Autism, An Extreme Challenge to Integrative Medicine. Part 1: The Knowledge Base

Parris M. Kidd, PhD

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for sameness, as seen in repetitive rituals or intense circumscribed interests.[1] Autistic children seem abnormally withdrawn, almost self-occupied, and out of touch with reality.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]

Parris Kidd, PhD (cell biology, University of California at Berkeley) – Contributing Editor, *Alternative Medicine Review*; health educator and biomedical consultant to the supplement industry.
Correspondence address: 847 Elm Street, El Cerrito, CA 94530

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.

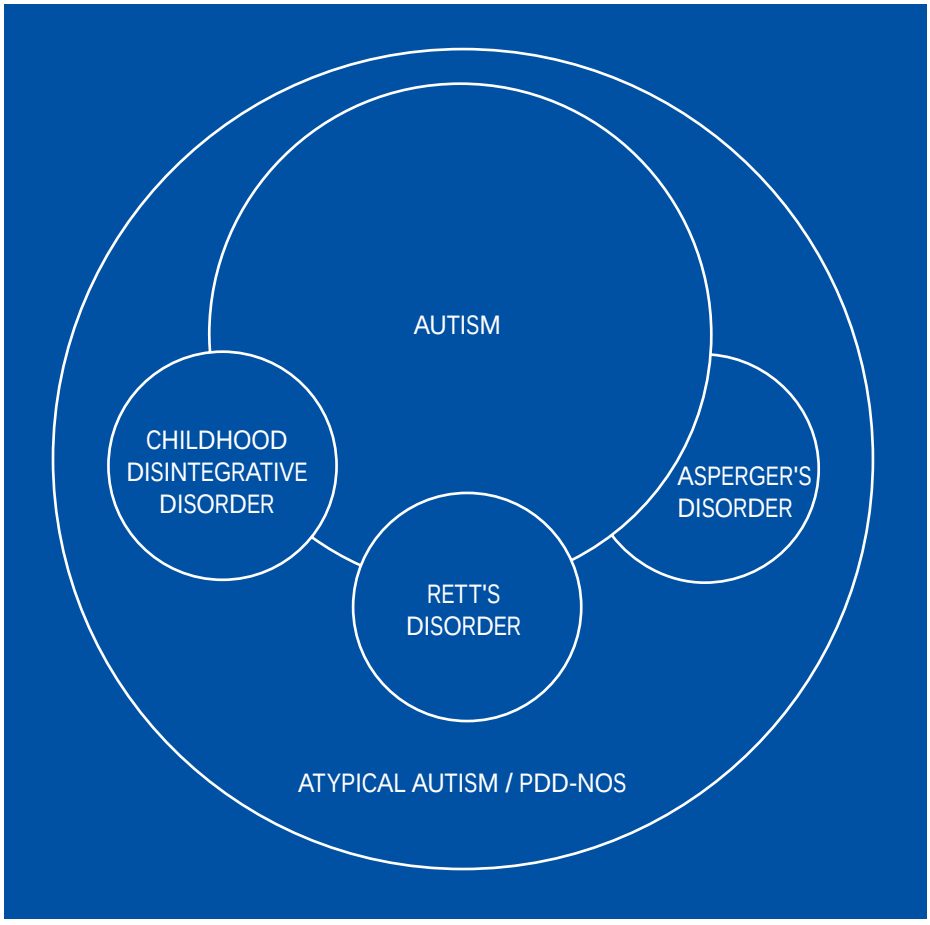
Emergence of the Disorder

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 Disorders*[16]



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.

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 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 epilepsy[17] 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 nonroutine 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.

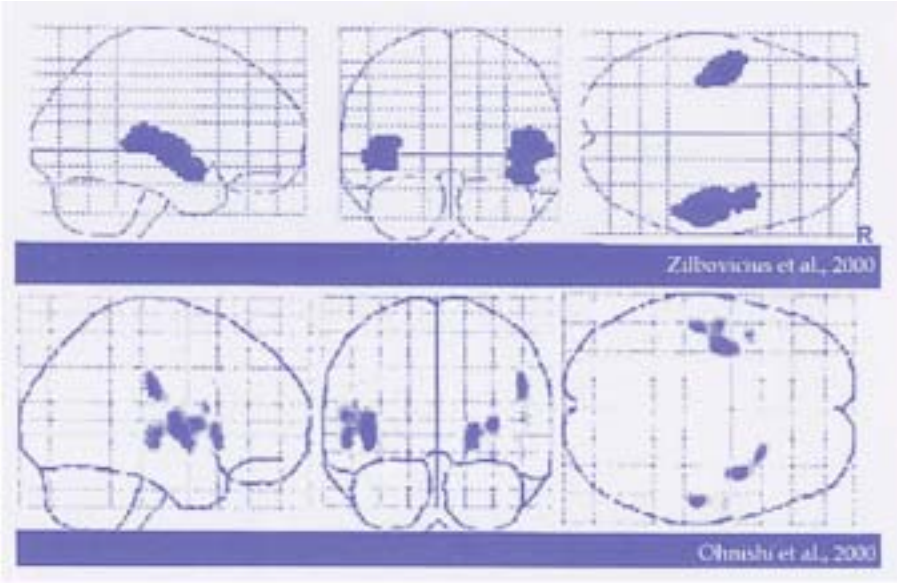
Structural magnetic resonance imaging has failed to detect consistent changes in autism.[9] In different studies, both atrophy and normal mass

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 study[37] 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 al[38] 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 al[39] 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 colleagues[40] 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 autism[9] 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 urinalysis).[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]

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%

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 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*

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

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 colleagues[70] 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'Eufemia[67] 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 exorphin 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 children[83] 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-1β, 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-a 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 sTNFRII, 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 al[93] 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 Warren[87] emphasize that many different inflammation-related mechanisms can be triggered or modulated by autoantibodies to damage the autistic brain.

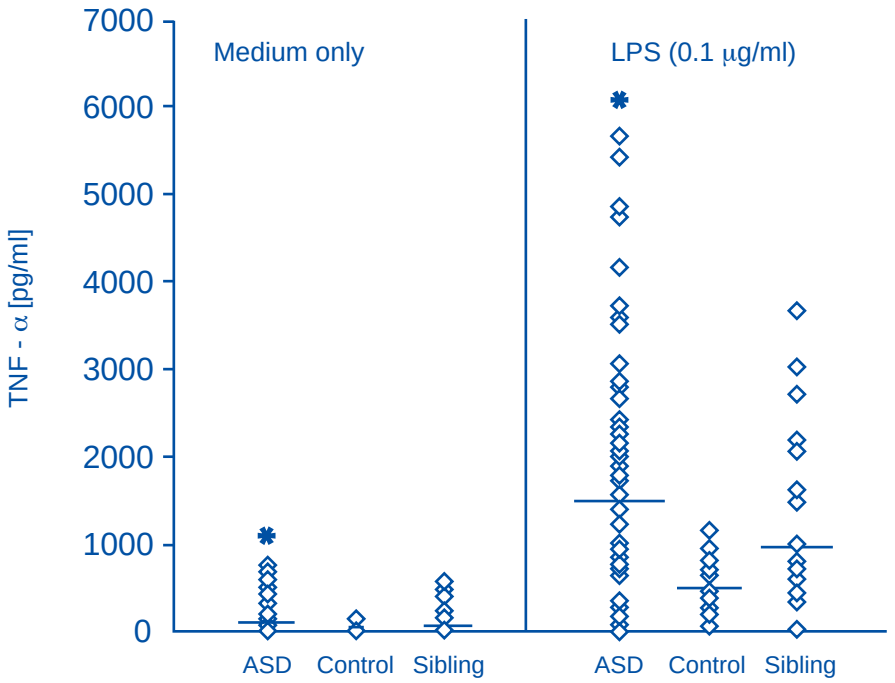
The data on abnormal immune system involvement in autism is fragmented but substantial. Further studies are needed to clarify the potential etiological contributions from immunogenetics, cytokine imbalances specific to the brain, and autoimmune potential from autoantibodies against brain biomolecules.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

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]

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

(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 assessed[100] 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 Symptomatologies

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 Killing[112]

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 quantitative 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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