GENESIS OF THE USE OF CORTICOSTEROIDS IN THE TREATMENT AND PREVENTION OF BRAIN EDEMA

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BACKGROUND: Since the groundbreaking article from the University of Minnesota in 1961 by Drs. Galicich, French, and Melby describing the use of dexamethasone for peritumoral cerebral edema, the use of corticosteroids in patients with brain tumors has become routine. Unfortunately, little has been reported regarding the environment that fostered arguably the greatest translational research contribution in the history of neurosurgery.

METHODS: During a pilot study to assess corticosteroid uptake in brain tumors, Dr. Galicich observed that patients given a large dose of corticosteroids just before craniotomy had a relatively benign postoperative course. This led, in October 1959, to the administration of high-dose corticosteroids to a patient with a large recurrent glioblastoma who was semicomatose and severely hemiparetic. The results were dramatic, with almost complete resolution of neurological deficit during a period of several days and marked reduction of midline shift on repeat angiograms. This finding prompted the studies that confirmed the efficacy of high-dose corticosteroids in reducing peritumoral brain edema in humans reported in the 1961 article.

RESULTS: After publication, a revolution in brain tumor management occurred because corticosteroid therapy markedly reduced the morbidity and mortality associated with brain tumors both in the United States and worldwide.

CONCLUSION: The combination of astute clinical observation and follow up by rigorous clinical research at the University of Minnesota resulted in one of the greatest contributions in the history of neurosurgery, rivaled only by the operative microscope in its effect on morbidity, and unsurpassed in reduction of mortality.

KEY WORDS: Brain edema, Brain tumors, Dexamethasone, Joseph H. Galicich, Lyle A. French, University of Minnesota

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After the 1961 publication of the groundbreaking article by Drs. Joseph H. Galicich (*Fig. 1*), Lyle A. French (*Fig. 2*), and James C. Melby from the University of Minnesota describing the results of the use of dexamethasone to treat peritumoral cerebral edema, the treatment and prevention of brain edema with high-dose glucocorticosteroids rapidly became routine, and led to a significant decrease in morbidity and mortality, particularly in neurosurgical oncology (2, 9). Although one of the greatest translational contributions in the history of neurosurgery, little has been reported of the atmosphere that fostered this work, which was published in *The Journal Lancet*, the precursor to the journal of the Minnesota State Medical Society and not to be confused with the British journal named *The Lancet*. To address this deficiency, the details of this breakthrough are featured in this report. Information was gathered from a comprehensive review of pertinent modern and historical records in print and electronic form.

Historical Vignette

Interest in the blood-brain barrier (BBB) and brain edema at the University of Minnesota began in the early 1950s with extensive laboratory and clinical research involving the use of fluorescent and radioactive tracers to assess the integrity of the BBB (3). Studies using these tracers intraoperatively to localize brain tumors extended into the early 1960s (3, 8, 10). Although this work was not directly related to the later corticosteroid discoveries, by fostering an interest and familiarity within the department of the interrelationships of the BBB, edema, and tumors, it was certainly a contributing factor. Additionally, not to be underestimated was the emphasis on and the full-fledged support of research by Drs. William T. Peyton and Lyle A. French. Motivated residents were in charge of the laboratory to a great degree and were essentially given free rein in the choice of projects and methods of study.

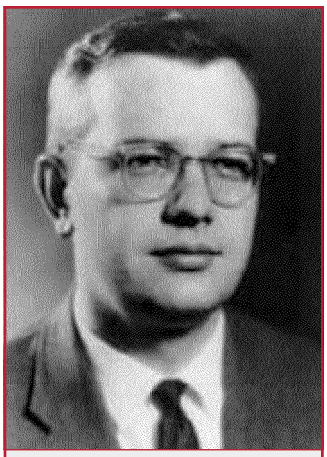

FIGURE 1. *Photograph of Joseph H. Galicich, M.D. Courtesy of the University of Minnesota Department of Neurosurgery.*

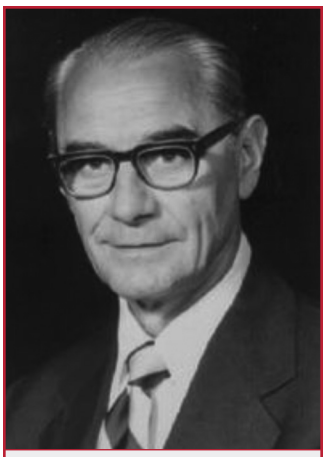

FIGURE 2. *Photograph of Lyle A. French, M.D., Ph.D. Courtesy of the University of Minnesota Department of Neurosurgery.*

In July 1958, Dr. Galicich, assigned to the laboratory in his first year of neurosurgery residency, began studies in mice that demonstrated a circadian periodicity in brain uptake of fluorescein that was the reciprocal of the adrenal corticosteroid rhythm concomitantly determined. This relationship strongly suggested a regulatory function of corticosteroids on the normal BBB and, by extension, the possibility of their use in treating the abnormally permeable BBB associated with brain edema. Further impetus influencing Dr. Galicich's decision to conduct a trial of corticosteroids in humans stemmed from a report of the possible oncolytic effect of corticosteroids on malignant gliomas from another institution.

As a first step in this study, Dr. Galicich sought to determine the concentration of corticosteroids safely achievable in brain tumors and the brain. At this juncture, he enlisted the help of endocrinologist Dr. James C. Melby, who suggested that along with the predominant natural human glucocorticosteroid, cortisol (hydrocortisone), dexamethasone (Decadron, Merck & Co., Inc., Whitehouse Station, NJ) should be studied as well. The choice of dexamethasone over other available corticosteroid analogs centered on two predominant advantages, namely its potency (e.g., more than 30 times that of cortisol in terms of adrenal replacement therapy) and the lack of salt-retaining properties because dexamethasone is essentially a pure glucocorticosteroid.

Before initiating the clinical study, large doses (40 mg) of dexamethasone were administered to dogs via intramuscular, intravenous, and intracarotid injection, as well as orally to a human volunteer (Dr. Galicich) to exclude any obvious acute adverse effects. The study, performed in patients predominantly undergoing craniotomy for brain tumors, revealed that the concentrations of cortisol and dexamethasone achieved in tumor, peritumoral white matter, and normal brain (canine and human lobectomy specimens) after intravenous administration of one or the other corticosteroid just before surgery were all equivalent to that achieved in temporal muscle. In addition, there was free exchange between circulating steroids and these tissues (unpublished data). The unusually benign clinical course of the patients in this clinical study strongly suggested to Dr. Galicich that administration of cortisol or dexamethasone had led to reduction or prevention of brain edema and encouraged him to study patients before they underwent surgery.

After these studies, the next pertinent event occurred in October 1959 in a semicomatose hemiparetic patient with a large recurrent temporal lobe glioblastoma. Dr. Galicich administered 40 mg of dexamethasone through the carotid artery as he obtained the cerebral angiogram. The result was dramatic. By the next morning, the patient was awake and had regained considerable strength in his affected limbs. With continued therapy (10 mg of dexamethasone every 6 h), the patient's hemiparesis continued to resolve over the next 4 days, and a repeat angiogram on the sixth day of treatment demonstrated marked resolution of the previously noted midline shift. These impressive results convinced Dr. French to allow Dr. Galicich to expand the study to treat every other patient with a precraniotomy brain tumor with dexamethasone. Close examination of the patients administered corticosteroids revealed that improvement in pretreatment deficits plateaued after 4 to 6 days. Although the initial treatment was 10 mg every 6 hours, the dosage was gradually reduced in successive patients. A dose–response curve revealed that patients achieved maximum improvement on 4 mg every 6 hours, but a significant number of patients failed to achieve an optimal clinical response with 2 mg every 6 hours. For this reason, dexamethasone (Decadron) was formulated in 4-mg tablets and 4 mg per ml, as it remains today.

The striking difference in the courses in most of the treated patients compared with the untreated group convinced all involved that it would be unethical to withhold corticosteroids in such patients. Subsequently, beginning early in 1960, high-dose corticosteroids were administered to all patients with tumors who were undergoing craniotomy and some who were undergoing craniotomy for other reasons. The expansion of the series allowed verification of the dose–response curve and, in due course, short-term study of the efficacy of other corticosteroids (cortisone acetate, cortisol, and prednisone) in a small number of patients. Although not rigorously quantified, all of these glucocorticosteroids were effective in decreasing neurological deficit when administered in doses equivalent to the standard dexamethasone regimen. Balance studies performed by Drs. Galicich and Melby determined that diuresis and occasional natriuresis were insignificant. In the short term (i.e., several weeks), few major complications were encountered.

At the same time, laboratory studies of dexamethasone were initiated to examine the effects of corticosteroids and the ultrastructural features of cerebral edema in animal models. These studies revealed not only the beneficial effects of corticosteroids on brain edema, but also that these effects preferentially targeted white matter rather than gray matter and enabled the astrocyte to be definitively differentiated from the oligodendrocyte with electron microscopy for the first time. These findings subsequently resulted in several significant peer-reviewed publications (4–7). The results of the initial randomized control

trial and the efficacy trial led to the publication of the landmark 1961 paper, a subsequent publication based on a larger series of patients (1), and subsequent approval of dexamethasone for brain edema by the United States Food and Drug Administration; it was the first drug ever successfully taken through the United States Food and Drug Administration approval process by neurosurgeons. After his residency, Dr. Galicich went on to become Chief of Neurosurgery at Memorial Sloan-Kettering Cancer Center and full Professor at Cornell University Medical College in New York before retiring in 1995.

After the 1961 publication, a revolution in neurosurgical and neurological care occurred as the introduction of corticosteroids markedly reduced mortality and morbidity in patients with brain tumors worldwide. A major consequence of these results was that patients were able to live long enough to benefit from the advances in resective surgery made possible by imaging improvements (computed tomographic and magnetic resonance imaging scans) and the introduction of the operative microscope.

CONCLUSION

The combination of astute clinical observation, and the courage to apply that observation in a novel manner to patient care and in the laboratory at the University of Minnesota, resulted in the genesis of arguably the greatest single contribution in the history of neurosurgery, rivaled only by the operative microscope in reduction of morbidity and unsurpassed with regard to improvement in neurosurgical mortality worldwide.

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Acknowledgments

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COMMENTS

It is important for all of us to know how we got to where we are today. So we read with great interest the article by McClelland and Long describing what they correctly call "arguably the greatest translational research contribution in the history of neurosurgery." We too have an additional interest in this very nice history. One of us (JBP) worked with Joe Galicich during his tenure as Chief of the Neurosurgery Service at Memorial Sloan-Kettering Cancer Center. The other (PHG) is now Chair of the new Department of Neurosurgery, which evolved from this Service.

It does not diminish the contribution of Galicich and French to point out that their observation had some precursors. As early as 1945, Prados et al. (3) noted that when the brain was exposed to air, the blood-brain barrier failed, and brain edema developed. If the brain was sprayed with adrenal extract, the blood-brain barrier remained intact, and the brain did not swell. Several years later in 1952, Ingraham et al. (2) recognized that cortisone and adrenocorticotropin smoothed the postoperative course of patients after surgery for craniopharyngioma. In 1957, Kofman et al. (4) gave prednisone to 20 patients with brain metastases after noting a striking relief of neurologic symptoms in a patient with breast cancer and brain metastasis who was given the drug to suppress adrenal function. They noted amelioration of the neurologic symptoms in the other patients and concluded that this was an effect of steroids on inflammation and edema. These observations might have come to naught and we still might be seeing high mortality from neurosurgery were it not for the seminal observations described in the article by McClelland and Long. It requires a prepared mind to take the observation of a circadian periodicity in brain uptake of fluorescein and translate that into treatment of brain tumors with corticosteroids.

Galicich was recruited from Yale to be Chief of the Neurosurgery Service at Memorial Sloan-Kettering in 1973. At that time, the neurology and neurosurgical units were combined. All patients were worked up by the neurology housestaff and seen by the neurology attending before and after surgery. This gave the neurologists a unique opportunity to see exactly how patients fared after surgery. They fared very well. Galicich was a meticulous surgeon and the neurologists came to expect that our patients with brain tumors, whether primary or metastatic, would have no significant complications from surgery. We were always surprised when the occasional complication occurred.

Before his arrival at Memorial Sloan-Kettering, we used prednisone to treat brain edema. Needless to say, we switched to the time-honored dexamethasone, 4 mg every 6 hours. When Joe retired, he left a mature service ready to receive new developments by his successor.

Great discoveries probably always have a price. Although steroids dramatically ameliorate the symptoms of brain edema and cause little trouble during brief treatment, many patients require the drug for long periods and have the well-known serious side effects of the drugs. Over the years, many attempts have been made to find substitutes for corticosteroids; most have failed. Most significant among these failures would be once promising agents such as 26-aminosteroids, difluoromethylornithine, and boswellic acids (1, 6, 7). Recent reports suggest that corticotropin-releasing factor may possess steroid-sparing effects on peritumoral brain edema in patients with primary or secondary brain tumors (5). Even so, this will not diminish the extraordinary contribution of Galicich and French.

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The use of corticosteroids in neurosurgery is widespread and now taken for granted. When I was a resident, I can remember some of the older attendings talking at times about what a miracle steroids were in neurosurgery. They also commented on the significant reduction of patients being taken back to the operating room postoperatively after a craniotomy with the introduction of steroids. So it was with great interest that I read of the history of the neurosurgical use of corticosteroids. These most certainly were miracle drugs when they were introduced, and the authors have clearly reviewed the historical details. Most interesting to me was the fact that Dr. Galicich was a "first year neurosurgical resident" when he did this work—what a great start to a neurosurgical career!

James T. Goodrich
Bronx, New York

The astute clinical observation by Dr. Galicich in a pilot study to assess the effect of cortical steroid uptake in a patient's brain tumor led to its ultimate and beneficial use in treating, both medically and surgically, patients with brain tumors. This translational bit of clinical therapy is one of the major contributions to safer surgical management and medical treatment of brain tumors. It has certainly aided tremendously in both the management and surgical treatment of brain tumors.

Lycurgus M. Davey
New Haven, Connecticut

This article elegantly reminds us of the validity of the adage that "chance favors the prepared mind." Joe Galicich was able to make an observation that ultimately revolutionized many aspects of neurosurgical practice and altered outcomes in a dramatic fashion. This kind of singular observational advance was described by William Sweet in his celebrated article, "The Difference between Zero and One."

It is important to recall the extraordinary milieu in which this discovery was made. Lyle French had created a quintessential Academic Department of Neurosurgery, with faculty and residents who were imbued with a drive for excellence and a pioneering spirit that were enviable. The article reminds us that careful clinical observation followed by scientific analysis can still lead us to major advances in the clinical care of our patients.

Edward R. Laws, Jr.
Boston, Massachusetts

This is a wonderful description of what I agree is arguably the "greatest translational research contribution in the history of neurosurgery." It is a magnificent example of how astute clinical observation and meticulous laboratory investigation led to an outcome that has had a profound and lasting effect on neurosurgical practice. This is an example of how a neurosurgery resident changed the course of surgical practice and should be studied by all surgeons and their residents.

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