

Autism, An Extreme Challenge to Integrative Medicine.

Part 1: The Knowledge Base

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Abstract

Autism, archetype of the autistic spectrum disorders (ASD), is a neurodevelopmental disorder characterized by socially aloof behavior and impairment of language and social interaction. Its prevalence has surged in recent years. Advanced functional brain imaging has confirmed pervasive neurologic involvement. Parent involvement in autism management has accelerated understanding and treatment. Often accompanied by epilepsy, cognitive deficits, or other neurologic impairment, autism manifests in the first three years of life and persists into adulthood. Its etiopathology is poorly defined but likely multifactorial with heritability playing a major role. Prenatal toxic exposures (teratogens) are consistent with autism spectrum symptomatology. Frequent vaccinations with live virus and toxic mercurial content (thimerosal) are a plausible etiologic factor. Autistic children frequently have abnormalities of sulfoxidation and sulfation that compromise liver detoxification, which may contribute to the high body burden of xenobiotics frequently found. Frequent copper-zinc imbalance implies metallothionein impairment that could compound the negative impact of sulfur metabolism impairments on detoxification and on intestinal lining integrity. Intestinal hyperpermeability manifests in autistic children as dysbiosis, food intolerances, and exorphin (opioid) intoxication, most frequently from casein and gluten. Immune system abnormalities encompass derangement of antibody production, skewing of T cell subsets, aberrant cytokine profiles, and other impairments consistent with chronic

inflammation and autoimmunity. Coagulation abnormalities have been reported. Part 2 of this review will attempt to consolidate progress in integrative management of autism, aimed at improving independence and lifespan for people with the disorder.

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Introduction

In 1943 the psychologist Leo Kanner published case histories of a childhood developmental disorder he called autism. He defined three symptom patterns: (1) failure to use language for communication, (2) abnormal development of social reciprocity, and (3) desire for sameness, as seen in repetitive rituals or intense circumscribed interests.¹ Autistic children seem abnormally withdrawn, almost self-occupied, and out of touch with reality. As a group they score significantly lower on measures of adaptive or life skills than the general population.²

Individuals with autism tend to have extreme difficulty learning from experience and modifying their behavior to accommodate varying situations.² Coping with the unpredictability of the social world is especially demanding, even overwhelming, for adults with autism; associated anxiety exacerbates the problem.² Adult individuals with autism have life outcomes that range from complete dependence to (rarely) successful employment. Most are able to benefit from structured training programs with marked improvement in their quality of life.³

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Autism has become epidemic in the industrialized societies. In the United States, autism was relatively rare until the early 1990s, after which its prevalence increased by at least double, and more likely 3-5 times.² Similar steep increases in prevalence have been recorded in the United Kingdom.⁴ The gender ratio is 3-4:1 boys to girls.² Since every autistic child has a major impact on the family, school system, and community, this epidemic calls for compassion, sensitivity, and maximum assistance from society as a whole.

There is a great deal of debate in the healthcare world over the existence of an autism epidemic and the possible contributing factors. Parents, supported by progressive healthcare professionals, are on one side pointing at vaccines manufactured with known toxic ingredients. On the other side are governmental and private organizations seemingly unwilling to institute reform. The annual monetary cost of autism in the United States is estimated to be \$26 billion.⁵

From the clinical-biological perspective, this disorder or spectrum of disorders, is extremely complex and multifaceted. Its expression, pathology, etiology, and management rank it among the most perplexing disorders known. Autism challenges the intellect and research skill of investigators obtaining funding support to investigate it. Yet despite all the limitations, real progress has been made within the last decade toward helping autistic people become productive members of society.

The Autism Research Institute, founded by Dr. Bernard Rimland, and its Defeat Autism Now! (DAN!) initiative, have successfully advanced medical management of autism to the degree that some children largely recover and can have somewhat normal lives.^{6,7} Within the broader medical community, diagnosis and assessment have also markedly improved, as have the pace and intensity of research. This review (Part 1 of 2) seeks to define the features of the disorder and its core abnormalities. Part 2 will address the variety of approaches to its medical management, along with priorities for future research.

Diagnosis, Classification, Epidemic Prevalence

The modern concept of autism recognizes Kanner's "classic autism" as autism, autistic disorder or AD, and subsumes this within a broader category called autistic spectrum disorders or ASD. For the physician these distinctions can be hard to make. In this review, use of the term autism will refer to AD and the broader category will be referred to as ASD, unless otherwise specified.

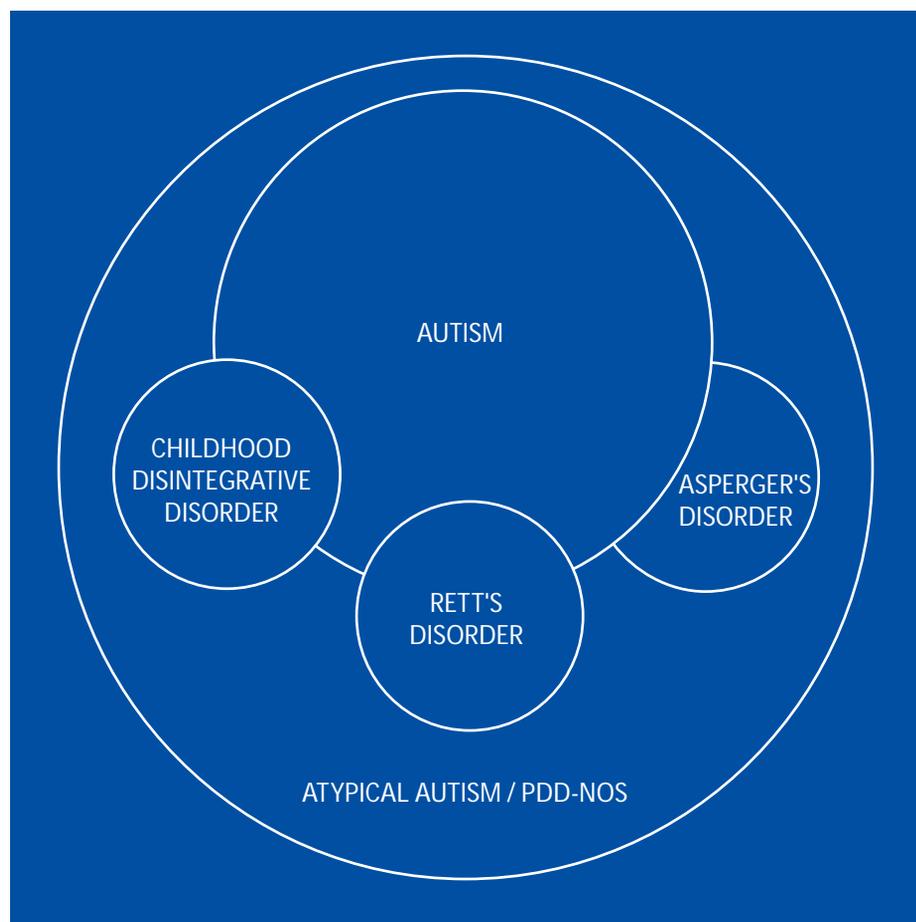
Emergence of the Disorder

Autism begins very early in life. Almost all autistic patients are normal in physical appearance, but physiologic abnormalities can become evident within mere months of birth.⁸ The three primary symptom patterns first defined by Kanner manifest by 36 months. This characteristic triad may be accompanied by sensory and motor dysfunctions, or by cognitive or other mental processing deficits.⁹ Neurological abnormalities dominate autism.

In the majority of autism cases the disorder first becomes apparent as a parent notices the growing child is not using words to communicate, even though the child usually can recite the alphabet. In a minority of cases, autism appears as developmental regression: parents report their child was developing normally, then regressed – occasionally abruptly – in language, sociability, and play.¹⁰ In rare cases motor skills also regress. After a plateau that lasts for some months, development resumes, but in most cases never returns to its previous level.

Some autistic children make little progress throughout their life, remaining nonverbal, severely withdrawn, and mentally deficient, while others fare better, although complete recovery is rare.¹¹ While 75 percent of AD cases are mentally retarded, only 50 percent of ASD cases exhibit retardation. As many as one in 10 autistics are savants – gifted in areas such as music, drawing, memorization, or calculations. They have "islands of genius" in skills that require attention to detail, memory, or computations such as calendrical calculating or perfect pitch.^{12,13} Tentative suggestions have been made that risk of autism may be greater

Figure 1. Conceptual Interrelationships of the Autistic Spectrum Disorders¹⁶



Diagnosis and Classifications

Autism is diagnosed generally at around two years of age, when the child should begin to participate in organized social activities. Social deficits become evident when the child is compared with peers of the same age. The young child with autism is unlikely to seek out others when he is happy, show or point to objects of interest, or call his parents by name. The child is, in a sense, abnormally self-occupied. During preschool years, repetitive behaviors begin to develop. These could include using peripheral vision to look at lines or wheels, or peculiar hand and finger movements.

From the early infant stage, children with autism are likely to be developmentally delayed. Trained observers can detect movement abnormalities at four months.¹⁵ The

autistic child is observed to be less adept at making eye contact with another person, has poor ability to make facial expressions, and is less able to coordinate his vocalizations with his intentions, compared to children within the normal developmental range.⁸

in families where one or both parents has selected a field of interest emphasizing focus and attention to detail.¹⁴

Persons with autism have reduced life expectancy.⁵ Those with the most severe mental retardation tend to die soonest. Those with mild or no mental retardation still die earlier than the general population, most often from seizures, nervous system dysfunction, drowning, or suffocation (all rates more than three times higher than the general population). Deaths due to epilepsy are 24 times that of background; many of the deaths by drowning involve heart attacks, perhaps related to adverse effects from medications.

In concept, the diagnosis of autism has not changed since formulated by Kanner, but there have been evolutionary changes in how the symptom patterns are interpreted and assessed. Recognizing that no two cases are alike, even within the same family, it has become more useful to view autism as a spectrum of disorders, classified autistic spectrum disorders with Kanner's "classic" autism at the core (Figure 1).

All the autistic spectrum disorders feature deficits in communicative and social skills, but they vary in symptom pervasiveness, severity, onset, and progression over time. For the purposes of this review, the term ASD is considered synonymous with pervasive developmental disorders (PDD). The category ASD includes at its core AD, overlapping with Asperger's disorder (Asperger's syndrome, AS), childhood disintegrative disorder (CDD), and Rett's disorder (Rett's syndrome, RTT). All these are enveloped by pervasive development disorder not otherwise specified (PDD-NOS, also called atypical autism).¹⁶ It is not uncommon for these ASDs to occur concurrently within the same family.

Physical Characteristics and Co-Morbid Conditions

Early reports of an association between autism and epilepsy¹⁷ helped implicate biological rather than mere psychogenic factors in the etiology of autism. Epilepsy may occur in up to 30 percent of individuals with autism. Although its peak onset is during early adolescence, it may also occur in infancy.² Infantile spasms that involve the brainstem may initiate autistic symptoms. Landau-Kleffner syndrome features epileptiform activity, abrupt loss of language, and autistic symptomatology.¹⁸

Epidemiological studies indicate that currently at least 25-30 percent of people with autism have associated medical conditions.¹⁹ Among the most prevalent are sensory impairment (blindness and/or deafness), tuberous sclerosis, neurofibromatosis, and epilepsy, all of which predominate among those with the most severe mental retardation. Hearing loss may be more prevalent than previously reported, and may be linked to abnormal brainstem auditory-evoked responsiveness.²⁰

Rising Prevalence of Autism and ASD

The statistics on occurrence of AD and ASD strongly suggest these disorders have become epidemic. From surveys conducted prior to the 1990s, nationwide prevalence in the United States

was estimated at about 5 per 10,000 for AD and 20 per 10,000 for total ASD.²¹ By 1997, the prevalence of autistic spectrum disorders was estimated to be 40-50 per 10,000.² In one community, Brick Township in New Jersey, the frequency of ASD may have reached 1 in 150.²²

Some experts argue that such increased prevalence of AD/ASD is only apparent because of changes in diagnostic criteria and improvements in early detection. But the documented minimal doubling – perhaps quadrupling – of prevalence within a little more than a decade seems too extreme to be attributed only to improved diagnosis.

Sidney M. Baker, MD, and Richard A. Kunin, MD, pioneers in autism management, have independently listed factors that have become more prominent in “developed” societies between 1950 and 2000, and which they strongly suspect have contributed to the autism upsurge.^{23,24} They both have identified the following factors: increased antibiotic use; mercury exposure by injection in infancy; increase in combined live viral vaccines and the numbers of vaccinations; increased soil depletion leading to vitamin/mineral deficits; decreased omega-3 and -6 essential fatty acids in the diet; and greater exposure to xenobiotic toxins.

From 1987 to 1998, the number of children being treated for autism in California jumped 273 percent.²⁵ A nationwide figure for 1991 to 1997 was 556 percent. Whatever the limitations of the statistics in regard to determining the real prevalence of these disorders, the data starkly indicate there is considerable need for societal attention to autism. Hopefully, the most polar advocates on both sides of the prevalence debate could agree on one point: that communities, schools, and the healthcare systems are being confronted with the challenge to raise, educate, and otherwise manage ever-increasing numbers of children with profound functional impairments.

The Defining Abnormalities

Most experts agree the neurological problems seen in autism seem to stem, not primarily from the senses, but from interpretation of the world.²⁵ When normal people view an array of objects, for example, they infer social relationships among the objects. Rather than see a room, they see individual details within it. Autistic people tend to see shapes and objects as isolated. They also have trouble interpreting faces, sometimes gazing at the mouth rather than the eyes, as normal people usually do. The autistic child would more often describe his father as a man who is tall and wears glasses, rather than as his father who is kind and works hard.²⁵

The ability to understand facts but not relate them to concepts is another common symptom. Children with autism may learn a particular task yet be unable to generalize it to other situations. Their difficulty in processing information on the higher levels extends to their motor activity as well. They can have trouble kicking balls, writing, or tying shoes.²⁵

Possible Information Processing Deficits

Several theories have been posited as to the processing mechanisms that may be affected in autism. One is weak central coherence.²⁶ Autistic individuals generally demonstrate remarkable skill on the Block Design subtest from the Wechsler Performance Scale. The hypothesis is that autistics fail at holistic processing of an image, instead remaining focused on its individual parts. Thus on Block Design, they do not reconstruct the overall form of the image and as a result find it easier to see the component parts.

An alternative to weak central coherence has been the executive dysfunction hypothesis.²⁷ Executive functions are typically used for non-routine problem solving, and would include such mental operations as planning, working memory, maintenance and shifting of attention, and inhibition of inappropriate responses. Executive function deficits could potentially explain the repetitive and rigid behaviors of ASD, and the impaired

ability for social interactions, which typically require flexible and immediate evaluation, then selection of appropriate responses to multidimensional information.²⁸

The most recently favored hypothesis for social cognitive impairment in autism features theory of mind.²⁹ It suggests that autistics fail to appreciate the representational theory of mind and instead think of mind on too literal a basis. For example, the autistic child shown a milk carton filled with paper clips may conclude the carton really was manufactured to carry paper clips. Children normally can correct such “false beliefs” by the time they reach age four. Children with ASD typically do not pass this stage until their verbal mental age is at least eight years.

Neuropathologic Findings Inconsistent

To date only about 30 autopsies of autistic brains have been formally reported. The limited autopsy studies have not uncovered any consistent differences between autistic brains and nonautistic brains. Microscopic pathology and structural imaging studies have also failed to confirm differences. But very recently advanced functional imaging has succeeded in defining a pattern of abnormalities in autism.

Neuropathological examinations have at one time or another pointed to possible abnormalities in the brainstem, the cerebellum, and limbic structures, including the hippocampal formation, amygdala, septal nuclei, mammillary nuclei, and anterior cingulate cortex;³⁰ however, the majority of neuropathological studies have failed to confirm any differences from normal brains.³¹

Three different groups have reported abnormalities of the cerebellum, especially loss of Purkinje cells.⁹ Loss of cerebellar Purkinje cells is seen frequently in seizure disorders, so it would be important to conclusively determine whether these cells are depleted in autistic subjects without a history of seizure disorders.

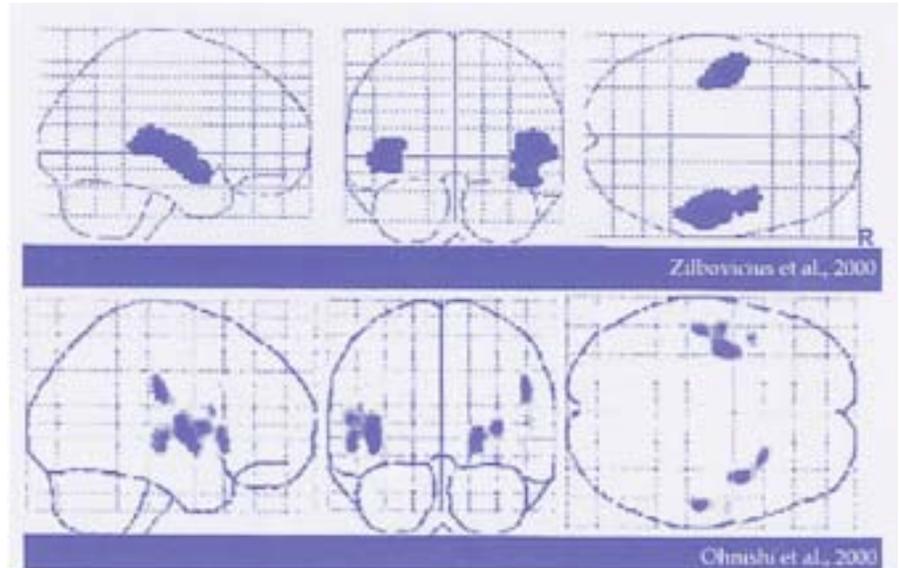
Structural magnetic resonance imaging has failed to detect consistent changes in autism.⁹ In different studies, both atrophy and normal mass

have been reported in the cerebellum. A few studies reported subtle abnormalities in the amygdala, while many reported normality.³¹ As well, studies that reported reductions of the hippocampus, mesial temporal lobe, or caudate nucleus in autistic subjects have been counterbalanced by others that found no change.^{31,32}

Functional brain imaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), initially made little progress over structural imaging. But with the second generation of instrumentation has come greatly improved resolution and data filtering. Now two groups have independently reported abnormalities of blood flow in the temporal lobes of autistic children. In addition, activation studies have revealed abnormal patterns of cortical activation.

Both PET and SPECT allow accurate measurements of cerebral glucose metabolism and/or blood flow. Measurements can be performed at rest or during the performance of specific sensory, motor, or cognitive tasks. The first good functional study was published in 1995. Zilbovicius and collaborators imaged regional cerebral blood flow in five “primary” autistic children (subjects free of epilepsy or other neurological complications), first at the age of 2-4 years then three years later.³³ They found that perfusion of the frontal lobes at the earlier age matched the pattern of perfusion in much younger normal children, and concluded these children had delayed frontal lobe metabolic maturation.

Figure 2. *Abnormally Low Blood Perfusion of the Temporal Lobes in Childhood Autism, Mapped from Two Separate Studies*



Dark areas indicate low regional cerebral blood flow at rest, as viewed from the right, the back, and the top of the brain. Top: Results from 21 autistic children.³⁴ Bottom: Results from 23 autistic children.³⁵ From Boddaert and Zilbovicius.³²

In 2000, using PET imaging, Zilbovicius et al detected significant temporal hypoperfusion in 21 autistic and 10 control children.³⁴ Careful data analysis confirmed that 16 of the 21 autistic children (77%) were lower than the controls; of these, four were unilaterally affected and 12, bilateral. These investigators then imaged another 12 autistic children and successfully confirmed the first result. That same year Ohnishi et al published a SPECT study of 23 autistic and 26 control children that detected significant hypoperfusion in the fronto-temporal region.³⁵ These two sets of results are so closely similar they are virtually superimposable on each other (Figure 2).

The evidence is now clear that autistic children, free of other major neurological conditions, manifest abnormally low blood flow in the temporal cortex.³³⁻³⁵ Neurologically, dysfunction in these regions could explain almost all the symptoms (perceptive, emotional, and

cognitive) observed in primary autism. The temporal associative regions are highly connected to the frontal and parietal lobes and the limbic and associated sensory systems. The temporal lobe is believed to be central to the processing of numerous environmental signals, as well as for the further conversion of these signals into structured patterns of neural activity that bring meaning to the world around us.

Indirect corroboration of this key finding comes from observations that individuals with temporal lobe pathology (epilepsy, herpes simplex encephalitis) sometimes manifest autistic behavior.³² In children with infantile spasms, temporal lobe hypometabolism is strongly associated with later emergence of autism symptoms.³⁶ Similar observations were made of children with tuberous sclerosis and from experiments conducted with primates.³²

Functional Imaging During Cortical Activation

Activation studies measure local changes of cortical blood flow or blood oxygenation, reflecting the variation of synaptic activity in response to sensory, cognitive, or motor stimulation. PET, SPECT, and fMRI activation studies suggest that autistic subjects activate different brain regions than controls, indicating they have different cerebral circuit configurations.³² Garreau et al conducted the first such SPECT study³⁷ and found that in response to auditory stimuli, autistic children activated the right posterior associative cortex while the control group activated the left side. Muller et al³⁸ reported similar findings in adult autistic males.

An auditory activation PET study was performed in autistic adults during passive listening to speech-like stimuli.³⁹ The autistic subjects showed significantly higher activation of the right posterior temporal lobe. Applying the same auditory model to children, Boddaert et al³⁹ detected significantly lower activation of the left temporal lobe. Altogether, the activation findings suggest autism is associated with abnormal activation of the left temporal cortex. Since this is the region thought to handle brain organization for language,

the functional findings are consistent with autistic subjects' language impairment and inadequate behavioral response to words.³²

Boddaert and Zilbovicius also described other types of activation studies with autistic children and adults.³² All the PET studies are consistent with disorganized establishment of neural circuits. Baron-Cohen and colleagues⁴⁰ tested the social intelligence (theory of mind) of autistic adults. Two sets of images were presented: (1) photographs of eyes, for the subject to guess whether each was a man or a woman and (2) photographs of people, for the subject to describe the mental state of the person in the photograph. The nonautistic control subjects activated both the fronto-temporal neocortical regions and non-neocortical regions, including the amygdala, hippocampus, and striatum. The autistic subjects activated the frontal neocortex less extensively, and failed to activate the amygdala. In other studies, autistic subjects failed to activate a cortical face area when attempting to assess facial expressions. The amygdala and cerebellum were not activated during processing of emotional facial expressions.

In summary, state-of-the-art functional brain imaging has established that autistic individuals exhibit abnormal temporal lobe function. Dysfunctional connections between these regions and the fronto-parietal zones could explain the cognitive abnormalities; to the limbic system, the emotional abnormalities; and to the auditory regions, the sensory perception abnormalities. Functional imaging detected abnormal activation patterns sufficient to suggest more or less widespread disorganization of cortical networks in the autistic brain.

Candidates for the Etiopathology of Autism

The etiopathology of AD/ASD is almost surely multifactorial. Although it is probably not an inborn error of metabolism, a genetic susceptibility almost surely exists. During the last 40 years, autism has been linked with many etiologies, including various inborn errors; genetic abnormalities such as fragile X syndrome; rubella and other

pathogens; and many other factors.⁴¹ Genetic predisposition, metabolic abnormalities, and abnormalities of the gastrointestinal, hepatic, and immune systems all appear to be markedly involved.

Genetic Predisposition

A solid body of evidence indicates genetics plays a primary role in autism, probably not as inborn error(s) but as a strongly predisposing factor.⁴² There is compelling evidence for high, very likely multigenically-determined, heritability as evidenced by the 50-percent concordance rate for monozygotic twins, versus about three percent for dizygotic twins.⁹ Further, the rate of autism among the siblings of an affected child is 3-6 percent, a rate 50-100 times higher than the general population.⁴³ This degree of genetic conditioning of autism exceeds genetically-conditioned diseases such as Alzheimer's, asthma, diabetes, and schizophrenia. These data are also consistent with the existence of multiple (probably between 3 and 20) susceptibility genes for autism.^{25,42}

The likelihood that autism is strongly determined by heredity has stimulated much recent research. A small proportion of autistic individuals (no more than 10-15 percent) demonstrate comorbidity with known genetic conditions including tuberous sclerosis, neurofibromatosis, fragile X syndrome, and chromosomal abnormalities. As many as 25 percent of fragile X cases display autistic-like symptoms that nonetheless are distinct from AD. Other X-linked gene mutations, such as in the MECP2 of Rett's disorder, may contribute to subsets of AD.

The chromosomal disorder most frequently found (up to 3 percent) in recent large samples of AD has been a maternal duplication of 15q11-q13, a region on chromosome 15 linked to other developmental disorders. While featuring mental retardation, these distinctly differ from AD, but a distance effect from this zone has not been ruled out. Several genome-wide gene screens have already been published on autism⁹ and a number of candidate gene regions are under scrutiny. Of these the most suspicious is a relatively large region on chromosome 7 (7q31-35). The 7q31 zone has been independently linked to a speech-

language disorder (SPCH1). A gene, FOXP2, has been identified from this zone and is being actively investigated.

Developmental/Teratologic

Several lines of evidence implicate an early brainstem injury in autism.⁴⁴ Minor physical anomalies of the ear are found in as many as 45 percent of autistic children, and point to a possible insult during ear development during the latter part of the first month of gestation.⁴⁵ Rodier and colleagues have developed a body of work that supports thalidomide exposure as a teratogenic factor in autism. Some 30 percent of children exposed to thalidomide during neural tube closure (days 20-24) developed autism, probably primarily related to brainstem damage.⁴⁶ Such cases usually display ear anomalies, including hearing loss, and Moebius syndrome (facial paralysis and a lack of eye abduction). Rodier explored the mechanisms in animal models and suggested many such individuals should show brainstem abnormalities at autopsy.⁴⁷

Metabolic Abnormalities

A number of inborn or acquired metabolic abnormalities may manifest as AD, ASD, or quasi-autistic syndromes. Biochemist Jon Pangborn, also the father of an autistic child, has reviewed these in a compilation of the applicable biochemical assessments.⁴⁸ The most prominent of the abnormalities are phenylketonuria (PKU) variants, histidinemia, adenylosuccinate lyase deficiency, purine synthesis deficiencies, inosine phosphate dehydrogenase weakness, Lesch-Nyhan Disease, adenosine deaminase deficiency, and ADA binding protein weakness.

Pangborn is also skilled at assessing amino acid analysis data from ASD cases with variable or non-inborn metabolic dysfunction. In a survey of 62 autistic children, he found taurine deficiency most predominant (62% on urinary analysis).⁴⁸ Deficiencies of lysine (59%), phenylalanine (54%), and methionine (51%) were trailed by deficiencies of tyrosine, leucine, glutamine, valine, and asparagine, in that order. In addition to amino

acid analyses he also strongly recommends elemental analyses from red cells and hair, and liver detoxification assessment using urinary caffeine, acetaminophen, and salicylate (aspirin) clearance.

Serotonin is a monoamine brain transmitter that is one of the earliest to appear in the developing brain. It also plays a role in regulating brain development.⁴⁹ Elevated blood serotonin is one of the most consistent abnormalities in autism, documented in more than 20 studies to date.⁵⁰ Up to 40 percent of ASD cases feature abnormally elevated blood serotonin.⁵⁰ Certain serotonin receptors may be supersensitive, which may contribute to repetitive behaviors.⁴⁹ Paradoxically, serotonin excess can result in lowered responsiveness to serotonin, due to feedback down-regulation of the receptors.⁴⁹ But some areas of the autistic brain can have decreased serotonin concentrations while other areas are abnormally elevated, perhaps corresponding to abnormal development of brain networks.⁴⁹

Warren and Singh measured serotonin in 20 autistic subjects and correlated the blood levels with genetic typing. They linked the blood serotonin elevation to a combination of MHC (major histocompatibility complex) genes on chromosome 6, a chromosome previously linked to autism.⁵⁰ The genes potentially involved are known to regulate immunity, and are often associated with immune deficits and autoimmune disorders.

Organ Abnormalities in Autism: Detoxification Impairments

While there are a seemingly unending number of theories seeking to explain the cause of autism, one category of abnormalities occurs with close to 100-percent frequency – abnormal liver detoxification.

Importance of Sulfoxidation and Sulfation to Health

The P450 detoxification system that is most concentrated in the liver uses sulfation as one pathway for the detoxification of endogenous and exogenous substances. Enzymes draw on a pool of sulfate to convert phenolic substances to

their water-soluble sulfate salts for subsequent excretion. Most of the sulfate substrate comes from sulfoxidation of the amino acid cysteine. Sulfation is important for the excretion of endogenously produced substances such as steroids, bile acids, and catecholamine neurotransmitters.⁵¹ Impaired sulfation also seriously compromises the ability to excrete xenobiotics from the body.

Sulfation and sulfoxidation capacities are known to vary substantially among individuals, and to be highly genetically conditioned.⁵² Sulfoxidation capacity (activity of the enzyme cysteine dioxygenase) can be roughly determined from the metabolism of the drug S-carboxymethyl-L-cysteine (SCMC).⁵¹ About 65 percent of the population test as “good metabolizers” of SCMC, 32.5 percent as “poor metabolizer.” And 2.5 percent are classed as “non-metabolizers.”⁵³ Despite limitations of this specific test, it seems clear that up to 2.5 percent of the general population have genetic polymorphisms that render them virtually unable to convert cysteine to inorganic sulfate.

Inorganic sulfate is important for many physiological functions. The liver relies on its sulfate pool to neutralize phenolic substances, chemicals common in foods and contaminants (exogenous) and also routinely produced in the body (endogenous). Endogenous compounds that are sulfated for excretion include the hormones progesterone and dehydroepiandrosterone (DHEA), and the catechol neurotransmitters dopamine and epinephrine. One exogenous substrate is acetaminophen (Tylenol®), an all-too-frequent cause of liver damage.

When sulfation is impaired or a high dose of acetaminophen is ingested, the resultant overload can deplete glutathione stores and result in liver injury or failure. Endogenous substrate overload, as from high estrogen during pregnancy or from use of estrogen-containing birth control pills, can further reduce liver sulfation capacity.^{54,55}

In addition to the liver's heavy reliance, the gastrointestinal (GI) tract also relies on sulfate availability for its essential functions. The gastrointestinal mucosa must have sulfate available in order to conduct “first-pass” neutralization of potentially toxic bacterial fermentation

products (e.g., from protein), foodborne phenolics, and manmade xenobiotics. The mucosa presumably receives most of its sulfate supply from the blood, within which sulfate levels are homeostatically controlled by kidney conservation.⁵⁶

Human studies have documented inadequate sulfation capacity in some individuals.⁵¹ The model drug used for this test is usually acetaminophen. Ultimately, three measures confirm sulfate metabolism abnormalities.

These are impaired sulfoxidation (from the SCMC test), impaired sulfation (from the acetaminophen test), and an elevated cysteine-to-sulfate ratio in the blood. To date these abnormalities are manifest in rheumatoid arthritis, as well as in the neurological diseases Alzheimer's, Parkinson's, motor neuron disease, and autism.⁵⁷

Abnormalities of Sulfoxidation and Sulfation in Autism

Reduced metabolism of SCMC, impaired sulfation, and an elevated cysteine-to-sulfate ratio have been reported in autistic children by Waring and collaborators, working in cooperation with parent groups in both the United Kingdom and the United States.⁵⁷

Alberti, Waring, and colleagues did a pilot study in which they measured acetaminophen

Table 1. Xenobiotic Overload (based on the maximum acceptable adult values) in Blood. Modified from Edelson and Cantor.⁴¹

Xenobiotic	%Children	% Adult Maximum
One or more xenobiotics	89%	>100%
Ethyl- or Methyl- benzenes	78%	111-1800%
2- or 3- Methylpentanes	55%	106-400%
Xylenes	44%	139-928%
Toluene	17%	367-10,000%
Benzene	17%	260-1160%
n-Heptane	17%	270-440%
Styrene	11%	200-400%
Trichloroethylene, Chloroform, Dieldrin	5%	325-1900%

clearance by 20 autistic children, diagnosed as AD and "low-functioning," against 20 age-matched controls.⁵⁸ Among the autistic subjects 18 of 20 were impaired, while among the controls 19 of 20 were normal (p value < 0.00002). In another 40 autistic children not directly compared, 37 of 40 showed a similar degree of sulfation impairment. In total, of 60 autistic children examined, 55 were markedly impaired (92 percent). The investigators suggested their findings should help explain why many autistic children are "triggered" by foodstuffs, particularly foods (e.g., bananas, chocolate, cheese and other fermented products) with relatively high profiles of phenolic amines such as dopamine, tyramine, and serotonin.

Additional support for this interpretation came when Waring and others found that the activity of phenylsulfotransferase (PST), the enzyme catalyzing the sulfation of acetaminophen, was

abnormally low in autistic children as measured from the blood platelets. This was more direct proof of a systemic incapacity of autistic subjects to detoxify endogenous and exogenous phenols and amines via sulfation.⁵⁹

These systemic impairments of sulfation in autistics threaten the stability of the catecholamine transmitter systems, the integrity of the gut lining, and heighten vulnerability to foodborne or pollutant xenobiotic overload. In this scenario a substance as ubiquitous as pyrethrin (a common ingredient of pesticides) could become neurotoxic, and many commonly-employed pharmaceuticals (including Tylenol®) could switch from (apparent) friend to foe. Endogenously produced steroid hormones could generate metabolic imbalances with the potential for long-term harm. Depletion of the endogenous sulfate pool could limit the biosynthesis of necessary substances such as bile acids (for digestion) or glycosaminoglycans (for joints and connective tissues). Backed-up dopamine and norepinephrine could auto-oxidize to nonspecifically reactive, free radical-type molecular species with great potential to damage the nervous system.

Cysteine is a known excitatory amino acid. In that portion of the population who cannot readily transform it to sulfate, there might be real potential for cysteine to become synergistic with exogenous excitotoxins such as excitatory food constituents or anticholinesterase agents and other neurologically-toxic insecticides, ubiquitous in the environment.

Ongoing research into multiple chemical sensitivity, ulcerative colitis, and non-IgE delayed food sensitivity, suggests that impaired sulfation of ingested phenolics and phenolic food constituents may well be causally linked with intolerance to foods and xenobiotics.^{51,57,59}

Excessive Accumulation of Xenobiotic Pollutants

Edelson and Cantor reported in 1988 that a group of 20 autistic children, ages 3-12, exhibited abnormal liver detoxification profiles.⁴¹ Blood analyses for identification of specific xenobiotic agents revealed toxic overload, defined as

significantly in excess of the established adult acceptable maximum values, in 16 of 18 of these children (Table 1).

Subsequently this sample population was expanded to include 56 children, 43 males and 13 females, mean age 6.54 years.⁴¹ All 56 subjects had abnormally high heavy metal burden; of these, 55 expressed liver detoxification malfunctions and 53 had one or more toxic chemicals in excess of the adult maximum reference range.

A recent review by this author explored the likelihood of linkages between the variety of toxins extant in the modern environment and the marked increases in childhood abnormalities.⁶⁰ The environment is suffused with organic pollutants. Pesticide spraying is still routine in many school districts. Heavy metals, organohalide pesticides, herbicides, fumigants, and a wide range of aromatic and aliphatic solvents have been linked to abnormalities in behavior, perception, cognition, and motor ability during early childhood. Children exposed acutely or chronically to aluminum, arsenic, cadmium, mercury, or lead are often left with permanent neurological sequelae. Lead can cause developmental delay and mental retardation. Studies on lead serve as a model for other toxic metals, and seemingly lead toxicity has no lower threshold of damage.⁶¹

The typical modern home is not a clean, protected environment.⁶² Chemicals embedded in carpets and wall materials; dust, molds, germs; lead in paints and radon contamination; pollutants in the air, water, and foods, all can be toxic to the developing infant. Children are especially vulnerable, due to their relatively immature detoxification capacities. Studies of infants prenatally exposed to mere "background" environmental levels of such pollutants consistently report changes in neurodevelopmental parameters.⁶³ Literally all the residents of industrialized countries now carry measurable amounts of several xenobiotic pollutants in breast and other tissues.

Abnormal Metallothionein Function

The healthy body carries an array of proteins which naturally chelate, and therefore buffer, zinc, copper, and other redox-active metals.⁶⁴

Table 2. Common Abnormalities on Stool and Digestive Analysis seen in Autism

<p>1. Digestive function: Deficient chymotrypsin; fat malabsorption</p>
<p>2. Metabolic abnormalities: Imbalanced short-chain fatty acids, also indicative of possible bacterial imbalance (dysbiosis)</p>
<p>3. Symbiotic beneficial bacteria: Marker species of Lactobacillus and Bifidobacterium often low or lacking, occasionally also E. coli</p>
<p>4. Bacterial imbalances: Streptococcus species, Staphylococcus species, hemolytic E. coli, Enterobacter</p>
<p>5. Possible pathogens: Candida excess, Blastocystis, Klebsiella, Bacillus species, Staphylococcus aureus, others</p>

These are called metallothioneins (MTs), due to their extraordinary metal-binding capability because of the many sulfhydryl (—SH) groups they contain. Their synthesis is inducible at the gene level, allowing some adaptation of the system to increased demand. MTs are the body's primary protection against toxic metals – Hg, Pb, Cd – and exposures to heavy metals normally lead to their adaptive up-regulation. Separate MTs guard the brain and gastrointestinal tract against heavy metal overload. It is likely that MT impairment would result in imbalances of heavy metals.

William Walsh, PhD, at the Pfeiffer Treatment Center, examined 503 patients diagnosed with ASD (318 autistic disorder, 23 Asperger's, 162 PDD with autistic features).⁶⁵ He found a significantly higher copper:zinc ratio in the ASD

group compared to healthy controls matched for age and gender ($p < 0.0001$). Walsh asserts that 99 percent of ASD cases were affected and that copper:zinc imbalance leads to emotional instability, attention deficit and hyperactivity, neurotransmitter imbalances, and impairment of hippocampus and amygdala function.

Walsh also asserted that elevated toxic metals are seen in 92 percent of autism cases, malabsorption in 85 percent, under-methylation in 45 percent, over-methylation in 15 percent, and pyrrole disorder in 20 percent of cases.⁶⁵ He discussed in depth a number of likely pervasive consequences for intestinal function, immunity, and brain function from an overloaded or otherwise inadequate MT system – examples, MTs appear to be involved in regulating brain nerve cell growth and in the GI production of enzymes that digest casein and gluten. Walsh also made available protocols aimed at MT system restoration and overall management of autism.

Organ Abnormalities: Gastrointestinal

The gastrointestinal system is a central source of symptom triggering in the autistic child and most autistic children have significant GI pathology.⁶⁶⁻⁶⁹ Common symptoms include diarrhea and/or constipation, abdominal pain, gas, bloating, and burping and gastro-esophageal reflux. Horvath and colleagues⁷⁰ found reflux esophagitis in 69 percent of an autistic sample, duodenal inflammation in 67 percent, low carbohydrate digesting enzymes (lactase) in 58 percent, and abnormal pancreatic response to secretin in 75 percent.

Stool Analysis, Digestive Function, Dysbiosis

Stool appearance is often abnormal in ASD, and stool cultures often reveal a variety of abnormalities (Table 2).^{48,71}

Pathogenic organisms can directly attack the GI tract, but many also generate a variety of toxins (detected by urine organic acid testing) that can have systemic effects. Shaw reported finding a wide array of abnormal organic acids in urine

samples from autistic children.⁷² In one case, a boy with apparent regressive autism following repeated courses of antibiotics showed abnormally elevated levels of tartaric acid in the urine. The boy responded positively to treatment with antifungal medication (Nystatin) and concomitantly the urine tartaric acid level dropped.

Tartaric acid is a potentially harmful approved food additive. It can appear in the urine of autistic children at very high levels, and the source is unclear but Shaw suggests it could be a product of breakdown of arabinose in the gut. Arabinose is a sweet-tasting aldose sugar that occurs in some foods, most notably apples. It has the potential to undergo Schiff-type cross-linkage reactions with proteins and thereby disrupt function. Elevated urine arabinose has been linked with yeast overgrowth (*Candida* species). Shaw reported analyzing urine from more than 95 autistic children and 20 age-matched controls and finding the mean arabinose levels to be five times higher than controls. The data presented was sketchy and no statistical analysis was performed.⁷² Shaw claims when children with abnormally high urine arabinose are treated with antifungal medication, the arabinose levels fall.

Dysbiosis is an almost routine consequence of antibiotic treatment, commonly used in young children for ear and other infections. Many parents have reported their healthy child became autistic following a course of antibiotic therapy; Galland documented one instructive case history.⁷³ A high-sugar/high-carbohydrate diet can encourage fungal growth (*Candida* or other less common species) and further contribute to the vicious cycle of dysbiosis.

Intestinal Lining Abnormalities, Leaky Gut

Inborn or neonatally-acquired weaknesses may predispose to gut lining dysfunction, with subsequent impairments of digestive, absorptive, or barrier functions. Secretin is a small protein (polypeptide) secreted by cells of the small intestine. It is a hormone whose function is to stimulate the pancreas to release bicarbonate, which creates an alkaline environment in the small

intestines, allowing the digestive enzymes later secreted by the pancreas to work optimally. Secretin therapy is under active development for ASD children with GI pathology. One study found 75 percent of the children had insufficient secretin production.⁷⁰

The mucus barrier may be poorly formed, as when glycosaminoglycan (GAG) synthesis is impaired by metabolic sulfation defects.⁷⁴ As the system functionally fails to cope with certain food constituents such as gluten, casein, or other large proteins or carbohydrates, incompletely digested fragments are likely to penetrate the mucus barrier and reach the epithelium. There, the Gut-Associated Lymphoid Tissue (GALT) can be bombarded with high doses of antigenic or other biologically active molecules. Past this stage, unless the GALT system can be protected against such inappropriate stimulation, frank inflammatory and/or autoimmune damage to the GI lining is initiated. A vicious cycle is generated, whereby the lining's integrity is compromised. Using a standard two-sugar test for intestinal permeability, D'Eufemia⁶⁷ documented abnormally increased permeability in 9 of 21 (43%) autistics.

For the autistic child with abnormal GI permeability, clinically significant damage may be averted or at least minimized if a gluten-free, casein-free diet can be implemented. Here, improvement of symptoms following step-by-step elimination of suspect foods is the only real test of success. Improvement with a casein-free diet can be seen within three weeks and usually predicts success of a gluten-free diet, which often takes longer than three months.⁷⁵

Penetration of Opioid Stimulants; the Opioid Excess Theory

Panksepp in 1979 proposed an "opioid excess" theory of autism. Other researchers have found opioid peptides ("exorphins," derived from partially-digested food proteins) in the urine of autistic individuals.^{48,76-78} Molecules this size do not normally cross the gut mucosa. Reichelt and colleagues working in Norway reported significantly higher levels of exorphins in urine from 315 autistic children from eight different countries

compared to 143 normal children. The mean levels were almost twice as high in the autistics ($p < 0.001$).⁷⁸

Another group based in the United Kingdom focused their opioid investigations on peptide effects on the dopamine transmitter system. They examined urine from 25 autistic adults and found abnormally high levels in 21 of them (84%) when compared to 20 healthy controls. However, they found essentially the same pattern in individuals with other mental handicaps, and expressed doubt this finding could be specific for autism.⁷⁹

Reichelt et al recently updated the opioid excess theory of autism.⁷⁸ They found exorphins opioids derived from casein and gluten crossed the blood-brain-barrier and caused “social indifference” symptoms in experimental animals, as well as inability to differentiate essential from non-essential stimuli. They found a peptide in urine from autistics that increased platelet content of serotonin, which is also a common finding in autism. Altered serotonin availability has been linked to “insistence on sameness,” reminiscent of ASD. They attempt to rationalize all the other characteristics of autism according to this model, suggesting that autism is based in a genetic error of peptide digestion, perhaps of the enzyme diaminopeptidase IV,⁷² and that the brain stimulant activity of the exorphins can explain most, if not all, autism symptomatology. Further clinical research will establish the relative correctness of this hypothesis.

Distinctive Enterocolitis Associated with Autism

In 1998, Wakefield and collaborators in the United Kingdom reported finding measles virus antigens in the intestinal linings of children with autism. They tentatively linked the presence of this antigen to recent measles-mumps-rubella (MMR) vaccination.⁶⁶ This sparked a torrent of criticism. In 2001 their team of 12 researchers reported on a blinded comparison among 21 consecutively evaluated autistic children with bowel disorders (manifesting as abdominal pain with constipation or diarrhea), eight children without

intestinal pathology, 10 non-ASD children with ileal lymphoid nodular hyperplasia (LNH), 15 with Crohn’s disease, and 14 with ulcerative colitis.⁶⁸ Histology demonstrated lymphocytic colitis in the ASD children, albeit less severe than classical inflammatory bowel disease (IBD). However, basement membrane thickness and mucosal gamma cell density were significantly increased over the other comparison groups, including IBD. Intraepithelial lymphocyte numbers and CD3, plasma cell, and CD8 cell counts were also markedly increased. The investigators concluded their findings pointed to a lymphocytic enterocolitis in ASD, possibly skewed in the T-helper 2 (TH2) dominant (autoimmune) direction.

In a recently published paper, 11 of the same investigators extended this line of inquiry from the colon to the duodenum.⁶⁹ They compared duodenal biopsies in 25 children with regressive autism to 11 with celiac disease, five with cerebral palsy and mental retardation, and 18 histologically normal controls. Histology revealed increased numbers of enterocytes and Paneth cells in the autistic children. The duodenal lining also had increased lymphocyte proliferation, crypt cell proliferation, and more T cells. The investigators were particularly struck by the finding of increased IgG deposition on the epithelial cell surfaces, accompanied by complement C1q. This novel form of enteropathy in the regressed autistic children was not seen in the other conditions. The researchers believe this pattern is suggestive of autoimmune lesions and distinctive for autism.

Organ Abnormalities: Immune Dysfunction

There is substantial evidence to suggest the immune system plays an important role in the pathogenesis of autism.^{66,80,81} All the arms of immunity are abnormal, and some or all of the abnormalities may have a genetic basis.⁸²

Cell-mediated immunity is often abnormal in autism. Abnormalities of macrophages, B cells, T cells, and natural killer (NK) cells have been reported.⁸¹ NK cell numbers are decreased in approximately 40 percent of these children⁸³ and CD4+ T cells decreased in

approximately 35 percent.⁸¹ Among 20 autistic children examined in detail by Gupta's group, 13 of them (65%) had CD4+ "helper" cells shifted away from TH1 towards TH2. This generally indicates a skewing of immune system balance toward autoimmunity. Warren's group had similar findings.⁸⁴ Both findings should be replicated with larger samples. However, the collective data is strongly consistent with a likelihood of autoimmune abnormality in at least a subset of ASD patients.

Turning to humoral immunity, serum immunoglobulin classes and subclasses are often altered.⁸¹ Complement deficiencies are sometimes found, especially of the C4B complement protein;⁸⁵ which apparently have a genetic basis.^{82,86}

The healthy digestive tract is coated with mucus that carries high levels of immunoglobulin A (IgA). Quantitatively, IgA is the most prominent immunoglobulin in the body and its rate of synthesis exceeds that of all the other immunoglobulins combined.⁸⁷ Warren and collaborators found decreased serum IgA in 8 of 40 (20%) individuals with autism.⁸⁸ IgA deficiency predisposes to autoimmune disease.

The literature suggests that at least a subset, perhaps 35-45 percent, of the autistic population has pervasive problems with immunity.⁸⁹ Autoantibodies to brain have been reported from autistic children,⁹⁰ as well as antibodies directed against specific neural self-antigens. Gupta's group reported finding anti-MBP (myelin basic protein) and anti-NAFP (neuron-axon filament protein) in 50-70 percent of their patients.^{81,91} In 1991, Singh et al reported cytokine and other abnormalities suggestive of autoimmunity.

Later research substantiates that cytokine profiles can be off-balance in autism. In a small sample Gupta's group found tumor necrosis factor-alpha (TNF- α), a potent proinflammatory cytokine, was significantly increased.⁹¹ In 2001, Jyonouchi and collaborators reported testing 71 ASD children aged 2-14 years and comparing them with healthy siblings and other controls.⁹² They found 27 of the ASD children (38%) had significantly higher levels of TNF- α and other

proinflammatory cytokines (interleukin-1 β , interleukin-6) compared with control children.

In the Jyonouchi study a majority of the ASD children (40/71, 56%) and their siblings produced abnormally high amounts of TNF- α upon physiologic stimulation (Figure 3). A minority of the ASD children (7/71, 10%) produced abnormally low amounts of TNF- α after stimulation.

Another 13 percent (9/71) had apparent poor regulation of TNF- α in that they produced normal amounts of the TNF- α cytokine but abnormally low amounts of sTNFR_{II}, a cytokine that normally helps counter-regulate TNF- α . In total 79 percent exhibited aberrant TNF- α characteristics and 83 percent overproduced one or more of three proinflammatory cytokines. The investigators concluded that a majority of their ASD children exhibited excessive or poorly regulated innate immune responses. The study data also indicate seemingly healthy siblings may share this tendency yet not become autistic.⁹²

One useful indicator of increased activity of TNF- α and other proinflammatory cytokines is urinary pterin levels (neopterin and biopterin). These are also predictably raised by autoimmune activation in the body. Messahel et al⁹³ analyzed urine from 14 AD children, 21 siblings, and 16 controls. They found significant elevation of both substances in autistic children, and intermediate elevation in their siblings. Their results also confirmed that as AD children get older their pterins may be less elevated. These findings were taken to indicate that autoimmune activation may be a contributing factor in typical or "classic" autism, shared to some degree by nonautistic siblings.

Detractors of this line of investigation argue autism cannot be inflammatory because characteristic cellular infiltrates are not found in the brain, and cannot be autoimmune because demyelination has not been found in the brain.⁹⁴ Actually, there are published case reports of demyelination in autism, and Burger and Warren⁸⁷ emphasize that many different inflammation-related mechanisms can be triggered or modulated by autoantibodies to damage the autistic brain.

The data on abnormal immune system involvement in autism is fragmented but substantial. Further studies are needed to clarify the potential etiological contributions from immunogenetics, cytokine imbalances specific to the brain, and autoimmune potential from autoantibodies against brain biomolecules. Better understanding should lead to strategies for rebuilding or rebalancing the immune system

Coagulation Abnormalities

An increasing number of integrative physicians report finding coagulation abnormalities in their autistic patients. According to Jeff Bradstreet, MD and Jerry Kartzinel, MD, “Many autistic children (and their family members) show significant abnormalities in blood coagulation.”⁹⁵ They suggest lack of oxygenation due to compromised blood supply stemming from coagulation might explain some of the symptomatology seen in autism. A laboratory panel known as ISAC (Immune System Activation of Coagulation) may be useful for assessment purposes.⁹⁶ They also have found vasospasm to be prevalent in autistic patients.

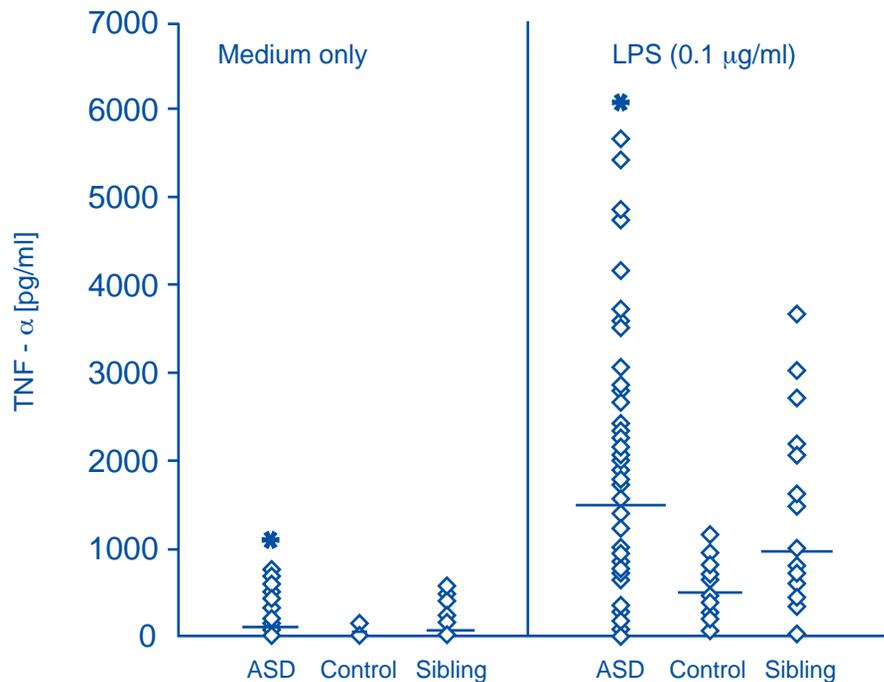
Carol Ann Ryser, MD, has had substantial clinical experience with this phenomenon in chronic fatigue patients, and reports similar findings in autism patients. She suggests inflammation can trigger the conversion of circulating fibrinogen to fibrin deposits, which

then adhere to the linings of the capillaries and other small vessels to occlude blood flow through them.⁹⁷ Richard Kunin, MD, has also reported clotting abnormalities in autistic patients.²⁴ Treatment with heparin will usually normalize the coagulation parameters.

Do Vaccines Cause Autism?

The issue of whether vaccinations cause or contribute to autism is one of the most controversial and contentious in this field. Those who advocate a connection note that sharp increases in autism prevalence in California

Figure 3. *TNF- α levels Produced by PBMCs (peripheral blood mononuclear cells) from ASD Children, Developmentally Normal Healthy Siblings, and Control Children*



Left, at baseline. Right, following stimulation with lipopolysaccharide (LPS). Horizontal bars represent median values. (*) Significantly higher than controls ($p < 0.001$). From Jyonouchi et al.⁹²

(which has 10 percent of the U. S. population) and the United Kingdom roughly parallel increases in the number of vaccinations given to children until the age of two (currently as many as 32 different vaccinations are given). They also claim parallels with the introduction of the MMR vaccine.

In California a sharp rise in autism began to be evident in the mid-1980s. A statewide study published in 1999 reported a 273-346 percent increase during the period from 1987-1998, depending on whether the “classic” Kanner-type diagnosis or the more inclusive “autistic spectrum” diagnosis was applied.⁴ Rimland makes the point that when reporting and publication delays are taken into consideration, the reported rise from 1987 may actually have begun as much as five years earlier, possibly around 1982. This would place the rise much more proximate to 1978, the year the MMR vaccine was introduced into California on a large scale.⁴

Introduction of the MMR vaccine into California is also linked to an important change in the pattern of onset of autism. According to data on many thousands of cases, collected since 1965 by the Autism Research Institute of California, prior to the early 1980s the majority of autism cases had onset at birth. Since that period far more cases of autism began to manifest around 18 months, the time after birth when most children receive the MMR vaccine.⁴

Contemporary vaccination programs involve more than 30 inoculations administered to the child between the ages of 12 and 24 months.⁴² Thus a large number of foreign proteins are introduced, sometimes as three different attenuated viruses in one vaccine (as with MMR). Often there may be insufficient time between vaccinations for the child’s immune response to return to baseline. Side effects of these vaccinations include allergic reactions, autoimmunity, and rarely, full development of clinical viral disease (from infection by attenuated viral particles of the vaccine).⁴²

Transfer of Measles from Vaccine to Recipient?

Many parents of autistic children and a number of medical experts believe the MMR vaccine is the culprit behind autism. In one in six children it causes fever 7-12 days following immunization, and one in 3,000 develop febrile seizures.⁹⁸ Thrombocytopenia occurs in one child per 30,000. Sensory-neural hearing loss and gait disturbance has been associated with use of attenuated live measles vaccine as found in the MMR; joint arthralgia or arthritis has been linked to the rubella component.⁹⁹

A possible mechanism to connect the MMR vaccine with autism was advocated by Wakefield and his colleagues in 1998.¹⁰⁰ They reported on 12 children who had undergone autistic-type regression soon after they received the MMR vaccine. These children had gastrointestinal symptoms, such as diarrhea and abdominal pain, and histopathological exam of the intestinal lining seemed to reveal the presence of measles virus. The cases were classed as a possibly new, inflammatory bowel syndrome, and tentatively linked to acquisition of measles virus from the MMR vaccine (albeit attenuated and having minimal infectivity). Another group confirmed the measles strain DNA was consistent with vaccine being the source.¹⁰¹

This study came under sharp criticism on many points, including its lack of rigorous controls. Nonetheless, its findings were provocative. Many critics totally dismissed this study, but in 2002 Korvatska and collaborators wrote of the MMR vaccine, “...it is difficult to believe that exposure to a vaccine may be more severe than to the virus itself. There is still a possibility of unaccounted interactions between the three related attenuated viruses during simultaneous infection.”⁴²

MMR Vaccine Safety Remains Unproven

Some of the defenders of MMR vaccine were perhaps uninformed that this vaccine was never subjected to adequate safety assessment prior to being released for use in large populations of children. In a letter to the journal *Lancet*, Wakefield stated that the entire MMR prelicensure

safety testing lasted only three weeks.¹⁰⁰ In any case, the usual design of prelicensure vaccine trials fails to generate data on rare reactions (i.e., less than one per 1,000 doses), reactions with delayed onset (i.e., 30 days or more after vaccinations), or reactions in subpopulations.¹⁰² Postlicensure evaluation of vaccine safety (after it has gone into use) is the only option.

However postlicensure reporting of adverse vaccine events has little practical usefulness.¹⁰² It relies on passive reporting – a clinician must voluntarily decide to submit a report. Under-reporting of such single case events is believed to be notoriously widespread. Adequately designed, prospective studies intended to pursue a link between the MMR (or any vaccine) and an adverse event pattern are practically nonexistent.

Some experts have decried efforts by concerned observers to criticize the use of MMR, sometimes alluding to “victimization” of the pertussis vaccine in the 1970s. Wakefield made the important point that the pertussis vaccine did cause neurological problems, to the extent of at least 80-percent disablement, in about 900 children. Large financial compensations were legally assessed¹⁰⁰ that provided impetus to replace the particular vaccine formulation with a safer version. Opponents of the current MMR vaccine suggest it could be made safer in its triple form, or else split into its three components to be given in three separately spaced shots.

Adding to the biological possibilities of vaccine damage comes a toxic possibility – the deliberate inclusion of toxic mercury in many of them.

A Likely Mercury Connection with Autism

During the same period that autism rates were showing a steep rise, many vaccines (although not the MMR) carried the toxic metal mercury. The vaccine makers chose as a preservative thimerosal, which contains the highly toxic compound ethylmercury. In recent years an outcry from parents resulted in reformulation of most (although not all) vaccines to exclude thimerosal. Although influential parties continue

to deny possible connections, uncanny similarities exist between the known patterns of mercury’s toxicity to children and those of autism.

Close Parallels in Mercury and Autism Symptomatology

Early in the twentieth century, mercury was used as a constituent of teething lotions and diaper powders. A disease called acrodynia appeared in young children and was christened “pink disease” because it turned the facial skin pink and simulated blushing. After a long process of denial and obfuscation, mercury was confirmed responsible for pink disease.¹⁰³ Other information on mercury toxicity patterns comes from victims of mercury-contaminated fish (Japan-Minamata disease), grain (Iraq, Guatemala, Russia), or from more individualized instances as with Mad Hatter’s disease (named so because beaver hat makers used mercury in the processing).¹⁰⁴⁻¹⁰⁶ The symptom patterns of these conditions overlap with those that characterize autism, as summarized in two pages of detailed comparisons painstakingly compiled by Bernard and her colleagues.¹⁰⁷

Scrutinizing these tables of detailed comparisons, even the most skeptical and rigorous observer would be struck by the close resemblances. The psychiatric and physical disturbances, speech and language deficits, sensory abnormalities, motor disorders, and cognitive impairments of autism, all resemble mercury poisoning. The similarities continue when looking at the most unusual behaviors, for example, movement disturbances that are worse on the right side of the body; over- or under-reaction to sound; and the flapping motions, originally thought so unique to autism that they were recommended as a diagnostic marker for the disorder.¹⁰⁷

Moving from the clinical expression of autism to its known biological features, again the parallels with mercury poisoning are remarkable. The biochemical abnormalities of autism, including low glutathione and sulfate levels, abnormal antioxidant enzyme activity, mitochondrial dysfunctions, and disruptions of purine and pyrimidine metabolism, are all paralleled by mercury toxicity.¹⁰⁷ The immune system parallels include greater propensity to

allergies and asthma and autoimmune overactivation with skewing toward TH2 imbalance and reduced NK cell function.

The brain and other central nervous system similarities between ASD and mercury toxicity include dysfunction in the amygdala, hippocampus, basal ganglia, and cerebral cortex; destruction of neurons from the cerebellum; and brainstem abnormalities. Demyelination is evident in both conditions. The brain's electrical patterns are similarly abnormal, with epileptiform and subtle, low amplitude seizure activities.

Temporal Connections Between Mercurial Vaccines and Autism

In most children affected by autism, symptoms become noticeable between four and 18 months after birth.⁷⁷ Vaccines containing thimerosal with a 50-percent content of ethylmercury typically were given in repeated administrations that began at infancy and continued until 12-18 months of age. Mercury toxicity typically begins gradually, first as sensory- and motor-related problems, then as speech and hearing deficits, then progresses into the full panoply of impairments.

Mercury was introduced into vaccines in the 1930s, which is approximately when the first cases of autism were recorded. Between 1970 and 1990 autism incidence doubled, from one in 2,000 to one in 1,000, coinciding with the rise of the DPT vaccines packing thimerosal. In the late 1980s and early 1990s, two new thimerosal vaccines, the HIB (*Haemophilus Influenzae* Type B) and Hepatitis B, were added to the schedule; perhaps coincidentally, this was about the time the sharp increase in autism began.¹⁰⁸ Some vaccines also contain aluminum,¹⁰⁹ which could compound mercury's toxicity.

In the State of California, there is a close correlation between increased autism from the late 1980s onward and cumulative mercury exposure through multiple vaccinations.¹¹⁰ The U.S. Centers for Disease Control, recipient of public trust for prevention of disease, has admitted that cumulative mercury exposure to children through vaccination exceeds known "safe" exposure levels.^{108,111} In late 2001, the prestigious Institute of Medicine, which advises the United States on

health issues, conceded an autism link with mercury is "biologically plausible," and recommended that thimerosal be removed from vaccines.¹¹¹

Autistic Children Have Impaired Capacity to Detoxify Mercury

Almost 100 percent of autistic children show impaired liver detoxification. Many also have poor metallothionein status, therefore lowered capacity to neutralize mercury and other heavy metals. Mercury is a powerful oxidant with partial free radical character; it depletes cellular antioxidants, especially glutathione, the core intracellular protectant.¹¹² The P450 detoxifying enzymes of the liver rely heavily on adequate availability of glutathione.

Mercury is also a potent poison to many enzyme systems, especially those that rely on sulfhydryl groups for their catalytic activity.¹⁰⁶ ATPases, ion transport enzymes crucial to cell-level homeostasis, are highly vulnerable. Mercury binds tightly with selenoproteins – glutathione peroxidases and other selenium-dependent enzymes – thereby endangering antioxidant defense. Mercury also has other potentially toxic effects, such as inducing autoantibodies to myelin and other cell constituents, and poisoning mitochondria.¹¹² In fact, mercury is one of the most potent toxins known, involving virtually every known pathway for inhibition.

New Study Establishes Thimerosal Mercury Link with Cell Killing¹¹²

A new study just being published (August 2002) makes a definitive, mechanistic link between thimerosal and cell damage or death in the exposed individual. Makani, Gupta, and colleagues subjected cultured human T cells (Jurkat) to thimerosal. They found thimerosal's mercury ingredient (ethylmercury) specifically caused apoptosis of these cells. The cells became depleted of the core antioxidant glutathione, their mitochondria became decompensated, and the cells died. The exposure levels at which thimerosal killed these human immune cells were low and well within the ranges likely attained in vaccinated children.

Skeptics of the mercury theory of autism sometimes inquire, with nearly all U.S. children being immunized, why only a few would develop autism. The experiences with acrodynia/pink disease and other human models of mercury intoxication illustrate that the effects of mercury are highly variable (1,000-10,000-fold) in its effects on the individual. Acrodynia, for example, afflicted only one in 500 among children who received similar, comparatively low mercury exposures.¹⁰⁶ Mercury seems to strike harder at certain genotypes that have higher propensity to autoimmune disorders, of which autism seems to be one example. Also, low-dose mercury exposure damages far more boys than girls, consistent with the gender imbalance of autism.¹¹³

Parent-Driven Progress in Autism Management

Following the first definitive report on autism by Kanner in 1943,¹ research on the disorder was largely descriptive: symptoms were catalogued with efforts made to pinpoint the brain areas and functions that might be affected. Drugs that had been developed for other applications were tested for symptom reduction, with little success. For decades little progress was made, until 1967 when Bernard Rimland, PhD, founded the Institute for Child Behavior Research (ICBR).¹¹⁴

As a father of an autistic child, Rimland understood the need for immediate assistance to individuals with the disorder. He intensively studied the scientific literature and used the Institute as an international clearinghouse for information on autistic children. He solicited information and case reports from parents, who are on the front lines of the battle against autism; and from health professionals, some who also had children with autism. Soon the ICBR was able to help parents to help their children. Drugs did little to help, but intensive, carefully planned, highly structured behavior modification did help.¹¹⁴

By 1987 the ICBR had in its data bank detailed case history information on 9,600 autistic children from 40 countries, gleaned from hundreds of professionals.¹¹⁴ They had collected more than 3,500 completed questionnaires with quanti-

tative feedback from parents on a variety of drugs, nutrients, and other treatments. The various treatments were scored, then ranked in terms of the ratio of number of autistic children helped to the number made worse. The first such ranking, from 318 parent questionnaires, scored vitamin B6 and magnesium as having the best “benefit-to-harm” ratio.

In 1968 the ICBR began to conduct prospective studies of vitamin therapy for autism. The first study employed large doses of vitamin B6, niacinamide, pantothenic acid, and vitamin C, the four treatments ranked most favorably by the parents.¹¹⁴ Treating 200 children over four months, it yielded significantly positive results, with vitamin B6 appearing to provide the most benefit. Subsequent trials by the ICBR and other parties found vitamin B6 and magnesium made a particularly beneficial combination, with no adverse effects. The ICBR has since evolved into the Autism Research Institute (ARI).⁶ The ARI now has the largest database in the world on autism, with upward of 34,000 cases.¹² Parents participate in the ARI at every level, including research and publication in peer-reviewed journals.

In 1995 the ARI initiated another breakthrough in autism research and medical management. A conference was convened at which 30 scientists and physicians specializing in autism founded Defeat Autism Now! (DAN!). Since then several other conferences have been held, with consensus reports published, periodic physician training manuals, and a manual on biomedical assessment options.⁷ As with the original ICBR and ARI, the activities of DAN! have once again sparked further advances in diagnosis and treatment of autism.

In 1997, the U.S. National Institutes of Health (NIH) began a five-year, \$42-million network of collaborative research programs for autism. In September 2001, construction began on a \$39-million state-of-the-art comprehensive clinic and research center to diagnose, treat, and study children with autism. Located at the University of California at Davis, it is largely a product of parent advocacy.²⁵ At parents’ insistence, all the comprehensive raw data generated at this facility – Medical Investigation of Neurodevelopmental

Disorders (MIND) Institute – will be shared with autism investigators around the world.

Conclusion

Until recently autism has been a puzzling disorder with a limited knowledge base and, as a consequence, its management was largely empirical. But now signs have emerged that point toward a possible pattern for this disorder. Hypofunctioning of the brain's temporal lobe regions, leading to compromise of this region's networking with other regions, can account for the core neurological symptomatology. Pervasive detoxification impairments, documented in a high percentage of children with the disorder, are consistent with the abnormally high xenobiotic load they carry and their heightened susceptibility to mercury, aluminum, and other toxic metals. Poor systemic detoxification performance may account for the apparent abnormal autoimmune tendency in this population.

The autistic child may be a casualty of the toxicity of modern society. Potential triggering factors such as antibiotic overdosing, overvaccination, and prenatal xenobiotic overload could interact with each other and with a high heritability component to account for the development of dysbiosis, leaky gut, and other GI abnormalities known to fuel systemic autoimmune reactivity. These and other triggers are so broadly threatening to human metabolism that they could also account for virtually all the other abnormalities seen in autistic spectrum disorders. Whether any one "cause" of autism will be established remains an open question; as the research deepens the theory of opioid excess will compete with other theories.

Much new research needs to be conducted on autism before this putative pattern can be fully confirmed. Many parents feel they cannot afford to wait for the normally snail's-paced progression of good science. Thus (to their credit) they are driving the pace of research into this devastating disorder. The limited, fragmentary data of today could soon become a body of knowledge that would allow for fuller confidence in detailed management protocols. Crucial challenges, such as a better neurological grounding of the disorder's subtypes, could be overcome within a few years. Part 2 of

this review will cover the current state of the art in autism treatment, which is consolidating into a model of integrative medical management.

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Autism, An Extreme Challenge to Integrative Medicine. Part II: Medical Management

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Abstract

Autism and allied autistic spectrum disorders (ASD) present myriad behavioral, clinical, and biochemical abnormalities. Parental participation, advanced testing protocols, and eclectic treatment strategies have driven progress toward cure. Behavioral modification and structured education are beneficial but insufficient. Dietary restrictions, including removal of milk and other casein dairy products, wheat and other gluten sources, sugar, chocolate, preservatives, and food coloring are beneficial and prerequisite to benefit from other interventions. Individualized IgG or IgE testing can identify other troublesome foods but not non-immune mediated food sensitivities. Gastrointestinal improvement rests on controlling *Candida* and other parasites, and using probiotic bacteria and nutrients to correct dysbiosis and decrease gut permeability. Detoxification of mercury and other heavy metals by DMSA/DMPS chelation can have marked benefit. Documented sulfoxidation-sulfation inadequacies call for sulfur-sulphydryl repletion and other liver p450 support. Many nutrient supplements are beneficial and well tolerated, including dimethylglycine (DMG) and a combination of pyridoxine (vitamin B6) and magnesium, both of which benefit roughly half of ASD cases. Vitamins A, B3, C, and folic acid; the minerals calcium and zinc; cod liver oil; and digestive enzymes, all offer benefit. Secretin, a triggering factor for digestion, is presently under investigation. Immune therapies (pentoxifyllin, intravenous immunoglobulin, transfer factor, and colostrum) benefit selected

cases. Long-chain omega-3 fatty acids offer great promise. Current pharmaceuticals fail to benefit the primary symptoms and can have marked adverse effects. Individualized, in-depth clinical and laboratory assessments and integrative parent-physician-scientist cooperation are the keys to successful ASD management.

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Introduction

The first part of this two-part series documented myriad abnormalities typical of autism and autistic spectrum disorder (ASD).¹ Despite their bewildering array, most of these abnormalities are amenable to medical intervention.² In part II of the series the medical management of autism is reviewed.

Conventional medicine has largely failed autistic individuals and their families. Autism went through a long period during which institutions hesitated and parents struggled to find any means to help their children. Some of these parents were scientists and physicians. They carefully observed their children and built cooperative networks to share experiences. They implemented various interventions such as diet, vitamins, behavioral modification, and specialized education. As a result, autism has emerged as a model of successful integrative medicine.

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Integrative autism management was first driven by the efforts of Rimland³ and the Autism Research Institute,⁴ then by its offshoot DAN! (Defeat Autism Now!),⁵ a collaborative network founded in 1995 by Rimland and 29 other scientists, parents, and physicians – many additionally motivated by being parents of autistic individuals. DAN! has generated an extensive collection of conference reports, practitioner referral services, assessment tools, and intervention protocols with the objective of transforming the autistic child into a productive adult.⁵ DAN! supports the current research consensus that autism is primarily organic in origin, while understanding that many of its features respond to psychological interventions.⁶ Brevity dictates that behavioral interventions and special education not be reviewed herein, except to state their utility for the autistic child is well established.⁷

In part I of this review,¹ it was documented that every ASD child has some combination of clinical and laboratory abnormalities (Table 1). Clinical improvement is difficult to achieve without individualized assessment of these abnormalities.^{1,2,6}

Getting Started: Recruiting the Parent

While complex medical assessments are in progress, a parent can do (or learn to do) many things to help the child. Parents can be pacesetters in helping the child become productive and happy, and can begin by keeping a day-to-day record of the child's life.

Table 1. Clinical and Laboratory Findings in Autism¹

Congenital: inborn errors of metabolism; prenatal susceptibilities; differing genetic load interacting with combinations of these factors
Biochemical peculiarities: impaired sulfoxidation capacity; multiple nutritional deficits
Central Nervous System (CNS): altered sensitivity to, and abnormal processing of, sensory and expressive information; neurotransmitter imbalances, sometimes with abnormal transmitters such as exorphin peptides
Gastrointestinal tract (GI): impaired digestion, bowel flora alterations, food intolerances, "leaky gut" – increased permeability to poorly digested food particles, peptides, microbial toxins, and other antigenic and metabolically active substances
Liver: impaired detoxification capacity, often with low cysteine, taurine, or glutathione levels
Immune system: abnormal hypersensitivity; abnormal antibody- and cell-mediated processes; pro-inflammatory cytokines; autoimmune antibody imbalance

Many parents have learned the value of detailed record keeping. Sidney Baker, MD, advises, "Do not depend on medical professionals to keep a clear record. Doctors generally keep lousy records."² He suggests organizing copies of lab results, consultation reports, and flow sheets of treatments and symptom progress. His published protocol provides blanks of a symptom flow sheet and a treatment list.² The Autism Brain Tissue Program circulates a set of "Quick Tips" to parents for keeping track of medical records.⁸ Suitably equipped, parents can be the physician's eyes and ears. Taking daily notes on the child's personal habits, diet, sleep patterns, and any changes, however miniscule, will help the physician more closely monitor the child's status. One essential early step is to change the child's diet.

Dietary Revision, the First Phase

Among practitioners familiar with autism, there is strong consensus that modifying the diet and the gastrointestinal system sets the stage for the success of other treatments, and therefore should come first.² Parents have found that, by closely regulating their child's diet, they can observe improvement, and that when dietary constraints are relaxed, the child often worsens. The recognition in recent years of a gut-immune-system-brain axis of pathology further supports this priority.⁹

Food Additives, Colorings, Sweeteners, Preservatives

Food additives can be a particular problem for autistic subjects. Although many of the worst offenders have been banned, others remain in the food supply. Two organizations, critical of irresponsible food additives, that publish useful information in this area are the Center for Science in the Public Interest¹⁰ and the Feingold Association.¹¹

Artificial coloring agents can have carcinogenic or mutagenic effects. Simple sugars and artificial sweeteners have adverse behavioral effects in some children. Lab tests (urine organic acids⁶) reveal abnormal carbohydrate chemistry in most autistic children. Baker urges the parent to test the sugar-avoidance diet by tapering off slowly over three weeks (to avoid withdrawal symptoms), then reintroducing sugar for five days, watching the results.² Whether or not the child has a strong adverse reaction to sugar reintroduction, Baker advises sugar in the diet be decreased because it is food for many potentially harmful intestinal dwellers.

For ASD children unusually food sensitive, the Feingold Diet is likely to be highly beneficial¹¹ by systematically excluding additives, colorings, salicylates, and preservatives. This and other more restrictive diets for integrative management of ADHD (attention deficit hyperactivity disorder) were previously reviewed.¹² Baker has published a list of additives least likely to affect ASD subjects.²

Removing Casein and Gluten Foods from the Diet

There is a great deal of evidence that foods containing casein or gluten contribute significantly to ASD and should be eliminated from the diet. In well-conducted studies, as many as 80 percent of ASD subjects improved following strict dietary exclusion of these proteins.^{13,14} Implementation of a strict casein- and gluten-free (CFGF) diet almost always leads to symptomatic improvement, and lays the foundation for a diet that can markedly benefit the condition.

It has been suggested that the adverse brain effects associated with dietary casein and gluten are likely due to opioid-acting peptides (small amino acid polymers, also called exorphins) metabolically generated from these proteins.¹⁵ In their Sunderland Protocol for autism, Shattock and Whiteley note that clinical improvement often occurs on the CFGF diet even when laboratory tests fail to detect such peptides in the urine.¹⁴ They suggest autistic subjects could be biochemically processing casein and/or gluten into other bioactive derivatives not being detected; or, while urinary levels measure normal, the quantities reaching the CNS could be high, perhaps due to abnormal permeability of the blood-brain barrier. Yet another possibility they suggest is children subjected to oxygen deprivation or other perinatal brain insults may have heightened vulnerability to even "normal" levels of the offending peptides.

Reichelt et al studied 15 ASD subjects (5 girls and 10 boys, age 3-17 years) for one year after implementing casein and gluten restriction.¹⁶ They reported that 13 of 15 showed some degree of behavioral improvement and none got worse, as judged from parent-teacher consensus. Seizure activity was decreased in 3 of 4 subjects; gross motor behavior improved in 13 of 15; social contact increased in 10 of 15; eye contact improved in 9 of 15; ritualistic behavior decreased in 8 of 11; language improved in 10 of 13; and sleep patterns normalized in 9 of 11. These investigators concluded that incomplete digestion of casein or gluten-gliadin by digestive peptidase enzymes could be a biochemical cause of autistic syndromes.

Since abrupt simultaneous removal of casein and gluten from the diet can cause withdrawal symptoms, a two-step phased withdrawal is appropriate. The first phase is removal of casein via removal of milk and other dairy products. From a 1995 trial, Lucarelli et al reported 66 percent of subjects showed benefits from this intervention.¹⁷ Benefits can manifest quickly – usually within 2-3 days in young children or 10-14 days in adults. However, a much longer period is required for casein to be fully cleared from the body.

Shattock and Whiteley documented the known metabolic dangers to children from consuming cow's milk.¹⁴ Milk consumption is linked to increased autism incidence among the immigrant population in Sweden as compared to the indigenous population.¹⁸ Some children are clearly addicted to cow's milk and will drink large quantities. Symptoms linked to casein intake include projectile vomiting; eczema, particularly behind the knees and in the crook of the elbow; white bumps under the skin; ear discharges and infections; constipation, cramps, and/or diarrhea; and respiratory disorders resembling asthma. Shattock and Whiteley report that casein withdrawal symptoms can be severe, especially in young children.¹⁴

Some higher-functioning ASD children voluntarily cease casein intake, apparently sensing it is not good for them. Gluten products, on the other hand, stir strong cravings and children are less likely to refuse them.¹⁹ Gluten exclusion requires the removal of several common cereals from the diet, wheat, barley, rye, and oats, in particular; but many other foods contain hidden gluten.¹⁹⁻²¹ The elimination process usually takes a minimum of 3-4 weeks, and a trial period of three months is appropriate. The urinary gluten profile persists for much longer than does the casein profile, and correspondingly the withdrawal effects are usually milder in severity than casein's, but typically more prolonged.

Full clearance of dietary casein-gluten symptoms is a long-term process. Withdrawal can be evident for three months or longer.¹⁶ Whiteley's group¹⁹ found a mere 26-percent reduction in urinary levels of gluten after a five-month exclusion diet. In some cases dramatic improvement

emerged a full 7-9 months after initiating the diet, but maximal improvement can require up to two years of rigid dietary exclusion. Shattock and Whiteley advise against adding these foods back into the diet, since severe opioid symptoms could result.¹⁴

Sensitivities to Other Foods

Whereas children with neurodevelopmental disorders frequently have sensitivities to common foods, ASD children seemingly have extreme sensitivity to a wide range of foods. These sensitivities may contribute to the perceptual and processing difficulties that typify autism, yet are difficult to objectify. The classic allergy symptoms such as stuffiness, eczema, wheezing, and itching may be absent, yet cognition and behavior remain affected.²

Once the main sources of food intolerance – casein, gluten, and gliadin – are removed from the diet, other foods may emerge as sources of symptoms. Parents, particularly those who keep food diaries, can often associate the child's consumption of a particular food with deterioration in behavior, sleep patterns, or performance. Beef, pork, rice, and potatoes are only occasionally implicated; whereas, foods that consistently cause problems are eggs, tomatoes, eggplant, avocados, red peppers, soy, and corn. Seroussi²¹ described how corn was revealed as a problem food only after strict removal of gluten and casein from the diet. If a particular food is suspected, it should be removed from the diet for a trial period of at least three weeks and any improvements noted. On being reintroduced into the diet, it will likely trigger an exacerbation of symptoms.

Even immune-mediated food allergy diagnosis can be challenging.⁶ Hospital-based laboratories often test for food allergy by measuring antibody levels, in particular IgE antibodies. But the food allergies seen in autism usually are not of the IgE-mediated, immediate hypersensitivity type that typically feature hives or sudden symptom onset. Rather, they tend to take hours or days to develop and often require cumulative exposure to the offending food. This suggests the allergy is mediated mainly by IgG rather than IgE antibodies.

Baker and Pangborn conducted two double-blind, placebo-diet controlled studies using IgG-ELISA (Enzyme-Linked Immunosorbent Assay) testing by reliable laboratories. Both trials demonstrated significantly better symptom reduction in subjects avoiding IgG-reactive foods versus IgG-nonreactive foods.^{2,6}

Food intolerances and sensitivities – a wide spectrum of reactions to foods or food constituents, sometimes highly nonspecific and not necessarily immune-mediated – are sometimes erroneously equated with food allergies, which by definition are immune mediated. While screening for serum antibodies can be a useful means to screen for suspected food allergens, it is unlikely to detect the full range of food sensitivities. For example, in the study mentioned above, Reichelt and collaborators¹⁶ examined 15 ASD subjects for serum antibodies to dietary proteins by ELISA (IgA and IgG) and for abnormal protein-peptide complexes in the urine. Just one-third of the subjects (5 of 15) scored abnormally high at baseline for antibodies to casein, gluten, or gliadin. They implemented dietary restriction of casein and gluten foods, and after six months urinary levels of protein-peptide complexes were down in every subject. After one year, 13 of 15 subjects were improved in at least some of 14 symptom categories. Although not double-blind, this study supports two other studies on casein and gluten restriction in which up to 80 percent of subjects improved.^{13,14}

While food allergy testing is confined to immune-mediated mechanisms, and can miss a much broader spectrum of food intolerances and other sensitivities, the basic approach to food allergy management closely resembles that for food intolerance; i.e., eliminate the food from the diet as completely and as early in life as possible. Thus, for the treating clinician, systematic dietary elimination of suspect foods is likely to have more clinical value than painstaking laboratory assessments for food allergy.

Perhaps due to wide-ranging difficulties with foods, children with autism are typically “picky” eaters who will often accept only a restricted range of foods. Further dietary restrictions

and removal of staple elements of the diet are likely to result in reduced intakes of vitamins, minerals, and other essential nutrients. Therefore, a nutrient supplementation regimen is always appropriate.

Nutrients Most Likely to Benefit Autism

A variety of nutrients have been reported as deficient or imbalanced in autistic children, with wide variability from child to child. Relatively little controlled research has been conducted on the benefits of dietary supplementation for the disorder. However, since 1967, the Autism Research Institute (ARI) has collected and periodically publishes semi-quantitative ratings of various nutrients.²²

The ARI developed the Treatment Effectiveness Survey questionnaire and provides them to parents, asking for a rating of each nutrient, drug, dietary modification, or other biomedical intervention. These are now available online.²³ Parents are asked to score “made better,” “made worse,” or “no effect.” Periodically the ratings are tabulated, and a “Better:Worse” ratio (B:W ratio) derived for the number of children parents judged got better versus worse. The cumulative nutrient data from 21,500 parents were summarized in April 2002.²⁴ This section covers those nutrients that, from clinical trials and/or the ARI’s B:W ratios, seem to offer the best benefit:risk ratio.

Multiple Vitamin-Mineral Supplements

Individuals with autism typically have poor nutritional status. They often have poor digestion (approximately 25 percent have chronic diarrhea; 25 percent have constipation).²⁵ Many have intestinal inflammatory conditions that limit nutrient absorption.²⁶ Often beneficial bacteria in the intestines are depleted, so fewer vitamins are produced by these friendly symbionts (vitamin B12, biotin, and vitamin K, in particular).¹ Rimland asserts that adults and half of ASD children benefit from multivitamin supplementation.²²

In 2000, Vogelaar reported on the nutrient status of 20 autistic children.²⁷ Over 50 percent of subjects had low levels of vitamins A, B1, B3, and B5, and biotin; minerals selenium, zinc, and magnesium; essential amino acids; and two essential fatty acids (omega-3 eicosapentaenoic acid (EPA) and the omega-6 dihomo-gamma-linolenic acid (DGLA)). Other clinicians report frequent deficiencies of vitamins B6 and B12 and folate. In 2002, Adams reported on a double-blind, placebo-controlled trial supplementing a multivitamin-mineral complex to 16 autistic children for three months.²⁵ Blood levels of vitamins B6 and C were significantly increased, and sleep and bowel patterns (parents' scores) were significantly improved. Multivitamin-mineral supplements for ASD children should not be supplemented with copper because it is one mineral they often have in excess.²⁸

Vitamin B6 and Magnesium

Vitamin B6, in its active form of pyridoxal-5-phosphate (P5P), is an essential cofactor for a majority of metabolic pathways of neurotransmitters, including serotonin, gamma-amino-butyric acid (GABA), dopamine, epinephrine, and norepinephrine. Magnesium is an essential macromineral required for a wide range of enzyme-catalyzed metabolic pathways. Rimland recently reviewed 18 autism studies conducted with vitamin B6, especially in combination with magnesium,²² and concluded that all provided positive results with no significant adverse effects. While no cures of autism by vitamin B6 are known, many cases of remarkable improvement have been documented.

A 1988 paper by Rimland provided an in-depth review of the history of vitamin B6 for autism.²⁹ In 1966, Heeley and Roberts reported vitamin B6 corrected abnormal tryptophan metabolism in 11 of 19 autistic children.³⁰ In 1968, Bonisch (cited in Rimland, 1988²⁹) reported vitamin B6 (100-600 mg per day) improved behavior in 12 of 16 autistic children. According to Rimland, three of Bonisch's subjects spoke for the first time while participating in this open trial.

After conducting an exploratory, non-controlled study in the early 1970s,³¹ in 1978 Rimland published the findings from a small double-blind trial that involved 15 children with autistic symptoms.³² In this trial only half the children involved qualified as ASD by current criteria.³² In this crossover trial, each child received vitamin B6 at a dose of 2.5-25.1 mg/kg body weight/day (75-800 mg per day) or a placebo. Following a complex, five-phase protocol, each child continued taking whatever vitamins, minerals, or drugs they had been receiving prior to the study and the duration of B6 dosing was individualized. Rimland stated they also received "several hundred" mg per day of magnesium and a B-complex vitamin to guard against overdosing with B6.²² Statistically significant benefits emerged from this trial, including better eye contact, less self-stimulatory behavior, more interest in surroundings, fewer tantrums, and better speech.³² Rimland began to suspect for many children autistic symptomatology might be a type of vitamin B6 dependency syndrome.²⁹

Following these promising findings, LeLord and colleagues were persuaded to further the research on vitamin B6 and magnesium for autism.²⁹ By 1981, after completing a number of studies, these researchers concluded vitamin B6 used with magnesium was a breakthrough autism intervention for about half the cases they studied.^{33,34} Urinary homovanillic acid (HVA) levels fell, an indication of improved metabolism of dopamine; and average evoked potentials (AEP), a measure of sensory processing ability, also were improved.³⁴

Rimland recently reviewed 18 studies on high-dose vitamin B6 for autism,²² with positive outcomes. Eleven were double-blind, placebo-controlled trials. One small study with negative outcome was criticized by Rimland for "obvious bias."^{35,36} Conducted by Findling et al, its sample size was 10 children.³⁵ Its design was double-blind, and included a crossover but no washout period was allowed between the B6 and placebo phases. Rimland³⁶ pointed out that the full outcome data were not provided. The authors admitted this study could not rule out benefit for vitamin B6 and magnesium in autism.

Taken together, the studies seem to establish that vitamin B6 can benefit as much as half of children and adults with autism, and that its efficacy and safety are improved when combined with magnesium. None of these studies reported any significant adverse effects, even though the vitamin B6 doses ranged as high as 1,000 mg per day. Rimland emphasized that thousands of autistic people have been taking large daily doses of vitamin B6 (as much as 1,000 mg) for decades without experiencing problems. One publication reported on seven cases of peripheral neuropathy from daily intakes of more than 2,000 mg vitamin B6.³⁷ These patients were not taking magnesium or other B vitamins, as usually recommended when taking large vitamin B6 doses; nor were they taking the active form – P5P – that has not been associated with toxicity. In a later study, doses of 30 mg/kg/day of B6 as pyridoxine hydrochloride (equivalent to as much as 2,100 mg for a 70 kg adult) were administered with 10 mg/kg/day of magnesium lactate to 11 autistic children for eight weeks; behavior significantly improved and no adverse effects were evident.³⁸ The latest ARI parent ratings in 2002²⁴ reported a B:W ratio for vitamin B6 used alone of 4.1:1, for magnesium alone 5.2:1, and for the combination of vitamin B6 plus magnesium, 11:1.

Cases of hereditary impairment of pyridoxine metabolism have been described, sometimes manifesting as seizure disorder and autism symptomatology.³⁹ Conversion of vitamin B6 to its active form P5P by the liver can be compromised in some autistic children. For these cases P5P supplementation may work more effectively, although hyperactivity is a possible adverse effect.⁴⁰ An intake threshold for achieving benefit may be approximately 200 mg vitamin B6 (as pyridoxine) and 100 mg magnesium per day for the 70 kg individual.⁴¹ In any case, the cumulative results from the double-blind trials and numerous other studies and case history reports are consistent with impressive efficacy of the combination of vitamin B6 and magnesium for autism, superior to either nutrient alone.^{38,42-44}

Dimethylglycine

Dimethylglycine (DMG) is an orthomolecule present in small amounts in foods, and is an important methyl donor with antioxidant character. Early feedback from parents promoted interest in DMG for autism; however, to date only three small autism studies with DMG are available.

Kun administered DMG to 39 autistic children (age 3-7 years) for three months;²² benefits were reported for 31 (80%). Kern and collaborators conducted a four-week, double-blind, placebo-controlled trial on 37 children age 3-11 years.⁴⁵ Both the DMG and placebo groups improved but with no significant difference between the two groups. The short period of this trial may have been insufficient for the full DMG benefits to emerge. Similarly, Bolman and Richmond⁴⁶ conducted a small, double-blind, short-term trial with low-dose DMG (125-375 mg/day) and found no significant results. The parent B:W ratio for DMG is currently 5.9:1, from 4,547 questionnaires.²⁴

The nutrient TMG (trimethylglycine; betaine) has a third methyl group, and some experts believe it could prove more clinically effective than DMG. To date the B:W ratio is less favorable for TMG, at 3.1:1 (182 questionnaires). It may be that DMG does more for the autistic subject than merely supporting methylation. Both these nutrients may best be taken earlier in the day to avoid the rare possibility of interference with sleep.

Rimland recommends children be started on DMG at a low intake (60 mg per day with breakfast), then titrated up to 500 mg per day. DMG usually begins to show benefit after 1-4 weeks and, in an occasional case, has had dramatic results within the first 24 hours. Although speech is the most consistent benefit, behavior might also improve. Seizures have been ameliorated by DMG, an important benefit since an estimated one-third of ASD subjects have seizures by adulthood.⁴⁷ Occasionally an ASD child will experience transient hyperactivity; administering folic acid and vitamin B12 with DMG lessens the likelihood of this effect.⁴⁸

Folic Acid

Folic acid is essential to numerous metabolic pathways. Its current B:W ratio is 11:1, from 1,100 questionnaires. Several researchers report folic acid has favorable effects on patients with autism associated with fragile X syndrome. LeJeune pioneered folic acid treatment of fragile X and, according to Rimland,²⁹ obtained favorable results on several non-fragile X autistic children by giving relatively large doses of folic acid (0.5-0.7 mg/kg/day).

Calcium

Bradstreet and Kartzinel report calcium and magnesium deficiency is common in autistic children.¹⁴ Landgrebe and Landgrebe found 22 percent of an autistic children sample had low 24-hour urinary calcium excretion.⁴⁹ ARI parents gave calcium a B:W ratio of 14:1 (988 questionnaires).

Vitamin B3 (Niacin/Niacinamide)

As with vitamin B6 and folic acid, this vitamin supports numerous pathways that sustain and renew the body's tissues. The current B:W ratio is 9:1.

Vitamin C

Vitamin C has a reputation for its involvement in a plethora of metabolic, antioxidant, and bio-synthetic pathways, and as a cofactor for certain enzymes necessary for neurotransmitter synthesis. In a double-blind trial for 30 weeks, vitamin C (8 g/70 kg body weight/day) improved total symptom severity and sensory motor scores.⁵⁰ Its current parent B:W ratio is an excellent 16:1, from 1,306 questionnaires.

Zinc

Among its many functions, zinc is needed for the development and maintenance of the brain, adrenal glands, GI tract, and immune system. Serotonin synthesis relies on zinc-activated enzymes; and zinc is also essential for antioxidant enzyme activity and other proteins important for growth and homeostasis. Breeding experiments with rodents indicate a zinc deficiency in the mother can

be passed on to the offspring and negatively influence immunity and brain development.⁵¹ Zinc currently has a very favorable B:W ratio, 17:1 from 835 questionnaires.

Zinc operates in a relationship with copper, i.e., when zinc levels go down, copper levels often go up. Bradstreet and Kartzinel assert zinc is deficient in 90 percent of ASD cases and copper in excess in 90 percent of cases.¹⁴ Walsh analyzed copper and zinc in the blood of 318 ASD subjects and reported finding abnormally elevated copper:zinc ratios in 85 percent.⁵² A smaller sampling of 22 subjects had 100-percent incidence of abnormally high, unbuffered copper (unbound to ceruloplasmin proteins) – about four times normal. Walsh's findings corroborate recommendations by Adams²⁵ and others that autistics should exclude copper from their multiple vitamins.

Essential Fatty Acids

Essential fatty acids (EFAs) function as homeostatic constituents of cell membranes, helping to relay signal information from outside the cell to the cell interior and are precursors to eicosanoids that influence other cells, similar to hormones. The longer-chain, 20- and 22-carbon species are crucially important for prenatal and postnatal brain development.⁵³

Biologically, the 18-carbon EFAs linoleic acid (omega-6) and alpha-linolenic acid (omega-3) qualify as vitamins since deficiency states are known. Some adults can generate the longer-chain EFA from the shorter-chain fatty acids, but infants are highly limited in this capacity.⁵⁴ Significantly, the C22:6 omega-3 (docosahexaenoic acid, DHA) and the C20:4 omega-6 (arachidonic acid, AA) occur in ample quantities in breast milk (around 4:1 omega-6 to omega-3). This confirms a major role for EFAs in postnatal development.

Essential fatty acids, particularly the omega-3s, are deficient in other neurodevelopmental disorders, including ADHD, dyslexia, and dyspraxia. These conditions have a striking degree of symptomatic, familial, etiopathological, and other biological overlap with the autistic spectrum.⁵⁵ Recently, in a unique workshop held at Inverness, Scotland, it was proposed

that abnormalities of fatty acid and phospholipid metabolism could help account for many features common to these conditions and to other neuropsychiatric disorders such as schizophrenia, bipolar disorder, and depression.⁵⁶

Studies on EFA deficiency in autism are few, but with consistent results. Bradstreet and Kartzinel found omega-3 fatty acids are deficient in nearly 100 percent of ASD cases.¹⁴ Vancassel and collaborators reported DHA 23-percent reduced, total omega-3s 20-percent reduced, and omega-6s unchanged in plasma phospholipids.⁵⁷ Hardy and Hardy studied 50 children with the more inclusive diagnosis Pervasive Developmental Disorder (PDD), and reported almost 90 percent omega-3 deficient via red cell analysis.⁵⁸

Controlled trials testing EFAs for their role in autism are clearly overdue. Stoll has outlined a research agenda that might be appropriate.⁵⁹ Still, physicians report autistic patients benefit from omega-3 supplementation. Fatty acid supplements (nature unspecified) currently have a B:W ratio of 12:1. Megson reported cod liver oil (CLO), rich in omega-3 EFAs and vitamins A and D, provided substantial benefit for autism.⁶⁰

Vitamin A

Vitamin A is especially important for cell growth and differentiation, especially in epithelial tissues of the gut, brain, and elsewhere. Megson reported on 60 children to whom natural vitamin A from CLO was administered for three months or longer.⁶⁰ Some cases exhibited marked improvement within days; core autism symptoms, such as language, eye contact, ability to socialize, and sleep patterns, were consistently improved. Megson noted that the natural vitamin A found in CLO is mostly in the “trans” form but about 12-percent is in the “cis” configuration, which is entirely lacking in synthetic vitamin A. Megson hypothesizes the cis-vitamin A of CLO is unblocking central retinoid receptors in the brain and G-alpha signal transduction proteins to which they are attached.

Although cod liver oil is unlikely to provide a sufficiently high content of omega-3 fatty acids to correct the extent of deficiency extant in

developmentally impaired children, and the possibility of vitamin A toxicity limits its upper dosing level, it still has good clinical value. It is important to avoid CLO contaminated with mercury and other heavy metals. The B:W ratio for CLO is 14:1, and for vitamin A (probably mostly the synthetic form) 22:1.²⁴ To the extent that the parent feedback ratings have meaning, a comparison of these specific ratios might cast doubt on the importance of natural as opposed to synthetic vitamin A.

Other Nutrients with Possible Autism Benefit

Bradstreet and Kartzinel claim poor diet results in vitamin, antioxidant, and fiber deficiencies in close to 100 percent of children with autism.¹⁴ Supplementation with vitamins as well as conditionally-essential nutrients such as taurine, coenzyme Q10, and carnitine may provide benefit.

Carnitine is an amino acid indispensable for energy generation. Although it is produced in the body, it may require supplementation. Valproate, a drug prescribed for seizures, is known to deplete carnitine.⁶¹ In one open-label study carnitine benefited patients with Rett Syndrome, a developmental disorder that shares features with autism.⁶² Constipation and self-abuse decreased while mood improved. A small, double-blind trial with 35 Rett Syndrome patients demonstrated clear improvement in well-being.⁶³

The pterin substances, biopterin and its precursor neopterin, are nutrient orthomolecules found naturally in body fluids, including urine. During periods of immune activation (as with autoimmune exacerbation) their levels in urine are increased.⁶⁴ Biopterin, in its reduced form (5,6,7,8-tetrahydrobiopterin, R-BH4), is a limiting factor for the biosyntheses of dopamine, epinephrine, and serotonin. Autistic children, particularly those six years or younger, can have relatively low R-BH4 in their cerebrospinal fluid (CSF) and abnormally high urine R-BH4, indicating increased loss from the body. Also, the enzyme (dihydropteridine reductase) that recycles biopterin into its biologically active reduced form, R-BH4, is lower in au-

tistic children younger than 12 years. In a pilot study, six autistic children, age 3-5 years, were treated with R-BH4 for three months.⁶⁵ All parents reported improvement in language, eye contact, and sociability. The CSF levels of R-BH4 were significantly increased. Positron emission tomographic (PET) findings were equivocal. The investigators suggested further investigation of R-BH4 therapy in autism.

Inositol is a precursor for the synthesis of phosphatidylinositol (PI), a phospholipid that is part of a complex cellular transmission pathway that facilitates serotonin receptor function. In double-blind trials it has been found safe and beneficial for depression, panic disorder, and obsessive-compulsive disorder. In a small, double-blind trial with nine autistic children, no significant benefits emerged.⁶⁶ The investigators conceded their efficacy measures were crude and suggested inositol be re-investigated.

Magnesium sulfate (Epsom salts) can benefit the autistic child through a novel route of delivery. A parent reported her child's oppositional behavior disappeared overnight after a bath in Epsom salts.⁶⁷ Other parents who used the treatment soon reported improvements in speech, mood, cooperation, and motor development.

Second Phase: The Medical Workup

Autism is not a condition that can be managed by frequent visits to a routine medical practice. Finding a physician experienced with ASD can be challenging, but is aided by the Autism Research Institute's referral service.⁴ Veteran DAN! practitioners Baker and Pangborn⁶

Table 2. Recommended Laboratory Evaluation of Autistics^{6,68}

- Blood chemistry screen, including thyroid tests
- Complete blood count
- Urinalysis
- Serum ferritin and iron
- Amino acid screen (urine)
- Organic acid screen for inborn errors of metabolism (urine)
- PKU screen, routine in the United States but not in some other countries
- Chromosome studies—Fragile X, Rett, Lesch-Nyhan (when indicated)
- MRI, CAT scan, or X-rays (when indicated)
- Electroencephalogram (when indicated)
- Landau-Kleffner screening (when indicated)

recommend a series of tests be undertaken promptly following diagnosis (Table 2).

Ruling Out Genetic and Metabolic Predispositions

The issue of genetic predisposition to autism has great clinical relevance and was reviewed in depth in part I. Autism undoubtedly has a strong heritability component, and sophisticated, noninvasive genotyping on siblings and other relatives will sometimes yield fruitful leads concerning the ASD subject's symptom patterns.²⁰

A number of congenital enzymatic weaknesses (inborn errors of metabolism) can mimic or contribute to ASD symptomatology (Table 3). Amino acid analysis can often give clues to their presence. Altogether, these abnormalities amount to compromised formation and balance of purines and pyrimidines that provide the bases of RNA and DNA.⁶⁸ Page discussed the sometimes-successful use of metabolites to override the metabolic weakness and improve autistic-like symptoms.⁶⁹

Table 3. Inborn Errors of Metabolism that Mimic or Contribute to Autism or ASD. From Pangborn^{6,68} and others⁶⁹

- PKU variants
- 5-Phosphoribosylpyrophosphate deficiency
- Fragile X
- Inosine 5-phosphate dehydrogenase weakness
- Histidinemia/Histidinuria
- Lesch-Nyhan disease
- Adenosine deaminase (ADA) weakness
- Adenylosuccinate lyase deficiency
- ADA binding protein weakness
- 5'-Nucleotidase superactivity
- Dihydropyrimidine dehydrogenase deficiency

Amino Acid Abnormalities

At least two-thirds of autistics have abnormal amino acid levels, as measured in 24-hour urine or fasting blood plasma. High phenylalanine is rarely seen (one per several thousand autistics) but can occur without overt phenylketonuria (PKU), which may be observed in children from countries that do not test for PKU at birth. High histidine (histidinuria and usually concurrent histidinemia) is seen in one per 250-500 autistics, and also can mimic autism. High urine levels of several amino acids (generalized hyperaminoaciduria) almost always indicate toxic chemical exposure and consequent liver damage. Such is also attributable to heavy metal contamination and Wilson's disease, Fanconi syndrome, cystinosis, fructose intolerance, galactosemia, and several other hereditary disorders.⁶

Low urine threonine suggests malabsorption. In maldigestion, anserine and carnosine are high, while the essential amino acids are low. Anserine and carnosine may also be high due to zinc insufficiency. When citrulline, methionine, ethanolamine, and phosphoethanolamine are elevated, functional magnesium deficiency is likely. Elevated sarcosine indicates toxic exposures and/or folate deficiency. And,

when detoxification capacity is limited, the cysteine/cystine ratio, and methionine, taurine, and glycine levels tend to be abnormal.

The essential sulfur amino acid methionine is occasionally found to be low, more frequently in subjects age four years or younger. Cysteine, another sulfur amino acid important for the formation of glutathione and taurine, is often low in young autistics and high in those older than five years. Since glutathione (GSH) is often low in ASD, a flaw in cysteine's incorporation into GSH could be involved. Cysteine abnormalities also would be consistent with the impaired sulfation and metallothionein synthesis often found in ASD.¹ Overall, the evidence suggests frequent impairment(s) in the pathway:

Methionine ⇒ S-adenosylmethionine ⇒ S-adenosylhomocysteine ⇒ cystathionine ⇒ cysteine ⇒ taurine

Pangborn found taurine deficiency is common in autistic children, reaching a 62-percent frequency on 24-hour urine analysis.⁷⁰ When taurine is low bile function is low, which can cause maldigestion and impaired liver detoxification capacity. Taurine is also a potent antioxidant, osmotic buffer in the brain and elsewhere, a pro-homeostatic neurotransmitter, and an immunoprotectant.

Glutamine is an energy source for enterocytes of the small intestine, helps form nicotinamide for energy transfers and glucosamine for connective tissue, and contributes to purine and pyrimidine nucleotides. Glutamine is also a building block for GSH. Glutamine is low in some autistics, particularly in those with an aversion to meat or poultry.

Autistic subjects who poorly metabolize tryptophan can carry its potentially toxic metabolite indoylacrylic acid (IAA) in their blood. IAA would normally be detoxified by combining it with glycine to make indoylacryloylglycine (IAG). Organophosphate pesticide contamination may shunt tryptophan down the IAG pathway.⁶

Tryptamine, found in tomatoes and all types of bananas, may also raise IAG levels. Certain citrus fruits also may contain tryptamine-like substances. Assays for IAG are not routinely available and are easily contaminated.

Clostridium bacteria that can produce neurotoxins in the intestines can also elevate IAG. A minimally absorbable antibiotic such as vancomycin can be useful,⁷¹ especially if given concomitantly with a high-potency probiotic re inoculation.⁷²

The DAN! assessment manual lists the laboratories best qualified to perform assays, and the pharmacies that custom-blend formulations for correcting measured abnormalities. They also list cautions to be observed when prescribing amino acid mixtures.

*Peptide Abnormalities*⁶

Peptides (small polymers of amino acids) act as regulatory or signal molecules, affecting a variety of neurotransmitter systems that regulate behavior. Certain peptides can be abnormally elevated in the urine of ASD subjects.⁷³ For example, as previously mentioned, high urinary levels of the dipeptides anserine and carnosine generally indicate poor digestive function.

Certain food-derived peptides have endorphin-like effects on the dopamine neurotransmitter system, and to differing extents also the cholinergic, serotonergic, noradrenergic, and GABAergic systems. In 1979, Panksepp suggested incompletely digested peptides with opioid activity could be causative in autism.⁷⁴ Thus began the “opioid excess” theory of autism alluded to in part I of this review. In 1981, Reichelt and colleagues reported abnormal peptides with opioid activity in the urine of 22 of 25 autistics studied.⁷³ Gillberg later found excessive levels of endorphin-like substances, later coined exorphins, in the CSF of autistics.⁷⁵

Dietary exorphins are peptides produced from incomplete digestion of casein or gluten foods – casomorphins, gluteomorphins, and gliadomorphins⁴ – all with powerful endorphin-opiate activity in the brain. Effective digestive

breakdown of these substances normally relies on only one, highly specialized peptidase enzyme called dipeptidyl-peptidase IV (DPPIV). Congenital weakness in DPPIV function was linked to autism by Stubbs in 1982.⁷⁶ The DPPIV enzyme is also highly sensitive to mercury and organophosphate xenobiotics.⁶ This metabolic weakness may be a cause of ASD by enhancing absorption of exorphins, leading to adverse reactions in the brain and to immune dysregulation.⁶⁸

In 1990 Shattock et al reviewed the various mechanisms by which opioid peptides may initiate perceptual impairment, stereotypic behaviors, self injury, and other autistic behavior.⁷⁷ They discussed how the blockade of dopamine receptors by opioids can result in spillage of dopamine into the CSF, or into the urine predominantly as homovanillic acid. High CSF and/or urine HVA is a frequent finding in subgroups of ASD children, and is an indicator of possible CNS insufficiency of dopamine.⁷⁷

To decrease the possibility of abnormal peptide production from foods, protein digestion can be improved by supplementing with digestive enzymes and betaine hydrochloride (HCl).⁴⁸ Since enzyme supplementation does not guarantee inhibition of exorphin production from casein and gluten foods, a strict casein- and gluten-free diet should still be considered.

Correcting Gastrointestinal Abnormalities

Many ASD individuals have GI abnormalities (see part I of this review). Maldigestion and malabsorption are common and combine with dysbiosis that commonly results from repeated antibiotic treatment. Chronic inflammation of the GI tract afflicts at least half of ASD subjects sampled, whether or not symptoms manifest.⁷⁸ Melmed et al reported that a study of 385 autistic people found 46 percent had chronic diarrhea, constipation, or other GI symptoms.⁷⁹ Horvath et al reported on 36 ASD children with chronic diarrhea, gas, abdominal discomfort and distension.⁸⁰ More than two-thirds had GI inflammation, associated with impaired digestive enzyme activity.

In 2002, Wakefield's group published a provocative overview of a pattern designated autistic enterocolitis,²⁶ featuring motility disorder combined with inflammation. They reported impressive improvement from the use of 5-aminosalicylates and a limited diet, including casein and gluten elimination, to decrease inflammation. The dysmotility could be due to exorphin actions directly on the GI tract. They discussed a scenario in which exorphins, such as gluteomorphin or gliadomorphin from wheat and beta-casomorphin from milk, escape digestion by the DPPIV enzyme due to gut damage. These substances can either be absorbed, reach the bloodstream, and travel to the CNS; or act locally to directly impair the intestinal wall motility.

Integrative practitioners have worked closely with laboratories to develop comprehensive assessments of GI abnormalities.^{20,68} One result of this effort is the comprehensive digestive and stool analysis (CDSA) that includes tests for digestive function (undigested food, for example), metabolic function (particularly short-chain fatty acids that reflect probiotic activity), microbiology (from bacterial culture), mycology (presence and types of yeasts and other fungi), and parasitology. The Biomedical Assessment manual from DAN! lists laboratories that offer CDSAs.²⁰

Frequent findings in autism are discussed below, together with some of the corrective approaches suggested by Baker and Pangborn in the DAN! assessment manual.⁶ For a more comprehensive list of options this manual should be consulted directly.

Bolte⁸¹ suggested the possibility of a subacute, chronic tetanus infection of the gut as an underlying cause of autism in some individuals. *Clostridium tetani* is a ubiquitous anaerobic bacterium that is opportunistic in the gut and produces a potent neurotoxin. This toxin can move from the intestine to the brain via the vagus nerve. Antibiotic treatment should be accompanied by high-potency probiotic replacement.

Correction of Intestinal Hyperpermeability (Leaky Gut)

The luminal-facing surface of the intestinal wall is only a few cell layers thick, yet it must function to efficiently absorb nutrients while acting as a barrier to prevent other intestinal contents from entering the bloodstream. A variety of insults can increase the permeability of this layer. A 1996 study by D'Eufemia⁷⁸ found that 43 percent of a sample of autistic children had increased intestinal permeability or "leaky gut" syndrome.

Inflammation commonly causes increased intestinal permeability.²⁶ Nutritional deficiencies; localized food intolerance or allergic responses; infection, *Candida* overgrowth, parasites; oxidant or inflammatory xenobiotic toxins; and drugs such as aspirin that can damage the protective mucus all may contribute to leaky gut. Integrity of the gut should be corrected before other modalities can optimally benefit autism.

The test for permeability is based on the differential absorption of two inert (non-metabolized) substances. Mannitol, a sugar alcohol, has low molecular weight and routinely passes across the healthy intestinal epithelium, later to be excreted in the urine. The lactulose molecule is larger and normally is not absorbed but passes with the feces. A urine-based test can detect signs of potential intestinal hyperpermeability from the amount of each of these two substances that reaches the urine.

Measures to correct intestinal hyperpermeability include correcting other intestinal abnormalities such as pancreatic insufficiency, dysbiosis, *Candida* or other fungal overgrowth, parasites, and so on. The diet should be redesigned to increase protein and fiber intake and lower digestible carbohydrates,² and constipation should be treated. When diarrhea occurs, viral activity should be considered and treated if indicated, but often this improves as reactive foods are eliminated. The amino acid L-glutamine can be supplemented, as a direct source of energy for the damaged enterocytes. To ensure the most efficient food digestion to minimize allergenicity, digestive enzymes with defined protease, amylase, and lipase activities can be comprehensively

supplemented. Betaine HCl supplementation may be useful and secretin therapy could be an option.

Effect of Secretin in Autism

Secretin is a small protein substance (27-amino acid polypeptide), a neuropeptide hormone normally secreted by cells of the upper intestinal tract. It is secreted in response to a bolus of food entering the stomach and stimulates the pancreas to release bicarbonate, which raises the pH of the intestinal environment so that the digestive enzymes later secreted by the pancreas can work optimally. It also stimulates release of bile from the liver and pepsin from the stomach. With GI disturbances reported in two-thirds of autistic children,⁸⁰ use of secretin supplementation seems rational. In laboratory rats, receptors for secretin were found throughout the brain, and secretin injected into the brain was demonstrated to activate the amygdala.⁸²

A “secretin craze” began in 1998, when reports circulated from an uncontrolled trial with just three autistic children.⁸³ Its findings indicated secretin therapy might dramatically improve socialization and communication abilities along with GI symptoms. Several controlled clinical trials of secretin since completed yielded mixed results. Single or double intravenous doses were not consistently beneficial under double-blind or other controlled conditions, but investigators were unable to rule out the possibility a subgroup of children may benefit. A meta-analysis conducted in 2000 left open the possibility of a response rate to secretin of one child in 10.⁸⁴

Drawing on an unpublished secretin study, Bradstreet and others have asserted that severely autistic children respond better to secretin than those only mildly autistic.¹³ Improvements were claimed for behavior, eye contact, and spontaneous communication. But in a double-blind, placebo-controlled, phase II, multi-dose trial conducted by the manufacturer,⁸⁵ parent ratings of significant improvement were not corroborated by professional raters. In Japan secretin is used intramuscularly (i.m.) as ulcer therapy. Shaw referred to a Japanese double-blind trial, using i.m. secretin, that claimed benefit of core symptoms

in 75 percent of a sample of autistic children.⁸⁶ This product was less purified, and Shaw suggested other enzymes in the preparation may have conferred additional benefits beyond those of secretin alone.⁸⁶

Herlihy⁸⁵ and Shaw⁸⁶ recently summarized the current information on secretin. Despite the lack of clear benefit found in controlled trials to date, case histories continue to suggest it may have utility for special cases. Secretin can be administered by oral, intravenous, intramuscular, or transdermal routes. Transdermal application is a highly convenient means of delivery and may be effective.⁸⁷ Secretin is safe and adverse effects are usually minor.⁸⁴ It is currently in phase III trial assessment.

Another hormone from the small intestine, cholecystokinin (CCK), works similarly to secretin. But sulfation deficits as seen in many autistics can compromise CCK’s activity.⁸⁸ CCK was reported by parents to be efficacious when taken by mouth. However, Shaw states that CCK can cause harm if handled inappropriately; the dosing and timing of its administration are critical and it should only be used under a physician’s supervision.⁸⁶

Heavy Metal Detoxification

The biochemical profile of autism frequently features heavy metal overload, complicating impaired detoxification, as documented in part I of this review.¹ The affected detoxification pathways are sufficiently understood that rational intervention with nutrients can effect clinical improvement. The heavy metal burden can be reduced by oral chelation. But for these interventions to have lasting benefit, ongoing exposure to heavy metals and other toxins must be lowered to as near zero as possible.

With toxin overload and intolerance to chemicals so common in ASD individuals, a “zero tolerance” stance is essential to medical progress.⁸⁹ Home, school, and other locales frequented by the ASD individual should be purged of toxic materials.⁹⁰

Mercury Chelation

Heavy metals contaminate the everyday environment and could contribute to ASD. While lead, cadmium, arsenic, and aluminum are suspects, the evidence for mercury as a causative factor is somewhat stronger.^{1,91} The visual disturbances, motor/coordination defects, and immune dysfunctions of autism are reminiscent of mercury poisoning.^{28,91} Young children have been exposed to mercury through vaccination at levels that exceed the U.S. Environmental Protection Agency's (EPA) safe limit.⁹² The mercury-based preservative thimerosal is widely used in medical solutions (e.g., RhoGam injection for Rh-sensitive mothers) and still contaminates some vaccines.⁹² Seafood intake or dental amalgams can load the pregnant woman with mercury, some of which may be transferred to the developing fetus. A number of practitioners report virtually all their autism cases show improvement following oral chelation for heavy metal removal.^{28,93}

Mercury continues to permeate the environment; air, water, and foods (especially marine fish) are contaminated, and mercury vapor from dental amalgams is a major emission source.²⁸ Mercury is toxic via many mechanisms. It depletes glutathione and other antioxidants, destroying antioxidant defenses; it impairs enzyme and receptor function; it poisons mitochondria, robbing the cells of energy; and it causes three-dimensional changes in proteins and other biomolecules, sometimes transforming them to autoantigens that promote autoimmunity. Mercury as thimerosal must be considered extremely toxic, inhibiting biological enzymes at very low concentrations. It likely has synergistic toxicity with aluminum, copper, and other heavy metals also present in the medical preparation.

In autistics, body mercury load is not directly reflected in results from hair analysis. For reasons still not understood, many ASD subjects exhibit lower hair mercury than the non-ASD population.²⁸ Some other, more esoteric tests for mercury intoxication are detailed by Cathcart⁹⁴ and by Laidler for the ARI's Mercury Detoxification Consensus Group.²⁸ Mercury appears to bind so tightly to proteins and other biomolecules that it is hard to dislodge, particularly in the tissues of

individuals afflicted with detoxification abnormalities. Following exposure, some mercury may be loosely bound and possibly detectable in the urine for a few weeks to months. After that the mercury becomes tightly bound to enzymes and other proteins, and is distributed to the liver, kidney, brain, and other organs with little remaining in the blood, hair, or urine. The best option for detection is a provoked urine excretion challenge, using a chelating agent that clears mercury via the urine.

Clearance of mercury from the tissues is a prerequisite for "fixing" homeostatic balance, detoxification capacity, and overall health status of the ASD subject. The best mercury chelators are DMSA (2,3-dimercaptosuccinic acid; succimer) and DMPS (2,3-dimercapto-1-propanesulfonic acid). DMSA is approved by the U.S. Food and Drug Administration (FDA) to treat lead poisoning in children, and is regarded as safer and better proven for this population. However, DMPS may work better for some subjects, including those who do not yield urine mercury with DMSA.⁹⁵ Lead, cadmium, arsenic, antimony, and other metals are also chelated by these agents and cleared via the urine; therefore, the urine analysis may show a number of toxic metals.²⁸ Some practitioners also monitor stool mercury levels during detoxification treatment.

To be conducted safely and effectively, mercury chelation is best entrusted to a qualified practitioner. Serious adverse side effects are rare but can occur, so professional monitoring and assessment is essential. For the subject to be considered for detoxification most physicians require:⁴⁸

- ◆ **Normal creatinine clearance**
- ◆ **No allergic reaction to a small sample of chelating agent**
- ◆ **Discontinuation of vaccines containing thimerosal**
- ◆ **Removal of mercury-containing amalgams (more of a concern with DMPS than DMSA)**
- ◆ **Vitamin, mineral, fatty acid deficiencies corrected**
- ◆ **Intestinal/GI health assessed and restored**

- ◆ **Seafood consumption cut (some sources may be allowed)**
- ◆ **Casein- and gluten-free diet**

The active detoxification process begins with the choice of chelating agent. Most often the first choice will be DMSA, due to more ample clinical experience with its use. Prior to starting the patient on DMSA, CBC and liver transaminase enzyme tests should be performed to obtain a baseline in the unlikely event the patient has an adverse reaction.²⁸ Blood urea nitrogen (BUN), creatinine, and creatinine clearance help establish normal renal function. As DMSA begins binding mercury, levels of this and other heavy metals should appear in the urine.⁹⁶ The schedule involves “on and off” cycles, in which the chelator is applied for a few days, then a rest period is taken for a longer period to allow for replenishing of essential trace minerals lost in the chelating process. The most common cycle is three days on and eleven days off the chelators (3/11); but 3/4, 5/9, or even alternating-days cycles have been used. The recommended dose is generally 10 mg/kg/day (total) in three divided doses between meals; higher doses may be used if the patient is monitored and accompanied by colonics.^{28,48,92} If adverse effects manifest, the dose can be lowered and given more frequently.

Cathcart, who uses a modification of the Holmes protocol,⁹² advocates that DMSA blood levels should be kept elevated throughout the day for best results.⁹⁴ He recommends DMSA at 6 mg/lb/day, in a time-release form prepared by compounding pharmacies. Serious adverse effects of DMSA are rare (for details consult the ARI Mercury Detoxification Consensus Group²⁸). Toxic epidermal necrolysis and Stevens-Johnson syndrome are absolute contraindications to DMSA therapy.

After the DMSA on/off cycle has been repeated several times, the urine should be tested for the progress of mercury clearance. Cathcart recommends this be done once per month.⁹⁶ He observes after 3-5 months the urine mercury usually falls to zero. This should mark the end of the body compartment clearance. Then comes a second phase, clearing mercury from the brain.

Since DMSA crosses the blood-brain barrier but does not readily extract tightly bound mercury from brain tissues, the Holmes and Cathcart protocols rely on DMSA to clear the body mercury first, then concentrate on the less accessible brain mercury by adding alpha-lipoic acid (ALA) to the DMSA. ALA is a potent glutathione repletor that readily enters cells and easily crosses the blood-brain barrier. A slow-release DMSA-ALA can be used.⁹⁶ During this phase urine mercury measurements and chelation are continued until mercury levels fall to zero. This protocol can be used to remove other heavy metals, including lead, cadmium, arsenic, and bismuth.⁹⁴

In 2001, Holmes reported at a DAN! conference on 152 ASD children, ages 1-18 years, treated with a detoxification protocol.⁹² She documented improvement in 83 percent of the total sample (126/152), but with a strong age gradient. Ninety-one percent of subjects ages 1-5 years demonstrated improvement; whereas, only 28 percent of those age 18 and above showed improvement. No one experienced marked improvement. Holmes noted that behavior sometimes worsened before improvement was noted. In some cases CNS autoantibodies and IgE-mediated allergies cleared following mercury clearance. Most common side effects of the chelation process were diarrhea and fatigue. Less common side effects included abnormal blood counts, liver enzyme elevation, and mineral abnormalities. The most rapid responders were younger children and those with a history of normal development followed by regression to autism.

Nutrient Support During Chelation

The DMSA chelation process can be very taxing on the patient because minerals other than toxic heavy metals are invariably chelated and require replacement by supplementation. Further, some minerals and vitamins actually assist the detoxification process. ALA not only may help chelate heavy metals but is important for replenishing GSH levels. Other nutrients to supplement during chelation are outlined in Table 4.²⁸ Aluminum apparently is not chelated by DMSA.

Table 4. Nutrient Supplementation for Heavy Metal Detoxification in Autistic Individuals²⁸

- A hypoallergenic multiple vitamin daily, during both chelation and non-chelation phases
- A hypoallergenic multiple mineral, during the chelation off days (should exclude copper)
- Alpha-Lipoic acid (ALA), preferably in combination with chelator⁹⁶
- Zinc – 2 mg/kg body weight/day, maximum 50 mg/day, only during chelation off days
- Selenium – 1-4 mcg/kg/day, preferably as L-selenomethionine
- Vitamin C – 4,000 mg/day up to bowel tolerance⁹⁴
- Vitamin E – 6 IU/kg/day, as mixed tocopherols. Soy sensitivity is possible
- Coenzyme Q10 – 100 mg/day
- Vitamin B6 – up to 500 mg/day, or P5P – up to 100 mg/day
- B complex, including generous folate and B12
- Glycine – 150-250 mg/day
- Melatonin – up to 0.1 mg/kg at bedtime, as a sleep aid when indicated

Brudnak makes a strong case that probiotics Lactobacilli and Bifidobacteria can assist with mercury detoxification.⁹⁷ The hypothesis is probiotics take up organic mercury from their surroundings, then convert highly toxic Hg²⁺ to Hg(0) via a redox reaction. Hg(0) is hydrophobic and volatile, allowing it to escape the bacterial cell into the intestinal lumen.

Clinical signs that can improve following mercury chelation include dilated pupils, increased heart rate, a mercury rash, excessive sweating, knee jerks, hand flapping, and others. Laboratory results that can indicate improvement include pyruvic acid (blood or urine), porphyrins (urine), glutathione (red cells), blood immune system markers (IgE, IgG, NK cells), and plasma sulfate levels. Some children improve while on DMSA, then regress whenever they discontinue it, even during the “off days” of the predetermined dosing cycle. The full significance of this pattern is not yet understood.²⁸

The ARI Consensus Group recommends that the supplements cysteine/cystine, N-acetylcysteine (NAC), and chlorella and other algae not be supplied during mercury detoxification.²⁸ They also caution that full benefits from mercury detoxification are unlikely if GI symptoms and especially dysbiosis were not previously corrected.

Liver Detoxification Support Following Mercury Clearance

In addition to mercury overload, the autistic population is documented to have higher xenobiotic pollutant load.¹ Edelson has reviewed a substantial body of evidence indicating environmental toxic exposure plays a role in the etiology of autism. He reports some patients have regained near-normal function after meticulous detoxification.⁹⁸

The cytochrome p450 system of detoxification is vulnerable to mercury poisoning. With mercury no longer present, the liver can restore its pathways of detoxification. GSH is the single most important resource for the p450 pathways⁹⁹ and is often found deficient in ASD individuals. This nutrient is absorbed into the cells of the intestinal mucosa, but does not enter the liver intact.⁹⁹ Since it does enter the intestinal mucosal cells intact, it may be useful for individuals with inflammatory intestinal symptoms. To best replete liver GSH, its precursors can be given, including glutamine, N-acetylcysteine, alpha-lipoic acid, and glycine. Phosphatidylcholine is also hepatoprotective as it is the primary phospholipid in hepatic cell membranes.¹⁰⁰

For the majority of ASD subjects, impaired sulfur metabolism places further stress on the liver. Sulfation is one of four major means for p450 phase II conjugation of xenobiotics, along with glutathione, glucuronic acid, and glycine.¹⁰¹ When sulfation fails these other pathways must take up the slack. Molybdenum, an essential trace mineral, is a cofactor for sulfite oxidase, the main sulfation enzyme, and magnesium also assists with sulfur metabolism. Methylsulfonylmethane (MSM) is a safe and effective sulfur source. Taurine, a sulfur-containing amino acid, is an antioxidant, bile salt constituent, and secondary p450 conjugant.

As previously established from non-autistic populations,¹⁰² poor sulfation capacity is linked to poor metabolism of dietary phenols. Pangborn advises that ASD subjects be shielded from phenolic xenobiotics (e.g., “Lysol” cleaner) and that foods high in phenols, such as bananas, onions, and coffee should be considered suspect.⁶⁸

Define and Treat Immuno-Inflammatory Imbalances

Inflammatory and immune hyperactivity states have considerable mechanistic overlap, and evidence links inflammatory cytokine imbalance to autoimmunity, both of which appear to contribute to ASD.^{1,103,104} In a recent review, Rimland and McGinnis conclude there is “clear-cut evidence of activation of the immune response system” in autism.¹⁰⁴ They further corroborate the argument that vaccines contribute to depressed immunity, autoimmunity, and inflammatory activation commonly seen in autism. Fortunately, from research on cardiovascular disease, arthritis, and other immuno-inflammatory diseases, nutritional interventions have emerged that show promise to help mitigate immuno-inflammatory imbalances in ASD populations.^{104,105}

Proteolytic enzymes such as bromelain and papain are well-documented anti-inflammatories and may well contribute to dampening inflammatory cascades in autism. Used in combination with other digestive enzymes and cofactors, they contribute to improved digestive efficiency and the correction of malabsorption.⁴⁰

Jyonouchi and colleagues¹⁰³ have documented inflammatory imbalance in ASD subjects by using measures of tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-6 (IL-6). The antioxidant vitamins C and E, and GSH may help lower these *in vivo*, but currently the most promising approach is generous dosing with long-chain, omega-3 fatty acids (LCFA-3),¹⁰⁵ in particular, EPA and DHA, appropriately screened for absence of mercury or other pollutants.

Ongoing work with clinical and animal models of inflammatory over-activation has established that inflammation can be inhibited by loading the cell membranes with LCFA-3. The omega-6 to omega-3 EFA balance in cell membranes helps determine the pro- to anti-inflammatory balance of eicosanoids the membranes can produce. Once produced, eicosanoids help regulate cytokine balance.^{104,105} Given that many, if not most, autistic children appear to produce excessive amounts of TNF-alpha and other pro-inflammatory cytokines,¹⁰³ it is reasonable to expect the anti-inflammatory LCFA-3s should offer benefit.

The rationale for LCFA-3 benefits – resetting the balance of prostaglandins and cytokines – can be extended to the management of pro-inflammatory coagulation states.¹⁰⁶

Treating Coagulation Abnormalities

Several integrative practitioners have reported seeing coagulation abnormalities in autistic children.^{14,107,108} ISAC (Immune System Activation of Coagulation) is the test panel most often used.¹⁰⁹ The rationale is that inflammation can trigger the conversion of circulating fibrinogen to fibrin deposits that then adhere to linings of the capillaries and other small vessels to occlude blood flow. The indicated treatment is usually heparin,¹⁰⁹ although LCFA-3 might prove efficacious in this situation as well, but may take months to demonstrate efficacy.^{104,105}

Bradstreet and Kartzinel reported finding vasospasm in autistic patients, which they treated successfully with Nimotop, a calcium channel blocker.¹⁴ This condition also might respond to long-term LCFA-3 dosing.

Immune-Based Treatments

Immune-based treatments include transfer factor (TF), pentoxifyllin (PXF), intravenous immunoglobulin (IVIG), and colostrum. Transfer factor is a low-molecular weight mix of molecules produced by white cells. Fudenberg,¹¹⁰ in an open-label study, treated autistic children ages 6-15 years with TF prepared from parents of children with autism. More than half of these children had autoantibodies to myelin basic protein (MBP), and half of them had depressed lymphocyte responsiveness to mitogens.¹ After TF administration a majority of this sample showed significant symptomatic improvement. Food sensitivities and symptoms associated with *Candida* overgrowth also decreased.

PXF is a drug approved in the United States for treatment of intermittent claudication, but also has immunomodulatory effects. Although it can affect many cytokines, it primarily suppresses TNF-alpha production.¹¹¹ TNF-alpha is one of the most pleiotropic and pluripotent cytokines known, and is consistently pro-inflammatory.¹¹² It is produced systemically, including by microglia and astrocytes of the brain, and is a suspected major contributor to inflammatory and/or autoimmune brain pathologies.^{113,114} An agent that effectively modulates TNF-alpha has potential efficacy for diverse neurodegenerative diseases.

In addition to cytokine-modulating effects, PXF has a number of other potential benefits for ASD subjects. Its hemorheologic properties include vasodilation, reduced platelet aggregability, and enhanced blood flow. It enhances serotonergic nerve transmission and can enhance long-term potentiation of electrical stimulation, a mechanism associated with learning and memory. Gupta and collaborators reviewed PXF's clinical features and several preliminary uncontrolled trials in autism.¹¹² Of a total 115 autistic patients treated with PXF, one-third experienced benefit. The most consistent benefits were increased attention and speech, improved sociability and behavior, and amelioration of seizure activity. Adverse effects, in a few patients, included nausea, vomiting, low blood pressure, headache, and (rarely) transient excitation or sleep

disturbance. The researchers concluded pentoxifyllin warranted further investigation for autism under double-blind conditions.

Intravenous immune globulin (IVIG) is prepared plasma using a highly involved purification process, from plasma donated by a large pool of donors (2,000-10,000), and contains predominantly monomeric IgG. IVIG has been used to treat a variety of antibody deficiency and autoimmune disorders, including neurological conditions such as chronic inflammatory demyelinating neuropathy and Guillain-Barre syndrome. This latter condition, like autism, features anti-MBP autoantibodies.¹¹¹ Since this material is in short supply, priority is normally given to children who exhibit failure to thrive, have significant serum autoantibodies or immune dysfunction, exhibit seizure disorders, or fail to respond to heavy metal detoxification programs.¹⁴

IVIG may work by correcting antibody deficiency, inhibiting TNF-alpha and perhaps other pro-inflammatory cytokines, or blocking an autoimmune response. In autism there are several clues that molecular mimicry and other autoimmune processes are operative. Among these are elevated urinary neopterin and biopterin, most likely resulting from TNF-alpha stimulation of immune cells.¹¹⁵ Serum autoantibodies to MBP were found in 58 percent (19/33) of autistic children.¹¹⁶ In a related study anti-brain autoantibodies reached 27 percent for IgG-type and 36 percent for IgM-type.¹¹⁷ Torrente et al reported finding autoantibodies bound to the surfaces of intestinal epithelial cells in children with regressive autism.¹¹⁸ A shift of T-helper cells from T-helper 1 to T-helper 2 – often seen in autoimmune conditions – was also reported in 13 of 20 children in a small study, as reviewed by Gupta.¹¹¹

Gupta's group conducted a small, six-month study with IVIG on 10 autistic children ages 3-12 years.¹¹⁹ IVIG was well tolerated and symptoms improved in a majority of patients. Behavior became calmer, eye contact improved, and in a few patients expressive speech improved. Children under five years showed more improvement and faster response.

Colostrum, the fluid expressed by the nursing breast for the first few days following birth, is another immune support agent under active scrutiny for possible benefit to autism.¹²⁰ Colostrum contains a wide range of immunoglobulins that generally boost immunity; antibodies, and other less specific antiviral factors; glycoproteins that inhibit the attachment of unwanted bacteria to the intestinal mucosal lining; significant amounts of the cytokine interleukin-10 (IL-10), transforming growth factor-beta (TGF-beta), and other potent anti-inflammatory factors; and various growth factors that promote cell growth, lymph node and other immune organ maturation, intestinal IgG production, and tissue repair. Interest in colostrum may be justified by the report of low levels of insulin-like growth factor I (IGF-1) in the CSF of children with autism;¹²¹ and by the presence of maternal autoantibodies in the neonatal infant.¹²²

Autism Pharmacotherapy

The autistic spectrum has been notoriously difficult to study in controlled fashion for numerous reasons, including extreme symptom heterogeneity, the need for long-term monitoring, and the complexities of doing research with children, particularly disabled children.¹²³ With the central problems of autism (lack of communication and social connection, for example) practically unresponsive to medications, pharmacological intervention has been restricted to efforts to manage symptoms such as aggression, self-injury, inattention, and stereotypical movements.¹²⁴ The ARI B:W ratings suggest most of these medications demonstrate poor performance.²⁴

Dopamine Antagonists

The dopamine receptor antagonists, or neuroleptics, are the class of drugs that have been most extensively applied to autism, haloperidol (Haldol) being the most studied.¹²⁵ With short-term use (four weeks), this drug was found consistently superior to placebo in decreasing motor stereotypy, hyperactivity, withdrawal, and negativism. Side effects included dystonic reactions, acute

dyskinesia, Parkinsonism, akathisia, and autonomic and cardiovascular symptoms. With long-term use (six months), haloperidol is effective in up to 70 percent of ASD children, but the adverse effects can be severe and include tardive or withdrawal dyskinesias in up to 29 percent of the children, anxiety and depression, sedation, restlessness, and lethargy. Weight gain that does not necessarily resolve when dosing is ceased can also occur. Haloperidol currently has a B:W ratio of 0.9:1.

Other dopamine receptor antagonists generally parallel haloperidol in their benefit-to-risk profiles.¹²⁵ The newer, "atypical neuroleptics" block both dopamine (D2) and serotonin (5-HT2) receptors and have more favorable side effect profiles. Clozapine initially looked promising; however, its B:W ratio is currently 0.4:1. Risperidone currently has the best benefit-to-risk profile, with a B:W ratio of 2.8:1.

A series of open-label clinical studies in children, adolescents, and adults has documented risperidone's promising clinical improvements.¹²⁵ In adults it was effective in reducing irritability, aggression, and repetitive and affective symptoms. The most prominent side effect reported was mild sedation. With children there was significant clinical improvement; however, up to 29 percent had adverse effects, including increased anger, aggression, and agitation; mild sedation; weight gain; restlessness; occasional liver damage; and dyskinesias.

In 2002 a placebo-controlled trial of risperidone involving 101 children was published in the *New England Journal of Medicine*.¹²⁶ Finding significant improvement of irritability and overall clinical impression in 69 percent of the drug group (12% for the placebo group), the investigators claimed the best degree of improvement ever seen for a medication to mitigate the behavioral symptoms of autism. Adverse effects included increased appetite and weight gain, averaging six pounds; fatigue and drowsiness; dizziness; and drooling.

Psychostimulants

Methylphenidate (Ritalin®) is the archetype for this pharmacological class, being the first line of drug treatment for hyperactivity, inattentiveness, and impulsivity, as occurs in ADHD (Attention Deficit/Hyperactivity Disorder).¹² Subjects with autism sometimes experience symptoms of ADHD, such as hyperactivity and distractibility. Ritalin's severe adverse effect profile was reviewed;¹² its B:W ratio is 0.7:1.

Tricyclic Antidepressants

Tricyclic antidepressants have mixed effects in autism. Clomipramine (Anafranil) reportedly improves stereotypic and self-injurious behaviors, anger and aggression, impulsivity, and social relatedness.¹²⁵ In controlled trials it proved superior to desipramine, a tricyclic noradrenergic reuptake inhibitor. But in a double-blind comparison trial with haloperidol, clomipramine was no more effective than placebo and subjects experienced severe adverse effects. Clomipramine can be cardiotoxic and exacerbate seizure disorders. Its current B:W ratio is 1:1, identical to that for desipramine.

NMDA Receptor Antagonists

N-methyl-D-aspartate (NMDA) receptors are a subclass of glutamate receptor that likely play a role in organizing brain circuitry during early development. Toxic or other adverse influences on NMDA receptors during brain development could conceivably contribute to ASD. Amantadine is an NMDA-receptor antagonist that may be marginally effective for hyperactivity and speech improvement.¹²⁷ Adverse effects include insomnia, sleepiness, tremors, confusion, poor concentration, depression, orthostatic hypotension, and hallucination (only at high dosages). This drug has antiviral effects, including against viruses that can affect behavior.¹²⁸

Serotonin Up-Regulators

Serotonin receptor agonist drugs have offered little benefit in autism. Fenfluramine, a halogenated amphetamine that boosts serotonin levels and blocks dopamine receptors, showed initial promise; later it was found ineffective and neurotoxic and was removed from the market.¹²³

Buspirone (Buspar), a serotonin 5T1 α -receptor agonist with anxiolytic and mildly antidepressant effects, has undergone only uncontrolled studies.¹²⁵ It can reduce affective lability, anxiety, and sleeping problems in disorganized and hyperaroused, autistic children. In developmentally disabled adults with autism, it can relieve anxiety, temper tantrums, aggression, and self-injurious behavior. Its B:W ratio is 1.2:1.

Fluvoxamine (Luvox) and fluoxetine (Prozac) are selective serotonin reuptake inhibitors (SSRIs), both of which may work better for autistic adults than children. Luvox may benefit repetitive behavior in adult subjects, but in children its benefits were insignificant and adverse effects quite severe.¹²⁵

Prozac, a more potent and selective SSRI than Luvox, may benefit obsessiveness and anxiety in autistic adults, but probably not compulsive behavior.¹²⁵ Another SSRI, sertraline (Zoloft), may also benefit adults. Children are likely to exhibit restlessness, anxiety, agitation, and insomnia in response to SSRIs. Prozac currently has a 1.2:1 B:W ratio, Zoloft a 1.1:1 ratio.

Naltrexone, Opiate-Receptor Antagonist

Autism has been consistently linked to opioid hyperactivation, whether from exogenous (food-derived peptides)¹⁹ or endogenous sources.¹²⁵ Naltrexone blocks the binding of heroin, morphine, or other opiates to brain receptors, and has been used since the early 1970s for drug addicts. Initial trials looked encouraging; however, it lost its allure after double-blind trials.¹²³ It may minimally reduce overactivity, but can worsen stereotypic behavior and has a bitter taste that affects compliance. The B:W ratio is 1.5:1.

Drugs Affecting Noradrenergic Receptors

Clonidine is a presynaptic alpha-2 adrenergic receptor agonist that up-regulates adrenergic transmission.¹²³ It may reduce hyperactivity, impulsivity, and irritability in the short term; but tolerance develops over time. Adverse effects include drowsiness, decreased activity, and hypotension. Its B:W ratio of 2.2:1 is better than most other autism drugs.

Miscellaneous Pharmacological Agents

When an autistic child exhibits a cyclic pattern or a bipolar mood disorder is suspected, treatment with lithium can be helpful.¹²⁵ Lithium may also be helpful for aggressive and self-injurious behavior. Its B:W ratio is 1.1:1.

Epilepsy afflicts 20-30 percent of children with autistic disorder,¹²⁵ and the anticonvulsant carbamazepine (Tegretol) can be useful. For antiseizure activity it has a good B:W ratio of 4.5:1. For its effects on mood and aggressive, irritable, or explosive behavior in autistic children, the ratio falls to 1.3:1. Valproate (Depakene) similarly has a B:W rating of 4.6:1 for seizures and 1.3:1 for calming behavior.

Judging from the existing knowledge base for autism, drug treatment may be most useful when symptoms associated with autism such as hyperactivity and inattention, aggression and self-injury, stereotypical behavior, rigidity, and anxiety interfere with psychosocial functioning or with other treatment approaches.

Conclusion

Autism continues to increase in prevalence, and remains an extreme challenge to medical management. Medically, autism's expression is so individualized that its management requires individualized care that only integrative medical practice can offer. Ethical integrative management supports parents' initiatives to explore options that offer negligible risk and any degree of benefit for the child. A ten-phase protocol for parent-physician collaboration for autism is presented in Table 5.

Nutrients predictably have broader effects and better benefit-to-risk profiles than drugs. The integrative practitioner, however, cannot always shun the use of drugs. As one example, many are forced to treat a substantial percentage of their patients with antifungal drugs if *Candida* overgrowth becomes intransigent. With a child's future at stake, it is appropriate to use the most effective therapies, within the acceptable limits for adverse effects. Integrative physicians usually give nutrients a chance before turning to drugs.

Evidence is accumulating that LCFA-3 status is deranged across a spectrum of neurodevelopmental disorders – from learning disorders and ADHD through the autistic spectrum. A newly published double-blind, placebo-controlled trial showed definitive, albeit incomplete, benefit from LCFA-3 for ADHD.¹²⁹ Since the LCFA-3s function as components of membrane phospholipids and preliminary evidence indicates the phospholipid phosphatidylserine (PS) benefits ADHD,¹⁰⁷ a trial of LCFA-3 and PS for autism is an attractive recommendation.

Autism remains a challenge to basic and clinical researchers. More in-depth studies are needed to clarify the relative contributions to ASD symptomatology from the perspective of: (1) genetic predispositions interacting with toxins or other etiologic triggers;¹ (2) maternal toxic burden, maternal antibodies against the child's antigens, and prenatal contribution to autism risk;¹²² (3) interactions between immune or detoxification impairment and vaccinations;¹⁰⁴ (4) pro-inflammatory cytokine imbalances in relation to anti-inflammatory nutrient status;¹⁰³ (5) likelihood of co-synergy between the intestinal, CNS, and immune abnormalities;^{9,26} and (6) contribution of autoimmune mechanisms to the overall condition¹²² and prospects for controlling such mechanisms.¹⁰⁵

In many difficult medical conditions treatment strategies can emerge that at first seem irrational but eventually may prove themselves. In autism one of these strategies may be bioresonance therapy, the use of frequency-customized sound waves to treat certain features of the disease. Careful and responsible investigation of this technique is currently underway.¹³⁰

Table 5. Ten-phase Integrative Protocol for Autism Management

1. Establish diagnosis, taking in-depth history. Initiate partnership with caregivers to implement detailed home record keeping.
2. Explore behavioral modification in cooperation with school and caregivers.
3. Supervise casein- and gluten-free, additive-free dietary modifications, tracked with food diary. Begin supplementation with multivitamin-mineral, vitamins B6, B12, and folate; magnesium; DMG; and omega-3 fatty acids.
4. Educate parents and all caregivers on zero tolerance for toxins. Test for mercury, other metals, and organochlorine pollutants as indicated.
5. Implement mercury chelation removal and nutrient support for detoxification.
6. Assess GI abnormalities: malabsorption, dysbiosis, intestinal hyperpermeability. Assess for gastritis-duodenitis-colitis and IgG/IgE food allergy testing. Supplement digestive enzymes, high-potency probiotics, prebiotics, glutathione, other GI nutrients.
7. Once detoxification and gastrointestinal healing is complete, test for vitamins, minerals, amino acids, essential fatty acids, and supplement as appropriate.
8. Check liver detoxification function; replenish liver support nutrients.
9. Test for immune system abnormalities: low white blood cell counts, antibody deficiencies, decreased lymphocyte proliferative response, cytokines, autoimmunity. Consider using nutritional and specialized immune therapies.
10. Periodically retest laboratory values and adjust management as indicated.

The ASD population is making steady advances toward improved quality of life and increased prospects for productivity. The marked degrees of benefit experienced by ASD patients have become a model for other challenging medical conditions that defy understanding. Spurred

by parent activism, practitioner commitment, and innovative organizational support, progress in understanding and treating autism has come from the power inherent in the integrative model of medical management.

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