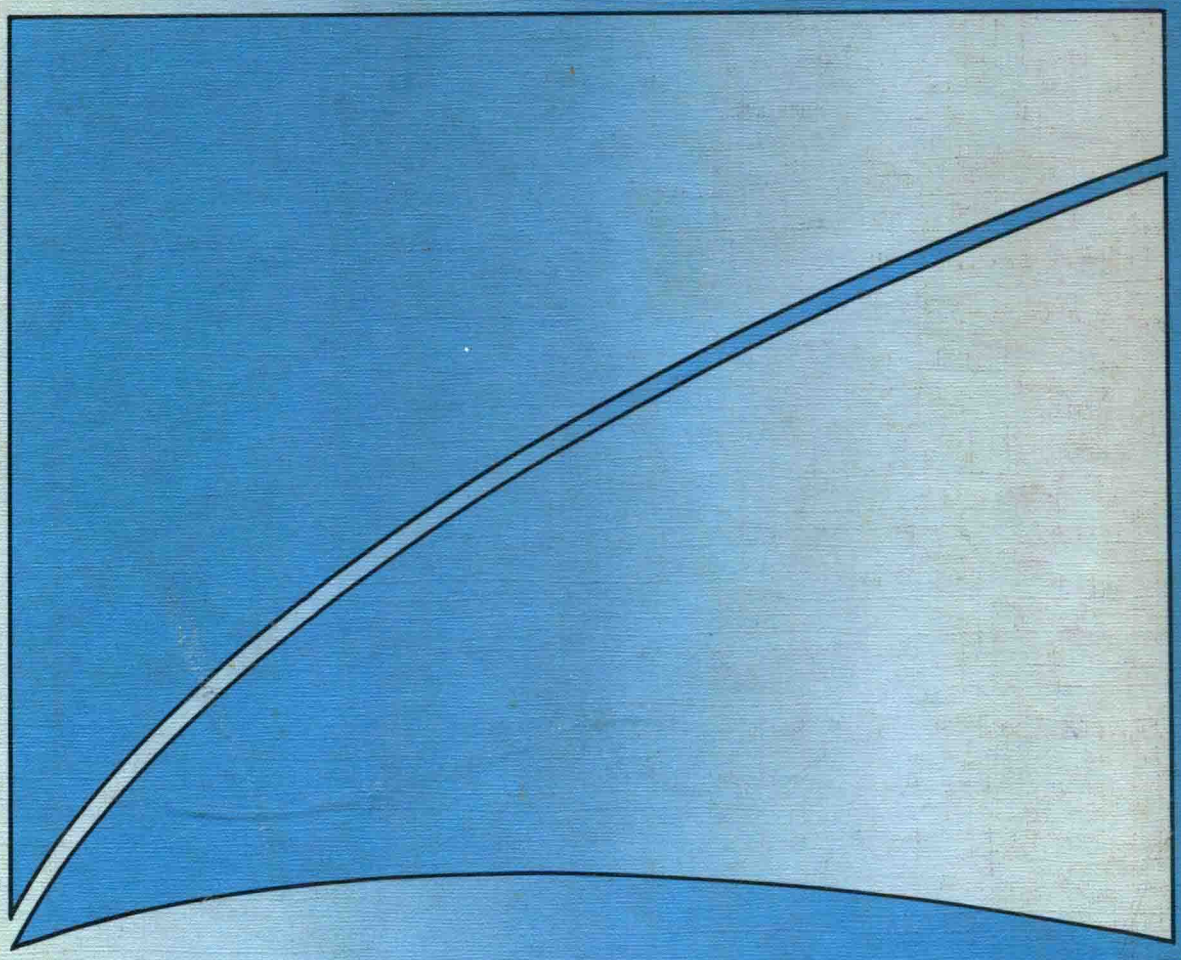
RATIONAL POLYPHARMACY

Editors: R.W. HOMAN, I.E. LEPPIK, E.W. LOTHMAN, J.K. PENRY and W.H. THEODORE



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Rational Polypharmacy

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Preface

Throughout most of history, treatment of epilepsy has usually involved the use of many agents in combination, that is, polytherapy. Although today we may regard many of the historical treatment with disdain, horror, or humor, their proponents often rationalized their combinations with references to various theories of the causes of epilepsy and described, sometimes in eloquent detail, how these concoctions would influence the various factors contributing to the development of seizures. Monotherapy is actually a relatively new development, having received most of its backing in the 1970's (Leppik and Sherwin 1977, Porter 1989).

Galen considered idiopathic epilepsy to be caused by "the production of the thick humor accumulating in the cerebral ventricles and obstructing the psychic pneuma" [Tempkin 1971]. The chief aim of his treatment was the "evacuation of phlegmatic humor" by use of various combinations of purgative medicaments, and bleeding and prevention of reaccumulation of phlegmatic humors by diets avoiding foods

Until this century, there was no scientific method for developing and testing agents for the treatment of epilepsy. Physicians would often, from analogy to other conditions, try remedies which appeared to affect systems thought to be important in the onset of seizures. Locock chose potassium of bromide in the 1860s to treat women with seizures because he had read that this substance, when tried by a German physician on himself, had caused impotence. The remarkable success of bromide led Locock to conclude that his theory of the causes of seizures was indeed true because it was effective.

The first treatment for epilepsy developed by testing substances in laboratory models was phenytoin during 1937 and 1938. One of the widely advertised treatments for epilepsy during that era is illustrated in Figure 1. This "rational" preparation consisted of bromide ("accepted as the chief depressor of reflex excitability"), arsenic ("assists the nutrition of the nervous system"), and picrotoxin ("which regulates the nerve centers, particularly those of the Bulb"). Shortly after the introduction of phenytoin, it became popular to use it in combination with phenobarbital (Cohen et al, 1940)

A hallmark study in the use of antiepileptic drugs in combination was reported in 1955. In this carefully done experiment, rats were given phenytoin (diphenylhydantoin) and phenobarbital alone and in combination and then tested in the maximum electroshock seizure (MES) model. Using probit analysis to determine the ED_{50} of the agents used alone and in combination, it was found that the most potent treatment was phenytoin and phenobarbital given in combination 2 hours before MES (Weaver et al, 1955). This lent a rational basis to the use of the combination of phenytoin and phenobarbital, which were thought to act synergistically.

The experiments of Weaver and his collaborators were repeated in the early 1970's with the advantage of having the ability to measure the concentrations of phenytoin and phenobarbital in brain and plasma. These studies again demonstrated that the most potent treatment was the use of both phenytoin and phenobarbital administered two hours before MES. However, measurements of the concentrations in brain indicated that the effect was additive, rather than synergistic (Leppik and Sherwin, 1997). The reason for the

observed synergy based on doses was found to lie in two pharmacokinetic facts. First, the half-life of phenytoin in the male Sprague-Dawley rats is one half hour. Secondly, although phenobarbital is an induce of phenytoin metabolism, when these two are given simultaneously to an uninduced liver, phenobarbital inhibits phenytoin metabolism (Kutt and Wallace). Thus, a lower dose of phenytoin is needed when it is given with phenobarbital two hours (four half-lives) before MES testing to have the same concentration when given alone.

The concept of monotherapy clinical practice became popular in the mid-1970s and 1980s (Reynolds et al, 1976). A number of reasons for preferring monotherapy over polypharmacy have been advanced (Porter,1989). These include: avoidance of adverse drug-drug interactions, improved compliance, reduced adverse effects, and reduced risk of teratogenicity.

The short reign of the popularity of monotherapy is being challenged by "rational polypharmacy" based on the concept that the use of two or more antiepileptic agents with different mechanisms of action may be more beneficial than "mindless" monotherapy. The validity of these reasons for use of monotherapy forces recognition that monotherapy is still preferable to polypharmacy, rational or not. This volume addresses areas in which monotherapy may be made more rational, and proposes that rational polypharmacy is the natural extension of rational monotherapy. Numerous issues are explored which need further delineation with a goal of a comprehensive antiepileptic drug management program to be developed for each patient.

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Neurobiology as a basis for rational polypharmacy Section Overview for Rational Polypharmacy Conference

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During the past two decades several concepts have evolved to the point of becoming guiding principles in the clinical use of pharmaceutical treatments for epilepsy and seizures. Current practice recognizes the need for accurate diagnosis (establishing the presence of seizures as opposed to other types of 'spells' and the proper classification of them with respect to seizure types and epileptic syndromes) and the use of agents appropriate for the particular diagnosis. These principles emerged from a wealth of advances in clinical epileptology and clinical pharmacology of antiepileptic drugs. Furthermore, the principle of monotherapy emerged, driven by clinical experience in the 1970s. At this time the profiles of clinical efficacy of antiepileptic drugs had not been elucidated nor had the classification schemes for seizures and epileptic syndromes been formulated. Accordingly, an appropriate drug, in terms of seizure suppression, was often not matched with the clinical condition. Consequently, patients were frequently treated with polypharmacy. This approach, combined with the lack of readily available blood level monitoring of antiepileptic drugs, led to frequent toxicity. The move to monotherapy grew out of this context and, in combination with the advances mentioned above, led to successful treatments for many patients. However, up to a third of patients today do not achieve adequate control of their seizures with medications. In these individuals, the standard approach is to try two or more medications, each used as monotherapy, and then resort to multiple concurrent medications. Yet, guidelines for such polypharmacy have not been established.

In parallel with the progress in the clinical realm cited above, tremendous strides were made in our knowledge of the basic neurobiology behind seizures and epilepsy. Advances in this realm include: the development and refinement of animal models that are counterparts of specific seizure types in humans (including acute seizure models and chronic epilepsy models); the development and refinement of animal models and test systems useful in identifying new anti-epileptic agents; identification of new agents for treating epilepsy and seizures; a broadened understanding of the mechanisms of action exerted by many of the anti-epileptic drugs in current use; identification of the circuits involved in various types of seizures; elucidation of fundamental alterations that distinguish the normal brain from the epileptic brain and exploration of how the various stages of maturation (neonate, youth, adult, senescence) impact on seizures and epileptogenesis. Such information will be useful in developing ideas and guidelines for polypharmacy.

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From considerations of the basic science of seizures and epilepsy, a broad domain emerges in which the term polypharmacy can be applied. Conceptually, a variety of phenomena are subsumed in the term epileptogenesis (Fig. 1). These include: processes in the chronically epileptic brain which make it susceptible to spontaneous recurrent seizures; processes during a seizure that lead to its full expression; the sequence of events enacted after a seizure is over that influence the brain for a finite period of time or indefinitely; and interactions between the processes just mentioned with the events that occur during maturation and involution of the brain. Indeed, there is a multiplicity of points on the spectrum of pathophysiology at which one could potentially intervene therapeutically, i.e. at which polypharmacy would be appropriate. Moreover, it should also be emphasized that for each of the general categories mentioned in the spectrum of pathophysiology, multiple processes occur. Thus, even if one restricted treatment to a single 'site' on the spectrum of pathophysiology, there is the possibility of polypharmacy. At present the scope of such proposed polypharmacy is speculative; for many of the types of processes identified, drugs have not yet been developed and our knowledge of the basic science is rudimentary. However, the considerations just raised provide a theoretical framework for a broader, and more effective, treatment for epilepsy, including the cases that remain refractory to current therapeutics.

In fact, at least one of the theoretic principles raised above has become incorporated into current thinking. Based on the discussion above, one can distinguish *ictogenesis* (processes involved in initiation, elaboration, and extension [in time and space] of seizures) from *epileptogenesis* (processes involved in augmented propensity for spontaneous seizures of in the progression in severity of seizures or their resistance to medical therapy). In this regard then, an *anti-ictal drug* (i.e. one suppressing seizure expression) would be distinguished from an *anti-epileptogenic drug* (i.e. one opposing one or more aspect of epileptogenesis). The proposed term anti-ictal drug would replace the term anti-epileptic drug in current usage. While displacing an established term that many are familiar with and comfortable,

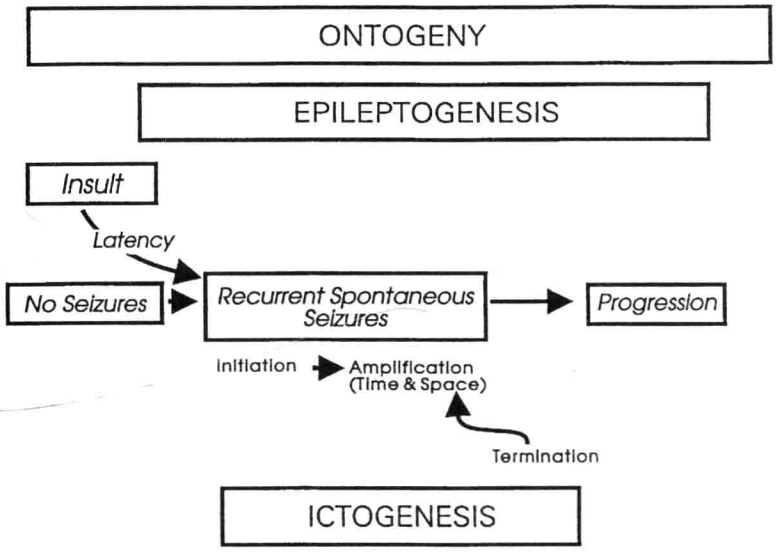

Fig. 1. Spectrum of pathophysiology for seizures and epilepsy. Each individual seizure, whether an isolated, 'provoked' seizure or a seizure as part of epilepsy, can be separated into phases in which seizure initiation occurs and in which seizure elaboration, involving spread in time and space, occurs. In addition, certain processes serve to terminate a seizure; when these fail, status epilepticus ensues. The term *ictogenesis* is applied to the just-mentioned processes in aggregate. The term *epileptogenesis* subsumes ictogenesis, but also involves processes that take place before the first seizure occurs to render the epileptic brain susceptible to spontaneous recurrent seizures, processes that serve to intensify seizures and to make them more refractory to therapy (progression).