Autism spectrum disorders (ASD) are among the most puzzling forms of developmental disability. This term refers to a spectrum of pervasive developmental disorders sharing deficits in three major domains: social relatedness and interactivity, communication, and restricted interests and/or stereotypic or repetitive behaviors with difficult transitions. Studies have investigated genetic factors, neurologic, immunologic, and early environmental insults. ASD are lifelong, often severe disorders impacting all facets of individual, family, and community function. Relationships are disrupted, and socially inappropriate behaviors are prominent. Often these children do not cope well with change, making it difficult for families to go out

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in public places. Children may become aggressive, self-injurious, or resort to self-stimulatory behaviors, which serve to calm them. Although the underlying causes of ASD have not been clarified, several promising interventions have been developed utilizing behavioral techniques, educational programs, and pharmacotherapy to address the symptoms of this disorder. The prognosis for truly normal function is guarded, even with availability of standard therapies, a factor often leading to parental desperation and the willingness to invest in newer approaches to treatment. Effective evidence-based services may also not be available or in short supply. Standard therapies may require much time to see progress, and therefore some parents may be willing to grasp at the promise of a “quick fix.”

Scientifically unsupported therapies lack a foundation based on objective, controlled research, using methods standardized within biological or medical science. Therapies such as these are often used either in conjunction with evidence-based medical treatments (complementary therapies) or might be used instead of the standard medical practice (alternative therapies). Use of these therapies date back to early folk medicine and are often based upon belief systems stemming from religious faith. Although the use of non-standardized home remedies for minor illnesses is widespread, the emphasis in modern-day medicine has been treatment that is evidence-based. There has been a growing trend toward the use of scientifically unsupported approaches, especially within the fields of chronic illness and developmental disabilities.

In 1992, the U.S. government established the National Center for Complementary and Alternative Medicine (NC- CAM) through the National Institutes of Health. The NCCAM recognizes five domains of complementary and alternative medicine: alternative medicine systems (eg, Chinese medicine), mind-body interventions (eg, meditation), biologically-based medicine (eg, megavitamin therapy), body-based therapies (eg, sensory integration therapy), and energy therapies (eg, magnet therapy) (see Table).

The prevalence of complementary and alternative therapy usage in children with chronic illness, developmental disabilities, and emotional problems is high.1-3 These treatments are often promoted commercially. They also generally lack objective, evidence-based studies to support their claims of efficacy, often relying upon unproven theories with results that are usually based upon anecdotal cases. Commercial Web sites or publications, instead of peer-reviewed, scientific journals, are the vehicles promoting the information to the public. Therapies reaching the attention of the media may then be sensationalized, furthering their promotion. Often pediatricians find themselves in a difficult position imposed by a parent requesting their endorsement of an unsubstantiated treatment.4 Recent studies found the use of CAM to range between 50% to 92% in the ASD population.5-6 Within the ASD population, 50% of biologically-based therapies utilized by parents involved dietary changes.7 Seventy-six percent of parents using dietary modifications felt that these had been of some benefit for their affected child. In the category of body-based therapies, chiropractic therapy was most commonly used; however, there was no real reported benefit. Various therapies were reported by parents as helpful in relaxing the child diagnosed with ASD, and these included therapeutic horsetack therapy (hippotherapy), massage, music therapy, and sensory integration therapy.

This article will focus on many of the biologically and non-biologically based alternative or complementary therapies used in the treatment of ASD (see Sidebar, page 500).

### BIOLOGICALLY-BASED THERAPIES

#### Diets: The Brain-Gut Connection

The potential relationship between gastrointestinal symptoms and autism has been the basis of much investigation in this population. Valicenti-McDermott et al8 reported a higher than expected frequency of gastrointestinal symptoms and food selectivity in a sample of 50 children with ASD. Increased symptoms such as diarrhea, reflux, constipation, bloating, etc., have been reported with frequencies of 9% to 50% in this population.9 Increased levels of serotonin, a primary gut neurotransmitter, have been found in the plasma of people with autism, but it is not clear that this is linked to the gastrointestinal symptoms.10 In a small, double-blinded, placebo-controlled study reviewed by Erickson,11 famotidine (Pepcid) was administered to children with ASD and gastrointestinal symptoms. Improved behavior was noted; however, four of the nine children noted to have behavioral improvement had undiagnosed gastroesophage-
al reflux disorder, which may have been a factor in their improvement.

Dietary manipulation in the treatment of developmental or behavioral problems is not a new concept. The origin of this practice is beyond the scope of this article. However, more recent dietary practices based upon presumed associations with nutritional excesses and deficiencies and possible effects on behavior evolved in the 1920s, with the suggestion of excessive sugar consumption and the development of hyperactivity and impulsivity. The Feingold diet,\textsuperscript{12} which became popularized in the 1970s, was largely based upon these theories.

In the 1970s, Panskepp\textsuperscript{13} proposed that malabsorption of casein (a milk protein) and gluten (a wheat protein) might be responsible for manifestations of autism via altered cerebral neurotransmitter metabolism. The protein metabolites from milk and wheat products were postulated to be absorbed through a “leaky gut” and to act centrally as endogenous opioids; however, the relationship between opioid activity and the development of autism remains speculative. The finding of increased peptides in the urine of children with autism\textsuperscript{14} is controversial, as is the proposal that a gluten- and casein-free diet can decrease urinary peptides, resulting in increased social interactivity among autistic children. Despite the lack of definitive data, the use of the gluten-/casein-free diet is widespread with many anecdotal testimonials of its success.

Erickson\textsuperscript{11} also reviewed the use of the ketogenic diet in a small population of children with autism. Although improved behavior was noted, the study was not controlled. Dietary limitations, such as those imposed by selective elimination diets, may impose additional stress on children and their families and hypothetically may result in nutritional deficiencies.

In 1998, Horvath’s report on improved developmental/behavioral function following secretin administration to children with gastrointestinal complaints and symptoms of autism added to the growing number of theories of brain-gut interaction based upon gastrointestinal proteins acting as central neuropeptides in the brain.\textsuperscript{15} However, despite the initial excitement of secretin as a treatment in ASD, multiple definitive data, the use of the gluten- and casein-free diet is widespread with many anecdotal testimonials of its success.

IS IT VIRAL?

Levy and Hyman’s 2005 review\textsuperscript{22} cited investigational reports of evidence of early infection, chronic inflammation, or autoimmune disorders as possible etiologic factors in ASD. They commented that prenatal and neonatal exposure to viruses is postulated to alter brain development; however, studies of viral exposure failed to show an inflammatory response in the brain. Antiviral agents have been proposed as a treatment strategy; however, no specific virus has been identified, and no publication has addressed antiviral therapies in terms of efficacy or safety in ASD.

In 1998, Wakefield\textsuperscript{16} reported on 12 cases of children with GI abnormalities...
and lymphonodular hyperplasia, and eight of the 12 children allegedly demonstrated symptoms of autism reported to develop soon after receipt of an MMR vaccination. Although Wakefield did not prove an actual causal connection between autism and MMR, public concern nonetheless exploded after this was reported on 60 Minutes. Madsen et al used national-registry data on autistic disorders in Denmark (a national cohort study including 537,000 children) found no association between the MMR vaccine and the subsequent diagnosis of autism. In March 2004, 10 of Wakefield’s co-authors published a formal retraction of the suggestion of a link between MMR and autism in The Lancet. The U.S. Institute of Medicine report co-sponsored by the National Institutes of Health and the Centers for Disease Control and Prevention concluded that there is no evidence linking the MMR vaccine with autism.

**IS IT BACTERIAL?**

Sandler et al used the antibiotic vancomycin in a small study of 11 children with autism and diarrhea whose stools were colonized with a different clostridium species than controls. It was suggested that neurological symptoms might result from altered gut integrity on the basis of toxins in altered colonic flora. However, outcome parameters of this study were not totally blinded, and the children’s behaviors may have improved because of improved bowel function alone.

**IS IT FUNGAL?**

In the 1980s, anecdotal reports implicated overgrowth of the yeast *Candida albicans* in precipitating some cases of autism. Crook suggested the overgrowth of yeast to be secondary to antibiotic use or ingestion of processed sugars. *Candidal* overgrowth was, however, not documented by endoscopic study. The yeast theory popularized the use of treatments to reduce yeast colonization, which included the use of probiotics (acidophilus, lactobacillus), dietary modification (reduction of refined sugars), and the use of antifungal agents like nystatin and fluconazole.

**IS IT PRIMARY IMMUNODEFICIENCY?**

Levy and Hyman reviewed three small case series of ASD with equivocal results after intravenous immunoglobulin G (IVIG) administration. However, because of the small risk of blood-borne infection and side effects of IVIG, they recommended that this agent be used for diseases where there was documented benefit.

**IS IT HEAVY METAL TOXICITY?**

Bernard et al drew attention to similarities between symptoms of autism and mercury toxicity, suggesting a connection between environmental sources of mercury and the development of autism. However, mercury poisoning is characterized by severe movement disorders and peripheral nerve damage, none of which is typically found in children with ASD. Nonetheless, media reports led to requests for mercury testing because of growing concerns of possible toxicity. Mercury, a heavy metal found in the environment, accumulates in internal organs. Therefore, blood and urine assays do not always reveal mercury exposure. Hair trace analysis, which has not been standardized, is not considered to be a reliable assay for mercury toxicity because of differing rates of hair growth, variable hair composition, and because shampoo, hair products, exposure to sun, and drying all serve to leach out substances from hair. Thimerosal, an ethylmercury based preservative once used in many vaccines in the United States (including the MMR vaccine), was suggested as a possible cause of autism in a subpopulation of immunized children. Other sources of mercury such as that contained in thermometers, mercury amalgams in tooth fillings, and some fish came under scrutiny in the search for environmental precipitants of autism symptoms. Pregnant women were issued warnings against excessive fish consumption, and amalgam removal was even suggested. Madsen et al examined the use of thimerosal-containing vaccines and ASD in Denmark, where thimerosal was removed from vaccines in 1992. This study demonstrated that despite removal of thimerosal from vaccines, the numbers of autism cases continued to rise at the same rate as prior to its removal. Studies of children who received heavy metal chelation failed to demonstrate improved neurodevelopmental function on follow-up. More ominous was the documentation of two deaths in children in the United States (one of whom had autism) because of hypocalcemia and cardiac arrest after undergoing chelation therapy. The American Academy of Medicine rendered a 2004 statement against the use of chelation therapy in ASD.
VITAMINS AND NUTRITIONAL SUPPLEMENTS

Nutritional supplements have also been popularized in the treatment of symptoms in children with ASD. Megavitamin therapy gained popularity in the 1960s with Linus Pauling’s theory linking mental illness and inborn errors of metabolism. A variety of vitamins (vitamins A, C, B6, magnesium complex, folic acid, B12) and minerals have been advocated.

Vitamin B6-magnesium complex has been the most heavily promoted of the vitamin therapies for ASD. Vitamin B6 (pyridoxine) has been advocated because of its cofactor role in the production of the neurotransmitters: serotonin, norepinephrine, epinephrine, dopamine, and GABA. Magnesium may have an additive effect on this. Rimland reported decreased behavioral outbursts in autism with vitamin B6-magnesium supplementation, based on more than a dozen studies at that time, many of which were not blinded or adequately controlled. In a review of the literature in 2002, Nye and Brice concluded that no recommendation could be made for this treatment based upon the scant data available. Caution is advised because excessive intake of pyridoxine is associated with peripheral neuropathy. Excessive magnesium concentrations are associated with the development of seizures.

Vitamin A, such as that found in cod liver oil, is promoted as improving immune function and vision in children with autism; however, no data are available. Excessive use of Vitamin A can lead to hepatotoxicity and increased intracranial pressure.

Vitamin C (ascorbic acid) was reported in one trial to decrease stereotypic behaviors significantly in a study of residential students with autism; however, this study was never replicated. Vitamin C in excessive doses has the potential to cause diarrhea and renal stones.

Vitamin B12 treatment was recommended based upon data from a small, controlled study of 20 children with autism found to have lower plasma concentrations of the antioxidants methionine, homocysteine, total glutathione, cysteine, and S-adenosylmethionine as compared with controls. Administration of subcutaneous vitamin B12 and oral folinic acid to patients with ASD is based on the premise that these individuals have compromised antioxidant defenses with an inability to detoxify environmental contaminants. This study suggested that as plasma concentrations of the antioxidants increased, behaviors were noted to improve; however, further studies have not replicated this data.

Dimethylglycine (DMG, a nutritional supplement) is metabolized to the excitatory neurotransmitter, glycine, within the liver. There have been reports of an old Russian study, which suggested enhanced language skills in developmentally disabled children who were administered DMG; however, two well-controlled and blinded studies in ASD failed to demonstrate a difference between DMG and placebo.

Omega-3 fatty acids or polyunsaturated fatty acid (PUFA) is a popular treatment for a variety of developmental problems including attention-deficit/hyperactivity disorder, dyslexia, developmental coordination disorder, and ASD. The results of controlled treatment trials have been mixed and are hard to interpret because of differing formulations of the essential fatty acids and different populations treated. Larger clinical trials are needed to corroborate the findings of a few reports of improved behaviors.

Oxytocin intranasally and intravenously may have significant positive effects on repetitive behaviors and social cognition in adult autism patients; however, the significance of these results needs further investigation as studies on adults cannot be generalized to children.

Other Supplements

Levy and Hyman reviewed data on other supplements such as tryptophan, tyrosine, cyproheptadine, D-cycloserine, and carnosine. There is need for additional research to support the use of these supplements.

NONBIOLOGICAL INTERVENTIONS

Sensory Integration Therapy

Ayres, an occupational therapist, postulated in 1979 that children with ASD have deficits in the brain areas
In 1998, the AAP issued a statement from the Committee on Children with Developmental Disabilities to demonstrate FC as replicable or valid. Numerous controlled and blinded studies have failed to demonstrate FC as replicable or valid. In 1998, the AAP issued a statement from the Committee on Children with Disabilities highlighting the lack of scientific data to show FC to be effective.43

Facilitated Communication

Facilitated communication (FC) refers to an intervention utilizing either a computer or typewriter device in which another individual, the facilitator, guides the hand of a nonverbal individual. This technique was originally used to assist physically disabled individuals.42 Numerous controlled and blinded studies have failed to demonstrate FC as replicable or valid. In 1998, the AAP issued a statement from the Committee on Children with Disabilities to demonstrate FC as replicable or valid. Numerous controlled and blinded studies have failed to demonstrate FC as replicable or valid. In 1998, the AAP issued a statement from the Committee on Children with Disabilities highlighting the lack of scientific data to show FC to be effective.43

SUMMARY

Our understanding of ASD has changed over the past decades, and diagnostic tools have assisted in earlier identification and referral for intervention. Appropriate intervention appears to impact positively on overall outcome for a pervasive developmental disorder for which there is currently no known cure. Novel and controversial therapies will come and go, and therefore physicians should familiarize themselves with these interventions, as advice about these alternative approaches will be sought. Discussions of nontraditional therapies should include the placebo effect, possibly undesirable, or potentially dangerous outcomes of a treatment, and the importance of scientifically sound research studies of that treatment. Addressing the use of complementary and alternative therapies in families with medically-compromised or developmentally disabled children is crucial to providing complete care to the patient and in the maintenance of a medical home.

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