should be suspected when hyperammonemia is associated with acidosis, ketosis, and low bicarbonate level. Topiramate and phenobarbital favor hyperammonemia, because of inhibition of cerebral glutamine synthetase; topiramate also inhibits carbonic anhydrase, leading to hyperammonemia by affecting the urea cycle. Polytherapy, including topiramate, phenobarbital, phenytoin and carbamazepine, should be avoided with VPA. Hyperammonemia leads to an increase in cerebral glutamine, which produces astrocyte swelling and cerebral edema. The EEG shows continuous generalized slowing, a predominance of theta and delta activity, occasional bursts of frontal rhythmic delta, and triphasic waves. Prompt diagnosis and treatment with supplements of carnitine can lead to a favorable response. (Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. **Acta Neurol Scand** July 2006;114:1-7). (Respond: Dr Nuria Segura-Bruna, Servei de Neurologia, Hospital del Mar, Passeig Maritim, 25-29, 08003, Barcelona, Spain).

COMMENT. In contrast to the above report and others, Beghi E et al (**Epilepsia** 1990;31:346-352) found a significant correlation between serum ammonia level and VPA dosage. A review of 132 fatal cases of valproate hepatotoxicity worldwide found that 65% were developmentally delayed, 75% were taking additional AEDs, and 65% were below 2 years of age (Konig St A, et al. **Epilepsia** 1994;35:1005-1015). In a report of 29 valproate case fatalities in the US between 1986 and 1996, risk factors also included young age (1:600 risk <2 years), and coincident metabolic disorders (Alpers' disease). (Bryant AE III, Dreifuss FE. **Neurology** 1996;46:465-469). Metabolic testing is recommended in young children (<2 years) with developmental abnormalities before prescribing VPA.

A review of the role of valproate therapy in the treatment of pediatric epilepsy emphasizes its superior efficacy and minimizes its toxicity (Aldenkamp A et al. **Acta Neurol Scand** August 2006;114 (Suppl 184):1-13). Given the number of fatalities reported in the past two decades, the potential adverse effects of valproate deserve at least equal attention and caution. The risks of valproate in the prophylaxis of febrile seizures, for example, outweigh the benefits (Wheless JW et al. **J Child Neurol** 2005;20(Suppl 1);S34-S35), and in pediatric epilepsy, careful monitoring is mandatory. The FDA-approved indications for valproate are complex partial seizures + other seizure types and simple and complex absence seizures (as monotherapy or adjunctive therapy); mania in adults; and migraine prophylaxis in adults (Golden AS, Haut SR, Moshe SL. Nonepileptic uses of antiepileptic drugs in children and adolescents. **Pediatr Neurol** June 2006;34:421-432).

ATTENTION DEFICIT DISORDERS

RESPONSE OF ADHD WITH GIANT SEP TO VALPROATE

Three boys, ages 4.5, 6, and 6.7 years, with attention deficit/hyperactivity disorder (ADHD) associated with giant somatosensory evoked potentials (SEP), who responded well to extended-release valproate (ER-VPA), are reported from the University of Tokushima Graduate, and Miyoshi Medical Clinic, Higashikagawa, Japan. Of 20 children with ADHD, 17 boys and 3 girls, ages 3 to 13 years, 6 showed giant SEPs, defined as peak-peak amplitude of N20-P25 that exceeded 10mcV, on median nerve stimulation. Three also had Tourette's

syndrome and were excluded. Of the 3 responders, 2 had the hyperactive-impulsive subtype of ADHD, and 1 had the ADD + HI combined type. All 3 had abnormal EEGs showing focal discharges in frontal areas. Two had received methylphenidate previously without benefit. ER-VPA was administered in one daily dose (9.5 to 18.8 mg/kg) each morning. Serum VPA concentrations ranged from 26 to 58 mcg/ml. Total ADHD-rating scale (RS-IV) scores were decreased following treatment with VPA, and the hyperactive-impulsive (H-I) symptoms were controlled more effectively than the inattentive type. Pretreatment and treatment scores for H-I decreased from 26-11, 22-10, and 26-25, for patients 1, 2, and 3, whereas those for inattention were 9-6, 9-9, and 24-21, respectively. SEP amplitudes following median nerve stimulation were decreased to normal voltage in two patients after VPA treatment. (Miyazaki M, Ito H, Saijo T, et al. Favorable response of ADHD with giant SEP to extended-release valproate. **Brain Dev** July 2006;28:470-472). (Respond: Dr Masahito Miyazaki, Department of Pediatrics, Miyoshi Medical Clinic, 813-1 Otani, Higashikagawa 769-2513, Japan).

COMMENT. The authors recommend a trial of ER-valproate in children with ADHD, especially those with the hyperactive-impulsive subtype, when associated with giant somatosensory evoked potentials. It should be noted that the responders also had epileptiform EEGs, with frontal localization, areas known to be involved in ADHD. Giant SEPs may reflect hyperactivity and decreased GABA in the sensorimotor cortex, and g-aminobutyric acid (GABA) enhancers such as clonazepam and valproate would be expected to reduce amplitude of giant SEPs and benefit hyperactive-impulsive behavior. In methylphenidate nonresponders, somatosensory evoked potentials should be tested, and treatment with VPA given consideration. GABAergic dysfunction as well as dopaminergic mechanisms are postulated in the etiology of ADHD. The risks of valproate therapy and the necessity for monitoring with blood level and other laboratory tests could deter its frequent use in ADHD practice.

Predictors for persistent hyperactive behavior in 2 to 7 year-olds included maternal prenatal smoking, child male gender, maternal depression, and hostile parenting. In a population-based sample, 7 children in 100 were classified as hyperactive at both the 2-year and 7-year evaluations. Preventive intervention is recommended for high-risk families. (Romano E et al. **Pediatrics** June 2006;117:2101-2110).

TRIAL OF DEXMETHYLPHENIDATE (FOCALIN) ER IN ADHD

The efficacy and safety of dexmethylphenidate extended release (d-MPH-ER) was compared to placebo in 97 patients (ages 6-17 years) with attention-deficit/hyperactivity disorder (ADHD) in a multicenter, randomized, double-blind, two-phase study reported from New York State Psychiatric Institute, New York. The once daily dose of d-MPH-ER was flexible (5-30 mg/kg) for 5 weeks, and the patients' final optimal dose (mean, 24.0 +/- 7.1 mg/day) was maintained during the last 2 weeks of the 7-week trial. Conners ADHD/DSM-IV Scale-Teacher version (CADS-T) total score improved significantly compared with placebo ($p<.001$), and 67.3% of patients were much improved on a Clinical Global Impressions-Improvement (CGI-I) Scale at final visit versus 13.3% of placebo patients ($p<.001$). Drug-related adverse events were spontaneously reported by 49.1% patients taking d-MPH-ER vs 25.5% of placebo-treated patients ($p=.01$). Decreased appetite was drug-