Ellen R. Grass Lecture: Present at the Beginning: Ellen Grass and the Evolution of Modern Concepts Regarding EEG and Epilepsy

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Ellen R. Grass Lecture:
Present at the Beginning: Ellen Grass and the Evolution of Modern Concepts Regarding EEG and Epilepsy*

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ABSTRACT. Ellen Grass was a remarkable woman whose efforts on behalf of neurophysiology, epilepsy, and physiological technology contributed importantly to the development of neuroscience in the United States during the middle third of the 20th century. She initially provided an important link between a remarkable group of Harvard physiologists and her husband, Albert, a brilliant engineer whose innovative equipment played a critical role in accelerating advances in neurophysiology and, later, EEG and epilepsy. Mrs. Grass herself observed and personally facilitated much of the clinical and basic neuroscience research during this period, when the modern framework for a scientific understanding of epilepsy and EEG was established. She also supported the development of professional societies relevant to these areas, including ASET, the American EEG Society, the American Epilepsy Society, and the Epilepsy Foundation of America.

KEY WORDS. EEG, Ellen Grass, epilepsy, neurophysiology, neuroscience.

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INTRODUCTION

It is my great privilege and honor to give the 2007 Ellen R. Grass Lecture. It is a privilege because ASET, which I first knew as the American Society of EEG Technologists, was an important part of my professional life early in my career. For many years I was an examiner for ABRET, the American Board of Registration of EEG Technologists, and I later served as a member of that Board. I also chaired the Joint Review Committee on Education in EEG Technology, which accredited schools of EEG technology. As a resident in neurology and later as a postdoctoral fellow in EEG and epilepsy, I quickly learned how important – indeed, essential – technologists are to the kind of high-quality EEG recordings that are necessary for accurate EEG interpretation and meaningful clinical-electrographic correlations. At Stanford University, where I trained, I was fortunate to work with, and learn from, a group of highly skilled technologists, one of whom was Kathleen Mears, who died far too young, but whose contributions and memory are appropriately commemorated by a lectureship that bears her name at the annual ASET meeting.

ELLEN R. GRASS

And it is an honor, because I knew Ellen Grass well and can say without exaggeration that she was one of the great persons I have known (Figure 1). She was a formidable but very kind, unassuming, generous, and supportive woman who preferred to work behind the scenes to achieve her objectives. Her New England background gave her a certain reserve and a practical “roll up the sleeves and get to work” approach to most things. In remarks Dr. Madison Thomas once made in introducing her, he commented that Mrs. Grass’s two most frequent questions were apt to be, “How can I help?” and “What needs doing?”. Some of her oldest friends knew her as “Robbie” (her maiden name was Robinson), but she was “Mrs. Grass” to almost everyone else. Indeed, it was many years before I had nerve enough to call her “Ellen,” even though she had been asking me to do so for some time.

I knew Mrs. Grass in four different but related contexts. First at EEG meetings, beginning about 1971, where she was usually at her company’s booth helping EEGers obtain the best equipment for their needs. She was always interested to speak with young people and ask if there was anything she could do for them. Second, she was equally visible at meetings of the American Epilepsy Society (AES) and always ready to articulate the needs and perspective of patients and their families. Her many important contributions to AES were recognized formally in 2000, when she received a unique Award for Extraordinary Contributions to the field of epilepsy. Third, I knew her through her work with the International Bureau for Epilepsy, an organization she served as President and that later named her Honorary President for life in recognition of her many contributions. Finally, I knew her at the
Epilepsy Foundation of America, which she helped create from three predecessor organizations in the late 1950s, and where she still served on the Board of Directors when I was elected in 1984. It was quite typical that when there wasn’t enough money to fund a worthwhile project of the Foundation (such as developing a cross cultural program for Native Americans), Mrs. Grass quietly made up the difference.
FIG. 2. Professor Hans Berger in 1925 at the age of 52, one year after he began his work on the human EEG. Reproduced from Gloor (1969) Clinical Neurophysiology, Supplement 28, with the permission of Elsevier Ltd.
Through the International Bureau and Epilepsy Foundation, Mrs. Grass played a critically important role in the development of the epilepsy volunteer movement, both in the United States and around the world.

As electroneurodiagnostic technologists, you should know how much Mrs. Grass cared for your field and your contribution to high-quality clinical electrophysiology. She was an Honorary Member of ASET, and she received the first Medallion of the Canadian Association of EEG Technologists. She wrote knowledgeably about EEG technology in such papers as “The technician’s responsibility to the hospital”; “Technological aspects of EEG in the determination of death”; and “Verifying electrocerebral silence: a technological challenge.” She was an early and enthusiastic supporter of ASET and of certification of EEG technologists, both of which were part of a larger goal that she and her husband shared, namely to standardize procedures for recording EEGs and to raise the quality of both EEG technology and interpretation. Thus, the Grass Instrument Company helped ASET in many ways, including with annual contributions to its support.

**BOSTON’S CONTRIBUTIONS TO EEG AND EPILEPSY**

Ellen’s husband, Albert, was a graduate of the Massachusetts Institute of Technology (MIT) and a brilliant engineer. He and Ellen made a marvelous team. They met in 1935 in Harvard’s Department of Physiology, which was home to a group of remarkable individuals interested in the new field of electrophysiology applied to the nervous system. By this time, Hans Berger’s reports of recording human “brain waves” (Gloor 1969) had been validated, and the opportunities for neuroscience and clinical application seemed almost limitless (Figures 2 and 3). At Harvard, Walter B. Cannon, Hallowell Davis (in whose laboratory Mrs. Grass once worked), and Alexander Forbes were among the scientists. William G. Lennox, Houston Merritt, and Tracy Putnam were the clinicians with access to patients. Albert Grass built the robust and technically innovative EEG machines that allowed the brain’s electrical activity to be recorded and studied in both animals and humans. Dr. Frederic Gibbs, who had observed Berger’s techniques in Germany, and his wife Erna, a former German EEG technologist, became the world’s leading authorities on
clinical EEG through an extraordinarily prolific output of methodical, descriptive research studies.

EPILEPSY AND EEG – CLINICAL CORRELATIONS

The period from about 1935 to 1960 was a golden age for epilepsy and EEG in the United States. The remarkable collaborative efforts of Albert Grass, William Lennox, and the Gibbses (Figure 4) resulted in a steady stream of major contributions that shaped many of our modern concepts related to EEG and epilepsy. From an even broader perspective, it is not an exaggeration to say that in the middle third
of the 20th century – the period when Mrs. Grass was most directly involved in epilepsy and EEG – efforts to determine the neural origin of EEG activity were the principal focus for neuroscientists interested in the physiology of the mammalian cortex. Let me summarize some of the major discoveries of that time as they relate to EEG and epilepsy.

Toward the end of the 19th century, Hughlings Jackson’s work at the National Hospital, Queen Square, in London inaugurated the modern era of the scientific study of epilepsy. Jackson (Figure 5) was the first to propose that specific brain areas gave rise to different and characteristic types of seizures. In addition to the by then well known grand mal and petit mal seizures, Jackson’s careful observations of patients with epilepsy led to the recognition of focal motor seizures (Jacksonian seizures) arising from primary motor cortex (Jackson 1932), and uncinate fits (Jackson 1888), later termed psychomotor epilepsy by VanGieson (1924) which were linked to the medial temporal lobe (Jackson 1899). Jackson and others realized that psychomotor seizures, which were characterized by what he called “dreamy states” with sensory hallucinations, were a kind of “intermediate” seizure type that was neither petit mal on the one hand, nor grand mal on the other, and thus a third distinct form of epileptic seizure.

Beginning in about 1935, EEG recording added a new dimension by enabling clinical observations of seizure phenomena in patients to be correlated with different EEG patterns. Thus, it was discovered that generalized rhythmic fast activity accompanied the tonic phase of a grand mal seizure, while repetitive generalized spike-wave or polyspike-wave bursts were associated with the synchronous muscle jerks of the clonic phase (Gibbs et al. 1936). Interictally, the EEGs of patients with grand mal (idiopathic generalized) epilepsy were found to have generalized spikes, spike-wave or polyspike-wave discharges (in the early days, these were sometimes called “larval seizures”). Children with petit mal epilepsy had sustained 3 Hz spike-wave activity during absence attacks (Gibbs et al. 1935). And patients with psychomotor (complex partial) seizures were found to have initial flattening of temporal EEG activity on one side followed by rhythmic 4 to 6 Hz activity in the same area (Gibbs et al. 1937, Jasper et al. 1951). Interictally, the majority of patients with temporal lobe epilepsy had focal sharp wave discharges over the anterior temporal region, especially during sleep (Gibbs and Gibbs 1947, Gibbs et al. 1948).

NEURAL BASIS OF EEG ACTIVITY

The Origin of EEG Waves

Seminal early studies of the physiological basis of EEG activity came from Lord Adrian, George Bishop, Herbert Jasper, the collaborative work of Edward W.
Dempsey and Robert S. Morison, B. Renshaw, HT Chang, and John Eccles. By the early 1950s, there was accumulating evidence and growing acceptance that the generator sources for EEG waves were principally postsynaptic potentials (for historical review, see Pedley and Traub 1990). Individual action potentials, familiar from studies of peripheral nerves, do not contribute directly to EEG activity, mainly because their short duration does not favor synchronous, in-phase summations or participation of distant charged membranes in passive current flow. In contrast, synaptic potentials, although of much lower voltage than action potentials, are associated with widely distributed extracellular current flow, involve a larger amount of membrane surface area, and are of much longer duration (Figure 6). Spontaneous EEG activity occurs when currents flow across charged neuronal membranes as a result of synaptic activity. Differences in the polarity of EEG waves at the scalp depend on the relative position of recording electrodes with respect to current sources and sinks representing, respectively, the positive and negative ends of a dipole. It is likely that cortical pyramidal cells, which have long processes oriented perpendicular to the cortical surface, thus corresponding to a model of stationary vertical dipoles, are the major contributors to EEG potentials. EEG waves represent the “average” behavior of large numbers of neurons that are engaged in relatively synchronous activity (Creutzfeldt et al. 1966). Thus, there is a good correlation between postsynaptic potentials and evoked potentials, sleep spindles, and epilepti-
form discharges. However, non-rhythmic EEG waves correlate poorly with the activity of individual neurons. This is to be expected, because the activity of individual neurons may deviate from the “average” behavior of a larger ensemble of neurons. The more neurons that are engaged in the same rhythmic activity, the more probable it is that a particular EEG pattern (e.g., sleep spindles or alpha rhythm) reflects the activity within a given neuronal aggregate.

**The Origin of EEG Rhythmicity**

Rhythmic EEG waves result from circuits within the brain that predispose groups of neurons to oscillate collectively. Oscillatory behaviors are now well known properties of certain neurons and circuits, both in invertebrates and vertebrates (Selverston and Moulins 1985, Traub et al. 1999). There are many cortical oscillators that allow information exchange among different regions, as well as oscillatory circuits that link cortical and subcortical neurons. Cortical oscillations can range from very slow (periods of seconds to even minutes) to very fast (up to 500 Hz or even higher). Faster frequencies were largely unknown in the early days of EEG technology, when mechanical recording systems limited upper frequency range fidelity. Today, gamma frequencies (about 25 to 50 Hz) are being studied extensively, especially in relation to learning and perception, and both fast (80 to 200 Hz) and ultra fast (200 to 500 Hz) oscillations (or “ripples”) are emerging as important contributors to understanding both normal brain function (Buzsáki et al. 1992, Jones et al. 2000) and epilepsy, including seizure onsets (Fisher et al. 1992, Traub 2003, Staba et al. 2002).

Neurophysiological oscillatory behaviors are readily apparent in routine EEG, as illustrated by the alpha rhythm, sleep spindles, and 3 Hz spike-wave discharges. A critical oscillatory circuit for these phenomena involves the cerebral cortex, the reticular nucleus of the thalamus, and specific thalamic relay nuclei (Snead 1995, Steriade et al. 1993, Kostopoulos 2001). The behavior of this circuit depends on three key elements: 1) reciprocal connectivity between the thalamic reticular nucleus and thalamic relay nuclei; 2) GABAergic control by the reticular nucleus of inhibitory postsynaptic potential (IPSP) duration in relay neurons and, thus, the timing of circuit oscillations; and 3) synchronous network discharges made possible by calcium-dependent bursts in both reticular and relay neurons (see Chang and Lowenstein 2003 for review).

It is important to remember that EEG has significant limitations, both clinically to a certain extent, but especially as a tool for studying physiological mechanisms in the brain. These derive from the fact that inferences or conclusions based on EEG data depend on interpretation of cortical events occurring close to the surface. Information about subcortical or brainstem contributions is, at best, limited and indirect. Because most network interactions and information processing take place in the
depths of the cortex, this is a serious constraint on its utility. Additional useful data can be obtained using intracranial electrodes and magnetoencephalography (MEG), but there are still major problems with sampling and spatial resolution. Most recently, functional magnetic resonance imaging (fMRI) has been combined with EEG to add further details about neuronal networks associated with EEG signals (Leal et al. 2007, Zijlmans et al. 2007). Nonetheless, the challenge that remains is what has been termed the "reverse engineering problem." That is, trying to infer cellular and synaptic events from signals that are complex composites of multiple, and often widespread, processes. For full discussion of these issues, see Nunez (1981).

The Pathophysiologica Basis of Epileptiform Discharges

Epileptiform discharges are indicators of an individual’s susceptibility to seizures. This is because they reflect a specific underlying cellular abnormality. Experimental studies in animals have demonstrated that EEG spikes or sharp waves are associated with synchronous paroxysmal depolarizing bursts occurring in cortical neurons (Figure 7) (Prince 1978). The long-lasting hyperpolarization that typically follows each burst results in the surface slow wave that usually follows each spike or sharp wave (the spike-wave complex) (Prince 1968, Prince 1978). The bursts also trigger inhibitory activity in the surrounding cortex ("surround inhibition"), which helps restrict the spread of epileptiform discharges (Prince and Wilder 1967). Surround inhibition also probably contributes to the intermittent slowing often seen in an epileptic EEG focus. EEG spikes and sharp waves occur when large numbers of neurons burst synchronously. Spikes (faster, more stereotyped waveforms) result when the neurons are tightly engaged and burst in very close synchrony with each other. Sharp waves (slower, more variable waveforms) result when the bursting in different neurons is less synchronous and spread out over a longer interval.

THE GRASS FOUNDATION AND ITS CONTRIBUTIONS TO NEUROSCIENCE AND NEUROPHYSIOLOGY

A history of the Grass Foundation and its origins has been written by Dr. Steven J. Zottoli, Professor of Biology at Williams College and a Trustee of the Foundation. The following comments are based on Dr. Zottoli’s article (2001), which is available as a PDF file at http://www.grassfoundation.org/about/origins.html.

The Grass Charity Trust was created in 1948 by Albert and Ellen Grass to evaluate and prioritize the growing number of requests for financial support of brain, especially physiological, research. In 1955, the Grass Foundation was established "to assist in advancing knowledge principally in the field of neurophysiology, and
FIG. 7. Cellular correlates of EEG spikes. Each EEG spike (top traces in A and B) is associated with a paroxysmal depolarizing burst (bottom traces in A and B) that occurs in neurons in the epileptogenic focus. Reproduced from Prince (1968) with permission of Elsevier Ltd.

including allied fields ...” In 1958, the assets of the Grass Charity Trust were donated to the Grass Foundation. While very much the child of Albert and Ellen Grass, the Foundation’s particular focus and unique perspective were deeply rooted in their earlier experience and continued links to scientists who had worked in Harvard’s Department of Physiology earlier in the 20th Century. Indeed, founding trustees of the Grass Foundation included Alexander Forbes, Robert S. Morison, Fred Gibbs, and Arturo Rosenblueth, all of whom were members of that Department. Harvard Medical School was also represented by William Lennox, who was located first at Boston City Hospital and then at the Children’s Hospital. Slightly later, other early Trustees with a Harvard physiology background included Donald B. Lindsley, George H. Acheson, and Fiorindo Simeone.

The signature program of the Foundation has been the support of summer fellows at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. Over the years, many of the Grass fellows have become leaders in neuroscience, including David Potter, Ricardo Miledi, Stanley Crain, Michael Bennett, Charles Stevens, Stephen Kitai, Bernice Grafstein, Zach Hall, Robert Wurtz, Allen Selversten, Denis Baylor, David Prince, and Dale Purves, to name only a few between 1951 and 1970. Apart from the exceptional quality of the program, two remarkable aspects have been the loyalty of former fellows to the Foundation and its continuing interests, and the sense of a special common experience that links one generation of fellows to another. The degree to which these features distinguish the program are almost unique in my experience. For many fellows, I think – at least in the past – this was due to the personal embodiment of the program in Albert and, especially, Ellen Grass.
The Foundation also supports named lectures at the MBL, Society for Neuroscience, American Physiological Society, and American Epilepsy Society, as well as grants, prizes, and courses through the MBL, Society for Neuroscience, Society of Neurological Surgeons, the International Brain Research Organization and, most recently, the American Neurological Association. In 1999, Mrs. Grass established the Albert and Ellen Grass Endowed Directorship of the Marine Resources Center at the MBL.

THE GRASS INSTRUMENT COMPANY: ONE LIKE NO OTHER

There may never have been another company like the Grass Instrument Company. It developed out of a growing demand for equipment to record neurophysiological, including EEG, activity for research purposes. The relationship that had developed between the Harvard investigators and Albert and Ellen Grass (Figure 8) was initially a scientific collaborative one. Ellen’s experience with experimental work allowed her to assist Albert in meeting the scientists’ needs for whatever amplifier, galvanometer, or other instrumentation was necessary for their experiments. Ellen also had wonderful people skills that would later, as the Company grew and became a flourishing commercial enterprise, be invaluable in interfacing with customers and understanding what they wanted. After the Second World War, there was rapid growth of EEG as an aid to neurological diagnosis, and EEG machines and polygraphs became essential to clinical research in epilepsy and sleep. Grass instruments could be found in every research and clinical laboratory in North America and in many other countries as well. Instruments were designed to meet the needs of investigators, and they were renowned for their durability and reliability. For over 30 years, Grass instruments were the gold standard for EEG and other physiological recordings. If not an absolute monopoly, there was no question that the Grass Instrument Company dominated the field. Serious competition did not appear until the mid-1970s, and even then, Grass continued to be the major player for at least another decade.

What no other instrument company of similar kind has ever had was the personal relationship with customers: technologists, clinicians and neuroscientists. Many knew Albert; everyone knew Mrs. Grass. I doubt there is a neurophysiologist of my generation who did not, at one time or another, receive a piece of equipment on loan from the Company, and not infrequently, those “loans” became permanent.

CONCLUSION

I hope I have given you some idea of who Ellen Grass was, and how large a role she, her husband, and their company and Foundation played in the early development of clinical EEG as a diagnostic and investigative tool, and in the
development of neuroscience as a discipline. It is wonderful that ASET remembers Mrs. Grass through this annual lecture, and in consideration of whom it memorializes, you should ensure – at least going forward – that only the very best are asked to give it.

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