

Silas Weir Mitchell on Epilepsy Therapy in the Late 19th to Early 20th Centuries

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ABSTRACT: Silas Weir Mitchell (1829-1914), one of the fathers of American neurology, is well known for many contributions to neurology. However, his efforts in epilepsy are overshadowed by his other accomplishments. Mitchell introduced a new bromide preparation, lithium bromide, as a viable therapy. His most widely accepted contribution to the field was the introduction of inhaled amyl nitrite for early termination of seizures accompanied by an appropriate aura. Despite the prevalent views on lifestyle modification as a treatment for epilepsy during this time period, as well as Mitchell's own development of the "rest cure" for certain disease states, he was not a proponent of these types of interventions for epilepsy, nor did he support interventions focused on other organ systems, such as abdominal or gynecologic surgery. Mitchell had distinct opinions on the treatment of epilepsy, and helped to advance its therapeutics during his career.

RÉSUMÉ: Silas Weir Mitchell sur le traitement de l'épilepsie de la fin du XIX^e siècle au début du XX^e siècle. Silas Weir Mitchell (1829-1914), l'un des pères de la neurologie américaine, est bien connu pour ses nombreuses contributions à la neurologie. Toutefois, ses efforts dans le domaine de l'épilepsie restent dans l'ombre de ses autres réalisations. Mitchell a introduit une nouvelle préparation à base de bromure, le bromure de lithium, comme traitement viable. Sa contribution la plus largement acceptée dans ce domaine a été l'introduction du nitrite d'amyle inhalé pour l'arrêt précoce des crises convulsives accompagnées d'une aura appropriée. En dépit des idées prévalentes à cette époque-là sur le rôle de la modification du mode de vie dans le traitement d'épilepsie et de la propre élaboration par Mitchell de la « cure de repos » pour certaines affections, il n'a pas suggéré ces types d'interventions pour l'épilepsie et il n'a pas, non plus, soutenu des interventions se concentrant sur d'autres systèmes, telles que la chirurgie abdominale ou la chirurgie gynécologique. Mitchell a eu une opinion personnelle sur le traitement d'épilepsie et a contribué aux progrès de son traitement tout au long de sa carrière.

Keywords: History of neurology, epilepsy, Silas Weir Mitchell

doi:10.1017/cjn.2014.42

Can. J. Neurol. Sci. 2014; 41: 769-772

Silas Weir Mitchell (Figure) was one of the fathers of American neurology. He was born the third of nine children to John Kearsley Mitchell, a prominent Philadelphia physician and chemistry professor, and Sarah Henry Mitchell, a homemaker. A lackluster student prior to his medical education, he graduated from Jefferson Medical College in 1850 and, following a year studying physiology under Claude Bernard in Paris, began a general medicine practice in Philadelphia.¹ Although he was active in toxicology and physiology research, including performing important work with snake venom, he failed to obtain chair positions in the Department of Physiology at both the University of Pennsylvania and Jefferson Medical College, and so he remained clinically active in medicine throughout his life.²

With the outbreak of the Civil War, he first gained significant exposure to neurologic diseases. His experiences during the war would transform his interests, and subsequently he focused his practice on neurology.³ He is most well known for his work *Injuries of Nerves and Their Consequences*, as well as descriptions of erythromelalgia and complex regional pain syndrome, the latter he named causalgia.¹ In addition to his medical science contributions, he was also a renowned literary author in his time, and described neurologic disease, including seizures, in a number of his works.⁴ Although he was a prolific author and

preeminent neurologist, his views on and contributions to the treatment of epilepsy are relatively obscured by his other accomplishments.

METHODS

We searched the publications of Silas Weir Mitchell with attention to those that focused on epilepsy, topics potentially related to epilepsy, seizures, or treatment of seizures or epilepsy. We compared his ideas to common practice at the time through the search of period medical textbooks, *materia medica*, and medical journals. We also reviewed his relationship with other prominent neurologists of the time period.

RESULTS

Standard treatments

Starting in the late 1850s and extending through the early part of the 20th century, bromides were a common therapy for

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RECEIVED MARCH 26, 2014. FINAL REVISIONS SUBMITTED JUNE 30, 2014.

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Figure: Silas Weir Mitchell (1829-1914). Photo courtesy of the National Library of Medicine.

epilepsy. Mitchell was as familiar with bromides as any neurologist of the time period. He published on bromides using cautious tones. In 1870, he pointed out cases of severe skin ulceration associated with bromide use.⁵ By 1896, he expanded his observations to include cardiac manifestations, depression, and psychosis attributable to bromide toxicity or preparation.⁶

He was not without his belief in bromides, though, as in 1870 he published the introduction of lithium bromide. He preferred lithium bromide over other bromide preparations as he claimed it held a higher concentration of bromide, was better tolerated, and was a better hypnotic than potassium bromide.⁷ Lithium bromide was just one of many bromide salt preparations available by the turn of the century⁸ and was cost prohibitive, often costing as much as four times the other bromide salts.⁷ Eventually, lithium was found to be a useful mood stabilizing agent. If Mitchell noticed mood or behavioral effects in his patients taking lithium bromide, he did not report it. He did feel that bromides in general were useful in the treatment of “nervousness” or as a “general nerve tonic,” but this was not specific to lithium.⁹

Some physicians were suspect of lithium bromide’s efficacy compared to the more widely used potassium preparation. “I have watched its effects...but have not been able to trace any superiority in its action,” wrote Sir William Gowers.¹⁰ Despite others’ misgivings, lithium bromide remained a favorite of Mitchell’s throughout the remainder of his career.¹¹

Novel therapeutics

In 1872, Mitchell published an account of using amyl nitrite specifically to arrest a seizure following the onset of an aura. He recounted a patient who had recurrent seizures despite employing typical treatment methods at the time, including bromides, chloroform, strychnia, valerianate of quina, zinc, blistering, and arm ligature. As the patient had an aura that provided significant warning time, Mitchell had him attempt seizure abortion with inhaled amyl nitrite. Mitchell proclaimed that the patient felt “The spasm ceasing, the attack at once, and for the first time in his experience, was cut short.”¹²

As amyl nitrite gained exposure, more physicians began reporting its efficacy. In 1873, Sir James Crichton-Browne, a renown Scottish psychiatrist, published his experience with amyl nitrite in epilepsy, lauding its benefits, without mention of Mitchell’s previous descriptions.¹³ This did not escape Mitchell’s attention. In 1875, he expanded his case experience with amyl nitrite and sharply noted that “It seems to be unknown in England that it had long been used...in America. I infer this from the fact that Dr. Crichton Browne...does not allude to its previous successful employment in this country.”¹⁴ Mitchell seems to have carried this with him, bringing up again in 1894 that “Several authors have written as to this, especially in England, without any reference to the original paper.”¹⁵ This may have been somewhat troublesome to Mitchell since he had spent time in London and had an amicable relationship with at least one prominent English neurologist, John Hughlings Jackson. The two exchanged correspondence and shared patients,¹⁶ and Mitchell even dedicated his 1881 text *Lectures on Diseases of the Nervous System, Especially in Women* to Hughlings Jackson.¹⁷

Although Mitchell was bolstered by the abortive success of amyl nitrite, he was aware of its limitations due to the short time of action and admitted that “it does not seem to possess, in most cases, any capacity to lessen the probability of a return of fits.”¹⁴ In 1880, he teamed with Edward Reichert, professor of physiology at the University of Pennsylvania, to investigate potassium nitrite as a long-acting alternative to amyl nitrite, and together they published a detailed physiologic report.¹⁸ Mitchell sampled potassium nitrite himself to assess its clinical effects:

Having made several like testings, I took within a half hour 10 grains. This in 25 minutes sent my pulse to 120, flushed my face, and my hands also, and caused a sense of intra-cranial throbbing. In a word, the potassium nitrite caused all the symptoms which are more abruptly developed by amyl nitrite.¹⁸

He aimed to publish his clinical experience with alkaline nitrites in his epilepsy patients,¹⁸ but no manuscript ever came to press. Amyl nitrite would continue to be used by physicians for many years, with Gowers proclaiming, “Of methods of arresting fits...nitrite of amyl is the most frequently (though not invariably) successful.”¹⁹

Nonpharmacologic measures

Mitchell perhaps best described his outlook in 1912 when he delivered an address regarding the treatment of epilepsy:

We must, I am sure, feel a sense of therapeutic despair whenever a case of ordinary epilepsy appears for treatment at a clinic – nor does wealth make the situation much better...The ingenuity of therapeutics has gone bankrupt in the effort to find drug cures for epilepsy.¹¹

Of course, so-called “drug cures” were not the only therapies available. Mitchell remained active well into his eighties, and commented on nonpharmacologically-based treatments during the twilight of his career. Mitchell was long well known as a champion of the “rest cure” for the treatment of neurologic diseases, particularly neurasthenia.¹ The treatment itself consisted of rigid control of the patient’s life, physically, nutritionally, and emotionally, so that they were unencumbered by anxiety. Along those lines, there were virtually as many lifestyle treatments for epilepsy as there were physicians to recommend them. English neurologist Sir J. Russell Reynolds, who had expertise in epilepsy, thought that “Salted meats, pastry, preserved vegetables, and cheese” should be avoided as “dyspepsia may at any time be the occasion of a particular attack.”²⁰ Later, Gowers recommended “regular action of the bowels” with the thought that constipation would lead to an increase in seizures.¹⁰ William P. Spratling, an American epileptologist and superintendent of the Craig Colony for Epileptics in New York, wrote in 1904 that certain patients “are better for not attending the drama and other places of amusement that excite the emotions” as these could trigger seizures. Spratling also included a list of foods to eat and foods to avoid.²¹ Mitchell, on the other hand, made no recommendations regarding the use of any lifestyle modification in epilepsy and, instead, commented that, “I do not agree with my friends upon the tremendous necessity for regulating the hours, diet, exercise, and everything else of confirmed epileptics.” He was adamant that, “It is undesirable to tie these patients down to rigidity in all sorts of directions.”²²

By the turn of the century, non-neurologic organ systems were still considered as an etiology and potential focus of treatment for some seizures. Spratling details the use of “abdominal section” for treatment particularly in women, ruling that “If the attacks came on about puberty...and occurred thereafter in close conjunction with the menstrual epoch,” then hysterectomy and salpingo-oophorectomy may be beneficial.²¹ While Mitchell recognized a catamenial component such that “Epileptic attacks are apt to return at the menstrual period with greater frequency than at others, and in certain persons (epileptics) the attacks never occur save when they appear either just before, just after, or during the monthly flow,” he did not recommend related surgical procedures as a treatment. “In no case seen by me,” Mitchell announced, “has ablation of ovaries and termination of menstruation cured epilepsy.” Mitchell came to the conclusion that, “Epilepsy truly...due to abnormal states of the sexual apparatus is rarely (I am tempted to say never) seen.”²³

Clinical context

Though knowing Mitchell’s thoughts regarding the etiology of epilepsy would help gain insight to his opinions regarding treatment, he shared little about any ideas he may have had in that regard. This is despite a relationship with Hughlings Jackson, who was active in the theory of somatotopic localization and seizure pathophysiology,²⁴ as well as Mitchell’s personal background in physiology.²

Mitchell recognized the role of head trauma as a cause of epilepsy relatively early in his career, noting the association in soldiers during the Civil War.²⁵ Still, in Mitchell’s first discussion of amyl nitrite as an abortive therapy, he clearly agreed with a common thought of the day by attributing the patient’s epilepsy to sexual vices, stating he had partaken in “...great excess, and that the punishment was distinctly born of the offence.”¹² As he found continued success in employing amyl nitrite against seizures, he posited a vascular theory that “A condition of vasal spasm” was associated with seizure onset and thus aborted by inhalation of the vasoactive drug.¹⁴ Even this explanation remained ultimately unsatisfactory to him and, in 1912, he openly questioned, perhaps in frustration, the etiology of seizures:

It is conceivable that in nerve centres normal or abnormal substances may accumulate until they result in irritative symptoms and discharges of neural energy. But how then could this sequence be arrested by a mere sensory stimulation, like a ligature on an arm, or by abruptly dilating the cerebral vessels with amyl? The explosions would only be put off for the minute; the activating poison would remain.¹¹

DISCUSSION

Silas Weir Mitchell contributed to the therapeutic armamentarium of epilepsy during his career. Despite his personal feelings about the failure of available treatments, Mitchell remained optimistic enough to help advance the field. He introduced what he felt to be a more tolerable bromide in an attempt to make palatable therapy more widely available. His use of amyl nitrite specifically as a pharmacologic seizure abortive expanded on the idea of arresting seizures in the early stages. Mitchell was not without his vanity; however, and was quick to comment when first Crichton-Browne and then other English physicians subsequently supported amyl nitrite without referencing his 1872 description. Amyl nitrite was well-received and widely used during the late 19th and early 20th centuries but his ultimate plans, to bring longer-acting oral nitrites into the clinical sphere, did not come to fruition.

Mitchell generally carried the same views regarding epilepsy as his contemporaries but had a particular point of departure when it came to nonpharmacologic interventions. Lifestyle measures and diet were popular methods of treatment during Mitchell’s time. Mitchell’s development and proponency of his rest cure indicates that he did believe lifestyle measures could be used therapeutically for some disease states. Interestingly, he did not feel any lifestyle interventions were useful in epilepsy.

Mitchell died in 1914 having never seen what he would consider an adequate therapy for epilepsy. Mitchell’s bold proclamation of bankrupt ingenuity and personal despair regarding the treatment of epilepsy came in 1912, after a lifetime of medicine. His calls for better therapies did not go unheard as phenobarbital was introduced that year,²⁶ signaling the beginning of a slow change in the availability of effective epilepsy therapies.

STATEMENT OF AUTHORSHIP

DB contributed to the study conception and design, interpretation of data, and drafting and revising the manuscript. CB

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DISCLOSURES

DB reports no disclosures.

CB serves as a Book Review Editor for *Neurology* and as a Contributing Editor to *Headache Currents*.

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