

Chapter 2

History of Cannabis as Medicine: Nineteenth Century Irish Physicians and Correlations of Their Observations to Modern Research

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Abstract Cannabis or hemp has been employed medicinally in Ireland since at least the Anglo-Saxon era, more than 1000 years ago. Its use came to the fore, however when William B. O'Shaughnessy, an Irish physician in India, became familiar with the versatility of Indian hemp in the treatment of rheumatic diseases, tetanus, cholera and epilepsy in 1838. His knowledge, acquired through application of the scientific method combining ethnobotanical teachings, animal experimentation and clinical observations in humans, was quickly shared with colleagues in Ireland and England. This led in turn to rapid advances in therapeutics by Michael Donovan in neuropathic pain states, Dominic Corrigan in chorea and trigeminal neuralgia, Fleetwood Churchill in uterine hemorrhage, and Richard Greene in the use of cannabis as a prophylactic treatment of migraine. In each instance the observations of these past treatments are examined in light of 21st century advances in pathophysiology so that their rationale and scientific basis are clarified. The venerable Irish tradition of cannabis research is being carried on contemporaneously by numerous prominent scientists with the promise of important advancements yet to come.

2.1 Introduction

2.1.1 *Ancient Antecedents: The Celts, the Lacnunga, and Irish Hemp*

Recent evidence supports that Ireland was settled by Neolithic peoples of Near Eastern origin in the 4th millennium BCE (Cassidy et al. 2016), but we know little of their use of food or fiber plants at that time. Their arrival predates any possible migration by Celtic people in the Mesolithic era. A Celtic archeological site in what

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is now Hungary, dating to the 1st Century BCE revealed carbonized seeds of hemp, *Cannabis sativa* L. (Dalnoki and Jacomet 2002). Cannabis came to the British Isles during the Roman era, at the latest, according to archeological and pollen records, where it became an important grain, fiber source and medicinal (Dark 2000). Hemp was one of numerous herbal ingredients applied topically in a “Rite for Salve, Partly Irish” contained in the 10th century Anglo-Saxon medico-religious text, the *Lacnunga* (Grattan and Singer 1952) (p. 123). Notwithstanding this reference, other citations of hemp in the ethnobotanical and folk medicine of Ireland are difficult to document. While its cousin, hops, *Humulus lupulus*, was adopted early (Allen and Hatfield 2004), this reference contains no information on hemp, nor does a venerable predecessor on ethnobotany of Ireland (Moloney 1919). Hemp was grown for fiber in Ireland in the early 19th century, at which time it was estimated that 14,000 tons were required to supply Great Britain in a year of peace (Besnard 1816), the author advising that Ireland contribute more to its provision as a better crop than flax linen. It was also stated of a local hemp fabric sample (p. 21), “This hemp [grown in Bunnratty, Ireland] possessed all the qualities of the Italian, and was particularly well adapted for fine Works.”

2.2 William Brooke O’Shaughnessy and Indian Hemp

William Brooke O’Shaughnessy must stand as the pre-eminent giant of cannabis science in the 19th century. His background and accomplishments have been well documented, due in no small part to his genius and innovation in multiple fields: chemistry, toxicology, ethnobotany, clinical medicine, and telegraphy (Gorman 1984, 1983; Coakley 1992; Mills 2003; Russo 2005). He was born in Limerick, Ireland in 1809, and lived in Ennis, County Clare before leaving for Edinburgh, from which he received his medical degree in 1829. He then moved to London and quickly established a reputation as a forensic chemist and toxicologist, publishing a landmark correspondence paper on cholera in the *Lancet* in 1831, demonstrating that the severe diarrhea of that disease produced dehydration, hypernatremia, electrolyte wastage and acidosis. This letter was reproduced *in toto* (Coakley 1992) (p. 151), and led directly in the following year to the successful salvage of 8 of 17 cholera victims in Scotland by Latta and Lewins utilizing intravenous saline. Ironically, this treatment then languished for six decades before its resumption in the latter 19th century. Cholera was to figure prominently once again in O’Shaughnessy’s therapeutic experiments subsequently, however.

Despite this early celebrity, as an outsider subject to political factors, O’Shaughnessy was unable to procure a practitioner’s medical license in London. As a result, he accepted a position as assistant surgeon with the East India Company and embarked for the subcontinent, eventually becoming the first chemistry professor of the Calcutta Medical College. By 1837, he had published a *Manual of Chemistry*, of which it was said (Gorman 1983) (p. 109–110), “this book reflect that most important ingredient necessary in the make-up of the colonial scientist- the

ability to adapt native human and material resources to the exigencies of the time, the place, and the purpose of any specific undertaking.” By all accounts, he was a patient and generous teacher to his Indian acolytes, in a quotation attributed to Corbyn related to the stellar test performance of his charges (Gorman 1983) (p. 113), “Such an examination is highly creditable to the pupils and especially to their teacher: indefatigable, eloquent, and devoted to the science, he is admirably adapted for the post he fills.”

O’Shaughnessy was subsequently responsible for the historical watershed moment for Indian hemp as his experiments yielded “the definitive account of cannabis of the early nineteenth century” (Mills 2003) (p. 39). This seminal work was first presented as a lecture read before the Medical and Physical Society of Calcutta on October 2, 1839, then published with the imposing title, *Extract from a Memoir on the Preparations of the Indian Hemp, or Gunjah, (Cannabis Indica) their effects on the animal system in Health, and their utility in the Treatment of Tetanus and other Convulsive Diseases, in two parts in one regional journal* (O’Shaughnessy 1839), then another (O’Shaughnessy 1838–1840), then republished in England in 1843 (O’Shaughnessy 1843b), and finally as the initial entry in a modern 20th century compendium (Mikuriya 1973). His approach to investigation was seemingly comprehensive and unusual for the era, providing a template for future research, as he presented an introduction to the subject, a botanical description of the plant, outlines of the various cannabis preparations available in India including *bhang* (low-grade cannabis leaves and fertile flowers), *ganja* (unfertilized female inflorescences), *charas* (cannabis resin, better known as hashish) and *majoon*, a hemp-based oral confection. He then gave a historical review of the plant’s uses with a nod to his collaborating scholars who assisted with translation of ancient texts, applying a critical review of ancient and modern Sanskrit and Unani (Arabic) medical authorities, the writings on cannabis of his British antecedents in India, and while cognizant of their moral objections to the drug, he did not eschew consideration of contemporary Indian folk medicine applications for it. Rather he applied these clues to direct new clinical experiments of cannabis effects in dogs, in which excess doses produced ataxia, and in ruminants, which seemed fairly immune to untoward effects, finally after assays in a menagerie of other creatures, turning to a series of experimental trials in human subjects with careful titration of dosages. His medical students also joined in the bioassays.

These trials supported benefit cannabis in a wide range of human maladies: cholera, rheumatic diseases, delirium tremens and infantile convulsions. In “rheumatism” cannabis resin in solution was given to three hospitalized patients. One proceeded to sing, declare himself fit and call for more food before falling asleep. When then examined, he was insensitive to pain and his limbs remained waxen and doll-like in any position placed—the first demonstration of catalepsy due to cannabis, the latter phenomenon now recognized as a key part of the cannabinoid tetrad (along with hypomotility, analgesia, and hypothermia) (Pertwee 1972; Fride and Sañudo-Peña 2002). One other patient also slept, while the third was alert, seemingly well and symptom-free. Two of the three were seemingly

“cured” by the treatment and discharged after three days. A fourth elderly patient became loquacious, musical and ravenous of appetite, quite enjoying the experience during his stay. Aphrodisia was an additional manifestation. All patients improved clinically, and none suffered significant sequelae despite the comedy-drama on the wards. This account may be supported in part by modern findings of the utility of cannabis-based medicines in rheumatoid arthritis, as evidenced by the efficacy of nabiximols in reduction of morning stiffness and pain and the Disease Activity Score-28 (Blake et al. 2006), and specifically that of cannabidiol in its effects on tumor necrosis factor-alpha (Malfait et al. 2000).

These initial results convinced O’Shaughnessy to essay the effects of cannabis in rabies, a disease which, then as now, is almost universally fatal with no effective treatment once its symptoms take hold. A compelling case study documented the patient’s torturous course three weeks after a bite by a rabid dog. The patient was anxious, diaphoretic, tachycardic and unable to drink. Any effort to imbibe provoked paroxysms so severe that his doctor was unable to watch. After cannabis treatment was initiated, in contrast, the patient was able to chat, suck an orange, and finally sleep. The next day, the paroxysms returned, but with further dosing, he was even able to eat. The pattern continued over four days until a peaceful stupor was followed by his final passage. While the patient was not saved, the great value that cannabis brought as a palliative agent was clear to O’Shaughnessy, as (O’Shaughnessy 1842) (p. 596):

—the awful malady was stripped of its horrors; if not less fatal than before, it was reduced to less than the scale of suffering which precedes death from most ordinary diseases.—I am not however rash enough to indulge the hope which involuntarily forces itself upon me, that we will ever from this narcotic derive an effectual remedy, for even a solitary case of this disease-but next to cure, the physician will perhaps esteem the means which enable him ‘to strew the path to the tomb with flowers’ and to divest of its specific terrors the most dreadful malady to which mankind is exposed.

These words remain as true and valid in the 21st century as they were in the 19th.

The experiments with Indian hemp extended to O’Shaughnessy’s students. Small doses increased the pulse, made the countenance glow, and rendered the appetite extraordinary, while the mind was filled with vivid and grandiose thoughts provoking loquacious exposition, expansive yarns and attendant mirth that their instructor likened to the Delphic Oracles. Modern medical education certainly pales in comparison.

Attention was turned next to victims of a local cholera epidemic, the ravages of which were quite familiar to the professor from his experiences with the London epidemic. Several patients were treated, their diarrhea stopped and stimulant benefits were noted. A durwan (guard) of the campus was initially dehydrated and nearly pulseless once stricken, but sufficiently recovered after one cannabis treatment to resume his post the next day. Subsequently, cannabis became a mainstay of 19th century treatment for the disease, which is eminently rational given the integral part that the endocannabinoid system plays in the enteric nervous system,

regulating both gastrointestinal secretion and propulsion (Pertwee 2001; Izzo et al. 2003; Izzo and Sharkey 2010).

Contemporaneously, in the era before immunizations became available, tetanus was essentially fatal in virtually every case (Russo 2014). O'Shaughnessy treated three patients, with each surviving the tetanic paroxysms, while one died subsequently of gangrene in a vain attempt to preserve a limb. The administration of frequent doses of cannabis soothed the spasms, allowing patients to eat and drink until effects of the toxin passed, often many weeks later. Colleagues including his cousin Richard (O'Shaughnessy 1842) saved half of their affected patients, miraculous for the time. In his later account (O'Shaughnessy 1842), this success was extended to treatment of affected horses. Similar application to human patients spread to Europe and North America, and its use remained in India through the 20th century despite its prohibition elsewhere (Dastur 1962). This indication of cannabis for tetanus seems eminently sensible today, given that the disease still claims a million victims annually with a mortality of 50% (Rowland 2000) and with an awareness of our of current knowledge on pathophysiology:

- (1) Muscle tone is under tonic control of the ECS. CB₁ agonists reduce spasticity, while antagonists such as SR141716A (Rimonabant) exacerbate it (Baker et al. 2000).
- (2) CB₁ receptors are densely represented in cortical and basal ganglia areas sub-serving motor control and their corresponding cerebellar counterparts (Glass et al. 1997).
- (3) Endocannabinoid functions are also prominent in interneurons of the spinal cord (Farquhar-Smith et al. 2000) and neocortex (Bacci et al. 2004) that may relate to pathophysiological mechanisms of spasticity.
- (4) Cannabis-based medicines are clinically effective treatments for spasticity in multiple sclerosis and cerebral palsy (Novotna et al. 2011).
- (5) Nabiximols is now approved in 29 countries for the former disorder and has shown signs of benefit in early clinical trials in the latter syndrome in children.

Given the successes with other paroxysmal disorders, O'Shaughnessy essayed it in infantile convulsions in a desperate situation wherein the child was could not be nourished, was wasting away, and all conventional approaches had failed (O'Shaughnessy 1842). Initial success was followed by recurrences of seizures. Heroic doses became necessary. Despite the apparent development of tolerance, the child withstood cannabis doses that rendered adults cataleptic. This notwithstanding the treatment eventuated in recovery (p. 603): "The child is now (17 December) in the enjoyment of robust health, and has regained her natural plump and happy appearance."

While little can be proven from one case, in a disorder that sometimes remits on its own, the narrative is illustrative of the fact that younger children are quite tolerant to the intoxicating effects of THC (Russo 2014; Gottschling 2011), and that cannabis, particularly cannabidiol, has prominent anticonvulsant effects

(Porter and Jacobson 2013; Friedman and Devinsky 2015; Rosenberg et al. 2015; Russo 2016a).

O'Shaughnessy also applied cannabis to treatment of *delirium tremens*, the terrifying syndrome produced by alcohol withdrawal, finding it far more effective than the usual approaches of opium or wine, observing it assuaging the patients' terror and modulating the mood into restful sleep. Similar successes were noted by other practitioners that followed, and have led to reconsideration of cannabis in modern treatment (Mikuriya 2004). Once more, cannabidiol appears very promising as a treatment for addiction to various substances (Russo 2011).

O'Shaughnessy suffered exhaustion in 1841, and took a sick leave in England, providing a watershed for that country's scientists' knowledge of cannabis. He brought a large supply of cannabis herbal material with him from Calcutta, and generously provided this to physicians throughout the Great Britain in the form of Squire's Extract, a tincture of Indian hemp. Practitioners in India, Europe and North America subsequently extended cannabis indications to numerous other conditions. However, issues arose. O'Shaughnessy himself noted that patients reacted differently to the medicine in England (Anonymous 1843). While others tended to attribute this to ethnic differences in pharmacological susceptibility, O'Shaughnessy posited quite wisely that a loss of potency from long transport in tropical weather required that aggressive titration to the point of effect might be necessary to see similar success in England (O'Shaughnessy 1843a). He also suggested acid drinks as an antidote to intoxication (Russo 2011).

In 1842, his *Bengal Dispensary* was published (O'Shaughnessy 1842), a monumental work of 794 pages that combined the ethnobotanical observations of his British predecessors in India, with Ayurvedic lessons, and his own observations on the indigenous *materia medica*. In 1843, he became a fellow of the Royal Society and returned to India the following year, turning his attention to engineering matters, eventually establishing the electric telegraph in India, and receiving a knighthood for his contribution in 1856. In 1860, he returned to England, enigmatically changing his name legally to William O'Shaughnessy Brooke, and retiring to the countryside. He was said to succumb to "senile asthenia" in 1889.

O'Shaughnessy's impact on the development of cannabis as medicine was paramount, as his early lectures in England led directly to its widespread adoption there, on the Continent and in North America, with each new report attesting to his contribution, and extending therapeutic applications for the "new" agent. In Ireland, such medical luminaries as Robert Graves, the discoverer of the hyperthyroid condition that bears his name, and Sir Philip Crampton, "probably the most flamboyant Irish surgeon of the nineteenth century." (Coakley 1992) (p.101) adopted the "new" treatment. William Wilde, himself a physician and father to the literary great, Oscar Wilde, also alluded to O'Shaughnessy's work on cannabis in the 1844 edition of his travelogue to the Near East (Wilde 1840). To this day, O'Shaughnessy is often remembered as the modern father of cannabis therapeutics. His contribution has been commemorated by the adoption of his name as the title of a newspaper devoted to that discipline, *O'Shaughnessy's*, available in print and online: <http://www.beyondthc.com/>.

2.3 Michael Donovan and Neuropathic Pain

This outstanding scientist was not a physician, but rather a chemist and licensed apothecary, as he frequently protested during his career (Cameron 1886). In 1820, he became Professor of Chemistry, Pharmacy, and Materia Medica of Apothecaries' Hall, a medical school in Dublin, and was well versed in all these disciplines. In 1832, his *Treatise on Chemistry*, a 401 page widely-adopted text was published (Donovan 1832). He was noted to be "an excellent classical scholar," and of his writings, it was characterized as "examples of the best style of scientific literature." (Cameron 1886) (p. 537).

Though not the first to publish on cannabis after O'Shaughnessy's return to Great Britain, Donovan was an early adopter of the new cannabis preparations, and a trailblazer in its application to therapeutic challenges, publishing his findings first in a rare 1844 monograph (Donovan 1844), and in a journal article similarly titled the next year (Donovan 1845), with an added appendix documenting further developments. After effusive praise for his predecessor, Donovan presented an impressive case series of patients to whom he provided cannabis after failures of available agents in patients with neuropathic, musculoskeletal and migraine pain. The latter has been extensively reviewed elsewhere (Russo 2001). Donovan described the advent of the new drug (Donovan 1845) (p. 368):

If the history of the Materia Medica were to be divided into epochs, each determined by the discovery of some remedy of transcendent power, the period of the introduction of Indian hemp into medicine would be entitled to the distinction of a new era.—The public and the Profession owe a deep debt of gratitude to Professor O'Shaughnessy, whose sagacity and researches have brought to light a medicine possessed of a kind of energy which belongs to no other known therapeutic agent, and which is capable of effecting cures hitherto deemed nearly hopeless or altogether impracticable.

He continued on, describing morphological distinctions between Indian hemp and the familiar European specimens, highlighting the utter dearth of resin produced by the latter, and documenting how personal bioassay experiments with local hemp tinctures made of his own hand were devoid of obvious psychoactive effect (p. 370), "I therefore conceive that domestic hemp is thus proved to be destitute of the principle which renders the Indian plant so desirable an excitant to the voluptuous people of the East." Of O'Shaughnessy's cases, he noted (p. 378–9):

To me they appear the evidences of a glorious triumph achieved over one of the most dreadful maladies that can afflict human nature [tetanus].—In violent and generally fatal diseases, it is the custom of some, in the plenitude of assumed wisdom, to meet the proposal of a new remedy with a derisive smile, and its reported success with scepticism or sarcasm.—The reflecting portion of the Profession will decide for themselves, whether, as ministers of relief to the sick, they are at liberty to withhold an impartial trial to a medicine of such proved power. I content myself with expressing my belief that Indian hemp will one day or another occupy one of the highest places amongst the means of combating disease.

Donovan thus expresses an opinion that applies equally well to the contemporary scene almost 200 years later.

Donovan commenced his therapeutic experiments with locally available samples, but found most quite weak, noting much improved results with material directly from O'Shaughnessy. He began by treating his own lower extremity neuralgia, achieving relief of the pain, but with a curious side effect (p. 381), "There was this peculiarity of the relief obtained, that I walked without much consciousness of the motion of my legs, or indeed of having legs at all: I felt as if they did not belong to me." These personal bioassays were continued in sufficient number and frequency to ensure that he was quite familiar with the salutary and adverse effects of the drug. His efforts proceeded on behalf of a man bedridden for weeks with sciatica who managed to overcome an episode of sedation and imagining a non-existent person in the room to waken the next day with vastly diminished pain that remitted nicely over the long term. Another woman long plagued by neuralgia of a foot and leg weathered a bout of tachycardia and the "notion that she was attacked with a fit of insanity" (p. 387), but was pain-free after an hour, and remained so thereafter. A patient of Robert Graves, best known as the discoverer of the eponymous hyperthyroid condition, was described as suffering a neuralgia afflicting various bodily parts successively. Unfortunately, she suffered faintness and cold, without relief. However, another patient in Graves' care experienced relief of headache and third great alleviation of intractable neuralgic pain.

A patient with teeth and neck pain was cured thereof after two doses. Another gentleman suffering excruciating lower jaw and cheek pain that permanently remitted after several doses. A reverend with facial neuralgia bouts appreciated decreased frequency and duration of attacks less than a reduction in intensity. A woman with rheumatic arm and thumb pain had marked benefit in symptoms after a few doses, while another elderly woman with rheumatic leg pain enjoyed its attenuation, but not the attendant giddiness and palpitations. Two other women with toothache found initial, but not lasting relief with the drug. In another two patients with facial pain, functional abrogation was attained after administration.

Other cases demonstrated variable success, but a final patient with sciatica unresponsive to laudanum was administered Indian hemp by the afore-mentioned Sir Philip Crampton, a veritable character, of whom it was said (Coakley 1988) (p.97), "When advanced in years, Crampton was heard to boast one day that he had swam across Lough Bray, ridden into Dublin and amputated a limb before breakfast." In his patient, cannabis treatment produced, "sound, comfortable and uninterrupted sleep for seven or eight hours. On awakening, he had almost perfect relief; and five doses more so completely subdued the pain that it gave him little further trouble." (p. 399). Donovan summarized his findings as follows (p. 399):

In the foregoing details, I have not made a selection of the successful cases out of many, but have faithfully recorded all those that come under my observation, of which the termination was distinctly known. It may be seen that far more than the majority of them were cured evidently by the agency of the hemp, and that all the rest were more or less relieved.

He went on to discuss preparations, favoring the strong tincture, and warn of the sometimes alarming psychotropic effects of the drug, which need be explained to the patient and "bystanders."

In the appendix to the 1845 article (Donovan 1845), Donovan presented a case history from Abraham Colles, “the most outstanding Irish surgeon of the nineteenth century,” (Coakley 1992) (p. 55), best remembered for his description of the distal radial fracture that still carries his name. His patient had an inflamed knee with ulceration, partial dislocation and ankylosis producing pain that no amount of opiates would diminish. A tranquil night resulted and Indian hemp was continued until the joint healed. Finally, another reverend presented with facial pain with all the signs of trigeminal neuralgia including an inability to shave the area. After treatment, he was able to move his jaw without provoking pain, his appetite returned, and over time the pain was substantially diminished, even after discontinuation of the drug.

Donovan’s successes in migraine and a variety of neuropathic pain syndromes were a landmark at the time and included the first reports of cannabis treatment for trigeminal neuralgia, which to this day remains a thorny therapeutic challenge. Modern studies of neuropathic pain support application of cannabis-based medicines for both central (Rog et al. 2005) and peripheral forms (Nurmikko et al. 2007), reviewed (Russo and Hohmann 2013), while extensive anecdotal information and basic science provide a rationale for use in headache (Russo 2001; Russo 2004) and rheumatic disorders (Malfait et al. 2000; Blake et al. 2006).

As a footnote, Donovan continued his experiments with cannabis, publishing a later account in 1851 documenting another personal experience plus success in two additional cases of facial neuralgia (Donovan 1851). He remarked on the striking differences in patient’s reactions to similar doses and opined (p. 183):

The difficulty, or rather impossibility, of determining what would be an effective dose for a patient of whom the practitioner has had no experience, with reference to the intensity of the pain and the susceptibility of the patient, has greatly limited the employment of this important medicine. From all I have seen of its effects, I conceive that the most prudent mode of proceeding is to begin with a small dose, and slowly increase it night, noon and morning, until the pain give way, or until it be proved that it will not give way, even when the sensorium becomes affected.

In 1870, this brilliant practitioner retired, much to the nostalgic consternation of colleagues (Anonymous 1870), and died in 1876, age 85.

2.4 Corrigan and Chorea

Dominic Corrigan was born in Dublin in 1802, was educated at Edinburgh, graduating in 1825. After a colorful early career that included a stint as a grave-rober supplying medical school anatomy laboratories, he is best known for his work on aortic valvular disease (“Corrigan’s pulse”) (Coakley 1988). After returning to Dublin, he practiced in various facilities, including Richmond Hospital, to which he

rode each morning on horseback (Coakley 1988). In 1845, his experiences with cannabis were documented in three young girls between the ages of 11 and 16, and all of whom had been afflicted by choreic movements of the face and body for prolonged intervals without relief from medical treatment. All were treated with cannabis tinctures in titrated doses until responses were noted, and the chorea remitted in each after five to six weeks of treatment, even though the third had been so afflicted for more than 10 years and required tolerated heroic doses of the drug (Corrigan 1845a). In none of the cases were there any encephalopathic signs supporting cognitive impairment that would suggest that a degenerative disorder was operative. These three cases would be absolutely consistent with a diagnosis of Sydenham chorea, a post-streptococcal autoimmune acquired movement disorder, now quite rare, but one that can be associated with long-lasting or even permanent effects. The response of these patients points strongly to a disturbance of the endocannabinoid system that was effectively treated by cannabis. This is hardly surprising given the density of CB₁ receptors in the basal ganglia (Glass et al. 1997). Other forms of chorea, such as Huntington disease, have been far more recalcitrant to benefit (Consroe et al. 1991; Fernandez-Ruiz et al. 2011). These lessons may well demonstrate possible application of cannabis-based medicines to related immunologically-mediated acquired neurological disorders such as PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) or PANS (pediatric acute-onset neuropsychiatric syndrome).

Corrigan also reported on an adult woman whose trigeminal neuralgia (“*tic douloureux*”) pain in the face, head and neck of three-four years’ duration was abrogated a course of cannabis tincture. Of the four cases, Corrigan stated (Corrigan 1845a) (p. 144), “In the Indian hemp we have, I believe, a valuable addition to our stock of medicines acting upon the nervous system.” He continued (p. 144), “It possesses a property of considerable value as a sedative, that even in an over dose, it does not cause dryness of the tongue and derangement of the digestive organs, such as follow on the use of opium.” Corrigan thus noted the critical ability of this medicine to treat various symptoms, allowing sleep, as has been subsequently documented in modern clinical trials (Russo et al. 2007). Additionally, Corrigan noted the variability of dosing and need for titration in each individual (p. 144), “While the Indian hemp has much to recommend it, there are circumstances connected with it that require to be well borne in mind. The first of these is its very variable effects on different individuals.” He went on to note several-fold variability in required doses, with markedly different tolerance, a lesson still applicable in current treatment (Russo et al. 2015). Corrigan’s observations were subsequently republished the same year (Corrigan 1845b), and a decade later in France (Corrigan 1855).

Corrigan was subsequently knighted, became a baronet, and liberal Member of Parliament before his death in 1880 (Coakley 1988).

2.5 Fleetwood Churchill and Uterine Hemorrhage

Fleetwood Churchill was born in Nottingham, England in 1808, and trained in Edinburgh, London and Dublin. He was a premier obstetrician-gynecologist of the time (Coakley 1988). The first modern citation of cannabis for uterine hemorrhage was documented as a serendipitous discovery (Churchill 1849) (p. 512):

We possess two remedies for these excessive discharges, at the time of the menses going off, which were not in use in Dr. Fothergill's time. I mean ergot of rye, and tincture of Indian hemp.—The property of Indian hemp, of restraining uterine haemorrhage, has only been known to the profession a year or two. It was accidentally discovered by my friend, Dr Maguire of Castleknock, and since then it has been extensively tried by different medical men in Dublin, and by myself, with considerable success. The tincture of the resin is the most efficacious preparation, and it may be given in doses of from five to fifteen or twenty drops three times a day, in water. Its effects, in many cases, are very marked, often instantaneous, but generally complete after three or four doses. In some few cases of ulceration in which I have tried it on account of the haemorrhage, it seemed to be equally beneficial.

Given the prominence of his textbook, Churchill's discovery and endorsement ensured that cannabis attained an eminent place in Ob-Gyn practice in the 19th century (Russo 2002). After a successful career and publication of a well-known pediatric text, Churchill died in 1878.

2.6 Richard Greene and the Scourge of Migraine

According to a "Celtic Royal Genealogy" (Greene 1899) and 1891 British Census Records, Richard Greene was born in Boston, USA in 1843 to an Anglo-Irish family, and graduated from Edinburgh in 1868 (Anonymous 1898). He subsequently practiced in England in the Sussex Lunatic Asylum before becoming superintendent of the Berry Wood Asylum in Northampton, where he was deemed not only an able administrator, but expert landscape gardener. His 1872 publication (Greene 1872) was quite influential and widely cited in recognizing the preventative value of cannabis in prevention of migraine, wherein he found it (p. 267) "nearly always productive of more or less benefit to the patient." In six case studies, excellent results were obtained despite the fact that two patients were less than fully compliant in administering prescribed daily doses. One of those responded to an acute migraine attack with a higher dosage. The other incomplete responder may have been related to the patient's lifestyle choices as an (p. 268), "inveterate tea and coffee drinker [who] could by no means be persuaded to give up the use of these wretched stimulants." This documents an important modern concept, that of "analgesic rebound," such that caffeine, aspirin, acetaminophen/paracetamol and opiates will perpetuate chronic daily headache and exacerbate migraines rather than reduce them (Dodick 2006). Greene summarized the initial experience in his patients (Greene 1872) (pp. 269–270):

These will show that though *Cannabis Indica* may often fail to cure, it scarcely ever fails to effect some improvement even in the most apparently hopeless cases;—this drug may be taken for very many months in comparatively large doses without producing any unpleasant effects or in any way injuriously affecting the economy.—

In the above cases, however, no drug whatever was used excepting the *Cannabis Indica*. Two years later (Greene 1874), while he enjoyed no success utilizing cannabis in epilepsy treatment, he noted (p. 96–97),

—Indian hemp has a singularly happy influence in the majority of cases of sick headache—.

Greene continued to utilize cannabis similarly over a long interval, subsequently opining that it had not been properly utilized among his peers, (Greene 1888), “Since 1872 I have often prescribed it, and I have yet to meet with a case in which at least some improvement does not follow the careful and continuous use of the drug.” Three additional accounts were outlined (p. 36):

Case I.- A female, aged fifty-three. Has been a martyr to this disease for twenty-five years; the attacks recurring very frequently. It was rare that eight days passed without one. In this case improvement began almost immediately; and the attack are not only less severe, but are reduced to once a month.

Case II.- Female, aged thirty-five. Had suffered from migraine for twelve years. She did not remember during that time ever being three weeks without an attack, and was ill of three days. Her, too, improvement began very soon after the treatment, and in eight weeks she considered herself cured.

Case III.- Female, aged thirty-seven. This patient has had sick headache for many years. The attacks came on weekly, and lasted two days. After a few weeks’ treatment she was much better, and has now been months without an attack.

He added in commentary (p. 36):

It should be noted that the treatment here advocated afresh is not merely a palliative one during the paroxysm, like the use of guarana, caffeine, hypodermic morphine or nitrite of amyl inhalations, but is often curative and nearly always gives some lasting relief.

Greene outlined his therapeutic strategy, the need for a prolonged course, and contextualized the morbidity of the disorder (p. 37):

It is necessary to persevere with the treatment for at least many weeks.—when decided relief is felt there is not much fear but that perseverance in the treatment will follow the improvement, as migraine is the reverse of a pleasant companion, and often unfits its victim for an active life several days in every month.

He conclude by addressing concerns of long-term usage of cannabis (Greene 1888) (p. 38), “Unlike opium, no craving for further doses follows its medicinal use, and apparently it can be given up without the slightest effort at any time.” The latter observation is echoed by findings in modern practice (Robson 2005; Notcutt et al. 2012).

Richard Greene left practice in ill health in 1898 (Anonymous 1898). Along with his predecessor, Donovan, he may be seen as a pioneer of cannabis treatment of

migraine, a diagnosis which remains extremely problematic today, and whose pathophysiology seems intimately related to a disturbance of the endocannabinoid system (Russo 2001; Russo 2004; Sarchielli et al. 2007; Akerman et al. 2007; Akerman et al. 2003; Akerman et al. 2004; Russo 2016b).

2.7 Conclusion: Contemporary Cannabis Research in Ireland

The research pioneered by Irish physicians in the 19th century paved a path that after a long hiatus is now being pursued afresh by modern researchers. A story in the *Irish Times* in 2015 has outlined these new investigative initiatives (King 2015). Researchers such as David Finn, Eric Downer, Veronica Campbell, Michelle and Roche, Saoirse O’Sullivan and others are carrying on a proud Irish tradition of enquiry that holds great promise for therapeutic advances with cannabis. It is hoped that the lessons of the past will help to guide their investigations toward future benefits in the treatment of recalcitrant maladies.

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