

## New antiepileptic drugs

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**N**EW medications are the best hope for tens of thousands of patients in the United States—and many more worldwide—for control of their epileptic seizures. Only a few patients whose disease is currently refractory to available medications can be considered for surgical intervention; other nonmedical therapies such as bio-feedback appear to have a similarly limited role. This paper examines a few of the issues related to the development of new antiepileptic drugs (AEDs) and considers some of the data on the most important of these new compounds. Current therapy has been reviewed in detail elsewhere.<sup>1,2</sup>

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### EARLY ANTIEPILEPTIC DRUGS

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In the nineteenth century, bromides were widely used as antiepileptic agents. In the United States, the modern history of AEDs begins in 1912 with the introduction of phenobarbital, a synthetic sedative-hypnotic drug which was shown to reduce seizure frequency (*Table 1*).<sup>3</sup>

As it proved to be more effective and less toxic than potassium bromide, phenobarbital soon became the drug of choice. Since the barbituric acid molecule is easily modified, many analogues of phenobarbital were synthesized, of which approximately 50 were marketed in the first 35 years of this century. One of these analogues, mephobarbital, demonstrated good antiepileptic activity and was marketed in the United States in 1935.<sup>4</sup>

In the absence of experimental models of seizures

that could be used to test anticonvulsant activity, the discovery of the antiepileptic effect of bromide and phenobarbital was serendipitous. Later, with the development of seizure models, the search for new AEDs was based on scientific screening programs.

The year 1937 marked the beginning of the experimental evaluation of promising anticonvulsant chemicals prior to clinical use. Employing a seizure model based on a new electroshock technique for producing convulsions in animals,<sup>5</sup> Merritt and Putnam<sup>6,7</sup> screened a group of compounds supplied to them by Parke-Davis and discovered the anticonvulsant properties of phenytoin, then called diphenylhydantoin. Because phenytoin was well tolerated by laboratory animals, it was subjected to clinical trials in 1938 and marketed that same year. The absence of a sedative effect and the dramatic control of seizures observed when phenytoin was added to barbiturate therapy were the key factors in its rapid marketing. In addition, its entry into the market was not delayed by regulatory requirements, since at that time the introduction of new drugs was controlled by the Federal Food and Drugs Act of 1906, which mandated that drugs be accurately labeled but required proof of neither safety nor efficacy.<sup>8</sup>

The reliability and quantitative capacity of Merritt's method demonstrated the feasibility of testing new chemicals for anticonvulsant activity.<sup>4</sup> Administration to humans, a more costly, time-consuming, and risky procedure, was reserved for the most effective experimental compounds that emerged from animal testing programs. In addition, the process through which phenytoin came onto the market demonstrated that academic investigators could work successfully with the pharmaceutical industry, encouraging a relationship that flourished for the next 20 years.

In 1944, Richards and Everett<sup>9</sup> reported that trimeth-

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**TABLE 1**  
ANTIEPILEPTIC DRUGS MARKETED IN THE UNITED STATES

| Year Introduced | International Nonproprietary Name | U.S. Trade Name | Company     |
|-----------------|-----------------------------------|-----------------|-------------|
| 1912            | phenobarbital                     | Luminal         | Winthrop    |
| 1935            | mephobarbital                     | Mebaral         | Winthrop    |
| 1938            | phenytoin                         | Dilantin        | Parke-Davis |
| 1946            | trimethadione                     | Tridione        | Abbott      |
| 1947            | mephénytoin                       | Mesantoin       | Sandoz      |
| 1949            | paramethadione                    | Paradione       | Abbott      |
| 1950            | phethenylate*                     | Thiantoin       | Lilly       |
| 1951            | phenacemide                       | Phenurone       | Abbott      |
| 1952            | metharbital                       | Gemonil         | Abbott      |
| 1952            | benzchlorpropamide†               | Hibicon         | Lederle     |
| 1953            | phensuximide                      | Milontin        | Parke-Davis |
| 1954            | primidone                         | Mysoline        | Ayerst      |
| 1957            | methsuximide                      | Celontin        | Parke-Davis |
| 1957            | ethotoin                          | Peganone        | Abbott      |
| 1960            | aminoglutethimide‡                | Elipten         | Ciba        |
| 1960            | ethosuximide                      | Zarontin        | Parke-Davis |
| 1968            | diazepam                          | Valium          | Roche       |
| 1974            | carbamazepine                     | Tegretol        | Geigy       |
| 1975            | clonazepam                        | Clonopin        | Roche       |
| 1978            | valproic acid                     | Depakene        | Abbott      |
| 1981            | clorazepate dipotassium§          | Tranxene        | Abbott      |

\* Withdrawn in 1952.

† Withdrawn in 1955.

‡ Withdrawn in 1966.

§ Approved by the FDA as an adjunct.

adione, a potent analgesic compound that was to become the first antiabsence drug, prevented threshold seizures induced by pentylenetetrazol (PTZ) in rodents. They also showed that these seizures were prevented by phenobarbital, but not by phenytoin.<sup>9</sup> Goodman et al<sup>10</sup> confirmed these results and demonstrated that phenytoin and phenobarbital modified the pattern of maximal electroshock (MES) seizures while trimethadione did not. These findings indicated the varying anticonvulsant actions of these drugs and the qualitative difference between threshold and maximal seizures.<sup>4</sup>

Interestingly, all AEDs developed from 1912 to 1960 were based on a simple heterocyclic ring structure (Figure 1).

During this period, genuinely novel structures were ignored in the development of AEDs; instead, attention centered on the hydantoins, barbiturates, oxazolinediones, succinimides, and acetylureas.<sup>4</sup> By the late 1960s, for a variety of reasons, very few innovative AEDs were under development.<sup>11,12</sup> In an effort to reverse this trend, the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke, in collaboration with other investiga-

tors, began in 1968 to conduct controlled clinical trials of seven drugs, many of which were already marketed abroad.<sup>4</sup> Between 1974 and 1978, three of these drugs—carbamazepine, clonazepam, and valproic acid—were approved as primary antiepileptic agents; clorazepate dipotassium was marketed in 1981 as an adjunctive drug. These efforts by the Epilepsy Branch became known as the Antiepileptic Drug Development (ADD) Program. Since its inception this program has encouraged the search for new AEDs by conducting and/or funding screening programs for new compounds, toxicity testing for advanced and promising preclinical compounds, and clinical trials. As a result, waning interest in the

United States in new medical therapies for epilepsy has been replaced by a productive coalition of government, industry, and academia.<sup>12</sup>

#### PRECLINICAL DRUG DEVELOPMENT

All drugs currently in use have some effect in either MES or PTZ models, even though many were not discovered by experimental means. Furthermore, drugs tend to be profiled clinically as a function of their effectiveness in these two models. Phenytoin, which is effective in partial and generalized tonic-clonic seizures, is effective against MES but not against PTZ (when used as a threshold test). Ethosuximide, which is effective against absence seizures in humans, has more effectiveness against PTZ. These two tests—considered by some to represent together the final common pathway for many epileptic seizures—have been further refined and used to screen more than 12,000 compounds in the ADD program of the Epilepsy Branch.<sup>4</sup> The screening is performed in a progressively more sophisticated manner, with the elimination of less promising compounds at each step.<sup>13</sup>

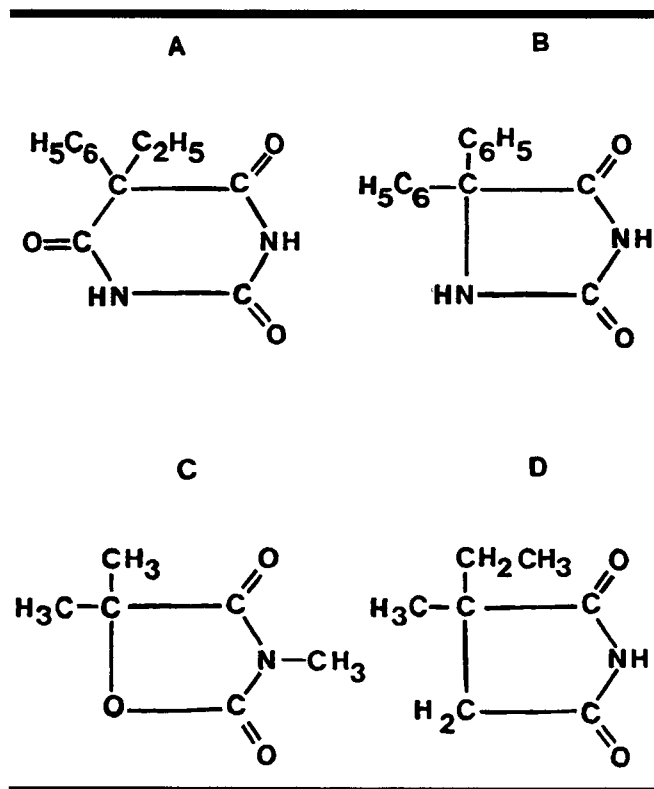


FIGURE 1. Heterocyclic ring structure: phenobarbital (A); phenytoin (B); trimethadione (C); ethosuximide (D).

One of the major arguments against the use of MES and PTZ is that the mechanisms by which drugs work against these empirical tests are obscure. It is argued that, using more basic and more rational approaches, we might be able to find better, more effective drugs. The counter argument is that we simply do not sufficiently understand the basic mechanisms of epileptic seizures to be certain which drug effect to seek, or whether any effect—once documented—is in fact a mechanism of action. Even when a potential drug is developed by rational methods, additional problems arise regarding clinical testing, since one cannot predict in which subgroup of the epileptic syndromes the new drug should be tested. On the other hand, discovery of a clinically effective drug which would be ineffective in MES and PTZ screening would open a whole new field for basic and clinical investigation.<sup>13</sup>

In the past decade, however, new avenues for the rational development of more effective AEDs have been pursued. Such development has progressed through two fundamental phases, the earliest of which

was the search for drugs that act—by various mechanisms—to enhance neuronal inhibition. The second and more recent phase of rational approach to AED development has been the effort to find drugs that diminish neuronal excitation. These approaches have been considered in some detail by Meldrum.<sup>14</sup>

#### CLINICAL DRUG DEVELOPMENT

A potential drug must successfully undergo a variety of clinical studies before being approved for use by the general public. These studies may include early tolerance and pharmacologic trials in normal volunteers as well as pilot studies of potential efficacy, but the controlled trial to evaluate efficacy is usually the most difficult and the most important. In any clinical trial, the peculiarities of the disorder being treated must be examined. Clinical trials in epilepsy, therefore, have to be designed to deal with the characteristics of that complex disorder. Of primary importance is the realization that many different syndromes are included in the epilepsies, so that, to be meaningful, data must be collected from a differentiated group of epileptic persons. Patients are usually categorized according to clinical seizure type. Fortunately, this categorization is based upon very empirical information and correlates well with the various therapeutic measures. Clinical seizure types are usually classified according to the 1981 International Classification of Epileptic Seizures,<sup>15</sup> and the resulting data serve as a first step in obtaining a modicum of homogeneity in the patients included in the clinical trial.<sup>11</sup> A number of critical variables (Table 2) must be considered when controlled clinical trials of AEDs are planned.<sup>16</sup>

#### PROMISING ANTIEPILEPTIC DRUGS UNDER DEVELOPMENT

In the past ten years, numerous compounds have reached various stages of preclinical and clinical investigation; each of these compounds has had some claim to being antiepileptic. But to summarize the status of such compounds is difficult. First, the data are not easy to obtain, especially for preclinical compounds concerning which a pharmaceutical company has little to gain by providing information. Some potential preclinical compounds have recently been described.<sup>17</sup> Secondly, information can very quickly become out-of-date, especially because toxic effects eliminate drugs from further clinical exposure. Finally, since the routes

**TABLE 2**  
VARIABLES TO BE CONSIDERED IN A CONTROLLED CLINICAL TRIAL OF PATIENTS WITH EPILEPSY

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| Patients   |
| Type of epilepsy determined by preclinical testing |
| Patient selection                                  |
| Seizure type                                       |
| Seizure frequency                                  |
| Exclusion criteria                                 |
| Concomitant medications                            |
| Dose of the test compound                          |
| Bias control and study design                      |
| Protocol   |
| Randomization                                      |
| Blinding   |
| Placebo vs active control                          |

by which compounds are evaluated are heterogeneous, the developmental stage of a particular compound can be difficult to ascertain. Data on a few selected compounds that are or have been significant in clinical studies in the United States can be summarized here. The compounds are listed in alphabetical order.

*Felbamate* is a dicarbamate closely related to meprobamate, a sedative-hypnotic compound. Unlike meprobamate, felbamate in higher dosages is not attended with sleepiness but rather with nausea and vomiting, suggesting that felbamate has a nonsedative central action. The drug has been developed primarily on the basis of its antiMES activity in rodents. This activity is approximately four times less potent than that of phenytoin or of carbamazepine, but felbamate is exceedingly nontoxic, and adult patients can often tolerate 3,000 mg per day or more.

Two randomized, double-blind trials of felbamate are under way. In one, a multicenter study involving the University of Virginia and the University of Minnesota, patients with partial seizures are being evaluated in a two-period crossover design. The study is essentially completed, and data are being analyzed. In the second study, being conducted at the National Institutes of Health in Bethesda, more severely affected patients with partial seizures are participating in a three-period crossover design. This study should be completed in 1988. Additional data on felbamate are available.<sup>18</sup>

*Flunarizine* is a defluorinated piperazine derivative that was originally introduced for vertigo and migraine. It has the intriguing effect—and possible mechanism of action—of being a calcium channel blocker. In many patients, this drug has an extraordinary half-life of more than two weeks. It has been studied clinically in epileptic patients since 1978. Following pharmacoki-

netic studies at UCLA, the Epilepsy Branch of the National Institutes of Health is undertaking a five-center (California, Michigan, Ohio, Virginia, and Massachusetts) parallel-design study of flunarizine. A total of one hundred patients are expected for this study. Patients must have uncontrolled partial seizures; concomitant medications will be phenytoin and/or carbamazepine. Additional data on flunarizine are available.<sup>19</sup>

*Gabapentin* is an amino acid which is related to gamma-aminobutyric acid (GABA). It moves through the blood-brain barrier and is thought to exert its antiepileptic effect by interfering with the action of excitatory amino acids such as aspartate. It should be noted, however, that only limited data are available describing the drug's mechanism of action; seizure-type specificity is difficult to determine from the available preclinical data. Numerous studies of this drug are under way, both in Europe and in the United States. Many of these studies are controlled, and efficacy data should emerge within the next several years. Additional data on gabapentin are available.<sup>20</sup>

*Lamotrigine* is a phenyltriazine derivative that was developed in an effort to find antifolate drugs, on the hypothesis that compounds that interfere with folate metabolism may be antiepileptic. Although lamotrigine has only weak antifolate activity, it is effective against MES in rodents. Data from several completed controlled trials in Europe are encouraging. A five-center controlled study is under way in the United States, and long-term studies are planned. If the drug proves effective, marketing might begin within five years in the United States. Additional data on lamotrigine are available.<sup>21</sup>

Org 6370 is an amino-benzobicyclononene derivative with activity against both MES and PTZ in rodents. The drug has an active metabolite that is probably of considerable significance. Early clinical studies in Europe and in at least two centers in the United States have demonstrated its safety. Controlled clinical trials are planned. Additional data on Org 6370 are available.<sup>22</sup>

*Oxcarbazepine* is closely related to carbamazepine, but since its mechanism of action does not include an epoxide metabolite, it may be less toxic. Large clinical trials are nearing completion in Europe; but because of the limited differences between this drug and carbamazepine, no studies are currently planned in the United States. Additional data are available on oxcarbazepine.<sup>23</sup>

*Progabide* acts by direct stimulation of the GABA



receptors. Its acid metabolite shows similar activity. Although usually referred to as a GABA agonist, progabide is considered by some to be a GABA pro-drug. Early clinical trials of progabide were promising. Sufficient data have been accumulated to permit marketing of the drug in France; applications are pending in several European countries; and clinical studies have been initiated in Japan. Two multicenter studies in the United States, however, suggested a limited benefit/risk ratio, causing studies in this country to be discontinued. Additional data on progabide are available.<sup>24</sup>

*Vigabatrin*, gamma-vinyl GABA, is an irreversible inhibitor of GABA-transaminase and, in animals, induces increases in brain GABA concentrations. Its mechanism, therefore, is presumably one of increased inhibitory synaptic activity. In numerous clinical studies in the United States and Europe, initial efficacy data are encouraging. Because of myelinic lesions in the brains of animals, however, additional studies in the United States have been stopped by the Federal Food and Drug Administration. The significance of these lesions remains uncertain; trials of vigabatrin are progressing in Europe, and human safety data continue to be encouraging. Additional information is available on vigabatrin.<sup>25</sup>

*Other new compounds* are currently in clinical trials, but activity with them is slow. Some data are available for clobazam, denzimal, eterobarb, flupirtine, milacemide, MK-801, nafimidone, stiripentol and zonisamide in Meldrum and Porter.<sup>17</sup> Other drugs which have been evaluated—at various stages—in human beings are RO 15-1788 (Roche), topiramate (McNeil), and ralitoline (Warner-Lambert).

#### SUMMARY

In contrast with the situation only a decade ago, a profusion of new potential AEDs has been introduced for world-wide clinical testing. Which, if any, of these compounds will be added to the physician's armamentarium against epileptic seizures is unknown, but the continuing flow of testable compounds augurs well for the future.

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