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Introduction

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Tracy Putnam and Houston Merritt wrote six papers together in the four years between 1937 and 1941. At the time of the first paper, Putnam was 43 years old and Merritt was 35. Their papers were to transform the treatment of epilepsy and crucially affect the development of neurology as a scientific discipline and as a clinical specialty.

Merritt and Putnam did not work in a vacuum. Both had been attracted to the Neurological Unit of the Boston City Hospital (BCH) by Stanley Cobb. At BCH there were others who were already well known for work on epilepsy, including William Lennox, Fred and Irma Gibbs, and Paul F. A. Hoefer. Lennox, an astute clinician and geneticist, was later responsible for the introduction of trimethadione. Fred and Irma Gibbs worked with Albert Grass to develop the first diagnostic electroencephalographs for the study of epilepsy (1); the EEG machine at BCH was probably the first one in this country to be used for clinical studies. Before anyone had conceived the term "Clinical Research Center" there was one for epilepsy at BCH. When Cobb moved to the Massachusetts General Hospital in 1934, Putnam became Director of the Neurological Unit at BCH.

When Merritt and Putnam started their work, the only drugs available to treat seizures were bromide salts and phenobarbital, and both were limited by sedative effects. The first paper of Putnam and Merritt (2) appeared in 1937 and described their method for determining the seizure threshold of cats, a modification of the method described earlier by the redoubtable E. A. Spiegel of Philadelphia and one described in Russia by Kransnogdorsky. The apparatus was simple: a 45-volt radio battery, a 50-ohm potentiometer, a commutator that was operated by a motor, and an ammeter (Fig. 1). Current passed from an occipital electrode to a mouth electrode. Under these conditions, the convulsive threshold for each animal was between 6 and 15 milliamperes.

In that first paper, Putnam and Merritt showed the difference between sedative and anticonvulsant effects of a drug. For instance, a dose of sodium bromide that was sufficiently hypnotic to keep a cat from walking raised the convulsive threshold by 50%; in contrast, a dose of phenobarbital that caused similar symptoms trebled or quadrupled the threshold. The drug then called diphenylhydantoin (now, phenytoin) had already been tested and proved to be the one with "greatest anticonvulsant activity and the least hypnotic activity."

A year later, the sequence of authors was reversed (3) when Merritt and Putnam described the effects of numerous drugs on seizure threshold in the cat. Phenytoin

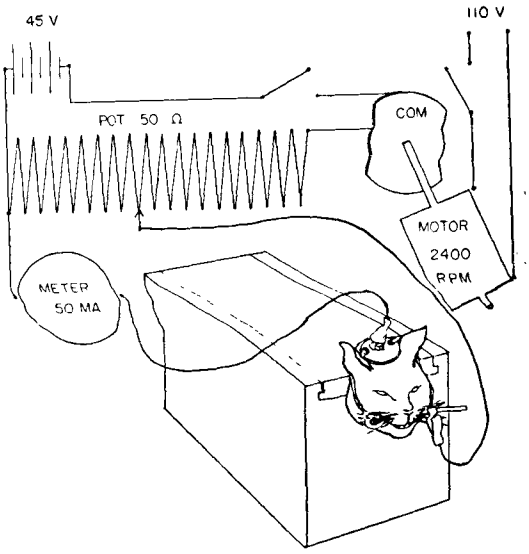

FIG. 1. Diagram of the wiring employed, permitting an interrupted current of determined amperage to be applied through an animal's head to determine the threshold for convulsions. (Reproduced with permission from ref. 2.)

was more effective than phenobarbital as an anticonvulsant and less soporific. A few other drugs were also effective in this test but, for one reason or another, they have still not been clinically successful. Merritt and Putnam recognized the similar molecular configuration of the drugs that were effective anticonvulsants; some other drugs also had similar structure but paradoxically were not effective. They concluded: "There is no reason for believing that the ideal anticonvulsant drug has yet been found." (The problem of structure and function of these drugs remains, and the molecular or cellular basis of the anticonvulsant action is not yet understood, perhaps because there is still so much to be learned about the biochemistry and physiology of the single epileptic neuron or the complex interactions of different sets of neurons during a seizure.)

In the third paper (4), also published in 1938, they demonstrated the clinical efficacy of phenytoin in human patients. By 1939 (5), they recognized the range of effective dose as 0.2-0.6 gm daily and they also recognized the major toxic effects: ataxia, rash, and hypertrophy of the gums. The next paper came in 1940 (6); they had extended their experience from 144 to 267 patients and now analyzed the effects of seizure type on the results (Tables 1–3). Phenytoin completely relieved "psychic equivalent seizures in 12 of 19 patients (62%)" and all seizure types

TABLE 1. *Effect of sodium diphenyl hydantoinate on psychic equivalent seizures in 39 patients with frequent attacks who have been treated for a period greater than two months*

	Psychic equivalents alone	Psychic equivalents associated with grand mal	Total	Per cent
Completely relieved	12	12	24	62
Greatly decreased	5	4	9	23
Moderately decreased	2	4	6	15
Total	19	20	39	100

(Reproduced with permission from ref. 6.)

TABLE 2. *Effect of sodium diphenyl hydantoinate on grand mal convulsive seizures in 227 patients with frequent attacks who have been treated for a period greater than two months*

	Grand mal alone	Grand mal associated with		Total	Per cent
		Petit mal	Psychic equivalents		
Completely relieved	74	51	12	137	60
Greatly decreased	16	12	3	31	14
Moderately decreased	16	10	3	29	13
No change	18	10	2	30	13
Total	124	83	20	227	100

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benefited to some extent. Similar success figures were achieved for grand mal but 13% of the patients in this category did not improve at all, and the general lack of effect of phenytoin on petit mal was recorded.

In the sixth and last paper, published in 1941 (7), Putnam and Merritt attempted to analyze the effective molecular structures. None of the other drugs they studied had a major clinical effect, but the way to test new drugs had clearly been shown.

After this triumphant accomplishment, Putnam and Merritt went separate ways. In 1939, Putnam became Professor of Neurology and Professor of Neurosurgery at Columbia University and Director of both services at the Neurological Institute of New York. In addition to epilepsy, he worked on the neuropathology of multiple sclerosis and championed a vascular theory of that disease. He had been trained surgically by Harvey Cushing and, at the Neurological Institute, he evaluated surgical therapy for hydrocephalus and for movement disorders. In an obituary of Putnam (8), Merritt wrote: "He (Putnam) was received with a certain degree of coolness by some members of the staff, and his attempts to act as professor of both neurology and neurosurgery were not appreciated by some of them." According to local legend, this was another of Merritt's understatements.

Personal tragedy also marred that time for Putnam and he left New York in 1947, to become Director of Neurology at the Cedars of Lebanon Hospital in Los Angeles. Putnam's research and writing stopped and he did not attend scientific meetings; little more was heard from him nationally until he died in 1975, at age 81.

TABLE 3. *Effect of sodium diphenyl hydantoinate on petit mal convulsive seizures in 104 patients with frequent attacks who have been treated for a period greater than two months*

	Petit mal alone	Petit mal associated with grand mal	Total	Per cent
Completely relieved	6	34	40	39
Greatly decreased	4	17	21	20
Moderately decreased	1	20	21	20
No change	10	12	22	21
Total	21	83	104	100

(Reproduced with permission from ref. 6.)

Merritt's career, by contrast, flourished. He moved to New York in 1945, first as Director of Neurology at Montefiore Hospital and then as successor to Putnam in 1948 as Director of the Neurology Service at the Columbia–Presbyterian Medical Center. When Merritt died in 1979, at age 77, several obituaries (9–14) recorded his contributions as premier clinician, editor of the *Archives of Neurology,* author of the standard *Textbook of Neurology* for a generation, skilled administrator, and counselor to the newborn National Institute for Neurological Diseases and Blindness.

Putnam's last years were truly a pity, but the work that he and Merritt did together will live forever and we can be grateful for their several achievements:

1. They devised a simple and reliable method to test drugs of anticonvulsant effect.
2. They showed that anticonvulsant effects in cats accurately predicted effects in humans; phenytoin was the first anticonvulsant drug to be tested in animals before it was given to human subjects.
3. They showed that anticonvulsant and sedative effects of drugs could be separated.
4. They showed that a single drug might be much more effective in treating some seizure types than others. This not only had therapeutic implications for choice of drugs to treat individual patients; it also implied that the pathogenic mechanisms of different types of seizure were also different.
5. They discovered the efficacy of phenytoin and—45 years later—this drug is still a mainstay of treatment.
6. Their work opened the way to the development of other anticonvulsant drugs.

These were monumental landmarks in the history of epilepsy, pharmacology, and neurology. We have good reason to celebrate their achievements in this first Merritt–Putnam Symposium.

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