ARIZONA STATE UNIVERSITY

AUTISM / ASPERGERS RESEARCH PROGRAM

Summary of Dietary, Nutritional, and Medical Treatments for Autism – based on over 150 published research studies

By James B. Adams, Ph.D.

Director, ASU Autism/Asperger's Research Program

http://autism.asu.edu

2013 Version

AUTISM RESEARCH INSTITUTE

Autism is Treatable

Summary of Dietary, Nutritional, and Medical Treatments for Autism – based on over 150 published research studies

By James B. Adams, Ph.D.

2013 Version
see http://autism.asu.edu or www.autism.com for future updates.

Overview

This document is intended to provide a simple summary for families and physicians of the major dietary, nutritional, and medical treatments available to help children and adults with autism spectrum disorders. The discussion is limited to those treatments which have scientific research support, with an emphasis on nutritional interventions. This report excludes psychiatric medications for brevity. The dietary, nutritional, and medical treatments discussed here will not help every individual with autism, but they have helped thousands of children and adults improve, usually slowly and steadily over months and years, but sometimes dramatically.

This summary is primarily based on review of the scientific literature, and includes over 150 references to peer-reviewed scientific research studies. It is also based on discussions with many physicians, nutritionists, researchers, and parents. This summary generally follows the philosophy of the Autism Research Institute (ARI), which involves trying to identify and treat the underlying causes of the symptoms of autism, based on medical testing, scientific research, and clinical experience, with an emphasis on nutritional interventions. Many of these treatments have been developed from observations by parents and physicians.

ARI Survey of Parent Ratings of Treatment Efficacy and Safety
Most of the treatments listed on the following pages were evaluated as part of the Autism Research Institute (ARI) survey of over 27,000 parents on their opinion of the effectiveness of various treatments for children with autism. For a full copy of the latest ARI Survey, see the last page. (For Asperger's see www.autism.com).

Almost all the treatments listed here generally have a much lower rate of adverse effects than psychiatric medications, according the ARI Survey of Parent Ratings. However, adverse effects are possible with any treatment, and in a few cases special Safety Notes are mentioned for particular treatments.

Other Interventions:
Behavioral interventions, such as Applied Behavior Analysis (ABA), can also be very helpful to children with autism, and are recommended to be used in conjunction with dietary, nutritional, and medical treatments. Similarly, speech therapy, sensory integration, physical therapy, occupational therapy, and a good educational program can be very important. Finally, social interventions such as play with parents/siblings, play dates and social groups can be very helpful in building social understanding, relationships and skills. Dietary, nutritional, and medical therapy may help improve the efficacy of these other interventions, by improving brain and body health and making it easier for the child to learn.

Note about Author: James Adams is a President's Professor at Arizona State University, where he directs the ASU Autism/Asperger's Research Program (http://autism.asu.edu), which focuses on researching the biological causes of autism and how to treat and prevent it. He has published over

25 articles on autism, including studies of vitamins, minerals, essential fatty acids, amino acids, carnitine, neurotransmitters, toxic metals, detoxification, oxidative stress, glutathione, sulfation, gastrointestinal bacteria, immune system regulation, seizures, and sleep disorders in children and adults with autism. He has a Ph.D. in Materials Engineering and is Program Chair of Materials Engineering at ASU, but now focuses his research on autism due to having a daughter with autism. He is a member of the graduate faculty in Chemistry and Biochemistry at ASU. He also serves as the President of the Autism Society of Greater Phoenix since 2000, and co-leader of the Scientific Advisory Committee of the Autism Research Institute.

Reviewers:
We thank the many experts who reviewed different sections of this Summary (see list below), and special thanks to Stephen Edelson and Jane Johnson for reviewing the entire Summary.

Tapan Audhya, Ph.D. – Vitamins/Minerals, High-Dose B6/Mg
Kelly Barnhill, CN, CCN (Nutritionist) – Healthy Diets
Gordon Bell, Ph.D. – Essential Fatty Acids
Marvin Boris, M.D. – Immune System Regulation
Richard Frye, M.D., Ph.D. – Carnitine; Melatonin; Thyroid; HBOT
Jill James, Ph.D. – Methylation/Glutathione/Oxidative Stress
Harumi Jyonouchi, Ph.D. – Food Sensitivities, GFCF Diet
Rafail Kushak, Ph.D., Dr.Sc. – Digestive Enzymes
David Quig, Ph.D. – Gut Treatments – Antifungals, Probiotics; Amino Acids
Rosemary Waring, Ph.D. – Sulfation

Additional Reading

Nutritional Supplement Use for Autistic Spectrum Disorder, by Jon B. Pangborn, Ph.D., published by Autism Research Institute 2012.

Acknowledgements

I would like to thank the many ARI doctors, nutritionists, researchers, parents, and others who have helped provide information on treatments for autism, with special thanks to Jon Pangborn, Ph.D., and Tapan Audhya, Ph.D.

Dedication

This summary is dedicated to the memory of Bernard Rimland, Ph.D., for his pioneering work on autism research and advocacy, and for inspiring many others to follow in his footsteps. Thank you Bernie.

Donations

I encourage you to support research on new treatments for autism by donating to the Autism Research Institute at www.autism.com – your donations can make a difference.

Changes to the 2013 Edition

We have made many updates to this version based on new research, but the general list of treatments is very similar to the original 2007 Edition (Summary of Biomedical Treatments for Autism).

The major changes are more research studies on treatments listed previously, and the addition of new therapies including:

Carnitine (for mitochondrial support to make energy)
NADH (for oxidative stress/glutathione/methylation)
Ribose (for oxidative stress/glutathione/methylation)
N-Acetyl-Cysteine
Hyperbaric Oxygen Therapy

Also, each section was reviewed by an expert in that area (see Reviewer list above).

Disclaimers

This summary is not intended as individual medical advice, and people should consult their physician or nutritionist for how to best treat their individual child. Autism is a spectrum disorder, and a treatment that helps one individual may not help others. This summary represents the personal views of James B. Adams, and does not necessarily represent the views of Arizona State University, Autism Research Institute, Autism Society, or any other organization.

The Autism Research Institute's mission is to provide scientific information about evidence-based treatments to parents and professionals. However, ARI does not endorse any specific intervention described in this summary paper or referred to in other sources.

Treatment Order

We have listed the various treatments in approximate order of what is typically recommended, but every child is different, and initial assessment by a physician and/or nutritionist may suggest a different order. Also, some physicians and nutritionists have their own preferences as to order of treatment. The key point to remember is to assess the effect of each treatment on each individual, by careful assessment of behavioral symptoms and through testing if possible.

This Summary includes the following sections:

- Improve Diet
- Food Sensitivities
- GFCF Diet
- Vitamin/Mineral Supplements
- High-Dose Vitamin B6 and Magnesium
- Essential Fatty Acids
- Gut Treatments
    - Antifungals
    - Probiotics
    - Digestive Enzymes
- Amino Acids
- Carnitine
- Melatonin
- Thyroid Supplements
- Sulfation
- Methylation/Glutathione/Oxidative Stress
- Immune System Regulation
- Hyperbaric Oxygen Therapy

Finding a Physician

Some of the treatments listed here do not require physician oversight, such as shifting to a healthier diet or beginning a vitamin/mineral supplement. However, it is helpful to work with a knowledgeable physician, especially for medical testing and prescription medications. This Summary is designed to be taken to your physician so you can discuss tests and treatments with them. A knowledgeable nutritionist can also be very helpful.

There are some clinicians who specialize in treating individuals on the autism spectrum. Some of them are excellent, some are reasonable, and others are questionable. Several organizations post lists of clinicians by geographic area, including the Autism Society of America, Autism Speaks, and MAPS. We recommend asking other parents in your local community to help you find the most appropriate clinician for your child. In addition, ARI posts a list of questions to ask when interviewing potential clinicians.

Example of a Personal Checklist for Biomedical Treatments

The treatments are listed in the order we generally recommend, but the order can be tailored to the individual and their specific needs and symptoms.

Currently Doing It – what effects?	Tried It In Past – what effect?	Considering for Future – any questions?	**Treatments**
			Healthy Diets
			Food Sensitivities
			GFCF Diet
			Vitamin/Mineral Supplements (or Juicing)
			High-Dose Vitamin B6 & Magnesium
			Essential Fatty Acids
			Gut Treatments **Antifungals** **Probiotics** **Digestive Enzymes**
			Amino Acids
			Carnitine
			Melatonin
			Thyroid Testing/Supplementation
			Sulfation
			Methylation/Glutathione/Oxidative Stress
			Immune System Regulation
			Hyperbaric Oxygen Therapy

Understanding Research

We still need a lot more research on the causes of autism and how to treat it. However, we believe that there is now enough evidence for the treatments listed in this Summary that it is reasonable to consider them as treatment options, since they are likely to be beneficial to some individuals with autism and generally have a low risk of adverse effects.

In this Summary we cite over 150 published research studies. In a few places we also cite some unpublished work which we think provides additional insight, but is not as rigorous.

Placebo-controlled treatment studies

For treatment studies, the highest quality studies are randomized, double-blind, placebo-controlled studies. This means that the researchers took a group of subjects and randomly assigned half to a treatment and half to a placebo (no treatment), but neither the participants nor the researchers knew who was in each group. Evaluations are done at the beginning and end of the study, and then the code is broken to determine if the treatment group did better than the placebo group.

"Single-blind" studies are similar in design and quality, except that only the evaluators (and not the participants) are blinded as to which group they are in.

Open Label treatment studies

An "open label" study is a lower quality study. It means that everyone receives the treatment, and knows that they received it. Unfortunately, due to the "placebo effect," behavioral scores usually improve just by the hope involved in being in a study, and so it is usually unclear if improvements from open-label studies are real or imagined. Open label studies are useful to demonstrate safety, to determine the type of possible benefit, and sometimes they are used to gather data on changes in medical test results (biomarkers). If an open label study has very promising results, it is then useful to follow up with a placebo-controlled study.

ARI Survey Data

Survey data is subject to both the placebo-effect and possible biases in collecting the data. However, an advantage of the ARI Survey of Parent Ratings of Treatment Efficacy and Safety is that it includes responses from over 27,000 families, and it involves comparisons of many different treatments (which is rarely done in traditional studies). So, although there is some "placebo effect" such that benefits may be somewhat over-estimated, it can provide useful insight into potential relative benefits of one type of study vs. another.

Individuality

It is important to remember that autism is a heterogeneous condition, and recent research suggests there are probably several subtypes of autism. There are likely different genetic and environmental factors associated with each subgroup. So, it is unlikely that any one treatment will apply to everyone with autism. However, most of the treatments here will probably help many children and adults with autism. In some cases medical testing or nutritional assessment can be very helpful as a guide as to whether or not a treatment is likely to be helpful.

Pediatric Reference Ranges

In interpreting personal lab results for children, it is important that the lab use pediatric reference ranges, not adult reference ranges. Otherwise, the test results are usually invalid and misleading, and it is better to not do the test. It is very important to check this, as many labs do NOT have pediatric reference ranges. Ideally, the lab should have multiple pediatric reference ranges, as a 3-year-old is very different from a 16-year-old for most medical tests.

Healthy Diets

Rationale: Humans need certain essential nutrients for their bodies to function, including vitamins, minerals, essential fatty acids, and amino acids (from protein). A balanced diet rich in vegetables, fruits, protein, and certain fats is important to help provide those key nutrients.

Explanation of Diet:

- Consume 3-4 servings of nutritious vegetables and 1-2 servings of fruit each day. (Corn is not a vegetable, it is a grain; potatoes have only limited nutritional value, especially if fried). Fruit juice is less healthy than eating the whole fruit, but better than soda.
- Consume at least 1-2 servings/day of protein (meat, chicken, eggs, nuts, beans). If child shows periods of irritability between protein meals, consider smaller protein snacks given more frequently.
- Greatly reduce or avoid added sugar (soda, candy, etc.).
- Avoid "junk food" – cookies, fried chips, etc. – they contain empty calories.
- Greatly reduce or avoid fried foods or foods containing transfats.
- Avoid artificial colors, artificial flavors, and preservatives.
- If possible, eat organic foods as they contain lower levels of pesticides. Organic milk and chicken contain higher levels of essential omega-3 fats. If eating non-organic food, wash fruit and vegetables well if eating the outside, and consider peeling the outer layer.

Benefits:

- Vegetables and fruits contain essential vitamins, minerals, and phytonutrients to improve and maintain mental and physical health.
- Protein is needed to provide amino acids, which are the building blocks for neurotransmitters and many other key amino acids and proteins in the body.
- Reduction in sugar intake can prevent rapid rises and falls in blood sugar, which can cause irritability and difficulty concentrating.
  Kohlboeck G, et al. Food intake, diet quality and behavioral problems in children: results from the GINI-plus/LISA-plus studies. Ann Nutr Metab. 2012;60(4):247-56.
- Artificial colors and flavors can irritate some sensitive individuals, causing behavioral and other problems.
- Organic foods have lower levels of pesticides, and one study found that people living near areas with higher usage of agricultural pesticides had a significantly higher risk of having a child with autism. Pesticide use inside the home is probably a similar concern.
  Roberts EM et al., Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ Health Perspect. 2007 Oct;115(10):1482-9.
  Shelton et al., Tipping the balance of autism risk: potential mechanisms linking pesticides and autism. Environ Health Perspect. 2012 Jul;120(7):944-51.

Duration: Lifelong healthy diet.

Research:
Most children in the US consume insufficient amounts of vegetables and fruits, leading to decreased levels of many essential vitamins and minerals.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Removed Sugar	2%	46%	52%	4589
Feingold Diet	2%	40%	58%	1041

A randomized, double-blind, placebo-controlled study of food additives found that they increased hyperactivity in typical children. This was a large study of 153 3-year-old and 144 8/9-year-old typical children, and found that either artificial colors or sodium benzoate (a food preservative) at levels typically found in foods caused hyperactivity.

McCann et al, Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. Lancet. 2007 Nov 3;370(9598):1560-7. Erratum in: Lancet. 2007 Nov 3;370(9598):1542

Individuals with autism appear to be more sensitive than the general population, since they often lack the sulfate needed to detoxify food additives and preservatives (see Sulfation section).

A major study reviewed the reported benefits of organic foods. It analyzed a total of 17 studies in humans and 223 studies of food content/contamination. The major differences were:
1) Organic foods rarely had detectable levels of pesticides (7%) compared to conventional foods (37%). Two studies found that children on organic diets had lower levels of pesticides in their urine.
2) Organic milk and organic chicken had higher amounts of certain essential omega-3 fatty acids. Similarly, two studies of mothers found that those who ate mostly organic dairy and meat products had higher levels of beneficial essential fatty acids in their breast milk compared to mothers on more conventional diets.
3) Vitamins and most minerals were present in similar amounts in organic foods vs. conventional foods. However, organic foods had higher levels of phosphorus, an essential mineral.

Smith-Spangler C et al., Are Organic Foods Safer or Healthier Than Conventional Alternatives? A Systematic Review, Ann Intern Med. 2012;157 Crystal Smith-Spangler,

For more information on diets avoiding unsafe food additives, go to: www.feingold.org

Food Sensitivities and Allergies

Rationale: Many children with autism have food sensitivities, due to abnormalities in their digestive and/or immune systems. If food is not fully digested into individual sugars, amino acids, etc., then the partly digested food can cause the immune system in the gut to react to those foods. This reaction is much more likely to occur if there is inflammation of the gut.

Immune reactions can involve an immediate allergic reaction (mediated by IgE antibodies), or they can be delayed by several hours to 1-2 days due to other parts of the immune system being involved (so-called non-IgE mediated food allergy).

Immediate-type responses can range from mild to severe, and may involve hives, respiratory problems such as choking/wheezing, diarrhea, vomiting, dizziness/feeling faint, or even severe reactions such as anaphylaxis.

For delayed-type food allergy, symptoms are typically limited to GI tract, but may involve headaches, migraines, or other reactions. For example, some patients with celiac disease (immune reaction to wheat mediated by IgA antibodies) may develop migraines in addition to severe gut inflammation.

Testing:

Observation (clinical diagnosis):
According to the 2010 US Guidelines for food allergy testing (Boyce et al 2010) and the European Food Allergy Diagnostic Criteria (Burks et al 2012), the gold standard for diagnosis of food allergy is observation, involving two steps:

1) Resolution of chronic symptoms after elimination of the offending food from the diet, which may take several days to 2-3 weeks for delayed-type food allergy, and
2) Recurrence of symptoms with reintroduction of the offending food.

For children with autism, symptoms may include changes in behavior, which may be due to pain and discomfort caused by reactions to food allergens.

Safety Note: If the food causes a severe reaction or anaphylaxis shock, then reintroduction of foods should only be done in a physician's clinic or hospital.

Boyce, J.A., et al. (2010). Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol 126, 1105-1118.

Burks, A.W., et al. (2012). ICON: Food allergy. J Allergy Clin Immunol 129, 906-920.

Diet Log: Keep a diet log, and look for a pattern between symptoms and foods eaten in the last 1-2 days. For delayed-type food allergies, the association between intake of the food allergens and clinical symptoms are much less evident, so a diet log is helpful to recognize associations in delayed-type food allergies.

Blood and skin testing: Food allergen specific IgE testing by blood testing (called RAST) or skin prick testing can be helpful to detect immediate-type food allergies. These tests are readily available but have a high frequency of false positive results (i.e., many safe foods will be falsely reported as being allergens), so they should only be used as a guide as to possible foods to consider removing and then reintroducing. These tests do NOT help diagnose delayed-type food allergies. Blood IgG testing for food allergens is available but is of questionable reliability.

Patch testing: This involves use of a special patch to hold the food on the skin on the back for 48-72 hours, to check for delayed reactions – this may correlate with delayed-type cellular immune

reactivity to food proteins. However, validity of skin patch testing to food allergens is unclear, so it is best used as a possible guide of foods to consider removing.

Again, commercially available laboratory testing is limited, especially for delayed-type food allergies. For delayed-type food allergies, the current gold standard for diagnosis is removal of the suspect food, followed by reintroduction, as discussed above.

In severe cases of food allergy, the diagnosis procedure can involve an elimination diet of the most common reactive foods. For non-IgE-mediated food allergies, soy and milk products are the most common. For IgE-mediated food allergies, egg, milk, and peanuts are the most common. Grains such as wheat, rye, barley, oats, and corn can sometimes be allergens also. If there is improvement after removing several foods, then try challenging with one suspect food every 4 days, to see if any can be added back in. Some children may also be sensitive to artificial colors, flavors, and preservatives, and sensitivity to those can be assessed in the same way.

Explanation of treatment:

- Avoid foods that cause allergic reactions or symptoms
- Consider other methods to heal the gut – many food allergies will disappear when gut inflammation is healed.
- May consider using a 4-day diet rotation, in which a given food is only eaten 1 day every four days, so that there is less likelihood of developing an allergy to it (this is a method typically used for patients with eosinophilic esophagitis and some patients with severe reactions to food proteins, but there is not a good scientific rationale and this method is still controversial).

Benefits:

Removing allergic foods can result in a wide range of improvements in some children, including gastrointestinal and improvements in behavior and attention.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Food Allergy Treatment	2%	31%	67%	1294
Rotation Diet	2%	43%	55%	1097
Removed Chocolate	2%	46%	52%	2264
Removed Eggs	2%	53%	45%	1658

Duration: Some food allergies (like peanuts) seem to be lifelong, whereas others can disappear when gut inflammation is healed and/or the gut immune system develops tolerance to the offending food.

Research:

A study by Vojdani et al. found that many children with autism have food allergies.

Vojdani A, et al., Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. Nutr Neurosci. 2004 Jun;7(3):151-61.

There are also 3 studies by Jyonouchi et al, which found that children with autism had more hypersensitivities to food allergens than did typical children, which seemed to contribute to gut problems.

Jyonouchi et al., Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. Neuropsychobiology. 2005;51(2):77-85.

Jyonouchi et al., Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. J Pediatr. 2005 May;146(5):605-10.

Jyonouchi et al., Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. Neuropsychobiology. 2002;46(2):76-84.

A study by Lucarelli et al found that an 8-week diet that avoided allergic foods resulted in benefits in an open study of 36 children.

Lucarelli et all, Food allergy and infantile autism. Panminerva Med. 1995 Sep;37(3):137-41.

Three studies have demonstrated that children and adults with autism often have low levels of digestive enzymes for sugars and carbohydrates, especially the sugar in milk, which reduces the ability to digest those foods (see section on Digestive Enzymes).

Three studies have demonstrated that some individuals have increased intestinal permeability, so that large sugar molecules that normally would not be absorbed are able to pass through the intestinal wall into the blood stream. This "leaky gut" may allow other partly digested foods to pass into the body, potentially causing an allergic or immune response to those foods. It is unclear if this test for sugars is relevant to proteins since they are absorbed by a different mechanism.

de Magistris L et al., Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. J Pediatr Gastroenterol Nutr. 2010 Oct;51(4):418-24.

D'Eufemia P, Celli M, Finocchiaro R, et al.: Abnormal intestinal permeability in children with autism. Acta Paediatr 1996,85:1076–1079.

Horvath K, Zielke H, Collins J, et al.: Secretin improves intestinal permeability in autistic children. J Pediatr Gastroenterol Nutr 2000, 31(suppl 2):S30–S31.

There are many studies of gastrointestinal problems in children and adults with autism (see reviews by Buie et al 2010 and Coury et al 2012), and inflammation of the gut will greatly increase the likelihood that the immune cells in the gastrointestinal tract will react to foods.

Buie, T., et al. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics 125 Suppl 1, S1-18.

Coury DL et al (2012) Gastrointestinal Conditions in children with Autism Spectrum Disorder: Developing a Research Agenda, Pediatrics V130, Supplement 2 pp S160-168.

Limitations of IgG blood testing

Two studies found that IgG blood testing was not clinically relevant to the general population for identification of food allergies.

Hochwallner, H et al. (2011). Patients suffering from non-IgE-mediated cow's milk protein intolerance cannot be diagnosed based on IgG subclass or IgA responses to milk allergens. Allergy 66, 1201-1207.

Mitchell, N., (2011). Randomised controlled trial of food elimination diet based on IgG antibodies for the prevention of migraine like headaches. Nutr J 10, 85. (NEGATIVE RESULTS)

Gluten-Free, Casein-Free Diet (and often corn-free and soy-free)

Rationale: It is important to note that human digestive systems have not evolved on a diet containing high amounts of wheat and dairy products. Humans are the only animal who drink milk as adults, and the only ones to drink the milk of another animal. Cow's milk is a perfect food for baby cows, but not for humans or infants.

Over the last several hundred years, wheat has been bred to greatly increase its gluten content, and a typical US diet contains far higher amounts of wheat than humans were eating 1000-10,000 years ago. Gluten (in wheat, rye, barley, and possibly oats) and cow's milk proteins (including casein, β lactoglobulin, α-lactoalbumin which are present in all dairy products, including milk, yogurt, cheese, ice cream, caseinate) can cause several problems:

1. They are common food allergens (see previous section), causing both immediate- and delayed-type food reactions.
2. Many individuals with autism have low levels of lactase, the enzyme needed to digest lactose (the sugar in milk). This results in bacteria consuming the lactose, resulting in painful gas, bloating, and diarrhea.
3. Certain peptides from gluten and casein can bind to opioid-receptors in the brain, and can have a potent effect on behavior (like heroin or morphine), causing problems including sleepiness, giddiness, inattention/"zoning out," and aggressive and self-abusive behavior. Like opioids, they can be highly addictive, and a lack of them can cause severe behaviors. This problem appears to be due to an inability to fully digest the gluten and casein peptides into single amino acids, and due to inflammation of the gut, which allows the gluten and casein peptides to enter the bloodstream and reach opioid receptors in the brain. However, the evidence for this "opioid hypothesis" is limited.
4. Consumption of dairy products can cause the immune system to create antibodies against a similar protein in the body, the folate transport receptor, which carries folic acid into the brain. Individuals with cerebral folate deficiency have benefitted from a dairy-free diet.

Explanation of Treatment:

- Total, 100% avoidance of all gluten products and all dairy products. Even small amounts, like a bite of a cookie, can cause allergic problems if the individual has immediate-type IgE-mediated food allergy. Symptoms caused by delayed-type food allergy may be more dependent on dose. Many foods have trace contamination with gluten; e.g., French fries and raisins are dusted with wheat powder to keep them from sticking, so it can be very difficult to avoid all foods and contaminated foods. In recent studies, extensively heated proteins (milk and egg) can be better tolerated in patients with immediate-type milk and egg allergy.

- Digestive enzymes may be helpful, especially if there is an accidental exposure, for delayed type food allergy, although efficacy is not well proven. In case of immediate type food allergy, digestive enzymes will not be effective.

- Children with autism may also benefit from removing corn and/or soy products. It is of note that soy protein is highly immunogenic. In children with Food Protein Induced Enterocolitis Syndrome (FPIES, a condition in which food proteins cause inflammation of the gut) the most common causative food proteins are cow's milk protein and soy protein.

Benefits:

Children who most crave dairy and/or wheat, and who eat a lot of it, are most likely to benefit. Casein-free diets usually produce benefits within a month, and sometimes within a week. Gluten free diets usually take 1-3 months to produce benefits. In some children there is a worsening of symptoms for a few days (similar to a drug withdrawal) followed by improvement.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Gluten- and Casein-Free Diet	3%	28%	69%	3593
Casein-Free Diet	2%	44%	55%	6950
Wheat-Free Diet	2%	43%	55%	4340

Duration: At least until problems in the gut are addressed, and possibly lifelong.

Safety Note: It is important that a **calcium-and-vitamin-D supplement** be taken while on a dairy-free diet unless a child has an exceptionally nutritious diet rich in calcium. (Vitamin D is essential for calcium absorption from the gut).

Testing:

A trial of the GFCF diet is the best test, as it is the only way to determine if the diet will help a particular individual. At least one month of avoiding dairy and 3 months of avoiding gluten is recommended.

Immediate-type food allergies to milk proteins and gluten can be detected by ELISA in the blood or by prick skin testing, but the testing often yields false positive results, and does NOT test for delayed-type food allergies.

In patients with celiac disease, IgA antibody against deaminated gliadin (wheat protein) and anti-IgA antibody against tissue transglutaminate (autoantigen cross-reactive to deaminated gliadin) can be detected in the blood.

Research:

Reichelt has conducted several studies that have found abnormal peptides in the urine of people with autism, and he has conducted long-term treatment studies that found significant improvement from a GF/CF diet. Cade found that long-term use of digestive enzymes was beneficial, but that the GFCF diet was even more helpful.

Cade's large study of 150 children with autism found that 87% had IgG antibodies (allergy) to gluten, vs. 1% of the age and gender-matched controls, and 90% had IgG antibodies to casein, vs. 7% of the controls. (Note that IgG testing may yield false positives, and is of limited validity, but the difference between the two groups was striking). He also studied 70 autistic children who followed a GFCF diet for 1-8 years, and found that 81% improved significantly by the third month, with improvements continuing over the next 12 months. Large improvements were observed in social isolation, eye contact, mutism, learning skills, hyperactivity, stereotypic activity, and panic attacks. Among the 19% who did not improve, about 1/3 of them were not following the GFCF diet, and had lots of gluten and casein peptides still in their blood.

Cade R, Privette M et al. "Autism and Schizophrenia: Intestinal Disorders" Nutr. Neurosci 3 (2000) 57-72. Published by Overseas Publishers Association, (OPA) N.V.

Knivsberg AM, Reichelt KL, Nodland M. Reports on dietary intervention in autistic disorders. Nutr Neurosci. 2001;4(1):25-37. Review.

Single-blind study of 10 children with autism found that 8 benefitted from a GFCF diet.

Knivsberg et al. A randomised, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci. 2002 Sep;5(4):251-61.

A 12-week, double-blind, cross-over study of a GFCF diet in 15 children with autism did not find significant benefits, but parents reported benefits that were not identified by the testing.

Elder et al, The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006 413-420.

A 12-month, randomized, single-blind, placebo-controlled GFCF diet involving 54 children with autism found statistically significant benefits in communication subscores (ADOS evaluation) in the GFCF diet group compared to the control group. The parents (who were not blinded) also reported benefits in social interaction, daily living skills, inattention, and hyperactivity.

Whitely et al, The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. Nutr Neurosci. 2010 Apr;13(2):87-100.

Overall, most of the above studies (except a small, short one by Elder et al) found that the GCFC diet was beneficial for children with autism. More research is needed to determine if the primary problem with these foods is immediate-allergy, delayed allergy, lactose intolerance, possible opioid effect, or other factors, since in all these studies, characterization of food sensitivities in the study subjects were lacking.

Other Diets:

Several other diets are being investigated currently. One alternative diet is the Specific Carbohydrate Diet (SCD), which involves avoiding all carbohydrates and most sugars (except monosaccharides in fruit). This diet is reasonable to consider in patients who do not respond well to a gfcf diet because some individuals with autism have low levels of digestive enzymes for certain sugars and carbohydrates (see Digestive Enzyme section). For more information on this diet, see www.pecanbread.com. It is recommended that an experienced nutritionist assist you with implementing the diet, as some individuals have done poorly on a poorly-implemented version of the diet.

For more information on GFCF and other diets, go to:

Autism Network for Dietary Intervention: www.autismndi.com

Books on how to implement GFCF and other Special Diets

Special Diets for Special Kids, by Lisa Lewis

The Kid-Friendly ADHD & Autism Cookbook, Updated and Revised: The Ultimate Guide to the Gluten-Free, Casein-Free Diet by Pamela Compart M.D., Dana Laake R.D.H. M.S. L.D.N., Jon B. Pangborn Ph.D. F.A.I.C. and Sidney MacDonald Baker M.D. (Apr 1, 2012)

Nourishing Meals by Alissa Segersten and Tom Malterre

Digestive Wellness by Elizabeth Lipski

Vitamin/Mineral Supplements

Rationale: In order to be classified as a "vitamin" or "essential mineral," many studies were conducted that showed that the lack of that vitamin or mineral resulted in disease or even death. The RDA is the minimum amount required to prevent disease, but may be less than the amount needed for optimal mental and physical health. Most people in the US consume less than the Required Daily Allowance (RDA) of one or more vitamins and minerals. For example, many women lack enough calcium and iron, leading to osteoporosis and anemia, respectively.

Explanation of Treatment:
Vitamins and minerals are available in vegetables, fruits, meat, and other sources. However, the typical U.S. diet is lacking in key vitamins and minerals, so many people need to take a supplement.
Juicing: One option is to use a juicer to make fresh vegetable/fruit juice, and storing it for up to a few days in an airtight glass container. Fresh vegetable/fruit juice is a rich source of vitamins, minerals, and other nutrients. Commercial juices are "pasteurized" or heated to destroy bacteria, which also causes a loss of some nutrients, especially vitamins.

Typical juicing grinds the vegetables/fruit and strains out the pulp. Grinding vegetables/fruit one time provides only about half of the original vitamins/minerals, so after the first juicing it is useful to soak the pulp for about 15 minutes in a small amount of pure water (about 10% of the amount of liquid initially squeezed out), and then grind the pulp again – this will yield most of the remaining vitamins/minerals. The disadvantage to juicing is a loss of fiber (the soluble fiber remains, but the insoluble fiber is removed, and both are beneficial).

An alternative method is to use a special blender which grinds the pulp into very small chunks, resulting in no loss of fiber. This results in a thicker consistency (which can be addressed by adding water). Vitamix is one popular brand.

The advantage of juicing is that it is often a very easy and tasteful way to get healthy nutrients into children who don't eat fruits/vegetables. Some of the healthiest vegetables to use include cabbage, spinach, carrots, broccoli, parsley, and oregano, mixed with a small amount of fresh fruit for flavor and other nutrients. Organic vegetables and fruits are preferred, as they have less toxic pesticides. 8 ounces/day should be enough for most children and adults, depending on their intake of other vegetables and fruits.

Supplements: Vitamin/mineral supplements are largely unregulated, and some supplements do not contain what they claim, contain impurities, and/or use forms that are poorly absorbed. Some companies choose to participate in the Dietary Supplement Verification Program (DSVP) of the United States Pharmacopeia (USP) - that program verifies that the contents of the supplement match the label. Check for a USP or DSVP label, or go to http://www.usp.org/USPVerified/ to check a product.

- Most supplements do not contain all the essential vitamins and minerals, or do not contain enough of them.
- Several good choices for broad-spectrum vitamin/mineral supplements include the following, listed in alphabetical order:
  Awaken Nutrition's Agape
  Brainchild's Spectrum Support (used in the Adams et al 2004 study)
  Kirkman's Super Nu Thera (very high in vitamin B6), and Kirkman's Spectrum Complete.
  Yasoo's Syndion (used in the Adams et al 2011 study).
  However, some of those supplements do not contain enough calcium or magnesium, which is also very important to supplement, and they do not contain iron, which some young children and teen girls/women may need.

- Either folinic acid or methyl-tetra-hydrofolate should be used for supplying vitamin B - folic acid is not sufficient for children with autism, according to one research study.
  James SJ, Cutler et al., Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr. 2004, 80(6):1611-7.
- Calcium supplements are especially important if a person is on a dairy-free diet.
- Iron supplements are needed by some typical children as well as children with autism, but should only be given if a test indicates a need, as too much iron can also be a problem.
- In general, nutritional supplements are a good way to boost key nutrients lacking in the diet, and to provide extra amounts that may be needed to overcome metabolic problems.

Testing:

Most vitamin and mineral levels can be tested using blood samples taken while fasting. Health Diagnostics is one of very few companies that can measure the level of all vitamins. Many commercial labs can measure the level of most minerals, most of which can be measured reliably in Red Blood Cells (RBC). Calcium is best measured in the urine, preferably with a 24-hour urine collection. Some laboratories also offer functional assessments of the need for vitamins and minerals based on blood and/or urine testing. Measure iron with serum ferritin.

Recommended Dosages:

We recommend the following dosages for people with autism as a reasonable level to start with. However, some individuals may need more or less depending on their diet and metabolic needs, and testing can help determine optimal supplement levels.
Note that vitamins and minerals can have a potent effect on body function and behavior, so start at a low dose (1/10 of that below) and then gradually increasing over 3-4 weeks.

Iron should be added only if a test indicates a need for iron – this is a common problem in children under 5 years. Low iron is a leading cause of mental retardation in the US, and 40% of infants under the age of 2 have low iron (and so do 40% of women of child-bearing age). Most girls/women who are menstruating should take supplemental iron. However, too much iron can be harmful, so testing is important.

The dosage below should be adjusted up or down by bodyweight; ie, half for a 30-lb child, and double for 120 pounds and above.

The following recommendations are based on the results of a published study that measured the effect of a multi-vitamin/mineral supplement on children with autism.

Adams JB et al., Effect of a Vitamin/Mineral Supplement on Children with Autism, BMC Pediatrics 2011, 11:111

The recommendations are similar to what was used in the Adams et al 2011 study, but slightly modified based on the results of that study. We recommend starting at a low dose, and gradually increasing over several weeks – some individuals may be better with half or ¾ dose.

VITAMINS	Recommended Supplement (for 60 lb child)	RDA (4-8 yr)	Upper Limit
Vitamin A (as mixed carotenoids)	6000 IU carotenoids[a] (equivalent to 3000 IU Vit. A)	400 mcg (1333 IU)	900 mcg (3000 IU)
Vitamin C (ascorbic acid)	500 mg	25 mg	650 mg
Vitamin D	1000 IU (some individuals may need more, especially if little exposure to direct sunlight)	5 mcg (200 IU)	Children - 50 mcg (2000 IU) Teens/Adults – 100 mcg (4000 IU)

Vitamin E (including mixed tocopherols)	250 IU	7 mg (10.5 IU)	300 mg (450 IU)
Vitamin K	55 mcg	55 mg	ND
B1 (thiamin HCl)	30 mg	0.6 mg	ND
B2 (riboflavin)	40mg	0.6 mg	ND
B3 (niacin/niacinamide)	15 mg niacin 20 mg niacinamide	8 mg	15 mg
B5	25 mg	3 mg	ND
B6	40 mg[b]	0.6	40 mg
B12 (methylcobalamin or cyanocobalamin)	600 mcg	1.2 mcg	ND
Folic Acid	800 mcg of folinic acid or methyltetrahydrofolate (not folic acid, which is insufficient for children with autism)	200 mcg	400 mcg
Biotin (d-biotin)	300 mcg	12 mcg	ND
Choline	250 mg	250 mg	1000 mg
Inositol	100 mg	n/a	n/a
MINERALS			
Calcium	300 mg (may need more if on dairy-free diet)	800 mg	2500 mg
Chromium	70 mcg	15 mcg	ND
Copper	0-400 mcg[c]	440 mcg	3000 mcg
Iodine	100 mcg	90 mcg	300 mcg
Iron	0[d]	10 mg	40 mg
Lithium	300 mcg[e]	n/a****	n/a
Magnesium	250 mg	130 mg	110 mg[f]
Manganese	0-1 mg[g]	1.5 mg	3 mg
Molybdenum	100 mcg	22 mcg	600 mcg
Phosphorus	0 (eat fruits & vegetables)	500 mg	3000 mg
Potassium	50 mg	1500 mg	n/a
Selenium	40 mcg	30 mcg	150 mcg
Sulfur (MSM)	500 mg; or, take Epsom Salt baths	n/a	n/a
Zinc	10-20 mg	5 mg	12 mg

a) Carotenoids are only converted to vitamin A as needed, so this level is safe even though it is at the Tolerable Upper Limit

b) Some children and adults may benefit from much higher dosages, see section on High Dose Vitamin B6.

c) Some children with autism have slightly elevated copper, so either low or no supplementation is sufficient for most children with autism.

d) Iron should be added on an individual basis only if serum ferritin tests reveal a need for iron, or for girls/women who are of menstruation age. Suggest 5-10 mg of iron chelate for 4 weeks, followed by half that dosage afterwards

e) For magnesium, the UL is the amount for supplements and does not count food sources
f) Estimated daily intake of lithium in food is 1900 mcg/day for adults.
g) One study found that children with autism have slightly elevated manganese, so either low or no supplementation is sufficient for most children with autism.

Duration: Lifelong, although improving diet and healing gut may reduce the need for supplementation.

Safety Note: Most vitamins are water soluble, and excess amounts of them will be safely excreted in the urine. Some vitamins (vitamins A, D, E, K) are fat soluble, and excess amounts of those can build up in the body and cause toxicity if taken at high levels (above what we recommend) for a long time.
Excess amounts of minerals can cause problems, and the upper limits listed above should not be exceeded without consultation with a physician or nutritionist.
Start with a low dose (1/5 of that listed above), and gradually increase over 1 month.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Vitamin A	2%	54%	44%	1535
Calcium[E]:	3%	60%	36%	2832
Folic Acid	5%	50%	45%	2505
Magnesium	6%	65%	29%	301
P5P (Vit. B6)	13%	37%	51%	213
Vitamin B3	4%	51%	45%	1192
Vitamin B6 alone	8%	63%	30%	620
Vitamin B6 with Magnesium	4%	46%	49%	7256
Vitamin B12 (methyl, subcut.)	6%	22%	72%	899
Vitamin C	2%	52%	46%	3077
Zinc	2%	44%	54%	2738

Research – Vitamins:

One large comprehensive study found that children with autism had lower levels of several vitamins (especially biotin) and some minerals (lithium, calcium, and magnesium) and impairments in sulfation, methylation, glutathione, ATP, and oxidative stress, compared to neurotypical children of the same age. The severity of autism was strongly associated with the level of certain vitamins and minerals.

Adams JB et al., Nutritional and Metabolic Status of Children with Autism vs. Neurotypical Children, and the Association with Autism Severity, Nutr. Metab (Lond) 2011 Jun 8:8(1):34.

One study in China found that most children with autism had inadequate intake of folic acid, vitamin B6, calcium, vitamin A, vitamin C, and zinc, based on estimating dietary intake from diet logs (not as accurate as blood measurements).

Xia W et al., A preliminary study on nutritional status and intake in Chinese children with autism. Eur J Pediatr 2010, 69(10):1201-6.

One study in Romania found normal levels of vitamin B12 and folate in children with autism compared to controls, but low levels of plasma glutathione, consistent with the Adams et al 2011 study. In other words, it seems that children with autism need extra amounts of vitamin B12 and folate to have normal glutathione.

Paşca SP et al., One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders. J. Cell. Mol. Med. 2009, 13(10):4229-4238.

One study found that children with autism had high levels of plasma vitamin B6 pre-supplementation, and this finding was confirmed in a follow-up study (Adams 2006), suggesting a metabolic imbalance in B6. (See section on High-Dose Vitamin B6 for more info.)

Adams JB, Holloway C.J: Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. Altern Complement Med. 2004, 10(6):1033-9.

Adams JB, George F, Audhya T: Abnormally high plasma levels of vitamin B6 in children with autism not taking supplements compared to controls not taking supplements. J Altern Complement Med. 2006, 12(1):59-63.

One study of vitamin D status in Egypt found that young children with autism had lower levels of vitamin D compared to age-matched controls. However, the Adams et al 2011 study did not find any difference between vitamin D levels in children with autism in the US and neurotypical children in the US. Low levels of vitamin D are a concern for the general population, since vitamin D is made by the body only when exposed to direct sunlight, and nowadays people spend more time inside or shielded from the sun.

Meguid NA, Hashish AF, Anwar M, Sidhom G: Reduced serum levels of 25-hydroxy and 1,25-dihydroxy vitamin D in Egyptian children with autism. J Altern Complement Med. 2010, 16(6):641-5.

One study in Slovakia found that children with autism had significantly higher levels of vitamin C and beta-carotene, but normal levels of vitamin A and vitamin E, compared to older teen controls. This is consistent with the Adams et al 2011 study.

Krajkovicova-Kudlackova M et al. Plasma concentration of selected antioxidants in autistic children and adolescents. Bratisl Lek Listy 2009, 110(4): 247-250.

Many studies have demonstrated that children with autism have substantial oxidative stress, suggesting either a low level of key antioxidants or an increased need for them. (See section on oxidative stress.)

Research – Minerals

One large comprehensive study found that children with autism had lower levels of some minerals (lithium, calcium, and magnesium) compared to neurotypical children of the same age. The severity of autism was strongly associated with the level of certain vitamins and minerals.

Adams JB et al., Nutritional and Metabolic Status of Children with Autism vs. Neurotypical Children, and the Association with Autism Severity, Nutr. Metab (Lond) 2011 Jun 8:8(1):34.

Another study also found that young US children with autism (and their mothers) had unusually low levels of lithium compared to neurotypical children and their mothers. Lithium is receiving increasing recognition as possibly being an essential mineral, as low levels are associated with psychiatric and immunological disorders.

Adams JB et al., Biol Tr El Res 2006, 110:193-209.

Two large studies of iron status found that young US and Canadian children with autism had anemia in 8% and 16% of cases, respectively.

Latif A et al., Iron Deficiency in Autism and Asperger Syndrome. Autism 2002, 6:103.

Dosman CF et al., Ferritin as an indicator of suspected iron deficiency in children with autism spectrum disorder: prevalence of low serum ferritin concentration. Dev Med Child Neurol. 2006, 48(12):1008-9.

One small study of minerals in red blood cells found that young Canadian children with autism had lower levels of RBC selenium and RBC molybdenum than neurotypical children of the same age [24], but similar levels of most other minerals.

Jory J and McGinnis W: Red-Cell Trace Minerals in Children with Autism. American Journal of Biochemistry and Biotechnology 2008, 4(2):101-104.

A small study of zinc and copper in plasma found that British children with autism had similar levels to neurotypical children.

Jackson MJ and Gerard PJ: Plasma Zinc, Copper, and Amino Acid Levels in the Blood of Autistic Children. J Autism Childhood Schizophrenia 1978, 8(2):203-208

In contrast, a study of Turkish children with autism found that they had lower levels of zinc in plasma and RBC compared to neurotypical children.

Yorbik O, Akay C, Sayal A, Cansever A, Sohmen T, Cavdar AO: Zinc Status in Autistic Children J. Trace Elements Experimental Medicine 2004, 17:101-107.

Research – Treatment

A large, randomized, double-blind placebo-controlled study found that a similar strong, balanced multi-vitamin/mineral supplement resulted in modest but statistically significant improvements in the Average Change of all symptoms on the Parent Global Impressions-Revised, and significant improvements in subscores in expressive language, tantrumming, hyperactivity, and overall symptoms. The supplement improved the level of many vitamins and minerals. There were also many improvements in metabolism, including improvements in oxidative stress, methylation, glutathione, sulfation, plasma ATP. The children with low levels of vitamin K and biotin (both made by gut bacteria) improved the most.

Adams JB et al., Effect of a Vitamin/Mineral Supplement on Children with Autism, BMC Pediatrics 2011, 11:111

One open-label study [49] found that micronutrient supplementation was comparable or more effective than treatment with pharmaceuticals in terms of improvements in the Childhood Autism Rating Scale, Childhood Psychiatric Rating Scale, Clinical Global Impressions, and Self-Injurious Behavior.

Mehl-Madrona L et al., Micronutrients versus standard medication management in autism: a naturalistic casecontrol study. J Child Adolesc Psychopharmacol 2010, 20(2):95-103.

One small randomized, double-blind, placebo-controlled study published found that a strong, balanced multi-vitamin/mineral supplement resulted in improvements in children with autism in sleep and gut function, and possibly in other areas.

Adams JB et al., Pilot study of a moderate dose multivitamin-mineral supplement for children with autistic spectrum disorder. J Altern Complement Med. 2004 Dec;10(6):1033-9.

One study found that high-dose vitamin C (1.1 g per 10 kg bodyweight) helped children with autism.

Dolske MC et al., A preliminary trial of ascorbic acid as supplemental therapy for autism. Prog Neuropsychopharmacol Biol Psychiatry 1993 Sep;17(5):765-74.

High-Dose Vitamin B6 and Magnesium

Rationale: There are over 20 studies of vitamin B6 with Magnesium for autism, including 12 double-blind, placebo-controlled studies, making it one of the most studied nutritional treatments for autism. Almost all of these studies found that 30-40% of children and adults with autism benefited from high-dose supplementation of vitamin B6 with magnesium. Vitamin B6 is required for over 1113 enzymatic reactions, including the production of major neurotransmitters (serotonin, dopamine, and others), glutathione (needed for detoxification), and hemoglobin (carries oxygen in blood). Magnesium is used to prevent the possibility of hyperactivity, which can occur if the vitamin B6 is taken by itself.

Most of the studies used dosages of about 8-15 mg/pound of B6 (maximum of 1000 mg). Only 1 study used a lower dosage (1.3 mg/pound), and that is one of the few studies that found no benefit.

An unpublished study by Audhya steadily increased the dosage of vitamin B6 from 1 to 10 mg/pound. They found that at least 3 mg/pound was needed to begin to see benefits, and 6 mg/pound was enough for most children to see benefit.

The reason why many children and adults benefit from high-dose vitamin B6 is still unclear, but a possible explanation is that some children and adults with autism have both 1) a decreased ability to convert vitamin B6 to its active form, and 2) defective enzymes for making key neurotransmitters that require an unusually high amount of the active form of vitamin B6.

Adams JB, Holloway C.J: Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. Altern Complement Med. 2004, 10(6):1033-9.

Adams JB, George F, Audhya T: Abnormally high plasma levels of vitamin B6 in children with autism not taking supplements compared to controls not taking supplements. J Altern Complement Med. 2006, 12(1):59-63.

Treatment: Based on a review of all the research, Dr. Bernard Rimland recommended a dosage of about 8 mg/pound of vitamin B6 (maximum of 1000 mg) and half as much magnesium. However, he emphasized that some individuals with autism need somewhat more or less.

Test: There is not yet a lab test to determine who will benefit from high-dose vitamin B6, although measurements of low neurotransmitters might be a possible clue. The best test is simply a 2-month trial, slowly increasing the dose from 1 mg/pound bodyweight to 8 mg/pound bodyweight of B6, and half as much magnesium.

A test for B6-deficiency is a measurement of 4-pyridoxic acid in urine. Normally about 50% of dietary vitamin B6 is excreted as 4-pyridoxic acid. Vitamin B6-deficient subjects have undetectable levels of 4-pyridoxic acid in their urine, making it a useful diagnostic test of vitamin B6 status; on a B6-deficient diet, levels drop to <5% within 5 days.

Absorption of vitamin B6

Only non-phosphated forms can be absorbed orally. Luckily, phosphated forms are converted into non-phosphated forms by alkaline phosphatase in the intestinal membrane.

Non-phosphated forms are then absorbed by passive diffusion, primarily in the jejunum (gut). Absorption is non-saturable (very large amounts can be absorbed).

Physicians Desk Reference (PDR) on Nutritional Supplements 2001.

Forms of vitamin B6

There are six different forms of vitamin B6, including three unphosphated forms and their corresponding phosphated forms. All forms can be converted to one another, and should result in increases in the active forms (PLP and (for a few reactions) PMP).
The six forms of vitamin B6 are:
Pyridoxine (PN) & Pyridoxine 5-Phosphate (PNP)
Pyridoxal (PL) & Pyridoxal 5-Phosphate (PLP)
Pyridoxamine (PM) and Pyridoxamine 5-Phosphate (PMP)

ARI survey data reports a slightly higher rate of adverse effects for PLP (11%) than for other forms of B6 (8%, or 4% if given with Mg). Analysis of their survey data suggests that some children do better on unphosphated forms (pyridoxine HCL), and some do better on the phosphated forms (PLP). Both forms should be well absorbed and have similar effects.

So, we suggest first starting with pyridoxine HCL; if it is not effective, consider switching to PLP. All research studies to date have only investigated high-dose pyridoxine HCL for autism, and none have involved high-dose PLP.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Magnesium	6%	65%	29%	301
Vitamin B6 (pyridoxine HCl)	8%	63%	30%	620
Vitamin B6 with Magnesium	4%	46%	49%	7256
P5P (Vit. B6)	11%	40%	48%	920

Safety: High dose B6 should always be taken with magnesium to prevent possible hyperactivity (which occurs in about 20% of cases when high dose B6 is taken without magnesium).
High dose supplementation of vitamin B6 with Mg in children and adults with autism appears to be very safe.
In very rare cases (less than 1 in 1000) high dose vitamin B6 can cause temporary numbness in fingers and toes. Stopping supplementation generally results in full recovery.

For more info: A summary of vitamin B6 studies in autism is available at www.autism.com

Essential Fatty Acids

Rationale: Essential fatty acids (EFAs) are critical nutrients for humans. They exist in the cell membrane of every cell, and roughly 20% of an infant's brain is composed of essential fatty acids. Mother's milk is very rich in essential fatty acids, but some infant formulas lack this key ingredient needed for brain development.

Two general categories of essential fatty acids are omega-3 and omega-6. Omega-3 fatty acids have relatively short shelf lives, so commercial food processing often hydrogenates or partially hydrogenates them, which provides long shelf life but eliminates their nutritional value. Thus, over 80% of the US population has low levels of omega-3 fatty acids – this is one of the most widespread nutritional problems in the US.

Low levels of EFAs are associated with a wide range of psychological disorders, including depression, post-partum depression, bipolar disorder (manic/depression), and Rett's syndrome (similar to autism). Most importantly, four published studies have found that children with autism have lower levels of omega–3 fatty acids than the general population.

- *S. Vancassel et al., Plasma fatty acid levels in autistic children, Prostaglandins Leukot Essent Fatty Acids 2001 65:1-7.*
- *Bell et al Essential fatty acids and phospholipase A2 in autistic spectrum disorders. Prostaglandins Leukot Essent Fatty Acids. 2004 Oct;71(4):201-4.*
- *Wiest et al Plasma fatty acid profiles in autism: a case-control study Prostaglandins Leukot Essent Fatty Acids. 2009 Apr;80(4):221-7.*
- *Bell et al 2010, 7The fatty acid compositions of erythrocyte and plasma polar lipids in children with autism, developmental delay or typically developing controls and the effect of fish oil intake. Br. J. Nutri. 103 1160-7.*

Explanation of Treatment:
One of the best sources of omega-3 fatty acids is fish, which obtain them from algae and plankton in the sea. Unfortunately, many fish are high in mercury and other toxins, especially the large predators (shark, swordfish, and tuna) that are at the top of the food chain and consume smaller fish. Smaller fish with shorter lifespans, such as salmon and shrimp, have lower levels of mercury, but it depends where they come from. So, it is generally safer for children to obtain essential fatty acids from fish oil from small fish, since little mercury is stored in the oil. Because fish oil (and fish) spoil readily, it is important to obtain a high-quality oil that does not smell or taste rancid, and it should be kept refrigerated. A high-quality fish oil should have only a mild taste.

Two of the major omega-3 fatty acids are eicosapentaenoic acid (EPA) & docosahexaenoic acid (DHA). DHA is critical for early brain development, and EPA is useful for later development and is an important anti-inflammatory mediator.

Recommended dosages (based on the amount of omega-3's, not the total amount of oil which will contain other oils):
Omega-3: 20-60 mg/kg (600-1800 mg for a 30 kg, or 60 lb, child). For younger children, use a supplement richer in DHA, and for older children and adults, use a supplement richer in EPA.
Omega 6: ¼ as much omega-6 as omega-3; so, if taking 1000 mg of omega-3's, then 250 mg of omega-6. It is important to maintain a balance of omega-3 and omega-6. Most people eating a typical western diet receive sufficient omega-6 but are lacking in omega-3; however, some may need a little extra omega-6 when taking an omega-3 supplement.

Flax seed oil is also a source of omega-3 fatty acids, but the form it provides (alpha linolenic acid) must be converted by the body to the active form (EPA and DHA), and that conversion process is

slow in humans. There have been some reports that children with autism respond poorly to flax seed oil, so we generally recommend fish oil instead.

Cod liver oil (or other fish liver oil) is a good source of omega-3 fatty acids, and also provides good amounts of vitamin A and vitamin D. However, vitamin A intake from all supplements should not greatly exceed the RDA intake (see vitamin/mineral section) for extended periods, since excess amounts will be stored in the liver and could affect liver function. (Carotenes are pre-vitamin A and are not a problem.)

Testing: The level of essential fatty acids can be measured in the red blood cell membrane. However, because most people in the US have low levels of omega-3's, it is desirable to reach levels at the top of the "normal" range. Also, it is better to measure the absolute amount of each fatty acid, rather than just the percentage of each.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Fatty Acids	2%	39%	59%	1680

Safety:
One unpublished study by Audhya of 400 children with autism found that about 1-2% had a severe behavioral reaction to fish oil within a few days, resulting in extreme behavioral problems. These symptoms disappeared within a few days after stopping intake. Blood testing revealed that these children had a carnitine deficiency (see section on Carnitine), which is needed to carry long-chain fatty acids into the mitochondria, and to transport short and medium chain fatty acids out of the mitochondria. Supplementation with low dose carnitine (about 200 mg/day) allowed the children to tolerate fish oil without any problem. Since the major source of carnitine is beef and pork, people who avoid those foods may want to start with very low doses of fish oil, and if there is a problem add a carnitine supplement or eat beef or pork regularly.

Research:
There are a huge number of scientific studies showing that humans need EFAs, and that most people in the US do not consume enough. As mentioned above, 4 studies found that children with autism have lower levels of omega-3 fatty acids than do typical children, many of whom are not consuming enough.

There have been nine treatment studies for children/adults with autism, six positive and three inconclusive or negative. Most of the studies have been short, and did not pre-screen for children with low EFA levels. It is likely that fish oil will be most beneficial to children who do not eat fish regularly, and it could be that long treatment (12 months) is needed for full benefits to be observed.

<u>Positive studies</u>
A 90-day open trial of essential fatty acids in 18 children with autism found significant increases in language and learning skills.

Patrick L and Salik R, The Effect of Essential Fatty Acid Supplementation on Language Development and Learning Skills in Autism and Asperger's syndrome. Autism/Asperger's Digest: Research Article – Jan/Feb 2005.

One unpublished study by Adams et al. found that 2 months supplementation of fish oil (rich in DHA) led to significant improvements in sociability and other areas, especially in children and adults who consumed 0-1 servings of fish/month.

One unpublished open study by Audhya et al. was a 9-month treatment study of several hundred children. They found little improvement by 6 months, but substantial improvements by 9 months. The largest improvement was in gut function (verified by pre and post endoscopies in many cases), but also improvements in other areas.

An open-label study of 30 children with autism found that fish oil supplementation led to improvements in EFA levels, and 2/3 of the participants had improvements in their autistic symptoms.

Meguid et al, Role of polyunsaturated fatty acids in the management of Egyptian children with autism. Clinical Biochemistry 41 (2008) 1044–1048

One study found that fish oil supplementation improved omega-3 levels in children with autism.

Bell JG et al, The fatty acid compositions of erythrocyte and plasma polar lipids in children with autism, developmental delay or typically developing controls and the effect of fish oil intake. Br J Nutr. 2010 Apr;103(8):1160-7.

One small randomized, double-blind, placebo-controlled 16-week treatment study found that the combination of DHA (an omega 3 EFA) and arachidonic acid (an omega 6 EFA) led to significant improvements in communication and social withdrawal. (There is a concern that western diets already contain sufficient arachidonic acid.)

Bent et al.,. Effects of large doses of arachidonic acid added to docosahexaenoic acid on social impairment in individuals with autism spectrum disorders: a double-blind, placebo-controlled, randomized trial. J Clin Psychopharmacol. 2012 Apr;32(2):200-6.

Negative/Inconclusive studies

One small double-blind, placebo-controlled treatment study by Amminger et al. found that fish oil might have some benefit in reducing hyperactivity, but the numbers were too small to be statistically significant.

Amminger et al. Omega-3 Fatty Acids Supplementation in Children with Autism: A Double-blind Randomized, Placebo-controlled Pilot Study. Biol Psychiatry. 2006 Aug 22.

In an open-label 6-week study of 19 young adults with severe autism, there was no benefit of EFA supplementation on autistic symptoms or problem behaviors.

Politi et al, Behavioral Effects of Omega-3 Fatty Acid Supplementation in Young Adults with Severe Autism: An Open Label Study Archives of Medical Research 39 (2008) 682-685

In a small randomized, double-blind, placebo-controlled 12-week treatment study of young children with autism, the treatment group did not improve significantly more than the placebo group on hyperactivity (the primary outcome measure).

Bent et al., A Pilot Randomized Controlled Trial of Omega-3 Fatty Acids for Autism Spectrum Disorder. J Autism Dev Disord. 2011 May;41(5):545-54.

For more info on essential fatty acids:

see www.nordicnaturals.com; www.ghs.co; www.barleans.com

Gut Treatments: Digestive Enzymes

Rationale: The body normally produces a variety of digestive enzymes to break large food molecules into smaller ones that can be absorbed. Different enzymes are needed for different types of protein, carbohydrates, and fats. Children with autism sometimes have low levels of certain enzymes, or less active enzymes, or both – enzyme problems are especially common in children with gut problems (chronic constipation or diarrhea).

One digestive enzyme, DPP4, is easily deactivated by small amounts of toxins including mercury and organophosphates (pesticide sprays). DPP4 is needed to digest some peptides from casein and other substances that can have an opioid-like effect.

Treatment: Take a digestive enzyme with each meal, usually at the start of the meal. Use enzymes that are as complete as possible. Proteases are needed for protein, lipases for fats, and disaccharidases and other enzymes for carbohydrates.
Note that we recommend digestive enzymes in addition to special diets, and they should not be used instead of special diets. If a child has a problem digesting wheat or dairy products, it is best to just avoid them, and use the digestive enzymes as a precaution against unknown exposures.

Testing:
Symptoms of pain, gas, and discomfort after eating dairy products is a strong indicator of a lack of digestive enzymes for milk, or a delayed-type food allergy to it.
If an endoscopy is conducted to investigate chronic gastrointestinal problems, it is highly recommended to include a biopsy to test for digestive enzymes – this is a routine test in most hospitals, and can easily be done as part of the endoscopy.
A Comprehensive Digestive Stool Analysis may reveal whether some types of foods are not being digested well, suggesting a problem with specific digestive enzymes, but the reliability of the test is limited.

Research

Gut Problems are Common in Autism
There are many studies of gastrointestinal problems in children and adults with autism (see review by Buie et al 2010), and most of the studies indicate that chronic gastrointestinal problems (constipation, diarhea, abdominal pain, esophagitis, etc.) are common and should be evaluated and treated.

Buie, T., et al. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics 125 Suppl 1, S1-18.

Lack of Digestive Enzymes
Studies by Horvath et al. 1999, Williams et al 2011, and Kushak et al 2011 have found that many children with autism and major gastrointestinal problems have low levels of enzymes needed to digest sugars/carbohydrates, especially lactase, the enzyme needed to digest lactose (the sugar in milk). Insufficient lactase would result in gas, pain, and diarrhea after consuming milk products. Their studies involved tissue biopsies taken during an endoscopy, so these were from children/adults with substantial gastrointestinal problems – problems with digestive enzymes are probably less likely in individuals without obvious gastrointestinal symptoms.

One large study by Horvath, et al (1999) evaluated disaccharidase (sugar) activity from endoscopic biopsies in 90 children with autism. They found that 49% had at least one deficient enzyme activity, and 20% had deficiencies in two or more disaccharidase enzymes. "Lactase and maltase deficiencies were the most frequent, followed by low activity of sucrase, palatinase, and glucoamylase. All of the children with low enzyme activity had loose stools and/or gaseousness."

Horvath K et al, Gastrointestinal abnormalities in children with autistic disorder," J. Pediatrics 135 no. 5 (1999) 559-563.

Horvath K and Perman JA "Autistic disorder and gastrointestinal disease," Curr. Opinion in Pediatrics, 14 (2002) 583.

A small study by Williams et al 2011 also found substantial decreases in disaccharidases, resulting in abnormal gut bacteria.

Williams BL et al., Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS One. 2011;6(9):e24585. Epub 2011 Sep 16.

A new large study at Harvard Medical School (Kushak et al 2011) involving intestinal biopsy samples of 199 children and adults with autism (ages 22 months to 28 years) found that many had deficiencies in disaccharidases (enzymes for digesting simple sugars). Specifically, they found that 62% had deficiencies in lactase, 16% were deficient in sucrase, and 10% were deficient in maltase. The problems seemed to be equally common in children and adults, suggesting that these problems are lifelong.

Kushak RI et al., Intestinal disaccharidase activity in patients with autism: effect of age, gender, and intestinal inflammation. Autism. 2011 May;15(3):285-94. Epub 2011 Mar 17.

Treatment Studies

One open-label treatment study involved a 12-week trial of a digestive enzyme. The digestive enzyme included enzymes for proteins, peptides, casein, and phytic acid. 46 participants started the study, and 17 dropped out, including 6 who stated adverse effects and others for various reasons including lack of benefit. This was a rather high drop-out rate. The 29 who finished the study reported improvements in many areas, especially socialization and hyperactivity, and half reported improvements in digestion.

Brudnak MA et al. Enzyme-based therapy for autism spectrum disorders -- is it worth another look? Med Hypotheses. 2002 May;58(5):422-8.

However, another digestive enzyme treatment study found no benefit. This was a more rigorous randomized, double-blind, placebo-controlled, cross-over study lasting 6 months and involving 43 participants. It involved a digestive enzyme designed to digest proteins and peptides (small proteins), not carbohydrates or sugars. The digestive enzymes were well tolerated, but there were no statistically significant clinical improvements on any symptoms.

Munasinghe et al., Digestive Enzyme Supplementation for Autism Spectrum Disorders: A Double-Blind Randomized Controlled Trial J Autism Dev Disord (2010) 40:1131–1138

The two studies listed above were for digestive enzymes focused on proteins, not sugars and carbohydrates. According to three studies by Horvath et al 1999, Williams et al 2011, and Kushak et al 2011, children with autism have a problem digesting sugars and carbohydrates, and especially milk sugar (lactose). So, there is a need for a treatment study to investigate digestive enzymes designed to digest sugars and carbohydrates, especially lactase.

Finally, the ARI survey data (which involves many different brands of digestive enzymes) suggests that digestive enzymes can be helpful and are generally well-tolerated. The Specific Carbohydrate

Diet (which includes avoidance of most sugars and all carbohydrates except for monosaccharides) also seems likely to be beneficial for people lacking digestive enzymes for those foods, but there are no formal research studies on it yet (see ARI survey data below).

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Digestive Enzymes	3%	35%	62%	2350
Specific Carbohydrate Diet	7%	22%	71%	537

Gut Treatments: Anti-fungals and Probiotics

Rationale: The human gut contains a large number of bacteria (10x more gut bacteria than cells in the entire body). Most of these gut bacteria are beneficial, helping with food digestion and water balance, producing some vitamins, and limiting the growth of harmful bacteria and yeast.

One of the most striking differences in the medical history of children with autism is that several studies have reported much higher use of oral antibiotics (usually for ear infections) in infancy of children with autism compared to controls. These oral antibiotics will destroy most of the beneficial gut bacteria, and thus increase the risk of overgrowth of harmful bacteria and/or yeast.

Harmful bacteria and yeast produce toxins that can severely affect mental functioning and behavior; alcohol is just one of many toxins that yeast can produce, and is a good example of a yeast toxin that can severely affect behavior. It seems that the best way to treat these problems is with a combination of antifungal diet, antifungal medications (if yeast are present) and probiotics (beneficial bacteria). These can help restore normal gut function. Antibiotics should only be considered as a last resort in most cases, as ARI survey data suggest they are more likely to cause harm than help.

Treatment:
Anti-fungal Diet: Yeast feed on sugar and simple carbohydrates, so reducing or avoiding those foods is important. Also, it can be helpful to avoid foods containing yeast or yeast products, including fruit juice, vinegar (in ketchup and other foods), leavened foods (bread, pizza, bagels, rolls), cheese, and mushrooms (a type of yeast/fungus).
Duration: Dr. Sidney Baker recommends a trial for 5-14 days, followed by a high exposure to see if the diet makes a difference. If so, continue long-term.

Anti-fungal Medications: There are several prescription and non-prescription anti-fungal treatments, and sometimes several need to be tried before finding an effective one for a given strain of yeast. Nystatin is the safest because it is not absorbed, but many yeast are now resistant to it. Diflucan, Sporanox, Lamisil, and Nizoral are alternatives to which yeast are less likely to be resistant, but since they are absorbed into the body they have a very small chance of overtaxing the liver, and liver enzymes should be checked every few months if they are used long-term. (Note that there is no published research supporting this approach, merely the clinical experience of some MDs.) Some non-prescription antifungal treatments include capryllic acid, oregano concentrate, citrus seed extract, undecylenic acid, and pau d'arco.
Duration: Dr. Sidney Baker recommends a series of high-dose trials of 2-3 weeks for each antifungal, followed by the next one until you find one that works.
Die-off reaction: When yeast are killed, they can release all their toxins at once. This can cause a temporary "die-off" reaction lasting a few days, followed by good improvement when the toxins leave the body. Activated charcoal can be taken to absorb these toxins and reduce side-effects.

Probiotics: Probiotics are mixtures of one or more beneficial bacteria that are normally present in the gut. Many probiotics contain only a few billion Colony Forming Units (CFU's), but some strong probiotics contain 30-75 billion CFU's, and some prescription probiotics contain up to 500 billion CFU's. The higher-dose products are more likely to be able to reach the gut and recolonize it with good bacteria. If high-dose probiotics continue to be needed, this may suggest pancreatitis or other serious dysfunction is present.

Duration: Very little is known about optimal types and dosages of probiotics. We recommend gradually increasing to a high dose until benefit is observed, and then consider a lower maintenance dose.
Testing: One simple and very useful test is to look at the stool, since half of the stool is bacteria. The stool should be a medium/dark brown and well-formed, with 1-3 bowel movements/day.

Use antibiotics only with great caution: One round of oral antibiotics typically kills off over 99% of beneficial gut bacteria, but has little or no effect on yeast or many types of bad bacteria, which then thrive due to lack of competition from beneficial bacteria. Oral antibiotics often cause overgrowths of bad bacteria and yeast, and are suspected as the cause of many of the gut problems in autism. Several studies have shown that children with autism had, on average, a much higher usage of oral antibiotics than typical children in their first few years of life.

Lab Testing: A Comprehensive Digestive Stool Analysis (available from Genova Diagnostics or Doctor's Data) will reveal the amount of some types of normal and abnormal bacteria and yeast. Some labs offer individualized susceptibility testing, to determine which anti-fungals are most effective against the patient's particular yeast.
Urinary organic acid testing can be done to check for abnormally high levels of metabolites from yeast, although the reliability of this test is unclear.

Individuals with chronic gastrointestinal problems should consider a consult with a gastroenterologist (a doctor who specializes in gastrointestinal problems), who may recommend an endoscopy or other testing. Endoscopies should include a biopsy to evaluate digestive enzymes (see Digestive Enzyme section) – this testing is now widely available.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Antifungals[C]: Diflucan	5%	34%	62%	1214
Antifungals[C]: Nystatin	5%	43%	52%	1969
Antibiotics (not recommended)	33%	50%	18%	2507
Candida diet	3%	39%	58%	1141

Research – Oral Antibiotics Over-used

Five studies have reported much higher usage of oral antibiotics during infancy of children with autism vs. controls, usually for treating ear infections (possibly suggesting an impaired immune system). Commonly used oral antibiotics eliminate almost all of the normal gut bacteria, which play an important role in the breakdown of plant polysaccharides, promoting gastrointestinal motility, maintaining water balance, producing some vitamins, and competing against harmful bacteria. Loss of normal gut flora can result in the overgrowth of harmful bacteria/yeast, which can in turn cause constipation and other problems.

Konstantareas MM, Homatidis S: Ear infections in autistic and normal children. Journal of Autism and Developmental Disorders 1987, 17(4):585-594.

Niehus R, Lord C: Early medical history of children with autism spectrum disorders. Journal of Developmental and Behavioral Pediatrics 2006, 27(2):S120-S127.

Adams JB et al., Analyses of Toxic Metals and Essential Minerals in the Hair of Arizona Children with Autism and their mothers, Biol Tr El Res 2006, 110:193-209.

Adams JB et al., Mercury, Lead, and Zinc in Baby Teeth of Children with Autism vs. Controls J Toxicol Environ Health 2007, 70(12):1046-51.

Adams JB et al., Mercury in First-Cut Baby Hair of Children with Autism vs. Typically-Developing Children. 2008, 90(4):739-753.

Research – Treatment

A small open-label treatment study by Sandler et al with a potent non-absorbable antibiotic (Vancomycin) found temporary improvement in gut function and behavior, but the gains were lost when the treatment was stopped. These mixed results may be due to the inability for antibiotics to destroy spores produced by clostridia or other bacteria. This study demonstrated the importance of abnormal gut bacteria, and the difficulty in treating them long-term.

Sander et al, Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol. 2000 Jul;15(7):429-35.

Research on Gut Bacteria

Historically it has been very difficult to assess gut bacteria, because there are about 1000 different types of bacteria in each person's gut, and standard culture methods can only assess a few dozen of them. However, new DNA-based methods are rapidly changing the ability to assess gut bacteria.

Two small studies by Finegold, et al found some limited evidence of abnormal anaerobic bacteria, primarily increases in clostridia. They did not test for AGNB. A study by Parracho, et al also found increased amounts of clostridia.

Song Y, Liu C, Finegold SM. Real-time PCR quantitation of clostridia in feces of autistic children. Appl Environ Microbiol. 2004 Nov;70(11):6459-65.

Finegold et al, Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. 2002 Sep 1;35 (Suppl 1):S6-S16.

Parracho HM et al., Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol. 2005 Oct;54(Pt 10):987-91.

One study of 58 children with autism vs. 39 controls found that the severity of gut problems strongly correlated with autism severity. Individuals with gut problems had much worse scores on the ATEC subscales of speech, social, sensory cognitive, and health/physical behavior. That study found some abnormalities in gut bacteria, including decreased levels of bifidobacteria (an important beneficial bacteria) in children with autism compared to controls. However, they did not find elevated yeast (by culture or microscopically) in stool samples.

Adams JB et al., Gastrointestinal Flora and Gastrointestinal Status in Children with Autism -- Comparisons to Neurotypical Children and Correlation with Autism Severity, BMC Gastroenterology 2011, 11:22 (16 March 2011).

Two small studies using DNA-based methods to investigate all gut bacteria have been conducted, but yielded dissimilar results – much larger studies are needed. One study (Finegold et al 2011) found increased levels of desulfovibrio bacteria in children with autism, while another study (Williams et al 2012) found Sutterela bacteria in half of the 23 children with autism but not in any of the 9 controls.

Finegold SM et al., Pyrosequencing study of fecal microflora of autistic and control children., Anaerobe. 2010 Aug;16(4):444-53. Epub 2010 Jul 9.

Williams BL et al., Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS One. 2011;6(9):e24585. Epub 2011 Sep 16.

Amino Acids

Rationale: Protein is made of long strands of individual amino acids. When protein is digested properly, digestive enzymes split the long protein molecule into small peptides and individual amino acids, which the body can absorb. Those amino acids can then be reassembled to make a wide array of critical substances, such as neurotransmitters, hormones, enzymes, antibodies, immunoglobulins, glutathione, and many other substances. Amino acids are the "building blocks" of life.

Some children with autism have self-limited diets that are low in protein, and some have digestive problems that limit their ability to digest protein into individual amino acids. Either of these problems can lead to insufficient amino acids.

Treatments:

1) Ensure diet contains sufficient protein (two 4-oz servings/day).
2) Consider digestive enzymes (with proteases and peptidases) to more completely digest the protein into individual amino acids
3) Give "free-form" amino acids; "free-form" means that the amino acids exist as individual molecules, rather than part of a large protein molecule that needs to be digested. General amino acid supplements are available, and they can also be customized by a compounding pharmacy.

Testing:

Amino acids can be tested either from blood (when fasting for 10 hours) or from a urine sample (24 hour is best). Fasting blood plasma reveals circulating levels of amino acids related more to metabolism than to diet/digestion. 24-hour urine amino acid analysis shows what's in excess or not usable and what's deficient, if kidney transport is normal. Urine has to be interpreted carefully, as high levels in the urine can indicate "wasting" or excessive excretion, resulting in a low body level. Amino acid levels very greatly with age, so it is important to use a lab that has age-specific reference ranges, or the results will be incorrect and misleading.

It may also be useful to measure levels of neurotransmitters in platelets (blood), as low levels of neurotransmitters can be treated by supplementing with amino acids and vitamins/minerals, allowing the body to build their own.

Research:

One study of 56 children with autism and 45 neurotypical controls of similar age and gender found that the autism group had significantly lower levels of several amino acids, including tryptophan (needed to make serotonin) and phenylalanine and tyrosine (needed to make dopamine). The children with autism also had higher levels of glutamate, an excitatory neurotransmitter, which may relate to seizures, stimming, and other problems in children with autism. There was a lot of variation within the autism group, so individual testing of amino acids is recommended.

Adams JB et al., Nutritional and Metabolic Status of Children with Autism vs. Neurotypical Children, and the Association with Autism Severity, Nutr. Metab (Lond) 2011 Jun 8:8(1):34.

Several other studies of amino acids in children with autism have been conducted, but they have generally been flawed due to small sample size, lack of an overnight fast, and lack of controls of similar age (plasma amino acid levels vary substantially with age).

Carnitine

Rationale:

Carnitine is a substance in the body that carries fuel (long-chain fatty acids) into the mitochondria (energy-producing organelles inside every cell in the body). It also carries potentially toxic organic acids out of the mitochondria and cell so they can be eliminated from the body. Mitochondria produce ATP, a major fuel for the body and the brain. So, carnitine is important for energy production to fuel the body and the brain.

Carnitine can be made by the body to a limited extent, but much of it comes from our diet, especially beef and pork. People who eat limited amounts of beef and pork are at higher risk of carnitine deficiency. Carnitine is widely used as an over-the-counter nutritional supplement, and it is also available by prescription (it is approved by the FDA for treating carnitine deficiency caused by certain genetic diseases).

Testing

Carnitine levels can be measured in the blood, but for children it is important to have a pediatric reference range. (Many labs do not.)

If a person is not eating beef or pork, then they are at higher risk of carnitine deficiency (other protein sources, such as chicken, have only 5% or less of the amount of carnitine present in beef). Vegetarians are especially at risk of carnitine deficiency.

Treatments

Carnitine is available as both l-carnitine and acetyl-l-carnitine. Both forms are useful sources of carnitine, and the body can convert them to one another. However, several double-blind, placebo-controlled studies have found that acetyl-l-carnitine is helpful for improving cognitive functioning and memory in adults with Alzheimer's, so it is possible that the acetyl-l-carnitine form is more beneficial due to the acetyl group, which can help make acetylcholine, an important neurotransmitter. Acetyl-l-carnitine has also been found to be neuroprotective.

The amount used in the autism treatment study by Geier et al 2010 (see below) was 50 mg L-carnitine/kg bodyweight/day up to 1 g/day, and dosages of 0.5 to 2 g/day are common. We suggest starting at a lower dosage, and gradually increasing over several weeks.

About 60% of carnitine in food is absorbed, vs. only about 15% from supplements. So, consuming 9 oz of beef or 1 g of carnitine supplement results in about the same absorption of carnitine.
Physicians Desk Reference (PDR) for Nutritional Supplements, 2001, P. 255.

Safety

A study by Geier et al (2011) found that carnitine supplementation was generally very well-tolerated, with rare side effects of irritability and stomach discomfort, and only 1 of 19 children withdrew due to side-effects. The risk of adverse effects may be reduced by gradually phasing in the dosage over several weeks. A 1-g dose of carnitine is about equivalent to eating a half-pound

of steak, which is not a significant concern. Common adverse effects include diarrhea and fishy smelling stools.

Research

Several studies have suggested that mitochondrial disorders are common in children with autism – see review by *Rossignol DA and Frye RE, Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012 Mar;17(3):290-314.*

Note that the term "mitochondrial disorders" is used to denote a generalized impairment of mitochondrial function, and are generally not as severe as "mitochondrial disease," which involves specific severe genetic abnormalities. One important factor for normal mitochondrial function is carnitine, which transports fatty acids into the mitochondria for energy production. However, mitochondrial disorders can be caused by many factors, and carnitine deficiency is only one possibility.

One study found decreased levels of carnitine in children with autism (Filipek et al 2004); however, that study only compared against laboratory reference ranges, which are of limited validity.

Filipek et al., Relative carnitine deficiency in autism. J Autism Dev Disord. 2004 Dec;34(6):615-23.

A recent double-blind, placebo-controlled 3-month study (n=30) found that supplementation with carnitine was beneficial. Specifically, that study found significantly greater improvements in the Childhood Autism Rating Scale (CARS) and Clinical Global Impressions (CGI) scores in the treatment group compared to the placebo group. In addition, scores significantly improved in cognition, marginally in speech, and non-significantly in total and sociability scores on the ATEC. L-carnitine therapy significantly increased serum carnitine concentrations, and significant correlations between changes in serum free-carnitine levels and positive clinical changes were observed. Study subjects generally tolerated L-carnitine therapy.

Geier DA et al., A prospective double-blind, randomized clinical trial of levocarnitine to treat autism spectrum disorders. Med Sci Monit 2011 Jun;17(6):PI15-23.

Overall, the literature suggests that mitochondrial disorders are common in autism, and carnitine supplementation may help improve mitochondrial function. Other supplements for mitochondrial therapy include vitamins, minerals, CoEnzyme Q10, and essential fatty acids, which work together to improve mitochondrial function.

Melatonin

Rationale: Many children and adults with autism have sleep problems, including falling asleep, nighttime waking, and early waking. These sleep problems have a strong correlation with gut problems, and healing the gut seems to reduce many of those sleep problems.
However, if sleep problems continue, supplementation with melatonin can help. Melatonin is the hormone the body naturally produces at nighttime to regulate sleep. It is formed from the neurotransmitter serotonin, so low serotonin levels can cause low melatonin levels.

Testing: The best test for melatonin is simply a trial of it, if a person has continuing sleep problems not due to other causes (see below).

Treatment: Melatonin production is reduced by light, and even a simple nightlight can greatly decrease melatonin production. So, first try eliminating all sources of light.

For problems falling asleep, first try a behavioral approach, including a regular nighttime routine (at a fixed time, begin bath/shower, brush teeth, story, etc.). Also, be sure to eliminate caffeine and reduce sugar intake at nighttime.

If sleep problems persist, start with 1 mg of melatonin (0.5 mg for children), and increase up to 2-5 mg if necessary (1-5 mg for children). If waking occurs during the night, then try a time-release form rather than increasing the dose. 2 mg time-release can be better than 5 mg all at once. However, in general it is not effective for night time waking, so other treatments may be necessary if time-release melatonin is not effective.

Safety: Melatonin seems to be exceptionally safe; high dosages in animals produce no toxicity, and a study of 1400 women taking 75 mg/day for up to 4 years with no adverse effects. Children with autism have been documented taking up to 25mg at bedtime without adverse effects. In fact, animal studies suggest that long-term use of melatonin can increase lifespan 20%, presumably due to its strong antioxidant effect.

One study of children with ADHD and insomnia who were followed for approximately 4 years revealed no serious adverse effects associated with long-term use of melatonin; after 4 years, 65% still used it regularly, 12% occasionally, and 9% no longer needed it.

Hoebert M, et al. "Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia". J. Pineal Res. 47 (1): 1–7. 2009

Research
Melatonin problems have been extensively studied in children with autism, and there are nine studies that found abnormalities in melatonin levels and/or melatonin cycle in children with autism. Five randomized, double-blind, placebo-controlled trials have been conducted, and Rossignol and Frye conducted a meta-analysis of those five studies. They found that melatonin improved falling asleep and sleep duration (30 minutes more than placebo), but not night-time awakening. The side effects of melatonin were reported to be minimal or none.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Melatonin	8%	26%	66%	1687

Overall, melatonin seems like a safe and effective therapy for sleep problems for many children with autism.

For more info, see the review by *Rossignol and Frye, Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol 2011 Sep;53(9):783-92.*

Thyroid Supplementation

Rationale: About 5-10% of the general population has a thyroid disorder requiring supplementation, and that percentage may be higher in autism. Poor thyroid function due to lack of iodine is the major cause of mental retardation in the world, resulting in over 80 million cases of mental retardation, and decreased energy level. Poor thyroid function can be caused by other factors as well.

Iodine is required for normal thyroid functioning, and a major national study (NHANES) found that levels of iodine fell more than 50% from the early 1970's to the early 1990's, presumably due to decreased use of table salt (which is one of the major sources of iodinized salt). Non-iodinized salt is used in most processed foods (potato chips, crackers, etc). Therefore, iodine deficiency is an increasing concern today.

Hollowell, JG et al., 'Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994)', J Clin Endocrinol Metab 83(10): 3401-8 (1998).

Testing:
If individuals do not use iodinized salt or take a vitamin/mineral supplement containing iodine, then they are at high risk of iodine deficiency.

The most accurate testing is a blood measurement of thyroid hormones and iodine level.

Thyroid hormone is measured as part of the newborn screening to rule out congenital hypothyroidism and to start treatment early in life if necessary, in order to prevent mental retardation. If a child has not had a newborn screening test or has symptoms of hypothyroidism in infancy, it is important to check thyroid hormones immediately.

A simple initial assessment can be done by measuring body temperature before waking. A low body temperature is a possible indicator of too low a level of thyroid function. Overall low energy/activity, low muscle tone, constipation, brittle hair, dry hair and developmental delays can also be a possible indicator of a thyroid problem, but could be caused by other factors also.

Treatment:
If iodine levels are low, then one can begin with iodine supplementation. If that does not normalize thyroid levels, then one can consider thyroid supplements. We recommend natural thyroid supplements derived from animals, as they will provide a complete thyroid source (both T3 and T4 hormones). Synthetic thyroid supplements contain only T4.

It is important to treat low thyroid conditions as early as possible, to prevent the risk of mental retardation.

Some individuals have thyroid dysfunction due to thyroid autoantibodies or congenital abnormalities in thyroid development, so an evaluation by an endocrinologist is important if abnormalities in thyroid function are suspected.

Duration:
Usually 1-2 months of supplementation are needed to observe an increase in energy level and body temperature. Supplementation may be needed long term unless the problem with thyroid development is resolved.

SAFETY CAUTION: Too much thyroid hormone can cause weight loss, anxiety and other problems, so thyroid levels should be monitored regularly if taking a supplement.

Research:
. There have been several studies of thyroid function and autism.

One study reported a high incidence of thyroid abnormalities in parents of children with autism
Megson MN. Is autism a G-alpha protein defect reversible with natural vitamin A? Med Hypotheses. 2000 Jun;54(6):979-83.

One study found abnormal thyroid function in young adults with severe autism correlated with impaired verbal communication.
Nir I et al., Brief report: circadian melatonin, thyroid-stimulating hormone, prolactin, and cortisol levels in serum of young adults with autism. J Autism Dev Disord. 1995 Dec;25(6):641-54.

One study found reduced levels of thyroid hormones (TSH) in children with autism (n=41) vs. controls.
Hashimoto T et al., Reduced thyroid-stimulating hormone response to thyrotropin-releasing hormone in autistic boys. Dev Med Child Neurol. 1991 Apr;33(4):313-9.

There was also one small study (n=14) that found normal levels of TSH in children with autism, but that study did not have a control group.
Abbassi V et al., Triiodothyronine (T3) concentration and therapy in autistic children. J Autism Child Schizophr. 1978 Dec;8(4):383-7.

One study found that many children with autism have unusually low levels of iodine in their hair, which possibly suggests a low level in their body and need for more.
Adams JB et al., Analyses of toxic metals and essential minerals in the hair of Arizona children with autism and associated conditions, and their mothers. Biol Trace Elem Res. 2006 Jun;110(3):193-209.

One study found that most children with autism had normal levels of iodine in their urine (normalized by creatinine) compared to controls, but 25% of the children with autism had unusually low levels (below the reference range).
Adams JB et al., Nutritional and Metabolic Status of Children with Autism vs. Neurotypical Children, and the Association with Autism Severity, Nutr. Metab (Lond) 2011 Jun 8:8(1):34.

Overall, the reports of abnormal thyroid function in most of the studies are consistent with findings of low iodine, and it is possible that impaired thyroid function is a cause of some of the symptoms of autism in some children, especially language impairment and mental retardation.

Sulfation

Rationale: Sulfate is used for many functions in the body, including detoxification, maintaining the lining of the gut, and hormone production. Some children with autism have a low level of sulfate in their bodies due to a variety of reasons, including poor absorption in the gut, excess loss in the urine, or poor recycling of sulfate by the kidney, or oxidant stress and inflammation can shut down cysteine dioxygenase, which throttles the cysteine -> sulfate route.

Testing: Blood testing can be used to check for levels of free and total plasma sulfate, and this is probably the more reliable test. Plasma cysteine can also be informative. (Urine testing of free and total sulfate may be useful to look for excessive loss of sulfate, but this is only one of several possible causes of low sulfate in the body, and should not be solely relied on to assess sulfate status).

Alternatively, since Epsom salt baths are very safe, one could simply try them for up to several weeks and look for improvements in behavior and functioning (see below).

Treatment:
Tapan Audhya evaluated many different ways to increase plasma sulfate levels in children with autism who had low levels. The two most effective methods were oral MSM (500-2000 mg depending on size and sulfate level) and Epsom Salt (magnesium sulfate) baths – 2 cups of Epsom salts in warm/hot water, soak for 20 minutes, 2-3x/week. A few children did not tolerate MSM, but Epsom salt baths are generally very well tolerated.

T. Audhya, Role of Sulfation, presentation at Autism/Asperger's Conference in Anaheim, CA, February 2007.

Many parents and physicians have anecdotally reported that Epsom salt baths were beneficial to their children. However, there is less experience with MSM for children with autism, and more research is needed.

Research – Sulfate and Autism

Sulfur is the fourth most common mineral in the body [Chang, 2007]. Most sulfate is produced *in vivo* by metabolism of cysteine [Stipanuk et al 2010]. Sulfation is important for many reactions, including detoxification, inactivation of catecholamines, synthesis of brain tissue, sulfation of mucin proteins which line the gastrointestinal tract, and more. The measurement of total plasma sulfate involves many substances in the plasma, including neurotransmitters, steroids, glycosaminoglycans, phenols, amino acids, peptides, and other molecules.

Low free and total plasma sulfate in children with autism has been reported in three studies [Waring et al 1997; Geier et al 2009; Adams et al 2011], and is consistent with four studies [Waring et al 1997; O'Reilly et al 1993; Alberti et al 1999; Horvath et al 2002] which found that children with ASD had a significantly decreased sulfation capacity compared to controls, based on decreased ability to detoxify paracetamol (acetaminophen, the active ingredient in Tylenol). The finding of low plasma sulfate is also consistent with a large study that found high sulfate in the urine of children with autism [Waring and Kovsra 2000], as sulfate wasting in the urine partly explains low levels in the plasma.

Research – Treatment

One study [Waring and Klovsra 2000] also reported high levels of urinary sulfite in children with autism, suggesting that there was a problem of converting sulfite to sulfate in the mitochondria. In 38% of cases (14/38) urinary sulfite and sulfate levels improved by giving 50 mcg of molybdenum (an essential mineral), presumably since the enzyme for converting sulfite to sulfate (sulfite oxidase) contains molybdenum.

One study [Adams et al 2011] involved treatment with a multi-vitamin/mineral supplement that included molybdenum and MSM. After three months of treatment, there was a substantial increase in both free and total sulfate in the plasma, but levels were still below normal. This suggests that additional treatment, such as Epsom salt baths, are necessary to normalize sulfate levels.

References

Chang, Raymond Chemistry, Ninth Edition, 2007. McGraw-Hill. p. 52.

Stipanuk MH, Ueki I. Dealing with methionine/homocysteine sulfur: cysteine metabolism to taurine and inorganic sulfur. J Inherit Metab Dis. 2011 Feb;34(1):17-32. Epub 2010 Feb 17.

Waring RH, Ngong JM, Klovrza L, Green S, Sharp H: Biochemical Parameters in Autistic Children. Dev Brain Dysfunct 1997, 10:40-43.

Geier DA, Kern JK, Garver CR, Adams JB, Audhya T, Geier MR: A prospective study of transsulfuration biomarkers in autistic disorders. Neurochem Res. 2009, 34(2):386-93. Erratum in: Neurochem Res. 2009, 34(2):394.

O'Reilly BA and Warning RH: Enzyme and Sulphur Oxidation Deficiencies in Autistic Children with Known Food/Chemical Sensitivities. J. Orthomolecular Medicine 1993, 8(4):198-200.

Alberti A, Pirrone P, Elia M, Waring RH, Romano C, Alberti A, Pirrone P, Elia M, Waring RH, Romano C: Sulphation deficit in "low-functioning" autistic children: a pilot study. Biol Psychiatry. 1999, 46(3):420-4.

Horvath K and Perman JA: Autistic disorder and gastrointestinal disease. Curr Opin Pediatr 2002, 14:583-587.

Waring RH and Klovrza LV: Sulfur Metabolism in Autism. J. Nutritional & Environmental Medicine 2000, 10:25-32.

Therapies for Methylation/Glutathione/Oxidative Stress

Rationale: Many children with autism have impairments in methylation, glutathione, and oxidative stress, which are all closely connected metabolically (see figures 1 and 2).

Methylation is the process of donating a methyl group (CH_3, or a carbon atom with three hydrogens attached) to another molecule, like DNA, RNA, proteins, phospholipids, and neurotransmitters, which basically can turn them on or off. The primary methyl donor in the body is SAM (S-adenosylmethionine), and several studies have shown it to be low in autism.

Glutathione is the primary antioxidant in the body, and it is also an important defense against toxic metals (it binds to them and is excreted with them in the bile and urine). It also indirectly supports many metabolic reactions, including DNA synthesis/ repair and protein synthesis. Every cell in the body and every system in the body is affected by glutathione, especially the immune system, nervous system, gastrointestinal tract, and lungs. Glutathione is a tri-peptide made from three amino acids – cysteine, glycine, and glutamate, and is the major antioxidant and detoxification system in cells. The amount of cysteine precursor is usually the limiting factor in how much glutathione is made by the body. Some cysteine is made from SAM, so low levels of SAM can result in low levels of cysteine. Several studies have found that children with autism have low cysteine and low glutathione, probably due in part to low SAM.

Oxidative stress occurs when too many free radicals are produced and glutathione antioxidant capacity is insufficient. Free radicals are highly-reactive molecules that can attack any cell in the body, interfering with their function and causing damage. One common cause is when mitochondria (energy-producing organelles in every cell of the body) are functioning incorrectly when they "burn" oxygen when it reacts with "fuel" (sugars, fats, etc) to make energy. Glutathione and other anti-oxidants can reduce oxidative stress by quenching free radicals, but they need to be recycled after each time they act. Several studies have demonstrated that children with autism often have impaired mitochondrial function, impaired glutathione recycling, and increased oxidative stress.

Treatment:
There are many ways to improve SAM, glutathione, and oxidative stress, but some are more effective than others. They include:

<u>Less-effective methods:</u>

1) Oral glutathione: Only about 10% of oral glutathione is absorbed, so this method is not very effective at raising body levels. One small study of children with autism found that oral doses of 15 mg/kg bodyweight led to a 19% increase in reduced (active) glutathione in plasma, and increased the total level of glutathione in whole blood by 12%. However, it did not improve the level of oxidized glutathione in plasma, so oxidative stress was still high.
   Kern JK et al., A clinical trial of glutathione supplementation in autism spectrum disorders. Med Sci Monit 2011 Dec 1;17(12):CR677-682

2) Transdermal glutathione: Glutathione is a relatively large molecule, and is not easily absorbed through the skin. One small study of 13 children found that a transdermal dose of 350-500 mg

led to an 11% increase in reduced (active) glutathione in plasma, and a 9% increase in the level of total glutathione in whole blood. However, there was little change in the level of oxidized glutathione in plasma (4% decrease).

Kern JK, et al., A clinical trial of glutathione supplementation in autism spectrum disorders. Med Sci Monit 2011 Dec 1;17(12):CR677-682

3) IV glutathione: One study of high-dose intravenous glutathione found that it did raise levels, but that the half-life in the body was only about 20 minutes, so it does not last long (but the effects probably last longer).

Aebi S et al., High-dose intravenous glutathione in man. Pharmacokinetics and effects on cyst(e)ine in plasma and urine. European Journal of Clinical Investigation 1991, 21:103-110.

More effective methods

1) Vitamin C: 500 mg of vitamin C was found to raise RBC glutathione levels 50% in college students.

Johnston et al, Vitamin C elevates red blood cell glutathione in healthy adults. Am J Clin Nutr. 1993 Jul;58(1):103-5.

2) Folinic Acid/TMG/methyl-B12: A treatment study of 8 young children with autism found that 800 mcg of folinic acid and 1000 mg of TMG normalized SAM and partially improved levels of cysteine, total glutathione in plasma, and ratio of oxidized to total glutathione. Adding subcutaneous injections of Vitamin B12 (methyl-cobalamin) resulted in normalization of levels of SAM, cysteine, total glutathione in plasma, and the ratio of oxidized to total glutathione levels.

James SJ, Cutler et al., Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr. 2004, 80(6):1611-7.

A larger treatment study of 48 children with autism involved the use of 800 mcg of folinic acid and subcutaneous injections of vitamin B12 (methylcobalamin), but no TMG. The children were pre-screened to verify that they had methylation and/or glutathione problems (75% of those screened met criteria). The treatment did not significantly improve SAM, but cysteine levels did increase to normal. Total and reduced glutathione increased partially, but remained lower than normal. Oxidized glutathione improved to near-normal levels. The ratio of total glutathione to oxidized glutathione improved partially but was still below normal. This was an open-label study, and some improvements in behavior were mentioned but not reported.

James SJ et al., Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009, 89(1):425-30.

So, it appears that the 2004 study, which included TMG, yielded more beneficial results than the 2009 study. TMG, or trimethylglycine, contains three methyl groups that can be donated, and likely supports methylation function and thereby improves SAM (which improved in the 2004 study, but not in the 2009 study).

3) Multi-Vitamin/Mineral Supplement: A randomized, double-blind, placebo-controlled study of 141 children and adults with autism investigated an oral multi-vitamin/mineral supplement designed for individuals with autism. 54 of the children also had measurements of nutritional status at the beginning and end of the study, including measurements of methylation, glutathione, and oxidative stress. The supplement normalized SAM, and substantially improved another biomarker of methylation (plasma uridine). The supplement also partially improved reduced and oxidized glutathione, but the levels remained somewhat abnormal. Another marker of oxidative stress, plasma nitrotryrosine, also improved substantially but remained slightly abnormal.

Behavioral changes were investigated for all participants, and the treatment group improved significantly more than the placebo group as evaluated by the Parent Global Impressions-Revised, including modest but statistically significant improvements in the Average Change of all symptoms on the Parent Global Impressions-Revised, and significant improvements in subscores in expressive language, tantrumming, hyperactivity, and overall symptoms.

This study also reported that children with autism compared to neurotypical children had significantly lower levels of NADH, the active form of vitamin B3, which is needed to recycle oxidized glutathione to reduced (active) glutathione. The vitamin/mineral supplement normalized levels of NADH, and this at least partially explains the improvement in the ratio of oxidized to reduced glutathione, and improvements in overall oxidative stress

Adams JB et al., Effect of a Vitamin/Mineral Supplement on Children with Autism, BMC Pediatrics 2011, 11:111

4) NADH: NADH is the active form of vitamin B3, and is an important co-factor for many enzymatic reactions in the body. One study found that children with autism had normal levels of vitamin B3, but significantly low levels of NADH (Adams et al 2011). One small treatment study of 8 children with autism investigated the effect of 2 weeks of supplementation with 5-10 mg/day NADH (the active form of vitamin B3). It resulted in significant improvements in SAM to near-normal levels. It significantly improved levels of reduced glutathione, but did not significantly improve levels of oxidized glutathione.

   Freedenfeld S et al., Biochemical Effects of Ribose and NADH Therapy in Children with Autism, Autism Insights, 2011:3 3-13

5) Ribose: D-ribose is a naturally occurring sugar that is a key structural component of DNA, RNA, NADH, NADPH, and many other important molecules in the body. It is a commonly used nutritional supplement. One small treatment study of 8 children with autism investigated the effect of 2 weeks of supplementation with 5 g/day ribose. It resulted in significant improvements in SAM, but levels were still somewhat low. It slightly improved levels of reduced glutathione, but did not significantly improve levels of oxidized glutathione.

   Overall, the effects of NADH supplementation were similar to the effects of ribose supplementation. Both treatments increased levels of NADH (by 22% and 18%, respectively) and greatly increased levels of ribose (173% and 222%, respectively).

   Freedenfeld S et al., Biochemical Effects of Ribose and NADH Therapy in Children with Autism, Autism Insights, 2011:3 3-13

6) DMSA: Toxic metals such as mercury can greatly decrease the body's ability to make glutathione, and removing toxic metals seems to normalize glutathione levels. One study investigated treatment with oral DMSA, a medication that is FDA-approved for treating lead poisoning in infants and children. Phase 1 of the study involved giving 3 doses of oral DMSA each day for 3 days (10 mg/kg bodyweight per dose). Levels of glutathione in RBC were measured previous to treatment, and 1-2 months after treatment. Initially, many children with autism had levels that were much below or much above that of the adult reference range, but after treatment they had levels that were almost all within the adult reference range; i.e., those with initially low levels increased towards normal, and those with high levels decreased towards normal. It appeared that high levels of RBC glutathione were associated with high levels of toxic metals (perhaps the body made more glutathione to respond?) and low levels of glutathione were associated with mercury (which inhibits production and decreases levels of glutathione). This treatment was safe and effective, and seemed to improve behavior.

Adams JB et al., Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: Part A--medical results. BMC Clin Parmacol. 2009 Oct 23:9:16

Adams JB, et al., Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part B - behavioral results. BMC Clin Pharmacol. 2009 Oct 23;9:17.

7) N-acetyl-cysteine (NAC). NAC is a form of cysteine, an amino acid that is the rate-limiting factor in the production of glutathione. NAC is more resistant to water absorption during storage, so it is often used instead of cysteine. One randomized, double-blind, placebo-controlled study investigated treatment of children with autism with NAC. Dosage was 900 mg every day for the first 4 weeks, then 900 mg twice daily for 4 weeks and 900 mg three times daily for 4 weeks. The treatment group had significantly more improvement in irritability than the placebo-group. There were no measurements of glutathione, but it is a critical component of glutathione and probably raised levels of glutathione.

Hardan AY, et al., A Randomized Controlled Pilot Trial of Oral N-Acetylcysteine in Children with Autism Biol Psychiatry. 2012 Jun 1;71(11):956-61. Epub 2012 Feb 18.

Additional Research:

Figure 1 shows a schematic of the methionine cycle, which leads to the production of SAM. Methionine is available from most dietary sources of protein (beef, chicken, nuts, etc). It is also made in the body by recycling homocysteine, which requires vitamin B12 and folinic acid. Methionine is converted to SAM to SAH to Homocysteine. Homocysteine is then either recycled to methionine or converted into cystathionine, some of which eventually becomes glutathione.

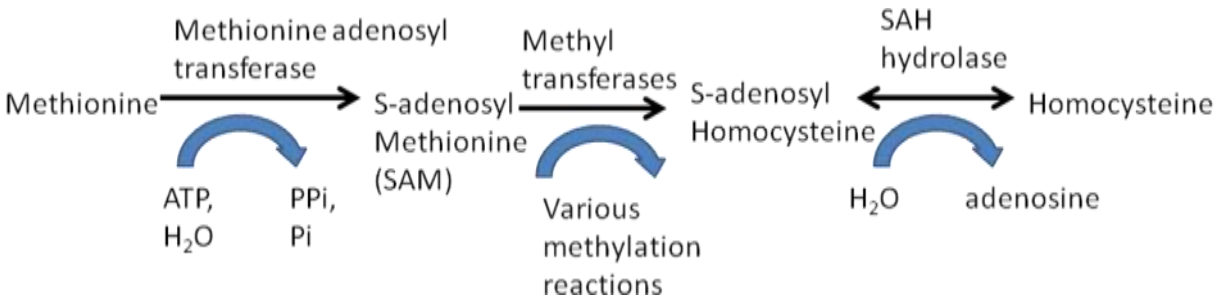
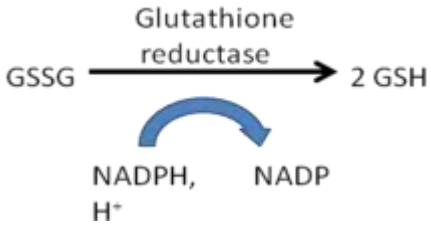


Figure 2 Reduction of GSSG to GSH (net result of a more complex process which involves FADH). NADH is the enzymatic co-factor needed to recycle glutathione.



Immune System Regulation

Rationale: Several studies have found abnormal immune function in autism, generally with shift to Th-2, and some evidence for auto-immunity.

Molloy et al., Elevated cytokine levels in children with autism spectrum disorder, J. Neuroimmunol 172 (2006) 198-205.

Testing: One standard test (available from any medical laboratory) is a measurement of total immunoglobulins (antibodies) and their subclasses. Decreased levels of IgG or subclasses of IgG provide evidence of immunodeficiency.

Treatments: More research on effective treatments for normalizing the immune system in children with autism is needed. If lab testing reveals abnormal immune function, current possible treatments include intra-venous immunoglobulins (IVIG), Actos (pioglitazone), and low-dose naltrexone.

Research:

IVIG: Gupta et al., found IVIG benefited 4 of 10 children, with 1 case of marked improvement. This is a very expensive treatment, as the immunoglobulins (antibodies) need to be collected from hundreds or thousands of human donors, but it may be covered by insurance if there is evidence of immune deficiency.

Gupta et al., Treatment of children with autism with intravenous immunoglobulin. J Child Neurol. 1999 Mar;14(3):203-5.

Twenty-six autistic children received intravenous gamma globulin (IVIG) every 4 weeks for 6 months at a dose of 400mg/Kg. Aberrant behaviors, speech, hyperactivity, inappropriate stims and social interactions significantly improved. However 22 of the 26 children regressed within 4 months after discontinuing IVIG. Anecdotal reports from clinicians suggest that 12 months or longer therapy is needed for long-term benefits.

Boris m, Goldblatt A, Edelson SM; Improvement in children with autism treated with intravenous gamma globulin. Journal of Nutritional & Environmental Medicine, Dec 2005; 15(4): 169-176.

PANS (Pediatric Acute-onset Neuropsychiatric Syndrome, formerly known as PANDAS**)** is the term used to describe a subset of children and adolescents who have sudden-onset Obsessive Compulsive Disorder (OCD) and/or tic disorders, and in whom symptoms worsen following infections (in the case of streptococcus, the term "PANDAS" is still used). The OCD and tic symptoms are accompanied by a variety of other neuropsychiatric symptoms, including separation anxiety, "anxiety attacks," irritability, extreme mood swings, temper tantrums, and immature behaviors (like talking "baby talk"), hyperactivity, problems with attention and concentration, handwriting changes, and problems with math, reading and other school subjects. It is present in some children with ASD. The diagnosis is made from symptoms alone; in the case of PANDAS, which comes from strep, elevated ASO (Antistreptolysin Antibodies) and/or antiDNAse antibody levels can be helpful; if the throat culture is positive, a single course of antibiotics will usually get rid of the strep infection and allow the PANDAS symptoms to subside. A treatment for both PANS and PANDAS is IVIG. This therapy is covered by many insurance carriers and may be an additional method for children with ASD to be covered for IVIG. Also, prophylactic antibiotic therapy is sometimes recommended to prevent further strep infections. For more information, see http://intramural.nimh.nih.gov/pdn/web.htm

ACTOS: ACTOS (pioglitazone) has multiple effects, including the ability to decrease inflammation. An open study of ACTOS in 25 children with autism for 3-4 months found substantial improvements

in irritability, lethargy, stereotypy, and hyperactivity, with greater benefits in the younger children. Doses were 30 mg (younger children) and 60 mg (older children).

Boris et al., Effect of pioglitazone treatment on behavioral symptoms in autistic children, accepted in J. Neuroinflammation 2007.

However, the ARI survey data (below) suggests that it is only rarely beneficial.

Safety Concern: The FDA has issued a "black box" warning that ACTOS may increase the risk of congestive heart failure, fluid retention, and edema (swelling due to fluid build-up under the skin).

Low-dose naltrexone:

Naltrexone is a medication used to block the opioid receptor in the brain, and therefore is used to treat opioid addiction by preventing the euphoric effect of opioids like morphine and heroin. There have been 14 clinical trials of naltrexone for children with autism. A review paper by Elchaar et al. reported "Naltrexone has been used most commonly at doses ranging from 0.5 to 2 mg/kg/day and found to be predominantly effective in decreasing self-injurious behavior. Naltrexone may also attenuate hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. Patients may also exhibit improved attention and eye contact. Transient sedation was the most commonly reported adverse event."

Elchaar et al., Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. Ann Pharmacother. 2006 Jun;40(6):1086-95. Epub 2006 May 30. Review.

It has been suggested that low-dose naltrexone, at about 3-5 mg/day (much lower than the doses mentioned above) may be beneficial to children with autism and may improve the regulation of their immune system. More research is needed.

ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
IVIG	7%	39%	54%	142
Actos	19%	60%	21%	140
Low-dose naltrexone	11%	52%	38%	190

Based on the ARI Survey Data, IVIG seems the most likely to be beneficial, followed by LDN, with Actos having the lowest % better and the highest % worse. However, this is only survey data from relatively small numbers of families. More research is needed.

TRICHURIS SUIS THERAPY: Eggs of the pig whipworm (Trichuris suis) have been used for treatment of certain immune-system disorders including inflammatory bowel diseases, multiple sclerosis and food allergies, due to their immunomodulatory effects (ability to modulate the immune system). The therapy appears to generally be safe because the worms can only exist for a short time in human digestive tracts. Some physicians have used it for patients with autism, but there is no formal research yet on its use for individuals with autism, so it should be viewed as an experimental therapy for autism.

Summers RW et. al., Trichuris suis therapy in Crohn´s disease, Gut 2005: 54:87-90;

Summer. et al.; Trichuris suis therapy for active ulcerative colitis. a randomized controlled trial gastroenterology april 2005 .

Jouvin MH, Kinet JP. Trichuris suis ova: testing a helminth-based therapy as an extension of the hygiene hypothesis., J Allergy Clin Immunol. 2012 Jul;130(1):3-10; quiz 11-2. Review.

Hyperbaric Oxygen Therapy (HBOT)

Rationale: There is substantial evidence of decreased blood flow in brains of most children with autism, suggesting a need for more oxygen. HBOT is an effective method to temporarily increase oxygen levels throughout the body. It is effective for improving general wound healing, and might help with gut inflammation, brain inflammation, and similar problems that are common in children with autism.

Treatment: Typically 40 1-hour sessions, 1-2x/day, in a chamber with 30% increased air pressure (1.3 atm), which temporarily increases level of oxygen in the body. A face mask with pure oxygen is sometimes used as well (regular air is only 22% oxygen). Higher pressures of 1.5-2 atm are sometimes used, but there is concern regarding excessive oxidative stress at higher partial pressures. Additional treatment hours are sometimes considered if the initial therapy is beneficial.

Testing: Currently it is unclear what tests may indicate who is the best candidate for HBOT.

One small study of 18 children with autism found that HBOT therapy was able to substantially reduce levels of C-Reactive Protein (CRP, a marker of inflammation), primarily in the 3 children with elevated levels. So, this might be a useful biomarker, but more research is needed.

Rossignol DA, et al., The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study. BMC Pediatr 2007, 7:36.

Safety Concerns:

1) Glutathione: One small study found that HBOT therapy decreased levels of plasma glutathione, which are already low in children with autism, so it is recommended to first normalize glutathione prior to starting HBOT. This is consistent with the notion that HBOT can increase reactive oxygen species, especially at higher partial pressure.

Rossignol DA, et al., The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study. BMC Pediatr 2007, 7:36.

2) Primary Mitochondrial Disease: A small percent of children with autism also have primary mitochondrial disease. According to an expert on mitochondrial disease, Robert Naviaux, MD, PhD: "Hyperbaric oxygen therapy is contraindicated in children with primary mitochondrial disease and has led to serious injury and death in some patients. Primary mitochondrial disease is characterized by gene defects that make cells unable to use oxygen to produce energy. Forced exposure to high levels of oxygen under these circumstances, when the cells cannot use oxygen, can result in large increases in oxygen free radical production, tissue oxidative damage, and no neurologic or metabolic benefit… The Scientific Advisory Board of the United Mitochondrial Disease Foundation (UMDF) addressed this issue in 2007, and this expert opinion was published in Mitochondrial News 12: 1 and 20, 2007."

3) Seizures: There have been some anecdotal reports of seizure onset following HBOT, but this has not been confirmed in a published study. A published parent survey of the effect of different treatments on individuals with autism and seizures included a small sample of 36 people who had tried HBOT. The survey found that HBOT possibly had a small beneficial effect on reducing seizures, a very low rate of adverse effects, and possible improvements in several areas, primarily communication.

Frye RE, et al., Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey, BMC Pediatrics 2011, 11:37.

Research on Treatment:

There are several open-label studies of HBOT therapy for children, and most suggest that HBOT therapy might be helpful, but one open-label study with rigorous pre/post assessment showed no benefit. There are also two randomized, double-blind, placebo-controlled studies, with one study showing statistically significant benefit in one of the measures but not the others, and the other study showing no benefit. Two recent reviews of these studies are Rossignol, et al 2012 and Ghanizadeh 2012.

Rossignol DA, et al, Hyperbaric oxygen treatment in *autism* spectrum disorders, *Med Gas Res.* 2012 Jun 15;2(1):16.

Ghanizadeh A Hyperbaric oxygen therapy for treatment of children with autism: a systematic review of randomized trials Med Gas Res. 2012; 2: 13

Open-label studies:

Three small open-label studies involved 6-10 children with autism, and they generally reported some improvements in autistic symptoms and therapy was well tolerated.

Rossignol DA, Rossignol LW: Hyperbaric oxygen therapy may improve symptoms in autistic children. Med Hypotheses 2006, 67(2):216-228.

Chungpaibulpatana J, et al., Hyperbaric oxygen therapy in Thai autistic children. J Med Assoc Thai 2008, 91(8):1232–1238.

Bent S, et al., Brief report: Hyperbaric oxygen therapy (HBOT) in children with autism spectrum disorder: a clinical trial. J Autism Dev Disord. 2012 Jun;42(6):1127-32.

One open-label study involved eighteen children with autism, ages 3-16 years, who received 40 hyperbaric sessions (45 minutes each) over 9 weeks. Six children received 1.5 atmospheres (atm) and 100% oxygen, and 12 children received 1.3 atm and 24% oxygen. Both groups had modest improvement in social responsiveness (communication, motivation, and mannerisms) and overall autism severity (language, sensory/cognitive, and health/physical behavior). Pre and post blood tests revealed a large improvement in CRP (C-Reactive Protein, a general marker of inflammation), primarily in the 3 children who had very high levels. Measurements of oxidized glutathione (GSSG) did not change, but measurements of total and free glutathione decreased, which is unfavorable. This suggests that glutathione therapy should be done prior to HBOT. HBOT therapy was generally well tolerated.

Rossignol DA, et al., The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study. BMC Pediatr 2007, 7:36.

One open-label study used a multiple baseline design, in which symptoms are assessed several times before and after treatment (this is more rigorous than typical open-label designs). The study involved 16 children with ASD who received 40 HBOT sessions (1.3 atm, 24% oxygen) over approximately 56 days. There was no improvement in any symptoms, as measured by behavioral analysts directly observing the children.

Jepson B, et al., Controlled evaluation of the effects of hyperbaric oxygen therapy on the behavior of 16 children with autism spectrum disorders. J Autism Dev Disord 2011, 41(5):575-588.

Randomized, Double-blind, placebo-controlled treatment studies:

One randomized, double-blind, placebo-controlled study followed 62 children undergoing 40 treatment sessions (1.3 atm, 24% oxygen, 10 sessions/week). 55 participants completed the study, which was conducted at multiple sites. Compared to the placebo group, the treatment group had significantly greater improvements on the Clinical Global Impressions (CGI) scale rated by the clinicians. For the parent evaluations, the treatment group had slightly more improvements on the

CGI, ABC, and ATEC scales, but the differences between treatment and placebo groups were not statistically significant.

Rossignol DA, et al: Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. BMC Pediatr 2009, 9:21.

Another randomized, double-blind, placebo-controlled study involved 46 children with autism undergoing 80 sessions (1.3 atm, 24% oxygen, 6-10 sessions/week). 34 participants completed the study (most of the withdrawals were due to travel time to the clinic, not adverse effects). In this study both groups were also receiving intensive ABA therapy (109 hours/month). This study involved extensive pre and post assessment of autistic symptoms, including both direct observations of behavior and standardized questionnaires. Overall, there was no difference in improvement in any of the behavioral assessments, suggesting that HBOT therapy was not significantly beneficial.

Granpeesheh D, et al., Randomized trial of hyperbaric oxygen therapy for children with autism. Research in Autism Spectrum Disorders 2010, 4:268-275.

Research on decreased blood flow in brains of children with autism:

Many studies have investigated blood flow in the brains of individuals with autism with brain scans (PET, SPECT, and fMRI), and they have generally found decreased blood flow (hypoperfusion) in several parts of the brain. Only one study (Zilbovicius et al 1992) was negative, possibly due to lower quality of the imaging available at that time. Most of these studies involved small numbers of participants and even fewer controls, but in total they provide substantial evidence for hypoperfusion existing in most individuals with autism. One small study included children and adults with autism, and found that the older individuals had worse hypoperfusion than the younger ones. One study of 45 children with autism found that the degree of decreased blood flow in one part of the brain (left superior temporal gyrus) correlated modestly with more severe autism scores (primarily with restricted/repetitive behaviors). One study (Ohnishi et al 2000) found that impairments in communication and social interactions correlated with decreased blood flow in one part of the brain, and that "obsessive desire for sameness" correlated with decreased blood flow in another part of the brain. Overall, hypoperfusion seems to be a very common problem in children and adults with autism, and likely has a large effect on their symptoms and cognitive function. The cause of the hypoperfusion is unknown, but may relate to inflammation of blood vessels leading to restricted blood flow. Effective treatments for this problem are sorely needed.

Zilbovicius M, et al., Regional cerebral blood flow in childhood autism: a SPECT study. Am J Psychiatry 1992, 149(7):924–930. (21 children with autism and 14 controls)

Zilbovicius M et al., Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography. Am J Psychiatry 2000, 157(12):1988–1993. (21 children with autism compared to 10 children with mental retardation)

Ohnishi T, et al., Abnormal regional cerebral blood flow in childhood autism. Brain 2000, 123(Pt 9):1838–1844. (23 children with autism compared to 26 non-autistic controls matched for age and IQ)

Starkstein SE, et al., *SPECT findings* in *mentally retarded autistic individuals, J Neuropsychiatry Clin Neurosci. 2000* Summer; *12*(*3*):370-5. (30 children with autism and mental retardation compared to 14 children with mental retardation).

Wilcox J, et al., Brain perfusion in autism varies with age. Neuropsychobiology. 2002;46(1):13-6. (14 individuals with autism age 3-37 years and 14 age-matched controls)

Meresse G, et al., Autism severity and temporal lobe functional abnormalities. Ann Neurol. 2005 Sep;58(3):466-9. (45 children with autism)

Ito H et al., Findings of brain 99mTc-ECD SPECT in high-functioning autism--3-dimensional stereotactic ROI template analysis of brain SPECT. J Med Invest. 2005 Feb;52(1-2):49-56. (15 children with autism, 5 children with epilepsy)

Gupta SK, Ratnam BV. Cerebral perfusion abnormalities in children with autism and mental retardation: a segmental quantitative SPECT study. Indian Pediatr. 2009 Feb;46(2):161-4. (10 children with autism, 5 typical children)

Sasaki M, et al Brain perfusion SPECT and EEG findings in children with autism spectrum disorders and medically intractable epilepsy. Brain Dev. 2010 Oct;32(9):776-82. Epub 2010 Jul 1. (15 children with autism)

Yang WH et al., Regional cerebral blood flow in children with autism spectrum disorders: a quantitative ^{99}mTc-ECD brain SPECT study with statistical parametric mapping evaluation. Chin Med J (Engl). 2011 May;124(9):1362-6. (23 children with autism, 8 controls)

Duchesnay E, et al., Feature selection and classification of imbalanced datasets: application to PET images of children with autistic spectrum disorders. Neuroimage. 2011 Aug 1;57(3):1003-14. Epub 2011 May 10. (45 children with autism, 13 control children)

Research on effect of HBOT on brain hypoperfusion

HBOT has been reported to at least temporarily improve brain hypoperfusion in two open-label studies of other conditions (veterans with post-concussion syndrome and patients with various chronic brain injuries).

Harch P, et al. A Phase I Study of Low Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post Concussion Syndrome and Post Traumatic Stress Disorder. J Neurotrauma 2012, 29(1):168-185.

Golden ZL et al., A: Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. Int J Neurosci 2002, 112(2):119–131.

Formal research studies of the possible effect of HBOT on brain hypoperfusion in individuals with autism are needed to determine if it is helpful. Investigation of the effect on inflammation, such as elevations of CRP, would also be very useful.

Summary

Autism is a very complex disorder, and involves many genetic and environmental factors that are not well-understood. However, there are many biomedical abnormalities that have been identified, and most can be treated to some degree. By following the testing and treatments outlined above, many individuals will improve to some degree, usually slowly and steadily over months and years. Sometimes one treatment shows great benefit, but it is more common that each treatment helps a small amount. However, the cumulative effect of multiple treatments can be substantial.

Much of the research on biomedical interventions has focused on children. Research is needed to understand their effectiveness on teenagers and adults on the autism spectrum, but it seems likely that many of the treatments listed here will also be helpful to teens and adults.

Much more research is needed to improve on these treatments and to determine which individuals are most likely to benefit from a given treatment, and to discover new treatments.

For more information, I encourage you to go to the website of the Autism Research Institute (www.autism.com) and attend their conferences.

Please consider filling out the ARI Treatment Effectiveness Survey at www.autism.com, to share your experiences with other families.

To read case studies of children who have greatly improved from biomedical approaches, see "Recovering Autistic Children" by Stephen Edelson, Ph.D., and Bernard Rimland, Ph.D., available from www.autism.com.

I encourage you to support research on new treatments for autism by donating to the Autism Research Institute at www.autism.com – your donations can make a difference.

Good luck in your journey.

James B. Adams, Ph.D.
http://autism.asu.edu