The Neurology of Autism

Mary Coleman,
Editor

OXFORD UNIVERSITY PRESS

The Neurology of Autism

This page intentionally left blank

The Neurology of Autism

Edited by Mary Coleman

OXFORD
UNIVERSITY PRESS

2005

OXFORD
UNIVERSITY PRESS

Oxford University Press, Inc., publishes works that further
Oxford University's objective of excellence
in research, scholarship, and education.

Oxford New York
Auckland Cape Town Dar es Salaam Hong Kong Karachi
Kuala Lumpur Madrid Melbourne Mexico City Nairobi
New Delhi Shanghai Taipei Toronto

With offices in
Argentina Austria Brazil Chile Czech Republic France Greece
Guatemala Hungary Italy Japan Poland Portugal Singapore
South Korea Switzerland Thailand Turkey Ukraine Vietnam

Published by Oxford University Press, Inc.
198 Madison Avenue, New York, New York 10016
www.oup.com

Oxford is a registered trademark of Oxford University Press

Library of Congress Cataloging-in-Publication Data
The neurology of autism / edited by Mary Coleman.
p. cm.
Includes bibliographical references and index.
ISBN-13 978-0-19-518222-4
ISBN 0-19-518222-7
1. Autism—Pathophysiology. I. Coleman, Mary, 1928-
RC553.A88N53 2005
616.85'882—dc22 2004020708

9 8 7 6 5 4 3 2 1

Printed in the United States of America
on acid-free paper

This book is dedicated to Richmond S. Paine

Richmond S. Paine, M.D., was a giant of pediatric neurology. He formed a large department of pediatric neurology at the Children's Hospital of Washington, D.C., in the early 1960s. Before that, he had been in close touch with those in Europe—people like André Thomas, Albrecht Peiper, and Ronnie Mac Keith—who were contributing as pioneers to the field of child neurology. As a teacher, he was a splendid example of how a professional should be rich with curiosity yet rigorous about the scientific approach. To study with him was a constant intellectual adventure; he had the gifts of clarity and patience. To his patients, he brought the best in diagnosis and treatment. He was gentle with the children and much appreciated by their parents.

His distinguished teaching attracted students from around the world. Three of the authors of this book—Mary Coleman, Michele Zappella, and Yoshiko Nomura—benefited from his creative erudition.

In the case of Mary Coleman, the brilliant teaching of Richmond Paine changed her planned specialty from adult to pediatric neurology. He also handed her Bernard Rimland's book on autism with a recommendation to read it, sparking a lifelong interest in this subject.

Michele Zappella entered the department as a fellow in Neurology. He remembers how generous Paine was with him: for example, initially, until Zappella could find a place to live in town, Paine took him into his home for several days as if he were a son. Subsequently, Paine favored Zappella's research in all possible ways, allowing him to write various articles and a book on congenital encephalopathies, the first one written in Italian in which Richmond Paine wrote a good introduction. He also supported Zappella's initial interest in child psychiatry and allowed him to attend the corresponding department in the afternoons. In the following years, when Zappella began to deal with children with autism, Rich-

mond's teaching was the basis upon which it was possible to imagine new subgroups and syndromes.

Yoshiko Nomura came to Children's Hospital of Washington, D.C., with the dream of learning from Richmond Paine after having been fascinated by his original works. Although greatly disappointed that he was gone when she arrived, her learning from the team left behind by Richmond Paine determined her career.

Acknowledgments

The authors wish to thank the Morton B. and Blanche S. Prince Philanthropic Fund; Carol and Harvey Eisenberg; Tahma Metz, Executive Director of the Purine Research Society; Dr. Phillip L. Pearl; and Dr. Masaya Segawa, Director of the Segawa Neurological Clinic for Children. They also wish to thank Catharine Carlin and Jennifer Rappaport of Oxford University Press.

This page intentionally left blank

Preface

"Costumeless consciousness, that is he" said Emily Dickinson (Johnson 1963). Was she thinking of a child with autism or Asperger syndrome? These beautiful children may indeed reveal their feelings for all to see; they do share an incompetence for being deceitful. But in many other ways, they can be quite different. Some are gentle and passive while others can become angry or hyperactive; some are quite clumsy and while others are astonishingly graceful and balanced; some stun us with their brilliant savant skills even while otherwise functioning at much lower cognitive levels. Who are these enigmatic children?

To address this and other questions regarding the children who have been given the diagnosis of autism or Asperger syndrome, this book turns to neurological analysis. As discussed in chapter 1, autism and Asperger syndrome appear to be variations of the same neurodevelopmental syndrome, a vast syndrome with many different etiological factors. Whether all the cases labeled as PDD-NOS belong inside this huge syndrome, however, is far from clear. Chapter 2 takes a look at the components of the impaired neural networks that might underlie the presentation of autistic symptoms. Of particular interest is the dysfunction of the cerebellum and its circuits in so many of these children (chapter 3). The neurological signs and symptoms that can be found in children with autism/Asperger include abnormal cranial circumferences (chapter 4), epilepsy, changes of muscle tone, stereotypies, and mutism (chapter 5). The appendix contains a neurological examination form specifically designed for the examination of patients with autism/Asperger.

The field of autism today is focused on several problem areas. One is whether autism has been increasing in recent years. The reasons for this perception and a review of the historical prevalence rates in chapter 6 suggest that autism has never been a very rare disorder. Another topic of great interest is whether autism

is reversible. Chapter 7 looks at the natural course of those diseases that have a transient autistic phase, using Rett syndrome as an example. Chapter 8 then reviews reports of reversible autistic behavior.

Finally, there is a review of therapies, alternative (chapter 9) and educational/medical (chapter 10). As discussed in these treatment chapters, many different therapies fill the landscape of helping the appropriately worried parents of these children. Parents often are overwhelmed by information. When you have many medical therapies, often contradictory, two possibilities exist. One is that the correct therapy for that disease has yet to be identified. The history of medicine is replete with incidents in which multiple, unsatisfactory therapies are offered until the single effective treatment for a single disease is discovered. The second possibility is that there is no such thing as one medical treatment because autism is not one disease after all but a syndrome, a final, common pathway of many, many different diseases, each of which may require its own medical therapy. In such cases, accurate diagnosis must precede therapy.

The authors of this book wish to recognize that the present level of knowledge about autism has been greatly aided by the heroic parents of children with autism, who have kept pushing the professionals to do better. What strength so many of these parents have! Among the parents of children with the autistic syndrome are the parent professionals, individuals with graduate training in many scientific fields. There are many such parents; they have organized schools and centers actively involved in supporting research, as well as seeking better diagnosis and treatment. When the medical history of autism is written, an unusual historical development will be noted: that several of the most important and seminal intellectual contributions in the field have been made by the parents of the patients themselves. One such example is Bernard Rimland, Ph.D., of the United States, who wrote the first comprehensive book challenging the psychoanalytic theory that autism was caused by poor mothering (Rimland 1964). He presented the case for a biological dysfunction of the brain and deduced that autism was a cognitive dysfunction. He studied the genetic basis of autism by comparing monozygotic and dizygotic twins. Another such parent professional is Lorna Wing, Ph.D., of England who made major clinical contributions to both autism (the triad of social impairment [Wing & Gould 1979], DISCO [Wing et al. 2002]) and Asperger syndrome by helping pull it from the dustbins of medical history (Wing 1981). She also has done groundbreaking work on catatonia in autism (Wing & Shah 2000).

The quantity and quality of research into autism has increased dramatically in the past few years, concomitant with the development of technical advances in imaging the brain and in molecular genetics; many of the questions posed in this volume may be better understood soon.

REFERENCES

Johnson TH (1963) *The poems of Emily Dickinson*. Cambridge, Mass.: Belknap Press. Poem 1454.

Rimland B (1964) *Infantile Autism; The syndrome and its implications for a neural theory of behavior*. Englewood Cliffs, N.J.: Prentice Hall.

Wing L (1981) Asperger syndrome: a clinical account. *Psychological Medicine* 11:115–129.

Wing L, Gould J (1979) Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *Journal of Autism and Developmental Disorders* 9:11–29.

Wing L, Leekam SR, Libby SJ, Gould J, Larcombe M (2002) The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability, and clinical use. *Journal of Child Psychology and Psychiatry* 43:307–325.

Wing L, Shah A (2000) Catatonia in autistic spectrum disorders. *British Journal of Psychiatry* 176:357–362.

This page intentionally left blank

Contents

Contributors

Catalina Betancur, MD, PhD
Faculté de Médecine
Université Paris XII
Paris, France

Mary Coleman, MD
Emeritus Clinical Professor of Pediatrics (Neurology)
Georgetown University School of Medicine
Washington, D.C., USA

G. Robert DeLong, MD
Professor of Pediatrics (Neurology)
Duke University Medical Center
Durham, North Carolina, USA

Christopher Gillberg, MD, PhD
Professor of Child and Adolescent Psychiatry
University of Göteborg, Sweden and University of London, UK

Yoshiko Nomura, MD
Segawa Neurological Clinic for Children
Chiyoda-ku, Toyko, Japan

Lorenzo Pavone, MD
Professor and Chairman of Pediatrics
Department of Pediatrics
University of Catania
Catania, Italy

Martino Ruggieri, MD, PhD
Senior Lecturer
Institute of Neurological Science
Italian National Research Council
Assistant Professor of Pediatrics
Department of Pediatrics
University of Catania
Catania, Italy

Michele Zappella, MD
Director of the Clinic of Neuropsychiatry
General Hospital di Siena
Siena, Italy

This page intentionally left blank

The Neurology of Autism

This page intentionally left blank

Chapter 1
Introduction

Mary Coleman and Catalina Betancur

It was 1866 in Londontown. The doctors, coming into their own beside the surgeons, had begun to classify diseases of the brain and help create the specialty of neurology. However, many children were hard to classify because they had something terribly wrong in brain function; they had great difficulty learning and were called idiots. Idiocy was an epithet, barely a disease entity, and a neglected one at that. But all that began to change when Dr. John Langdon Down (1866) published a paper pointing out that children who were classified as idiots and had enlarged tongues protruding from their mouths did not necessarily all have the same form of idiocy. They might have had the same major symptom (mental retardation), be the same age when it became obvious that something was wrong (usually after 18 months of age), and share a striking feature (the appearance of macroglossia), but he announced that they did not all have the same disease. Dr. Langdon Down wrote that one group had mongolism, a name he chose because of the appearance of the children's eyelids, and the other group had cretinism, a disease known today as infant hypothyroidism. This paper ushered in a new era of medical interest in these children, which also led to more humane care.

Almost a century and a half later, in the twenty-first century, over 2000 different disease entities have been described in which patients have mental retardation. Mental retardation is a series of neurodevelopmental syndromes due to chromosomal, genetic, infectious, endocrine, and toxic etiologies; in almost all cases, the disease process is underway prior to birth. Regarding genetic disease, when mutation of a single gene is both necessary and sufficient to cause disease, it is called a monogenetic trait; it is now known that over 200 of the mental retardation diseases are classified as monogenetic diseases (Zechner et al. 2001). The disease entities of the mental retardation syndromes have been generally grouped together into two major categories: syndromic and nonsyndromic men-

tal retardation. These categories refer to syndromes in which there are multiple congenital anomalies and mental retardation (the MCA/MR syndromes) versus those syndromes without either major congenital anomalies or facial and other stigmata.

Does this story have any relevance to autism? The history of autism does not cover as many years. It was first identified by Leo Kanner in 1943 and thought to be a single psychiatric disease; he defined it as a behavioral disease entity beginning when children are very young. A recent study has suggested that autism may be already underway at the time of birth in almost all the children. In a study of archived neonatal blood, Nelson and colleagues (2001) found that the levels of certain neurotrophins and certain neuropeptides were higher in 99% of the children who were later diagnosed as autistic than they were in control children. These molecules were brain-derived neurotrophic factor (BDNF), neurotrophin 4/5 (NT4/5), vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP). The study by Nelson and colleagues also found similar elevations of the neurotrophins and neuropeptides in 97% of children who later were diagnosed with mental retardation, including those with Down syndrome. *It is of great interest that no measurement distinguished the children with autism from those with mental retardation, although these measurements did distinguish them from children who later were diagnosed with cerebral palsy and from normal controls.*

This study suggests that the autistic syndromes, like the mental retardation syndromes, begin prior to birth in the overwhelming number of cases. It adds one more piece of evidence that autism is a member of the family of neurodevelopmental syndromes with maturational disturbances and may be the behavioral stepsister of the mental retardation syndromes.

In fact, the autistic syndromes share many of the characteristics of the mental retardation syndromes. Both groups of syndromes begin to impair the brain in almost all cases during the gestational neurodevelopmental time frame; they are both present at birth but are not usually clinically apparent. They both have family histories with inheritance patterns that sweep across the landscape of genetics, from classical Mendelian to maternal inheritance patterns to trinucleotide repeat disorders to large numbers of sporadic cases. Twin, family, and linkage data and case histories reveal that the inheritance pattern in autism is very complex (for review, see Folstein & Rosen-Sheidley 2001). Although a percentage of children in both groups of syndromes develop epilepsy, the autistic syndromes actually include a higher prevalence of children with seizure disorders than do the population with severe mental retardation syndromes (Gillberg & Coleman 2000a). Children with autism do not have the same neuropsychological profile as youngsters classified as retarded; nevertheless, IQ is the single best predictor of outcome in both syndromes (Gillberg & Coleman 2000b). And, most important, the two syndromes overlap in the majority of children who are classified as

autistic (Jacobson & Janicki 1983; Bryson et al. 1988); in most studies IQ is below 70 in 70% of individuals who are defined as having autism.

THE TIMING OF AUTISM

If autistic traits develop because of neurodevelopmental missteps, when during gestation does that occur? Neuroembryology is a very complex phenomenon although neurodevelopment of the brain seems to occur gradually and seamlessly. Rice and Barone (2000) and many others have noted evidence of critical periods of vulnerability in the developing nervous system (these periods are topics of important future research). In the case of autism, data obtained from several groups of children with autistic characteristics show evidence that the disease process can be initiated in all three trimesters (Rodier et al. 1996; Coleman 1994; Yamashita et al. 2003). (There is some postnatal evidence, too [Minshew 1996].) As evidence from these trimesters is reviewed, one useful way to look at this neurodevelopmental problem might be to classify the autistic syndromes with the same general terms that are used to classify mental retardation syndromes, that is, syndromic or nonsyndromic. However, in both mental retardation and autism, the concept of stigmatized versus nonstigmatized children is in reality a bit too stark. Certainly in autism a continuum from minor to major physical stigmata can be seen. In syndromes with large numbers of patients, it often is apparent that the variable degree of phenotypic manifestation between individuals could be represented as a continuum from the full disease to even minor or undetectable expression. The concept of syndromic autism versus nonsyndromic autism will be presented here as a structural framework in which to tentatively place the disease entities.

The first trimester, primarily a time when the body and face are formed, would be the time of syndromic autism, the period when MCA/MR syndromes are initiated. It has been demonstrated that some of the MCA/MR syndromes that include an autistic subgroup, such as the Möbius sequence, thalidomide embryopathy, or the CHARGE association (coloboma, heart defect, atresia of the choanae, retarded growth and mental development, genital anomalies, and ear malformations and hearing loss), may begin as early as 20 to 24 days postfertilization. In addition, in an autism autopsy case, Rodier et al. (1996) identified a shortening of the brain stem, a defect that could have occurred only during neural tube closure. In the development of the cerebral cortex, 6 to 8 weeks of gestational age are called the embryonic period. Children with autism and a grossly abnormal stigmata examination are 10 times more likely to be diagnosed with a known genetic syndrome and are twice as likely to have structural abnormalities in their brains than children with autism without gross stigmata (Miles & Hillman 2000).

A large number of MCA/MR syndromes include a subgroup of children with autism (table 1-1A). Estimates of the number of children with autism who have these syndromes vary widely from 7% to 37%, indicating either a different pop-

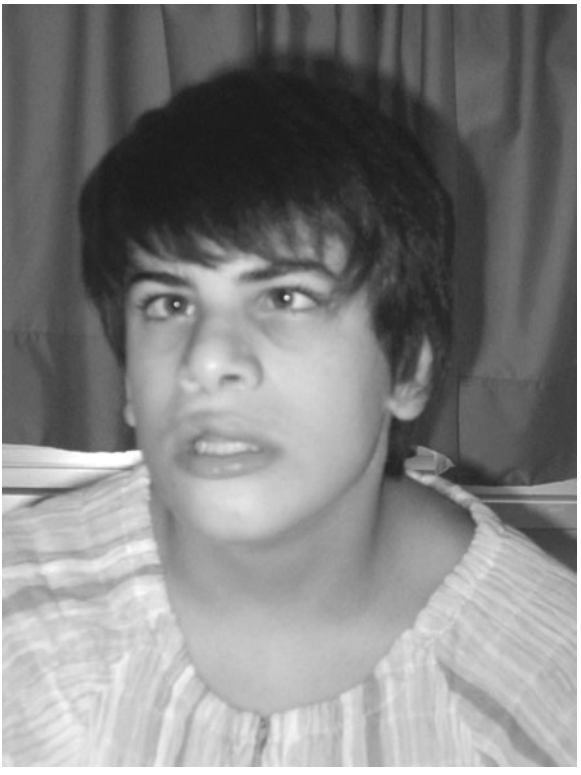

Figure 1.1 Fourteen-year-old girl with syndromic autism, ectodermal dysplasia, MR.

ulation mix, or a different method of selection by the investigators. Around 12% is a reasonable working estimate for population-based surveys (Kielinen et al. 2004). The relevant question in each MCA/MR syndrome is whether the syndrome is somehow related to autistic symptoms or whether the affected children have two completely separate syndromes, the MCA/MR syndrome and a second autistic syndrome. Each syndrome must be evaluated separately, because the majority of children in most of the MCA/MR syndromes in which autistic patients have been reported do *not* have autistic features.

In the MCA/MR syndromes that are very rare and include few cases of autism, a reasonable assumption could be that, in a coincidental double syndrome, an unlucky child described with autistic features perhaps did have the syndrome by chance. If the child also has established autism stigmata that differ from those of other children with the particular syndrome, this weighs in favor of coincidence instead of relevance; the unlucky patient likely has two separate disease entities.

Table 1-1 Some of the double syndromes in which a subgroup of patients meeting autistic criteria has been described

A. Multiple congenital anomalies/mental retardation (MCA/MR) syndromes

Angelman syndrome	Möbius sequence
CATCH 22	Neurofibromatosis 1
CHARGE association	Noonan syndrome
Cohen syndrome	Orstavik 1997 syndrome
Cole-Hughes macrocephaly syndrome	Rett syndrome
Cowden syndrome	Rubinstein-Taybi syndrome
15q11-q13 duplication syndrome	Smith-Lemli-Opitz syndrome
de Lange syndrome	Smith-Magenis syndrome
Down syndrome	Sotos syndrome
Ehlers-Danlos syndrome	Steinert's myotonic dystrophy
Fragile X syndrome	Timothy syndrome
Goldenhar syndrome	Tuberous sclerosis complex
Hypomelanosis of Ito	Turner syndrome
Lujan-Fryan syndrome	Williams syndrome

B. Neurological syndromes

Dysmaturational syndrome with familial complex tics
Joubert syndrome
Leber's congenital amaurosis
Mitochondrial syndromes, including the HEADD syndrome
Neuroaxonal dystrophy variant
Tourette syndrome/autism
X-linked creatine transporter defect

C. Psychiatric syndromes

Anorexia nervosa/autism
Infantile autistic bipolar subgroup

An example is the case of a boy with Myhre syndrome, who met the DMS-IV criteria of autism and exhibited several symptoms that are not usually found in the syndrome (Titomanlio et al. 2001). In addition to peculiar skin histology not typically described in Myhre syndrome, he also had hypertelorism and partial cutaneous syndactyly of the second and third toes. These are stigmata singled out in studies of minor physical anomalies in children with nonsyndromic autism. These facts weigh in favor of two separate disease entities in this boy.

However, other MCA/MR syndromes, such as the disease process of the tuberous sclerosis complex, may be more prone to creating autistic symptoms in their population. Epidemiological studies suggest that 43–86% of individuals with the tuberous sclerosis complex have a pervasive developmental disorder similar to autism (Harrison & Bolton 1997), and this disease alone may account for from 1% to 4% of children with autism in some series (Smalley 1998). It is possible

Figure 1.2 Fourteen-year-old boy with nonsyndromic, high-functioning autism.

that the autistic symptoms in some of these children may spring from the underlying disease process, such as the number, location, and size of the brain tubers of the tuberous sclerosis complex (Humphrey et al. 2004), which also can be a source of epileptic foci (Chugani et al 1998). Because they are much more thoroughly studied, the MCA/MR syndromes can be helpful in highlighting information that may underlie autistic symptoms. However, it must always be kept in mind that each of these syndromes has many other nonautistic symptoms, and it is only by putting together the information from many different disease entities that some form of standardized picture might come to light.

Several syndromes in which autistic features are part of the initial description of the syndrome have been reported. Examples are HEADD syndrome (hypotonia, epilepsy, autism, and developmental delay) and Orstvik 1997 syndrome (macrocephaly, epilepsy, autism, stigmata, and mental retardation) (Orstavik et al. 1997; Fillano et al. 2002; van Karnebeek et al. 2002). Evidence of mitochondrial dysfunction and mitochondrial DNA (mtDNA) deletions has been found in chil-

dren with HEADD syndrome. It is too early to be sure, but apparently almost all patients diagnosed with these new syndromes would be considered autistic. Even so, each child with a double syndrome of both autism and any MCA/MR syndrome should be evaluated as an individual; this has both genetic counseling and treatment implications.

While on the topic of MCA/MR syndromes, it should be noted that a child with autism does not have to possess major anomalies or major stigmata to have a disease entity that began in the first trimester. Some minor stigmata can be traced to the first trimester (Rodier et al. 1997b). Sometimes the syndrome is missed because the stigmata and skin lesions that characterize the children's faces are not always apparent in infancy and early childhood. Examples of this delayed diagnostic phenomenon are reported in tuberous sclerosis, Cohen syndrome, and chromosome 22q11.2 deletion syndrome. Yet another possibility is the recent revelation that a child may be clinically classified as having nonsyndromic autism and also have a mutation on the same gene affected in a MCA/MR syndrome (Turner et al. 2002); this is the same phenomenon that is seen in syndromic and nonsyndromic forms of mental retardation (Nokelainen & Flint 2002).

The second trimester is believed to be a time when many of the neurodevelopmental errors that lead to nonsyndromic autism occur. The period from 8 to 20–24 weeks of gestational age including the end of the first as well as the second trimester is the fetal period of brain development. When autism was first being studied, it was noted how beautiful and unstigmatized many of these children were. This may even have been a factor in the initial blaming of the parents who were raising such normal-looking children. But as soon as any systematic research was conducted on this question, it became clear that children with autism who looked unstigmatized were more likely to have minor physical anomalies than control children matched for age, sex, and socioeconomic status (Steg & Rapoport 1975; Walker 1976; Campbell et al. 1978; Links et al. 1980; Rodier et al. 1997a). The timing of formation of these minor anomalies spans from the first trimester to the beginning of the second trimester. In these studies, the single most common minor anomaly in these studies found in autism was an ear anomaly characterized by particularly low seating and posterior rotation of the ears. This anomaly was even more common in children with autism than in children with mental retardation. Other minor anomalies found in children with autism by more than one of these studies were partial or full syndactyly of the second and third toes and a slight hypertelorism.

It is far from clear in which trimester to place the infantile forms of neurological (table 1-1B) and psychiatric disorders (table 1-1C) already defined in older populations. Because these beautiful children have so few stigmata, these categories temporarily go into the second trimester lists. The issue will become clearer disease by disease as the neuroanatomical and genetic basis of the primary disorders are better understood.

In a prospective study of prenatal factors comparing children who developed

autism with normal and mentally retarded controls, statistically significant second-trimester bleeding was limited to the mothers of children with autism (Torrey et al. 1975). There are a few reported cases of accurately timed infections in mothers of children who later developed autism. In children with autism and congenital rubella (Chess 1977) or congenital cytomegalovirus (Ivarsson et al. 1990), the maternal infections occurred in the second trimester. Maternal autoimmune diseases in the second trimester also may increase risk (Croen et al. 2005).

Malformations of cortical development due to abnormal neuronal and glial proliferation are seen in neuroectodermal diseases, such as tuberous sclerosis. Evidence of neuronal migration aberrations is found in many MRIs of children with both autism and Asperger syndrome. (See chapter 2 for references.) Table 1-2 lists some of the diseases in which these neuroembryological errors are found. Both genetic and infectious etiologies can cause these aberrations. They are primarily second trimester phenomena.

Relatively few patients with autism are thought to have injuries to the central nervous system initiated during the third trimester. The period extending from 24 weeks of gestation until the time of birth is called the perinatal period by embryologists of the central nervous system. The children with autism that have been documented with third trimester insults appear to be mostly affected by infections, such as symptomatic congenital cytomegalovirus infection (Yamashita et al. 2003).

The perinatal and postnatal periods are times when errors established earlier may be expressed or new insults may affect brain function. After the advent of birth, the brain continues to grow, change, and be vulnerable owing to the persistence of some limited neurogenesis, elimination of neurons through apoptosis or programmed cell death, postnatal proliferation and pruning of synapses, and activity-dependent refinement of neuronal connections (Johnston 2004).

Table 1-2 Disease entities in which both neuronal migration and autistic symptoms have been reported

MCA/MR syndrome	*Type of neuronal migration disorder*
de Lange syndrome	heterotopia
Ehlers-Danlos syndrome	heterotopia
Hypomelanosis of Ito	polymicrogyria, heterotopia
Neurofibromatosis, type 1	polymicrogyria, heterotopia
Rett syndrome	nodular heterotopia perisylvian cortical dysplasia
Smith-Lemli-Opitz syndrome	polymicrogyria, rare
Sotos syndrome	neuronal heterotopia
Tuberous sclerosis complex	heterotopia

Reference: Hennekam & Barth (2003)

THE NOSOLOGY OF AUTISM

So in this neurodevelopmental syndrome, the question arises as to how we are going to diagnose children with this core social disorder in the future. One encouraging development is that, in psychiatry and neurology as in all of medicine, nosology is rapidly improving so that diagnosis and treatment can be more individualized. It is now possible to expand the traditional clinicopathological method of general diagnosis into a more comprehensive study of the disease during the lifetime of the individual through chromosomal studies, molecular genetics, brain imaging, electrophysiology, and many other technologies. However, the symptoms of central nervous system disease, showing through an underlying personality structure, remain particularly difficult to interpret. This is especially so in the case of the young child with autistic symptoms.

It has been 60 years since the behavioral syndrome of autism was first described, yet problems of nosology remain. Most physicians working with these patients would agree that current testing instruments to define the symptoms of autism (table 1-3) are clinically useful and appropriate. Autism involves multiple developmental domains; it compromises a wide range of socioemotional, language, and other cognitive skills. However, many patients do not fit exactly into the designated criteria of autism or Asperger, and their condition is called atypical autism or pervasive developmental disorder not otherwise specified (PDD-NOS). Are children with specific language disorders mistakenly being put into a pool with autism? Another unsettled question refers to patients currently classified as having the very rare Childhood Disintegrative Disorder. This is a topic in itself: A family of 2 half-brothers, 1 with autism and 1 with Childhood Disintegrative Disorder, has been described (Zwaigenbaum et al. 2000).

Very important work has been done to recruit populations of children with autism that are as psychiatrically homogeneous as possible for research purposes. Nevertheless, a number of unsolved issues remain in play. These problems are not just academic; they have implications for infant and childhood learning programs, as well as pharmacological approaches.

One persistent nosological challenge is to determine whether Asperger syndrome and autism are variations of the same disease, a question posed by Lot-

Table 1-3 Current instruments that can be used to diagnose or assess the severity of patients with autistic symptoms

Autism Diagnostic Interview–Revised (ADI-R)
Autism Diagnostic Observation Schedule–Generic (ADOS-G)
Childhood Autism Rating Scale (CARS)
Diagnostic Interview for Social and Communication Disorders (DISCO)
Diagnostic and Statistical Manual of Mental Disorders (*DSM–IV*) criteria
The ICD-10 Classification of Mental and Behavioral Disorders (ICD–10) criteria