CHAPTER 20

Medical Aspects of Autism

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It is now unequivocal that neurobiological dysfunction is causative in autism. Although a number of disorders have been potentially associated with autism, the extent and nature of these associations have traditionally been the subject of much debate (Rutter, 1996). Wing and Gould (1979) found relatively lower rates of known medical problems in their autistic sample relative to nonautistic subjects (17% versus 71%, respectively). Further, disorders such as phenylketonuria (PKU) and tuberous sclerosis were found only in the nonautistic group. Tuchman, Rapin, and Shinnar (1991) compared groups of children with autism to those with developmental language disorder and found similar rates of medical conditions, about 5%, across groups. Similarly, Fombonne and du Mazaubrun (1992) noted that autistic children and those with special educational needs did not differ in the frequency of most medical conditions, including congenital rubella or chromosomal abnormalities. Of note, the autistic group was significantly less likely to have Down syndrome or cerebral palsy, and all cases of neurofibromatosis and PKU were found in the nonautistic group.

In a series of studies, Bolton et al. (1991) and Rutter, Bailey, Bolton, and Le Couteur (1993) conducted extensive evaluations on 151 individuals with autism and found that 8.1% of these cases showed medical conditions that were likely to be causal factors of autism, including fragile X syndrome (FXS), bilateral deafness, cerebral palsy, multiple congenital abnormalities, and chromosomal anomalies. About 3.8% had other medical concerns that were considered less likely to be etiologic factors. The overall rate of medical conditions, 11.9%, is similar to the rate found in a study of medical conditions in twins with autism (12.9%; A. Bailey et al., 1991). Although some found that IQ is not related to medical risk (Steffenburg, 1991), others found more medical conditions among autistic persons at lower IQ levels. For example, in an epidemiologic study of autism, Ritvo et al. (1990) demonstrated that medical conditions were more frequent in persons with severe mental retardation, which is consistent with other reports (Rutter, Bailey, Bolton, & Le Couteur, 1994; Wing & Gould, 1979). The possibility of finding any associated medical condition rises with increasing degrees of mental retardation—approaching 50% among persons at the severe and profound levels of cognitive dysfunction (Scott, 1994). More recent studies corroborate the findings of these earlier studies (Barton & Volkmar, 1998; Challman, Barbaresi, Katusic, & Weaver, 2003; Fombonne, du Mazaubrun, Cans, & Grandjean, 1997; C. Gillberg & Billstedt, 2000; Kielinen, Rantala, Timonen, Linna, & Moilanen, 2004; Lauritsen, Mors, Mortensen, & Ewald, 2002;

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Shevell, Majnemer, Rosenbaum, & Abrahamowicz, 2001; Skjeldal, Sponheim, Ganes, Jellum, & Bakke, 1998).

In summary, traditional studies have found variable rates of medical conditions in autism, ranging from 5% to 33%. The first edition of this text (1987) reviewed associated medical conditions in the chapter titled, "Neurologic Functioning" (pp. 133–147). The accompanying table (p. 138) listed almost 40 disorders that had been reported in only "one or more" (p. 137) cases of autism, but the text detailed, very briefly, less than a dozen of these, including then-newly described Rett syndrome (Hagberg, Aicardi, Dias, & Ramos, 1983). In contrast, the second edition (1997) included a chapter dedicated to associated medical conditions (pp. 388–407), which selectively focused on only four syndromes, two commonly co-occurring with autism (FXS and tuberous sclerosis complex [TSC]) and two with seemingly uncommon associations with autism (Down and Williams syndromes).

AUTISM AND MEDICAL CONDITIONS: VIEWING THE RELATIONSHIP FROM BOTH SIDES OF A SEMANTIC COIN

It would appear, at first glance, that this corresponding chapter in this third edition could be titled either "Medical Conditions Associated with Autism" or "Autism Associated with Medical Conditions." *Medical conditions* can refer either to broader classes of medical signs and symptoms or to specific disorders and syndromes. Additionally, the term *medical condition* does not specify the presumed population under study, for example, a cohort with a specific medical disorder or a cohort with autism. The premise traditionally used for significant "associated medical conditions" has been of *specific disorders or syndromes* occurring *within populations of autistic individuals.*

Since the first edition was published in 1987, a wealth of information about autism has emerged, much of it initially anecdotal (e.g., case reports) but increasingly empirical. Concurrently, the concept of autism is evolving from the singular *autistic disorder* into the pleural *autistic spectrum disorders* (ASDs). As a result of this ongoing ontogeny, in tandem with rapid genetic progress, more and more disorders and syndromes are now recognized to be behaviorally on the autistic spectrum. As specific genotypes are identified within the spectrum of autism and related conditions, it is likely that many, if not most, cases will be related to a specific medical (genetic) disorder or syndrome.

The original chapter title, "Medical Conditions Associated with Autism," must now be revised to include both vantage points. It has therefore been updated to "Medical Aspects of Autism" and is addressed as two, now complementary, topics: (1) medical signs and symptoms in children presenting with autism and (2) comorbid autism in children presenting with specific disorders or syndromes.

This seemingly unconventional approach incorporates presumably rarer disorders whose prevalence may be marginal within an autistic population; for example, many children presenting with TSC are autistic, but few children presenting with autism have comorbid TSC. Particularly in medical settings where experience with ASDs is less common, there has been a tendency for medical specialists to focus less on behavior and more on specific signs and symptoms. As a result, many children with the classic hallmarks of autism in addition to their other medical diagnoses may not be correctly diagnosed and thereby served. For example, Howlin, Wing, and Gould (1995) eloquently championed the importance of recognizing autism specifically in children with Down syndrome. Although autism diagnoses are typically made in the preschool years, they noted much later ages of autistic diagnoses in Down syndrome cases, as well as in all cases of Down reported in the literature (range from 7 years to adulthood). This "diagnostic overshadowing" of sorts creates unnecessary stress for families and prevents them from using supports and interventions available to families with an autistic child. Even though most of the following disorders and syndromes are uncommon in samples of individuals with autism, they should always be considered in the range of diagnostic possibilities.

This chapter begins with a brief outline of the appropriate medical evaluation for individuals with an ASD, then discusses the medical symptoms commonly seen in autism and the specific disorders presenting with an autistic

behavioral phenotype. A resource list for parents and professionals is provided at the end of the chapter.

THE MEDICAL EVALUATION IN AUTISM*

The medical evaluation in autism consists of a careful physical and neurologic examination with selected laboratory testing.

Physical and Neurologic Examination

The *head circumference* in autistic children is larger than is found in typically developing children (Aylward, Minshew, Field, Sparks, & Singh, 2002; A. Bailey et al., 1995; Bolton et al., 1994; Courchesne, Carper, & Akshoomoff, 2003; Davidovitch, Patterson, & Gartside, 1996; Fidler, Bailey, & Smalley, 2000; Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Ghaziuddin, Zaccagnini, Tsai, & Elardo, 1999; C. Gillberg & de Souza, 2002; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Woodhouse et al., 1996). The same has been noted with postmortem brain weights (A. Bailey et al., 1993, 1998; Bauman, 1992, 1996; Bauman & Kemper, 1994, 1997). Only a small proportion of autistic children have frank macrocephaly/megalencephaly, but the distribution of the measures is clearly shifted upward with the large majority falling above the 50 percentile with the mean approximately at the 75 percentile (A. Bailey et al., 1995; Bolton et al., 1994; Courchesne et al., 2003; Davidovitch et al., 1996; Filipek, Richelme, et al., 1992; Lainhart, 2003; Lainhart et al., 1997; Rapin, 1996b; Woodhouse et al., 1996). Some investigators have noted that the large head circumference correlates with higher IQ (Filipek, Richelme, et al., 1992; Miles et al., 2000). The large head circumference is not necessarily present at birth but may appear in early to mid-childhood with increased rates of growth (Lainhart et al., 1997; Mason-Brothers et al., 1987; Mason-Brothers et al., 1990). It also appears that the head circumference is normal by adolescence and adulthood (Aylward et al., 2002), as is postmortem brain weight by adulthood (Bauman & Kemper, 1997). *This phenomenon of large head size in autistic children is readily acknowledged, and barring lateralizing signs on the remainder of the examination, routine neuroimaging work-up for the finding of a large head alone in autism is not warranted.* Several reports also show a higher prevalence of microcephaly in autism, which is associated with abnormal physical morphology, medical disorders, lower IQ, and seizures (e.g., Fombonne et al., 1999; Miles et al., 2000).

Sensorimotor function is commonly problematic in autistic individuals and most severe in those with lower cognitive function (Noterdaeme, Mildenberger, Minow, & Amorosa, 2002; Rapin, 1996b; S. J. Rogers, Bennetto, McEvoy, & Pennington, 1996). Sensory issues are very common, particularly sensory seeking, oral sensitivity, and low endurance (Baranek, 1999; Baranek, Foster, & Berkson, 1997; Bernabei, Fenton, Fabrizi, Camaioni, & Perucchini, 2003; Watling, Deitz, & White, 2001). Sensory-processing abilities are aberrant in 42% to 88% of autistic individuals and include preoccupation with sensory features of objects, over- or under-responsiveness to environmental stimuli, or paradoxical responses to sensory stimuli (Kientz & Dunn, 1997). Hypotonia was noted in about 25% of 176 autistic children and in 33% of 110 nonautistic mentally retarded children, while spasticity was found in less than 5% of either group (exclusionary criteria for this sample included the presence of lateralizing gross motor findings; Rapin, 1996b). Motor apraxia was noted in almost 30% of autistic children with normal cognitive function, in 75% of retarded autistic children, and in 56% of a nonautistic retarded control group (Mari, Castiello, Marks, Marraffa, & Prior, 2003; Rapin, 1996b; J. H. Williams, Whiten, & Singh, 2004). The presence of *observed* motor stereotypies was noted in over 40% of autistic children (in contrast to a much higher prevalence by parental report) and in over 60% of those with low IQ, but in only 13% of the nonautistic control group (Rapin, 1996b). Hand or finger mannerisms, body rocking, or unusual posturing is reported

* Portions of this section are taken with permission from Filipek et al. (1999, 2000).

in 37% to 95% of individuals and often manifests during the preschool years (Lord, 1995; Rapin, 1996b; S. J. Rogers et al., 1996).

In a large longitudinal study of autistic children, over 6% also had a sibling with autism (Rapin, 1996a). The overall *recurrence risk estimate* for ideopathic autism—the percent chance that a younger sibling will also develop the disorder—varies from about 3% to 7% (A. Bailey, Phillips, & Rutter, 1996; Bolton et al., 1994; Piven et al., 1990; Ritvo, Jorde, et al., 1989; Smalley, Asarnow, & Spence, 1989). However, there are gender differences to this risk estimate: If the first autistic child is male, the recurrence risk estimate ranges from about 4% to 7%, but if female, the recurrence risk estimate ranges from 7% to 14.5% (Jorde et al., 1991; Ritvo, Jorde, et al., 1989). The risk of having a second autistic child, therefore, is approximately 50-fold higher than in the general population. These risk estimates are based on the older prevalence rates of approximately 4 per 10,000 and, therefore, cannot reflect the fact that many families choose not to have more natural children subsequent to receiving a diagnosis of autism. Regardless, it is the physician's responsibility to inform parents of this recurrence risk when a child is diagnosed with autism.

Definitive Hearing Test

Every child presenting with a receptive language deficit should receive a definitive hearing test. Audiologic assessment should occur early in the differential diagnostic process and use a battery of tests including behavioral audiometric measures, assessment of middle ear function, and electrophysiologic procedures (American Speech-Language-Hearing Association, 1991). If audiology cannot be performed adequately, brainstem-evoked responses should be performed (Filipek, Accardo, et al., 2000; Filipek et al., 1999).

Lead Level

Children with developmental delays who spend an extended period in the oral-motor stage of play (where everything goes into their mouths) are at increased risk for lead toxicity, especially in certain environments. The prevalence of pica in this group can result in high rates of substantial and often recurrent exposure to lead and, possibly, other metals (Shannon & Graef, 1997). Several studies report the neurobehavioral effects and behavioral toxicity of lead and its potential clinical relevance in patients with autism. Mean blood lead concentration was notably higher in 18 children with autism than in 16 nonautistic children or in 10 normal siblings; 44% of the autistic and psychotic children had blood lead levels greater than two standard deviations above the mean for normal controls (Cohen, Johnson, & Caparulo, 1976). In three of six reported cases of lead poisoning in children with autism, developmental deviance seemed to have been present before the possible impact of lead toxicity, while in two, the lead poisoning may have contributed to the onset or acceleration of developmental symptomatology (Accardo, Whitman, Caul, & Rolfe, 1988). A more recent chart review found that 17 children with autism were treated for plumbism over a 6-year period from 1987 to 1992. When compared with a randomly selected group of 30 children without autism who were treated during the same interval, the children with autism were significantly older at diagnosis and had a longer period of elevated blood lead levels during treatment; 75% were subsequently reexposed despite close monitoring, environmental inspection, and either lead hazard reduction or alternative housing (Shannon & Graef, 1997). Therefore, all children with delays or who are at risk for autism should have a periodic lead screen until the pica disappears (Centers for Disease Control and Prevention, 1997; Shannon & Graef, 1997).

Karyotype and DNA Analysis for Fragile X

The newer cytogenetic methods of karyotyping and molecular analyses for FXS and the implications of a cytogenetic or molecular diagnosis for other family members justify their routine inclusion in the diagnostic evaluation of a child with autism (American College of Medical Genetics: Policy Statement, 1994; A. Bailey, 1994; Bauer, 1995; Dykens & Volkmar, 1997; Rutter, Bailey, Simonoff, & Pickles, 1997; Rutter et al., 1994; Schaefer & Bodensteiner, 1992).

Metabolic Testing

A wide range of biochemical determinations have been performed in urine, blood, and cerebrospinal fluid in an attempt to identify a specific metabolic abnormality in individuals with autism. Included are studies of inborn errors in amino acid, carbohydrate, purine, peptide, and mitochondrial metabolism, as well as toxicological studies. The reported co-occurrence of autistic-like symptoms in individuals with inborn errors of metabolism has led to consideration of screening tests as part of the routine assessment of patients with severe developmental impairment (Steffenburg, 1991). However, the percentage of children with autism who prove to have an identifiable metabolic disorder is probably less than 5% (Dykens & Volkmar, 1997; Rutter et al., 1994, 1997). Most of the biochemical analyses are useful at present *only as research tools* in the ongoing effort to understand the biology of autism.

Metabolic testing or consultation clearly is indicated by a history of lethargy, cyclic vomiting, early seizures, dysmorphic or coarse features, mental retardation, or, if mental retardation cannot be excluded, questionable newborn screening or birth out of the United States because of the potential absence of newborn screening and maternal public health measures. As recommended by the American College of Medical Genetics, selective metabolic testing should be initiated only in the presence of suggestive clinical and physical findings (Curry et al., 1997). However, as described later in the section titled Mitochondrial Disorders, recent findings may ultimately lead to future recommendations for screenings of lactate, pyruvate, ammonia, and free and total carnitine (Filipek, Juranek, Nguyen, Cummings, & Gargus, in press).

Electroencephalography

The association among electroencephalogram (EEG) abnormalities, seizures, and developmental regression is described in Chapter 18 (this *Handbook,* this volume). An adequate EEG should be performed *with prolonged sleep to Stages III and IV* in any child who presents with suspicion of developmental regression (Dykens & Volkmar, 1997; Tuchman, 1995; Tuchman & Rapin, 1997; Tuchman, Rapin, & Shinnar, 1991). However, some neurologists are routinely performing sleep EEGs on autistic children at diagnosis and are finding subtle abnormalities in many, often localized to the temporal lobes. It is unclear whether the children with the abnormalities are those who would eventually develop clinical seizures, and these findings along with the potential benefits of valproate therapy need to be systematically evaluated.

Neuroimaging Studies

A review of the many neuroimaging reports in autism noted a very low prevalence of focal lesions or other abnormalities, none of which localized consistently to be more than coincidental findings (Filipek, Kennedy, & Caviness, 1992). In a subsequent study using magnetic resonance imaging (MRI), the prevalence of lesions in autistic children was equal to that in the normal control volunteers (Filipek, Richelme, et al., 1992). However, cortical migration malformations have been reported on MRI in *a small number of* high-functioning autistic or Asperger subjects, including polymicrogyria, schizencephaly, and macrogyria, without collective preference for a particular lobe or hemisphere (Berthier, 1994; Berthier, Starkstein, & Leiguarda, 1990; Piven et al., 1990). It is unclear whether these findings of cortical dysplasias are more prevalent in autism than is currently recognized, as another study of 63 developmentally disabled children did not note dysplasias (Filipek, Richelme, et al., 1992). Regardless, unless lateralized findings are present on neurological examination, conventional clinical computed tomography (CT) or MRI scans are not indicated in the routine diagnostic evaluation of autism or any of the developmental disorders. Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) are presently used only as research tools and are not indicated in the diagnostic evaluation of autism.

Tests of Unproven Value

There is inadequate evidence to support routine clinical testing of individuals with autism for hair analysis for trace elements (Gentile, Trentalange, Zamichek, & Coleman, 1983;

Shearer, Larson, Neuschwander, & Gedney, 1982; Wecker, Miller, Cochran, Dugger, & Johnson, 1985), celiac antibodies (Pavone, Fiumara, Bottaro, Mazzone, & Coleman, 1997), allergies (in particular, food allergies for gluten, casein, candida and other molds; Lucarelli et al., 1995), immunological or neurochemical abnormalities (Cook, Perry, Dawson, Wainwright, & Leventhal, 1993; Singh, Warren, Averett, & Ghaziuddin, 1997; Yuwiler et al., 1992), micronutrients such as vitamin levels (Findling et al., 1997; LaPerchia, 1987; Tolbert, Haigler, Waits, & Dennis, 1993), intestinal permeability studies (D'Eufemia et al., 1996), stool analysis, urinary peptides (Le Couteur, Trygstad, Evered, Gillberg, & Rutter, 1988), thyroid function (Cohen, Young, Lowe, & Harcherik, 1980; T. Hashimoto et al., 1991), or erythrocyte glutathione peroxidase (Michelson, 1998).

MEDICAL SIGNS AND SYMPTOMS ASSOCIATED WITH AUTISM

The more common signs and symptoms associated with autism include perinatal factors, hearing loss, food and gastrointestinal problems, immunologic abnormalities and sleep disorders.

Perinatal Factors

Early studies indicated that autism may be associated with increased but mild obstetrical risk factors (Bryson, Smith, & Eastwood, 1988; Deykin & MacMahon, 1980; Finegan & Quarrington, 1979; Folstein & Rutter, 1977a, 1977b; C. Gillberg & Gillberg, 1983; Levy, Zoltak, & Saelens, 1988; Lord, Mulloy, Wendelboe, & Schopler, 1991; Mason-Brothers et al., 1987, 1990; Nelson, 1991; Piven et al., 1993; Tsai, 1987). However, the strong influence of maternal parity/reproductive stoppage accounted for differences in at least two of these studies (Lord et al., 1991; Piven et al., 1993) and was not necessarily appropriately considered in the others. Subsequently, Zambrino, Balottin, Bettaglio, Gerardo, and Lanzi (1995) found that the obstetrical optimality score was lower only in those autistic children with central nervous system (CNS) damage; and Bolton, Murphy, Macdonald, Whitlock, Pickles, et al. (1997) noted an increase of only mild obstetrical complications independent of maternal age or parity, which makes a causal relationship unlikely. Specifically, no associations were found between autism and maternal factors, such as vaginal bleeding, infection, diabetes, toxemia, use of pitocin, age, or prior abortions (Bolton, Murphy, Macdonald, Whitlock, Pickles, et al., 1997; Cryan, Byrne, O'Donovan, & O'Callaghan, 1996; Fein et al., 1997; Gale, Ozonoff, & Lainhart, 2003; Ghaziuddin, Shakal, & Tsai, 1995; Piven et al., 1993; Rapin, 1996a). There were also no associations noted between autism and gestational age, forceps or caesarian delivery, neonatal depression, need for intensive care or mechanical ventilation, neonatal seizures, or prolonged neonatal hospitalization (Bolton, Murphy, Macdonald, & Whitlock, 1997; Piven et al., 1993; Rapin, 1996a).

More recent studies simply add more conflicting data to the debate. Juul-Dam, Townsend, and Courchesne (2001) noted that their autism cohort had a higher incidence of uterine bleeding, a lower incidence of maternal vaginal infection, and less maternal use of contraceptives when compared with the general population; the pervasive developmental disorder–not otherwise specified (PDD-NOS) cohort showed a higher incidence of hyperbilirubinemia. The authors concluded that interpretation of these data "is difficult, as the specific complications with the highest risk of autism represented various forms of pathologic processes with no presently apparent unifying feature" (p. E63). Wilkerson, Volpe, Dean, and Titus (2002) noted that different perinatal factors and maternal medical conditions contributed to the risk of autism: prescriptions during pregnancy, length of labor, viral infection, abnormal presentation at delivery, low birthweight, maternal urinary infection, high temperatures, and depression. In a population study in Sweden, Hultman, Sparen, and Cnattingius (2002) reported yet additional factors as being associated with the risk of autism: daily cigarette smoking, maternal birth outside Europe or North America, caesarean delivery, being small for gestational age, Apgar scores below 7, and congenital malformations. In contrast, Klug, Burd, Kerbeshian, Benz, and Martsolf (2003) examined parental, prenatal, and perinatal risk factors and found that the cohort with autism was quantitatively less

influenced by 15 specific risk markers than were fetal alcohol and sudden infant death syndromes; only low-magnitude risk markers (low birthweight, child malformations, and low level of maternal education) were mildly but significantly elevated for autism, producing odds ratios of less than 2.4. Again, differing diagnostic methods for autism and differing risk factor assessments can account for at least some of the discrepancies noted.

Only one report has examined the incidence of autism in survivors of neonatal intensive care units (NICU; Matsuishi et al., 1999). In this study, 90% of almost 6,000 NICU survivors born between 1983 and 1987 were followed neurodevelopmentally at 2 to 3 and 5 years of age. Eighteen were diagnosed with *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised (*DSM-III-R;* American Psychiatric Association, 1987) autistic disorder. The only risk factor identified of the 28 factors examined was meconium aspiration syndrome. The mean incidence for autism in the NICU survivors was 34 per 10,000, which is more than twice that found in two previous studies in the same geographic region in Japan (Matsuishi et al., 1987; Ohtaki et al., 1992). However, note that these referenced epidemiological studies were performed more than 15 years ago, during the same time frame as those performed by Ritvo, Freeman, et al. (1989) and do not reflect current prevalence rates.

Hearing Loss

Many children diagnosed with autism are first described by parents as acting "as if deaf." However, the vast majority of children with autism are found to have normal hearing function. Rosenhall, Nordin, Sandstrom, Ahlsen, and Gillberg (1999) performed audiological evaluations on 199 children and adolescents with autism and found that pronounced to profound bilateral hearing loss or deafness was present in 3.5% of all cases, a prevalence greater than that seen in the general population but similar to that seen in individuals with mental retardation. However, the rate of hearing loss in this study was equivalent across all levels of cognitive functioning. In contrast, hyperacusis was commonly found and affected almost 20% of the autistic sample. As recommended by the practice parameters for screening and diagnosing autism (Filipek, Accardo, et al., 2000; Filipek et al., 1999), audiological evaluations or evoked potentials should be performed on all children with autism so that, if indicated, appropriate referrals can be made for aural habilitation.

Feeding Disturbances and Gastrointestinal Problems

Feeding habits and food preferences of children with autism are traditionally unconventional and were even at one time considered as part of the diagnostic indicators (Ahearn, Castine, Nault, & Green, 2001; Ritvo & Freeman, 1978). However, this specific aspect of the constellation of atypical behaviors has not received much formal study. Ahearn et al. (2001) studied 30 children with autism using the procedures developed by Munk and Repp (1994) for classifying feeding problems in the developmentally disabled. Just over half of the sample lived at home with their parents, the remainder lived in community group homes for the disabled, and all attended the same private educational and treatment program. More than half showed low levels of food acceptance, with 13% refusing all foods presented to them. However, the authors acknowledged caution in interpreting these results, as there were no comparison groups of either typically developing children or those with other developmental disabilities. Field, Garland, and Williams (2003) also noted food selectivity by type (62%) and by texture (31%); all three children with food refusal (12%) also had gastroesophageal reflux. Food selectivity "by type" was significantly higher for children with autism, and food refusal and oral motor problems were significantly lower than found in children with other developmental disorders. Bowers (2002) performed an audit of referrals of autistic children to a dietetic service over a 3-month period and found that, despite selective food preferences in 46%, the majority of children had intakes that met or exceeded dietary reference values.

Although there have been reports of gastrointestinal (GI) complaints in children with autism dating back more than 30 years (e.g., Goodwin, Cowen, & Goodwin, 1971; Walker-Smith & Andrews, 1972), such problems have

become a significant focus of study in recent years. Lightdale, Siegel, and Heyman (2001) surveyed 500 parents of autistic children; almost 50% reported loose stools or frequent diarrhea. In an epidemiologic study, Fombonne and Chakrabarti (2001) found that 19% of children with autism reported GI symptoms, with constipation identified in 9%. Molloy and Manning-Courtney (2003) found that, of 137 children with autism diagnosed with the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000), 24% had a history of at least one chronic GI symptom and 17% had diarrhea; they found no association between GI symptoms and autistic regression.

Some reports from gastroenterologists have stated that GI symptoms occur in 46% to 84% of children with autism (Horvath, Papadimitriou, Rabsztyn, Drachenberg, & Tildon, 1999; Horvath & Perman, 2002a, 2002b). However, in these studies, most of the autistic samples had been referred to the gastroenterologists for preexisting GI complaints, thus limiting the generalizability of the data. Afzal et al. (2003) noted moderate or severe constipation to be more frequent in the autistic group referred for GI symptoms than in control subjects with abdominal pain (36% versus 10%); over 50% had moderate to severe recto-sigmoid loading than did controls (24%). Milk consumption was the strongest predictor of constipation in the autistic group; stool frequency, gluten consumption, soiling, and abdominal pain were *not* predictive of constipation.

Sandler et al. (2000) hypothesized that, in children with "regressive"-onset autism who had antecedent antibiotic exposure followed by diarrhea, endogenous intestinal microflora might be disrupted by neurotoxin-producing bacteria. Eleven children received a trial of vancomycin, leading to only short-term improvement of autistic symptomatology in 8 of the 10 children. There was no control group in this study, and the raters were *not* blinded as to the hypotheses being tested. Finegold et al. (2002) went on to investigate intestinal microflora and found a higher prevalence of clostridia in the stools of children with autism than in control children, all of whom were presumably referred for GI procedures.

Kuddo and Nelson (2003) reviewed the literature and noted that the frequency of GI symptoms in autistic children is not as common as the GI literature might suggest. Taylor et al. (2002) noted an 8% rate of chronic constipation, which is similar to that estimated for the general childhood population (Loening-Baucke, 1998). Black, Kaye, and Jick (2002) performed a nested case-control study in the United Kingdom and found that both 9% of children with autism and 9% of children without autism had a history of GI complaints, producing an odds ratio of 1.0 (no effect) for autism with GI complaints. Peltola et al. (1998) also noted no association of ASD and GI symptoms over a 14-year period in Finland. DeFelice et al. (2003) found no relationship between autism and GI immune dysregulation by investigating intestinal cytokines; in fact, intestinal levels of interleukin (IL)-6 and IL-8 were lower in patients with ASD than in age-matched controls. Whiteley (2004, p. 9) also noted that "only a minority" of participants with autism in their study showed some bowel problems.

A. J. Wakefield et al. (1998) first reported an apparent link among GI disease, developmental regression, and the measles-mumps-rubella (MMR) vaccine *in 10 autistic children.* These authors published over a dozen additional studies apparently supporting their initial report (Ashwood et al., 2003; Furlano et al., 2001; Kawashima et al., 2000; O'Leary, Uhlmann, & Wakefield, 2000; Torrente et al., 2002; A. J. Wakefield, 1999, 2002, 2003; A. J. Wakefield & Montgomery, 1999; A. J. Wakefield et al., 2000, 2002; J. Wakefield, 2002). While the ensuing international controversy and the direct effect of these studies on the drop in the rates of immunization of children is beyond the scope of this chapter, it should be noted that the majority of these authors have recently retracted their initial interpretation that there is a causal connection between the onset of autistic symptoms and the MMR vaccine (Murch et al., 2004).

It was of great interest when a case series claimed that three autistic patients with GI complaints had dramatic improvement in the core symptoms of autism after receiving the hormone secretin as part of a diagnostic endoscopy (Horvath et al., 1998; Larsen, 1998). Subjective improvement was noticed, particularly in areas of eye contact, alertness, and language capacities. Subsequently, 15 empiric

studies were performed and found no positive effects of either porcine or human recombinant secretin on autistic symptomatology (Carey et al., 2002; Chez et al., 2000; Coniglio et al., 2001; Corbett et al., 2001; Dunn-Geier et al., 2000; Kern, Van Miller, Evans, & Trivedi, 2002; Levy et al., 2003; Lightdale, Hayer, et al., 2001; Molloy et al., 2002; Owley et al., 2001; Roberts et al., 2001; Robinson, 2001; Sponheim, Oftedal, & Helverschou, 2002; Unis et al., 2002); in fact, in one study, autistic symptoms worsened (Robinson, 2001).

Immune Factors

Interest in the potential relationship between the immune system and autism arises given the various cases reported in which infections (and possibly altered immune response) are associated with the development of autism (Marchetti, Scifo, Batticane, & Scapagnini, 1990; Menage et al., 1992; Singh, Warren, Odell, Warren, & Cole, 1993; Warren, Margaretten, Pace, & Foster, 1986). However, the few studies conducted have yielded inconsistent or contradictory findings and are discussed in recent review articles (Hornig & Lipkin, 2001; Korvatska, Van de Water, Anders, & Gershwin, 2002; Krause, He, Gershwin, & Shoenfeld, 2002).

Sleep Disturbances

Sleep disturbances have been a recognized feature of autism for over 25 years, particularly abnormalities in sleep-wake cycles (Hoshino, Watanabe, Yashima, Kaneko, & Kumashiro, 1984; Inanuma, 1984; Ornitz, 1985; Tanguay, Ornitz, Forsythe, & Ritvo, 1976; see also Didde & Sigafoos, 2001; Richdale, 1999; and Stores & Wiggs, 1998, for reviews). Studies find that the majority of children with autism have sleep problems, often severe, and usually involving extreme sleep latencies, lengthy nighttime awakenings, shortened night sleep, and early morning awakenings (Honomichl, Goodlin-Jones, Burnham, Gaylor, & Anders, 2002; Patzold, Richdale, & Tonge, 1998; Richdale & Prior, 1995; Schreck & Mulick, 2000; Wiggs & Stores, 2004). Children with autism also have more unusual and obligatory bedtime routines, for example, requiring that parents hold them, lie down with them, or sit beside their bed; all family members go to bed at the same time; or curtains or bedclothes be positioned in a certain way. If these routines are not performed exactly, the result is usually a tantrum or other angry outburst. As might be expected, only the autistic children studied *always* followed their bedtime routine (Patzold et al., 1998), and the presence of sleep problems was significantly associated with parental stress (Richdale, Francis, Gavidia-Payne, & Cotton, 2000). Schreck, Mulick, and Smith (2004) suggested that both the quantity and quality of sleep per night predicted overall autism scores, as measured by the Gilliam Autism Rating Scale (GARS; Gilliam, 1995), social skills deficits, and stereotypic behaviors. According to Wiggs and Stores (1996), it is uncertain whether sleep disorders in children with autism cause daytime maladaptive behaviors, simply allow them to continue, or worsen preexisting problems.

Hering, Epstein, Elroy, Iancu, and Zelnik (1999) compared the results of parental questionnaires with electronic movement activity recordings (actigraphy) in three groups of children: Group 1: autistic children whose parents reported sleep difficulties, Group 2: autistic children whose parents did not report sleep difficulties, and Group 3: typically developing children. The initial questionnaires showed that 50% of children in Group 1 had sleep disorders versus only 20% in Group 2 and none in Group 3. When sleep was quantified using actigraphy, there were no differences in patterns of sleep between Groups 1 and 2 except for more early morning awakenings in Group 1. These findings support the need for objective study methodologies in these samples.

Diomedi et al. (1999) compared polysomnograph parameters in adult autistic individuals, who demonstrated a significant reduction of rapid eye movement (REM) sleep, increased interspersed wakefulness, and increased number of awakenings with reduction of sleep efficiency relative to normal controls (see Harvey & Kennedy, 2002, for a comprehensive review of polysomnography in autism and other developmental disabilities). Elia et al. (2000) noted that the total time in bed and total sleep time were significantly lower in autistic individuals, who also had a higher density of muscle

twitches, which correlated with some psychological indices of autism from the Psychoeducational Profile-Revised (Schopler, Reichler, Bashford, Lansing, & Marcus, 1990) and the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Rochen-Renner, 1988).

Thirumalai, Shubin, and Robinson (2002) identified REM sleep behavior disorder in almost half of 11 autistic children studied. Usually seen in elderly males, the diagnostic criteria include movements of the body or limbs associated with dreaming (REM), potentially harmful sleep behavior, dreams that appear to be acted out, and sleep behavior that disrupts sleep continuity (American Sleep Disorders Association, 1997, pp. 177–180). Additional studies on this topic are needed because pharmacologic treatment may ameliorate some of the effects of this specific sleep disorder.

AUTISM ASSOCIATED WITH SPECIFIC DISORDERS OR SYNDROMES

Autism is now associated with many more specific disorders or syndromes than previously known, many more than the traditionally recognized tuberous sclerosis and fragile X syndrome (Table 20.1).

Tuberous Sclerosis Complex

TSC is a neurocutaneous disorder that affects as many as 1 in 6,000 to 10,000 individuals and is characterized by benign tumors (hamartomas) and nongrowing lesions (hamartias) in the brain and in many other organs such as the skin, kidneys, eyes, heart, and lungs (Curatolo, Verdecchia, & Bombardieri, 2002; Kandt, 2003). Depigmented macules (shaped like an ash leaf; Fitzpatrick, 1991) are usually the first sign of the disease, which are often visualized only with the use of an ultraviolet Wood light. Facial angiofibroma, formerly called adenoma sebaceum, and shagreen patches over the lower back are also characteristic but often do not appear until late childhood or early adolescence (Webb, Clarke, Fryer, & Osborne, 1996). The major intracerebral lesions are the tubers, which consist of histogenic malformations of both neuronal and glial elements with giant heterotopic cells, characteristically located in the subependymal regions and in the cortex (Braffman & Naidich, 1994; Harrison & Bolton, 1997; Truhan & Filipek, 1993). These tumors are variably expressed, resulting in a phenotype that ranges from only mild skin manifestations to severe mental retardation and intractable epilepsy (Curatolo et al., 2002; Kandt, 2003; Short, Richardson, Haines, & Kwiatkowski, 1995). Between 50% and 60% of affected individuals are mentally retarded and 80% have seizures; those with mental retardation invariably have seizures (Gomez, Sampson, & Whittemore, 1999).

TSC is an autosomal dominant disorder caused by mutations in either of two genes: TSC1 on chromosome 9q34 producing hamartin and TCS2 on chromosome 16p13.3 producing tuberin (Curatolo et al., 2002; OMIM™, 2000). It has been puzzling that two separate genotypes could be associated with apparently identical phenotypes. It is now known that hamartin and tuberin must bind together into a protein complex to regulate mTOR (mammalian *t*arget *o*f *r*apamycin) in a critical signaling pathway to control cell size and proliferation (Lewis, Thomas, Murphy, & Sampson, 2004; McManus & Alessi, 2002; for a review, see Kwiatkowski, 2003).

The phenotypes of TSC1 and TSC2 have been considered to be identical in character. However, recent studies indicate that there may be differences in severity between the two genotypes. TSC1 accounts for 85% to 90% of familial cases, while TSC2 is responsible for 70% of sporadic cases. It also appears that individuals with TSC2 may more likely be mentally retarded than those with TSC1 (P. J. de Vries & Bolton, 2000; A. C. Jones et al., 1997, 1999; van Slegtenhorst et al., 1999; Zhang et al., 1999) and, therefore, more likely to have severe seizures. Lewis et al. (2004) noted that the presence of a TSC2 mutation carried a significantly higher risk of low IQ, autistic disorder, and infantile spasms than a TSC1 mutation. The odds ratio of low IQ in TSC2 has been reported as 2.44 (P. J. de Vries & Bolton, 2000) and 3.5 (Lewis et al., 2004), the latter adjusted for a history of infantile spasms. It would make sense, therefore, that individuals with TSC1 with a potentially milder phenotype would be more likely to reproduce and contribute to familial lines of

Table 20.1 Other Syndromic Associations

47, XYY		Abrams & Pergament, 1971 Nielsen, Christensen, Friedrich, Zeuthen, & Ostergaard, 1973 Nicolson, Bhalerao, & Sloman, 1998 Weidmer-Mikhail et al., 1998
CHARGE association (coloboma, heart defect, choanal atresia, retarded growth and development, genital hypoplasia, ear anomalies		Fernell et al., 1999
Chromosome 2q37 deletion syndrome		Ghaziuddin & Burmeister, 1999 Smith et al., 2001
Chromosome 13 deletion syndrome		Steele, Al-Adeimi, Siu, & Fan, 2001 Smith et al., 2002
Chromosome 22q13 terminal deletion syndrome		Prasad et al., 2000
Cohen syndrome		Chandler, Moffett, Clayton-Smith, & Baker, 2003
Cornelia de Lang syndrome		Berney, Ireland, & Burn, 1999
Pediatric epilepsy syndromes		Besag, 2004
Infantile spasms/West syndrome		Askalan et al., 2003
Aristaless-related homeobox gene (ARX) syndrome		Stromme, Mangelsdorf, Scheffer, & Gecz, 2002 Sherr, 2003
Fetal alcohol syndrome		Aronson, Hagberg, & Gillberg, 1997
FG syndrome (mental retardation, large head, imperforate anus, congenital hypotonia, and partial agenesis of corpus callosum)		Ozonoff, Williams, Rauch, & Opitz, 2000
Goldenhar syndrome		Landgren, Gillberg, & Stromland, 1992
Histidinemia		Kotsopoulos & Kutty, 1979
Hypomelanosis of Ito		Akefeldt & Gillberg, 1991 Zappella, 1993 Pascual-Castroviejo et al., 1998
Infections	Congenital	Chess, 1971 Stubbs, 1978 Yamashita, Fujimoto, Nakajima, Isagai, & Matsuishi, 2003
	Acquired	Ghaziuddin, Al-Khouri, & Ghaziuddin, 2002 Ghaziuddin, Tsai, Eilers, & Ghaziuddin, 1992 C. Gillberg, 1991 C. Gillberg, 1986 Domachowske et al., 1996
Joubert syndrome		Ozonoff, Williams, Gale, & Miller, 1999 Raynes, Shanske, Goldberg, Burde, & Rapin, 1999
Kleinfelter's syndrome		Kielinen et al., 2004
Lesch-Nyhan syndrome		Nyhan, James, Teberg, Sweetman, & Nelson, 1969
Neurofibromatosis Type 1		C. Gillberg & Forsell, 1984 P. G. Williams & Hersh, 1998 Fombonne et al., 1997
Smith-Lemli-Opitz syndrome		Tierney et al., 2001 Goldenberg, Chevy, Bernard, Wolf, & Cormier-Daire, 2003
Thalidomide embryopathy		Stromland, Nordin, Miller, Akerstrom, & Gillberg, 1994 Stromland, Philipson, & Andersson Gronlund, 2002
Turner syndrome		Skuse et al., 1997 El Abd, Patton, Turk, Hoey, & Howlin, 1999 Donnelly et al., 2000

TSC (A. C. Jones et al., 1997; Lewis et al., 2004). However, the jury is still out with respect to differential representation of autism in the TSC1 and TSC2 genotypes.

Autistic symptoms were first described in patients with TSC a decade before Kanner's classic delineation of infantile autism (Critchley & Earl, 1932). These early noted symptoms included stereotypies, absent or abnormal speech, withdrawal, and impaired social interactions. TSC has since been strongly associated with autism, and estimates range from 17% to over 65% of individuals with TSC who are also autistic, identified more frequently in those with mental retardation, most commonly with epilepsy (Curatolo et al., 1991; I. Gillberg, Gillberg, & Ahlsen, 1994; Gutierrez, Smalley, & Tanguay, 1998; Harrison & Bolton, 1997; Hunt & Shepherd, 1993; Kandt, 2003; Riikonen & Simell, 1990). The reverse, the number of autistic individuals with TSC, has been estimated between 0.4% and 4% in epidemiological studies (C. Gillberg, Steffenburg, & Schaumann, 1991; Lotter, 1967; Ritvo et al., 1990; Smalley, Tanguay, Smith, & Gutierrez, 1992). This rate increases to 8% to 14% in autistic subjects with epilepsy (C. Gillberg, 1991; Riikonen & Amnell, 1981).

Fragile X

As the most common inherited cause of mental retardation, FXS is second only to Down syndrome in terms of a known chromosomal cause of mental retardation. FXS is characterized by macroorchidism, large protruding ears, and moderate to severe mental retardation (for recent reviews, see Hagerman, 2002; Kooy, Willemsen, & Oostra, 2000; and Willemsen, Oostra, Bassell, & Dictenberg, 2004). In over 99% of the cases, this syndrome is caused by an unstable amplification (excessive triplet repetition) of cytosine (C) and guanine (G) within the FMR1 gene on chromosome Xq27.3 (Verkerk et al., 1991). The range of ~5 to ~44 CGG triplet repeats is considered to be a normal finding, ~45 to 54 repeats is considered the intermediate "gray zone," and ~55 to 200 repeats is considered the premutation state producing carriers who may or may not be affected. Above a threshold of approximately 200 to 230 repeats with an abnormal methylation pattern, no FXS protein (FMRP) is produced and people are fully affected with FXS (Maddalena et al., 2001). Prevalence of the full syndrome is 2.4 per 10,000 in males and 1.6 per 10,000 in females; prevalence of the premutation carrier status is 12.3 per 10,000 in males and 38.6 per 10,000 in females (Dombrowski et al., 2002).

FXS is associated with numerous distinctive neuropsychological deficits, which are not analogous with the overall cognitive impairment (Bennetto & Pennington, 2002; Loesch, Huggins, & Hagerman, 2004). Loesch et al. (2004) reviewed the correlations between FMRP depletion and deficits of cognitive and executive function on both genders with FXS using the Wechsler Adult Intelligence Scale-III (WISC-III, Wechsler, 1997). The Digit Span and Symbol Search subtests in both sexes and Picture Arrangement subtest in females showed that subjects were particularly affected by FMRP depletion, suggesting deficits in the cognitive constructs of processing speed, short-term memory, and attention. Although females are usually less affected than males because of the presence of the second unaffected X chromosome (Loesch et al., 2004), 50% to 70%, nonetheless, demonstrated significant cognitive deficits (B. B. de Vries et al., 1996), which correlated with the ratio of cells in which the normal X chromosome is activated (B. B. de Vries et al., 1996; Riddle et al., 1998; Tassone et al., 2000) and FMRP levels (Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997).

Premutation carriers, both male and female, have traditionally been thought to be entirely unaffected. It is surprising, however, that a premutation phenotype has recently been recognized. Hagerman et al. (2001) and Jacquemont et al. (2003, 2004) reported a syndrome of progressive intention tremor, cerebellar ataxia, executive function deficits, and brain atrophy (FXTAS) in asymptomatic older males with the FXS premutation status. Additional documented signs include short-term memory loss, cognitive decline, parkinsonism, peripheral neuropathy, proximal muscle weakness, and autonomic dysfunction. The late onset of this syndrome is due to an age-related penetrance, giving such carriers an age-adjusted 13-fold increased risk of combined intention

tremor and gait ataxia (Jacquemont et al., 2004). Most recently, Hagerman et al. (2004) reported five female premutation carriers with symptoms of FXTAS, but none demonstrated the dementia noted in the males with FXTAS. In addition, females with the premutation had an increased (~20%) incidence of premature ovarian failure and early menopause, which has not been reported in females with the full FXS mutation (Murray, 2000; Sherman, 2000).

The early descriptions of FXS focused on fully affected males and their many autistic features. These features included poor eye contact; language delay, perseveration, and echolalia; self-injurious behaviors; motor stereotypies (e.g., hand flapping and body rocking); hypersensitivity to auditory stimuli or environmental change; tactile defensiveness; preoccupations with a narrow range of stimuli; and poor social relating (August & Lockhart, 1988; Borghgraef, Fryns, Dielkens, Pyck, & Van den Berghe, 1987; Fryns, Jacobs, Kleczkowska, & Van den Berghe, 1984; C. Gillberg, Persson, & Wahlstrom, 1986; Hagerman, Jackson, Levitas, Rimland, & Braden, 1986; Meryash, Szymanski, & Gerald, 1982). In the previous edition of this text (1997), over 30 studies were noted describing the prevalence of autism in FXS and vice versa (Dykens & Volkmar, 1997). The prevalence rates for FXS in autistic samples ranged from 0 to 16%, with a median of about 4%, while the prevalence rates of autism in fragile XFXS samples varied considerably, from 5% to 60%. Some researchers asserted that their prevalence rates of FXS and autism—16% to 20%—far exceeded the 4.5% to 7% of severely and mildly retarded males with FXS, concluding that FXS was strongly associated with autism (Blomquist et al., 1985; Fisch, Cohen, Jenkins, & Brown, 1988; C. Gillberg & Wahlstrom, 1985). In contrast, others claimed that their ~3% to 5% prevalence rates of autism and fragile XFXS were no higher than the rate of FXS among mentally retarded males (Payton, Steele, Wenger, & Minshew, 1989; Watson et al., 1984); therefore, the argument was that FXS should not increase the risk of autism above and beyond the risk associated with mental retardation. Subsequent work supported this latter position. A. Bailey et al. (1993) found that only 1.6% of their autistic population had FXS, and Einfeld, Molony, and Hall (1989) found comparable rates of autism in appropriately matched groups of FXS and non-fragile XFXS males. Summarizing data across 40 studies, Fisch (1992) found virtually identical pooled proportions of FXS in autistic males and in mentally retarded males in general. These studies suggested that autism and FXS indeed may co-occur, but the prevalence of these cases is much lower than originally thought, and that FXS is not a major etiologic factor in autism.

The debate continues, with data that support both sides of the argument. O. Hashimoto, Shimizu, and Kawasaki (1993) noted no association between FXS and autism in their cohort. Klauck et al. (1997) found that 139 of 141 patients with autism were negative for the full syndrome. Only one multiplex family accounted for the positive FXS testing in their cohort: the mother with a premutation, one female autistic child who was heterozygous, and two male children with full mutations—one autistic with mental retardation and one with normal cognition and mild learning disabilities. Maes, Fryns, Van Walleghem, and Van den Berghe (1993) described males with FXS as having stereotypic movements, disturbing language patterns, social avoidance reactions, and eccentric peculiarities, but also showing social openness and sensitivity; however, there was no difference in the general levels of autistic behaviors between the mentally retarded males with and without FXS. Turk and Graham (1997) reported that their FXS cohort also did not demonstrate more autism than the comparison group with idiopathic mental retardation; however, both groups demonstrated more autism diagnoses (~70% to 80%) than did a second comparison group with Down syndrome (~30%). They concluded that FXS demonstrates a characteristic autistic-like phenotype of communication and stereotypic disturbances with delayed echolalia, repetitive speech, and hand flapping.

D. B. Bailey, Hatton, Mesibov, Ament, and Skinner (2000), using the CARS (Schopler et al., 1988), reported that FXS boys without autism showed a relatively flat developmental profile in contrast to the varied, uneven profiles and more severe cognitive difficulties seen in FXS with autism; FXS without autism also demonstrated more social competence

and temperaments that were similar to typically developing children. They subsequently noted that the expression of the FXS protein (FMRP) accounted for less variance in developmental level in FXS than did the comorbidity of autism, suggesting that autism in FXS may come from a second hit predisposing to autism (D. B. Bailey, Hatton, Skinner, & Mesibov, 2001; also postulated by Feinstein & Reiss, 1998).

S. J. Rogers, Wehner, and Hagerman (2001) used the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and the ADOS-G (Lord et al., 2000) to evaluate FXS in comparison to non-FXS autistic and other developmentally disabled children and reported two FXS subgroups: One-third of the FXS group met the stringent criteria for autism and were very similar to the non-FXS autistic cohort, while the remaining two-thirds of the FXS group were not autistic and were very similar to the group with other developmental disabilities. Philofsky, Hepburn, Hayes, Hagerman, and Rogers (2004), also using the ADOS and ADI for autism diagnosis, reported that the FXS/autism cohort was more impaired in nonverbal cognition and receptive and expressive language relative to the FXS children; receptive language function was similarly poor in children with autism, regardless of FXS status. Kau et al. (2004), again using the ADI, noted that the FXS/autism cohort was more cognitively impaired and demonstrated more aberrant behaviors but, notwithstanding, was less impaired in the reciprocal social domain than the autistic cohort without FXS. The authors proposed a Social Behavior Profile (SBP) as a distinct subphenotype of FXS, which may share mechanisms with autism.

The extent of association of autism and FXS is still unknown. As stated by Mazzocco et al. (1998):

> . . . despite the specificity of autistic behavior among fragile X males and females, these behaviors (a) are not seen in all children with the disorder, (b) range in severity across individuals with the disorder, and (c) may be seen among individuals with fragile X regardless of whether they meet *DSM* criteria for autistic disorder. (p. 326)

This issue may be resolved with current studies that are using the gold standard autism diagnostic instruments (ADOS-G and ADI-R) so that variability in mode of diagnosis should no longer be a confounding factor in this debate.

Down Syndrome

Down syndrome is the most common chromosomal cause of mental retardation, originally occurring in approximately 1 in 800 live births (Hook, 1982); more recently, with available options for prenatal diagnosis and elective termination, it has decreased to approximately 1 in 1,000 live births (Bell, Rankin, & Donaldson, 2003; Iliyasu, Gilmour, & Stone, 2002; Olsen, Cross, & Gensburg, 2003). Although once considered implausible, the comorbidity of autism and Down syndrome is not rare (Bregman & Volkmar, 1988; Ghaziuddin, 1997, 2000; Ghaziuddin, Tsai, & Ghaziuddin, 1992; Howlin et al., 1995; Wakabayashi, 1979; Wing & Gould, 1979). In fact, Down's original phenotypic description (Down, 1887/1990, pp. 6–7) of Mongolism certainly gives credence to the concept that comorbidity of Down syndrome and autism has always existed:

> These children have always great power of imitation and become extremely good mimics . . . I have known a ventriloquist to be convulsed with laughter between the first and second parts of his entertainment on seeing a Mongolian patient mount the platform, and hearing him grotesquely imitate the performance with which the audience had been entertained. They have a strong sense of the ridiculous; this is indicated by their humorous remarks and the laughter with which they hail accidental falls, even of those to whom they are most attached. Another feature is their great obstinacy—they can only be guided by consummate tact. No amount of coercion will induce them to do that which they have made up their minds not to do. Sometimes they initiate a struggle for mastery, and the day previous will determine what they will or will not do on the next day. Often they will talk to themselves, and they may be heard rehearsing the disputes which they think will be the feature of the following day. They in fact, go through a play in which the patient, doctor, governess, and nurses are the *dramatis personae*—a play in which the patient is represented as defying and contravening the wishes of those in authority.

In epidemiological studies, the prevalence of Down syndrome in individuals with autism ranges from none to 16.7% (see Fombonne, 2003, for review). Large-scale studies that

screened samples with Down syndrome for autism found relatively low rates of autism, ranging from 1.0% to 2.2%. However, other series have reported that as many as 10% of subjects with Down syndrome also meet criteria for autism (Ghaziuddin, 1997; Ghaziuddin et al., 1992; C. Gillberg et al., 1986; Lund, 1988; Wing & Gould, 1979).

Howlin et al. (1995) eloquently championed the importance of recognizing autism in children with Down syndrome. Although autism diagnoses are typically made in the preschool years, they noted later ages of autistic diagnoses in all cases reported in the literature (range from 7 years to adulthood). This singular diagnostic view creates unnecessary stress for families and prevents them from using supports and interventions available to families with an autistic child.

Reasons for the lack of recognition of autistic signs in Down syndrome are unclear. The stereotyped personality of individuals with Down syndrome is outgoing, affectionate, easygoing, placid, cheerful, highly social, and verbal—like "Prince Charming" (Gibbs & Thorpe, 1983; Menolascino, 1965). Some mothers describe their children with Down syndrome with a wide range of personality features (C. Rogers, 1987; Wishart & Johnston, 1990). While some children are easygoing, others are more active and distractible, with difficult temperaments (see Ganiban, Wagner, & Cicchetti, 1990, for a review). Yet, children with comorbid Down syndrome and autism are very different from other children with Down syndrome, demonstrating classic deficits in sociability, immediate and delayed echolalia, poor developmental progress in communication skills, motor stereotypies and ritualistic behaviors or interests, and adaptive behaviors. Even though autism may not be common in Down syndrome, it should be considered in the range of diagnostic possibilities for all individuals with this syndrome.

Rates of other psychiatric disorders are low for persons with Down syndrome, even as compared to groups with other types of developmental delay (Collacott, Cooper, & McGrother, 1992; Grizenko, Cvejic, Vida, & Sayegh, 1991; Myers & Pueschel, 1991). Some children, however, may be prone to attentional difficulties, overactivity, oppositionality, and anxiety (Gath & Gumley, 1986; Myers & Pueschel, 1991; Pueschel, Bernier, & Pezzullo, 1991). Further, adults with Down syndrome are particularly vulnerable to Alzheimer-type dementia (Bush & Beail, 2004).

Williams-Beuren Syndrome

Williams-Beuren syndrome (WBS) is a rare disorder first described over 40 years ago (Beuren, Apitz, & Harmjanz, 1962; J. C. Williams, Barratt-Boyes, & Lowe, 1961) and caused by a microdeletion on chromosome 7q11.23 that includes the gene for elastin (OMIM™, 2000). Persons with WBS often show a distinctive cognitive profile, hyperacusis, supravalvular aortic stenosis, hypercalcemia, and characteristic facial features described as "elfin-like" (Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Osborn, Harnsberger, Smoker, & Boyer, 1990; Pober & Dykens, 1996). Although WBS is thought to affect about 1 in 20,000 people (Pober & Dykens, 1996), the most recent epidemiological study in Finland noted a prevalence of 1 in 7,500 individuals (Stromme, Bjornstad, & Ramstad, 2002). The association between WBS and autism has not yet been widely studied, and there are only a few cases of comorbidity formally reported in the literature (C. Gillberg & Rasmussen, 1994; Reiss, Feinstein, Rosenbaum, Borengasser-Caruso, & Goldsmith, 1985). Individuals with WBS were almost twice as likely to be diagnosed with a psychiatric disorder characterized by anxiety, preoccupations, wandering, being overaffectionate, and seeking attention, and having difficulty with interpersonal interactions, with sleep disorders, and hyperacusis, than were controls who were matched for degree of cognitive deficit (Einfeld, Tonge, & Florio, 1997).

WBS and autism have traditionally been thought to show opposing patterns of cognitive strength and weakness. By definition, individuals with autism have poor verbal and nonverbal communication skills (see Chapter 12, this *Handbook,* this volume). In contrast, despite significant early language delay, many individuals with WBS have been described as showing relative sparing of expressive language and linguistic functioning, including high-level

syntax and semantics (Bellugi, Marks, Bihrle, & Sabo, 1988), storytelling and narrative enrichment strategies involving affective prosody and a sense of drama (Reilly, Klima, & Bellugi, 1990), and a reliance on stereotypic, adult phrases (Udwin & Yule, 1990). However, nonverbal, perceptual skills are typically weak in WBS, often with marked difficulties in visual-spatial processing, especially integrating details into a whole. Yet, certain visual-spatial skills seem well preserved even within this area of deficit. In particular, persons with WBS generally excel on facial perception and recognition tasks (Bellugi, Wang, & Jernigan, 1994; Udwin & Yule, 1991). They often look intently at the faces of both strangers and familiar people (Bellugi, Bihrle, Neville, Doherty, & Jernigan, 1992; Bertrand, Mervis, Rice, & Adamson, 1993), although they solve face-processing tasks by different cognitive processes (Grice et al., 2001). (For reviews, see Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; and W. Jones et al., 2000.)

Recently, investigators have more specifically characterized atypical language development in WBS. Mervis (1999) noted that referential language precedes referential pointing in WBS, and the developmental vocabulary spurt occurs prior to spontaneous exhaustive sorting, the opposite of what is seen in typical language development. Toddlers with WBS also do not spontaneously use the pointing gesture in free-play situations. Laing et al. (2002) reported that despite superficially good social skills, children with WBS were deficient at both initiating and responding to triadic interactions (e.g., child-interlocutor-object), which are essential for instrumental and declarative joint attention and for referential uses of language; they did show proficiency at dyadic interactions (e.g., face to face), however. It has been suggested that children with WBS may be less interested in objects and more interested in faces than typical children (Bertrand et al., 1993). The WBS group was also impaired on the comprehension and production of referential pointing, despite vocabulary levels higher than those of typically developing children of the same mental age, which could not be explained on the basis of fine motor impairments (Laing et al., 2002). The authors thereby challenged the published claims that individuals with WBS have "preserved linguistic and social skills."

Tager-Flusberg and Sullivan (2000) reported on the dissociation of the social-cognitive and social-perceptual components of theory of mind in WBS, with relative sparing of the latter. Children with WBS did poorly on false-belief understanding (social-cognition) tasks but were able to provide mental-age-appropriate explanations for another person's behaviors and to discriminate and match facial expressions of emotion (social-perceptual tasks). Laws and Bishop (2004) demonstrated that children with WBS indeed have difficulties with social relationships and a semantic-pragmatic language disorder (described by some as "loquaciousness"), particularly with inappropriate initiation of conversation and the use of stereotyped conversation. They produce less coherent narratives and conversation despite having syntactic abilities equivalent to normal controls, and they score low for conversation rapport. They also have a restricted range of interests, specialized factual knowledge, and usual vocabulary. The authors (2004, p. 45) even suggested that:

> Far from representing the polar opposite of autism, as suggested by some researchers, Williams syndrome would seem to share many of the characteristics of autistic disorder.

Further research in WBS will elucidate whether the extent of shared characteristics would enable official inclusion on the autistic spectrum.

Mitochondrial Disorders

Coleman and Blass (1985) first reported an association of lactic acidosis with autism over 20 years ago, which was corroborated by Laszlo, Horvath, Eck, and Fekete (1994). Lombard (1998) postulated a mitochondrial etiology for autism based on, among other things, his unpublished anecdotal observations of carnitine deficiency. Functional neuroimaging methodologies have also related autism and deficient energy metabolism in the brain (Chugani, Sundram, Behen, Lee, & Moore, 1999; Levitt et al., 2003; Minshew, Goldstein, Dombrowski, Panchalingam, & Pettegrew,

1993). Graf et al. (2000) reported a family with a group of neurologic disorders associated with the mitochondrial DNA G8363A transfer ribonucleic acid $(RNA)^{Lys}$ mutation; of four family members affected, one child was also severely autistic. Ramoz et al. (2004) reported linkage and association of the mitochondrial aspartate/glutamate carrier SLC25A12 gene with autism. Filiano, Goldenthal, Rhodes, and Marin-Garcia (2002) reported a group of 12 children presenting with hypotonia, intractable epilepsy, autism, and developmental delay (HEADD syndrome), who demonstrated reduced levels in specific mitochondrial respiratory activities encoded by mitochondrial DNA, with a majority also showing mitochondrial structural abnormalities. Pons et al. (2004) recently reported five patients with autism who had concurrent A3243G mitochondrial (mt)DNA mutations and mtDNA depletion syndromes. This mutation typically causes mitochondrial encephalopathy, lactic acidosis, seizures, hearing loss, and strokes (MELAS syndrome) with ragged red fibers in skeletal muscle. Four of these five patients were ascertained because a maternal relative was identified with the mutation, not because they presented with symptoms consistent with a mitochondrial disorder. Clark-Taylor and Clark-Taylor (2004) reported a child with autism who also had an abnormal acyl-carnitine profile with elevations of unsaturated fatty-acid metabolites C14:1 and C14:2 and ammonia and alterations of tricarboxylic acid cycle energy production. Filipek et al. (in press) reported that free and total carnitine and pyruvate were significantly reduced while ammonia, lactate, and alanine levels were considerably elevated in 100 autistic children. The relative carnitine deficiency in these patients, accompanied by slight elevations in lactate and significant elevations in alanine and ammonia levels, is suggestive of mild mitochondrial dysfunction, and the authors hypothesized that a mitochondrial defect might be the origin of the carnitine deficiency in these autistic children.

Lerman-Sagie, Leshinsky-Silver, Watemberg, and Lev (2004) reviewed the literature on the association of autism and mitochondrial disorders:

> Mitochondrial diseases are probably a rare and insignificant cause of pure autism; however, evidence is accumulating that . . . mitochondrial disorders can present with autistic features. Most patients will present with multisystem abnormalities (especially neurologic) associated with autistic behavior. (p. 381)

Nevertheless, because our knowledge of mitochondrial function and dysfunction is presently expanding exponentially and concurrently with our knowledge of the neurobiology and genetics of autism, further research is indicated to elucidate the validity and extent of mitochondrial dysfunction in individuals with autism.

Isodicentric Chromosome 15q Syndrome

A chromosomal duplication syndrome found in autism involves the proximal long arm of chromosome 15q11-q13 (IDIC 15). The duplication is usually maternally inherited and involves the area roughly corresponding to the Prader-Willi/Angelman critical region (PWACR) of approximately four million base pairs. The additional genetic material may be interstitial (within one chromosome 15, producing 46,XY) and may or may not be inverted, producing a trisomy (three copies) of 15q11-q13. Or, the additional material may form a separate marker chromosome (47,XY), producing a tetrasomy (four copies) of this region. Although the prevalence of duplications of the PWACR is estimated to be similar to that of deletions in this region, 1:15,000 (Mohandas et al., 1999), the phenotype of the duplication syndrome has become appreciated only within the past 8 to 10 years.

This syndrome is one of the most frequent of the currently identifiable chromosomal disorders associated with autism, occurring in between 1% and 4% of autistic individuals (Browne et al., 1997; Konstantareas & Homatidis, 1999; Schroer et al., 1998). The clinical phenotype in autism is highly variable, ranging from profound psychomotor retardation to normal nonverbal cognitive scores (Filipek, Smith, et al., 2000). Rineer, Finucane, and Simon (1998) noted that, of 29 individuals with IDIC 15, 20 met criteria for autism using the GARS (Gilliam, 1995); those autistic IDIC

15 differed from the GARS autistic norming group only on having better social function as measured by the social interaction subscale, which corresponds to the anecdotal experience of this author and other investigators (Catherine Lord, personal communication). More than 100 individuals with autism and this chromosomal anomaly have been reported in the literature to date (Baker, Piven, Schwartz, & Patil, 1994; Battaglia et al., 1997; Bolton et al., 2001; Borgatti et al., 2001; Bundey, Hardy, Vickers, Kilpatrick, & Corbett, 1994; Cheng, Spinner, Zackai, & Knoll, 1994; Cook et al., 1997; Estecio, Fett-Conte, Varella-Garcia, Fridman, & Silva, 2002; Fantes et al., 2002; Flejter et al., 1996; C. Gillberg, Steffenburg, Wahlstrom, et al., 1991; Gurrieri et al., 1999; Hotopf & Bolton, 1995; Hou & Wang, 1998; Keller et al., 2003; Konstantareas & Homatidis, 1999; Lauritsen, Mors, Mortensen, & Ewald, 1999; Ludowese, Thompson, Sekhon, & Pauli, 1991; Mann et al., 2004; Mao & Jalal, 2000; Moeschler, Mohandas, Hawk, & Noll, 2002; Rausch & Nevin, 1991; Repetto, White, Bader, Johnson, & Knoll, 1998; Rineer et al., 1998; Sabry & Farag, 1998; Schroer et al., 1998; Silva, Vayego-Lourenco, Fett-Conte, Goloni-Bertollo, & Varella-Garcia, 2002; Ungaro et al., 2001; Webb et al., 1998; Weidmer-Mikhail, Sheldon, & Ghaziuddin, 1998; Wisniewski, Hassold, Heffelfinger, & Higgins, 1979; Wolpert et al., 2000; Woods, Robinson, Gardiner, & Roussounis, 1997; Yardin et al., 2002).

Filipek et al. (2003) reported mitochondrial dysfunction in two autistic children with isodicentric 15q syndrome. Both had uneventful perinatal courses, normal EEGs and MRI scans, moderate motor delay, pronounced lethargy when ill, severe hypotonia, and modest lactic acidosis. On muscle mitochondrial enzyme assays, each had pronounced mitochondrial hyperproliferation and a partial respiratory chain block most parsimoniously placed at the level of complex III, suggesting candidate gene loci for autism within the PWACR that affect pathways influencing mitochondrial function.

Some investigators have recently questioned whether fluorescent in situ hybridization (FISH) studies should be performed in addition to high-resolution karyotype in all cases of autism to detect duplication of 15q (Keller et al., 2003; Yardin et al., 2002). In addition to its association with autism, Longo et al. (2004) reported isodicentric 15q11-q13 duplications in 3 of 63 (4.7%) patients with Rett syndrome in addition to the MECP2 deletions.

Angelman/Prader-Willi Syndromes

Described as "sister imprinting disorders" (Cassidy, Dykens, & Williams, 2000), Angelman and Prader-Willi (PWS) syndromes are each the result of either a deletion or uniparental disomy (UPD) in the PWACR of chromosome 15 (see Clayton-Smith & Laan, 2003, for a review). Angelman syndrome, coined the "happy puppet syndrome" (Bower & Jeavons, 1967), presents with severe motor and intellectual retardation, ataxia, hypotonia, epilepsy, absence of speech, and unusual "happy" facies (OMIM™, 2000). Evidence is strong that the gene for Angelman syndrome is the E6-associated protein ubiquitin-protein ligase gene (UBE3A), which suggests that Angelman syndrome is the first recognized example of a genetic disorder of the ubiquitin-dependent proteolytic pathway in humans (Kishino, Lalande, & Wagstaff, 1997; OMIM™, 2000). Steffenburg, Gillberg, Steffenburg, and Kyllerman (1996) reported that all four children with Angelman syndrome ascertained in a population study met behavioral criteria for autism. Trillingsgaard and Stergaard (2004) found that 13 of 16 children with Angelman met ADOS-G (Lord et al., 2000) criteria for an ASD; however, the authors noted that autism might have been overdiagnosed in their sample because of the extremely low cognitive levels of the children with Angelman. C. A. Williams, Lossie, and Driscoll (2001) noted that some children with ASD may be misdiagnosed with Angelman, particularly with negative genetic testing for Angelman. Thompson and Bolton (2003) reported one case of Angelman syndrome and paternal UPD and described the milder Angelman symptomatology associated with UPD as including a lack of autistic features.

PWS is characterized by obesity, muscular hypotonia, mental retardation, short stature,

hypogonadotropic hypogonadism, and small hands and feet. It appears that PWS results from UPD or deletion of the paternal copies of the imprinted small nuclear ribonucleoprotein polypeptide N (SNRPN) and necdin genes and possibly others as well (OMIM™, 2000). Veltman et al. (2004) found that maternal UPD cases of PWS would be more likely to exhibit ASD than would cases with deletions in the PWACR. Therefore, the extent of the associations of Angelman and PWS with autism remains unclear, particularly the differential effects of UPD as compared with deletions of the responsible genes.

Velocardiofacial Syndrome

Shprintzen, Goldberg, Young, and Wolford (1981) first described velocardiofacial syndrome (VCFS), which is characterized by cleft palate, cardiac malformations (usually a ventricular septal defect), typical facies (tubular nose, narrow palpebral fissures, and retruded jaw), learning disabilities and/or mental retardation, microcephaly, short stature, CNS vascular malformations, and seizures (Coppola, Sciscio, Russo, Caliendo, & Pascotto, 2001; OMIM™, 2000; Perez & Sullivan, 2002; Roubertie et al., 2001). VCFS is now known to be caused by a microdeletion on chromosome 22q11.2. It is also known as CATCH 22 and chromosome 22q11 deletion syndromes, and its prevalence is estimated at 1 per 4,000 (Bassett & Chow, 1999).

There is an extremely high prevalence of neuropsychiatric disorders in VCFS involving over 50% of the reported cases. Gothelf and colleagues reported that 16% to 25% will develop psychotic disorder by adolescence; the prevalence of schizophrenia in VCFS is 25 times that of the general population (Gothelf & Lombroso, 2001; Gothelf, Presburger, Levy, et al., 2004; Gothelf, Presburger, Zohar, et al., 2004). Up to 40% meet criteria for attention deficit/hyperactivity disorder, and 33% for obsessive-compulsive disorder. Over half of the cases in some series were mentally retarded (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001).

The most characteristic behavioral phenotype is that of a nonverbal learning disorder, with verbal IQ scores significantly greater than nonverbal, despite almost universal severe early language delay (Bearden et al., 2001; Niklasson et al., 2001; Wang, Woodin, Kreps-Falk, & Moss, 2000; Woodin et al., 2001). A marked deficit in visuospatial memory has been documented in these children, producing the described mathematics disabilities. In addition to the selective deficit in visuospatial memory, Bearden et al. (2001) found a dissociation between visuospatial and object memory and noted the similarity of the VCFS cognitive profile with WBS (Bearden, Wang, & Simon, 2002).

Kozma (1998) was the first to report comorbid autism in VCFS, with associated severe mental retardation. Niklasson et al. (2001; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2002) found that more than 30% of their VCFS subjects were also autistic, 50% had "autistic traits," and more than 50% had mental retardation; only 6% of their sample had a normal IQ and were free of neuropsychiatric disorders. Scherer, D'Antonio, and Rodgers (2001) noted a sparse vocabulary and pattern of sound types and very low mean babbling length relative to other communication measures, differing qualitatively and quantitatively from that found in Down syndrome. Glaser et al. (2002) noted uniquely lower receptive language function relative to expressive language ability; they also found parent-of-origin effects, with those with a deletion of paternal origin scoring higher on language measures than those with a deletion of maternal origin.

Möbius Syndrome

Möbius syndrome maps to chromosome 13q12.2-q13 and is characterized by brainstem maldevelopment resulting in congenital unilateral or bilateral paresis of the facial (7th) cranial nerve. There is variable involvement of other cranial nerves, usually the abducens (6th), but also possibly the trigeminal (5th), glossopharyngeal (9th), or hypoglossal (12th). There is associated mental retardation, orofacial and limb malformations, and musculoskeletal defects (Möbius, 1888; OMIM™, 2000).

Several reports noted the co-occurrence of autism and Möbius syndrome (C. Gillberg &

Winnergard, 1984; Larrandaburu, Schuler, Ehlers, Reis, & Silveira, 1999; Ornitz, Guthrie, & Farley, 1977), while others described difficulties in communication, social interactions, and maladaptive behaviors without specific diagnoses of autism (Giannini, Tamulonis, Giannini, Loiselle, & Spirtos, 1984; Meyerson & Foushee, 1978). In an early report, C. Gillberg and Steffenberg (1989) noted autistic behaviors in about 40% of individuals with Möbius syndrome. One autistic child, whose brainstem neuropathology noted virtual absence of neurons in the facial nerve nucleus, was also described as having little facial expression and may have also had Möbius or a similar syndrome (Rodier, Ingram, Tisdale, Nelson, & Romano, 1996).

Johansson et al. (2001) found an ASD in 40% of their cohort with Möbius syndrome, using the ADI-R (Lord et al., 1994), with mental retardation in one-third of the subjects. Bandim, Ventura, Miller, Almeida, and Costa (2003) used the CARS (Schopler et al., 1988) to diagnose autism in one-third of their cohort; the average CARS score for the autistic individuals was 40.4, in the severe range, while the average for the nonautistic individuals was 18.4. Stromland et al. (2002) reported comorbid autism in 24% of their cohort with Möbius, using the ADI-R (Lord et al., 1994).

Although Möbius syndrome has an identified genetic locus, there have been reports of an association of Möbius after in utero exposure to misoprostol, a prostaglandin analogue used to prevent and treat GI ulceration from nonsteroidal anti-inflammatory medications (Pastuszak et al., 1998); misoprostol is also available over the counter in some countries and used to self-induce abortions (Gonzalez et al., 1998).

Phenylketonuria

Autism has been associated with several inborn errors of metabolism, primarily PKU (Folstein & Rutter, 1988; Friedman, 1969; Miladi, Larnaout, Kaabachi, Helayem, & Ben Hamida, 1992; R. S. Williams, Hauser, Purpura, DeLong, & Swisher, 1980). Almost half of one cohort with PKU had autistic symptomatology (Bliumina, 1975), and 2% to 5% of autistic children in two other cohorts were found to have untreated PKU (Lowe, Tanaka, Seashore, Young, & Cohen, 1980; Moreno et al., 1992). In contrast, other studies have found essentially no significant abnormalities in metabolic tests in autistic individuals (Johnson, Wiersema, & Kraft, 1974; Perry, Hansen, & Christie, 1978; Pueschel, Herman, & Groden, 1985). In the study by Lowe et al. (1980), the autistic symptoms in the children with PKU improved after initiation of dietary therapy.

Rutter et al. (1997) stated that because untreated PKU is very rare, it must be an even rarer cause of autism. However, reliance on newborn screening programs alone may give a false sense of security, particularly in regions with large immigrant populations. A 4-year-old child, born in the Middle East and diagnosed with autism by both a child psychiatrist and child neurologist in the United States, presented with undiagnosed PKU after her newborn brother was identified on routine newborn screen (Gargus & Filipek, n.d.). In addition, despite extremely strict dietary control of his PKU and frequent normal serum phenylalanine levels when followed in metabolic clinic, the younger child also met *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (*DSM-IV;* American Psychiatric Association, 1994), criteria for Asperger syndrome (Filipek, unpublished observation). Baieli, Pavone, Meli, Fiumara, and Coleman (2003) reported that 2 of 35 individuals with classic PKU who were diagnosed late in infancy (before newborn screening became common) met criteria for autism, using the ADI-R (Lord et al., 1994) and the CARS (Schopler et al., 1988); none of the 62 children identified by newborn screening and on dietary treatment met criteria for autism. In addition, in the group of 144 with mild hyperphenylalanemia due to causes other than classic PKU, one boy had Asperger syndrome with normal IQ, and one retarded child with tetrahydropterin deficiency met criteria for autism. Again, in a sample of individuals with autism, finding undiagnosed and untreated PKU is rare; however, in a sample of individuals with PKU, up to 5% may be autistic.

Congenital Blindness and Deafness

Autistic symptomatology has been anecdotally associated with congenital blindness (CB) for

decades; in some studies, up to 30% of children with CB were also described as being autistic (Chase, 1972; Fraiberg, 1977; Fraiberg & Freedman, 1964; Keeler, 1958; Norris, Spaulding, & Bordie, 1957; Wing, 1969; as cited in reviews by Cass, 1998; Hobson & Bishop, 2003; Hobson, Lee, & Brown, 1999). S. J. Rogers and Newhart-Larson (1989) reported a diagnosis of autism in all five boys studied with Leber's congenital amaurosis. Ek, Fernell, Jacobson, and Gillberg (1998) found that 56% of premature babies with retinopathy of prematurity (ROP) had both autistic disorder and mental retardation, and, of those, one-third had coexistent cerebral palsy. In comparison, only 14% of those with hereditary retinal disease had autistic disorder. Janson (1993) postulated that, in blind children with ROP, a behavior pattern of unresponsitivity and stereotypic object manipulation emerges between 12 and 30 months to distinguish autistic and nonautistic children with CB. Msall et al. (2004) followed children with ROP at ages 5 and 8 years and found that 23% had epilepsy; 39%, cerebral palsy; and 44%, learning disabilities. Of the children with no or minimal light perception or totally detached retinas bilaterally, 9% were autistic, as compared with only 1% of those with more favorable visual status.

Cass, Sonksen, and McConachie (1994) reported that, of an entire sample of over 600 congenitally blind children of differing etiologies, only 17% demonstrated no evidence of additional disabilities and were developing normally at age 16 months when first studied. Subsequently, 31% had a regression in their development at between 16 and 27 months of age; children who regressed tended to have disorders of CNS/optic nerve/retina while children who did not regress had a purely optical cause for their blindness (e.g., congenital cataracts or glaucoma). The more "central" pathophysiology of the blindness in the regression cohort was subsequently confirmed by neuroimaging studies; the children with developmental regression had more CNS lesions than those who did not regress (Waugh, Chong, & Sonksen, 1998).

Brown, Hobson, Lee, and Stevenson (1997) reported that almost half of their sample with CB met criteria for autism and that, even in CB without autism, there were significantly more "autistic features" than seen in matched, sighted children. Brown et al. (1997) and Hobson et al. (1999) compared congenitally blind (of various etiologies) and sighted autistic children and noted remarkably similar clinical features. The mean CARS score (Schopler et al., 1988) was 27.8 (without Item VII, visual responsiveness, scored) for the CB children with autism. The authors' clinical impression was that blind autistic children were less severely impaired than sighted autistic children; none were abnormal in listening response (Item VIII), but most were markedly abnormal in body (IV) and object use (V). Therefore, they noted the close similarities and possible subtle distinctions between the two autistic groups. Hobson and Bishop (2003) went on to evaluate 18 CB children between 4 and 8 years of age who did not meet *DSM-IV* (American Psychiatric Association, 1994) criteria for autism and had an IQ > 55; teacher impressions were used to divide the sample into "more social" (MS, $N = 9$) and "less social" (LS, $N = 9$) groups. In the MS group, the highest CARS score was 15.5 (lowest possible score is 14 without rating Item VII), and no individual item was rated higher than 0.5 above normal. In contrast, in the LS group, the CARS scores ranged from 17.5 to 27.5 (mean 22.3 + 3.6). Four of the subjects had Leber's congenital amaurosis and were all placed into the LS group; almost half of the subjects had ROP and were spread across both groups.

The comorbidity of autism and congenital blindness has received relatively meager attention in the autism research literature. Diagnosis of autism in children with CB is particularly difficult. As Cass (1998) asked:

> . . . distinguishing normal from abnormal social-communication development in children with visual impairment is an even more complex problem. Is it possible to use diagnostic tools more firmly rooted in *ICD-10* criteria such as the Autism Diagnostic Interview (ADI) and the Autism Diagnostic Observation Schedule (ADOS; Le Couteur et al., 1989; Lord, 1991)? Again, there are major problems with this approach since these instruments focus (entirely appropriately for diagnosis in the sighted) on highly visual dependent behaviors such as referential eye gaze, eye gaze for social purposes, protodeclarative pointing and symbolic play, all of which

are either delayed or absent in normally developing children with visual impairment. (p. 129)

Gense and Gense (1994) tried to develop guidelines, using an educational approach, for children with CB and autism, but to date no pragmatic approach to autistic children with CB has been developed. Hobson et al. (1999) proposed several theoretical questions that need to be addressed on a larger scale to formally investigate the associations between autism and CB:

(a) Is the syndrome of autism in blind children to be clearly demarcated from autism-like clinical manifestations in nonautistic blind children, given that there appears to be a gradation in the number, quality, and severity of abnormalities shown by different children? (b) How far is it appropriate to consider each of the clinical manifestations as autistic-like, when such abnormalities might arise on the basis of quite different psychopathological mechanisms? (c) When blind children present with a constellation of clinical features and a picture that approximates to the syndrome of early childhood autism, is this picture distinguishable from that of autism in sighted children? If it is, might the distinguishing features afford insight into the developmental psychopathology of autism itself? (p. 46)

The incidence and prevalence of hearing impairment in children is 11 to 12 per 10,000 (Boyle et al., 1996; Kubba, MacAndie, Ritchie, & MacFarlane, 2004), and the rate steadily increases with age (Boyle et al., 1996). The comorbidity of hearing impairment and autism may be higher than expected (Gordon, 1991; Jure, Rapin, & Tuchman, 1991). Jure et al. (1991) performed a chart review of 46 children diagnosed as deaf and autistic; nearly 20% had normal or near-normal nonverbal cognitive function, and only 20% had severe mental retardation. The severity of the autistic behaviors correlated with the level of cognitive impairment but not to the level of hearing loss. In almost 24%, the diagnosis of comorbid autism did not occur for over 4 years after the diagnosis of deafness; and in another 22%, the diagnosis of hearing impairment was delayed for many years after the diagnosis of autism. Because the diagnosis of the comorbid condition (e.g., autism in the deaf or deafness in the autistic) is often delayed, remediation is often suboptimal and ineffective.

Roper, Arnold, and Monteiro (2003) evaluated deaf autistic, deaf learning disabled, and hearing autistic children. There were no differences across the groups in the age at which parents first suspected a developmental or hearing problem or when the hearing deficit was diagnosed. However, the deaf autistic children were first diagnosed with deafness at a mean of 1 year of age (range 6 months to 2½ years), but not diagnosed with autism until a mean of 15 years of age (range 5 to 16 years) despite parental suspicions averaging 7 months of age (range 2 to 18 months). In contrast, the hearing autistic children were diagnosed at a mean of 7½ years of age (range 4 to 11 years), albeit late since their parents' suspicions averaged 18 months of age (range 3 months to 5 years). There were no differences in the current levels of autistic behaviors demonstrated by the deaf or hearing autistic groups, which is consistent with the previous findings of Garreau, Barthelemy, and Sauvage (1984). The authors also noted no discriminating characteristics of the deaf autistic individuals that would have facilitated earlier recognition of the autistic symptoms. Therefore, early recognition of hearing impairment in autistic children and of autism in deaf children is essential for the provision of an appropriate intervention strategy for these children (Ewing & Jones, 2003).

Fetal Anticonvulsant/Valproate Syndrome

Although the syndrome was described earlier (Chessa & Iannetti, 1986; DiLiberti, Farndon, Dennis, & Curry, 1984; Paulson & Paulson, 1981), Ardinger et al. (1988) confirmed that the multiple congenital anomalies and developmental delay noted in infants exposed to valproic acid (VPA) in utero represented a definitive *fetal valproate syndrome* (FVS). The clinical features include craniofacial, cardiovascular, urinary tract, genital, digital, and respiratory anomalies, and meningomyelocele. Up to 90% have developmental delay.

Several subsequent papers reported autism in children with FVS (Bescoby-Chambers, Forster, & Bates, 2001; Christianson, Chesler, & Kromberg, 1994; Moore et al.,

2000; Samren, van Duijn, Christiaens, Hofman, & Lindhout, 1999; G. Williams et al., 2001; P. G. Williams & Hersh, 1997). Christianson et al. (1994) first reported FVS in two sibling pairs. In the first family, the dose of valproate was halved when the first pregnancy was confirmed and phenytoin was added; in the second pregnancy, valproate was continued at the mother's usual dose. Although both children demonstrated many of the classic dysmorphic findings associated with fetal anticonvulsant syndrome (epicanthal folds, synophrys, upturned nasal tip with anteverted nares, and long philtrum), the older child was developmentally normal while the younger child was classically autistic with additional craniofacial anomalies. The authors suggested that there may be a valproate dosage effect in FVS, which was corroborated by Samren et al. (1999).

Four of the 57 children with fetal anticonvulsant syndromes reported by Moore et al. (2000) were reported to have autism (two exposed to VPA alone, one to VPA and phenytoin, and one to carbamazepine and diazepam). Two additional children were diagnosed with Asperger syndrome (one exposed to VPA and one to VPA, phenytoin, and a benzodiazepine). Eight additional cases were reported (Bescoby-Chambers et al., 2001; G. Williams et al., 2001; P. G. Williams & Hersh, 1997), one with Asperger syndrome and seven who met *DSM-IV* or *International Classification of Diseases (ICD-10)* criteria for autistic disorder.

CONCLUSION

Studies of relatively strictly defined autistic disorder have generally revealed low rates of medical conditions that might be associated with autism; the broadened view of ASDs forces us to revisit this issue. This chapter provided a summary of the medical aspects of this complex disorder from complementary perspectives, reinforcing the complexity of the ASDs and strengthening the bridge between evidence-based medicine and clinical application. Providers and investigators in all clinical and research disciplines should become familiar with the medical aspects of autism. When a child with an ASD is seen, providers need to consider all potential associated medical disorders and syndromes, both relatively common and rare. They also need to consider associated signs and symptoms that the family will confront, such as sleeping and feeding disturbances. In addition, when a provider sees a child with a rare syndrome or disorder, the child's behavioral phenotype must be considered: Does this child have autism or another neurobehavioral disorder? These deliberations will improve the recognition of autism and the role of associated medical factors and ultimately best serve the children and their families.

Cross-References

Issues of diagnosis are addressed in Chapters 1 to 6; genetic factors are discussed in Chapter 16; neurobiological aspects of the disorder are discussed in Chapter 18.

RECOMMENDED READING LIST FOR PARENTS AND PROFESSIONALS*

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* Portions of this section were taken with permission from Volkmar & Wiesner (2004).

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