CHAPTER 2

What Causes Autism?

The earliest descriptions and discussions of autism, not surprisingly, focused on today what we might call "classical" autism—that is, autism as strictly defined and much less on what we would now think of as autism spectrum disorders or the broader autism phenotype, as it is sometimes called. As we mentioned in the first chapter, Kanner's first paper on autism was very influential in several different ways although some of his first observations have been modified over time. His description of autism was unusually clear about t what he saw as the central features present in autism (problems in social interaction and unusual responses to the environment). He also was clear in suggesting that autism was congenital; that is, children were born with it although we now know that sometimes children seem develop autism in the first years of life. Kanner speculated that autism was not associated with intellectual disability (mental retardation) because children did well on some parts of intelligence quotient (IQ) tests. Some aspects of his report misled people, for example, into thinking parents of children with autism might somehow cause the disorder. The early (and mistaken) notion that autism was more common in families where parents were more successful indirectly contributed to a very unfortunate development in the 1950s: blaming the parent (usually the mother) for the child's troubles. Bruno Bettleheimof the University of Chicago advocated removing children from the home in an attempt to address what he saw as the fundamental problem. The idea that parents somehow caused autism damaged a generation of parents who felt responsible for their child's difficulties. However, beginning in the 1960s, and particularly in the 1970s, research began to show that autism was a brain-based disorder.

As children with autism were followed over time, it was clear that many of them—perhaps 20% or so—would develop seizures. Other children exhibited unusual features on neurological examination such as persistent "primitive" **reflexes** (which are present at birth but typically disappear in children after a few months). Some studies reported that children with autism were more likely to

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have had complications either before or during birth. Still other studies reported associations of autism with a number of medical conditions that were known to affect brain development. Most importantly, it became clear that autism has a strong **genetic** aspect. Although we still don't know the absolute cause of autism, the best evidence suggests that autism is a brain-based disorder with a very strong genetic component. Although the exact genetic cause (or causes) is not known, we are much closer to finding genes than we were even a few years ago.

Genetic Causes of Autism

In the 1970s, an article written by some prominent **geneticists** suggested that there was no genetic contribution in autism. However, autism was relatively rare and the data was very limited. Shortly thereafter, a very important paper by Susan Folstein and Michael Rutter (1977) appeared, which suggested that rates of autism in identical (or monozygotic) twins were much high than rates in same-sex fraternal (or dizygotic) twins.[1] Identical twins have identical genes, while fraternal twins share only some genes. The implication of this finding was that there was potentially a very strong genetic contribution in autism. A number of studies have now shown that this is the case(see Rutter, 2005 for a detailed discussion). Several different additional findings have emerged.

As scientists began to look into the issue of the genetics of autism, it became apparent that rates of autism were increased in the brothers and sisters of children with autism. Rates reported vary between 1 in 10 and 1 in 50. This does not seem like a very high rate *unless* one realizes that the rate of classical or strictly defined autism in the general population is between 1 in 800 and 1,000 or so and that, although autism is by no means common in siblings of autistic children the rate is clearly increased— relative to the general population.

GENETICS OF AUTISM

Strong role for genetic factors suggested by:

- High rates of concordance in identical twins (if one twin has it, the other one is very likely to have it).
- Increased risk for autism in siblings (2–10%) (this is significantly greater than the population rate).

[1]Monozygotic or identical twins are always same sex of course but genetic studies of fraternal twins with autism have generally focused on same-sex twin pairs because of the gender difference in autism, or, put another way, these studies have typically not used boy-girl fraternal twin pairs because of this sex difference.

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What genes are involved?

- It appears that multiple genes contribute to autism.
- Attempts are under way to identify these genes.

What happens once genes are identified?

- It will be possible to develop animal models.
- We will better understand how the genes work in the brain.
- There may be implications for diagnosis and screening.

Other work also began to look at associated problems in siblings and suggested than even when siblings did not have autism, they did seem to have an increase in other problems, including language and learning difficulties. It still is not exactly clear what is inherited in autism. It is possible that what is inherited is a more general predisposition to difficulties rather than to autism as such. Recent work on family members also suggests that there may be higher rates of mood and anxiety problems in family members as well as, perhaps, more social difficulties.

Although research has increasingly highlighted the importance of genetic factors in autism, final answers are not yet in. The genetics of autism is not straightforward or very simple, and it appears that multiple genes are probably involved; estimates of the number of genes range from 4 to 20 or even more. To make life more complicated, it may also be the case that not all forms of autism have the same genetic basis but might come about in other ways; for example, there might be a specific problem at the moment of conception when some genetic material might be lost or a genetic change (**mutation**) might occur. It might be that other things are involved, for example early birth difficulties might interact with a genetic predisposition to cause autism. Major efforts are now under way to identify potential genes in autism. Genes that may be involved (known as "candidate genes") are presently being investigated. It seems likely that some genetic cause (or causes) of autism will be identified over the next few years.

Seizure Disorders and Electroencephalographic Abnormalities

One of the important things that helped doctors realize parents weren't to blame for autism was an increasing awareness of the higher-than-expected risk autistic children had for developing seizures. Seizure disorders (also referred to as **epilepsy** or **convulsions**) are a group of conditions that result from abnormal electrical activity in the brain. The symptoms of seizure disorder are quite varied. They can range from brief episodes where the child seems to "tune out" to

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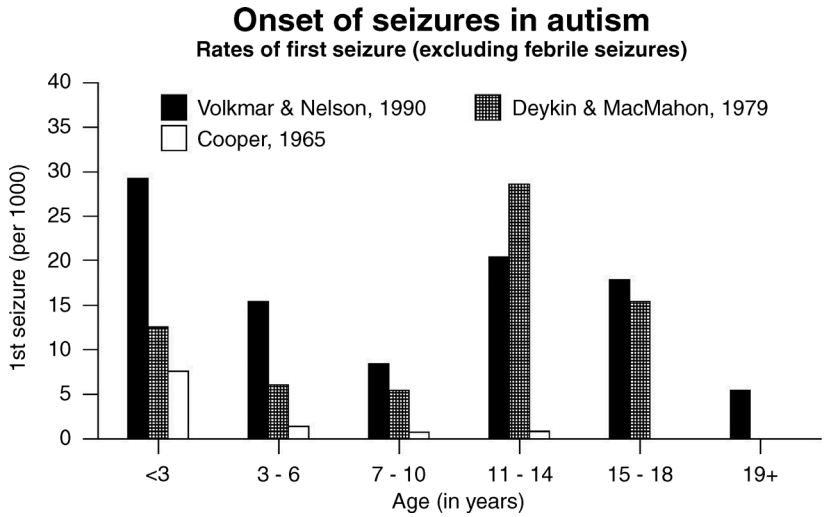

FIGURE 2.1 **Rates of first seizure in two samples of individuals with autism**

(Volkmar & Nelson, 1990; Deykin, & MacMahon, 1979) and a normative British sample (Cooper, 1965).

much more obvious convulsions where the child falls to the ground, loses consciousness, and has alternating periods of muscle contraction and relaxation. There are many different kinds of epilepsy (see chapter 12).

One of the ways doctors look for seizure activity is through the **electroencephalogram** (or **EEG**), which measures electrical activity in the brain. Both early and more recent studies suggest that as many of 50% of individuals with autism have abnormalities in their EEGs; findings on the EEG are diverse and not specific to autism, but the higher rates of abnormality are, of course, suggestive of some basic problem with the way the brain is "wired." In the "normal" population of children, rates of first seizure are highest around the time of birth and then greatly decrease over time. Figure 2.1 presents information from two studies of children with autism or autism and pervasive developmental disorder not otherwise specified (PDD-NOS), as well as data from a large normative sample of British children. The rates for developing seizures are higher in children with classical autism.

Other Neurological Problems

A number of other neurological problems are observed in autism. Again, these are of many different types; not every child has every problem, and some children will have none. Some children with autism have delays in the development of hand dominance (preference for right or left hand) later than typically developing

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children. They can also have general decreases in muscle tone in the body and be somewhat "floppy" as babies (technically called **hypotonia**). Sometimes individuals with autism have unusual reflexes; often, these are reflexes that are usually seen only in very young babies but can persist into adulthood in individuals with autism. For example, if the doctor brings a reflex hammer toward the baby's mouth, she may start to suck as if anticipating the bottle or breast; this *visual rooting reflex* is sometimes seen even in adults with autism, whereas in most people it disappears very early in childhood. Other problems may be seen in the way that individuals with autism walk or with their posture.

Neuroanatomy and Brain Imaging Studies

Various methods can be used to study the brain, ranging from actual studies of brain tissues obtained at the time of death (postmortem studies) to studies of the living and active brain through **functional magnetic resonance imaging (fMRI)**. A number of findings deserve mention. Both autopsy and brain imaging studies have suggested that at least some individuals with autism have increased brain size and that this develops in the first year or so of life. Several studies have suggested the possibility that there are some alterations in brain structure, particularly in those parts of the brain that process more emotional or social information (the limbic system) and possibly in the cerebellum. The **cerebellum** is the part of the brain that, among other things, helps coordinate and control movement. One investigator has, in particular, noted specific changes in the cerebellum in individuals with autism; unfortunately, other investigators have generally not been able to find this.

AREAS OF POSSIBLE BRAIN INVOLVEMENT IN AUTISM

Areas of Possible Difficulty	Functions
Prefrontal cerebral cortex	Social thinking
Hypothalamus	Attachment behaviors
Amygdala	Social orientation, emotional learning
Fusiform gyrus	Face recognition
Middle temporal gyrus	Recognition of facial expression
Pulvinar	Emotional relevance

In the last few years, several interesting findings have emerged from studies of functional neuroimaging in autism. A paper from our (Yale) group documented that children with autism and Asperger's syndrome seem to process the information in faces differently in the brain; basically, they use the object processing areas,

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whereas most of us use a very specialized face processing center in the brain. This may be one of the reasons that faces don't seem to have the same "specialness" for people with autism that they do for typically developing people. It might also account for an interesting finding in autism—people with autism do just as well identifying faces upside down as opposed to right side up. After about 6 months of age, typically developing babies (and people in general—try this with your driver's license the next time you go through the airport screener!) have real trouble identifying upside-down faces (known as the *facial inversion effect*).

Another, possibly related finding is that higher functioning individuals with autism—and, for that matter, many babies with autism—tend to look at mouths rather than eyes and the upper parts of the face when watching very intense social interactions. Our group originally demonstrated this by having very able people with autism and typically developing viewers watch clips from the movie classic *Who's Afraid of Virginia Woolf* and discovered great differences in how the very cognitively able viewers with autism watched the movie. In contrast to typically developing viewers, who spend more time looking at the eyes and top half of the face, the viewers with autism tended to focus on mouths and objects (the latter usually more or less totally extraneous to the plot of the movie). This is demonstrated visually in Figures 2.2 and 2.3. Figure 2.2 shows the differences in visual

FIGURE 2.2 **Visual focus of an autistic man and a normal comparison subject showing a film clip of a conversation.**

Typically developing person (top line) goes back and forth between the eyes in viewing a social scene; a high-functioning person with autism goes back and forth between the mouths of the speakers.

Reprinted, with permission, from Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Defining and quantifying the social phenotype in autism. American Journal of Psychiatry, 159, 895–908.

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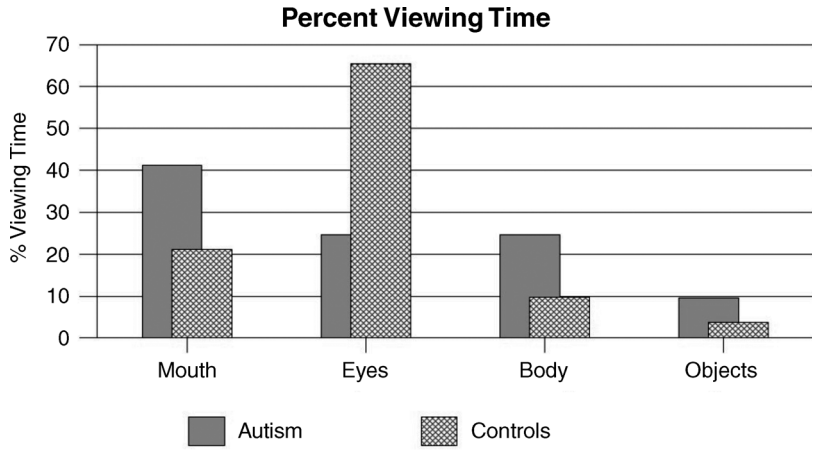

FIGURE 2.3 **Percent viewing time spent focused on mouth, eye, object, and body regions in viewers with autism and typically developing persons.**

All differences are significant.

Data adapted, with permission, fromA. Klin, W. Jones, R. Schultz, F. Volkmar, & D. Cohen. (2002). Visual fixation patterns during viewing naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 39*(9), 809–816.

scanning of a viewer with autism (bottom line), who focuses on mouths (and then only on the person speaking), versus the typical viewer, who focuses on the eyes. Figure 2.3 shows the data for groups of cases—there is actually no overlap of the groups in terms of where they watch. Given that most (maybe about 90%) of the important social information is conveyed in the top half of the face, it is probably not such a surprise that viewers with autism are missing most of the relevant action. These differences in visual tracking seem to develop very early (see chapter 7) and may be a reflection of different brain mechanisms used to process social information. This is a very active area of research right now.

Neurochemistry

Nerve cells use different kinds of chemicals to communicate with each other. A number of these systems have been studied in autism, and there is some suggestion of alterations in these systems. Most of the work has centered on the chemical **serotonin** (also sometimes referred to as 5-HT or 5-hydroxytryptamine). A number of studies have shown that levels of serotonin in the blood are often increased in individuals with autism. Unfortunately, the relationship between blood levels and brain levels of this chemical are not always clear. Other studies

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have focused on the chemical **dopamine**, which is involved in parts of the brain that control movement and is part of a broader system that relates to levels of alertness and what is technically called *arousal*. Many of the drugs used to treat symptoms of autism affect these chemicals (see chapter 15).

NEUROCHEMISTRY OF AUTISM

Neural transmitter	Function, relevance to autism
Serotonin	Regulates sleep, mood, body temperature High levels in blood of many individuals with autism Affected by some medications
Dopamine	Control of motor functions One class of medicines used in autism (neuroleptics) block dopamine function
Norepinephrine	Involved in states of arousal, stress response, memory, and anxiety; affected by some medications

Risks During Pregnancy and Childbirth

Could autism be caused by problems during pregnancy, labor, and delivery? A number of studies have looked at this question. Generally, they have employed some rating scale that looks at the degree of risk during the pregnancy and/or during labor and delivery. Early studies seemed to show that there was an increased risk based on the use of these rating scales. Factors that seemed to be associated with increased risk for autism included older age in the mother, prematurity, and some other problems during labor and delivery. Several studies have also suggested that doctors or nurses may be more likely to notice something wrong with the newborn, even if it is very minor. This suggests an important point and a major problem in understanding whether problems during pregnancy or labor and delivery might cause autism; that is, it would be reasonable to assume that if there were something wrong with the child from the moment of conception that was picked up at birth, we might be seeing problems at birth that may result from some vulnerability in the child. Thus, it would be just as reasonable to assume that problems in the child cause difficulties in the pregnancy. The growing body of work on genetic factors in autism, which is discussed shortly, would be most consistent with this idea.

At the same time, it is reasonably clear that horrendous difficulties during labor and delivery, particularly when associated with severe fetal distress, won't *help* any child and have the potential to further cause trouble for a child who was going to have autism.

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Environmental Causes of Autism

Interest in the possibility that environmental factors contribute to autism stems from several sources, including reports of "cluster" cases, an assumption that the rate of autism has risen over time, and associations with potential environmental toxins like mercury (or thimerosal in vaccines). It is indeed clear that even in identical twins, while the rate of concordance for autism is high, it is not 100%.

However, as we discussed in chapter 1, it is not so clear that the rate of autism is increasing. It is reasonably clear that we are doing a better job of finding cases, that there is much more awareness of autism, and that we've changed the ways we diagnose autism and have expanded the number of children diagnosed. As we discuss in chapter 10, the vast majority of serious scientific studies have not supported the idea that vaccines (or thimerosal) cause autism. Furthermore, some of the evidence proposed for environmental factors is based on case reports, which are often difficult to interpret. For example, there was an early impression that autism was associated with congenital rubella infection, but, over time, these usually very delayed children looked less and less autistic. At present, there is not particularly strong evidence for specific environmental etiologies, although clearly more work is needed in this area. Some good summaries of work in this area are included in the reading list at the end of this chapter.

Medical Conditions and Autism

It took many years before people considered the possibility that autism was associated with some medical conditions, such as seizures. As autism came to be better recognized, it became associated with a number of other medical conditions, and there was interest in the possibility that some of these conditions *caused* autism. However, much of this work was based on **case reports**, wherein a doctor sends a letter or a short paper to a professional journal, which reports that autism is associated with_____syndrome (you can fill in the blank with essentially any known medical condition). Case reports have some value but also have many limitations since there is a bias for only positive reports to be published (similar to the situation with the regular media!). The issue is not whether you *ever* see autism and condition X, but whether in larger groups of individuals the frequency of condition X is significantly greater in autism than you would expect, given how common condition X is in the general population.

Another problem relates to the diagnosis of autism in the first place. Some researchers take a very broad view of autism; others, a more narrow one. If a broad view is taken, estimates of the rate of autism will naturally tend to be higher and there will be the impression that autism is more likely associated with other medical conditions. In other words, if a broader definition of autism

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is used, there will be more diagnoses of autism among people with severe and profound intellectual disability, in part because levels of repetitive movements and unusual behaviors are higher in this group of cases. Also in this group of cases, with lower IQs, about half the time there is an associated medical condition, and thus a condition that might contribute to the person's handicap is much more likely to be found, regardless of whether they have autism! Two rather different views emerge from the published research on medical conditions associated with autism. If a very broad view of autism is taken, perhaps one-third of cases of autism might be related to some condition; however, if a narrow view is taken, probably only 10% of cases are.

Various conditions have been identified as possibly being associated with autism, including **phenylketonuria**, **congenital rubella**, **tuberous sclerosis**, and **fragile X syndrome**. However, careful research has led us to rethink how strong these relationships are, and at present the strongest associations are with fragile X and tuberous sclerosis.

Fragile X Syndrome

Fragile X syndrome is a common syndrome associated with intellectual disability and, sometimes, with autism. It is probably second only to Down syndrome as the most identified genetic source of mental retardation. Fragile X syndrome particularly affects boys and has sometimes been associated with autism. All of us have 23 pairs of **chromosomes**. Boys have an X chromosome (from their mothers) and a Y chromosome (from their fathers). It is called fragile X syndrome because the X chromosome was noted to sometimes break or be "fragile" when examined. Because boys have only one X chromosome, they are more likely to have the disorder (i.e., there is no extra X to make up the difference). In girls, who have two X chromosomes, the disorder may be expressed in a somewhat milder form. Fragile X is one of the more common causes of intellectual disability/mental retardation, perhaps affecting 1 in 800 to 1,000 children.

Associated problems in fragile X syndrome include mild intellectual disability/mental retardation (although sometimes IQ is in the normal range). In addition, language problems, attentional difficulties, and symptoms suggestive of autism (problems with eye contact and self-stimulatory behaviors) may be observed. Boys with the disorder may have some unusual body features, such as large ears and genitals; the face may be long and narrow, and the palate (the roof of the mouth) may be unusually high and arched. Motor and learning problems are relatively common. Low muscle tone as well as dental and eye problems may be observed. Sometimes individuals with this condition have seizures.

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FRAGILE X SYNDROME

- Symptoms: social anxiety, "autistic-like" symptoms, and sometimes autism.
- About 1–2% of individuals with autism have fragile X.
- A simple blood test can be used to determine whether fragile X is present.
- Syndrome can be seen in boys and girls.
- The genetic basis of this condition has been well described.

Early reports suggested a very strong association between autism and fragile X syndrome, with claims that as many as 60% of individuals with autism had fragile X. There was much optimism that a genetic cause of autism had been found. However, subsequent (and better) studies have suggested that the association between fragile X syndrome and autism is not nearly as strong as it first appeared. In the early studies there was not careful attention to appropriate controls or to diagnosis of autism. Recent research indicates that between 1% and 2% of individuals with autism have fragile X; this rate is not much different from what would be expected from any sample of children with mild intellectual disability—that about 1% of individuals with fragile X have autism. Thus, although it remains important to consider testing for fragile X, the rate of the condition in autism is relatively small and accounts for only a very small subgroup of children with autism.

At the present time, the main impact of diagnosing fragile X relates to the implications for genetic counseling of parents and sisters of affected individuals; that is, the treatment of the child with autism and fragile X is no different than that for the autistic child without fragile X. However, for parents who know that they have a risk for subsequent children with fragile X, prenatal testing and termination of pregnancy (if that is an option for the parents) is available. In the past, the diagnosis of fragile X syndrome was made on the basis of an actual examination of the child's chromosomes, obtained through a blood sample and grown in a laboratory. This time-consuming and costly procedure has now been replaced in many centers by a more direct DNA test for the fragile X abnormality. The genetic that cause of fragile X has now been identified.

Tuberous Sclerosis

Tuberous sclerosis affects about 1 in 10,000 people and, although rare, has been noted to be significantly associated with autism. It is seen equally as frequently in boys and in girls. Symptoms include the growth of unusual tissue or benign tumors in the skin, eye, brain, and other organs. Over half of infants with the disorder will have white patches on their skin at birth. The tubers may be seen in

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the brain and can be detected by **computed tomography (CT)** or **magnetic resonance imaging (MRI)** scan. The tumors associated with this disorder are often seen in the preschool years and may increase in frequency during **puberty**. These growths are "benign" in the sense that, unlike cancer, they do not spread, but their effect on growth and development can be very serious. Individuals with this condition often have **developmental delay** and intellectual disability and seizures.

The disorder is inherited as an *autosomal dominant* trait, meaning that it is on the autosomes (i.e., not on the sex chromosomes) and that if you get one copy of this gene from either parent, you are likely to have the disorder. A gene for the disorder has been located on chromosome 9.

Although the effects of the disorder can be severe, the degree of severity in tuberous sclerosis is variable.Children with tuberous sclerosis may have speech delays and learning problems. They often have motor problems as well Sometimes the first symptoms are seen in infancy or early childhood, often with the onset of seizures. Between 50% and 60% of affected individuals show intellectual disability, and about 80% have seizures. Sometimes the findings include a specific abnormality in brain wave (EEG) testing. The seizures may include a specific kind of muscle spasm (myoclonic jerks). Sometimes individuals seem to be much less severely affected; it seems likely that this happens in some special circumstances, for example, as a result of spontaneous genetic change not inherited from the parents.

Interestingly, early reports on tuberous sclerosis appeared in the 1930s and described some problems suggestive of autism (which was not described until the 1940s!). These problems included stereotyped movement, abnormal speech, and social problems. Hyperactivity, aggression, and other behavior difficulties have also been reported.

In studies of individuals with autism, about 1–2% also have tuberous sclerosis; this figure is higher if only individuals with autism *and* seizures are included (about 8–12% of such cases may have tuberous sclerosis). But not every child with tuberous sclerosis has autism. The ratio of boys to girls in autism associated with tuberous sclerosis is about the same; this is in contrast to autism in general, where the rate of autism is clearly several times higher in boys than in girls. Sometimes tuberous sclerosis is not associated with intellectual disability; studies of this small subgroup do not seem to suggest high rates of autism or similar problems, but the final answers are not yet in. Promising work on the genetic causes of tuberous sclerosis is now underway.

Disorders of Metabolism: Phenylketonuria (PKU)

PKU is caused by a problem in the body's use of the amino acid phenylalanine. As a result, levels of this amino acid build up in the body and eventually are

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excreted in the urine. This disorder is rather rare, affecting about 1 in 10,000 babies. If it is not treated, PKU can cause severe intellectual disability, growth problems, and seizures. Although the baby may otherwise appear normal at birth, symptoms gradually develop, including problems in feeding and development. Fortunately, with the recognition of the cause of the disorder, doctors realized that the condition could be treated with a special diet that eliminates phenylalanine. This is one a handful of dietary treatments medically proven to have a major role in preventing/treating developmental problems. PKU is now screened for at birth in this country, since prompt treatment allows children with PKU to have normal and productive lives.

Early papers suggested that PKU was a risk factor for autism. However, more recent research has questioned this view. Well-controlled studies do not seem to suggest that there are higher-than-expected rates of PKU or other disorders of metabolism in autism. It seems likely that early reports of such associations probably equated "autistic features" (usually meaning stereotyped, self-stimulatory behaviors) with autism. It is still appropriate to consider screening children with severe developmental difficulties for inborn errors of metabolism, but there is not a clear relationship of these disorders to autism.

Congenital Infections

There have been some reports associating autism with infections either before or at the time of birth or shortly thereafter. The kinds of infections for which this have been claimed are quite varied and include congenital rubella, cytomegalovirus, herpes simplex, and human immunodeficiency virus (HIV—the AIDS virus). A few papers have also reported that there might be some association of autism with the time of year when children are born that might suggest some fluctuation in association with the prevalence of other infections. However, other studies have not seen such associations. Probably the most interest in terms of infection has centered around congenital rubella.

Congenital rubella occurs when a baby still in its mother's womb is infected with the rubella (German measles) virus. Women who have not had rubella or who have not had the immunization for it are at very high risk for having a baby with congenital rubella if they develop rubella while they are pregnant. The risk is greatest during the first 8 weeks or so of the pregnancy (a time when sometimes women may not realize they are pregnant).

The virus often does severe damage to the developing baby. The baby may be born with problems in the heart, eyes, and ears. The head may be small, and there may problems with other parts of the body. Hearing loss may develop; deafness and blindness are relatively common. Intellectual disability and various behavior problems may be observed. While a few children do not have symptoms, most

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do. Fortunately, greater awareness of the seriousness of this condition and the development of a vaccine have reduced the frequency of this condition. The vaccination of young children has been very helpful in this effort.

Early reports on congenital rubella suggested that these children often seemed to have autism. As we mentioned earlier in the chapter, there were a number of issues with this conclusion since these children had multiple problems—they were often deaf or had impaired vision and severe learning difficulties so being sure of the diagnosis was complicated. As with other conditions, the presence of **autistic-like** features was taken as suggestive of autism; however, follow-up studies have shown that over time the social and other problems of these children seem to improve in ways that would not be typical of autism.

Psychological Models of Autism

Following the error of the early "blame the parent" notion, speculation about how autism might be understood through psychology was held back in some important ways. Over the last two decades, new theoretical models have been proposed that try to understand the developmental and behavioral aspects of autism from the point of view of psychological development; it must be emphasized that this is an attempt to understand brain-based difficulties and *not* to blame the parents. These attempts are of some interest in terms of research and may, perhaps, lead to some treatment advances. It is important to realize that several rather different approaches have been used. One attempts to view the social problems in autism as one of many different difficulties caused by the same factor (or factors). The other view emphasizes the social difficulties as primary in some basic way, that is, as leading to other problems. These all have their pros and cons and none has, at least as yet, emerged as the "winner." At present, they all have something to offer in terms of alternative models of how we might understand autism.

The **Theory of Mind** approach has emphasized the idea that there is a basic problem for children with autism in empathizing with others, that is, having a "theory of mind," or theory of what motivations, intention, and so on, impact on the behavior of others. This approach, first proposed by Simon Baron-Cohen (see reading list) has been remarkably productive in terms of research. The simplicity and elegance of this theory have added to its attractiveness. There are, however, two problems with this model. One is that the severe difficulties in social interaction impact behaviors seen in very, very young children—children of a few weeks of age. This is a time well before the ability to "put yourself into the other's place" has really developed. Another problem is that many higher functioning individuals on the autism spectrum can do "theory of mind" tasks just fine, and yet these individuals are still very socially disabled.

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Another approach, termed the ***executive dysfunction hypothesis***, emphasizes deficits in "executive functions" (a topic we discuss in greater detail in chapter 6). The notion of executive functions refers, basically, to the whole range of abilities involved in planning and organization. For example, seeing the multiple steps involved in a complicated task, plotting a solution in terms of getting to the desired result, keeping the desired result in mind, and being able to work out alternatives when this is needed (Pennington & Ozonoff, 1996). Within this view, autism is related to difficulties in dealing with change and a tendency to engage in repetitive behavior and **perseveration** as well as to problems in developing planning and problem-solving abilities due to a lack of coordinated reasoning and ongoing adjustment to feedback (Ozonoff, 1997). As we discuss later in this book, there is no question that children with autism spectrum disorders often have severe problems in this area. From the point of view of a more general theory, however, there are some difficulties. Probably most importantly, difficulties in this area are not unique and specific to autism; that is, children with attention deficit hyperactivity disorder also have problems with organization (but don't have social troubles of the same type seen in autism).

A somewhat different theory proposes that the difficulties in autism relate to "**weak central coherence**." The idea here is that people with autism have trouble getting the "big picture" issue (Happé, Briskman, & Frith, 2001); they don't see the interconnections of things—a "not seeing the forest for the trees" problem. This theory would account for some of the people with autism who are gifted in one area but very deficient in another area. Although very attractive in many ways, the experimental evidence has been somewhat weak and contradictory. Other approaches, for example, Klin and colleagues (2003) focus more on the social difficulties being a primary cause of autism, with many of the symptoms arising from the limited interest in people and the negative consequences of brain and psychological development.

Understanding the Causes of PDDs Other than Autism

Our understanding of the causes of PDDs other than autism is not generally as far advanced as in autism, with the major exception of Rett's disorder. Again, we understand that all these conditions have a basis in problems in the brain. This is suggested by such things as rates of seizure disorder and, occasionally, other abnormalities as well. The role of genetic factors in Rett's syndrome is now clearly established, as a gene has been found to be involved in many cases (see chapter 13). Compared to Rett's syndrome, childhood disintegrative disorder is apparently less common and has been even less frequently studied. For many years doctors presumed that there was some specific medical process that could always

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be identified to explain why children developed normally for several years and then had a major deterioration. It is clear that this is the exception rather than the rule.Occasionally, such a process is identified that is similar, in some ways, to the dementias of adults (such as Alzheimer's disease, where there is progressive loss of functioning). Interestingly, however, in CDD behavior and developmental skills usually deteriorate and then stay at the same, relatively low level. This kind of plateau is not usually observed when a progressive medical condition is present. As in autism, the involvement of the brain is suggested by the high rates of EEG abnormality and seizure disorder. Information on brain structure and functioning is very limited, although research on this aspect of CDD is now under way. It is possible that the condition might develop in several different ways.

CHILDHOOD DISINTEGRATIVE DISORDER

Causes of Childhood Disintegrative Disorder

- Early impression of possible psychological causes seems wrong.
- The distinctive and unusual pattern of onset suggests some specific disease process.
- Most of the time, despite intensive searching, no specific medical cause is found.
- Occasionally the condition is associated with some neurological disorder similar in some ways to adult dementia, but this is not usually the case.

In Asperger's syndrome (AS) there have been several reports of associated abnormalities, but these are mostly based on reports of single cases rather than group studies. One interesting finding has been that Asperger's is frequently associated with **nonverbal learning disability** (NLD) and the difficulties in AS have been taken by some to suggest difficulties in the right part of the brain (in contrast to autism, where the presence of **language** problems has often been taken to suggest problems in the left part of the brain). Although research on the issue of genetic contributions in Asperger's is not as well advanced as that in autism there is already some evidence for a strong genetic component with high rates of social difficulty in members of the immediate family.

ASPERGER'S DISORDER

Causes of Asperger's Disorder

- Genetics:
  - Asperger commented on high rate of similar conditions in fathers.

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- Recent research does suggest higher rates of social problems in
- male relatives.
- Female relatives tend to have higher rates of anxiety and
- depression.
- It is possible that this is even more strongly genetic than autism.

- Brain functioning:
  - Association with Nonverbal Learning Disability Profile.
  - Suggestion that problems are more likely in the right cerebral cortex.

Research on the causes of PDD-NOS is the least advanced of all the PDD conditions. There is a strong suggestion of a possible genetic component, since many individuals with autism have relatives with language, learning, or social difficulties. It is possible that what we now see as PDD-NOS may, someday, be identified as a variant of autism—for example, one which comes about when some, but not all, the **genes** that cause autism are present. It is also likely that there really may be important distinctions within the broad group of PDD-NOS cases. For example, some cases may have more a genetic basis and may be more closely related to autism; others may have a different basis and might be close to other conditions (e.g., language or attentional problems). It is also possible that some combination of factors might cause PDD-NOS.

Summary

We have now come to appreciate that genetic factors are very much involved in autism. In some ways this has been a surprise, since early work did not seem to suggest a strong genetic basis. This early work was very limited, and only when the first studies of twins were done was the possible genetic basis of autism recognized. Studies of twins showed that if the twins were identical (with exactly the same genetic makeup) and if one had autism, there was a very high chance the other twin would as well; if the twins were fraternal (not exactly the same genetic makeup but sharing as many genes as any siblings would), the rate was much lower. As time went on, it also became clear that a range of other problems—in language and learning and social interaction—might be inherited. Active research around the world is being conducted to look for the genes that cause autism.

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QUESTIONS AND ANSWERS

1. **I have one child with autism and am thinking about having a second. What are the chances my second child could have autism?**

   In general, having had one child with autism increases your risk of having anotherby probably between 2% and 10%. This does not like sound like much of a risk until you think that roughly 1 child in a 800 to 1,000 in the general population has autism, which means your chances are substantially increased. We have seen families with three and four children with autism. Keep in mind that this is a question we can answer in general terms—for a specific answer relevant to you, speak with a genetic counselor, who can take into account all the special factors in your situation, such as family history.

2. **Are a brain scan and an EEG always necessary in evaluating a child with autism?**

   In general without a specific clinical reason to do it, the likelihood of finding something is small. If there are specific clinical reasons to do these tests, for example, if you suspect seizures or if the child's history and behavior are highly unusual, then they should be done.

3. **Are there any lab tests that diagnose autism?**

   At present, the answer is no. When genes for autism are found, there may be some such tests in the future. At the moment, the only additional lab test that makes sense is the test for fragile X (a blood test). Other tests may be needed, given the child's history and examination.

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4. **Can autism be diagnosed from an EEG?**

   No. Autism is diagnosed based on history and clinical examination. The EEG is useful in the diagnosis of seizure disorders, which are sometimes associated with autism.

5. **What will it mean if genes are found for autism?**

   A number of things will have to happen before the findings can translate into new treatments. These include discovering how the gene works and how it operates in development and in the brain, and development of an animal model. Developing an animal model is important, since this would help with understanding what is happening in the brain and give us more potential for testing possible treatments. There *may* be some important implications quickly for screening. There also *may* be some possibility of understanding the broader spectrum of autism and related conditions. Keep in mind that this is a very active area of research and that the answer to this question may change dramatically in the next several years.