Manucher Javid, Urea, and the Rise of Osmotic Therapy for Intracranial Pressure

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Therapy with hypertonic solutions is one of the mainstays of neurosurgical treatment for all types of neurological injury. Although the initial research with hypertonic agents in the early decades of the 20th century showed great promise for these agents to lower intracranial pressure, this research also showed a considerable rate of adverse effects and complications. By the 1940s and 1950s, hypertonic therapy had been discounted as unsafe and was rarely used in neurosurgery. In the late 1950s, Manucher J. Javid and Paul Settlage at the University of Wisconsin began experimenting with infusions of urea as an agent to control intracranial pressure. Their experiments were wildly successful, and urea became a drug of major importance to neurosurgeons worldwide in only a few years. This article chronicles the work of Javid and Settlage, including a discussion of the early research on hypertonic agents, the initial difficulty the Wisconsin researchers had in disseminating their results, the widespread acceptance that followed, and the impact that these discoveries had on the neurosurgical community. The prominent place that hypertonic agents now hold in the armamentarium of neurosurgeons is owed to the work of Dr Javid, as illustrated in this historical analysis.

KEY WORDS: History, Intracranial Pressure, Mannitol, Urea

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At the annual meeting of the Harvey Cushing Society in New Orleans on May 1, 1959, James Poppen, chief of neurosurgery at the Lahey Clinic in Boston, said, "This is a new epoch in neurosurgery. . .. Electrocautery, application of gelfoam, and now the introduction of urea in neurosurgery are the three great things that have happened during my career as a neurosurgeon." This comment about the importance of urea was echoed throughout the neurosurgical community at the beginning of the 1960s, and indeed, by that time, urea was in widespread international use for the control of intracranial pressure (ICP). Hypertonic agents such as mannitol and hypertonic saline continue to be a mainstay of therapy for elevated ICP today.

Neurosurgeons had recognized decades earlier that administration of hypertonic/osmotic agents had the effect of lowering ICP, but this practice was not in widespread use. Why did > 30 years pass between the discovery of the ICP-lowering effects of hypertonics and their acceptance into clinical practice? What occurred to change the practices of the entire neurosurgical community so quickly? This article endeavors to answer these questions through an exploration of the work of Manucher J. Javid at the University of Wisconsin in the 1950s, including a discussion of the work of Dr Javid, the history of hypertonic agents in neurosurgery up to that time, and the effect that the research, performed at the University of Wisconsin, had on the neurosurgical community worldwide.

ABBREVIATION: ICP, intracranial pressure

EARLY WORK

In 1919, Lewis Weed and Paul McKibben of the US Army Neurosurgical Laboratory at Johns Hopkins University published their observations on the response of the ICP of cats to intravenous injection of various substances of differing concentrations.[1] Their work had started as an attempt to study the salt concentration of cerebrospinal fluid (CSF) after intravenous injection of hypertonic saline, but the investigators were unable to recover CSF from the injected cats. They then conducted a series of experiments in which cats underwent CSF pressure measurement via manometry through the atlanto-occipital ligament. Weed and

McKibben noted that infusion of hypertonic solutions of 30% sodium chloride, 30% sodium sulfate, or saturated sodium bicarbonate led to a profound decrease in the CSF pressure of the animals, often to levels < 0. Conversely, injection of distilled water led to a doubling or tripling of the CSF pressure.

The significance of these findings was not lost on neurosurgeons, who at the time were keenly interested in methods to reduce brain bulk and to prevent the herniation of cerebral tissue on opening of the dura in patients with intracranial mass lesions, a condition referred to as fungus cerebri. As Harvey Cushing noted, "The fact established by Weed and McKibben might be adaptable to certain cranial operations, making them easier by lowering tension and diminishing brain volume."[2] Cushing collaborators Frederic Foley and Tracy Putnam repeated the experiments, confirming the findings, and went on to show that enteral doses of hypertonic solutions had nearly the same effect on ICP as intravenous doses.[2] By the 1930s, the action of hypertonic agents on ICP was understood to be a consequence of their diuretic/purgative effects. The diuresis was thought to lead to an osmotic gradient to draw fluid from the cerebral tissues.[3] Enthusiastic use of hypertonic agents in the treatment of brain injury followed these discoveries, accompanied by further research with other hypertonics such as dextrose, sucrose, glucose, and magnesium sulfate.[4-8] However, tempering the excitement were the warnings of both Weed and Foley, who had noted "severe cardiac and respiratory disturbance" on initial administration of hypertonic salt solutions and that "[d]eaths from these causes occurred in several experiments."[1,2] Additional reports of poor outcomes, including respiratory difficulty, convulsions, renal failure, and death, appeared in the 1930s, further increasing neurosurgeons' wariness of these agents.[9-11]

In 1933, Walter Dandy spoke unequivocally against the use of hypertonic solutions in head injury: "I feel quite confident that no patient has been saved by [this] method, and certainly many have been lost who might otherwise have survived."[12] Wilder Penfield's 1935 monograph, "The Principles of Physiology Involved in the Management of Increased Intracranial Pressure," included comments on the work of Weed and others on hypertonic solutions.[13] His conclusions are instructive about the attitude of neurosurgeons toward hypertonic therapy at the time.

It has been shown that this shrinking effect is transitory, disappearing often within the hour as measured by a needle left in the spinal canal, and some observers believe a greater pressure follows the temporary relief. Consequently, these procedures have recently become somewhat less frequently used.[13]

On the basis of the commentary from these 2 giants of neurological surgery and the quantity and content of reports in the medical literature regarding hypertonic solutions as treatment for elevated ICP, it is apparent that, although initially promising, these agents had fallen out of favor by the end of the 1930s.

MANUCHER JAVID AND UREA

In 1953, Manucher J. Javid joined Theodore Erickson to form the Division of Neurological Surgery at the University of Wisconsin. Dr Javid (Figure 1) was born in Tehran in 1922. He was inspired by his father, a pharmacist, to pursue a career in medicine and came to the United States in the early 1940s with plans to return to Tehran and establish a neurosurgery center in Iran. Dr Javid attended medical school at the University of Illinois College of Medicine and completed his residency training at Massachusetts General Hospital.[14] His early practice in Wisconsin involved a rigorous daily routine. After making morning rounds, he was responsible for the day's diagnostic studies, pneumoencephalograms, and carotid-puncture angiography. Starting in the early afternoon, he assisted with Dr Erickson's operations. Dr Javid's own operative cases would begin around 4 or 5 PM. Despite this demanding schedule, Javid made it a habit to attend the monthly University of Wisconsin research conference.

In July 1954, the lecture at this conference was presented by medical student Theodore Roberts (who went on to a distinguished career in neurosurgery, serving as the chairman of neurosurgery at the University of Utah and professor of neurosurgery at the University of Washington).[15] Roberts presented the research of anatomist Paul Settlage comparing the effects of glucose, sucrose, and urea on the ICP of monkeys.[16] Solutions of urea "produced more pronounced and more prolonged pressure drops than glucose

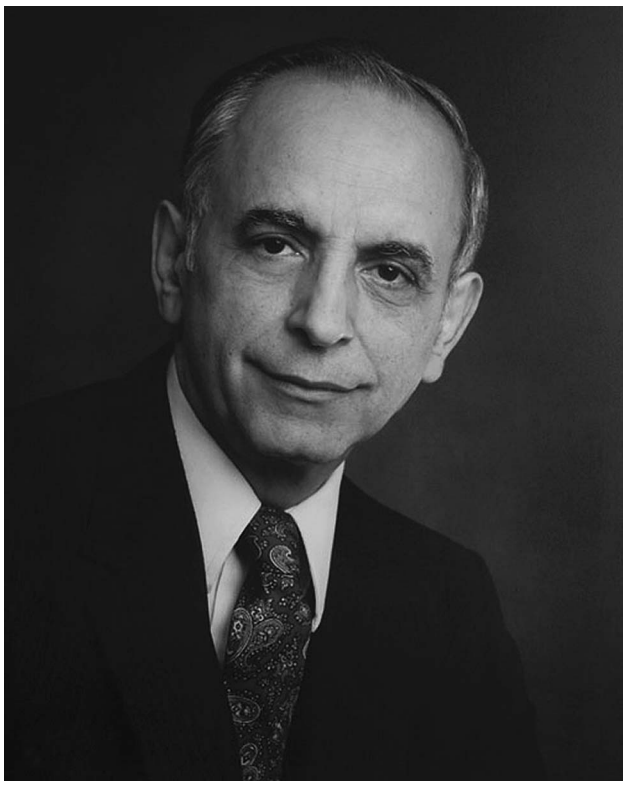

FIGURE 1. *Manucher J. Javid, MD.*

or sucrose," and although associated with rare local skin sloughing, there were no systemic toxic effects. For a neurosurgeon in the early 1950s, "the chief importance of raised intracranial pressure seems to be the mechanical problems which it creates. . . .[T]he brain under increased pressure will shift toward the artificial opening made by the surgeon in his effort at therapy."[17] Therefore, the only recourse for a surgeon operating on a tumor with significant brain edema was to operate quickly in the hopes of evacuating the mass lesion before cortical herniation and rupture or, in rare cases, to perform subtemporal decompression before addressing the tumor.[18] It was with this view of ICP in mind that Dr Javid watched the presentation of Settlage's work. For Javid, it immediately represented a potential solution to the problem of fungus cerebri with cortical rupture, one of the most vexing problems in neurosurgery since the time of Cushing.[19]

Javid approached Settlage immediately after the presentation and arranged a meeting with Frederick Schideman, the chair of pharmacology. Schideman recommended a 50-mg/kg initial dose of urea, but Javid, whose pharmacist father had always told him that pharmacologists were too conservative, decided on 100 mg/kg (personal interview, October 2010). Pure urea crystals were sterilized by washing with ether to prevent decomposition on heating and then dissolved in sterile water. (Later formulations involved dissolution in 5% dextrose to limit hemolysis.) The group constructed a proposal and won a grant of $85 from the department of surgery to fund the research.

With pharmacist Louis Busse providing the purified and sterilized urea, the first experiment took place on July 25, 1954, in the solarium of the State of Wisconsin General Hospital (Figure 2).[20] Dr Javid performed a lumbar puncture and connected a manometer to the needle in the lumbar cistern. Javid then administered urea and read pressure measurements while Settlage recorded data. The second patient was a sheriff and bartender from northern Wisconsin with a malignant brain tumor and severe headaches. After a discussion with the patient and family (no Institutional Review Board or written consent process existed at the time), Javid administered 100 mg/kg urea. The headache resolved immediately, accompanied by a profound decrease in ICP.[19] Trials on several more patients followed, with systematically increasing doses (up to 1 g/kg) and dramatic results, including return of spontaneous respiration in a handful of patients with cerebral herniation syndromes. In 1957, after initial experiences with > 2 dozen patients at the bedside, urea was used in the operating theater for the first time. Results were profound; according to Javid, "Rupture of the brain stopped with this drug."[19]

FIGURE 2. *University of Wisconsin Medical Science Center, formerly the State of Wisconsin General Hospital.*

GETTING THE WORD OUT

In 1950, Settlage submitted his preliminary work on monkeys to the National Research Council in an application for grant support. Despite the interest of neurosurgeons William Sweet and Henry Schwartz, a prominent biochemist on the committee "adduced a myriad of reasons why only a pathetic oaf would suggest anything so ludicrous. Putting back into the body the final waste product of protein metabolism could only be deleterious. . .."[21] In light of this interaction, one can imagine Settlage's excitement when, 4 years later, he was approached by Javid, who was clearly interested in the potential of his work.

Difficulties continued after the groundbreaking research had been initiated. At the meeting of the Interurban Neurosurgery Society in February 1955, discussion turned to severe brain injury and the ensuing edema. Javid was in attendance and now had an agent he thought represented a significant advance. However, the moderator of the meeting did not allow him to speak, and his work remained unknown (personal interview, October 2010). In both 1955 and 1957, Javid and Settlage submitted manuscripts to the American Neurological Association, only to have the work deemed not important enough for presentation at the meeting.[21]

In March 1956, results from the first 26 patients were published as a preliminary report in the *Journal of the American Medical Association*.[22] This report generated little interest. It was not until a presentation given by Dr Javid at the October 1956 meeting of the American College of Surgeons in San Francisco that the "floodgates were loosened."[23,24] Letters began to arrive from neurosurgeons around the country requesting urea preparations for use in their practices. The Wisconsin Alumni Research Foundation, to whom the rights of the urea compound had been licensed, quickly became overwhelmed by the demand and contracted with Travenol Laboratories in Morton, Illinois, to produce urea according to the Wisconsin method for widespread distribution. Tragically, just as the importance of his work was being recognized, Paul Settlage died in a canoe accident in Madison on April 20, 1957.[25]

The definitive publication of Javid and Settlage's work with urea came in 1958 in *Surgical Clinics of North America*, an issue devoted entirely to the University of Wisconsin.[26] Figures 3 and 4 depict reproductions of the original figures from this publication. Ironically, after initial difficulty garnering interest in his research, Dr Javid was criticized for publishing the final work in a journal of minor importance.

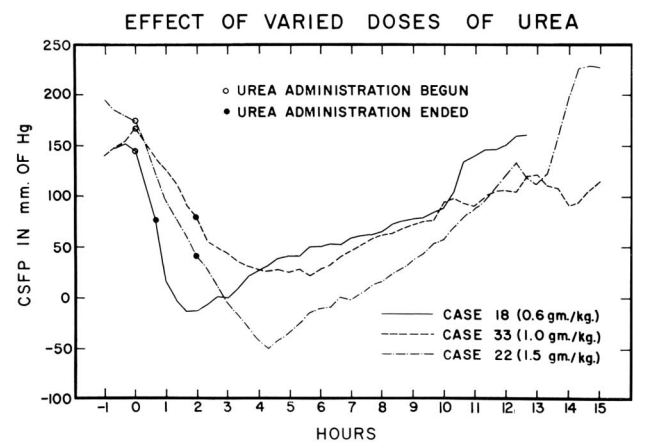

FIGURE 3. *Graph showing effect of urea administration over time on cerebrospinal fluid pressure (CSFP) in 3 cases. Reproduced with permission from Reference 26.*

IMPLICATIONS AND POPULAR RESPONSE

The New York Times reported in August 1958 the discovery of a "urea-sugar compound that has saved the lives of many patients suffering from increased brain pressure caused by concussions, fractures and other head and brain injuries."[27] A larger piece had appeared earlier in the month in the *Wisconsin State Journal*.[24] In < 2 years, urea had gone from a topic not worthy of presentation at scientific meetings to a discovery considered important enough to report in the popular press.

In January 1962, Nobel Prize–winning Soviet physicist Lev Landau suffered a head injury when his car was hit by a truck. The Soviet government flew Wilder Penfield from Montreal to Moscow to assist in treatment of the eminent physicist, who was reported to have suffered "clinical death" several times but was revived each time. Landau's obituary in *The Times* in 1968 notes that "British drugs were flown to the Russian capital."[28] What was the British drug? According to Javid, it was urea.

A year earlier, Dr Javid had presented his work with urea at the 1961 meeting of the International Congress of Neurological Surgery in Washington, DC. In the audience at the time was a visiting Russian scientist, most likely Alexander Arutyunov of the Kiev Scientific Research Institute.[29] The Russian showed great interest in urea and questioned Javid extensively after the presentation, noting that urea was not available in Russia and expressing a desire to make the compound widely available in the Soviet Union. When Landau was injured, urea remained unavailable. In Iran, it was reported that Khrushchev's personal plane had flown to London to pick up urea for use in treating Landau (personal interview, October 2010).

After the results of Javid's work became widely known, the use of urea spread rapidly through the neurosurgical community. By 1965, there was literature describing the use of urea for control of ICP in 12 languages. A PubMed search for "urea" and "intracranial pressure" reveals 150 publications between 1955 and 1980, the vast majority of which discuss the use of urea as treatment for elevated ICP. In 1961, building on the work of Javid, Burton Wise and Norman Chater published the first account of the use of mannitol as treatment for ICP.[30,31]

THE DECLINE OF UREA

The late 1950s and early 1960s saw great advances in the understanding of ICP and its management. The widespread availability of the strain-gauge pressure transducer allowed less invasive measurements of ICP that led to advances such as Lundberg's identification of pressure waves and elucidation of the effect of controlled respiration on brain bulk during surgery.[32-35] The discovery of the profound effect of corticosteroids on peritumoral edema by Galicich, French, and Melby led to a decrease in morbidity and mortality of operative treatment for brain tumors.[36] These

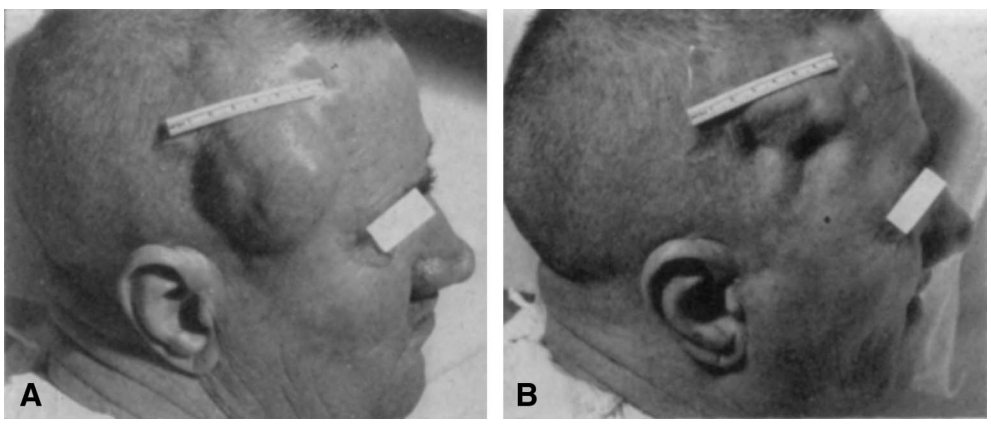

FIGURE 4. *A patient with pseudomeningocele after removal of a temporal glioma, demonstrating the effect of the administration of urea. Reproduced with permission from Reference 26.*

discoveries, coupled with the rise in popularity of mannitol, led to a decline in the use of urea over the next decades. Although urea, which has a molecular weight that is one third that of mannitol, provided a higher osmotic load per gram than mannitol and thus a theoretically faster and greater effect on ICP, it also was difficult to prepare, was not stable in solution, was difficult to store, and had a propensity for venous irritation.[37,38] Over the course of his career, Dr Javid used urea in > 3200 patients, published extensively on the uses of urea and its properties, and advocated for its use in a variety of diseases.[20] However, because mannitol proved to be sufficient for control of ICP, particularly in conjunction with other advances of the 1960s, the unfavorable characteristics of urea led to its decline and eventually cessation of production for clinical use.

CONCLUSION

Young neurosurgeons today are only minimally familiar with the problem of cortical rupture from intractable brain edema or elevated ICP. It is only the rare case of severe trauma or subarachnoid hemorrhage that generates elevation of ICP that cannot be managed with modern therapy at least well enough to allow safe craniotomy without cortical rupture. Before the introduction of urea, this was not the case. Despite knowledge of the physiological principles for > 3 decades, neurosurgeons had largely abandoned the use of hypertonic solutions. It is no doubt because of this prior experience that skepticism existed among neurosurgeons when Javid and Settlage initially presented their findings. Yet, their perseverance allowed them to overcome this inertia despite discouragement from the scientific establishment. Use of urea, followed by mannitol, exploded in the 1960s, transforming hypertonic solutions into the essential therapeutic tool that they are today.

Disclosure

The author has no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The author presents an excellent and accurate historical summary of the use of urea and hyperosmotic agents in the treatment of raised intracranial pressure. The author presents the story of Dr Javid and the original studies that determined the properties and risks of using hyperosmotic agents and their effects on intracranial pressure. In addition to providing an excellent comprehensive chronological rendering of the events that led to the discovery of the properties of urea in affecting intracranial pressure, this article integrates this information into the fabric of the time. It is important to note how this technique was integrated with the birth and growth of the use of mannitol and the subsequent methods of adjusting intracranial pressure with hyperosmotic agents.

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