Not knowing

Editorial

By all accounts child development specialists are diagnosing autism (used here for autistic spectrum/pervasive developmental disorders) with increased frequency. It is uncertain whether this is due to an actual increase in the incidence of autistic disorders or to the effects of broadened diagnostic criteria, heightened awareness of clinical variability, and increased utilization of developmental screening programs for preschoolers. It seems likely that all of these factors are involved and result in increasing numbers of parents bringing their children for evaluation of possible autism.

The initial consultation concerns three questions. The first, 'Does my child have autism?' is unfortunately usually the easiest to answer. Although precise characterization of the individual child's developmental status requires a detailed history, a period of observation and interaction with the examiner, and completion of a behavioral questionnaire or observation schedule, the diagnosis is often all too obvious in the waiting room. After confirming that the child's impairments meet appropriate criteria for autism, the second question follows, 'What can be done to help?' This leads to a discussion of the considerable value of early intervention followed by appropriate referrals to educational specialists and therapists and often some comments on the unproven role of alternative interventions including intravenous secretin, anti-yeast therapy, and elimination diets (see below). However, it is the third question 'What causes autism' that is most problematic and reminds me of Mark Twain's comment, 'I was gratified to be able to answer promptly, and I did. I said I don't know.'[1]

The lack of understanding of the etiology in of autism is due to a number of factors including the absence of a specific laboratory or brain imaging 'gold standard' for diagnosis and the lack of knowledge regarding the neuropathophysiology of autistic symptoms. Like other neurodevelopmental disorders including mental retardation and cerebral palsy, autism has no single cause and is associated with a number of possible etiologies including congenital infections, chromosomal disorders, genetic syndromes, and a variety of metabolic conditions. However, these putative causes are identified in only 10–20% of affected children, and even then pathophysiological mechanisms are largely unknown.

Currently the vast majority of individuals with autism have no identifiable etiology. Although family and twin studies indicate that genetic influences are important, many different genes are involved and the modes of genetic transmission are complex and incompletely understood. Additional data also indicate that environmental modulation of genetic factors plays a critical role. Considerable interest has centered on the possibility that genetic alterations may create vulnerabilities to 'second hit' phenomena from environmental, infectious, and immune-mediated processes in individuals with autism.

The study by Hunter et al. in this month's journal[2] concerns one such environmentally-related hypothesis which involves opioid peptide metabolism. This theory suggests that excess activation of CNS opioid receptors by increased endogenous or exogenous peptides may be pathophysiologically important in autism. Such peptides can reportedly be derived from dietary gluten or casein and access the circulatory system through intestinal mucosa damaged by gluten-sensitive enteropathy or vaccine-related injury. These circulating active peptides are then hypothesized to cross into the central nervous system where they interact with CNS opioid receptors and damage neural networks to produce autistic symptoms. Publicity of this theory has led to wide-spread use of gluten and casein elimination diets in children with autism as well as parental avoidance of measles-mumps-rubella immunization in many children without autism.

Within this context, the Hunter paper is important for two reasons. The study's failure to find abnormalities of opioid peptides in the urine or related enzyme concentrations in the plasma of a group of children with autism is noteworthy. In addition to failing to confirm prior research, these investigators found that the techniques used in previous publications to identify abnormal urinary peptides were not adequate to distinguish such compounds in their laboratory. This study, albeit in only a small group of children, therefore challenges one of the pathophysiological underpinnings of exclusion diets and immunization avoidance on both clinical and methodological grounds. Clearly further investigation is indicated to resolve these important discrepancies.

The confusion resulting from such conflicting data illustrates the situation with autism only too well. Lack of knowledge regarding pathophysiology inhibits understanding of diagnostic definitions, etiological relationships, and comorbidities as well as options for biological intervention. Enhanced understanding of the neurobiological mechanisms that produce the complex behaviors of autism will be required for preventive and therapeutic options based on scientific understanding. Only when the pathophysiology is understood will there be an answer to the parent's question 'What causes autism?' At present we still don't know.

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References

1. Twain, M. (1883) *Life on the Mississippi.* New York: Meridian/Penguin Books USA. p75
2. Hunter LC, O'Hare A, Herron WJ, Fisher LA. Jones GE. (2003) Opioid peptides and dipeptidyl peptidase in autism. *Dev Med Child Neurol* **45:** 121–8.