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WHERE WE ARE: OVERVIEW AND DEFINITIONS

Isabelle Rapin and Roberto F Tuchman

HISTORICAL BACKGROUND
The term “autism”, which was coined by Bleuler to characterize the negative symptoms and social alienation of individuals suffering from schizophrenia, was borrowed by both Kanner (Kanner 1943) and Asperger (Frith 1991) when they independently and almost simultaneously in 1943–44 described developmentally disabled children whose profound deficit in the ability to relate to others marked them as unique. It took close to 40 years for autism to be listed as such in the Diagnostic and Statistical Manual of Mental Disorders (DSM). The 3rd edition of the DSM (DSM-III; APA 1980) introduced the term “pervasive developmental disorder” to refer to a group of behaviorally defined developmental disorders that share symptomatology with classic autism as described by Kanner, which is labeled “autistic disorder” in both the DSM and the International Classification of Mental and Behavioural Disorders (ICD-10; WHO 1992). Over the next quarter century an exponential number of studies were carried out to refine the description of the behaviors that characterize affected individuals and, more recently, to investigate the causes (etiologies) of autism and the neurologic pathophysiology of its many behavioral manifestations.

DEFINITIONS (TABLE 1.1)
In this book, the term autism is used broadly and synonymously with pervasive developmental disorders (PDDs) or the autism spectrum disorders (ASDs), and not to refer specifically to autistic disorder (AD) as defined in the DSM and ICD manuals. The term spectrum implies a broad range of severity. We use autism (or ASD) in this book irrespective of the many potential biologic causes of this developmental disorder.

The subcategories under the broader label of PDD introduced in the DSM 4th edition, text revision (DSM-IV-TR; APA 2000) are an attempt to meet scientific (research) needs, as well as to allow for appropriate service development and administrative needs for individuals with autism and related disorders (Rutter and Schopler 1992). Still missing are more specific behavioral criteria to identify homogenous subgroups of individuals within the larger spectrum of autism, both for research and practical purposes.
What makes autism so distinctive that an experienced clinician or educator recognizes classic cases at a glance and rapidly suspects it even in less severely affected persons? Both Kanner and Asperger were impressed by the profound social ineptitude of the children they identified, their rigidity and resistance to change, their repetitive behaviors (stereotypies), and their unusual speech and often bizarre modes of communication – if they communicated at all. Both described children with extremely uneven cognitive abilities, in some of whom extraordinary accomplishments, especially in rote memory and visual skills, coexisted with profound deficits in common sense and reasoning. Psychiatrists and psychologists who spent decades studying affected individuals developed for the

### TABLE 1.1 Definitions*

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<thead>
<tr>
<th>Term</th>
<th>Abbrev.</th>
<th>Definition</th>
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<tr>
<td>Autism spectrum disorder</td>
<td>ASD</td>
<td>Refers to the entire range of severity of disorders with autistic symptomatology, irrespective of etiology or associated disabilities</td>
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<tr>
<td>Pervasive developmental disorder</td>
<td>PDD</td>
<td>Used synonymously with ASD</td>
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<tr>
<td>Autism, autistic</td>
<td>—</td>
<td>Used as short for ASD/PDD</td>
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<tr>
<td>Autistic disorder</td>
<td>AD</td>
<td>Used narrowly in its DSM-IV definition</td>
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<tr>
<td>Pervasive developmental disorder – not otherwise specified</td>
<td>PDD-NOS</td>
<td>Used narrowly in its DSM-IV definition, refers to the milder end of the ASD spectrum</td>
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<tr>
<td>Asperger syndrome</td>
<td>AS</td>
<td>Used narrowly in its DSM definition</td>
</tr>
<tr>
<td>Developmental and Statistical Manual of Mental Disorders</td>
<td>DSM</td>
<td>Refers to any of the editions if unspecified</td>
</tr>
<tr>
<td>International Classification of Diseases</td>
<td>ICD</td>
<td>Refers to any of the editions if unspecified</td>
</tr>
<tr>
<td>Idiopathic/primary autism</td>
<td>—</td>
<td>Autism without an ascertainable etiology in a non-stigmatized individual</td>
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<tr>
<td>Syndromic/secondary autism</td>
<td>—</td>
<td>Autism with a known or ostensible etiology, whether the individual is stigmatized or not</td>
</tr>
<tr>
<td>Non-syndromic autism</td>
<td>—</td>
<td>Autism without stigmata or known etiology</td>
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*See Table 1.3 for DSM-IV/ICD-10 correspondences.
DSM/ICD manuals (WHO 1993, APA 2000) a set of operationalized behavioral descriptors to enable investigators and clinicians alike to reach a satisfactory degree of diagnostic consensus.

The first and foremost domain is social skill and the ability to be sufficiently cognizant of others’ thinking to enable empathy and insight into what others may be thinking. The second domain is verbal and nonverbal communication, and, in young children, pretend play. The third domain is breadth of interests, behavioral flexibility, and the ability to switch activities and cope with the unexpected. The DSM IV-TR (APA 2000) includes a series of 12 descriptors of deficits, four in each of the three behavioral domains (Table 1.2). We stress that PDD/ASD diagnoses are behavioral; neither level of intelligence nor biologic criteria such as epilepsy, motor deficits, visual or auditory impairment, or a specific etiology is an exclusionary criterion for an ASD diagnosis.

### DSM/ICD SUBTYPES OF PERVERSIVE DEVELOPMENTAL DISORDERS

The ASDs encompass a wide range of symptoms, some or all of which vary greatly in

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**TABLE 1.2**

**DSM-IV-TR (2000) behavioral descriptors**

1. **Social interaction domain:**
   - (a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
   - (b) failure to develop peer relationships appropriate to developmental level
   - (c) lack of spontaneous seeking to share enjoyment, interests or achievements (e.g. by lack of showing, bringing, or pointing out of objects of interest)
   - (d) lack of social or emotional reciprocity

2. **Language, communication and imagination domain:**
   - (a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime)
   - (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
   - (c) stereotyped and repetitive use of language or idiosyncratic language
   - (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

3. **Behavioral flexibility domain:** restricted, repetitive and stereotyped patterns of behavior, interests and activities
   - (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
   - (b) apparently inflexible adherence to specific, nonfunctional routines or rituals
   - (c) stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
   - (d) persistent preoccupation with parts of objects
severity. The most recent DSM-IV and ICD-10 systems have adopted parallel and virtually identical names (and criteria) for the subtypes of PDD, as shown in Table 1.3. Diagnostic criteria for these subtypes of autism are based mainly on the number and distribution of behavioral descriptors, therefore on severity within a continuum, with some consideration of age of onset (or more realistically age at awareness of the disorder) (Table 1.4). These criteria were arrived at after field trials and international conferences of clinicians and researchers (mostly psychiatrists and psychologists, with little if any input from neurology) whose goals were to create a common language applicable worldwide and to define operational rules or criteria for classification. Achieving a consensus is critical for enabling clinicians and investigators to use a common diagnostic system when referring to individuals of all ages with autistic symptomatology. At least at present, the DSM subtypes, with the exception of Rett syndrome, do not fulfill criteria for any biologically specific disorder.

These behavioral classification systems are very much a work in progress and no doubt will continue to evolve as new information is accrued. It is likely, for example, that Rett syndrome, originally considered an ASD subtype, will be taken off the list in a future DSM-V inasmuch as its diagnostic criteria are no longer strictly behavioral. It is not that girls with Rett syndrome – at least during some phases of their illness – are not autistic, but that there is now a known biologic cause for their behaviorally defined autism. We stress the distinction between biologic and behavioral classifications, a distinction that does not in the least imply that individuals with known biologic etiologies do not have autism when their behavioral criteria put them on the spectrum. Biologic and behavioral classifications are not mutually exclusive but concurrent diagnoses.

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>ICD-10</th>
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<tr>
<td>Autistic disorder</td>
<td>Childhood autism</td>
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<td>Asperger’s disorder</td>
<td>Asperger syndrome</td>
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<tr>
<td>PDD-NOS</td>
<td>• Atypical autism (by age of onset, symptomatology, or both)</td>
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<tr>
<td></td>
<td>• Other pervasive developmental disorder</td>
</tr>
<tr>
<td></td>
<td>• Pervasive developmental disorder, unspecified</td>
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<tr>
<td>Childhood disintegrative disorder</td>
<td>Childhood disintegrative disorder (Heller syndrome)</td>
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<tr>
<td>Rett’s disorder</td>
<td>Rett syndrome</td>
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TABLE 1.3
Correspondence between DSM-IV and ICD-10 subtypes of pervasive developmental disorders (PDDs)
TABLE 1.4

DSM-IV-TR criteria for subtypes of PDDs based on the descriptors of Table 1.1*

<table>
<thead>
<tr>
<th>Criteria for autistic disorder (AD):</th>
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<tr>
<td>(a) Endorsement of a total of 6 (or more) descriptors from (1), (2) and (3), with at least 2 from (1), and one each from (2) and (3)</td>
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<tr>
<td>(b) Onset prior to age 3 years in social interaction, communicative language or imaginative play</td>
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<td>(c) The disturbance is not better accounted for by Rett’s disorder or childhood disintegrative disorder</td>
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<tr>
<th>Criteria for Asperger’s disorder (ASP):</th>
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<tr>
<td>(a) Endorsement of at least 1 (or more) descriptors from (1) and 1 (or more) from (3)</td>
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<tr>
<td>(b) Language not delayed, that is single words by age 2 years, communicative phrases used by age 3 years</td>
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<tr>
<td>(c) No significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than social interaction), and curiosity about the environment in childhood</td>
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<tr>
<td>(d) Criteria are not met for another specific PDD disorder or schizophrenia</td>
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<thead>
<tr>
<th>Criteria for pervasive developmental disorder–not otherwise specified (PDD-NOS):</th>
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<tbody>
<tr>
<td>(a) Endorsement of at least 1 (or more) descriptor from (1) and at least 1 (or more) from (2) or (3) or both but does not meet criteria for another specific PDD or schizophrenia, schizotypal or avoidant personality disorder, or age of onset. PDD-NOS includes atypical autism</td>
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<tr>
<th>Criteria for childhood disintegrative disorder:</th>
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<tbody>
<tr>
<td>(a) Entirely normal development, including sociability, language, play and adaptive behavior until at least age 2 years</td>
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<tr>
<td>(b) Clinically significant loss (before age 10 years) of previously acquired skills in at least 2 of the following areas:</td>
<td></td>
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<tr>
<td>(i) expressive or receptive language</td>
<td></td>
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<tr>
<td>(ii) social skills or adaptive behavior</td>
<td></td>
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<tr>
<td>(iii) bowel or bladder control</td>
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<tr>
<td>(iv) play</td>
<td></td>
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<td>(v) motor skills</td>
<td></td>
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<tr>
<td>(c) Endorsement of at least 1 (or more) descriptors from 2 or more of domains (1), (2) or (3)</td>
<td></td>
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<tr>
<td>(d) The disturbance is not better accounted for by another specific PDD or by schizophrenia</td>
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<tr>
<th>Criteria for Rett’s disorder:</th>
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<tr>
<td>Such significant progress in defining Rett syndrome has followed the identification of the MECP2 gene on the X chromosome in ~80% of affected girls, in an occasional severely affected boy, and in some older children and women with a broader phenotype that the DSM-IV criteria no longer apply. Postnatal slowing of head growth, postnatal appearance of prominent stereotypies, severe mental retardation with lack of or minimal language, and at least for a time lack of interest in interacting, severely impaired motor skills, development of epilepsy, and other somatic features such as hyperventilation, aerophagia, scoliosis, and cyanosed hands and feet are valid criteria for this diagnosis in girls with classic Rett syndrome. Rett’s is but one monogenic etiology of autism</td>
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*Numbers in parentheses refer to the behavioral domains listed in Table 1.1.
CAUSES OF AUTISM (ETIOLOGY)

Autism in its very broad spectrum of severity is now known to have many etiologies. The view of inept parenting as its cause, which dominated the first quarter century of its study, has been roundly discredited. It is now established that autism is but one among the (multi)dimensionally defined disorders of brain development that affect complex human behaviors. All are considered to reflect the dysfunction of widely distributed neuronal networks that interconnect widespread functionally disparate groups of neurons in the brain. The complexity of these networks is brought into focus by the fact that individual neurons are likely to be connected to many hundreds of other neurons, and that the strength of their interconnecting synapses is not fixed but varies greatly depending on the history of their functional connections and the influences of other ongoing influences on the brain. The specificity of these connections depends on which of many neurotransmitters links the neurons in a pathway and on the activity of many more modulators that influence synaptic transmission. The development and functions of these neurotransmitters, neuromodulators and their specific synaptic receptors are under the control of genes that turn on and off in orchestrated sequences. It is the plasticity of these complex widely distributed brain networks that accounts for the profound effects of the unique environmental influences, including education, to which the individual is exposed from prenatal life to his or her demise that modulates that individual’s behavior. The symptomatology of each developmental disorder depends on which nodes or larger parts of the network are dysfunctional and on the cascading consequences of the dysfunction for other networks, irrespective of the cause or etiology of the dysfunction.

This view of autism (multiple causes converging on a common neuropathogenesis) has a parallel in dementia. Like autism, dementia is defined on the basis of quantitative (dimensional) behavioral criteria, and it too has a broad range (spectrum) of severity. Dementia denotes loss of previously achieved cognitive and, eventually, sensorimotor abilities caused by any one (or more) of many underlying progressive brain degenerations. Dementia, like autism, has a large variety of causes (etiologies), among which Alzheimer disease of the elderly, unlike autism to date, has a well defined neuropathology and biochemical basis. Yet even Alzheimer disease has several distinct known – and no doubt other as yet undefined – mostly genetic etiologies, with a phenotype influenced to a greater or lesser degree by environmental contingencies such as prior level of education and current level of brain activity.

The cause of clinically defined autistic phenotypes is thus complex and multifactorial because it is generally both strongly genetic and environmentally influenced, with occasional entirely nongenetic causes as well (Muhle et al. 2004). Its largely multigenic inheritance greatly complicates attempts to link its behaviorally defined phenotype to its causal genes. In an attempt to decrease the complexity of genetic linkage studies, a recently adopted strategy is to use either biologic endophenotypes or biologic markers such as hyper serotoninemia or epilepsy, or behavioral endophenotypes such as a history of behavioral regression, stereotypies or language disorder, rather than the complex behaviorally defined
subtypes of the DSM/ICD systems in order to narrow the search for underlying etiologies (Gottesman and Gould 2003). The most recent, more efficient, strategy is to not search for individually linked genes but to use chip technologies to scan the entire genome for statistically linked groups of genes relevant to autism or autistic subtypes. The hope that drives all of these approaches is that tightly defined phenotypic subtypes will increase the likelihood of linking them to specific pathophysiologic mechanisms, and possibly even to particular etiologies.

“SYNDROMIC” AUTISM VS “IDIOPATHIC” (PRIMARY) AUTISM

Autism is a syndrome, not a disease in the sense that measles or sickle cell anemia is a disease, because despite its salient behavioral phenotype it lacks a unique etiology or specific pathology. Coleman (2005) and others use the term “syndromic” autism (others speak of “secondary” autism or autistic comorbidities – see Chapter 2) to refer to autism with a single defined cause or with readily discernible physical or imaging features or epilepsy. “Syndromic” autism is often – but not necessarily – associated with mental retardation. Examples of syndromic autism include tuberous sclerosis, Angelman syndrome, fragile-X syndrome (fra-X), the velo-cardio-facial syndrome resulting from a deletion of chromosome 22q11.2, and congenital rubella, among dozens of others. None of these etiologies is specific to autism because each of them encompasses a variable proportion of individuals with and without autism.

The term “non-syndromic” (or “primary” or “idiopathic”) autism, which applies when there are no physical stigmata or readily demonstrable biomarker, is not etiologically specific. “Idiopathic” autism encompasses mainly individuals whose etiologies remain unknown to date. Idiopathic autism might also include, at least transiently, individuals with a potentially definable but undiscovered etiology who have no physical stigmata, for example a young boy in whom fra-X or some metabolic disorder still lacks systemic signs, or even autism in a toddler with a history of regression without epilepsy (although the term “regressive autism” has recently been used to indicate a potential subgroup among children with ASD). Coleman (2005) and others use “idiopathic” autism with full awareness that it is no less organic or multifactorial because its cause(s) is (are) unknown. As etiologies are discovered one by one, the number of individuals with idiopathic autism will shrink. Clearly this nomenclature, like the behavioral nomenclature of the DSM/ICD systems, is a work in progress and will change as research advances.

COMORBID AND COEXISTING DISORDERS

Etiology is defined as the biologic cause of diseases and disorders. Causality is generally considered satisfied by the identification of a specific disorder known to produce some or most of the individual patient’s signs and symptoms if corroborated by a specific test such as the mutation of a gene, an image, or by the documented past history of a relevant illness. For example, the correlation between autism and intrauterine rubella or tuberous sclerosis is so well established that looking further for a causal explanation for the autism
would be considered superfluous, even though neither causes autism in the majority of affected individuals. The attribution is less convincing when the putative etiology is, for example, a history of uncomplicated preterm birth or of bacterial meningitis without discernable brain lesion, cognitive deficit or epilepsy as sequela. Might the condition be coincidental rather than causal, or only causal in a child with a pre-existing genetic vulnerability to autism, i.e. in such cases have a multifactorial etiology?

In addition to the core descriptors of the DSM/ICD systems, individuals with autism have a variety of other symptoms and signs. Some of them, like toe-walking and motor clumsiness, or sleep problems, or enhanced anxiety and deficient joint attention, are so frequent that they have come to be viewed as coexisting parts of the autistic phenotype even though they are not listed among the DSM/ICD descriptors of autism. Other neurologic deficits like epilepsy, Tourette syndrome, attention deficit disorder and, for that matter, mental retardation coexist too often with autism to be plausibly considered coincidental. Should they be thought of as separate comorbid disorders – on the grounds that each is considered a disorder in its own right in the DSM/ICD manuals – or are they but other manifestations of the underlying, more often than not multidetermined, cause of the individual’s autism?

Comorbidity implies that a complex phenotype results from the joint or independent expression of several independent genetic or nongenetic causes interacting on the developing brain. Comorbidity thus implies etiologic heterogeneity, in contrast to phenotypically coexisting symptoms which bespeak pathogenetic – but not necessarily etiologic – complexity. Coexistent social ineptitude with inadequate language and stereotypes signal a common, albeit most often polygenic or, more realistically, an environmentally influenced polygenic common cause. This common causation in no way implies that the phenotypic manifestations have a common pathogenesis in the brain, because there is incontrovertible evidence that the programming of motor movements, language and social skills engages distinct distributed networks.

The conceptual differences between comorbidity and coexistence are not as clear as we make them out to be. Take depression in an intelligent person with autism: depression might be comorbid with autism and be the consequence of co-inherited independent genes concerned with disordered oxytocin and serotonin metabolism affecting distinct cortico-subcortical networks; but an equally likely explanation is that the depression is the expected emotional consequence of inability to secure stable employment because of the inept social skills that characterize autism. But note that only a fraction of individuals with autism will become depressed in response to environmental adversity, therefore those who do may have inherited enhanced vulnerability to stresses, an environmentally modulated comorbidity. The possibility of genetically enhanced susceptibility to environmental insults that most persons would tolerate without persistent damage is being considered increasingly seriously with regard to immunologic, metabolic, toxic, infectious or stress contributors to the cause of autism.

There are two types of comorbidity: coincidental (unrelated, stochastic) and related.
The same phenotype, for example congenital deafness in an unstigmatized child with autism, might represent either a comorbid or a coexistent situation. Uncomplicated congenital deafness no more causes autism than autism causes deafness. If the deafness in this ASD child is due to homozygosity for connexin-26 mutation, this is an example of coincidental comorbidity of deafness with autism, but if the deafness is due to intrauterine cytomegalovirus infection, whose association with hearing loss and with autism is well documented, we are probably faced with coexisting symptomatology arising from a common etiology. Another clear example of coincidental comorbidity would be that of a child with Asperger syndrome and a congenital hemiplegia attributable to an intrauterine middle cerebral artery branch occlusion, because a unilateral focal brain lesion is most unlikely to be responsible for the ASD. The situation is much less clear in the examples of Tourette syndrome, bipolar disease, or attention deficit disorder with hyperactivity. It is even more controversial in the rather frequent situation of a child with autism who has non-autistic family members with developmental language disorders, given that impaired language is a core deficit of autism. The FOXP2 gene, which is mutated in at least one large family with a severe developmental language disorder (Lai et al. 2003), is considered by some investigators to be a susceptibility gene for autism in families in which the affected child and nonautistic family members have impaired phonologic skills (Wassink et al. 2001), an interpretation disputed by others (Newbury et al. 2002).

From a practical point of view, whether clinically distinct problems are coincidental or related is irrelevant. Each needs to be treated as such, but the possibility, as in the earlier example of depression, that one is the consequence of the other must be kept in mind. Even if they have unrelated causes, the existence of both in one person means that there will inevitably be interactions to be taken into account in planning intervention.

**COMPLEXITIES OF GENETIC ETIOLOGIES**

Clinical, neuropsychologic, electrophysiologic, imaging and other biologic research supports the view of autism (and other developmental disorders) as the expression of atypical brain development resulting in more or less widespread (and not necessarily etiologically specific) dysfunction of a complex widely distributed neural network. This *pathophysiologic view of developmental disorders* is the antithesis of a “disease” in the sense of a unique genetic or nongenetic biologic condition or of “brain damage” as a frequent cause of autism. Current genetic research, together with the strikingly skewed gender distribution to males (Baron-Cohen et al. 2005) and a less than 10% recurrence risk within sibships, points to a strongly gender-influenced polygenic etiology in the great majority of cases of “idiopathic” (primary) autism. The less than 100% concordance in both diagnosis and severity among monozygotic (MZ or single egg) twins who share 100% of their genes indicates that there are postconceptional epigenetic or environmental influences on the phenotype (Jiang et al. 2004).

Half of the human genome is involved in brain development and function. The
growth of the brain and its size, which depends on the differential growth of its different parts and their connectivity, including the many component parts of different neocortical and white matter areas and their subcortical relays, are under the control of specific gene cascades that are turned on and off in appropriate sequences. There are epigenetic regulatory networks, some of them controlled by genes like the \textit{MECP2} gene whose mutations are responsible for Rett syndrome, that influence the widely distributed neuronal networks and the growth of the synapses that interconnect them (Zoghbi 2003). More recently the focus has turned to unraveling the implications of normal and dysregulated components of a newly defined “second genome” (i.e. non-coding or micro-RNAs), whose role is to orchestrate genome-wide alterations in complex gene profiles and associated gene functional networks at play during neural development in both health and disease (Du and Zamore 2005). It has been known for several years that neurons, in addition to their classic action potentials, also have much slower integrative effects operating on gene expression on a time scale of minutes or even hours, and that these play a role in learning in response to environmental stimulation (Clayton 2000). Hormones exert effects on neuronal expression, some of which potentiate slow transcriptional responses (Vasudevan et al. 2005). The point of these few examples is that this vast array of continuous epigenetic regulatory systems is particularly malleable by environmental influences and will likely become amenable to currently evolving therapeutic interventions. It is also likely that these systems will provide insights into the gene–environment underpinnings of complex and previously intractable neurological disorders.

A host of cytogenetic abnormalities, single mendelian gene defects and mitochondrial abnormalities have been identified in occasional children with autism but, as not all carriers of these genetic abnormalities are autistic, other as yet unidentified interacting factors must come into play. For example, in tuberous sclerosis, one of the more common and better studied monogenic disorders with a high association with autism, it is probably not the gene defect per se but the burden and location of tubers (which is random as far as we know) that determine whether a carrier of a tuberous sclerosis mutation will or will not be autistic (Asano et al. 2001, Bolton 2004). As mentioned earlier, the fact that many blood relatives of individuals with autism are burdened by a variety of developmental non-autistic but related disorders also supports polygenic causation. In each individual the consequences of the mutation of one or multiple genes (or brain insults) are modulated by both the unique genetic background and the environmental experiences of the person, which goes far toward accounting for the wide variability of autistic phenotypes.

\textbf{LEVELS OF CLASSIFICATION}

Determining how various etiologies give rise to particular behavioral symptomatologies requires an understanding of the nature and location of their impacts on the brain. It is research not at the etiologic level but at the level of \textit{neurologic pathogenesis} and its interface with behavior that will illuminate the phenotype of autism. It is critical to keep these three
levels (symptomatology, pathophysiology, etiology) firmly in mind and not to jump from one to the other in discussing diagnosis. In other words, the cause (etiology) of the brain dysfunction does not provide a direct explanation for the behavioral phenotype; it is through their consequences for brain function that the many etiologies of autism cause deficiencies in behavior or other skills.

This may sound self-evident but it is common for these levels not to be kept separate. This results in incoherent hybrid classifications. For example, it makes no sense to speak of the differential diagnosis between autism (a behaviorally defined disorder with many different causes) and Rett or fra-X syndromes (diseases due to single gene defects), or to state that autism was mistakenly diagnosed in a child who turns out to have fra-X, when fra-X is a well documented etiology of ASD in some but not all the children carriers of expanded trinucleotide CGG repeats on the X chromosome. On the other hand it makes perfect sense to compare “idiopathic” autism (a behaviorally defined disorder with many different causes) to Rett or fra-X syndromes (single gene defects) or to compare commonalities in the behavioral phenotypes, MRIs or neurotransmitter levels in two distinct genetic disorders like Angelman and Williams syndromes.

CLASSIFICATION: CATEGORICAL VERSUS DIMENSIONAL DIAGNOSES

The DSM/ICD classifications are behavioral; they define disorders, not diseases in the medical sense. Many medical diseases are defined categorically: a person does or does not have the disease on the basis of a biologic criterion like an X-ray showing a fracture or a tumor, immunologic evidence or isolation of a virus, or a blood test revealing type I diabetes or sickle cell anemia. Categorical diagnoses remain dichotomous even though the severity of the disease may vary dimensionally depending on host factors, the intensity of the insult, or the degree to which different mutations inactivate a particular gene and variably decrease its product, with resultant variation in the phenotype. Other medical conditions like obesity or arterial hypertension are defined dimensionally on the basis of a measure like body mass index or blood pressure. As in the case of autism, diagnosis in these dimensionally defined morbid conditions is stipulated by an arbitrary cut in a continuum based on an agreed-upon distance of the measure from its norm. Like autism, they are also likely to be multiply determined conditions.

DSM/ICD diagnoses are designed to be categorical or mutually exclusive, in the sense that they attempt to separate behaviorally defined disorders as cleanly as possible from one another and from normality based on characteristic clusters of symptoms. In reality they are not categorical because a “diagnosis” of PDD versus not-PDD, which sounds dichotomous, rests on the presence of qualitative impairments in three behavioral domains – sociability, communication, and cognitive flexibility – and the term qualitative implies a subjective, graded – thus quantitative – judgment rather than a categorical yes/no criterion.

Not just the autistic vs not autistic diagnosis, but also the subtypes under the PDD umbrella such as autistic vs Asperger vs PDD-NOS (PDD–not otherwise specified) are
designed to be mutually exclusive or categorical. They are defined by the number of DSM/ICD qualitative behavioral descriptors endorsed on parent teacher, or clinician questionnaires, or by direct observation of the child, or both (Table 1.4), validated by the evaluation of an experienced clinician cognizant of the DSM/ICD criteria. The descriptors themselves are largely dimensional (e.g. how little interest in pretend play must a child display to endorse that criterion?). The distribution of responses to the descriptors brings in still another source of dimensional variability. For example, 6 endorsements, with at least 2 relating to sociability, 1 to language and play, and 1 to rigidity, together with symptom onset before age 3 years define DSM-IV autistic disorder (AD), but so might a total of 8 or 12 endorsements. A total of just 5 endorsements excludes AD but might mean either PDD-NOS or Asperger disorder depending on whether language was delayed or not; but so might 2 or 3, or even 6 or more endorsements if they were not distributed as required for a diagnosis of AD.

The consequence is that there is a range of both kind and severity of dysfunctions within PDD subtypes. One child might have a greater degree of social deficit and fewer repetitive behaviors, and the reverse might be the case with another child, yet both might fulfill criteria for AD. Such differences may reflect not just differences in severity of the underlying brain dysfunction but differences in what brain networks are affected. Consequently it is critical not to be satisfied with a DSM/ICD subtype diagnosis for research but to select rigorously homogeneous behaviorally defined groups of subjects or a specific endophenotype for studies like imaging or electrophysiology designed to elucidate the neurologic basis of ASD symptoms.

Extensive questionnaires like the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994), or brief screening questionnaires (Robins et al. 2001), or standardized observation schedules like the Autism Diagnostic Observation Schedule – Generic (ADOS-G) (Lord et al. 2000) or Childhood Autism Rating Scale (CARS) (Schopler et al. 1986) yield quantitative criteria for separating autistic disorder from less severe subtypes like Asperger and PDD-NOS and from a diagnosis of non-ASD. Major efforts were expended when the DSM/ICD and these other diagnostic instruments were developed to make the behavioral ratings or observations as objective as possible. All were field tested and standardized on a variety of clinically defined populations, yet agreement between behaviorally defined subtypes remains suboptimal (Zwaigenbaum et al. 2000) because behavior is inherently dimensional, which precludes an entirely sharply defined classification.

Individuals on the autism spectrum are distributed along a bell shaped (Gaussian) curve of severity, with prototypic AD cases most numerous in the center of the distribution. Diagnosis in the lowest, most severe tail of the curve overlaps with severe mental retardation (Berument et al. 2005), and diagnosis in the highest (non-retarded) tail is likely to overlap with other disorders like some developmental language disorders, obsessive–compulsive disorder, Tourette syndrome, schizoid personality, and even with normality. Indeed, there may be no sharp cut between a socially gauche, eccentric solitary
scientist and a gifted Asperger individual (Baron-Cohen et al. 2001). It is the degree to which the personality characteristics of the individual interfere with functioning in everyday life that decides whether the person is given a clinical diagnosis or dismissed as normal. The dimensionality of ASD diagnoses has become a big issue as school systems and insurance companies struggle to decide whether or not they will provide benefits to particular individuals. Diagnosis based on changing behavioral criteria, together with greater awareness of the ASDs by both professionals and the public, and heightened awareness that there are efficacious interventions for the ASDs have no doubt played a major role in the so-called autism epidemic (Fombonne 2003).

**CLINICAL COURSE OF AUTISM**

The behavioral manifestations of the ASDs change and generally improve with age. For example, as individuals enter into adulthood there is frequently an amelioration of the social isolation, although the poverty of social skills and impaired ability to make peer friendships is lasting (Howlin et al. 2000, 2004). Language and communication deficits too often endure into adulthood, and verbal skills in those who acquire speech may have permanent inadequacies in conversational skills such as turn taking, understanding the subtleties of language like jokes or sarcasm, and interpreting body language, intonation and facial expression. Stereotypies may decrease over time or become “miniaturized”, whereas abnormal body posture and gait abnormalities often persist. We know very little about the long-term effects of early intervention on many of the manifestations of autism and on outcome. Among the less severely affected individuals with autism there are a number who improve with little or no intervention, whereas progress in others is extremely limited despite intensive behavioral, educational and pharmacological intervention.

About a third of parents report an *early regression* of language and behavior, most often between 18 and 24 months, or later in the rare previously entirely normally developing child with disintegrative disorder in whom regression may occur as late as 10 years. There is no accepted definition of regression, and most studies documenting regression have been based on parent reports of their children losing single words or phrases, together with loss of sociability and of interest in playing with toys, and the appearance of behavioral rigidity and stereotypies. Investigators who examined family videotapes made prior to the identification of symptoms of autism often find signs of preexisting developmental differences (Osterling et al. 2002, Werner and Dawson 2005). There is some preliminary evidence that cognitive impairment is more likely in individuals with ASD who experienced a regression, although this is disputed (Kobayashi and Murata 1998, Kurita et al. 2004, Lord et al. 2004). There is also controversy regarding whether disintegrative disorder and autistic regression are discrete entities. There are almost no prospective studies on autistic regression, and its cause or causes remain unexplained. Regression is more profound in disintegrative disorder as the children regress in adaptive behaviors like toilet training and in overall cognitive ability; its prognosis for improvement is poor (Volkmar et al. 1997).
Overall, prognosis in autism is variable and depends most directly on its severity and underlying causes (Ballaban-Gil et al. 1996, Howlin 2003, Howlin et al. 2004). Early intervention programs for the child – but equally important, training of parents in how to deal more effectively with such difficult children – may make a difference and may produce long-lasting gains, as may the provision of social skills training as the need arises throughout childhood (Dunn 2005). We have very little empirical evidence to support any particular type of intervention, and no intervention fits universal needs, although the most effective behavioral and educational interventions share the common characteristics of intensity, frequency, structure, and being provided to toddlers and preschoolers (National Research Council 2001). We stress that our ability to predict outcome in very early childhood is limited. There are no systematic accounts or epidemiological studies to provide data regarding longevity or long term prognosis of older individuals with autism.

THE ROLE OF THE CHILD NEUROLOGIST IN THE ASSESSMENT AND TREATMENT OF CHILDREN WITH ASDs

There is no biologic test to validate the diagnosis of an ASD. The goal of the neurological examination is to assess what, if any, tests are needed, depending of course on the history and neurological examination. The initial work-up of an individual with autism should have a clear clinical goal. It will differ from the evaluation and tests required for a research protocol. There are evidence-based guidelines established for the diagnosis and evaluation of children with autism and related disorders (Volkmar et al. 1999a,b; Filipek et al. 2000; Committee on Children with Disabilities 2001). As is the case for children with mental retardation or dementia, a detailed developmental evaluation is always required. Other tests like a formal speech and language evaluation and neuropsychological assessment need to be carried out in selected children with autism in order to define their individual educational plans (IEPs) more precisely. The history and neurologic evaluation may mandate tests such as neuroimaging or neuropsychiologic investigations, or referral to a geneticist for cytogenetic studies, DNA tests for fra-X, Rett syndrome, and other known genetic conditions highly associated with autism, in the hopes of being able to provide a target medical treatment or genetic counseling. We stress that there is no such thing as a routine test battery for autism except in the context of a formal research protocol. Rigorous behavioral subgrouping for research is required if we hope to gain an understanding of the pathophysiology of the ASDs and make progress toward providing more specific biologically targeted interventions and prognosis.

Early identification of children with an ASD is essential for enhancing the efficacy of early intervention at a time when the brain is most plastic. No one treatment fits all. Subgrouping is required for management, which needs to be individualized and multidisciplinary. Besides specially trained educators it may involve a variety of therapists, a psychopharmacologist, and a social worker/child/family advocate.

The child neurologist plays a unique role in providing or interpreting genetic
information to parents, educating families, primary care physicians, other allied health professionals, and educators on the early signs of autism, what it is and is not, and what investigations and interventions are optimal. As child neurologists we have an understanding of the neurologic basis of autism, as well as being trained in the coordination of the multiple disciplines and individualized interventions that each child with ASD deserves. Because we are used to dealing with chronic diseases that affect the quality of the life of the affected individuals, and equally that of their families, we have not discharged our duty unless we have made sure that the family, as well as the child, have access to practical help and emotional support. We have organized this book from this perspective, emphasizing the need to understand both the neurobiological and clinical heterogeneity of autism, and have emphasized both medical and behavioral/educational interventions.

OUTLINE OF THE BOOK
In organizing this book by neurologists for neurologists, we have in this first chapter provided some general definitions, and discussed the terminology and concepts that have placed autism at the forefront of behaviorally defined complex disorders of the developing brain. There follows a discussion of the epidemiology of autism, pointing out how important it is to use a common language to determine the frequency of a problem. It is clear that autism is no longer considered a rare disorder, and clinicians are recognizing and making this diagnosis much more often than even 10 years ago. What is more controversial is the possibility that specific and yet unidentified risk factors may be accounting for the increased number of children diagnosed with ASDs. The next three chapters discuss what are considered the core symptoms of autism; they provide the clinical material that needs to be understood from the perspective of both the clinician managing a child with an ASD and the researcher trying to understand its neurobiologic basis. These chapters are followed by a review of the evidence that suggests that autism is a disorder of neuronal development, followed by discussions of the genetics, neuroanatomy and neuroradiology, neurochemistry, immunology, and neurophysiology of autism. Reviews of problems commonly associated with autism such as epilepsy, sleep disturbances, and sensory and motor deficits come next. Consideration is then given to the neuropsychological assessment of children with ASDs, medical and psychopharmacologic management, educational and behavioral interventions, and outcome. The concluding chapter briefly summarizes where we are now in our understanding of the neurology of autism, but more importantly it proposes a research agenda that ensures that child neurologists continue to have a positive impact on the lives of children and families coping with this complex disorder of neurodevelopment.

REFERENCES


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