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COMMENTARY

H. Steve White: A Champion for Contemporary Epilepsy Research

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Drug discovery remains a roller coaster ride with all its highs and lows and unexpected hurdles. Despite the advances in chemistry, pharmacology and molecular biology and the implementation of rational drug design paradigms, cumulative drug attrition rates remain near 90% for drug candidates entering human clinical trials [1]. It is against this backdrop that the success of the US NINDS Epilepsy Therapy Screening Program (ETSP; formerly called the Anticonvulsant Screening Program) in aiding new anti-seizure drug development is so remarkable. Since its inception in 1975, the ETSP has screened some 32,000 compounds for anticonvulsant properties. It has aided the development of 10 new clinical products and played a major role in evaluating 6 of these.

What has been the ETSP's formula for success and who has been behind these efforts? A retrospective analysis, at first glance, does not provide an immediate answer. Epilepsy has long been known to be a complex and heterogeneous disorder. In 1975, little was known of epilepsy's cause and our understanding of epilepsy genetics was in its infancy. New drug development was at a near standstill, and few epilepsy drug candidates were being advanced. Most emerging clinical agents were fashioned after existing drugs. Fortunately, the ETSP was under the leadership of scientists with vision, understanding, and passion. The ETSP's Ewart Swinyard and Harvey Kupferberg implemented a series of diagnostic phenotypic animal screens to identify new classes of anticonvulsants. They built into this testing paradigm, scope and rigor allowing the ETSP to identify effective novel agents while limiting false-positive responses. It is in this historical context that I wish to provide commentary of Professor H. Steve White's many contributions to today's management of epilepsy and to our understanding of this important disorder.

While the ETSP is in the Washington, DC, area, its Anticonvulsant Drug Development (ADD) Program's contract animal test facility is at the University of Utah. For several years, Dr. Harold Wolf was its principal investigator. Steve White joined the Utah team in 1985 as a senior scientist and became director in 2001. Today, he is a leading authority in the field. At the beginning of this year, Steve White stepped down as ADD's director and principal investigator. However, in his 15 years at that post, the FDA approved 8 new antiepileptic drugs, among these was lacosamide (Vimpat®), a drug discovered in my laboratory [2]. Over Steve's years at the ADD, I submitted more than 500 new chemical entities for screening in animals. We examined several novel series of anticonvulsant agents and published more than 30 papers that contained primary data secured at the ETSP. Our studies progressed positively from the information reported to us. We used this knowledge to advance new and valuable compounds and to probe existing pathways for drug function.

Science is built upon studies that provide informative, insightful, and reliable data. Here, Steve White has made extraordinary contributions to the epilepsy community. He has reported on the functional mechanism of a diverse set of small molecule and protein antiepileptic agents. Steve has developed and implemented new screening models for epilepsy that identify compounds with different mechanisms [3, 4]. Of particular relevance to today's research focus, he has introduced new phenotypic models designed to identify compounds that could affect disease

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progression, address treatment resistance, and, hopefully, provide cures [5]. Finally, Steve White has championed the expansion and streamlining of testing protocols to efficiently accommodate the needs of academic, governmental and pharmaceutical researchers. He has accomplished this even while some have questioned the use of phenotypic models in drug discovery and budgetary resources have been strained.

Research accomplishments aside, Steve White have been an authoritative, passionate, and eloquent spokesperson for the epilepsy community. He has taken leadership roles in the scientific circles that drive new epilepsy research at the NIH and for Citizens United for Research in Epilepsy. The impact of his continued efforts are seen in today's advances and will be in tomorrow's.

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