Introduction: Cannabis: From Pariah to Prescription

Ethan Russo

SUMMARY. Cannabis has been employed in human medicine for more than 4000 years. In the last century, political prohibition led to its disappearance from the conventional pharmacopoeia, but this trend is reversing due to the broad acceptance and application of this forbidden medicine by patients with chronic and intractable disorders inadequately treated by available therapeutics. This study addresses the "road back" for cannabis medicines, and reacceptance as prescription products.

Current pharmacology of the two primary therapeutic phytocannabinoids, THC and CBD, is reviewed with respect to herbal synergy and as pertains to treatment of pain, spasm and the wide range of therapeutic applications and adverse effects of cannabis.

In particular, the efforts of GW Pharmaceuticals to develop cannabis based medicine extracts (CBME) are documented including cultivation of genetically-selected medical-grade cannabis cloned strains in glass houses with organic and integrated pest management techniques, and their processing employing supercritical carbon dioxide extraction and winterization. These CBMEs are then available for formulation of dos-

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age forms including sublingual extracts and inhaled forms. An optional Advanced Delivery System (ADS) is also discussed.

KEYWORDS. Medical marijuana, cannabis, THC, cannabidiol, herbal treatment, alternative delivery systems, psychopharmacology

The *Journal of Cannabis Therapeutics* is pleased to mark with this the publication the transition of cannabis from a forbidden herb back into the realm of prescription medicine. Although a recognized and documented therapeutic agent for more than 4000 years (Aldrich 1997; Russo 2003; Russo 2001), cannabis became politicized in the early 20th century, leading to its ultimate prohibition in most industrialized nations. Cannabis was dropped from the *National Formulary* in the USA in 1941, and the *British Pharmacopoeia* in 1971. Reasons for the loss of cannabis as an available pharmaceutical were complex, related to a perceived risk of abuse, but also included formidable quality control issues such as lack of reliable or consistent supplies from India, idiosyncratic variability of patient responses to available preparations, and the advent of modern single product pharmacotherapy. The road back for cannabis medicines, as it were, has been a difficult and circuitous journey, beset by politics to a greater extent than science.

The essential features that characterize a prescription medicine require it to be of proven quality, consistency, clinical efficacy, and safety. For the last thirty-plus years, 85% of the world's research dollars for cannabis have been provided by the National Institute on Drug Abuse (NIDA), whose orientation has certainly not tended towards proof of therapeutic efficacy for this ancient herb. The lead has thus been taken by Europeans, whose medicine has never strayed quite so far from the realm of vegetable *materia medica*. Our account will document the progress of GW Pharmaceuticals, which, with full backing of the UK Home Office, has achieved the feat in five years of progressing from the idea of restoring cannabis to the pharmacy, all the way through to submission of a lead product for regulatory approval by the Medicines and Healthcare Products Regulatory Agency (MHRA, formerly the Medicines Control Agency).

As previously published two years ago (Whittle, Guy, and Robson 2001), many hurdles exist when considering the concept of how to produce a prescription cannabis product (p. 186):

- the concept of cannabis-based medicines as botanicals as opposed to pure cannabinoids;
- selective breeding of high yielding chemovars that produce an abundance of one particular cannabinoid;
- investigation of the pharmacological properties of various cannabinoids, i.e., cannabis is not just THC;
- variability of composition of cannabis. The geographical and genetic basis for variation in cannabinoid content of cannabis biomass and its control to give a standardised product;
- the quality aspects of cannabis biomass production;
- routes of administration and optimisation of formulations to achieve particular pharmacokinetic profiles;
- regulatory issues, including health registration, and international legal requirements;
- security packaging and anti-diversionary devices which can be used in connection with cannabis-based medicines in order to satisfy statutory requirements.

As is evident, the process of preparing a botanical for approval as medicine is comparable, but yet more complex than that for the New Chemical Entity (NCE), or novel synthetic pharmaceutical. A formidable barrier remains in the assignation and perception of cannabis as a drug of abuse. In the USA, cannabis was placed in the most restrictive category, Schedule I of the Controlled Substances Act in 1970, which encompasses drugs that are dangerous and addictive and lack recognized medical utility. It requires emphasis that this assignment was political and designed as a temporary, pending reassignment by the Shaffer Commission in 1972 (Abuse 1972). President Nixon rejected their recommendations of medical access and decriminalization before even reading the final report. Additionally, Schedule I assignation remains anachronistic (Haines et al. 2000). Many such drugs, including cannabis and LSD have had clear therapeutic indications in the past. Others, such as diamorphine (heroin), are forbidden in the USA, but retain legal pharmaceutical status in the UK. At least, controversy about such blanket proscriptions exists, and certainly with advancing knowledge, debate and reconsideration are required. A detailed analysis of the complexities of the cannabis question in the UK is available (Whittle and Guy

2003). The same publication outlines scientific evidence that cannabis based medicine extracts (CBME) may offer a distinct advantage over THC alone (Marinol®):

1. *Potentiation*. Based on a concept noted for endocannabinoids and their precursors called the "entourage effect" (Ben-Shabat et al. 1998; Mechoulam and Ben-Shabat 1999), various phytocannabinoid components, whether active (CBD, CBC) or relatively inactive (CBN) affect the cannabinoid receptor binding, pharmacokinetics and metabolism of THC. The same may be true of non-cannabinoid components, such as the essential oil terpenoids (McPartland and Russo 2001; Russo and McPartland 2003).
2. *Antagonism*. Cannabidiol mitigates side effects of THC (Karniol et al. 1975; Mechoulam, Parker, and Gallily 2002), including its intoxication liability. Additionally, other cannabis components may be helpful in this regard, e.g., terpenoids such as pulegone, 1, 8-cineole, and α-pinene may counter the short-term memory impairment engendered by THC (McPartland and Russo 2001; Russo and McPartland 2003).
3. *Summation*. A number of cannabis components may contribute to a certain therapeutic effect of THC (Williamson and Evans 2000; McPartland and Russo 2001).
4. *Pharmacokinetic*. For example, CBD alters the metabolism of THC by inhibiting its hepatic conversion to 11-OH-THC (Zuardi et al. 1982).
5. *Metabolism*. Whittle and Guy (2003) argue, as have others (Tyler 1994; Russo 2001) that due to co-evolution over the millennia, humans are better able to metabolize herbal preparations (i.e., cannabis) as compared to synthetic pharmaceuticals (i.e., synthetic cannabinoids).

Beyond the issues of regulation and rationale, the next step is to grow the plant. *Cannabis sativa*, despite its cosmopolitan propagation on the planet, is a rather exacting species insofar as optimal production of desirable medicinal cannabinoids is concerned. Such production is greatest in unfertilized female flowering tops, most commonly known as *sinsemilla* (Spanish, "without seed"), or *ganja*, the Sanskrit term for a process known in India for some 2500 years (Figure 1). THC production is increased by selecting certain strains and exposing them to ultraviolet light (Pate 1994). In the organization of the primary GW Pharmaceuticals production glasshouse, David Potter and Etienne de

FIGURE 1. Unfertilized female cannabis flower (photograph courtesy of GW Pharmaceuticals).

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Meijer have outlined additional important factors (Potter 2003; de Meijer 2003): high yield per area, high cannabinoid purity, high inflorescence to leaf ratio ("harvest index"), avoidance of diseases and pests, production of sturdy growth conducive to subsequent processing and ease of harvest.

Consistency is achieved by clonal propagation of cuttings from select strains called "mother plants," that yield shorter specimens with less waste stem material. Successful propagation occurs with 95% of cuttings (Figure 2).

A decision was made to produce different cannabinoid ratios for prescription CBMEs, through the use of separate high-THC and high-CBD strains, or their combination in a fixed-ratio. This work was initiated by HortaPharm B.V. a generation ago in Holland, and selected strains were developed there, and the seeds imported into the UK in 1998 (de Meijer 2003). The high-THC strain was originally produced by hybridization of ((Afghani $\times$ Mexican) $\times$ Colombian) genetics, said to be reminiscent of the commercial (if illegal) "Skunk #1" strain (Potter 2003). An initial 400 plants grown from seed were analyzed for cannabinoid concentration and purity, leading to five chemovars ("chemical varieties" or phenotypes) that were selected for commercial cultivation potential. A high-CBD strain was similarly selected from 1600 seeds yielding a selection of the best four chemovars. It has been determined that cannabis

FIGURE 2. Clonal growth in glasshouse (photograph courtesy of GW Pharmaceuticals).

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plant vigor, architecture, and glandular trichome density and metabolic efficiency in cannabinoid production are all polygenetically-determined traits, but affected by environmental factors (de Meijer 2003; de Meijer et al. 2003). Together, they determine the "cannabinoid quality." The chemovar is the primary determinant, however, of what cannabinoid ratios result. Additional line selection via repetitive self-fertilization has also been employed to maximize appropriate selection of both parents of a hybrid (de Meijer 2003).

In this particular instance, GW Pharmaceuticals chose to produce separate chemovars that selectively yield THC, CBD and THCV (83% theoretical maximum), CBC (76% theoretical maximum) or even CBG in relatively high amounts (de Meijer 2003). Although genetic modification (GM) of cannabis has often been discussed in certain quarters, it is abundantly clear from the above discussion that tremendous variation of chemical parameters is readily available with application of standard Mendelian genetic breeding techniques, and there is no rational reason for adding to the cannabis controversy by rendering it a genetically-modified organism (GMO).

As cannabis propagation and quality are subject to the vagaries of weather, all the more in a cloudy and wet northern clime, artificial light-

ing under glass was deemed the preferred method for pharmaceutical production in the UK. Mother plants are grown under high-pressure sodium (HPS) lights continuously at 75 watts/m^2 PAR (Photosythetically Active Radiation) (equivalent to 31,000 lux of natural sunlight) at 25°C in an organic compost ("leaf mould") to a height of 2 m, allowing pruning and the production of as many as 80 more cuttings for propagation (Potter 2003). The mother plant may be utilized for two or more "flushes" over the next few months before its vigor diminishes.

Clones are placed in peat pots after treatment with rooting hormone, trimming to retain one axial bud, and are grown out in polythene tunnels under high humidity with 24 hour light for two weeks until "potting up" (Potter 2003). Plants are continued under perpetual illumination for about three weeks until attaining a height of 50 cm, before shifting to a 12-hour light/12-hour dark critical day-length regimen to induce flowering.

All cultivation is performed in accord with Good Agricultural Practice (GAP) methods of the European Medicines Evaluation Agency in conjunction with rules of the UK Medicines Control Agency (Medicines Control 1997) for the production of a Botanical Drug Substance (BDS). [For the approved process of medicinal cannabis cultivation in the Netherlands, see the article in a prior issue of *Journal of Cannabis Therapeutics* (Anonymous 2003)]. Microbiological safety is crucial, and is a monitored function by regulatory agencies. In this instance GW Pharmaceuticals chose to use some minimal mineral sources of soil enrichment to avoid possible pathogen exposure from organic sources (Potter 2003). However, no pesticides whatsoever have been employed. Common pests are kept at bay by positive pressure in the glasshouses, and utilization of integrated pest management (IPM). Pests of concern have included spider mites (*Tetanychus* spp.) and onion (tobacco) thrips (*Thrips tabaci*). These are controlled through release of predatory mites, and kept at low level. For a comprehensive examination of the topic, the reader is urged to consult the superb *Hemp diseases and pests: Management and biological control* (McPartland, Clarke, and Watson 2000).

Fungal issues to date at the GW facilities have mainly pertained to grey mold (*Botrytis cinerea*) and powdery mildew (*Sphaerotheca macularis*). Control is achieved mainly by avoidance of high humidity close to time of harvest for the former, and increasing light pressure while avoiding excessive nitrogen exposure for the latter. When diseased plants do arise, affected specimens are destroyed.

While trials of outdoor cultivation were attempted with CBD-rich strains, daunting problems were encountered in the cool, damp British climate (Potter 2003).

Because cannabigerol (CBG) levels are dependent upon plant maturity, both the THC- and CBD-rich chemovars are harvested at the same growth stage at the onset of senescence, at which time the flowering tops representing 90% of the weight of the plants' aerial portions. Drying under a stream of dehumidified air from 25 down to 12% moisture content is then achieved under dark conditions to minimize cannabinoid oxidation (Whittle, Guy, and Robson 2001). The resultant mixture of dried unfertilized flowers, stalks and leaves yields 15% THC or 8% CBD in the respective chemovars (Figures 3, 4, and 5).

Interestingly, in the "raw" state, much of the THC and CBD are in the form of cannabinoid acids, THCA and CBDA, which are low in cannabinoid pharmacological activity. It is only after decarboxylation by progressive oxidation over time, after heating, or in the extraction process, that significant THC and CBD levels are produced and pharmacological benefits are obtained.

FIGURE 3. High CBD strain in GW Pharmaceuticals glasshouse (photograph courtesy of David Downs, PhD, GW Pharmaceuticals).

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FIGURE 4. High THC strain in GW Pharmaceuticals glasshouse (photograph courtesy of David Downs, PhD, GW Pharmaceuticals).

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Historically, cannabis extracts were ethanol-based, dating back to the experiments of O'Shaughnessy in India in the 19th century (O'Shaughnessy 1838-1840). GW Pharmaceuticals has opted for a more modern technique employing supercritical CO_2 extraction (Whittle, Guy, and Robson 2001). This has distinct advantages, as organic materials are extracted at approximately body temperature with retention of essential oil terpenoid components that seemingly contribute to medicinal effects of cannabis (McPartland and Russo 2001). Additionally, no solvent residue remains after the process. Although such extraction does include some waxy ballast, this is easily removed by "winterization," or chilling in an ethanol solution. The resultant liquid CBME is then ready for pharmaceutical preparation.

Whereas oral ingestion and smoking have been favored methods of application in the past, they are not likely to be the primary modes of administration in the future of clinical cannabis as a prescription medicine. Oral administration, such as with Marinol® (synthetic THC, or "dronabinol" in sesame oil) was introduced into the USA market in

FIGURE 5. Dried cannabis ready for processing (photograph courtesy of GW Pharmaceuticals).

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1986, but has been relatively little employed (Russo 2002). Reasons include expense, delayed onset of effects in the range of 90-120 minutes, lack of practical titration of dosage, and a pronounced tendency toward dysphoria or other mental complaints from being "too high." In part, this may relate to hepatic first-pass conversion of THC to 11-OH-THC, which may possess a higher degree of psychoactivity according to some authorities. Interestingly, the presence of CBD, which is present in natural cannabis, but obviously absent in Marinol®, impedes this hepatic conversion by inhibition of cytochrome P450 3A11 (Browne and Weissman 1981).

Although smoking of cannabis was an acknowledged delivery system in the past, with cigarettes from the Grimault et Cie Company among others, and endorsement by such experts as Walter E. Dixon in England (Dixon 1899, 1921) and Walther Straub in Germany (Straub

1931), it is highly unlikely that regulatory agencies such as the Food and Drug Administration (FDA) would ever approve a drug delivery system that produces bronchial irritation and contains pyrolytic end-products that are potentially carcinogenic (Tashkin et al. 2002). Vaporization technology presents a viable option, preserving as it does the rapid bronchial absorption of cannabis components, and retaining the ability to titrate dosage rapidly. It is in initial stages of investigation (Gieringer 1996; Gieringer 1996; Gieringer 2001; Russo and Stortz 2003). This approach will require both elucidation of the pharmacokinetics of the vaporization technique, and approval of the hardware as a medical device. As will be discussed, GWP has developed an inhaled device (patent application GB0126150.2) that employs a metallic or ceramic surface coated with CBME that is heated by electrical current. The process is triggered by inhalation, employing the Advanced Dispensing System (ADS) (*vide infra*) providing the advantages of smoked cannabis (rapid onset, ready dosage titratability), but without hazards posed by smoke particles or inhalation of solvents.

Inhaled, non-smoked delivery of isolated THC has been previously investigated (Tashkin et al. 1977), but curiously, the isolated molecule is quite irritating to the bronchioles and induces a cough reflex despite its notable bronchodilatory benefits (Williams, Hartley, and Graham 1976). Biophysical parameters for this method of delivery are exacting, and have been recently reviewed (Whittle, Guy, and Robson 2001). Particles of diameter greater than 10 μ fail to reach the bronchioles. Those below 1 μ are mostly re-expired. It is only those particles in the 1-2 μ range that stand the best chance to be absorbed from the alveoli. Inasmuch as THC is an extremely viscous molecule that sticks to any vessel, dispersion in a solvent such as alcohol or propylene glycol is most often necessary, and introduces its own adverse effect issues in pulmonary application. This search for modern alternatives to smoked cannabis continues, however, through the use of a metered dose inhaler (Wilson et al. 2002) for THC. Although some seemingly represent that THC represents the sum total of important pharmacological effects of cannabis (Wachtel et al. 2002), others counter (McPartland and Russo 2001; Russo and McPartland 2003) in contrast, that the presence of other phytocannabinoid and terpenoid component such as myrcene, with its analgesic and anti-inflammatory effects (Rao, Menezes, and Viana 1990; Lorenzetti et al. 1991), or α-pinene, which is also a bronchodilator (Falk et al. 1990), or apigenin, wich is a non-sedating flavonoid in cannabis (Viola et al. 1995), contribute demonstrably to its clinical attrib-

utes. This debate will continue, engendering as it does the basic conflict between single-component "modern" pharmacology, and old-fashioned but resurgent notions of phytotherapeutic synergy.

Suppository forms of cannabis have been documented as far back as Ancient Egypt (Mannische 1989; Russo 2002), and the Victorian era (Farlow 1889). Modern research effort has also revived the concept, most often with Δ^9-THC-hemisuccinate (Broom et al. 2001; Elsohly et al. 1991). This method lacks convenience, is less subject to allow titration of dosage, and may be cosmetically unacceptable, especially in particular American consumers.

Transdermal delivery of cannabinoids is an attractive possibility as consumers have found "patches" to be a convenient method of drug delivery via this parenteral, long-acting method. Problems with this method have been previously outlined (Whittle, Guy, and Robson 2001). In essence, they include the lipophilic nature of cannabis components, the need for carrier molecules or other facilitators of transdermal absorption, and results to date that approximate only 10% of necessary serum levels (Challapalli and Stinchcomb 2002). Finally, the gradient of transport of cannabinoids through the skin is such that a used patch would still retain 90% or more of initial dosage, and would thereby represent a theoretical diversion risk upon disposal.

GW Pharmaceuticals primary efforts to date have focused on an approach employing a sub-lingual or oro-mucosal spray of CBME in ethanol and propylene glycol solution. The oro-mucosal preparation employs a pump action aerosol spray (Robson and Guy 2003; Whittle and Guy 2003) (Figure 6). This dispersion of materials allows reasonably rapid absorption (45 minutes), preserving the ability to titrate dosage, avoiding excessive swallowing of material, and producing an area under the curve that is comparable to that for smoked or intravenous administration of THC (Whittle and Guy 2003). Experiments in the UK with a simple unadorned device have demonstrated no major compliance problems, nor diversion of CBME to the black market. There are no plans to introduce pharmaceutical products with CBME in the UK, Western European or British Commonwealth nations with added security devices. However, it is anticipated that such security would be a necessary prerequisite in the USA for Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) approval (Figure 7). Thus, an additional Advanced Delivery System (ADS) has been developed (Figure 8). The ADS is a hand-held computerized encrypted device which may (Robson and Guy 2003; Whittle and Guy 2003):

1. remind patients of times dosing is due
2. record daily patterns and fluctuations in doses employed
3. allow remote computer monitoring of dosage employed by researchers or clinicians
4. render the device secure, tamper-proof, and patient-specific through individual codes
5. allow delivery of a variety of dosage forms (e.g., CBME with THC-CBD 1:1 ratio for daily usage, with high-THC preparation for sudden bouts of pain)
6. be suitable for usage with controlled drugs such as methadone or diamorphine (heroin).

CLINICAL STUDY DESIGN

As will be seen subsequently, initial Phase I studies of CBME examined pharmacokinetics and adverse effects of the materials in normal

FIGURE 6. Pump Action Sublingual Spray as utilized in the United Kingdom (photograph courtesy of GW Pharmaceuticals).

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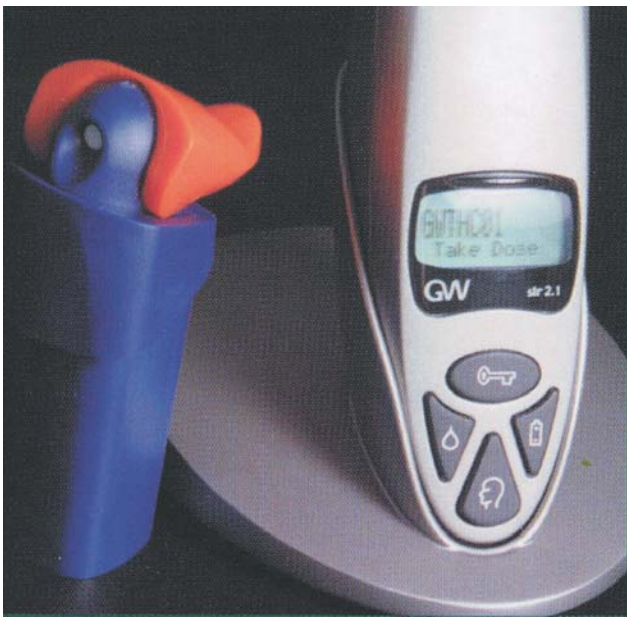
FIGURE 7. Sublingual spray as part of Advanced Delivery System (photograph courtesy of GW Pharmaceuticals).



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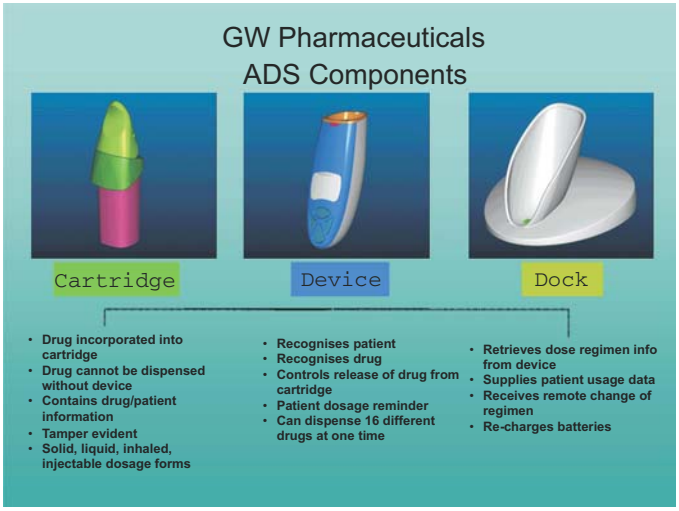
volunteers with monitoring of dose-response parameters, as well as pulse, blood pressure and subjective and objective assessments of intoxication. Although criticized, the current "gold standard" in pharmaceutical assessment is the double-blind randomized placebo-controlled clinical trial (RCT). An accepted variation in this approach that is worthwhile in contexts in which true blinding is difficult to achieve (as with cannabis) or in assessment of unpredictable diseases (such as multiple sclerosis) is presented by the N-of-1 trial design, achieved through a series of randomized, placebo controlled studies in which each subject serves as their own control (Guyatt et al. 1990). In fact, this approach to cannabis clinical trials was specifically endorsed by the American Institute of Medicine (Joy, Watson, and Benson 1999).

In assessing target conditions for initial studies, GWP relied on a survey of clinical cannabis patients and their conditions. In 1998, some 3516 self-selected patients who contacted the company were sent survey forms, of which 2458 were completed (70% response rate) (Robson and Guy 2003). Of 787 current or past cannabis users, the greatest rep-

FIGURE 8. Diagram of Advanced Delivery System (ADS) (courtesy of GW Pharmaceuticals).



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resentation was among patients with MS or various arthritic conditions. This contrasts with the situation in the USA, where HIV/AIDS is more highly represented, but where chronic pain remains a prime concern (Corral 2001; Gieringer 2001).

Another priority in selection of patients for clinical investigation involved a decision to study those with intractable conditions that had failed to be symptomatically controlled by available conventional pharmaceuticals. This was based on a philosophical decision to demonstrate that CBME would not merely be equal in efficacy to standard drugs, but rather, offer tangible advantages in difficult clinical contexts. A decision was also made to add CBME to patients' existing pharmaceutical regimens to provide a baseline comparison.

For MS patients, entry criteria included the presence of one or more poorly controlled symptom despite best available treatment: pain, spasm, spasticity, tremor or urinary difficulty, whether frequency, urgency, nocturia or incontinence (Robson and Guy 2003; Whittle and Guy 2003). Patient exclusions were similar to those employed in previous studies of cannabis or Marinol®: history of serious drug or alcohol abuse, schizophrenia, uncontrolled cardiovascular conditions including hypertension, impaired hepatic or renal function, and epilepsy. All na-

tional norms for clinical research and Guidelines for Good Clinical Practice (GCP) were followed.

Noting past historical data on individual idiosyncrasies of dosing and responses to cannabis by patients, a requirement was pursued to deliver initial THC:CBD 1:1 CBME dosages in open-label fashion with close monitoring, in an attempt to establish initial individual dose guidelines. This was then followed by randomized double-blind crossover comparisons of that preparation versus placebo and high-THC and high-CBD CBMEs. Subsequent monitoring employed an array of subjective measures (via visual analogue scales, or VAS) and objective measures on examination and laboratory study. Patients who demonstrated benefits in initial studies were given the option of entering long-term safety studies, and a majority of patient-subjects chose to do so (Robson and Guy 2003). The results of these trials form the basis for the remainder of this publication.

THC AND CBD: SUMMARY OF CURRENT KNOWLEDGE

Although this author has emphasized the biochemical and physiological contribution importance of other cannabis components (minor cannabinoids, terpenoids and flavonoids) to the medical therapeutic benefits of cannabis (McPartland and Russo 2001), it is clear from the data that exist to date that two entities provide the greatest effects: Δ^9-tetrahydrocannabinol and cannabidiol. A complete analysis of current knowledge is beyond our scope, but it is appropriate to briefly summarize current knowledge of their contributions (Table 1).

Receptor Effects

THC is a partial agonist at both CB_1 and CB_2 receptors (Pertwee 1998; Showalter et al. 1996). In contrast, CBD has little activity, and perhaps slight antagonistic activity at CB_1, while greater activity at CB_2 (Showalter et al. 1996). Of great importance, it has recently been demonstrated that cannabidiol stimulates vanilloid receptors (VR_1) with similar efficacy to capsaicin, and inhibits uptake of the endocannabinoid anandamide (AEA), and weakly inhibits its hydrolysis (Bisogno et al. 2001). These new findings have important implications in elucidating the pain-relieving and anti-inflammatory effects of CBD. In a

TABLE 1. Therapeutic/Adverse Effects of THC and CBD

Effect	THC	CBD	Reference
Receptor/Non-Receptor Effects			
CB_1 (CNS receptors)	++	±	(Pertwee 1998)
CB_2 (Peripheral receptors)	+	++	(Showalter et al. 1996)
Vanilloid Receptors	–	+	(Bisogno et al. 2001)
Anti-inflammatory	+	+	(Hampson et al. 1998)
Immunomodulatory	+	++	(Malfait et al. 2000; Cabral 2001)
CNS Effects			
Anticonvulsant	+	++	(Wallace, Martin, and DeLorenzo 2002; Carlini and Cunha 1981)
Muscle Relaxant	+	++	(Petro 1980)
Antinociceptive	++	+	(Pertwee 2001)
Catalepsy	++	++	(O'Shaughnessy 1838-1840)
Psychotropic	++	–	(Russo 2001)
Anxiolytic		+	(Zuardi and Guimaraes 1997)
Antipsychotic	–	++	(Zuardi and Guimaraes 1997)
Neuroprotective antioxidant activity	+	++	(Hampson et al. 1998)
Antiemetic	++	–	(Chang et al. 1979)/(Guy et al. 2002)
Sedation (reduced spontaneous activity)	+	+	(Zuardi and Guimaraes 1997)
Agitation (Alzheimer disease)	+		(Volicer et al. 1997)
Tic reduction	+		(Müller-Vahl et al. 1999)
Withdrawal effects (reduction)	+		(Cichewicz and Welch 2002; Reynolds 1890)
Migraine	+		(Russo 2001; Russo 1998)
Bipolar disease	+		(Grinspoon and Bakalar 1998)
Cardiovascular Effects			
Bradycardia	–	+	(Weil, Zinberg, and Nelsen 1968)
Tachycardia	+	–	ditto
Hypertension	+	–	ditto
Hypotension	–	+	(Adams et al. 1977)
Appetite/Gastrointestinal			
Appetite	+	–	(da Orta 1913)
Motility (slowed)	+		(Pertwee 2001)
Neonatal feeding (endocannabinoid)	+		(Fride 2002)
Anti-Carcinogenesis			
Melanoma (apoptosis, angiogenesis)	+		(Casanova et al. 2003)
Breast (prolactin receptor)	+		(De Petrocellis et al. 1998)
Glioma (apoptosis)	+	+	(Sanchez et al. 1998; Vaccani, Massi, and Parolaro 2003)
Leukemia (apoptosis)	+		(McKallip et al. 2002)
Pulmonary (blocks carcinogenesis enzymatically)	+		(Roth et al. 2001)
Pulmonary			
Bronchodilation	+		(Williams, Hartley, and Graham 1976; Tashkin et al. 1977)
Ophthalmological			
Intra-ocular pressure (reduced)	++	+	(Merritt et al. 1980; Jarvinen, Pate, and Laine 2002)
Night vision (improved)	+*		(Russo et al. 2003; West 1991)

Adapted and expanded from (Whittle, Guy, and Robson 2001; Whittle and Guy 2003).
* New indication. See final article in this publication.

manner of interpretation, CBD may be considered the first clinical agent that modulates endocannabinoid function.

Anti-Inflammatory and Immunomodulatory Effects

The benefits of cannabis and cannabinoids on inflammation have been extensively documented. The following are suggested as reviews (Hampson et al. 1998; Pertwee 2001; Burstein 1992; Russo 2001). Both THC and CBD have important roles in these observations. Of increasing interest is the recent demonstration that CBD possesses both anti-inflammatory and immunomodulatory benefits in an animal model of rheumatoid arthritis (Malfait et al. 2000). Although there has been great concern expressed as to immunological damage by cannabis, such effects are usually demonstrable in laboratory assays at levels 50-100 times the psychoactive dose (Cabral 2001). Deleterious clinical effects of cannabis in HIV (Abrams et al. 2002), and chronic medical usage (Russo et al. 2002) have not been demonstrated.

Central Nervous System Effects

Of prime importance in cannabinoid therapeutics is pain control or antinociception (Pertwee 2001; Russo 2001). One of the primary functions of the endogenous cannabinoid system is modulation of pain control, in parallel with the endogenous opioid and vanilloid systems. THC is the main contributor of cannabis to control of pain, via its actions on CB_1, which occur in key areas of the spinal cord, and brainstem. A purported "comprehensive" review of the analgesic effects of cannabinoids concluded that they have little demonstrated benefit (Campbell et al. 2001), but this pronouncement produced strong refutation (Russo 2001) and more considered subsequent support (Baker et al. 2003) in some quarters. Countless testimonials attest to the unique benefits of cannabis in difficult cases of neuropathic pain (Grinspoon and Bakalar 1997), and other unusual and intractable conditions, such as familial Mediterranean fever (Holdcroft et al. 1997).

The cataleptic effects of high doses of THC were noted by O'Shaughnessy in 1839 (O'Shaughnessy 1838-1840), and this effect remains part of the tetrad of behavioral effects sought in laboratory animals as a sign of cannabinoid activity.

Cannabis was noted to have anticonvulsant effects in the 19th century. Primary focus of therapeutic benefit on seizures of partial onset has focused on CBD (Carlini and Cunha 1981), while it was generally

believed that THC was proconvulsant. Epileptic patients have generally claimed otherwise (Corral 2001), and it was recently demonstrated that endocannabinoids modulate seizure thresholds, and that THC exerts an anticonvulsant effect, as well (Wallace, Martin, and DeLorenzo 2002).

Migraine is a neurochemical and vascular disorder of exceeding complexity, whose treatment remains extremely problematical. The multi-modality effects of cannabis seem to support its historical role in both symptomatic and prophylactic treatment (Russo 1998; Russo 2001). While THC has received the bulk of the attention in therapeutic application, this author's experience with Marinol® treatment would seem to support that the benefits on chronic migraine treatment do not mirror the high efficacy of historical claims in the Victorian era. Current discoveries of the endocannabinoid modulation and vanilloid receptor effects of CBD discussed above (Bisogno et al. 2001) would seem to support that cannabidiol is a necessary component to successful prophylaxis in migraine.

Antidepressant and anti-anxiety effects of cannabis date to ancient India in the *Atharva Veda*, and the Scythians (Herodotus 1998). Certainly, an antidepressant effect of cannabis has been observed in chronic disease (Herodotus 1998; Russo et al. 2002; Regelson et al. 1976). In general, THC is considered psychotropic, while CBD generally is not (reviewed in Russo 2001). Rather, cannabidiol is noteworthy for its anxiolytic, sedative and antipsychotic effects (Zuardi and Guimaraes 1997). Interestingly, THC (as Marinol®) was recently observed to produce weight gain and reduce agitation in demented Alzheimer disease patients (Volicer et al. 1997). Unfortunately, CBD was not examined, but very likely would have contributed to the clinical benefits. Anecdotal reports support benefit of THC in mood-stabilization in bipolar disease (Grinspoon and Bakalar 1998).

The antispasmodic effects of cannabis were observed in such diseases as tetanus in the 19th century, producing cures of fatal diseases, and palliation of chronic disorders (O'Shaughnessy 1838-1840). Muscle relaxant properties of cannabis in multiple sclerosis were noted more recently (Petro 1980; Grinspoon and Bakalar 1997), and have recently been reviewed in detail (Baker et al. 2003; Consroe 1998; Petro 2002). These will form the focus of many of the study results subsequently discussed in this publication. As if the muscle relaxant and anti-spasmodic benefits of cannabis were insufficient, it has recently been demonstrated that cannabinoid agonists positively influence the immunological parameters of demyelinating diseases such as experimentally allergic encephalomyelitis (Baker et al. 2000). In the past year,

a small clinical trial of THC and a cannabis extract was performed with 16 subjects. Neither was observed to reduce spasticity, and adverse events were reported in the extract group (Killestein et al. 2002). Numerous criticisms were subsequently voiced in this regard (Russo 2003). Among these were that the plant extract was poorly categorized; in fact, it contained a fixed ratio of THC to CBD with maximum doses of 5 mg of THC and 2 mg of CBD per day. The study additionally employed oral administration with no real dose titration. An additional study in Switzerland with more patients (57) and doses of up to 15 mg THC with 6 mg CBD divided tid has provided better results with reduction in spasms to the $p < 0.05$ level and no significant side effects vs. placebo (Vaney et al. 2002). A study of an even larger cohort of MS patients in the UK is pending publication.

Kirsten Müller-Vahl has pioneered the use of cannabis and THC in Tourette syndrome, demonstrating a marked reduction in tic behavior and obsessive-compulsive preoccupation (Muller-Vahl et al. 2003; Müller-Vahl et al. 1999).

The antiemetic effect of THC in morning sickness was noted as early as the 19th century (Wright 1862), and was further elucidated in the last two decades (Chang et al. 1979). A tremendous body of knowledge in this context that has been historically ignored was recently published in this journal (Musty and Rossi 2001). This pertained to state-sponsored studies in the USA in cancer chemotherapy. Pooling available data in some 768 patients, oral THC provided 76-88% relief of nausea and vomiting, while smoked cannabis figures supported 70-100% relief in the various surveys. Also worthy of inclusion here, an Israeli study of 8 children receiving highly emetogenic chemotherapy for hematological malignancies with oral Δ^8-THC (a trace and more stable component of cannabis) was 100% effective in allaying vomiting in 480 dose applications! Surprisingly, slight euphoria was noted in only one subject, causing the authors to surmise that the appreciation of the cannabis "high" is a developmental phenomenon. Shockingly, this study has never been followed by more similar investigations.

Surprisingly as well, it has just been demonstrated that CBD also has anti-emetic benefits in motion sickness in rodents (Guy et al. 2002), an indication that has wide implications, including space flight.

Although THC and cannabis are often attacked as productive of addiction, it is well documented from the 19th century that prominent physicians claimed benefit of Indian hemp in treatment of alcohol, morphine and cocaine dependencies (Reynolds 1890). As is becoming a recurrent

theme, the claims of the Victorian era are resonating with modern scientists who subsequently prove their biochemical and physiological basis. This benefit has been strikingly demonstrated in the laboratory, through "opiate-sparing" by THC (Cichewicz et al. 1999), and more recently, the effect of THC to mitigate opiate-withdrawal symptoms, and block the formation of dependency (Cichewicz and Welch 2002).

One of the most exciting and pressing areas of neurological investigation surrounds the emerging concept of neuroprotection. If one were able to prevent the progressive cell death of parkinsonism, amyotrophic lateral sclerosis, Alzheimer and Huntington diseases, the inevitable deterioration and ultimate demise that these disorders eventuate might well be mitigated or arrested. This is the promise that may accrue to THC and CBD from the research of Hampson et al. (1998) in their demonstration that these agents are capable of blocking NMDA receptors in glutamate toxicity.

Cardiovascular Effects

A pioneering study in 1968 documented transient tachycardia and hypertension induced by THC in experimental subjects (Weil, Zinberg, and Nelsen 1968). Overall however, a mild hypotensive effect of CBD is observed (Adams et al. 1977). Recently, concerns have been raised with respect to cannabis as an inciting influence in myocardial infarction (Mittleman et al. 2001), but no significant epidemiological basis is evident for such claims (Sidney et al. 1997).

Appetite/Gastrointestinal

The appetite stimulating power of cannabis and THC are among the most well known effects (or side effects). This phenomenon was first documented in the West by the physician and explorer, Garcia da Orta, in India in the 16th century (da Orta 1913), but repeatedly studied subsequently. It was this effect that led to an approved indication for THC (as Marinol®) in the USA in 1992. Recently, smoked cannabis and THC demonstrated benefits in appetite and weight gain in hospitalized AIDS subjects (Abrams et al. 2002).

THC slows gut motility (reviewed in Pertwee 2001), providing additional support to the known analgesic and anti-inflammatory benefits in such disorders as Crohn's disease, ulcerative colitis, and idiopathic bowel syndrome (spastic colon).

A much better understanding of the critical role of tonic endocannabinoid function in normal ontogeny has recently been elucidated when Ester Fride and colleagues investigated the role of anandamide in initiation of neonatal feeding, and inevitable demise with its blockade (Fride 2002). Therapeutic use in "failure-to-thrive" states and cystic fibrosis (Fride 2002) are obvious putative applications.

Anti-Carcinogenesis

Whereas, governmental pronouncements have long sought to indict marijuana and THC as contributors to the incidence of cancer, closer analysis has failed to demonstrate epidemiological support for significant danger, even with smoked cannabis (Ware and Tawfik 2001). Little publicity, in contrast, has accrued to an increasing number of studies that demonstrate anti-carcinogenesis by THC.

Legitimate concerns surround the use of smoked cannabis, and its contribution to pulmonary irritation, bronchitis symptoms, and possible neoplastic sequelae (Tashkin 2001). However, recent study indicates that THC and even cannabis smoke block the activity of a key enzyme in pulmonary carcinogenesis (Roth et al. 2001), perhaps explaining the observation that there are still no documented cases of lung cancer in cannabis-only smokers.

THC also has been demonstrated to promote apoptosis (programmed cell death) in malignant conditions including: leukemia (McKallip et al. 2002) via CB_2 stimulation, gliomas (Sanchez et al. 1998), and melanoma (Casanova et al. 2003), in which tumor angiogenesis is also inhibited. Additionally, two types of breast tumor cell lines were inhibited by THC (De Petrocellis et al. 1998), apparently via prolactin receptor effects. This is obviously a fertile area for further research.

Pulmonary

As noted above, the primary medical concerns about cannabis revolve around its pulmonary sequelae. It requires emphasis that these may be totally avoided through alternative delivery techniques. That notwithstanding, it seems that emphysematous deterioration, even in cannabis smokers, is a lower risk than previously surmised (Tashkin et al. 1997). Actual therapeutic application of THC in asthma, as previously attempted (Tashkin et al. 1977; Williams, Hartley, and Graham 1976), may soon become a reality with improved vaporizers or CBME applications.

Ophthalmological

The ability of cannabis and THC to lower intra-ocular pressure in glaucoma was serendipitously discovered in the late 1970s by a variety of patients and researchers (Randall and O'Leary 1998; Merritt et al. 1980). What is more compelling perhaps, in the long run, is the fact that there is more to glaucoma treatment than merely controlling pressure. Even effective management with conventional pharmacology fails to avert visual loss over time. Rather, an emerging concept supports that prospect that glaucoma represents a progressive vascular retinopathy that requires a neuroprotectant to preserve vision (Jarvinen, Pate, and Laine 2002). This is an area where cannabis and cannabinoids shine.

As will be discussed in the final entry in this publication, cannabis and cannabinoids also seem to have a role in improving night vision and in treatment of other degenerative eye conditions (Russo et al. 2003).

REFERENCES

Abrams, D., R. Leiser, J. Hilton, S. Shade, T. Elbeik, F. Aweeka, N. Benowitz, B. Bredt, B. Kosel, J. Aberg, S. Deeks, T. Mitchell, K. Mulligan, J. McCune, and M. Schambelan. 2002. Short-term effects of cannabinoids in patients with HIV-1 infection. Paper read at Symposium on the Cannabinoids, July 13, at Asilomar Conference Center, Pacific Grove, CA.

Abuse, United States Commission on Marihuana and Drug. 1972. *Marihuana: A signal of misunderstanding; First report*. Washington: U.S. Govt. Print. Off.

Adams, M. D., J. T. Earnhardt, B. R. Martin, L. S. Harris, W. L. Dewey, and R. K. Razdan. 1977. A cannabinoid with cardiovascular activity but no overt behavioral effects. *Experientia* 33 (9):1204-5.

Aldrich, M. R. 1997. History of therapeutic cannabis. In *Cannabis in medical practice: A legal, historical and pharmacological overview of the therapeutic use of marijuana*, edited by M. L. Mathre. NC: McFarland.

Anonymous. 2003. Guidelines for cultivating cannabis for medicinal purposes *[Voorschriften voor de verbouw van cannabis voor medicinale doeleinden]*. *J Cannabis Therapeutics* 3 (2):51-61.

Baker, D., G. Pryce, J. L. Croxford, P. Brown, R. G. Pertwee, J. W. Huffman, and L. Layward. 2000. Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 404 (6773):84-7.

Baker, D., G. Pryce, G. Giovannoni, and A. J. Thompson. 2003. The therapeutic potential of cannabis. *Lancet Neurology* 2 (May):291-298.

Ben-Shabat, S., E. Fride, T. Sheskin, T. Tamiri, M. H. Rhee, Z. Vogel, T. Bisogno, L. De Petrocellis, V. Di Marzo, and R. Mechoulam. 1998. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *Eur J Pharmacol* 353 (1):23-31.

Bisogno, T., L. Hanus, L. De Petrocellis, S. Tchilibon, D. E. Ponde, I. Brandi, A. S. Moriello, J. B. Davis, R. Mechoulam, and V. Di Marzo. 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 134 (4):845-52.

Broom, S. L., K. J. Sufka, M. A. Elsohly, and R. A. Ross. 2001. Analgesic and reinforcing proerties of delta9-THC-hemisuccinate in adjuvant-arthritic rats. *J Cannabis Therapeutics* 1 (3-4):171-182.

Browne, R. G., and A. Weissman. 1981. Discriminative stimulus properties of delta 9-tetrahydrocannabinol: mechanistic studies. *J Clin Pharmacol* 21 (8-9 Suppl): 227S-234S.

Burstein, S. 1992. Eicosanoids as mediators of cannabinoid action. In *Marijuana/ Cannabinoids: Neurobiology and neurophysiology of drug abuse*, edited by L. Murphy and A. Bartke. Boca Raton: CRC Press.

Cabral, G. 2001. Immune system. In *Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential*, edited by F. Grotenhermen and E. B. Russo. Binghamton, NY: Haworth Press.

Campbell, F. A., M. R. Tramber, D. Carroll, D. J. M. Reynolds, R. A. Moore, and H. J. McQuay. 2001. Are cannabinoids an effective and safe option in the management of pain? A qualitative systematic review. *Brit Medl J* 323 (7 July):1-6.

Carlini, E. A., and J. M. Cunha. 1981. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol* 21 (8-9 Suppl):417S-427S.

Casanova, M. L., C. Blazquez, J. Martinez-Palacio, C. Villanueva, M. J. Fernandez-Acenero, J. W. Huffman, J. L. Jorcano, and M. Guzman. 2003. Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. *J Clin Invest* 111 (1):43-50.

Challapalli, P. V., and A. L. Stinchcomb. 2002. In vitro experiment optimization for measuring tetrahydrocannabinol skin permeation. *Int J Pharm* 241 (2):329-39.

Chang, A. E., D. J. Shiling, R. C. Stillman, N. H. Goldberg, C. A. Seipp, I. Barofsky, R. M. Simon, and S. A. Rosenberg. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med* 91 (6):819-24.

Cichewicz, D. L., Z. L. Martin, F. L. Smith, and S. P. Welch. 1999. Enhancement of mu opioid antinociception by oral delta9-tetrahydrocannabinol: Dose-response analysis and receptor identification. *J Pharmacol Exp Ther* 289 (2):859-67.

Cichewicz, D. L., and S. P. Welch. 2002. The effects of oral administration of delta-9-THC on morphine tolerance and physical dependence. Paper read at Symposium on the Cannabinoids, July 13, at Asilomar Conference Center, Pacific Grove, CA.

Consroe, P. 1998. Brain cannabinoid systems as targets for the therapy of neurological disorders [In Process Citation]. *Neurobiol Dis* 5 (6 Pt B):534-51.

Corral, V.L. 2001. Differential effects of medical marijuana based on strain and route of administration: A three-year observational study. *J Cannabis Therapeutics* 1 (3-4):43-59.

da Orta, Garcia. 1913. *Colloquies on the simples and drugs of India*. London: Henry Sotheran.

de Meijer, E. 2003. The breeding of cannabis cultivars for pharmaceutical end uses. In *Medicinal uses of cannabis and cannabinoids*, edited by B. A. Whittle, G. W. Guy and P. Robson. London: Pharmaceutical Press.

de Meijer, E. P., M. Bagatta, A. Carboni, P. Crucitti, V. M. Moliterni, P. Ranalli, and G. Mandolino. 2003. The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics* 163 (1):335-46.

De Petrocellis, L., D. Melck, A. Palmisano, T. Bisogno, C. Laezza, M. Bifulco, and V. Di Marzo. 1998. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proc Natl Acad Sci U S A* 95 (14):8375-80.

Dixon, W. E. 1899. The pharmacology of *Cannabis indica*. *Brit Med J* 2:1354-1357.

_____1921. A manual of pharmacology. 5th ed. London: Edward Arnold & Co.

Elsohly, M. A., T. L. Little, Jr., A. Hikal, E. Harland, D. F. Stanford, and L. Walker. 1991. Rectal bioavailability of delta-9-tetrahydrocannabinol from various esters. *Pharmacol Biochem Behav* 40 (3):497-502.

Falk, A. A., M. T. Hagberg, A. E. Lof, E. M. Wigaeus-Hjelm, and Z. P. Wang. 1990. Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scand J Work Environ Health* 16 (5):372-8.

Farlow, J. W. 1889. On the use of belladonna and *Cannabis indica* by the rectum in gynecological practice. *Boston Med Surg Jl* 120:507-509.

Fride, E. 2002. Cannabinoids and cystic fibrosis: A novel approach. *J Cannabis Therapeutics* 2 (1):59-71.

_____2002. Cannabinoids and feeding: The role of the endogenous cannabinoid system as a trigger for newborn suckling. *J Cannabis Therapeutics* 2 (3-4):51-62.

Gieringer, D. 1996. Why marijuana smoke harm reduction? *Bull Multidisciplinary Assoc Psychedelic Stud* 6 (64-66).

Gieringer, D. 1996. Waterpipe study. *Bull Multidisciplinary Assoc Psychedelic Stud* 6:59-63.

_____2001. Medical use of cannabis: Experience in California. In *Cannabis and cannabinoids: Pharmacology, toxicology, and therapeutic potential*, edited by F. Grotenhermen and E. Russo. Binghamton, NY: Haworth Press.

Gieringer, D. H. 2001. Cannabis "vaporization": A promising strategy for smoke harm reduction. *J Cannabis Therapeutics* 1 (3-4):153-170.

Grinspoon, L., and J. B. Bakalar. 1998. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs* 30 (2):171-7.

Grinspoon, L., and J. B. Bakalar. 1997. *Marihuana, the forbidden medicine*. Rev. and exp. ed. New Haven: Yale University Press.

Guy, G. W., B. A. Whittle, F. A. Javid, C. Wright, and R. J. Naylor. 2002. An inhibitory role for cannabinoids in the control of motion sickness in *Suncus marinus*. Paper read at Symposium on the Cannabinoids, at Asilomar Conference Center, Pacific Grove, CA.

Guyatt, G. H., J. L. Keller, R. Jaeschke, D. Rosenbloom, J. D. Adachi, and M. T. Newhouse. 1990. The n-of-1 randomized controlled trial: Clinical usefulness. Our three-year experience. *Ann Intern Med* 112 (4):293-9.

Haines, T., C. D. Adler, T. P. Farley, E. B. Russo, L. Grinspoon, and R. W. Sweet. 2000. Living with our drug policy. *Fordham Urban Law Jl* 28 (1):92-129.

Hampson, A. J., M. Grimaldi, J. Axelrod, and D. Wink. 1998. Cannabidiol and (-)delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A* 95 (14):8268-73.

Herodotus. 1998. *The histories*. Translated by R. Waterfield and C. Dewald. Oxford [England]; New York: Oxford University Press.

Holdcroft, A., M. Smith, A. Jacklin, H. Hodgson, B. Smith, M. Newton, and F. Evans. 1997. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 52 (5):483-6.

Jarvinen, T., D. Pate, and K. Laine. 2002. Cannabinoids in the treatment of glaucoma. *Pharmacol Ther* 95 (2):203.

Joy, Janet E., Stanley J. Watson, and John A. Benson, Jr. 1999. Marijuana and medicine: Assessing the science base. Washington, DC: Institute of Medicine.

Karniol, I. G., I. Shirakawa, R. N. Takahashi, E. Knobel, and R. E. Musty. 1975. Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacol* 13 (6):502-12.

Killestein, J., E. L. Hoogervorst, M. Reif, N. F. Kalkers, A. C. Van Loenen, P. G. Staats, R. W. Gorter, B. M. Uitdehaag, and C. H. Polman. 2002. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurol* 58 (9):1404-7.

Lorenzetti, B. B., G. E. Souza, S. J. Sarti, D. Santos Filho, and S. H. Ferreira. 1991. Myrcene mimics the peripheral analgesic activity of lemongrass tea. *J Ethnopharmacol* 34 (1):43-8.

Malfait, A. M., R. Gallily, P. F. Sumariwalla, A. S. Malik, E. Andreakos, R. Mechoulam, and M. Feldmann. 2000. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci U S A* 97 (17):9561-6.

Mannische, L. 1989. *An ancient Egyptian herbal*. Austin: University of Texas.

McKallip, R. J., C. Lombard, M. Fisher, B. R. Martin, S. Ryu, S. Grant, P. S. Nagarkatti, and M. Nagarkatti. 2002. Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. *Blood* 100 (2):627-34.

McPartland, J. M., R. C. Clarke, and D. P. Watson. 2000. *Hemp diseases and pests: Management and biological control*. Wallingford, UK: CABI.

McPartland, J. M., and E. B. Russo. 2001. Cannabis and cannabis extracts: Greater than the sum of their parts? *J Cannabis Therapeutics* 1 (3-4):103-132.

Mechoulam, R., and S. Ben-Shabat. 1999. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: The ongoing story of cannabis. *Nat Prod Rep* 16 (2): 131-43.

Mechoulam, R., L. A. Parker, and R. Gallily. 2002. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol* 42 (11 Suppl):11S-19S.

Medicines Control, Agency. 1997. Rules and guidance for pharmaceutical manufacturers 1997: Orange Guide. London: Stationery Office Agency.

Merritt, J. C., W. J. Crawford, P. C. Alexander, A. L. Anduze, and S. S. Gelbart. 1980. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmol* 87 (3):222-8.

Mittleman, M. A., R. A. Lewis, M. Maclure, J. B. Sherwood, and J. E. Muller. 2001. Triggering myocardial infarction by marijuana. *Circulation* 103 (23):2805-9.

Müller-Vahl, K. R., U. Schneider, H. Kolbe, and H. M. Emrich. 1999. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *Am J Psychiatry* 156 (3):495.

Muller-Vahl, K. R., U. Schneider, H. Prevedel, K. Theloe, H. Kolbe, T. Daldrup, and H. M. Emrich. 2003. Delta9-tetrahydrocannabinol (THC) is effective in the treatment of Tics in Tourette syndrome: A 6-week randomized trial. *J Clin Psychiatry* 64 (4):459-465.

Musty, R. E., and R. Rossi. 2001. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. *J Cannabis Therapeutics* 1 (1):29-42.

O'Shaughnessy, W. B. 1838-1840. On the preparations of the Indian hemp, or gunjah *(Cannabis indica)*; Their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Transactions of the Medical and Physical Society of Bengal*:71-102, 421-461.

Pate, D. 1994. Chemical ecology of cannabis. *J Interntl Hemp Assoc* 2:32-37.

Pertwee, R. G. 2001. Cannabinoid receptors and pain. *Prog Neurobiol* 63 (5):569-611.

_____2001. Cannabinoids and the gastrointestinal tract. *Gut* 48 (6):859-67.

Pertwee, R.G. 1998. Advanced in cannabinoid receptor pharmacology in cannabis. In *Cannabis: The genus Cannabis*, edited by D. T. Brown. Amsterdam: Harwood Academic Publishers.

Petro, D. J. 1980. Marihuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics* 21 (1):81, 85.

Petro, D. J. 2002. Cannabis in multiple sclerosis: Women's health concerns. *J Cannabis Therapeutics* 2 (3-4):161-175.

Potter, D. 2003. Growth and morphology of medicinal cannabis. In *Medicinal uses of cannabis and cannabinoids*, edited by B. A. Whittle, G. W. Guy and P. Robson. London: Pharmaceutical Press.

Randall, R. C., and A. M. O'Leary. 1998. *Marijuana Rx: The patients' fight for medicinal pot*. New York: Thunder's Mouth Press.

Rao, V. S., A. M. Menezes, and G. S. Viana. 1990. Effect of myrcene on nociception in mice. *J Pharm Pharmacol* 42 (12):877-8.

Regelson, W., J. R. Butler, J. Schulz, T. Kirk, L. Peek, M. L. Green, and M. O. Zalis. 1976. Delta 9-tetrahydrocannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In Braude M. C., Szara S., ed. *Pharmacology of marihuana*. Vol 2. New York, Raven Press.

Reynolds, J. R. 1890. Therapeutical uses and toxic effects of *Cannabis indica*. *Lancet* 1:637-638.

Robson, P., and G. W. Guy. 2003. Clinical studies of cannabis-based medicine. In *Medicinal uses of cannabis and cannabinoids*, edited by B. A. Whittle, G. W. Guy and P. Robson. London: Pharmaceutical Press.

Roth, M. D., J. A. Marques-Magallanes, M. Yuan, W. Sun, D. P. Tashkin, and O. Hankinson. 2001. Induction and regulation of the carcinogen-metabolizing enzyme CYP1A1 by marijuana smoke and delta (9)-tetrahydrocannabinol. *Am J Respir Cell Mol Biol* 24 (3):339-44.

Russo, E. 1998. Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. *Pain* 76 (1-2):3-8.

_____2001. Cannabinoids in pain management. Study was bound to conclude that cannabinoids had limited efficacy. *Brit Med J* 323 (7323):1249-50.

_____2002. Cannabis treatments in obstetrics and gynecology: A historical review. *J Cannabis Therapeutics* 2 (3-4):5-35.

Russo, E. B., and J. M. McPartland. 2003. Cannabis is more than simply delta (9)-tetrahydrocannabinol. *Psychopharmacol (Berl)* 165 (4):431-2.

Russo, E. B. 2001. *Handbook of psychotropic herbs: A scientific analysis of herbal remedies for psychiatric conditions*. Binghamton, NY: Haworth Press.

_____2002. Role of cannabis and cannabinoids in pain management. In *Pain management: A practical guide for clinicians*, edited by R. S. Weiner. Boca Raton, FL: CRC Press.

_____2003. The history of cannabis as medicine. In *Medicinal uses of cannabis and cannabinoids*, edited by B. A. Whittle, G. W. Guy and P. Robson. London: Pharmaceutical Press.

Russo, E. B., M. L. Mathre, A. Byrne, R. Velin, P. J. Bach, J. Sanchez-Ramos, and K. A. Kirlin. 2002. Chronic cannabis use in the Compassionate Investigational New Drug Program: An examination of benefits and adverse effects of legal clinical cannabis. *J Cannabis Therapeutics* 2 (1):3-57.

Russo, E. B., A. Merzouki, J. Molero Mesa, and K. A. Frey. 2003. Cannabis improves night vision: A pilot study of dark adaptometry and scotopic sensitivity in kif smokers of the Rif Mountains of Northern Morocco. *Journal of Ethnopharmacology* (Submitted).

Russo, E.B., and M. Stortz. 2003. An interview with Markus Storz: June 19, 2002. *J Cannabis Therapeutics* 3 (1):67-78.

Russo, E. B. 2001. Hemp for headache: An in-depth historical and scientific review of cannabis in migraine treatment. *J Cannabis Therapeutics* 1 (2):21-92.

Sanchez, C., I. Galve-Roperh, C. Canova, P. Brachet, and M. Guzman. 1998. Delta9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. *FEBS Lett* 436 (1):6-10.

Showalter, V. M., D. R. Compton, B. R. Martin, and M. E. Abood. 1996. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): Identification of cannabinoid receptor subtype selective ligands. *J Pharmacol Exp Ther* 278 (3):989-99.

Sidney, S., J. E. Beck, I. S. Tekawa, C. P. Quesenberry, and G. D. Friedman. 1997. Marijuana use and mortality. *Am J Public Health* 87 (4):585-90.

Straub, W. 1931. Intoxicating drugs. In *Lane Lectures on Pharmacology*, edited by W. Straub. Stanford, CA: Stanford University Press.

Tashkin, D. P., S. Reiss, B. J. Shapiro, B. Calvarese, J. L. Olsen, and J. W. Lodge. 1977. Bronchial effects of aerosolized delta 9-tetrahydrocannabinol in healthy and asthmatic subjects. *Am Rev Respir Dis* 115 (1):57-65.

Tashkin, D. P., M. S. Simmons, D. L. Sherrill, and A. H. Coulson. 1997. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *Am J Respir Crit Care Med* 155 (1):141-8.

Tashkin, D. P., G. C. Baldwin, T. Sarafian, S. Dubinett, and M. D. Roth. 2002. Respiratory and immunologic consequences of marijuana smoking. *J Clin Pharmacol* 42 (11 Suppl):71S-81S.

Tashkin, D. P. 2001. Respiratory risks from marijuana smoking. In *Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential*, edited by F. Grotenhermen and E. Russo. Binghamton, NY: Haworth Press.

Tyler, V. E. 1994. *Herbs of choice: the therapeutic use of phytomedicinals*. New York: Pharmaceutical Products Press.

Vaccani, A., P. Massi, and D. Parolaro. 2003. Inhibition of human glioma cell growth by the non psychoactive cannabidiol. Paper read at First European Workshop on Cannabinoid Research., April 4-5, at Madrid.

Vaney, C., P. Jobin, F. Tschopp, M. Heinzel, and M. Schnelle. 2002. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis. Paper read at Symposium on the Cannabinoids, July 13, at Asilomar Conference Center, Pacific Grove, CA.

Viola, H., C. Wasowski, M. Levi de Stein, C. Wolfman, R. Silveira, F. Dajas, J. H. Medina, and A. C. Paladini. 1995. Apigenin, a component of *Matricaria recutita* flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. *Planta Med* 61 (3):213-6.

Volicer, L., M. Stelly, J. Morris, J. McLaughlin, and B. J. Volicer. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 12 (9):913-9.

Wachtel, S.R., M. A. ElSohly, R. A. Ross, J. Ambre, and H. de Wit. 2002. Comparison of the subjective effects of delta9-tetrahydrocannabinol and marijuana in humans. *Psychopharmacol* 161:331-339.

Wallace, M. J., B. R. Martin, and R. J. DeLorenzo. 2002. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. *Eur J Pharmacol* 452 (3):295-301.

Ware, M. A., and V. L. Tawfik. 2001. A review of the respiratory effects of smoked cannabis: Implications for clinical trials. Paper read at Symposium on the Cannabinoids, June 30, at El Escorial, Spain.

Weil, A. T., N. E. Zinberg, and J. M. Nelsen. 1968. Clinical and psychological effects of marihuana in man. *Science* 162 (859):1234-42.

West, M.E. 1991. Cannabis and night vision. *Nature* 351:703-704.

Whittle, B. A., and G. W. Guy. 2003. Development of cannabis-based medicines; risk, benefit and serendipity. In *Medicinal uses of cannabis and cannabinoids*, edited by B. A. Whittle, G. W. Guy and P. Robson. London: Pharmaceutical Press.

Whittle, B. A., G. W. Guy, and P. Robson. 2001. Prospects for new cannabis-based prescription medicines. *J Cannabis Therapeutics* 1 (3-4):183-205.

Williams, S. J., J. P. Hartley, and J. D. Graham. 1976. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax* 31 (6):720-3.

Williamson, E. M., and F. J. Evans. 2000. Cannabinoids in clinical practice. *Drugs* 60 (6):1303-14.

Wilson, D. M., J. Peart, B. R. Martin, D. T. Bridgen, P. R. Byron, and A. H. Lichtman. 2002. Physiochemical and pharmacological characterization of a delta (9)-THC aerosol generated by a metered dose inhaler. *Drug Alcohol Depend* 67 (3):259-67.

Wright, T. L. 1862. Correspondence. *Cincinnati Lancet and Observer* 5 (4):246-247.

Zuardi, A. W., I. Shirakawa, E. Finkelfarb, and I. G. Karniol. 1982. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacol* 76 (3):245-50.

Zuardi, A. W., and F. S. Guimaraes. 1997. Cannabidiol as an anxiolytic and antipsychotic. In *Cannabis in medical practice: A legal, historical and pharmacological overview of the therapeutic use of marijuana*, edited by M. L. Mathre. Jefferson, NC: McFarland.