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Invited Comment

Autistic Regression: Genes, Environment, or Both

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Autistic spectrum disorders (ASD), complex conditions of behavior and cognitive function, affect more children than either cancer or spina bifida [Filipek et al., 1999]. Epidemiologic studies conducted in the 1960s indicated that the prevalence of infantile autism, as defined by Kanner [1943], was approximately 1 per 2,000 [Lotter, 1967]. However, recent studies suggest that the prevalence of ASD may be considerably greater, as high as 1 per 500 [Filipek et al., 1999]. This corresponds to approximately 100,000 ASD cases among children under the age of 15 years in the United States. Although changes in diagnostic criteria may account for the increased prevalence of ASD, genetic predilections, environmental factors, or both, could contribute to the increasing frequency of childhood autism.

Children with ASD display impairments in socialization, impairments in verbal and nonverbal communication, and restricted and repetitive patterns of behavior [American Psychiatric Association, 1994]. The disorder is evident by three years of age, but early symptoms, such as absence of early babbling, failure to utter single words, and behavioral abnormalities, are usually noticeable by 18 months of age [Filipek et al., 1999]. Because there remain no biologic markers, e.g., serologic, electroencephalographic, computed tomographic, magnetic resonance imaging, or chromosome abnormalities, that universally detect children with ASD, behavioral screening instruments, such as the Checklist for Autism in Toddlers (CHAT), have essential roles in identifying young children with ASD [Filipek et al., 1999].

Genetic factors, as yet undetermined, have major roles in the etiology of autism. Environmental factors, such as infections or other exposures, could also participate in the pathogenesis of the disorder [Institute of Medicine, 2001]. Approximately 40% of children with autism regress, usually during their second year of life [Tuchman and Rapin, 1997]. Although a complex relationship may exist between autistic regression, epilepsy, and unusual epilepsy syndromes, such as the Landau-Kleffner syndrome, autistic regression is a poorly understood phenomenon [Filipek et al., 1999]. Thus, Wakefield et al. [1998] ignited considerable scientific and public concern when they reported 12 children with gastrointestinal disorders and developmental regression, and postulated that measles-mumps-rubella (MMR) vaccine administration could cause an autistic-like condition.

Several investigators subsequently closely examined the potential relationship between MMR vaccination and autism. They found no scientific evidence for such a relationship [Farrington et al., 2001; Kaye et al., 2001; Taylor et al., 2002]. The National Academy of Sciences' Institute of Medicine (IOM) considered the potential relationship of such widespread concern that the IOM convened the Immunization Safety Review Committee to review thoroughly the available data. To ensure an unbiased appraisal, the IOM excluded anyone who had "financial ties to vaccine manufacturers or their parent companies, previous service on vaccine advisory committees, or prior expert witness testimony or publications on issues related to vaccine safety" [Institute of Medicine, 2001].

The Immunization Safety Review Committee concluded that the evidence "favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders." They based their conclusion on four lines of evidence: 1) a consistent body of epidemiological evidence; 2) the initial case series and other reports were uninformative regarding causality; 3) biologic models linking MMR vaccine and ASD are fragmentary; and 4) the absence of an animal model linking MMR vaccine and ASD. However, the committee noted that this does not "exclude the possibility that MMR vaccine could contribute to ASD in a small number of children."

The study of Lainhart et al. [2002], in this issue, while not eliminating the lingering doubt raised by the IOM's study, does provide useful information regarding the potential genetic risk that underlies the etiology of regressive autism. Lainhart and her colleagues carefully assessed the parents of autistic children with and

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without regression to determine the prevalence of the "broader autism phenotype" among parents. They observed similar rates of this phenotype (27.8% among parents of children with regression versus 32.9% among children without regression; $P = 0.33$). The authors concluded that the genetic liability was increased uniformly among parents regardless of the autism phenotype in their offspring.

Lainhart et al.'s [2002] data demonstrate that genetic factors likely contribute in equal fashion to these differing autistic phenotypes. Their data also imply that environmental events are unlikely to be the sole cause of regressive autism. They do not eliminate, however, the possibility that environmental factors somehow participate in the pathogenesis of autism. The authors suggest that as yet undetermined environmental factors could act as additive factors. What are the precedents for this hypothesis?

Perhaps the most relevant and intriguing example of this interplay occurs in psychiatric and neurologic disorders associated with group A streptococcus (PANDAS) [Swedo et al., 1998]. At the conventional end of the post-streptococcal spectrum is Sydenham chorea, a disorder in which children or adolescents experience characteristic movement disorders but frequently have obsessive-compulsive behaviors [Stollerman, 2001]. At the more controversial end may be the modulation of tics, compulsions, and Tourette syndrome by intercurrent streptococcal infections [Trifiletti and Packard, 1999]. Clearly, much remains to be learned about the relationships of environmental factors and neuropsychiatric disorders.

Do the available data imply that parents should immunize their children? Absolutely. As stated by the IOM, "next to clean water, no single intervention has had so profound an effect on reducing mortality from childhood diseases as has the widespread introduction of vaccines" [Institute of Medicine, 1991]. Nonetheless, the current data also suggest that investigators must continue their search for the genetic factors that predispose to autistic spectrum disorders, problems of immense public health importance, and the environmental factors that may influence the clinical features of these disorders.

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