorption of fats and fat-soluble substances. Some autistic children are deficient in taurine and benefit from a supplementation of 250 – 500 mg/day. A maximum dose of 2 grams/day in adults and adult-sized children is recommended.

Glutathione: Glutathione is the keystone of the cellular anti-oxidant system and is often deficient in autistic children. Despite numerous rodent studies that show good systemic absorption of oral glutathione, the two human studies looking at oral absorption have shown it to be nil[30]. In humans, oral glutathione is readily absorbed by the gut mucosa, repleting its glutathione supply; the mucosa then breaks down the remaining glutathione. This may explain why oral glutathione has been of help to autistic children even when there is apparently no systemic absorption. Given the gut dysfunction found in many autistic children, oral glutathione 250 – 500 mg/day may be of significant help.

Supplements to be wary of

***Alpha*-Lipoic acid:** A dithiol fatty acid, *alpha*-lipoic acid is a native chelating agent but is also a powerful anti-oxidant. It has been extensively used in Germany to treat diabetic neuropathy with excellent results[31]. Its anti-oxidant effects may be particularly helpful in autistic children, since many of them show clear evidence of anti-oxidant depletion.

Alpha-lipoic acid is a natural product of human cells and so has minimal toxicity; doses of up to 25 mg/kg/day given over more than three years have been studied in adults with no detectable toxicity[32]. There is a theoretical concern that *alpha*-lipoic acid may bind to DMSA and reduce the availability of both, but this has not been seen clinically. Another concern is that *alpha*-lipoic acid reduces the removal of methyl-mercury by glutathione, which is a reason why it should be given with DMSA. There is also evidence that *alpha*-lipoic acid reduces copper excretion[33]. Since DMSA *increases* copper excretion[34] (it has been used to treat the copper intoxication of Wilson's disease[35]), this should not be a problem if *alpha*-lipoic acid is used with DMSA.

A serious concern with *alpha*-lipoic acid it is readily consumed by yeast, and its usage can often exacerbate intestinal yeast overgrowth. The risk of yeast overgrowth may be decreased by lowering the dose or by transdermal administration, although absorption by transdermal forms has not yet been established. A prior history of yeast infections is a contra-indication for use of alpha lipoic acid.

Cysteine/cystine: As sulfur-containing amino acids (cystine is the dimer of cysteine), both can bind to and mobilize mercury. Like *alpha*-lipoic acid, cysteine and cystine may worsen mercury

intoxication by spreading it to other tissues. Furthermore, cysteine and cystine are excellent culture media for the *Candida* genus of yeast and can promote or worsen intestinal candidiasis.

N-Acetyl-L-Cysteine (NAC): NAC should not be used initially or by itself with anyone suspected of having a significant body burden of mercury. Like *alpha*-lipoic acid, cysteine and cystine, NAC can bind with mercury and carry it across cell membranes. NAC is also a good culture medium for yeast, like its parent molecule, cysteine. Since many autistic children also have high cysteine levels, giving them NAC will only exacerbate this problem.

NAC is often recommended because it can rapidly increase intracellular glutathione levels[36,37]. For that reason, it can be tremendously useful in treating the antioxidant deficiencies seen in so many autistic children. NAC should be used either in conjunction with DMSA or after mercury detoxification is well under way. In addition, NAC should be used with extreme caution in children with elevated cysteine levels.

NAC should not be used orally, because it is a food for yeast and can frequently cause or exacerbate gastrointestinal problems. It can be given transdermally or nasally.

D-Penicillamine

D-Penicillamine is a cysteine-like amino acid (slightly different chemical structure) that has had several therapeutic uses. In Wilson's disease, D-penicillamine, which is also called "Cuprimine" (Merck), has been given as an oral chelating agent for lowering blood copper levels.[38] It has been found beneficial in some cases of rheumatoid arthritis where other modalities are ineffective.[39] In cystinuria, D-penicillamine participates in sulfhydryl-disulfide exchange with cystine.[40] This serves to reduce cystine levels by forming a cysteine-penicillamine disulfide which is excreted more readily in urine than cysteine. In heavy metal poisoning, D-penicillamine has been used for both lead and mercury removal,[41] , and it is also credited with removing arsenic.[42]

While removal of mercury, lead, copper and arsenic may sound like beneficial interventions for autistics, D-penicillamine also has possible, significant detrimental effects. First, it lowers cysteine levels by lowering blood cystine, and cysteine is often low or deficient to begin with in autism. By this process, D-penicillamine can also lower glutathione stores. Second, this drug is a pyridoxine antagonist. It complexes with the vitamin and impairs coenzyme function of vitamin B_6 (as pyridoxal 5-phosphate).[43] And nearly 50% of autistics need and benefit from vitamin B_6 (with magnesium) as a supplement.[44] Pathological side effects from use of D-penicillamine include: sensitivities (rash, fever), leukopenia, lymphadenopathy, proteinuria and nephritic syndrome, and a form of glomerulonephritis and immune dysregulation called Goodpasture's syndrome.[8] While the severe side effects are uncommon, the sensitivity problem is common (about one-third of users), and the cysteine and pyridoxine depletion are always occurring to some extent. Note also that all commercial forms of D-penicillamine are formulated to include lactose,[42] for which there is little tolerance in at least 60% of autistics. Therefore, D-penicillamine is not considered to be a preferred agent by DAN clinicians or researchers.

Use of N-acetyl-D,L-penicillamine has been mentioned as a less toxic and perhaps more effective alternative for mercury and heavy metal removal.[45] For a period of time (1990s) this was an "investigational drug", but insufficient clinical experience exists to decide about its use in autism.

Chlorella/other algae: Often touted as an herbal remedy for mercury poisoning, chlorella has been claimed to be able to bind to heavy metals. However, in a study recently conducted at the Southwest College of Naturopathic Medicine[46], they administered 10 g/day of chlorella to 15 people with mercury dental amalgams. The chlorella had no effect on fecal or urinary excretion of mercury after 3 or 8 days, based on a comparison of pre and post levels. Therefore, we do not recommend the use of chlorella.

End-of-treatment indications

Treatment should continue at least until urinary collections reveal only modest amounts of toxic metals. If one could assume that the benefits seen in autistic children were exclusively due to removal of toxic metals, then treatment could stop when toxic metal excretion dropped to the low part of the reference range. Since this may not be the sole mechanism of action, the decision to end treatment needs to be based on both laboratory and clinical evidence.

One obvious indication to stop treatment is when improvement ceases. Halt therapy when the child reaches a “plateau” and watch for any indication of regression. Some parents and practitioners may want to continue treatment for a few months after reaching a “plateau” in the hopes that a small amount of additional progress may occur. Alternatively, one could wait several months, and then restart therapy on a trial basis.

Obviously, if the child shows no significant progress during therapy or experiences regression, this would be another indication to stop treatment. Keep in mind that a significant number of autistic children will undergo some degree of regression during initial chelation treatment while later experiencing significant gains. If intestinal dysbiosis is not adequately treated prior to starting DMSA, any improvement from the DMSA may be masked when the intestinal dysbiosis worsens on exposure to a rich culture medium.

A number of children have shown significant improvement while taking DMSA, which regresses when they stop, even for the “rest period” of each cycle. These children need to be dealt with on a case-by-case basis, since there is insufficient clinical experience so far to recommend a course of action.

Future Research Needs:
There is a need for further research into new therapies that are more beneficial than those we currently have. For the current treatment options (DMSA, DMPS, TTFD) there is a need for formal clinical trials to evaluate the relative efficacy of the treatment options and to assess any potential side effects more fully. There is a need for some medications, such as DMPS and TTFD, to gain FDA approval so that physicians are more comfortable with their use. Most importantly, these studies are needed to convince skeptical physicians and parents of the importance of considering detoxification therapy for children with autism.

Disclaimers:

1. The therapies outlined in this monograph should not be used except by and under the supervision of a physician.
2. This is not a "stand-alone" protocol and must be preceded by correction of intestinal dysbiosis and nutritional deficiencies.
3. These therapies may not help all autistic children and may potentially make some autistic children significantly worse. Even those children who will ultimately benefit from these therapies may show transient deterioration during treatment.
4. The drugs and nutritional supplements discussed in this monograph, with the exception of DMSA (Succimer, Chemet®), antibiotics and prescription antifungals, are not approved by the United States Food and Drug Administration (USFDA). DMSA is currently approved by the USFDA only for children with lead poisoning.
5. The quality and purity of drugs and supplements that are not FDA approved will vary with different suppliers. All such drugs and nutritional supplements mentioned are allowed by the USFDA, but it does not guarantee their safety, purity or effectiveness.
6. The theories and medical models on which these therapies are based are not universally accepted in the medical community and are being vigorously studied by a number of researchers. The clinical evidence supporting these therapies is compelling but no well-controlled outcome studies have yet been performed; the evidence is largely based on clinical experience at this point.
7. The theories and therapies discussed in this monograph are subject to change without notice if significant clinical or research data indicates a need for change.

Disclaimers for medical practitioners:

1. Attempting mercury or other heavy metal detoxification before the patient's underlying gastrointestinal and nutritional problems are corrected will likely be disappointing to you and to the patient's family.
2. The dosing of the drugs and nutritional supplements in this monograph is within the limits supported by the majority of the peer-reviewed literature published as of December 2004. The maximum limits should be exceeded only if you have good reasons to do so.
3. At the present, it is impossible to determine which patients will benefit from these therapies with great accuracy. Some patients who seem to be perfect candidates will have no improvement and others who seem to have little to recommend the therapy will show marked improvement.
4. Obtaining written consent from parents for the use of non-FDA approved chelating agents is strongly recommended although not legally binding.
5. The treatment of autism is in a state of continual flux.

Disclaimers for parents and family members:

1. Many families are treating their autistic children with therapies similar to those listed in this monograph without involving a physician or other health care provider. That most of them do so without any adverse consequences is a testament to the safety of the drugs and supplements used. However, DMSA, DMPS and some of the supplements present a small but

non-zero risk of serious side effects. Life, in general, is a series of risks; the risk of serious side effects can be reduced by careful medical monitoring during treatment.

2. Not every physician is able or willing to carry out the therapies described in this monograph. Have a frank and open discussion with your physician or other medical practitioner before embarking on these treatments.
3. Despite miraculous case reports heard on the grapevine and on the Internet, these therapies will not work for every autistic person. Even those who do improve may have slow or incremental improvement.
4. In general, younger patients appear to respond more quickly than older patients, but this has not yet been adequately investigated.

Appendix A: Background on Mercury Toxicity

Toxicity of Mercury

Mercury is an extremely toxic substance, and very low levels of it (nanomolar) can cause neurological and other damage.

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR), gives the following summary about the symptoms of mercury toxicity in infants:[47]

- "Mercury is considered to be a developmental toxicant. … The symptoms observed in offspring of exposed mothers are primarily neurological in origin and have ranged from delays in motor and verbal development to severe brain damage."
- "The infant may be born apparently normal, but later show effects that may range from the infant being slower to reach developmental milestones, such as the age of first walking and talking, to more severe effects including brain damage with mental retardation, incoordination, and inability to move."
- "Other severe effects observed in children whose mothers were exposed to very toxic levels of mercury during pregnancy include eventual blindness, involuntary muscle contractions and seizures, muscle weakness, and inability to speak."
- "It is important to remember, however, that the severity of these effects depends upon the level of mercury exposure and the time of dose."

This summary is strikingly close to the symptoms of autism.

Three federal agencies have established "safe" limits for total exposure to mercury. Those limits are: the Environmental Protection Agency (EPA), 0.1 micrograms of mercury per kilogram bodyweight per day; Agency for Toxic Substances and Disease Registry (ATSDR), 0.3 µg/kg-day; and the Food and Drug Administration (FDA), 0.4 µg/kg-day. Thus, for an adult weighing 70 kg, the total safe exposure would be 7-28 µg/day.

Between 1890-1950, thousands of children in the US and other developed countries suffered from acrodynia, or pink disease. [48] The symptoms were very similar to autism, except that some cases were more severe and 20% of the children died. After 60 years, the cause was determined to be the use of a teething powder whose active ingredient was mercuric chloride. (J. Adams obtained 50-year-old samples of the powder and confirmed that it was in fact mercuric chloride, as stated on the label). The mercuric chloride was effective as a teething powder because the mercury is highly neurotoxic, and it numbed or killed the nerve cells in the gums. Only about 1 in 500 of the children exposed to the teething powder were affected, a similar ratio to the current incidence of autism. When the teething powder was removed from the market, the incidence of new cases dropped to zero. It took 60 years to make the connection of the disease to the mercury in the teething powder because symptoms of mercury toxicity do not usually occur until 2-3 months after exposure.

The problem of acrodynia due to mercury in infant teething powders in the first half of the twentieth century seems strikingly similar to the possible connection of autism and thimerosal in infant vaccines in the second half of the twentieth century, as will be discussed in more detail on the following pages.

Timing of the exposure is also a critical determinant of toxicity. For example, the developing fetus is 5-10 times more sensitive to mercury. Also, the human brain undergoes tremendous growth and maturation the first year of life. Mercury is known to interfere with these growth mechanisms. Exposures that occur during critical "Windows of Development" are more damaging.

There is tremendous inter-individual susceptibility to mercury and genetic make-up, age, sex, and health status all impact susceptibility. In adults a 78-fold variation has been reported and in infants this variation can be up to 10,000 fold. Metabolism and excretion can also vary widely. In animal studies, infants do not excrete mercury until weaned and a milk diet increases gastrointestinal absorption of metals. Adequate bile production is also necessary for excretion and is often not adequate in newborn infants. Gut flora also play a role in breaking down mercury for excretion, therefore antibiotic exposure will result in decreased excretion. Stress and illness are known to decrease glutathione levels which will also decrease excretion.

Mercury exposure at potentially dangerous levels is common in the US.

The three major sources of mercury exposure to children in the US are maternal seafood consumption, maternal dental fillings, and childhood vaccines.

Seafood Consumption: A recent report by the EPA [49] estimates that 1 in 6 women in the US has mercury levels that place their infants at increased risk of neurological damage; i.e., over 300,000 infants at risk each year. This is based on evaluation of blood levels of mercury of 1709 women who participated in the 1999-2000 NHANES (National Health and Nutrition Examination Survey). They found that women who regularly consumed fish (9 or more servings per month) had 7x as much mercury in their blood as women who did not consume fish.

In addition to the EPA, the FDA has also released their 2004 advisory regarding fish. They recommend that pregnant women not consume a single serving of some types of fish (shark and swordfish), and limit their consumption of other types. A single serving of shark or swordfish, which has on average 1 ppm of mercury, would contain 200 mcg of mercury in a typical 200 g serving.

Dental Amalgams: The most commonly used dental filling material in the US is mercury-silver dental amalgams, composed of 50% mercury. Many studies have showed that those fillings release mercury vapor, and that approximately 80% of that vapor is absorbed into the body [50]. The amount of mercury absorbed into the body is in the range of 1-10 mcg/day, depending on number of mercury dental amalgams. [51] [52] [53] This

amount of mercury is probably not harmful to most people by itself, but it adds to the overall body burden and increases the risk of additional exposures.

Thimerosal in Childhood Vaccines

Thimerosal, a preservative utilized in the production of numerous medications including infant vaccines and immune globulin products contains 49.6% ethyl mercury by weight. The history of thimerosal use in vaccines is complex. It was first used in the late 1930's, and as the number of vaccinations given to human infants increased, the amount of injected thimerosal increased. Thimerosal was removed from animal vaccines in the early 1990's. As part of an ongoing review of biological products, the Food and Drug Administration (FDA) announced in 1999 that infants who received multiple mercury-preserved vaccines may have been exposed to cumulative mercury levels in excess of Federal safety guidelines.In 1999, the AAP (American Academy of Pediatrics) recommended it be removed from childhood vaccines [54], and in 2001 the FDA asked (but did not require) vaccine manufacturers to remove it from childhood vaccines. Today, thimerosal has been removed from most but not all childhood vaccines. In September 2004, California passed legislation to ban thimerosal use in childhood vaccines, and several other states have passed similar laws.

Thimerosal is a mercury-based preservative (50% mercury) which was commonly used in most childhood vaccines until recently. Some examples of the thimerosal content of childhood vaccines includes Hep B (12.5 mcg), DTaP (25 mcg), HiB (25 mcg), and PCV (25 mcg). The HepB vaccine is given at birth, and assuming that the infant weighs 3.4 kg (7.5 pounds), then their "safe" exposure limit per the EPA is 0.34 mcg, so that their injection with HepB exceeds the recommended "safe" limits by a factor of 36; lower body weight infants are at higher risk, as vaccines are one of the rare medications where the dose does not depend on age or bodyweight (the same dose is given to an adult as a premature infant). If an infant were fully vaccinated in the 1990's, then they received approximately 237.5 mcg of mercury during their first 15 months of life.

It is interesting to note that thimerosal in vaccines was introduced in the late 1930's, only a few short years before Dr. Leo Kanner described a new mental disorder which differed "markedly and uniquely from anything reported" before. In its early history autism was diagnosed more frequently in affluent families, but became more evenly distributed socioeconomically by the 1970's. This apparent widening in demographics paralleled the increasing availability of vaccines to all children through federally sponsored programs. In the late 1980's and early 1990's the vaccine schedule was amended to include both Hepatitis B and HiB vaccines. Each of these vaccines was administered to infants 3 times during the first six-months of life. Their addition to the vaccine schedule potentially tripled an infant's exposure to mercury, should they receive all thimerosal-containing vaccines.

During the 1980's and 1990's, the Academy of Obstetrics and Gynecology recommended that all Rh- pregnant women receive a prophylactic dose of anti-Rho-D immune globulin during the pregnancy at 28 weeks gestation. Prophylaxis was also recommended for any invasive procedure like amniocentesis or villi sampling and for any episodes of bleeding during the pregnancy. With approximately 15% of the population being Rh- and many

women choosing to delay childbirth and opting to undergo invasive procedures necessary to identify chromosomal abnormalities, exposure to mercury prenatally has also increased over the past decade. It has been during this same time period, the 1980's and especially the 1990's, that we have witnessed a tremendous increase in the occurrence of autism spectrum disorders. Anti Rho-D exposure levels also varied widely from a low of 7.5 mcg to a high of 65 mcg per dose. At times multiple doses were administered throughout the pregnancy.

The potential toxicity of thimerosal in vaccines has only recently received attention, and there has been very little study of the effect of thimerosal in infant animals. The potential danger of thimerosal is highlighted by a 2004 study by Hornig et al [55], which investigated the effect of the injection of thimerosal into infant mice, at a dosage and dosage schedule equivalent to that given to a human infant at age 2, 4, 6, and 12 months of age (based on the thimerosal content of the HepB, DTaP, and HiB vaccines). She found that two strains of mice were completely unaffected, but the third strain of mice (a strain known to be susceptible to autoimmunity) suffered several major problems, including growth delay, reduced locomotion, exaggerated response to novelty, and abnormal development of neurons and synapses. This important recent study suggests that although most human infants would be unaffected by thimerosal at concentrations present in childhood vaccines, there may be a subset of genetically-vulnerable infants who could be damaged at dosages used in childhood vaccines. It is important to note that the families of autistic children often have immune disorders, suggesting that their children would be more vulnerable to thimerosal.

Toxicity of Thimerosal

Because there is little information on the toxicity of ethyl mercury (the form in thimerosal), much of the estimation of its toxicity is based on methyl mercury. However, a recent investigation by Burbacher (2004) in primates documented that ethyl mercury had a shorter half-life in the blood than methyl mercury, resulting in higher blood:brain ratios, and that it is rapidly converted to inorganic mercury, which is toxic and can stay in the brain for years. A study by Pichichero (2002) assessed blood levels of mercury in infants after exposure to thimerosal-containing vaccines and reported a level in a 2 month old infant of 20.55 nmol/L, five days after receiving only a 37.5 mcg exposure (but the level was probably even higher shortly after the injection). According to a letter to the editor written by Dr. Neal Halsey, a dose of 62.5 mcg could well have resulted in a peak blood mercury level of 48.3nmol/l. Applying Burbacher's newly reported brain to blood partition ratio predicted brain levels of mercury would be 217.35 ng/g. Given that Baskin *et al.* (2003) have documented DNA damage, caspase-3 activation, nuclear membrane damage and cell death in cultured adult human neurons and fibroblasts exposed to 201 mcg/l ethyl mercury after 6 hours or less of incubation, it seems likely that routine vaccination practices during the 1990's may have resulted in neurodevelopmental injury to some infants.

Similarly, a study by Waly *et al.,* (2004) documented that thimerosal, at low nanomolar concentrations, inhibited insulin like growth factor-1 (IGF-1) and dopamine stimulated methylation in human neuroblastoma cells, indicating its potential to disrupt normal growth factor control and methylation. Levels of thimerosal exposure that

produced these abnormalities were well below the documented levels found to occur in infants from exposure to thimerosal containing vaccines in the Pichichero investigation cited above. This investigation provides a molecular explanation for how increased use of vaccines could promote an increase in the incidence of autism.

Appendix B: Evidence of Mercury Toxicity in Autism

Symptoms: A landmark literature review paper by Bernard et al. [56] published in 2001 reported that all of the diagnostic criteria necessary for a diagnosis of autism were also observed in cases of mercury toxicity. For example, the major toxicity of mercury compounds is expressed in the central nervous system, although immune and gastrointestinal systems are also commonly affected. The same abnormalities in these systems have been found in children with autism. Mercury causes a pervasive disruption in the body by binding to sulfur which causes widespread dysfunction of enzymes, transport mechanisms and structural proteins. Therefore, clinical manifestations involve multiple organ systems with variable features and intensities. The same is true for autism.

Susceptibility to mercury appears to have a genetic component and boys are documented to be more affected than girls. Autism also occurs more frequently in boys than girls, with a ratio of approximately 4:1.

Mercury toxicity is known to cause speech and hearing deficits, including difficulty speaking and understanding speech. One of the primary features of autism is receptive and expressive language delay.

Sensory disturbances, including numbness in the mouth, hands and feet, sensitivity to loud noises, aversion to touch and over or under response to pain, are common manifestations of mercury toxicity. These same sensory disturbances are also common in children with autism.

Mercury exposure is known to cause cognitive impairment and difficulty with abstract ideas and complex commands, social withdrawal, anxiety and obsessive-compulsive behaviors. These same symptoms are also well documented in children with autism.

Mercury disrupts serotonin, dopamine, glutamate and acetylcholine neurotransmitters. These same abnormalities have been found in children with autism. Mercury in the brain targets the Purkinje cells and granule layer of the cerebellum as well as the amygdala and hippocampus, while other areas are spared. This same pattern of pathology has been found in autistic brains.

Mercury toxicity causes damage to the immune system and triggers autoimmune processes, including shifts in the Th2 lymphocytes. These same autoimmune processes are known to occur in autism. Mercury exposure can increase susceptibility to certain virus strains, which may be related to a decrease in NK cell function. A subset of autistic children have been found to have evidence of chronic viral infections, including measles virus. Mercury poisoning can cause gastrointestinal disturbances and inhibit digestive enzymes and peptides. Many children with autism develop gastrointestinal problems and have difficulty digesting dairy and wheat products.

In summary, the paper by Bernard et al. shows that all the symptoms reported in the literature for autism have also been reported in the literature for mercury toxicity, and vice versa. It seems very likely that some children suffering from mercury toxicity would be given the diagnosis of "autism," which is simply a label indicating they have a communication/behavior/social disorder of unknown cause. Mercury toxicity seems likely to be a cause of many cases of "autism."

Baby Hair: Holmes et al.[57] measured the level of mercury in the baby hair of children with autism compared to typical control children, all born between 1988-1999, with hair samples cut between 12-24 months. The typical children had 8x higher mean level of mercury in their hair. The children with autism had similar or higher exposure from the major sources of mercury (dental fillings, seafood consumption, thimerosal from vaccines), so the difference was not due to exposure to mercury. Since hair is a measure of excretion, it appears that the difference is due to a very limited ability of the children with autism to excrete mercury. Also, the severity of autism was strongly inversely correlated with the level of mercury, suggesting that the most severe children had the weakest ability to excrete mercury.

The Holmes et al. study has been replicated by Adams et al.[58] with the assistance of the National Institutes of Environmental Health Sciences (NIEHS, a branch of NIH). Their preliminary analysis found that children with autism had much lower levels of mercury in their baby hair, 0.36 ppm, vs. 0.85 ppm in the controls. However, they found that about 10% of the children with autism had unusually high levels in their baby hair, which probably indicates a high exposure. Overall, the Adams et al. preliminary results are generally consistent with the study by Holmes' et al, and support the hypothesis that children with autism have a limited ability to excrete mercury.

Low Cysteine/Glutathione: Mercury is normally excreted from the body by being bound to glutathione, and then excreted with the bile into the small intestine. A study by Clarkson et al. found that young monkeys had a much lower level of glutathione, and the level of glutathione closely correlated with their ability to excrete mercury. This is believed to also hold true in human children, such that there would be almost no excretion of mercury during the first six months of life, and it would likely take years?? to reach full production of glutathione.

There have been three studies (James et al,[7] Bradstreet et al.[59], Audhya et al.[60]) which have consistently demonstrated that children with autism have low levels of cysteine. Cysteine is the precursor to making glutathione, so low cysteine levels would result in low glutathione levels. Two of those studies also measured the level of glutathione in plasma, and found that it was approximately 50% lower in children with autism compared to age-matched controls. One of those studies (James et al)[7] measured the oxidation of glutathione, and found that children with autism had a higher ratio of oxidized (inactive) glutathione, presumably due to oxidative stress.

Oral Antibiotics and a Milk Diet: effect on mercury excretion

A study of rats found that oral antibiotics and milk both decreased the rate of methyl mercury excretion. Rats typically take 10 days to excrete half the mercury they are exposed to, but in rats on an all-milk diet (relevant to nursing infants) the half-life increased from 10 days to 30 days. In rats on oral antibiotics, the half-life increased from 10 days to over 100 days. In rats on both an all-milk diet and oral antibiotics, the half-life increased to 300 days. Humans excrete mercury more slowly than rats, so the effects would be larger there.

The reason for the decreased excretion rate is not known, but it may be due to alterations in gut bacteria. 90% of Hg excreted in feces is inorganic; bacteria tend to demethylate mercury, and yeast have the capacity to methylate mercury. Rosseneu et al.[10] have demonstrated that autistic children with chronic constipation/diarrhea have highly abnormal gut bacteria, including 10,000x higher amounts of E. Coli, which produces a potent endotoxin.

Several studies have found that children with autism had much higher usage of oral antibiotics during infancy than typical children, primarily due to ear infections. This is especially sad when one realizes that oral antibiotics have almost no benefit for ear infections (90% recovery with no intervention, vs. 95% with oral antibiotics), and the use of oral antibiotics greatly increases the risk of future ear infections.

In addition to reducing the excretion of mercury and altering gut flora, oral antibiotics greatly increase the toxicity of thimerosal to brain cells (Haley et al).[61]

Overall, infants have limited ability to excrete mercury, and children with autism have an unusually low ability to excrete mercury due to low glutathione and excessive oral antibiotics. Furthermore, antibiotics increase the toxicity of mercury.

High Mercury/Metal Body Burden: Urine, Blood, Teeth, Hair

Several methods have been used to investigate the level of mercury and other toxic metals in children with autism. Each method needs to be interpreted carefully, because they measure exposures at different times, but they generally reveal an elevated body burden of mercury and sometimes toxic metals.

DMSA Provocation: Bradstreet et al.[1] investigated the effect of giving DMSA to 221 children with autism compared to 18 controls. They used 10 mg/kg per dose, 3 doses per day, over 3 days, with a urine collection following the 9th dose. They found that the children with autism excreted 3 times as much mercury into their urine (which is where DMSA is excreted), but lead and cadmium levels were not significantly different. DMSA provocation is probably a measure of both recent and older exposures.

Baby Teeth: A preliminary report by Adams [62] of 14 children with autism compared to 11 controls found that the children with autism had normal levels of zinc, slightly elevated levels of lead, and 3x higher mercury in their baby teeth. Since baby teeth form in utero and grow during the first few years of life, they give a measure of early childhood exposure. Other studies of lead toxicity have demonstrated that lead levels in teeth correlate strongly with the symptoms of lead toxicity.

Blood: Audhya et al [60] has measured the level of toxic metals in red blood cells of children with autism compared to age-matched control children. He found that the levels of many toxic elements were elevated in the children with autism, including mercury. Blood is a measure of recent exposure, and an overall high level is consistent with low levels of glutathione. However, a study by Ip et al of mercury in the blood and hair found normal levels in children with autism (n=82) vs. controls (n=55). Their average age was 7 years, and since mercury has a half-life of only a few weeks in the blood before going

to organs, this is NOT a good way to check for earlier exposure during fetal development or infancy.[63]

Hair: A recent study by Adams et al.[64] of 51 autistic children compared to 40 typical children age 3-15 yr revealed essentially normal levels of toxic elements in their hair, taken from the most recent one inch at the nape of their neck. Hair is a measure of recent exposure, growing at a rate of about 1 inch per 1-2 months. A similar study by Ip et al also found normal levels of mercury in children with autism (n=82) compared to controls (n=55).[63] These results are difficult to interpret; they could indicate no abnormalities in metal exposure/excretion, or they could indicate a combination of high metal body burden and low glutathione, yielding an average excretion rate of toxic metals into hair. Again, as with blood, current hair levels is NOT a good way to check for exposure to mercury during fetal development or infancy.

Long-term Detoxification Therapy: Many DAN! physicians have reported that long-term use of detoxification in autistic children results in a high excretion of toxic metals, which tends to decrease after months of therapy. A variety of toxic metals are often excreted, with different metals being excreted at different times – this is not fully understood. Long-term detoxification therapy results in varying degrees of improvement, with younger children usually showing the most improvement, sometimes to the point of losing their diagnosis of ASD. However, despite thousands of positive reports from dozens of clinicians, there has not yet been a formal research study of the effects of long-term detoxification therapy.

Effect of Mercury on Metabolic Pathways

(Note: this is a scientific discussion of a complex subject; the bottom line is that mercury can injure several metabolic pathways including synthesis of methyl B12 and glutathione, so detoxification of mercury is likely to be beneficial).

Heavy metals, including the ethylmercury from thimerosal, have important effects on metabolic pathways that are involved with sulfur-containing amino acids (e.g. methionine, S-adenosylmethionine, S-adenosylhomocysteine, homocysteine and cysteine) sulfur-containing peptides (e.g. glutathione). The ability to clear metals from the body depends upon the levels of these thiols, especially the concentration of glutathione. Their lower levels of glutathione place autistic children at greater risk for heavy metal toxicity directed against the very system that defends them.

Research by R. Deth et al. has shown that heavy metals and thimerosal potently inhibit the activity of methionine synthase, which uses folate-derived methyl groups to convert homocysteine to methionine. This inhibition blocks the ability of insulin-like growth factor-1 (IGF-1) and dopamine to activate this enzyme, thereby interfering with the role of methylation in development and in the molecular mechanism of attention. Recently they found that the inhibitory effect of metals is directed at the glutathione-dependent synthesis of methylcobalamin (methylB12), which is required for methionine synthase activity in certain cell types (e.g. lymphocytes and some neuronal cells). Methylation function in these particular cells will therefore be most affected by heavy metals, especially in individuals whose genetic background makes them more vulnerable.

While more research is needed, their studies suggest that methionine synthase can

exist as a truncated, variant form that strictly requires methylcobalamin. Cells expressing only this form of the enzyme are the most vulnerable to heavy metals.

The ability of methylcobalamin administration to improve symptoms in many autistic children appears to confirm the importance of impaired folate-dependent methylation as a primary feature of the disorder. Furthermore, the fact that heavy metals and thimerosal potently impair methylcobalamin synthesis suggests that heavy metal toxicity could be an important cause of autism. Within this framework, lowering the levels of offending metals via chelation therapy represents an approach for re-activating methylation that could complement other metabolic interventions.

Epidemiology of Autism and Thimerosal in Vaccines:

There is a historical correlation of autism and thimerosal in vaccines. Thimerosal was first used in infant vaccines in the late 1930's, and the first cases of autism were diagnosed by Kanner shortly thereafter. As the number of thimerosal-containing vaccines given to children has increased, the incidence of autism has tended to increase. Some countries with low thimerosal use (such as Denmark) have much lower rates of autism than other countries that used high amounts of thimerosal (US).

There have been nine epidemiological studies of the link between thimerosal in vaccines and autism. Four published studies by the Geiers [65] [66] [67] have consistently found that children who received thimerosal in their vaccines had a 2-6x higher chance of developing autism than those who received thimerosal-free vaccines. Four published studies by groups affiliated with vaccine manufacturers have failed to find a link, [68] [69] [70] [71] and one was inconclusive, [72] but those studies are somewhat flawed. Three of the negative studies were in countries with much lower usage of thimerosal than in the US, and they had much lower rates of autism in those countries, so it is invalid to extrapolate those results to the US. One of the US studies initially stated in an internal report to the CDC that the children who received thimerosal in their vaccines had a 7-11x higher risk of developing autism, but the data was manipulated until the relative risk disappeared. In general, we believe the studies by governmental agencies and vaccine manufacturers are suspect, and an independent evaluation of the CDC database is needed.

Summary: Children with autism have a low ability to excrete mercury and other toxic metals, especially in infancy. This results in an increased body burden of mercury and other toxic metals, which probably is a major contributor to the development of autism in most of the children. Removal of those toxic metals from their body often results in reduction of the symptoms of autism, especially in younger children.

Appendix C: Other Tests to Determine Mercury/Metal Toxification

Other than looking for the heavy metals directly, one can look for evidence of their effects. Mercury and other heavy metals suppress the effect of a number of enzymes, some of which can be easily tested. The most commonly available of these is glucose-6 phosphodiesterase (G-6PD); a quantitative G-6PD activity may reveal levels intermediate between normal and deficient in heavy metal poisoning[73]. Of note, there has been one report of hemolysis in a patient with absolute G-6PD-deficiency[74], but DMSA has been used extensively in populations with a high incidence of G-6PD deficiency and sickle cell disease without problems. Less commonly available is glutathione reductase, which is also reduced in heavy metal poisoning[75]. Low glutathione levels in the red cells are not specific for heavy metal toxicity, but may be supporting evidence.

Another commonly available test is blood or urine pyruvic acid. Pyruvic acid can be elevated for a number of reasons, but mercury is notorious for interfering with the mitochondrial pyruvate dehydrogenase complex, where it binds to and deactivates the lipoic acid coenzyme, resulting in elevated pyruvic acid.

Mercury and other heavy metals interfere with heme synthesis, leading to urinary excretion of uroporphyrin and coproporphyrin. Mercury also causes production of pre-coproporphyrin, which may be considered a specific marker for mercury poisoning[76,77]. Analysis of uroporphyrin and coproporphyrin can be done at most clinical laboratories; pre-coproporphyrin analysis can also be done, but most laboratories do not routinely have that test available.

Mercury and other heavy metals (such as lead) can cause progressive myelin degeneration with the development of antibodies to myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP)[78,79]. While these changes are not diagnostic of mercury intoxication, they point to ongoing degeneration in the central nervous system.

Depletion or deficiency of the cellular antioxidant systems is seen in a number of autistic children. A common finding in autistic children is an abnormally low erythrocyte glutathione level. The potential causes for this deficiency in cellular antioxidant substances are myriad, ranging from congenital deficiency to toxins; heavy metals are well-documented causes of intracellular antioxidant depletion. Whether the cause is too little production, rapid consumption or a combination of the two, many of these children can benefit from exogenous antioxidant support. Since DMSA and many of the other supplements used to treat mercury and heavy metal intoxication are powerful antioxidants, this may be mechanism of action in some children who improve, especially those who show little excretion of toxic metals.

Since it is possible that neither removal of metals nor supplementing cellular antioxidants are the mechanism of action, an empiric trial of DMSA therapy may be warranted. This trial should be done for a limited time and without changing any other therapy, including

physical therapy, occupational therapy, speech therapy, etc. If no definitive results are seen in four to six weeks, discontinue therapy and look again for any changes.

Appendix D: Treating gut dysbiosis

A large number of autistic children have intestinal abnormalities, including abnormalities in gut permeability, defects or deficiencies in intestinal enzymes, and abnormal intestinal flora. Many of these factors are mutually reinforcing, so they are difficult to correct in isolation. The causes of these intestinal dysfunctions are hotly debated, but the leading theories are congenital enzyme dysfunction, secondary enzyme dysfunction due to toxins (*e.g.* mercury), viral injury, and yeast overgrowth. There are other theories and their exclusion here does not reflect on their merit or lack thereof.

Since no two autistic children are alike, the first step is to examine the stool to determine which specific organisms predominate and whether there are imbalances or pathogenic flora present. A stool culture (with fungal culture) will provide a great deal of information for a relatively minor output of effort and at a reasonable cost. A microscopic exam is also important, as some bacteria do not easily culture. A common finding is yeast overgrowth, with a fair number of children showing significant colonization with *Clostridium* species. Evidence of *Clostridium* may be seen in the stool sample (*C. difficile* antigen) or it may be detected by urine organic acid analysis. Elevated hydroxylated phenylproprionate (DHPPA) in the urine is a telltale marker of *Clostridium* overgrowth. Other abnormal bacteria found include *Pseudomonas* and other opportunistic pathogens.

However, stool culture and microscopic exam are not 100% reliable, so sometimes a diagnostic trial of one or more antifungals is useful.

Clinical experience has shown that an important first step in treating gut dysbiosis is to correct any coexisting constipation. Regular elimination will help reduce the fungal and/or bacterial load and will reduce the amount of endotoxins and exotoxins that are absorbed from the intestine.

Diet modifications are also important during the treatment of documented or suspected yeast overgrowth. Reducing the carbohydrate intake as much as possible has been correlated with improved success and fewer recurrences. At least one study of *Candida albicans* showed that the presence of sucrose, glucose, fructose, galactose or maltose in the culture media significantly increased the surface adherence of the yeast, a major determining factor in its pathogenicity[80]. In addition, *Candida* in the gut lumen, even without invasion of the intestinal mucosa, can decrease the intestinal absorption of sugar and water in experimental animals[81].

Yeast overgrowth can be treated in a number of ways; one reasonably gentle way is to administer live *Lactobacillus* by mouth. In moderate yeast overgrowth, the *Lactobacillus* can restore normal gut flora, which then suppresses yeast by competition. A number of herbal preparations, such as garlic, have been used to suppress yeast as well, and may help the *Lactobacillus* regain a foothold. When neither of these methods is sufficient, antifungal drugs are needed.

One drug commonly used is Nystatin, which is a polyene antibiotic produced by the bacteria *Streptomyces noursei*. When given by mouth, it is not absorbed to any significant extent and remains in the intestine; this keeps the drug where it is needed and minimizes any systemic effects. The usual dose schedule is one to two million units a day, preferably in divided doses. It should be given away from food or liquids to maximize it efficacy. Doses of up to 10 million units a day or more may be needed initially to eliminate yeast; maintenance doses of one or two million units a day for in excess of a year are common. Side effects are limited to nausea and gastrointestinal upset, usually only seen at doses over 5 million units daily. Since it is not absorbed, the yellow color of the drug will modify the stool color, which may alarm some parents if they are not forewarned.

However, since some yeast are becoming resistant to Nystatin, a useful alternative is Amphotericin B, since it is also a non-absorbable anti-fungal. It is available from compounding pharmacies.

For more persistent yeast overgrowth, the azole antifungals such as fluconazole (Diflucan®), itraconazole (Sporanox®) and ketoconazole (Nizoral®) can be a great help. The azole antifungals work by inhibiting the fungal cytochrome P-450 enzyme that catalyzes C-14 alpha-demethylation in the production of ergosterols. The equivalent human enzyme is much less sensitive to inhibition by azoles, but is affected somewhat. This inhibition may become clinically significant when given with another compound that is metabolized by that enzyme. Specific drug interactions have been reported with rifampin, coumadin, phenytoin, cyclosporine, theophylline, oral hypoglycemics, terfenadine, cisapride, and astemizole.

Note that the azoles also significantly lower the level of steroidal hormones, especially cortisol and testosterone. Lowering those hormones may account for some of the calming and better sleep anecdotally reported by parents.

Fluconazole is well absorbed when taken by mouth and so has the potential for systemic effects. One of these systemic effects is to get into the deepest crypts of the intestine and eradicate any yeast taking refuge there. Adverse reactions reported in children include vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Laboratory abnormalities of elevated transaminases and alkaline phosphatase were seen in 1.4% of children without any clinical findings. Adults undergoing prolonged fluconazole therapy reported headache (1.9%) and skin rash (1.8%). Rare anaphylactic reactions have also been reported as well as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).

Fluconazole has been used in children as young as six months for oropharyngeal and esophageal candidiasis. The recommended dosage is an initial loading dose of 6 mg/kg and doses of 3 mg/kg once a day. The daily dose may be up to 12 mg/kg/day but should not exceed a maximum of 600 mg/day. The duration of treatment depends on the clinical findings, but should be at least fourteen days. The longest reported therapy with fluconazole was 1,616 days.

Hepatocellular injury can be seen with any of the azole antifungals, but fluconazole has the lowest reported incidence. Still, serum liver transaminase levels should be followed carefully for any treatment lasting longer than 20 – 30 days. (Treatment with milk thistle may be beneficial for elevated liver enzymes). Side effects are not significantly different between drugs in this class, although fluconazole and itraconazole are often reported to have a lower incidence of side effects than ketoconazole[82]. Resistance to the azoles is becoming more of a problem, especially in patients who have repeated or prolonged treatment. Resistance to one azole drug usually, but not always, leads to resistance to them all[83,84].

Like yeast, overgrowth with *Clostridium spp.* or *Pseudomonas spp.* may also resolve with reintroduction of *Lactobacillus*. For those that do not resolve, oral therapy with vancomycin is tremendously effective. Vancomycin is a tricyclic glycopeptide antibiotic produced by *Amycolatopsis orientalis* (formerly *Nocardia orientalis*) which is not normally absorbed orally, so there is minimal risk of systemic effects. An oral form is available, but the powdered form used to prepare intravenous infusions is also readily available and is absolutely free of any potentially harmful additives or fillers. The recommended dosage is 40 mg/kg/day divided into three to four doses; the total daily dose should not exceed 2 grams. Treatment should last 7 – 10 days.

With the increased use of antibiotics, both bacteria and yeast are developing increasing drug resistance. For this reason, the stool culture should include the antibiotic sensitivities and any isolates.

For a fuller discussion, see Biomedical Assessment Options for Children with Autism and Related Problems, by Pangborn, J and Baker, SM, published by the Autism Research Institute.

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ARI/Form
Mercury-4/01

Mercury Detoxification Evaluation Form
Autism Research Institute

4182 Adams Avenue, San Diego, CA 92116
fax: (619) 563-6840; www.autismresearchinstitute.com

We are very interested in receiving comments and observations from parents of autistic children on the effects of the mercury detoxification process. Please make copies of this form and send a completed copy to the Autism Research Institute just before the child is started on the detoxification program. Send us follow-up reports monthly during the treatment. Findings will be reported on our web site and in the *Autism Research Review*. You may also obtain copies of this form on our web site, or you can complete this form electronically on our web site. You may track your child's improvement by entering the report every month on our web site, which will immediately give you your child's scores.

Name of Child _____ _____ ☐ Male Age _____ Date of Birth _____
Last First ☐ Female Today's Date _____

Functional Level:
Lo__ Med.__ Hi__ No. of Detox
_____ _____ Date Detox Started _____ Treatments _____
Form completed by Relationship

Address: _____
Street City State Zipcode Phone Fax E-mail

Age of onset: _____ Do you believe child's autism was caused by a vaccine? Yes / No If so, which? _____

Name of physician treating child: _____ City/State: _____

If your child has not yet begun a mercury detoxification procedure, please complete only section A.
For 30-day follow-up reports, complete both sections A and B.

Section A -- Current Status

Circle the appropriate value

No Problem	Is a Problem Mild	Mod.	Severe	Symptoms
0	1	2	3	Aggression. . . . .
0	1	2	3	Agitation/Irritability. . . . .
0	1	2	3	Awkward body movements . . .
0	1	2	3	Constipation . . . . .
0	1	2	3	Diarrhea. . . . .
0	1	2	3	Eating/feeding problems. . . . .
0	1	2	3	Inappropriate use of toys . . . . .
0	1	2	3	Irrational fears . . . . .
0	1	2	3	Lack of awareness . . . . .
0	1	2	3	Lacks eye contact. . . . .
0	1	2	3	Lacks speech . . . . .
0	1	2	3	Obsessive/OCD behaviors . . . .
0	1	2	3	Poor attention . . . . .
0	1	2	3	Poor finger/hand skills . . . . .
0	1	2	3	Repetitive, self-stim behaviors .
0	1	2	3	Seizures . . . . .
0	1	2	3	Self-injury. . . . .
0	1	2	3	Sleep disturbances . . . . .
0	1	2	3	Social deficits/withdrawal. . . . .
0	1	2	3	Sound sensitivity. . . . .
0	1	2	3	Speech/language deficits. . . . .
0	1	2	3	Temper tantrums . . . . .

Section B -- Detox Effects

Place an x *on the scales below to indicate detox effects. Please base your ratings on changes observed since the detox procedure was initiated.*

Made Worse	No Effect	Possibly Helped	Helped a Little	Helped a Lot	Greatly Improved
|----------	----------	--------	----------	----------	---------|

Please use the back of this form to tell us more about the benefits, if any, seen in the past month and about any adverse effects, if any, seen in the past month. Other comments and observations are also welcome.