Ceasing Antiquated Conceptions: A Telling of the Early and Evolving History of Epilepsy

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Abstract

The word *epilepsy* is derived from the Greek word *epilambanein*, meaning “to seize.” This term came to embody the disease as early descriptions characterized seizures as events in which the faculties of the mind and body were “seized” from the individual. This notion of seizing the mind and body’s faculties has in essence remained a constant throughout the evolution of epilepsy. The theories elucidating the significance of the event, however, have surely shifted with the times, reflecting an elegant battle among magic, science, and theology. Subsequent advents in clinical observation, diagnostic evaluation, and therapeutics unfurled many mysteries of the brain and revolutionized prevailing theories, landing epilepsy as it is known today far beyond the primitive and highly supernatural notions that predominated in antiquity.

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Essay

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The earliest accounts proposed seizures as a product of vengeance on sinners by the Goddess of the Moon, cap-

tured by the term *antasubbu*, meaning “hand of sin,” in Mesopotamian texts dating as early as 2,000 BCE, *anta-subba* in Babylonian texts a thousand years later, and *seliniasmos*, derived from the Greek name for the Goddess of the Moon, Selene [1]. Prevention and treatment, thus, included existing traditions for expiation of sin, measures for pleasing the deities, and magical therapies, such as incantations, drinking blood of the gladiators, and wearing amulets [2]. An esteemed Roman physician is noted to have mentioned a “practice of putting the patient into goat’s skin [goat skin was displeasing to deities], plunging him into the sea, and observing whether he sank or not; if the former, the diagnosis was positive.” The paradigm of demonizing epileptics as either possessed or as sinners predominated with concomitant stigmatization. The epileptic was deemed a bad omen and considered a contagion. The Romans, for example, referred to an epileptic attack as *morbus comitialis*, meaning “that which ruined an assembly of people,” and epilepsy itself as “the disease that was spit upon” [1].

The first formal rebuttal of the theories proclaiming a divine origin of epilepsy was in the form of a collection of medical writings known as *On the Sacred Disease*, thought to be authored by one of many anonymous physicians represented as Hippocrates around 400 BCE [2]. The author declared epilepsy a medical condition with the brain as the seat of the disease: “Its cause lies in the brain, a brain overflowing with a superfluity of phlegm. When the phlegm rushes into the blood vessels of the body it causes all the symptoms of the attack” [2, 3]. Temkin described the extent of the pathophysiology known at the time in exquisite detail in *The Falling Sickness*:

“When the air, in the respiratory process, reaches the brain, it deposits here its intelligence content and then goes on to the other parts. Therefore, the brain serves as the rational interpreter and messenger as long as it partakes of the breath. But if the air is cut off from the brain and the vessels, the person becomes dumb and unconscious; suffocation arises, which by its violence makes the excrements pass. As the lung is cut off from the breath, foams and effervesces cause frothing at the mouth. The small vessels of the eye beat vehemently, and so the eyes become distorted; in the legs, the incarcerated breath causes cramp and pain and makes the patient kick. In the hands, however, the blood stands still, and they become powerless and cramped. In case the flux is violent, the cold phlegm will congeal the blood, and the patient will die. Otherwise, it will be dispersed into the vessels and mixed with the blood, air will be taken in again, and then attack end” [2].

The text further condemned the claim of wizards and charlatans as “fundamentally impious” because it implicated the gods in breeding what was “unclean” [2]. Thus, the Hippocratic era marked the beginning of the liberation of medicine from the supernatural.

Epilepsy was again redefined centuries later by physician and philosopher Galen, who combined Hippocratic theories with new advances in anatomy and physiology to ultimately describe two types of seizures: primary idiopathic and sympathetic. Primary idiopathic seizures were those Galen attributed to accumulation of phlegm or black bile in the cerebral ventricles. It was believed that the cerebral ventricles harbored an individual’s psychic pneuma, and irritation at this locus would, thus, trigger generalized convulsions through activation of the nerves at their origin [3]. In other cases, Galen noted an origin that seemed to stem from elsewhere, namely, the stomach or extremities, referred to as sympathetic seizures. Galen famously evaluated a 13-year-old patient who described this sensation as a passing feeling from the leg to the head, characterized further as a “cool breeze,” from which the word “aura” was derived [3, 4]. This shift in the proposed mechanism was mirrored by treatment methods. Practices for containing phlegm (e.g., body binding), removing phlegm (e.g., trephining), and replacing phlegm (e.g., consuming various “purified” products) were the mainstays of treatment at the time [4].

The Dark Ages witnessed a return of the theories dating back to antiquity. With the rise of Christianity, epileptics were once again deemed possessed at the hand of the divine or the devil [4]. The moon remained a popular implication in epilepsy even as physicians transitioned to theories that were more scientific, which etymologically explains the advent of the word “lunatic” [2]. With the transition into the Renaissance, diagnostic evaluation required parsing out what was true epilepsy, possession, or hysteria [4]. By the 19th century, epilepsy, though acknowledged as rooted within the central nervous system, was thought to be attributed to heightened emotions, such as fear, sadness, or anger, hypersexuality, abnormal menstruation, pregnancy, head trauma, or heredity [5].

Finally, a cascade of exponential advancements resulted in the discovery of effective therapeutics. In 1857, at the meeting of the Royal Medical and Chirurgical Society in London where a case series of epilepsy was reviewed, Sir Charles Locock described his use of potassium bromide in the treatment of what he referred to as hysterical epilepsy after he observed it caused reversible impotence, believing it to quell sexual excitement, a postulated trigger for seizures at the time [6]. Other physician scientists observed and reproduced the effects of bromide therapy, crediting it with modifying intrinsic neural activity [6]. In 1912, the anti-convulsant properties of phenobarbital

were discovered serendipitously by a resident psychiatrist, Alfred Hauptman. Hauptman is said to have administered the drug to patients with epilepsy living nearby to improve the quality of his own sleep, as he was often kept awake by the sound of bodies falling from beds during tonic-clonic seizures. He quickly recognized its beneficial effects on the frequency of seizures in these patients with epilepsy [7]. Over the next few decades, early antiepileptic medications were added to therapeutic regimens [7].

Alongside these developments in therapy of epilepsy were advances in elucidation of pathophysiologic mechanisms. In the 19th century, Theodore Herpin composed a detailed account of clinical phenomenology of peripheral symptoms known today as epileptic auras in *Des Accés Incomplets D'Epilepsie* and suggested their origin as central based on their stereotypy [8]. Hughlings Jackson later and independently made similar observations but went further to describe how these peripheral symptoms reflected localization in focal epilepsy: "we shall ultimately be able not only to speak of certain symptoms as constituting genuine epilepsy or some variety of it, but of these or those particular symptoms as pointing to a 'discharging lesion' of this or that particular part of cortex" [9]. His development of the concept of somatotopic organization is an underpinning of past and present bedside neurology; his contribution was recognized by Jean-Martin Charcot, who later dubbed the eponym "Jacksonian march" [10]. In the latter half of the 19th century, Gustav Fritsch and Eduard Hitzig demonstrated electric stimulation of the cortex resulted in peripheral movements. Building on this and Jackson's observations, David Ferrier conducted extensive experimentation in animals to identify cortical centers and their motor-function correlates [11]. At the beginning of the 20th century, Harvey Cushing's intraoperative Faradic stimulation of epilepsy patients fostered cortical mapping in humans [12]. These works ultimately served as the basis for Wilder Penfield's homunculus in 1937 and revolutionized contemporary neurosurgery [12].

The concept of electrical discharge served as the basis for the invention of the greatest diagnostic tool for epilepsy, the electroencephalogram. Hans Berger, a neuropsychiatrist, devoted much of his career to recording human brain activity. He became enthralled with the subject when he experienced a near fatal injury in the German army, and his sister, many miles away, reported the danger Berger was in to their father, who promptly sent his son a telegram, which Berger felt reflected a telepathy of sorts [13]. Building on the work of Richard Caton and

Adolph Beck, who had already demonstrated electrical recordings from the brains of animals, Berger successfully recorded the first human electroencephalogram in 1924 [13].

Thus, the beginnings of the unveiling of this disease were made possible. The original theories of epilepsy are fascinating albeit somewhat disturbing and, while most have been debunked, the remaining mystery projects an exciting future in further investigation and lends a temporizing warrant for a little bit of magic.

Statement of Ethics

The authors have no conflicts of interest to declare.

Conflict of Interest Statement

Nadia Khalil has nothing to disclose. Selim Benbadis (last 3 years): consultant for Brain Sentinel, Cavigion, Ceribell, Eisai, Greenwich, LivaNova, Neuropace, SK biopharmaceuticals, and Sunovion; speakers bureau for Eisai, Greenwich, LivaNova, and Sunovion; national medical director for RSC Diagnostic Services (EEG); Florida medical director of Stratus/Alliance (EEG); member in Epilepsy Study Consortium; received grant support from Biogen, Brain Sentinel, Cavigion, LivaNova, Greenwich, Ovid, SK biopharmaceuticals, and Xenon; royalties as an author or editor for Emedicine-Medscape-WebMD and UpToDate; and editorial board for Epilepsy.com (Epilepsy Foundation) controversy section, Emedicine-Medscape-WebMD, Epileptic Disorders, Epilepsy and Behavior, and Expert Review of Neurotherapeutics. Derrick Robertson (last 3 years): consultant for Alexion, Biogen, Celgene, EMD Serono, Genentech, Novartis, Sanofi-Genzyme, and Teva Neuroscience; speaker bureau for Acorda, Alexion, Biogen, Celgene, EMD Serono, Genentech, Mallinckrodt, Novartis, Sanofi-Genzyme, and Teva Neuroscience; and grant support from Actelion, Biogen, EMD Serono, Genentech, Mallinckrodt, MedDay, Novartis, PCORI, Sanofi-Genzyme, Sun Pharma, and TG Therapeutics.

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Author Contributions

Nadia Khalil: major role in contributing to the content in paper and revising the manuscript for intellectual content. Selim Benbadis: major role in contributing to content in paper and revising the manuscript for intellectual content. Derrick Robertson: major role in contributing to content in paper and revising the manuscript for intellectual content.

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