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Introductory Chapter: Seizures and Its Historical Background

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1. Introduction

Seizures are a very common problem that accompany the humanity since its origin, and epileptic seizure (ES) was considered as a sacred disease for thousands of years, while for the past hundred year, a real knowledge of its etiopathogenetic mechanism is better known.

In one of the chapters of this book, an overview of genetic testing modalities and workflows taking into account genetic architecture of epilepsies is given, and practical aspects of genetic testing in epilepsies, including advantages/limitations and clinical utility of tests, are discussed.

Other chapters of this book aim to present in synthesized form the genetic, immunological, and environmental factors' role in the autoimmunity to epilepsy, as well as the therapeutic approach that has been used to control seizures, mainly where there is a suspected anti-neuronal-antibody circulation. A review of the work achieved during the last years in patients with this condition provides information and experience in the diagnosis and treatment of this epilepsy type. In this chapter, the authors conducted a systematic search of PUBMED, for articles published between 1990 and December 2016 using the search terms "autoimmune and epilepsy," "autoantibodies and epilepsy," NMDA and epilepsy, AMPA and epilepsy, and GAD and epilepsy. The list of identified articles was complemented by additional searches for relevant articles in the reference section of the publications captured by the initial search.

In another chapter, the authors estimated the prevalence of ischemic stroke (IS) in epileptic patients presenting subarachnoid neurocysticercosis (SNCC) and IS frequency among HIV-positive patients in three NCC subgroups. Finally, to determine if the odds of ischemic stroke are elevated in SNCC patients compared to patients with intraparenchymal NCC (INCC).

They determined whether the risk for IS is elevated in HIV-seropositive patients presenting with SNCC or intraparenchymal NCC (INCC) and evaluated if and when the potential interaction varies by location of NCC in the brain. Eligible epileptic patient's seropositive status was recorded, and cross associations for the independent variables (NCC status and HIV status) and outcome variables (IS event) were performed.

The authors compared the INCC SNCC group to the reference group; the odds of IS in PLWNCC were 2.0 and 2.6 times greater patients with SNCC and INCC, respectively. The frequency of IS was greater in HIV-positive patients in all three groups, but the risk was especially pronounced when seropositive epileptic patients were both NCC groups when compared with the reference group, subarachnoid space that risk increased three times more.

In the chapter entitled "Self-Reporting Technologies for Supporting Epilepsy Treatment," the authors conducted interviews, a literature review, an expert panel, and online surveys to assess the availability and quality of patient-reported data that is useful but reported as being unavailable, difficult for patients to collect, or unreliable during epilepsy diagnosis and treatment, respectively. Their results highlight important yet underexplored data collection and design opportunities for supporting the diagnosis, treatment, and self-management of epilepsy and expose notable gaps between clinical data needs and current patient practices.

The chapter entitled "Psychogenic Non-epileptic Seizures in Patients Living with Neurocysticercosis" analyzes the results of one study about patients presenting epileptic seizures and pseudo-seizures (psychogenic non-epileptic seizures [PNES]) and living with NCC done in rural South Africa. NCC is the leading cause of secondary epilepsy in developing countries where PNES is also a frequent problem, then to distinguish real seizures from PNES is a challenge. Therefore, the author reviewed the recent medical literature and compared it with their results and highlighted how to differentiate epileptic seizures from PNES.

2. Background history

The main clinical manifestation of NCC is ES; then the first human being presenting NCC also had ES. Probably the first human being infected by *Taenia solium* was the *Homo ergaster* [1, 2]. Therefore, the history of epileptic seizures began at the Lower Pleistocene (between 1.51 and 1.56 million years ago) when *H. ergaster* lived. Tapeworms that plague humanity originated in carnivores such as lions, hyenas, or African dogs and jumped to humans after they began eating their prey animals on the African savannah [2]. Modern humans share the same differences as *H. ergaster* with Asian *H. erectus*, leading the possibility that *H. ergaster* is the ancestor of later Homo population [2, 3]. In our opinion the first epileptic patient was a *H. ergaster*. Because the humans are the most important element in the *T. solium* transmission, we assumed that *H. ergaster* was the first transmitter of the tapeworms to the savage animals and from the infected animals, he got the infection with *T. solium* through their eggs and proglottids present in the contaminated water and/or food.

2.1. Ancient times

Seizure disorders, and the mysteries surrounding them, have been discussed for nearly 4000 years starting with Assyria, Akkadia, and Babylonia. Babylonians and Sumerians believed that it had supernatural causes like other diseases.

Many years after the *H. ergaster* disappeared, the habitants of earth continue being infected by *T. solium* suffered from NCC and, obviously, presenting ES. The earliest report of seizures is available in the *Sakikku*, a Babylonian cuneiform medical diagnostic text from 1067 to 1046 BC where the current description of epilepsy is named *miqtu* (“the falling disease”) [4].

According to Eadie and Bladin [5] “with the probable exceptions of the absence and myoclonic seizures of today’s generalized epilepsy, the *Sakikku* mentions probable examples of all the major contemporary classificational types of epileptic seizures. The fact the ancient and unknown author or authors of the *Sakikku* saw fit to bring such phenomena together in the account indicates recognition of the fundamental kinship of these phenomena. The ascribing of them all to *miqtu*, suggest that they were all taken to be various expressions of the same underlying disorder. Moreover, the authors (s) also distinguished between *miqtu* and a possible pseudo-seizure.”

Historically, people with epilepsy were considered to be demonically possessed, to be witches or even insane [6]. *The history of epilepsy and its treatment in the western world dates back at least 4 millennia to the ancient civilization of the Middle East. Past and present treatments have been empirical, usually reflecting the prevailing views of epilepsy, be they medical, theological, or superstitious. Ancient physicians relied on clinical observation to distinguish between epileptic syndromes and infer their cause* [7]. In this period other peoples also worked on the field of epileptic seizures such as Atreya the father of the Indian Medicine who wrote the *Charaka Samhita* (sixth century BC) [8]. The *Huang Di Nei Ching* was written by a group of Chinese physicians between circa 770 and 221BC; they wrote on epilepsy and delivered a description about an epileptic seizure (epilepsy mania) [9].

In 400 BC Hippocrates, the father of medicine, offered another point of view on epilepsy that it was just another natural disease and could be treated through natural methods. *On the Sacred Disease* was regarded as the oldest surviving medical account of epilepsy, where he argued that the epileptic seizures were not sacred in its origins [5]. He supported the use of medicine and control of the diet in order to cure this disease based on his theories of medical methodology. While his methods were hardly scientific, he was the first to consider epilepsy to be a natural disorder and would be the only one to do so for centuries. After the Greeks the Romans took a view similar to that of the Babylonians as to the nature of epilepsy [6].

Magiorkinis et al. [10] said that “The first formal description of epilepsy as a disease should be attributed to the father of medicine, Hippocrates of Kos, in his classic treatise *On the sacred disease* (Πετοκα τετονα νοουσου). In this book, Hippocrates disputes the divine origin of epilepsy by saying: “This disease is in my opinion no more divine than any other; it has the same nature as other diseases, and the cause that gives rise to individual diseases. It is also curable, no less than other illnesses.”

After Hippocrates, the experience on ES in Alexandrian, Roman, Middle East, and Asian medicine did not reach higher progress, but we should highlight the work done by Diocles of Carystus, Praxagoras of Cos, Pedanius Dioscorides, and Aurelius Cornelius Celsus (circa 30AD) who wrote “Epileptic fits are not difficult to bring to an end, when they have commenced before puberty, and whenever the sensation of the coming fit begins in some one part of the body. It is best for it to begin from the hands or feet, next from the flanks, worst of all from the head” [5]. Aretaeus the Cappadocian was the first to describe visual, olfactory, and auditory auras (second century AD). Aelius (Claudius) Galenus (131–201AD) gave a definition of epilepsy: *Yet if there is not only convulsion of the whole body, but also interruption of the leading functions, then this is called “epilepsy.”* Caelius Aurelianus differentiated two types of ES: deep sleep from convulsive (fifth century). Paul of Aegina, the last of Byzantine writers in the late sixth or early seventh century, also delivered a definition of ES as paraphrases of those of Galen did, but he recognized that seizures in eclampsia proceed from the uterus [5]. Nevertheless, to consider the *Ancient Chinese Medicine* among those great delivers of knowledge is mandatory, and the classification of ES in the *Zhu Bing Yuan Hou Lun* Theu in five types was a great advance [9].

2.2. Medieval times

From our historical review on NCC, we know that mysticism and dogmatism continue influence all scientific fields including medicine, and many diseases were considered as a consequence of demonic possession; then patients presenting ES were managed as warlocks and witches. Several physicians wrote about ES in this period worldwide, and almost all kept the same point of view from ancient Great and Romans. The most famous medieval Islamic writers were Abu Bakr Muhammad Ibn Zakariya al-Razi (85–925), known as Rhazes, and Abu Ali al-Husayn ibn Abd Allah ibn Sina (980AD) from Persia, known in the west as Avicenna [11]. However in this period, there were other writers with some different criteria about ES that should be mentioned: Arnold of Villanova (circa 1234–1311) who defined ES as an occlusion of the chief ventricle of the brain [12]. In 1305, Bernard of Gordon adverted to the possibility of the existence of simple partial seizures [5, 13]. In 1314, John of Gaddesden (circa 1280–1361) wrote about epilepsy in his *Rosa medicinae* considering that ES without convulsion is possible and proposed three forms of epilepsy – minor, medium, and major – assigning the synonyms true, truer, and truest. Minor epilepsy is attributed to the obstruction of arteries, medium epilepsy to the obstruction of the nerves, and major to an obstruction of the ventricles of the brain [14]. However, Antonius Guainerius (died circa 1450) considered that the presence of convulsion and foam at the mouth must be part of the clinical feature of ES [15]. According to Singer [16] Antonio Benivieni (1443–1502) wrote: “Though the disease called epilepsy is among the best known of diseases, yet many are unacquainted with it in the form of which I saw it recently in a young Aretine girl. When attacked she did exhibit the usual symptom of falling down, nor did she foam at the mouth, but she would just stand still, moving her head and neck from side to side as if trying to see something, yet dumb, deaf, and insensible. On coming to herself and being asked what she had been doing she did not know in the least.”

Beyerstein [17] suggests that the curious behavior of the possessed people described in the classic *Malleus Maleficarum* (published in Germany in 1487) is likely symptoms of epilepsy or Tourette’ syndrome. At the age 13, Joan of Arc experienced moments of ecstasy with light,

heard voices of saints, and claimed to see visions with angels, all probably symptoms of epileptic seizure [18].

The first acknowledgement of St. Valentine being a patron saint for people with epilepsy is printed in *The Nuremberg Chronicle*, an illustrated book printed in 1493. St. Valentine was known for healing people with epilepsy around Europe including southern Germany, eastern Switzerland, Austria, and northern Italy [19].

2.3. Brief history of ES during the renaissance and the enlightenment

In the XIV to XVII centuries (European Renaissance), the Sciences is realized from the Catholic Church's chains, and as a consequences of that, the number of writers with new criteria about ES increased remarkably, and also theories regarding the mechanism that causes the epileptic fits as well as new classifications of the disease came forth [10]. There were some peoples trying to differentiate epilepsy and demonism.

In 1549, some aspects on ES were written in the first book delivered "about neurology" (Pratensis: *De Cerebri Morbis*) according to Prestonk where the author adopted Galen's subdivision of epilepsy into three types [20].

By the end of the sixteenth century, Martinus Rulandus (1532–1602) delivered a booklet about now known as benign Rolandic epilepsy.

In the seventeenth century, Thomas Willis goes in front of the scientific revolution, and apart from his description about anatomy of the blood supply to the brain among other aspects, he wrote about ES describing the a typical tonic–clonic seizure as the characteristic epileptic convulsive phenomenon: "...The Epileptick fit or assault seems to be the only a universal and more cruel Covulsion..." [5]. Paracelsus (1493–1541 AD) dealt with epilepsy. He agrees that epilepsy may originate from the brain or the liver, the heart, the intestines, and the limbs but he also suspected that epilepsy of a sick priest derived from the presence of brain cyst [2]. Paracelsus views about the human nature and the construction of the human body from mercury, sulfur, and salt which led him to a different model for the causes of epilepsy. Ioannes Marcus Marci (1595–1667 AD), a Bohemian physician and scientist, broadened the definition of epilepsy "to any affection of the body where the victims are disordered in their minds, while the members [of the body], be it all, or some, or only one, are moved against their will" [10]. John Locke (1632–1704) worked on hysteria and epilepsy.

From the eighteenth century, we should highlight the work done by Herman Boerhaave (1669–1738), George Cheyne (1671–1743), and William Cullen (1710–1790) who wrote about spasmodic affections without fever together with tetanus and chorea or St. Vitus dance [5]. Samuel Tissot a Swiss physician (1728–1797) defined epilepsy as a convulsive illness in which every attack interferes with the senses and the understanding and is accompanied by convulsive movements of various degrees of severity involving many parts of the body [5].

Pedro de Horta a Mexican physician wrote the first book on epilepsy in the New World (1754) published in Madrid. The book contained a discussion of the distinctions to be drawn between the different medical disorders embraced by the conditions known locally as "Telele" and "Tembeleque" [21]. William Heberden, an English physician (1710–1801), included complex

partial seizures (which did not become secondarily generalized) and absence seizures in his concept of epilepsy.

2.4. Brief history of ES during the eighteenth and nineteenth centuries

Herman Boerhaave (1668–1738) provided a rather strict definition of epilepsy: “Epilepsy is the sudden abolishment of all vital functions with accompanying increase of mobility and convulsions in all body muscles,” whereas he adopts the Galenic classification of epilepsy [10].

The Dutch-Austrian Gerard van Swieten (1700–1772) wrote a chapter on epilepsy in which he described extensively the clinical characteristics of various forms of the disease and discusses epilepsy in comparison with apoplexy and hysteria [22]. By law, at that time peoples presenting ES (in Sweden) is prohibited to get married (1757).

The Swiss physician Simon August André David Tissot (1728–1787) published in 1770 the first major treatise on epilepsy that is considered to be a milestone in the scientific research on epilepsy. At the same time, he refused the theory of the influence of the moon on epileptic seizures and accepted the hereditary forms of epilepsy. The Italian naturalist Felice Gaspar Ferdinand Fontana (1730–1803), in a series of experiments on stimulation of the cerebral cortex with electricity, demonstrated that convulsions could be produced by pressure on the brain, but not by irritation of the dura, as commonly believed [23, 24]. Thomas Beddoes (1760–1808) described accurately the premonitory symptoms developing before the onset of an attack. Sir Charles Locock introduced the first generation of antiepileptic drug (AED), bromides (in 1850); since then it was the only available medication for treatment of ES for the next 50 years [19]. In November 30, 1893, the Ohio Hospital for patients presenting ES was opened.

Connecticut becomes the first American state to prohibit marriage for people with epilepsy (1895). House Bill 681 denied the rite of marriage, or to live together unmarried, to individuals 45 years old or younger who either had epilepsy or were a pauper, imbecile, or feeble-minded. Minimum prison sentence would be 3 years. Many states would follow with similar rules. This bill was repealed in 1953 with the passage of Public Act 254 [19].

The nineteenth century was the “golden era” of French medicine, and the English school of physicians also made a great contribution to the development of knowledge about ES. Marie Jean Pierre Flourens (1794–1867) established the basic rules regarding the irritability and sensibility of the central nervous system. The French psychiatrist Jean-Étienne Dominique Esquirol (1772–1840) worked on epilepsy and insanity and identified severe from light epileptic seizures (grand mal and petit mal). Based on a large amount of clinical data, postmortem reports, and his personal experience, Antoine Baron de Portal (1742–1832) concluded that anatomical dissection did not reveal any lesions either in the brain or other parts of the body from patients affected by ES.

From the English school of physicians, numerous writers performed a great contribution to the better knowledge of ES, and the list of most famous writers is as follows: (1) James Cowles Prichard (1786–1848), Richard Bright (1789–1858), Marshall Hall (1790–1857), Robert Bentley Todd (1809–1860), Astley Cooper (1768–1841), John Russell Reynolds (1828–1896), and William Richard Gowers (1845–1915) [5].

In the late 1800, and the beginning of 1900, many American states had colonies for patients presenting ES. The first colony was created in 1896 at the Shaker colony, Sonyea, New York (Craig Colony). Some colonies had facilities for education or vocational training to epileptic patients, while other had not those facilities, and patients remained in disadvantage conditions dealing with isolation, side effects, and poor prognosis [25].

In this period, some German and Dutch physicians reached high levels of development in research on ES. Karl Friedrich Burdach (1776–1847) made a remarkable job on anatomical abnormalities observed in the brain leading to ES. Friedrich Gustav Jakob Henle (1809–1895), writing in 1853, noted that epileptic convulsions were due to increase or decrease of blood flow in the hemispheres, and Wilhelm Griesinger (1817–1868), in 1868, *employed for the first time the term “psychomotor symptoms” in epileptoid conditions* [10].

2.5. Brief history of John Hughlings Jackson

Currently, the general community of epileptologists countrywide agrees that John Hughlings Jackson (1835–1911) is the father of modern epileptology. He was a very active researcher from 1861 to 1870, and almost all of his results have been confirmed by other authors. Based on his knowledge on anatomo-pathology, he studied patients with ES. His first publication from hospital records and review of the medical literature was made in 1861; 2 years later he reported his observation on focal seizures mainly in syphilitic patients and confirmed lesion on the brain contralateral to the focal ES. Jackson believed that loss of consciousness was secondary to disorder of the very highest level of the cerebral hemisphere and the seizures started at the lower levels and then spread to higher ones through interconnecting fibers as well as to neighboring cells of the same level. Jackson said: “I do not use the term cortical epilepsy because both epileptic and epileptiform seizures are, to my thinking, cortical fits... I formerly used the term epilepsy generically for all excessive discharges of the cortex and their consequences...” He mentions, writing in 1876, a number of expressions used by patients to describe those symptoms of the so-called ‘intellectual aura’, some of which resemble states known in modern psychiatry and neurology as ‘*déjà vu*’ [10].

2.6. Twentieth century

In 1903, Herman Bernhard Lundborg (1868–1943) published the first description of progressive myoclonic epilepsy [26].

In 1904, William P. Spratling described his job done at Craig Colony for years as the medical superintendent and named him as epileptologist because his services were rendered to epileptics. Today he is considered the first epileptologist in history [10].

Patients with seizures have been denied many rights throughout the ages including education and work training. In 1907, legislation denying immigrants with epilepsy (as well as tuberculosis and physical disabilities) was passed.

In 1906, Santiago Ramón y Cajal (1852–1934) from Spain received the Nobel Prize of Medicine as a reward of his efforts [27]. He made remarkable advances in the field of the microscopic structure of the central nervous system and described the histological structure of the neuron cell and its synapses.

In March 1907, Indiana was the first state to officially pass a eugenics law regarding to sterilization of individuals, including idiots and imbeciles, in state custody. Epileptic patients were not officially included in that statement, but in the early 1900s, terms such as idiots, imbeciles, and feeble-minded were used interchangeably when referring to people with ES. Many other states did the same and included people with ES as well. This law influenced Nazi eugenics during the Holocaust [19].

In September 1909, the ILAE held its first meeting and members from Algeria, the USA, and eight European countries attended. Ketogenic diet was used for the first time in the treatment of epilepsy in 1911 by the French physicians Guelpa and Marie. In 1912, during experimental-induced seizures, electric changes in the brain were noticed by Kaufmann, and at the same time, Alfred Hauptmann (1881–1948) synthesized phenobarbital, one of the first AED [28], whereas Walter Dandy (1886–1946) described in 1918 and 1919 pneumoventriculography and pneumoencephalography [10]. Years later, these radiographic tests were of great value in the management of peoples with ES. Everybody knows that people with ES are denied the right to serve their country during the WW I (1914–1918) and WW II (1939–1945).

In 1929, Hans Berger (1873–1941), a psychiatrist, developed the human electroencephalograph (EEG) in Germany. In 1932, Hans Berger informed about patients presenting tonic-clonic ES and an associated change on EEG in the postictal period (slow waves) and described the typical 3/s rhythmic spike-slow waves in patients with minor seizures. Its important application from the 1930s onward was in the field of epilepsy. The EEG also helped to find the origin of the ES, to differentiate different types of ES, and shows signals of brain damaged due to ES and expanded the possibilities of neurosurgical treatments, which became much more widely available from the 1950s onward in London, Montreal, and Paris [29]. The job on epileptic EEG done by Berger was completed by Frederic Andrews Gibbs (1903–1992) and Erna Gibbs (1904–1987) who in collaboration with William G. Lennox established the correlation between EEG findings and epileptic convulsions [30, 31]. Around the same time, the main progress in the history of ES is related to the development and introduction of new AED for a better management of epileptics. During the same period, H. Houston Merritt (1902–1979) and Tracy Putnam (1894–1975) discovered phenytoin and its effect on the control of epileptic seizures [32–35]. Phenytoin became the first-line AED for the control of partial and generalized tonic-clonic seizures and status epilepticus. In 1946, Richards and Everett added trimethadione to the list of AEDs mainly for the treatment of absence seizures [36].

During the 1950s, new drugs came up such as carbamazepine in 1953 [37], primidone in 1954, ethosuximide in 1958 by Vossen [38], sodium valproate in 1963 by Meunier et al. [39], and sultiame. Buchtal and Svensmark were the first ones in 1960 to measure the levels of the anti-epileptic drugs in the blood [40]. In 1967, valproate came up as a new promising antiepileptic drug. Valproate was initially synthesized in 1881 by Beverly Burton in the USA and was initially employed as an organic solvent [41]. Newer AED such as vigabatrin (1989), lamotrigine (1990), oxcarbazepine (1990), gabapentin (1993), felbamate (1993), topiramate (1995), tiagabine (1998), zonisamide (1989 in Japan and 2000 in the USA), levetiracetam (2000), stiripentol (2002), pregabalin (2004), rufinamide (2004), lacosamide (2008), eslicarbazepine (2009), and perampanel (2012) were included in the list of medicines to be prescribed [42]. The research on antiepileptic

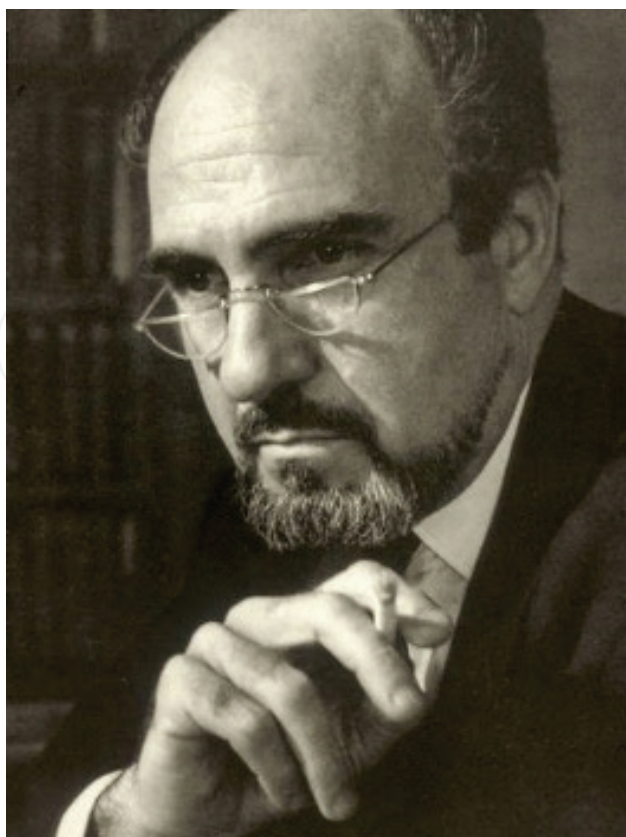


Figure 1. Henri Jean Pascal Gastaut (1915–1995) (adopted by public domain at <http://www.lennox-gastaut.de/Krankheitsbild.112.0.html>).

drugs is an active field, and many drugs are currently under development in clinical trials including eslicarbazepine acetate, brivaracetam, and retigabine [42].

One special space in this chapter should be dedicated to the memory of Henri Jean Pascal Gastaut (1915–1995) (**Figure 1**). He was an important and influential figure in the field of EEG whose work was intensified during the 1950s. He also worked with William Gray Walter (1910–1977) in Bristol learning the basics of EEG and discovered photic stimulation as an EEG seizure activator [42].

Gastaut also worked with Wilder Penfield (1891–1976) and Herbert Jasper (1906–1999) and investigated the role of thalamic reticular structures in the genesis of metrazol-induced generalized paroxysmal EEG discharges and developed the concept of centrencephalic seizures in 1949 [43]. Beyond any doubt Gastaut was one of the greatest European researchers in epileptology from our time.

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