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Chapter 2

The Pharmacological History of Cannabis

Ethan B. Russo

2.1 Introduction

The circumstances whereby cannabis was first used medicinally are lost in time and mystery. More than likely, it happened at many times and in many places with rediscoveries figuring prominently alongside the landscape of human peregrinations and conquests in a rapidly changing mosaic of Eurasian languages and cultures, a process this author has termed "cannabis interruptus" (Russo 2001b, 2004, 2007). As a ubiquitous "camp follower," cannabis accompanied the early nomads around the Old World for millennia, as they deciphered that certain plants were better for fiber, others for edible seed, while certain chemovars were pharmacologically superior. Rarely does a triple-purpose plant appear in nature, such as that discovered in Nepal (Clarke 2007).

The breadth of cannabis history does not lend itself to comprehensive treatment in a brief chapter. Rather, this effort will focus on a chronology (Table 2.1), followed by some possible new therapeutic directions.

2.2 Pharmacology of cannabis chronology

Table 2.1 Cannabis chronology

2700 BCE	Oral tradition in *Shen Nong Ben Cao Jing* notes hallucinatory effects, appetite stimulation, tonic and antisenility effects	Shou-Zhong 1997
c.2000 BCE	Cannabis seeds in Margiana, Proto-Zoroastrian site, part of religious rites	Sarianidi 1998
c.1800 BCE	30 citations from Ancient Sumeria and Akkadia for grief, epilepsy, neuralgia, and pediculocide	Babylon and Thompson 1903; Russo 2007; Thompson 1924; 1949
1534 BCE	*Ebers Papyrus*, Egypt, for vaginal contractions, ophthalmological conditions, etc.	Manniche 1989; Russo 2007
c.1500 BCE	*Atharva Veda* notes *bhanga* to "release us from anxiety"	Grierson 1894; Indian Hemp Drugs Commission 1894; Russo 2005
c.750 BCE	*Kaneh bosem* (aromatic cane) part of holy anointing oil of Hebrews (*Exodus* 30:22-25)	Alter 2004; Russo 2007

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Table 2.1 (continued) Cannabis chronology

700 BCE	Cannabis cache from Yanghai Tombs,Xinjiang; biochemical and genomic analysis demonstrate THC chemotype	Jiang et al. 2006; Russo et al. 2008
*c.*600 BCE	Persia: *Avesta* notes ritual use, and in combination to produce miscarriage	Darmesteter 1895
450 BCE	Intoxication in Central Asian funerary rites, subsequently documented in frozen tombs in Siberia	Artamonov 1965; Herodotus 1998; Rudenko 1970; Russo 2007
*c.*350 BCE	Carbonized cannabis found in Israeli cave by remains of woman dying in childbirth	Zias 1995; Zias et al. 1993
*c.*214 BCE	*Erh-Ya*, China describes dioecious status, superiority of males for fiber, females for intoxication	Carr 1979; Russo 2007
First century CE	"The juice extracted from it when green and instilled is appropriate for earaches"	Dioscorides and Beck 2011 (p. 248)
First century CE	Pliny the Elder notes *gelotophyllis* ("Leaves of laughter" from Bactria) producing hallucinations; also hemp infusion for looseness in beasts of burden, root for joint contractures and gout, herb for burns	Pliny 1951 (Book XX, Ch. 98, p. 298), 1980 (Book XXIV, Ch. 164, p. 117); Russo 2007
Second century CE	Galen notes leaves for flatus and seed juice for otalgia, chronic pain	Brunner 1973; Butrica 2002; Sethi 1868
Second century CE	Hua-Tho in China notes use in wine as surgical anaesthetic/analgesic	Julien 1849
Late second century CE	Egyptian *Fayyum Medical Book* for tumors	Reymond 1976; Russo 2007
*c.*550 CE	*The Syriac Book of Medicines*, for excess spittle, hemp plug for anal fissures	Budge 1913
570	Taoist incense	Needham and Gwei-Djen 1974
Eighth century	Psychoactivity noted, Jabir ibn Hayyan in Persia/Iraq	Lewis et al. 1971
*c.*850	In Persia, ibn Sahl uses compound medicine with flower juice intranasally for migraine, uterine pains, prevent miscarriage	Kahl 1994; Russo 2001b, 2002
875	In Iraq, muscle relaxant	Al-Kindi and Levey 1966; Russo 2007
Ninth century	*The Old English Herbarium* recommends pounded hemp or its sap for wounds, and for "pain of the innards"	Pollington 2000 (p. 301)
Ninth century	Ibn al-Baytar, Egypt, vermicidal, for neuralgia	Lozano 2001
*c.*900	Al-Razi, Persia, to stimulate hair growth	Lozano 2001
Tenth century	Hemp part of "holy salve" in Anglo-Saxon *Lacnunga*	Grattan and Singer 1952 (p. 123)
*c.*1000	al-Mayusi first mention in epilepsy, leaf juice intanasally	Al-Mayusi 1877; Lozano 2001

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Table 2.1 (continued) Cannabis chronology

Eleventh century	Roots for fever, tumors, herb juice for ears, and leaves for dandruff	Ibn Sina (Avicenna), 1294
Eleventh century	*Olde English Herbarium*, hemp and fat applied to breast to disperse swelling and purge diseased matter; herb when drunk to relieve pain of the innards	Vriend 1984
Twelfth century	In Spain, Sheshet Benveniste recommends *theriaca* with cannabis as tonic, curing sterility, repairing the womb, stomach and head	Barkai 1998
1158	Hildegard von Bingen, for headache, stomach slime, and compress for sores, wounds	Fankhauser 2002; Hildegard and Throop 1998
1200	*Anandakanda*, increasing longevity	Russo 2005
Thirteenth century	Italy, *Codex Vindobonensis 93*, ointment for breast swelling, pain	Russo 2002; Zotter 1996
Thirteenth century	ibn Rasul, headache and ear pains	Lewis et al. 1971
1542	Latin binomial: *Cannabis sativa*; root boiled for gout, raw for burns, wild hemp boiled, wrapped for tumors	Fuchs 1999
1546	Boiled root for sore muscles, stiff joints, gout, rheumatism, herb juice for colicky horses, raw on burns	Rabelais 1990
1563	Indian hemp engenders laughter, allays anxiety, increases appetite, improves work	Da Orta 1913
1570	Feckenham cites "hemmp" as part of honey/wine mixture for wounds, fistulae	Macgill 1990
1596	Li Shi-Chen: flowers for menstrual disorders, root juice for retained placenta, post-partum hemorrhage	Stuart 1928; Russo 2002
1597	Hemp for jaundice and colic	Gerard and Johnson 1975; Crawford 2002
Seventeenth century	In Far East, benefits on mood, gonorrhea, pleurisy, hernia	Rumpf and Beekman 1981
1621	Indian hemp produces ecstasy, laughter	Burton 1907
Eighteenth century	In India, *Makhzan al-adwiya*, leaf snuff for "deterging the brain," to remove dandruff and vermin, treat diarrhea, gonorrhea, powder for wounds, sores, herb to prolong life	Russo 2005
1712	Psychotropic effects in Persia, India	Kaempfer 1996
1751	*Medicina Britannica*, hemp precipitates menses, "against Pissing the Bed"	Short 1751 (p. 138)
1772	Linneaus summarizes cannabis: "narcotica, phantastica, dementans, repellens"	Linné 1772
1784	In Scotland, hemp oil for urinary burning, incontinence and "restraining venereal appetites"	Lewis 1794

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Table 2.1 (continued) Cannabis chronology

1830	Extract in wine for nervousness	Nees Von Esenbeck and Ebermaier 1830
1839	O'Shaughnessy studies Indian pharmacopoeia, tests dogs, then patients, for tetanus, rabies, epilepsy, rheumatoid disease	O'Shaughnessy 1838–1840
1843	Indian hemp treats cough in tuberculosis, pertussis, migraine, rheumatic joint pain, gout, morphine withdrawal	Clendinning 1843; Russo 2001b
1843	Treatment success in convulsions	Pereira 1843
1843	Hashish treats bubonic plague	Aubert-Roche 1843
1843	Testing in psychiatry	Moreau 1845
1845	In Ireland, Donovan treats migraine, neuralgia and musculoskeletal pain	Donovan 1845, 1851; Russo 2001b
1848	For neuralgia and sleep	Christison 1848
1849	Uterine hemorrhage	Churchill 1849; Russo 2002
1851	Enhances uterine contractions in labor	Christison 1851
1857	Tolerance and reverse tolerance described	Ludlow 1857
1860	Case report in bipolar disease	McMeens 1860
1860	Restores natural sleep in 1000 patients	Fronmüller 1860
1862	Life-saving in *hyperemesis gravidarum*	Russo 2002; Wright 1863, 1862
1860s	American Civil War, employed for war injuries, with opium for dysentery	United States. Dept. Of the Army. Office of the Surgeon General et al. 1990
1867	Delirium tremens treated with tincture	Tyrell 1867
1870	Melancholia, obsession and anxiety	Polli 1870; Russo 2001a
1883	Mental depression with insomnia	Strange 1883
1886	Ringer endorses for migraine prophylaxis, dysuria, urinary retention and dysmenorrhea	Ringer 1886
1887	Advantages over opiates, distancing from pain	Hare 1887; Russo 2001b
1887	For chronic daily headache	Mackenzie 1887a, 1887b, 1894
1888	Superiority in migraine, tremor of parkinsonism	Gowers 1888
1889	Suppositories for menopause	Farlow 1889; Russo 2002
1890	Touted for migraine, senility, dysmenorrhea, childhood convulsions, teething	Reynolds 1890; Russo 2001b, 2002
1890	Gastrointestinal pain	Sée 1890
1890	Delirium tremens and cyclic vomiting	Aulde 1890
1891	Cocaine, chloral hydrate and opiate addiction and "it calms the pain of clap"	Mattison 1891; Russo 2001a
1894	Migraine, syphilitic and functional gastrointestinal pain	Mackenzie 1894

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Table 2.1 (continued) Cannabis chronology

1897	Oromucosal activity	Marshall 1897; Russo 2007
1899	Pain, including herpes zoster	Shoemaker 1899
1900	Dysmenorrhea, malarial symptoms	Lewis 1900
1915	Most satisfactory remedy for migraine	Osler and Mccrae 1915; Russo 2001b
1934	Psychiatric sequelae reviewed, finding little lasting harm	Bromberg 1934
1942	Menstrual migraine	Fishbein 1942
1944	Loewe reviews cannabinoid pharmacology, structure-activity relationships	New York (N.Y.). Mayor's Committee on Marihuana. et al. 1944
1947	Duodenal ulcers	Douthwaite 1947
1964	Isolation, synthesis of tetrahydrocannabinol	Gaoni and Mechoulam 1964
1968	Landmark clinical investigation	Weil et al. 1968
1971	Cannabis decreases intraocular pressure	Hepler and Frank 1971
1975	THC antineoplastic in lung adenocarcinoma	Munson et al. 1975
1975	THC antiemetic, cancer chemotherapy	Sallan et al. 1975
1975	THC equi-analgesic to codeine	Noyes et al. 1975
1976	THC equals salbutamol as bronchodilatator	Williams et al. 1976
1981	CBD anticonvulsant in humans	Carlini and Cunha 1981
1981	THC reduces spasticity	Petro and Ellenberger 1981
1982	Cannabidiol reduces anxiety after THC	Zuardi et al. 1982
1985	Anti-inflammatory component, cannflavin A, discovered	Barrett et al. 1985
1985	Marinol®, synthetic THC, approved for chemotherapy nausea, US	
1988	Discovery of cannabinoid receptor, CB_1	Devane et al. 1988
1989	CB_1 a G-protein-coupled receptor	Matsuda et al. 1990
1991	Cannabis improves night vision in Jamaica and Morocco, subsequently experimentally demonstrated	Merzouki and Molero Mesa 1999; Russo et al. 2004; West 1991
1991	THC has 20 times anti-inflammatory power of aspirin, twice that of hydrocortisone	Evans 1991
1992	Discovery of endogenous cannabinoid, arachidonoylethanolamide (anandamide, AEA)	Devane et al. 1992
1993	CB_2 receptor identified	Munro et al. 1993
1993	CBD reduces anxiety	Zuardi et al. 1993
1993	Anandamide active in cannabinoid tetrad	Fride and Mechoulam 1993
1994	(Supra)normal development in infants born to mothers smoking in pregnancy	Dreher et al. 1994

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Table 2.1 (continued) Cannabis chronology

1995	Endogenous cannabinoid, 2-arachidonoylglycerol	Mechoulam et al. 1995; Sugiura et al. 1995
1995	Δ^8-THC safe, effective in nausea and vomiting in children on chemotherapy	Abrahamov and Mechoulam 1995
1995	CBD improves psychosis	Zuardi et al. 1995
1997	THC reduces agitation in dementia	Volicer et al. 1997
1998	GW Pharmaceuticals begins cultivation, UK	Guy and Stott 2005
1998	"Endocannabinoids" described: "relax, eat, sleep, forget, and protect"	Di Marzo 1998
1998	Endocannabinoid "entourage effect"	Ben-Shabat et al. 1998; Mechoulam and Ben-Shabat 1999
1998	THC, CBD, neuroprotective antioxidants	Hampson et al. 1998
1998	THC produces apoptosis in glioma	Sanchez et al. 1998
2000	CBD antagonizes tumor necrosis factor-alpha in rheumatoid model	Malfait et al. 2000
2001	CBD. TRPV1 agonist, fatty acid amide hydrolase-inhibitor, stimulator of AEA synthesis	Bisogno et al. 2001
2001	Clinical endocannabinoid deficiency syndrome hypothesized	Russo 2001a, 2001b, 2004a
2002	CBD antinausea effects	Parker et al. 2002
2003	First trial of Sativex® in multiple sclerosis symptoms	Wade et al. 2003
2003	Smoked cannabis in HIV/AIDS immunologically safe	Abrams et al. 2003
2003	THC, cannabis extract benefit mobility, subjective spasticity in MS	Zajicek et al. 2003
2003	THC improves Tourette symptoms without neuropsychological sequelae	Müller-Vahl et al. 2003a, 2003b
2004	Sativex® benefits pain	Notcutt et al. 2004
2004	Cannabis extracts reduce urological symptoms in MS	Brady et al. 2004
2004	Sativex®, high-THC extracts effective in brachial plexus avulsion pain	Berman et al. 2004
2004	THC reduces MS pain	Svendsen et al. 2004
2004	Cannabidiol increases wakefulness, counteracts THC sedation	Nicholson et al. 2004
2005	Sativex® approved in Canada for neuropathic pain in MS	Rog et al. 2005
2005	THCV CB_1 antagonist	Thomas et al. 2005
2005	CBD agonist at serotonin-1A	Russo et al. 2005
2006	CBD, other phytocannabinoids cytotoxic in breast cancer	Ligresti et al. 2006
2006	Sativex reduces pain, disease activity in rheumatoid arthritis	Blake et al. 2006

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Table 2.1 (continued) Cannabis chronology

2006	CBD enhances adenosine receptor A2A signaling	Carrier et al. 2006
2006	Efficacious in morning sickness	Westphall et al. 2006
2006	Hepatitis C patients using cannabis better adhere to treatment	Sylvestre et al. 2006
2006	Cannabis lowers lung cancer risk	Hashibe et al. 2006
2007	Sativex® in peripheral neuropathic pain	Nurmikko et al. 2007
2007	Sativex® approved in Canada in opioid-resistant cancer pain	Johnson et al. 2010
2007	Smoked cannabis in short-term trials of sensory neuropathy in HIV/AIDS	Abrams et al. 2007a
2007	Vaporization pharmacokinetics/pharmacodynamics comparable to smoking	Abrams et al. 2007b
2007	CBD antagonizes CB_1 in presence of THC	Thomas et al. 2007
2007	CBD reduces prions, toxicity	Dirikoc et al. 2007
2008	Benefit in short-term study of HIV neuropathy	Ellis et al. 2009
2008	CBD, CBG antibiotic for methicillin-resistant *Staphylococcus aureus*	Appendino et al. 2008
2008	β-caryophyllene, sesquiterpenoid, potent CB_2 agonist	Gertsch et al. 2008
2008	Cannabis effective in brief neuropathic pain trial	Wilsey et al. 2008
2009	Cannabichromene-predominant plant; concentrated as enriched trichome product	De Meijer et al. 2009; Potter 2009
2010	Sativex® approved UK, Spain for intractable spasticity in MS	Novotna et al. 2011
2010	Sativex® reduces pain in opioid-resistant cancer	Johnson et al. 2010
2010	THCV anticonvulsant	Hill et al. 2010
2010	Single inhalations reduce neuropathic pain	Ware et al. 2010
2010	Sativex® benefits urological MS symptoms	Kavia et al. 2010
2010	Cannabigerol a potent TRPM8 antagonist for prostate cancer	De Petrocellis and Di Marzo 2010
2010	THCV reduces hyperalgaesia in animals	Bolognini et al. 2010
2010	Cannabidivarin, THCV anticonvulsant	Hill et al. 2010; Jones et al. 2010
2010	Sativex® improves intractable nausea of chemotherapy	Duran et al. 2010
2010	THC attenuates breast cancer	Caffarel et al. 2010
2010	*Cannabis* genome published	Medicinal Genomics 2012; Van Bakel et al. 2011
2011	THC, CBD synergize with temozolomide reducing glioma growth	Torres et al. 2011
2012	CBD equals standard antipsychotic	Leweke et al. 2012

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2.3 Selected topics

2.3.1 Cannabis and tinnitus

In 1698, Nicholas Lémery wrote, "Hemp contains much oil, little salt, it is specific for burns, *for roaring in the ears*, to kill worms," (Lémery 1727, p. 109, translation EBR). Tinnitus is a nettlesome syndrome of myriad causes, notoriously recalcitrant to treatment. However, many attestations to the benefits of cannabis are posted online, and Grinspoon and Bakalar (1997) offered one case report, and another documents improvement in tinnitus associated with benign intracranial hypertension by tetrahydrocannabinol (THC) administration (Raby et al. 2006). These claims gain plausibility when it is considered that the cannabinoid receptor type 1 (CB_1) is expressed in cochlear nucleus cells, is downregulated in salicylate-treated rats (Zheng et al. 2007), and there is no epidemiological evidence of recreational cannabis usage increasing tinnitus (Han et al. 2010). Thus, there is preliminary evidence to support the contention that THC may be helpful, while Lémery's report suggests cannabidiol (CBD) may also be beneficial. The latter supposition is supported by indirect evidence. To whit, transient receptor potential vanilloid receptor (TRPV)-4 is expressed in inner ear hair cells (Lowry et al. 2009), wherein CBD is an agonist (Moran et al. 2011). Additionally, since CBD is also a TRPV1 agonist/desensitizer (Bisogno et al. 2001), and the expression of mouse RNA of TRPV1 is increased after kanamycin administration, while TRPV4 expression is diminished by this tinnitus-producing treatment, suggests that both vanilloid mechanisms may be operative. Therapeutic trials of cannabinoids in humans certainly seem warranted, particularly with a combination of THC and CBD.

2.3.2 Cannabis and tetanus

In 1838, in India when O'Shaughnessy began experiments, tetanus was virtually uniformly fatal, even in England (Cock and Wilks 1858). Gowers cited mortality of 90% decades later (Gowers 1888). Prior ethnobotanical use in India for this indication was not apparent in the literature (Ainslie 1813). O'Shaughnessy essayed it in three cases, all of whom survived the acute disorder, but with one succumbing to gangrene after refusing amputation (O'Shaughnessy 1838–1840). Frequent dosing relaxed spasmodic paroxysms, allowing nutrition/hydration until recovery ensued, sometimes weeks later. He described similar successes in colleagues' efforts, saving the lives of three of six affected people. One case report was detailed by his cousin (O'Shaughnessy 1842). Treatment failed in one case for another (Shaw 1843) in India, but in England, Miller saw success in a 7-year-old treated with cannabis tincture (Miller 1845), who tolerated well a dose that previously intoxicated an adult. Christison (1848) similarly endorsed for this and other spasmodic diseases. In South Carolina, Gaillard reported two survivors with *trismus nascentium*, the infantile form (Gaillard and Desaussure 1853). Another case in an 18-year-old required 110 doses before cure (Cock and Wilks 1858). Cannabis was utilized successfully in a 9-year-old girl in Honduras (Skues 1858). In 1863, a Union soldier survived a musket ball wound with compound radioulnar fractures, tetanus and gangrene after amputation, and cannabis tincture (United States. Dept. Of the Army. Office of the Surgeon General. et al. 1990, Vol. 12, p. 822). In India, another case was successfully treated with a combination of cannabis with smoked opium (Fayrer 1865). In a review article from St. Louis (Roemer 1873), it was observed, "As standard remedies, opium, cannabis indica and the calabar bean are entitled to the greatest confidence" (p. 377). In India, Khastagir documented five cures employing smoked cannabis for tetanus to avoid difficult oral administration, and to titrate effects to spasm severity (Khastagir 1878). Lucas suggested the same to the West (Lucas 1880). By the end of the century, it was stated, "The treatment of Tetanus by

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smoking GUNJAH (Indian Hemp) . . . promises to supersede all others in India" (Waring 1897, p. 252). As late as 1962 in India, *charas* (hashish) was still recommended (Dastur 1962).

Despite worldwide attempts at immunization, tetanus afflicts 100–200 Americans per year, and 1 million victims worldwide with a mortality exceeding 50% (Rowland 2000). Given these striking statistics, and the marked success of modern cannabinoid pharmacology in treating spasticity (Novotna et al. 2011), prospective treatment for tetanus with Sativex® certainly seems warranted, especially in developing countries where intensive care and mechanical ventilation for weeks at a time are unavailable.

2.3.3 Cannabis and burns

Pliny the Elder may have been first to write of the benefit of cannabis for this indication, "It is applied raw to burns, but it must be frequently changed, so as to not let it dry" (Pliny 1951, Book XX, Ch. 97, p. 298). Variations of this approach continued for many centuries, with occasional elaboration. Leonhart Fuchs noted, "The raw root, pounded and wrapped, is good for the burn" (translation courtesy of Franjo Grotenhermen) (Fuchs 1999). Rabelais advised, "If you want to cure a burn, no matter whether it be from boiling water or burning wood, just rub on raw Panguelion [hemp], just as it comes out of the earth, without doing anything else. But be careful to change the dressing when you see it drying out on the wound" (Rabelais 1990, Book III, Ch. 51, p. 371). Parkinson suggested, "Hempe . . . is good to be used, for any place that hath been burnt by fire, if the fresh juyce be mixed with a little oyle or butter" (Parkinson et al. 1640). Lémery noted hemp "specific for burns" (Lémery 1727). William Salmon described various preparations (Salmon 1710, p. 510):

> *XVIII. The Oil by Insolation, Infusion, or Decoction*. It is good to be applied to any place which is burn'd with Fire, and to remove inflammation in any part; so also if an Oil of Ointment is made, by mixing the fresh juice with Oil Olive, or Hogs Lard, or fresh Butter, it heals Burning of Scaldings after an admirable Manner.

Chomel (1782, pp. 369–370) preferred hemp seed for burns (and tumors), "This oil mixed with a little melted wax, is a good remedy for burns from which it appeases the pain" (translation EBR). Marcandier (1758, p. 41, translation EBR) recommended a mixture, "Crushed and ground fresh, with butter in a mortar, one applies to burns, which it soothes infinitely, provided it is often renewed." It is noteworthy that all these preparations save the roots employ European hemp, generally in its raw state. This suggests that further investigation of cannabidiolic acid be undertaken. If any is converted in processing to CBD, then certainly its activity as a TRPV1 agonist/desensitizer is germane in decreasing both attendant pain and apoptotic cell death after burns (Radtke et al. 2011).

2.3.4 Cannabis in pediatrics

This author has addressed this topic previously (Russo 2003), but with subsequent advances in cannabis-based therapeutics, the need to re-examine the issue is clear, in spite of any attendant controversy. It is a simple truism that any pharmacological agent released to general usage eventually finds application in children, and in fact, regulatory bodies in the European Union and US now require pediatric clinical trials for all newly approved pharmaceuticals. The questions then become, not whether to employ cannabis in children, but rather, how to do so safely and for what indications.

Actually, as the chronology attests, cannabis has been employed in children probably as long as in any other age group. This is additionally supported by ethnobotanical evidence. In Nepal,

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cannabis has been mixed with sweets to calm children while their mothers worked the fields (Fisher 1975). Cannabis candy is employed in Uzbekistan as an analgesic for boys undergoing circumcision (Benet 1975). In Jamaica, cannabis is an essential item of the folk pharmacopoeia. *Ganja* compresses are utilized for pain and wounds, even in neonates (Comitas 1975). *Ganja* tea and tonics are administered for marasmus, infantile diarrhea, teething, and as all-purpose remedies (Dreher 1982). Even noncannabis smokers believe the tea "brainifies" and maintains the young healthy (Dreher 1982, p. 72). Amongst Rastafarians, cannabis smoke may be passively blown towards infants to "make dem smart" and provide "wisdom and health" (Dreher 1982, p. 73). In Costa Rica in two children with asthma, one treated the malady by smoking cannabis, while the other abstained, and succumbed to the disease (Carter 1980). In Morocco, cannabis is combined with mint tea to expel intestinal worms in infants, while infantile diarrhea calls for passive smoke administration (Merzouki and Molero Mesa 1999).

Powdered cannabis in sugar was used in Berlin to treat paroxysmal coughing in children with pertussis (Dierbach 1828). In Calcutta, O'Shaughnessy included children in his trials, amongst them a 40-day-old infant with convulsions. After 20 days, "The child is now in the enjoyment of robust health, and has regained her natural plump and happy appearance" (O'Shaughnessy 1838–1840). Notice quickly spread throughout the British Empire and beyond. Ley followed upon this success by similarly treating a 9-month-old infant (Ley 1842). In England, Clendinning observed benefit of cannabis extract in cough of tuberculosis, and pertussis in a 9-week-old with reduced paroxysms and improved sleep.

Experimentation extended indications in children, including tetanus (*vide infra)*. In Ireland, success was observed in Sydenham's (post-streptococcal) chorea (Corrigan 1845). Benefits on acute and chronic migraine were evident in children (Anstie 1871; Russo 2001b). Reynolds noted the same, plus benefit in spasmodic dysmenorrhea, infantile convulsions, the "temper disease of Marshall Hall," and even infant teething (Reynolds 1890), the latter also espoused in India contemporaneously (Dymock et al. 1890). Its popularity is highlighted by the presence of cannabis in numerous patent medicines sold for children.

In the twentieth century, Morris Fishbein, editor of the *Journal of the American Medical Association*, espoused cannabis in childbirth to aid in a painless labor with no attendant adverse events for the baby (Anonymous 1930).

More recently, the late Ester Fride pioneered exploration of the role of the endocannabinoid system in early development, demonstrating it essential to early initiation of feeding and maternal bonding (Fride 2002b), suggesting application in cystic fibrosis (Fride 2002a), neurotrauma, degenerative diseases, and "non-organic failure to thrive" (Fride 2004, pp. 24–25):

> Developmental observations suggest further that CB_1 receptors develop only gradually during the postnatal period, which correlates with an insensitivity to the psychoactive effects of cannabinoid treatment in the young organism.

This statement is further supported by histological studies in human brain development (Glass et al. 1997), the frequent mention in the nineteenth-century literature that children often tolerated perfectly well heroic doses of cannabis medicines that would engender prostration in an adult, and similar attestations in modern clinical use. One compelling example of the latter is the clinical trial in Israel with Δ^8-THC, up to 0.64 mg/kg/dose, administered onto the tongues of children to allay nausea in chemotherapy, in which it was virtually totally effective and free of side effects (Abrahamov and Mechoulam 1995).

Similarly, in Germany, Lorenz published detailed case reports employing Marinol® (synthetic THC) 0.04–0.12 mg/kg/d in eight children severely affected with degenerative diseases, epilepsy,

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posttraumatic, and hypoxic encephalopathy (Lorenz 2004). Prominent positive results included reduced seizures, spasms, improved social interaction, and palliation in terminal cases. Another case series provides support (Gottschling 2011). Dronabinol (average dose 0.2 mg/kg/d) was administered to 13 severely neurologically impaired children, aged 7 months to 17 years with uniform benefit on spasticity and pain, and improved sleep in ten. No tolerance or dose escalation was apparent in treatment, up to 5 years. More than 50 patients from the age of 3 months were treated for nausea and inanition from chemotherapy. Marked benefit was noted with no serious side effects aside from one self-limited case of tenfold accidental overdose, and no withdrawal effects were seen even after abrupt withdrawal following months of therapy.

An entire book was devoted to a case study of a youngster with severe behavioral abnormalities, controlled by oral cannabis confections (Jeffries and Jeffries 2003), allowing more normal socialization and mainstream education. Numerous anecdotal accounts claim benefit of cannabis in attention-deficit hyperactivity disorder (ADHD) (Grinspoon and Bakalar 1997). As counterintuitive as this may seem, this author (EBR) saw many families and patients in clinical practice with independent attestation of benefits in ADHD. Support has been evident from animal models, wherein impulsive behavior was reduced by a CB_1 agonist (Adriani et al. 2003), or prenatal treatment of mothers with AM404 (inhibitor of cellular uptake of anandamide) to increase anandamide reduced hyperactivity in progeny (Viggiano et al. 2003). Clinical trials of both THC and cannabis (Müller-Vahl et al. 2003a, 2003b) have shown promise in treatment of tics and psychiatric symptoms in Tourette syndrome.

In animal experiments, high-dose THC attenuated induced insulitis and hyperglycemia in a diabetes model (Li et al. 2001), while CBD allowed a lower incidence of diabetes in mice (Weiss et al. 2006), was neuroprotective and retina-preserving in diabetic animals (El-Remessy et al. 2006), and attenuated myriad pathologies associated with diabetic cardiomyopathy (Rajesh et al. 2010). Clinical work in humans certainly seems indicated in type I diabetic children.

Application of cannabinoids for primary cancer treatment has been evident for centuries, and came to the fore once again after early experimental studies of THC in animals (Munson et al. 1975), and in treating human glioblastoma multiforme (Guzman et al. 2006). Recently, two detailed case studies with magnetic resonance imaging and histology have documented complete regression of pilocytic astrocytomas in children treated by their parents with cannabis (Foroughi et al. 2011). Certainly, if such treatment can be effected without psychoactive liability, whether with THC- or CBD-predominant preparations, future applications could be quite promising to achieve benefit with lower toxicity than with conventional chemotherapy. Additional possibilities are only limited by the imagination. Clinical cannabis will likely never be fully accepted in mainstream medicine until it can be proven safe and effective in serious disorders in children. To restate the issue, "If and when cannabis establishes its efficacy in pediatric diseases, it shall have achieved a fair measure of redemption from the derision it has elicited during the past century" (Russo 1998, p. 171).

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