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POTENTIAL THERAPEUTIC USEFULNESS OF MARIJUANA

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INTRODUCTION AND HISTORICAL BACKGROUND

The debate regarding the legalization or decriminalization of marijuana continues. In the United States, this controversial drug is considered by some to be a major drug of abuse; indeed, some allege that sale of marijuana constitutes the third largest "industry" in the United States. Why, then, would academic laboratories, governmental institutions, and the pharmaceutical industry place such a major emphasis on developing marijuana as a therapeutic agent? The reason is that useful therapeutic agents may someday be derived from *Cannabis sativa,* the plant from which marijuana is derived, or from synthetic cannabinoids, which are closely related structurally to active constituents of marijuana. There are already a variety of major drugs in the physician's armamentarium that are of botanical origin —morphine from *Papaver somniferum* (opium), digitalis from *Digitalis purpurea* (foxglove), ergots from infected rye grain, ephedrine from *Ma Huang,* atropine from *Atropa belladonna* (deadly nightshade), reserpine from *Rauwolfia serpentina* (Indian snakeroot), and curare from *Chondodendron tomentosum,* to cite a few.

Usage of marijuana for medical purposes can be traced back 5000 years. In 2737 B.C. the Chinese Emperor Shen Nung published a monograph describing the use of cannabis in treating several diseases, including asthma, migraine, and certain gynecologic disorders. In 1842, O'Shaughnessy (1), an army physician in India, published an extensive treatise on the use of cannabis in various medical conditions, and drew attention to its hypnotic, anticonvulsive, analgesic, antianxiety, and antitussive effects. Partly as a

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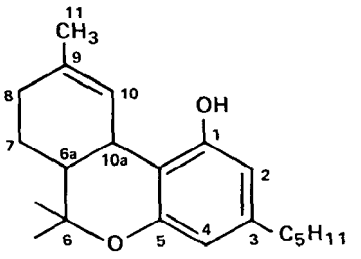
result of this early publication, cannabis was introduced into European medicine and subsequently into other areas of Western medicine, including the United States. Preparations such as tincture and extract of cannabis were recognized as official drugs and were listed in the *US Pharmacopoeia* from 1850 until 1942. However, although they remained in the *Pharmacopoeia* until 1942, their medical use was essentially abolished in 1937, when the Marijuana Tax Act was enacted.

Cannabis sativa contains a multitude of chemical constituents, including a novel group of chemicals called cannabinoids. More than 20 cannabinoids have been isolated from the plant and their chemical structures elucidated. Although Adams (2, 3) and Todd (4) speculated that a mixture of isomers of tetrahydrocannabinol were the active constituents of marijuana, Mechoulam and co-workers (5) isolated Δ^9-tetrahydrocannabinol (Δ^9-THC) from the plant and demonstrated it to be the major pharmacologically active constituent of cannabis. Δ^9-THC (Figure 1) is of special interest to scientists and clinicians because of its marked potency in producing pharmacologic effects, while possessing a low incidence of toxicity (that is, it has a large therapeutic index).

Many congeners of Δ^9-THC have been synthesized (Figure 2). Several have been administered to healthy volunteers for clinical pharmacologic evaluation and, to a lesser extent, to patients in therapeutic trials. Synhexyl, a compound similar to Δ^9-THC (it possesses a double bond in the $\Delta^{6a,\,10a}$ position and a *n*-hexyl group instead of a *n*-pentyl side chain), and DMHP, the dimethylheptyl side chain congener of synhexyl, were among the first synthetic cannabinoids evaluated in man (6–8). In man, these agents were found to be more potent than Δ^9-THC and marijuana and produced significant undesirable side effects. Thus they were not considered for further clinical evaluation.



Δ 9-THC

Figure 1 Chemical structure of Δ^9-THC.

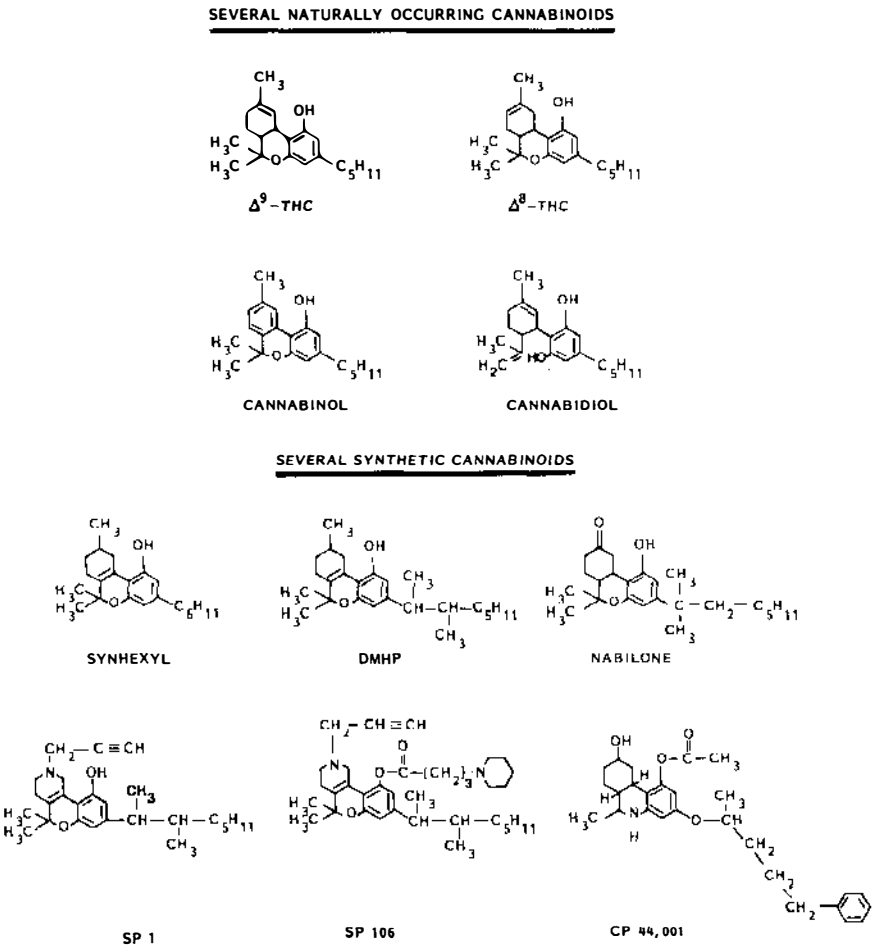


Figure 2 Structures of some naturally occurring and synthetic cannabinoids.

Nabilone (Figure 2), a cannabinoid with a ketone function at the 9 position, produces some effects associated with Δ^9-THC after administration to man, specifically those related to its CNS depression. However, in man, nabilone does not produce other effects associated with Δ^9-THC, notably tachycardia (9). In addition to minor modifications of the cannabinoid nucleus, compounds with major structural modifications have also been synthesized (Figure 2). Some of these agents, such as SP106 and CP-44,001, possess heterocyclic rings as well as other changes in the side chain. Both of these compounds are being evaluated in man as potential

therapeutic agents. Thus, major synthetic programs have been conducted in universities (2–5), government laboratories (10), and the pharmaceutical industry (11–15) to develop cannabinoid derivatives which might be useful therapeutic agents.

During the past decade, marijuana and the natural and synthetic cannabinoids have been investigated extensively in animals and man to assess their use as antihypertensives, analgesic-anti-inflamatory agents, anticonvulsants, antianxiety agents, antidepressants, sedative-hypnotics, antiemetics and appetite stimulants (as adjuncts in cancer chemotherapy), antitumor agents, antiasthmatics, and as drugs to treat glaucoma.

Much has been written in the press about experiences of marijuana users who claim that marijuana smoking produces a variety of positive effects, ranging from a prophylaxis for the common cold, to a cure for cancer. Since these anecdotal claims are based on limited experiences of biased observers, their validity still must be confirmed under conditions of responsible, rigorous clinical trials. Similarly, many early reports in the scientific literature pertaining to the clinical effects of marijuana were anecdotal. Only within the past 15 years (since the isolation of Δ^9-THC in 1964 and the development of synthetic compounds) have clinical trials been conducted using standardized drug dosages, sound clinical pharmacologic principles, and scientific criteria for evaluating data. The clinical research conducted during the last decade has been of a high caliber and has tended to utilize those recognized scientific principles, such as subject randomization, placebo comparison, and double-blind design involving either crossover or parallel studies.

SPECIFIC DRUG CATEGORIES IN WHICH CANNABINOIDS MAY POSSESS THERAPEUTIC POTENTIAL

Antiasthmatic

One of the earliest clinical effects of marijuana to be studied since 1964 has been its effect on the bronchopulmonary tree. Minimal animal data are available with regard to the effects of cannabis on pulmonary smooth muscle. Graham et al (16) compared the bronchodilator effects of Δ^9-THC and isoproterenol on the smooth muscle of the isolated guinea pig tracheal strip. The concentration versus response curve for Δ^9-THC paralleled that of isoproterenol; however, the concentration of Δ^9-THC required to produce effects comparable to isoproterenol was a thousandfold higher. In addition, propranolol, a β-adrenergic blocking agent, had no effect on the Δ^9-THC response, but abolished the effect of isoproterenol. They concluded that Δ^9-THC was a weak bronchodilator which acted by a mechanism different from that of the widely used bronchodilator catecholamines.

The initial observations that cannabis produced acute, prolonged bronchodilatation in normal, healthy subjects was reported by Vachon (17) and Tashkin et al (18). These investigators demonstrated that both smoking marijuana and ingesting Δ^9-THC resulted in decreased airway resistance and increased airway conductance. These effects were of longer duration than those produced by isoproterenol administration. Further studies were conducted to determine whether Δ^9-THC could produce bronchodilatation in chronic, stable bronchial asthmatics and in asthmatic patients in whom experimentally induced bronchospasm was produced by exercising or by inhaling methacholine. In both experimental conditions (18a–c), marijuana and Δ^9-THC administration reversed the bronchoconstriction; however, these effects were accompanied by adverse effects, including drug-related bronchospasm and behavioral effects (euphoria and sedation). Abboud & Sanders (19), noting the reports that orally administered Δ^9-THC produced prolonged bronchodilation in healthy volunteers and reversed bronchoconstriction in asthmatics, attempted to confirm these earlier studies using a double-blind randomized, crossover design and comparing the bronchodilatory effects of placebo and oral Δ^9-THC in normal subjects and patients with asthma. After the oral administration of Δ^9-THC (10 mg) to the normal volunteers, these investigators observed no statistically significant increase in maximal expiratory flow at 50% of vital capacity (V_{max} 50%). They did, however, find a slight but statistically significant increase in specific airway conductance (G_{AW}/V_1) 1 hr after drug administration, an effect which was indicative of bronchodilatation. In contrast, five of six of the asthmatic patients had variable changes in the G_{AW}/V_1 and V_{max} 50% values with mean changes not statistically different from the mean changes occurring after the placebo control treatment. The sixth patient developed severe bronchoconstriction 1.5 hr after Δ^9-THC administration. This was relieved promptly after inhalation of an aerosol preparation of a sympathomimetic amine. Many of their subjects and patients had significant CNS side effects, including mild euphoria, which on occasion was followed by an unpleasant hangover, and detached or dreamy feelings. They concluded that the oral administration of Δ^9-THC would have doubtful therapeutic value in treating asthma because its bronchodilatory action was mild and unpredictable, and was associated with significant, disturbing CNS side effects.

Graham et al (16) also studied the effect of orally administered Δ^9-THC (10 mg) in asthmatic patients. In these double-blind studies, salbutamol, a sympathomimetic amine widely used as a bronchodilator, was reported to be significantly better than either placebo or Δ^9-THC. Placebo and Δ^9-THC administration produced no statistically significant effects in several pulmonary function tests. When Δ^9-THC was given by aerosol, it had no beneficial effect on the asthmatic condition. Likewise, Bright et al (20) concluded that

the dilative effects of marijuana and Δ^9-THC did not occur in the clinically important airways (diameter < 2 mm), which contribute significantly to the bronchoconstriction accompanying asthmatic attacks, but in actuality, the dilative effect was occurring in larger airways such as the trachea and mainstem bronchi.

The question of the therapeutic benefits of cannabinoids as antiasthmatic agents remains unanswered. Although marijuana and Δ^9-THC appear to be unsuitable because of unacceptable CNS side effects and bronchoconstriction, Shapiro et al (21) presented a cogent argument that further studies with Δ^9-THC and other cannabinoids should be pursued vigorously because these drugs appear to act by mechanisms different from those of the presently available bronchodialators. As stated earlier, Δ^9-THC does not act as a β-adrenergic agonist, and its effects are not modified by the classical β-blocking agents (16, 22). In addition, Δ^9-THC does not appear to be exhibiting an antimuscarinic action (22). Shapiro et al (21) stated that "any drug which has a potentially new mechanism of action producing a therapeutic effect should be closely investigated; that drug may be effective when other drugs are ineffective, or synergistic effects with other drugs may be present." Moreover, the possibility exists that the synthesis of analogues of Δ^9-THC may result in the development of drugs that possess prolonged bronchodilatation without the adverse effects.

Therefore, it seems worthwhile to continue studying cannabinoids as bronchodilators, and to follow the initial leads generated in recent years. Synthesis of analogues of Δ^9-THC might result in the development of a drug that possesses a prolonged bronchodilative effect.

Anticonvulsant

The anticonvulsant properties of cannabinoids were reported in the modern scientific

demonstrated that constituents of marijuana were effective in attenuating seizures induced in rats by electroconvulsive shock (ECS). These early findings have been confirmed and extended by many investigators using various animal species (24–44). Δ^9-THC and phenytoin appear to act in a similar manner, both blocking and attenuating ECS-induced convulsions, shortening their duration, and raising the seizure threshold. Additional evidence that marijuana and Δ^9-THC might be useful anticonvulsants is that they have been shown to be effective in epileptic animal models, such as the epileptic baboon (41).

That Δ^9-THC has anticonvulsant effect is not universally accepted. Meldrum et al (42) reported that Δ^9-THC had no seizure-reducing effect in epileptic baboons. Moreover, several investigators have reported that

Table 1 Anticonvulsant effects of Δ^9-THC in laboratory animals[a]

Seizure type	Species	Major effects of Δ^9-THC on seizure
Maximal (tonic) electroshock seizures (MES)	Rat	Dose-response protection, generally (23–26)
	Mouse	Protection (partial and dose-response); tolerance develops to anticonvulsant effect (25, 27–31)
		No protection reported (32)
Electrically induced minimal (clonic) seizures	Rat	Protection against "kindled" seizures; tolerance develops to anticonvulsant effect (33, 34)
	Mouse	Elevation of 6-HZ- and not 60 HZ-electroshock seizure thresholds (EST) (25)
	Cat	Reduction of seizures induced by subcortical stimulation (35)
Electrically induced electrographic (EEG) seizures	Rat	Protection against cortical and subcortical EEG seizures, generally; tolerance develops to anticonvulsant effect (33, 34, 36)
	Cat	Reduction or enhancement of EEG seizures depending on stimulus strength (35, 37)
Pentylenetetrazol	Rat	No seizure protection and enhanced lethality (23)
		Protection of maximal seizures and no effect on minimal seizures and lethality of PTZ (24)
		Protection against minimal PTZ seizures only at toxic and lethal doses of Δ^9-THC (26)
	Mouse	Dose-response protection against minimal PTZ seizures (32)
		Partial protection against maximal seizures; no protection or enhancement of minimal seizures and lethality of PTZ:; strychnine seizures and lethality also increased (25, 27, 31, 38)
Audiogenic (clonic) and/or tonic seizures	Rat	Dose-response protection (24, 39)
	Mouse	Reduction in seizure susceptibility (40)
Photomyoclonic seizures	Baboon	Protection (41)
		No protection (42)
Reflex ("spontaneous") seizures	Gerbil	Protection; tolerance develops to anticonvulsant effect (43)

[a] Adapted from Consroe et al (44).

Δ^9-THC increases the seizure threshold and causes convulsions when administered in large doses to epileptic beagles and rabbits (44, 45).

Several cannabinoids other than Δ^9-THC, namely cannabidiol and cannabinol, are also said to possess anticonvulsant properties (46). Although larger doses of these drugs are required, they appear to have the advantage of not producing the adverse psychotomimetic effects associated with Δ^9-THC.

The clinical "efficacy" of marijuana as an anticonvulsant dates back to 1842 when O'Shaughnessy (1) used cannabis to treat epilepsy. In 1949, Davis & Ramsey (47) reported that synthetic THC homologues were effective in treating epileptic patients. However, these findings have been questioned by Feeney (45) because of the lack of details in the original report. No clinical studies have been reported to date which directly address the question whether or not Δ^9-THC has anticonvulsant properties in humans. However, a preliminary study suggests that cannabidiol may be an effective anticonvulsant agent (E. A. Carlini, personal communication); these studies need to be substantiated in larger clinical trials.

Although it has been suggested that Δ^9-THC or its congeners may be efficacious in treating convulsive disorders, several factors suggest that cannabinoids may not be therapeutically acceptable in these conditions. First, they produce other effects, including tachycardia and CNS side effects (sedation, euphoria, etc). Second, they may exacerbate convulsive disorders in susceptible individuals. Third, studies in animals suggest that tolerance develops to their anticonvulsant effects. This tolerance is probably a "receptor" tolerance, rather than a "metabolic" tolerance, since the latter type is thought not to occur with the cannabinoids [see review, Lemberger & Rubin (48)].

Antiemetic

In the anitemetic area, as has been the case for marijuana in general, clinical experiments preceded animal experiments. Many oncologists, and more specifically, specialists in cancer chemotherapy have related accounts of patients suffering from leukemia or Hodgkin's Disease who smoked marijuana and obtained relief from the severe nausea and vomiting associated with their subsequent intravenous cancer medication. Indeed, nausea and vomiting can be one of the most debilitating aspects of the treatment of these patients with cancer chemotherapeutic drugs. It also profoundly affects the physicians and nurses who are involved in providing total care to the patient because these adverse effects are viewed as iatrogenic.

The phenothiazines, which are widely used as antiemetic agents in other conditions, have only limited antiemetic utility in these patients, and in some cases are no more effective than placebo in suppressing the nausea and

vomiting induced by the chemotherapeutic agents. Sallan et al (49, 50) conducted a well-controlled, randomized, double-blind crossover study in cancer patients receiving chemotherapy who were known to be refractory to conventional antiemetics to determine whether Δ^9-THC would prevent vomiting in this patient population. Placebo treatment did not reduce the nausea and vomiting, whereas 12 of 15 patients responded favorably to Δ^9-THC. In five individuals, Δ^9-THC completely prevented vomiting and in seven patients it afforded partial relief. Three subjects did not experience any relief; neither did they experience a psychologic "high" (in contrast to the 12 responders), suggesting that the drug may not have been absorbed adequately. Although somnolence occurred in two thirds of the patients, it did not cause appreciable change in their level of activity. Two subjects experienced psychotomimetic symptoms with visual hallucinations.

After the development of the synthetic cannabinoid, nabilone, several controlled studies were conducted to assess its antiemetic effectiveness. Herman et al (51, 52) reported that nabilone, in a dose-related manner, significantly reduced the nausea and vomiting induced by cancer chemotherapy in 10 of 13 patients who had been refractory to conventional antiemetics. Einhorn and co-workers have reported similar beneficial effects with nabilone in cancer patients who were receiving *cis*-platinum (*cis*-diaminedichloroplatinum), a cancer chemotherapeutic drug which is regarded as one of the more emetic-producing agents used to treat cancer (52, 53). In all these studies, nabilone was well tolerated and, like Δ^9-THC, produced sedative effects. In contrast to Δ^9-THC, nabilone produced only minimal euphoric effects at doses that reduced nausea and vomiting. Additional side effects evidenced in some subjects included dizziness, decreased coordination, and postural hypotension.

The initial clinical reports regarding the potential benefits of nabilone in preventing nausea and vomiting of central origin in man prompted Borison and co-workers (54–56) to use several well-established emetic agents and anticancer drugs to investigate the antiemetic property of nabilone in cats. Nabilone was ineffective in preventing vomiting induced after the intravenous injection of nicotine. Though nabilone was effective in blocking vomiting in cats injected with apomorphine (intracerebroventricularly) or the digitalis glycoside deslanoside (intravenously), it did so at doses which were associated with pronounced behavioral disturbances. Nonetheless, nabilone was very effective in preventing emesis in cats who received the anticancer agents BCNU [1,3-bis-(2-chorethyl)-1-nitrososurea], mechlorethamine, and *cis*-platinum (*cis*-diaminedichloroplatinum). In contrast, prochlorperazine was ineffective in blocking mechlorethamine-induced emesis in this animal model. Thus it appears that nabilone and presumably other antiemetic cannabinoids (e.g. Δ^9-THC) are exerting their effects by a different

mechanism from that of the more conventional antiemetics. London et al (56) suggest that "the emetic suppresant action of nabilone is effected in the forebrain in association with its psychotropic influence to cause an inhibition of the vomiting control mechanism in the medulla oblongata through descending connections."

Thus, both clinical and animal studies indicate that certain cannabinoids have therapeutic potential in this area of medicine, where a great need for effective agents exists.

Appetite Stimulant

Street users have claimed that smoking marijuana increases one's appetite. Only anecdotal reports of this potentially useful effect (in debilitated individuals or patients suffering from chronic weight loss) had been available until Hollister et al (57) conducted a double-blind controlled study in which smokers of marijuana or placebo cigarettes were allowed unlimited access to a high caloric beverage. The subjects were unaware of the quantity of beverage they ingested during the study. These investigators observed an increase in caloric consumption in about half the subjects when comparing the placebo and the marijuana treatments, suggesting that Δ^9-THC did stimulate the appetite. However, there was a large variability among subjects, suggesting that use of marijuana as an appetite stimulant might not be of clinical significance. In contrast, some cancer patients receiving Δ^9-THC or nabilone as an antiemetic do note a definite increase in appetite and food intake (49, 51, 52). This may, however, be related more to an alleviation of their symptoms of nausea and vomiting rather than to a true appetite stimulant effect.

Regelson et al (58), while studying the psychologic effects and toxicity of chronic Δ^9-THC and placebo administration in cancer patients, reported that Δ^9-THC stimulated appetite and helped to retard the chronic weight loss frequently associated with cancer. Further studies in this area are needed to determine whether this effect can be beneficial to cancer subjects. Certainly one must consider the occurrence of possible side effects that the cannabinoids may induce (i.e. benefit to risk). Indeed, in the Regelson study, a significant percentage of patients failed to complete the two-week study because of unacceptable side effects.

Treatment of Glaucoma

Glaucoma, a disease of the eye characterized by an increase in intraocular pressure, is the second most common cause of blindness in the United States. Drugs used currently to treat glaucoma are the anticholinergic agents, β-adrenergic blocking agents, and the carbonic anhydrase inhibitor acetazolamide (Diamox®). However, some patients remain refractory to

these conventional agents and they may eventually become blind with progression of their disease.

The serendipitous finding that marijuana and Δ^9-THC decrease intraocular pressure was first reported by Hepler & Frank in 1971 (59). They were doing routine ophthalmologic examinations on healthy subjects participating in a major investigation of the chronic effects of cannabis in man when they noted that marijuana smoking lowered the intraocular pressure. These investigators expanded their studies, using a placebo-controlled, double-blind design in healthy volunteers who smoked either natural marijuana of known Δ^9-THC content, or synthetic Δ^9-THC, or who ingested synthetic Δ^9-THC. They found a dose-related and statistically significant reduction of the intraocular pressure immediately following either the inhalation or ingestion of marijuana or its cannabinoid constituents. Intraocular pressure was decreased about 30% from control values after an intermediate dose of marijuana containing 2% THC was used (60). Subsequent studies have confirmed the acute effect of Δ^9-THC in lowering intraocular pressure in healthy volunteers by oral, inhalation, and intravenous routes of administration (61–64). Hepler and co-workers also conducted chronic studies with marijuana and Δ-THC in healthy volunteers studied as inpatients hospitalized for up to 94 days. Again, they reported a consistent lowering in intraocular pressure (approximately 30%) following the inhalation of marijuana containing 2% Δ^9-THC. The effect persisted for 4–5 hr and no tolerance was noted with respect to this decrease in intraocular pressure throughout the 94-day study (65).

Hepler and co-workers (65, 66) next followed the intraocular pressure in glaucoma patients who were asked to smoke marijuana or to ingest Δ^9-THC. In preliminary experiments, the intraocular pressures in 7 of 11 patients were decreased substantially (averaging around a 30% decline). The intraocular pressures in the remaining four patients were not lowered by the drug, nor did they experience any behavioral effects; therefore, the investigators questioned whether these patients had mastered the technique of marijuana smoking to allow for pulmonary absorption of the drug. Further studies in a larger population of patients substantiated the finding that intraocular pressure decreased by about 25% after the ingestion of 10 or 20 mg of Δ^9-THC and by about 30% after smoking marijuana containing 1% to 4% Δ^9-THC. Moreover, the pressure-reducing effects of marijuana and Δ^9-THC were additive to the pressure reduction caused by conventional glaucoma medications, suggesting that the drug combinations would be especially useful. Cuendet et al (67) have also reported that Δ^9-THC lowers intraocular pressure in patients with glaucoma.

Following the initial report of the ability of marijuana and Δ^9-THC to lower intraocular pressure in humans, Green and co-workers used rabbits

to delineate the possible mechanism of this action of the cannabinoids (68–71). They demonstrated that intravenously administered Δ^9-THC lowered intraocular pressure by 25% and increased the total outflow facility of aqueous humor by 25%. This action is seen whether the cannabinoid reaches the eye via the topical or the systemic route. Extensive studies suggest that the effect of Δ^9-THC on intraocular pressure is mediated via the sympathetic nervous system, because the effect was modified by α- and β-adrenergic antagonists. They also suggested that Δ^9-THC acted proximal to the superior cervical ganglion, i.e. in the CNS (71). The studies in rabbits confirmed the findings in man that tolerance did not develop to the intraocular pressure lowering effect after topical administration of Δ^9-THC for up to 60 days (72). It is of interest that after the topical administration of ^{14}C-Δ^9-THC, the drug localizes in the cornea (a site from which it presumably can be further released, thus acting as a depot), the aqueous humor, and the iris. A substantial amount of radioactivity was also found in the iris of one eye after instillation of radiolabeled ^{14}C-Δ^9-THC into the contralateral eye; thus, drug was absorbed into the systemic circulation by topical instillation (72). In humans, the ingestion or inhalation of marijuana or Δ^9-THC has been accompanied by psychotropic and other pharmacologic effects. The findings that cannabinoids lower intraocular pressure after topical administration, and that a peripheral component may be in part responsible, offer encouragement that future research can develop a suitable cannabinoid for the treatment of glaucoma that will be devoid of systemic side effects.

Several synthetic cannabinoid derivatives have been studied for their effects in lowering intraocular pressure. Green et al (72, 73) investigated the effects of SP-1 and SP-106 (Nabitan®) in rabbits, and Stark et al (74) studied nabilone in rabbits and man. Preliminary studies suggest that these cannabinoids also lower the intraocular pressure. Although further research will be needed to determine whether agents of this type will be of value in treating glaucoma, the early findings are encouraging.

Psychopharmacologic Effects (Antianxiety, Antidepressant, Sedative-Hypnotic)

Marijuana smokers claim that a feeling of relaxation and tranquility occurs during and after the euphorigenic actions (for which the drug is consumed). This information is difficult to prove or dispute since it is—at best—anecdotal and very subjective. However, when clinical studies were conducted with marijuana and Δ^9-THC, it was apparent to trained observers that these drugs did produce some degree of relaxation and had sedative-hypnotic activity in healthy volunteers. No studies have been published to date ultilizing Δ^9-THC or marijuana in subjects with increased levels of anxiety.

However, nabilone's antianxiety effects have been studied. One study design involved an experimental anxiety paradigm, using normal volunteers with high levels of trait anxiety ("anxious normal" volunteers) who were tested on two anxiety-producing procedures: a mirror drawing test and the Stroop color-word test (75). Subjects received single oral doses of either placebo, diazapam (5 mg), or nabilone (2 mg) in a double-blind parallel study (12 subjects/group). Although both agents appeared to be superior to placebo, diazapam alleviated the experimentally produced anxiety more than the nabilone. Fabre et al (76) using a double-blind parallel study design, compared the effects of nabilone and placebo in patients suffering from psychoneurotic anxiety. Nabilone was administered in a dose of 3 mg daily (1 mg three times a day) for 28 days. This synthetic cannabinoid was found to be significantly superior to placebo in treating the anxiety. Nabilone was also reported by these investigators to "improve the psychic and somatic concomitance of anxiety as well as feelings of depression." Alleviation of anxiety occurred quickly, the patients reporting improvement within three days after starting medication.

Although nabilone was superior to placebo in this latter study, no conclusions can be made at this time regarding how it would compare to the benzodiazepines in patients suffering from psychoneurotic anxiety. Although the cannabinoids possibly could be highly effective, it is unlikely that they would replace the benzodiazepines in this patient population, because the latter group of drugs has been shown over the last two decades to be safe and efficacious and to produce minimal side effects.

The available data are conflicting in regard to the potential use of Δ^9-THC as an antidepressant medication. Kotin et al (77) were unable to detect any antidepressant activity for Δ^9-THC in a group of depressed patients. Feinberg et al (78) studied the effects of marijuana and Δ^9-THC, at relatively high doses, on EEG sleep parameters in humans and found that these drugs, like lithium, increased stage-4 sleep and decreased rapid eye movement (REM). Ablon & Goodwin (79) reported that Δ^9-THC, at doses of 5 to 40 mg daily for up to one week, produced dysphoria in patients who were categorized as suffering from unipolar depression, but not in patients who were suffering from bipolar depression. This finding suggested that further clinical trials might be considered in the latter group of depressed patients; interestingly, among depressed patients this group benefits to the greatest extent from lithium therapy.

Regelson and co-workers (80, 81) reported that Δ^9-THC had a beneficial effect on the symptoms of depression in advanced cancer patients. Whether this is a true antidepressant action or one due to the euphorigenic and/or tranquilizing effect of the drug is unclear. As stated by Regelson, "The depression and anxiety in cancer patients are by no means symptomatic of

an unstable personality or an endogenous depression; rather, they are clearly a common response to a catastrophic event that is extremely difficult to deal with and the usual reassurances of psychic energizers (antidepressants) have little or negative effects." This statement is consistent with the findings from the studies of Kotin et al (77) in which Δ^9-THC appears not to be an antidepressant in the classical sense, like the tricyclic antidepressants or the monoamine oxidase inhibitors. Thus, if Δ^9-THC is to be useful as an antidepressant, it would probably be of value in patients with reactive rather than those with endogenous depression.

As stated previously, Δ^9-THC and marijuana reportedly possess sedative-hypnotic activity. DiMascio and co-workers (82) reported that a beneficial sleep-inducing effect was seen in healthy volunteers to whom Δ^9-THC was given orally prior to retiring at night. After a low dose (10 mg) subjects fell asleep about 45 min sooner than they did after placebo medication. At higher doses (20–30 mg), the hypnotic effect was accompanied by a hangover of long duration and, in addition, some subjects experienced a continued euphoria after waking. These investigators conducted a second study (83), using doses of 5, 10, and 15 mg of Δ^9-THC, to further examine its potential hypnotic effects. The effects of these doses of Δ^9-THC on sleep patterns were compared to effects of placebo and chloral hydrate (500 mg). The results of this study were inconclusive because, although Δ^9-THC did not exhibit hypnotic activity, neither did chloral hydrate, the standard medication. Available cannabinoids have little therapeutic potential in treating CNS disorders such as anxiety, depression, or insomnia unless derivative compounds with fewer side effects can be synthesized. Agents used currently in medical practice are more efficacious and possess fewer side effects than the cannabinoids.

Analgesic and Anti-Inflammatory

Whether the cannabinoids have analgesic activity in animals or man is a controversial issue. Results from animal studies vary, apparently depending upon the analgesic test system. Δ^9-THC is active in the acetic acid writhing test, but is devoid of activity in the mouse and rat tail flick test at doses that do not produce marked sedation and behavioral effects. Moreover, some investigators have shown analgesic effects with Δ^9-THC in the rat and mouse tail flick tests (14, 84–86), whereas others have not observed analgesic effects unless they used doses that produced severe behavioral and psychomotor impairment (87). Wilson & May (88) reported that 11-OH-Δ^9-THC, a metabolite of Δ^9-THC, was an analgesic in the mouse hot plate test: It was equipotent with morphine and five times more potent than Δ^9-THC.

Some synthetic cannabinoids also possess antinocepetive activity in animal tests. Nabilone, SP1, SP106, and CP-44001 are active in several analgesic test models (13, 14, 89) In addition, the synthetic cannabinoid, 9-nor-9β-hydroxyhexahydrocannabinol (HHC), also possesses analgesic activity in the mouse hot plate test, the effect being equal to that of morphine (90). The synthetic cannabinoids do not appear to act as analgesics in animals by the same mechanism as the opiates. For example, CP-44001 does not bind to the opiate receptor despite the compound's potent analgesic activity in vivo (91). Furthermore, the analgesic effects of HHC and CP-44001 are not reversed by naloxone (91, 92), and no cross tolerance occurs between morphine and HHC (92). These animal studies suggest that cannabinoids may be discovered that possess strong analgesic activity without the addiction liability associated with the opiates.

The clinical data currently available on the analgesic activity of Δ^9-THC and the cannabinoids are equivocal. Noyes et al (93) demonstrated an analgesic effect of orally administered Δ^9-THC in patients suffering from advanced cancer who had pain associated with their disease. Subjects received either placebo or randomly allocated graded doses of Δ^9-THC (5–20 mg) in a double blind study. An analgesic effect of Δ^9-THC developed gradually and persisted for several hours. At the higher doses (15 and 20 mg), Δ^9-THC was significantly superior to placebo. However, analgesia was accompanied by significant side effects, including substantial sedation and mental clouding. The severity of the side effects was dose related. In contrast to the analgesic effects in cancer patients, Hill et al (94) were unable to detect analgesic activity after a moderate dose of Δ^9-THC (12 mg) was given to 26 healthy volunteers subjected to an experimental pain model (i.e. applying cutaneous electrical stimulation to the fingers). Δ^9-THC did not decrease the sensitivity (i.e. increase the threshold to painful stimulation); in fact, it sometimes heightened it (hyperalgesia). In addition, Δ^9-THC reduced the tolerance to pain. Furthermore, two case reports (95, 96) mention an increased sensitivity to pain in cancer patients who had smoked marijuana. These patients reported that the hyperalgesia coincided with the "high" and subsided 2–3 hr after the high had disappeared.

Although several of the synthetic cannabinoids are undergoing clinical evaluation as analgesics, preliminary indications are that they may produce analgesia at doses which also produce undesirable side effects. One cannot help notice that, in general, the doses at which many of the potential therapeutic uses of the cannabinoids seem to develop are close to those which produce side effects. Thus, while separations of pharmacologic activities have been seen among cannabinoids, thus far the therapeutic index has been, at best, marginally acceptable.

In addition to investigation of their analgesic activity, the cannabinoids have been evaluated as potential anti-inflammatory drugs. Δ^9-THC (10 mg/kg) caused a 40% inhibition of pore swelling in the carageenon-induced rat paw edema test. Likewise, in the adjuvant-induced polyarthritis model, the daily administration of Δ^9-THC (20 mg/kg) to rats inhibited the development of the disease (97, 98). The mechanism of this anti-inflammatory effect of Δ^9-THC has been investigated by Burstein and co-workers (99, 100). They showed that Δ^9-THC inhibited prostaglandin synthesis in an in vitro system (bovine and/or seminal vesicle microsomes) by reducing the conversion of arachidonic acid to prostaglandin E_2. Δ^9-THC also inhibits the in vitro formation of prostaglandin E_1 from 8,11,14-elcosatrienoic acid (101). In vivo studies have demonstrated that Δ^9-THC can prevent the arachadoic acid–induced increase in intraocular pressure in the rabbit eye (102). Presumably, this effect is the result of inhibition of the enzyme prostaglandin synthetase. Burstein has suggested that this action may also be involved in the activity of Δ^9-THC in certain other disease states, namely, asthma and glaucoma. Clearly, more studies should be performed to determine whether this observation is clinically significant.

Miscellaneous Uses

ANTITUMOR It appears from studies in animals that certain cannabinoids may possess antitumor activity. Harris and co-workers (103, 104) reported that several cannabinoids are active in vitro and in vivo against certain models of neoplasia in mice. For example, Δ^9-THC, Δ^8-THC, and cannabinol, when administered at relatively high doses (25–100 mg/kg orally), inhibited the growth of the primary Lewis lung adenocarcinoma (a solid tumor) in mice and increased the life span of these animals. In contrast, cannabidiol was not an effective antitumor agent. Although these results are exciting, they must be interpreted cautiously when extrapolating them to cancer chemotherapy in man. Clearly, additional studies are warranted to determine whether the cannabinoids could be useful oncolytic drugs.

ANTIHYPERTENSIVE Δ^9-THC and other cannabinoids can produce postural hypotension in man (6–8, 105, 106). Although this hypotension may be mild with the naturally occurring canabinoids such as Δ^9-THC, it can be more marked with some of the synthetic agents such as DMHP. In fact, this effect of DMHP occurs after doses which have only minimal behavioral effects (8). Postural hypotension can also occur after a large dose of nabilone (9, 51, 52). In animal studies, Birmingham et al (107, 108) demonstrated that Δ^9-THC and Δ^8-THC can lower blood pressure in rats with adrenal regeneration hypertension. Nahas et al (109) and Forney and co-workers

(110) have also observed lowered blood pressure in the spontaneously hypertensive rat after Δ^9-THC administration. Some but not all of these investigators report that tolerance develops to this antihypertensive effect.

Several groups of drugs exist which are beneficial in treating hypertension. The mechanisms by which these drugs act include the excretion of salt and water, interference with sympathetic nervous system function, direct vasodilation, β-adrenergic receptor blockade, and prevention of the formation of angiotensin. Initially, these agents are utilized alone in treating mild hypertension; however, in moderate to severe hypertension they are usually used in combinations. If cannabinoids lower blood pressure by a mechanism unrelated to those listed above, and if analogues can be synthesized that produce minimal side effects, then cannabinoids may present us with a new and unique approach to the treatment of hypertension.

CONCLUSIONS

The cannabinoids have been implicated as being useful in many clinical disorders which afflict man. These compounds were utilized for centuries as therapeutic agents, until their discontinuation in 1937. During the past decade a renewed interest in cannabinoids has occurred. Although marijuana has been utilized socially and experimentally by inhalation, the use of the crude preparation and its administration by this route do not appear practical. Δ^9-THC, the active constituent of marijuana, has been administered orally; however, it is chemically unstable and exists physically as a resin. Thus, problems exist with respect to reproducible absorption and the production of consistent and predictable pharmacologic effects. In addition, Δ^9-THC produces pharmacologic effects on many biologic systems, including the cardiovascular and the central nervous systems. This lack of tissue specificity suggests that Δ^9-THC would not be a useful therapeutic agent. However, synthetic cannabinol derivatives have been synthesized, some of which are crystalline, readily absorbed, and capable of producing reproducible effects. These derivatives appear to possess a greater degree of organ specificity and selectivity in their actions. Many of these agents may become new additions to our current therapeutic armamentarium, especially to reduce intraocular pressure in glaucoma and to reduce nausea and vomiting that often accompany treatment with cancer chemotherapeutic agents. However, no cannabinoids of current interest are devoid of adverse side effects and, thus, there is a continued need and impetus for close collaboration between chemists, pharmacologists, toxicologists, and clinical pharmacologists to develop useful drugs from this class of compounds which will benefit patients suffering from a variety of diseases.

Literature Cited

1. O'Shaughnessy, W. B. 1842. On the preparation of Indian hemp or gunjah. *Trans. Med. Phys. Soc. Bombay* 8: 421–61
2. Adams, R., Pease, D. C., Clark, J. H. 1940. Isolation of cannabinol, cannabidiol and quebranchitol from red oil of Minnesota wild hemp. *J. Am. Chem. Soc.* 62:2194–96
3. Adams, R. 1942. Marihuana. *Harvey Lect.* 37:168
4. Todd, A. R. 1942. The chemistry of hashish. *Sci. J. R. Coll. Sci.* 12:37
5. Gaoni, Y., Mechoulam, R. 1964. Isolation, structure and partial synthesis of active constituent of hashish. *J. Am. Chem. Soc.* 86:1646–47
6. Hollister, L. E., Richards, R. K., Gillespie, H. K. 1968. Comparison of tetrahydrocannabinol and synhexyl in man. *Clin. Pharmacol. Ther.* 9:783–91
7. Sidell, F. R., Pless, J. E., Neitlich, H., Sussman, P., Copelan, H. W., Sim, V. M. 1973. Dimethylheptyl-delta-6a,10a-tetrahydrocannabinol: Effects after parenteral administration to man. *Proc. Soc. Exp. Biol. Med.* 142:867–73
8. Lemberger, L., McMahon, R., Archer, R., Matsumoto, K., Rowe, H. 1974. Pharmacologic effects and physiologic disposition of delta-6a,10a-dimethylheptyl tetrahydrocannabinol (DMHP) in man. *Clin. Pharmacol. Ther.* 15: 380–86
9. Lemberger, L., Rowe, H. 1975. Clinical pharmacology of nabilone, a cannabinol derivative. *Clin. Pharmacol. Ther.* 18: 720–26
10. Wilson, R. S., May, E. L. 1974. 9-Nor-delta-8-tetrahydrocannabinol, a cannabinoid of metabolic interest. *J. Med. Chem.* 17:475–76
11. Pars, H. G., Razdan, R. K. 1976. Heterocyclic analogs of the cannabinoids. In *The Therapeutic Potential of Marihuana,* ed. S. Cohen, R. C. Stillman, pp. 419–37. New York: Plenum
12. Archer, R. A., Blanchard, W. B., Day, W. A., Johnson, D. W., Lavagnino, E. R., Ryan, C. W. 1977. Cannabinoids. 3. Synthetic approaches to 9-ketocannabinoids. Total synthesis of nabilone. *J. Org. Chem.* 42:2277–84
13. Mast, R. W., McIlhenny, H. M., Milne, G. M., Johnson, M. R. 1979. Behavioral effects and pharmacokinetics of nantradol hydrochloride, a potent cannabinoid-related analgesic. *Pharmacologist* 21:270
14. Dren, A. T. 1976. Preclinical neuropharmacology of three nitrogen-containing heterocyclic benzopyrons derived from the cannabinoid nucleus. See Ref. 11, pp. 439–55
15. Fahrenholtz, K. E., Lurie, M., Kierstead, R. W. 1967. The total synthesis of dl-delta-9-tetrahydrocannabinol and four of its isomers. *J. Am. Chem. Soc.* 89:5934
16. Graham, J. D. P., Davies, B. H., Seaton, A., Weatherstone, R. M. 1976. Bronchodilator action of extract of cannabis and Δ^1-tetrahydrocannabinol. In *The Pharmacology of Marihuana,* ed. M. C. Braude, S. Szara, pp. 269–76. New York: Raven: 536 pp.
17. Vachon, L., Fitzgerald, M. X., Solliday, N. H., Gould, I. A., Gaensler, E. A. 1973. Single-dose effect of marihuana smoke. *N. Engl. J. Med.* 288:985–89
18. Tashkin, D. P., Shapiro, B. J., Frank, I. M. 1973. Acute pulmonary physiological effects of smoked marihuana and oral delta-9-tetrahydrocannabinol in healthy young men. *N. Engl. J. Med.* 289:336–41

18a. Tashkin, D. P., Shapiro, B. J., Frank, I. M. 1974. Acute effects of smoked marihuana and oral delta-9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. *Am. Rev. Respir. Dis.* 109:420–28

18b. Tashkin, D. P., Shapiro, B. J., Lee, Y. E., Harper, C. E. 1975. Effects of smoked marihuana in experimentally induced asthma. *Am. Rev. Respir. Dis.* 112:337–86

18c. Vachon, L., Mikus, P., Morrisey, W., Fitzgerald, M., Gaensler, E. A. 1975. Bronchial effect of marihuana smoke in asthma. See Ref. 16, pp. 777–84

19. Abboud, R. T., Sanders, H. D. 1976. Effect of oral administration of delta-9-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects. *Chest* 70:480–85
20. Bright, T. P., Evans, M. A., Martz, R., Brown, D. J., Forney, R. B. 1973. Marihuana induced changes in pulmonary function. *Pharmacologist* 15:238 (Abstr.)
21. Shapiro, B. J., Tashkin, D. P., Vachon, L. 1977. Tetrahydrocannabinol as a bronchodilator. *Chest* 71:558–59
22. Shapiro, B. J., Tashkin, D. P. 1976. Effects of B-adrenergic blockade and muscarinic stimulation on cannabis bronchodilation. See Ref. 16, pp. 277–86
23. Loewe, S., Goodman, L. S. 1947. Anticonvulsant action of marihuana-active substances. *Fed. Proc.* 6:352

24. Consroe, P. F., Mann, D. P. 1973. Effects of delta-8 and delta-9-tetrahydrocannabinol on experimentally induced seizures. *Life Sci.* 13:429–39
25. Karler, R., Cely, W., Turkanis, S. A. 1974. Anticonvulsant properties of delta-9-tetrahydrocannabinol and other cannabinoids. *Life Sci.* 15:931–47
26. McCaughran, J. A., Corcoran, M. E., Wada, J. A. 1974. Anticonvulsant activity of delta-8- and delta-9-tetrahydrocannabinol in rats. *Pharmacol. Biochem. Behav.* 2:227–33
27. Chesher, G. B., Jackson, D. M. 1974. Anticonvulsant effects of cannabinoids in mice: Drug interactions with cannabinoids and cannabinoid interactions with phenytoin. *Psychopharmacologia* 37:255–64
28. Fujimoto, J. M. 1972. Modification of the effects of delta-9-tetrahydrocannabinol by phenobarbital pretreatment in mice. *Toxicol. Appl. Pharmacol.* 23:623–34
29. Garriott, J. C., Forney, R. B., Hughes, F. W., Richards, A. B. 1968. Pharmacologic properties of some Cannabis related compounds. *Arch. Int. Pharmacodyn. Ther.* 171:425–34
30. Karler, R., Cely, W., Turkanis, S. A. 1973. The anticonvulsant activity of cannabidiol and cannabinol. *Life Sci.* 13:1527–31
31. Sofia, R. D., Solomon, T. A., Barry, H. 1971. The anticonvulsant activity in delta-1-tetrahydrocannabinol in mice. *Pharmacologist* 13:246
32. Dwivedi, C., Harbison, R. D. 1975. Anticonvulsant activities of delta-8- and delta-9-tetrahydrocannabinol and uridine. *Toxicol. Appl. Pharmacol.* 31: 452–58
33. Corcoran, M. E., McCaughran, J. A., Wada, J. A. 1973. Acute antiepileptic effects of delta-9-tetrahydrocannabinol in rats with kindled seizures. *Exp. Neurol.* 40:471–83
34. Fried, P. A., McIntyre, D. C. 1973. Electrical and behavioral attenuation of the anti-convulsant properties of delta-9-THC following chronic administration. *Psychopharmacologia* 31:215–27
35. Wada, J. A., Sato, M., Corcoran, M. E. 1973. Antiepileptic properties of delta-9-tetrahydrocannabinol. *Exp. Neurol.* 39:157–65
36. Izquierdo, I., Orsingher, O. A., Berardi, A. C. 1973. Effect of cannabidiol and of other Cannabis sativa compounds on hippocampal seizure discharges. *Psychopharmacologia* 28:95–102
37. Feeney, D. M., Wagner, H. R., McNamara, M. C., Weiss, G. 1973. Effects of tetrahydrocannabinol on hippocampal evoked after discharges in cats. *Exp. Neurol.* 41:357–65
38. Turkanis, S. A., Cely, W., Olsen, D. M., Karler, R. 1974. Anticonvulsant properties of cannabidiol. *Res. Commun. Chem. Pathol. Pharmacol.* 8:231–46
39. Consroe, P. F., Man, D. P., Chin, L., Picchioni, A. L. 1973. Reduction of audiogenic seizure by delta-8- and delta-9-tetrahydrocannabinols. *J. Pharm. Pharmacol.* 25:764–65
40. Boggan, W. O., Steele, R. A., Freedman, D. X. 1973. Delta-9-tetrahydrocannabinol effect on audiogenic seizure susceptibility. *Psychopharmacologia* 29:101–6
41. Killam, K. F., Killam, E. K. 1972. The action of tetrahydrocannabinol on EEG and photomyoclonic seizures in the baboon. *5th Int. Congr. Pharmacol.* 124 (Abstr.)
42. Meldrum, B. S., Fariello, R. G., Puil, E. A., Derouaux, M., Naquet, R. 1974. Delta-9-tetrahydrocannabinol and epilepsy in the photosensitive baboon (Papio papio). *Epilepsia* 15:255–64
43. Cox, B., Ham, M. T., Loskota, W. J., Lomax, P. 1975. The anticonvulsant activity of cannabinoids in seizure sensitive gerbils. *Proc. West. Pharmacol. Soc.* 18:154–57
44. Consroe, P., Jones, B., Laird, H., Reinking, J. 1976. Anticonvulsant effects of delta-9-tetrahydrocannabinol. See Ref. 11, pp. 363–82
45. Feeney, D. M., Spiker, M., Weiss, G. K. 1976. Marihuana and epilepsy: Activation of symptoms by delta 9-THC. See Ref. 11, pp. 343–62
46. Carlini, E. A., Leite, J. R., Tannhauser, M., Berardi, A. C. 1973. Cannabidiol and Cannabis sativa extract protect mice and rats against convulsive agents. *J. Pharm. Pharmacol.* 25:664–65
47. Davis, J. P., Ramsey, H. H. 1949. Antiepileptic actions of marihuana-active substances. *Fed. Proc.* 8:284
48. Lemberger, L., Rubin, A. 1978. Cannabis: The role of metabolism in the development of tolerance. *Drug Metab. Rev.* 8:59–68
49. Sallan, S. E., Zinberg, N. E., Frei, E. 1975. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N. Engl. J. Med.* 293:795–97
50. Sallan, S., Zinberg, N., Frei, E. III. 1975. Oral delta-9-tetrahydrocannabinol (THC) in the prevention of

vomiting associated with cancer chemotherapy. *Proc. Am. Assoc. Cancer Res.* 16:144
51. Herman, T. S., Jones, S. E., Dean, J., Leigh, S., Dorr, R., Moon, T. E., Salmon, S. E. 1977. Nabilone: A potent antiemetic cannabinol with minimal euphoria. *Biomed. Express* 27:331–34
52. Herman, T. S., Einhorn, L. H., Jones, S. E., Nagy, C., Chester, A. B., Dean, J. C., Furnas, B., Williams, S. D., Leigh, S. A., Dorr, R. T., Moon, T. E. 1979. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N. Engl. J. Med.* 300:1295–97
53. Nagy, C. M., Furnas, B. E., Einhorn, L. H., Bond, W. H. 1978. Nabilone antiemetic crossover study in cancer chemotherapy patients. *Proc. AACR ASCO* 19:30
54. Borison, H. L., McCarthy, L. E., London, S. W. 1978. Cannabinoids and emesis. *N. Engl. J. Med.* 298:1480–81
55. McCarthy, L. E., Borison, H. L. 1977. Antiemetic activity of nabilone, a cannabinol derivative, reversed by Naloxone in awake cats. *Pharmacologist* 19:230
56. London, S. W., McCarthy, L. E., Borison, H. L. 1979. Suppression of cancer chemotherapy-induced vomiting in the cat by nabilone, a synthetic cannabinoid. *Proc. Soc. Exp. Biol. Med.* 160:437–440
57. Hollister, L. E. 1971. Hunger and appetite after single doses of marihuana, ethanol, and dextroamphetamine. *Clin. Pharmacol. Ther.* 12:44–49
58. Regelson, W., Butler, J. R., Schultz, J., Kirk, T., Peek, L., Green, M. L., Zakis, O. 1975. Delta-9-THC as an effective antidepressant and appetite stimulating agent in advanced cancer patients. In *Int. Conf. Pharmacol. Cannabis,* ed. S. Szara, M. C. Braude. Savannah: Raven
59. Hepler, R. S., Frank, I. M. 1971. Marihuana smoking and intraocular pressure. *J. Am. Med. Assoc.* 217:1392
60. Hepler, R. S., Frank, I. M., Ungerleider, J. T. 1972. Pupillary constriction after marihuana smoking. *Am. J. Ophthalmol.* 74:1185–90.
61. Shapiro, D. 1974. The ocular manifestations of the cannabinols. *Ophthalmologica* 168:366–69
62. Perez-Reyes, M., Wagner, D., Wall, M. E., Davis, K. H. 1976. Intravenous administration of cannabinoids and intraoccular pressure. See Ref. 16, pp. 829–32
63. Purnell, W. D., Gregg, J. M. 1975. Delta-9-Tetrahydrocannabinol, euphoria and intraocular pressure in man. *Ann. Ophthalmol.* 7:921–23
64. Cooler, P., Gregg, J. M. 1976. The effect of delta 9-tetrahydrocannabinol on intraoccular pressure in humans. See Ref. 11, pp. 77–87
65. Hepler, R. S., Frank, I. M., Petrus, R. 1976. Ocular effects of marihuana. In *Pharmacology of Cannabis,* ed. M. Braude, S. Szara. New York: Raven
66. Hepler, R. S., Petrus, R. J. 1976. Experiences with administration of marihuana to glaucoma patients. See. Ref. 11, pp. 63–75
67. Cuendet, J. F., Shapiro, D., Calanca, A., Faggioni, R., Ducrey, N. 1976. Action du delta-9-tetrahydrocannabinol sur l'ophthalmotonus. *Ophthalmologica* 172:122–27
68. Green, K., Podos, S. M. 1974. Antagonism of arachidonic acid-induced ocular effects by delta-tetrahydro cannabinol. *Invest. Opthalmol.* 13: 422–29
69. Green, K., Pederson, J. E. 1973. Effect of delta-9-tetrahydrocannabinol on aqueous dynamics and ciliary body permeability in the rabbit. *Exp. Eye Res.* 15:499–507
70. Green, K., Kim, K., Bowman, K. 1976., Ocular Effects of delta-9-tetrahydrocannibinol. See Ref. 11, 4:49–62
71. Green, K., Bigger, J., Kim, K., Bowman, K. 1977. Cannabinoid action on the eye as mediated through the central nervous system and local adrenergic activity. *Exp. Eye Res.* 24:189–96
72. Green, K., Bigger, J., Kim, K., Bowman, K. 1977. Cannabinoid penetration and chronic effects in the eye. *Exp. Eye Res.* 24:197–205
73. Green, K., Kim, K. 1977. Acute dose response of intraocular pressure to topical and oral cannabinoids. *Proc. Soc. Exp. Biol. Med.* 154:228–31
74. Stark, P., Fabre, L. F., Newell, F. W., Einhorn, L. 1978. Clinical and preclinical pharmacology of a synthetic cannabinoid, nabilone (Lilly Compound 109514). *Proc. 11th Meet. Coll. Int. Neuro-Psychopharmacol.,* Vienna, p. 34
75. Nakano, S., Gillespie, H., Hollister, L. 1978. A model for evaluation of antianxiety drugs with the use of experimentally induced stress: Comparison of nabilone and diazepam. *Clin. Pharmacol. Ther.* 23:54–62
76. Fabre, L., McClendon, D., Stark, P. 1978. Nabilone, a cannabinoid, in the treatment of anxiety: An open-label and double-blind study. *Curr. Ther. Res.* 24:161–69

77. Kotin, J., Post, R., Goodwin, R. 1973. Delta-9-tetrahydrocannabinol in depressed patients. *Arch. Gen. Psychiatry* 28:345–48
78. Feinberg, I., Jones, R., Walker, J., Cavness, C., Floyd, T. 1976. Effects of marihuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin. Pharmacol. Ther.* 19:782–94
79. Ablon, S., Goodwin, F. 1974. High frequency dysphoric reactions to tetrahydrocannabinol among depressed patients. *Am. J. Psychiatry* 131:448–53
80. Regelson, W., Butler, J., Schulz, J., Kirk, T., Peek, L., Green, M. L., Zakis, O. 1976. Delta-9-tetrahydrocannabinol as an effective antidepressant and appetite stimulating agent in advanced cancer patients. See Ref. 16, pp. 763–76
81. Butler, J. R., Peek, L. A., Regelson, W., Moore, M. M., Lubin, L. A. 1976. Treatment effects of delta 9-THC in an advanced cancer population. See Ref. 11, pp. 313–28
82. Cousens, K., DiMascio, A. 1973. Delta-9-THC as an hypnotic *Psychopharmacologia* 33:355–64
83. Neu, C., DiMascio, A. 1976. Hypnotic properties of THC: Experimental comparison of THC, chloral hydrate, and placebo. See Ref. 11, pp. 153–60
84. Grunfield, Y., Edery, H. 1968. Psychopharmacological activity of the active constituents of hashish and some related cannabinoids. *Psychopharmacologia* 14:200–10
85. Sofia, R. D., Nalepa, S. D., Harakal, J. J., Vassar, H. B. 1973. Antiedema and analgesic properties of delta-9-tetrahydrocannabinol (THC). *J. Pharmacol. Exp. Ther.* 186:646–55
86. Chesher, G. B., Dahl, C. J., Everingham, M. Jackson, D. M., Marchant, H., Starmer, G. A. 1973. The effect of cannabinoids on intestinal motility and their antinociceptive effect in mice. *Br. J. Pharmacol.* 49:588–94
87. Dewey, W. L., Harris, L. S., Kennedy, J. S. 1972. Some pharmacological and toxicological effects of *l-trans*-delta-8 and *l-trans*-delta-9-tetrahydrocannabinol in laboratory rodents. *Arch. Int. Pharmacol.* 196:133–45
88. Wilson, R. S., May, E. L. 1976. The role of 11-hydroxylation in tetrahydrocannabinol activity. See Ref. 16, pp. 137–38
89. Stark, P., Archer, R. 1975. Preclinical pharmacologic profile of a psychoactive cannabinoid. *Pharmacologist* 17:210
90. Wilson, R. S., May, E. L., Martin, B. R., Dewey, W. L. 1976. The 9-nor-4-hydroxyhexa hydrocannabinols. Synthesis, some behavioral and analgesic properties and comparison with the tetrahydrocannabinols. *J. Med. Chem.* 19:1165
91. Milne, G. M., Weissman, A., Koe, B. K., Johnson, M. R. 1978. CP-44,001, A novel benzo(c)quinoline analgesic. *Pharmacologist* 20:243
92. Harris, L. S. 1976. Analgesic and antitumor potential of the cannabinoids. See Ref. 11, pp. 299–312
93. Noyes, R., Brunk, S., Baram, D., Canter, A. 1976. Analgesic effects of delta-9-tetrahydrocannabinol. See Ref. 16, pp. 833–36
94. Hill, S. Y., Schwin, R., Goodwin, D. W., Powell, B. J. 1974. Marihuana and pain. *J. Pharmacol. Exp. Ther.* 188: 415–18
95. Allen, T. 1976. Tetrahydrocannabinol and chemotherapy. *N. Engl. J. Med.* 294:168
96. Nieburg, H. A., Margolin, F., Seligman, B. R. 1976. Tetrahydrocannabinol and chemotherapy. *N. Engl. J. Med.* 294:168
97. Sofia, R. D., Knobloch, L. C., Vassar, H. B. 1973. The antiedema activity of various naturally occurring cannabinoids. *Res. Commun. Chem. Pathol. Pharmacol.* 6:909–18
98. Sofia, R. D., Nalepa, S. D. Vassar, H. B., Knobloch, L. C. 1974. Comparative antiphlogistic activity of delta-9-tetrahydrocannabinol, hydrocortisone and aspirin in various rat paw edema models. *Life Sci.* 15:251–60
99. Burstein, S., Raz, A. 1972. Inhibition of prostaglandin E_2 synthesis by delta 1-tetrahydrocannabinol. *Prostaglandins* 2:369
100. Burstein, S., Levin, E., Varanelli, C. 1973. Prostaglandins and cannabis, II. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochem. Pharmacol.* 22:2905–10
101. Howes, J. F., Osgood, P. F. 1974. The effects of delta-9-THC and a water soluble derivative on PGE_1 synthesis on the corpus striatum. *Pharmacologist* 16:259
102. Green, K., Podos, S. M. 1974. Antagonism of archidonic acid–induced ocular effects by delta-1-tetrahydrocannabinol. *Invest. Ophthalmol.* 13:422–29
103. Harris, L. S., Munson, A. E., Friedman, M. A., Dewey, W. L. 1974. Retardation of tumor growth by delta-9-tetrahydrocannabinol. *Pharmacologist* 16: 259
104. Harris, L. S., Munson, A. E., Carchman, R. 1976. Anti-tumor properties of cannabinoids. See Ref. 16, p. 749

105. Weiss, J. L., Watanabe, A. M., Lemberger, L., Tamarkin, N. R., Cardon, P. V. 1972. Cardiovascular effects of delta-9-tetrahydrocannabinol in man. *Clin. Pharmacol. Ther.* 13:671–84
106. Beaconsfield, P., Ginsburg, J., Rainsbury, R. 1972. Marijuana smoking: Cardiovascular effects in man and possible mechanisms. *N. Engl. J. Med.* 287:209–19
107. Birmingham, M. K. 1973. Reduction by delta-9-tetrahydrocannabinol in the blood pressure of hypertensive rats bearing regenerated adrenal glands. *Br. J. Pharmacol.* 48:169–71
108. Birmingham, M. K., Bartova, A. 1976. Effects of cannabinol derivatives on blood pressure, body weight, pituitary-adrenal function, and mitochondrial respiration in the rat. In *Marihuana: Chemistry, Biochemistry and Cellular Effects,* ed. G. Nahas, pp. 425–38. New York: Springer
109. Nahas, G. G., Schwartz, I. W., Adamec, J., Manger, W. M. 1973. Tolerance to delta-9-tetrahydrocannabinol in the spontaneously hypertensive rat. *Proc. Soc. Exp. Biol. Med.* 142:58–60
110. Lewis, S. C., Neel, M. A., Brown, D. J., Forney, R. B. 1973. Vasodepressor response to delta-9-tetrahydrocannabinol in hypertensive rats. *Pharmacologist* 15:200 (Abstr.)