Serendipidity in Antiepileptic Drug Discovery

Gagandeep Singh¹, Loveleen Aggarwal²

The anti-epileptic drug boom following the 1990s was preceded by the sporadic discovery of medicinal compounds that were mostly tested by serendipity (Figure 1). Here, we recount the discoveries of three salient epilepsy medicines, bromides, phenobarbital and phenytoin and the scientists behind these discoveries.

Sir Charles Locock (1799-1875)

The era of modern treatment of epilepsy was ushered in by a report of “the treatment of 15 women with hysterical convulsions” presented in the Royal Medical Society in London in 1857. Sir Charles Locock was better known at that time as obstetrician to Queen Victoria of England. His observation that potassium bromide abolished seizures which occurred in 15 women with presumed hysterical seizures - thought to be hysterical because the seizures occurred in relation to their menstrual periods - but now now believed to be catamenial seizures.

Alfred Hauptmann (1881-1948)

Although the discovery of barbituric acid is credited to von Bayer, who received the Nobel prize for chemistry in 1905, it was Alfred Hauptmann who first noted it beneficial effect in people with epilepsy.

A German psychiatrist and neurologist, Alfred Hauptmann’s most important contribution is still the manuscript on the efficacy of phenobarbital as an antiepileptic, which was written in 1912 and is an excellent example of astute clinical observation. (Hauptmann, 1912).

In February 1912, Alfred Hauptmann, then a young clinical assistant in Freiburg, Germany, slept above the ward of patients with epilepsy. Annoyed by being kept awake by the noise of seizures at night, he gave them phenobarbital, which at that time had acquired reputation as a hypnotic. It was serendipitously that Hauptmann observed that not only were the inmates of the ward able to sleep, their seizures were also suppressed.

Hauptmann records that following his first serendipitous observation, he began systematically to examine the potential ofphenobarbital as an antiepileptic and concluded that Luminal was effective in the severest cases of epilepsy that went beyond the effect of bromides.

Unlike the rapid endorsement of bromide before, or of phenytoin later, by the medical community, phenobarbital was not quickly taken up internationally. This may have been partly because Hauptmann’s publication was in a relatively obscure German journal, or (more likely) because the 1914–1918 war disrupted international medical communication.

It was only in the early 1920s that the drug began to be used more widely as an antiepileptic, largely due to the works of British scientists like Golla, Holmes and Collier who also reported similar success with phenobarbital. In an often quoted study (1921), Golla compared bromide and phenobarbital in 125 patients and noted that “most patients found that they were far brighter and more cheerful after a change to Luminal from bromide treatment.”

Fig. 1: Timeline of anti epileptic drug discovery

¹Professor and Head, Department of Neurology, Dayanand Medical College & Hospital, Ludhiana, Punjab;
²Consultant Neurologist, Dhawan Hospital, Panchkula, Haryana
This new drug discovery jumped from nation to nation and pretty soon it was the drug of first choice in epilepsy treatment.

**Tracy Putnam (1894-1975) and Houston Merritt (1902-1979)**

Tracy Putnam came to work in Boston City Hospital in the mid-1930s and established an EEG research laboratory under the mentorship of Dr. Freidrick Gibbs, the legendary epileptologist. The laboratory was established in order to test the efficacy of potential agents in the treatment of epilepsy. The aim was to develop compounds more effective and safer than phenobarbital. This was the first example of systematically and orderly conducted series of investigations to discover newer epilepsy medicines inasmuch as the earlier ones were discovered by serendipity alone.

Tracy Putnam obtained several molecules from Parke Davis, found many to be efficacious but only one of them to be safe - phenytoin. He then approached Merritt Putnam, a junior doctor working in the neurological unit of Boston City Hospital to administer it to patients with epilepsy. This led to the publication of a series of papers between 1937 and 1942 that established phenytoin (Dilantin) as an effective anti-epileptic drug that is widely used in the treatment of epilepsy even today.

Following his work on phenytoin, Putnam went in to obscurity perhaps following the tragic death of his daughter. Merritt however, went on to become the Director of the Institute of Neurology at Columbia Presbyterian, New York form 1948 to 1967. He is perhaps best known for his textbook, “Merritt’s Neurology”, of which he was the sole author for the first four edition and which is in its thirteenth edition today, widely read by students across the world.

**References**