ACQUIRED APHASIA OF CHILDHOOD EPILEPSY, SHOWING UNILATERAL AUDITORY BRAIN STEM RESPONSE ABNORMALITIES

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The pathogenesis of acquired aphasia of childhood epilepsy (Landau-Kleffner syndrome) remains still hypothetical. We report a case of a four-year-old boy with this interesting syndrome, showing abnormal auditory brain stem response (ABR).

After a full-term gestation and uncomplicated birth, the patient developed normally until age three, when his mother noted his glassy-eyed appearance. Six months later, a speech disturbance was reported with a change to left-handedness. Then, motor skills and speech gradually deteriorated. At age four, seizures resembling petit mal absence appeared, and the electroencephalogram showed frequent bilateral spikes and slow waves dominant on the right side. He was treated with carbamazepine for epilepsy, but the symptoms continued with fluctuations. At the age of four years and six months he was admitted to our hospital, and diagnosed as having Landau-Kleffner syndrome, or acquired aphasia with epilepsy. The abnormal pattern of right-sided ABR was noted. After the administration of small doses of clonazepam, his apathic appearance disappeared dramatically, and his motor skill and verbal performance improved gradually. The ABR abnormality was also improved.

This case was compatible with Landau-Kleffner syndrome, but was unusual in several respects, including unilateral ABR abnormalities and mental deterioration in nonverbal as well as verbal performance. The pathogenesis of Landau-Kleffner syndrome will be discussed.

ACTH THERAPY IN INFANTILE SPASMS: EFFECTS ON CEREBROSPINAL AMINO ACIDS, HVA, 5-HYDROXYINDOLEACETIC ACID, AND HISTAMINE

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ACTH treatment has been used in infantile spasm (IS) for 30 years. It abolishes clinical seizures and electroencephalographic abnormalities in most cases, but the mechanisms are unknown. We followed the effect of ACTH treatment on the concentration of several neuroactive substances in the cerebrospinal (CSF) fluid of children with IS.

A group (n = 14) of such children (10 boys, four girls) with mean age of nine (range: three to 18 months) were treated with ACTH in cumulative doses from 840 to 3,860 IU (mean, 2,159) for 40 days (range: 35 to 44 days). Six and nine out of the 14 children received one or two antiepileptic drugs (phenobarbital, nitrazepam or carbamazepine) during the first and second CSF sampling, respectively. Concentrations of the following parameters in the CSF were measured before and after ACTH therapy: amino acids (also in plasma) with aminoacid analyzer, gamma-aminobutyric acid (GABA) with radioreceptor method, histamine with high-power light chromatography, and HVA and 5-hydroxyindoleacetic acid (5HIAA) fluorometrically.

A significant ($P < .05$) decrease of CSF GABA (about 26% of the basal level) was found after ACTH therapy in the IS children regardless of clinical response to ACTH, possibly because of the increased binding of GABA to receptors (Kendall et al, *Brain Res* 1982;236:365). No change was found in the concentration of other CSF amino acids, but serine level decreased significantly ($P < .05$) in plasma after ACTH therapy. CSF histamine, 5HIAA and HVA levels tended to decrease after ACTH, but the change was not significant.

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It seems that the present biochemical changes cannot be utilized to predict clinical response of IS children to ACTH.

PATTERN AND TYPE OF SEIZURE DISORDERS IN A SELECTED GROUP OF SAUDI ARABIAN CHILDREN

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The variety of types of seizure of multiple origin and disagreement on the definition and classification of epilepsy make epidemiologic study of epilepsy difficult. This hospital-based study reports a preliminary attempt to determine the burden of illness related to seizure disorders in children in the Eastern Province of Saudi Arabia. Data were obtained from the medical records of all children under 13 years of age with seizure disorders or with a history of convulsions, seen in the Emergency Room and the Department of Pediatrics, King Fahd Hospital of the University (KFHU), Al-Khobar, between 1981 and 1984.

During the period of study, 461 out of the 58,702 children seen at KFHU had seizure disorders. The frequency rate of seizures was 7.8/1000. Febrile seizures (23%) were the most frequent, particularly in children under six years of age; single seizure episodes were described in only 11%. Tonic-clonic seizures, encountered in 96 children (21%) were the commonest type in those above the age of six years. Myoclonic epilepsy was common (17%). Birth trauma was present in 19%, and mental retardation was an associated feature in 104 subjects (23%). Absence (petit mal) seizures were uncommon (2%).

AMANTADINE IN THE TREATMENT OF INTRACTABLE GENERALIZED SEIZURES IN RETARDED CHILDREN

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Tonic, atonic and myoclonic seizures in mentally retarded children are often intractable to most anticonvulsants. We designed a study to test the efficacy of amantadine in this particular population because of its previously reported success in the treatment of atypical absence and myoclonic seizures. We selected children who had (1) mixed seizure types (minor motor and major motor), (2) mental retardation, (3) electroencephalograms with slow and disorganized background and generalized or multifocal discharges, and (4) whose disease had been reported to be intractable to at least three different classes of anticonvulsants.

Six patients, 21 months to 12 years of age, met these criteria and were started on amantadine. Preliminary results showed a dramatic response in all cases within two weeks of initiation of the medication or dosage adjustment. Three patients have been seizure-free for over one year with dosages ranging from 0.9 to 5.9 mg/kg/day and serum levels ranging from 0.1 to 0.9 μg/mL. Another patient has had his seizures reduced by 90% for more than one year (7.6 mg/kg/day).

Two other children, for the first time since the onset of their seizure disorder, have been seizure-free for at least one month on dosages of 0.8 mg/kg/day and 3.2 mg/kg/day respectively. No significant side effects occurred in any of these patients.

Although the numbers are still small, these preliminary results indicate that amantadine, at lower dosages than were previously used, may be a promising anticonvulsant for the treatment of generalized seizure types occurring in children with mental retardation.

LASER SURGERY FOR INTRACTABLE EPILEPSY DUE TO BENIGN FORNICO-MAMILLARY GLIOMA

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A boy, 17 years of age, suffered from epilepsy since early childhood. During recent years, grand mal seizures predominated, though he had been treated with high dosages of antiepileptics. His intellectual and psychomotor development showed a slight decline, and it became increasingly difficult to keep his activities within socially tolerable limits. Computed tomography revealed a small tumor situated in the basal part of the third ventricle at the linkage of the right fornix and mamillary body.

The tumor has been attacked by a frontomedial subfrontal retrochiasmatic supraoptic approach. It has been partially removed, partially vaporized, while the

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right fornix and the anterior part of the mammillothalamic tract have been transsected by laser. Alternative approaches are discussed. The epilepsy and the psychomental situation of the patient have improved following the operation.

INTENTION MYOCLONUS IN PROGRESSIVE MYOCLONUS EPILEPSY

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Intention myoclonus in progressive myoclonus epilepsy (PME) is notoriously difficult to treat. Three patients with a very active myoclonus in an early stage of Lafora disease were treated with low-dosage L-5-hydroxytryptophan (L-5-HTP) (400 to 1200 mg/day), benserazide (50 to 150 mg/day), and levodopa (125 to 375 mg/day). Within a few weeks patients could walk, eat and drink again without any help. Levodopa accelerated the initiation of voluntary movements to near normal.

To facilitate insight into the targets of the given precursors, a (simplified) scheme of transmitter systems about the main projections of the striatum, input processing and the main output will be presented. The administration of L-5-HTP plus carbidopa has already been reported in the literature as therapy for myoclonus in various disorders. From a physiological point of view, the interaction between dopamine input and cholinergic interneurons in the striatum is of vital importance.

In the cortex-caudatum-pallidum-thalamus-cortex circuit the dopamine-acetylcholine balance plays a significant role. The intrinsic activity of the circuit is controlled by (a) nigral influences, (b) raphe nuclei, (c) cerebellar influences, and (d) indirectly by reticular influences. The raphe and cerebellar influences are to a considerable extent serotonin-mediated. The cortical motor output, based on information processing, is converted by subcortical structures into space-temporal patterns: thus, intention to movements → activation of preprogrammed circuits in basal ganglia and cerebellum → activation of motor neurons → execution of movements.

Preprogramming is a function of both basal ganglia and the cerebellum. *Transmission within the described circuits is mainly serotonin- and dopamine-mediated.* In intention myoclonus, this programming is disturbed.

SEIZURES PRECIPITATED BY HOT WATER IMMERSION

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It is well known that severe myoclonic epilepsy (SME) in infants, first delineated by Dravet in 1982, is often accompanied by seizures precipitated by hot water immersion. There are also scattered case reports of bathing-induced seizures (BIS) in the literature since Allen described such a case in 1945. However, no detailed investigation had ever been carried out, with analytical observation of the ictal phenomena of BIS.

The authors examined BIS by means of continuous electroencephalographic (EEG)-video monitoring together with rectal temperature (RT) recording, and also studied the effect of experimental bathing on RT in healthy subjects, the results of which will be reported.

Two infants with SME (age range, 10 to 20 months), three epileptic children with no history of BIS (31 to 40 months), and five healthy subjects (an infant, three children and an adult) as controls were subjected to the "bathing provocation test" which consists of dipping the body into a bathtub filled with hot water (40°C) for 11 minutes, or until the induced convulsion. EEG, electrocardiographic (ECG), RT and videotape recording were monitored throughout.

Generalized convulsions were induced without exception on three trials, nine to 17 minutes after starting immersion, in two SME babies. RT at the time of convulsions ranged from 38.1°C to 38.3°C. In healthy controls and epileptics without BIS, no seizure induction was observed. In the latter group, RT rose from the baseline (37.2°C) to the peak (38.2°C) within 14 minutes on average, the average speed of elevation being 0.08°C/minute. The last figure was nearly equal to that observed in SME cases, where seizures developed. The degree of RT elevation was correlated with the duration of immersion.

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CLONAZEPAM FOR THE LONG-TERM TREATMENT OF EPILEPSY IN CHILDREN? RESULTS FOLLOWING PROSPECTIVE WITHDRAWAL

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From September, 1983, to December, 1987, 51 children on long-term treatment with clonazepam (CZP) were admitted to the pediatric clinic of the epilepsy center in Bethel. We discontinued CZP in all children as a result of our observations, published in 1984, of frequent withdrawal symptoms and the development of tolerance to the anticonvulsive effect. A prospective study could be carried out in 40 of these children.

At the time of discontinuing treatment, CZP was no longer effective in 90% of the patients. Paradoxically, in more than 15%, a seizure-provoking effect of the drug was noted. In about 50% of the children, withdrawal symptoms occurred in the form of an increased number of seizures followed by spontaneous normalization, and/or general symptoms. The occurrence of withdrawal signs correlated with the CZP dosage and the period of CZP pretreatment, but not, however, with the rate at which the drug was discontinued.

Taking into consideration the experience of other authors, we recommend extreme caution in using CZP for long-term treatment of children with severe epilepsy.

BROMIDES: USEFUL FOR TREATMENT OF GENERALIZED EPILEPSIES IN CHILDREN AND ADOLESCENTS?

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Sixty-eight children and adolescents suffering from therapy-resistant grand mal seizures were treated with potassium bromide in addition to their existing medication. The reduction in seizures and the occurrence of side effects were carefully noted during adjustment of treatment. Serum concentrations were regularly determined.

The cohort included 12 patients with Lennox-Gastaut syndrome (LGS) with tonic clonic seizures (TCS), 25 patients with mainly TCS and other seizures (absences, complex focal), and 27 with grand mal epilepsy of early childhood (TCS-EC). Four patients were excluded for variable reasons.

A clear reduction in TCSs was observed in the overall group. The results were better among patients with TCS-EC, 33% of whom became seizure free. A reduction of seizures of 50% and more could be attained in the overall group, with TCSs in about 60%. There was no effect in children with LGS; one third of them showed a serious increase in tonic seizures.

The results taken in conjunction with the measured serum levels and documented side effects probably call for a correction of the so-called therapeutic range, as given in the literature.

Our study encourages us to include bromides yet again in planning the treatment of patients suffering from "therapy-resistant" TCSs.

NEONATE WITH CLINICAL SEIZURES AND AN ELECTROENCEPHALOGRAM REMARKABLY ACTIVATED BY SLEEP

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This presentation describes a neonate with clinical seizures and an electroencephalogram (EEG) remarkably activated by sleep. In the first month of life, recurrent serial sleep-associated seizures persisted despite anticonvulsant therapy. No adverse prenatal or perinatal events were documented. While awake, the neonate's responsiveness was depressed, he was hypotonic, and there was a high-pitched cry. Nonetheless, he fed without difficulty, and seizures were not frequent during wakefulness. The waking EEG showed a low amplitude, mixed frequency background without paroxysmal features. Initially there was a pattern of burst suppression during sleep, with repetitive sharp waves discharging from central foci. Later, during sleep, intermittent seizures of bicentral origin would alternate with background suppression. Intravenous pyridoxine failed to suppress paroxysmal discharges; diazepam exacerbated central discharges. Infantile myoclonic seizures later developed, and ACTH therapy was given. Jackknife seizures were associated with generalized sharp and slow wave discharges and electrodecremental responses. However, hypsarrhythmia was not noted. Serial cerebral imaging revealed prominent progressive

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cerebral atrophy. Extensive biochemical investigation documented only elevation of serum lactate on several occasions. Studies of oxidative metabolism in fibroblasts were normal. At 18 months of age, the patient's development was profoundly delayed, and he was visually impaired, with spasticity and frequent seizures.

ROLE OF POSITRON EMISSION TOMOGRAPHY IN PEDIATRIC EPILEPSY SURGERY

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Positron emission tomography (PET) with 2-deoxy-2[18F]fluoro-D-glucose (FDG) was performed in eight infants and children (aged 18 days to 14 years) undergoing surgical treatment for medically refractory epilepsy. Of the eight subjects, three underwent left cerebral hemispherectomy, two had right cerebral hemispherectomy, and three underwent focal cortical resection. In all eight patients, the distribution of glucose metabolic abnormalities seen with PET correlated well with electrographic localization of seizure focus. Computed tomography (CT) and magnetic-resonance imaging (MRI), however, were abnormal in only four of the eight subjects. In all five children undergoing cerebral hemispherectomy, PET revealed diffuse hypometabolism in the affected hemisphere with a normal pattern in the opposite hemisphere. In one child, ictal PET revealed hypermetabolism in the left frontal cortex, left striatum, and right cerebellum; a left fronto-temporo-parietal resection was performed. One neonate had relative hypermetabolism in the right temporal and occipital lobes, and left frontal lobe on ictal PET; this infant underwent right occipitotemporal cortical resection.

Interictal PET in another infant showed right occipitoparietal hypometabolism; a right occipitoparietal resection was performed. Although the extent of resection in these three subjects undergoing focal excision was determined with the guidance of intraoperative electrocorticography, the distribution of epileptic tissue matched precisely that depicted by PET in all three cases. Neuropathological correlation revealed that PET is a sensitive test capable of detecting cytoarchitectural disturbances in all four cases where CT and MRI failed to show any abnormalities. In addition, PET provides a unique and important assessment of the functional integrity of brain regions outside the area of potential resection.

LOCAL CEREBRAL METABOLIC RATES FOR GLUCOSE IN CHILDREN FOLLOWING CEREBRAL HEMISPHERECTOMY FOR INTRACTABLE EPILEPSY

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Using positron emission tomography (PET) with 2-deoxy-2[18F]fluoro-D-glucose (FDG), we have shown that cortical local cerebral metabolic rates for glucose (LCMRGlc) reach adult rates by two years of age, are 2.5 times adult rates by four years, begin to decline by nine years, and reach adult values by end of the second decade. The period of excessive LCMRGlc corresponds in time with "overdevelopment" of neuronal connectivity, reflecting central nervous system (CNS) plasticity. Cerebral hemispherectomy (CH), which is being performed with increasing frequency in children for uncontrolled epilepsy, results in remarkably little functional deficit. We measured LCMRGlc in the remaining hemisphere following CH in four children, three of whom had preoperative PET studies. PET was performed in the awake resting state with eyes and ears open. The first child underwent CH at age 18 months; LCMRGlc for most brain regions exceeded normal values for age preoperatively, and normalized by 22 months. The second patient had CH at age 14 years; LCMRGlc were subnormal preoperatively but normal nine months later. The third child underwent CH at age four; LCMRGlc were lower than normal preoperatively, but exceeded (range: 67 to 93 μmol/min/100 g) normal range (52 to 66 μmol/min/100 g) three months after surgery. The fourth child had CH at age one; LCMRGlc values at seven years were normal for age. Both pre- and postoperatively, the relative distribution of LCMRGlc among anatomical structures was normal. These studies demonstrate that the normal tendency of LCMRGlc to exceed adult rates between three and 16 years is maintained in the remaining hemisphere following CH. In patient 3, the very high values of LCMRGlc postoperatively may reflect com-

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pensatory mechanisms for normal "overdevelopment" in the single hemisphere. Serial PET studies in children following CH provide a means of assessing CNS plasticity and may be of prognostic value.

DISCHARGES WITH HORIZONTAL DIPOLES IN EPILEPTIC CHILDREN'S ELECTROENCEPHALOGRAMS

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Principles of volume conduction, employing the solid angle and a cortical generator with a dipole, have been used to explain phase reversals in the surface electroencephalogram (EEG). With electrocorticography, the "true" phase reversals arising from a vertical generator in the depth of a sulcus have lent support to the solid angle hypothesis. But focal epileptiform discharges displaying the features of a horizontal dipole from a vertical generator are considered to be extremely rare in a surface EEG.

We reviewed the EEGs of one year at the Child Health Center in an EEG laboratory averaging 1,250 EEG studies annually. We found that 20 children with seizure disorders displayed focal discharges with features of a vertical generator. This represented 6% of all EEGs manifesting an epileptiform abnormality. The linear "Bipolar" anterior-posterior montage appeared to correlate least with the features suggested by the "Referential" montage to an ipsilateral ear which showed "true" phase reversal. In particular, when a vertical generator is suggested and the anterior-posterior "Bipolar" montage pointed to a "central" focus, the "Referential" and "Bipolar" transverse montages indicated that the generator lay closer to the midfrontal electrode site. The results of neuroimaging studies will be presented.

The finding of phase reversals on the "Referential" montage was surprisingly more frequent than expected, and the correlations described may be relevant to the choice of montages in long-term EEG recordings.

IS PYRIDOXINE DEPENDENCY AN INBORN ERROR OF METABOLISM IN GENETIC EPILEPSY?

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It is suggested that relative pyridoxine dependency is an inborn error of metabolism characteristic of genetic predisposition to epilepsy. Some clinical cases of early pyridoxine use for treating epileptic children (salaam convulsions, uncontrolled behavior of epileptic origin) are considered. It was found that epilepsy-prone and epilepsy-resistant BALB/c mice substrains (specially bred) differ widely from each other in their response to thiosemicarbazide as a pyridoxine antagonist. BALB/c epilepsy-prone offspring treated with pyridoxine (5 to 10 mg/kg in drinking water) during lactation and infancy are found to be highly tolerant to different convulsants. Multitolerance to convulsants accompanies changes in the composition of brain plasmatic membrane phospholipids (PL). Inositol decrease but phosphatidylserine and phosphatidylcholine increase are noted in pyridoxine-treated as compared to non-treated offspring. The changes in brain stem membranes are greater than those in cortical membranes. Modulation of PL-signalling mechanism is most pronounced under subconvulsive (30 mg/kg) pentamethylentetrazole loading. The implication of the early use of pyridoxine as a preventive treatment for children of families at high risk of epilepsy is discussed.

PAROXYSMAL BEHAVIORS MISTAKEN FOR SEIZURES IN THE NEUROLOGICALLY IMPAIRED CHILD

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From analysis of video electroencephalograms (EEGs) of children suspected of having seizures, we identified neurologically impaired children who had symptoms which were mistaken for seizures. This report demonstrates the usefulness of video EEG in the characterization of other neurologically abnormal behavior and its differentiation from true seizures.

The 17 patients ranged in age from one month to 13 years of age. Four patients were in coma. One patient

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was lethargic postictally. Twelve patients had moderate to severe mental retardation and motor disabilities.

All patients' EEGs were obtained with time-locked simultaneous video recording. The episodes included the following symptoms: six patients had abnormal eye movements; four patients stared; five patients had repetitive mouth movements; two patients had abnormal respiratory movements; eight patients had tonic posturing; two patients had coarse tremors; two patients had sleep myoclonus; and four patients had other symptoms (tics, dystonia, excessive startles).

Several videotapes will demonstrate that although these episodes clinically were suggestive of seizures, no temporal correlation existed between the abnormal behaviors and epileptiform activity.

SURGERY IN INFANCY FOR PARTIAL SEIZURES

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Surgical intervention for drug-resistant partial seizures improves long-term prognosis in older children and adults, but there is little experience with surgery performed very early in life. Although we rarely recommend surgery for epilepsy in infants, resective procedures for partial seizures have been performed in five infants under one year of age during a nine-year period. In all cases, the decision to offer surgery was heavily influenced by medical and psychosocial factors.

All infants experienced frequent (10 to 80/day) seizures resistant to multiple antiepileptic drugs (AEDs) at therapeutic dosages. ACTH and a ketogenic diet had been tried unsuccessfully with two infants. Clinical seizures consisted of tonic upper extremity posturing with versive head and eye movements. Clonic hand movements and myoclonus occurred in two infants. Neurodevelopmental status was normal in one infant, delayed in two and indeterminate in two because of concurrent medical illness and AED toxicity. Brain imaging studies demonstrated a localized structural lesion in two infants, bilateral lesions in one and nonspecific atrophy in two. Scalp video/electroencephalographic (EEG) recording of ictal and interictal activity revealed unilateral regional seizure discharges in four infants and bifrontal seizure discharges in one. Electrocorticography and preoperative subdural EEG recording further localized seizure onset and assisted in surgical planning.

Complete resection of the seizure focus was accomplished in three infants (frontal corticectomy and prefrontal lobectomy) and partial resections were performed in two infants (lateral temporal lobectomy, bifrontal corticectomy with anterior callosotomy). All specimens demonstrated confirmed pathological abnormalities. The three infants with complete resections are seizure-free after four, four and 14 months. Both infants with partial resections experienced a significant reduction in seizure frequency at four and six years. Surgery did not functionally impair any of the infants.

From these limited data, we conclude that surgery for medication-resistant partial seizures in highly selected infants is safe and is associated with considerable improvement in long-term seizure status. However, many issues relating to case selection and surgical planning still need to be resolved.

INFANTILE GELASTIC EPILEPSY WITH HYPOTHALAMIC LESIONS

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"Gelastic epilepsy" is a term broadly used to indicate a seizure disorder in which laughter represents a prominent ictal manifestation. It constitutes a specific syndrome when associated with hypothalamic lesions but laughing or smiling is also observed in complex partial, tonic, and myoclonic seizures. Thus, the term needs further definition.

We followed three patients with onset in early infancy who presented with small paramedian masses protruding from the ventral hypothalamus. These proved to be infiltrating gliomas in two patients. In the third patient magnetic resonance (MR) imaging also showed an abnormally enlarged amygdala suggesting hamartoma. Ictal electrographic features were generalized. Video monitoring of ictal events showed a diphasic pattern consisting of initial stereotyped laughter followed by tonic and myoclonic manifestations.

None of these subjects had hypothalamic dysfunctions though biopsy with partial removal of the lesion was followed by transient endocrine deficiency. Anticonvulsants were not effective. Surgery and radiation were modestly and transiently helpful.

We propose to reserve the term "gelastic epilepsy" to seizures starting with a peculiar nonmirthful laughter as

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the initial ictal manifestation. A ventral hypothalamic mass should be sought in this group of patients. Recent evidence suggests that various diencephalic structures are responsible for seizure generalization. The hypothalamic region may be closely connected with centers or pathways responsible for the motoric integration of laughter (but not its emotional content), and myoclonic/tonic manifestations may represent secondary generalization.

TEMPORAL LOBECTOMY FOR COMPLEX PARTIAL SEIZURES BEGINNING IN CHILDHOOD

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From 1972 to 1984 at The Children's Hospital in Boston, 34 patients underwent temporal lobectomy for medically intractable complex partial seizures beginning in childhood. Mean age at onset was 6.4 ± 4.6 years, and the age at surgery was 18.8 ± 6.3 years (mean ± SD). For statistical analysis, patients were divided into two groups: those completely seizure-free and those with persistent seizures. Two factors appeared important in rendering patients seizure-free: the duration of the epilepsy and the pathological findings. There was a significant correlation between long duration of the seizure disorder and poor outcome (P = .05). Mean duration of seizures for patients with successful surgery was 9.9 ± 6.2 years and for those with persistent seizures was 19.3 ± 8.0 years (mean ± SD).

Regarding pathological findings, there were 19 patients with tumors (56%), seven with atrophic lesions (20%), two with AVMs (6%), four with nonspecific changes (12%), and two with hamartomas (6%). Less satisfactory outcomes were associated with diffuse gliomas extending beyond the resection limit, or nonspecific pathological changes. In patients with tumors, worse outcome was associated with longer duration of seizures. These data suggest that relief from intractable seizures beginning in childhood will be easier to achieve if surgery is performed early.

TRANSIENT RETARDATION OF EARLY POSTNATAL GROWTH WITH NORMAL STATURE AT 5.5 YEARS IN DRUG-EXPOSED CHILDREN OF EPILEPTIC MOTHERS

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Early postnatal growth rate and height at 5.5 years were investigated in 132 full-term children of epileptic mothers and 103 control children. One hundred seventeen children had been exposed to antiepileptic drugs (AED) during pregnancy: 48 to phenytoin monotherapy, 16 to carbamazepine monotherapy, 24 to barbiturates (all except one combined with phenytoin and/or carbamazepine), 27 to other combinations (excluding barbiturates) with phenytoin and/or carbamazepine, and two to other drugs. Maternal drug levels were available in 93% of the pregnancies, and were usually within or below the low reference range. The mean length increment of the AED-exposed children in the first postnatal month was significantly smaller than that of the nonexposed children of epileptic mothers or control children. The effect was seen in all AED-exposed subgroups. A normal growth rate was resumed by the second month. Weight gain in the first month was significantly reduced only in the barbiturate-exposed subgroup. The differences were not explained by birth measures, nutritional status at birth or feeding method. We suggest that the transient slowing of linear growth rate observed in the AED-exposed children results from a reversible suppression of the thyroid hormone system in the fetus and the newborn. The weight lag in the barbiturate-exposed subgroup was probably caused by feeding problems due to sedative drug effects. No permanent effect on growth was noted as the mean height at 5.5 years was normal in both the AED-exposed and nonexposed group.

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COMPARATIVE BIOAVAILABILITY OF CARBAMAZEPINE TABLETS, CHEWABLE TABLETS AND SUSPENSION

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Carbamazepine (CBZ) has a narrow therapeutic range, and bioavailability differences between dosage forms would have dramatic clinical consequences. We have compared the tablet (T), chewable tablet (C) and suspension (S) formulations from one manufacturer. In 10 volunteers, a single 200 mg dose of CBZ-T was compared to CBZ-C in a randomized crossover design. No differences between formulations were found for Ke, T_{max} and AUC. A statistically significant but clinically insignificant difference was observed in C_{max} (3.81 ± 0.81 *v* 4.64 ± 0.80 mg/L) with CBZ-C. CBZ-T was compared to CBZ-S in 18 epileptic children, ages two to 12, who were taking CBZ chronically in a randomized, double blind crossover design following two weeks of continuous dosing with each formulation. The total daily dosage was given bid with CBZ-T and tid with CBZ-S. CBZ-S had a significantly faster T_{max} (1.5 ± 0.8 *v* 3.7 ± 1.1 hour), but there were no differences in AUC, C_{max}, C_{min} or C_{max}/C_{min}. Power analysis revealed that the sample size was adequate. It is concluded that CBZ-T and CBZ-C may be interchanged. CBZ-S has comparable bioavailability to CBZ-T but has a more rapid rate of absorption. Therefore, the total daily dose of CBZ-S and CBZ-T will be the same after individualization of therapy, but CBZ-S should be given at least tid to avoid wide fluctuations in CBZ concentrations. These factors and the intra- and intervariability of CBZ absorption should be considered in selecting and choosing dosage forms and manufacturers.

IMPROVED CONTROL OF SEIZURE CLUSTERS WITH RECTAL DIAZEPAM AND LORAZEPAM

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Patients with poorly controlled childhood epilepsy frequently experience clusters (> two seizures/day) despite optimal medical management. These clusters often lead to emergency medical evaluation and/or hospitalization. Rectally administered benzodiazepines (BZDs) are rapidly absorbed and effective in aborting seizures. We used diazepam (DZM) ($n = 5$) or lorazepam (LZM) ($n = 2$) in seven patients with multiple seizure types, who ranged in age from three to 12 years. All patients were maintained on conventional antiepileptic drug therapy. The BZD was administered after the second seizure of the day in doses of 2.5 to 10 mg (0.1 to 0.54 mg/kg) for DZM and 0.6 to 0.76 (0.03 to 0.04 mg/kg) for LZM. Duration of treatment ranged from seven to 24 months, with a frequency of administration from once every four months to 10 times per month.

Response to treatment was evaluated retrospectively by chart review and questionnaire. All families felt that clusters were more easily controlled. Frequency of emergency room visits decreased by at least 50%. Three patients have required no further hospital admissions. Side effects were limited to drowsiness and short-term irritability. Tolerance was reported in one patient.

Home use of intermittent rectal BZDs may help to limit urgent medical treatment. This therapy affords parents a feeling of greater control and a more active role in their child's treatment. A prospective study is indicated.

RAPID INTRAVENOUS PHENOBARBITAL LOADING AND CARDIOVASCULAR STATUS

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We have previously reported that phenobarbital (PB) administered in sequential bolus doses is effective for the control of seizures in the newborn. This technique rapidly achieves serum concentrations of 40 μg/mL. Barbiturates, however, are generally regarded as having deleterious effects on cardiovascular (CV) status, making many clinicians reluctant to administer doses sufficient to achieve this serum level. To evaluate the effect of PB on CV status, we measured blood pressure (BP) and heart rate (HR) responses to PB infusion in 11 newborns (gestational ages 29 to 39 weeks). Subjects received 15 to 20 mg/kg of PB over a

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period of at least five minutes at infusion rates which did not exceed 25 mg/minute. This administration was repeated at 15-minute intervals until serum PB concentrations were between 60 and 100 mg/L. This occurred within 60 minutes. There were no adverse cardiovascular sequelae. Mean BPs prior to and after PB administration were 62/33 and 63/36 mmHg, respectively. Mean HR prior to and after PB administration was 151 bpm and 147 bpm. There were no significant differences between these values ($P < .1$ paired t test). These findings suggest that administration rate rather than serum concentration is responsible for the CV changes associated with PB infusion. It is also possible that CV instability associated with rapid drug administration is mediated by the delivery of high concentrations of propylene glycol. Graded intravenous loading of PB, however, appears devoid of cardiovascular toxicity even at serum concentrations of 60 to 100 mg/L.

TEGRETOL MALABSORPTION: A CASE REPORT

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Carbamazepine (CBZ) is commonly used to control generalized and complex partial seizures in children and adults. It is well tolerated, effective by oral administration, and lacks the unpleasant cosmetic and cognitive effects associated with phenytoin administration. Although its gastrointestinal absorption is slow and erratic, its bioavailability is usually high (75% to 85%). The fact that children often require higher dosages and achieve lower serum CBZ concentrations than adults suggests that children are "fast metabolizers". This presumption usually forms the basis for justifying high dosages in this population. We now demonstrate the first documented case of Tegretol (CIBA-GEIGY) malabsorption in a six-year-old Hispanic boy with intractable epilepsy. His seizure disorder began neonatally and consisted of tonic and myoclonic seizures with a multifocal paroxysmal electroencephalogram. Anticonvulsant therapy at the time of evaluation consisted of CBZ and primidone. Steady-state serum concentrations remained low (4.3 μg/mL) despite dosages of up to 85 mg/kg/day. Examination of the patient's feces revealed a whole 200 mg Tegretol tablet as well as some smaller pieces. These specimens were retrieved and shipped to CIBA-GEIGY Laboratories (Summit, NJ) for analysis and subsequently confirmed as their product. The intact tablet contained approximately 200 mg of CBZ. The patient was placed on low dose Tegretol chewable tablets, and the dosage was slowly increased to 57 mg/kg/day. Serum CBZ concentrations increased to a steady-state value of 9.4 μg/mL.

Our patient's circumstances underscore the need to distinguish between disorders of CBZ absorption and metabolism. This distinction could avoid potential drug toxicity if absorption patterns or drug preparations should change. Furthermore, a trial of chewable tablets should be considered for patients with serum CBZ concentrations which are persistently lower than expected.

SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY: SEIZURES AND RAGGED-RED FIBERS

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Succinic semialdehyde dehydrogenase deficiency (SSDD) is characterized clinically by nonprogressive ataxia, muscular hypotonia, psychomotor retardation, and seizures. The biochemical hallmark is the presence of gamma-hydroxybutyric acid (GHBA) in urine, serum and cerebrospinal fluid. We report, with video recordings, the clinical, biochemical and muscle biopsy features of a brother and sister with SSDD. Both children were the products of a nonconsanguineous relationship. They presented in infancy with profound hypotonia, psychomotor retardation and ataxia. Initial generalized akinetic seizures occurred at 20 months in the female, who was the older. Her initial electroencephalogram (EEG) showed diffuse bilateral slowing; follow-up interictal EEGs have been normal; diffuse atrophy was demonstrated on computed tomography (CT) scanning. The male child, who was the younger, had a generalized tonic-clonic seizure at 18 months, but interictal EEGs have been normal. Increased levels of GHBA were detected at six years and 20 months respectively. The diagnosis of SSDD was confirmed by decreased activity of lymphocytic SSDD; parental en-

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zyme activity was compatible with carrier status. Muscle biopsy specimens taken at two years in the female sibling showed evidence of myopathy with ragged-red fibers; the male sibling, who underwent biopsy at four months, had evidence of a nonspecific myopathy. The clinical features described, together with a review of the world literature, confirm that SSDD is inherited as an autosomal recessive disorder. Seizures occur with SSDD and may be related to disordered gamma-aminobutyric acid metabolism. To our knowledge, myopathy with evidence of ragged-red fibers has not previously been described in SSDD.

CLINICAL STUDY OF EPILEPTIC CHILDREN WITH FREQUENT SEIZURES

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The subjects were 98 children with an average age of 5.8 years. Their frequent seizures were categorized into the following groups: (1) seizures developing more than five times a day; (2) one to four seizures developing every day for one week or more; (3) one to four seizures a day developing weekly for one month or more.

The 98 patients were distributed as follows: 15.3% in group 1; 16.3% in group 2; 17.3 % in group 3; 43.9% in group 1+2; 4.1% in group 1+3; 3.1% in group 2+3. Tonic seizures (TS) were noted in 10.2% of the patients, simple partial seizures (SPS) in 12.2%, complex partial seizures (CPS) in 8.2%, absence seizures (AS) in 6.1%, minor seizures (MS) in 10.2%, tonic-clonic seizures (TCS) in 10.2%, unilateral seizures (US) in 7.1%, infantile spasms (IS) in 20.4%, and Lennox-Gastaut syndrome (LGS) in 15.3%.

We frequently observed cases of TCS in group 1, IS in group 2, SPS in group 3, and MS, IS, and LGS in group 1+2. Abnormal computed tomographic findings were observed in 37.8%. Of all the patients, 33.7% indicated DQ above 80, and 31.6% showed DQ under 30. Of 96 patients followed for the past one year or more, 32.3% (consisting chiefly of patients with AS and IS) had no seizures; 60.4% (chiefly patients with LGS, TS, US, SPS and CPS) continued to have seizures.

SELECTION FOR EPILEPSY SURGERY: SPECT SCANNING WITH ^{99}Tc-HM-PAO COMPARED WITH CLINICAL ELECTROENCEPHALOGRAPHIC AND NEURORADIOLOGICAL CRITERIA

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A prospective study of 25 children (16 girls, nine boys) with intractable epilepsy used SPECT scanning with ^{99}Tc-HM-PAO, which provides qualitative assessment of regional cerebral blood flow (rCBF) patterns. All patients had detailed clinical and electroencephalographic (EEG) examinations, computed tomography and magnetic resonance imaging, or cerebral angiography.

Mean age of patients was 8.8 years, (range, 11 months to 17 years). All had partial seizures on antiepileptic drugs, nine with and 12 without structural abnormalities, and four with secondarily generalized seizures.

Among the most common SPECT findings were a regional decreased rCBF with or without a focal increased rCBF, although normal scans were occasionally seen. Ictal and immediate postictal SPECT scans showed focal increased rCBF with or without regional decreased uptake. These SPECT findings showed a high correlation with scalp/sphenoidal EEG abnormalities: focal increased rCBF with epileptiform focus, and regional decreased rCBF with slow-wave disturbance of background activity. Pathological diagnoses in six patients included mesial temporal sclerosis (two), chronic focal encephalitis, Sturge-Weber, astrocytoma and unilateral megalencephaly (one each).

In the presurgical assessment of children with medically intractable epilepsy, SPECT scanning with 99Tc-HM-PAO can reveal abnormalities in rCBF that correlate well with seizure localization by clinical and EEG studies and may contribute to evaluation for surgical excision.

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TEMPORARY INTERRUPTION OF BENZODIAZEPINES FOR INTRACTABLE CHILDHOOD EPILEPSY

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Benzodiazepines (BZD) are thought to be among the most effective drugs for epilepsy, but they often become ineffective after long-term administration. We attempted drug holiday therapy with this class of drug for intractable childhood epilepsy. Thirteen epileptic patients, aged from three to 11 (mean, seven) years, whose seizures responded previously to a BZD, were included in this study. Eight cases were categorized as Lennox-Gastaut syndrome, three others as secondary generalized epilepsy, and two as partial epilepsy. Most patients had daily seizures; some had weekly seizures. The BZD was gradually decreased and eliminated from the antiepileptic formula during one or two weeks, and was readministered two to 10 days after cessation of the drug. Seizures were completely controlled for more than three months in four cases (excellent). Seizures decreased to less than 50% for more than one month in three cases (moderate), and this effect persisted for less than one month in five cases (poor). No effect was observed in one case. The periods of the drug holidays were 7, 8, 10 days and one year in excellent responders; 2, 6, and 7 days in moderate responders, 2, 3, 4 and 7 days in poor responders, and two days in the one unresponsive case. The effectiveness of this therapy may be related to the length of the drug holiday. This therapy should be considered for intractable seizures which have previously responded to benzodiazepines.

ABSENCE STATUS EPILEPTICUS CHARACTERIZED BY REPETITIVE ASYMMETRIC ATONIA: TWO CASES ACCOMPANIED BY SYLVIAN SEIZURES

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Two cases of absence status epilepticus characterized by repetitive asymmetric atonic episodes are presented. The patients were seven- and nine-year-old girls whose seizures started at three and seven years of age, respectively. Both had combined types of seizure including unilateral sylvian seizures and atonic absence. Interictally, each had contralateral rolandic spikes with increased frequency during sleep. They had no remarkable family history. Their neuropsychological development was normal except for slightly diffuse brain atrophy on computed tomography in the younger girl. Status in both patients consisted of discontinuous atonic absence, which was asymmetric and predominant in an upper limb, and was associated with simultaneously appearing diffuse spike and wave discharges with contralateral rolandic predominance on the electroencephalograms (EEGs). Moreover, on ictal EEGs during the status, their diffuse discharges were not symmetrical, since each predominant discharge almost always appeared first. In addition, the discharges in the ipsilateral rolandic area appeared later than those in other areas of the same hemisphere.

The asynchronization of the epileptic discharges in the bilateral hemispheres may be associated with the clinical symptom such as asymmetric atonia. This phenomenon suggests that the cerebral cortex plays an important role in the mechanism causing absence seizures in these cases.

DYSTONIC POSTURING IN COMPLEX PARTIAL SEIZURES: A NEW LATERALIZING SIGN

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Videotapes of 131 complex partial seizures (CPS) from 37 patients were reviewed blind without knowledge of electroencephalographic data. Thirty-one patients were seizure-free after temporal lobectomy. Unilateral dystonic posturing of an arm or leg was identified in 29 CPS from 13 patients. The dystonic posturing was contralateral to the side of seizure onset in 26/29 CPS. In the other three seizures from one patient, the ictal discharge switched from the left to the right temporal lobe, at which point contralateral dystonic posturing was noted. Subdural recordings in 7/29 seizures showed ictal discharge mainly in the basal temporal lobe with minimal spread to the cerebral convexity during the dystonic posturing. The posturing lasted a mean of 28 seconds and occurred during the first half of the seizure in two-thirds of the seizures. During the posturing,

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unilateral hand automatisms were seen in 22/29 seizures on the side opposite the dystonic limb. Version occurred in 8/29 seizures to the same side as the dystonic posturing.

Unilateral dystonic posturing is a reliable lateralizing sign in temporal lobe CPS. It may be generated by spread of the ictal discharge to deeper brain structures such as basal ganglia.

EPILEPSY IN CHILDREN IN RURAL KASHMIR INDIA

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A rural population of 63,645 living in a mountainous valley (Kuthar Valley) of South Kashmir, northwest India, was surveyed to determine the prevalence of major neurological disorders including epilepsy (called lath/mirgi/laran in the local language). The survey was made according to WHO protocol (1981). The diagnostic criteria of Hauser and Kurland (1975) were considered in cases of active epilepsy, and cases were classified according to ILAE (1981) on the basis of clinical data. In this population, 157 cases (95 males, 62 females) of active epilepsy were detected, for a crude prevalence rate of 2.47/1000.

Of these cases, 84 (56 male, 28 female) were under 14 years of age, for a prevalence rate of 3.18/1000. Mean age at onset was 2.77 years in males and 2.92 years in females. Mean duration of occurrence of seizures was 3.04 years in males and 4.71 years in females. Generalized seizures were found in 84.52%; 70.19% were receiving no antiepileptic drugs; 98.81% had been born in home delivery; 23.8% had associated mental retardation; and 7.14% had infantile hemiplegia.

REFLEX EPILEPSY EVOKED BY MENTAL ACTIVITY AND EPILEPSIA ARITHMETICES

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Decision making as a form of reflex epilepsy is rare. Epileptiform discharge evoked by mental arithmetic is very rare. Only two cases of electroencephalographic (EEG) abnormalities arising in the nondominant hemisphere have been reported. We report the case of an 18-year-old right-handed woman with a three-year history of attacks of strange feelings occurring spontaneously or triggered by thinking. The last fit terminated in automatic behavior and secondary generalized crisis. Five years previously, while playing, she experienced a loss of consciousness after right carotid compression. On EEG recording, an epileptiform activity appeared over the right frontotemporal area, while the patient was attempting difficult mental calculations. Complex mental tasks activated a right frontotemporal spike-and-wave focus. Full wakefulness and relaxation did not evoke any pathological activity, nor did sleep-EEG and hyperventilation. Paroxysmal discharges were not related to visual, tactile or auditory stimuli. No clinical events were registered during the different activation procedures. The patient's disease is well controlled by carbamazepine therapy.

We believe that the rareness of the case justifies further research for the sake of better understanding the mechanism underlying reflex epilepsy.

"NOT-SO-BENIGN" FAMILIAL NEONATAL SEIZURES: AN AUTOSOMAL RECESSIVE CONDITION

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We report three siblings, the only children of normal unrelated parents, all of whom experienced intractable seizures in the neonatal period. The seizures were apparent immediately after birth and were first noted in the delivery unit. Continuous spontaneous and stimulus-sensitive generalized or focal myoclonic jerks or shifting focal clonic movements were observed. The electroencephalogram (EEG) showed rhythmic central sharp waves on one occasion, but was usually normal despite persistent clinical seizures. The first born, a girl, was felt to have intractable seizures due to hypoxic ischemic encephalopathy. She died on the fourth day of cardiovascular collapse while on a ventilator. In the other two children, both males, the seizures persisted for the first three to four months of life; they gradually lessened both in frequency and amplitude of movement until they were observed only following a stimulus. From six months in one, and 19 months in the other,

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complex partial seizures developed, and their EEGs showed epileptic discharges of temporal lobe origin. Both children experienced at least one episode of status epilepticus in the second year. Both children, now at three and five years, are mildly mentally retarded. All investigations in the neonatal period were negative. Computed tomographic brain studies, TORCH and metabolic studies, and both intravenous pyridoxine 150 mg and an eight-week trial of oral pyridoxine 50 mg daily were unhelpful. This condition is to be distinguished from the more common autosomal dominant benign familial neonatal seizures and also from the more recently described "fifth day fits".

PATHOLOGY OF LESIONS RESECTED DURING SURGERY FOR INTRACTABLE SEIZURES OF PEDIATRIC PATIENTS

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Thirteen pediatric patients (1.5 to 17 years old) underwent surgical therapy for medically refractory seizure disorders at the UCLA Center for the Health Sciences during the years 1986 and 1987. Procedures performed included five total hemispherectomies, three subtotal hemispherectomies, four anterior temporal lobectomies and one corpus callosotomy. Pathologic studies of the surgically resected material were available on 12 of the patients. All total hemispherectomy resection specimens were characterized by extensive gliosis but with different patterns. In two specimens, large glial cysts were identified. A third resection specimen was characterized by extensive multifocal cortical gliosis with areas of status spongiosis. The remaining specimens contained areas of hamartomatous astrocytic proliferation. Three of the lesions also contained areas of loss of the normal cortical laminar architecture suggestive of a congenital malformation. Included in this latter group is one of the specimens with a large glial cyst which contained distinct areas of heterotopia in cortical areas remote to the cyst. Pathologic examinations have been completed on two of the three subtotal hemispherectomy specimens and revealed a large porencephalic cyst in one while the other appeared to be grossly normal. In spite of a normal gyral-sulcal pattern and normal gray-to-white-matter ratio, microscopic examination revealed areas of indistinct cortical laminar layering with large malaligned neurons containing clumped basophilic fibrillary material in the cytoplasm. These did not appear to be neurofibrillary tangles on Bielschowsky stain. Lesions identified in patients undergoing temporal lobectomy included two gangliogliomas with ganglioneuromatous differentiation, a grade II astrocytoma, and a porencephalic cyst. The corpus callosotomy was undertaken for seizures related to a previously resected oligodendroglioma.

DISSEMINATED CYTOMEGALOVIRUS IN A PATIENT WITH INFANTILE SPASMS TREATED WITH ACTH

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Congenital cytomegalovirus (CMV) infection has been implicated as a cause of infantile spasms. It has been demonstrated that CMV-specific cell-mediated immunity and interferon production are deficient in congenitally infected infants. ACTH, which is widely used in the treatment of infantile spasms, is known to cause immunosuppression. A case is presented of a child with suspected congenital CMV infection who died of disseminated CMV infection during ACTH therapy. The benzodiazepines have also been reported to be of benefit in treatment of infantile spasms. The mechanism of action of these medications is not known, but both ACTH and the benzodiazepines inhibit release of corticotropin releasing factor (CRF) from the hypothalamus. The resultant reduction in synthesis of proopiomelanocortin from the pituitary may serve as a common mechanism for the effect of these drugs on this condition. Valproic acid would also inhibit CRF release, and this might have a role in the management of infantile spasms. The risk of disseminated CMV infection in congenitally infected infants would appear to deter the use of ACTH. Use of benzodiazepines or, perhaps, valproic acid may be advisable in this group of infants.

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CLINICAL AND ELECTROENCEPHALOGRAPHIC CHARACTERISTICS OF CHILDREN WITH COMPLICATED FEBRILE SEIZURES

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Although complicated febrile seizures (CFS) (i.e., focal, prolonged, or multiple) represent 20% of febrile seizures (FS), and may be predictive of a future nonfebrile seizure, little attention has been focused on characteristics of children with a CFS that distinguish them from those with a simple FS. In a prospective study of 158 children with FS, 37 (23%) had one or more complicated features, including 15 focal, 20 multiple (more than one seizure in 24 hours), and seven prolonged (>25 minutes duration); five had two features each. These were age-matched to a random control population of 37 children with a simple FS, and compared for the following: sex, abnormal birth history, positive seizure history in parents/siblings, intake of possible seizure-precipitating medication in the 24-hour period prior to ictus, immediate postictal electroencephalographic (EEG) abnormalities. All had normal milestones/neurological examinations. Statistically significant findings were that more females had a focal component, and more males had multiple FS (80% *v* 33%, $P < .02$, and 85% *v* 50%, $P = .02$, respectively). No differences were demonstrated for abnormal birth history, including fetal distress, prematurity, primary cesarean section, eclampsia, breech, or nuchal cord (14 study/12 controls); prior sympathomimetic/antihistamine intake (9 study/8 controls); abnormal EEG (3/36 in study, 18 done within 24 hours of ictus; 2/34 controls, 23 within 24 hours); positive family seizure history (febrile: 11 in each group; nonfebrile: two study/0 control).

Thus, children with CFS had similar clinical and EEG characteristics compared to those with a simple FS. The cause of the male/female difference in focal and multiple FS is uncertain and merits further study.

A COMPARATIVE MONOTHERAPY TRIAL IN CHILDHOOD EPILEPSY

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The good prognosis for monotherapy in newly diagnosed epileptic patients is well established, and large scale comparative trials of efficacy and toxicity with different major anticonvulsant drugs have been undertaken. There is very little information on this subject for childhood epilepsy. We have undertaken a randomized, comparative trial of monotherapy with phenobarbitone, phenytoin, carbamazepine and valproate in 140 children aged three to 16 years with newly diagnosed epilepsy. Children were classified according to seizure type and the presence of additional handicaps. They were randomly assigned to a small dose of the starting drug, increasing into therapeutic blood level range if necessary. The mean duration of follow-up is 2.3 years (range, 0.5 to 5.8 years). Four percent have been lost to follow-up. In 10%, the starting drug was discontinued because of toxicity. This included six of the first 10 children treated with phenobarbitone. Phenobarbitone was therefore withdrawn from the study. Forty-three children were randomly assigned to carbamazepine, 42 to valproate and 45 to phenytoin. The overall value of monotherapy in children is similar to that in adults. Data on the comparative efficacy and toxicity of the drugs and on prognosis will be presented.

EPILEPSY WITH INDEPENDENT, MULTIFOCAL EPILEPTIFORM DISCHARGES IN CHILDREN

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Nineteen epileptic children showing more than one epileptic firing in at least two successive electroencephalograms (EEGs) were studied for an analysis of their clinical EEG, critical and intercritical condition and their longitudinal evolution. The results permitted us to define a malignant form of childhood epilepsy

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with precociously acquired brain lesions, characterized by frequent seizures with predominance of primitive patterns of fundamentally tonic type, severe neuropsychomotor impairment and independent multifocal spikes between seizures. We discuss the relationship of this form of epilepsy with other secondary generalized forms of epilepsy, such as West syndrome (hypsarrhythmia), and Lennox-Gastaut syndrome (slow spike-waves). We also discuss the benign character, multifocal EEG pattern in patients without multiple and/or bilateral structural modifications. On the basis of our findings and of a critical review of the literature, we conclude that patients with West and Lennox-Gastaut syndromes exhibit forms of partial epilepsy differing from that of our patients only in the diffuse character of the EEG discharges.

We propose that for this condition the following terminology be used: "malignant childhood epilepsy with independent multifocal spikes."

Etiologic Factors in Acquired Childhood Epilepsy

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We studied etiologic factors in a population of epileptic children treated at the Children's Neurology Clinic of the Faculty of Medicine of Botucatu, UNESP, Sao Paulo, Brazil, in 1985 and 1986. Patients' ages ranged from three months to 15 years. All etiologies were considered except genetic ones. A clinical history and electroencephalogram were obtained on each patient. The study population consisted of 197 well documented cases. The probable etiologic factors identified in 43.15% of the cases were neonatal anoxia, 43.57%; low birthweight for gestational age, 11.76%; cerebrospinal infections, 11.76%; intracranial calcifications, 8.23%; central nervous system malformations, 5.80%; head and skull injury, 5.80%; prematurity and anoxia, 4.70%; traumatic delivery, 2.35%; and other factors, 3.52%. Etiology could not be determined in 56.85% of cases. An outstanding feature was birthweight, which was one of the most frequent causes of acquired epilepsy, reflecting the socioeconomic conditions for our country, where prenatal and nutritional care are deficient. Partial type seizures were the most frequent (59%) and are traditionally considered to be due to organic or lesional etiology, reflecting an important factor of brain injury, even though etiology cannot be determined in many cases. We believe that in the present study, the possible etiologic factors identified as causes of acquired childhood epilepsy could be prevented if basic preventive programs were instituted.

Central Sensory Dysfunctions in Baltic Progressive Myoclonus Epilepsy

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Baltic progressive myoclonus epilepsy (PME), a degenerative form of PME of unknown etiology and clinically similar to Unverricht-Lundborg disease, is found particularly in Finland. In this study we demonstrate multimodal evoked potentials in Baltic PME. Thirteen ambulatory patients (16 to 35 years of age) and seven more severely affected patients (26 to 49 years) were studied by four-channel median nerve somato-sensory (SEP), pattern-reversal visual (VEP), and brain-stem auditory evoked potentials (BAEP). All patients received conventional anticonvulsant medication for PME and were cooperative.

In SEPs, enhanced cortical amplitudes were seen in ambulatory but not in more severely affected patients. Cortical peak latencies and especially the central conduction time (interpeak N20-N13) were progressively prolonged. VEPs showed symmetrical and progressive latency prolongations in the presence of normal electroretinograms. VEP amplitudes and shapes of responses were normal. Slight prolongations of interpeak I-V were seen in BAEPs in both patient groups. SEP and VEP latencies correlated with the clinical stage of the disease: the more severe the clinical stage, the more the latencies were prolonged.

In conclusion, multimodal dysfunction in impulse conduction along the central sensory afferent pathways was seen in Baltic PME. It cannot be explained by a drug effect, and it is suggested that it reflects interictal cortical hyperpolarization in Baltic PME.

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INTERACTION OF ZONISAMIDE WITH BENZODIAZEPINE AND GABA RECEPTORS IN RAT BRAIN

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The effects of zonisamide on ^{3}H-flunitrazepam binding and ^{3}H-muscimol binding were studied in Sprague-Dawley rat brain. The percent specific ^{3}H-flunitrazepam bound was decreased to 64.6 ± 5.6 and 91.9 ± 4.0% (mean ± SD, $n = 5$) by 10^{-3} M and 10^{-4} M of zonisamide, respectively. Scatchard analysis of the saturation study of ^{3}H-flunitrazepam binding with 10^{-3} M of zonisamide revealed an increased K_d with no change in B_{max}. No effect of zonisamide was seen on the enhancement by gamma-aminobutyric acid (GABA) of specific ^{3}H-flunitrazepam binding. As for the effects on GABA receptors, the percent specific ^{3}H-muscimol bound was decreased to 27.7 ± 10.4 and 68.3 ± 3.7% (mean ± SD) by 10^{-3} M and 10^{-4} M of zonisamide, respectively.

On the other hand, ^{3}H-zonisamide was found to bind in a saturable fashion in the crude synaptosomal fraction of whole rat brain. Linear regression analysis of the binding data in the Scatchard plot indicated a K_d of 90 nM, and a B_{max} of 1.40×10^3 fmol/mg protein. Competition studies revealed an inhibitory effect of clonazepam on specific ^{3}H-zonisamide binding. The enhancement effect of GABA was also seen on specific ^{3}H-zonisamide binding. These results suggest that the specific binding sites of zonisamide may have something to do with benzodiazepine and GABA receptors in rat brain.

IMMUNOLOGIC DISTURBANCE IN WEST AND LENNOX-GASTAUT SYNDROMES AND IN EPILEPSY WITH INDEPENDENT MULTIFOCAL SPIKES

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Cell-mediated and humoral immunity was investigated in 50 children with West syndrome, Lennox-Gastaut syndrome, epilepsy with independent multifocal spikes, and in 29 healthy controls. The test group consisted of patients aged between four months and 18 years, and the control group of children aged between two months and 18 years. Immunologic tests were planned to avoid interference with ACTH therapy. The study included determination of T and B peripheral blood lymphocytes, serum levels of IgG, IgA and IgM, skin sensitization with 2-4-dinitrochlorobenzene (DNCB), intracutaneous phytohemagglutinin (PHA), leucocyte migration inhibition test and lymphocyte blastic transformation in presence of PHA. In 44 of the patients, there was deficiency in cell-mediated immunity; in 17, immunoglobulin plasma levels were decreased. High levels of IgM and IgG were detected in 27 patients. Immunologic disturbances were more prominent in children with West syndrome. Our results also demonstrated that the impairment of cellular and humoral immunity varies from patient to patient. The degree of depression of cellular and humoral immunity was found to correlate with the patient's predisposition to infection. It is remarkable that cutaneous reaction to DNCB was the more sensitive parameter to detect immunodeficiency in our patients. A prospective study was performed in 22 patients, with yearly evaluations, the total periods of survey ranging from 11 months to eight years. No normalization of immunologic disturbances was noted.

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ELECTRODIAGNOSIS OF BALTIC PROGRESSIVE MYOCLONUS EPILEPSY

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Baltic progressive myoclonus epilepsy (BPME) is an inherited form of generalized epilepsy found predominantly in Finland. Its clinical features are characterized by stimulus-sensitive myoclonus, generalized tonic-clonic seizures, ataxia, intention tremor as well as a mild mental retardation. In this study, we demonstrate our experience with the typical electrophysiological findings in BPME. The electroencephalogram (EEG) is always abnormal in BPME. Generalized multi-spike wave discharges are common, especially during photic stimulation (PS). EEG also shows disturbance of background activity, which progresses during the course of the disease. Markedly increased theta power in spectral EEG is common for patients with a mild BPME. Myoclonus occurs spontaneously, but it is exacerbated significantly during PS and active movement. Myoclonic jerks usually occur without simultaneous spikes in EEG. Evoked potentials show a multimodal dysfunction of both the central sensory and visual pathways in BPME. Enhanced cortical somatosensory evoked potentials are seen in mildly affected patients but not in more advanced cases. ENMG and histopathological studies have shown occasional neuropathic changes in BPME. In conclusion, BPME has characteristic electrophysiological abnormalities which are helpful both in the differential diagnosis of the patients and in assessing deterioration associated with the disease.

INDUCED ELECTROCEREBRAL SILENCE FOR REFRACTORY STATUS EPILEPTICUS

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Refractory status epilepticus refers to continuous seizure activity which persists for more than six hours despite maximal dosages and therapeutic levels of at least three first-line anticonvulsants. Termination of convulsive status is critically important since continued electrical status epilepticus, even in the paralyzed patient receiving ventilation and oxygen, can result in cerebral cell death with neurologic sequelae or death of the patient.

Twelve pediatric patients (seven males and five females, ages three to 19 years) with refractory status epilepticus were treated with continuous infusions of short-acting anticonvulsants (thiopental, diazepam, lorazepam or midazolam) titrated to a physiologic end-point of appearance of an isoelectric tracing on a standard, continuously monitored electroencephalogram (EEG) at 2 μV sensitivity. The continuous infusion anticonvulsant was then titrated to maintain a burst-suppression to isoelectric tracing for 48 to 72 hours. Throughout the treatment period, the patient was maintained paralyzed and mechanically ventilated with continuous hemodynamic and respiratory monitoring.

The refractory status epilepticus was successfully terminated in all cases, although three patients required a second 48- to 72-hour induced electrocerebral silence period to terminate the status epilepticus. Two patients never regained consciousness after the termination of their status epilepticus and died six to eight weeks later. Both of these patients had been in status epilepticus for more than two weeks before successful treatment.

We believe that induced electrocerebral silence is an effective means of terminating refractory status epilepticus. The agent used to induce electrocerebral silence is less important than the physiologic end-point of burst-suppression to isoelectric EEG, which is then maintained for 48 to 72 hours.

WEST AND LENNOX-GASTAUT SYNDROMES AND OTHER EPILEPSIES WITH PORENCEPHALIC CYSTS

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At present, porencephalic cysts can best be demonstrated by computed tomography. Usually they result from perinatal cerebral thrombosis or hemorrhage, most often in the territory of the middle cerebral artery. Primarily neurologic deficits (such as hemiparesis) are combined with severe, often intractable epileptic seizures, as in the West syndrome, the Lennox-Gastaut syndrome, or other partial epileptic seizures.

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In cases of therapy-resistant seizures and/or generalized epileptic discharges in the electroencephalogram (EEG) (i.e., especially hypsarrhythmia and slow spike-wave paroxysms) we treated 17 patients in our clinic by neurosurgical intervention. This involved uncapping the cyst and fenestration to the lateral ventricle, though there were no displacing signs.

Almost all operations resulted in a very impressive improvement of the epileptic condition but less clearing of the motor deficits. As a result, for treatment of patients with West or Lennox-Gastaut syndromes, we would prefer surgical intervention to long-term therapy with ACTH or steroids. The long-term follow-up of the patients is documented by EEG and case reports.

COGNITIVE AND BEHAVIORAL EFFECTS OF ANTIEPILEPTIC DRUGS IN CHILDREN

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Cognitive effects (CE) and behavioral effects (BE) of antiepileptic drugs (AEDs) are known in adults, but few long-term comparative studies have been performed in children. CE and BE were compared in six-to-16-year-old children receiving chronic monotherapy with phenobarbital (PB), phenytoin (PHT) or carbamazepine (CBZ) and alternative AEDs at three centers. Subjects and controls were evaluated on the basis of AED levels, hematology, chemistry, electroencephalogram, neuropsychological, educational and clinical examinations, and behavior ratings by parents and/or teachers. Factors currently evaluated include baseline AED *v* final CBZ visit, parent/teacher Connors total score, parent global opinion, continuous performance task (CPT) reaction time, omission errors and commission errors, color naming, finger oscillation, WISC-R digit span, Knox cube, and digit vigilance time and errors. In comparing PB or PHT with CBZ treatment in 36 subjects, significant improvement was found on parent Connors score, digit vigilance errors, finger oscillation, color naming and CPT reaction time; also approaching significance were Knox cube and digit vigilance times. Thus with each subject serving as his or her own control, significant improvement was noted in comparing initial PB or PHT therapy with final CBZ visit in behavior, motor speed, reaction time, cognitive flexibility and impulsivity. There was no significant decrement on any test, but specific children showed variable areas of improvement, and individualized testing is necessary. Data from nearly 70 patients and controls will be reported.

"DIAPER CHANGING" EPILEPSY

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Reflex epilepsies have previously been described for many modalities of sensory stimuli, particularly in adults. Somatosensory stimuli are less commonly associated with seizures although the latter have been associated with hot water. An 18-month-old infant with developmental delay and a history of infantile spasms and myoclonic seizures in the first year of life began having frequent partial and generalized tonic seizures every time his diaper was changed. The electroencephalographic (EEG) pattern during this event showed rhythmic 8 Hz generalized activity arising out of high voltage slow background activity and was accompanied by clinical seizure. Videotape and EEG will be demonstrated, and response to therapy discussed.

VALPROATE THERAPY DEPRESSES FREE RADICAL SCAVENGING ENZYME ACTIVITY: A MECHANISM FOR INDUCTION OF ACUTE PANCREATITIS OR HEPATOTOXICITY

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Based upon our studies of free radical scavenging enzyme activities (FRSEA) in patients treated with valproic acid and other antiepileptic drugs (AED), we

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propose valproate (VPA)- induced acute pancreatitis and hepatotoxicity are directly related to decreased FRSEA. We quantitated the enzymatic activity of glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), glutathione transferase (GST), glutathione reductase (GSSR), and catalase in red blood cells (RBC) of epileptic patients receiving different AED combinations. Whole blood trace element concentrations of selenium (Se), copper (Cu), zinc (Zn), and manganese (Mn) were quantitated. Results were as follows with all enzyme activities expressed as mean ± SD in U/g Hb, and trace elements mean ± SD in μg/dL. Control ($n = 20$): GSH-Px 35.4 ± 3.8, Se 15.9 ± 1.6, SOD 2527 ± 269, Cu 93.0 ± 11.0; carbamazepine ($n = 26$): GSH-Px 33.7 ± 7.0, Se 13.1 ± 2.4 ($P < .05$), SOD 2410 ± 216, Cu 97.1 ± 15.5; phenytoin ($n = 22$): GSH-Px 35.7 ± 8.4, Se 13.1 ± 2.4 ($P < .05$), SOD 2381 ± 212, Cu 100.3 ± 21.7; valproic acid ($n = 13$): GSH-Px 30.1 ± 6.9 ($P < .05$), Se 11.1 ± 3.5 ($P < .001$), SOD 2288 ± 139 ($P < .001$), Cu 71.3 ± 13.3 ($P < .05$).

Results demonstrate that VPA mono- or polytherapy causes significant decreases in both GSH-Px and SOD activity which we suggest is secondary to total body store depletion of Se and Cu (the cofactors necessary for maximal GSH-Px and SOD activity) during VPA therapy. The FRSEA in VPA-treated patients operate at a significant deficit. When at any time during AED therapy the patient's body burden of free radicals is increased, the FRSEA become saturated and cannot compensate for the increased free radical production, free radicals are not scavenged, and cellular membrane damage occurs, precipitating acute pancreatitis or hepatotoxicity. We conclude the routine measurement of GSH-Px and SOD can be used to identify those patients at risk for VPA- induced idiosyncratic toxicity. We postulate patients receiving VPA therapy should receive supplementary trace elements to compensate for enhanced trace element clearance and decreased FRSEA.

"SHENG" AND "STEP" SHAPE OF ELECTROENCEPHALOGRAPHIC SPECTRUM IN PATIENTS WITH TYPICAL AND ATYPICAL ABSENCES

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Electroencephalographic (EEG) and spectral changes of 49 absence seizures from 10 patients and EEG and spectral changes with bursts of less than 2.5 Hz (atypical absence) were studied from four patients. EEG and spectral analyses were performed on an Alvar Reega 2000 for routine EEG, and Cartovar 2000 for numeric values of each Hz of 16 electrodes and their power spectra. Durations of 3 Hz spike-and-wave complexes were from four seconds to 27 seconds. In spectral parameters, the highest peak was in 3 Hz, then there were peaks in frequency of 6, 9, 12, 15, 18, 21, 24, 27, and 30 Hz, but in lower and different heights, which formed a "sheng" shape. "Sheng" is the Chinese name of a reed pipe wind instrument made of bamboo. This form of spectrum is quite different from the power spectra of the EEG of atypical absence which manifested as a "step" shape. The highest power was in 1 Hz, then in 2 Hz, etc., and looked like a "step". The patterns are so characteristic that they can easily be differentiated from each other and may be of some help in certain difficult cases.

ENDOCRINE COMPLICATIONS OF ACTH THERAPY OF INFANTILE SPASMS

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At the end of conventional ACTH therapy of infantile spasms, sudden deterioration of the infant's condition and even death are not rare. We followed 10 infants during and after carboxymethylcellulose ACTH therapy. Eighty IU was given at 8 a.m. for three weeks and 40 IU for two weeks, with tapering during therapy and termination at the end of the sixth week. During therapy, 24-hour urinary cortisol level increased 100-fold, morning plasma cortisol level did not increase, and plasma aldosterone level decreased slightly. After

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therapy, cortisol and AVP levels fell precipitously, with cortisol level remaining subnormal for more than two weeks. Plasma renin and aldosterone levels peaked abruptly. Urine flow decreased and body weight increased sharply. Plasma cortisol response to AVP remained decreased for more than two weeks. Plasma cortisol response to ACTH was shortened at three days and diminished at one to two weeks, indicating suppression of ACTH secretion. The risk at the end of ACTH therapy appears to be associated with (1) sudden subsidence of cortisol hypersecretion resulting in hypocortisolism and hypomineralocorticoidism; (2) abrupt activation of the renin-angiotensin-aldosterone axis subsequent to the hypomineralocorticoidism; and (3) impairment of water excretion subsequent to the hypocortisolism.

CORPUS CALLOSUM SECTION IN THE CHILD: A PROPOSED PROTOCOL

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Four children underwent corpus callosotomy to improve their seizure control. The children were aged three to 15 years (mean, 8.5 years), with medically intractable, secondarily generalized seizures (mean duration 5.4 years). All four patients had more than one seizure type (tonic, atonic, myoclonic, atypical absence, complex partial, and generalized tonic-clonic). All had histories of convulsive/nonconvulsive status epilepticus; three of the four had repeated episodes of status requiring frequent emergency treatment.

All patients had multifocal interictal epileptiform abnormalities with epileptiform fast or electrodecremental ictal electroencephalographic expression for the tonic seizures. The extent of callosotomy was dictated by the intraoperative transformation of epileptiform discharges from bilaterally generalized to lateralized as the section progressed from anterior to posterior. Two of the four patients had total corpus callosum sections verified by magnetic resonance imaging. No significant postoperative complications were experienced.

Generalized tonic drop attacks were reduced by more than 90%. (Preoperative *v* postoperative seizure frequency/month: patient #1, 70 *v* 2; patient #2, >200 *v* 0; patient #3, 1500 *v* 20; patient #4, 60 *v* 5; $P <$ .01.) Other seizure types were also dramatically improved postoperatively. No patient has experienced status epilepticus postoperatively. This information, combined with the adult experience of over 50 cases of corpus callosotomy at Minnesota, has resulted in a model protocol for variable corpus callosotomy. The model for the pediatric patient will be presented.

EPILEPTIC ACTIVITY OF THE OCCIPITAL LOBE

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We have analyzed the course of illness in 11 patients whose common electroencephalographic (EEG) characteristic was epileptiform activity in the occipital area. The first group comprised patients who presented bilateral amaurosis. In three of these cases, the occipital hypersynchronous EEG activity was merely a secondary symptom of ischemic hypoxia or of a degenerative process in the occipital visual cortex, and was not responsible for genesis of the actual blindness. In two further cases of monosymptomatic temporary loss of vision, it was difficult to make a differential diagnosis between ictal blindness (associated with status epilepticus amauroticus occurring in an occipital lobe epilepsy) and a migraine attack involving the basilar area. The second group comprised three patients with paroxysmal visual hallucinations of elementary type (illusions). In the only patient belonging to the third group, whose seizures were characterized by motor phenomena in the field of the ocular organs and tonic lateral movement of the bulbi of the eyes and the head, an occipital epileptic crisis with spread of discharges from the occipital lobe to the frontomesial surface should be assumed. The occurrence of complex partial seizures (generalized tonic-clonic attacks) in two patients of the fourth group, who had definite epileptiform EEG-activity in the occipital area, can be explained by a propagation of paroxysmal activity to the temporal lobe or to the motor cortex. This study illustrates the heterogeneity of clinical manifestations among patients with occipital epileptiform activity.

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PHARMACOKINETICS OF LORAZEPAM IN CRITICALLY ILL NEONATES WITH SEIZURES

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Our group recently conducted a pilot study of lorazepam in seven critically ill neonates with seizures. Cessation of seizure activity was achieved in all patients within five minutes, although seizures subsequently recurred in two patients. No apparent adverse side effects were seen. These results prompted the current study of the pharmacokinetics of lorazepam in neonates. Five severely asphyxiated infants with seizure activity have been studied thus far. After receiving informed consent, lorazepam 0.05 mg/kg IV was given as a one-time dose. Lorazepam levels were obtained at 0, 0.5, 1, 12, 24, 48 and 72 hours following injection. The results of data analysis indicate a mean distribution $t_{1/2}$ of 1.3 hours (n = 3 patients). The mean elimination $t_{1/2}$ was 31.7 hours (n = 5 patients). Treatment with other anticonvulsants such as phenobarbital and phenytoin did not appear to affect the pharmacokinetics of lorazepam.

STATUS EPILEPTICUS, INTRACRANIAL PRESSURE, AND COMPUTED TOMOGRAPHY FINDINGS

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A fifteen-year-old boy with an uneventful medical history presented with a generalized convulsive status epilepticus. Treatment was partially successful, but an epilepsia partialis continua persisted. Within six months, two periods of generalized convulsive status epilepticus recurred; during the last period, the patient died. This patient showed temporary hypodensities on the computed tomography scan, corresponding to local maximal epileptic discharges.

Apart from this, it was noted that epileptic discharges during a generalized "convulsion" (the patient was paralyzed, ventilated and sedated) caused a significant rise in intracranial pressure with a serious drop of the cerebral perfusion pressure.

During life a definitive cause of this patient's severe epilepsy was not established. Neuropathologic examination revealed an intensive pathological process, almost entirely confined to the cerebral cortex, suggestive of Alper's disease.

PEDIATRIC COCAINE INTOXICATION AND GENERALIZED SEIZURES

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Clinical evidence in adults and experimental evidence in rats have linked cocaine use to the occurrence of seizures. We report three pediatric patients, one infant and two adolescents, who presented to our emergency room with a first-onset afebrile seizure and whose routine urine toxicology screens were positive only for cocaine. Their seizures were all generalized, brief convulsive fits. There was no clinical evidence for intravenous drug abuse. The ages of these neurologically normal patients made onset of idiopathic epilepsy quite unlikely. No other possible etiology for the seizures was found except that in one of the adolescent patients, theophylline toxicity was also present. No seizures have recurred in the one patient who has returned for follow-up. Since substance abuse is widespread among our patient population and is frequently denied, toxicology screens during the last six months have been obtained routinely on our pediatric patients who present with the first afebrile seizure. With the ever increasing widespread use of illicit drugs, especially crack, a high index of suspicion of substance abuse, even by proxy, is required in the acute evaluation of a first-onset afebrile seizure, especially outside the idiopathic epilepsy age group. It has been suggested that cocaine may be the causative agent for seizures in pediatric patients; and at the very least it seems very likely that the abuse of some substance (if not cocaine) was responsible for these patients' seizures.

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PERTUSSIS IMMUNIZATION AND THE ONSET OF EPILEPSY AND FEBRILE CONVULSIONS

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There is some agreement that febrile seizures may occur with pertussis immunization, but controversy exists regarding the relationship to epilepsy. Prior to April 1, 1970, children in Denmark received diphtheria, tetanus and pertussis vaccine (DTP+Pol) at five, six, seven, and 15 months of age. Starting April 1, 1970, and continuing to the present, children have received monovalent pertussis vaccine at five and nine weeks and at 10 months of age. The diphtheria-tetanus vaccination continued at five, six and 15 months. Change in the pertussis vaccination schedule allowed a retrospective epidemiologic study examining the relationship of the time of onset of neurologic disorders with the time of pertussis immunization in two populations of children who received pertussis immunization at different ages. The charts of 2,743 children, aged 0 to 24 months, with febrile convulsion or epilepsy were reviewed, 1,153 from the period prior to change in pertussis immunization, and 1,666 after that time. Six hundred and ten cases of epilepsy with onset between 28 days and 24 months of age were reviewed; 318 were in the first period and 292 in the second. There was no relationship between the age of onset of epilepsy and the scheduled age at administration of pertussis vaccine. Of the 2,209 subjects with febrile seizures entered into the second study, 835 were in the first period, and 1,374 in the second. There was a very clear association between febrile seizures and the scheduled age of administration of pertussis vaccine ($P = .004$).

In this study, pertussis immunization was statistically related to the occurrence of febrile seizures but was not related to the onset of epilepsy.

FOCAL CENTRAL NERVOUS SYSTEM LESIONS AS A CAUSE OF INFANTILE SPASMS

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Infantile spasms are known to have many etiologies but a common pattern of seizures, electroencephalographic (EEG) abnormalities and a poor prognosis for development. The prognosis is improved if the seizures are controlled early. We present five children with infantile spasms who had focal lesions in the central nervous system (CNS) as the cause of the seizures. The focal lesions were discovered only after intensive study of some of the patients.

The five infants (four girls, one boy) had the onset of seizures at one to eight months of age. All had typical infantile spasms associated with either hypsarrhythmia or modified hypsarrhythmia. Three of the infants had focal seizures that predated the infantile spasms by one to four months. Treatment terminated the infantile spasms in all cases, but other seizures persisted. Computed tomography (CT) was definitely abnormal in only one case, a child with a porencephalic cyst; two others had enlarged lateral ventricles. Magnetic resonance (MR) imaging provided no additional information. Positron emission tomography revealed focal abnormalities in all five cases; four had supratentorial/cortical lesions, and one had a hypothalamic hamartoma. Focal EEG abnormalities were observed in three cases. Four of the patients' seizures are controlled at this time. Two are controlled with medical therapy, two required surgery. One had a focal resection; the other had hemispherectomy.

We conclude that infantile spasms may be the result of focal CNS lesions. Focal lesions may be present even with normal or nonspecific CT and MR studies. In children with infantile spasms, aggressive work-up is indicated to demonstrate focal abnormalities which may be surgically remediable. This is especially true if there is asymmetry in the seizures or EEG. Positron emission tomography may demonstrate focal abnormalities even when CT and MR do not.

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THERAPY OF INFANTILE SPASMS WITH SODIUM VALPROATE

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In a controlled study, 22 children with recently manifested infantile spasms (symptomatic, 18, idiopathic, four) were treated with sodium valproate (VPA). Prior to the application of VPA, a loading test (gas chromatography and mass spectroscopy) was performed with this agent for detection of abnormal patterns of VPA metabolites in serum and urine. VPA was then applied in increasing dosage until infantile spasms were controlled or a maximum dose of 100 mg/kg/day was reached. If VPA did not at least reduce seizure frequency significantly after a trial of four to six weeks, dexamethasone was added to VPA. In case of focal seizures, carbamazepine was given in addition to VPA. After three months of therapy, 16 children were free of seizures (VPA monotherapy, 14); in four further patients, seizure frequency was reduced to less than 25%. VPA dosages ranged between 40 and 100 mg/kg/day (mean, 74). After six months of therapy, seizure control was reached in 20 of 22 patients (VPA monotherapy, 16). There were seven relapses in six children during the first seven months of therapy. Mean observation time was 16.5 months (range, six to 36 months). Adverse effects included transient symptoms of gastrointestinal distress and/or sedation early in therapy. Muscle hypotonia was noticed in nearly all children. Thrombocytopenia purpura occurred in seven children, chiefly in association with an upper respiratory tract infection, and disappeared after dosage reduction.

This study shows that VPA monotherapy in high dosage is effective for treatment of infantile spasms.

FOCAL EPILEPTIC ACTIVITY DURING INDUCED SLEEP IN THE SECONDARY LENNOX-GASTAUT SYNDROME

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In the present report we describe the localization, morphology and frequency of focal epileptic discharges during induced sleep in children with secondary Lennox-Gastaut syndrome. Patients were examined monthly over periods of time varying from one to nine years. On each visit, patients were given electroencephalographic examination during phases II and III of sodium secobarbital-induced sleep. Of the 15 patients studied, three had no focal epileptic activity. Eleven patients showed more than one type of discharge during follow-up. Spikes and sharp waves were the most common findings. We found no reports of regions of higher incidence of focal discharges in patients with Lennox-Gastaut syndrome. Our study showed that the regions most often involved were the central, parietotemporal, temporal, parietal, occipital and parasagittal regions, in decreasing order of frequency. Of the epileptic activities recorded in our patients, the most frequent was spike. We noted that the different discharges occurred preferentially in definite regions: spikes in the central regions, sharp waves distributed uniformly, and spike-wave complexes mainly in the parietotemporal regions. Focal epileptic discharges are not a constant occurrence, but are present during certain phases of evolution and disappear during others. Over successive examinations, and sometimes even during the same examination, focal discharges change their site of occurrence. The present study was conducted in order to demonstrate that the secondary Lennox-Gastaut syndrome can be considered a form of secondarily generalized multifocal epilepsy.

USE OF CROSS CORRELATION IN THE DISPLAY OF PAROXYSMAL EVENTS IN CHILDHOOD ABSENCE EPILEPSY

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Electroencephalographic (EEG) correlates of epileptic seizures vary in regard to their scope as well as in regard to their topographic distribution. Visual analysis is limited by the delay caused by the writing system, the pen time line alignment and especially by the chart speed. In addition, these paroxysmal EEG correlates often are of such structural complexity as far as time and topography are concerned that visual analysis is overtaxed. Classification in categories, therefore, orients itself on prototypal patterns of the EEG. Complexity is not sufficiently taken into consideration, particularly regarding the dynamic of paroxysmal changes. For these reasons, a computer-assisted software package

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using cross correlation techniques has been developed, which examines and quantifies paroxysmal changes. Absence seizures usually are associated with a bilaterally synchronous and symmetrical discharge of rhythmic spike and wave complexes. This paroxysmal activity occurs bilaterally, beginning abruptly and synchronously in both hemispheres. The spike-waves have the same shape and amplitude at homologous leads in the two hemispheres. They have their highest amplitude under the fronto-central leads. The frequency of the spike-wave complexes is three per second at the beginning of the discharges and may slow to 2.5 to two per second towards the end. An identifying characteristic of "fast spike-wave" discharges for particular patients was noted as well as many individual variations from patient to patient. The relative amplitude of the spike-waves, the leads which are first involved (usually the anterior ones), and the shapes of the patterns vary.

First results of mapping the time/space relationship of paroxysmal EEG-events as well as of inter- and intraindividual variation will be presented.

USE OF FAMILY THERAPY IN THE TREATMENT OF PSEUDOSEIZURES

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Psychological seizures that are unconsciously produced (pseudoseizures) have been described as difficult to diagnose and more problematic to treat. The issue of pseudoseizures in adolescents is further complicated because the patient is embroiled in a difficult developmental transition, which often can lead to further helplessness and depression.

Pseudoseizures are fraught with helplessness. Such feelings in physicians may lead to anger at and rejection of the patient. Family helplessness in providing for the child can lead to anger at the medical establishment; and the helplessness of the patient leads to anger at the world and/or depression.

Because of the multiplicity of feelings generated by this illness, families frequently "shop" from neurologist to neurologist when a possible psychological aspect of the illness is suggested. This is due, to a great extent, to the desire of the family to find a physical reason for pseudoseizures, and a long history of denying underlying tension and avoiding conflicts. The family then becomes increasingly frustrated and rigid at the time of the initial psychosocial interview. For all these reasons, they require support, understanding and immediate direction regarding the role of seizures in the family group.

Family therapy is effective in treating pseudoseizures since it aids in addressing unresolved conflicts while redeveloping family confidence. Family therapy provides an opportunity to demonstrate dramatically the correlation between seizures and the stress causing them, while developing parental understanding of emotional boundaries and individual growth. Thus, a greater sense of differentiation between parent and child can evolve along with an extinction of the symptom (pseudoseizure).

THE SIGNIFICANCE OF ELECTROENCEPHALOGRAPHY IN FEBRILE CONVULSIONS

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A series of 1,500 children admitted consecutively to one pediatric department with a first febrile convulsion will be presented. Electroencephalography (EEG) has been performed one month, one year and two years after the first convulsion. These results have been correlated to perinatal history as well as to circumstances around the febrile convulsion.

The presentation will concentrate on the correlation between EEG results and family history of febrile convulsion and/or epilepsy and the possibility of a later development of epilepsy.

ALTERNATE-DAY NITRAZEPAM THERAPY IN MYOCLONIC AND ASTATIC SEIZURES

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Nitrazepam (NTZ) has been effective in the treatment of some patients with myoclonic, astatic, and atypical absence seizures as well as in infantile spasms. Recurrence of seizures has been observed in up to 30% of those with an initial response to NTZ, and increasing dosages have raised the frequency of toxicity.

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We have studied five patients, 11 months to 25 years of age, with myoclonic and astatic seizures, three of whom had Lennox-Gastaut syndrome. Prior to starting on NTZ, these patients had received various antiepileptic drugs including ACTH, valproic acid (VPA) and clonazepam (CZP), without long-lasting beneficial effects.

NTZ was begun as an alternate-day regimen in two patients; the other three received daily doses for two, four and 12 months respectively before they were switched to the alternate-day plan. The NTZ dose was 0.15 to 0.9 mg/kg/day in two to three divided doses given every other day. At the onset of NTZ therapy, two patients had high therapeutic levels of carbamazepine and VPA, and two had high therapeutic levels of VPA and CZP respectively. One patient was taking VPA and phensuxamide. These drugs were continued during NTZ treatment.

A 50% to 100% reduction in seizure frequency occurred within one to three months of NTZ treatment in all patients and has continued for six to 24 months.

We have found that alternate-day NTZ therapy is effective in some patients with myoclonic and astatic seizures and that it may help to avoid the development of tolerance to the drug and hence allow longer-term efficacy.

Impact of Antiepileptic Drugs on Cognitive Function in Children

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Although many variables in epilepsy, including site and frequency of seizures, age at onset of seizures, and severity of seizures, obviously have an impact on cognitive function, in recent years the role of anticonvulsant drugs has become of importance. Many studies in adults have now been carried out, showing that polytherapy is more likely to impair cognitive abilities than monotherapy, but that differences exist between the anticonvulsants in monotherapy. The main contrasts are between the more deleterious effects of phenytoin and phenobarbital, and the minimal effects of carbamazepine. In this paper, results from recent studies in children will be presented. Four groups of children have been examined, two control groups (one with and one without epilepsy), a group of children with increases in anticonvulsant dosing and a group with decreases in such dosing. Automated presentation of psychological tests was performed, and children were tested on three occasions, the first session being before drug changes and the second two following change at three and six months respectively. Results from these studies will be presented, as will information derived from this study on differences between children on polytherapy and monotherapy, and between children on carbamazepine or sodium valproate monotherapy. It is concluded that, in general, the results obtained in adults also apply to children with regard to the effect of anticonvulsant drugs on cognitive function.

Epileptiform Electroencephalographic Activities at the Centromedian Thalamic Nuclei in Patients with Generalized Seizures

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Centromedian (CM) epileptiform electroencephalographic activities were recorded in children and adolescents with nonconvulsive and tonic-clonic generalized seizures. Through implanted recording-stimulating electrodes used for seizure control, CM epileptiform activities were consistently correlated to widespread surface cortical activities and clinical symptoms. Unilateral CM double-spike complex discharge preceded, continued through and lasted the duration of the contralateral CM and bilateral surface cortical discharges and symptoms of the fully developed nonconvulsive generalized seizures. Unilateral CM fast-slow-fast paroxysmal discharges preceded and continued through those of the contralateral CM and bilateral surface cortical regions at the onset; while sharp-slow wave complexes at both CM and surface were recorded together at the clonic phase of the convulsive tonic-clonic generalized seizures. Individual spike-wave complexes from the surface frontal region, however, preceded those at CM and other cortical regions during the nonconvulsive and clonic generalized seizures.

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MYOCLONIC EPILEPSIES IN THE FIRST YEAR OF LIFE

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Since Chevrie and Aicardi reviewed convulsive disorders in the first year of life (*Epilepsia* 18, 1977), interest in their study has steadily grown because of the great incidence of epilepsy during this period of life.

Although valuable advances have been achieved in the classification of seizures, epilepsies and epileptic syndromes, convulsive disorders of infancy pose several problems in classification since some of them are still being defined. This is the case with myoclonic epilepsies of infancy; therefore, attempts to deepen our knowledge of their clinical features and evaluation of their relevance seem worthy.

From a population of epileptic children with seizure onset during the first year of life, those affected with myoclonic seizures have been selected and their follow-up reviewed. The clinical, electroencephalographic, radiologic, biochemical and therapeutic aspects of eight patients with idiopathic or secondary myoclonic seizures have been analyzed in order to identify aspects of relevance to clinical classification, neuropsychological evaluation, and prognosis in such matters as seizure evolution and response to treatment. Myoclonic seizures are far from being a single entity. It is of the utmost importance to delineate the spectrum of syndromes and recognize the prognosis they imply for the afflicted children.

EARLY ONSET THERAPY OF INFANTILE SPASMS

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Early detection has proven crucial for the mental prognosis of infants with infantile spasms (IS), which may be missed in symptomatic cases with preexisting retardation. Additional mental deterioration resulting from late detection and delayed implementation of effective therapy may then be falsely attributed to the underlying cerebral lesion. An approach for identifying infants at risk for IS of presumed pre- or perinatal etiology by neonatal polygraphic tracing was established.

Polygraphic tracings of 549 high-risk newborns (1976–1980) were retrospectively reevaluated: the tracings of the 25 newborns with later manifest IS could be described by a compound electroencephalogram (EEG)-risk score comprising six bioelectrical and two behavioral items. If at least four out of these eight items scored positive, IS developed in every single case. In 1981–1982, the risk score was prospectively applied to the polygraph tracings of 378 newborns; IS was correctly predicted in 12 infants. There was no false positive or negative prediction. From 1983 on, we started early onset of ACTH-therapy in 35 infants with informed consent of parents on the following conditions: at least two polygraphic tracings with positive risk score, evolution of behavioral symptoms which might be early seizure symptoms, and lack of contraindications.

Infants with EIEE are no longer included in this approach. With other infants, developmental outcome at the end of the first year of age is promising; with early onset of therapy, more than half reach a developmental quotient above 50 as compared to 10% treated with conventional onset therapy.

REGIONAL BRAIN DISTRIBUTION OF CARBAMAZAPINE IN KAINIC ACID-INDUCED SEIZURES IN RATS

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Kainic acid (KA)-induced seizures in rats are a model of limbic seizures in humans. Carbamazepine (CBZ) is effective for the treatment of limbic seizures. The association between concentrations of CBZ in brain regions and antiepileptic effects is unknown. Female Wistar rats were given CBZ 40 mg/kg IP mixed with either 15 mg/kg KA ($n = 20$) or saline control ($n = 5$). At 90 minutes after treatment, five KA-treated rats without obvious behavioral seizures, five KA-treated rats with seizures, and five control rats were killed. Blood and six brain areas (cortex, brain stem, cerebellum, thalamus, hippocampus, striatum) were collected. Concentrations (mg/L) were measured by EMIT (Syva).

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There was a significant difference ($P < .05$) in CBZ serum levels between seizure-free, KA-treated rats (38.1 ± 12.9) and control rats (19.2 ± 11.3), but there was no difference in serum CBZ in KA-treated rats with or without seizures. There were also significant differences ($P < .05$) in hippocampal CBZ between KA-treated, seizure-free (9.7 ± 1.5), KA-treated with seizures (5.5 ± 0.7) and control groups (5.1 ± 3.5). These data suggest that hippocampal CBZ levels in KA-treated rats are more reliable indicators of antiepileptic effect than serum levels of CBZ. Since the focus of KA-induced convulsions is in the hippocampus, the sites of CBZ action may also be in the hippocampus. Variation in brain distribution may be related to differences in antiepileptic effects in rats or humans.

TRIAL OF ANTIEPILEPSIRINE IN CHILDREN WITH EPILEPSY

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Antiepilepsirine (AES) is a new antiepileptic drug (AED) first derived from a Chinese folk remedy, now chemically characterized and synthesized. Its chemical structure is different from those of presently available AEDs. Animal experiments demonstrate significant activity for AES, but there have been few clinical studies.

A 6.5 month, add-on, double blind, placebo (Pbo)-controlled, randomized, crossover study was conducted in 58 epileptic children (aged one to 14 years) whose disease was refractory to treatment with current AEDs. Seizure frequency was recorded, and blood was obtained for measurement of AES and AED serum levels.

A total of 34 children completed the study (parents of 24 children refused the crossover). Seizure control is summarized in the table below:

		Controlled		Partial		No Effect	
Seizure Type	n	AES	Pbo	AES	Pbo	AES	Pbo
Tonic-clonic	21	5	3	10	5	6	13
Partial + polytype	13	0	0	0	3	10	10

There was a significant difference in seizure frequency between AES and placebo ($\chi^2 = 4.71$, $P < .05$) for the 21 patients with tonic-clonic seizures. There were no differences between serum levels of other AEDs and no serious side effects were observed despite AES dosages as high as 10 mg/kg/day. AES shows promise as a new AED.

CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDIES OF POSTENCEPHALITIC EPILEPSY

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We reviewed records of 62 patients with acute encephalitis admitted to our institution during 1975 to 1987 and examined the correlation between clinical and laboratory findings during the acute phase and postencephalitic epilepsy. Three subgroups emerged from the states after the acute phase; group I: 17 cases with seizures; group II: nine cases without seizures who showed electroencephalographic (EEG) seizure discharges; group III: 36 cases without seizures who showed no EEG seizure discharges. The age of onset ranged from 23 days to 14 years 11 months (mean age, five years). The duration of follow-up was six months to 10 years, average one year 10 months. The infecting organism was identified in 19 patients. Convulsions during the acute phase were observed in 100% of patients in group I, 88% of those in II and 73% of those in III, while status epilepticus was found in about half the patients in I and only 23% in III. There was no fixed relationship between cerebrospinal fluid abnormalities and postencephalitic epilepsy. EEG seizure discharges during the acute phase were almost three times as frequent in I and II as in III. The final follow-up EEG showed negative spikes in 76% of patients in I, 100% in II, but 0% in III. General and focal slowing of activity was also found most frequently in patients in I. The type of seizures after the acute phase in I were six cases with generalized tonic-clonic, two with Lennox-Gastaut syndrome and nine with partial seizures. Convulsions and EEG seizure dis-

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charges during the acute stage were the most significant prognostic sign of postencephalitic epilepsy.

RELATIONSHIP OF VALPROATE DOSE AND 3 HZ SPIKE-AND-WAVE COMPLEXES IN PATIENTS WITH ABSENCE SEIZURES

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The aim of the study is to evaluate the relationship between a valproate dose and 3 Hz spike-and-wave (S-W) complexes. We reviewed electroencephalographic recordings of 18 patients (eight male; 11 female) with absence seizures before and after taking sodium valproate. Ages ranged from four to 11 years. The duration of 3 Hz S-W complexes was between two and 37 seconds. The number of bursts ranged from two to 15. The dosage of valproate which controlled the clinical seizures and suppressed the bursts of 3 Hz S-W complexes was from 10 to 47 mg/kg, or 0.3 to 0.8 g/day. It was seen that the dosage needed for controlling the clinical seizures has no relationship with the duration and number of 3 Hz S-W complexes. The dosage of valproate for absence seizures control in the majority of our cases was 20 mg/kg; in only four cases was more than 30 mg/kg required. It appears that in Chinese patients with pure absence seizures the dosage of valproate needed is lower than that in Caucasians.

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