When starting with VPA the great problem of drug interactions is avoided. Treating patients with intractable epilepsy has shown that VPA may be effective in all seizure types regardless of the EEG findings. However, generalized paroxysms of spike-and-wave complexes in the EEG are a good prognostic sign, especially when fairly regular. Side effects are few when using enteric-coated tablets, but toxic effect may be serious. Drug fasting serum level monitoring is mandatory, especially when VPA is given in combination with other antiepileptic drugs, as interactions with these are pronounced. Optimal clinical effect is usually seen on serum levels between 300 and 600 μmol/l, which may be obtained by giving 10–20 mg/kg daily, assuming that the patient is receiving VPA monotherapy, which always should be aimed at. Comedication may have to be withdrawn to obtain therapeutic serum levels of VPA due to drug interactions.

THE EFFICACY OF VALPROIC ACID AS COMPARED WITH PHENYTOIN IN THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED TONIC-CLONIC SEIZURES. B. J. Karas and B. J. Wilder (Neurology Service, Veterans Administration Medical Center, and University of Florida College of Medicine, Gainesville, FL 32602).

We evaluated the efficacy of valproic acid (VPA) as compared with phenytoin (PHT) in the treatment of patients with newly diagnosed generalized tonic-clonic seizures. Twenty-five patients, 7 females (19–56) and 18 males (19–65) were entered into the 6-month study. All patients had tonic-clonic seizures occurring at a frequency of four or more per month. In addition to generalized tonic-clonic seizures, 7 patients had additional seizure types (myoclonus, absence, complex partial, and atonic). Seventeen patients were randomized to receive valproic acid and 8 phenytoin. Doses ranging from 500–2,000 mg/day of VPA (20–29 mg/kg/day), and 300–500 mg/day of PHT (2.5 to 5 mg/kg/day) were titrated over a month's time or until adequate seizure control was achieved.

VPA was found to be equally as effective as PHT in controlling these newly diagnosed tonic-clonic seizures. There was one treatment failure in each group. Both patients had complex partial seizures that required the addition of another antiepileptic drug. Plasma levels of VPA and PHT ranged between 50–115 μg/ml and 8–24 μg/ml respectively.

Side effects associated with VPA included a mild hand tremor in 70% of patients, mild gastrointestinal disturbances in 40% and transient weight gain in 20% of patients. Pertinent laboratory studies included transient liver function elevations occurring upon initiation of VPA and mild decrease in platelet and fibrinogen levels. No patient experienced severe side effects.

In the PHT group many patients complained of early morning and late evening sedation. One patient was dropped due to a hepatotoxicity reaction. Another patient, placed on PHT as emergency treatment before entering the study, suffered a serum sickness reaction. The patient subsequently responded well to VPA therapy.

Valproic acid is equally as effective as phenytoin in controlling patients with primary generalized tonic-clonic seizures and produces much less sedation.

PHENYTOIN BIOAVAILABILITY AND KINETICS IN NEWBORNS. Blaise F. D. Bourgeois and W. Edwin Dodson (St. Louis Children's Hospital, Department of Pediatrics and Neurology, St. Louis, MO 63110).

The relative contribution of initial concentration, age and enteral absorption on phenytoin (PHT) kinetics during the neonatal period was investigated. PHT apparent half-life (t_{50}) was measured 26 times in 14 infants aged 2 to 36 days. PHT was given i.v. 15 times and orally 11 times. The PHT t_{50} ranged from 140.0 h in a 2-day-old to 3.0 h in a 36-day-old. Whereas the t_{50} correlated with initial concentration (C_i) in patients 9–21 days old ($r = .96$, $p < 0.001$) and in patients more than 3 weeks old ($r = .88$, $p < 0.01$), there was no correlation during the first week of life. t_{50} varied inversely with age. After controlling for the effect of C_i there was a threefold decrease in the t_{50} between the first ($t_{50} = 61.4 \pm 49.3$ h) and fourth week ($t_{50} = 19.1 \pm 3.16$ h) of life.

We also investigated the absorption of PHT administered orally to newborns. We developed a mathematical model that allows estimation of PHT bioavailability at any baseline level, does not require the patient to be in steady state, and that also corrects for the effect of varying t_{50}. By using this model on eight different occasions, we found an average bioavailability of 69.7% with a range of 48.2 to 100%.

Thus, phenytoin levels in newborns are unpredictable and should be checked frequently. The relation between C_i and t_{50} of PHT changes rapidly during the first month of life. The changes in the t_{50} due to maturation and/or recovery from illness cause, on the average, a threeefold increase in dosage requirements. Because of reduced bioavailability of phenytoin in newborns, a 1.5-fold increase in dose may be required on the average when switching from i.v. to oral therapy. For newborns treated with PHT intravenously during the first week of life then switched to oral administration, the combined effect of changing t_{50} and incomplete oral absorption may cause an average increase in dosage requirements of 4.5 times between the first and fourth week of life, if the same serum levels of PHT are to be maintained.

MEDROXY PROGESTERONE TREATMENT OF WOMEN WITH UNCONTROLLED SEIZURES. Richard H. Mattson, Pamela Edwards Klein, Burton V. Caldwell, and Joyce A. Cramer (Epilepsy V.A. Medical Center, West Haven, CT and Yale University School of Medicine, New Haven, CT).

Reports of an association between the menstrual cycle and seizure frequency have been defined to show exacerbation of epilespy when progesterone levels are lowest. An increase in seizure frequency in epileptic women with anovulatory cycles has also been reported (*Epilepsia* 1981; 22:262). Animal models have indicated that progesterone increases seizure thresh-

old. For these reasons a trial of synthetic progesterone treatment has been undertaken. Fourteen women with uncontrolled seizures were followed for at least three consecutive menstrual cycles to document seizure frequency and anticonvulsant drug compliance. The women were then treated with medroxy-progesterone acetate (Provera) for an average of 13 months. During the treatment period there were no changes in antiepileptic drug levels.

The 6 women who showed the effects of progesterone therapy with secondary amenorrhea had a significant 50% decrease in seizure frequency. No one reported an increase in seizure frequency. Women were discontinued from Provera treatment due to no improvement (3) or continuous menstrual bleeding (5). No significant side effects were observed. Six women are continuing on Provera treatment.

These preliminary results suggest that Provera treatment may be useful in decreasing seizure frequency for some women with uncontrolled seizures.

DISCONTINUATION OF ANTIEPILEPTIC DRUGS: PRELIMINARY REPORT OF A PROSPECTIVE RANDOMIZED STUDY OF TWO YEAR VERSUS FOUR-YEAR SEIZURE-FREE INTERVALS, AND NINE-MONTH VERSUS SIX-WEEK TAPER SCHEDULES. Stanley J. Rothman, Darrell V. Lewis, Jr., Robert S. Greenwood, John A. Messenheimer, Jr., and Harriet V. Rothman (Departments of Pediatrics and Neurology, Duke University Medical Center, Durham, NC 27710, and University of North Carolina Memorial Hospital, Durham and Chapel Hill, NC).

Although the practice of discontinuing antiepileptic drug treatment in childhood seizure disorders is commonplace, no prospectively acquired data exist regarding the proper seizure-free interval or the proper medication taper schedule. We have prospectively randomized our seizure-free patients seen by the pediatric neurology services at Duke University and the University of North Carolina—Chapel Hill. Drug compliance has been confirmed by antiepileptic drug serum levels prior to tapering. Assignment to the 4-year and 2-year seizure-free groups was random, as was assignment to the 9-month and 6-week taper groups. All of the children are being followed prospectively while either waiting to be tapered, tapering, or having been already tapered. (See table below.)

Our preliminary results indicate that there is no difference in recurrence risk between the 2-year and 4-year group. Electroencephalographic findings and other factors that may be pertinent to assessment of recurrence risk will be discussed.

Two years seizure free may be sufficient in a large proportion of children with childhood epilepsies. Rapid tapering schedules over a 6-week period may also be sufficient in most circumstances.

CHANGES IN NEUROPSYCHOLOGICAL TEST PERFORMANCE FOLLOWING IMPROVED SEIZURE CONTROL AND ELIMINATION OF BARBITURATE ANTIEPILEPTIC DRUGS. Bruno Giordani, J. Chris Sackellares, Sarah M. Miller, Thomas P. Sutula, T. J. Boll, F. E. Dreifus, and Stanley Berent (Departments of Neurology and Psychiatry, University of Michigan, Ann Arbor, MI 48109, and Departments of Neurology and Psychiatry, University of Virginia, Charlottesville, VA 22908).

Application of intensive diagnostic and therapeutic techniques in the treatment of patients with previously refractory seizures can result in significant reduction of seizures and elimination of unnecessary antiepileptic drugs (Sutula et al., *Neurology* 1981; 31:243). In this study, 26 patients with previously refractory seizures were evaluated before and after intensive treatment in a specialized epilepsy unit to assess the effects of this treatment upon cognitive, perceptual, motor, and memory function. Subjects were administered a battery of neuropsychological tests upon admission to the epilepsy unit and 6 months later. Formal statistical treatment indicated significant improvement in a number of these behavioral variables. There was significant correlation between improved test performance and reduction in the number of antiepileptic drugs and with withdrawal of barbiturates. Improved test performance did not correlate with reduction of seizure frequency. These results suggest that reduction of polypharmacy and elimination of barbiturates may play a significant role in improving functional capacity of patients with refractory seizures.

DEVELOPMENT OF TOLERANCE TO PHT AND CBZ DETECTED BY NEUROPSYCHOLOGICAL PERFORMANCE. Thomas E. Beniak, Ilo E. Leppik, Therese E. Bowman, Ruth B. Loewenson, and Robert J. Gumnit (University of Minnesota, Minneapolis, MI 55455).

To determine whether tolerance to unwanted effects of antiepileptic drugs (AED) develops during chronic therapy, a battery of 10 neuropsychological tests was administered to 24 patients with complex partial seizures near the beginning (B) and near the end (E) of a six-month study block. Patients were randomly as-

Group	Total	To be tapered	Tapering	Tapered	Seizure recurrence
2 yr/6 wk	24	3	3	14	4
2 yr/9 mos	21	3	11	6	1
4 yr/6 wk	23	9	3	10	1
4 yr/9 mos	13	7	4	1	1
	81	22	21	31	7