William Walsh, PhD is the president of the Walsh Research Institute in Naperville, Illinois. Dr. Walsh received his PhD in chemical engineering and is an internationally recognized expert on biochemical imbalances. An early collaboration with Carl Pfeiffer, MD, PhD, led to advanced nutrient protocols for normalizing body chemistry and brain chemistry in the 1980s. This work led to establishment of the Health Research Institute and Pfeiffer Treatment Center in Illinois in the 1980s. Dr. Walsh is the director of an international program for training physicians in advanced nutrient therapy for behavior disorders, mental illness, and autism. In 1999, he was the first to discover that undermethylation is a distinctive feature of autism spectrum disorders. His recent autism research includes chemical analysis of autism brain tissues, abnormalities in hormone chemistry, studies focusing on oxidative damage and oxidative stress, and the role of epigenetics. He is the author of a new book titled *Nutrient Power.*

OXIDATIVE STRESS, UNDERMETHYLATION, AND EPIGENETICS – THE BERMUDA TRIANGLE OF AUTISM

The bottom line is that autism is treatable and recovery is possible.

By William J. Walsh, PhD

INTRODUCTION

Over the past 50 years, autism has transformed from a rare childhood disorder to a major epidemic impacting one in every 110 children in the United States, according to the Centers for Disease Control. Fifty years ago, most school teachers experienced one or two autism cases in their entire career. Today, teachers learn of new cases each month. For several decades, the increasing numbers were attributed to better efficiency of diagnosis. However, this cannot explain the continuing sharp increases from 1990 forward, during which time the syndrome of autism has become well-known throughout the medical field.

Until 1960, most autism cases involved clear symptoms at birth. During ensuing decades, however, regressive autism rates gradually increased and now represent about 80% of cases. The reason for increased prevalence of regressive autism is considered by many to be unknown. In typical regressive cases, children develop normally until age 16-22 months and then a fairly sudden and shocking decline in functionality occurs. Typical cases involve loss of speech, a divergent gaze, odd repetitive movements, disinterest in parents and siblings, and emotional meltdowns. Most parents are horrified upon receiving a diagnosis of autism and being told the condition is incurable and will lead to a lifetime of severe handicap. This scenario is still common in mainstream medicine, with many families advised to institutionalize their child. Fortunately, many doctors and families have refused to accept this dismal verdict and have engaged in promising exploratory treatments, based on available scientific evidence.

In my experience with 6,500 children on the autism spectrum, thousands of families have reported exciting improvements, with hundreds reporting complete recovery. Many of my medical colleagues have achieved similar successes. The bottom line is that autism is treatable and recovery is possible.

Some of the mysteries of autism have been resolved by new research. For example, it is now clear that high oxidative stress and undermethylation are distinctive features of this disorder. In addition the emerging science of epigenetics is providing insights into the underlying causes of autism.

ALTERED BIOCHEMISTRY IN AUTISM

Autistic children exhibit distinctive chemical imbalances not present in the general population. By 1999, I had collected 50,000 chemical assays of blood and urine for autistic children and was invited by Dr. Bernard Rimland to present the findings at a think tank in Cherry Hill, New Jersey. The assembled audience of autism researchers and clinicians was familiar with my findings of: (a) zinc deficiency; (b) copper overload; (c) B-6 deficiency; and (d) elevated toxic metals. However, the group expressed great surprise at data indicating that more than 90% of autistics were undermethylated. Subsequent research by Dr. S. Jill James, Dr. Richard Deth, and others has shown that undermethylation

is a distinctive feature of autism. By 2010, a wealth of biochemical information has been collected by autism researchers throughout the world. Table 1 lists biochemical abnormalities found in autism spectrum disorders. All of these imbalances are associated with oxidative stress.

Table 1
Biochemical Features of Autism
(partial list)

- Low glutathione (GSH) and cysteine
- Undermethylation
- Elevated mercury, lead, and other toxins
- Copper overload and insufficient ceruloplasmin
- Deficiency of zinc and selenium
- Elevated urine pyrroles
- Depressed metallothionein (MT) protein levels
- Elevated carboxyethylpyrroles

AUTISM BRAINS ARE DIFFERENT

Researchers have identified differences in brain structure and organization in autistic persons. Harvard studies have shown that primitive areas of autism brains are immature, having failed to complete development of brain cells and synaptic connections. This knowledge suggests that therapies aimed at completion of brain development may be a high priority. Dr. Manuel Casanova has reported abnormalities in the cortex of autism brains, especially narrowing of "minicolumn" arrays of cells. Dr. Woody McGinnis and colleagues have reported threadlike accumulations of damaged fats in autism brains, indicating oxidative damage. Dr. Eric Courchesne found that many autistic children experience a rapid acceleration in brain size during the first year of life. Approximately 25% of autistics have unusually large heads. All of these findings suggest that early intervention is of critical importance, since brain abnormalities that develop in the initial years may persist throughout life. The plasticity of brain cells and synapses is greatest in infancy and early childhood, and exciting progress is possible during this window of time.

We all start life with billions of short, dense brain cells that are immature. Brain development involves four basic phases: (1) pruning of some brain cells to make space for growth of other cells; (2) growth of neurons, axons, dendrites, and other cell components; (3) growth inhibition once a brain cell is fully mature; and (4) development of synaptic connections. Researchers have reported an excessive number of short, undeveloped brain cells in the cerebellum, pineal gland, hippocampus, and amygdala of autistics, but not in other brain locations. These are areas with little or no protection from the blood-brain barrier, suggesting that chemical insults or excessive oxidative stress may have stunted brain development. The net result is an immature brain with reduced capability for learning, speech, and socialization.

The brain area with the most pronounced immaturity in autism is the cerebellum, which is responsible for smooth, controlled movements. A majority of autistics exhibit odd repetitive movements, possibly due to an impaired cerebellum. Another affected brain area is the amygdala, which enables a person to develop socialization skills. Deficits in socialization are a hallmark of autism, and an immature amygdala may be part of the problem. The hippocampus partners with Wernieke's area and Broca's area in the development of speech. Mutism and speech delay are common in autism and a poorly functioning hippocampus may be responsible.

Fortunately, the ability to develop immature brain cells and new synapses continues throughout life. This capability enables many paralyzed stroke victims to recover and also offers hope for autistic children. The speed with which new brain cells and synapses are developed is extremely rapid until about age three when a gradual slowing occurs. Clinicians working with autistic children are aware of the critical need for early intervention. In my experience, greater progress can be achieved in one month with a 2-year-old, than in 6 months with an 8-year-old. Doctors and parents need to be aware that immediate action is essential once a diagnosis of autism has been made in order to maximize benefits. However, intervention can be beneficial at any age. For example, a Connecticut mother told me that her 17-year-old daughter began to speak after 30 days of MT-Promotion therapy.

Autism brains also appear to be afflicted with significant inflammation that may inhibit brain development and cause a myriad of symptoms including irritability, speech delay, sleep disorders, cognitive delay, and increased head size. The sudden regression experienced by many children may be caused by events that result in brain inflammation.

BIOCHEMICAL THERAPIES

Table 2 lists popular biochemical therapies that have produced countless reports of significant improvement in autism spectrum patients. It seems highly significant that most of these therapies produce an antioxidant effect. It's also interesting to note that Risperdal, the

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> “The environmental triggers for autism continue to be hotly debated, but there is general agreement on one thing: the recipe for autism is a combination of an inherited predisposition and severe environmental insults prior to age three.”

most popular psychiatric medication in autism treatment, has antioxidant properties. However, it must be noted that Risperdal is a powerful anti-psychotic medication that has never been tested for safety in young children.

All of the treatment systems listed below have acquired a cadre of enthusiastic supporters, but none of these have been adopted by mainstream medicine.

Table 2
Popular Biochemical Therapies for Autism *(partial list)*

- Methyl-B12 and other methylation therapies
- Vitamins and minerals
- Transdermal glutathione
- Casein-free, gluten-free diet
- Chelation (removal of toxic metals)
- Metallothionein-Promotion therapy
- N-Acetylcysteine and alpha-lipoic acid
- Therapies to combat yeast overgrowth
- Antibacterials and antifungals
- Decoppering protocols
- Amino acid supplements
- Digestive enzymes
- Secretin
- Hyperbaric oxygen therapy

GENETICS, EPIGENETICS, & ENVIRONMENT

There is an undeniable hereditary component to autism, with about 60-90% concordance in identical twins, compared to less than 10% for fraternal twins. Since concordance is less than 100%, a significant environmental component must exist. Many people ask, “How can there be an epidemic of a genetic disorder?” Spontaneous DNA abnormalities occur about once in every 500,000 cell divisions, and DNA mutations usually require centuries to develop. Consequently, the consensus belief is that the increased rates of autism are due to changes in the environment over the past 70 years. More than two dozen environmental theories have been suggested, including increased vaccinations, toxic metal exposures, changes in the water supply, industrial food processing, changes in family dynamics, and more. The environmental triggers for autism continue to be hotly debated, but there is general agreement on one thing: the recipe for autism is a combination of an inherited predisposition and severe environmental insults prior to age three.

The emerging science of epigenetics is providing a new and persuasive explanation for increasing autism rates. Until recently, a person’s genetic characteristics were thought to be cast in concrete at the moment of conception. We now know this is only partially true, and that a person’s chemical environment can determine which genes are expressed and which are silenced. Epigenetics is a rapidly growing field that investigates alterations in gene expression that do not involve changes in DNA sequence. Methyl is a dominant chemical factor in epigenetics, and nearly all autistics are undermethylated. This suggests that autism may be predominantly epigenetic in origin rather than a result of genetic modifications (DNA polymorphisms). This theory is supported by the fact that epigenetic processes are far more sensitive to environmental insults than genetic processes.

All cells in the human body contain an identical copy of DNA with the potential for producing many thousands of proteins. However, the proteins expressed in liver cells are very different from those of skin cells, pancreas cells, etc. Epigenetics refers to differences in tissue environment that enable production of certain proteins while preventing formation of others. Certain biochemicals have a powerful role in determining which genes are expressed or silenced and a balance between these factors is essential for proper development after conception.

DNA consists of billions of proteins that form a double helix ribbon that is about 6 feet in length. Amazingly, this DNA is packed into a tiny ball that is about one-hundredth of a millimeter in diameter and neatly fits inside the nucleus of every cell. This fragile double helix is wrapped around tiny globs of protein called “histones” in a configuration known as “beads on a string.” The acidic DNA tends to adhere to millions of histones that are alkaline. The histone-DNA beads are called “nucleosomes,” and an array of nucleosomes is termed “chromatin.” Each nucleosome consists of eight histone proteins, with “tails” that extend out of its core as shown in **Figure 1**. The two primary epigenetic processes are (a) direct methylation of DNA at cytosine residues; and (2) histone modification as illustrated in **Figure 2**. For years, scientists believed histones provided a support framework for the fragile DNA but didn’t have an active role in gene expression. Researchers recently established that genes can be turned on or off depending on which chemicals react with the histone tails. In many cases, the ability to express a specific gene (produce a protein) depends on a competition between methyl and acetyl groups at histone tails. In general, methylation tends to inhibit expression and acetylation promotes expression as shown in **Figures 3** and **4**. A total of 63 different core histone proteins have been identified,

> “… a person’s chemical environment can determine which genes are expressed and which are silenced.”

and a complex "histone code" is under investigation. In summary, undermethylation is a chemical imbalance that can alter epigenetic bookmarking of hundreds of genes and may be responsible for many aspects of autism.

OXIDATIVE STRESS AND METHYLATION – THE CHICKEN OR THE EGG?

There is an exquisite interrelationship between oxidative stress and methylation. Excess oxidative stress tends to deplete glutathione, impair the one-carbon cycle, and cause undermethylation. On the other hand, undermethylation can reduce production of glutathione, cysteine, and metallothionein and cause oxidative overload. A genetic or acquired deficiency in either factor can produce a deficiency in the other.

After studying the methyl status of more than 20,000 persons, I've learned that undermethylation runs in families and is associated with obsessive-compulsive tendencies, competitiveness, high career accomplishment, seasonal allergies, and low serotonin activity. The incidence of undermethylation is very high in many populations, including doctors, lawyers, corporate executives, engineers, scientists, and professional athletes. Undermethylation is also more prevalent in college populations and in affluent neighborhoods. Social mobility has increased during the past 50 years, and there has been a great increase in the number of undermethylated men and women who marry each other. I believe that this has caused a great increase in the number of parents prone to producing autistic children, Low methyl levels in utero and in the fetus itself would: (a) increase the likelihood of epigenetic errors; and (b) increase vulnerability to toxic metals and other sources of oxidative stress. This "reverse social entropy" may be a contributing factor in the autism epidemic.

A CLUE FROM THE PAST – THALIDOMIDE BABIES

Deformed thalidomide children of the 1960s had an unusually high incidence of autism. It was eventually learned that this autism occurred only if the anti-nausea pill was taken between days 20-24 of gestation. This is the time period when the lion's share of epigenetic bookmarking is established. Thalidomide was taken throughout pregnancy by thousands of women, suggesting that this narrow time frame is a period of heightened sensitivity to autism-causing environmental insults. This suggests that psychiatric medications and mercury-containing flu vaccines could increase autism risk during this brief time interval.

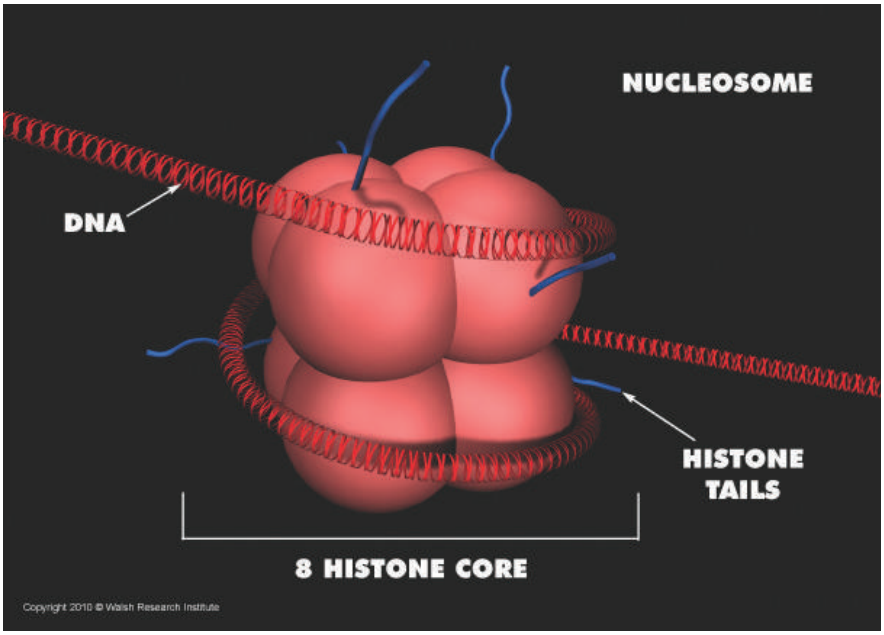

FIGURE 1

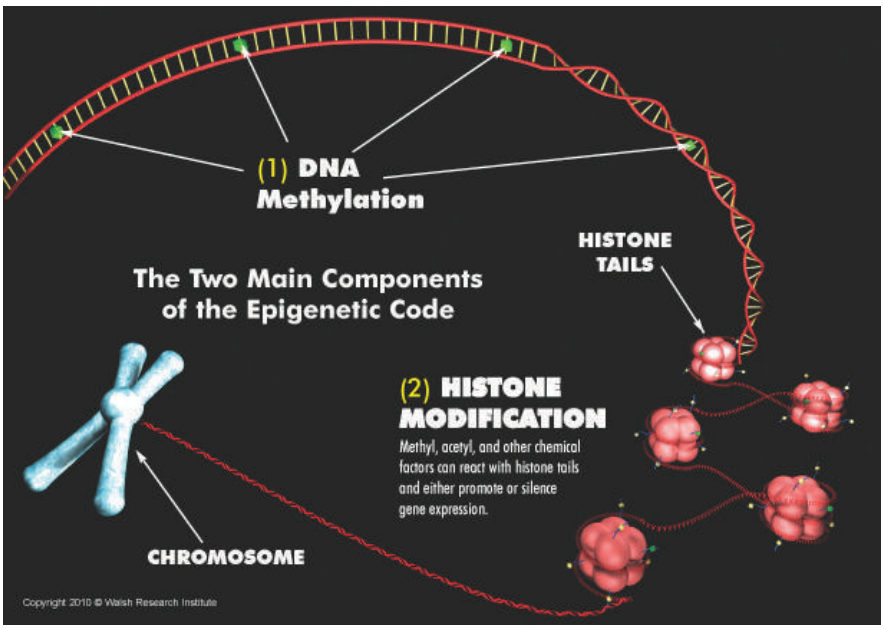

FIGURE 2

Most pregnancies are undetected at this early stage, and effective autism prevention may require women of childbearing age to avoid exposure to toxic metals and other sources of teratological harm.

TRANSGENERATIONAL EPIGENETIC INHERITANCE

There is mounting evidence that certain epigenetic defects can be transmitted to future generations by a process called "transgenerational epigenetic inheritance" (TEI). More than 100 TEI conditions have been identified in early research and many more are anticipated. Animal research has provided solid evidence of TEI, and there are early convincing

"In summary, undermethylation is a chemical imbalance that can alter epigenetic bookmarking of hundreds of genes and may be responsible for many aspects of autism."

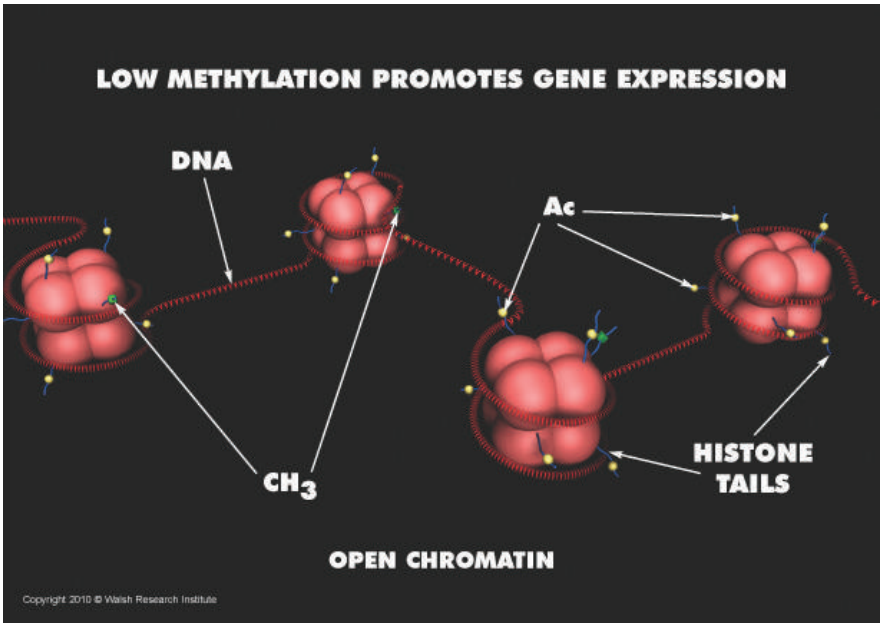

FIGURE 3

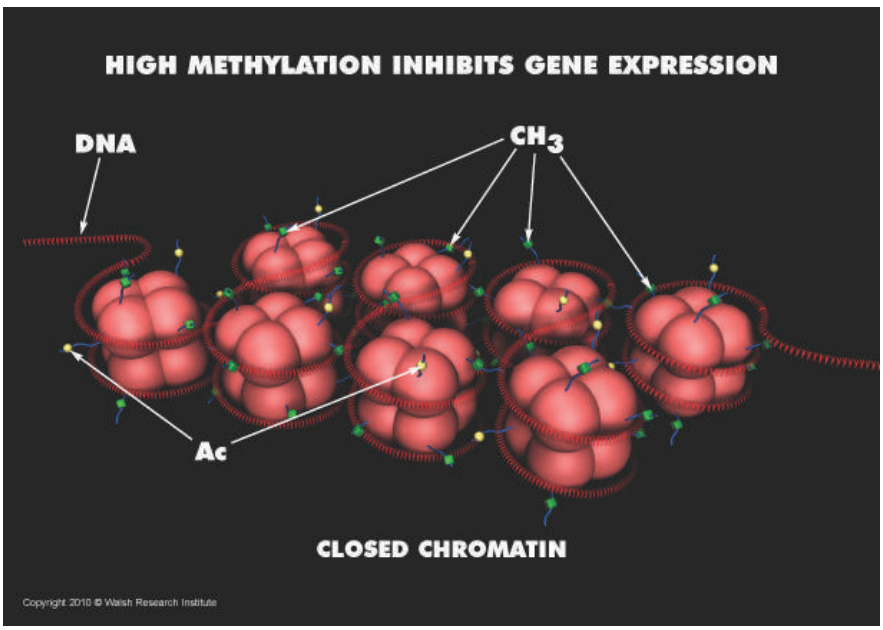

FIGURE 4

> "... therapies aimed at development of new brain cells, synapses, and minicolumns should have the highest priority."

indications of TEI in humans. Environmental insults during days 20-24 of gestation may not only harm the fetus, but also transfer autism predisposition to the next three or four generations. It appears that TEI defects may be a contributing factor in the autism epidemic.

THE AUTISM REGRESSION EVENT

Although experts are able to detect subtle autism tendencies by studying early video tapes, the regressive deterioration that often occurs during year two needs explanation. I have met hundreds of parents who reported very rapid regressions, including cases in which vaccinations, illnesses, or known toxic exposures were not involved. The global nature of the regressions often include loss of speech, odd repetitive movements, divergent gaze, sudden intolerance to certain foods, and extreme personality change. It seems clear that a major EVENT has occurred within the brain and perhaps throughout the entire body. In the absence of effective treatment, the devastating symptoms of autism can persist throughout a lifetime.

Two other medical conditions that involve sudden global regressions are Wilson's disease and schizophrenia. An important difference is that autism develops before brain development has been completed. Wilson's disease and autism are similar in that both are conditions of severe oxidative stress, with extreme depletions of the protective proteins metallothionein and glutathione. In Wilson's, gradual worsening of oxidative stress can progress until the MT and GSH antioxidant functions are overwhelmed, resulting in sudden inability to transport copper from the liver. The median age of onset of Wilson's disease is 17 years, and rapid deterioration in physical and mental functioning is common. In another example, schizophrenia involves excessive oxidative stress and usually entails a sudden onset (or mental breakdown), usually between ages 16-26.

AN OXIDATIVE STRESS MODEL OF AUTISM

In the history of science, progress has often been hastened by the development of theories that attempt to explain the mechanisms of poorly understood phenomena. In this spirit, I present the following model of autism that is largely based on the research advances and dedicated efforts of others.

1. The heritable component of autism derives from a combination of DNA polymorphisms and epigenetic defects. The relative contribution of these factors is unknown.
2. The primary harm from genetic/epigenetic defects involves weakened ability to cope with oxidative stress.
3. In utero environmental contributions to autism are primarily epigenetic in nature.
4. Post-partum triggers for autism include toxic exposures, immune challenges, and other environmental insults that increase oxidative stress.
5. The body's natural protectors against oxidative stress (e.g., glutathione, metallothionein, selenium, super oxide dismutase, ceruloplasmin, and cysteine) are gradually weakened until a threshold is reached in which their effectiveness collapses. This event results in a sudden increase in oxidative stress and inflammation within the brain.
6. In regressive autism, the sudden increase in

oxidative stress and inflammation can cause a rapid decline in mental functioning (e.g., loss of speech, behavioral changes, and divergent gaze).

7. Autism symptoms persist unless powerful antioxidant therapy is provided.
8. Rampant oxidative stress impairs protein digestion and weakens intestinal and blood-brain barriers.
9. Sharply reduced metallothionein activity greatly slows development of brain cells, resulting in an immature brain.
10. Severity of autism depends on the relative progress in brain development prior to inundation by oxidative stress.
11. If untreated, excessive oxidative stress can result in gradual loss of brain cells and mental retardation by age 20.
12. Antioxidant therapies together with applied behavior analysis (ABA) offer the promise of a better life for autistic children. If started in earnest prior to age four, a greater possibility of recovery exists.

WHAT IS A FAMILY TO DO?

Early intervention is essential to optimal progress; intensive treatment must begin soon after diagnosis. Autism involves a brain that has not completed the maturation process, and brain cells may have been damaged by early environmental insults. In either case, therapies aimed at development of new brain cells, synapses, and minicolumns should have the highest priority. Treatments to increase metallothionein and glutathione levels would hasten advances in brain development. Brain inflammation can retard progress and must be overcome. Diets free of casein and gluten proteins may quickly reduce inflammation and produce immediate benefits. Behavioral therapies such as ABA can stimulate the development of new synapses and minicolumns, and are especially effective when coupled with antioxidant therapies. This is an example of Hebb's Rule: "Brain cells that fire together, wire together." In addition, children on the autism spectrum must be provided a pristine environment that is free of unnecessary sources of oxidative stress. Families must never give up and constantly remember that *"Autism is Treatable and Recovery is Possible."*