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Reflections on a Career in Epilepsy

A "triple threat" career in epilepsy surgery

When I was an adolescent, as adolescents will, I mused about my career, deciding that I wanted to help people with disease and also discover new knowledge. I had wanted to be a physician since I was very young, although I do not know why, for no immediate relatives were physicians, and my only contacts with doctors had been routine visits. Since my older brother also became a physician, there was probably some covert family influence. Yet looking back on my career now at the end of my eighth decade, those adolescent musings pretty well describe much of it. My interest in the brain is more readily explained: an influence of my father, a professor of child psychology and parent education (despite my brother's and my view that there was a large gap between theory and practice), and in medical school at the University of Iowa by an excellent neuroanatomy course of Dr. W. R. Ingram, and neurology clerkship under Dr. Adolph Sahs, augmented by a summer rotation on the neurology service of the Massachusetts General Hospital with Drs. Raymond Adams and C. Miller Fisher. Up to this point, I had received an excellent clinical exposure to neurology, but very little to neurosurgery, and essentially none to research, nor had I any special interest in epilepsy.

The decision to become a neurosurgeon rather than a neurologist was not made until my internship at the King County Hospital (now Harborview Medical Center) in Seattle. There, I came in contact with Dr. Arthur Ward, Jr., who would become my mentor. Dr. Ward had an unusual background and had established an unusual neurosurgical training program. His undergraduate training had been in the neurophysiologic laboratories of Yale directed by Dr. John Fulton. There, Ward had been persuaded that he should become a neurosurgeon so that he could carry out similar observations in humans. That he did, with his neurosurgical residency at the Montreal Neurological Institute (MNI) under Wilder Penfield. Subsequently, he was appointed the first head of Neurosurgery at the new University of Washington (UW) Medical School, establishing a division combining clinical neurosurgery, research, and teaching (the "triple threat" career), with a particular emphasis on epilepsy surgery. To this end, he also set up an epilepsy clinic and an EEG laboratory and had begun to perform a few epilepsy operations, using the Penfield technique of awake operations with electrocorticography (ECoG) and electrical stimulation mapping (ESM). This was the career I wanted; I became his eighth neurosurgical resident.

However, during my residency and subsequent experience on the Surgical Neurology Branch of NIH, I had very little exposure to epilepsy surgery. Indeed, except for the MNI during the 1950s and 60s, none of the institutions that were considered epilepsy centers, including those, were averaging as many as 10 cases yearly [1]; I saw two during my four-year residency. Resective epilepsy surgery was so rarely done that one insurer in Washington State called it experimental and would not pay for it. At that time, the major focus of "functional" neurosurgery (as opposed to neurosurgery for structural lesions such as tumors or aneurysms) was on stereotaxic surgery for dyskinesias, predominately thalamotomy for parkinsonism. Dr. Ward had an active practice in that area, so I performed those operations during my residency and became acquainted with the use of ESM effects on the dyskinesia to place the lesion. I also began to question what I had been taught about the brain organization for language, for I noticed that after left thalamotomies, some patients had an aphasia that was absent after right thalamotomies, even though both groups were equally sleepy post-op, when the then generally accepted view was that the thalamus had no relation to language apart from the level of alertness.

In my two years at the Surgical Neurology Branch of NIH, I worked most closely with Dr. John Van Buren, who was performing thalamotomies with chronic electrodes implanted in the thalamic target from a posterior approach. He was investigating ESM effects on the dyskinesia and a measure of alertness in these patients. I persuaded him to allow me to also examine ESM effects on language as assessed with object naming. My colleague in this was a neuropsychologist, Paul Fedio. These electrodes passed through the superior lateral portion of the pulvinar, at that time functionally "terra incognita". We evoked interference with naming from those contacts in the left brain, the first effort to map language representation in the thalamus (and my first major paper [2], still occasionally cited as there are few subsequent observations in this region). Dr. Fedio and I also devised a measure of recent verbal memory to use with pulvinar ESM and observed interference with both encoding and retrieval portions of that task. Subsequently, I returned to Seattle on the UW neurosurgical faculty and, there, extended those studies, finding differential effects from different parts of the left lateral thalamus, including enhancement of memory retention with anterior lateral thalamic stimulation during memory encoding, findings recently reviewed [3].

The shift in the focus of both my clinical and research activities to epilepsy surgery was a result of two events. One was the advent of L-DOPA therapy for parkinsonism in the late 1960s, which greatly decreased the volume of thalamotomies. The other was Dr. Ward obtaining NIH funding for a UW comprehensive epilepsy center in 1976. This increased the resources for caring for patients with difficult-to-control seizures, including inpatient chronic EEG seizure monitoring, which was particularly useful for identifying a focus of seizure onset and, thus, potentially useful for epilepsy surgery in that pre-MRI era. This resulted in a major increase in our volume of epilepsy surgery, performed principally by Dr. Allen Wyler (to 1985) and myself, so that by the time I retired from clinical practice a decade ago, I had performed between 900 and 1000 therapeutic resections for epilepsy in patients from 4 to 70 years old: all tailored resections, the majority to intraoperative

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findings acquired during "awake" surgery, and the majority temporal lobe resections.

In the late 1980s, we evaluated a temporal lobe resection sample of this experience that had follow-ups of 5 years and for a portion, 10 years. This was compared with a matched cohort of patients managed medically in our clinic over the same periods. Our Epilepsy Center included a neuropsychology program under Dr. Carl Dodrill and a vocational rehabilitation unit under Dr. Robert Fraser, so we also had pre- and postoperative neuropsychologic assessments (for a portion) and postoperative quality of life (QOL) and vocational outcomes for these patients. The continuously seizure-free rate was significantly and substantially greater in both the 5- and 10-year follow-up surgical groups than in the matched cohort [4]. The only deficit on Dr. Dodrill's battery of tests for patients with epilepsy was in verbal memory after left temporal resections. Quality-of-life improvement was related to being seizure-free. Vocational outcome at follow-up was also significantly better in the surgical group for those with at least some employment in both hours worked and earnings, particularly when surgery had been performed before the patient had reached their mid-twenties [5].

By the mid-1980s, this increased interest in epilepsy surgery was shared nationally by neurologists specializing in epilepsy, the first Palm Desert conference in February 1986 reflecting this renaissance of interest [6]. But this was not true of most neurosurgeons, who considered epilepsy surgery as an exotic activity not part of "main stream" practice or training. I had made some effort to change this, beginning as early as 1979 when I presented a talk on epilepsy surgery to a plenary session of the American Association of Neurological Surgeons, with subsequent continuing medical education and textbook articles including an invited 1987 article in the Journal of Neurosurgery [7]. However, as late as 1993, when I was chairman of the American Board of Neurological Surgery, no questions related to epilepsy surgery were part of any of the Board's exams. I was finally able to move epilepsy surgery into mainstream neurosurgery training when I became a member of the Residency Review Committee for Neurosurgery of the ACGME, the accrediting body for neurosurgical training programs (1994–7). Insuring that residents were exposed to an adequate number of cases in the different areas of neurosurgery was a major concern of that committee. As an "add on" to my effort to obtain quantitative data to support those judgments, I included numbers of cases of resective epilepsy surgery performed. With those data, programs with no exposure were identified and "cited" for this deficiency. This has had the desired effect, most programs now providing some experience in epilepsy surgery and a minimum standard for that included in the current neurosurgical training requirements.

The shift in my clinical activities was associated with a shift in the focus of my ESM research, now to the cortex exposed during epilepsy surgery. Those ESM investigations of cognition were multidisciplinary, with psychologists Harry Whitaker, Catherine Mateer, and later David Corina as my colleagues. The interference effect on higher functions used to map cortical language representation was apparently first described by Penfield in the mid-1940s. His reported experience [8] includes some dominant hemisphere aphasic responses outside of classical language areas, and individual subjects with several sites of interference separated by areas without effects, particularly in the temporal lobe, but he did not recognize the surgical implications of these observations and concluded that he was using ESM much less frequently as he could predict "speech limits" anatomically [8, p. 104]. Dr. Ward, like many Penfield trainees, used stimulation to identify motor cortex and, occasionally, a frontal site of speech arrest, but not ESM for language localization elsewhere. Our study of ESM effects in the left dominant hemisphere on a more standardized set of measures of object naming and with constant current stimulation showed that most patients had one or more very focal sites of interference frontally or temporoparietally, but that across the population, the variance in location of these sites was so large that except for the inferior frontal cortex immediately anterior to face motor cortex, no other region could be reliably related to language. Indeed, one-third of that series had no language-related sites in the superior temporal gyrus [9]. Moreover, we were able to show that avoiding encroaching on those sites, but not anatomic landmarks, predicted whether language deficits occurred post-op [10,11]. These cortical surface sites even identified the effects of removal of the buried cortex and white matter in that gyrus. This meant that we were sometimes able to safely do resections in classical language areas, but in other patients not in what was considered safe anatomically outside those areas. In the late 1980s, my colleague Mitch Berger, who performed most of our resections for intrinsic gliomas, approached me about learning the language mapping technique to use in those resections, which I taught him. Dr. Berger went on to popularize the technique among oncology neurosurgeons, and it became the standard method for planning resections near the language cortex to reduce the risk of post-op aphasias, and has remained so, for modern functional neuroimaging has not provided the necessary information [12]. The widespread use of ESM for this purpose was facilitated by the development of an easy to use constant current stimulator designed to my specifications (OCS-1, originally from Radionics, now Integra).

In addition to the practical application of those ESM findings, we made observations related to the underlying neurobiology of language, including differences in patterns of ESM localization related to gender, verbal ability, and age [9,13]. We looked for evidence of plasticity in the location of ESM sites, by mapping patients who were partially recovered from aphasias [14], and in remapping of sites after intervals of as much as 20 years (unpublished data). Contrary to some recent reports of remapping in tumor patients, we found little evidence of plasticity. We also examined ESM localization of other language-related functions, including second languages [15,16], sign language [17–19], word and sentence reading [20], nouns compared with verbs [21,22], semantic categories, recent verbal memory [23,24], motor speech movement mimicry, and speech sound discrimination [10,25]. As with object naming, sites related to the different functions were often quite localized in individual patients, but with substantial variation in their location across the sampled population (reading [20], memory, [24]). Some of this differential localization was surprising: in one patient, there was a posterior temporal site where fruits could not be named but tools and clothes were unaffected, with a site 1 cm away with the reverse pattern (Case 0006, unpublished). The pattern for the first five functions we had assessed was similar, a perisylvian "core" common to multiple aspects of language surrounded in the frontal, temporal, and parietal lobes by sites related to only one of the sampled tasks [25]. Sites with ESM effects on recent memory were largely separate from those with language effects [25]. In the temporal lobe, ESM interference was with the encoding and storage phases of memory; in the frontal lobe, it was with the retrieval phase. The other exception was a substantial overlap of ESM effects on motor speech movement and speech sound discrimination, both frontally and temporoparietally, rather than the expected frontal motor, posterior temporal sensory separation [10,25]. Temporal effects were for sequences of movements, frontal for single movements. We suggested that the specializations for language in humans may have arisen between preexisting cortical motor speech sound decoding and recent memory systems [26]. The effects of ESM in the nondominant hemisphere on several visuospatial functions, including face, line angle, shape matching and memory, and recognition of face emotional expression were also examined, relating the latter to the posterior middle temporal gyrus [27]. All these findings were of particular interest to neuropsychologists and were also part of my 2002 Lennox lecture to the American Epilepsy Society.

With my success in using ESM effects on naming to reduce the risk of language deficits with a resection, I thought that tailoring resections to ESM effects on the cortical representation of recent memory might be a way to reduce the post-op verbal memory deficits. Although some early findings supported this [24,28], later experience did not. After 1990, our medial temporal resections were tailored to the extent of