

Marijuana and Health

Report of a Study
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7 THERAPEUTIC POTENTIAL AND MEDICAL USES OF MARIJUANA

There has been growing interest in the possibility that cannabis and its derivatives will be valuable for the treatment of several medical and psychiatric conditions. The 97th Congress, for example, introduced a bill (H.R. 4498) "to provide for the therapeutic use of marijuana in situations involving life-threatening or sense-threatening illness and to provide adequate supplies of marijuana for such use."

Most of the putative therapeutic effects of cannabis are believed to be mediated by the central nervous system. These include effects on appetite, nausea and vomiting, epilepsy, muscle spasticity, anxiety, depression, pain, and on glaucoma, asthma, and the symptoms of withdrawal from alcohol and narcotics. The literature on these and other therapeutic actions believed mediated by the central nervous system will be reviewed in this chapter.

In general, the committee finds that cannabis shows promise in some of these areas, although the dose necessary to produce the desired therapeutic effect is often close to one that produces an unacceptable frequency of toxic (undesirable) side-effects. What is perhaps more encouraging than the therapeutic effects observed thus far is that cannabis seems to exert its beneficial effects through mechanisms that differ from those of other available drugs. This raises the possibility that some patients who would not be helped by conventional therapies could be treated effectively with cannabis. A second possibility is that cannabis could be combined with other drugs to achieve a therapeutic goal, but with each drug being used at a lower dose than would be required if either *were* used alone. As a result, fewer side-effects would be expected to occur. It may be possible to reduce side-effects by synthesizing related *molecules* that could have a more favorable ratio of desired to undesired actions; this line of investigation should have high priority, because such synthetic derivatives may ultimately have widespread therapeutic use.

GLAUCOMA

Glaucoma is the leading cause of blindness in the United States. The term is used to describe a group of ocular diseases characterized by an increase in intraocular pressure, which damages the optic nerve and leads eventually to loss of vision. The disease affects over two million Americans of age 35 or older. Although there is increasing risk of glaucoma with increasing age, there are forms that develop in infancy. The National Society to Prevent Blindness (1980) also estimates that 300,000 new cases are diagnosed each year.

Treatment of glaucoma depends on the type and cause. It may be pharmacological or surgical. Surgery is useful treatment in relatively few cases; there is a high incidence of failure and serious complications may occur. Available antiglaucoma drugs are effective in regulating intraocular pressure in many patients, and are the mainstay of treatment in the most common form of glaucoma, but there are some adverse side-effects. Some patients are refractory to present forms of treatment and become blind as the disease progresses; for them, there is a particularly urgent need to find effective drugs.

Cannabis (the crude drug), Δ -9-THC (the pure compound), and some other cannabinoid derivatives lower intraocular pressure when administered by various routes, such as inhalation, oral, or intravenous. However, adverse side-effects of cannabis and Δ -9-THC also have been reported. Most patients with glaucoma are elderly, and have a reduced tolerance for many of these side-effects. Even without the adverse side effects, smoking, oral, and intravenous routes of administration are not suitable for the long term. For example, to give adequate control for intraocular pressure, four marijuana cigarettes per day of 2 percent Δ -9-THC would be necessary; this amount is considered heavy usage and could pose a serious health problem in long-term use. Therefore, topical application would be the most salutary route of administration for the patient who needs continuous treatment.

Human Studies

Interest in using cannabis for the treatment of glaucoma was first stimulated by the observation of Hepler et al. (1971, 1972) that intraocular pressure decreased when healthy human subjects smoked cannabis (0.9 percent and 1.5 percent Δ -9-THC content) using an ice-cooled water pipe. (See Green, 1979, for an extensive literature review.)

A study of the acute ocular effects of cannabis in 429 subjects showed there was a dose-related and statistically significant reduction of intraocular pressure following the smoking or ingestion of cannabis containing 1, 2, or 4 percent Δ -9-THC (Hepler et al., 1976a). The amount of pressure decrease was in the range of 30 percent for the cannabis that contained 2 percent Δ -9-THC. Nineteen hospitalized subjects who smoked cannabis of 1 or 2 percent

Δ -9-THC content were observed for 35 days and another 29 subjects were observed as in-patients for a total of 94 days. There was a consistent drop in intraocular pressure in those smoking the 2 percent cannabis and the reduction appeared to last 4 to 5 hours (Hepler et al., 1976a). The authors noted that there did not seem to be much of a cumulative effect on size of pupils or upon intraocular pressure response. Studies by other investigators have confirmed this effect of cannabis and Δ -9-THC in causing reduction of intraocular Pressure in humans (Shapiro, 1974; Purnell and Gregg, 1975).

Perez-Reyes et al. in 1976 investigated the effect of intravenous infusion of six cannabinoids in healthy volunteers. Delta-8-THC, Δ -9-THC, 11-hydroxy- Δ -9-THC, cannabinol, cannabidiol, and 8-8-hydroxy- Δ -9-THC were tested on healthy subjects with normal intraocular pressure; Δ -8-THC, Δ -9-THC, and 11-hydroxy-THC caused the greatest reduction in pressure. Of these Δ -8-THC caused the largest decrease in intraocular pressure, with the least number of psychological side-effects.

In a preliminary study of 11 human glaucoma patients who smoked marijuana (1, 2, and 4 percent) or ingested Δ -9-THC (15 mg), intraocular pressure was lowered an average of 30 percent in 7 out of 11 patients (Hepler et al., 1976a). Another study showed that most patients had a decrease in intraocular pressure after ingestion of 15, 20, or 30 mg of Δ -9-THC and after smoking cannabis containing 1, 2, and 4 percent Δ -9-THC (Hepler et al., 1976b).

Ideally, the synthesis of a preparation that could be applied topically to the eye would be most desirable for humans, because this would allow for self-administration. However, initial studies in humans with a topical preparation of Δ -9-THC have not shown a consistent effect on intraocular pressure (Merritt et al., 1981). More work needs to be done on this possibility.

Animal Studies

While animal studies have supported the observation that Δ -9-THC lowers intraocular pressure after oral and topical administration in rabbits (Green et al., 1977a,b; 1978), and after intravenous administration in the cat (Inneme et al., 1979), the reduction in intraocular pressure is not completely understood. It may result in part from a central nervous system effect, and in part through action on the adrenergic system in the eye, probably mediated by the neurotransmitter norepinephrine.

Side-Effects

Marijuana and Δ -9-THC given orally, intravenously, or in cigarettes to control glaucoma cause systemic side-effects, such as increase in heart rate, decrease in blood pressure, and psychotropic effects. Some of these side-effects are significant enough to pose problems, particularly in patients with glaucoma, who are usually elderly. But

on the other hand, some of these effects may disappear as tolerance (decreased response with repeated use) develops.

Tolerance to the Intraocular Pressure Reducing Effect

No tolerance was detected to the ocular effects of cannabis in rabbits after 1 year's topical instillation of the synthetic cannabinoids **SP-1**, **SP-106**, and **SP-204** (Green and Kim, 1977; Green et al., 1977b). **Hepler** et al. (1976b) noted a ceiling effect in humans, in that the smoking of 22 cannabis cigarettes did not result in a significant decrease in eyeball pressure as compared with a subject who smoked only 2 cigarettes. The area of tolerance will need further study, especially if a cannabinoid preparation with a satisfactorily high ratio of therapeutic to side-effects can be found.

Summary

Cannabis, **Δ-9-THC**, other cannabinoid derivatives, and their synthetics, reduce intraocular pressure in humans when smoked, or given intravenously or orally. However, there are systemic side-effects as well as psychotropic effects that are of concern. It is not yet clear whether an effective topical preparation can be developed that will not have these side-effects. Future work should determine whether synthetic cannabinoids or cannabinoid analogues can be found that will be effective in treating glaucoma without causing side-effects.

ANTIEMETIC ACTION

- Certain cancer chemotherapeutic agents regularly produce nausea and vomiting after oral or intravenous administration. Those that are most severe in that respect are cisplatin, actinomycin **D**, **adriamycin**, **cyclophosphamide**, methotrexate, and the nitrosoureas. Other anti-cancer compounds may produce nausea less regularly or in less marked fashion.

Because cancer chemotherapy now can produce increased survival in patients with some neoplasms (recurrent or metastatic breast cancer, small cell carcinoma of the lung, ovarian cancer, and others) and substantial cure rates in several (acute lymphoblastic leukemia, Hodgkins disease, germ cell tumors of the testis, etc.) nausea and vomiting that interfere with patients' willingness to continue therapy can be a life-threatening side-effect. Even for those willing to endure the symptoms, they can be extremely unpleasant and debilitating.

Established antiemetics (prochlorperazine and other **phenothiazines**) are not very effective against drug-induced **emesis**, and there is a need for new and more reliable antiemetic agents. **Metoclopramide**, a derivative of **procainamide**, has recently been shown to be

more effective than prochlorperazine in certain situations and seems promising (Gralla et al., 1981).

The suggestion that cannabis might have some useful antiemetic activity in this setting arose about 1973, when patients receiving intensive chemotherapy for acute leukemia observed that their "social" use of cannabis appeared to reduce their customary nausea and vomiting.

Clinical Investigations

Several controlled studies have been reported. In one of the early ones (Sallan et al., 1975), Δ -9-THC in 15- or 20-mg doses by mouth was compared with a placebo in a randomized double-blind crossover trial in 22 patients whose nausea and vomiting had been shown refractory to other antiemetics. In 14 of 20 courses of treatment, patients obtained "complete or partial relief" with Δ -9-THC; in none of 22 courses did patients report benefit with the placebo. It was observed that the antiemetic effect of Δ -9-THC occurred only in association with the "high," and it was necessary to maintain the "high" in order to maintain the antiemetic effect.

In another controlled trial (Chang et al., 1979), 14 of 15 patients with osteogenic sarcoma treated with high-dose methotrexate had less nausea and vomiting with Δ -9-THC than with the placebo. In that study, patients with other tumors being treated with cytoxan and adriamycin did not respond as well. That report and others like it suggested that the antiemetic effect of Δ -9-THC against those chemotherapeutic agents that are moderate in their emetic potential (e.g., methotrexate) was pronounced, but that Δ -9-THC was less effective against those agents with severe emetic properties. In a similar study (Lucas and Laszlo, 1980), 38 of 53 patients with nausea and vomiting refractory to other antiemetics reported good results with Δ -9-THC. Among the failures were those treated with cisplatin, which has been characterized as one of the most emetic agents used in cancer chemotherapy.

In comparison with prochlorperazine, Δ -9-THC has also been reported to be more effective in preventing nausea and vomiting (Ekert et al., 1979; Sallan et al., 1980).

In a larger study (Frytak et al., 1979), of 116 patients treated with 5-fluorouracil and methyl-CCNU, Δ -9-THC was said to be no more effective than prochlorperazine. In that study, in which nearly all patients were older than those in the other reported trials, the majority of patients considered the other side-effects of Δ -9-THC so unpleasant that they preferred either prochlorperazine or the placebo.

Another cannabinoid, a synthetic, nabilone, has been provided to several investigators for evaluation as an antiemetic agent; it has been licensed for use in Canada for treatment of nausea associated with cancer treatment. In the largest clinical study to date (Herman et al., 1979), nabilone was compared with prochlorperazine in a double-blind crossover trial. It was found more effective than

prochlorperazine. The patients in that study preferred nabilone to prochlorperazine; the predominant side-effects were somnolence, dry mouth, and dizziness. Hallucinations occurred in a few patients. Euphoria of the type associated with cannabis was infrequent in that study. However, a study in dogs has revealed previously unrecognized late **neurologic** effects of nabilone at high doses (Archer et al., 1981). Monkeys and rats did not show similar toxic effects with long-term administration of nabilone (Archer et al., 1981), and further studies will be necessary to clarify the safety of this new agent.

Levonantradol is yet another synthetic cannabinoid, related to Δ -9-THC, which has been shown in preliminary clinical studies to have antiemetic action in patients with refractory **chemotherapy**-induced emesis (Diasio et al., 1981).

Uncontrolled Use of Δ -9-THC

In response to public and political pressures, the National Cancer Institute, the United States Drug Enforcement **Agency**, and the Food and Drug Administration have agreed to a program whereby the National Cancer Institute is making Δ -9-THC available through the pharmacies of approximately 500 teaching hospitals and cancer centers to physicians who wish to use Δ -9-THC in treating the nausea and vomiting of patients receiving cancer chemotherapy. This broad, uncontrolled **program**, in which no data other than the reporting of severe reactions are to be collected, may make it extremely difficult to obtain continuing valid evaluations of the effectiveness of Δ -9-THC in the management of nausea and vomiting due to cancer chemotherapy. Although the extent of use of Δ -9-THC under this program is difficult to evaluate, informal communication with the National Cancer Institute indicates that Δ -9-THC has been supplied in substantial quantities to several hundred hospital pharmacies. The problem is further complicated by the fact that the legislatures of 23 states have authorized the use of cannabis by any physician for the management of nausea and vomiting due to cancer chemotherapy. It is expected that little reliable information will be derived from such use.

Summary

There seems little doubt that Δ -9-THC and other cannabinoids are active against the severe nausea and vomiting produced by cancer chemotherapeutic agents. The extent of this activity, its relation to other antiemetics, and its relation to the other effects of the cannabinoids have not yet been accurately determined.

Cannabis **leaf**, smoked or eaten, is also antiemetic but its activity has been even less well determined than that of Δ -9-THC. Studies with other synthetic cannabinoids have barely begun and much remains to be learned in this field.

APPETITE STIMULANT

It has been stated by "social" users that the smoking of cannabis increases appetite. On that basis, there have been sporadic attempts to use it in patients with advanced cancer to overcome their customary debilitating weight loss.

In several of the studies in which Δ -9-THC was used as an antiemetic in patients receiving cancer chemotherapy, they were reported to have increased appetite and food intake. At this time, it is not certain whether that increase was due merely to relief of nausea and vomiting or to stimulation of appetite. One comparison of habitual marijuana users and controls matched for age and educational background showed increased caloric intake and weight gain among the users (Greenberg, et al., 1976). Furthermore, a double-blind controlled study (Hollister, 1971) of smokers of cannabis or placebo cigarettes provided with unlimited quantities of a high-caloric beverage indicated an increase in caloric consumption in those using cannabis compared with those using the placebo; however, the variability was very large and there was some question that cannabis could be considered a clinically significant appetite stimulant.

In another study of the psychological effects of Δ -9-THC in patients with advanced cancer, it was observed that Δ -9-THC appeared to stimulate appetite and retard weight loss (Regelson et al., 1976). In that study many patients refused to complete the 2-week trial because of unacceptable side-effects from Δ -9-THC.

The evidence to date suggests that there may be some influence of cannabis on appetite. However, it is not possible to separate that from the effect on nausea and vomiting. Further studies are in progress in cancer patients whose course is not complicated by nausea and vomiting.

ANTICONVULSANT ACTION

A large number of animal studies have been conducted using cannabis as an anticonvulsant. These can be divided into several categories. The first to be discussed will be maximal electroshock seizures (MES)* both in the rat and mouse (Loewe and Goodman, 1947; Sofia et al., 1971; Fujimoto, 1972; Consroe and Man, 1973; Karler et al., 1973; Chesher and Jackson, 1974; Karler et al., 1974; McCaughran et al., 1974; Karler and Turkanis, 1976; Consroe and Wolkin, 1977; Turkanis et al., 1977). In these studies there is a clear dose-response effect in the protection to MES conferred by cannabinal (CBN) and cannabidiol (CBD). Tolerance to the effect has frequently been reported. However, the tolerance noted with cannabinoids is similar to that seen with phenytoin (DPH). Further, even though tolerance to phenytoin develops with MES, this has not been shown to

*Electrical shock of maximum intensity to cause a major seizure.

be a clinically significant phenomenon. In these studies it is generally found that CBN is less effective against **MES** and against **audiogenic** seizures, the latter produced in rodents by loud noise, than CBD. In addition, Turkanis et al. (1977) have emphasized the fact that CBD acts more like DPH than other anticonvulsants and hence would be expected to be effective against major seizures rather than against minor seizures.

There is also extensive animal literature that CBN and CBD will protect against electrically induced, minimal (kindling) seizures (Corcoran et al., 1973; Fried and McIntyre, 1973; Izquierdo et al., 1973; Turkanis et al., 1977, 1979). Reduction of seizures produced by **subcortical** electrical stimulation in the cat has been reported (Wada et al., 1973). There appears to be much less effect on **pentylentetrazol-induced** seizures (Consroe and Man, 1973; Turkanis et al., 1979). Any effect of CBN and CBD on such seizures occurs with maximal toxic doses (Turkanis et al., 1974). Protection against **audiogenic** seizures (Consroe et al., 1973) and against reflex seizures in the gerbil (Cox et al., 1975) have been reported.

Human studies are largely anecdotal and conflicting. There is one study by Cunha et al. (1980) in which 15 patients suffering from partial complex epilepsy with a temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, **200-300 mg** of CBD or placebo daily. The drugs were administered for as long as 4 1/2 months. Throughout the study, clinical and laboratory examinations, electroencephalograms, and electrocardiograms were performed at **15- to 30-day** intervals. The patients continued their anticonvulsant medications taken before entering the study, on which all them had previously experienced uncontrolled seizures. All patients tolerated CBD well, and there were no signs of toxicity or serious side-effects. Four of the 8 CBD subjects remained nearly free of convulsions during CBD treatment and 3 other patients demonstrated partial improvement in their clinical condition. Cannabidiol was ineffective in 1 patient. The placebo group showed no alteration of seizure frequency. A series of 8 healthy volunteers given CBD showed no effects of the drug.

Summary

There is substantial evidence from animal studies to indicate that cannabinoids are effective in blocking both kindling seizures and **MES**, and this is particularly true for CBD. **MES** is a standard testing procedure for evaluation of anticonvulsant drugs. This is strong support for further investigation into the utility of CBD in human epilepsy. The one available carefully controlled human study is in accord with this review.

MUSCLE RELAXANT ACTION

There are widespread, anecdotal reports that cannabis is effective in relieving muscle spasm or spasticity. Petro (1980) has reported such effects in two cases and has carried out a double-blind study of the administration of Δ -9-THC on spasticity (Petro and Ellenberger, 1981). They reported that 10 mg of Δ -9-THC significantly reduced spasticity by clinical measurement and that quadriceps **electromyograms** demonstrated a decrease in interference pattern in four patients with primarily extensor spasticity. These are preliminary observations, but they suggest that further and more rigorous investigations of the use of cannabinoids in spasticity should be suggested to test their therapeutic effectiveness.

ANTIASTHMATIC EFFECT

Intensive, chronic smoking of concentrated cannabis produces several adverse effects on the airways, including mild bronchoconstriction. But acute smoking of cannabis as well as the ingestion of Δ -9-THC **produces** bronchodilation in normals and in subjects with chronic, clinically stable bronchial asthma of minimal to moderate severity (Tashkin et al., 1974). These bronchodilator effects were also investigated in individuals in whom an asthmatic attack was induced experimentally by exercise or methalcholine (Tashkin et al., 1975). Immediately after the development of **bronchospasm**, subjects smoked a cigarette containing 500 mg of cannabis assayed at either 1 or 2 percent Δ -9-THC.

Methalcholine inhalation promptly caused significant **broncho-**Constriction (an average decrease in airway conductance of 40-55 percent) and significant hyperinflation (mean increases in thoracic gas volume of 35-43 percent). After placebo smoking or saline inhalation, airway conductance increased only modestly, remaining significantly less than initial control values for 30 to 60 minutes, and thoracic gas volume decreased only gradually, remaining significantly increased for 15 minutes. However, after 2 percent cannabis, and after isoproterenol, there was a prompt return of airway conductance and thoracic gas volume to control values.

Exercise in the asthma-prone individual resulted in average decreases in airway conductance of 30-39 percent and average increase in thoracic gas volume of 25-35 percent. After placebo or saline, there was only a gradual return to control values during 30-60 minutes, but after cannabis, airway conductance and thoracic gas volume returned promptly to preexercise values. Four of the subjects who had previously used cannabis could detect pleasurable sensations after smoking cannabis, which distinguished these effects from those of the **placebo** cigarette. In that sense these experiments were not strictly blind. The four subjects who had no previous experience with cannabis did not experience any central nervous system effects but did note mild **somolence** or light-headedness after cannabis. The results of this study suggest that any bronchial irritant effects of

placebo cannabis smoke were not sufficient to aggravate or perpetuate existing acute **bronchospasm** to an extent greater than that which might result from the irritant effect of inhaled saline. The results also demonstrate that inhaled Δ -9-THC causes a prompt and complete sustained reversal of methacholine-induced bronchospasm and correction of the associated **hyperinflation**. These effects were not significantly different from those observed after isoproterenol, although there was a tendency toward a greater degree of bronchial dilation after isoproterenol. Similarly, after inhalation of Δ -9-THC, there was a prompt return of airway conductance and thoracic gas volume during exercise-induced bronchospasm to the preexercise value. After exercise the effects of 10 mg Δ -9-THC was **not** as efficacious as 1.25 mg isoproterenol.

The way in which Δ -9-THC induces bronchial dilation has not been determined, but previous studies have shown that this effect is not mediated by beta-adrenergic stimulation or inhibition of muscarinic receptors (Shapiro et al., 1973). A vagolytic mechanism is **possible**, as suggested by other studies carried out on the dog salivary gland (Cavero et al., 1972) and on guinea pig ileum (Gill et al., 1970).

Although ingestion of Δ -9-THC in a sesame oil vehicle has produced **bronchodilation** in asthmatic patients (Tashkin et al., 1974), less dilation was noted than after smaller doses of Δ -9-THC delivered by smoking. Its significant **bronchodilator** effect notwithstanding, Δ -9-THC does not appear to be suitable for therapeutic use, because of its psychotropic effects and possibly other side-effects. However, other cannabinoid compounds such as cannabidiol and cannabidol do not produce the central nervous system effects of tachycardia characteristic of cannabis (Hollister, 1973) and deserve further investigation for possible **bronchodilator** activity.

ANTI-ANXIETY EFFECT

Users of cannabis have often reported that the drug produces feelings of relaxation and calmness, and some have reported its use to reduce anxiety. A problem with evaluating cannabis as an anti-anxiety drug, however, is that some subjects report increased anxiety or panic after using cannabis (see Chapter 6). For example, Regelson et al. (1976) found less tension and apprehension in cancer patients after cannabis **use**; but 6 of 59 subjects receiving Δ -9-THC reported such side-effects as severe dizziness, confused thinking, dissociation, and concern **over loss** of sanity. In normals, Pillard et al. (1974) found no effects of cannabis on experimentally induced anxiety. Nabilone, a synthetic cannabinoid, was found to reduce experimentally induced anxiety in normal volunteers but it was less effective than **diazepam** (Nakano et al., 1978). Nabilone was found to be more effective than placebo in patients with psychoneurotic anxiety (Fabre et al., 1978).

There **are very** few studies of cannabis effects on anxiety. There is no indication at this time that cannabis or nabilone are

more effective or reliable than currently available antianxiety medication.

ANTIDEPRESSANT EFFECT

Regelson et al. (1976) reported a significant reduction in **self-rated** depressive symptoms in cancer patients treated with **Δ -9-THC**. However, in a carefully controlled trial with four bipolar and four **unpolar** depressed patients, Kotin et al. (1973) found no anti-depressant activity.

ANALGESIC ACTION

Several animal models have been used to show analgesic effects of cannabis and its analogues (for example, Grunfeld and Edery, 1969; Sofia et al., 1973). Human studies have been conflicting. Milstein et al. (1975) found increase in tolerance to experimentally induced pain after smoking cannabis, while Hill et al. (1974) were unable to detect effects using a different kind of experimental pain. **Noyes** et al. (1976) found a reduction in pain reports by **cancer** patients given oral **Δ -9-THC**; Regelson et al. (1976) also studied cancer patients and found no significant changes in pain after **Δ -9-THC**.

Those subjects who show analgesic effects of cannabis also show other pharmacological effects such as mental clouding. The literature does not indicate a specific effect of cannabis on pain pathways nor does it suggest that cannabis is likely to be more effective than currently available analgesics.

ALCOHOLISM

Cannabis has been proposed as a treatment for alcoholism (**Scher**, 1971) based upon case reports and on the observation that cannabis and alcohol were generally not used together. A systematic evaluation (Rosenberg et al., 1978) failed to find cannabis useful in alcoholism. Moreover, recent surveys (see Chapter 2) indicate that currently the abuse of cannabis and alcohol are frequently combined.

OPIATE WITHDRAWAL

Early clinical reports suggested that cannabis might be useful in suppressing the symptoms of opiate withdrawal (Birch, 1889; Thompson and Proctor, 1953). Recently a series of animal studies (**Hine** et al., 1975a,b; Bhargava, 1976) have found that **Δ -9-THC** suppresses many of the behavioral manifestations of withdrawal precipitated by naloxane in morphine dependent rodents. This effect is enhanced by **cannabidiol (CBD)** (**Hine** et al., 1975a,b), but **CBD** is not effective alone.

There are no reports of systematic evaluations of cannabis as a treatment of opiate withdrawal in human beings. The animal studies do not present evidence that cannabis is likely to be more effective than currently available treatments for opiate withdrawal.

ANTITUMOR ACTION

There is very little information about the effects of cannabis on **neoplasms**. In one study (Harris et al., 1976), minor effects were seen on the Lewis Lung Tumor but not in L1210 leukemia. In another study (White et al., 1976), it was found that Δ -9-THC inhibited tumor DNA replication somewhat. In that same study, cannabidiol appeared to have a growth enhancing effect on the Lewis Lung Tumor. These limited studies do not support a view that Δ -9-THC has a useful effect in inhibiting tumor growth.

SUMMARY

Cannabis and its derivatives have shown promise in the treatment of a **variety** of disorders. The evidence is most impressive in glaucoma, where their mechanism of action appears to be different from the standard drugs; in asthma, where they approach isoproterenol in effectiveness; and in the nausea and vomiting of cancer chemotherapy, where they compare favorably with phenothiazines. Smaller trials have suggested cannabis might also be useful in seizures, spasticity, and other nervous system disorders. Effective doses usually produce psychotropic and cardiovascular effects and can be **troublesome**, particularly in older patients,

Although marijuana has not been shown unequivocally superior to any existing therapy for any of these conditions, several important aspects of its therapeutic potential should be appreciated. First, its mechanisms of action and its toxicity in several diseases are different from those of drugs now being used to treat these conditions; thus, combined use with other drugs might allow greater therapeutic efficacy without cumulative toxicity. Second, the differences in action suggest new approaches to understanding both the diseases and the drugs used to treat them. Last, there may be an opportunity to synthesize derivatives of marijuana that offer better therapeutic ratios than marijuana itself.

RECOMMENDATIONS FOR RESEARCH

The committee believes that the therapeutic potential of cannabis and its derivatives and synthetic **analogues** warrants further research along the lines described in this chapter. There also may be significant heuristic benefits to be derived from the study of the biological mechanisms by which these compounds act.

Some therapeutic promise seems to be offered by synthetic cannabinoid analogues. The committee recommends that particular attention be paid to the treatment of chemotherapy-induced nausea and vomiting in cancer patients because current management of this important and widespread problem is inadequate and preliminary studies suggest that cannabinoids may have some special advantage. Cannabinoids or their analogues also may find a place in the management of resistant glaucoma, of severe intractable asthma, and of certain forms of seizures that are resistant to standard therapy. Continued carefully contracted clinical trials in these areas seem worthwhile at this time, as do studies of the usefulness of cannabinoids in the treatment of muscle spasticity.

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Appendix

D

PARAQUAT ISSUE

Paraquat is a herbicide that is used throughout the **world**. It is available in an aerosol form, granules, and a water-soluble **concentrate**. As a result of accidental or suicidal swallowing of the water-soluble concentrate, more than 500 human fatalities have occurred (Harley et **al.**, 1977). In contrast, neither inhalation of the spray nor ingestion of paraquat granules has been shown to be of clinical importance (Fairshter and Wilson, 1975).

About 60 percent of the marijuana consumed in the United States is grown in Mexico. Since 1975, in the attempt to reduce the illegal production of marijuana, the Mexican government has been spraying marijuana fields from airplanes. The herbicide kills the treated plants within 1 or 2 days. Marijuana producers have resorted to harvesting the plants soon after spraying, minimizing exposure to sunshine, so that they are not destroyed. The paraquat persists on the dried leaves. Samples of marijuana confiscated at the **U.S.-Mexico** border have disclosed that about 21 percent of the confiscated marijuana was contaminated with paraquat in varying concentrations.

Paraquat damages the lungs, heart, kidneys, adrenal glands, central nervous system, liver, skeletal muscle, and spleen. **In** general, all effects but those on the lungs are transitory. The changes in the lungs of humans after ingestion appear to be dose-related: small amounts of the swallowed chemical may cause modest and reversible lung damage; in contrast, larger quantities cause lethal pulmonary fibrosis. An important element in paraquat toxicity is the fact that it is concentrated in the lungs where it does particular damage to the alveolar lining. **In** many respects, probably including the mechanism by which it damages the lungs, its effects resemble those of oxygen toxicity but seem to be less reversible (Smith and Heath, 1976).

With respect to marijuana, the use of paraquat as a herbicide entails the possibility of risk to two populations: (1) those who **spray** the paraquat and the workers in the fields who are exposed to an environment containing the paraquat spray, and (2) the marijuana smoker. **To** date, no toxic effects attributable to paraquat, **per se**, have been proved in either population. However, the observations thus far relate to the acute hazards of paraquat inhalation and do

not provide any assurance about the long-term effects. Indeed, observations on other inhaled toxins suggest that exposure for many years may be prerequisite for the development of clinical disability.

An important question with respect to the toxic effects of paraquat on the lungs is how much of the paraquat survives combustion and is transferred in the smoke to the gas-exchanging surfaces of the lungs. Studies conducted by NIDA indicate that as much as 0.2 percent of the paraquat in a marijuana cigarette appeared in a condensate of smoke prepared under laboratory conditions. The results suggested that a typical marijuana cigarette contaminated at approximately 500 ppm--a reasonable degree of contamination--would produce smoke containing up to 1 mg of paraquat. This experimental evidence has led to the prediction that a human smoker of five marijuana cigarettes per day would expose the lungs to approximately 5 mg of paraquat. Laboratory evidence derived from hamsters suggests the possibility of damaging the distal part of the airways (the bronchioles and the proximal alveolar ducts) by this exposure. These experiments and predictions suggest that an individual who continued to smoke paraquat-contaminated cigarettes would be a candidate for serious lung injury. The prospect probably would be greatly heightened by the toxic effects of the combusted marijuana.

There are only a few observations of experimental animals that bear directly on the effects of inhaled paraquat (Kimbrough and Gaines, 1970; Zavala and Rhodes, 1978). These suggest that similar lesions are produced by ingested paraquat and by paraquat introduced into the airways. For example, the introduction of minute quantities of paraquat dichloride intrabronchially, in concentrations ranging from 10 mg to 100 mg, elicited focal pulmonary edema, hemorrhage, and fibrosis (Zavala and Rhodes, 1978). The smaller doses are within the range to which a smoker of marijuana contaminated by paraquat might be exposed. However, the experimental evidence is not entirely relevant on several accounts: (1) paraquat arriving at the lung surfaces by inhalation from contaminated air or after smoking must be carried in the form of smoke, gas, or small droplets, because larger droplets, such as the aerosols used in agriculture, are apt to precipitate out in proximal airways, which are protected by cilia and mucus; (2) the intrabronchial installation of paraquat in a solution provides a different pattern of access to the gas-exchanging surfaces of the lungs than does inhalation of smoke, gas, or droplets; (3) because of its water solubility, paraquat that escapes pyrolyzation during smoking would be expected to be taken up by the tracheal bronchial tree and its branches before reaching the alveoli unless carried in the form of smoke, gas, or small droplets.

In essence, the evidence concerning the injurious effects of paraquat inhaled after either spraying or smoking is too meager for conclusions. The observations available since 1975 have not proved that paraquat, per se, is harmful to the lungs. On the other hand, the clinical experience to date, coupled with the increasing understanding of the biochemical basis for paraquat toxicity, raises the serious possibility that continued exposure to inhaled paraquat is likely to be harmful to the lungs, that the predominant effect