Hemp for Headache: An In-Depth Historical and Scientific Review of Cannabis in Migraine Treatment

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ABSTRACT. Cannabis, or ''marijuana,'' has been employed in various forms throughout the millennia for both symptomatic and prophylactic treatment of migraine. This document examines its history of medicinal use by smoking and other methods in ancient cultures, including the Chinese, Indian, Egyptian, Assyrian, Greek and Roman, as well as in the Islamic world, and its subsequent adoption by Renaissance and Industrial Age Europeans.

The most prominent physicians of the age in the century between 1842 and 1942 preferred cannabis to other preparations in migraine treatment, and it remained part of Western pharmacopoeias for this indication throughout the period. The writings of this era are examined in great detail in an effort to emphasize useful medical documentation that has subsequently been forgotten.

In modern times, ethnobotanical and anecdotal references continue to support the efficacy of cannabis for headache treatment, while biochemical studies of THC and anandamide have provided scientific justification for its use via anti-inflammatory, serotonergic and dopaminergic mechanisms, as well as by interaction with NMDA and endogenous opioid systems. These are examined in detail.

The author feels that this collective evidence supports the proposition that experimental protocols of cannabis usage in migraine treatment should go forward employing modern controlled clinical trials.

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INTRODUCTION

Throughout medical history, drugs of choice for various indications have changed by the decade, or in recent times, annually. Once having fallen out of favor, few drugs ever resume a favorable opinion. Only a handful has remained popular for decades.

Modern physicians are not cognizant of the prominence that cannabis preparations once held in the practice of medicine. Its departure from Western formularies was due in part to problems with quality control, but more particularly to political biases. As has been recently stated (Notcutt, Price, and Chapman 1997, p. 551), ''Unfortunately, almost no clinical research into the use of cannabinoids for pain relief has taken place, primarily because of the legal difficulties in conducting such trials in patients.''

Despite its reputation as a ''drug of abuse,'' far more dangerous medications than cannabis remain in our formularies because of their specific medical indications. Thus, we retain opiates for analgesia, amphetamines for treatment of narcolepsy and attention deficit hyperactivity disorder, etc. Thalidomide, which was banned due to its teratogenic effects, may be revived as a mainstream cancer chemotherapeutic with appropriate safeguards. Even the leech is once more a therapeutic and research tool.

This review will examine the history of cannabis use for headache treatment, along with its scientific basis and possible future as a ''new'' therapeutic agent. It represents a more in-depth attempt at covering this topic as compared to prior publications (Russo 1998; Russo 2001). A recent purported ''comprehensive review'' of medical marijuana provided only one brief paragraph on migraine (Gurley, Aranow, and Katz 1998), with no early historical data documenting the extensive use of cannabis in migraine treatment.

The current narrative is divided into sections: The Ancient and Classical Worlds, Middle Ages and Islamic World, Renaissance Europe, Industrial Age Western Medical Usage, Modern Ethnobotanical Data, and Recent Research on Cannabis and Cannabinoids. Discussion will focus on issues of headache and analgesia, while that on

political issues will be cited only as pertinent. Safety issues with respect to cannabis have been discussed briefly in a prior publication (Russo 1998). Reviews may be found in the following (Ashton 1999; Hall, Solowij, and Lemon 1995; Zimmer and Morgan 1997). Extensive bibliographies on cannabis have been published by the United Nations (1965), Gamage and Zerkin (1969), Waller et al. (1976), and Abel (1979). Excellent reviews of ''medical marijuana'' appear in the literature by Mikuriya (1969; 1973), Grinspoon and Bakalar (1997), Mathre (1997), Zimmer and Morgan (1997), British Medical Association (1997), Zimmermann, Bayer, and Crumpacker (1998), Rosenthal, Gieringer, and Mikuriya (1997), and the Institute of Medicine (Joy, Watson, and Benson 1999).

THE HISTORY AND ETHNOBOTANY OF CANNABIS IN HEADACHE TREATMENT

Archeological records substantiate a longstanding mutual association of man and cannabis. It is a member of the plant family, Cannabaceae, with botanical origin in Eastern or Central Asia (de Barge 1860; Candolle 1886). Subsequent authors have often felt that no truly wild hemp exists at this time, and that all modern strains derive from cultivated forebears whose feral ancestor is now lost. Modern analysis has placed the center of diversity for cannabis in Central Asia, possibly in the Pamir plain (Camp 1936), border regions of Kazakhstan, Mongolia, Northwest China and the Russian Far East (Bouquet 1950), or in the Himalayan foothills (Sharma 1979).

The number of species in the *Cannabis* genus remains controversial. Some botanists retain all members as one polymorphic species, while others (Emboden 1981; Schultes and Hofmann 1980; Schultes et al. 1974) have exhaustively documented three species: *sativa*, *indica*, and *ruderalis*. All specimens contain the psychoactive chemical delta-9-tetrahydrocannabinol (THC) to some degree, generally *indica* being most potent, and *ruderalis* least. Additional taxonomic data of interest, particularly with reference to drug strains/species in Afghanistan (*C. afghanica*), ratios of cannabis components tetrahydrocannabinol (THC) to cannabidiol (CBD), and possible true wild plants, is discussed a book by Clarke (1998).

Ancient and Classical Worlds

It is claimed that cannabis use occurred in central Europe by the Bylony culture as much as 7000 years ago (Kabelik, Krejei, and Santavy 1960). Physical evidence for its early employment in 1896 in Wilmersdorff (Brandenburg), Germany in the form of a funerary urn that contained cannabis leaves and fruit (Busse 1897), subsequently dated to the 5th century BCE (Andrews and Vinkenoog 1967; La Barre 1980). According to Ames (1939), Hartwich (1911) interpreted the urn contents to represent early use as an inebriant.

China

Use of cannabis fibers to make hemp has been documented as early as 4000 BCE in China by Carbon-14 dating (Li 1974), and has been maintained continuously up to the present day. Its seed grain was an ancient human foodstuff, which may have lead to an early recognition of its medicinal use. The first records may occur in the *Pên-tsao Ching*, a traditional herbal written down in the 1st or 2nd centuries, but based on the oral traditions passed down from the Emperor Shên-nung in the third millennium BCE. The text noted that the plant fruits ''if taken in excess will produce hallucinations (literally ''seeing devils'') (Li 1974, p. 446). The *chuan* pictograph for cannabis, or *Ma*, is easily recognized as harvested plants hanging inverted in a shed.

Julien (1849) submitted a controversial report of powdered cannabis use as an early surgical anesthetic in the early 2nd century.

Indications of cannabis for headache do not seemingly appear in China until a later time (see Ethnobotany section).

India

The *Atharva Veda* of India, dated to between 1400 and 2000 BCE referred to a sacred grass, *bhanga*, as an herb to allay anxiety (Indian Hemp Drugs Commission 1894). The *Sushruta Samhita* cites medicinal references to cannabis dating to 600-400 BCE (Sushruta 1991). Dwarakanath (1965) asserted that cannabis has been employed in folk medicine from the 4th to 3rd centuries BCE. He noted Ayurvedic preparations called *Rasachandrika vati* and *Mahalakshmivilasa rasa*, said to contain cannabis indicated for (p. 17), ''Diseases of the head

including neuralgic headaches, haemicrania etc. (Shiroaroga) [term for migraine].''

Other authors stated (Muthu 1927) (p. 27), ''The Hindus also used the fumes of burning Indian hemp (*Cannabis indica*) as an anaesthetic at a period of great antiquity . . .'' and (Sanyal 1964, p. 61), ''They also used the fumes of burning Indian Hemps (Cannabis Indica) as an anaesthetic from ancient times . . .''

One controversy frequently discussed in literature on the subject concerns the issue of whether actual smoking as a method of drug delivery occurred in the Old World before the European ''re-discovery.'' In a discussion of Indian drugs including cannabis, Walker (1968) addressed the issue, citing many early medical works [such as the *Sushruta Samhita* (Sushruta 1991)] and a variety of herbs, including those with indication for headache.

A modern observation may address the relative dearth of archeological evidence on the smoking issue. Clarke (1998, p. CS5) has described and illustrated a technique whereby cannabis is sieved to produce resin powder which is hand rolled into a ''snake'' that may be smoked without additional paraphernalia, and potentially leaving nothing but ash.

Egypt

Although many authorities have claimed an absence of cannabis in Ancient Egypt, Nunn (1996) cited six supporting experts that it was employed (Mannische 1989; Ghalioungui 1987; Charpentier 1981; von Deines and Grapow 1959; Faulkner 1962; Dawson 1934) as an agent termed *shemshemet*, administered via oral, rectal, vaginal, and local routes, and by fumigation.

Mannische (1989) also has cited evidence of cannabis use in Ancient Egypt in the Pyramid Texts of the mid 3rd millennium BCE Physical proof includes discoveries of hemp remnants in the tomb of Akhenaten (Amenophis IV) around 1350 BCE, and cannabis pollen in the tomb of Rameses II, who died in 1224 BCE.

Persia

The *Zend-Avesta*, the holy book of Zoroastrianism, which survives only in fragments dating from around 600 BCE in Persia, alludes to

the use of *Banga* in a medical context, which is identified as hemp by Darmesteter (*Zend-Avesta* 1895).

Assyria

Medical use of cannabis in Ancient Assyria has been claimed in numerous sources, though has remained controversial. Thompson (Thompson 1924, 1949) documented 29 citations of cannabis in the ancient Assyrian library of Ashurbanipal. These attested to cannabis' analgesic and psychogenic effects by various methods including fumigation. Citations date to the second millennium BCE and pertain to *A. ZAL. LA* in Sumerian, and *azallû* in Akkadian. Through philological arguments the author concluded (Thompson 1924, p. 101), ''The evidence thus indicates a plant prescribed in AM [Assyrian manuscripts] in very small doses, used in spinning and rope-making, and at the same time a drug used to dispel depression of spirits. Obviously, it is none other than hemp, *Cannabis sativa*, L.'' Specifically (Thompson 1949), hemp, or *azallû*, was employed to bind the temples (possibly for headache?).

Israel/Judea/Palestine

Longstanding debate has occurred as to the veracity of cannabis use in the Bible. Benetowa (1936) proposed its presence on a strong philological basis in a Polish/French paper. Her data was re-presented a few decades later (Benet 1975, p. 40):

> Both in the original Hebrew text of the Old Testament and in the Aramaic translation, the word *kaneh* or *keneh* is used either alone or linked to the adjective *bosm* in Hebrew and *busma* in Aramaic, meaning aromatic. It is *cana* in Sanskrit, *qunnabu* in Assyrian, *kenab* in Persian, *kannab* in Arabic and *kanbun* in Chaldean. In Exodus 30:23, God directs Moses to make a holy oil composed of ''myrrh, sweet cinnamon, kaneh bosm and kassia.'' In many ancient languages, including Hebrew, the root *kan* has a double meaning–both hemp and reed.

To expand on this base, the same etymological roots apply to the word cannabis in Scythian and Latin, *kannabis* in Greek, *canevas* in Old

French, *quannab* in Celtic, and *canvas* in English (cannabis hemp was the original source for canvas material). Additionally, we see *cáñamo* in Spanish, *cãnhamo* in Portuguese, *chènevis* in French, *canapa* in Italian, *khanapiz* in old Germanic language, and *konoplya* in Russian.

Although the issue of its biblical presence has been hotly debated, physical evidence of medicinal cannabis use in 4th century Israel/Palestine was recently discovered (Zias et al. 1993).

Ancient Greece and Rome

The historian Herodotus, circa 450 BCE, described how a Central Asian tribe called the Massagetae on Persia's northeastern border sought an altered state of consciousness as a group experience (Herodotus 1998) (Book 1, Verse 202), with the smoke of the fruit of an unidentified burning plant. Another passage (Book 4, verses 73-75) is explicit in use of the word cannabis in description of a similar ritual performed by the Scythian tribe somewhere north of the Black Sea.

In the 1st century of the Common Era, Dioscorides published his *Materia Medica*, perhaps the first pharmacopoeia in the Western World, describing the analgesic role of cannabis (Dioscorides 1968) (3.165) (p. 390), ''Cannabis is a plant of much use in this life for ye twistings of very strong ropes, . . . but being juiced when it is green is good for the pains of the ears.''

In the 2nd century, the Greek physician Galen expounded on medical indications, mainly gastrointestinal (Brunner 1973), but also noted of cannabis (Galen) (100.49, p. 350), ''If consumed in large amounts, it affects the head by sending to it a warm and toxic vapor.''

Subsequently, Oribasius elaborated on this point (Oribasius 1997, Book I, v. 32, p. 65), ''The seed of hemp is difficult to digest and bad for the stomach, causes headaches, and is unwholesome; it is somewhat heating.'' These unsubstantiated side effect claims were to be echoed by Middle Eastern and European authors for some 15 centuries.

The Middle Ages and Islamic World

The medicinal use of cannabis as and herbal treatment or *hashish* has been well documented in early Islamic texts (Lozano Camara 1997). Jabir ibn Hayyan observed a psychoactive effect in the *Kitab al-Sumum* (''Book of Poisons'') in the 8th century (Lewis et al. 1971).

In the 9th century, Sabur ibn Sahl, a Nestorean Christian physician in Persia cited use of cannabis five times in his dispensatorium, *Al-Aqrabadhin Al-Saghir* (Kahl 1994, p. 68), the earliest known document of Arabic pharmacology. According to Dr. Indalecio Lozano (personal communication, 2000), ibn Sahl offered four recipes for compound medicines containing cannabis. The third of these comprised a large number of ingredients, and was used to treat a variety of aching pains, specifically migraine and headache. He prescribed that the compound medicine of many items (or *theriac*) be mixed with juice of cannabis (*ma al-sahdanay*) and then should be instilled into the patient's nostril. This represents the earliest unequivocal, direct citation of cannabis use for migraine that the author has been able to document. The prescription dictates administration by a parenteral route, intranasally, which circumvents the oral pitfalls of oral migraine treatment due to the nausea, emesis, and gastroparesis of that disorder.

Abu Mansur ibn Muwaffak in 10th century Persia in his work *Kitab al-abniya 'an haqa'iq al-adwiya* (''Book of the Foundations of the True Properties of Remedies''), described the use of cannabis fiber for making rope, and the plant to treat headache according to two sources (Lewis et al. 1971; Levey, 1973), although a translation of the German text seems to echo Galenic warnings that it produced headache (Kobert 1889).

Cannabis also figured in the medical writings of Avicenna (ibn Sina) in the 10th century, wherein the inebriating effects of the plant leaves were noted (Ainslie 1826), those of Simeonis Sethi, a Byzantine scholar in the 11th century (Sethi 1868), and Maimonides in the 12th century (Meyerhof 1940; Maimonides 1979). Also in the 12th century, Al-Biruni noted (Biruni 1973, p. 346), ''Galen says: 'The leaves of this plant [Indian hemp = cannabis] cure flatus–Some people squeeze the fresh (seeds) for use in ear-aches. I believe that it is used in chronic pains.' ''

Throughout the Islamic Age, a definite ambivalence reigned concerning cannabis pitting its medicinal effects against its inebriating actions, which were arguably contrary to Muslim precepts. The first known government sanction on cannabis occurred at the behest of King al-Zahir Baybars at the close of the 13th century (Hamarneh 1957). Nevertheless, Umar ibn Yusuf ibn Rasul persisted in suggesting cannabis for ear and head pain (Lewis et al. 1971).

Some centuries later, the use of an electuary named *bars*, or *barsh*,

containing a variety of herbs with or without cannabis, swept the Arab world. Though maligned, and outlawed, it retained numerous medical indications, including treatment of persistent headache (Lozano Camara 1990).

The 17th century Persian medical text *Makhzon-ul-Adwiya*, or *Makhzan al-adwiya*, described cannabis in its various preparations, as an intoxicant, stimulant and sedative, but also (Dymock 1884, p. 605), ''The leaves make a good snuff for deterging the brain . . .'' This source also recommended a poultice of its boiled roots (Kaplan 1969, p. 175) ''for allaying neuralgic pains.''

Renaissance Europe

Hildegard von Bingen, the 12th century abbess, musician, and herbalist wrote of cannabis in her *Physica*, stating (Fankhauser 2001, p. 34):

> Whoever has an empty brain and head pains may eat it and the head pains will be reduced. Though he who is healthy and full of brains shall not be harmed by it.–He who has an empty brain shall be caused pain by indulging in hemp. A healthy head and a full brain will not be harmed.

European awareness of the psychoactivity of cannabis was rekindled with the writings of Garcia da Orta, who visited India in the 16th century, and noted its sedative and appetite-stimulating properties in his 1563 book (da Orta 1913).

Contemporaneously, Rabelais wrote of cannabis in his *Gargantua et Pantagruel*, including an excellent botanical description of the plant and its medicinal uses (Robinson 1946; Rabelais 1990). Prosper Alpinus (Alpin 1980) visited Egypt in 1591 and documented the use of cannabis as an inebriant and visionary drug.

Medicinal uses persisted in England. In 1640, in the *Theatrum Botanicum*, *The Theater of Plantes* (Parkinson 1640), John Parkinson indicated (p. 598), ''The decoction of the roote is sayd to allay inflammation in the head, or any other part, the herbe it selfe, or the distilled water thereof performeth the like effect;''

Culpeper echoed similar wording in his famous herbal (Culpeper 1994, p. 183), ''The decoction of the root allays inflammations of the head, or any other parts; the herb or the distilled water of it, does the same.'' Other European documentation of psychoactive and medicinal

usage of cannabis was provided by Ange de Saint-Joseph (Ange de Saint-Joseph 1681), Berlu, in his 1690 book, *Treasury of Drugs* (Flückinger 1879), Georg Everard Rumpf (Rumpf and Beekman 1981), Rheede (Rheede 1678-1692), Chardin (Chardin 1711), Engelbert Kaempfer in his *Amoenitatum Exoticarum Politico-Physico-Medicarum* (Dolan 1971; Kaempfer 1996), and Lemery (Lemery 1733).

In his book, *Traité du Chanvre*, Marcandier (1758) noted pertinent inebriating and anti-inflammatory effects of cannabis (pp. 40-41), ''Its root, boiled in water, and smeared in the form of a cataplasm, softens and alleviates joints of the fingers that are retracted, It is quite strong against gout, and other swellings of nervous, muscular and tendinous parts.''[translation EBR]

Linnaeus cited these uses of *Cannabis sativa* in his *Materia Medica* (Linné 1772, pp. 213-214), ''narcotica, phantastica, dementans, anodyna, repellens.'' This supports the concept that earlier scientists understood not only the psychotropic properties of cannabis, but also recognized its analgesic value. Bergius noted a distinction between the psychoactive effects of cannabis grown in the Orient as compared to European samples (Bergius and Hesselberg 1782).

After the Napoleonic campaign in Egypt, cannabis usage was popularized through the literary works of Silvestre de Sacy (Sacy 1809), and subsequently, Moreau (1845), Gautier (1846), and Baudelaire (1860), patrons of *Le Club des Hachichins*.

Industrial Age Western Medical Usage of Cannabis

The medical use of cannabis, or what became known as ''Indian hemp'' was reintroduced to the West, yet again, in 1839 (O'Shaughnessy 1838-1840). His treatise on the subject dealt with the apparent symptomatic and analgesic utility of a plant extract administered to patients suffering from rabies, cholera, tetanus, and convulsions.

The earliest specific citation on cannabis use in headache treatment in modern Western medicine seems to be from London (Clendinning 1843), shortly after Indian hemp came to England. He began experiments in 1842 (p. 191), on a ''medical man of forty-four;'' one may assume, Dr. Clendinning himself. In an initial assay before bed, he slept six hours versus his usual three to four, and suffered no indigestion, nor other bodily derangements. In a second trial (p. 192):

> Being frequently incommoded by rheumatic irritation in the head, producing frightful dreams, troublesome nightmare, megrims [archaic word for migraine], headaches, &c., he took 20 minims of the tincture of hemp, with *3fs*. spir. ammon. arom. at bed time, and with effects similar in kind to those experienced on the former occasion. He has since taken *3fs*. of the tincture, with ammonia, for a similar head affection, and with very satisfactory effect.

Clendinning described his results of treatment with 18 patients, three of whom suffered headaches. In each case, tincture of Indian hemp provided relief, even in cases of morphine withdrawal (p. 209):

> I have no hesitation in affirming that in my hand its exhibition has usually, and with remarkably few substantial exceptions, been followed by manifest effects as a soporific or hypnotic in conciliating sleep; as an anodyne in lulling irritation; as an antispasmodic in checking cough and cramp; and as a nervine stimulant in removing languor and anxiety, and raising the pulse and spirits; and that these effect have been observed in both acute and chronic affections, in young and old, male and female.
>
> In reply to the latter question, I should say that these useful, and in several cases most salutary effects have been obtained without any important drawback or deduction on account of indirect or incidental inconveniences.

Back in India that same year, Shaw (1843, p.77) commented on a patient who had been ‘‘in hospital frequently of late with cephalalgic affections induced by intemperance.’’ A tincture of *Cannabis indica* alleviated all his symptoms including an attack of cholera.

In Ireland, Donovan (1845) was effusive in his praise for the new therapeutic tool, summarized results of his colleagues, then described his own extensive trials, mainly in patients with neuropathic and musculoskeletal pain (pp. 389-391):

> The next case is that of a lady who laboured under a severe attack of browach [read ‘‘browache’’], which for several days had come on a nine o’clock in the morning, and went off about one. ‘‘The pain (she described) was not sharp, but heavily intense, with a slight throbbing.’’ She tried several remedies in vain; at length I

> directed her to take three drachms of tincture of the herb [cannabis], about one hour before the accession of the pain. The following is her own account of the effects, written at may request:- ‘‘Although feeling giddy, and indisposed to exertion, I got up an hour after taking the medicine, and went down stairs a little unsteadily. During breakfast I felt my head occasionally nodding, in that sudden way which one experiences while dozing in a chair . . . I had next to no pain over my eye, yet was constantly putting up my hand to where the pain had been; my reason as constantly telling me the pain was gone. . . . finally, after dozing a few minutes, awoke quite well about four o’clock. I have not had any return or tendency to return of the pain.’’
>
> Dr. Graves by accident saw this lady in the singular state above described. Notwithstanding her apprehensions, she in a day or two after called on me to inquire if she should take more of the medicine, with a view to securing herself against a return of the browach; but of course none was given her.
>
> The next case was that of William Dunn, a stout peasant, living near Slane, subject to a violent pain in the head, which attacked him at intervals of about a month.

This gentleman was also administered tincture of Indian hemp resin. He experienced a variety of unusual bodily sensations, some arguably due to the prescription, others likely secondary to the migraine (p. 391):

> ‘‘. . . He thought his eyes would burst out of his head; and that he would be bruised, and blown up the chimney. Every thing appeared very bright. Then he would bet a few moments’ ease when it would commence its rig again.’’ This lasted about three hours and a half, during which the pain was not felt, but then returned a little. Finally, he fell asleep; slept eight hours, and was perfectly well, except that he was ‘‘weak and dull.’’ The poor man’s alarm was so great that he sent for his priest; but this did not prevent his coming to Dublin for another dose against his next attack.

In neither case were the parties totally dissuaded from subsequent pursuit of this new remedy on account of possible side effects. Donovan described two other cases pertaining to headache. In one, it was

one of a constellation of symptoms relieved by cannabis. In the other (p. 394):

> The case of the Reverend R. H–11, is thus stated by himself: the tincture of Indian hemp was prescribed for him by Dr. Aickin: ‘‘I had so bad an attack of pain in the head (to which I have been subject for some years), that I resolved to try your dose. The pain was so acute at one side of the forehead, that it awoke me before day-light, and continued unabated until about half an hour after I took the Indian hemp, when the pain gradually died away. The only effect produced beside this was a drowsiness which lasted all the day, during the greater part of which I slept, with out at all interfering with my night-sleep, which was, perhaps, rather improved by it. I also remarked, that instead of having some remains of the pain and weight in the head, as at other times, after a severe attack the pain was gone completely, and left no uneasiness after it.’’

Donovan summarized with the following comments (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.

That same year, two cases of chorea with headache were described (Taylor 1845). One case was associated with mitral valvular disease, (likely Sydenham’s post-streptococcal chorea), while the other might have been due to that disease, trauma or functional causes. All headache symptoms were alleviated by tid dosing with tincture of *Cannabis indica*.

Christison (1851) reviewed the topic of Indian hemp at length. In addition to endorsing its benefits in treating tetanus, and augmenting labor, he reported marked benefit in treatment of neuralgic pain, which many authors of the time conceived of as including migraine.

In 1855, G. Martius published a German essay with an extensive bibliography of medicinal properties of cannabis (Martius 1855).

In 1860, an American doctor stated (Owen 1860, p. 281), ‘‘Canna-

bis Indica, when properly administered in small doses, serves to strengthen the constitution, affords an increase of mental activity, and increase of appetite, enables one to endure fatigue, alleviates pain . . .''

Over the next decades, authorities recognized cannabis as helpful for various conditions, including headache. John Russell Reynolds was eventually to become Queen Victoria's personal physician. He reported his successes with Indian hemp (Reynolds 1868). Several of his patients suffered headaches, whether due to migraine, syphilis, or spasm, but all obtained benefit in his hands. One misused the prescription Squire's extract (p. 154):

> A young lady, whose violent head-aches had been much relieved by doses of gr. 1/3, repeated a dose too soon, felt almost immediate freedom from pain, and started with some friends to a whitebait dinner at Blackwall. Unaccustomed to the steam-boat, to whitebait, and to wine, she shortly began to be extremely lively in conversation, then to ''clip her words,'' and suffer from confusion of vision; but whether in this case the result was due to previous head-ache, to the steam-boat, to whitebait, hock, or Indian hemp, I could never satisfactorily determine.

In another case, there were no such misadventures (p. 19):

> A young lady, age 19, of highly nervous temperament, but with no evidences of hysteria, has suffered from attacks of hemicrania, of great severity, for a period of 18 months. Change of air, various tonics, and alteratives have been tried without avail. The attacks are of almost daily frequency, the general health has become enfeebled, she dreads every kind of exertion and amusement for fear that it should induce the pain. Cannabis Indica was given in gr. 1/3 doses, thrice daily, and after the second day the attacks may be said to have completely ceased; for there have not occurred more than two since that time, and these in each instance arose from the sudden discontinuance of the medicine. It is now more than 14 months, and no medicine has been taken for the last eight.

Reynolds theorized (p. 160):

> This medicine appears capable of reducing over-activity of the nervous centres without interfering with any one of the functions

> of organic, or vegetal life. The bane of many opiates and sedatives is this, that the relief of the moment, the hour, or the day, is purchased at the expense of to-morrow's misery. In no one case to which I have administered Indian hemp, have I witnessed any such results.

Another contemporary citation is that of Anstie (1871, p. 190):

> From 1/4 grain to 1/2 grain of *good* extract of cannabis, repeated in two hours if it has not produced sleep, is an excellent remedy in migraine of the young. It is very important in this disease, that *the habit of long neuralgic paroxysms should not be set up;*

Richard Greene was widely recognized for advocating the prophylactic treatment of migraine with daily doses of *Cannabis indica*. His experience over two years caused him to label it (Greene 1872, p. 267) ''nearly always productive of more or less benefit to the patient.'' He presented six case studies with impressive responses. The two least responsive patients seemed to be non-compliant with the daily regimen. One, however, successfully treated acute migraine attacks with a double dose of cannabis. The other incomplete response (p. 268) occurred in an, ''inveterate tea and coffee drinker [who] could by no means be persuaded to give up the use of these wretched stimulants.'' Thus, from an early date, Greene was able to note the effect known to contemporary neurological practice as ''analgesic rebound,'' that is the tendency of certain agents, when used habitually to perpetuate rather than abrogate chronic headaches.

Overall, Greene stated of his case studies (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. . . . As a rule, it will be sufficient to prescribe one-third of a grain [of the alcohol extract] every night or every night and morning, and it may be increased to two-thirds of a grain. . . . In the above cases, however, no drug whatever was used excepting the Cannabis Indica.

In the same journal, Anstie (1872) also recommended Indian hemp for acute migraine relief in a lecture on its treatment.

Liveing (1873) was the author of a popular book on migraine, but failed to mention cannabis as a treatment modality. Despite positive review the next year (Allbutt 1874), the following criticism was offered (p. 319), ‘‘If we discover anything lacking in this book it is in this chapter [on migraine treatment], where Dr. Living, instead of being always better informed than ourselves, seems scarcely more than abreast of the general knowledge on the subject.’’ Allbutt then proceeded to fill in the gaps on treatments that deserved greater investigation and endorsement, ‘‘Nitrite of amyl is one of these, and one from which I have been led to hope something; others are ergot of rye, cannabis indica, and digitalis.’’

The noted American neurologist, Silas Weir Mitchell espoused cannabis for migraine (Mitchell 1874, p. 70):

> It is necessary at times to do something to give immediate relief to the too prolonged pain, and in these cases a combination of cannabis indica and morphia answers very well; but in a disease so wearisome and long, it is well to be more than cautious in ordering narcotics.

Also in 1874, a popular textbook, *Practical Therapeutics* stated of cannabis (Waring 1874, p. 159):

> Of a good extract, gr. 1/4 to gr. 1/2, rarely gr. j, in the form of pill, is very effective in some forms of neuralgia, particularly *Clavus hystericus* [a lancinating type of pain along the sagittal aspect of the head] and *Migraina*. Even in the severest and most intractable forms it often palliates greatly. It should be given every night, whether there be pain or not.

These continued claims support both acute and prophylactic indications of cannabis for migraine.

Edouard C. Seguin, the President of the New York Neurological Society, gave a speech espousing the preventive benefits of cannabis for migraine that was frequently cited for the next 40 years (Seguin 1878, 1877). To quote (p. 1):

> Briefly stated my thesis is THAT BY THE LONG-CONTINUED USE OF CANNABIS INDICA, MIGRAINE OR SICK-HEAD-

> ACHE MAY BE CURED, MUCH RELIEVED, OR MIGIGATED IN SEVERITY.

Seguin indicated that he had applied techniques suggested by Greene in the intervening several years, and with good success. He felt this approach unique in (p. 4), ‘‘treating the disease, of the supposed fundamental pathological state in the nervous system.’’ In comparing cannabis to alternative treatments, he stated (p. 5), ‘‘I never allow my patients to take opium or morphia themselves in this disease.’’ His approach to migraine was as follows (p. 6):

> The principle of the treatment is to keep the nervous system steadily under a slight influence of cannabis for a long period of time; . . .
>
> I give adult females one-third of a grain of the alcoholic extract of cannabis indica before each meal, increasing the dose after a few weeks to one-half grain. Males can generally begin with one-half grain, and it is well to give them three-quarters grain in two or three weeks. These doses must be taken with the greatest regularity, just as faithfully and regularly as bromides in epilepsy. Indeed, when beginning such a treatment, I usually obtain a promise from the patient that he will regularly take the pills for a period of three months.
>
> As a rule, no appreciable immediate effect is produced by the above doses, though I have known lightness of the head and slight confusion of mind to result from an initial dose of one-half grain three times a day.
>
> Under this apparently and essentially simple plan of treatment, I have known what may be termed excellent results to be obtained. . . . I feel certain that about one-half of my cases have been relieved. . . . The majority of patients relieved have obtained months of freedom from attacks while taking the remedy.

Seguin’s rare document was reviewed the next year in the *British Medical Journal*. The article contained direct quotations and comments (Anonymous 1879):

> When we consider the vast aggregate of suffering which this malady occasions, and, we fear we must add, the unsatisfactory methods of treatment hitherto proposed, at least in many of the

> severer forms of the affection, where relief is most urgently called for, we think Dr. Seguin's concluding appeal to his professional brethren ''to give the cannabis treatment of true migraine a critical trial,'' is abundantly justified.

Day (1880, p. 312) expounded on headaches in a book of the era. Diagnostic categories for its presentations were quite distinct from those recognized today: Day barely mentioned migraine. Nevertheless, ''tincture of cannabis indica'' was prescribed in association with ''the headache of cerebral hyperaemia'' and ''neuralgic headache.''

In the French literature, Michel (1880) extensively reviewed and endorsed the success of cannabis in treating neuralgic afflictions.

Lothrop (1880) reported on the benefits of cannabis in persistent hemicrania. After paying homage to Greene and Seguin, he indicated the principle of treatment (p. 200):

> What the bromides and belladonna are to Epilepsy, cannabis indica is to migraine; not that either of these medicinal agents or any combination of them will cure every case that may come under observation, but they will relieve many. . . . Success here is only obtained by persevering effort. Failure is often complained of, when on inquiry the agent has not had a fair trial;

He offered a case study (p. 201):

> A case is in hand in which hereditary influences bore a prominent part in its causation; in which the skill of the most eminent men in the metropolis had failed to afford any relief, the patient finally resigning herself to the suffering which seemed inevitably to be entailed upon her at each menstrual epoch, the only hope of relief being in the approach of the climacteric which was many years in the future. Hemicrania in its severest form, with nausea, insomnia always followed each menstruation. Life was indeed burdened with the anticipation fulfilled with never-varying certainty of two or three days in each month of suffering from which there seemed no escape, and hence no relief. The prolonged use of cannabis indica of the period of one year, has afforded such relief that the nervous system has had time to regain long-lost vigor, and the patient is in better health than for many years. Other cases might be cited confirmatory of the utility of the agent. Is

> the question asked, Has the remedy ever failed in my hands? And I can answer that it has not in any case in which its prolonged use has been made. The trouble is in the want of perseverance to the patient, not in the efficacy of the remedy.

A self-styled ‘‘Country Doctor’’ stated of *Cannabis indica* treatment (Anonymous 1883, p. 992), ‘‘Last winter I had four patients, who found a one grain dose of the extract quite specific in warding off attacks of migrainous headache. For months this had been the case.’’ Another observed (Lawrence 1883, p. 177), ‘‘undoubted value which attaches to cannabis Indica in megrim, . . .’’

Spender (1884) felt that newer was not always better (p. 1145):

> But I wish to lay special stress on the prophylactic treatment of migraine. Before the days of chloral and the bromine salts, Indian hemp was much more in fashion than it is now; and I often recommended a dose of Indian hemp and of quinine to be taken every night during the intervals of the neuralgic attacks. It is doubtful whether any combination of more modern drugs promises better successes; and we must remember that our aim is gradual alleviation rather than sudden cure.

In a review of headache (Sinkler 1886), in relation to migraine treatment, the author stated (pp. 413-414):

> Cannabis indica is probably the most potent remedy which is at our command. Its effects are most decided, and many cases of hemicrania have been cured by this means alone. It must be given for a long time, and in some instances it is necessary to give gradually-increasing doses up to the physiological effects. The drug must be of good quality, otherwise we need expect no good from it. . . . Occasionally, an impending attack can be warded off by the administration of caffeine, guarana [caffeine-containing seed extract of the Amazonian tree, *Paullinia cupana*], or cannabis indica. Cannabis indica may be given in doses of a quarter of a grain of the extract every two hours until relief is obtained.

Sydney Ringer, the inventor of the physiological intravenous fluid that bears his name, devoted a book chapter to the plant (Ringer 1886, p. 562):

> Cannabis indica is one of the most valuable remedies for megrim or sick headache. It appears to act on the nervous centre whence this headache springs. It is found serviceable both in cases associated with little or no nausea, and in cases accompanied by severe vomiting. It is useful in attack accompanied with spectra [visual disturbance in migraine]. It is most useful, in my experience, in preventing the attack, not in arresting them when once they have begun. It is sometimes useful in those severe continuous forms of headache lasting for weeks; but it is especially effective when from fatigue, anxiety, or change of life the attacks become much more frequent; then the drug gradually, and indeed sometimes quickly, lengthens the interval, and at last brings back the attacks to their old periodicity, or even extends the intervals between the seizures. It need hardly be said that cannabis will not cure these patients. I have given this drug weeks or months continuously, in dosed of one-third to one-half grain twice or thrice daily. . .
>
> Subsequent experience has fully confirmed the favourable opinion of it just expressed; no single drug have I found so useful in migraine. . . . Not only is cannabis indica useful in the interparoxysmal period to prevent headaches, but a third to half a grain of the extract given at the commencement of an attack will sometimes cut short the paroxysm.

Hobart Hare published an article that dealt with the indication of cannabis for migraine treatment in detail (Hare 1887, pp. 225-226):

> CANNABIS INDICA has been before the profession for many years as a remedy to be used in combating almost all forms of pain, yet, owing to the variations found to exist as to its activity, it has not received the confidence which I think it now deserves. At present certain improvements made in the method of obtaining the extract from the crude drug have very materially increased its reliability, so that by selecting an article made by a responsible firm we may be fairly sure of receiving a preparation in which we can place confidence. Within a few years this drug has become particularly prominent in connection with its use in migraine, particularly when used in conjunction with gelsemium [*Gelsemium sempervirens* (L.) Ait. Loganiaceae, yellow jessamine. This is now recognized as toxic, but is retained in some

modern homeopathic remedies.], although of the two remedies the hemp is by far the most active agent in subduing the pain and preventing other attacks.

. . . I have certainly seen very severe and intractable cases of migraine successfully treated by this remedy, not only in regard to the attack itself, but by acting as a prophylactic. The best use of the remedy under such circumstances is as follows, in case the drug obtained be fairly active. If the attacks are frequent then the remedy should be used constantly in small doses, in such a way that the patient is not conscious of any influence of the drug, and about 1/8 of a grain of the solid extract may be taken night and morning, or, if this produces any tendency to sleep, the whole amount may be taken at night. At the beginning and during the attack it should be freely administered, until either the pain is diminished or very marked symptoms of its physiological action assert themselves; and that this line of treatment is not one calculated to produce serious results is proved by my own experiments, and by the fact that so far no case of fatal poisoning from its ingestion has been recorded as occurring in the human being.

. . . Cases of migraine treated in this way, when the disease does not depend on any distinct organic lesion, are in a large proportion of instance either entirely cured or greatly benefited, the attacks even when they recur being considerably farther apart.

. . . The advantages in its use over that of opium consist chiefly in the absence of prostration and nausea after its ingestion, and in the partial lack of soporific power which it possesses as compared to the opiate, for in certain cases sleep is not always desirable when pain is to be removed. That cannabis indica has, however, marked powers as a soporific is not to be denied. Added to these advantages is the fact of its failure to produce serious symptoms even if very large doses be taken, although I have found the efficient dose of a pure extract of hemp to be as powerful in relieving pain as the corresponding dose of the same preparation of opium.

. . . During the time that this remarkable drug is relieving pain a very curious psychical condition sometimes manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and

> less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing.

Stephen Mackenzie stated (Mackenzie 1887, p. 97):

> Indian hemp is well known as a sedative, and enjoys a considerable reputation–not so large, however, as is deserves–in the treatment of headache. . .
>
> The headache to which I wish to draw attention is of a dull, continuous, or subcontinuous character, attended sometimes with paroxysmal exacerbations.

Mackenzie went on to describe this syndrome at length. It is this author's opinion that he was describing ''chronic daily headache,'' an evolutive subset of migraine. Mackenzie felt of Indian hemp, ''In the majority of cases, it cures the complaint.'' Once more, he employed an alcohol extract, in doses similar to those above cited (p. 97):

> Given in these doses, usually no inconvenience is experienced by those taking cannabis indica; but a few patients have complained of a feeling of slight confusion or giddiness, not in any way so annoying as the condition for which it was administered.
>
> The length of time over which treatment has to be continued varies in different cases; usually, it extends over several weeks, but rebellious cases may require a treatment of two or three months. As the malady recedes, the dose should be reduced, and it is advisable to continue the administration of the remedy for a week or two after the headache has disappeared.

Four case studies were described at length, one that of a medical student who pursued the Socratic method (p. 98), ''He has since himself administered the drug to others suffering in like manner.''

The following year, Greene (1888) opined that Indian hemp had not received its due recognition in migraine treatment, particularly in England. He revisited the topic with the benefit of 16 years of additional usage, ''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.'' He cited 3 representative cases (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.

Greene commented (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.

He chose to differ with Seguin (p. 37), ''In reviewing both, I am confident that in my hands recovery has more frequently followed cannabis indica in migraine than bromides in epilepsy.'' Greene reiterated his observation of the safety of cannabis and his dosing regimen suggestions over the long term (p. 37):

> 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.

A doctor in India wrote of *Cannabis indica* (McConnell 1888), and how proper storage was key to therapeutic response (p. 95):

> Where care is taken in this respect, the therapeutic value of the drug in certain affections of the nervous system–tetanus, neural-

> gia, migraine &c.–and its powerful effect in controlling uterine haemorrhage (menorrhagia, &c.) has been repeatedly recorded by competent observers, and its employment for the relief of such affections is well understood and more or less extensively resorted to.

William Gowers was one of the founding fathers of modern neurology. For treatment of migraine, he wrote (Gowers 1888, p. 1188), ''Most relief is afforded to the pain by a good dose (thirty or forty grains) of bromide, and its effect is increased by the addition of five or ten minims of tincture of Indian hemp.'' For treatment of ''headache,'' he stated:

> Sedatives are very uncertain in their influence. Opium and morphia are seldom useful, and often do more harm than good, in consequence of the indirect effect of the constipation that is produced. Gelsemium and Indian hemp frequently lessen the pain, the former chiefly in neuralgic forms about the front of the head, the latter not only in neuralgic, but in anaemic, and also other ill-defined forms of headache.

Little (1888) recommended for ''migrainous headache'' fresh air, exercise, healthy diet, bathing (p. 56):

> And among drugs the combination which has appeared to me to do most good is a pill containing one-twelfth of a grain of arseniate of sodium, one-sixth of a grain of extract of indian hemp, one-third of a grain of extract of bella-donna, and two grains of valerianate of zinc, taken after breakfast and dinner.

Farlow (1889) discussed use of rectal preparations of cannabis (Farlow 1889). Although many of the author's concepts concerning the pathophysiology of gynecological problems seem quite dated a century later, he stated (p. 508), ''Cannabis has few equals in its power over nervous headaches such as women with pelvic troubles are subject to.''

In India, Watt attributed the following quotation on cannabis to a Dr. E. G. Russell in Calcutta (Watt 1889, p. 124), ''Valuable as a remedy for sick headache, and especially in preventing such attacks.''

In the USA, Wharton Sinkler (Sinkler 1890) once again reviewed

migraine for a medical newspaper. He observed an unusual feature of the disorder, its tendency to afflict some sufferers weekly on the same day (p. 57), ‘‘Cannabis indica was given in increasing doses and the patient was greatly relieved. The periodicity of the attacks was broken up and the intervals became from eight to ten weeks.’’ In another case, he documented (p. 57):

> I gave him cannabis indica and regulated his diet and the attacks were very much relieved in frequency and severity. The Sunday attacks recurred for about nine months. . . . He now very rarely has attacks and they are not so severe as formerly.

Sinkler summarized (p. 59):

> Cannabis indica, which has been given in migraine for many years, still holds a prominent place among the medicinal agents used in its treatment. For myself, I may say that I consider it of more value in the majority of cases of migrainous headache than in any other headache. It must be given for some length of time and the dose should be increased until slight toxic symptoms are felt.

A few weeks later, in the same journal, Aulde (1890) affirmed the prophylactic benefit of extract of Indian hemp in frequent migraine, but reminded readers of its utility and efficacy in acute settings (p. 118), ‘‘For the emergency, to relieve the pain and place the patient in a favorable condition, I cannot speak too highly of an assayed preparation of cannabis indica . . .’’ His patient had suffered inexorably from a three week attack.

Tirard (1890) commented on ‘‘toxic effects’’ of cannabis (p. 723). His case pertained to a 48 year-old man prescribed the tincture for ‘‘migraine and lassitude.’’ The same day, Dr. Tirard was summoned to see the patient for anxiety symptoms, after ingesting some 2 1/2 times the prescribed dose. Nevertheless, the patient was easily reassured, and it was reported, ‘‘He has since taken the ordinary dose on several occasions, not only without any toxic effects, but with marked relief of migraine and of the ordinary symptoms of business worry.’’

Benefits of cannabis were also reported in France (Lailler 1890), including its use in migraine.

The *Lancet* published an article on *Cannabis indica* by J. Russell

Reynolds 22 years after his initial report (Reynolds 1890), ‘‘Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess.’’ In relation to its use in headache, Reynolds said, ‘‘Migraine: Very many victims of this malady have for years kept their suffering in abeyance by taking hemp at the moment of threatening, or onset of the attack.’’

In Germany in 1890, a commercial product was marketed called *Migränin* containing 1% cannabis extract and unspecified active organic substances (Fankhauser 1996, p. 163).

In the following year, the *British Medical Journal* published a short report, ‘‘On the Therapeutic Value of Indian Hemp’’ (Suckling 1891), which stated (p. 12):

> In migraine the drug is also of great value; a pill containing 1/4 gr. of the extract with or without a 1/4 gr. of phosphide of zinc will often immediately check an attack, and if the pill will be given twice a day continuously the severity and frequency of the attacks are often much diminished. I have met with patients who have been incapacitated for work from the frequency of the attacks, and who have been enabled by the use of Indian hemp to resume their employment.

In *A Text-Book of Materia Medica and Therapeutics* (Cowperthwaite 1892), once more *Cannabis indica* was indicated for migraine treatment.

The same year, it was written of cannabis (Mattison 1891) (p. 266), ‘‘. . . its most important use is in that opprobrium of the healing art-migraine.’’ Mattison paraphrased the work of many authors on the subject as above presented, but then drew from his own experience (pp. 270-271):

> Failure with hemp is largely due to inferior preparations, and this has had much to do with its limited use. It should never be called inert till full trial with an active product proved it. . . . In headache, periodical or long continued, one half to two grains solid extract may be given each hour or two till the attack is arrested, and then continued in a similar dose, morning and night, for weeks or months. It is important not to quit the drug during a respite from pain.
>
> I close this paper by asking attention to the need of giving

> hemp in migraine. Were its use limited to this alone, its worth, direct and indirect, would be greater than most imagine. Bare in mind the bane of American women is headache. Recollect that hemp eases pain without disturbing stomach and secretions so often as opium, and that competent men think it not only calmative, but curative. Above all remember the close genetic relation of migraine relieved by opium, to a disease that spares neither sex, state nor condition.
>
> . . . Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence.
>
> My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic.

Mackenzie (1894) reviewed an additional seven years of cannabis in headache treatment in a French journal (pp. 399-400):

> It exerts a favorable action in all forms of headache, whether of a purely functional nature or due to an organic affection. Thus, I have often succeeded in completely calming by Indian hemp the violent headaches occasioned by brain tumors. In these cases, sometimes *Cannabis indica* acts altogether better than morphine administered by subcutaneous injection, sometimes it is inferior to it as an analgesic. It may interrupt at its debut, or when it has persisted a certain time; its prolonged usage is capable of diminishing the frequency and intensity of the migraine attacks.
>
> . . . I have convinced myself that *Cannabis indica* calms well the cephalic pains of chronic uremia.
>
> . . . In some twenty years that I have employed Indian hemp, I have registered very few failures in the treatment of the particular form of cephalalgia that I have come to describe [chronic daily headache]: I may likewise say that the success of this treatment has been striking precisely in the most inveterate and seemingly particularly rebellious cases.
>
> . . . The feeble symptoms of intoxication sometimes provoked by Indian hemp need not cause us to renounce the use of this precious medicament. In effect, a long experience has demonstrated to me, I repeat, that these accidents are absolutely excep-

> tional. They result either from an idiosyncrasy, or variability in the grade of the drug in its active principle. [translation EBR]

Cannabis in its various forms remained the focus of intense debate. Because of concerns of its dangers, the British and colonial authorities in India organized the Indian Hemp Drugs Commission (1894) to examine all aspects of the issue. Its members, after exhaustive investigation and testimony exceeding 3000 pages, found no reason medically or economically to outlaw the plant or its use. Two pertinent excerpts follow (Kaplan 1969, p. 176, p. 483):

> Witnesses refer to the use of the drugs [*bhang*, *ganja*, *charas*] in the treatment of ''brain fever,'' cramps convulsions of children, headache, hysteria, neuralgia, sciatica, and tetanus.
>
> . . . *Tinctura Cannabis Indicae*
> . . . Sedative, anodyne, and hypnotic, has been used with success in megrim and delirium, also in menorrhagia and dysmenorrhoea.

Brookes (1896) continued to tout cannabis in migraine. His patient was a young woman who suffered severe attacks every one two weeks. He place her on a prophylactic daily regimen as previously recorded (p. 338):

> This treatment has been carried out with the strictest regularity nearly two months, during which period the patient has been absolutely free from a recurrence of pain. . .
>
> I may add I observed no dizziness, or any constitutional derangement, either at the beginning of treatment or during its course.

That year, a brief case report documented a self-limited case of cannabis overdose in a 12 year-old (Attlee 1896), easily treated, and in which his prolonged headache was alleviated.

Fox (1897) also touted cannabis for headache (p. 307):

> I understand by migraine a periodical nerve storm. . . . For the relief of the paroxysms antipyrin and phenacetin have often been in my experience successful. . . . But I am accustomed to rely

> much upon cannabis indica, having had a pretty large experience of this remedy. The extract, often combined with cascara sagrada [*Rhamnus purshianus* DC Rhamnaceae, a laxative], has controlled many, if not most, cases of migraine. . . . I prefer to use the fresh extract, and have in a good many instances given it to the point of intoxication. This, however, does no permanent harm.

An American 1898 drug handbook stated the following quaint prose under ''Actions and uses'' for cannabis (Lilly 1898, p. 32):

> Not poisonous according to best authorities, though formerly so regarded. Antispasmodic, analgesic, anesthetic, narcotic, aphrodisiac. Specially recommended in spasmodic and painful affections; for preventing rather than arresting migraine; almost a specific in that form of insanity peculiar to women, caused by mental worry or moral shock.

That year, a case report documented symptoms of cannabis overdose in a young woman whose headache was relieved, but who had nonetheless administered a second dose after 4 hours (Roche 1898).

At the turn of the last century, Shoemaker (1899) reported two supportive case studies from Philadelphia. One pertained to a 26 year-old male whose attacks of hemicrania were incapacitating, lasting 48 hours (p. 485):

> Cannabis indica brought him more relief than he had obtained from any other substance. Convinced by experience, he had recourse to this remedy as soon as he felt the slightest promonition of and attack. He would sometimes succeed in aborting a paroxysm and upon other occasions the severity of an attack would be much mitigated.

In the other case, the concomitant occurrence of migraine and dysmenorrhea was successfully treated with cannabis (p. 484), ''In migraine, hemicrania, or sick headache the use of this remedy is often productive of excellent results.''

In *The New American Family Physician* by (Lyman, Jones and Belfield 1899), the authors recommended for headache (p. 340):

> Where there is no evident disturbance of digestion to account for the difficulty, and where the individual is ''nervous,'' the following prescription may be given:

> Extract of guarana, - - - - - - - - - 40 grains
> Extract of cannabis indica, - - - 30 grains
> Citrate of caffeine, - - - - - - - - - 60 grains
>
> Mix, and make 40 pills; take one pill, and repeat the dose after two hours if not relieved.

Contemporaneously, a British pharmacologist extensively studied cannabis (Dixon 1899), recognizing its value as an appetite stimulant, supporting its current indications in the cachexia of cancer chemotherapy and HIV-positive patients. Dixon also lauded smoked cannabis (p. 1356):

> In cases where an immediate effect is desired the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, and exhaustion a few inhalations produce an almost immediate effect, the sense of depression, headache, feeling of fatigue disappear and the subject is enabled to continue his work, feeling refreshed and soothed. I am further convinced that its results are marvellous in giving staying power and altering the feelings of muscular fatigue which follow hard physical labour. . .
>
> Hemp taken as an inhalation may be place in the same category as coffee, tea, and kola [*Cola acuminata* or *C. nitida* Sterculiaceae, tropical African trees whose nuts contain caffeine]. It is not dangerous and its effects are never alarming, and I have come to regard it in this form as a useful and refreshing stimulant and food accessory, and one whose use does not lead to a habit which grows upon its votary. . .
>
> Like any stimulant or sedative narcotic, hemp may be abused as when taken to produce an intoxicant or deliriant effect, but this abuse is rare and there is reason to believe has been grossly exaggerated. . .
>
> I believe it to be an exceedingly useful therapeutic agent, one not likely to lead to abuse, and producing in proper dosage no untoward after-effects.

The latter comments are pertinent in terms of later allegations of an ‘‘amotivational syndrome’’ attached to people who engage in daily use of cannabis. Apparently, physicians of the age noted no such effect employing hemp preparations in their patients.

In a note added in proof, the editor stated (p. 1357), ‘‘Dr. R. B. Wild remarked that cannabis indica–was also of value in certain cases of functional headache.’’

Lewis (1900) reported on *Cannabis indica* (p. 250), ‘‘In migraine, hemicrania, neuralgias, and headache due to eye-strain, it may be used with marked success.’’

In a contemporary text (Wood and Wood 1900), the authors stated (p. 166), ‘‘In full doses in *neuralgic* pains, it certainly often gives relief. . . . As first suggested by Seguin, hemp extract, administered for months continuously in such dosed as will keep just within the limit of distinct physiological effects, is often effective in *migraine*.’’

Marshall (1905) opined that other medicines had supplanted cannabis for some indications but (p. 451), ‘‘It appears, however, to be useful in headache of a dull continuous character. The extract in the form of pills is usually administered.’’

In 1906, a popular treatise continued to discuss smoking as a mode of medical application (Allbutt and Dixon 1906) (p. 965), ‘‘the drug, generally as ganja, may be smoked, when the symptoms come on almost immediately but do not last so long.’’

It was also noted of Indian hemp (Allman 1911) (p. 765), ‘‘In full doses it certainly gives relief in acute neuralgic pains, . . .’’

As late as 1915, Sir William Osler, the acknowledged father of modern medicine stated of migraine treatment (Osler and McCrae 1915) (p. 1089), ‘‘Cannabis indica is probably the most satisfactory remedy. Seguin recommends a prolonged course of the drug.’’ This statement provided continued support of its use for both acute and prophylactic treatment.

Ratnam (1916) repeated Dixon’s quotation in reference to the therapeutic effects of smoked cannabis for headache treatment.

In 1918, *The Dispensatory of the United States of America* stated (Remington et al. 1918, p. 280), ‘‘For its analgesic action it is used especially in pains of neuralgic origin, such as *migraine*, but is occasionally of service in other types.’’ This language was retained in the 21st edition in 1926, and the 1937 22nd edition continued to refer to an indication for cannabis in ‘‘migrainic headaches.’’

By this time in the 20th century, cannabis was suffering a political downturn. In 1914, it was dropped from the pharmacopoeia of Ceylon (Sri Lanka), over the vociferous objections of its adherents, such as Ratnam (1920) and others. His points of debate included passionate

defenses of its medical benefits, and poignant political arguments based on multiple facts and figures comparing its benignity to the dangers of other ''recreational'' drugs. Ultimately, Ratnam addressed a remaining clinical need for cannabis (p. 42):

> ''In some cases where there is continued pain in the head lasting for a length of time, Cannabis Indica seems to help and this may be given either in the form of extract or tincture. There is no danger in it. . . . The long continued use of this drug will sometimes relieve these headaches when other things seems to fail.'' The above authoritative statement was made by Sir T. Lander Brunton, M.D., D.Sc., L.L.D., F.R.S., Physician to St. Bartholomew's Hospital and Lecturer on Pharmacology before the British Medical Association without a dissentient voice.

In the German literature, cannabis use by extract or smoking was held to be an ''outstanding agent'' (Dinand 1921, p. 71) (translation Schloesser).

Hare (1922) continued to advocated use of cannabis noting (p. 181), ''For the relief of *pain*, particularly that depending on nerve disturbance, hemp is very valuable.'' He went on to state, ''In true *migraine* with hemianopsia this treatment is often most effectual in aborting the attack. The prevention of further attack is to be attained by the use of smaller amounts of the cannabis during the intervals . . .'' An examination of alternative medications listed in that edition is illuminating: ammonium benzoate, amyl nitrate, bromide of potassium, croton chloral, gelsemium, phenacetin, salicylic acid, and sodium phosphate. Most have passed into obscurity, or are considered ineffective, or even toxic in modern practice.

Dixon (1923) revisited the issue of smoked cannabis, and decried the poor quality of drug available in England. His independent bioassays revealed effects of smoking imported *ganja* and *charas* lasting only one half-hour. Doubtless, many patients and clinicians were lead to believe in the herb's inefficacy by such experiences.

In the years that followed, cannabis came to be perceived as a drug of abuse, smoked by certain minorities in the USA as ''marijuana'' or ''marihuana.'' In an article provocatively entitled ''The Weed of Insanity'' the author nevertheless conceded (Bragman 1925, p. 416), ''It has some value in the relief of migraine.''

The following year, Stevens (1926) remained a convinced user of cannabis for migraine (p. 1115):

> Cannabis indica is sometimes very useful, when a reliable preparation can be secured. Two drops of the fluid extract may be given every half hour until the pain abates or until slight dizziness or mental confusion appears. Even larger doses may be used, if necessary. Morphin should never be employed, except as a last resort.

In a definitive tome of the era (Solis-Cohen and Githens 1928) it was stated (pp. 1704-1705):

> Cannabis is of great service in certain cases of migraine not dependent upon, nor aggravated by, eyestrain. It may be given in dose of 1/4 to 1/2 grain (0.015 to 0.03 Gm.) of the extract, repeated in two hours if sleep has not been produced. According to Mattison, the persevering use of the remedy twice a day for weeks or months, will in many cases, especially in the young, blot out this neurotic taint.

At this time, Walther Straub, Professor of Pharmacology of the University of Munich retained interest in the titration available by the smoking route (Straub 1931, p. 16), ‘‘More time is required for the enjoyment of hashish than for opium, but less than for alcohol. It requires still better dosing, and here the empirical instinct found that the safest dose can be attained by smoking the substance.’’

In a comprehensive review article on headache, Henry Alsop Riley stated (Riley 1932, p. 515), ‘‘Cannabis indica has been much used in the treatment of migraine.’’

Despite its contemporary political downturn in popularity, Fantus (1933) reviewed therapeutic techniques, recommending (p. 879), ‘‘fluid-extract of cannabis,’’ ‘‘One teaspoonful in water every two hours until relieved. (For migraine.)’’

Bastedo (1937) decried the variability of quality of cannabis in his textbook, but noted (p. 460), ‘‘A good preparation of it may allay nervous excitability, as after sexual or alcoholic excesses, may lessen the pain of neuralgia or migraine, and may promote sleep (in the presence of pain).’’

In 1937, marijuana was rendered essentially illegal in the USA

(Baum 1996; Bonnie and Whitebread 1970). Cannabis had become a phytochemical scapegoat for a perceived social problem, and research on its medical uses was substantially curtailed. The American Medical Association vigorously opposed this development (Cary 1937).

Despite this political event, in 1938 Robert Walton published a comprehensive review of cannabis with botanical, historical, chemical and political discussions (Walton 1938). After addressing the issues of its purported abuse, and consequent legislation, he went on to discuss its utility in migraine, citing many of the above sources. He referred to twelve major authorities on its efficacy, and one from a detractor (Beckman 1938) (p. 595), ''The U.S.P. extract of cannabis (better known as Cannabis indica) formerly enjoyed the reputation of being almost specific when used in a pill containing 1/6 to 1/4 grain (0.01-0.015 Gm.), not to be too often repeated, but has latterly fallen into a probably deserved disrepute.''

In 1941, cannabis preparations were dropped from the *United States Pharmacopoeia* (*USP*) and *National Formulary* (*NF*), but the following year, the editor of the *Journal of the American Medical Association* still advocated oral preparations of cannabis in treatment of menstrual (catamenial) migraine (Fishbein 1942) (p. 326):

> In this instance the patient may be given either sodium bromide or fluidextract of cannabis three days before the onset of the menstrual period, continued until three days after the menstrual period.
>
> . . . The dose of the fluidextract of cannabis is five drops three times daily, increased daily until eleven drops, three times daily, are taken. Then the dosage is reduced by one drop daily until five drops are taken three times daily and so on.

As a seeming afterthought, he added, ''Ergotamine tartrate may also be given.'' The latter medicine remains in the migraine armamentarium, some 60 years later, but he considered it inferior to cannabis.

Thus, as demonstrated, cannabis was touted in the mainstream Western medical literature for a full century as a, or the, primary treatment for migraine.

Modern Ethnobotanical Data

Despite political issues in the USA, medical use of cannabis continued elsewhere. In 1947, an ethereal extract of cannabis was employed

for migraine treatment in Argentina (Kabelik, Krejei, and Santavy 1960). Cannabis was recommended as a homeopathic remedy for migraine in 1956 in East Germany (Auster and Schafer 1955).

In Tashkent in the 1930's, cannabis or *nasha* was employed medicinally, despite Soviet prohibition (Benet 1975) (pp. 46-47), ''A mixture of lamb's fat with *nasha* is recommended for brides to use on their wedding night to reduce the pain of defloration. The same mixture works well for headache when rubbed into the skin; it may also be eaten spread on bread.''

Smith (1911) documented its utilization in China, where cannabis remained a useful item in the pharmacopoeia (pp. 90-91), ''Every part of the hemp plant is used in medicine; the dried flowers, the achenia, the seeds, the oil, the leaves, the stalk, the root, and the juice.''

Burkhill (1935) noted continuing usage of *ganja* flowering tops as one ingredient in a pill for headaches in Malaya. Perry and Metzger (1980) referred to ongoing use of cannabis in China to treat migraine, much the same as noted in Thailand (Dhavadee 1987). In other areas of Southeast Asia its use remains popular (Martin 1975, p. 70):

> Everywhere it is considered to be of analgesic value, comparable to the opium derivatives. Moreover, it can be added to any relaxant to reinforce its action. Cooked leaves, which have been dried in the sun, are used in quantities of several grams per bowl of water. This decoction helps especially to combat migraines and stiffness; taken before sleep and before meals, it relaxes the nerves.

A very recent study documents the ethnobotanical uses of cannabis by the Hmong minority in the China-Vietnam border region (Gu and Clarke 1998). The authors described its medical usage (p. 6):

> Some herbal remedies are used by the Hmong, and cannabis seeds, leaves and stalks are used for various indications. Raw seeds are thoroughly chewed and used as a poultice in the forehead for headache relief . . .
>
> Some older Hmong men may rarely smoke cannabis to ''relieve discomfort,'' but they are not daily smokers.

Analgesic effects of cannabis have remained noteworthy in the folk medicine of North Africa (Boulos 1983). As late as 1957, despite

governmental regulation in that country, cannabis drugs retained a role in the indigenous medicine of India (Chopra and Chopra 1957, p. 12), ‘‘The concentrated resin exudate–is considered valuable in preventing and curing sick-headaches, neuralgias and migraine . . .’’

Nadkarni (1976) observed (p. 203), ‘‘The concentrated *resin* exudates–is valuable in preventing and curing sick-headaches, neuralgias, migraine . . .’’ In a subsequent treatise entitled *Indigenous Drugs of India* (Chopra 1982) the authors stated (p. 91), ‘‘Cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness. There is little definite knowledge of the therapeutic effects produced, but in some persons it appears to produce euphoria and will often relieve migraine headaches.’’

In discussing the native use of cannabis and opium products by village doctors in India, who provided 80% of the population with their medical care, the author of a report to the United Nations felt a legitimate role for them was still present (Dwarakanath 1965) (p. 19):

> These drugs should be allowed to be used by Ayurvedic and Unani [Arabian tradition] physicians until such time as the benefits of modern medicine are extended to rural areas. Banning their use by the large mass of Ayurvedic and Unani physicians for therapeutic purposes may create a vacuum which may not be easily filled for a long time to come.

Another book about medicinal plants of India stated (Dastur 1962) (p. 67):

> Charas is the resinous exudation that collects on the leaves and flowering tops of plants [equivalent to Arabic *hashish*]; it is the active principle of hemp; it is a valuable narcotic, especially in cases where opium cannot be administered; it is of great value in malarial and periodical headaches, migraine–Charas is usually given in one-sixth to one-fourth grain doses.

In a more recent review of Ayurvedic medicine (Kapoor 1990), the author echoed the above indications but recommended doses of (p. 97), ‘‘*ganja* [flowering tops of female cannabis plants]–1-2 gr; *charas*–1/2 gr.’’

Similarly, in Nepal, cannabis remains useful for headache treatment. According to Drs. Purushottam Shrestha and Narendra Nath

Tiwari (personal communication, July 2000), the *Bhavparaksh Nighantu* (Misra 1988) describes a technique by which flowering tops of cannabis are powdered, hung in muslin above a pot of boiling cow's milk, and then fried in *ghee* (clarified butter). Headache suffers, especially women, take 60-125 mg a day of the treated material.

Dr. Farid Alakbarov reports cannabis use in migraine in Azerbaijan (Alakbarov 2000) (personal communication, June 2000).

Even today in Iran, the indication for cannabis for headache is retained. Zargari (1990, p. 434-438, translation courtesy of H. Akhani and M. O'Yarhossein) notes *Cannabis indica* products ''can be used to relieve nervous pains and rheumatism . . .'' An alcoholic extract with two other ingredients is also compounded as a ''prescription for recovering [from] migraine pains . . .''

Examples are also to be found in the New World. In Colombia the analgesic effects of a cannabis tincture were observed (Partridge 1975, p. 161), ''the knowledge that cannabis can be used for treatment of pain is widespread . . .'' Rubin et al. documented extensive medical usage of cannabis for a variety of conditions in Jamaica (Rubin 1976; Rubin and Comitas 1972), including headache. Extensive interviews revealed that *ganja* tea was commonly acknowledged to treat headache. Interestingly, among 43 subjects interviewed about their first exposure to smoked cannabis, headache was the only side effect among many suggested symptoms that failed to be claimed. Only one subject noted headache on any subsequent exposure (Lambros Comitas, personal communication, July 2000).

Ultimately, a modern study of chronic use of cannabis has been undertaken in Costa Rica (Carter 1980), detailing medicinal use for asthma, but also (p. 24), ''The simple smoking of marijuana is claimed by users to have a number of additional medical benefits. It is said to cure headaches, hangovers, loss of appetite, impotence, depression and general malaise.'' The adoption of cannabis for headache in cultures remote from its Eurasian origins is particularly noteworthy. Separate citations of identical medicinal claims for a plant for the same indication is widely acknowledged in ethnobotany as strongly supporting clinical efficacy (Russo 1992).

Recent Research on Cannabis and Cannabinoids

In the next two decades, marijuana moved to center stage of Western consciousness, not as a medicinal agent, but rather as a perceived

drug of abuse. Research resumed only slowly, with occasional anecdotal reports by patients of cannabis' benefits on their illnesses.

A popular treatise on marijuana noted medicinal effects (Margolis and Clorfene 1969, p. 26), ''You'll also discover that grass is an analgesic, and will reduce pain considerably.''

The eminent psychopharmacologist, Solomon Snyder, wrote a popular, but scientifically noteworthy review of cannabis during this era (Snyder 1971, p. 10):

> Migraine headaches can be so incapacitating that, besides easing the acute pain, it is important to attempt to prevent future attacks or at least reduce their frequency and severity. In modern medicine these two tasks are the province of two different types of drugs. Ergot derivatives, such as ergotamine, alleviate acute migraine headaches, while methysergide (Sansert)–which, interestingly, is a close relative of LSD–is used to ward off future headaches. There are indications that cannabis may fulfill both roles.

Snyder examined cannabis' pros and cons as an analgesic (p. 14):

> In one important way, opiates are better than cannabis. They are stronger pain-killers. For the excruciating colicky pain produced by a kidney stone or the crushing chest pain of an acute heart attack, morphine is a blessing. For these conditions, cannabis is much too weak. But its relatively weak pain-relieving action could not possibly account for the neglect of cannabis in modern medicine. For there are many conditions, such as migraine headaches or menstrual cramps, where something as mild as aspirin gives insufficient relief and opiates are too powerful, not to mention their potential for addiction. Cannabis might conceivably fulfill a useful role in such conditions.

President Nixon convened a National Commission on Marihauna and Drug Abuse that recommended decriminalization of cannabis use, and further medical research (United States Commission on Marihuana and Drug Abuse 1972, p. 222):

Therapeutic Uses

> RECOMMENDATION: INCREASED SUPPORT OF STUDIES WHICH EVALUATE THE EFFICACY OF MARIHUANA IN

> THE TREATMENT OF PHYSICAL IMPAIRMENTS AND DISEASE IS RECOMMENDED
>
> Historical references have been noted throughout the literature referring to the use of cannabis products as therapeutically useful agents. Of particular significance for current research with controlled quality, quantity and therapeutic settings, would be investigations into the treatment of glaucoma, migraine, alcoholism and terminal cancer.

The findings of this commission were largely ignored by the administration.

In 1974 began a series of studies that formally examined effects of cannabis on pain. Noyes and Baram (1974) described case studies of five patients who voluntarily employed it to treat their painful conditions. Three of these had chronic headaches. Case 2 pertained to a graduate student who found smoked cannabis to be almost as effective at treating acute migraine as an ergotamine/phenobarbital preparation. The cannabis also seemed to reduce attack frequency (unlike his usual combination that can produce analgesic rebound).

In Case 3, a housewife had successfully treated headache with cannabis smoking for a year with ‘‘immediate and lasting relief’’ she considered superior to aspirin (p. 533). Case 5 pertained to another graduate student, who over two years found that smoked cannabis relieved headaches about 70% of the time (comparable to the best standard pharmaceuticals at present).

A similarly composed research group compared the analgesic effect of THC was compared to codeine (Noyes et al. 1975). In short, 10 mg of oral THC reduced subjective pain burdens by similar decrements to 60 mg of codeine, as did 20 mg of THC vs. 120 mg of codeine. This supports the observations of Hobart Hare almost one century earlier. Subjects in this experiment tolerated 10 mg of THC well, but 20 mg produced sedation and psychic disturbances in some relatively elderly cannabis-naïve subjects.

Another government-sponsored commission evaluated *Marijuana and Health* (Institute of Medicine 1982), their findings echoing those of prior studies (p. 150):

> Cannabis and its derivatives have shown promise in the treatment of a variety of disorders. The evidence is most impressive in

> glaucoma, . . . in asthma, . . . and in the nausea and vomiting of cancer chemotherapy. . . . Smaller trials have suggested cannabis might also be useful in seizures, spasticity, and other nervous system disorders.
>
> . . . The committee believes that the therapeutic potential of cannabis and its derivatives and synthetic analogues warrants further research. . .

Greater governmental cooperation in the development of research protocols in humans was suggested, but the US government printed only 300 copies of the report (Mathre 1997).

In ''Health Aspects of Cannabis,'' Hollister (1986) addressed possible medical indications, but his direct experience with cannabis use in migraine was not broad (p. 16):

> *Migraine:* This indication has not been studied systematically in recent years, although it has a long history. In one patient I treated, the mental effects sought socially caused the patient to abandon treatment. Innumerable successful treatments for migraine have been reported at one time or another.

Mechoulam (1986) published *Cannabinoids as Therapeutic Agents*, wherein the author stated and then inquired (p. 16):

> For the medical scientist use of cannabis as a therapeutic agent in the past may serve as a clue to future drug development. Many of the therapeutic properties of cannabis have been verified with pure natural or synthetic cannabinoids. In several fields, however, no modern work exists. The most blatant examples are the antihelmintic, anti-migraine, and the oxytocic effects. Are we missing something?

The following year, another article dealt with the headache issue more directly (el-Mallakh 1987). Entitled ''Marijuana and Migraine,'' three cases were discussed in which abrupt cessation of frequent, prolonged, daily marijuana smoking was followed by recurrent migraine attacks. One patient noted subsequent remission of headaches with a return to episodic cannabis use, while the two others employed ''conventional drugs'' successfully. THC's peripheral vasoconstrictive actions in rats, or its action to minimize serotonin release from the

platelets of human migraineurs (Volfe, Dvilansky, and Nathan 1985), were felt to be possible explanations of its therapeutic effects.

The book *Marihuana: The forbidden medicine* (Grinspoon and Bakalar 1993) included an entire section on migraine. One clinical vignette documented the medical odyssey of a migraineur through failures with standard pharmaceuticals. Over a period of 18 years, she found that a little smoked cannabis and rest for 30 minutes allowed her to return to work. Both of her daughters subsequently treated their attacks in similar fashion, but her mother resisted due to its illegality.

The *American Journal of Public Health* issued a particularly strong plea for access to therapeutic cannabis (Anonymous 1996, p. 441), acknowledging its role in ''decreasing the suffering from chronic pain.''

Recently, the debate on the subject of ''medical marijuana'' has extended to the World Wide Web. One posted document (Mikuriya 1997) is ''Chronic Migraine Headache: five cases successfully treated with Marinol and/or illicit cannabis.'' Two patients were prescribed dronabinol (synthetic THC) for their headaches with improvement, but some degree of side effects, or difficulties with overwhelming cost. Both switched to marijuana, with an improved clinical response and decreasing frequency and severity of attacks. Another family of three women smoked marijuana acutely with good success in aborting headache, often in the prodromal phase.

A second Web document entitled ''Cannabis Medicinal Uses at a 'Buyers' Club' '' (Mikuriya 1995) examined the indications that prompted patients to seek out this treatment. Of the 57 people interviewed, eleven identified migraine as the culprit condition that prompted their decision to self-medicate with cannabis.

In another Internet document, the author (Terwur 1997) described regular successful treatment of migraine attacks and associated symptoms with cannabis resin in a fashion that did not produce inebriation.

Petro (1997) offered a published account on cannabis use in migraine in which a 34-year-old woman found superior relief and prophylaxis with cannabis as compared to beta-blockers, opiates or ergots. Frequency dropped from 3-4 attacks to one per month.

A British group recently reviewed their clinical experience employing the synthetic cannabinoid, nabilone, as an analgesic, including neuropathic pain (Notcutt, Price, and Chapman 1997). Nabilone is employed orally, but causes drowsiness and dysphoria. Several pa-

tients cited better pain relief with smoked cannabis, with fewer side effects. Nabilone was also estimated to cost 10 times as much as street cannabis. The authors stated (Notcutt, Price, and Chapman 1997, p. 554), ''Cannabis can be cloned and grown to yield a cocktail of cannabinoids of known and repeatable concentrations. The illogicalities are evident.'' They closed by observing (p. 555):

> we must not lose sight of the fact that there are a large number of patients with chronic pain who might benefit from this group of drugs [cannabinoids]. Currently their options for analgesia are limited or non-existent. This is particularly poignant when one considers the history and safety of cannabis.

Hollister (2000) recently reviewed indications for cannabis. On the one hand, he states (p. 5), ''for exploratory purposes, any patient with pain unrelieved by conventional analgesics should have access to smoked marijuana if they so desire.'' A few paragraphs later, however, he decries, ''New drugs for migraine are aimed at pathogenetic mechanisms rather than symptomatic treatment. Virtually no literature exists that support this use of marijuana.''

Despite this view, the *PDR for Herbal Medicines* (Medical Economics Company 2000) lists *Cannabis sativa* under its Indications Index for migraine headache (p. I-103), and states (p. 501), ''Current literature on phytotherapeutic drugs cite as indications for Indian hemp: . . . migraine; . . .''

ALTERNATIVE DELIVERY SYSTEMS

Alternative smoke delivery systems have been investigated for cannabis (Gieringer 1996; Gieringer 1996). Reportedly, vaporization of marijuana makes it possible to deliver even high doses of THC to the lungs of a prospective patient far below the flash point of the cannabis leaf, thus reducing smoke, tar and other possible carcinogens. However, the standard marijuana joint remained about as effective as any examined smoking device, including those employing water filtration, in providing a favorable ratio of THC to tar and other undesirable by-products. A standardized smoking procedure for use of cannabis in medical research has been described (Foltin, Fischman, and Byrne 1988).

Suppository preparations of cannabis have been used to advantage in the past, and may be an acceptable alternative route of administration for the migraineur, although the advantage of dose titration would be lost. GW Pharmaceuticals in the UK is researching nebulized and sublingual preparation with whole cannabis extracts.

THE DISCOVERY OF ENDOGENOUS CANNABINOIDS AND BIOCHEMICAL MECHANISMS OF CANNABINOIDS

Recently, scientists have provided elucidation of the mechanisms of action of cannabis and THC with the discovery of an endogenous cannabinoid brain receptor, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda*, or ''bliss'' (Barinaga 1992; Devane et al. 1992; Marx 1990; Matsuda et al. 1990). Anandamide has an inhibitory effect on cyclic AMP mediated through G-protein coupling in target cells, which, though widespread in the brain, cluster in nociceptive areas (Herkenham 1993). Preliminary tests of its pharmacological action and behavioral activity support similarity to THC (Fride and Mechoulam 1993). Pertwee (1997) has examined the pharmacology of cannabinoid receptors in detail.

Additional research has elucidated mechanisms of therapeutic action of the cannabinoids pertinent to migraine, which are examined system by system.

CANNABINOIDS AND SEROTONERGIC SYSTEMS

Serotonergic mechanisms have long been implicated in migraine pathogenesis and treatment. This mechanism has been specifically targeted in the development of the triptan drugs (Humphrey, Feniuk, and Perren 1990). THC reduces serotonin release from the platelets of human migraineurs (Volfe, Dvilansky, and Nathan 1985). Cannabis has also been reviewed in the French literature (Spadone 1991). Among other points, the author indicated (p. 21):

> As to serotonin, the synthesis of 5-HT is stimulated by THC (possibly by intermediary augmentation of corticosteroids) as well as brain 5-HT content. Synaptosomal uptake seems inhibited, while release is favored. [translation EBR]

Anandamide and other cannabinoid agonists inhibit rat serotonin type 3 (5-HT_3) receptors (Fan 1995). This receptor acts as a mediator of emetic and pain responses. The dearth of cannabinoid receptors in the area postrema (Herkenham et al. 1990; Fride and Mechoulam 1996) coupled with the clinical effectiveness of cannabinoids as antiemetics (Abrahamov and Mechoulam 1995), support such an alternative mechanism.

Recently, Boger demonstrated an 89% relative potentiation of the 5-HT_{1A} receptor and a 36% inhibition of the 5-HT_{2A} receptor responses by anandamide (Boger, Patterson, and Jin 1998). 2-AG or arachidonylglycerol (another endocannabinoid) inhibited 5-HT_{2A} by 28%. Similar effects by THC are likely. These observations support efficacy for cannabinoids in acute symptomatic migraine treatment (agonistic activity at 5-HT_{1A} or 5-HT_{1D}) and in prophylactic treatment of chronic headache (antagonistic activity at 5-HT_{2A}) (Peroutka 1990a and 1990b).

In a similar vein, Kimura et al. (1998) showed that high concentrations of anandamide decreased serotonin and ketanserin binding (the latter being a 5-HT_{2A} antagonist). Additionally, 11-OH-delta-8-THC and 11-oxo-delta-8-THC metabolites of cannabis modified serotonin receptor binding.

Ultimately, the author and colleagues have recently demonstrated pertinent serotonin receptor activity of the essential oil of cannabis (Russo et al. 2000). Dilutions of these terpenoid components of up to 20,000 in buffer produced displacements of at least 50% of ^{3}H-ketanserin from the cloned 5-HT_{2A} receptor, while the same material displaced ^{3}H-8-OH-DPAT from the 5-HT_{1A} receptor at least 50% in dilutions up to 400. This activity provides important evidence for putative synergistic activity of cannabis essential oil components with THC in the preventive and symptomatic treatment of migraine.

DOPAMINERGIC SYSTEMS

The importance of dopaminergic mechanisms in migraine treatment has received recent emphasis (Peroutka 1997). Dopamine blocking drugs such as chlorpromazine and haloperidol can be very effective stand-alone or adjunctive agents in migraine, but are significantly sedating.

Ferri et al. (1986) were able to demonstrate that 6-hydroxydopa-

mine, which causes degeneration of catecholamine terminals, was able to block THC antinociception. Stefano and his team showed that anandamide stimulates nitric oxide formation in lower animals through inhibition of presynaptic dopamine release (Stefano et al. 1997). They stated (p. 63), ''cannabinoids and their endogenous effectors play a prominent role in the regulation of catecholamine release in invertebrates . . .'' Many cannabinoid mechanisms demonstrate teleological preservation, and similar effects in higher mammals may well be operative. In a recent review (Mechoulam, Fride, and Di Marzo 1998) (p. 12), a number of studies were cited as demonstrating that cannabimimetic drugs cause ''inhibition of the dopaminergic nigrostriatal system.''

Müller-Vahl and her colleagues cited previous work (Mailleux and Vanderhaeghen 1992) in their examination of cannabinoid effects on the dopaminergic system (Müller-Vahl et al. 1998, p. 504), ''cannabinoid receptors were found to be co-localized both with dopamine D_1 receptors on striatonigral dynorphin/substance-P-containing neurones and with dopamine D_2 receptors on striatopallidal enkephalinergic neurones.'' This and subsequent work by her group (Müller-Vahl et al. 1999) demonstrates that cannabis is able to induce a considerable decrement in the movement disorder of patients with Tourette syndrome. This suggests a possible dopamine blocking effect of THC, which may be clinically relevant without significant sedation, but whose mechanism remains to be elucidated. Similar effects of THC on the dopaminergic system may be equally pertinent to migraine treatment.

Leweke et al. (1999) demonstrated elevated levels of anandamide and palmitylethanolamide (PEA) in schizophrenic patients, stating (p. 1666), ''anandamide may act as a local modulatory signal to offset dopamine-induced psychomotor activation.'' Given the tendency of schizophrenics to ''self-medicate'' with cannabis, there is support for their statement that their findings, ''may reflect a homeostatic adaptation of the endogenous cannabinoid system to neurotransmitter imbalances that involve dopamine.'' Conjecturally, THC may similarly modulate dopaminergic imbalances in migraine, and deserves study.

INFLAMMATORY MECHANISMS

Anti-inflammatory claims for cannabis date back to the Sumerians binding the head with the herb (Thompson 1949). Modern authors

(Burstein 1992; Evans, Formukong, and Evans 1987; Formukong, Evans, and Evans 1988, 1989) have examined the relationship between cannabinoids and inflammation. It is well known that anti-inflammatory drugs may ameliorate migraine, perhaps through effects on the ''sterile inflammation'' of that disorder, as well as effects on the arachidonate cascade. McPartland (2000) provides an excellent summary and analysis (McPartland 2000).

Burstein et al. (1973) demonstrated that THC and other cannabinoids could inhibit prostaglandin E-2 synthesis, and that the aromatic moiety seemed to be the critical portion. In 1979, it was experimentally demonstrated that smoked cannabis reduced platelet aggregation (Schaefer et al. 1979).

Cannabichromene is often the second most abundant cannabinoid in marijuana after THC (Turner and ElSohly 1981). CBC proved superior in its anti-inflammatory capabilities to phenylbutazone. The authors stated (p. 283S), ''it is obvious that the THC content of marihuana cannot be used to adequately describe the pharmacologic activity of the drug.''

Evans (1991) further analyzed structure-activity relationships of cannabinoids, stating (p. S65), ''Experiments involving oral administration of THC suggested that THC was 20 times more potent than aspirin and twice as potent as hydrocortisone.'' Also observed was the action of CBD as a dual cyclooxygenase and lipoxygenase inhibitor in various assays. Hampson et al. (1995) were able to demonstrate that anandamide and metabolites are substrates for brain lipoxygenase.

Although some authors have reported THC as an inhibitor of tumor necrosis factor (TNF) production, Klein et al. (1998) noted that levels of the latter might rise or fall depending on the cells and culture system selected.

In a recent review (Fimiani et al. 1999), the authors analyze the respective roles of opiate, cannabinoid and eicosanoid signaling through a common nitric oxide coupling. They note (p. 27), ''Delta-9-THC blocks the conversion of arachidonic acid into all metabolites derived by cyclooxygenase activity, whereas it stimulates lipoxygenase, resulting in an increase in lipoxygenase products.'' The COX inhibition of THC may in fact be selective for the COX-2 isozyme, as more fully discussed by McPartland (2000). Clinically, no increased incidence of gastric ulceration in chronic cannabis users has been observed (Stefanis, Dornbush, and Fink 1977; Rubin and Comitas

1975; New York (City), Mayor's Committee on Marihuana, Wallace, and Cunningham 1973), thus supporting its likely selectivity for COX-2. One essential oil sesquiterpene component of cannabis, caryophyllene, has a gastric cytoprotective effect (Tambe et al. 1996).

The above authors (Fimiani et al. 1999) also noted the morphine-cannabinoid system modulates the eicosanoid cascade and its pro-inflammatory cytokine activity through induction of nitric oxide synthesis, averting damaging effects on tissues. They summarized (p. 30), ''Thus, we can surmise cannabinoid-morphine systems are down-regulators of inflammatory processes in an attempt to restore homeostasis.''

Additionally, cannabis seed has likely dietary benefits as an anti-inflammatory agent. It is a rich source of linolenic acid, which promotes formation of anti-inflammatory metabolites, as well as providing significant amounts of gamma-linolenic acid, inhibiting the formation of pro-inflammatory products from arachidonate (Conrad 1997; Wirtshafter 1997; Russo 2000).

Flavonoid components of cannabis may potentiate anti-inflammatory activity. Cannflavin A and B inhibited prostaglandin E-2 production in human rheumatoid synovial cells 30 times more potently than aspirin (Barrett, Scutt, and Evans 1986). Apigenin, a flavonoid common to cannabis and German chamomile (*Matricaria recutita* L. Asteraceae), had important anti-inflammatory actions on interleukin, TNF, carrageenan-induced edema and by inhibition of up-regulation of cytokine-induced genes (Gerritsen et al. 1995). Quercetin, another flavonoid in cannabis, serves as an antioxidant, and inhibits hydrogen peroxide-mediated NF-kappaB activity (Musonda and Chipman 1998).

Finally, various terpenoid essential oil components of cannabis demonstrate anti-inflammatory effects at physiologically appropriate levels (McPartland and Mediavilla 2001). Burstein et al. (1975) have examined the essential oil fraction of cannabis, demonstrating eugenol as potent in prostaglandin inhibition. Alpha-pinene and caryophyllene have proven to demonstrate anti-inflammatory activity in the rat hind-paw edema model from carrageenan or by PGE-1 (Martin et al. 1993).

CANNABINOID INTERACTIONS WITH OPIATES AND ENDOGENOUS OPIOIDS

In ''Cellular Effects of Cannabinoids'' (Martin 1986), the author reported that naloxone did not block the analgesic properties of these substances, supporting a non-opioid mechanism.

THC experimentally increases beta-endorphin levels (Wiegant, Sweep, and Nir 1987). Depletion of endorphins has been measured in the CSF of migraineurs during attacks (Fettes et al. 1985), and may contribute to hyperalgesia and photophobia. Early exposure to THC in rat pups boosted adult levels of beta-endorphins in specific brain areas, while also raising substance P (Kumar et al. 1990). The pertinence to human patients is unclear. Mailleux and Vanderhaeghen (1994) have also demonstrated that THC regulates substance P and enkephalin mRNA levels in the basal ganglia. Manzanares et al. (1998) have shown THC is able to promote increases in beta-endorphin in rats.

Meng and his group (1998) demonstrated that THC is involved in an analgesic brainstem circuit in the rostral ventromedial medulla that interacts with opiate pathways. They observed (p. 382), ''the release of endogenous opioids in the RVM mediates both the inhibition of 'on' cells and the antinociception seen after activation of neurons in the midbrain periaqueductal grey.''

Cichewicz and her group (1999) have suggested an opiate sparing effect of THC might be employed clinically in pain patients, echoing claims of the 19th century pioneers of Indian hemp.

Many analgesic effects of cannabinoids cannot be reproduced by opiates, however, particularly in cases of neuropathic pain (Hamann and di Vadi 1999). Especially in migraine, opiates may aggravate the condition, or even promote its appearance *de novo* (Nicolodi 1998). Therapeutic doses of morphine were unable to relieve migraine attack and increased hyperalgesia in migraineurs when administered in headache-free intervals. Additionally, 65% of chronic opiate users developed migraine during or subsequent to their addiction.

Meng's results are discussed above (Meng et al. 1998). In a recent publication Manzanares et al. (1999), cited that chronic cannabinoid administration could similarly promote hypothalamic production of beta-endorphin. This effect may be important with respect to autonomic and chronometric effects of migraine.

MIGRAINE, CANNABINOIDS, AND THE PERIAQUEDUCTAL GRAY

In 1996, researchers demonstrated antinociceptive effects of delta-9-THC and other cannabinoids in the periaqueductal gray matter in

rats (Lichtman, Cook, and Martin 1996). The PAG is a putative migraine generator area (Goadsby and Gundlach 1991; Raskin 1988), and is integral to ascending and descending pain pathways, fear and anxiety (Behbehani 1995).

Weiller et al. (1995) examined migraineurs during attacks with positron emission tomography (PET), demonstrating various sites of regional blood flow increase. Those increases persisted in brainstem areas, including the PAG, after successful treatment of the attacks with sumatriptan. The authors posited migraine to reflect an imbalance in activity of brainstem centers mediating vascular tone and antinociception. Similarly, Castro et al. (1997) demonstrated a differential tritiated sumatriptan binding in human PAG, again supporting the crucial nature of that locus in migraine pathophysiology.

Manzanares et al. (1998) suggested that cannabinoid-mediated antinociception in the PAG is produced by activation of endogenous opioids. This is further supported by the fact that subchronic THC administration elevates proenkephalin gene expression in the PAG.

A very recent analysis (Walker et al. 1999), has demonstrated that electrical stimulation of PAG in the rat stimulated anandamide release and CB_1 receptor-mediated analgesia. The system was tonically active, and cannabinoid antagonists produced hyperalgesia. The authors posited that this cannabinoid modulated pain system would support the prospect of approaches with cannabinoids to opiate-resistant syndromes.

NMDA, GLUTAMATE AND MIGRAINE

A trigeminovascular system has long been implicated as subserving pain, inflammatory and vascular effects of migraine. An important neurochemical link of the NMDA/glutamate system to trigeminovascular nociception in migraine has been reviewed in detail (Storer and Goadsby 1999). In essence, painful stimuli in the head produce transmission in the trigeminocervical complex through both NMDA and non-NMDA-mediated mechanisms. One of the observed mechanisms of the triptan drugs in migraine is their ability to block glutamate release and trigeminocervical transmission through modulation of $5\text{-}HT_1$ receptor subtypes. The authors called for newer agents that would affect this system without vascular side effects of the triptans.

Shen et al. (1996) elucidated basic mechanism of cannabinoids in

glutamatergic systems. Through G-protein coupling, cannabinoid receptors inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release. This effect was noted with endogenous and synthetic cannabinoid receptor agonists, and was felt to be key to their analgesic responses. ''Psychotomimetic'' or rather, dissociative side effects of strongly active agents on the NMDA system (e.g., phencyclidine, ketamine) were noted, while (p. 4333), ''better tolerated drugs appear to be less efficacious inhibitors of glutamate activation, but retain neuroprotective efficacy, consistent with reduction, but not abolition, of glutamate receptor activation.'' Natural cannabinoids fit this profile, as demonstrated in a subsequent study (Shen and Thayer 1999), wherein THC served as a partial agonist acting presynaptically via CB_1 to modulate glutamatergic transmission through a reduction without blockade.

Similarly, Hampson and colleagues demonstrated a 30-40% reduction in delta-calcium-NMDA responses by THC (Hampson, Bornheim et al. 1998), which was eliminated by a cannabinoid antagonist. This group has subsequently provided elegant demonstration of the ability of the THC and cannabidiol components of cannabis to act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA and kainate receptors (Hampson, Grimaldi et al. 1998). These effects seemed to occur independently of cannabinoid receptors, and support presumptive benefit in cerebral ischemia, as observed in migraine infarction. The natural cannabinoids were more potent in their anti-oxidant effects than either alpha-tocopherol or ascorbic acid.

Italian researchers Nicolodi and Sicuteri (1995) have recently elucidated the role of NMDA antagonists in eliminating hyperalgesia in migraine and possibly other conditions in a series of articles. They demonstrated that ketamine was able to ameliorate migraine both acutely and prophylactically through NMDA blockade. A ''secondary hyperalgesia'' in these patients, manifested by an increased response to noxious stimuli in areas adjacent to the pain was also diminished. They suggested NMDA blockade as a remedy for chronic daily headache (Nicolodi, Del Bianco, and Sicuteri 1997), and related mechanisms of pain in defects of serotonergic analgesia in fibromyalgia (Nicolodi, Volpe, and Sicuteri 1998), which is frequently comorbid. In a most recent study (Nicolodi and Sicuteri 1998), they elucidate mechanisms by which a genetic predisposition (''tertiary hyperalgesia'')

may lead to a ''chronicization'' of migraine through NMDA stimulation. Gabapentin and ketamine were suggested as tools to block this system and provide amelioration. Given the above observations and relationships, it is logical that prolonged use of THC prophylactically may exert similar benefits, as was espoused in cures of chronic daily headache claimed in the 19th century with regular cannabis usage (Mackenzie 1887).

This concept is bolstered by examination of another series of articles by Richardson and her group. One study examined peripheral mechanisms (Richardson, Kilo, and Hargreaves 1998), wherein cannabinoids acted on CB_1 to reduce hyperalgesia and inflammation via inhibition of neurosecretion of calcitonin gene-related peptide (CGRP) in capsaicin activated nerve terminals. This is akin to mechanisms of ''sterile inflammation'' observed centrally in migraine where CGRP is felt to be an important mediator. At the spinal level, her group noted an antihyperalgesic effect of cannabinoids (Richardson, Aanonsen, and Hargreaves 1998a), mediated by CB_1. Additionally, experimental cannabinoid receptor blockade induced a glutamate-dependent hyperalgesia, suggesting a tonic activity of cannabinoids in averting such a development. Once more, an inhibition of CGRP release was noted with anandamide. On this basis, they suggested the clinical of cannabinoids in disorders (p. 152) ''characterized by primary afferent barrage.'' Inasmuch as an increased potency of cannabinoids was observed in hyperalgesia (p. 152), ''may mean that there are dosages of cannabinoids that would be effective as antihyperalgesic agents but subthreshold for the untoward psychomimetic effects.'' This is reminiscent of Dixon's patients, able to return to work after treating their headaches with a few inhalations of cannabis (Dixon 1899).

Elaborating on these themes, Richardson noted that a decrease in lumbar cannabinoid receptor numbers correlated with hyperalgesia (Richardson, Aanonsen, and Hargreaves 1998b), and could provide an etiology for certain chronic pain states, especially those unresponsive to opiate treatments, stating (p. 456), ''Accordingly, drugs that activate cannabinoid receptors or gene therapy directed at increasing activity of the cannabinoid system may have therapeutic use in treating certain types of chronic pain.''

An even more recent study (Li et al. 1999) supports these contentions. The synthetic cannabinoid agonist, WIN 55,212-2 was employed

to block capsaicin-induced hyperalgesia in rat paws much as has been observed for THC in formalin treatment paradigms. The authors stated (p. 30), ''These studies support the notion that cannabinoids can block hyperalgesia at doses which do not produce analgesia or affect motor function.'' They continued (p. 31), ''low doses of cannabinoids may represent a novel therapeutic approach for alleviating hyperalgesia–without the unwanted side effects typically associated with these compounds.''

Ultimately, Ko and Woods (1999) examined local THC administration and its activity on capsaicin-induced pain in rhesus monkeys. Once more, THC effectively reduced pain, which was blocked by a CB_1 antagonist. THC was effective by injection, at a dose that produced no behavioral change or sedation. The authors observed (p. 322), ''Cannabinoid agonists may be effective treatments for nausea associated with chemotherapy, pain, migraine and epilepsy.'' Critics may point out that the above studies examine peripheral and spinal mechanisms, but are not applicable to supraspinal systems. This seems unlikely. Maneuf et al. (1996) were able to show a tonic activation of the cannabinoid system serving to reduce GABA uptake in the globus pallidus.

The above studies, taken ensemble, provide intriguing evidence that cannabinoid systems may prove to integral to nociceptive pathways in migraine pathogenesis.

SYNERGISM AND THE ENTOURAGE EFFECT

Another potent endogenous cannabinoid with analgesic effects has recently been described (Calignano et al. 1998). Palmitylethanolamide (PEA) is released with from a phospholipid in conjunction with anandamide. The two compounds achieve a 100-fold synergism on CB_1 type peripheral receptors in cutaneous tissues. It has also been shown that endogenous cannabinoids and their inactive metabolites combine to boost physiological responses (the ''entourage effect'') (Mechoulam and Ben-Shabat 1999). Given the likely contributions of cannabis flavonoids and essential oils to therapeutic effects on mood, inflammation and pain reviewed in (McPartland and Pruitt 1999), one can easily see support for Dr. Mechoulam's quotation (Mechoulam and Ben-Shabat 1999, p. 136), ''This type of synergism may play a role in the widely held (but not experimentally based) view that in

some cases plants are better drugs than the natural products isolated from them.''

ONTOLOGICAL CONJECTURE ON THE CANNABINOIDS IN MIGRAINE

Migraine is relatively uncommon before age 10, and very much so before age 5. When present, it may be manifested as ''acephalic migraine,'' or migraine without pain, or as a number of other *formes frustes* such as cyclic vomiting, abdominal pain, or paroxysmal vertigo. The reason for this developmental quirk has never been elucidated.

A detailed developmental mapping of cannabinoid receptor binding in humans has been performed (Glass, Dragunow, and Faull 1997), and may shed light on this issue. Cannabinoid binding is low in the brainstem except for the substantia nigra, spinal trigeminal and tractus solitarius nuclei and the periventricular gray matter, demonstrating an interesting homology with sumatriptan binding in the human brain (Castro et al. 1997). In the adult, midbrain central gray binding of tritiated CP55940 was 21 ± 12 femtomoles/mg of tissue, whereas, in the neonate, the value was 157 ± 11, some 7.5 times greater (Glass, Dragunow, and Faull 1997). Similar increased density of cannabinoid binding is seen in other areas. A decremental decline in cannabinoid binding was observed developmentally.

Given the reported role of the PAG in pain modulation and migraine, it is interesting to conjecture that this decline in its cannabinoid binding allows the subsequent development of migraine pain in the older child or adult. The emesis and abdominal pain of migraine appear early in its ontogeny, but it is clear from previous study that this mechanism is not mediated by cannabinoid receptors.

What of other phenomena of the young? Could it be that the eidetic images, childlike wonder and ready laughter of youth are a manifestation of their greater expression of cannabinoid function? As adults are we consigned to suffer the pain, and lose the intensity of image and imagination? This conjecture is surely worth considering.

VALUE AND PLACE OF CANNABIS IN MIGRAINE TREATMENT

The information reviewed above indicates that cannabis has a long established history of efficacy in migraine treatment. Clinical use of

the herb and its extracts for headache has waxed and waned for 1200 years, or perhaps much longer, in a sort of *cannabis interruptus*.

It is only contemporaneously that supportive biochemical and pharmacological evidence for the indication is demonstrable. Cannabis' unique ability to modulate various serotonergic receptor subtypes, inhibit glutamatergic-mediated toxicities, simultaneously provide anti-inflammatory activity and provide acute symptomatic and chronic preventive relief make it unique among available treatments for this disorder.

This author's personal experience in communicating with several hundred migraineurs who have employed cannabis is that 80% have noted improvement, often with complete symptomatic relief. That this has occurred without any quality control of the herb whatsoever is most compelling. Many report the ability to titrate their dosage through smoking so that they achieve relief without cognitive or motor impairment. The latter is not the case with oral THC (''dronabinol'' or Marinol®), whose slow and variable gastrointestinal absorption and conversion to more intoxicating metabolites (11-hydroxy-delta-9-THC) have made it a poorer choice for most migraineurs.

Reports of surveys of undertaken by Dr. Tod Mikuriya on 2480 patients served by the Oakland Cannabis Buyers' Club indicate that 127 or 5% sought cannabis for primary treatment of chronic migraines (Gieringer 2001).

CANNABIS, AND THE IDEAL DRUG FOR MIGRAINE

Some years ago, this author mused on the pharmacological attributes of an ''ideal drug'' for headache treatment (Russo 1992). Based on contemporary knowledge, these included: stimulatory activity on 5-HT_1 receptors for acute relief, antagonistic activity on 5-HT_2 receptors for prophylactic benefit, antagonism of 5-HT_3 receptors for antiemesis, boosting of depleted endorphin levels, inhibition of substance P, freedom from gastrointestinal upset, and reasonable cost. Nowadays, we might add inhibition of NMDA receptor activity and CGRP release. It seemed wise to consider that no single agent that met these requirements existed, or could even be conceived. Currently, that judgment requires revision. Cannabis, particularly considered as an admixture of THC, other cannabinoids, flavonoids and essential oils,

seems to fulfill all of these criteria. That proof is offered historically, with anecdotal case studies, and with examination of its biochemical basis. Now all that is required in clinical correlation in modern controlled conditions.

FINAL THOUGHTS

Migraine remains a serious public health issue despite the recent development of 5-HT_{1D}-agonist medications. In the USA, an estimated 23 million Americans suffer severe migraine. Of those, 25% have four or more episodes per month, and 35% have one to three severe headaches each month (Stewart et al. 1992). An estimated 14% of females, and 8% of males miss some part a day of work or school each month due to headaches (Linet et al. 1989). Migraine has been estimated to account for an economic impact of $1.2 to $17.2 billion annually in the USA in terms of lost productivity (Lipton and Stewart 1993).

Although sumatriptan has effected an admirable advance in treating acute migraine, problems remain. While rapidly active subcutaneously, its oral absorption is relatively slow, and absorption of any agent by this route may be notably impaired or impossible in the migraineur. One may inadvertently treat the headache attack too early: sumatriptan and its analogues are ineffective when administered in the ‘‘aura phase’’ of classic migraine (Bates et al. 1994; Ferrari and Saxena 1995). Despite its status as the current most effective agent in acute migraine treatment, injected sumatriptan (Imitrex®) has been ineffective in up to 30% of patients, or has produced undesirable side effects for up to 66% (Mathew 1997). Headache recurrence after triptans remains a common clinical pitfall. Unfortunately, repetitive dosing, and development of agents with longer half-lives does not totally solve the problem (Ferrari and Saxena, 1993, 1995). It is a curious feature of sumatriptan that it is said to pass the blood-brain barrier poorly. Some researchers posit that the condition itself results in easier passage of the molecule. Newer agents with improved central nervous system penetration have been synthesized, but have not notably improved efficacy. Some may result in more frequent chest and throat tightness, numbness, tingling, anxiety, and other side effects (Ferrari and Saxena 1993, 1995). Most importantly the triptan class of medica-

tions does not reduce the frequency of migraine attacks. The older drug dihydroergotamine, has some prophylactic benefit but is best administered intravenously, and is not well tolerated by some. Thus, the triptans, however impressive, may represent a therapeutic dead end. Considering these shortcomings, alternative treatment agents remain an important priority.

Based on the above review, it is convincingly the case that ''medical marijuana'' deserves formal scientific scrutiny for migraine treatment. Such clinical trials may reveal whether cannabis fulfills current criteria as a safe and effective treatment for migraine. Smoked cannabis would be preferable to butorphanol nasal spray (Stadol-NS®), which has remained an unscheduled drug approved in the USA for migraine treatment notwithstanding its addictive potential and attendant morbidity and mortality (Fisher and Glass 1997).

Although evidence suggests that delta-9-THC is primarily responsible for clinical benefits of cannabis smoking in migraine, investigation of the effects of different cannabis strains rich in tetrahydrocannabivarin (THCV), delta-8-THC, or certain flavonoids and monoterpenes may be clinically fruitful. Use of high potency material for smoking, or alternative delivery systems may provide improved cost-benefit ratios. Solving the above issues may render cannabis or future synthetic cannabinoids well suited to migraine treatment. Given the multiple mechanisms by which cannabis affects migraine pathophysiology, it may come to pass that the disorder is eventually recognized as an endocannabinoid deficiency disease, or a disorder of cannabinoid regulation.

In closing, a unique dance of medical science and politics is occurring that will soon decide whether herbal cannabis (a derivative, or synthetic analogue) will rise like the legendary phoenix to resume an ancient role as a remedy for migraine and neuropathic pain.

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