This series of 10-year updates in child and adolescent psychiatry began in July 1996. Topics are selected in consultation with the AACAP Committee on Recertification, both for the importance of new research and its clinical or developmental significance. The authors have been asked to place an asterisk before the 5 or 6 most seminal references.

M.K.D.

Pervasive Developmental Disorders: A 10-Year Review

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ABSTRACT

Objective: To summarize recent advances about the nature, diagnosis, and treatment of pervasive developmental disorders.


Results: Clinical and genetic studies support expansion of the concept of autism to include a broader spectrum of social communication handicaps. The prevalence of autism is approximately 1 per 2,000; the prevalence of autism and Asperger's disorder together is 1 per 1,000. The Checklist for Autism in Toddlers is a useful screening instrument for 18-month-old children; the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule are instruments of choice for research. Although twin and family studies clearly support genetic factors as important in autism, linkage analysis studies indicate that many genes may be involved. There is no one treatment of choice. Social-pragmatic approaches, augmented by individualized strategies and social coaching, may be best for teaching social communication skills. Pharmacological interventions have a limited role in improving social communication, but selective serotonin reuptake inhibitors and atypical neuroleptic medications may help ameliorate aggression, hyperactivity, and other secondary problems. Conclusions: Private and government agencies must continue to support basic and applied research. J. Am. Acad. Child Adolesc. Psychiatry, 2000, 39(9):1079–1095. Key Words: pervasive developmental disorders, autism, Asperger's disorder, review.

A review of the National Library of Medicine database indicates that more than 2,000 articles about autism and Asperger's disorder have been published over the past 10 years. This does not include books and book chapters about autism, which number in the hundreds. This review differs from the Practice Parameters (American Academy of Child and Adolescent Psychiatry, 1999) in that it focuses primarily on research, and especially on studies that have been clinically important in the past decade. This review will focus on research issues and controversies, especially as they answer clinical questions.

PERVASIVE DEVELOPMENTAL DISORDERS

Five diagnoses are included under pervasive developmental disorders (PDDs) in DSM-IV (American Psychiatric Association, 1994). These are autism, Rett's disorder, childhood disintegrative disorder (CDD), Asperger's disorder (ASP), and pervasive developmental disorder not otherwise specified (PDD-NOS) (including atypical autism). Autism is the prototypic disorder in the category. For convenience, Rett's and CDD will be discussed first.

Rett's Disorder

The diagnostic criteria for Rett's disorder derive from those agreed upon by an international work group in 1988 (Rett Syndrome Diagnostic Criteria Work Group, 1988). There is an initial period of normal development, including normal prenatal head circumference. Between 5 months and 4 years there is a deceleration of head growth, followed by a loss of hand skills and the appearance of stereotypic hand-wringing movements. Social skills and
expressive and receptive language development also deteriorate at 2 or 3 years of age. Ataxia and apraxia become prominent, and gait becomes broad-based and jerky, with stiff legs and side-to-side swaying. Breathing dysfunctions may be severe.

The prevalence rate of Rett's disorder is approximately 1 in 10,000 to 15,000 females (Hagberg, 1985). A British survey (Kerr et al., 1997) found an annual mortality rate of 1.2%. Forty-eight percent of deaths occurred in persons already debilitated by respiratory and motor dysfunctions. There was a 26% incidence of sudden and unexpected death.

There is a 100% concordance of Rett's disorder in monozygotic twins and a 100% discordance in dizygotic twins. Because Rett's disorder occurs almost exclusively in females, it was proposed that the syndrome was caused by an X-liked dominant mutation with lethality in hemizygous males. On the basis of previous family studies indicating a locus at Xq28, Amir et al. (1999) found that mutations in a gene called MeCP2 are responsible for nearly a third of the Rett cases. Previous studies had shown that MeCP2 plays a role in the epigenetic regulation of gene expression. The manner in which the gene defect leads to the myriad of Rett's disorder defects is unknown, but study of mice in whom the MeCP2 genes are knocked out shows that they develop symptoms similar to Rett's disorder symptoms (Gura, 1999).

Childhood Disintegrative Disorder

In 1930, Heller described a disorder that he called infantile dementia (Heller, 1969). The children in question had 2 to 4 years of normal development, after which they markedly regressed in social, communicative, and adaptive skills. The condition has been associated with various medical conditions including metachromatic leukodystrophy and Schilder's disease, but in most cases no specific neuropathological process has been identified. A recent comparison (Mouridsen et al., 1998) of 13 cases of disintegrative psychosis (defined as having normal or near-normal development for several years followed by the loss of social skills and speech) showed that compared with 39 matched autism cases, significantly more children with disintegrative disorders had developed seizures (77% versus 33%). As part of the DSM-IV field trials (Volkmar and Rutter, 1995), 26 children with CDD were compared with a group of children with autism. The median age of onset for the children with CDD was 36 months (range 24–70 months). The sex ratio did not differ in the 2 groups, but children with CDD were more likely to be mute and to have an IQ score of less than 40. The age of onset is the most important differentiating characteristic. The prevalence of CDD is considered to be much lower than that of autism.

Autism, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (Including Atypical Autism)

The DSM-IV field trials have established that autism is one of the most robust diagnoses in the system, with a sensitivity of 0.82 and a specificity of 0.87 (Volkmar et al., 1994). Of the almost 1,000 cases studied in the DSM-IV field trials for PDD, 163 cases appeared to fit within the category but did not meet all of the criteria for autism. These were given a subthreshold diagnosis of either PDD-NOS or "atypical autism." In some instances this diagnosis was given because insufficient information was available about peer relationships or imaginative play, but 38 cases failed to meet the strict criteria for autism (Klin et al., 1995a) despite having some degree of autistic-like symptoms. The existence of "autistic-like" or "subthreshold" cases had already been anticipated in the literature. Asperger's case histories (Asperger, 1991) are very similar to what is currently called high-functioning autism or autism spectrum disorder. Even as young children, many of Asperger's patients had normal language development, but their facial expression, prosody, and social gestures were often deficient, as was their social interaction. They lacked an "intuitive knowledge" of how to approach others. If highly intelligent, they might become intensely interested in one or two subjects, such as astronomy, genealogy, or geology. Some were able to use this knowledge quite successfully, so that despite their very inept social skills they became quite successful in earning a living. In addition to having normal language development, persons with ASP are described as having delayed motor milestones and motor clumsiness but no significant delays in cognitive development or in development of age-appropriate self-help skills and adaptive behavior.

Atypical autism is often used to designate persons with PDD whose symptoms developed after 30 months of age or who show atypical or subthreshold symptoms. Two studies (Ghaziuddin et al., 1994; Manjiviona and Prior, 1995) compared persons with high-functioning (IQ > 70) autism (HFA) and ASP. Neither motor impairments nor clumsiness distinguished HFA from ASP subjects. Cognitively, children with ASP have better Verbal and poorer
Performance scores than children with HFA on standardized IQ tests (Ehlers et al., 1997; Klin et al., 1995b). Other studies have investigated whether expert clinicians can reliably classify subjects into HFA or ASP groups. In one (Eisenmajer et al., 1996), a logistic regression analysis was used to determine which variables from a standard checklist of items best predicted clinician's diagnosis. Among family and developmental variables, only delayed language onset predicted diagnosis. The ASP group also had significantly higher verbal mental age than the autistic subjects. In a further study (Mahoney et al., 1998), data from the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), IQ, and other clinical instruments were independently assessed by 3 experienced raters, each of whom then made a separate, blind diagnosis. The clinicians had little difficulty differentiating autism from ASP but had more difficulty identifying children with atypical autism. A latent class analysis showed that the average error rates of the 3 raters for a differentiation of atypical autism from autism were unacceptably high. Sevin et al. (1995), using a number of instruments, studied 34 children with autism and autistic-like conditions. Four subgroups were identified. They differed mainly in their IQ and the severity of their social handicaps. The authors concluded that while the children's symptoms were quantitatively different, they did not represent discrete categories.

Additional attempts to identify new entities within PDD have not fared well. Wing (1997) proposed a “triad of subtypes” based on social interaction, communication, imagination, and behavior. The subtypes were aloof (persons who actively avoid interaction), passive (who accept social interaction but do not seek it), and active but odd (who accept social interaction but interact in odd and eccentric ways). Volkmar et al. (1989a) classified autistic persons into Wing subtypes using questionnaire-based information gathered from teachers or caretakers. Although clinicians were able to reliably group both autistic and nonautistic cases into the 3 subtypes, the subtypes were mainly related to IQ. Lower-functioning individuals were mostly classified as aloof, and the highest-functioning ones exhibited features of the active but odd group. The passive category fell between these two extremes. As such, it appears that a classification based on IQ alone would have been as useful as one using Wing's subtypes. Other investigators who studied Wing's system (Borden and Ollendick, 1994; Castellio and Dawson, 1993; O'Brien, 1996) showed that although it can be used to reliably group persons with PDD, the clinical and experimental usefulness of the exercise is uncertain. Few clinicians appear to be using it in their everyday work.

**Nonverbal Learning Disorder.** Nonverbal learning disorder (NVLD) is a diagnostic category developed outside of the DSM-IV nomenclature by Rourke (1989). It is characterized by deficits in perception, psychomotor coordination, visual-spatial organization, nonverbal problem-solving, and appreciation of conceptual incongruities and humor. The neuropsychological model of hemispheric specialization has been invoked to categorize NVLD as a form of right hemisphere dysfunction. Previously, a similar cluster of neuropsychological traits had been identified as learning disability of the right hemisphere (Denckla, 1999). Klin et al. (1995b) compared ASP and NVLD. They found a robust overlap between the neuropsychological profiles of persons with ASP and those with NVLD, suggesting that from a clinical viewpoint, the groups are quite similar. On a related topic, Siegel et al. (1996) examined whether rigorously diagnosed HFA subjects had a uniform pattern of Performance versus Verbal scores on the WISC-R. They found no characteristic Performance–Verbal relationships, though autistic subjects did tend to have lower Comprehension and higher Block Design subtest scores.

**Multiple Complex Developmental Disorder.** This category, which has also been called multiplex learning disorder and multidimensionally impaired disorder, may include children labeled in the 1950s and 1960s as having atypical developmental disorder, symbiotic psychosis, and borderline conditions of childhood. Although the clinical features of multiple complex developmental disorder (MCDD) include symptoms of autism, especially social and interpersonal difficulties, persons with MCDD also show disturbed anxiety modulation and peculiarities in thinking and language (Klin et al., 1995a; Kumra et al., 1998; Towbin et al., 1993). Using standardized instruments, a retrospective chart review indicated that in comparison with children with dysthymia or with conduct disorder, children with MCDD had earlier symptom onset, earlier age of first hospitalization, higher psychopathology scores on the Child Behavior Checklist, poorer peer relationships, and greater psychopathology (Towbin et al., 1993). Compared with subjects with very-early-onset schizophrenia (VEOS), subjects with MCDD are similar to the VEOS subjects in the proportion of family members having schizotypal or paranoid personality disorder and in their not being able to understand what they read despite...
having adequate word recognition skills. They differ from the VEOS group in that they have a less deviant pattern of autonomic reactivity and no progression to schizophrenia. However, 3 of the 11 subjects in the MCDD group received the diagnosis of schizoaffective disorder (bipolar type) at 2-year follow-up. The investigators noted that only transient features of PDD were found in the MCDD group (Kumra et al., 1998). In a more direct comparison (Van der Gaag et al., 1995), 105 MCDD subjects were retrospectively compared with 32 HFA subjects. Each child was rated on 189 developmental, behavioral, neurological, cognitive, and affective items. In comparison with MCDD subjects, HFA subjects had significantly poorer social interactions and more stereotyped and rigid behaviors, while the children with MCDD had significantly more psychotic thinking, anxiety, and aggression. Research indicates that children with MCDD do show differences from children with autism or ASP, but it is not clear that the category is unique. Perhaps MCDD represents an early manifestation of major affective disorder or schizophrenia.

AUTISM AND SOCIAL COMMUNICATION

Our understanding of the development of children's social and emotional interactions with others in the first 2 years of life has been substantially augmented in the past 2 decades. Newborn infants come into the world with an innate set of behavioral propensities that maximize the infant's interaction with caretakers. Children, like other higher primates, emit various innate, universal, facial expressions (Izard, 1994; Malatesta and Izard, 1984) and can discriminate their mother's face from that of a stranger (Field et al., 1984). Newborn infants can discriminate and imitate facial expressions (Field et al., 1983). Affect attenuation (Szajnberg et al., 1989) describes a phenomenon in which an infant expresses affect and a mother responds cross-modally, matching duration, intensity, and rhythm. Mothers talk to their infants in “motherese,” using exaggerated tone of voice, body language, gestures, and facial expressions. Their infants learn to respond with their own set of nonverbal communicative behaviors. Mother-infant vocal interactions, which tend to be overlapping around 7 to 13 weeks of age, change to an alternative to-and-fro pattern by 18 weeks. At 2 to 4 months of age, 30% of children automatically follow their mother's line of sight to an object, but by 14 months of age all children do so, without verbal prompting or gesture on the part of their mother (Scaife and Bruner, 1975). Faced with an experimental “visual cliff,” 12-month-old infants learn to look to their mother's face to determine what they should do (Sorce et al., 1985). If their mothers pose joy or interest, the children will cross; if the mothers pose fear or anger, few infants cross.

Persons with classic forms of autism may fail to engage in the nonverbal social communication interactions typically seen in young children (Baron-Cohen et al., 1993; Sigman and Capps, 1997). It is not that autistic children fail to attach to their caretakers or that they avoid proximity. Like normal children and children with Down syndrome, children with autism are clearly attached to their mothers and they attempt to remain close to them (Dissanayake and Crossley, 1996). In the Ainsworth Strange Situation they seek proximity and contact with their mothers as much as normal children matched on age and IQ (Rogers et al., 1991). What they do not do, however, is engage in attention-sharing behaviors, such as pointing or showing objects (Sigman et al., 1986). We have no evidence that this is because autistic persons fail to perceive normally: they can distinguish between pictures of objects and various sounds as well as age- and IQ-matched nonautistic subjects (Hobson, 1986), and they appear not to have any deficits in perception of faces as stimulus objects (Volkmar et al., 1984). They do not seem to recognize the emotional and contextual meaning of facial expression, gesture, and the nonverbal vocalizations of emotion (Hobson, 1986).

In comparison with children with “mental handicap” matched on mental age, autistic children fail to use the speaker's direction of gaze to orient themselves to objects (Baron-Cohen et al., 1997). In comparison with children with Down syndrome (Attwood et al., 1988), autistic persons rarely use emotional gestures, even though they usually can initiate them upon request. Autistic children are better at expressing their physical needs than at engaging in eye contact or pointing and showing an object to someone else (Mundy et al., 1992). They may recognize and label emotions demonstrated to them, though less well than normal children (Yirmiya et al., 1992). Autistic children do not chat, nor do they become proficient at give-and-take conversation, even when they develop language.

Put succinctly, persons with autism do not show joint attention (McArthur and Adamson, 1996), and they fail to develop a theory of mind (Baron-Cohen, 1995). Joint attention develops prelinguistically, and it involves a triadic coordination of attention between the infant, another person, and an object or event. In its narrowest definition,
theory of mind signifies an understanding that people have minds which differ from their own and that one can learn from others by reading their social signals and listening to what they say. Not all autistic persons lack a theory of mind in an absolute sense, but even those who have normal intelligence and language may fail to acquire social knowledge. They do not know the social (pragmatic) rules of interpersonal communication (e.g., how do you start a conversation, choose a topic of discourse, take turns or end a conversation, etc.) nor can they correctly impute motives to others, understand another’s goals, or respond with alacrity to the nonverbal signals of others. The autistic person’s lack of social knowledge is shown by the inability to form context-relevant communicative intentions (Eaves, 1993), engage in spontaneous symbolic play (Jarrold et al., 1993), or generate original actions in play (Lewis and Boucher, 1995), despite the ability to follow instructions in play.

It should be noted that deficits in theory of mind are not specific to autism, but may be found in severely hearing-impaired children (Russell et al., 1998) and in persons who have Down syndrome (Yirmiya et al., 1996; Zelazo et al., 1996). The difference between autistic and hearing-impaired or Down syndrome children may be that the latter two groups do not show deficits in joint attention.

RATING SCALES

Two popular rating scales for PDD are the Childhood Autism Rating Scale (CARS) (Schopler et al., 1988) and the Autism Behavior Checklist (ABC) (Krug et al., 1980). Both have good interrater reliability. The CARS contains 15 items and uses a 7-point Likert scale ranging from 1.0 to 4.0, with intermediate values between units. The ABC has 57 items which are rated as either absent or present. Several studies have compared the CARS and the ABC (Eaves and Milner, 1993; Sevin et al., 1991). In both instances the CARS was superior to the ABC in correctly identifying autistic subjects; however, the study of Eaves and Milner appears to have been biased in that the CARS was scored from direct observation whereas the ABC was scored from parent report.

Two new interviews, the ADI-R (Lord et al., 1994) and the ADOS (Lord et al., 1989), have been published in the past decade. The ADI-R is a standardized investigator-based interview intended for use in the diagnosis of the PDDs. It consists of a series of initial questions about schooling, treatment history, and family constellation, followed by inquiries about social skills, communication, and play; questions about restricted and repetitive behaviors; and questions about general behavioral difficulties. Raters use probes to formulate their queries and are required to record specific instances and examples of the behaviors on which the rating is based. Each question is scored on an anchored 0 to 3 scale, with 0 being normal and 3 being severe disability. An algorithm permits overall scores to be calculated for the 3 diagnostic categories for autism in the DSM-IV. The ADI-R is both reliable and valid (Lord et al., 1994). The ADOS (Lord et al., 1989) is a standardized protocol for the observation of social and communicative behaviors associated with autism. It consists of a series of structured and semistructured “presses” for social interaction, initiated by the rater, accompanied by coding of specific target behaviors and by general ratings about the quality of social and interpersonal behaviors. The interrater reliability of the instrument is good. A diagnostic algorithm has been developed for the ADOS. The ADOS was originally developed for use with verbal children, but a Prelinguistic version has since been published (PL-ADOS) (DiLavore et al., 1995).

Several additional instruments have been proposed for use in autism and in developmental disorders, including the Kiddie-Infant Descriptive Instrument for Emotional States (Trad et al., 1992), the Behavioral Summarized Evaluation (Barthelemy et al., 1992), the Parent Interview for Autism (Stone and Hogan, 1993), and the Real Life Rating Scale (Freeman et al., 1986). None has been used in more than a few projects to date.

It appears that for screening purposes, the CARS may be the best instrument: it is easily learned and administered, has good interrater reliability, and seems to have reasonable sensitivity in distinguishing autistic from nonautistic subjects. For research purposes, only the ADI-R and the ADOS/PL-ADOS can be considered adequate. Their advantages are that they provide a very detailed view of social, language, and interpersonal functioning (in addition to information about restrictive and repetitive behaviors), and they have algorithms for overall diagnosis as well as for each of the 3 DSM-IV autism domains. Their drawback is that raters must be fully trained and they are time-consuming to administer (up to 2 hours for the ADI-R and 45 minutes for the ADOS and PL-ADOS).

AUTISM AS A SPECTRUM DISORDER

The spectrum model views autism as a disorder whose manifestations can vary from severe to mild. The model
might, of course, be incorrect. Autism could represent several discrete genetic disorders with a common overlapping phenotype. Nonetheless, the spectrum model is a way of making sense of those individuals, including relatives of persons who are autistic (Piven et al., 1994), who have significant impairments in social knowledge and pragmatic communication and whose behaviors, interests, and activities are socially nonfunctional but whose symptoms are not severe enough to meet the criteria for autism.

One recent attempt to study the model used “social communication” as the spectrum variable, with the ADI-R and the ADOS serving as rating instruments (Robertson et al., 1999; Tanguay et al., 1998). A factor analysis of the “social communication” items resulted in a 3-factor solution, with symptoms falling into 3 domains: affective reciprocity, joint attention, and theory of mind. Affective reciprocity was thought to represent the behavioral propensity of the children to use facial, gestural, vocal, and body language cues in 2-way communication with others. Theory of mind appeared to represent “social knowledge” in the broad sense. The most severely affected autistic children had moderate to severe abnormalities in all 3 domains, while children with ASP and PDD-NOS had better affective reciprocity scores than joint attention or theory of mind scores. The least impaired subjects were ones whose impairments were mostly in theory of mind. Although the results are interesting, the study is preliminary and needs replication and improvement.

COMORBIDITY STUDIES

General Medical Conditions

A thorough review of the literature (Rutter et al., 1994) has concluded that most cases of autism are not secondary to, or associated with, specific medical disorders. When concomitant medical disorders are found, they are seen most often in profoundly retarded autistic persons or in atypical cases of autism which differ from ones diagnosed using DSM-IV criteria. With the discovery that fragile X syndrome is caused by a CGG triplet repeat insertion in the region near the FMR-1 gene at Xq27, it has been possible to identify accurately how many persons with autism have a Fra-X mutation. The number is no more than 2% to 5% (Bailey et al., 1993). Examination of multiplex autism families (i.e., ones in which there are 2 or more autistic probands) has established that none of the FMR-1 mutations identified to date is associated with autism (Gurling et al., 1997; Hallmayer et al., 1994). Autism and atypical autism have been reported in approximately 40% of persons with tuberous sclerosis (Gutierrez et al., 1998; Hunt and Shepherd, 1993), but mostly in autistic persons who have moderate to severe mental retardation and/or a seizure disorder. Bolton and Griffiths (1997) found that the number of tubers seen on magnetic resonance imaging (MRI) was correlated with degree of mental retardation. Eight of the 9 patients with autism or atypical autism in their sample had tubers located in the temporal lobes, in contrast to none of the nonautistic patients. There have also been a few reports of autism in Williams syndrome (Gillberg and Rasmussen, 1994) and in neurofibromatosis (Williams and Hersh, 1998), but the coincidence of autism and these disorders is quite rare. Although an association has been postulated between celiac disease and autism, a study (Pavone et al., 1997) of 120 patients with celiac disease indicated none had DSM-III-R symptoms of autism, nor was there evidence of celiac disease among 11 autistic patients. Stefanos et al. (1995) described a 6-year-old child with profound expressive-receptive aphasia whose language and behavior had regressed at 22 months. They diagnosed both PDD-NOS and Landau-Kleffner syndrome (Mouridsen, 1995). Corticosteroid therapy led to amelioration of his language and social deficits. Subsequent correspondence (Volkmar et al., 1996) established that the child did not appear to have autism (though he had some symptoms of PDD-NOS) nor did he have classic Landau-Kleffner syndrome, inasmuch as his EEG was normal. A major issue raised by this report was whether it is medically justifiable to treat young autistic children with high-dose steroids whose effect on brain development may not be entirely benign.

Other Psychiatric Disorders

Several studies have reported a higher incidence of major depression and social phobia in the first-degree relatives of persons with autism (Bolton et al., 1998; Piven et al., 1991; Piven and Palmer, 1999; Smalley et al., 1995). The latter reported that 37% of 96 first-degree relatives of autistic probands had a major depressive disorder, compared with 11% of the 45 relatives of control subjects. Likewise, the frequency of social phobia in the relatives of the autistic persons was 20%, 10 times higher than in the relatives of controls. Sixty-four percent of the depressed parents had their first episode prior to the birth of the autistic child.
PREVALENCE RATES

Within the past 30 years there have been some 20 epidemiological studies of autism (see Fombonne et al., 1997; Honda et al., 1996). Fombonne et al. calculated that the mean estimated prevalence rate for all the studies was 4.8 per 10,000, or approximately 1 per 2,000 persons. Recently, however, much higher prevalence rates have been reported by several groups—as much as 1 per 250 persons. If the increase were real it could be alarming, though no persuasive reason has been advanced to explain it. A comparison of studies reported in the past decade shows that they differ greatly in screening methods, diagnostic instruments, and diagnostic criteria. If one examines them in terms of diagnostic criteria, there appears to be a possible explanation for the differing results. Three projects, one from France (Fombonne et al., 1997), one from Norway (Sponheim and Skjeldal, 1998), and one from Japan (Honda et al., 1996) used strict ICD-10 Research Diagnostic Criteria. The French group reported a prevalence rate for autism of 1 per 2,000 and of 1 per 600 for autism and other PDDs taken together. The Norwegian group reported a prevalence rate of 1 per 2,000 for autism. In contrast, the Japanese investigators reported a prevalence rate of roughly 1 per 500. But they also noted that more than 50% of their subjects had IQ scores greater than 85, which suggests that their population may have been more akin to HFA than to most cases of DSM-IV autism. Three studies have been reported in which less rigorous criteria were used: Bryson et al. (1988) used the ABC and other nonstandard criteria, Sugiyama and Abe (1989) used the more liberal DSM-III criteria, and Ehlers and Gillberg (1993) used a set of criteria specifically designed for the diagnosis of ASP. All 3 studies reported prevalence rates for autism ranging from 1 per 250 to 1 per 1,000. A parsimonious explanation for the apparent increase in the prevalence of autism is that higher rates include varying numbers of persons with atypical autism, ASP, and PDD-NOS as well as autism. A conservative estimate for the prevalence of autism would appear to be 1 per 2,000 persons, and for autism plus ASP, 1 per 1,000 persons.

SCREENING INFANTS AND CHILDREN FOR AUTISM

There has been a consensus among clinicians that if treatment is started by 24 to 36 months of age, the prognosis in autism may be better than if treatment is postponed until age 4. If true, early diagnosis would be very important. The Checklist for Autism in Toddlers (CHAT) (Baron-Cohen et al., 1992) has been developed to screen for autism. Initial studies indicate that the key psychological predictors at 18 months of a later diagnosis of autism are the presence of 2 or more of the following: lack of pretend play, lack of protodeclarative pointing, lack of social interest or social play, and lack of joint attention. Sixteen thousand British 18-month-old children were screened with the CHAT, with follow-up studies at 20 and 42 months (Baron-Cohen et al., 1996; Charman et al., 1997; Cox et al., 1999). Almost all children identified as autistic at 18 months were found to have either autism or a major language delay by 42 months. But the CHAT appears to lack sensitivity at 18 to 20 months, i.e., it missed 60% of the children who were later found to be autistic. An unrelated study (Lord, 1995) emphasized how important it is to use direct observations of the infant as well as parental descriptions when screening for autism in infants.

ANTECEDENT FACTORS INFLUENCING THE DEVELOPMENT OF AUTISM

Season of Birth

Two recent studies (Bolton et al., 1992; Mouridsen et al., 1994) used complex time-series analysis to examine seasonal variations in the births of persons with autism. Such variations might point to seasonal factors such as infections, weather, or diet as important in autism. No consistent seasonal trends emerged. Mouridsen et al. examined season of birth in 328 children with autism, autism-like conditions, or "borderline child psychosis." Children with autism had a significantly greater incidence of births in March and in August, and those with autistic-like conditions were most often born in May and November. It would seem that if there are seasonal influences on the development of autism, these are fairly weak and inconsistent.

Severe Early Global Deprivation

After the fall of the Ceaucescu regime in Romania, a large number of children were discovered to be living under extremely poor conditions in institutions, many of them having been placed there in early infancy. There is no evidence that any child was sent to an institution because of an existing handicap. The conditions in the institutes ranged from poor to appalling. A cohort of such children arrived in the United Kingdom in the early
1990s (Rutter et al., 1998). A randomly selected, age-stratified sample of 165 of these children are being systematically monitored. Of 111 children assessed at age 4 and again at age 6, some showed an attachment disorder (O’Connor et al., 1999) and 7 children (6.3%) met the criteria for autism on the Autism Screening Questionnaire, an instrument based on the ADI. They appeared to be quite similar to autistic children in general, but further evaluation and follow-up revealed important differences. Three of the children were severely retarded, but despite this they had learned some sign language, which they spontaneously used to communicate, and 2 made considerable social approaches, albeit deviant in quality. What these findings emphasize is that very severe social deprivation may occasionally lead to social and emotional handicaps that meet the diagnostic criteria for autism.

Antecedent Neuropsychological Deficits

Minshew et al. (1997) administered a battery of neuropsychological tests to 33 rigorously diagnosed autistic persons of normal intelligence and compared them with normal controls. Autistic persons had intact or superior performance in tasks measuring attention, simple memory, simple language, and visual-spatial domains. In contrast, they were impaired in skilled motor tasks, complex memory, complex language, and reasoning. This profile of deficits will need refining before it can be of use in understanding the nature of autism.

Executive functions (EF), which are defective in persons with frontal lobe damage, have been defined as the ability to maintain an appropriate problem-solving set for the attainment of future goals. They include the ability to formulate goals, to plan an action sequence to reach the goals, and to maintain memory traces needed for these processes. Even this concept may still be too broad for the understanding of a specific disorder such as autism. A recent review (Pennington and Ozonoff, 1996) concluded that EF deficits are consistently found in both attention-deficit/hyperactivity disorder and autism, but not in conduct disorder. Other investigators have reported more specific EF deficits in autism: impairment in cognitive flexibility (Ozonoff et al., 1994) and in shifting cognitive set (Hughes et al., 1994). Pennington and Ozonoff (1996) argued that EF deficits may underlie theory of mind deficits and cite an intriguing study (Price et al., 1990) of 2 individuals who sustained widespread prefrontal damage early in development. Neither was autistic, but both exhibited severe deficits in interpersonal role-taking, a task which is also markedly impaired in autism and ASP.

NEUROBIOLOGICAL STUDIES IN AUTISM

Genetic Studies

Twin and Family Studies. Several studies have confirmed Folstein and Rutter’s (1977) findings of a markedly increased concordance of infantile autism in monozygotic (MZ) compared with dizygotic (DZ) twins. In a study of 21 twin pairs, Steffenburg et al. (1989) found the concordance rate for autism (using DSM-III criteria but without standardized diagnostic interviews) to be 91% for MZ and 0% for DZ twins. Bailey et al. (1995) reexamined the subjects seen in the first British twin study of Folstein and Rutter, adding subjects to increase the number of pairs to 48 and using the ADI for diagnosis. They found that 60% of MZ twins and 0% of DZ twins were concordant for the ICD-10 diagnosis of autism. When they examined a broader spectrum of related cognitive and social abnormalities, they found that 92% of the MZ twins versus 10% of DZ twins were concordant. Behavioral and cognitive manifestations of autism were also compared both within and between pairs. The variation was as great within MZ twin pairs as between pairs. Because MZ twins share all of their genes, this finding suggested that the varying symptoms seen in autism were not a result of different sets of genes acting to produce different clinical features. It appears that autism is under a high degree of genetic control, but what is inherited is a broader spectrum of related cognitive and social abnormalities (Bailey et al., 1995).

Family studies suggest that there is an increased loading for both autism and autistic-like disorders in the first-degree relatives of persons with autism (Bolton et al., 1994; Piven et al., 1997a,b; Spiker et al., 1994; Szatmari et al., 1996). These studies used the ADI and the ADOS for diagnosis, with the addition of other structured interviews for broader symptom assessment. Bolton et al. (1994) reported an increased family loading for autism and for more broadly defined PDDs in the siblings of 99 autistic probands compared with the siblings of Down syndrome subjects. They also found evidence for a lesser variant of autism, comprising more subtle communication/social impairments or stereotypic behaviors, but not mental retardation alone, in 12.4% to 20.4% of the autism siblings, compared with 1.6% to 3.2% of the Down syndrome siblings. Szatmari et al. (1996) found a high intraclass correlation of social behavior abnormalities (measured
using the Vineland and the ABC) between affected children from the same families, but a low correlation between affected and unaffected siblings. Piven et al. (1997a,b), using a semistructured family history interview, reported higher rates of social and communication deficits and stereotypic behaviors in the relatives in families with multiple-incidence autism in comparison with relatives in Down syndrome families. They also reported that the parents of autistic subjects had higher rates of aloof, rigid, hypersensitive, and anxious personality traits and of speech and pragmatic language deficits. They also had more limited friendships. Taken together, these studies suggest that there are genetic factors which influence the development of autism and that these factors can result in a variety of subtle and not-so-subtle social and communication deficits and stereotypic behaviors.

Chromosome Studies and Linkage Analysis. Using data from 38 multiplex families, Hallmayer et al. (1996) performed a sib-pair linkage analysis between autism and 35 microsatellite markers on the X chromosome. None of the lod scores reached a positive level of significance, leading them to conclude that there was no major gene effect on the X chromosome causing autism. Because 2% to 5% of persons with fragile X show symptoms of autism, several projects have investigated whether autistic children might show abnormalities in the FMR gene or in the fragile X region (Gurling et al., 1997; Holden et al., 1996; Vincent et al., 1996). None have been found. Sporadic reports of single-case abnormalities in other chromosomes are questionable. Exceptions are the numerous reports of deletions and duplications of chromosome 15, especially in the 15q11–13 region (see Cook, 1998). No candidate genes have been identified, however. Investigators from the International Molecular Genetic Study of Autism Consortium carried out a 2-stage genome search for susceptibility loci for autism on 87 affected sib pairs and 12 non-sib affected relatives (International Molecular Genetic Study of Autism Consortium, 1998). The highest lod scores were obtained for regions on chromosome 7q and 16p, with lesser scores of interest on chromosomes 4, 10, 19, and 22. Another multicenter group (Risch et al., 1999) reported that the results of their linkage analysis studies were compatible with a model specifying a large number of loci (>15), and less so with models specifying fewer than 10 loci. They concluded that the task of identifying genetic abnormalities by positional cloning of susceptibility loci using linkage analysis could be a formidable one and that other approaches may be necessary.

Neuropharmacological Studies

Although various neuropharmacological substrates in autism have been investigated in the past several decades, most abnormal findings have not been substantiated. Convergent findings in the past decade from behavioral neuroscience, platelet, pharmacological, and genetic studies indicate the involvement of serotonin in many of the symptoms of autism (Cook and Leventhal, 1996). Circulating blood serotonin is carried on the platelets; but despite numerous studies, the reason for the increased serotonin levels in the platelets remains unknown. Hyperserotonemia in autism may be heterogenous, with one subgroup of subjects having increased 5-HT uptake and another group having decreased 5-HT2 binding (Cook et al., 1993). That autistic persons have autoantibodies to brain serotonin receptors (Todd and Ciaramello, 1985) was initially exciting. Two studies have not confirmed it (Todd et al., 1988; Yuwiler et al., 1992). Singh et al. (1997) reported that autistic children’s plasma inhibits the specific binding of serotonin to its receptor, which they interpreted as indicating the presence of serotonin-blocking antibodies. Two recent studies focused on the serotonergic receptor gene. Herault et al. (1996) reported no differences in allele and genotype frequencies for the 5-HT2a receptor, but Cook et al. (1997) found evidence of linkage and association between the serotonin transporter gene and autistic disorder. The latter finding could not be replicated (Klauck et al., 1997).

Electroencephalography and Event-Related Potentials

Persons with autism are likely to show more EEG abnormalities than are seen in a normal population, but the findings are varied, are nonspecific, and do not lead to a better understanding of the nature of brain dysfunction in the syndrome. Advances in EEG techniques have not overcome the inherent shortcomings of the technology: brain activity at any one electrode represents the summed activity of numerous electrical generators whose location is difficult to pinpoint, and uncontrolled and often unquantifiable changes in subject attention may greatly affect the EEG or event-related potential (ERP) response. Few EEG and ERP studies have been reported in the past decade. Those that have appeared (Buchwald et al., 1992; Dawson et al., 1988, 1995; Strandburg et al., 1993) have led to no more than modest increases in knowledge. Even brainstem evoked responses, which are relatively simple to record and whose neural generators are known, have led to negative or inconclusive results (Klin,
They remain an excellent tool with which to study hearing acuity, however.

**Neural Imaging**

MRI studies of autistic persons in the past 15 years have not identified or confirmed brain abnormalities in autism (see Deb and Thompson, 1998). Courchesne et al. (1994) reported cerebellar vermian hypoplasia or hyperplasia in subgroups of autistic persons, but others (Garber and Ritvo, 1992; Kleiman et al., 1992; Piven et al., 1997c) have not been able to confirm this finding. Autistic persons have been reported to have larger third ventricles and smaller caudates than normal subjects (Jacobson et al., 1988), abnormal forebrain structures (Gaffney et al., 1989), smaller right anterior cingulate gyrus (Haznedar et al., 1997), and smaller parietal lobes (Courchesne et al., 1993). Skepticism is warranted with regard to neural imaging results.

**Neuropathological Studies**

Kemper and Bauman (1993) and Raymond et al. (1996), who used whole-brain serial sections, reported increased neuronal density in the hippocampus, amygdala, and limbic system in 6 brains of persons who had autism. They also reported decreased numbers of Purkinje cells and evidence of a fetal cerebellar circuity. In a study of 4 autistic brains, Ritvo et al. (1986) reported lower Purkinje cell counts. Bailey et al. (1998) examined brain tissue from 6 mentally handicapped persons with autism. Four of the brains were megaloecephalic, and they found developmental abnormalities, including evidence of abnormal neuronal cell migration, in the brainstem and cerebellum. Numbers of Purkinje cells were reduced in the adult cases. Kemper and Bauman’s finding of elevated neuronal density was not confirmed. Although the number of subjects in each of these investigations was small, the coincidence of certain findings, in particular the low Purkinje cell count, is intriguing. The difficulty of obtaining suitable study material may constrain the development of this line of research.

**Study of Brain Volume**

There has been a convergence of evidence in the past decade in support of the observation that an unexpectedly large portion of autistic persons (ranging from 14% to 30%) have a marked increase in head circumference (Davidovitch et al., 1996; Fombonne et al., 1999; Woodhouse et al., 1996). Increased head circumference has not been correlated with IQ, verbal ability, seizure disorder, or medical illness. Using retrospective data, Lainhart et al. (1997) found that the macrocephaly was not present at birth, but developed in early and middle childhood. Two MRI studies (Piven et al., 1995, 1996) confirmed the increase in brain volume. The former reported that the increase was present in the temporal, parietal, and occipital, but not frontal lobes. The cause of the increase in size has not yet been explained, but longitudinal MRI studies of the phenomena are warranted.

**TREATMENT OF AUTISM AND ASPERGER’S DISORDER**

**Social and Behavioral Therapies**

It is generally accepted that early intervention, tailored to the child’s individual patterns of strengths and handi- caps, can enable a child to develop better social and emo- tional relationships, learn better communicative skills, and decrease the intensity of stereotypic and bizarre behaviors. There is no one treatment that works with everyone, though some treatments may be more effective than others in improving social, interpersonal, and pragmatic skills. In some parts of the United States there is still a severe shortage of teachers trained to meet the needs of autistic children. There is also a lack of understanding by educators that early intervention is important and that persons with HFA or ASP have special needs. There are few comparison studies between methods of treatment and few investigations designed to identify when and where a particular approach works best. While it is beyond the scope of this article to review specific techniques of therapy, important studies, as well as theoretical issues, will be reviewed.

**Treatments Not Shown To Be Effective.** Auditory integration training (AIT) (Stehli, 1991) entails listening to 10 hours of music which has been filtered to dampen frequencies to which the person is hypersensitive. A pilot study (Rimland and Edelson, 1995) reported that AIT decreased subject irritability, stereotypy, and hyperactivity 3 months after treatment, but statistical flaws (the baseline measures of the control and experimental groups were significantly different) make it difficult to assess the validity of these results. Bettison (1996) found that AIT significantly improved psychometric and social ratings for both AIT subjects and controls (the latter listened to unfiltered music), without there being any significant between-group differences. Gillberg et al. (1997) reported no significant changes in autistic symptoms as a result of AIT.

In facilitated communication, the facilitator guides the arm, wrist, or fingers of the autistic person as he/she types.
messages on a keyboard. Nonverbal and intellectually handicapped autistic persons have been reported to have become suddenly capable of sending emotionally moving and grammatically complex messages to their parents, but studies have shown that the messages come largely from the facilitator and not from the handicapped person (Bomba et al., 1996; Eberlin et al., 1993; Smith et al., 1994).

Two other treatment programs, daily life therapy, practiced in the Higashi schools (Gould et al., 1991), and Kaufman's "Options" (Kaufman, 1981), have been championed on the basis of anecdotal observations and testimonials, but neither has been subject to rigorous scientific study.

**Massed, Discrete-Trial Learning Versus Intense Social-Pragmatic Teaching.** Recent passionate debates about the merits of one or other school of treatment for autism appear to reflect 2 fundamentally different approaches to teaching. Each may be useful in certain circumstances (see Prizant and Wetherby, 1998, for a detailed discussion). Massed, discrete-trial learning (also called teacher- or therapist-centered learning or traditional behavioral learning) focuses on teaching discrete and objectively defined behaviors, skills, and facts; the teaching structure is highly prescribed; the focus of the learning is determined by the teacher-therapist; predetermined criteria are provided for correctness of the response; initial focus is on adult control and child compliance; rewards are given for correct answers or behaviors; "aversive stimuli" may be given for incorrect answers or inappropriate behaviors; and teaching is largely directed through oral language. In contrast, social-pragmatic teaching (also called child-centered therapy, pivotal-behavior therapy, or incidental teaching) emphasizes following the child's attentional focus and motivations; it builds on the person's current repertoire of social and communicative behaviors (even if this is only nonverbal); it uses visual, verbal, and tactile cues; it seeks to motivate learning through shared emotional experiences; it relies on naturally occurring events rather than a set curriculum; and it views the child as an active learner and social participant. The former is perhaps best suited to teaching discrete skills and facts, such as vocabulary and grammar or reading and mathematical concepts. The latter appears similar to the way in which very young children learn joint attention, pragmatic language skills, and theory of mind and social knowledge. As such, it appears to be a more suitable approach to teaching persons with autism, especially very young persons, the core social skills they lack. Applied behavior analysis or the Lovaas approach, at least in terms of its earlier descriptions (Lovaas, 1987; Maurice, 1994), appears to be a prototypic example of the massed, discrete-trial learning, while treatments advocated by Greenspan (1995), Rogers and Lewis (1989), Lewy and Dawson (1992), or McGee et al. (1992) are examples of social-pragmatic teaching. What must be kept in mind is that proponents of the various named therapies (including the Lovaas treatment) may have evolved their approaches to the point at which they now include elements of both discrete-trial learning and social-pragmatic therapy. Clinicians and parents must ask therapists for a specific description of their philosophy, goals, and techniques if they are to judge properly whether the treatment is suitable for a particular child.

**Discrete Elements of Treatment.** Most autistic children need a combination of individual teaching strategies and broad educational goals. Social and interactional handicaps, intellectual and language deficits, and motor skill abnormalities require expert remedial approaches (Mundy and Crowson, 1997). "Challenging" behaviors (e.g., aggression, self-injury, and ritualistic stereotyped activities) must be dealt with (Dawson et al., 1998; Howlin, 1993). Some children learn better if materials are presented visually rather than verbally (Hodgdon, 1996; Quill, 1997). Autistic persons may be treated in special Head Start programs or therapeutic preschools, assisted by home therapy programs administered by their parents. They may benefit from the newer technologies designed for augmented communication. Memory devices (as simple as a felt-board with coded symbols) may relieve the anxiety of not knowing what is next in their daily routine. Some will benefit from social coaching, as represented by Gray's Social Stories and Comic Strip Conversations (Gray and Garand, 1993). Social coaching can be given by teachers, teacher's aides, or even the child's peers (McGee et al., 1992). Treatment should begin early and may need to be continued, in one form or another, into adulthood as described in Project TEACCH (Mesibov, 1997).

**Pharmacotherapy of Autism**

There is, as yet, no medication that is effective in treating the social and relationship problems in autism. Stimulants may be effective in treating impulsivity, overactivity, and short attention span. Traditional antidepressants, mood stabilizers, and antianxiety medications may be used as they would be in a nonautistic population. Unfor-
fortunately, we know little about the long-term effects of some of the newer, and perhaps more promising, medications for autism. The continuing arrival of new psychotropic agents, as well as the increased use of the present ones, suggests that many more medication studies will need to be carried out in the coming years.

What follows is a brief review of the pharmacological interventions for which there are sufficient experimental data, either with regard to their effectiveness or lack thereof.

**Vitamin B₆ and Magnesium.** Proponents (Rimland, 1988) of megavitamin treatment for autism frequently cite the study by Martineau et al. (1988) as supportive of their belief. In fact, only 30% of the children in that study showed improvement, most to only a modest degree. Two recent reviews (Kleijnen and Knipschild, 1991; Pfeiffer et al., 1995) concluded that there are no data to back the megavitamin claims. A recent double-blind, placebo-controlled study concluded that high-dose pyridoxine and magnesium were ineffective in ameliorating autistic behaviors (Martineau et al., 1988).

**Flunitrazepam.** Originally proposed as a treatment for autism because it lowers blood serotonin levels, and initially greeted with excitement, it has proven disappointing. While it may lead to modest decreases in hyperactivity, it is not useful in ameliorating other symptoms (Campbell et al., 1990; Feldman et al., 1999; Willemsen-Swinkels et al., 1996, 1999). Naltrexone is not effective in reducing self-injurious behavior (Willemsen-Swinkels et al., 1995; Zingarelli et al., 1992) or in increasing learning (Campbell et al., 1990; Kolmen et al., 1995).

**Clonidine.** β-Blockers were initially suggested as a treatment for self-injurious behaviors. Studies of their use in autism (Fankhauser et al., 1992; Jaselskis et al., 1992) indicate that although clonidine can effect a modest reduction in hyperactivity and irritability, it is less beneficial in ameliorating social behaviors. Drowsiness has been reported as a main side effect.

**Secretin.** Secretin, an endogenous gastrointestinal polypeptide, was widely touted in 1999 as a treatment for the social and communication handicaps of autism. Controlled studies (Sandler et al., 1999) have found single-dose secretin to be ineffective for this purpose.

**Corticosteroids.** Although recommended by Stefanos et al. (1995), there is little evidence that the treatment is effective (Volkmar et al., 1996). The effect of long-term use of steroids on brain development is not known.

**Antidepressants.** Although imipramine and desipramine were initially popular for treatment of depression, aggression, and irritability in autism, potential cardiovascular side effects and a realization that they are not very effective have led to their being supplanted by clomipramine. A double-blind study (Gordon et al., 1993) reported that clomipramine was superior to both desipramine and placebo in reducing stereotypies, anger, and compulsive behaviors and that both tricyclics were superior to placebo in decreasing hyperactivity. A second double-blind study (Brodkin et al., 1997) reported that 18 of 33 subjects receiving clomipramine experienced a decrease in repetitive thoughts and behaviors, and in aggression, and that the social relatedness of a few subjects also seemed to improve. Three patients, 2 of whom were known to have epilepsy, had a seizure while being treated. The results of an open trial of clomipramine (Sanchez et al., 1996) indicated that the target symptoms of stereotypies and aggression improved in only 1 of 6 subjects. One child developed acute urinary retention while taking the medication. With the advent of the selective serotonin reuptake inhibitors (SSRIs), there has been a shift of interest to these medications, though as yet there have been too few SSRI studies to permit any conclusions to be reached. SSRIs appear to be moderately effective in decreasing hyperactivity, restlessness, and agitation and in decreasing obsessive thoughts and preoccupations (Awad, 1996; Cook et al., 1992; McDougle et al., 1998; Posey et al., 1999). No one SSRI has been shown to be superior for these purposes.

**Neuroleptics.** Older neuroleptics were not found to be especially effective in treating autism (Campbell and Cueva, 1995), and their potential to produce tardive dyskinesia (Campbell et al., 1997) has limited their use. Of the newer "atypical" neuroleptics, risperidone has been the most frequently studied (McDougle et al., 1997; Nicolson et al., 1998; Perry et al., 1997). These studies, which were all open-label trials, indicate that risperidone may be effective in reducing hyperactivity, impulsivity, obsessive preoccupations, and aggressiveness. It may also increase socialization in some children. The major side effect of risperidone has been weight gain. In a 12-week open-label study of olanzapine (Potenza et al., 1999), of the 7 patients who completed the study,
6 were judged to be responders on the basis of their improvement in hyperactivity, repetitive behaviors, self-injurious behaviors, and social relatedness (Potenza et al., 1999).

In summary, it appears that pharmacological interventions have a limited role to play in improving the social and communication handicaps of persons with autism and ASP. They may be helpful in decreasing hyperactivity and impulsivity and in reducing aggression and obsessive preoccupations. The SSRIs appear to be well suited for this role, though there have been too few studies to confirm this or to identify which SSRI medication may be best. Except for their propensity to induce weight gain, the atypical neuroleptics also appear promising in this regard.

**FUTURE CONSIDERATIONS**

Studies of the development of social communication in normal persons and of the role of social communication deficits in autism have been important milestones in our understanding of autism in the past 15 years. Currently, genetic and molecular biological studies appear very promising, but recent results indicating that many genes may influence the phenotypic manifestations of the disorder suggest that it may be many years before they bear fruit. If specific genes are identified, there can be hope for very early identification of persons at risk. Brain imaging studies using functional MRI could be promising, but we will first need to better understand normal brain–behavior relationships.

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TANGUAY


The Dynamics of Alcohol and Marijuana Initiation: Patterns and Predictors of First Use in Adolescence. Rick Kosterman, PhD, J. David Hawkins, PhD, Jie Guo, PhD, Richard F. Catalano, PhD, Robert D. Abbott, PhD

Objectives: This study, guided by the social development model, examined the dynamic patterns and predictors of alcohol and marijuana use onset. Methods: Survival analysis and complementary log-log regression were used to model hazard rates and etiology of initiation with time-varying covariates. The sample was derived from a longitudinal study of 808 youth interviewed annually from 10 to 16 years of age and at 18 years of age. Results: Alcohol initiation rose steeply up to the age of 13 years and then increased more gradually; most participants had initiated by 13 years of age. Marijuana initiation showed a different pattern, with more participants initiating after the age of 13 years. Conclusions: This study showed that: (1) the risk of initiation spans the entire course of adolescent development; (2) young people exposed to others who use substances are at higher risk for early initiation; (3) proactive parents can help delay initiation; and (4) clear family standards and proactive family management are important in delaying alcohol and marijuana use, regardless of how closely bonded a child is to his or her mother. Am J Public Health 2000;90:360-366. Copyright 2000 by the American Public Health Association.