

Hallmarks in the History of Epilepsy: From Antiquity Till the Twentieth Century

Emmanouil Magiorkinis, Kalliopi Sidiropoulou
and Aristidis Diamantis
*Office for the Study of History of Hellenic Naval Medicine,
Naval Hospital of Athens,
Greece*

1. Introduction

1.1 First reports on epilepsy

The history of epilepsy is intervened with the history of humanity. One of the first descriptions of epileptic seizures can be traced back to 2,000 B.C. in ancient Akkadian texts, a language widely used in the region of Mesopotamia. The author described a patient with symptoms resembling epilepsy:

*his neck turns left, his hands and feet are tense and his eyes wide open, and
from his mouth froth is flowing without having any consciousness.*

The exorciser diagnosed the condition as 'antasubbû' (the hand of Sin) brought about by the god of the moon (Labat, 1951).

Later reports on epilepsy can also be found in Ancient Egyptian medical texts. The Edwin Smith surgical papyrus (1700 B.C.) refers to epileptic convulsions in at least five cases (cases 4, 7, 29, 40, 42). Descriptions of epilepsy can also be found in ancient Babylonian texts; epileptics are thought to be afflicted by evil spirits. (Longrigg, 2000). The *Sakikku*, one of the oldest Babylonian medical texts (1067-1046 B.C.), refers to epilepsy with the terms 'antasubba' and 'miqtu'. The translated Babylonian text describes unilateral and bilateral epileptic fits, the epileptic cry, the incontinence of feces, the description of simple and complex epileptic seizures, the epileptic aura and narcolepsy (Eadie & Bladin, 2001). The Hamurabbi code (1790 B.C.) also refers to epilepsy. The code states that a slave could be returned and the money refunded, if *bennu*, another word for epilepsy (Stol, 1993), appeared within the month after the purchase. In Indian medicine, Atreya attributed epilepsy to a brain dysfunction and not to divine intervention. In the *Caraka Saṃhitā Sutra* (6th century B.C.), he defines epilepsy as:

*"paroxysmal loss of consciousness due to disturbance of memory and [of] understanding of mind
attended with convulsive seizures"* (Pirkner, 1929).

In the Indian text, four different kinds of epilepsy are described along with a description of premonitory symptoms and a type of epilepsy called 'Abasmara', in which the patients lose their memories.

¹ One can easily note the similarity between the Akkadian word *antasubbû* and the Babylonian *antasubba*

1.2 Epilepsy in ancient Greece: the era before Hippocrates

The nosological entity of epilepsy is found under many names in Ancient Greek texts: seliniamos (σεληνιασμός), sacred disease, Herculan disease (because it affected the semi-god Hercules) or demonism. After all, the word 'epilepsy' (επιληψία) originates from the Greek verb "epilambanein" (επιλαμβάνειν), which means 'to seize, possess, or afflict'. The disease was initially called sacred, because of the belief for its divine origin. In his work *Lithica*, Orpheus describes eloquently the vengeance of Mene, goddess of the Moon, in the form of epilepsy (Gottfried et al., 1805):

*".... to prove them sufferers from the sacred ill
For quickly will they bend and forwards tilt,
As to earth it draws them. Smear'd by froth
From their own mouths, hither and tither will they turn,
And wallow on the ground. For filled with anger towards them
She laughs to see their woe, Mene, the horrid and swift"*

Ancient Greeks considered epilepsy to be a 'miasma'² (μίασμα) which was cast upon the soul. Considered a divine punishment for sinners, an aura of mysticism and superstition surrounded epilepsy; the disease was connected with *Selene* (Σελήνη), the goddess of the Moon, since people who offended her were afflicted with epilepsy. Depending on the special symptoms of the epileptic seizure, the Greeks would attribute the fits to a different deity such as Cybele, Poseidon, Mars, Hekate, Hermes or Apollo. According to the Hippocratic texts, for example, if the symptoms included teeth gnashing or convulsions on the right side, then epilepsy was attributed to Cybele, whereas if the patient screamed like a horse, then god Poseidon was to blame (Hippocrate, 1849c).

According to Plutarch (50-120 A.D.), all babies in ancient Sparta were examined by the 'Lesche' (Λέσχη), a council of the elder of Sparta; epileptic babies were left to Apothetae, a short chasm of the mountain Taygetus (Plutarch, 1914). Heraclitus of Ephesus (535-475 B.C.) makes the first reference to the term 'sacred disease', however, not for describing epileptic seizures (Laertius, 1853). Alcmaeon of Croton (6th B.C.) was the first of the Greek physicians to ascertain that the brain was the organ where 'hegemonicon' (ηγεμονικόν)³ is founded, the source of memory and thoughts (Diels, 1906). Democritus of Abdera (5th B.C.) wrote a book on epilepsy (*Περί επιληψίας*) which now is extinct, suggesting that the brain is the center of the soul and that cognition and senses were one and the same, originating from the same force (Plutarch, 1888). Herodotus of Hallicarnassus (484 - 425 B.C.), the father of history, in the third book of his work *The Histories* (Thaleia) indirectly refers to epilepsy afflicting the Persian King Cambyses II, whose erratic behavior, according to Herodotus, could be attributed either to the retribution of an aggrieved god or to the so-called 'sacred disease'. Herodotus also noticed the hereditary nature of the disease (εκ γενεής) (Herodotus, 2000).

1.3 Epilepsy in the Hippocratic corpus

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* (Περί ιεράς νόσου). 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,

² Miasma: a greek word for pollution, a noxious form of 'bad air'

³ Hegemonicon comes from the word hegemon which means sovereign.

unless by long lapse of time it be so ingrained as to be more powerful than the remedies that are applied" (Hippocrate, 1849b)

Hippocrates was also the first who attempted a scientific approach toward the study of epilepsy by suggesting possible etiology and therapy for the disease. He was the first to attribute the etiology of epilepsy to brain dysfunction (Hippocrate, 1849a), stressing the role of heredity in the disease. Among others, Hippocrates will describe the disease accurately, including its unilateral nature and the symptoms of aura (Hippocrate, 1849d). Hippocrates calls epilepsy the "great disease", the originator of the term 'grand mal.' He also describes symptoms reminiscent of psychomotor epilepsy and temporal lobe fits (Hippocrate, 1849e). The view of Hippocrates for the origin of epileptic convulsions and their association with life in utero is also interesting. He states unequivocally that "its birth begins in the embryo while it is still in the womb" (Hippocrate, 1849h). Among the predispositional factors that can lead to a epileptic fit are: (a) the changes of the winds and of temperature, (b) the exposition of the head to sun, (c) crying, and (d) fear. Prognosis is also worse, when the disease is manifested in early age (Hippocrate, 1849g), but, for older people, the prognosis is better (Hippocrate, 1849f). In his other treatise, *Injuries of the Head*, Hippocrates notes that head injuries often lead to convulsions, introducing the idea of traumatic epilepsy (Hippocrate, 1849i).

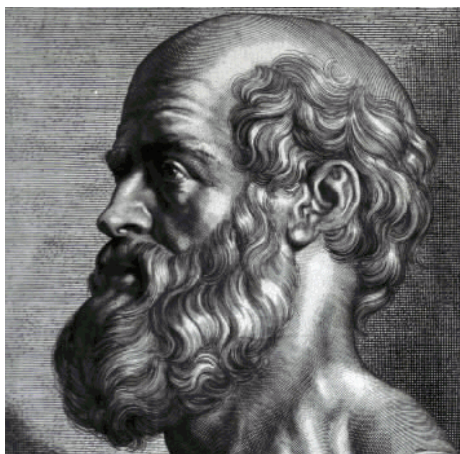


Fig. 1. Hippocrates of Kos (460 BC - ca. 370 BC)

1.4 Epilepsy in Alexandrian and Roman medicine

Medicine in the post-Hippocratic era did not make important achievements as far as the treatment of the disease is concerned. Diocles of Carystus employed the use of various remedies such as phlebotomy, whereas Praxagoras of Cos prescribed extreme remedies such as the cauterization (Drabkin, 1950).

On the other hand, Plato (428/427 BC - 348/347 BC), in his *Laws*, suggests specific punishment for people selling slaves with epilepsy, in parallel with the Hamurabi code of the Babylonians (Plato, 1871). During the Roman period, the proceedings of the Senate were interrupted or postponed, whenever a senator was struck by epilepsy during a session because epilepsy was considered a bad sign from the Gods. For that reason Romans called epilepsy *morbus comitialis*, since an epileptic attack tended to spoil the day of the *comitia*, the assembly of the people.

Various philosophers will refer to epilepsy such as the Pliny the Elder, in his *Naturalis Historia*, suggesting magical remedies such as the rubbing of patient's feet with menstrual blood (Pliny, 1856), Pedanius Dioscorides (40-90 A.D.) describing 45 different substances used as remedies for epilepsy (Temkin, 1971a) and Aurelius Cornelius Celsus who calls epilepsy, in his writings, *morbis comitialis* and suggests as a cure sexual intercourse for boys or the warm blood of slain gladiators in obstinate cases (Celsus, 1935).

One of the most important works of this period is that of Aelius Galenus or Claudius Galenus (131-201 AD) who systemized nosology and described epilepsy with accuracy in his classic treatise *Medical Definitions* (Galen, 1821c). He was able to discern three forms of epilepsy: (1) idiopathic, attributed to primary brain disorder (an analogue to grand mal epilepsies), (2) Secondary forms, attributed to disturbance of cardiac function transmitted through the flow of liquids secondarily to the brain (epilepsy by sympathy), and (3) a third type attributed to disturbance of another part of human body which is secondarily transmitted to the brain (probably Jacksonian epileptic seizures). Galen accurately sets the brain as the organ afflicted by the disease, and, most importantly, he described the aura, a greek word which originally means 'breeze', in his *De locis affectis* referring to the symptoms of a case of a 13-year-old boy (Galen, 1821a). Galen also differentiates epilepsy from tetanus because with epilepsy the whole body participates with a loss of consciousness (Galen, 1821b).

Aretaeus of Cappadocia (1st/2nd century AD) was the first to describe premonitory symptoms of epilepsy, such as hallucinations that occasionally precede epileptic seizures; he noted that fetid odors, luminous circles of diverse color, noises from the ears, tremors and sensations in the hands or feet may occur before the seizure. He also noted the tendency of seizures to recur, once established, and the phenomenon of epileptic insanity (Aretaeus, 1856a). After the fall of the epileptic to the ground, Aretaeus, distinguished three main periods: manifestation, abatement, cessation. The manifestation is characterized by insensibility and tonic and clonic convulsions. At the end of the abatement stage, patients appear to suffocate, with its concomitant signs including erection of the genital. During the abatement stage, the patients unconsciously discharge urine, excrement, and semen, a hallmark symptom that discerns epilepsy from hysteria. Then, a flow of froth ends the suffocation. At the end of the abatement stage, they arise with the seizure having ended. During cessation period, patients still have various signs of physical and mental discomfort (Aretaeus, 1856c). Aretaeus gives an excellent description of 'grand mal' epilepsy in his text (Aretaeus, 1856c), as well as the first description of the so-called 'epileptic personality' (Aretaeus, 1856b).

Soranus of Ephesus (1st/2nd century AD) also referred to epilepsy without making any contribution to the understanding of the disease.

2. Epilepsy in the dark ages

2.1 Medieval times and medicine

The Medieval times is characterized by a domination of mysticism and dogmatism in all fields of science, including Medicine. Physicians tended to believe that diseases such epilepsy, hysteria and psychoses were the result of demonic possession; for that reason epileptics were treated as witches and warlocks. Many medieval mosaics, frescoes, miniatures and paintings depict the exorcism of a particular disease/devil by a particular saint. Beyerstein suggests that the curious behavior of the possessed people described in the classic *Malleus Maleficarum* (15th century AD) is likely symptoms of epilepsy or Tourette's

syndrome (Beyerstein, 1988). Beginning at age 13, Joan d'Arc experienced moments of ecstasy with light, heard voices of saints, and claimed to see visions with angels, all probably symptoms of epileptic seizure (d'Orsi & Tinuper, 2006).

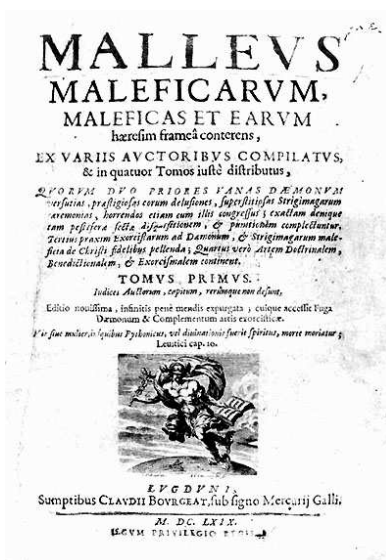


Fig. 2. Malleus Maleficarum (Lyon edition, 1669)

Another aspect on epilepsy during the Medieval times, was the theory that epilepsy was a contagious disease. The epileptics, considered to be possessed, were excused from oblation and Eucharist because they would desecrate the holy objects and would infect the common plate and cup (Dolger, 1933). Epilepsy was also included in the infectious diseases enumerated in the verse of the so-called *Schola Salernitana*, where it was named *pedicon* (Martin, 1922). Berthold of Regensburg, attributed the infection of the 'falling evil', as epilepsy was commonly called during this period, to the contagious character of the patient's evil breath. A connection of epilepsy with astrology was also a very popular theory in medieval times. Pagans believed that epilepsy was a vengeance of the goddess of the moon. The waxing moon supposedly heated the atmosphere surrounding the earth, which in turn melted the human brain and provoked the attack (Temkin, 1971c).

2.2 Epilepsy and the catholic church

Inevitably, many saints of the catholic church dealt with epilepsy. For example, St. Hildegard of Bingen (1098-1179 AD) distinguished between two kinds of epilepsy: a vengeful wrath sets the blood in motion causing one type of epilepsy while patients with unstable or low morals suffered the a second type (Hildegard, 1903). Saint Valentine, whose name in German originates from the phrase 'fall net hin' (Valentin) ('do not fall down'), was considered as patron of the epileptics (Kluger & Kudernatsch, 2009). Saint John the Baptist, was also connected with the disease, probably because his head fell to the ground after his decapitation by Herod (Budrys, 2007). St John was originally the patron of the dancing mania, and later, St. Vitus, a christian martyr of Sicily, became the specific saint of this neurosis and St. John of

epilepsy. The three wise men from the biblical tale of Jesus' birth also had a reputation as patrons of epilepsy mainly because they fell down before the divine child and offered gifts (Kerler, 1905). On the other hand, the Greek Orthodox Church has the example of St. Tychonas of Cyprus who was considered to have cured many possessed people.

2.3 Byzantine and Arab physicians

One should also note the views of famous byzantine physicians such as Oribasius of Pergamum, Aetius Amidenus, Alexander of Tralles and Paulus of Aegina on epilepsy. Overall, byzantine doctors recapitulate the theories of Ancient Greek physicians and further systemize the nosology of the disease by reporting interesting cases of epileptic patients. It is of note, though, that Alexander of Tralles (525-605 AD), in his treatise *Twelve books on Medicine*, takes an orthologic approach considering epilepsy a brain disturbance and reject extreme procedures such as trephination (Tralles, 1878). Paulus of Aegina (7th century AD), according to Economou and Lascaratos, was the first Byzantine doctor who provided a clinical description of the epileptic fits, and also described a clinical condition that resembles *status epilepticus* (Economou & Lascaratos, 2005).

Arab doctors seem also to recapitulate the theories of Galen and Hippocrates without making any significant progress. Interesting descriptions of epileptic seizures can be found in the texts of Rhazes (Temkin, 1942) and those of Abulcasis (936 - 1013 AD) who also refers to cases of epilepsy due to daemonic possession (Abulcasim, 1519). He will also make important observations on traumatic epilepsy, correctly associating fractures of the skull and brain compression with the malady (Africanus, 1536-1539). Masoudi (late 10th century AD) refers to epilepsy of traumatic origin by noting that an obstruction of the brain may be the result of a compression from a fracture of the skull accompanied by severe pain (Abbas, 1523), whereas Avicenna (981-1037 AD), one of the most influential scientists in the Middle ages, supports the theory of blockage of humors as a possible mechanism of epileptic convulsions (Avicenna, 1999).

Constantinus the African (1020-1087 AD), a translator of Greek medical and Islamic texts, advises the parents of epileptics to take the patient to church during the second week following Whitsuntide (Pentecost) and expose them to the Friday or Saturday Mass (Temkin, 1971d).

2.4 Physicians of the Western Europe

Among the most influential physicians are Arnold of Villanova, famous physician, alchemist and magician, Bernard of Gordon, a teacher in Montpellier from 1285 to 1307, and John of Gaddesden, physician to Edward II of England. Arnold of Vilanova (1240 - 1311), perpetuates superstitious views emphasizing the dependence of the disease on the star constellations and especially the moon. (Vilanova, 1585b). He also notices that 'the true epilepsy is engendered with phlegm; spurious epilepsy by black bile mixed with phlegm' (Vilanova, 1585a). Bernard of Gordon (1303) suggested as therapy that a priest should recite a Gospel passage, which it should be written down to be carried by the patient as an amulet (Gordon, 1542). John of Gaddesden (1280-1361 AD) distinguishes 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 (Gaddesden, 1595). Giovanni Michele Savonarola of Padova (1385 - 1466 AD) adopts a similar classification with different

terms: primitive, antecedent and conjoint (Savonarola, 1547), as well as Matthaeus Platearius in his *Practica brevis* adding two clinical varieties that are distinguished as 'maior and 'minor' epilepsy (i.e., grand mal and petite mal) (Serapion, 1530).

3. Views on epilepsy in renaissance and enlightenment

The end of the Medieval times and the beginning of the European Renaissance (14th-17th century) is marked with an exceptional production of literature regarding epilepsy. Science, emancipated from the restraints of the Catholic Church will undoubtedly make important progress; in the field of epilepsy, almost all the prestigious and famous physicians of the era deal with the disease.

Various theories will be proposed regarding the mechanism that causes the epileptic fits as well as new classifications of the disease will come forth. For example, Petrus Forestus (1522-1597 AD), a Dutch physician, notes that the part of the body that epilepsy originates, leads to different manifestations. There is also a tendency to differentiate epilepsy and daemonism; in his *Daemonum investigatio peripatetica* (Peripatetic investigation of demons) Andreas Caesalpinus (1519-1603 AD), an Italian natural philosopher, tries to differ epileptic seizures and daemonic possession (Caesalpinus, 1593).

One of the most famous physicians of this period, 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. Paracelsus views about the human nature and the construction of the human body from mercury, sulfur and salt led him to a different model for the causes of epilepsy (Paracelsus, 1922-1933a). However, in his essay he clearly sets God above all, and stresses that the physician should ask for divine help in the treatment (Paracelsus, 1922-1933b). 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.' Thus, he tied cases of epileptic convulsions with mental manifestations (Marci a Kronland, 1678). Levinus Lemnius (1505-1568 AD), famous Dutch physician and student of Vesalius, all stressed the natural origin of the disease and rejected any theological superstitions (Lemnius, 1658).

Other physicians who also dealt with epilepsy include Charles Le Pois (1563-1636 AD), consultant physician to Charles III of France, who rejected previous theories such as those postulated by Petrus Forestus suggesting that peripheral organs led to epilepsy (Le Pois, 1733). Joannes Ambianus Fernelius (Jean François Fernel) (1497-1558), a French astrologist and physiologist, who supported the theory that poisonous vapors affected the brain and led to epileptic fits, and rejected the medieval belief about the contagious nature of epilepsy (Fernelius, 1577).

An important treatise of the period is that of Jean Taxil's *Traicté de l'épilepsie*, that summarize the knowledge around epilepsy, including its causes and various remedies; he was the first Renaissance doctor who seriously doubted demonic possession (Taxil, 1602).

William Harvey (1585-1657 AD) will be the first who will make important advances for the establishment of neurology as clinical speciality with his descriptions of various neurological disorders including epilepsy (Brain, 1959; R. Hunter & MacAlpine, 1957). An interesting theory on epileptic convulsions is that of Thomas Willis Thomas Willis (1621 - 1675) who assumed the existence of a '*spasmodic explosive copula*'. For Willis 'The convulsive disease for the most part, takes its origin from the head (Willis, 1684). In his *De morbus*

convulsivis (Morbid convulsions) Willis places the cause of epilepsy in the brain, but differed with his predecessors who pointed to the middle of the brain itself or the meninges. His hypothesis suggested that since the brain is of a weak constitution, a strong *spasmodi copula* distills from the blood to the brain leading the animal spirits that lie in the middle of the brain to explode. The explosion of animal spirits cause all the mental symptoms of the epileptic attack, and a series of similar explosions occur along the rest of the nervous system to bring about the convulsions of the body (Willis, 1682).

Interesting cases of epileptic patients appear during this period too. For example, Martinus Rulandus (1532-1602), German physician and alchemist, describes the case of a 40-year-old man suffering from epilepsy and mania. A woman considered to be a witch was accused of causing evil to this man, but during her confession she claimed that she could not cure him. So, Ruland was called and he managed to cure him by bloodletting, sternutatory and a strong cathartic (Rulandus, 1580). Thomas Erastus (1524-1583), a Swiss theologian, documents the case of a girl with characteristic psychomotor symptoms of epileptic convulsions. After convulsing, she wandered around the room for almost half an hour and the people who were around could not stop her. After the event she could not remember anything that happened (Erastus, 1581). Felix Plater (1536-1617), as referred by Tissot, describes a young man whose malady started with a headache, stubborn insomnia and deterioration of his faculties and ended with frequent convulsive attacks and emaciation. The post-mortem dissection revealed tumor in the anterior part of the brain (Tissot, 1770a). Charles Drélincourt (1633-1694), finally, was the first to provoke epileptic convulsions experimentally by driving a needle into the fourth ventricle of a dog's brain (Drelincurtius, 1682).

4. Epilepsy during the 18th and 19th century

4.1 The work of 18th century physicians on epilepsy

The beginning of the 18th century is marked by the work of doctors of the Dutch medical school founded by Herman Boerhaave and his pupil Gerard van Swieten. 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 (Boerhaave, 1761). The Dutch-Austrian Gerard Van Swieten (1700-1772) wrote a chapter on epilepsy in which he describes extensively the clinical characteristics of various forms of the disease and discusses epilepsy in comparison with apoplexy and hysteria. (Temkin, 1971b).

The first major treatise on epilepsy was written by the Swiss physician Simon August André David Tissot (1728-1787). Published in 1770, the *Traite de l'epilepsie* is considered to be a milestone in the scientific research on epilepsy. Tissot completely rejects the influence of the moon on epileptic seizures, accepts the hereditary forms of epilepsy, and states that it is the duty of the epileptic to remain unmarried (S. Tissot, 1770b). Among his extreme views about epilepsy is the belief that masturbation could cause epileptic seizures (S. Tissot, 1770b).

The French medical school of the 19th century took lead in the fields of neurology and psychiatry, and, therefore, were the main driving force on epilepsy research. Jacques-Louis Doussin Dubreuil (1762-1831) tried to explain the influence of various emotional states on epilepsy (Doussin-Dubreuil, 1825), whereas Louis Maisonneuve, a pupil of Philip Pinel (1745 - 1826), stated that 'epilepsy like all chronic diseases can be studied well only in hospital', stressing the variety of clinical manifestations of epilepsy (Maisonneuve, 1803).

Physicians of the British medical school also dealt with epilepsy such as Thomas Beddoes (1760–1808), who described accurately the premonitory symptoms developing before the onset of an attack, (Maisonneuve, 1804) William Cullen (1712–1790), who included epilepsy as one of the spasmodic affections without fever, together with tetanus and chorea or St. Vitus dance (Cullen, 1778–1784). Finally, the first experimental provocation of convulsions was done in Italy. 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 (Garrison, 1935; Marchand & Hoff, 1955).

4.2 The 19th century: The “golden era” of French medicine and the contribution of the English school of physicians

4.2.1 The French medical school

The progress of the French medical school is marked by a peak during the 19th century. Marie-Jean-Pierre Flourens (1794–1867) established the basic rules regarding the irritability and sensibility of the central nervous system, noting that different functions can be attributed to different parts. His contribution is decisive for the research on epilepsy, since the loss of consciousness and the voluntary movements in epileptic attacks would imply the involvement of the cerebral lobes, were it not for the participation of the medulla that Flourens found (Flourens, 1823). The French psychiatrist Jean-Étienne Dominique Esquirol (1772–1840), distinguished severe from light epileptic seizures (*grand mal* and *petit mal*) and worked with his pupils Bouchet and Cazauvieilh, on epilepsy and insanity. A later study by his students Bouchet and Cazauvieilh revealed a high frequency of epileptic attacks among patients considered to be insane (Esquirol, 1838). In 1827, Antoine Baron de Portal (1742–1832) published his clinical experience based on a large amount of clinical data and post-mortem reports, admitting that in many cases of epilepsy, dissection did not reveal any lesions either in the brain or other parts of the body (Portal, 1827b). He also makes important notes on the so-called *furor epilepticus*. He noticed this clinical status appeared before the onset of the epileptic seizure, as well as after; a patient in this condition could even commit murder (Portal, 1827a). Louis François Bravais (1801–1843) in his thesis defines epilepsy from a new basis, that of ‘hemiplegic epilepsy’, during which convulsions attack one side of the body followed by paralysis, whereas he is considered to be the first to describe of what was later called Jacksonian convulsions (Bravais, 1827). François-Emmanuel Foderé (1764–1835), renowned French physician and expert in forensic medicine, will discuss what he calls ‘periodic delirium’, which is clearly epileptic mania (Foderé, 1798). Charles-Édouard Brown-Séquard (1817–1894) managed to provoke epileptiform convulsions by transverse section of the lateral half of the spinal cord in animals (Brown-Séquard, 1857). Théodore Herpin (1799–1865) will publish 300 cases on epilepsy, providing insights on the symptoms preceding the onset of major seizures, the initial symptoms with which major attacks began and the minor attacks appearing in the intervals between complete attacks. Herpin also describes epilepsies with intellectual disturbances and with immediate loss of consciousness. (Herpin, 1867).

One should also note the important contribution of the French psychiatrists on the psychomotor symptoms of epilepsy. Bénédicte Augustin Morel (1809–1879) noted that irritability and anger are the salient features of the epileptic personality (Morel, 1852–1853). Epileptic fury, according to Morel, appears in two forms: either before or after the epileptic

attack or independently “like lightning and being condensed in terrible deeds” (Morel, 1852-1853). Jules Falret (1824–1902) will divide the mental disorders found in epileptics in three categories: premonitory symptoms, symptoms of the epileptic personality and epileptic insanity. Falret was also able to identify intellectual disturbances during the epileptic attack in cases where the patient did not lose consciousness, whereas he divided the mental disorders of the third type into *petit mal intellectuel* and *grand mal intellectuel*. (Falret, 1860).

4.2.2 The British medical school of the 19th century

The contribution of the British Medical school is equally important. James Cowles Prichard (1786–1848), notes that the ‘epileptic delirium’ appears when the patient revives from the comatose state consequent of a seizure, but it can also appear without any previous fit, whereas he describes the typical symptoms of epileptic mania (J. C. Prichard, 1822a). Prichard describes other states of mental confusion, suggesting they are like somnambulism or epileptic ecstasy:

‘A more unusual circumstance in the history of epilepsy is the appearance of a species of somnambulism, or of a kind of ecstasis, during which the patient is in an undisturbed reverie, and walks about, fancying himself occupied in some of his customary amusements or avocations. This takes place during the waking as well as the sleeping hours’.

His observations are the forerunners of the concept of ‘psychic equivalents of epilepsy’ (James Cowles Prichard, 1822b). Prichard was also the first to establish the term ‘partial epilepsy’ in the literature, devoting to the topic an entire chapter in his treatise, called ‘Of local convulsion or partial epilepsy’.

Richard Bright (1789–1858) attempted to combine anatomical data with clinical cases, and was able to show changes in the cortex of the cerebral hemispheres (R. Bright, 1831a). Bright supported the theory that the gray matter of the brain was the main functional part of the cerebral hemispheres, referring to the discoveries of Foville (Richard Bright, 1831b). Marshall Hall (1790–1857), on the other hand, suggested that epilepsy was due in part to anemia of the medulla and that paroxysmal discharges arose from the brain (M. Hall, 1851; Marshall Hall, 1852). Robert Bentley Todd (1809–1860), physician in King’s College Hospital, in an experiment to determine the seat of epilepsy, observed discrete movements on the face of a rabbit upon stimulation of the cerebral hemispheres, but he did not appreciate the significance of his experiments, for he maintained that movement was the concern of structures from the corpora striatum rostrally. In 1836, Astley Cooper (1768–1841) reported his findings on provoking epileptic seizures by temporary anaemia, without the loss of blood. (Cooper, 1836).

John Russell Reynolds (1828–1896), was the first to identify ‘epilepsy proper’ with idiopathic epilepsy, to which, he believed, ‘the name of epilepsy ought to be applied’ (Reynolds, 1861b). His major account on epilepsy was published in 1861 entitled *Epilepsy: Its Symptoms, Treatment and Relation to Other Chronic Convulsive Diseases* (Reynolds, 1861a), which is considered to be a milestone in the English epileptology. Reynolds employs the terms ‘epileptiform’ or ‘epileptoid’ for seizures resembling epilepsy, rejecting, in that way, the existence of renal or uterine epilepsy and epilepsy from tumor of the brain; he claims that we ‘find these confounded together with simple or idiopathic affection’ (Reynolds, 1861a), adopting indirectly Delasiauve’s theories about idiopathic epilepsy (Delasiauve, 1854) as epilepsy of cerebral origin with unknown pathology. Reynolds support also the theory about positive and negative symptoms arising from brain pathology (Pearce, 2004), earlier than his successor, Jackson; negative effects are associated with direct impact on structural pathology

that damaged or destroyed tissue, whereas positive symptoms are more remote effects of pathology arising from 'altered nutrition' that the pathology produced in surviving tissue. Reynolds also refers to the epileptic aura without attempting to explain its pathogenesis. William Richard Gowers (1845-1915), also contributed substantially into the understanding of the pathogenesis of the disease. During those lectures, Gowers presented and reviewed the clinical features of a series of 1,500 cases who observed and treated them in person. Those cases were published in some of the most prestigious contemporary medical journals (Gowers, 1880), and, then, he expanded further those findings in his monograph entitled *Epilepsy and other chronic convulsive disorders* (1881), including a series of 3,000 cases of epilepsy which covers every possible clinical feature of epilepsy (Gowers, 1881).

4.2.3 The Dutch and German medical school of the 19th century

Research into epilepsy was also advanced by the work of German and Dutch physicians of the era. Karl Friedrich Burdach (1776-1847), anatomist, physiologist and embryologist, published a series of 1,911 anatomical abnormalities observed in the brain. According to his data, the lateral ventricles were most frequently affected, with 86 out of 476 cases, of which 63 consisted of serous effusion (Burdach, 1826).

Friedrich Gustav Jacob Henle (1809-1895), writing in 1853, noted that epileptic convulsions are provoked by an increased turgor at the base of the brain, and that the loss of consciousness depends either on increase or decrease of blood flow in the hemispheres. (Henle, 1846). The same year, Adolf Kussmaul (1822-1902) along with Adolf Tenner published the classic treatise on epileptiform convulsions (Kussmaul & Tenner, 1859), whereas in 1859, Hörung, a German physician, in his dissertation entitled *Über Epilepsie*, described a case of a young man who had grand mal attacks as well as many mild attacks during which he had complete lapses of memory (Horing, 1859). Wilhelm Griesinger (1817-1868), in 1868, will employ for the first time the term 'psycho-motor symptoms' in epileptoid conditions. (Griesinger, 1868-1869).

4.3 Therapies on epilepsy

The most important advance in anti-epileptic therapy of this period is the introduction of bromide potassium in the treatment of epilepsy by Edward Sieveking, in 1857 (Sieveking, 1857), a treatment further supported by Charles Locock (1799-1875) and especially Samuel Wilks (Richard Hunter, 1959-1960; Wilks, 1861). Locock described the anticonvulsant effect of bromides, although the earliest studies on the effects of various drugs as anticonvulsants were performed by Albertoni (1882), on animals with induced seizures (Albertoni, 1882). Extreme methods of therapy are still perpetuated such as trephining of the skull was supported by Charles-Édouard Brown-Séquard, Benjamin W. Dudley (1785-1870), John Saw Billings (1838-1913) and Paul Broca (1824-1880), most of whom had applied surgical therapy in various cases (Billings, 1861; Broca, 1867; Smith, 1852). Other surgical procedures suggested have been tracheotomy, by Marsall Hall (M. Hall, 1841), and cauterization of the larynx with nitrate of silver, by Brown-Séquard (Brown-Séquard, 1853).

5. The age of John Hughlings Jackson

John Hughlings Jackson (1835-1911), is beyond any doubt the father of modern epileptology. His clinical observations from 1861 to 1870, which came well before the experimental reports of Eduard Hitzig (1839-1907) and David Ferrier (1843 -1928), were confirmed ultimately by Hitzig and Ferrier (Fritsch & Hitzig, 1870).



Fig. 3. John Hughlings Jackson (1835-1911), father of modern epileptology

Jackson studied epilepsy on a pathological and anatomical basis. He initially believed that focal convulsions were due to a discharging lesion from damage to nerve cells. He also believed, at first, that the part of the brain involved was the region of the corpus striatum or the convolutions near to it. In 1861, Jackson published his first paper containing reports from hospitals and from the medical literature (Jackson, 1861), whereas, in 1863, he observed about unilateral convulsions that 'in very many cases of epilepsy and especially in syphilitic epilepsy, the convulsions are limited to one side of the body; and, as autopsies of patients who have died after syphilitic epilepsy appear to show, the cause is obvious organic disease on the side of the brain, opposite to the side of the body convulsed, frequently on the surface of the hemisphere' (Jackson, 1863).

In 1864, Jackson published his an important in which he discusses the symptoms of aphasia (Jackson, 1864). Jackson thus offered a new explanation about epileptic seizures that differed that of his predecessors who claimed the seat of the disease lay in the medula oblongata.

In the following years, Jackson's views regarding the involvement of the corpus striatum in the genesis of seizures evolved rapidly. Jackson distinguishes four factors involved in the final cause of convulsions: the 'seat of the internal lesion', the functional cause of the change, the pathological process which brought about the functional change (embolus, tumor, syphilis or other cause) and the various circumstances that trigger the paroxysm (Jackson, 1931-1932a, 1931-1932b).

In 1866 Jackson discussed the mechanisms of various forms of epilepsy noting that 'in cases of sudden and temporary loss of consciousness in which convulsive movements were slight, or perhaps absent, the disorder of function was chiefly in the range of the anterior cerebral artery' (Jackson, 1866). For cases of loss of consciousness, he believed the disorder to be located 'in the very highest nervous centres of the cerebral hemisphere' (Jackson, 1931-1932b). As far as the mechanisms involved, genuine epilepsy was not different from unilateral epilepsy. He later refined his definition of epilepsy, suggesting an scientific and an empirical classification; in terms of anatomy and physiology epileptic vertigo, petit mal and grand mal were due to differences of a discharge 'beginning and spreading from the

same parts of the brain' (Jackson, 1931-1932b). Empirically, he distinguished three classes of epilepsy proper from which the epileptiform or epileptoid group, including convulsions beginning unilaterally, unilateral dysaesthesia (migraine) and epileptiform amaurosis, had to be differentiated (Jackson, 1931-1932b).

In his lecture *On Convulsive Seizures* Jackson presented the most advanced form of his theory on epilepsy. According to Jackson, the central nervous system can be divided into three levels: (a) the lowest level, which consists of the spinal cord, the medulla oblongata and the pons, representing the most rough and simple movements; (b) the 'motor province' consisting of the 'motor region of the cerebral cortex (Rolandic region) and of the ganglia of the corpus striatum representing complex movements of all parts of the body; and (c) the highest level formed by the centers of the prefrontal lobes ('the organ of mind') (Jackson, 1931-1932b). Fits beginning at the lower levels can spread to higher ones through interconnecting fibers as well as to neighboring cells of the same level. Jackson considered therefore middle level fits to correspond to *epileptiform* seizures and highest level fits to *epileptic* seizures. Jackson was careful to clarify his use of terms, however: '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... I now use the term epilepsy for that neurosis which is often called "genuine" or "ordinary" epilepsy, and for that only' (Jackson, 1931-1932b). Epileptiform convulsions, according to Jackson, start from a definite place in the brain and always begin with a signal symptom which localizes the original discharging lesion. The symptoms can be either be sensory or motor depending on the part of the brain where discharges take place, since according to Jackson all levels are sensorimotor. Discharging lesions are diseased because of 'morbid nutrition', and those cells who are discharged, lose their function and temporarily form a 'negative lesion' (Jackson, 1931-1932b). Sensory or/and motor symptoms are present in each epileptic or epileptiform seizure; in epileptic seizures paralysis is generalized, whereas in epileptiform seizures it is located in certain parts of the body.

To explain post-epileptic states, Jackson suggests the four-layer theory of higher levels, though this theory was not supported by any anatomical data, as Jackson admits. He thought that discharges afflicting the first layer are responsible for impaired consciousness, the second for a single loss of consciousness, as in the case of epileptic mania, and the third for coma without affecting the vital operations (Jackson, 1931-1932b).

Jackson also refers to the 'dreamy state' some patients experience before the onset of the epileptic fits. 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': 'Old scenes revert, I fell in some strange place, a dreamy state, a panorama of something familiar and yet strange, if I were walking alone and had a fit, I should think "Oh, I saw that before" (Jackson, 1931-1932b).

6. Epilepsy in the twentieth century

Before the end of the 19th century, in 1898, William Letchworth (1823-1910) and Frederick Peterson (1859-1938) will organize the National Association for the Study of Epilepsy and the Care and Treatment of Epileptics in the US (Letchworth, 1901). At the beginning of the 20th century, William Spartling will be the first to use the term 'epileptologist' for a

physician specializing in epilepsy. Cajal will describe neurons and synapses, a hallmark finding in the history of Neurology; in 1906, he will receive the Nobel prize for his discoveries.

In 1903, the first description of progressive myoclonic epilepsy by Herman Bernhard Lundborg (1868-1943) will be published (Lundborg, 1903), whereas Gowers will publish his famous book *The Borderlands of Epilepsy* (Gowers, 1903)

In 1912, Kaufmann will notice the electric changes in the brain during experimentally induced seizures (Kaufman, 1912), whereas in the same year Alfred Hauptmann (1881-1948) will synthesize phenobarbital, one of the first anti-epileptic drugs (Hauptmann, 1912). Two years later Napoleon Cybulski (1854 - 1919) and Jelenska-Macieszyna (Cybulski & Jelenska-Macieszyna, 1914) will publish the first photographs of electroencephalography, whereas Walter Dandy (1886-1946) will describe in 1918 and 1919 pneumoventriculography and pneumoencephalography (Dandy, 1918, 1919a, 1919b). During the 1920's, William Gordon Lennox (1884-1960) and Cobb will focus on the effects of starvation, ketogenic diet and altered cerebral oxygen in seizures and they will publish their first monograph (Lennox & Cobb, 1928).



Fig. 4. Alfred Hauptmann (1881-1948)

In 1929, Hans Berger (1873-1941) will report human brain waves (Berger, 1929), confirmed later by Adrian and Matthews (Adrian & Mathews, 1934). In 1932, Berger reported sequential postictal EEG changes after a generalized tonicoclonic 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 (Berger, 1932, 1933). His work on epileptic EEG will be completed by Frederic Andrews Gibbs (1903-1992) and Erna Gibbs (1904-1987) who in collaboration with William G. Lennox will establish the correlation between EEG findings and epileptic convulsions (Gibbs et al., 1935; Gibbs et al., 1937; Gibbs et al., 1936). During the same period, H. Houston Merritt (1902 - 1979) and Tracy Putnam (1894-1975) will discover phenytoin and its effect on the control of epileptic seizures publishing their results in a series of papers (Merritt & Putnam, 1938a, 1938b, 1939, 1940). Phenytoin will become the first-line medication for the prevention of partial and tonic-clonic seizures and for acute cases of epilepsies or status epilepticus. Important advances will also be made on the fields of epileptic surgery by Wilder Penfield (1891-1976) who applied the Foerster method of removing epileptogenic

lesions on an epilepsy patient (Penfield & Steelman, 1947). The concept of eugenics will become an issue in the control of epilepsy; in 1936, the American Neurological Association Committee for the Investigation of Eugenic Sterilization will publish a report (Myerson et al., 1936) stating that sterilization of epileptics should be voluntary, conducted under supervision and only with patient consent.

Kliver and Bucy will show, in 1939, that changes in behavior in monkeys may be associated with temporal lobe lesions (Kliver & Bucy, 1939), whereas in 1941 Jasper and Kershmann will prove that the temporal lobe is the site of origin of psychomotor seizures (Jasper & Kershmann, 1941). Percival Bailey (1892-1973) is the first to attempt temporal lobectomies for psychomotor seizures and the first to use electro-corticography for intra-operative localization (Bailey & Gibbs, 1951).

In 1946, a new anti-epileptic drug trimethadione was reported by Richards and Evertt to prevent pentylentetrazol induced seizures (Richards & Everett, 1946). Other important advances in the field of epileptology were the development of a stereotactic human brain atlas by Talairach and Bancaud and the discovery of γ -aminobutyric acid (GABA) by Roberts and Frankel in 1949 (Roberts & Frankel, 1950).

The beginning of the 1950's is marked by the establishment of the National Institute of Neurological Diseases and Blindness (NINDS). William Penfield will perfect and establish his surgical procedures as a treatment of choice in intractable epilepsy, especially of neocortical regions (Penfield & Baldwin, 1952; Penfield & Flanigin, 1950; Penfield & Steelman, 1947), whereas one should also mention the method of hemispherectomy introduced by Roland Krynauw in 1950 (Krynauw, 1950). Bailey and Gibbs in 1951 will employ the EEG as a guide to perform temporal lobe surgery (Bailey & Gibbs, 1951), whereas in 1953, Murray Falconer in London introduced the en bloc anterior temporal lobe resection and the term mesial temporal sclerosis (Falconer et al., 1953). In 1954, Penfield will publish with Herbert Jasper, an eminent neurophysiologist, one of the great classics in neurology, *Epilepsy and the Functional Anatomy of the Human Brain* (Penfield & Jasper, 1954). An important and influential figure in the field of Epileptology who become active during this period was Henri Gastaut. He was the founder of International EEG Federation and, in 1953, became head of the Marseille Hospital Neurobiological laboratories. His contribution in the study of epileptology was monumental; he defined five major human EEG patterns (lambda waves, pi rhythm, mu rhythm, rolandic spikes and posterior theta rhythm) (Naquet, 1996a, 1996b). During this decade, new drugs will come up such as carbamazepine in 1953 (Schindler & Häfliger, 1954), ethosuximide in 1958 (Vossen, 1958), sodium valproate in 1963 (Meunier et al., 1963).

In 1961, the International Bureau for Epilepsy (IBE) was established. In 1966, Surgeon General William Stewart will create the Surgeon General's Public Health Service Advisory Committee on the Epilepsies, whereas, in 1969, the Society for Neuroscience was established. Important advances will be made in the field of neuroscience and in the physiology of synapses by Eccles, Kandel, Spencer, Speckman, Purpura, Meldrum and others. During this period important EEG studies will be conducted in animals mainly by Prince and his research team demonstrating the spikes and waves associated with synchronous paroxysmal depolarizing bursts occurring in cortical neurons (Matsumoto & Marsan, 1964a, 1964b; Prince, 1968a; Prince & Futamachi, 1968), and the spike-wave complex (Prince, 1968b). In 1968, Murray Alexander Falconer (1910-1977) will recognize the importance of hippocampal sclerosis in temporal lobe epilepsy (Falconer, 1968). James Kiffin

Penry (1929-1996), in 1969, will publish his treatise *Basic Mechanisms of the Epilpsies* and afterwards *Antiepileptic Drugs, Neurosurgical Management of the Epilepsis, Complex Partial Seizures and their Treatment* and *Antiepileptic Drugs Mechanisms of Action*. Although carbamazepine and valproate were available in Europe during the 60s, no other drug was licensed in the US.

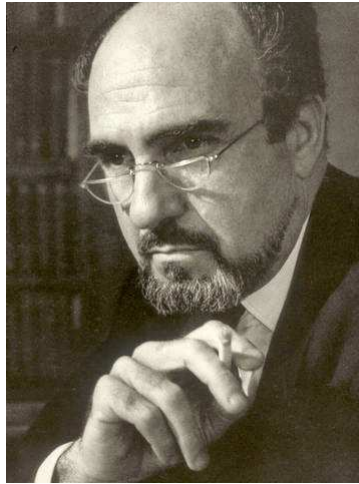


Fig. 5. Henri Gastaut (1915 -1995)

In 1970, Penry and Cereghino were employed in designing clinical trials for anti-epileptic drugs (AEDs). Carbamazepine was the first drug to be licensed by the FDA based on the results of clinical trials. Charles Pippenger (1939-) developed methods for measuring blood levels of AEDs (Painter et al., 1978), whereas Fritz Dreifuss (1926-1997) worked on video-monitoring of absence seizures and helped in the classification of various epileptic conditions (Penry et al., 1975). An important development in the field of neuroscience was that of Erwin Neher (1944-), who invented the patch clamp method to measure the flow of current through single-ion channels (Neher et al., 1978). Prince *et al* will make the first studies of cellular phenomena of epileptic events in the human cortex (Schwartzkroin & Prince, 1978; Wong & Prince, 1978, 1981). Meldrum will prove that the assumption connecting brain damage from seizures as a result of hypoxia, is wrong (Meldrum & Horton, 1973a, 1973b; Meldrum et al., 1973); he demonstrated that the excessive excitatory activity is responsible for the brain cellular loss.

The advent of the new decade, the 1980s, was marked by huge advances in the fields of neuro-imaging techniques, such as the CT, MRI, PET-scanning, and video-EEG monitoring. Epileptics are being evaluated psychologically and socially and before 1990, Quality of Life tools were developed. During the 1990s, the decade of the brain, the Global Campaign Against Epilepsy, launched in 1997 by the WHO, ILAE and IBE brought epilepsy out of the Shadows improving diagnosis, treatment, prevention and social acceptability. Various changes regarding the epileptic brain damage will also be studied, such as the mossy fiber sprouting and synaptic reorganization (Houser et al., 1990; Sutula et al., 1989; Sutula et al., 1988) (Tauck & Nadler, 1985). In 1993, Gabapentin (Neurontin) marketed in the US as the first AED which is not metabolized in the liver.

The most important evolution, however, in the field of epileptology during the last twenty years was the connection between genetic factors and epilepsy; in 1989 Leppert was the first to identify the link between chromosome 20 and idiopathic human epilepsy syndrome in a family with benign familial neonatal convulsions (Leppert et al., 1989). The growing evidence on the connection between various genes and epilepsies is the cutting edge of modern epilepsy research, and in the next decades new exciting discoveries are going to change epileptology (Baulac & Baulac, 2010).

7. Conclusions

The fascinating history of epilepsy is connected with the history of humanity; early reports on epilepsy go back to the ancient assyrian and babylonian texts, scanning a period of almost 4,000 years. The first hallmark in the history of epilepsy are the Hippocratic texts which set in doubt the divine origin of the disease. Major advances in the understanding of epilepsy will come much later, during the 18th and 19th century; theories on epilepsy during this period are formulated on a solid scientific basis and epileptics are for the first time treated as patients and not as lunatics or possessed. During this period, experimental studies were conducted as well as advances made in the pathology of the disease and the connection of epilepsy with various psychiatric symptoms. The work of John Hughlings Jackson was preceded by a plethora of studies by Dutch, German, English and French physicians who evolved scientific thought and performed thorough studies on epilepsy. The advent of the 20th century led to the in-depth understanding of the mechanisms of the disease, the development of effective drugs and neuro-imaging methods. Last but not least, one should mention the important advances in the molecular biology of the disease and the connection of various genes with various forms of epilepsy.

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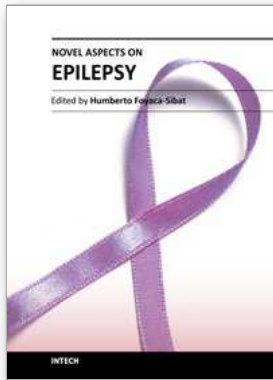
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Novel Aspects on Epilepsy

Edited by Prof. Humberto Foyaca-Sibat

ISBN 978-953-307-678-2

Hard cover, 338 pages

Publisher InTech

Published online 12, October, 2011

Published in print edition October, 2011

This book covers novel aspects of epilepsy without ignoring its foundation and therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis as a leading cause of epilepsy in developing countries. We are looking forward with confidence and pride in the vital role that this book has to play for a new vision and mission. Therefore, we introduce novel aspects of epilepsy related to its impact on reproductive functions, oral health and epilepsy secondary to tuberous sclerosis, mitochondrial disorders and lisosomal storage disorders.

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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
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Phone: +86-21-62489820
Fax: +86-21-62489821

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