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Review

# A review of recent reports on autism: 1000 studies published in 2007

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ABSTRACT

From 1000 studies published in 2007 on all aspects of autism, those that reached clear conclusions or included quantitative data were selected for this review. Possible etiologies include elemental metals, especially the inconsistent evidence regarding mercury from the vaccine preservative thimerosal, not used after 2001, and chromosomes and genes with the conclusion that autism has a complex genetic architecture. Also, various parental conditions are considered, as are many different abnormalities in the central nervous system, especially underconnectivity within the cortex. Furthermore, deficiencies in mirror neurons have been proposed, leading to the "theory of mind" explanation that autistic children tend to disregard others. In addition, various global deficiencies, like an increase in inhibitory synaptic transmission, are proposed. Characteristics of these children include selective (inward) attention; underresponsiveness; stereotyped repetitive motor behavior; increased head size, weight, and height; various cognitive and communicative disorders; and also epilepsy. Therapy has emphasized risperidone, but some atypical antipsychotic medications have been helpful, as have robotic aids, massage, hyperbaric oxygen, and music. Nearly every conceivable problem that a child could have can be observed in these unfortunate children.



## 1. 1. Introduction

Autism has been defined as a condition involving: (1) problems of social communication, (2) inflexible language and behavior, and (3) repetitive sensory–motor movements [1]. Some investigators [2] have emphasized that there is a continuum in this type of disorder, and the term *autism spectrum disorders* has become useful. The present reviewer had previously published EEG data suggesting that the autistic child may have a diminished number of corticocortical fibers [3]. This publication was followed by a review emphasizing one firm finding in autism of underconnectivity [4]. The present review attempts to deal with all aspects of autism by collating the most recent 1000 reports on the topic, all published in 2007. Reports that were only general and came to no clear conclusion on autism or dealt mainly with related disorders are not included in this review, whereas those that provided relevant data or drew clear conclusions are mentioned.

## 2. Identification of autism

The Children's Communication Checklist has been often used for screening [5], but some authors [6] have found that the Developmental Checklist—Early Screen has a high sensitivity, although a low specificity. There are a number of reports that screening with the Checklist for Autism in Toddlers (CHAT) is very useful [7].

## 3. Prevalence

In one national study [8] involving 2685 patients with autism, the prevalence was 1 in 150 children (0.7%), relatively low in Alabama and high in New Jersey. There was an increase in whites, compared with blacks and more in males than females (ratio of 3.4–6.5), but with more cognitive changes in females. An additional survey (in Iran) was taken among 2000 children and a higher prevalence of 1.9% was reported by another group [9]. Other investigators [10] reported no difference between blacks and whites, a slightly lower male:female ratio (2.8–5.5), and an earlier study also reported a relatively high prevalence in New Jersey [11]. One study [12] concluded that any proposed increase in rate was likely related to substitute diagnoses. Another group [13] dealt with the possibility of an increased prevalence and claimed that any higher values may be related to an increase in prenatal exposure to severe natural storms.

## 4. Etiology

### 4.1. Metallic elements

#### 4.1.1. Possible positive evidence

A significant controversy in autism has been whether the mercury in thimerosal, a preservative often used until 2001 in some

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vaccines, could contribute to the development of autism. One study [14] concluded that a *possible* causal role for mercury should be considered, and another study [15] concluded that prenatal mercury poisoning from the mother should also be considered. Mercury poisoning has also been considered in two reports that suggested that autistic children demonstrated ineffective excretion or elimination of this element [16,17].

#### 4.1.2. Negative evidence

Four studies [18–21] disclaimed any involvement of mercury through thimerosal (not used after 2001), and one other study [22] concluded that generally no heavy metals were in any way involved. Two other studies [23,24] considered that the amalgam from tooth fillings also was not involved. Finally, Brown et al. [25] concluded that vaccines were now safer than ever.

Another element, iron, was under consideration by Dosman et al. [26], who suggested that children should be checked for its deficiency.

### 4.2. Chromosomes

Many different chromosomes have been mentioned in relation to autism. Marui et al. [27] considered chromosome 7q21.3–q22.1 first viewed at the NPTX2 locus (neuronal Pentraxin II), but this locus was eventually considered insignificant. Chromosome 11p12–p13 and neurexins with a glutamate-related gene were emphasized in another report [28] whereas 16p13.1 was mentioned by Ullmann [29]. Another group [30] believed that autism may be similar to Prader–Willi syndrome and that the chromosome in the 15q11–q13 region may be involved in both conditions. Chromosome 17 was emphasized in another study [31], likely involving genes MYO1D, ACCN1, and LASP1. Multiple chromosomes have also been mentioned, for example, 1, 9, and 16 [32] and also 2, 4, 6, 7, 10, 15, 16, 17, 19, 21, and 22 [33]. Finally, Yang and Gill [34] implicated regions 1q21–q44, 2q24.1–q31.1, 3q21.3–q29, 6q14.3–q23.2, 7q21.1–q36.2, 16p12.1–p13.3, and 17q11.1–q21.2.

Also mentioned was duplication of chromosomes like dup 7q11.23 [35] and dup 17p11.2–p11.2 [36], confirmed by another group [37]. Finally, duplication of 22q11.2 has also been proposed [38]. In summary, many different chromosomes have been implicated, especially chromosomes 15–17, but clearly the evidence at present is that autism is polychromosomal.

### 4.3. Genes

One of the genes most often mentioned was an epigenetic defect leading to decreased MECP2 expression, encoding methyl CpG-binding protein 2 [39]. Thatcher et al. [40] also claimed that MECP2 may play a role in chromosomal organization in the developing brain and thus could be involved in autism. Finally, Coutinho et al. [41] concluded that MECP2 may play a role in the etiology of autism, but only very rarely.

The human ENGRAILED 2 (EN2) gene has been implicated in the Chinese Han population [42]; another report claimed it was one of single-nucleotide polymorphisms (SNPs) of EN2 (rs1861972) that could influence the risk of autism [43].

Li et al. discussed only a possible involvement of the RELN gene [44], considered a good candidate for susceptibility to autism, as also suggested by Ashley-Koch et al. [45]. PTEN gene sequencing should be considered in any child with autism and macrocephaly, according to one group [46], and also mentioned by other investigators [47] who concluded that the gene played a role only infrequently.

GABA genes have also been under consideration. One group [48] claimed no association whatsoever, at least in Japanese, and Solis-Anez et al. [49] concluded that the GABA receptor B3 subunit gene GABRB3 by itself could not have a phenotypic effect, but, joined to other variants, it could explain the autistic phenotype.

Some general comments have been made about possible genetic effects. For example, from the family histories of 164 children with autism, Brimacombe et al. [50] noted an underlying presence of genetic factors, whereas Herman et al. [51] claimed only a 10% yield from genetic tests. Nicholas et al. [52] mentioned anomalies of clock genes, those that participated in regulating biological rhythms. In particular, they implicated the SNPs npas 2 and per 1, and with npas 2, significance was found between markers rs1811399 and rs2117714. Within per 1 the important region was between rs2253820 and rs885747. Silverman et al. [53] emphasized the polymorphic rs2056202 of a glutamate carrier gene. The problem of designating any given gene was well illustrated by a report [54] that concluded that gene expression data support a genetic predisposition to autism on the basis of at least 11 genes involved. Other investigators [55] have demonstrated low-level aneuploidy as a new genetic risk factor, associated with genomic imbalances, appearing as chromosomal mosaicism. Finally, Zhao et al. [56] emphasized that there are two types of genetically determined dominant transmission: (1) in sporadic autism in low-risk families, but with high penetrance in males, and (2) in high-risk families, mainly in females who are unaffected but carry the causative mutation. At least 17 other specific genes have been mentioned in 17 other studies.

In summary, nearly 30 different genes have been implicated, especially MECP2, the promotor methylation gene, but autism likely has a complex genetic architecture.

### 4.4. Parental conditions

Cannell [57] has indicated that severe vitamin D deficiency in the mother might be involved in autism, and thus, the avoidance of sunlight could be a problem. Another group [58] concluded that autism may be associated with prenatal exposure to severe natural storms, and other investigators [59] have implicated anti-thyroid agents producing a maternal low thyroid level. Two studies [60,61] provided evidence that advanced age of the parents increases the risk of autism. Maternal relatives with increased mood and anxiety disorders and paternal relatives with learning and attention-deficient disorders may be associated with an increased risk [62] of autism in the children. However, no difference was found in the prevalence of autism among the relatives of affected males versus females [63]. On the other hand, assisted conception seemed to diminish the risk of autism [64].

### 4.5. Central nervous system conditions

The present reviewer has previously published EEG data on autism and concluded that patients with this disorder likely have a deficiency of corticocortical fibers [3]. Later, this conclusion was supported by a review of other central nervous system data that confirmed a firm finding of underconnectivity in autism [4]. The present review does not, therefore, include further data on this same finding.

#### 4.5.1. Frontal cortex

The orbital frontal area, associated with the amygdala and the superior temporal gyrus, was implicated in one study [65] that concluded that the latter regions are involved in the diminished moral judgments characterizing autism. Other studies [66] have demonstrated deficiencies in the performance of various other psychological tasks from impairment of the same orbital frontal area, in relation to the amygdala and also the relationship of the dorsolateral prefrontal area with the hippocampus. Kleinhans et al. [67]

also emphasized the frontal area, especially the left, in the claim that there was a diminished *N*-acetyl aspartate (NAA) in many cortical regions, as also mentioned by DeVito et al. [68]. Abnormal brain overgrowth, especially in the frontal areas, was emphasized by another group [69]. Anterior to the frontal area is the (medial) prefrontal region, which Wang et al. [70] concluded was abnormal in autism and accounted for the abnormal facial expressions. The same area was implicated in the many commission errors made by high-functioning autistic persons [71]. Another group [72] concluded that an increased coherence was found for theta rhythms, especially in the frontal and temporal areas, and coherence was reduced in the alpha activity between the frontal and all other scalp regions. On the basis of MRI data, Salmond et al. [73] reported abnormalities in bilateral frontal areas and also in the fusiform gyrus and the cerebellum.

#### 4.5.2. Amygdala–hippocampus

As previously mentioned [66] the amygdala, in relation to the orbital frontal area, and the hippocampus with the prefrontal area have been considered abnormal in autism. Also, the amygdala was viewed as dysregulated to account for the poor integration of the internal milieu with the social environment [74]. Another possible linkage was the disrupted serotonergic innervation of the hippocampus and the resulting behavioral changes [75]. Dager et al. [76] reported, in some patients with autism, an alteration of the hippocampal shape with an inward deformation of the subiculum.

#### 4.5.3. Gray–white volume

Investigators like Casanova [77] have emphasized as significant not a given cortical area, but change in the gray:white ratio and an increase in brain volume. Another group [78] also reported an increase in the radiating white matter volume to account for the functional impairment of motor skills. Any change in volume would likely occur after birth, as Hobbs et al. [79] have maintained that fetal head size was normal at least during the second trimester.

#### 4.5.4. Serotonin

As mentioned above, abnormal behavior in autism has been viewed as related to the disrupted serotonergic innervation of the hippocampus with the cerebral cortex [75]. Other groups [80] have also concluded that autism is accompanied by central serotonergic hypoactivity, possibly playing a role in the pathophysiology of autism. Casanova [81] has also reported serotonergic abnormalities, but added the significance of minicolumnopathy as a smaller width of cortical columns compared with normal.

#### 4.5.5. Minicolumns

The latter author and his colleagues [82] have concluded that diminished minicolumn width within the cortex may help to explain the focused attention in the savant abilities of some autistic patients.

#### 4.5.6. Mirror neurons

Mirror neurons are those that are active not only when a person moves [83], but also on observation of movement of another person [84]. The latter author, Altschuler, concluded that these neurons were dysfunctional in autistic children and help to explain the problem of the "theory of mind," the appreciation of thoughts and feelings of others that are viewed by some as deficient in autism. One possible example of deficient mirror neurons may be seen in contagious yawning, which is a normal phenomenon but is rare in autistic persons [85].

#### 4.5.7. Global deficiencies

Yip et al. [86] concluded that a slight increase in glutamic acid decarboxylase [67] mRNA occurred in Purkinje cells of the cerebellum, affecting inhibition onto the dentate nuclei and leading to a change in cognitive–motor behavior. Other groups [87] concluded that in general, an increase in inhibitory synaptic transmission occurred without a change in excitatory synapses, helping to explain autism. Other global changes were a delay in brain-derived neurotropic factor [88] or a global lack of integration as a result of brain enlargement [89] and a decrease in neuronal progenitor cells [90] that affect the development of synaptogenesis and neural networks. The mesencephalon was implicated by an increase in the interpeak latency between peaks III and V of the brainstem auditory evoked potential [91]. Finally, other investigators [92] pointed to many structural brain abnormalities involving the cerebellum, limbic system, frontal and temporal cortices, corpus callosum, and basal ganglia.

### 4.6. Systemic disorders

#### 4.6.1. Autoimmune disorder

Some investigators have concluded that autism is associated with an autoimmune response to dietary protein [93] or an increase in autoantibodies specific to the brain [94]. Another group [95] has demonstrated significantly low levels of platelet–endothelial adhesion molecules in autism, which likely plays a role in the immune system as a marker for inflammatory changes. Chez et al. [96] showed an elevation of cerebral spinal fluid tumor necrosis factor $\alpha$ in patients with autism.

#### 4.6.2. Growth and hormonal factors

Other data would argue for a diminished growth factor, including the insulin-like growth factor type 1(IGF-1) [97] or epidermal growth factor [98]. Still other data suggest an increase in many growth-related hormones [99].

#### 4.6.3. Electrolyte disorders

Krey and Dolmetsch [100] concluded that one problem in autism is calcium ($Ca^{2+}$)-regulated signaling proteins, whereas Dosman et al. [26] suggested an iron (Fe) deficiency. Others [101] have concluded that a subset of autistic persons may have a central nervous system folate deficiency.

### 4.7. Oxidative stress

Deth et al. [102] concluded that oxidative stress, initiated by environmental factors, may lead to impaired methylation and neurological deficits secondary to reduced synchronizing neural networks. Kern and Jones [103] have provided some confirmation in the form of evidence for oxidative stress and toxicity, resulting in possible neuronal insults in autism.

### 4.8. High testosterone level

The fetal androgen theory suggests that high levels of androgens increase the risk of developing autism. One group [104] concluded that play preference in boys versus girls provides partial support for the latter theory. To add further evidence, Bohm et al. [105] described a test for unusually high testosterone levels in amniotic fluid at 14 to 20 weeks of pregnancy that could provide evidence for or against the theory.

### 4.9. Other

In a study from Portugal, one group [106] reported a relatively high prevalence of autism in the Azores, also with an unexpectedly high rate of mitochrondrial–respiratory chain disorders. The presence of infantile spasms in infants added to the prevalence of autistic patients of whom 30% fit the definition of autism [107]. Birth

order was relevant according to another group [108], showing that firstborns had significantly worse scores for repetitive behavior and, therefore, were possible candidates for autism.

### 4.10. Summary of etiology

The 9 categories and 12 subcategories listed here for the possible etiology of autism are testimony to either the multiple causes of this disorder or to the ignorance of the "real" cause. Consideration has been given to the unlikely mercury poisoning through the preservative thimerosal; many different chromosomes, especially 15–17, and the even larger number of genes, especially MECP2; various parental conditions; and many central nervous system conditions involving frontal cortex, amygdala, hippocampus, temporal lobe, gray–white volume, serotonin levels, diminished minicolumns, absence of mirror neurons, and global deficiencies. Also under consideration were various systemic factors, growth and hormonal changes, and electrolyte disorders, especially involving $Ca^{2+}$. Finally, oxidative stress and high testosterone levels have also been implicated, as was underconnectivity in the central nervous system.

## 5. Characteristics of autistic patients

### 5.1. Attention

One group [109] chose "selective attention" (usually inward) as one of the major characteristics of patients with autism, similar in some ways to the term "a deficit in focused attention" (usually outward), used by another group [110]. These latter characteristics are similar to the "underresponsiveness" and the poor "seeking" behavior proposed by still other investigators [111]. Clifford and Dissanayake [112] have specified not just impaired attention, but designated impaired joint attention in particular. Naber et al. [113] have agreed that joint attention was impaired at the age of 2 years, but claimed that this specific impairment disappeared around 42 months of age.

### 5.2. Motor impairments

Dewey et al. [114] concluded that motor coordination and also gesture performance were abnormal. On the other hand, other investigators [115] concluded that global motion perception was not impaired. Vanvuchelen et al. [116] agreed that there was perceptual motor impairment in these children, but a cognitive weakness was not the problem. Other investigators [117] pointed to the general problem of fine motor control, and yet others [118] were more specific in emphasizing repetitive, stereotyped motor behavior [119]. Kates et al. [120] concluded the autistic persons exhibited more motor stereotypes, rituals, repetitive use of objects, and less make-believe play. Another group claimed [121] that there was no link between repetitive behavior and measures of central coherence. A slightly different emphasis was placed by Ming et al. [117], who concluded that a decrease in fine motor control was a major problem, along with programming deficits. Another group [122] emphasized that such movements were often preceded by a lateral glance. With all of the movement problems of the autistic persons, Buckner and Vincent [123] summarized the situation as "unrest at rest."

### 5.3. Abnormal facial perception

One group [124] characterized the facial perception problems as a diminished recognition of facial affect, and others [125] concluded that an abnormal cortical network accounted for this abnormal facial perception. McCleery et al. [126] specified that the magnocellular pathway was involved in this abnormal processing. Sasson et al. [127] added that schizophrenics share with autistics the abnormality of failing to use facial information for assessing emotional content in social scenes. On the other hand, Wilson et al. [128] claimed that the pattern of familiar facial recognition was not a specific defect in autistics, and Chawarska and Volkmar [129] admitted that abnormal facial processing was a problem for toddlers, but that the problem disappeared during early schooling.

### 5.4. Abnormal eye movements

One group [130] referred to the reduced eye contact with others to account for the diminished ability to discriminate between genuine and posed smiles. Other investigators [131] viewed one particular eye movement problem as a decrease in lip reading, resulting in a decrease in speech integration. Finally, Clifford and Dissanayake [112] claimed that an abnormal gaze was present at 6 months and became more severe later at 2 years of age.

### 5.5. Mirror neurons: Theory of mind

As previously mentioned, mirror neurons are those cells within the central nervous system that are active not only during one's own performance, but also when observing someone or something else. They are viewed as deficient in autistic persons. Theory of mind refers to the ability to understand and predict the behavior or the emotion of others [132,133]. The deficient mirror neurons in autism are viewed as contributing to the problem of the theory of mind [134]. Mason and his colleagues [135] were specific about the low functional connection within the theory of mind network and also between the latter network and the language network of the left hemisphere. It seems likely that the impaired imitation seen in autistic persons [136] is related to these deficient mirror neurons.

### 5.6. Head size

Chiu et al. [137] concluded that head circumference was normal at 1 year of age, but at 30 months the size was 27% above the norm and then returned to normal again at 5 years of age. Agreement came from Van Daalen et al. [138], who also found head size normal at 1 year, but with an increase in body length, concluding a disproportionate growth in general. Fukumoto et al. [139] provided details of head circumference before the first year of life. They found the head size normal at birth, but with a marked increase in the first month, peaking at 6 months, and then with a smaller difference from normal at the end of the first year. Body length and weight began to increase at 3 months at a rate smaller than that of head circumference. Other investigators [140] have provided similar details. A smaller head circumference was found from birth to 2 weeks, much larger at 10–14 months, and the greater size at 2 years was associated with poorer performance, especially deficient visual performance. Also, autistic children were longer and heavier beginning at 1–2 months. Thus, some, but not all studies reported an increase in head size, length, and weight in the first and second years.

### 5.7. Sensory impairments

One group [141] reported that autistic persons had auditory orienting deficits, but these impairments could not be explained by a sensory deficit, but instead by social orienting. Other investigators [142] used the neurophysiological phenomenon of mismatch negativity to establish abnormal automatic processing. Bennetto et al. [143] reported impairments in both olfactory and taste identifica-

tion. A few studies have dealt with tactile responses. Pernon et al. [144] reported a strong positive valence to tactile stimuli, which excited patients with autism. Another group [145] also dealt with emotional aspects of tactile stimuli, reporting both hyper- and hyporesponsivity to touch, viewed not as a perceptual sensory problem, but as an emotional disorder. Cascio et al. [146] provided further evidence for enhanced responsiveness by an increased sensitivity to vibration and thermal pain, but with normal perception. Kern et al. [147] have summarized perception in general by concluding that all the main modalities and multisensory processing are affected so that sensory dysfunction is global in autistic children.

### 5.8. Inflammatory disorders

DeMattei et al. [148] have provided evidence that the majority of patients with autism have gingivitis, dental plaque, and other oral conditions. Finegold [149] has emphasized the importance of intestinal bacteria, specifically Clostridia, by pointing to some cases of relapse in autism after discontinuation of an antimicrobial agent and also providing a possible (unexplained) increased incidence of autism. A high prevalence of *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in autism was emphasized by another group [150], and in general, Becker [151] compared the parallel aspects of autism and inflammatory disorders to support an immune-based hygiene hypothesis in autism. Bransfield et al. [152] added further evidence by pointing to mothers with Lyme disease and children with autism, whose antibiotic treatment for occasional *Mycoplasma* often had resulted in improvement in autism symptoms. Other investigators [153] have provided some negative evidence on the emphasis on inflammatory disorders by claiming that "autistic enterocolitis" may not be a verifiable entity. Instead, ileal lymphoid hyperplasia may be prevalent in children with autism, but also may be found in children with food allergies and severe constipation.

### 5.9. Others

#### 5.9.1. Communication disorders

Luyster et al. [154] used the Communicative Development Inventory to predict autism. Their conclusion was that scores at age 2 were predictive, but at 3 years these scores were even more predictive. McCann et al. [155] dealt with a specific aspect of communication, namely, prosody. They reported that all children with (high-functioning) autism had difficulty with at least one aspect of prosody, correlating well with deficits in expressive and receptive language. Finally, another group [156] explored the failure to respond to one's name and reported that this failure at 1 year of age was highly suggestive of autism, but at 2 years, 89% of the children who failed to respond turned out to have autism.

#### 5.9.2. Cognitive impairments

One group [157] dealt generally with cognitive impairment and reported that through intervention, IQ improvements correlated with reduction in autism symptoms. In general, cognitive ability was associated with the severity of the autism. Lombardo et al. [158] acknowledged that autism was associated with the interpersonal social domain, but also investigated possible impairment in intrapersonal self-reference. The autistic children exhibited reductions in memory of themselves, self-focused attention, and empathy measures. Thus, autistic children showed broad impairments in both self-referential cognition and empathy. Another group [159] studied ways of learning words and reported that performance on intention tasks was the most powerful predictor of vocabulary. Mayes and Calhoun [160] compared the Versions III and IV of the Wechsler Intelligence Scale for Children (WISC) and reported that Version IV was an improvement over III for autistic children because Version IV better captured their problems in visual reasoning strength and identified their weaknesses in attention, graphomotor, and processing speed. Pellicano [161] dealt with the aforementioned theory of mind and its relationship to executive function in autism. He concluded that there was a significant correlation between these two functions and that impairment in executive function was likely an important factor in the advancement of the theory of mind explanation in autism. Bogte et al. [162] also studied executive function, but reported negative results in that no deficit was found in presetting response inhibition, set shifting, and a priori planning in autistic patients. Another group [163] attempted to differentiate adults with (high-functioning) autism from those with Asperger syndrome. Verbal and Performance differences on the Wechsler Adult Intelligence Scale (WAIS) could not distinguish between the two, but the WAIS-III Factor Scale and Subtest Patterning provided a more valid indicator. Finally, Whitehouse et al. [164] investigated whether the deficient encoding of verbal information was due to poor attention to semantic rather than phonological attributes. The group reported that there was no support for deficient semantic encoding in autism.

#### 5.9.3. Relationship to testosterone

The androgen theory of autism proposes that autism is in part related to elevated fetal testosterone levels. One group [165] reported that autistic females had more hirsutism, bisexuality, irregular menstrual cycles, dysmenorrhea, polycystic ovarian syndrome, severe acne, epilepsy, tomboyism, and *family* history of ovarian, uterine, and prostate tumors. Furthermore, mothers of autistic children had similar abnormalities, demonstrating hormone abnormalities in these women with autism were also seen at times in their own mothers. Falter et al. [166] hypothesized that autism was an extreme version of the male brain, caused by high levels of prenatal testosterone. Use of a controversial index of prenatal testosterone, second digit:fourth digit length ratio in the hand, revealed no differences related to these levels, failing to confirm that autism represents an extreme male brain. On the other hand, Geier and Geier [167], on the basis of morning blood samples of 70 patients with autism, reported significantly increased levels of serum testosterone, serum free testosterone, percentage free testosterone and androstenedione in the autistic group. Surprisingly, females had higher overall mean relative testosterone and also relative free levels than males. As a possible reflection of extreme male behavior Montes and Halterman [168] studied bullying in autistic children. Only if these patients also had attention-deficit hyperactivity disorder was there an increased prevalence of bullying among children with autism.

#### 5.9.4. Epilepsy

Hara [169] pointed out that "idiopathic" autism (without major complications before the diagnosis) is well known to be a risk factor for epilepsy. His goal was to clarify the characteristics of epilepsy in autism, the onset of seizures, seizure types, EEG findings, and the outcome of the epilepsy. Furthermore, this author explored the differences between autism with epilepsy and autism without epilepsy. One hundred thirty individuals with autism were followed for more than 10 years and were evaluated nearly every year, up to ages 18–35. The age at onset of epilepsy ranged from 8 to 26 years, and two types of seizures were observed: (1) partial attacks with secondarily generalized seizures, and (2) generalized seizures from the onset. Among the patients with seizures, 61% had partial seizures and 39% generalized seizures. In the group without epilepsy, 18% exhibited epileptiform activity, and 68% of those with epilepsy revealed this same type of activity before the onset of their clinical epilepsy. This value of 68% is similar to the 59% reported by the present reviewer [3] a few years earlier.

One of the important findings in the latter study [3] was that 19% of autistic children had spikes on their EEGs, but without any clinical epilepsy; in the study by Hara the value was nearly the same at 18%. These data indicate that autism is closely associated with epilepsy, but especially with the typical electrographic expression, the epileptiform discharge. This reviewer [3] argued that because nearly one-fifth of patients with autism had spikes, but no clinical attacks, these data may reflect *focal* changes as spikes, but without appropriate *spread* from the focus to initiate a clinical attack. Therefore, a deficiency in the autistic brain may be a paucity of corticocortical fibers to explain the absence of such spread, consistent with later data, especially functional MRI data on the firm findings of underconnectivity in autism.

Hara found no differences in sex ratio or past history of febrile seizures between the epileptic and nonepileptic groups. Differences did, however, occur in that the epileptic group had lower IQs, lower social maturity scores, and higher frequency of prescribed psychotropic medications. One of his final conclusions was that epilepsy was one of the negative factors in cognitive, adaptive, and behavioral outcomes for individuals with autism.

Another group [170] set out to describe autism in a cohort of children under 1 year of age with a history of unprovoked seizures. Over an 8-year period, 102 children had such seizures between 28 days and 1 year of age, and 82% participated in the study with a surprising larger number of females (56) than males (28). Although 37% were investigated for possible autism, only 7% were given the diagnosis. All of these autistic patients had mental retardation, and one-half had congenital brain abnormalities. The final conclusion was that the prevalence of autism is higher in children with a history of seizures in the first year of life than it is in the general population. Also, there are indicators that these children may have a higher prevalence of congenital brain abnormalities and more often are female than other children with autism.

#### 5.9.5. Social involvements

Impairment in social interaction in autism was studied by Dichter and Belger [171], who used directional gaze in autistic children while they processed social–cognitive stimuli. The authors reported hypoactivation (from functional MRI) of frontal, parietal, and anterior cingulate regions in autistic children during these stimuli. Other investigators [172] concluded that sociability impairments may be partly assigned to dysregulation of the GABAergic system, especially in the amygdala. Similar conclusions were reached by Endo et al. [173], who claimed that abnormality in the amygdala–hippocampal region is related to the social impairment. Another social issue in autistic patients is mealtime behavior, which was studied by another group [174], who showed that the Brief Autism Mealtime Behavior Inventory was a reliable instrument. Stokes et al. [175] dealt with social issues by demonstrating that older autistic individuals relied less on peers and friends for social and romantic learning, were likely to engage in inappropriate courting behavior, and also paid too much attention to celebrities and strangers. Finally, other investigators [176] reported that the siblings of children with autism tended to manifest atypical social and communication development, leading to an increased risk of social and behavioral adjustment problems and lack of closeness in the sibling relationships.

#### 5.9.6. Various other conditions

Quality-of-life (QOL) issues of parents were studied by Mugno et al. [177] who concluded that parents of high-functioning autistic patients had a lower QOL than parents of those with a typical autistic disorder. A similar study was done by another group [178] was a follow-up 5 years after the diagnosis of autism. Outcome was good in 27%, but poor in 26% with a very restricted life, no occupation, and no friends, worse for males. McDermott et al. [179] studied injuries in these children and reported a high rate of poisoning and head, face, and neck injuries, including those that were self-inflicted. Other investigators [180] dealt with dream content, reporting that autistic children had fewer recollections, fewer bad dreams, and dreams with less emotional content. Finally, Stroganova et al. [181] studied EEG rhythms and reported a relatively large amount of prefrontal delta slow waves and a diminished capacity of the right temporal cortex to generate EEG rhythms.

#### 5.9.7. Summary of characteristics of autistic children

One of the major characteristics of these children is selective attention, a deficit in *appropriate* focused attention, underresponsiveness, and poor seeking behavior. For motor impairments, disorders in coordination and in fine motor control and repetitive or stereotyped motor behavior were evident. Abnormal processing of facial perception usually occurred, especially as a diminished recognition of facial affect. One reason for the latter may well be the reduced eye contact with others, in addition to an abnormal gaze. One of the interesting concepts in autism is the theory of mind, likely associated with deficient mirror neurons. The reference is to the inability to understand and predict behavior or emotion in others because of deficient neurons that normally are active when observing someone or something else. Changes in head size are controversial. Most of the evidence would indicate normal size at birth, but an increase beginning early in infancy and observed at 1.5–2 years, in association with poor performance. Increases in length and weight are observed as early as 1–3 months. Sensory impairments include auditory orienting deficits and olfactory and taste disorders, but an increased sensitivity to vibration and thermal pain. Inflammatory and infectious disorders include evidence for occasional Clostridia, *Mycoplasma*, and *Chlamydia* infections. Evidence of communicative disorders include deficits in expressive and receptive language, as well as in prosody, and also the failure to respond to one's own name, especially at 2 years of age. Cognitive impairments include self-referential cognition and attention empathy, poor executive function, and deficient encoding of verbal information. Some evidence supports the androgen theory of autism, especially because autistic women and their mothers often manifest more hirsutism, tomboyism, and bisexuality. Blood samples have often shown increased testosterone and androstenedione levels. Epilepsy, mainly as partial attacks, has often been observed, and epileptiform discharges were seen in nearly one-fifth of patients who had no seizures as an example of a focal discharge, but without spread to an ictal event, leading to the concept of underconnectivity in autistic children. Impaired social interaction has been tied to hypoactivation of frontal, parietal, and anterior cingulate regions or a deficiency in the GABAergic system, leading later to inappropriate courting behavior and attention to celebrities and strangers. Other characteristics include poor outcome in 5 years for at least one-fourth of patients and an increase in many types of injuries, especially of the head, face, and neck.

## 6. Other related disorders

### 6.1. Obsessive–compulsive disorder

Bejerot [182] has stated that autism in its milder forms may be clinically similar to obsessive–compulsive disorder (OCD). Neuropsychological deficits are common in OCD, and odd personalities with paranoid avoidant OCD traits may have autistic traits. Cath et al. [183] pointed out that OCD and social anxiety disorder (SAD) frequently co-occur in patients with autism. Patients with comorbid autism and OCD/SAD scored (on the Autism Questionnaire) intermediate between controls and the pure OCD group, with the conclusion of an overlap between autism and both OCD and SAD.

### 6.2. Prader–Willi syndrome

One group [30] discussed Prader–Willi syndrome with an absence of gene expression from the paternally inherited copy of chromosomes in the q11–q13 region. Also, this syndrome involves obsessive–compulsive symptoms, disruptive, repetitive behavior, and also social deficits. Thus, there are phenotypic similarities between autism and Prader–Willi syndrome.

### 6.3. Klinefelter syndrome

Other medical conditions are known to occur in 10–25% of patients with autism. Jha et al. [184] showed that Klinefelter syndrome is sometimes associated with autism, concluding that autistic features are more common in Klinefelter syndrome than generally believed.

### 6.4. Rett syndrome

Young et al. [185] concluded that many cases initially diagnosed as autism turn out to be Rett syndrome, as both conditions involve disruptive social and language development accompanied by repetitive, nonpurposeful stereotypic hand movements. Females with p.R306C or p.T158M mutations in the MECP2 gene were likely to have an initial diagnosis of autism, but the specific diagnosis of Rett syndrome at a later age.

### 6.5. Anorexia nervosa

Zucker et al. [186] claimed that patients with anorexia nervosa often develop symptoms of autism in a chronic course with impaired interpersonal processes and deficits in social–cognitive relationships.

## 7. Later changes

### 7.1. Psychological and social factors

Sterling et al. [187] studied adults with autism and reported that 43% showed depressive symptoms, especially those with higher rates of other psychiatric symptoms, but with greater cognitive ability and fewer social impairments. Billstedt et al. [188] studied social interaction problems in patients 13–22 years after the diagnosis of autism and concluded that the latter problems were still present in the majority, as were persistent perceptual problems. However, behavioral impairments were much more variable in adulthood, and odd responses to sensory stimuli were very common.

### 7.2. Anatomy

Cranial circumference was measured by Sacco et al. [189] in 241 patients with autism up to 16 years of age. The distribution of this measurement was very significantly skewed toward larger head sizes. Circumferences in the >75th percentile were associated with more impaired adaptive behavior, but surprisingly with less impairment in IQ and motor and verbal language development. These larger head sizes were associated with a positive history of allergic/immune disorders, both in the patients and in their first-degree relatives. The authors concluded that these larger head sizes point toward pathogenetic links with immune dysfunctions, possibly associated with increased cell progression and decreased apoptosis. Keller et al. [190] were concerned with the structural integrity of white matter at ages 10–35, and reported lower fractional anisotrophy (a measure of white matter integrity) within and near the corpus callosum and in the right retrolenticular portion of the internal capsule. Thus, reductions in the structural integrity of white matter persisted into adulthood.

### 7.3. Heritability

One group [191] studied 370 twins at age 18 and their siblings, stating that earlier studies had reported high heritability for autistic traits in childhood, but this study extended the findings into late adolescence. Although males had higher autism scores, the genes affecting autistic traits appeared to be the same across the sexes.

## 8. Need for a better understanding of autism

Schmitz and Rezaie [192], in considering the need to better understand autism, pointed out that pre- and postnatal developmental abnormalities involve multiple regions of the brain. These include the cerebral cortex, cortical white matter, amygdala, brainstem, and cerebellum. Their emphasis now is to examine various aspects of *cellular* pathology affecting the brain in autism. Müller [193] viewed autism as a "distributed disorder," including genetic, neuroanatomical, neurofunctional, and behavioral aspects. "Localizing" models have not been promising, but interactions during development between affected functional networks and atypical behavior further complicate the neurological bases, resulting in an "exponentially distributed profile." Müller reminds us of the evidence for underconnectivity, but calls for more anatomical studies, such as diffusion-tensor imaging tractography. Jones et al. [194] saw a different need, that is, teaching children with autism how to develop their spontaneous responses. The development of these effective interventions to address the social communicative needs of these children will be crucial to their quality of life.

## 9. Therapy

### 9.1. Drugs

#### 9.1.1. Risperidone

Jesner et al. [195] scanned the medical literature for results on the use of risperidone in autistic children. They reported the benefits as lessened irritability, repetition, and social withdrawal. The most prominent adverse effect was weight gain, and the authors pointed out that a single standard outcome measure was lacking to allow adequate comparison between different studies. Scott and Dhillon [196] also dealt with risperidone, claiming that it reduced irritability and other behavioral symptoms with adverse events of mild to moderate intensity, including weight gain, somnolence, and hyperglycemia. One of their conclusions was that the long-term safety of risperidone remained to be determined. Gencer et al. [197] compared and contrasted risperidone with haloperidol, concluding that risperidone led to a greater reduction on the Clinical Global Impression Scale and improvement on the sensory motor and language subscales and, in addition, scores on the Aberrant Behavior Checklist. Weight gain was observed more frequently in the haloperidol group so that, in general, risperidone was more efficacious and well tolerated than haloperidol. Another group [198] determined the efficacy of risperidone (up to 2 mg/day), added to piracetam (up to 800 mg/day), a modulator of glutamate receptors. Their conclusion was that the combination of this antipsychotic medication and a glutamate agent, piracetam, resulted in improvement in Aberrant Behavior Checklist scores. These results indicated, to the authors, the synergistic effects of these two medications.

*9.1.2. Atypical antipsychotic drugs*

One group [199] studied olanzapine, ziprasidone, quetiapine, and aripiprazole by checking Medline databases from 1966 to February 2007. Their conclusion was that these drugs have some efficacy in improving certain behavioral symptoms, especially aggressiveness, hyperactivity, and self-injurious behavior. Positive conclusions were strongest for olanzapine, compared with quetiapine, but both had weight gain and sedation as adverse events. Aripiprazole demonstrated efficacy in only a limited case series with minimal adverse events. However, the investigators claimed that these drugs did not affect the core symptoms of autism.

*9.1.3. Antibiotics*

Adams et al. [17] have discussed how oral antibiotics may partially explain changes in various symptoms in autism. The investigators checked levels of mercury, lead, and zinc in baby teeth and reported higher than normal levels of these metals in autistic children. These children had higher usage of antibiotics during years 1–3 and these drugs likely inhibited the excretion of mercury due to alteration of gut flora. This latter problem may also partially explain the high incidence of chronic gastrointestinal problems in autism.

*9.1.4. Memantine*

Chez et al. [200] hypothesized that memantine, as a antagonist of the *N*-methyl D-aspartic acid (NMDA) glutamate receptor, may block the effects of excessive glutamate, including neuroinflammatory activity. In 151 patients over a 21-month period, language function, social behavior, and self-stimulatory behaviors improved. So far, chronic use has appeared to have no serious side effects.

*9.1.5. d-Lysergic acid diethylamide*

Because there is renewed interest in the use of psychedelic drugs for therapeutic purposes, Sigafoos et al. [201] reminds us that the justification for using *d*-lysergic acid diethylamide (LSD) was often based on default logic that other treatments had failed. The authors also remind us of the important lessons learned in the 1960s and 1970s in the use of this drug.

*9.1.6. Pharmacotherapy in general*

Myers [202] stated that psychotropic medication and agents with glutamatergic or cholinergic mechanisms may warrant further investigation, and in particular, valproate, atomoxetine, $\alpha_2$-adrenergic agonists, and olanzapine seemed to be promising. One of the conclusions was that impact on the core features of autism was, however, very limited. Oswald and Sonenklar [203] found that during one year, 83% of autistic children were prescribed at least one drug from 125 different therapeutic classes. The seven most prescribed classes were antidepressants, stimulants, tranquilizers/antipsychotics, anticonvulsants, hypotensives, anxiolytic/sedative/hypnotics, and benzodiazepines. At 8 years of age, 70% of children with autism had received some form of psychoactive medication in a given year.

*9.2. Acupuncture*

Yan et al. [204] reported on 40 children with autism who underwent 60–90 sessions of acupuncture. In the treatment group 55% showed marked effectiveness, in contrast to only 15% of the controls. Total scores in development, imitation, and cognition were especially improved. Wang et al. [205] studied 60 children who received electroacupuncture plus behavior therapy, compared with behavior therapy alone. The total effective rate was 87% for the combination of therapies, compared to 57% in the behavior group. A significant enhancement in sensation, association, body, and self-care was seen, especially with electroacupuncture plus therapy, but this combination did not improve intelligence.

*9.3. Massage*

As sensory impairments often occur in autism, Silva et al. [206] evaluated (Qigong) massage for 5 months in 13 patients aged 3–6 years. Compared with untreated children, the treated ones experienced improvement of their sensory impairment, demonstrating increased social and basic living skills. Those with bowel and sleep abnormalities also improved with treatment.

*9.4. Robots*

Pierno et al. [207] were aware that autistic children usually had social deficits and these could be bypassed by interacting with robots, which could possibly trigger imitative behavior. The patients could react to either a human or a robotic arm performing a reach-to-grasp action. The children with autism were facilitated when primed by a robotic, but not by a human arm movement. The opposite was found in normal children. Thus, interaction with robots had an effect on visuomotor priming processes.

Billard et al. [208] used "Robota," a mini-humanoid robot, to assess imitation ability and to teach children simple coordinated behavior and also discussed the use of robots in general for rehabilitation of children with autism.

Kozima et al. [209] called their creature-like robot "Keepon," which was capable of expressing attention by directing its gaze and emotions, including "pleasure" and "excitement." The children approached Keepon and interacted with it and, later, with adult caregivers, in the pleasure and surprise modes they found in the robot. The authors concluded that the robot's minimal expressiveness helped the children to understand socially meaningful information, which then activated their motivation to share these interests and feelings with others.

Participants in another study [210] performed a prespecified hand action in response to either a human or a robotic hand. Compatible trials were those in which the stimulus and response actions matched and the effect was greater when responses were made to human than to robotic actions. Thus, the group with autism exhibited a larger bias to the human hand, in contradistinction to other studies indicating a bias to robots.

*9.5. Electroconvulsive therapy*

Only one study [211] has reported that catatonia, seen in 6% of children with autism, can be successfully treated with electroconvulsive therapy, which improved both autism and catatonia in adolescent identical twins.

*9.6. Hyperbaric oxygen therapy (HBOT)*

A number of studies have shown that children with autism have increased oxidative stress and inflammation (see Sections 4.7 and 5.8). Thus, 18 children were given 40 sessions of hyperbaric oxygen therapy (HBOT), either 1.5 atm of 100% oxygen or 1.3 atm of 24% oxygen [212]. Neither group showed changes in plasma oxidized glutathione, a marker for oxidative stress. A trend toward improvement was seen in the mean level of C-reactive protein, and in addition, parental observations indicated improvement in motivation, speech, and cognitive awareness.

*9.7. Music*

Kern et al. [213] reported that a therapist composed a song for each child and these songs assisted the children in entering the

classroom, greeting others, and engaging in play. Boso et al. [214] used 52 weekly 60-minute music therapy sessions including singing, piano playing, and drumming. At the end, improvements were noted on both the Clinical Global Impression and Brief Psychiatric Rating scales.

### 9.8. Costs

One group [215] estimated the medical expenditures for autism, including the cost of therapies. Children with autism exceeded the average medical expenditures of those without autism by $4110–6200 per year. On average, costs were 4.1–6.2 times greater for children with autism than for those without autism. The *median* expenditures were 8.4–9.5 times greater, indicating increased use of medical services and increased costs in autism.

## 10. Summary

Autism is a disorder involving problems of social communication, inflexible language, and behavior and also repetitive sensory–motor movements. These unfortunate children have nearly every problem a child could have. The correct diagnosis is often made with screening tools, like the Checklist for Autism in Toddlers. The prevalence is 1 in 150 children, but likely relatively high in New Jersey.

Possible etiologies include metallic elements, although the mercury in thimerosal, a preservative previously used in vaccines, is likely not involved. Many chromosomes and genes (especially MECP2) have been implicated, but autism is likely polygenic with a complex genetic architecture. Parental conditions that may be significant include vitamin D deficiency, anti-thyroid medication, advanced age, and relatives with learning and mood disorders. Central nervous system conditions are varied, but considerable evidence exists for underconnectivity of cortical regions. Especially involved are the frontal cortex, amygdala, hippocampus, and temporal cortex. An increase in radiating white matter volume has also been reported, as has serotonergic hypoactivity. Minicolumns in the cortex are likely diminished, as are mirror neurons that are active not only during one's own movements but also during the movements of others. These factors refer to the theory of mind explanation of autism, that these children have a deficient appreciation of the thoughts and feelings of others. Many examples can be given of global deficiencies in the brains of autistic children, including an increase in inhibitory synaptic transmission, delay in brain-derived neurotropic factor, global lack of integration from brain enlargement, and many structural abnormalities. There is some evidence for the involvement of autoimmune, hormonal, and electrolyte factors. Oxidative stress and toxicity have also been mentioned. One view of autism is that it represents an extreme male brain with high testosterone levels.

The characteristics of children with autism are many, including selective (inward) attention, underresponsiveness, and poor seeking behavior. Perceptual motor impairment and stereotyped repetitive motor behavior are usually present, as are abnormal facial perception and abnormal eye movements. Head size usually is increased, as are weight and height. Sensory impairments involve all modalities. There is evidence for inflammatory and infectious disorders. Communicative disorders represent the essence of autism and many types of cognitive impairment can be found. A relationship to testosterone includes various male characteristics in some females, supporting the androgen theory of autism. Epilepsy is found in many of these children, but epileptiform activity, in particular, is often seen on the EEG, even in nonepileptic children. Social involvements are critical with a significant risk of social and behavioral adjustment problems with others. Autism may have some relationship to obsessive–compulsive disorder, Prader–Willi syndrome, Klinefelter syndrome, Rett syndrome, and anorexia nervosa. Later changes show that the reduction in the structural integrity of white matter persists into adulthood.

There is a need for more information on developmental abnormalities, especially cellular pathology and underconnectivity.

Therapy has emphasized risperidone, but some atypical antipsychotic drugs, memantine, and acupuncture have been studied, as have massage, robotic aids, electroconvulsive therapy, hyperbaric oxygen therapy, and music.

As mentioned above, nearly every conceivable problem a child may have can be observed in these unfortunate children with autism.

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