1 Introduction: epilepsy

Gregory D. Cascino

Department of Neurology, Division of Epilepsy, Mayo Clinic, Rochester, MN, USA

1.1 Epilepsy care: beginnings of observation and recognition

Epilepsy historically has been one of the most commonly recognized and distinct neurological disorders [1, 2]. In fifth-century BC Greece, Hippocrates, the father of medicine, made several profound observations regarding epilepsy that have survived many centuries [1]. He was a follower of the Greek god of medicine Asclepius whose symbol of a serpent-entwined staff has been representative of medical practice to the present. On the island of Cos in the Aegean Sea, Hippocrates observed patients with a malady referred to as the "sacred disease." He indicated that seizures appeared no more *divine* or spiritual than any other illness. Hippocrates also implicated the brain as the site of seizure onset and recognized the genetic predisposition in selected patients. Galen was another outstanding physician of Greek origin who was born in 129 AD and was influenced by the teachings of Hippocrates. Upon traveling to Rome he made several seminal observations in medicine and introduced the term "aura" to describe the patients' symptoms that recognized the onset of a seizure. Initially Galen recognized the abdominal complaints that may occur in patients prior to the impairment in consciousness. The aura was compared to a "breeze" that may indicate an oncoming weather storm.

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Epilepsy in the Middle Ages was considered to be emblematic of the *absence* of a spiritual or divine presence [1, 2]. The paroxysmal behavior was thought to be related to an external evil force that was possessing the soul of the unfortunate individual. The removal of "demons" was necessary to control the "convulsions" that gripped the patient. Later, patients were often isolated from the general population and placed in institutions or epilepsy colonies. The segregation of people with epilepsy had a profoundly negative impact on the ability of these individuals to successfully integrate and live in "normal" society.

1.2 Epilepsy care: initial understanding and treatment

The contemporary care of patients with seizure disorders began with the pivotal observations and writings of John Hughlings Jackson (1835–1911), the father of epilepsy, at the National Hospital for Diseases of the Nervous System including Paralysis and Epilepsy in Queen Square, London [1–4]. Jackson influenced the Scottish neurologist Sir David Ferrier working in London to confirm the relationship between nervous system physiology and structure to better elucidate the pathophysiology associated with seizures [4]. Ferrier performed electrical stimulation of the motor cortex in the dog providing evidence that focal motor seizures were associated with excitation of the precentral gyrus [1–4]. Prior to the works of Jackson in the mid nineteenth century, there was considered to be only one prominent seizure type, the generalized tonic-clonic seizure. There was a broad consensus that the "grand mal seizure" involved the lower brainstem or upper cervical cord, or both structures. Jackson postulated that the cerebral cortex was the site of seizure onset and that the ictal behavior correlated with the region of functional anatomy. A focal or lateralized neurological abnormality may indicate the region of hemisphere of seizure onset. Further, he introduced the concept of partial epilepsy indicating that "*part*" of the cerebral cortex was involved in seizure onset [3]. This area of cerebral cortex was considered to be abnormal resulting in a focal neurological deficit and seizure activity. The potential therapeutic importance of Jackson's brilliant conclusions was that surgical treatment may be effective as an underlying pathology or structural lesion was presumed to be associated with the site of epileptogenesis [4]. Resection of the lesional pathology was entertained as an effective means of rendering the patient seizure-free [4]. These seminal observations occurred prior to the development of electroencephalography (EEG), neuroimaging, or use of antiepileptic drug therapy. Subsequently, beginning in 1886 Dr. Victor Horsley, a young surgical colleague of Hughlings Jackson, performed neurosurgical procedures for epilepsy in patients at the National Hospital [4]. The localization of the epileptogenic brain tissue was based on the ictal semiology, the neurological examination, and knowledge of functional neuroanatomy. The efforts of Jackson and colleagues began the

rewarding and productive relationship between neurology and neurosurgery in the management of patients with intractable epilepsy [4].

1.3 Epilepsy care: the Mayo Clinic

Dr. Willam J. Mayo and Dr. Charles H. Mayo, the brothers who founded the group practice in Rochester, Minnesota, were close colleagues of the "fathers" of contemporary neurosurgery, Dr. Harvey Cushing of Johns Hopkins University and later Harvard University, and Dr. Charles H. Frazier of the University of Pennsylvania [5, 6]. The strong relationship between Dr. Cushing and the Mayos lasted until the time of the brothers' deaths in 1939 [6, 7]. Dr. C. Mayo published his initial experience with neurosurgery in 1891 [8]. The importance of seizures as a diagnostic symptom of neurological disease and the effect of neurosurgery on seizure tendency were recognized. Ultimately, in 1917, Dr. Alfred W. Adson became the first full-time neurosurgeon at the Mayo Clinic [5]. The growth of neurology and neurosurgery at this institution were forever intertwined during this period as Dr. Walter D. Shelden had come to the Mayo Clinic in 1913 and founded the neurology section. Perhaps most importantly, Dr. Adson had insisted that neurosurgery should be a separate department from surgery and a unique subspecialty at the Mayo Clinic. Advances in diagnostic technology would be necessary to expand the care of patients with epilepsy.

The first EEG study at the Mayo Clinic was performed by Dr. E.J. Baldes, a biophysicist, on Dr. Charles LeVant Yeager who was a Mayo neurology fellow in 1936 [9]. Dr. Yeager was an amateur radio operator who became interested in the works of Hans Berger when the first publication of EEG appeared in 1929. He personally translated the 10 works of Berger on EEG into English. Dr. Frederick Moersch, one of the pioneers in neurology at the Mayo Clinic, had visited Nobel Laureate Lord Edgar Douglas Adrian's laboratory working on EEG at the University of Cambridge in 1935, and encouraged development of this innovation in Rochester, MN [9]. The initial EEG recordings were performed at the Rochester State Hospital and the laboratory was subsequently moved to Saint Marys Hospital. The development of EEG at the Mayo Clinic was selected by Dr. Henry Woltman, the section head of neurology, as Dr. Yeager's "research project." Working closely with Dr. Adson the diagnostic utility of EEG was analyzed in patients with known intracranial lesions. Dr. Adson had insisted that only the ages of the patients and not the clinical information be made available to the EEG readers. The results of EEG studies in a series of patients demonstrated the favorable diagnostic importance of the "new" technique for structural localization compared to other studies, for example, ventriculography and pneumoencephalography. EEG was also demonstrated to assess the seizure tendency in these individuals and indicate the likely site of seizure onset.

After World War II the clinical and basic research activities of the EEG laboratory were expanded. The recruitment in 1948 of Dr. Reginald G. Bickford from the University of Cambridge increased the research interests of EEG to include the evaluation of patients with seizure disorders [9]. Dr. Bickford had worked with E.D. Adrian and EEG pioneer Dr. W. Grey Walter during the war and had had the opportunity to perform intracranial EEG recordings in patients with penetrating head injuries undergoing neurosurgical treatment [9, 10]. He brought to the Mayo Clinic his interest in reflex epilepsy and intracranial EEG recordings. Therefore, Rochester, MN was one of the earliest centers in North America performing these depth electrode recordings in patients with seizure disorders. A symposium on "intracerebral electrography" was held in 1953 summarizing the outcome of these studies in patients with epilepsy [10]. Beginning in 1948, Dr. Bickford and colleagues also performed motion picture recordings for diagnostic classification of seizures and nonepileptic events. Dr. Donald W. Klass started as neurology resident at the Mayo Clinic in 1953 and went on to become head of the EEG section in 1967 [11]. Dr. Klass had described the epileptogenic potential of several paroxysmal EEG patterns and recognized the benign nature of selected discharges. Importantly, he also educated a generation of neurologists in EEG interpretation [9].

In 1968, Dr. Frank W. Sharbrough joined the staff at the Mayo Clinic after completing his training at the University of Michigan and serving in the military. His interests included routine EEG, intraoperative EEG monitoring during cerebrovascular surgery and epilepsy surgery, evoked potentials, and use of computer applications to monitor neurophysiological techniques. Focal cortical resections for patients with epilepsy and excisions of potentially epileptogenic lesions were performed by several neurosurgeons including Dr. Ross H. Miller who served as chair of the department of neurosurgery (1975–1980) and performed over 4000 operations for intracranial tumors [5]. Surgical treatment for intractable partial epilepsy achieved a significant advance with the arrival of Dr. Edward P. Laws, Jr. at the Mayo Clinic in 1972 [5]. Dr. Laws was trained in neurosurgery at the Johns Hopkins University by the renowned neurosurgeon Dr. A. Earl Walker and collaborated with famed electroencephalographer, Dr. Ernst Niedermeyer. At the Mayo Clinic he was a prominent academic neurosurgeon and educator actively involved in epilepsy surgery as well as resection of pituitary tumors and craniopharyngiomas [12, 13].

In 1973 the Mayo Clinic was the first institution in the United States to have an x-ray computed tomography (CT) scanner installed [14]. The use of CT and the subsequent development of magnetic resonance imaging (MRI) had a profound effect on the evaluation of patients with epilepsy. The pivotal importance of MRI in identifying structural abnormalities and the potential for performance of intraoperative imaging to guide surgical procedures and implantation of intracranial electrodes had an enormous impact on the care and management of epilepsy.

In 1984, Dr. Patrick J. Kelly joined the staff in neurosurgery [5]. After his neurosurgery residency he completed training at the Hospital Sainte Anne in Paris with the founder of stereotactic neurosurgery, Dr. Jean Talairach. The emergence of the new imaging technology and Dr. Kelly's experience combined for the use of stereotactic neurosurgical procedures to resect epileptogenic lesions and for computer-assisted placement of intracranial depth electrodes [15, 16]. Stereotactic "lesionectomy" was particularly useful for intra-axial lesions involving functional cerebral cortex [15].

The last decade of the twentieth century was remarkable for major advances in neuroimaging at the Mayo Clinic that significantly improved the ability to care for patients with intractable seizure disorders. Colleagues in neuroradiology, neurology, neurosurgery, and nuclear medicine were critical for the development of MRI hippocampal formation volumetry and subtraction ictal single photon emission computed tomography (SISCOM) [17, 18]. The former structural neuroimaging study has proven beneficial in correlating quantitative hippocampal atrophy with neuronal cell loss, neuropsychometric studies, and seizure outcome in patients undergoing temporal lobe surgery for intractable epilepsy [17]. The latter functional neuroimaging procedure has been adapted to the evaluation of patients with nonlesional partial epilepsy or if the preoperative evaluation has conflicting findings regarding the localization of the epileptogenic zone [18].

The practice of epileptology at the Mayo Clinic is predicated on the motto for medical care since the pioneer practice of Dr. William W. Mayo in the nineteenth century: "The needs of the patient always come first." At the three Mayo Clinic sites in Arizona, Florida, and Minnesota the goals of epilepsy treatment are to reduce seizure tendency and improve the quality of life enabling the individual to become a participating and productive member of our society.

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