Chapter

Introductory Chapter: Epilepsy—The Long Journey of the Sacred Disease

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1. Introduction

Epilepsy is the most common neurological disorder globally, affecting approximately 50 million people of all ages [1]. It is one of oldest diseases described in literature from remote ancient civilizations 2000–3000 years ago. Despite its old description and its wider spread, epilepsy is still surrounded by myth and prejudice which can be overcome only with great difficulties. These myths and prejudice might have its historical origin. The aim of this introductory chapter is to follow the origin of epilepsy in ancient cultures, highlight the myth and stigmatism associated with epilepsy, and follow the major milestone in its development as a disease entity. The term epilepsy is derived from the Greek verb epilambanein, which by itself means to be seized and to be overwhelmed by surprise or attack. Therefore, epilepsy means a condition of getting over, seized, or attacked [2].

2. The major milestones in the history of epilepsy

The history of epilepsy goes together with the history of humankind in the globe. The earliest recorded account of epilepsy can be traced to the earliest civilization developing in Mesopotamia (the old name of the country IRAQ) almost 2000–3000 BC. These earliest establishments include the Sumerian, Babylonian, Assyrian, and Akkadian civilizations. The first description of epilepsy was written in the Akkadian language about 2000 BC in which the author described a condition similar to epileptic seizures in a patient. He described a patient whose neck turns to the left side, with his hands and feet being tense, with his eyes widely opened, and with his mouth drooling froth without him knowing. The condition diagnosed as antasubbû translated as the hand of sin brought about by the god of the Moon [5].

In a tablet from the Babylonian series (1067–1046 BC) present in the Babylonian collection of the British Museum(47,753), we find a report containing a detailed description of the symptoms of the condition known today as epilepsy with the supernatural forces suggested as an etiology (**Figure 1**). This table is written in Neo-Babylonian script dated approximately at the middle of the first millennium BC [4]. In this tablet, epilepsy was called Sakikku miqtu ("falling disease"), and the author describes various signs for the diagnosis, treatment, and prognosis of epilepsy. The etiology of epilepsy was presumed to be the effect of demons, evil spirits, and ghosts, and features of generalized seizures, simple and complex partial seizures, gelastic seizures, nocturnal epilepsy, febrile seizures, status epilepticus,

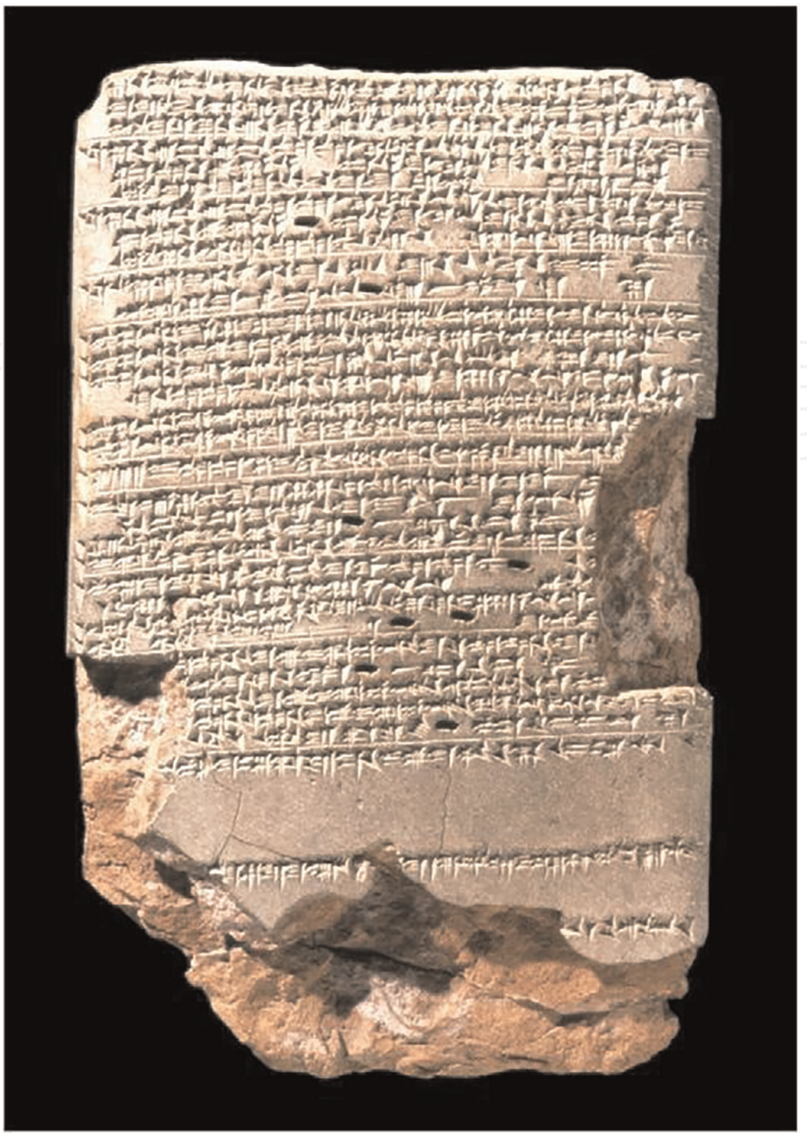

Figure 1.
British Museum Babylonian collection; Epilepsy tablet (47753) is an important Neo-Babylonian manuscript of Tablet 26 of the Diagnostic Handbook, the canonical Akkadian medical diagnostic series, composed of 40 tablets arranged into six chapters. This tablet gives symptoms of epilepsy and assigns disease names and etiologies to the various ways that the symptoms present themselves. Adopted by public domain at http://cdli.ox.ac.uk/wiki/doku.php?id=tablet_on_epilepsy.

chronic epilepsy, narcolepsy, and postictal states were described. This is by far the first written account of epilepsy [6, 7]. The king Hammurabi in his legislation (1790 BC) also refers to epilepsy (**Figure 2**). The legislation stated that a person with epilepsy could not marry, or testify in court, and a slave could be returned and the money refunded if bennu appeared within the month after the purchase. According to the researcher Marten Stol, bennu is another term for epilepsy [8].

The ancient Egyptian civilization medical reports (1700 BC) also contribute to the history of epilepsy by reporting five separate patients who shudder exceedingly. Probably these were the first reports of focal epilepsy following cortical irritation caused by examination or probing of wound or from an injury, e.g., gaping wound of the head. The last represents the earliest description of posttraumatic epilepsy [3].

In Greek civilization, epilepsy was referred to by many names including seliniasmos, sacred disease, Herculean disease, and demonism. These names related either to the etiology of the condition or to a figure. The scariness of the disease in Greek civilization may be related to the belief that epilepsy is vengeance of Mene,

Figure 2.
The Hammurabi Obelisk containing his legislation (1790 B.C.). From the Louvre collection. Adopted by public domain at https://www.pinterest.com/pin/178173728990949335/.

Goddess of the Moon, on those with epilepsy and its cure could be of divine origin [3]. On the other hand, it might reflect the ambiguity of the disease, affecting body and mind, inspires, and has an Apollonian aspect. It is also considered as a disease of the genius since men like Persian King Cambyses II (522 BC), the Roman emperor Caesar, and the hero Hercules are said to have had epilepsy [3].

The father of the medicine, Hippocrates (**Figure 3**), in his book *On the Sacred Disease* (400 BC) (although still a controversy exists about the book authorship), who raised the first dispute about the divine origin of the epilepsy, had said "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." Hippocrates argued that epilepsy originates in the brain when an excess of phlegm enters the blood and is not of divine nature. He criticizes previous doctors who attribute epilepsy to divine intervention by stigmatizing them as magicians and charlatans [9]. Hippocrates was also the first to attempt a scientific approach toward the study of epilepsy by suggesting a possible etiology and therapy for the disease. He suggests brain dysfunction and heredity factors play a role in the etiology of epilepsy [10, 11].

By calling epilepsy as the great disease, he originates the term grand mal, and by linking convulsion to head injuries, he gives the base for the term posttraumatic epilepsy. He noticed that injury affecting the left side of the head could produce a right-sided convulsion. He describes the symptoms of focal seizures and suggests

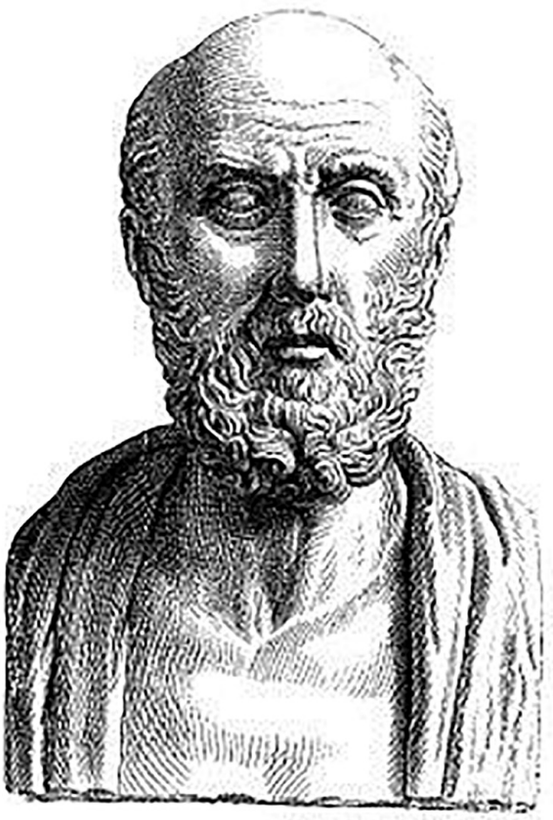

Figure 3.
Hippocrates wrote on the sacred disease 400 B.C. Adopted from the free domain https://en.wikipedia.org/wiki/Hippocrates.

many precipitating factors, among these are changes in the winds and temperature, exposure of the head to the sun, crying, and fear, and also he gives a prognostic clue by suggesting that disease manifesting at an early age has worse prognosis, and for older peoples, the prognosis is better. He considered epilepsy a curable disease unless if it is of long duration and ingrained as to be more powerful than the remedies that are applied [12]. Furthermore, Hippocrates in his book *On the Sacred Disease* described the first neurosurgical procedure, a craniotomy. He said craniotomy should be performed at the opposite side of the brain of the seizure in order to spare patients from "phlegmad" that caused the disease [13]. Many other famous Greek philosophers also wrote about epilepsy in their works like Plato (428–348 BC), who suggested in his laws a specific punishment for people selling slaves with epilepsy. Also Aristotle (384–322 BC), in his works *Problems*, *On Sleep and Waking*, and *Ethica Nicomachea*, presented his theories and views about epilepsy that had impressed many physicians in the post-Hippocratic and even Medieval era which had led the Catholic Church to validate his teaching and work and consider it as indisputable and beyond any criticism [3, 14–16]. The dominance of the Catholic Church during the era of the Middle Ages led to the continued existence of religious and magic beliefs about epilepsy.

In the old Chinese civilizations, also there are some references to the disease. Old Chinese physicians discuss a condition similar to generalized convulsions, T'ien-Hs'ien (770–221 BC). They thought that emotional shock bore by the mother during pregnancy is the cause for epilepsy in a child. Later on, Chinese scientist tries to classify seizures according to the age at onset, clinical symptoms, and the possible etiology. During the Tang dynasty (682 AD), two different classifications were proposed on the basis of the resemblance of noises a patient might utter during seizures to voices of animals and different organs as presumed sites of seizure origin [17, 18].

3. Epilepsy evolution as a disease entity

The first liberation of epilepsy from religious theories such as divine punishment or possession was made in the eighteenth and nineteenth centuries [19, 20]. In these centuries, a tremendous advance in the research on epilepsy with great emancipation from religious superstitions was made. At the beginning of the eighteenth century, epilepsy was regarded as idiopathic disease derived from brain and other internal organs. The work of William Culen (1710–1790) and Samuel A. Tissot (1728–1797) builds up the bases of the modern epileptology, and they described different types of epilepsies.

At the beginning of the nineteenth century, French physicians started to publish their research in the field of epileptology. Maisonneuve (1745–1826) [21], Calmeil (1798–1895) [22], and Jean-Etienne Dominique Esquirol (1772–1840) are among the famous physicians who work in this field. Maisonneuve stressed the importance of hospitalization of epileptic patients, categorized epilepsy into idiopathic and sympathetic, and described the so-called sensitive aura of sympathetic epilepsy. Esquirol distinguished between petit and grand mal and along with his pupils Bouchet and Cazauvieilh studied systematically insanity and epilepsy, conducting clinical and postmortem studies [19, 20]. In the second half of the nineteenth century, the etiology and pathophysiology of epilepsy and the topographic localization of epileptic seizures were stressed on. At that time important works were published by prestigious physicians such as Theodore Herpin (1799–1865) in 1852 and 1867, Louis François Delasiauve (1804–1893) in 1854, John Russell Reynolds (1828–1896) in 1861, and Sir William Richard Gowers (1845–1915) in 1881 [19].

The physiologist Fritsch (1838–1927) and the psychiatrist Hitzig (1838–1907) give the first proof that the brain was the origin of epilepsy. They presented experiments in which they provoked seizures by electric stimulation in the brain cortex of dogs [23]. An English neurologist, John Hughling Jackson (1835–1911), studied the pathological and anatomical bases of epilepsy extensively, and he set the scientific bases of epileptology. Jackson in 1873 defined epilepsy as the name given for occasional, sudden, excessive, rapid, and local discharges of gray matter. The presence of localized lesions on the cortex involved by epilepsy was the core of his studies on convulsions [19].

A Spanish pathologist, histologist, and neuroscientist, Santiago Ram'ony Cajal (1852–1934) at the beginning of the twentieth century, made an important advance in the field of the microscopic structure of the brain and nervous system. He was awarded with the Nobel Prize in 1906 for his advancement in the description of the structure of the neurons and synapses by employing the Golgi staining in the study of the nervous system. The famous book *The Borderlands of Epilepsy*, published by Sir William Richard Gowers in 1907, focuses on vagal and vasovagal attacks, faints, vertigo, migraine, and some sleep symptoms, especially narcolepsy.

Lennox (1884–1960) and Cobb (1887–1968) during the 1920s studied the effects of starvation, ketogenic diet, and altered cerebral oxygen in seizures. In their published monographs entitled "Epilepsy from the Standpoint of Physiology and Treatment" and "Epilepsy and Related Disorder" and their important paper summarizing their research entitled "The Relationship of Certain Physiochemical Processes to Epileptiform Seizures), they concentrate on the effects of various stimuli to the generation of epileptic convulsions. Most of these studied stimuli, as starvation, ketogenic diet, and lack of oxygen, give negative results. [24–26]. The relationship of behavioral changes to temporal lobe lesion was discovered during the 1940s by Klüver (1897–1979) and Bucy (1904–1992) who noticed this association on monkeys. Jasper (1906–1999) and Kershmann in 1941 proved that the temporal lobe is the site of origin of psychomotor seizures [27].

In 1969, James Kiffin Penry (1929–1996) published important treatises such as the series Basic Mechanisms of the Epilepsies and afterward Antiepileptic Drugs, Neurosurgical Management of the Epilepsies, Complex Partial Seizures, and their Treatment and Antiepileptic Drugs Mechanisms of Action and Advances in Epileptology. In the same year, Gastaut managed to organize a meeting in Marseilles attended by 120 members of the International League Against Epilepsy (ILAE), and preliminary classification of epilepsies was presented to a commission on the terminology of epilepsy. The General Assembly of the ILAE accepted the first publication of clinical and electroencephalographic classifications of epileptic seizures [28–30].

A great milestone in the understanding of epilepsy was by recording abnormal electrical discharge associated with seizures. The first scientist who notices electric changes in the brain during experimentally induced seizures, associating epileptic attacks with abnormal electric discharges, was a Russian physiologist, Kaufman (1877–1951), in 1912. In the same year, Pravdich-Neminsky (1879–1952), a Ukrainian physiologist, published the first animal EEG and the evoked potential of the mammalian (dog) [31]. The theories of the association of electric stimuli and brain activity inducing seizures dated back to the nineteenth century from the work of Fritch (1838–1927) and Hitzig (1838–1907), Caton (1842–1926), and Adolf Beck (186–1942) who did their experiments by inducing seizure in dogs, rats, and rabbits, by applying electric stimuli on the animals' cortex [30].

Hans Berger (1873–1941), a German neurologist, reported the first record of human EEG in 1929 (**Figure 4**). In 1932, he reported sequential postictal EEG changes after a generalized tonic-clonic seizure, and in 1933, he published the first example of interictal changes and a minor epileptic seizure with 3/s rhythmic waves in the EEG [32, 33]. Initially, his work was confronted by controversies and suspicions within the scientific society, but later Adrian (1899–1977) and Matthews

Figure 4.
Hans Berger, the first who record EEG in human. Adopted from the free domain https://neupsykey.com/historical-aspects-of-eeg/.

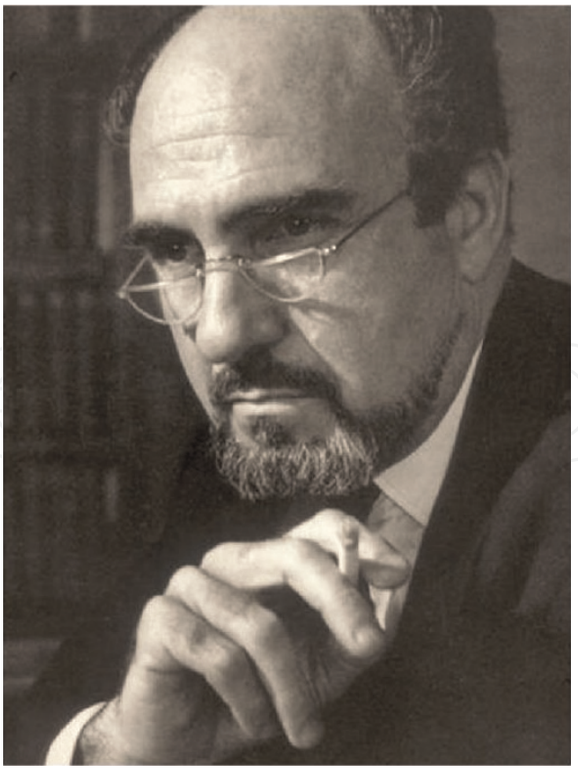

Figure 5.
Henri Jean Pascal Gastaut; the first who discover the photic stimulation as an EEG seizure activator and describe two syndromes adopted his name. Adopted from the free domain https://openi.nlm.nih.gov/detailedresult.php?img=PMC4158257 ERT2014-582039.002&req=4.

confirmed his results. The work of Berger on epileptic EEG was completed by an American neurologist Frederic Andrews Gibbs (1903–1992), and his wife and technician Erna Leonhardt-Gibbs (1904–1987), who is in collaboration with Lennox, establishes a correlation between EEG findings and epileptic seizures [34, 35]. In 1941, Gibbs and Lennox published the *Atlas of Electroencephalography* in which they included also mechanical and mathematical analyses of EEG [36].

Henri Jean Pascal Gastaut (1915–1995) did the great advance in the field of EEG in the 1950s (**Figure 5**). He discovered the photic stimulation as an EEG seizure activator and studied the role of thalamic reticular structures in the genesis of metrazol-induced generalized paroxysmal EEG discharges and developed the concept of centrencephalic seizures. Furthermore, he founded the International EEG Federation, and, in 1953, he became the head of the Marseilles Hospital Neurobiological Laboratories establishing a school of neurology that dominated for the next decades. He participated in the foundation of many education centers and research units. Also, he defined five major human EEG patterns (lambda waves, pi rhythm, mu rhythm, rolandic spikes, and posterior theta rhythm) and described two clinical syndromes that carried his name: Gastaut syndrome (a type of photosensitive epilepsy) and the Lennox-Gastaut syndrome (severe childhood encephalopathy) [37].

4. Evolution of anticonvulsant therapy

Herbal and chemical substances were the major therapy for epilepsy before the second half of the nineteenth century. In 1857, Sir Locock (1799–1875) discovered the anticonvulsant and sedative effect of potassium bromide, and he starts to treat his patients with this substance. Since that time, potassium bromide became the first drug of choice in the treatment of epilepsy, until the discovery of phenobarbital

by a German physician, Hauptmann (1881–1948), in 1912. The drug company Bayer, under the brand name Luminal, introduced phenobarbital to the market. Hauptmann used phenobarbital as a sedative for his epileptic patient, and he discovered that their epileptic attacks were susceptible to the drug. The absence of the sedative effect of phenytoin, the next drug used as antiepileptic, leads to the delay of its use as anticonvulsant until 1938 despite its synthesis by Heinrich Biltz (1865–1943) in 1908. It was introduced as an anticonvulsant by Merritt (1902–1979) and Putnam (1894–1975) in 1938 under the name Dilantin. Phenytoin substitutes potassium bromide and phenobarbital as the first-line drug of choice for the prevention of partial and tonic seizures and for the treatment for acute cases of epilepsies and status epilepticus [38–42].

A new antiepileptic drug was introduced in 1946 under the name of trimethadione. Richards and Everett report the use of trimethadione to prevent pentylenetetrazol- induced seizures and for the treatment of absence seizures. In the 1950s, a set of new antiepileptic drugs were introduced: carbamazepine in 1953, primidone in 1954, ethosuximide in 1958, and sodium valproate in 1963 [43]. Serum level of antiepileptic drugs was first introduced in 1960 by Buchtal and Svenmark [44]. Other antiepileptic drugs were introduced in the 1970s, including clobazam, clonazepam, and piracetam. The last decade of the twentieth century and the early years of the twenty-first century mark the beginning of the use of new antiepileptic drugs. Among these drugs are vigabatrin (1989), lamotrigine (1990), gabapentin (1993), felbamate (1993), topiramate (1995), tiagabine (1998), zonisamide (1989 in Japan and 2000 in the USA), levetiracetam(2000), pregabalin (2004), rufinamide (2004), lacosamide (2008), eslicarbazepine (2009), and perampanel (2012). The field of anticonvulsant drugs is dynamic and in the last two decades a new generation of antiepileptic drugs introduced to the market, and there are a number of very new antiepileptic drugs which are under various stages of drug development such as brivaracetam and retigabine. The aim of the researches in this field is to improve tolerance and effectiveness of the drugs and to improve the quality of the life of the patient through improvement in the pharmacokinetics, safety, and efficacy of these drugs.

The role of diet in the management of epilepsy dated back to the era of Hippocratic were fasting and other types of diet used for the treatment of epilepsy [13]. The use of ketogenic diet (diet full with fat and low in protein and carbohydrates) for the treatment of epilepsy started in 1911 by two French physicians, Guelpa and Marie, who reported a decrease in the number of seizures in 20 children and adults with epilepsy when treated with ketogenic diet [45]. In 1922, an American physician, Hugh Conklin, stresses the importance of the ketogenic diet in the management of epilepsy since he believed that epilepsy caused by toxins damages the brain cell. He had a personal interest in ketogenic diet and tried to treat his nephew, who suffered from drug-resistant epilepsy, by this method. By using ketogenic diet, he had encouraging results. Since that time, many authors published many papers, but none explained the anticonvulsive mechanisms of ketogenic diets [46, 47].

In 1831, the first neurosurgical operation for an epileptic patient with brain abscess was done by Heyman [30]. Posttraumatic epilepsy was the most common indication for the operations done at that time. At the beginning of the twentieth century, a great advance in neurosurgical operations for epileptic patients is done, started by Dandy (1886–1946) who introduced hemispherectomy in 1923 and continued by Gibbs and Lennox in 1938 who introduced the notion of operating the epileptogenic focus [31, 48]. A further advance in the surgical procedure for epileptic patients was done by Penfield, Jasper, and Theodor Brown Rasmussen (1910–2002). They introduce the Foerster method for removing epileptogenic lesions in epileptic patients, invented Montreal procedure (using local anesthesia to

remove part of the skull and expose brain), and published one the greatest classics in neurology, *Epilepsy and the Functional Anatomy of the Human Brain*, in 1954 [49, 50]. On the other hand, Van Wagenen and Herren (1897–1961) introduce the procedure of callosotomy, and Bailey (1892–1973) attempts temporal lobectomies for psychomotor seizures [51, 52].

The early introduction of EEG and the use of electrocorticography for intraoperative localization and later on the advent of modern diagnostic techniques such as MRI, PET, and SPECT was an important advance in the development of surgical techniques and approaches. Recently the application of microsurgery and the use of multiple transaction and gamma knife had revolutionized the neurosurgical operations for epileptic patients.

5. Misconception about epilepsy

Throughout the history of epilepsy, many misconceptions and wrong beliefs about the disease are conveyed. Some of these are referred to earlier in this chapter. These misconceptions and beliefs are variable in different parts of the world, from society to society and era to era, and it may lead to rejection, denial of education, and isolation in both developed and developing countries.

In the antiquity, one of the popular beliefs was that epilepsy is a contagious disease. People used to spit at a person with seizure and refuse to use the same dish. These beliefs continued in the Middle Ages where the clergy and synods of the early Christian church separated the possessed from the faithful because they thought that the possessed would desecrate the holy objects and would infect the sharing dishes and cups [53]. Berthold of Regensburg (1220–1272), a thirteenth-century-preacher, added breath as a rout of infection, and he warns people not to talk or bath with patients with seizures since the contagious nature of the infection is transmitted through the evil breath [4]. The beliefs that epilepsy is an infectious process continued until the eighteenth century [54].

Figure 6.
Avicenna (Ibn Sina) (A) and Abubakr Muhammad ibn Zakariyya al-Razi (B) written manuscripts about epilepsy, which had great influences on the students and universities in Eastern and Western world till the 18 century. Adopted from the free Domain http://www.muslimphilosophy.com/sina/gal/IS-gal-16.htm and https://www.researchgate.net/figure/Portrait-of-Abubakr-Muhammad-ibn-Zakariyya-al-Razi-or-Rhazes-865-925-CE_fig1_236331515.

Other wrong beliefs were that people with epilepsy were demoniacs and that seizures caused by an unclean dumb and deaf spirit were common among priests in the old Christian world. These beliefs can be attributed to the biblical story of Jesus healing a boy with symptoms of an epileptic seizure. In the medieval Islamic era, we cannot find referring to epilepsy as caused by demons in any of the scientific texts of epilepsy written in that era. The two famous Islamic physicians, Avicenna and Mohammed Ibn Zakariya AL-Razi (**Figure 6**), had written manuscripts about epilepsy, which had great influences on the students and universities in Eastern and Western world till the eighteenth century [55]. Nowadays, still, misconceptions and wrong beliefs are prevalent and widely spread among societies from developing and developed countries throughout the world.

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