

# NEURO IMAGE

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## EPILEPSY

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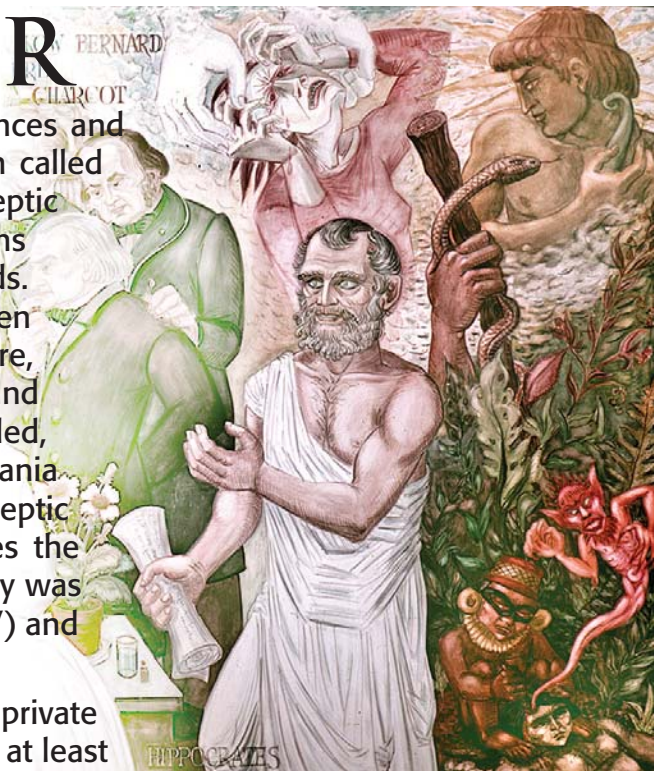


# FROM THE EDITOR

In the past, epilepsy was associated with religious experiences and even demonic possession. Apocryphally, epilepsy has been called the "Sacred Disease" because people thought that epileptic seizures were a form of attack by demons, or that the visions experienced by persons with epilepsy were sent by the gods. However, in many cultures, persons with epilepsy have been stigmatized, shunned, or even imprisoned; in the Salpêtrière, the birthplace of modern neurology, Jean-Martin Charcot found people with epilepsy side-by-side with the mentally retarded, those with chronic syphilis, and the criminally insane. In Tanzania to this day, onlookers will not touch a person having an epileptic attack, owing to fear of demons, even if the seizure causes the person to fall into the cooking fire. In ancient Rome, epilepsy was known as the Morbus Comitialis ('disease of the assembly hall') and was seen as a curse from the gods.

Stigma continues to this day, in both the public and private spheres, but polls suggest it is generally decreasing with time, at least in the developed world; Hippocrates remarked that epilepsy would be considered divine only until it was understood.

*One Beelzebub*



(Image above) A section of the *Advance of Neurology* mural, painted by Mary Filer; note just to the right of Hippocrates, the demon being released by a patient's brain by the first neurosurgeon. (Below) One of the many gargoyles protecting the Cathédrale Notre Dame de Paris

## Greetings

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Herzliche Gruesse

Afectuosamente

Amicalement Bäst Hälsningar

O Genki De

Saluti affettuosi

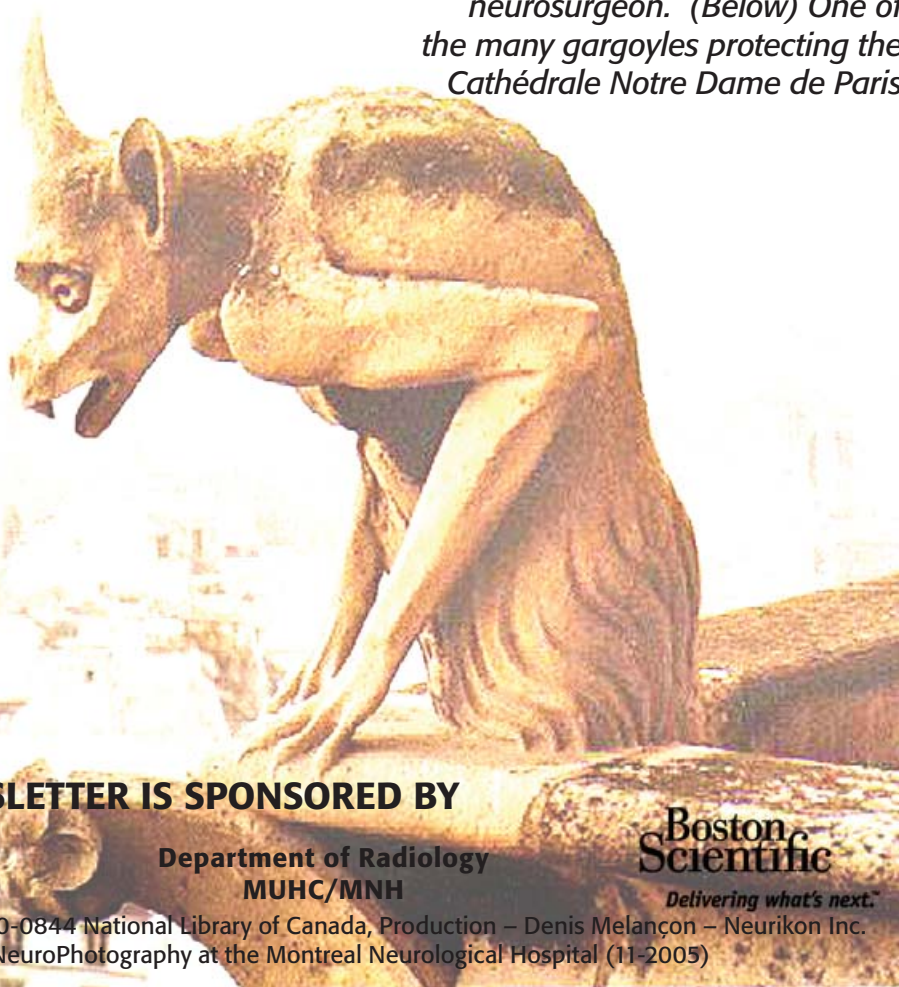
Saudações Namaste

Filika Respetos

As-salaam alaykum

Cordialmente

敬意



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# TEMPORAL LOBE EPILEPSY AND THE ARTS

Dejà vu  
Dejà vécu  
Dejà visité

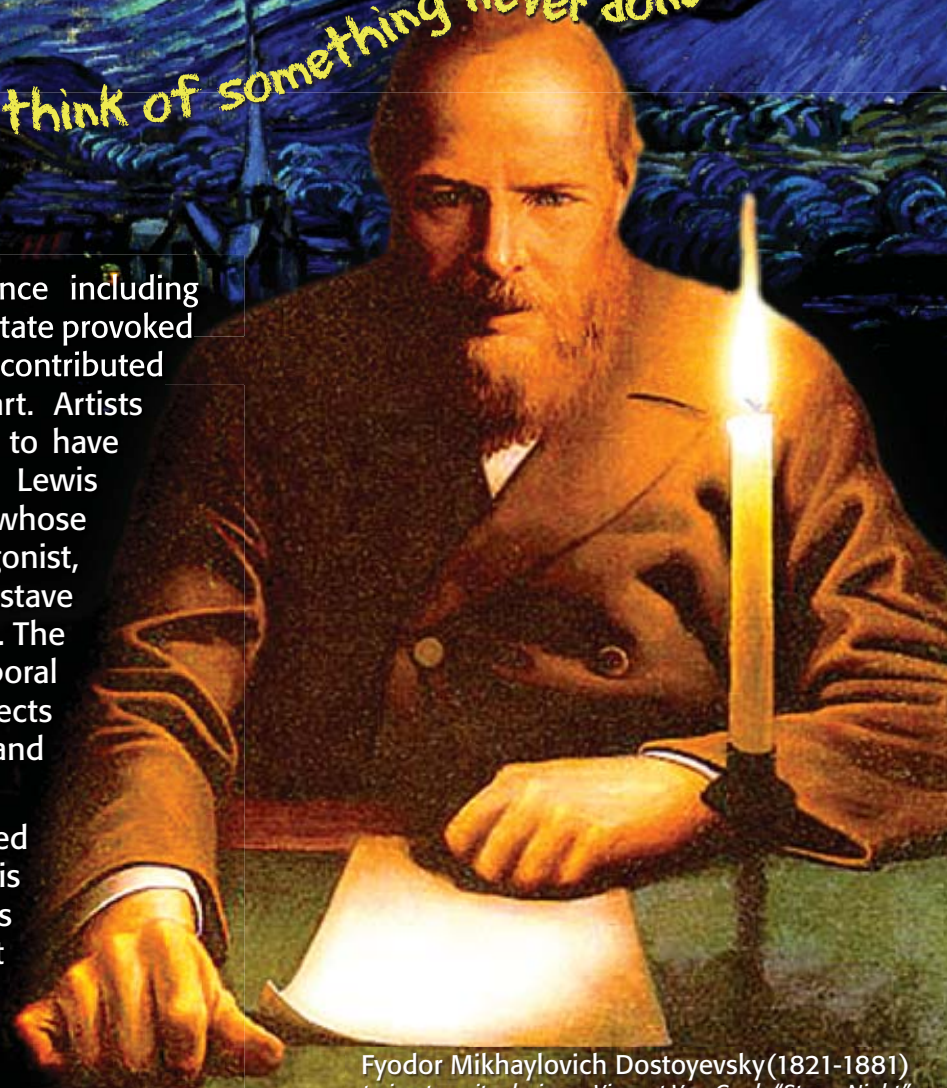
Been there  
Done that

Haven't I been down this road before?

I need to think of something never done before.

The intense emotions, sensory experience including vibrancy of colors, and particular mental state provoked by temporal lobe abnormalities may have contributed to the creation of significant works of art. Artists known (with varying degrees of certainty) to have had TLE include Charles Dodgson (a.k.a. Lewis Carroll), Edgar Allen Poe, Dostoevsky (whose novel *The Idiot* features an epileptic protagonist, Prince Myshkin), Vincent Van Gogh, Gustave Flaubert, Soren Kierkegaard and Sylvia Plath. The contemporary author Thom Jones has temporal lobe epilepsy. The left temporal lobe affects comprehension, naming, verbal memory and other language functions.

More than anyone else, Dostoyevsky used his own illness and suffering as a theme in his writing. The writer made many people in his stories and novels have epilepsy. The most well-known figure is Prince Myshkin in the novel *'The Idiot'*. This character also reveals most about Dostoyevsky's own illness.



Fyodor Mikhaylovich Dostoyevsky (1821-1881)  
trying to write during a Vincent Van Gogh "Starry Night"

# HISTORY OF SURGERY FOR TEMPORAL LOBE SEIZURES<sup>1</sup>

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## The Anterior and Lateral Temporal Cortex

The emergence at the MNI in the early 1950s of surgery for seizures related to the temporal lobe opened a new era for what has now become the most frequent surgical approach for the surgical treatment of epilepsy. There were several phases in the development of such surgery, each distinguished by a substantial increase in knowledge about the pathophysiology of seizures arising from the temporal lobe. Penfield and Flanigin (1950) reviewed 68 temporal lobe operations carried out at the MNI from 1939 to 1949, which had arrested or controlled seizures in over one-half of the patients. The resections in this series were limited mainly to the anterolateral temporal cortex; in only 10 cases was the uncus removed and in only two was a part of the hippocampus also removed. Bailey and Gibbs (1951) in the meantime performed antero-lateral cortical removal in a series of patients, with no encroachment on mesial temporal structures because Bailey was aware of the severe behavioural deficits in monkeys after bilateral mesial temporal ablations as reported by Klüver and Bucy beginning in 1939 (Herman and Stone, 1989). This limited anterolateral approach was also supported by the pre-operative localization offered by EEG, either antero-lateral temporal, anterior Sylvian, or fronto-temporal (Gibbs, Lennox and Gibbs, 1936). Related experimental studies at the MNI were thus directed to clarify the connections of the temporal pole (Stoll et al, 1951; Ajmone-Marsan and Stoll, 1951) This is also well illustrated by similar antero-lateral temporal localization of ECG foci registered by Jasper and two young neurosurgeons (Jasper, Pertuiset and Flanigin, 1951) in thirty-nine of the same series of patients reported by Penfield and Flanigin in 1950. In only a few patients was EEG abnormality detected in the inferior and mesial part of the temporal lobe. (Fig. 1)

<sup>1</sup> For references see: Feindel W. Role of brain science in the evolution of epilepsy surgery. *McGill Med J* 1:160-174,1995 and Feindel W. *Epilepsy Surgery in Canada*. Chap 12 In: Lüders H., Najm I., Bingaman W.; *Textbook of Epilepsy Surgery* Abingdon, UK: Taylor and Francis, 2006.

## IMPORTANT INVESTIGATORS OF EPILEPSY

### Galen (129 - approx. 200)

According to Galen there are three forms of epilepsy: "In all forms it is the brain which is diseased; either the sickness originates in the brain itself,... or it rises in sympathy into the brain from the cardiac orifice of the stomach... Seldom, however, it can have its origin in any part of the body... and then rises to the head in a way which the patient can feel..."

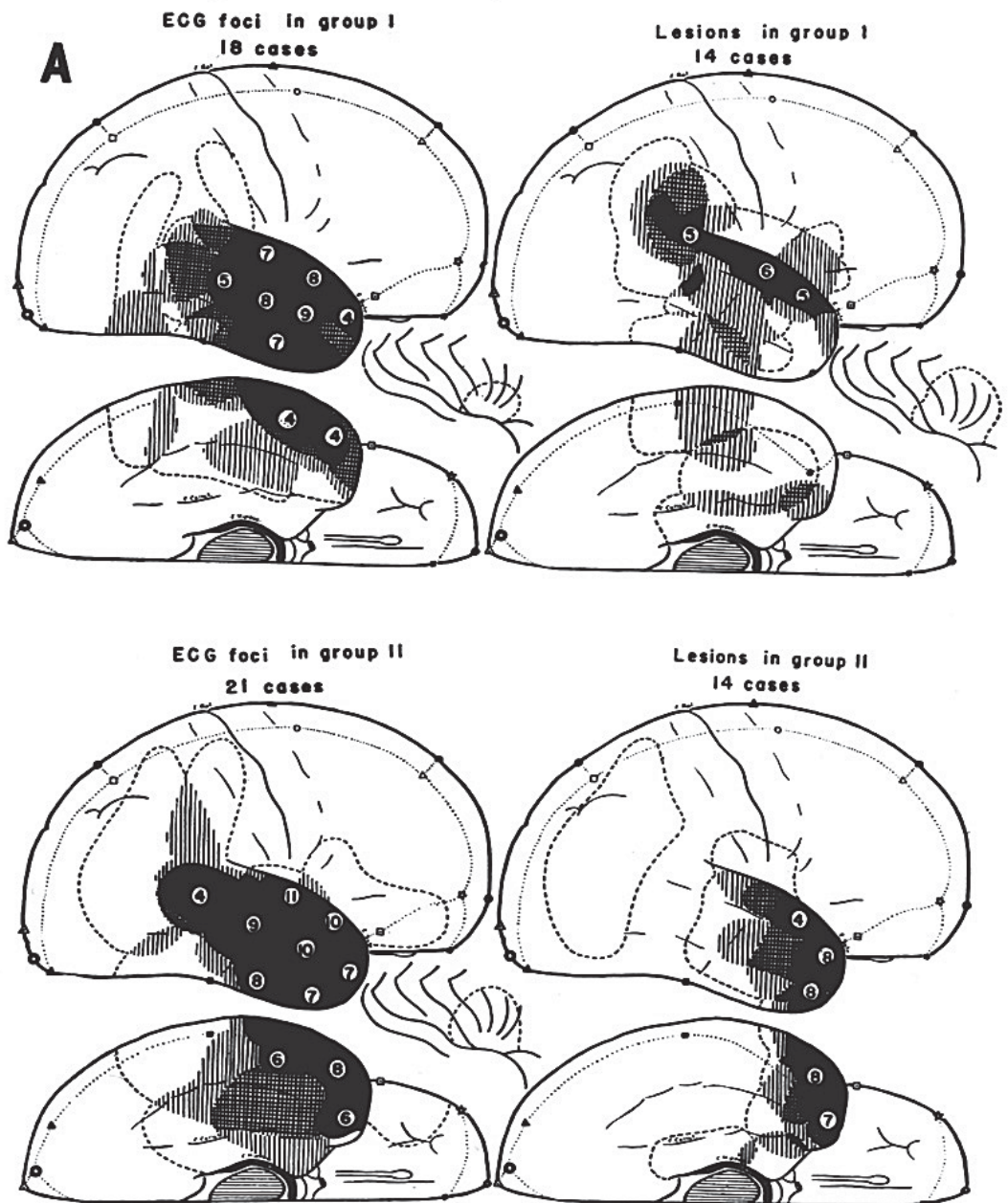
Case description: "I heard the boy say that his condition began in his lower leg and then moved up through the thigh, the groin and side of the chest above the affected thigh up to the neck and then to the head. As soon as [the condition] reached this part, he said that he was no longer aware of himself. When the doctors asked what the movement into the head was like, [another] boy said ... the movement upwards was like a cold breeze (aura)."



# The Mesial Temporal Region

The success rate of just over 50% in the two major surgical series, reported from Montreal by Penfield and Flanigin (1950) and from Chicago by Bailey and Gibbs (1951) indicated that resection limited to the antero-lateral temporal cortex did not eliminate all the epileptogenic tissue in many patients. Indeed in some cases persistent seizures led Penfield to persevere and carry out a second operation. In these, he extended the resection, under electrocorticographic control, sometimes posteriorly along the lateral temporal cortex (if on the nondominant side for speech) and also included more of the uncus and hippocampus (Feindel, 1991).

A second phase in the surgical approach to temporal lobe seizures unfolded rapidly in the early 1950s. Clues from experimental animal studies by Gastaut et al. (1951) and Kaada (1951) and from stimulation at operation (Liberson et al., 1951; Kaada and Jasper, 1952) pointed to the mesial and inferior surfaces of the temporal lobe for the origin of the epileptic



**Figure 1** Localisation of EEG foci and lesions reported by Jasper, Pertuiset and Flanigin in 39 patients operated upon for temporal lobe seizures by Penfield. The maximum changes, areas indicated in black, involve mainly the antero-lateral cortex of the temporal lobe

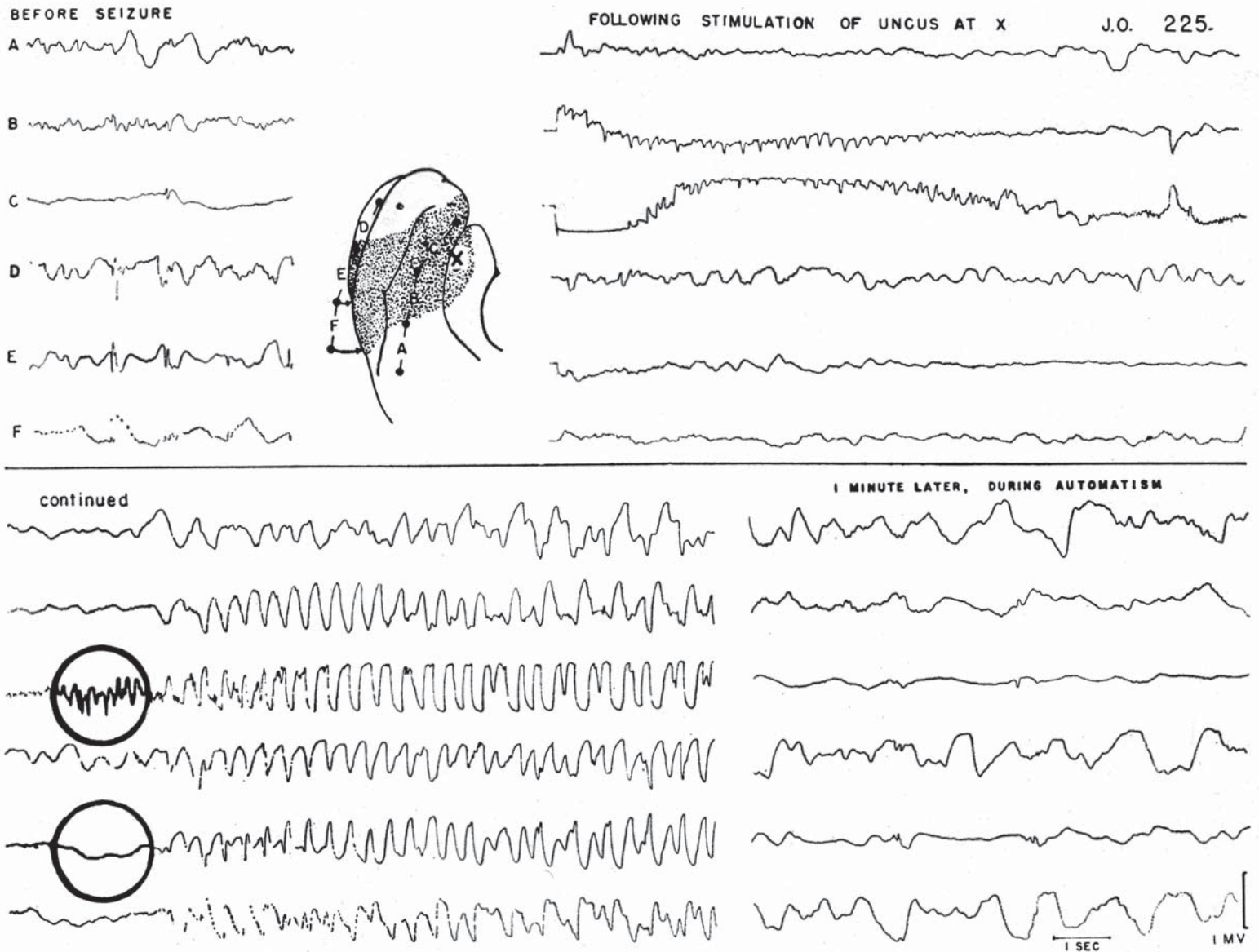
## IMPORTANT INVESTIGATORS OF EPILEPSY



### Jean-Martin Charcot (1825-1893)

One of the founders of modern neurology. Students came from all over the world to study under him in Paris, including Freud in 1885. Charcot used hypnosis as a diagnostic tool in his study of hysteria and influenced Freud's views on the origin of neurosis. Charcot made a number of important medical discoveries and even has a disease named after him (neurogenic arthropathy is also known as Charcot's joints). Charcot believed that he had discovered a new disease, which he called "hystero-epilepsy." (conversion disorder) The symptoms included "convulsions, contortions, fainting, and transient impairment of consciousness."\* He showed his students several examples of this new disease during his rounds at Salpêtrière Hospital.

attack. Penfield noted instances where stimulation in the uncinat region produced auras of the patients' attacks. In one such instance, a seizure with automatism was recorded consisting of low voltage fast activity followed by 3 per second waves to spread from the stimulation point to involve a wide region of the temporal cortex. (Fig. 2). These findings led Penfield in this case to extend his resection to include the mesial temporal region.



**Figure 2** ECG in patient J.O. before and after stimulation of uncinat cortex by Penfield (Jasper et al, 1951)

## IMPORTANT INVESTIGATORS OF EPILEPSY



### **John Hughlings Jackson (1835-1911)**

**E**nglish physician who pioneered the development of neurology as a medical specialty during the reign of Queen Victoria. Jackson first became interested in neurology when he became a staff member of the National Hospital Queen Square. There began his first stimulation in the study of seizures. He gained importance, not only based on his description of a certain seizure pattern "Jacksonian Epilepsy," but on his formulation of concepts, even principles, that explain paroxysmal seizures of all types. John Hughlings Jackson has been called the "father of English neurology." Jackson made a number of scientific discoveries in several areas of higher nervous activity and language, and contributed greatly to the study of various types of epilepsy.

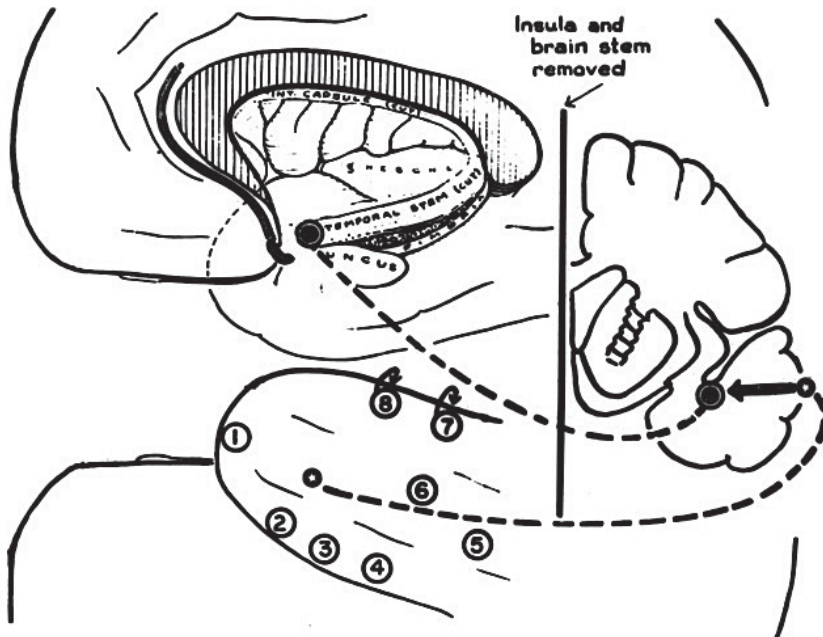
## Stimulation responses from the claustramygdaloid complex

The most substantial indication that the mesial temporal region was a crucial zone for the generation of temporal lobe seizures came in a third phase of surgical studies. This was the reproduction of the patient's habitual auras and other typical features of these attacks by anatomically directed depth stimulation or stimulation under direct vision at operation within and around the amygdala involving also the ventral claustrum and the anterior insula (Feindel, Penfield and Jasper, 1952). The resulting seizure discharges on corticography were seen to spread rapidly to encompass not only the temporal cortex but the exposed frontal parietal cortex.

In 1951, the surgical findings in the first patient in this series, initiated convincing evidence for the role of the amygdaloid region in temporal lobe seizures (Feindel and Penfield, 1954).

### Case Report Patient P.S., Age 26

He had a difficult birth and, from the age of 12, attacks which began with a vision of coloured lights, a "shock in the head", after which he became unresponsive, fumbled with his clothes and would later have no memory of his actions during this period. Pre-operative EEG study showed abnormal spike activity over the lateral and inferior temporal regions on the right side. At operation, a depth electrode was directed through the second temporal convolution 3.5 centimetres from the tip of the temporal lobe toward the region of the amygdala. One of his typical small attacks was produced with the electrode tip deep in temporal-insular sulcus, with electrodes recording from the lateral and inferior surface of the temporal lobe (Fig. 3). Epileptic spikes were suddenly replaced by low voltage rapid activity, the patient was seen to stare and become unresponsive to questioning, while he plucked at the anaesthetist's coat and



**Figure 3** Brain drawing to show electrode positions (in numbered circles) and depth stimulation in the amygdaloid region (black circles) from patient P.S.

made chewing movements. His appearance was much like that seen in his habitual attacks. The electrographic changes lasted a minute and a half, at which time the patient appeared to have recovered, but seemed unaware of the attack (Fig. 4). There was smallness and toughness of the first temporal convolution and mesial

## IMPORTANT INVESTIGATORS OF EPILEPSY



### **Hans Berger** (1873-1941)

**B**erger's research interest was centered on intracranial blood circulation and electrical activity of the brain. He studied Richard Caton's work on action potentials in animals and developed an instrument that measured and recorded electrical activity. In 1924, he measured the first electrical activity of the human brain as an electroencephalogram (EEG). He reported that the brain generates electrical impulses or 'brain waves'. The brain waves changed dramatically if the subject simply shifted from sitting quietly with eyes closed (alpha waves) to sitting quietly with eyes opened (beta waves).

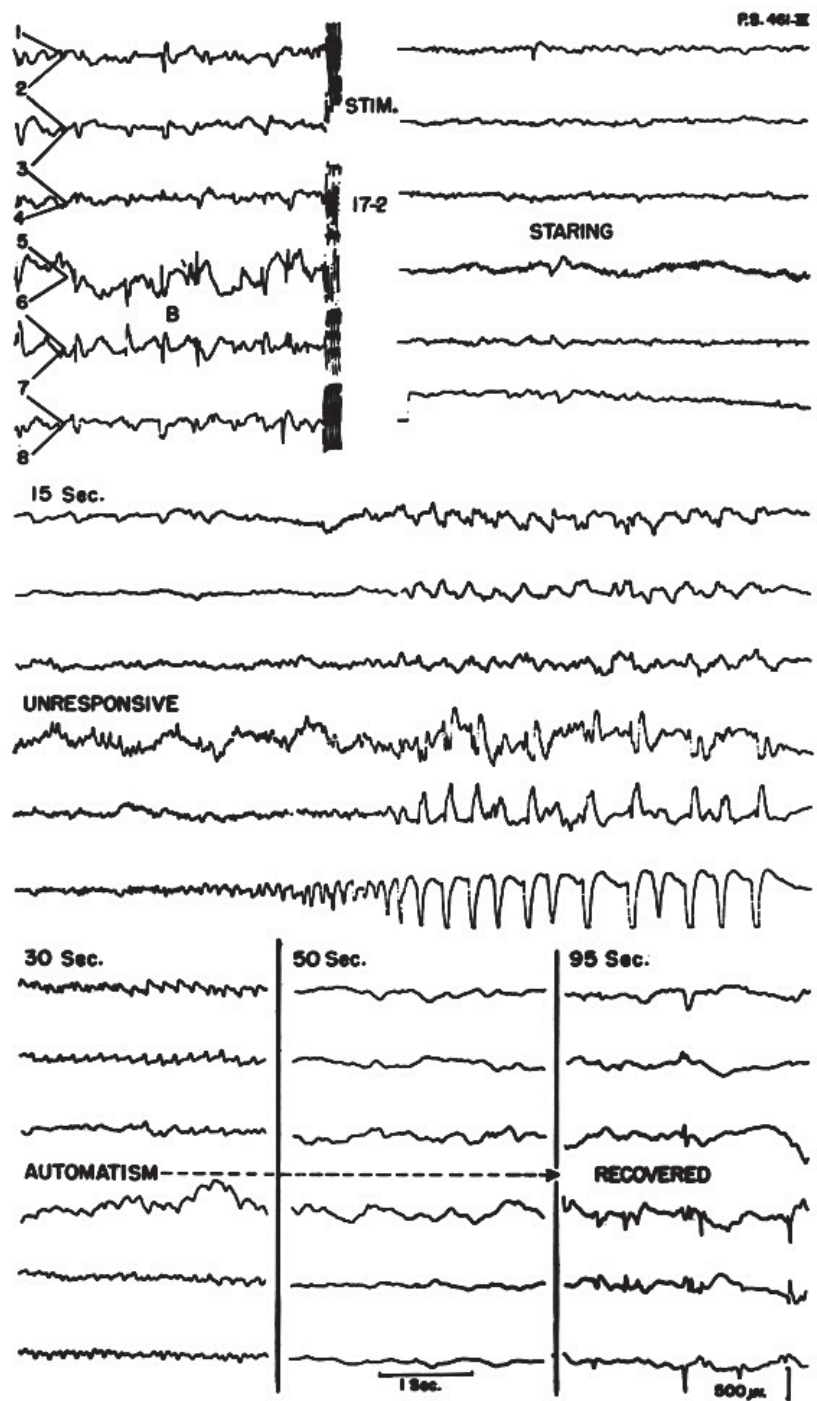
After his findings were confirmed, the electroencephalogram was launched into use for the study of normal and abnormal human brain activity. The EEG revolutionized neurological and psychiatric diagnosis and made possible specialized research in the neurological sciences. Today, the EEG is used in the clinical diagnosis of epilepsy, serious head injuries, brain tumors, cerebral infections, and various degenerative diseases of the nervous system.

temporal region, as well as a zone of gelatinoid tissue about the size of a small walnut deep in the temporal lobe, lateral and inferior to the ventricle and encroaching on the amygdala. Microscopically, this showed dense astrocytic gliosis. On later review, the neuropathologist interpreted this as a grade I astrocytoma. Resection included 6 cm. of antero-lateral cortex, as well as the mesial temporal region (amygdala; hippocampus) harboring the lesion. The patient continued free of attacks for 37 years later, with no reappearance of the tumor.

### The role of the claustramygdaloid complex

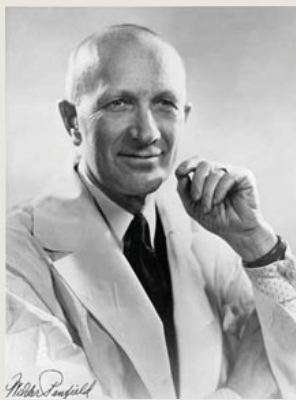
In 15 other patients from that same study, similar features of automatism and amnesia were reproduced by stimulation in the peri-amygdaloid region (Fig.5). This first examination of stimulation and electrographic responses from the human amygdala demonstrated its role in visceral responses such as fear and its critical relation to recent memory (Feindel, Penfield and Jasper, 1952). It was noted that these findings corresponded to the localization for "a particular variety of epilepsy" that had been proposed by Hughlings Jackson and others, just before the turn of the century: "the discharge-lesions in these cases are made up of some cells, not of the uncinate gyrus alone, but of some cells of different parts of a region of which this gyrus is part - a very vague circumscription, I admit - the uncinate region" (Jackson and Colman, 1898). The rich network of connectivity subtended by the amygdala offered a

**Figure 4** ECG showing rapid low-voltage activity from the temporal lobe and then return of the prestimulation spike activity. The patient P.S. had automatism and amnesia for the episode. Compare with Figure 2.



## IMPORTANT INVESTIGATORS OF EPILEPSY

### Wilder Penfield (1891-1976)



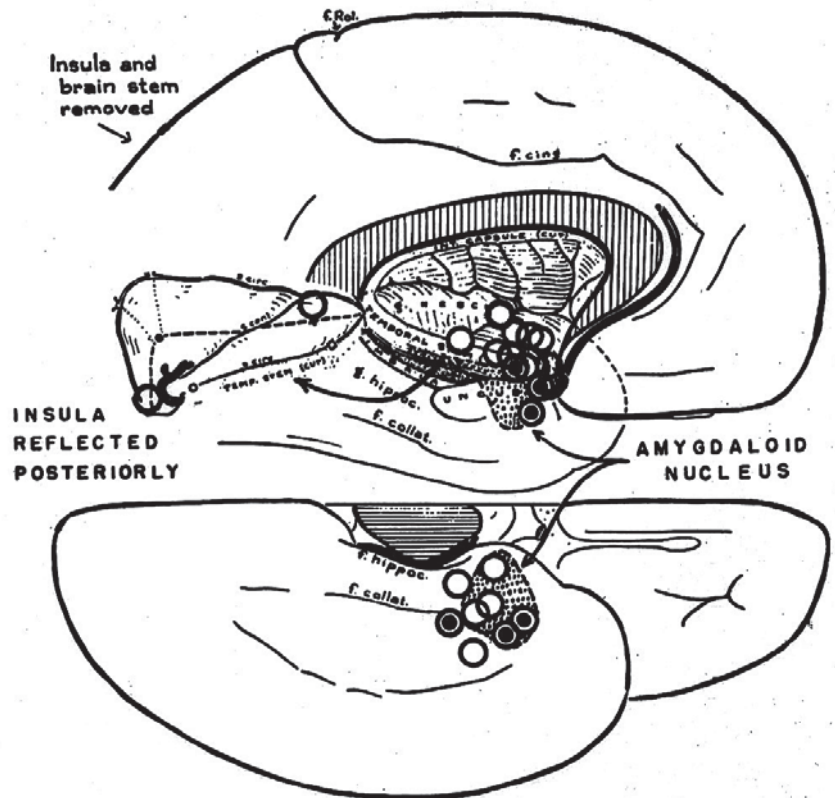
World-famous brain surgeon, Penfield reflected toward the end of his long, productive life that "the only certain virtue" that came into the world with him at his birth in Spokane, Washington on January 26, 1891 was "tenacity of purpose."

Penfield had a passionate desire to unlock the mysteries of the human brain. He revolutionized the techniques of brain surgery and made major discoveries about human cognition, memory, speech and sensation.

Penfield's medical exploration began with the causes and treatment of epilepsy, which was considered incurable. In 1934 he set up the Montréal Neurological Institute, which brought together surgeons and scientists for co-operative projects in the research, diagnosis and surgical treatment of brain disorders. (Photo by Yosef Karsh, 1953)



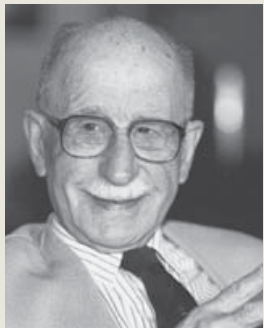
valid explanation for many of the characteristic clinical features of “uncinate” attacks described by Jackson (Feindel and Penfield, 1954). Thus, the patient’s epigastric aura, sometimes associated with a sense of fear, was reproduced from stimulation either of the amygdala itself or of the adjacent anterior insular cortex, which would later be shown to be physiologically associated with gastric movement (Penfield and Faulk, 1955). The various emotional, autonomic, and visceral responses likewise seemed explicable because of the robust anatomical pathways then known from the amygdala to the septal and hypothalamic regions. The initial feature of brief tonic movement with some temporal lobe attacks could be effected by the amygdaline efferent pathways to the striatum; chewing and swallowing movements could be explained by connections with the brain stem. The interference of the epileptic discharge with memory recording, characterized by the profound postictal amnesia, could reasonably be related, it was proposed, to the amygdala-hippocampal connection as well as the projection of the amygdala to the reticular system of the brain stem (Feindel and Gloor, 1954). Curiously, stimulation of the hippocampus



**Figure 5** Sites of stimulation from 16 operations that produced features of temporal lobe seizures such as epigastric area, fear, memory disturbance, automatism and amnesia.

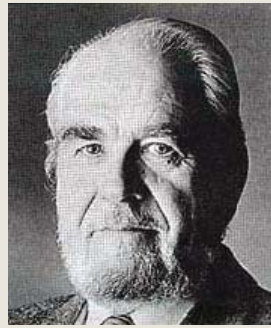
## IMPORTANT INVESTIGATORS OF EPILEPSY

### Herbert Jasper (1906-1999)



Jasper pioneered the application of the electroencephalogram (EEG) for the study of the electrical activity of the brain and used this technique in studies of consciousness, learning and particularly the examination of epileptic discharge. He utilized microelectrode recordings from single brain cells and combined this technique with microchemical analyses to study cortical and sub-cortical activity. Jasper conducted the first electroencephalograph (EEG) in the US in 1935. He led the Montreal Neurological Institute’s neurophysiology and EEG labs from 1939 to 1961, at the request of Wilder Penfield, MNI’s founder. He had impressed Penfield with his EEG skills on the exposed human brain while Penfield operated. Jasper also co-wrote an important text on epilepsy with Penfield. Among many other awards, he received the Albert Einstein Prize from the World Cultural Council in 1996. Today he is still recognized as one of the world’s leading neurophysiologists.

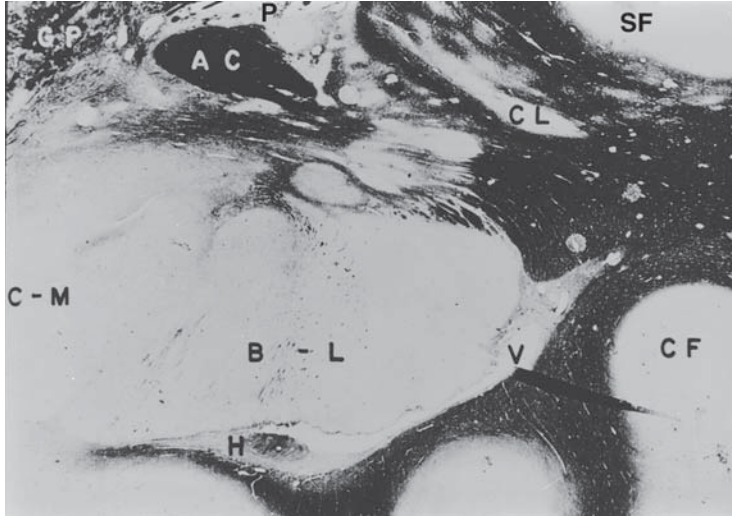
### Peter Gloor (1923–2003)



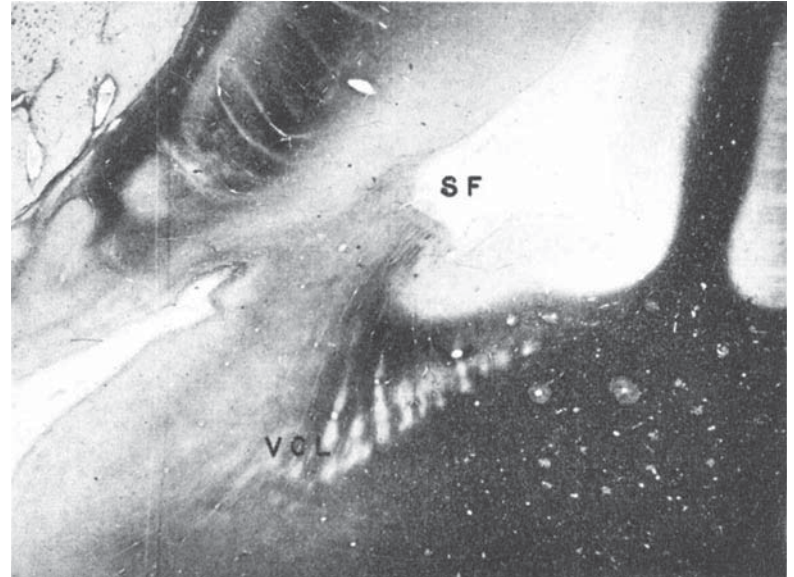
Born in Switzerland, Pierre Gloor received his medical education at the University of Basel, and carried out postgraduate work in neurology and neurosurgery at l’hôpital Louis Pasteur in Colmar, France. He joined McGill’s Montreal Neurological Institute in 1952 as a fellow in electroencephalography and neurophysiology, where he studied with Wilder Penfield and Herbert Jasper, receiving his Ph.D. from McGill in 1957. He had inexhaustible scholarly curiosity and planned a comprehensive synthesis of all that is known about the temporal lobe and the limbic system, a subject that continually fascinated him. He did this in his usual thorough manner, involving many trips to the original Yakovlev anatomic archives in Washington. This resulted in his magnum opus, *The Temporal Lobe and The Limbic System*, published by Oxford University Press.

directly at operation in the Montreal experience rarely produced such responses, even though epileptic abnormality might sometimes be recorded from the anterior part of the structure (Gloor and Feindel, 1963).

Thus, this evidence indicated that the amygdala and the juxtaposed gray matter, including the ventral claustrum and the anterior insular cortex, could generate temporal lobe seizures; this provided a physiological hypothesis that explained for the first time many of the clinical aspects of these attacks (Figures 9A & 9B). It also indicated that the peri-amygdaloid zone should be removed in the surgical resection in order to produce the most beneficial outcome. This critical role of the peri-amygdaloid region in mesial temporal seizures became confirmed in many later studies, as summarized for example in the monograph by Gloor in 1997.



**Figure 6** Enlarged view of the claustramoamygdaloid complex which shows the Sylvian fissure (SF), claustrum (CL), anterior commissure (AC), globus pallidum (GP), centro-medial and baso-lateral nuclei of the amygdala (C-M, B-L) hippocampus (H), ventricle (V), and collateral fissure (C-F).



**Figure 7** A more anterior coronal section shows the Sylvian fissure (SF) and grey matter of the ventral claustrum (VCL). This section relates to the site of the depth stimulation shown in Figure 3.

## IMPORTANT INVESTIGATORS OF EPILEPSY

### H. Houston Merritt (1902-1979)



**H**is contributions to neurology were countless. Among the most important was the discovery of the anticonvulsant properties of phenytoin (Dilantin); the technique he used, along with Tracy Putnam, to identify this compound ushered in the modern era of drug therapy for epilepsy. He also was the sole author of the first five editions of Merritt's

Neurology; this popular textbook is as of this writing (2005) in its tenth edition. His early work on the normal properties of the cerebrospinal fluid (CSF) was updated and published by one of his students, Robert Fishman, in a text that is the acknowledged standard on the topic.

### William G. Lennox (1884-1960)



**A**n American neurologist who was a pioneer in the use of electroencephalography (EEG) for the diagnosis and treatment of epilepsy. He was the author of *Epilepsy and Related Disorders*, and had a lasting effect on our understanding of this illness. He postulated that epilepsy was not a

unitary condition and that neuronal chemistries differed from one form of the disease to another. A leader in the use of electroencephalography in epilepsy, he described the first nearly pathognomonic EEG pattern and demonstrated specific features for each of the three most common types of seizure. His pioneering investigations into the biochemical basis of epilepsy helped to identify pathological mechanisms in epileptic attacks. Lennox stood alone in his belief, now generally accepted, that the genetics of epilepsy could be understood only through a multifactorial mode of inheritance.

# EPILEPSY TODAY

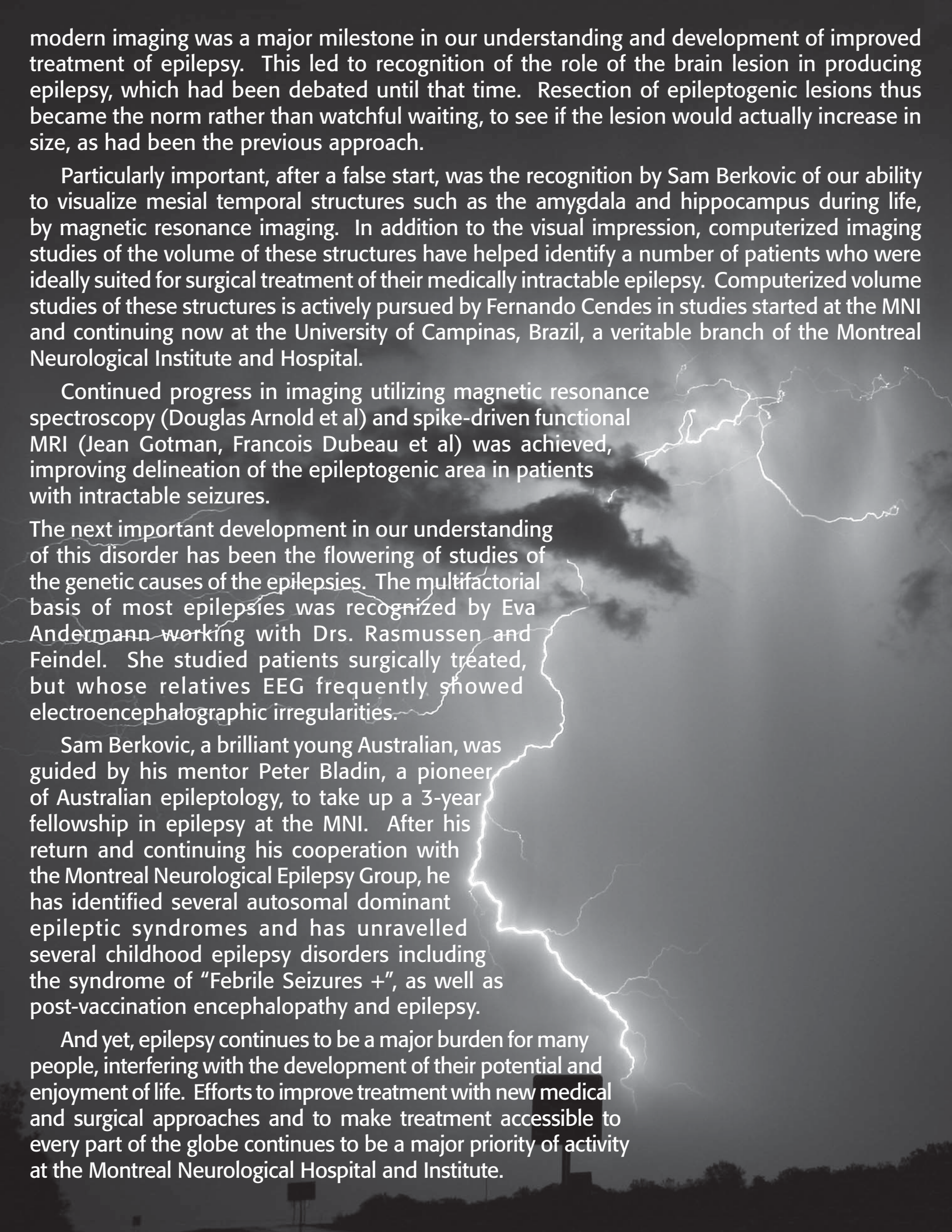
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There has been great progress in our understanding and treatment of epilepsy over the last century. Antiepileptic medications emerged at the end of the 19th century with bromides, initially used to diminish sexual drive. In 1912 Phenobarbital was introduced and it remains the drug of choice in many parts of the world because of its prolonged action and low cost. Because of cognitive side effects, attempts have continued to look for better antiepileptic medications. As a result of a series of trials of various compounds, Phenytoin (Dilantin) was identified by Merritt and Putnam. Fifty years later this drug is still widely used and is particularly valuable for the treatment of partial and generalized seizures. It was followed by the development of Valproic acid or Depakene, particularly useful for the treatment of photosensitivity in generalized epilepsy, and by Carbamazepine and others.

In recent years several new antiepileptic compounds have emerged. Their mode of action has, for the most part, been clarified as modifying the function of channels traversing the membrane of neurons. The newer antiepileptics seem to have fewer side effects compared with the older, established, agents. In over 2/3 of patients with epilepsy the recurrence of seizures can be controlled by the use of antiepileptic medications. The goal for the future is rational therapy which would further improve seizure control by acting on identified causative neurophysiological and neurochemical mechanisms.

Given the intractability of epileptic seizures in many individuals, a search for other approaches led to the development of the surgical treatment of epilepsy pioneered at the MNI by Penfield, Rasmussen, Feindel, Olivier and their groups. Following the flowering of electroencephalography, well described by Feindel in this publication, the development of



modern imaging was a major milestone in our understanding and development of improved treatment of epilepsy. This led to recognition of the role of the brain lesion in producing epilepsy, which had been debated until that time. Resection of epileptogenic lesions thus became the norm rather than watchful waiting, to see if the lesion would actually increase in size, as had been the previous approach.

Particularly important, after a false start, was the recognition by Sam Berkovic of our ability to visualize mesial temporal structures such as the amygdala and hippocampus during life, by magnetic resonance imaging. In addition to the visual impression, computerized imaging studies of the volume of these structures have helped identify a number of patients who were ideally suited for surgical treatment of their medically intractable epilepsy. Computerized volume studies of these structures is actively pursued by Fernando Cendes in studies started at the MNI and continuing now at the University of Campinas, Brazil, a veritable branch of the Montreal Neurological Institute and Hospital.

Continued progress in imaging utilizing magnetic resonance spectroscopy (Douglas Arnold et al) and spike-driven functional MRI (Jean Gotman, Francois Dubeau et al) was achieved, improving delineation of the epileptogenic area in patients with intractable seizures.

The next important development in our understanding of this disorder has been the flowering of studies of the genetic causes of the epilepsies. The multifactorial basis of most epilepsies was recognized by Eva Andermann working with Drs. Rasmussen and Feindel. She studied patients surgically treated, but whose relatives EEG frequently showed electroencephalographic irregularities.

Sam Berkovic, a brilliant young Australian, was guided by his mentor Peter Bladin, a pioneer of Australian epileptology, to take up a 3-year fellowship in epilepsy at the MNI. After his return and continuing his cooperation with the Montreal Neurological Epilepsy Group, he has identified several autosomal dominant epileptic syndromes and has unravelled several childhood epilepsy disorders including the syndrome of "Febrile Seizures +", as well as post-vaccination encephalopathy and epilepsy.

And yet, epilepsy continues to be a major burden for many people, interfering with the development of their potential and enjoyment of life. Efforts to improve treatment with new medical and surgical approaches and to make treatment accessible to every part of the globe continues to be a major priority of activity at the Montreal Neurological Hospital and Institute.