ABSTRACT

Because speech is usually delayed or absent in children born with autism, and lost when seemingly normal children regress into autism, impairment of the left hemisphere of the brain is implicated. Executive functions of planning and impulse control are often impaired or absent, and autistic children are emotional, impulsive, musical, and artistic – right hemisphere attributes. Children with the autistic disorder Asperger syndrome, by contrast, speak timely with good grammar and logic, but without emotion or empathy. These observations argue Asperger syndrome is a distinct disorder of left-hemisphere laterality, with little right-hemisphere communication. Autism (including high-functioning autism) looks like a disorder of right-hemisphere laterality, though with some left-hemisphere specialization. Dysconnections and atypical anatomical, functional, neurochemical, and blood flow asymmetries have been reported. Evidence that the antitoxin/antioxidant glutathione matures myelin as well as sustains release of the primary vasodilator nitric oxide argues glutathione depletion is a key mechanism in autistic disorders – keeping brain blood flow low, myelin immature, and hemispheres dysconnected and asymmetric.

INTRODUCTION: LEFT HEMISPHERE HYPOTHESIS OF AUTISM

Geschwind and Galaburda ... point out that the left hemisphere normally completes its development later than the right hemisphere and is thus subjected to prenatal influences, some of which can be detrimental, for a longer period of time.... A 'pathology of superiority' was postulated, with compensatory growth in the right brain as a result of impaired development or actual injury to the left brain. Treffert DA Savant Syndrome [1]

Certain aspects of autism are obvious though little understood. As different as autistic behavior looks from child to child, it is recognizably autistic. Herbert noted autistic behavior has been seen in many disorders, including metabolic, allergic, digestive, and epileptic conditions. “What is it about brain biology that may allow many different underlying biological mechanisms to produce a set of behaviors that look so similar?” she asked [2]. One explanation may be that these disorders all elicit a stress response, shifting brain dominance to the right hemisphere – first responder to threats present and potential [3]. Do rightward dominance shifts induce autistic behavior because autism is a disorder of right-hemisphere asymmetry? But then what explains persons with the autistic disorder Asperger syndrome, who appear left-hemisphere dominant?

Signs of left hemisphere impairment are delayed or absent speech in children born with autism, and loss of speech when apparently normal children regress into autism. Executive functions of planning and impulse control are usually deficient or absent, and these children (and adults) are emotional, impulsive, musical, and artistic – right hemisphere attributes.

Tucker and Williamson, in their monumental Asymmetric neural control systems in human self-regulation (1984), reported early conclusions about hemispheric laterality [4]: “Finding that the two hemispheres take opposite approaches to problem solving – the left hemisphere structures information analytically and the right hemisphere perceives holistically – Levy (1969) speculated on the origins of hemispheric specialization: Analytic and synthetic cognitive processes may have evolved in specialized hemispheres because they are inherently incompatible, requiring different forms of neural organization.... When an analytic perceptual or conceptual structure is required, the left hemisphere seems to be called upon, even with nonverbal stimuli. In contrast, the right hemisphere’s contributions appear most important when a global or holistic organization of the stimulus information is necessary.... The left hemisphere excels at tasks that require the ordering of cognitive operations sequentially, whereas the right hemisphere appears more adept at parallel processing.”

They noted considerable evidence the right hemisphere is essential for emotional communication: “Right-hemisphere lesions disrupt the patient’s ability to understand emotion conveyed by facial expression or tone of voice. Certain
right-hemisphere lesions cause speech to become monotonous, without meaningful affective intonation. . . . The right hemisphere’s skill in dealing with the nonverbal, analogical representation of information seems requisite to emotional communication.... Some evidence suggests that the left hemisphere may normally control and inhibit emotionality.”[4] [my emphasis]

Brogaard and Marlow discussed the left hemisphere hypothesis of autism, and differences between autism and Asperger syndrome. Asperger children speak without delay, with proper grammar and logic: “The different patterns of left-versus-right-sidedness in different individuals with autism line up with the old distinction between autism and asperger syndrome. On the old classification, autism required marked language deficits, whereas asperger syndrome did not. Many children diagnosed with asperger syndrome exhibit the same social difficulties, adhere to a rigid routine, and so on, but perform normally or above normal in left-brain activities like complex language, reasoning, mathematics and sensory integration. . . . The left hemisphere hypothesis ... also explains regimented behavior, unusual attention to or avoidance of sensory input, social impairment and enhanced low-level perceptual memory processing. Studies show enhanced activation in the amygdala, the main fear-processing center, in autistic subjects during attended face processing and other types of sensory processing. This suggests that autistic individuals may be processing too much emotionally relevant information ....”[5] [my emphasis]

Schreibman distinguished Asperger children from autistic children by their unusual use of language: “[C]hildren with Asperger’s Disorder are likely to exhibit deviance as opposed to delay in language and communication. It has been noted that while they are not delayed in the acquisition of language form (semantics, syntax, phonology), other aspects of their communication are distinctly disordered. These other aspects relate to the use of language, generally referred to as pragmatics. Their use of language for social intercourse may be characterized by one-sided, pedantic, egocentric ‘conversation’ in which they are quite verbose regarding a topic of their own (perhaps idiosyncratic) interest. Their conversation is typically devoid of real emotion and may be largely objective and practical. . . . [I]ndividuals with Asperger’s Disorder exhibit fewer symptoms of social difficulties, and their social problems, while clinically significant, are not as severe as those seen in individuals with autistic disorder. Whereas children with autism may at best be passive or aloof in social situations, and at worst actively avoidant of social contact, children with Asperger’s tend to be just socially clueless.”[6]

Floris and colleagues revisited the left hemisphere hypothesis of autism [7]: “Many people with ASC [autism spectrum conditions] show a pattern of deficits in skills ascribed to the left hemisphere, such as language, communication and symbol use, whilst appearing relatively unimpaired in right hemisphere functions such as visuospatial abilities.... Further evidence for this ‘left hemisphere dysfunction’ theory stems from neuroimaging studies showing a reversal of asymmetry in language-related regions such as the inferior lateral frontal cortex ....

“There is a close link between cerebral lateralization and connectivity, with more strongly lateralized brains relying on less inter-hemispheric transfer.... One of the most reliable findings is that consistently right-handed men have a smaller corpus callosum than non-consistently right-handed men.... [O]ne might assume that hemispheric lateralization might not only relate to callosal size but also co-occur with callosal asymmetries. As there is an inverse relationship between cortical asymmetry and corpus callosum volume, global callosal size reductions (in association with greater hemispheric and functional lateralization) may be mediated by regional right or leftward callosal reductions, depending on which hemisphere exhibits dominance....

“Rightward asymmetry of several callosal subregions such as the splenium, the rostral body and the posterior midbody were associated with increased symptom severity.... Contrary to the other results, asymmetry of the rostrum did not show rightward disadvantage. Rostral rightward asymmetry was instead associated with higher IQ scores and less severe communication impairment.... This raises the question of whether not only impairments in high functioning autism, but also strengths of the condition such as high IQ or good systemizing skills, might be related to the same atypical pattern of lateralization in the same way.”[7]

Ozonoff proposed the primary deficit in autism is impairment of the frontal lobes and their executive functions of impulse control, planning, and flexible thinking: “Some features of autism are reminiscent of the executive function deficits that follow frontal injury. The behavior of autistic people often appears rigid and inflexible; many children with autism become distressed over trivial changes in the environment and insist on following routines in precise detail. They are often very perseverative, focusing on one narrow interest or repetitively engaging in one stereotyped behavior. They may be impulsive, having trouble delaying or inhibiting responses.... Finally, autistic people often seem narrowly focused on details and have difficulty ‘seeing the big picture.’”[8] Yet analysis of detail is a left hemisphere function, and “seeing the big picture” (gestalt) a right
hemisphere attribute [5]. Evidence indicates the left hemisphere also has executive functions (see Evaluation).

ANATOMICAL AND FUNCTIONAL HEMISPHERIC ASYMMETRY IN AUTISM

Jayasundar and Raghunathan reported early asymmetries detected in healthy human brains: “In right-handed subjects, almost all the regions in the brain, such as frontal, parietal, temporal, occipital, thalamus and cerebellum ... exhibit both structural and functional asymmetries. For example, in the frontal lobes, variability of the gyral pattern has been found to be greater in the left hemisphere. In the parietal lobes, associated with a lower sylvian point, the left post central gyrus, particularly its lower portion, is wider than the right. In the temporal lobes, which have been most extensively studied because of their reported role in speech and language, the planum temporale has been found to be consistently larger in the left hemisphere.... In general, a greater density of cells has been reported in the left than in the right hemisphere and the left is more extensively fissured than the right.”[9]

Herbert and colleagues used magnetic resonance imaging (MRI) to measure partial/whole-brain volume asymmetries in children with high-functioning autism [10]: “[A]symmetries were masked with larger units of analysis but progressively more apparent with smaller units .... [A]utism ... had a greater aggregate volume of significantly asymmetrical cortical parcellation units [PUs] (leftward plus rightward), as well as a substantially larger aggregate volume of right-asymmetrical cortex .... [T]he shift in right : left ratios of volume asymmetry is driven wholly in autism ... by an increase in aggregate volume of asymmetrical PUs on the right....

“Since the bulk of interhemispheric cortical communication relies on information transfer via the corpus callosum, these larger brains with their disproportionately smaller corpus callosum sizes may experience greater than normal constraints on interhemispheric transfer of information .... Moreover, the white matter volume increase driving the larger total brain volumes ... shows a regional bias, with larger radiate white matter and a sparing of deep white matter.... This possible disproportionate increase in intra-hemispheric connections, along with a bottleneck in inter-hemispheric linkages, should further increase the likelihood of functional lateralization and anatomical asymmetry.”[10] [my emphasis]

A year earlier Herbert et al. observed: “The radiate white matter enlargement that we have found ... has important implications for pathogenesis and developmental timing.... The radiate volumetric increase is most likely the footprint of a pathogenic process that in some way altered the development of later-myelinating white matter.... The distribution of volume changes is not consistent with an increased number of cortical neurons driving an increase in axon number but instead suggests a process that alters some nonaxonal component of white matter, possibly myelin.”[11]

A pervasive rightward shift in functional hemispheric laterality in autistic children and adolescents was reported by Cardinale and colleagues. Using functional MRI (fMRI), they detected rightward asymmetry in visual, auditory, motor, language, executive, and attentional networks: “Hemispheric asymmetry is a fundamental feature of human brain organization. Differences in the columnar organization between hemispheres support an early-onset specialization of the left in fast temporal analysis of auditory and other sensory information.... The results of our study suggest that atypical rightward asymmetry may be a general feature of brain organization in ASD, affecting many different functional brain systems.”[12]

Wittling concluded the human stress response resides largely in the right hemisphere: “The right hemisphere is endowed with a unique response system preparing the organism to deal efficiently with external challenges. Therefore, both the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenomedullary axis seem to be under the main control of the right hemisphere.... [N]eural systems mediating arousal, vigilance, and outward-directed attention are more efficiently represented in the right hemisphere. With respect to emotional responses, this hemisphere is activated highly by psychosocial stress and negatively appraised situations.”[3] Does this rightward shift from stress explain why many different disorders show autistic behavior [2]? But stress doesn’t provoke autistic behavior in healthy children – or does it?

Forrester and colleagues studied lateralized hand preferences in ASD children [13]: “Recent evidence suggests that ASD is likely to have an early developmental onset characterized by hypo-lateralization of brain function for expressive and receptive language processes long before there is visible behavioral evidence of language impairment.... [T]ypically developing children have a right hand dominance for hand actions to objects and a left hand dominance for hand actions for self-directed behaviors [SDBs], revealing a possible dissociation for functional specialization of the left and right hemispheres .... Children with autism demonstrated mixed-handedness for both target conditions, consistent with the hypothesis that there is reduced cerebral specialization ....”
They noted usual handedness patterns: “It is commonly reported that the human population exhibits approximately 90% right-handedness and, within the right-handed population, approximately 95% of individuals have language-processing regions situated in the left hemisphere of the brain .... Additionally, 70% of left-handers also demonstrate left cerebral hemisphere dominance for language .... [H]and dominance (left or right) for manipulative tasks (e.g. drawing) has been associated with typical neurodevelopment, whereas inconsistent hand dominance has been associated with significantly lower developmental assessment scores in children .... A growing body of evidence now indicates that reduced cortical lateralization is associated with impaired cognitive function and can manifest behaviorally as mixed-handedness.... [C]hildren with ASD who possess either left or right hand dominance, generally tend to have stronger language capabilities, compared with mixed-handed children with ASD....

“A functional dissociation between hand preference for controlling hand actions for object manipulation and SDBs is consistent with an evolutionary functional distinction between the two hemispheres such that the left hemisphere is dominant for structured sequences of actions (e.g. tool use and language), and the right hemisphere is dominant for actions that are the manifestation of emotive processing (fight or flight).... In humans, the right hemisphere hypothesis considers the right hemisphere to be dominant in all forms of emotional expression and perception, while the valence theory posits that the left hemisphere dominance is ... for positive affect and right hemisphere dominance for negative affect.”[13] Soper and Satz described “ambiguous handedness” in persons with autism[14].

Eyler and colleagues used fMRI to study lateralized responses to spoken language in sleeping 2–3-year-olds later diagnosed with autism. They found unusually weak responses in the left temporal cortex, unusually strong responses in the right temporal cortex: “Results indicated that at-risk toddlers later diagnosed as autistic display deficient left hemisphere response to speech sounds and have abnormally right-lateralized temporal cortex response to language; this defect worsens with age, becoming most severe in autistic 3- and 4-year-olds.... [W]hereas typical toddlers show the expected pattern of left side dominance in response to stories, toddlers with autism exhibit reversed or absent laterality patterns. Specifically, toddlers with autism display stronger activation on the right ... in the anterior portion of the superior temporal gyrus, the brain region most strongly responsive to language sounds in typically developing toddlers. This abnormal lateralization is consistent with studies of older autistic children and adults.”[15]

ASYMMETRIC LOW BRAIN BLOOD FLOW

Ohnishi and colleagues determined regional cerebral blood flow (rCBF) in autistic children in relation to symptoms: “Decreases in rCBF in autistic patients ... were identified in the bilateral insula, superior temporal gyrus and left prefrontal cortex.... [P]atients’ behaviours could be classified into two syndromes: (i) impairments in communication and social interaction; and (ii) an obsessive desire for sameness. Factor I ... was associated with altered cCBF in the left medial prefrontal regions, including the anterior cingulate gyrus.”[16] Meresse and colleagues found low blood flow in the superior gyrus of the left temporal lobe in ASD children: “The more severe the autistic syndrome, the more rCBF is low in this region, suggesting that left superior temporal hypoperfusion is related to autistic behavior severity.”[17]

Burrioni and colleagues detected global and asymmetric reduction of brain blood flow in autistic children: “[A] significant difference was also observed for the right-to-left asymmetry of hemispheric perfusion between the control group and autistic patients with a right prevalence greater in autistic ... children. Our data show a significant decrease of global cerebral perfusion in autistic children ... and the existence of left-hemispheric dysfunction, especially in the temporo-parietal areas devoted to language and the comprehension of music and sounds.”[18]

Degirmenci and colleagues detected asymmetric hypoperfusion in autistic children (AC) and their family members: “Hypoperfusion was seen in the right posterior parietal cortex in three AC, in bilateral parietal cortex in one AC, bilateral frontal cortex in two AC, left parietal and temporal cortex in one AC, and right parietal and temporal cortex in one AC. Asymmetric perfusion was observed in the caudate nucleus in four AC.... In parents of AC, significant hypoperfusion was noted in the right parietal and bilateral inferior frontal cortex. In siblings of AC, perfusion in the right frontal cortex, right nucleus caudate and left parietal cortex was significantly decreased.”[19]

Floris et al. concluded: “These alterations of typically occurring asymmetries are corroborated by findings based on single photon emission computed tomography [SPECT], and positron emission tomography [PET] showing atypical or reversed cerebral blood flow in frontal language regions. Other brain regions have been implicated, too. Computerized tomography scanning reveals increased cerebral blood flow in the right temporal and right parietal lobes.”[7] Herbert suggested swollen astrocytes and microglia constricting capillaries might explain brain hypoperfusion in ASD[20].
Geschwind and Galaburda (1985) proposed that fetal testosterone slows development of the left hemisphere in male infants: “(1) [L]eft-handedness is usually found to be more common in men than in women. (2) The developmental disorders of language, speech, cognition, and emotion, eg, stuttering, dyslexia, and autism are strongly male predominant. (3) Women are on the average superior in verbal talents while men tend on the average to be better at spatial functions. (4) Left-handers of both sexes and those with learning disabilities often exhibit superior right-hemisphere functions. (5) Left-handedness and ambidexterity are more frequent in the developmental disorders of childhood. (6) Certain diseases are more common in non-right-handers, eg, immune disorders. The human brain is asymmetrical even in fetal life with a pattern resembling that seen in adult life .... There is probably some influence that slows the growth of parts of the left hemisphere so that ... the corresponding regions on the right side develop relatively more rapidly. It is postulated, on the basis of the higher frequency of sinistrality and of learning disorders in men, that this influence is related to male sex, eg, testosterone or some factor related to it.”[21]

Asperger observed that the autistic personality is an extreme variant of normal male intelligence [22]. Pursuing the implications, Baron-Cohen and colleagues presented six clues that fetal testosterone (FT) is high in children with autism: (a) FT induces ring fingers longer than index fingers (low 2D-4D ratio); (b) girls with high levels of adrenal testosterone before birth have more autistic traits than their sisters; (c) as FT increases, behaviors characteristic of autism increase; (d) evidence of hypermasculinization; (e) precocious puberty in boys; (f) elevated levels of serotonin [23]. Excessive testosterone before birth, they explained, exaggerates the normal tendency of male brains to be larger than female brains – a difference caused by white matter tracts within cerebral hemispheres enlarging at the expense of white matter tracts connecting the hemispheres.

Brogaard and Marlow emphasized asymmetry of the inhibitory neurotransmitter serotonin in ASD, which processes fear in the amygdala: “Reduced serotonin increases amygdala activity ... by being coupled to ... GABA, which is the brain’s main inhibitory chemical. When the serotonin levels are high enough, the GABA system is activated, and that inhibits fear.... Several studies have suggested that autism may be a syndrome of one of the brain’s two hemispheres, with decreased synthesis of serotonin in the left (or sometimes the right) hemisphere.... More recent PET studies of serotonin synthesis have confirmed the abnormal asymmetry of cortical serotonin synthesis in children with autism. The studies found cortical asymmetries of serotonin synthesis affecting the left or right cortex. In one study serotonin synthesis was decreased in the frontal lobe in 90 percent of cases.”[6] [my emphases]

Jayasundar detected by magnetic resonance spectroscopy (MRS) brain asymmetries of N-acetyl aspartate (NAA), creatine/phosphocreatine, and choline in healthy right-handed males: “Significant interhemispheric differences in the distribution of metabolites were observed for all the regions studied [parietal, occipital, temporal, frontal, thalamus, and cerebellum].... [A]ll the metabolites showed a consistent right-shift in thalamus and frontal regions and a left-shift in cerebellum and parietal regions.... While both structural and functional asymmetries have been reported in thalamus, asymmetric blood flow to the cerebellar hemispheres in resting volunteers has been reported ....”[24]

AMYGDALA HYPOTHESES OF AUTISM

Considerable evidence implicates the amygdala in autism – a gray matter structure in the temporal lobe of each hemisphere intimately involved in fear and the stress response. Amygdalae are larger in normal males than in females, with many androgen receptors [25]. Mosconi and colleagues used MRI to measure amygdala volumes in boys and girls with autism 18 to 35 months old; their right and left amygdala volumes were significantly larger than controls [26]. Schumann and Amaral studied autistic male brains post mortem, detecting early proliferation of neurons in the amygdala: “[T]he amygdala of children with autism reaches adult size before adolescence, whereas typically developing children undergo a progressive growth of the amygdala through adolescence.... [W]e found that younger children with autism plus mental retardation had a 16% larger right amygdala and a 13% larger left amygdala than typically developing controls.... We found that young children with autism on average have a 16% larger amygdala than controls, whereas young children with Asperger syndrome have a 9% larger amygdala than controls.”[27]

Baron-Cohen and colleagues [28] also implicated the amygdala, viewing autism as a primary impairment of the “social brain” described by Brothers (1990), comprised of the amygdala, orbito-frontal cortex, and superior temporal sulcus and gyrus: “In humans the most common emotion following amygdalar stimulation is fear, accompanied by its autonomic manifestations (dilation of the pupils, release of adrenalin, and increased heart rate).... [T]he left amygdala appears to be specifically activated in emotion processing. The autism group appears not to perform the task using the amygdala, but
instead place a greater processing load on temporal lobe structures, specialized for verbally labelling complex visual stimuli and processing faces and eyes. This may arise as a compensation for an amygdala abnormality.... [In terms of neurochemistry, the amygdala has the highest density of benzodiazepine/GABAa receptors in the brain, and also has a substantial set of opiate receptors. It contains serotonergic, dopaminergic, cholinergic and noradrenergic cell bodies and pathways.... The fMRI study provides strong evidence of the role of the amygdala in normal social intelligence, and abnormality of the amygdala in autism.... If there is an role of the amygdala in normal social intelligence, and pathways.... The fMRI study provides strong evidence of the role of the amygdala in normal social intelligence, and abnormality of the amygdala in autism.... If there is an role of the amygdala in normal social intelligence, and pathways.... The fMRI study provides strong evidence of the role of the amygdala in normal social intelligence, and abnormality of the amygdala in autism.... If there is an role of the amygdala in normal social intelligence, and pathways....]

Dziobek and colleagues, revisiting the amygdala hypothesis, found little association between amygdala volume and emotional and social cognition in adults with Asperger syndrome (AS), but an association with repetitive behaviors [29]. They noted volume measurements might not detect microstructural variations: “[P]ost-mortem studies of individuals with autism have revealed an increased cell packing density and smaller neuronal size in limbic regions including the amygdala... [W]e know that in healthy individuals there is usually a close association between amygdala volume and overall brain size. Consequently, the dissociation between amygdala volumes and brain size in the individuals with AS may be indicative of structural abnormalities in the amygdala.”

Markram and colleagues proposed an alternate theory of amygdala dysfunction in autism – intense world syndrome: “The current version of the amygdala theory of autism assumes a hypo-functional amygdala, which leads to lack or inappropriateness of social behavior in autism. In this view, autists fail to assign emotional significance to their environment and for this reason are not interested in others, do not attend to faces, and fail to engage in normal social interaction. However, based on the result in the VPA [valproic acid] model of autism and observations obtained in autistic humans, we propose that this view may be not correct and that quite to the contrary, the amygdala in the autistic individual may be hyper-reactive which leads to rapid excessive responses to socio-emotional stimuli. In this view, the autistic person would be overwhelmed with emotional significance and salience. As a consequence, the subject would want to avoid this emotional overload and would have to withdraw from situations, such as social encounters, which are rich in complex stimuli.”[30][my emphases]

WHY ARE AUTISTIC CHILDREN TIMID?

Despite extensive observations corroborating the extreme male brain theory of autism [23] – e.g. masculinization of these children, aggressive violent behavior, precocious puberty in boys, even high testosterone in amniotic fluid – two anomalies remain unexplained. First, as Markram et al. observed, children with autism are often extremely anxious, even timid, in the presence of others. According to Konner [31] early pioneers of autism research Niko and Elisabeth Tinbergen detected signs of fear in these children in social situations, and “reasoned that exceptionally timid children might be at risk for developing the disorder if they grew up in a sufficiently threatening – or perhaps for them, merely a very intrusive – social environment.” Konner noted infants do not fear strangers nor separation from mother until about four to six months old, when the nerve tracts of the limbic system myelinate rapidly. Markram et al: “Kanner’s original case studies (1943) suggested that some of the autistic children he observed exhibited abnormal anxiety levels and phobias. More recent studies have also suggested abnormally high anxiety levels and phobias in children with ASD and their relatives.”[30]

Because testosterone allays fear [31], why are autistic children anxious, even timid, in the presence of others? One explanation may be prenatal stress, which elevates maternal and fetal adrenal androstenedione, a weak androgen precursor of testosterone (and estrogen) that suppresses testosterone release from the fetal testes. Ward: “[I]t appears that stress causes an increase in the weak adrenal androgen, androstenedione, from the maternal or fetal adrenal cortices, or from both, and a concurrent decrease in the potent gonadal androgen, testosterone.”[32] Release of androstenedione and testosterone from the testes is triggered by luteinizing hormone from the pituitary – which high adrenal androstenedione suppresses by negative feedback. Androstenedione becomes testosterone in peripheral tissues including the brain, or becomes estrone then estradiol, the primary estrogen [33]. Jasuja and colleagues: “Administration of 1500 mg 4-androstenedione daily to hypogonadal men significantly increased serum androstenedione, total and free testosterone, estradiol, and estrone levels and suppressed SHBG [steroid hormone binding globulin] ....” [34]

Jacklin and colleagues assessed timidity in infants by their reaction to fear-provoking toys. Low timidity in boys was associated with higher levels of testosterone at birth – but not androstenedione [35]. Taylor and colleagues studied effects of adrenal steroid precursors androstenedione (4-A)
on sexual behavior in male rats: “These results suggest that DHEA and 4-A are not merely precursors of sex hormones, and provide support for these steroids influencing the brain and behavior in a unique fashion that is dissimilar from the effects of TS [testosterone] on male sexual behavior.”[36].

Geier and Geier found that ASD children had high levels of serum/plasma DHEA and testosterone, and low levels of methionine, cysteine, glutathione, and other cysteine metabolites. They noted DHEA can convert to androstenedione and then testosterone, or be sulfated to the “normally favored storage molecule” DHEAS. Because sulfation of DHEA requires glutathione as cofactor, they proposed that glutathione deficiency in these children causes less DHEA to convert to DHEAS and more to androstenedione and testosterone [37]. DHEAS from the fetal adrenal cortex is the most common precursor of placental estrogens critical to fetal growth and maturation [38] – including maturation of myelin.

Do prenatal stress and sulfate/glutathione depletion masculinize the brain of a male fetus via weak androgens – and myelinate via inadequate estrogens? Is a brain differentiated by androstenedione and DHEA more timid – and dysconnected – than a brain differentiated by testosterone and estradiol? An amygdala differentiated by androstenedione and DHEA more reactive and fearful?

Another challenge to high prenatal testosterone is the certainty the brain overgrowth of autism happens after birth, not before. Courchesne and colleagues found that children with autism have smaller heads at birth, then a sudden excessive increase in head size beginning a few months after birth and lasting six to 14 months: “[O]ur study found evidence of neonatal brain undergrowth followed by rapid and excessive postnatal brain growth beginning in the first few months that precedes the clinical behavioral onset of autism.”[39] This sounds like postnatal catch-up growth in infants born prematurely or whose fetal head growth was restrained [40]. Or was it triggered by the usual testosterone surge from the testes in male infants a few months after birth [41]? Courchesne et al. didn’t mention the surge; some of the infants they studied were girls.

Herbert [42] reviewed the pathology of these large brains in ASD: disproportionate proliferation of white matter, yet diminished connectivity, and neuroinflammation and astrogliosis. She and her colleagues previously found the increased brain volume was confined to the subcortical white matter, especially in the frontal lobes, and did not include the deep white matter, e.g. corpus callosum: “This lack of expected association between radiate compartment and corpus callosum volume suggests that the white matter volume increase predominantly involves short and medium-range corticocortical connections within hemispheres, with less, if any, involvement of connections between hemispheres.”[11]

Intra-hemispheric white-matter tracts are testosterone-dependent, inter-hemispheric white-matter tracts estrogen-dependent [23]. If postnatal brain overgrowth in ASD is catch-up growth, overgrowth of testosterone-dependent structures implies prenatal undergrowth of the structures. Yet lack of estrogen might also explain smaller brains at birth. But then why doesn’t postnatal brain overgrowth favor estrogen-dependent structures?

HEMISPHERIC DYSCONNECTION AND ISOLATION

The landmark study and theory by Just and colleagues (2004) of language comprehension in high-functioning autistics speaks for itself [43]: “One of the enigmas of autism in high-functioning individuals is the juxtaposition of some domains of preserved or even enhanced cognitive function, coupled with domains of deficit. In particular, previous behavioural studies of the processing of language in high-functioning autistic individuals have reported a preserved or even enhanced ability in the narrower-scope task of reading individual words, coupled with a deficit in the broader-scope task of processing grammatically complex verbal instructions ... thus epitomizing in microcosm the enigma of autism....

“In a number of previous studies, LIFG (left inferior frontal gyrus) or, more informally, Broca’s area, was involved in a number of processes that could play an integrating role in sentence comprehension .... A second key area in sentence comprehension is the more posterior LSTG (left superior and middle temporal gyrus), or more informally, Wernicke’s area, which has particularly been associated with lexical processing.... A PET study of sentence listening in five high-functioning autistic participants showed less left-lateralization (compared with the control group) in the peri-sylvian and temporal areas. Moreover, a morphometric study has shown that these two areas, LIFG and the posterior LSTG, show a reversal of the usual left–right size asymmetry in high-functioning autistic boys (ages 7–11 years), in whom the left-hemisphere homologue is smaller than the right....

“The autistic participants showed significantly more activation in LSTG and significantly less activation in LIFG, as compared with the control participants. A plausible interpretation of this finding is that ... autistic participants
engage in more extensive processing of the meanings of the individual words that comprise a sentence, manifested as more LSTG (Wernicke’s areas) activation, which is consistent with their hyperlexicality or unusual strength in processing single words. At the same time, the autistic participants showed less activation in LIFG than the control group. LIFG ... is associated with semantic, syntactic and working memory processes, all of which serve to integrate the meanings of individual words into a coherent conceptual and syntactic structure. The reduced activation in this region is consistent with the finding that high-functioning autistic participants are impaired in their ability to process the meaning of complex sentences. . . .

“We propose that autism is a cognitive and neurobiological disorder marked and caused by underfunctioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels.... The theory predicts that any facet of psychological or neurological function that is dependent on the coordination or integration of brain regions is susceptible to disruption .... The dissociation between intact or enhanced simple abilities and impaired higher order abilities is a recurring profile across cognitive and neurological domains in autism including the motor, memory, language, abstract reasoning and probably also sensory domains.” [43]

Geschwind and Levitt proposed a unifying model for autistic disorders based on frontal lobe disconnection: “[H]igher-order association areas of the brain that normally connect to the frontal lobe are partially disconnected during development. This concept ... can accommodate the specific neurobehavioral features that are observed in autism, their emergence during development, and the heterogeneity of autism etiology, behaviors and cognition.”[44] Nordahl and colleagues, scanning the corpus callosum by MRI, concluded: “In older children, adolescents and adults with ASD, the corpus callosum is consistently reported to be smaller, with decreased fractional anisotropy and reduced interhemispheric functional connectivity.”[45] [my emphasis]

The anterior commissure may be as dysconnected in ASD as the corpus callosum. Guyton and Hall: “[T]he anterior commissure plays an important ... role in unifying the emotional responses of the two sides of the brain.... Fibers in the corpus callosum provide abundant bi-directional neural connections between most of the respective cortical areas of the two cerebral hemispheres except for the anterior portions of the temporal lobes; these temporal areas, including especially the amygdala, are interconnected by fibers that pass through the anterior commissure.”[46]
Distinguishing Aspergers from HFA clinical. Roy and colleagues [50]: “The prevalence of Asperger’s syndrome in childhood is estimated at 0.02% to 0.03%. Asperger’s is far more common in boys ... with a sex ratio of 8:1.... Since the core symptoms of Asperger’s syndrome persist throughout patients’ lifetimes, we can assume that Asperger’s syndrome is probably not much less common in adults....

“Because of their lack of empathy, persons with Asperger’s syndrome may have difficulties to make contact with potential partners in an appropriate way. In a developing or existing relationship they may appear selfish or cold.... In early childhood autism according to Kanner, the inability to make contact in a nonverbal manner is often accompanied by incomprehensible or lacking speech. Affected children display extensive stereotypical and unusual activity patterns. The clinical impairment in Kanner autism is more pronounced than in Asperger autism. The distinction of Asperger’s syndrome from the so-called high functioning autism has been much discussed. Compared with patients with early childhood autism, high functioning autists have greater intellectual and better social and communicative abilities, but overall their cognitive and speech development is delayed....

“The executive functions comprise skills such as planning and monitoring one’s own actions, inhibiting impulses, focusing attention, and flexible searching for problem solving strategies. In patients with Asperger’s syndrome, the executive functions are often impaired. The patients are inflexible in their attention and can use newly acquired behaviors only with difficulty.”[50]

speech. Semanticists Faust and Kenett investigated the unusual speech of Asperger children and adults [51]: “[W]e suggest that language is always a whole brain process and thus processing any type of language, including metaphors, requires integration between systemized, more rigid semantic processing associated with the left hemisphere (LH) and more flexible semantic processing associated with the right hemisphere (RH)... This continuum includes LH hyper-rigid and rule-based semantic processing on one extreme (e.g. in persons with Asperger syndrome (AS), and RH chaotic and over-flexible semantic activation on the other extreme (e.g. in persons with schizophrenia)....

“At the morphological level, there are a few distinct asymmetries between the LH and the RH, such as the LH impaired or isolated right hemisphere. What evidence supports or disputes this argument?

Asperger syndrome before DSM-V

Lehnhardt and colleagues summarized the diagnosis of adult Asperger syndrome published in DSM-IV [49]:

“Disturbance of social interaction
The main feature is a lack of intuitive understanding of the rules of interpersonal relations. From early childhood on, the affected person stands out as socially isolated with little interest in initiating or maintaining friendships, particularly with age peers. The existing types of social contact may be eccentric or highly self-centered. Family members often perceive the affected person as cool and selfish, but also as highly reliable, honest, and free of cultural or sexist prejudice. There are marked difficulties in the appropriate assessment of the context of social situations (“weak central coherence”) and in the assumption of other people’s emotional perspectives—i.e., empathy, which is the ability to recognize other people’s feelings, intentions, and attitudes, to create an image of them in one’s own thoughts and emotions, and to feel them vicariously. Another way to characterize this is as an impaired ability to ‘mentalize’ ... an impaired ‘theory of mind.’

Impaired communication
There is a marked impairment in the perception, interpretation, and implementation of mutually modulated, context-driven nonverbal communication, e.g., facial expressions, prosody, body posture, and gesticulation. Eye contact may be noticeably elusive, or, alternatively, fixed, without being used for communicative purposes. Despite possessing highly developed language skills in terms of grammar and vocabulary, the affected person lacks understanding of social-pragmatic content (e.g., implicit requests, set phrases) and semantic content (e.g., irony, metaphor), so that communication tends to be highly formalistic.

Limited interests and repetitive behavior patterns
The affected person’s interests and activities are characterized by intense involvement in highly circumscribed areas (e.g., the collection and cataloguing of specific types of information), interest in rule systems and structures (e.g., language syntax or tables), and a lack of social context. Limited cognitive flexibility can manifest itself in unusual devotion to orderliness and in the introduction of rituals into everyday life that must be rigidly adhered to; when these rituals are interrupted, anxiety arises.”[49]
of gray to white matter and the RH having relatively more white matter and a higher degree of functional interconnectivity. At the micro-anatomical level, LH neurons have smaller input fields than RH neurons in language related brain areas. This difference in input fields may be related to more specific, fine, neural processing in the LH compared to less specific, coarser processing in the RH.”[51]

**problem solving.** Sahyoun and colleagues studied verbal vs. visuo-spatial problem-solving in high-functioning autism vs. Asperger syndrome [52]: “We designed a reasoning task involving a variety of pictorial puzzles that differed in the extent to which they necessitated the use of language or visuospatial processes to solve them.... Individuals with autism exhibit specific communication impairments before age 3, in the form of delayed or lack of expressive language, whereas individuals with ASP appear to develop language normally in these early years. Although not a DSM-IV diagnosis, high-functioning autism (HFA) is viewed as a subtype of autism with no overall cognitive impairment .... Studies have documented epidemiologic, psychological, genetic, motor, and neurobehavioral differences between HFA and ASP . . . .

“The present study demonstrated differences between the two ASD ... in processing efficiency and strategies in pictorial reasoning. Typically developing participants appeared to benefit from the availability of both visuospatial and linguistic processing routes .... Participants with high-functioning autism showed an increased processing efficiency in favor of visuospatial mediation when this strategy was available .... Asperger syndrome participants ... appeared to have used both verbal mediation and language-independent fluid reasoning ability in reasoning . . . .”[52]

**brain blood flow.** Yang et al. reported: “There was a significant reduction in rCBF in the bilateral frontal lobe (frontal poles, arcula frontal gyrus) and the bilateral basal ganglia in the autism group, and a reduction in the bilateral frontal, temporal, parietal, legumina nucleus and cerebellum in the AS [Asperger] group compared to the control. In addition, asymmetry of hemispheric hypoperfusion in the ASD group was observed. Inner-group comparison analysis revealed that rCBF decreased significantly in the bilateral frontal lobe (42.7%), basal nucleus (24.9%) and temporal lobe (22.8%) in the autism group, and in the bilateral cerebellum (22.8%), basal nucleus (19.3%) and right thalamencephalon (16.6%) in the AS group (P <0.05). Conclusions. The decrease in rCBF in ASD is a global event, which involves the bilateral frontal, temporal, limbic system and basal ganglias. Asymmetry of hemispheric hypoperfusion was more obvious in the AS group than the autism group, which indicates a different neurobiological mechanism from that of autism.”[48] [my emphasis]

**personal reports.** Ryan and Räisänen asked 16 Asperger adults how they felt living in a “neurotypical” world [53]: “All participants described a constant feeling of not belonging.... Participants recounted experiences from childhood and talked about how their interests differed from those of their peers; they enjoyed more individual, structured play and found team games, like football, or imaginary games, like ’cops and robbers’, problematic because the rules were unclear or interpreted flexibly by other children. Imaginary play was difficult to comprehend....

“Participants suggest that typical others found it hard to understand how they felt or to make sense of their emotional detachment and yet participants felt enormous pressure to try to reduce such differences, make sense of the social world and try to fit in.... [T]his extract highlights the way in which the participant knew what the problem was but did not have the appropriate symbolic capacity to resolve it. He was not able to put himself in the shoes of his partner to have some idea of how she felt.... They were, effectively, at the centre of an ontological crisis on a daily basis and their experiences suggest an intense ‘autistic emotion’ arising from this awareness and the accompanying fragile, precarious position they occupied in many social settings.”[53]

**EEG.** Duffy and colleagues measured “EEG coherence” (brain connectivity) of Asperger vs. autistic children 2 to 12 years old: “Although there are no agreed upon neuro-imaging criteria to diagnose ASP, there have been a number of studies that raise the potential for this possibility.... The study’s second goal was to determine if the 26 subjects with ASP were, nonetheless, systematically separable from the larger population of 430 subjects with ASD.... [T]he subjects with ASP were indeed significantly separated (P ≤0.0001) from the ASD population; 92.3% (24 out of 26) of those with ASP were classified as ASP rather than as ASD. These results show that subjects with ASP, although associated with the broader autism spectrum population, manifested significant physiological differences in EEG connectivity ... to distinguish them from the subjects with ASD.”[54]

**amygdala.** As noted, Schumann and Amaral found young children with autism had a 16% larger amygdala than controls, whereas young children with Asperger syndrome had a 9% larger amygdala than controls [27].
gray and white matter. McAlonan and colleagues used MRI to measure gray matter volumes in children with high-functioning autism or Asperger syndrome: “Children with HFA had significantly smaller grey matter volumes in subcortical, posterior cingulate and precuneus regions than the Asperger’s group. Compared to controls, children with HFA had smaller grey matter volumes in predominantly fronto-pallidal regions, while children with Asperger’s had less grey matter in mainly bilateral caudate and left thalamus.... When the groups were combined we confirmed a mixed picture of smaller grey matter volumes in frontal, basal ganglia, temporal and parietal regions.” [55]

McAlonan et al. subsequently measured white matter volumes: “White-matter volumes around the basal ganglia were higher in the HFA group than ASP and higher in both autism groups than controls. Compared with controls, children with HFA had less frontal and corpus callosal white matter in the left hemisphere; those with ASP had less frontal and corpus callosal white matter in the right hemisphere with more white matter in the left parietal lobe.... HFA involved mainly left hemisphere white-matter systems; ASP affected predominantly right hemisphere white-matter systems.”[56] [my emphasis]

Are Asperger children/adults left-hemisphere lateralized and right-hemisphere isolated because they have more left-hemisphere white matter than right? Are high-functioning (and other) autists right-hemisphere lateralized and left-hemisphere isolated because they have more right-hemisphere white matter than left? Or does gray matter asymmetry determine laterality? Asymmetric brain blood flow? Yet autists see left-hemisphere details better than right-hemisphere big pictures [8,43]; Aspergers too lack planning and impulse control [50].

Ozonoff and Griffith: “The proposed visual–spatial deficits of AS [Asperger] individuals, as well as their difficulties producing and interpreting facial expressions, gestures, and prosody, have led to the hypothesis that the right hemisphere is dysfunctional in AS. Conversely, lateralization work has suggested that the left hemisphere is damaged in autism. This suggests a very appealing hypothesis, namely that AS and HFA result from different patterns of unilateral brain dysfunction. Unfortunately, however, this right-hemisphere-left-hemisphere dichotomy does not account for all data. First, it has long been evident that classically autistic children exhibit deficits typically considered right hemisphere in origin .... Second, recent studies have documented left-hemisphere damage in AS.”

[57] DISCUSSION: DO HEMISPHERIC DYSCONNECTION AND LOW BRAIN BLOOD FLOW IN AUTISM HAVE A COMMON CAUSE?

Another enigma in children with autistic disorders is consistently low brain blood flow despite frequent hyperexcitability – as if neurovascular coupling has failed. When neurons fire they release molecules that dilate nearby blood vessels, notably neuronal nitric oxide (NO). Attwell and colleagues: “Synaptic release of glutamate activates neuronal NMDA (N-methyl-D-aspartate) receptors, resulting in Ca2+ entry into neurons and activation of neuronal nitric oxide synthase (nNOS). This releases NO, which dilates vessels ....”[58]

Reynell and Harris reviewed explanations for the apparent failure of neurovascular coupling in autism, including depletion of neuronal nitric oxide [59] [see also Evaluation]. The problem is that nitric oxide appears high in these children, to judge from high levels of metabolites nitrite and nitrate in blood [60]. The source of this nitric oxide appears to be inducible nitric oxide synthase (iNOS) [61] induced in brain microglia, astrocytes, and other cells as part of the inflammatory/immune response. Two constitutive forms of nitric oxide synthase continuously present in blood vessel endothelial cells (eNOS) and neurons (nNOS) synthesize and release lesser amounts of endothelial and neuronal nitric oxide.

Frye and colleagues recently tested nitric oxide metabolism in ASD children using sapropterin, a synthetic form of tetrahydrobiopterin (BH4), a cofactor for NOS [61]. Confirming the successes of Naruse and colleagues with sapropterin, Frye et al. found sapropterin improved communicative language in these children, which they attributed to stabilization of nitric oxide metabolism. But sapropterin also stimulates release of neuronal and endothelial nitric oxide [62]. Furthermore, induced nitric oxide commonly compensates depletion of constitutive nitric oxide [63], and nitrite acts as a reservoir “pool” to regenerate nitric oxide by reduction [64].

Most intriguing is fresh evidence that glutathione (GSH) – already heavily implicated in ASD as primary antitoxin and antioxidant [65] – sustains nitric oxide release as well as matures myelin!

McKinley-Barnard and colleagues studied effects of combined citrulline and glutathione supplements on nitric oxide in healthy athletes: “Nitric oxide (NO) is endogenously synthesized from L-arginine and L-citrulline. Due to its effects on nitric oxide synthase (NOS), reduced glutathione (GSH) may protect against the oxidative reduction of NO.... Intracellular glutathione exists in both the oxidized disulfide...
form (GSSG) or in reduced (GSH) state; the ratio between GSH and GSSG is held in dynamic balance depending on many factors including the tissue of interest, intracellular demand for conjugation reactions, intracellular demand for reducing power, and extracellular demand for reducing potential. In some cell types, GSH appears to be necessary for NO synthesis and NO has been shown to be correlated with intra-cellular GSH. GSH stimulates total L-arginine turnover and, in the presence of GSH, NOS activity is increased. This suggests that GSH may play an important role in protection against oxidative reaction of NO, thus contributing to the sustained release of NO. Therefore, combining L-citrulline with GSH may augment the production of NO.”[66] [my emphasis]

Monin and colleagues reported glutathione is necessary to mature myelin in children: “We found that GSH levels measured in the medial prefrontal cortex are positively associated with white matter integrity in the cingulum bundle of young healthy subjects and early psychosis patients.... Taken all together, these data suggest the presence of a critical developmental period during which a proper redox regulation and GSH levels are required for myelination processes. Adverse events during early life are risk factors for the psychopathology and myelin development. This also suggests that there are several critical periods during which environmental risk factors could impact the normal development of myelin. Indeed, transient changes in GSH levels induced by environmental insults during pre-, peri- and post-natal periods may have an impact on oligodendrocyte maturation, consequently affecting later structural connectivity.”[67] [my emphasis]

A pathogenic scenario

This evidence clearly speaks for itself. It says that depletion of glutathione at critical periods of a child’s development by any of the toxins and oxidants implicated in autism – e.g. mercury, aluminum, lead, hydrogen peroxide, and especially acetaminophen (Tylenol) – can delay or prevent maturation of myelin and limit release of nitric oxide, primary vasodilator in the brain. Immature myelin may explain disconnected brain hemispheres; lack of nitric oxide explains low brain blood flow despite hyperexcitability. Do these pathologies induce atypical brain asymmetries – and autism? Are they reversible?

GLUTATHIONE IN AUTISM

James and colleagues studied transmethylation and transsulfur-ation pathways in children with ASD: “Relative to the control children, the children with autism had significantly lower baseline plasma concentrations of methionine, SAM, homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of SAH, adenosine, and oxidized glutathione. This metabolic profile is consistent with impaired capacity for methylation (significantly lower ratio of SAM to SAH) and increased oxidative stress (significantly lower redox ratio of reduced glutathione to oxidized glutathione) in children with autism.”[68]

As noted, Geier and Geier proposed that glutathione deficiency in ASD causes less DHEA to convert to DHEAS and more to androstenedione and testosterone [37]. Adams and colleagues found the severity of autism was associated with the body burden of toxic metals and red blood cell glutathione levels [69]. Chauhan and colleagues reported: “The present study examines the concentrations of glutathione (GSH, reduced form; and GSSG, oxidized form) and the redox ratio of GSH to GSSG (marker of oxidative stress) in different regions of brains from autistic subjects and age-matched control subjects. In the cerebellum and temporal cortex from subjects with autism, GSH levels were significantly decreased ... with a concomitant increase in the levels of GSSG .... There was also a significant decrease in the levels of total GSH (tGSH) ... in the cerebellum, and ... in the temporal cortex of subjects with autism. In contrast, there was no significant change in GSH, GSSG and tGSH levels in the frontal, parietal and occipital cortices in autism versus control group.... These findings indicate that autism is associated with deficits in glutathione antioxidant defense in selective regions of the brain.”[70]

McAlonan and colleagues, however, found brain GSH levels similar to controls in normally intelligent males with ASD, nor did GSH levels correlate with clinical severity [71]. Is glutathione depletion primarily a problem in childhood?

Frye and James: “Decreased GSH concentration and GSH/GSSG ratio, and increased GSSG concentration have been reported in plasma, peripheral blood mononuclear cells, lymphoblastoid cells lines, brain tissue and mitochondria of individuals with ASD. Some studies have demonstrated a reduction in total GSH in plasma and whole blood, but this biomarker appears to be more variable than the other measures of GSH. Although low plasma concentrations of GSH precursor metabolites ... have been reported, a decrease in plasma and intracellular concentration of cysteine is the only consistent finding across studies.”[72]

Frye and colleagues tested the benefit of methylcobalamin and folinic acid in autistic children: “A greater improvement in glutathione redox status was associated with a greater im-
provement in expressive communication, personal and domestic daily living skills, and interpersonal, play-leisure, and coping social skills.... The significant behavioral improvements observed and the relationship between these improvements to glutathione redox status suggest that nutritional interventions targeting redox metabolism may benefit some children with autism.”[73]

Kern and colleagues reported effects of oral and transdermal glutathione on sulfur metabolites in ASD children: “The oral treatment group showed significant increases in plasma reduced glutathione, but not whole-blood glutathione levels following supplementation. Both the oral and transdermal treatment groups showed significant increases in plasma sulfate, cysteine, and taurine following supplementation.” They noted oral glutathione is poorly absorbed, and can’t enter cells; glutathione needs to be synthesized within cells [74]. A pharmacologist suggested N-acetylcysteine (NAC) or whey protein for glutathione precursors [75]. My 2006 PDR warned against denatured whey protein: “When subject to heat or shearing forces (inherent in most extraction processes), the fragile disulfide bonds within the peptides are broken and the bio-availability of cysteine [rate-limiting amino acid in GSH] is greatly diminished.”[76]

ARI pediatrician John Green (MD) has used NAC for ASD extensively for 15 years – orally, iv, and topically: “It is a potent GSH support, being the rate limiting step in GSH synthesis, and is consumed molecule for molecule in detoxification. Hardan at Stanford did a study of pharmaNAC in ASD children, dosing from 900 to 2700 mg/day in stepwise fashion, and demonstrated significant neurologic improvements. It is also a competitive amino acid in glutamate transport, and could thus be calming.... Clinically, responses are very split, with an almost equal number of patients showing agitation vs. enhanced cognitive function in others. I start with 900 mg and move up as able. We tested five different preparations with a biochemist, and found the commercial preparations have very little actual NAC, being composed instead of congeners, cysteine, and degradation products. It is very fragile, oxidizes upon opening the bottle, so is of limited antioxidant value, though may still contribute to GSH synthesis. The pharmaNAC preparation is blister packed, so that the stability is much more secure.”[77]

acetaminophen vs. glutathione

Shaw (2013) presented compelling evidence that acetaminophen (Tylenol) depletes glutathione in autism, asthma, and other disorders [78]: “The characteristic loss of Purkinje cells in the brains of people with autism is consistent with depletion of brain glutathione due to excess acetaminophen usage, which leads to premature brain Purkinje cell death.” Shaw observed that Cuba vaccinates all their children, especially against measles, yet their autism incidence is only 1/300th of ours in the U.S. [US: 1 in 68; Cuba: 1 in 20,000!]. What’s the difference, according to Shaw? Cuba prohibits over-the-counter Tylenol, and only rarely allows acetaminophen prescribed for vaccination, because acetaminophen is limited by the U.S. embargo.

Deth noted acetaminophen (like mercury) readily binds selenium-containing proteins that underlie the glutathione system [79]. By depleting glutathione, acetaminophen may effectively deplete glutamine, because glutamine enters cells more readily than glutamate, thus often provides glutamate to synthesize glutathione [80]. Main et al. noted: “Glycine and glutamine are key compounds for the biosynthesis of glutathione obtained through dietary sources.”[65]

Schultz and colleagues found via a parent survey that children given acetaminophen for pain/fever of the measles-mumps-rubella vaccine (MMR) became autistic much more often than children given ibuprofen [81]. They noted sulfation by the liver is the primary pathway to detoxify acetaminophen in children younger than ten. When sulfation is impaired [consistently in ASD] acetaminophen oxidizes to a toxic metabolite that requires glutathione to detoxify. Thus acetaminophen depletes the liver’s sulfate and glutathione.

Schultz concluded the autism epidemic in this country began in 1980, when the Centers for Disease Control and Prevention (CDC) warned the American public that aspirin could cause Reye’s syndrome in children, and everyone switched to acetaminophen [82]. Pangborn too implicated 1980 as the year our epidemic began, based on thousands of parents’ reports to the Autism Research Institute (ARI) [83]. Previc concluded: “The incidence of autism has risen 10-fold since the early 1980s, with most of this rise not explainable by changing diagnostic criteria.”[84] Orlowski and colleagues compellingly debunked the association of aspirin with Reye’s syndrome [85,86].

Bauer and Kriebel noted recommendations that acetaminophen (paracetamol in the UK) be given before and after circumcision [87]: “These guidelines include the suggestion of a first dose ... two hours prior to the procedure, and doses every 4–6 hours for 24 hours following the procedure. Thus newborn males often receive 5–7 doses ... during the developmentally vulnerable initial days of life.” They also cited evidence that may explain more children born autistic –
by the early 1980s about 42% of American women used acetaminophen during the first trimester of pregnancy: “The rate climbed to over 65% in the early 1990’s, where it has essentially remained through 2004.”

Bilbo and colleagues commented on Schultz’s parent survey: “[A] particularly informative observation ... was made when the use of acetaminophen was found to be associated with the development of autism with an odds ratio of about 8 ... compared to ibuprofen. The odds ratio climbed to a factor of about 20 when only those cases of children with regression were considered. This original study has been subsequently supported by other studies and plausible mechanisms explaining the role of the drug in the pathogenesis of autism have been put forth. Thus, the potentially strong and very plausible association of acetaminophen but not ibuprofen with autism, coupled with the very recent introduction of acetaminophen into Western culture, provides extremely compelling evidence that autism is, at least in part, a modern pandemic.”[88]

**IS AUTISM REVERSIBLE?**

Herbert argued that autism can hardly be a permanent structural disorder, since infectious fever often relieves autistic behavior dramatically [20,89]. Fluid diets before surgery had similar effect [90], as does severe stress – e.g. panic [91] or a broken bone [92]. Herbert concluded autism is a “chronic dynamic encephalopathy” – an ongoing active reversible brain pathophysiology [20,89].

Fever’s phenomenal benefit, first published formally by Sullivan in 1980 [93], continues to tantalize parents and practitioners [94,95,96] – yet its physiology/biochemistry have never been investigated. Zimmerman noted 80% of parents in Curran et al. [95] reported their child improved during fever on one or more Autism Behavior Checklist categories: “In clinical care, approximately 30% of parents report that their children with ASD improved dramatically during fever ... their symptoms are so obvious the family recognize them immediately.”[97] Evidence of improvements hours before fever [92] implicate release of free glutamine (and taurine) from skeletal muscles [98]. Fasting (e.g. fluid diets) also releases glutamine as provisional fuel.

More challenging to explain is brief dramatic relief of autistic behavior by severe stress [91,93], since ordinary stress aggravates [99]. Ordinary stress too releases free glutamine from muscles, but plasma glutamine falls because so many cells require it. Does severe stress release sufficient glutamine to tip the balance? Or is the decisive factor epinephrine from the adrenal medulla? Sympathetic beta-stimulation by epinephrine moves calcium and taurine into excitable cells; intense beta-stimulation by epinephrine [e.g. fever, panic] reverses this shift [100].

Considerable evidence argues glutamine is decisive here. Glutamine is normally the most abundant amino acid in blood, yet is consistently low in plasma of ASD children, and often low in their brain, despite frequent high blood and brain ammonia [96,101]. Glutamine is alternative fuel in brain neurons and astrocytes, especially during hypoglycemia, and primary fuel in rapidly replicating cells, e.g. blood vessel endothelial cells and intestinal enterocytes [96]. Children with high brain glutamine from urea cycle disorders rarely show autistic behavior [102].

ARI practitioners commonly give ASD children oral glutamine to heal their intestines – from 250mg to 8g/day – but only two reported improved behavior [96]. Verzella gives 5–7g/day of oral glutamine after cleansing their intestines of pathogens like bacteria and yeast: “Multifactorial and multisystemic is the condition, so that the improvement has different aspects in different children. Most common: sedation, less stereotypes, better sleep, more concentration.”[103] Pangborn recommended the natural substances thyme, oregano, and Goldenseal to cleanse intestines [104]. Some ARI practitioners reported increased excitability from glutamine (one reported seizures) – probably because some glutamine readily breaks down to glutamate, ammonia, and other toxins in the intestines [104]. Oral glutamine may be more stable taken as the dipeptide glutamine/alanine (e.g. Sustamine).

Glutamine’s primary value in ASD may be as immediate precursor of citrulline – precursor of arginine, only substrate for the primary vasodilator nitric oxide. Deutz observed: “[A]bout 80–90% of the citrulline is derived from the gut glutamine to citrulline conversion. Therefore, whole body citrulline production is related to the quantity of gut glutamine conversion to citrulline, and is most likely influenced by the amount of active gut tissue.”[105] Does intestinal inflammation in ASD limit conversion of glutamine to citrulline?

Most arginine ingested as protein is taken up by the liver; citrulline bypasses the liver and forms arginine in the kidneys, increasing systemic arginine [106]. Citrulline has other advantages as a source of arginine for ASD. Cynober and colleagues noted citrulline stimulates protein synthesis when dietary protein is low [e.g. casein/gluten-free diets] and provides sufficient arginine for constitutive nitric oxide but not induced nitric oxide [107]. Citrulline is also safer in large doses than arginine [106]. Watermelon and its juice, rich in citrulline and arginine, may be effective alternatives to supplements [108].
Woeller has given ASD children 5–10g/day of creatine (arginine + glycine) without adverse effects [109]. Taurine too dilates blood vessels, by stimulating release of endothelial nitric oxide [110]. The ARI recommended 250–500mg/day of taurine for ASD children, up to 2g/day for adults and adult-sized children [111].

EVALUATION

[You cannot have a genetic epidemic ... ]

Martha Herbert [112]

Blaming autism on epigenetics when our practical understanding of epigenetics is still so minimal hardly explains anything.

Martha Herbert [113]

How can brain nitric oxide be low in ASD when blood nitrite is high? About 70% of nitrite normally derives from ammonia, a common problem from intestinal bacteria and intestinal glutamine in ASD children may be needed to feed – and heal – enterocytes. One sign ASD myelin is immature is decreased fractional anisotropy, a measure of the degree that parallel layers of myelin restrain perpendicular water diffusion. Beaulieu: “[S]tudies of cerebral white matter development in human neonates and infants in vivo have shown, in general, a decrease in the mean diffusivity and an increase in the degree of anisotropy with maturation.”[120] [my emphasis]

ASD myelin may be immature from insufficient conversion of testosterone (and androstenedione) to estradiol, to judge from testosterone-dependent white-matter tracts within hemispheres larger than estrogen-dependent tracts between hemispheres. Does postnatal catch-up growth favor testosterone-dependent structures because its conversion to estradiol remains impaired? Sulfate [121] and glutathione depletion [37] may be decisive here, or depletion of the enzyme aromatase – inhibited by mercury and other metals, which bind sulfhydryl groups on its cysteine residues [122], and by bisphenol A [123]. Central nervous system myelin normally may not mature fully until late adolescence and adulthood [124].

Are executive functions in autism disabled by left hemisphere or frontal lobe [8] impairments/dysconnections? Rinehart and colleagues found that left-hemisphere dysfunction in children with high-functioning autism “is most prominent on executive function tasks, thus implicating a specific disruption of the frontostriatal circuitry. No such hemispheric deficit was uncovered for the [Asperger] group.... Executive functioning reflects the role of the frontostriatal region in coordinating cognitive-motor output so that behavior is well-timed, planned, adaptable, appropriate, and relevant.”[125]

BRAIN SEROTONIN AND NEURONAL NITRIC OXIDE SYNTHASE

Serotonin is an unusual neurotransmitter because it inhibits distally as well as locally – like a hormone. Inactivation of serotonin at synapses requires uptake by the serotonin transporter (SERT) – why uptake inhibitors are calming. Brogaard and Marlow pointed out that high brain serotonin also triggers release of GABA, the brain’s primary inhibitory transmitter [6].

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Reynell and Harris: “[G]lobal serotonin synthesis is abnormally low in children with autism but, in adolescence, it increases gradually to 1.5 times the level in adult controls. ... Because serotonin is thought to produce a basal constriction of blood vessels, either a decrease or an increase in serotonergic activity could change vessel tone, and thus alter the vessel response to the vasodilators released by a given amount of neuronal activity.”[59] [my emphasis] Is brain serotonin low in ASD because neuronal nitric oxide is low?

Zürcher and colleagues, recently reviewing PET and SPECT studies of ASD, concluded: “The majority of ... studies reported decreases in 5-HT2a receptor and SERT compared to controls in various brain regions including the cingulate cortex, the medial prefrontal cortex, thalamus, temporal and parietal lobes ....”[126] Girgis and colleagues used PET to measure brain serotonin receptor 5-HT2A and the serotonin transporter in 17 Asperger adults [127]: “5-HT2A receptor availability was numerically, but not statistically, greater in the Asperger’s Disorder group in every ROI [region of interest]... Based on results of treatment, imaging, biochemical, and challenge studies that suggest deficiencies of central nervous system serotonin in ASD, the study hypothesis was that 5-HT2A receptor availability might be increased in patients with Asperger’s Disorder, reflecting a compensatory upregulation of these receptors.... [E]thical concerns preclude administration of radioactivity to children and adolescents (i.e., due to their age), and to individuals who are more severely affected with psychiatric illness ....” [127]

Albrecht and Jones noted glutamine accumulation in the brain stimulates transport of tryptophan (serotonin’s precursor) and other neutral amino acids (NAA) across the blood-brain barrier [129]: “In particular, there is strong evidence for enhanced Gln/tryptophan exchange across the BBB in acute and chronic liver failure.” They cited evidence that high intracellular concentrations of glutamine in brain microvessels stimulate uptake of other NAA.

Chanrion and colleagues detected reciprocal interaction between the serotonin transporter and neuronal nitric oxide synthase [130]: “The present study ... demonstrates that SERT-mediated 5-HT uptake enhances the enzymatic activity of nNOS in cells coexpressing SERT and nNOS, revealing a reciprocal functional interaction between these protein partners.... A physical interaction between SERT and nNOS was a prerequisite for the activation of nNOS on 5-HT uptake. Interestingly, NO production induced by 5-HT uptake was not mediated by an influx of Ca2+.... According to the present findings, increased nNOS levels would lead to intra-cellular sequestration of SERT, thereby preventing excessive 5-HT uptake and enhancing 5-HT neurotransmission. In conclusion, this study demonstrates that the physical association of nNOS with SERT provides a molecular substrate for a reciprocal modulation of their functional activity and reveals an intracellular signaling pathway initiated by 5-HT that does depend on the engagement of serotonergic receptors, but is mediated by its reuptake by SERT. A loss of the inhibitory influence of nNOS on the activity of SERT ... may conceivably be involved in the pathogenesis of psychiatric disorders, including depressive states and enhanced aggressiveness and impulsivity ....”[130]

Garthwaite commented on this study [131]: “[T]he results of Chanrion et al. raise a number of important questions about the role of nNOS in the regulation of 5-HT transmission. 5-HT neurons appear to fire mainly in a regular slow manner in vivo. This firing pattern should lead to a tonic level of extracellular 5-HT within the brain regions innervated by the axons, the concentration being set by the transporter activity. By diminishing the amount of SERT in the cell membrane, binding of nNOS should adjust extracellular 5-HT upward. In effect, nNOS would be acting like an endogenous antidepressant.”[131] [my emphasis]

CONCLUSIONS – res ipsa loquitur

Considerable evidence argues the brain hemispheres of autistic children and adults are chronically dysconnected and atypically asymmetric in anatomy, function, neurochemistry, and blood flow. This is most obvious when persons with Asperger syndrome are contrasted with high-functioning autists. Aspergers appear left-hemisphere lateralized for most functions, with little right-hemisphere communication; autists appear right-hemisphere lateralized, though with some left-hemisphere specialization. Autists see LH details better than RH gestalts; Aspergers too lack executive functions. Thus brain laterality in autistic disorders may be different for different functions, yet consistently atypical.

Another enigma in autistic disorders is global/asymmetric low brain blood flow despite frequent hyperexcitability – as if neu-rovascular coupling has failed from lack of nitric oxide, the primary vasodilator, or its substrate arginine. Is too much arginine taken up by the liver to detoxify ammonia? One test is oral citrulline, which bypasses the liver and forms arginine in the kidneys, increasing systemic arginine. Glutathione precursors sustain release of nitric oxide and spare glutamine...”
as precursor of citrulline. Evidence that glutathione also matures myelin argues glutathione depletion is a key mechanism in autism – keeping brain blood flow low, myelin immature, and brain hemispheres disconnected and asymmetric.

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