epilepsy treated in the Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, and the Department of Neurology, Stamford Hospital, Stamford, CT. The daily dose varied from 500 mg in six patients to 1750 mg in one (average 893 mg). Acetazolamide was less effective in controlling myoclonus than in the control of generalized tonic-clonic seizures. Six (43%) of 14 adults with generalized seizures responding to acetazolamide developed renal calculi. (Resor SR, Resor LD. Chronic acetazolamide monotherapy in the treatment of juvenile myoclonic epilepsy. Neurology Nov 1990; 40:1677-1681).

COMMENT. The frequency of renal calculus as a side effect of chronic acetazolamide therapy in the adults in this study is alarming and sufficient to contraindicate its use. In children, however, renal calculus is a rare side effect of acetazolamide, and this report in adults should not negate the efficacy and clinical use of acetazolamide in the treatment of childhood epilepsy.

In a double blind, placebo controlled trial of acetazolamide in 14 children, ages 6 months to 11 years, an anticonvulsant effect was demonstrated in all patients. Both generalized tonic-clonic and myoclonic seizures were reduced in frequency and in eight patients the maximal reduction in seizures was more than 75%. The control of generalized tonic-clonic seizures was superior to that of the myoclonic type. Acetazolamide monotherapy was used in two patients and additional antiepileptic drugs were continued in the remainder. Tolerance to the effect of acetazolamide shown in eight patients was a greater limiting factor than toxicity in this study. Polyuria and nocturnal enuresis were the only renal side effects and renal calculus did not occur. (Millichap JG. Anticonvulsant action of acetazolamide (Diamox) in children. Neurology 1956; 6:552-559). Acetazolamide treatment of absence seizures reviewed in 620 children and young adults provided complete control in 50% and a 3/4 or greater reduction in an additional 26%. Side effects were reported in 60 (10%) patients and renal calculus occurred in one, a 20 year old adult. (Millichap JG, Aymat F. Treatment and prognosis of petit mal epilepsy. Ped Clin N Amer 1967; 14:905-920).

MECHANISMS OF ANTIEPILEPTIC DRUG ACTION

The mechanisms of antiepileptic drug action are reviewed from the University Pediatric Epilepsy Program and Division of Pediatric Neurology, University of Minnesota Hospital, Minneapolis, MN. Phenytoin, carbamazepine, and valproic acid decrease sustained repetitive firing of action potentials at therapeutic concentrations. Unlike phenytoin and carbamazepine which block the sodium channel, valproic acid blocks sustained repetitive firing by activation of calcium-dependent, potassium conductance. Phenytoin and carbamazepine also have the ability to block post-tetanic potentiation, an effect mediated by blocking the sodium channel. Benzodiazepines and

barbiturates enhance GABA-mediated inhibition. Other mechanisms of antiepileptic drug action include inhibition of calcium influx, inhibition of excitatory receptors, or excitation of inhibitory receptors. Glutamate and aspartate are the major excitatory neurotransmitters in the central nervous system and glutamate binds to excitatory receptors, including N-Methyl D-aspartate (NMDA). NMDA receptors which regulate channels permeable to sodium and calcium and are blocked by magnesium play a role in the pathogenesis of some forms of epilepsy. Lamotrigine is an NMDA antagonist with antiepileptic potential. (Talwar D. Mechanisms of antiepileptic drug action. Pediatr Neurol Sept/Oct 1990; 6:289-295).

COMMENT. This excellent review of antiepileptic drug action might also include acetazolamide, a carbonic anhydrase inhibitor with an anticonvulsant mechanism that is unique and not shared by the drugs noted in the review. Acetazolamide is a sulfonamide containing a free-SO_2NH_2 group which is essential for inhibition of carbonic anhydrase. The anticonvulsant effect of acetazolamide is not abolished by nephrectomy and is independent of the action of the drug on the kidney and the resultant metabolic acidosis. The anticonvulsant effect is correlated directly with the inhibition of brain carbonic anhydrase. (Millichap JG et al. Mechanism of the anticonvulsant action of acetazolamide, a carbonic anhydrase inhibitor. J Pharm Exp Ther 1955; 115:251-258). The inhibition of carbonic anhydrase located in glial cells results in CO_2 accumulation and changes in acid-base and electrolyte balance that reduce neuronal excitability.

GENERIC SUBSTITUTIONS FOR ANTIEPILEPTIC DRUGS

The hazards and problems of generic substitutions for antiepileptic drugs are reviewed in a Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Neurology Nov 1990; 40:1641-1643) and are discussed by Nuwer MR et al (Neurology Nov 1990; 40:1647-1651). According to the present Federal guidelines for manufacturers a generic product may be approved as equivalent to a brand name product even if it produces widely varying bioavailability in some individuals. Implicit in the FDA guidelines is the assumption that a ± 20% change in mean steady-state serum concentration of antiepileptic drugs can be tolerated safely. However, there is no scientific evidence to support this assertion. When substitution of different formulations of an antiepileptic drug occurs, the patient is put at risk of drug intoxication or breakthrough seizures. Generic substitution of drugs such as phenytoin and carbamazepine which have a narrow therapeutic range is especially problematic.

COMMENT. Economic benefits because of lower cost of generic substitutions may be outweighed by the need for more frequent serum concentration determinations and costs of follow-up visits.