0031-6997/86/3802-0151$02.00/0
PHARMACOLOGICAL REVIEWS

Vol. 38, No. 2
Printed in U.S.A.

Cannabinoid Pharmacology*,†

WILLIAM L. DEWEY

Department of Pharmacology/Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

I. Introduction

A NUMBER of review articles (116, 166) and books (38, 119, 177–179, 210) have been published in recent years which describe some of the pharmacological effects of cannabinoids. These articles have been written by many of the leaders of this field; therefore, an attempt will not be made in this review to restate all the work which has been carried out with this important group of compounds. Also, certain pharmacological aspects of these drugs will not be described in this review, either because they are discussed in another article in this series, or because there has not been much new work since the last time this aspect of the pharmacology of the cannabinoids has been reviewed. For instance, the effects of the cannabinoids at the molecular level are discussed by Martin (182a), the clinical pharmacology of cannabinoids by Hollister (129a), and the metabolism and pharmacokinetics by Agurell and his colleagues (5a) as parts of this series. The effects of cannabinoids on the immune system were reviewed recently by Munson and Fehr (207), and little additional work has been done in the area of the toxicity of cannabinoids since our last review appeared in 1977 (116). Additionally, Rosenkrantz published a detailed review of the toxicological effects of cannabinoids in 1983 (235). The objective of this review will be to evaluate specific reports, allowing a critical assessment of proposed mechanisms of action for the pharmacological effects of these interesting substances. In some instances, very detailed discussions are presented because there has been considerable work carried out on that specific aspect of the pharmacology of these chemicals. In other cases, such work has led to the hypothesis that one or another of the cannabinoids might be useful as a

* Portions of this work were supported by grants DA-03672 and DA-00490 from the National Institute on Drug Abuse.

† This article is one of a series of five stimulated by a symposium held in conjunction with the Fall Meeting of the American Society of Pharmacology and Experimental Therapeutics at Louisville, August 18–20, 1982. The assistance of William L. Dewey as consulting editor is gratefully acknowledged.

therapeutic agent in man. One could conclude that more emphasis has been placed on studies suggesting a therapeutic use than on the abuse liability of these drugs. This is surprising when one considers the widespread abuse of this material as reported by the National Institute on Drug Abuse (96).

It is clear from the extensive literature in this field that the cannabinoids have a multiplicity of effects. However, little if any conclusive evidence has been presented which shows that the cannabinoids affect any peripheral system without working at least indirectly through the central nervous system (CNS). That is to say, there are no pharmacological effects of the cannabinoids in whole animals for which the mechanism has been shown to be due to something other than altering central nervous system function. There have been a number of studies of the effects of cannabinoids on cells in culture and in a number of different *in vitro* assays. The cannabinoids are not without effect on these systems and these observations suggest that, in fact, the cannabinoids could have direct effects on peripheral organs. In many sections throughout this review, an objective of the author will be to elucidate the general concept as to whether an effect is mediated centrally or is the direct action of the cannabinoid on peripheral systems.

II. Compounds

It has been suggested that there are 426 chemical entities in the marihuana plant. Of this total, more than 60 of them are cannabinoids (283). In this review, I will restrict my comments to the cannabinoids found in marihuana which have been studied to the greatest extent. These are Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabidiol (CBD), and cannabinol (CBN). Because of the extensive number of substances found in marihuana, and in particular the large number of cannabinoids, it is quite possible that these different cannabinoids might be working synergistically, additively, or possibly even antagonistically in animals when marihuana itself or a crude extract of the plant is administered. These interactions are discussed in some detail in Section XII, "Drug interaction." When one reads the literature one must be very acutely aware of what substance has been administered. Did the authors administer marihuana, smoke from marihuana, or an extract of marihuana, or have they in fact injected one of the active constituents, and if so, which one? Another aspect of the marihuana literature which can be somewhat confusing is the use of two different numbering systems for these compounds. A detailed discussion of this issue is presented in the review by Razdan (230a) in this series. However, it is important to reiterate here that Δ^8-THC is exactly the same compound as Δ^{1-6}-tetrahydrocannabinol, and Δ^9-THC is exactly the same compound as Δ^1-THC. Throughout this review, the dibenzopyran nomenclature will be used, i.e., Δ^9-THC, Δ^8-THC, etc.

Another aspect of the cannabinoids worthy of mention in a general way has to do with the differing pharmacological effects of the various isomers of the active constituents of marihuana. As previously pointed out in a number of review articles and mentioned in the review by Razdan in this series (230a), there are a number of different isomers of Δ^9-THC. Unless otherwise specified, I will be talking about the (−)-*trans* isomer of Δ^9-THC and the (−)-*trans* isomer of the Δ^8-THC in all cases. It is the (−)-*trans* isomer of these compounds which appears naturally in the plant, and it is this isomer of these two cannabinoids which has the greatest pharmacological activity (78).

III. Vehicle

One of the major problems encountered by researchers working with cannabinoids has been the choice of an appropriate vehicle. The physical and chemical characteristics of these substances are such that they have limited solubility in aqueous solutions. The cannabinoids are very lipid soluble and hydrophobic. Many of the compounds, including Δ^9-THC, are difficult to handle in that they are a gummy-type material which is best described in appearance as similar to "rubber cement." This makes it difficult to accurately weigh small amounts and prepare suspensions for injection. Many vehicles have been used for the administration of cannabinoids including alcohol, dimethyl sulfoxide (DMSO), the propylene glycols, polyvinylpyrrolidine (PVP), Tween 80, and serum albumin. Emulphor was first used by Cradock and colleagues (59) for the intravenous injection of Δ^9-THC. This non-ionic surfactant has become a very popular vehicle for cannabinoids in animal studies as well as in clinical trials. Differences in the potency of a specific compound in different studies in the literature may be due to the different vehicles that were used. For example, many investigators have studied the effects of cannabinoids when dissolved in ethyl alcohol. It is clear that both ethyl alcohol and cannabinoids are predominantly CNS depressants, and therefore it is not surprising that these two substances might act at least additively, and possibly synergistically, when injected together. A more thorough discussion of the interaction of these two abused drugs is presented later in this chapter. We and others have bound Δ^9-THC and other cannabinoids to serum albumin, in order to obtain an even suspension, before injection into animals. One of the problems with this vehicle is that the Δ^9-THC is bound to the albumin, and equilibrium is established between the albumin injected and the albumin in the bloodstream. Obviously, some of the cannabinoid is bound and not available for the target tissue. In most procedures, Δ^9-THC is less potent when injected as an albumin suspension than when it is solubilized or suspended in another vehicle. For instance, we have reported that Δ^9-THC is considerably more active in the mouse hot-plate test if administered in Triton X-100, rather than serum albu-

min (74). The widest discrepancy appears in the effects of Δ^9-THC when injected in alcohol and when injected in serum albumin. These examples may be considered to be the two extremes of the problem of choosing a vehicle for cannabinoids. One shoud be very critical when reading the literature and keep in mind the importance of the effects of different vehicles on the potency of the cannabinoids. To the best of my knowledge, there has never been a case where the vehicle has changed the qualitative effects of cannabinoids in animals, only the quantitative aspects.

Borgen and Davis (24) reported that the vehicle used could also be important for both the onset and duration of action. These investigators also found that suspensions of Δ^9-THC in polyvinylpyrrolidone, polysorbate-80, and a polysorbate-65-sorbitan monolaurate were effective when they were administered subcutaneously or intraperitoneally. However, Δ^9-THC was poorly absorbed by either route when it was administered in olive oil (24).

The choice of a suspending agent is especially important for studying cannabinoids in isolated organ bioassays. These compounds have been shown to be active in a number of these test systems, but exact potencies are difficult to determine due to the different characteristics of the suspending agent being used (74). Some of the vehicles which have been used are tissue solubilizers which interrupt normal biological functions. Alcohol is not an appropriate vehicle for these studies since the cannabinoid comes out of solution when the absolute alcohol is diluted out in the aqueous electrolyte solution used in these assays. Although DMSO has been used, it is important that the appropriate controls be included since DMSO alters the passage of materials across various biological membranes.

As indicated above, one of the major problems with pharmacological investigations of Δ^9-THC and other cannabinoids has been the lack of water solubility of the constituents of the plant and of many of the synthetic analogs. The pharmacological characteristics of the first cannabinoid with increased water solubility were published in 1972. Esters of the phenyl hydroxyl group were shown to possess biological properties qualitatively similar to those of Δ^9-THC (300). However, some caution should be used since the increase in water solubility of these compounds is limited. It is still questionable whether these esters are in fact in solution in aqueous media, or if minute micells are formed. Alcohol helps put these substances into solution. A cannabinoid with adequate water solubility has not appeared at this time.

IV. Overt Behavioral Effects

The overt behavioral effects of cannabinoids in man are quite complex. The subjective effects of cannabis ingestion include: excitement and dissociation of ideas, enhancement of senses, errors in judgment of time and space, damage to emotions, fixed ideas of delusions, irresistible impulses, illusions, and hallucinations. These subjective effects are accompanied at appropriate doses with a decrement in psychomotor performance (176), an interference in attention span and a loss of efficiency in memory (65, 70), and a reduction in physical strength (128, 131). Any of these effects of cannabinoids in man are very difficult to quantitate in experimental animals, yet cannabinoids have been shown to produce a rather unique syndrome of effects on the free ranging behavior of a wide variety of animal species. These behavioral changes are characterized at low doses as a unique mixture of depressant and stimulatory effects and at higher doses as predominantly CNS depression. The behavioral effects of Δ^9-THC and related cannabinoids in mice have been euphemistically termed the "popcorn" effect. That is, groups of mice are in a sedated state with little or no movement until a stimulus causes one mouse to jump (hyper-reflexia). This animal falls on another mouse which in turn jumps so that this repeated hyper-reflexic jumping looks like corn popping in a machine. Subsequently, all mice will be sedated until another stimulus reinitiates the process. Often, stimulation is also seen at the higher doses prior to the onset of the depression. This may be due to the initial lower blood level and therefore lower concentration of cannabinoid at the site of action. The depressant effects of the psychotomimetic cannabinoids (those that produce a psychological high in man) differ from the CNS depression induced by barbiturates, major tranquilizers, and other CNS depressants. A state of hyper-reflexia or hyper-stimulation is observed during the depressive portion of the syndrome. This unique syndrome has been useful to predict which chemical analogs of the constituents of marijuana would have psychotomimetic activity in man. Higher doses of cannabinoids produce a much more classical type of depression in rodents including catalepsy (114, 170, 220).

All of the cannabinoids that have been tested cause CNS depression at some dose, but all do not produce the typical cannabinoid syndrome. The purpose of many of the overt behavioral assays has been to differentiate between the dose that produces psychotomimetic effects and those doses which produce only depressant effects. The corneal areflexia test in rabbits was used widely at one time to predict the psychotomimetic effect of cannabinoids but is not used to a great extent at this time (110, 170, 286). The dog static ataxia assay, as first described by Walton (291) and modified by Dewey et al. (75) and later by Martin and his colleagues (186), has been an excellent predictor of psychotomimetic activity for all cannabinoids which have been tested in man [see review by Razdan in this series (230a)]. Edery and his colleagues (86, 87) have studied the effects of cannabinoids on overt behavior in the rhesus monkey and have used this model to differentiate doses which produce psychotomimetic effects from those which produce general CNS depressant characteristics. Generally, what has

been seen in both dogs and monkeys following administration of psychotomimetic cannabinoids is depression which, as mentioned above, is accompanied by a state of hyper-reflexia.

Animals medicated with Δ^9-THC sleep for a considerable period of time during the 24 h after administration. When aroused, some hyper-reflexia can be observed throughout this prolonged period. There are many effects of the cannabinoids which have a very long duration of action, which suggests that there is a slow elimination of these compounds from the body [for detail, see the review written by Agurell et al. in this series (5a)].

Δ^9-THC and other psychotomimetic cannabinoids have been tested in a number of laboratories for their effects on the spontaneous activity of rodents. As expected from the overt behavioral data generated from other species, the general effect that is observed is a decrease in spontaneous activity. CBN and CBD are less potent than Δ^8- or Δ^9-THC in this test system, although at high doses they also produce a pronounced decrease in spontaneous activity. For years, it was not possible to differentiate psychotomimetic cannabinoids from those that do not produce psychotomimetic effects utilizing this test procedure. Recently, Martin (181) reported that cannabinoids which did not produce hypoactivity at doses less than 20 mg/kg did not produce effects in other animal species known to be predictive of psychotomimetic effects in man. This would be an important bioassay for new cannabinoids, since experiments in mice are faster, less costly, and more acceptable than procedures which require the use of dogs or monkeys. Similarly, all cannabinoids produce a decrease in body temperature at some dose, but this test in itself is not useful for identifying cannabinoids void of psychotomimetic activity. Martin and coworkers (186) have combined dose-response curves in the mouse spontaneous activity and hypothermia assays with the dog static ataxia test to generate a profile of activity for compounds expected to have cannabinoid-like activity.

There appears to be some selectivity for compounds from different classes even in such nonspecific tests as spontaneous activity. Both Δ^9-THC and morphine have been shown to decrease spontaneous activity in rats. The effect of morphine in these animals was reversed by naloxone; however, naloxone was ineffective in reversing the depression induced by Δ^9-THC. An antagonist to the effects of Δ^9-THC has not yet been identified. When animals were treated chronically with these drugs, tolerance developed to the locomotor depressive activities of both morphine and Δ^9-THC (276). The possibility of the development of cross-tolerance was not investigated in these experiments.

The effects of cannabinoids on behavior in a social setting have been investigated. A dose of hashish extract containing 20 mg of Δ^9-THC/kg weakened the dominant position of the dominant mouse when it was the only one given the extract. Tolerance developed to the effect within three administrations. There was no change in dominance when all three mice in the group were given this dose of the extract (241). The effect of cannabinoids on dominance has also been investigated in monkeys who were housed in groups of four (237). In each group, some animals were more dominant while others were more subordinate in their behavior. A daily dose of 2.4 mg/kg of Δ^9-THC was given for up to 3 mo to dominant monkeys in some groups and subordinate animals in others. This dose of Δ^9-THC was chosen because in pilot experiments it produced a state of tranquilization without ataxia. The acute effects of the cannabinoid on these animals included increased irritability which the experimenters associated with stress. The long-term administration of the cannabinoid produced a number of changes in social behavior (such as a decrease in play, an increase in nonsocial activity, and an increase in self-directed behavior) which were considered to be long-term effects of the drug and not due to the last injection of the cannabinoid. These latter effects were seen only during chronic drug administration. They were observed at a significant period of time after the acute effect of the drug had worn off. The authors hypothesized that the individual differences observed were in response to long-term THC treatment and could be associated with an alteration of sensitivity at central noradrenergic receptors. They proposed that chronic Δ^9-THC increased the sensitivity to stress induced by increases in catecholamines (237) However, a marked effect of Δ^9-THC on catecholamines in the brain has not been established. Subtle changes following chronic treatment as proposed by the authors have not been investigated. In another series of experiments, some of the high ranking monkeys in a free ranging group were medicated chronically with Δ^9-THC. The administration of the cannabinoid to a few of the high ranking monkeys decreased the distance among various members of the group, but these decreases in distance were not limited to the medicated animals only. Although the average distances between monkeys were less after Δ^9-THC, there was more variability in the distances. These effects were observed following either acute or chronic treatment, as well as following the end of the drug administration period (35). One could interpret these results to suggest that the cannabinoid increased the social behavior of all the rhesus monkeys in the group by decreasing the aggressiveness of the medicated animals.

Overt behavioral assays more than any others have been used to test the hypothesis that certain constituents of marijuana might have either additive or antagonistic activities with each other. This has been found to be the case, and therefore the ratio of the quantity of each constituent is a major factor in the different potencies observed for one plant source *versus* another. One had to study various combinations of synthetic supplies of

the constituents to clarify this point. The interaction of the active constituents of marijuana has been exceedingly interesting and is described in Section XII, "Drug Interactions." Suffice it to say at this point that the multiple effects of the many constituents of marihuana and their interactions emphasize even more strongly the point made earlier that one cannot compare the effects of a marihuana extract to the effects of one of its constituents.

Considerable interest emerged concerning the question of whether Δ^9-THC caused behavioral effects in itself or if it had to be metabolized to 11-OH-Δ^9-THC to be active (167). There have been many studies which document the role of 11-hydroxy-Δ^9-THC in many species (36, 127, 129, 130, 164, 168, 197, 199, 219). Both compounds produced overt behavioral changes in mice, and 11-OH-Δ^9-THC was found to be more potent than the parent compound (50). Ford and his colleagues (97) reported that, in the monkey, the onset of the behavioral effects of 11-hydroxy-Δ^9-THC is much less than the onset of the behavioral effects of an equally active dose of Δ^9-THC. 11-Hydroxy was 3 times more potent than Δ^9-THC and had a shorter duration of action. 11-Hydroxy-Δ^9-THC was absorbed more quickly than Δ^9-THC and reached its peak brain and plasma levels faster. These data indicate that the differences in the behavioral effects of Δ^9-THC and its 11-hydroxy metabolite were accompanied by a difference in absorption and disposition of the compounds (97).

Other work has shown that synthetic cannabinoids which cannot be converted metabolically to 11-OH-Δ^9-THC or any other known metabolite of Δ^9-THC produce a behavioral syndrome similar to that produced by Δ^9-THC. These results also suggest, but do not prove, that a metabolic conversion of Δ^9-THC is not required for it to produce behavioral effects in animals and man. Additional support for the hypothesis that Δ^9-THC need not be converted to a metabolite to produce behavioral effects was supplied by the study of Carney et al. (43). These investigators showed that Δ^9-THC produced marked behavioral effects in the squirrel monkey following an injection into the cerebroventricle. They also showed that Δ^9-THC was not metabolized following its injection by this route of administration.

As indicated throughout this and other reviews in this series, a great many analogs of Δ^9-THC have been synthesized and tested for their behavioral effects in animals. One of the objectives of these experiments has been an attempt to separate activities of this interesting series of compounds. One of the more successful approaches to this have been the investigations of abnormal Δ^8-THC and abnormal CBD, analogs in which the phenolic hydroxyl and the side chain is interposed. They were studied for their effects on overt behavior in normal dogs and on the cardiovascular system in anesthetized dogs. Abnormal CBD contained potent hypotensive activity in the anesthetized dogs, but did not exhibit the psychotomimetic effects produced by Δ^8-THC, or the sedative effects produced by cannabidiol in dogs (4).

In summary, as one might expect, there are a number of similarities between the effects of cannabinoids in experimental animals and in man. Clearly, the stimulant aspect of the overall CNS depression induced by the cannabinoids is unique to this class of psychotomimetic agents. Granted, a number of drugs that are predominantly CNS stimulants or predominantly CNS depressants can produce the opposite effect at a narrow range of doses or in certain circumstance. For instance, the excitement state of anesthetic induction is a prime example. It is only the psychotomimetic cannabinoids that produce a constant state of hyper-reflexia throughout the overall CNS depression. This occurs in all species tested, yet it is manifested in different aspects of the behavioral syndrome.

V. Aggressiveness

Considerable anecdotal information suggests that the ingestion of marihuana by humans leads to an amotivational syndrome. This is more likely to occur with a CNS depressant than with a drug that is a generalized stimulant of the central nervous system. One of the most studied behavioral effects of the cannabinoids is an investigation of their effects on aggressive behavior. Based on the amotivational syndrome suspected in man, one might expect a decrease in aggressiveness by this group of compounds in experimental animals. Interestingly, the vast majority of the data indicates that Δ^9-THC and other cannabinoids increase aggressiveness, at least in rodents.

Injections of cannabinoids have been used to induce an aggressive state in animals which were then used as a model to investigate the effects of other drugs or modalities on the aggressive state (285). Cannabinoids have been shown to induce muricide activity in rats (106, 107). This effect was greater in animals kept in isolation than in those grouped in a cage.

The chronic administration of marihuana extract or Δ^9-THC produced aggressiveness in rats that had been food-deprived for 20 h. Although the injection of large amounts of glucose did not alter the aggressiveness once it was induced by the cannabinoid, glucose given orally prior to the exposure of the cannabinoids blocked the development of this behavior. The aggressiveness was potentiated when the animals were mantained at a low temperature of 14°C. The authors suggested that the stress of the hunger, rather than the lack of specific nutrients (hypoglycemia or acidosis), was a factor responsible for the inducement of the aggressive behavior following the chronic administration of the cannabinoids (40).

The injection of 6-hydroxydopamine increased marihuana-induced aggressive behavior in REM-sleep-deprived rats. Dopamine injections into the lateral cere-

broventricle did not alter the aggressive behavior in these rats, but the intraventricular injection of norepinephrine significantly decreased this aggressive behavior. These results led the authors to suggest that marihuana might sensitize the dopamine system, which in turn inhibited the norepinephrine system, thereby producing the increased aggressiveness in these animals (209). Studies by Carlini and Lindsey (41) showed that the Δ^9-THC-induced aggression in REM-sleep-deprived rats involved both brain dopamine and serotonin systems.

The cholinergic nervous system has been implicated in cannabinoid-induced aggression, in that very large doses (50 to 100 mg/kg) of atropine sulfate significantly decreased the aggressive behavior induced by cannabis extract in REM-sleep-deprived rats. This effect was dose-related, but a dose of 25 mg/kg was without effect. Scopolamine at a dose of 20 mg/kg also decreased the aggressive behavior. The quarternary atropine analog, atropine methyl nitrate, did not alter the fighting behavior of these animals. These authors suggested that their evidence supported the hypothesis that the antiacetylcholine drugs were responsible for the decrease in aggressive behavior induced by the chronic administration of the extract. They also suggested, however, the possibility that the high doses of these anticholinergic drugs inhibited the dopaminergic system which has been suggested to be an important factor in the inducement of aggressive behavior in rats (72). Similarly, doses of 50 and 100 mg/kg of Δ^9-THC produced an increased flight response to aggression in mice in a social behavior experiment (61). Doses of 0.5 and 1 mg/kg of Δ^9-THC reduced schedule-induced aggression in pigeons (46).

Doses from 5 to 40 mg/kg of Δ^9-THC and a number of alcoholic extracts of marihuana produced a dose-related increase in aggressiveness in rats that had been deprived of REM-sleep for 96 h. The duration of action of Δ^9-THC in this test was up to 4 h. The authors concluded that cannabinoids can produce opposite effects depending on the conditions of the animal. That is, normally these compounds produced depression in rats, yet irritability and aggressiveness was observed in stressed animals (6).

Δ^8- and Δ^9-THC both produced a decrease in the aggressiveness of mice or Chinese hamsters induced by isolation. Tolerance did not develop to the suppressant effects of Δ^8- or Δ^9-THC. This lack of tolerance to the depressant effect of the cannabinoids in these experiments, as opposed to the marked tolerance shown in many other studies, was suggested to be due to the effect of metabolites in the other paradigms whereas the parent compound was thought to be the active constituent in these aggressive studies (270). There are few data from other studies to support this hypothesis.

Although the effects of cannabinoids on aggressiveness have received considerable attention, a clear picture of the effects of cannabinoids on this syndrome has not emerged. Generally, cannabinoids induce aggressiveness in laboratory animals and, at least at some doses, cannabinoids potentiate aggressiveness in laboratory animals induced by other modalities such as foot-shock, hunger, etc. Attempts to identify an insult to a specific neurotransmitter system by cannabinoids as the cause of the induced aggression have not been fruitful. Of course, this is also true for most effects of most drugs on complex behaviors such as aggression. It is clear that the effects of cannabinoids on aggressiveness in laboratory animals is not predictive of their effects in man.

VI. Behavioral Pharmacology

As one might expect from the overt behavioral studies, the predominant effect of Δ^9-THC and other cannabinoids on stimulus-controlled behavioral patterns in laboratory animals is to produce central nervous system depression. This is manifested as a decrement of behavior in most animal species. However, as was also pointed out in the experiments on overt behavior, Δ^9-THC and other psychoactive cannabinoids produce a behavioral state that has a stimulatory component. In essence, some reflexes are heightened. The behavioral effects of the cannabinoids have been characterized in a great many studies involving conditioned behavior. Black and his colleagues (18) have shown that dimethylheptylpyran at the low dose of 0.3 mg/kg caused a decrease in the ability of a pigeon to peck a key for a food reward for a fixed-interval schedule. Studies by McMillan and his colleagues (191) and other workers have confirmed this depressant effect of Δ^9-THC. It has also been shown that other constituents of marihuana including Δ^8-THC, CBD, and CBN are also active in these procedures. Yet again, the potencies of Δ^9- and Δ^8-THC far exceeded those of the other naturally occurring cannabinoids. It was obvious from these studies that the cannabinoids had a very good therapeutic ratio. That is, they altered stimulus-controlled behavior at doses below those which produced other effects and much below those which were toxic to the animal. It is important to point out that this safety ratio for the cannabinoids has been shown for many of their pharmacological effects. By and large this is due to their low toxicity more than to a marked pharmacological potency.

Carlini (39) reported that acute administration of a marihuana extract decreased the performance of rats in the pole-climbing test and in the operant behavior of water-deprived rats maintained on an intravenous schedule for a positive reward. This same dose of the extract reduced aggressiveness in mice induced by isolation. Tolerance developed to the effects of the cannabis extract in all of these paradigms.

High doses of cannabis extract in pigeons increased responding in a color discrimination task but did not alter accuracy (242). Yet doses of Δ^9-THC within the effective range for humans caused a decrease in total

operant timing responses and behavioral accuracy in chimpanzees (51).

The acute administration of Δ^9-THC at doses of 0.5 or 4 mg/kg did not alter depth perception in rats. Chronic administration of these doses of the cannabinoid for 22 days did not produce an effect on this response (102). These results differ from reports that marihuana intake alters depth perception in man.

The intraperitoneal administration of either 5 or 15 mg/kg of Δ^9-THC did not have a significant effect on passive avoidance in rats. There was an effect of the 5 mg/kg dose on retention using an active retest procedure. However, the authors concluded that the drug had more of an effect on performance than on retention (202).

Black and his colleagues reported in 1970 (18) that a dose of 10 mg/kg of Δ^9-THC in pigeons significantly decreased the rate of responding on a multiple schedule of positive reinforcement. They also showed that tolerance developed to these effects when this dose of Δ^9-THC was administered at 1-wk intervals (18). Tolerance to the effects of a drug given at such long intervals was not known. The long half-lives of Δ^9-THC and its metabolites most probably contribute to this unusual property of the cannabinoids.

Ferraro and Grilly (92) demonstrated that the administration of 1 or 4 mg/kg of Δ^9-THC decreased both accuracy and speed of performance of chimpanzees in a delayed matching to sample task. Tolerance did not develop to this effect when these doses were given daily for up to 6 wk. Also, they did not observe a change in behavior which would indicate a withdrawal syndrome following the end of the chronic administration of the drug (92). The intramuscular injection of doses of Δ^9-THC ranging from 0.5 to 2.0 mg/kg produced a dose-related reduction in accuracy and rate of responding in squirrel monkeys trained to press either a two- or five-colored key sequence (32). Tolerance developed to the effects of Δ^9-THC on both accuracy and rate.

Cross-tolerance between ethyl alcohol and Δ^9-THC was demonstrated in rats trained in a one-way avoidance paradigm. Both compounds depressed behavior when given acutely. Tolerance developed to these effects and when the ethyl alcohol was given to Δ^9-THC-tolerant animals or when Δ^9-THC was given to the ethanol-tolerant animals, cross-tolerance was observed (211).

Aversive effects of 1 to 32 mg/kg of Δ^9-THC were demonstrated in a dose-related fashion in rats deprived of water and given a saccharin solution immediately prior to the oral or intraperitoneal injection of the cannabinoid (88).

It is clear from the behavioral studies described above and even more so from the overt behavioral studies, that there are two types of cannabinoids, both of which produce central nervous system depression as their predominant effect. One of these groups is made up of the cannabinoids that produce a behavioral depression accompanied by a stimulatory component. This group of compounds is best typified by Δ^9-THC. The other group is best exemplified by CBD and CBN, which at high doses also produce central nervous system depression, but without a stimulatory component. It has been proposed that the cannabinoids which produce a stimulatory component or a heightened reflex component in their behavioral effects are those that produce psychotomimetic effects in man. For many years, the overt behavioral studies in dogs and monkeys have been used as assays for the behavioral effects of cannabinoids. In recent years, an additional bioassay has been used to characterize the behavioral effect of cannabinoids, with the major objective of differentiating the two types of cannabinoids. This relatively new procedure, the drug discrimination test, has been used to identify compounds to which animals will generalize from the cue of a training drug. Rats or monkeys are taught to differentiate between the cue of a training drug and the cue induced by vehicle. After the animal has learned to differentiate the drug cue, the experimental drug is administered. The ability of the animal to generalize from the training drug to the experimental drug indicates a similarity in the cues of the two drugs. Investigators hypothesized that the Δ^9-THC cue was related to its psychotomimetic activity in man. This hypothesis was supported by the results of a number of studies in which metabolites of Δ^8- and Δ^9-THC and other constituents of marihuana were tested to determine whether the cue of these agents would be generalized in animals trained to discriminate Δ^9-THC. When dose-response curves were generated, the cue of the compounds which had been shown to have psychotomimetic activity in man were found to be generalized to the Δ^9-THC cue.

Balster and Ford (8) reviewed the discriminative stimulus properties of cannabinoids. They concluded that stimulus generalization studies have promise as a bioassay to screen cannabinoids for Δ^9-THC-like activity, or psychotomimetic properties. This generalization did not extend to psychotomimetic drugs from other classes (33). Drug discrimination based on Δ^9-THC in animals has been shown to be a sensitive and specific assay for identifying Δ^9-THC-like behavioral effects of drugs (98). Recently, Semjonow and Binder (240) used the drug discrimination paradigm to compare the potency of Δ^9-THC to that of Δ^{9-11}-THC, an interesting cannabinoid analog which is being investigated as a tool to elucidate the molecular effects of cannabinoids on a number of physiological functions, including effects on the brain and on the cardiovascular system.

It is clear from the effects of cannabinoids in the wide variety of procedures used in the studies reviewed in this section that stimulus-controlled behavior is one of the most sensitive to all measures for the cannabinoids. The cannabinoids have been shown to have depressant effects

in these procedures at doses comparable to those used by man. In some cases, even lower doses have been effective.

VII. Body Temperature

Δ^9-THC, like most central nervous system depressants, has been shown to produce hypothermia in a dose-response fashion in most laboratory animal species. Some tolerance to the hypothermic effect of Δ^9-THC in rats has been reported (268). Δ^9-THC also lowered the body temperature of animals with elevated temperatures due to the injection of yeast. Δ^9-THC was more potent in hyperthermic animals than in euthermic animals. Orally administered Δ^9-THC was not an analgesic when the nociceptive stimulus was pressure applied to both normal and the yeast-implanted inflamed paws. Δ^9-THC was also inactive in blocking the carrageenan-induced edema in the inflamed paw model. These studies showed that although Δ^9-THC lowered body temperature in both normal and hyperthermic animals, it did not have the anti-inflammatory or analgesic potency of a number of nonsteroid analgesics. These results plus the fact that Δ^9-THC produced CNS depression at these doses imply that the effects of Δ^9-THC are in the CNS and are not due to its ability to release ACTH or adrenal steroids (157).

The intraperitoneal injection of 10 mg/kg of Δ^9-THC to mice produced hypothermia which lasted for 5 or 6 h and had a peak response at 1 to 2 h (13). This peak hypothermia was much less than the maximum hypothermia induced by chlorpromazine, reserpine, or other major tranquilizers. The low magnitude of the hypothermia induced by cannabinoids has been a characteristic of most studies. Δ^9-THC produced a dose-related hypothermia in mice at doses of 5 to 100 mg/kg. The effects of various drugs that alter the brain neurochemistry on the hypothermic effect of the cannabinoid caused the authors to suggest that serotonergic mechanisms were involved (66). These doses were much higher than the minimal effective doses of Δ^9-THC required to induce CNS depression. Bloom and Kiernan (23) reported that Δ^9-THC produced hypothermia at an ambient temperature of 10 or 20°C but not at 31°C. The hypothermia was not responsible for the alteration in brain catecholamines produced by Δ^9-THC.

The injection of 10 or 20 mg of Δ^9-THC directly into the preoptic area of the hypothalamus induced a decrease in body temperature in mice which was maximal 30 min after administration. Δ^9-THC apparently acts selectively within the regulatory system in this area. The hypothermic doses of Δ^9-THC decreased heat production in response to cold and altered behavioral thermal regulation. These data support the view that the hypothermic effect of Δ^9-THC in mice is a central effect since there is no evidence that the decrease in temperature is due to an increase in heat loss caused by a decrease in peripheral vasomotor tone (222).

Recently, Pertwee reviewed (221) the effects of cannabinoids on body temperature, and he also concluded that the site of the hypothermic effect of Δ^9-THC was in the brain. More specifically, he proposed that the cannabinoids alter the thermal input in the thermoregulatory centers of the brain. It is clear from the review by Pertwee, as well as from the other studies referred to in this section, that Δ^9-THC and other cannabinoids produce marked hypothermia only at doses which are above those that produce minimal behavioral effects.

VIII. Tolerance

An early study in humans (292) demonstrated an increased sensitivity to repeated exposures to marijuana. However, the majority of the data generated to date clearly show that a pronounced tolerance develops to most of the pharmacological effects of marihuana and to the effects of each of the individual cannabinoids that have been studied in detail. The tolerance is observed in most animal species and in human experimental procedures. Pronounced tolerance to Δ^9-THC was first demonstrated by McMillan and his colleagues (196). They demonstrated that the effect of repeated injections of Δ^9-THC, which had inhibited a conditioned response in pigeons, decreased on repeated administrations. Subsequent experiments demonstrated that the tolerance was large and had a fast onset of action as well as a very long duration (195). Cross-tolerance among cannabinoids has also been demonstrated. The phenomenon of tolerance to the pharmacological effects of Δ^9-THC was soon thereafter demonstrated in a number of laboratory animal species, including dogs, mice, rats, and monkeys (193). The work of McMillan et al. (79, 194) demonstrated that the pronounced tolerance of the cannabinoids was a true pharmacodynamic tolerance and not due to an alteration in absorption or metabolism of the parent compound. Subsequent work by Martin and his colleagues (184) demonstrated that the tolerance was not due to an alteration in the disposition of the parent compound or its metabolite in intracellular organelles in dog, rat, or mouse brain neurons. Characteristics of the tolerance which develops to Δ^9-THC in a number of pharmacological procedures were reviewed by McMillan et al. (193).

One of the distinct features of the tolerance that develops to cannabinoids, as opposed to the tolerance demonstrated for opiates and other compounds, is the very long duration of the tolerance after cessation of the drug. When dogs were injected once a day for 8 days with doses of Δ^9-THC and then not treated for 11 days, administration of a dose of Δ^9-THC which was effective in drug-naive dogs, produced very little change in the overt behavior of these animals. This prolonged tolerance has now been demonstrated in many species. Although as mentioned above, there is considerable cross-tolerance demonstrated among various cannabinoids, cross-tolerance between individual cannabinoids and other classes of drugs is not wide spread. Nonspecific cross-tolerance

among various types of CNS depressants and the cannabinoids has been reported.

Tolerance did not develop to the depressant effects of Δ^8- or Δ^9-THC on isolation-induced aggressiveness of mice or Chinese hamsters (270). Tolerance also did not develop to the depressant effect of Δ^9-THC on either accuracy or speed of performance in a delayed matching-to-sample task (92). We found that tolerance did not develop to the stimulatory effects of Δ^9-THC on ACTH secretion when the cannabinoid (10 mg/kg) was administered daily for 5 days. This dose produced significant secretion of ACTH after either one or five daily injections (80).

Black and his colleagues (18) demonstrated that tolerance developed to the rate-suppressing effects of Δ^9-THC when the cannabinoid was administered once per week for 7 wk.

The oral administration of marihuana extract distillate containing 20 mg/kg of Δ^9-THC produced a significant decrease in the integrated electroencephalogram (EEG) which was maximal after one or two daily doses. The effect decreased gradually with the effect almost completely gone following the twelfth daily dose. However, tolerance was not seen to these EEG effects when the drug was given only once per week over a 30-wk period. Tolerance developed to most, but not all, of the effects of cannabinoids on EEG. Tolerance did not develop to the high voltage "spindle-like" activity induced by marihuana extract in either dosage schedue (224).

As mentioned in an earlier part of this review, cross-tolerance between ethyl alcohol and Δ^9-THC has been demonstrated in a number of studies in rodents (211, 218, 243–245, 257, 258, 265). Recently, Hine (123) reported evidence for two-way cross-tolerance for both the analgesic and bradycardic effects of Δ^9-THC and morphine in rats. Tolerance developed rapidly to each agent, but cross-tolerance to the THC-induced bradycardia was seen only in those rats completely tolerant to this effect of morphine. There have been a number of reports of the lack of complete cross-tolerance between Δ^9-THC and morphine (20, 21). Although the magnitude of tolerance to cannabinoids was similar to that seen with morphine, cross-tolerance was not seen between morphine and Δ^9-THC in pigeons on a fixed-ratio 30 fixed-interval 5 (FR30 FI5) schedule of food reinforcement (195). Additional well-controlled studies are needed to clarify the discrepancy in these reports. A clarification of the issue of cross-tolerance between opiates and cannabinoids is important since its resolution might shed some light on the question of whether cannabinoids induce antinociception by acting through endogenous opioid peptides acting on opiate receptors.

The intraperitoneal injection of 10 mg/kg Δ^9-THC daily for a period of 1 or 2 wk resulted in tolerance to the acute effects of the cannabinoid on body weight and body temperature but not to its depressant effect on motor activity. Rats injected intraperitoneally for 28 days with 10 mg/kg of Δ^9-THC did not show the bradycardia and hypotension which was observed in animals given vehicle for 28 days prior to the intravenous injection of the same dose of Δ^9-THC. Tolerance also failed to develop to the pressor actions of the intravenous Δ^9-THC. The pressor response induced by the intravenous injection of norepinephrine was similar in animals given vehicle injection or 10 mg/kg of Δ^9-THC for the 28 days (2).

Carlini (39) reported that tolerance developed to the depressant effect of marihuana extract in the rat pole-climbing, operant behavioral task, and aggressiveness test.

Tolerance was observed to develop to the behavioral effects of Δ^9-THC when administered intravenously to mongrel dogs. The magnitude of this tolerance exceeded 300-fold. However, there was no withdrawal symptomatology observed at the end of this chronic daily administration of Δ^9-THC, suggesting that physical dependence did not occur. In a second experiment, tolerance could be observed when the cannabinoid was injected only once every 8 days, indicating the long half-life of Δ^9-THC in this species. In this regard, the cannabinoids differ markedly from morphine and most other opiates since most of the opiates need to be given at least daily and usually every 6 h to induce marked tolerance (75). These differences are obviously due to different pharmacokinetic properties of the various drugs. The cannabinoids, as a class of compounds, have a very long duration of action and an even longer half-life in animals and man.

The mechanism underlying the development of tolerance to Δ^9-THC is an interesting problem due to the fact that it has been hypothesized that Δ^9-THC had to be converted to an active metabolite for its pharmacological activity. A thorough investigation into the possible role of a metabolic factor in this pronounced tolerance was studied in detail. It was shown that the marked tolerance which developed to Δ^9-THC in a number of animal species was not due to an alteration in blood or brain levels of the cannabinoid or its major metabolite. A thorough investigation of these parameters has been carried out and the conclusion from all of these studies is that the tolerance is pharmacodynamic in nature (79, 192, 194).

The administration of radiolabeled Δ^9-THC to tolerant and nontolerant dogs was followed by measurement of levels of Δ^9-THC in various brain areas. In subsequent studies, the intracellular distribution of the cannabinoid was carried out in an attempt to determine if the tolerance that developed to Δ^9-THC was due to an alteration of either brain or subcellular distribution of the compound. The results of this investigation to determine the effect of biodisposition of Δ^9-THC on the pronounced tolerance showed that Δ^9-THC was equally distributed,

not only throughout various brain areas, but also intracellularly in brain tissue in both the tolerant and nontolerant dogs. One of the surprising discoveries in this series of experiments was that the uptake of radiolabeled cannabinoids was higher in central gray areas than in central white. The white areas are those areas which contain the myelin, and the lipid-soluble cannabinoids were expected to be concentrated in these substances, rather than in the neurons or gray tissue (184).

In subsequent studies using mice and rats, it was shown that the chronic treatment of Δ^9-THC, which produced marked behavioral tolerance in these species, also is not due to an alteration in brain levels or to an alteration of the subcellular distribution of the cannabinoids in these species (77). As many of the studies described above indicate, tolerance develops readily to Δ^9-THC and marihuana extract. Much less work has been carried out on the ability of tolerance to develop to other cannabinoids. Tolerance and cross-tolerance developed at the same rate to equally active doses of Δ^9- and 11-OH-Δ^9-THC in rats (97).

An understanding of the mechanisms responsible for the tolerance of the cannabinoids must wait until there is some clarification as to the existence of THC receptors. It is a logical possibility that the tolerance is due to an increase in the number of receptor sites or an up-regulation of the receptors. It should be pointed out, however, that the mechanism of tolerance to ethanol or other depressant drugs has not been elucidated at this time.

IX. Dependence

In spite of the fact that pronounced tolerance has been shown in many species and to many of the pharmacological effects of the cannabinoids, the development of physical dependence is more open to question. Many investigators have proposed that a withdrawal syndrome was observed following the abrupt cessation of chronic treatment of monkeys or rats with cannabis (69, 71, 152, 153, 223, 250, 255). Others have suggested that cannabinoid dependence has developed in monkeys (31, 92, 93) since the cessation of chronic administration of Δ^9-THC led to a disruption of the pattern of ongoing behavior. Fredericks and Benowitz (101) suggested that a withdrawal syndrome appeared in rhesus monkeys after the intravenous infusion of 0.5 mg/kg of Δ^9-THC every 6 h for 3 wk. This syndrome consisted of an increased number of gross movements, eye contact, and greater frequency and duration of teeth-baring. A behavioral syndrome characterized by writhes, backward kicks, and wet shakes was observed in rats treated daily for 5 or 10 days with Δ^9-THC and then given an injection of imipramine, clomipramine, or fluoxetine, all drugs which inhibit the uptake of biogenic amines, on day 6 or 11. The severity of these behaviors appeared to correlate with the potency of the compound to inhibit reuptake or biogenic amines. The authors suggested that tryptaminergic mechanisms are involved in a withdrawal syndrome following chronic cannabinoid treatment (268, 289). However, it should be noted that this behavioral syndrome has not been recorded in most experiments utilizing chronic cannabinoid treatment. Yet, these authors reported that if they injected Δ^9-THC just prior to the biogenic amine uptake inhibitor, the withdrawal syndrome was less than if vehicle was injected (288). The most critical experiment needed to define the behavioral effects as a true withdrawal syndrome is to reverse these effects with an injection of Δ^9-THC after they have appeared. Yet this has not been seen in all experiments. Ford and his coworkers (97, 98) showed that the tolerance to Δ^9-THC amounted to some 1800-fold, and when they discontinued the administration of this high dose of drug to the pigeon, the rate of responses decreased. This was at first interpreted to be an indication of withdrawal symptomatology. However, as stated above, one of the criteria for the demonstration of physical dependence is the disruption of the withdrawal symptomatology when the agent is readministered to the animal. When active doses of Δ^9-THC were injected in these pigeons, the behavior did not return to the control level. Similarly, neither Leite and Carlini (164) nor Harris et al. (117) saw a withdrawal syndrome after the abrupt cessation of chronic administration of Δ^9-THC in rats and monkeys, respectively. These results suggest that physical dependence did not occur.

A test used to determine the opiate-like dependence liability of compounds is to determine if they will substitute for morphine in monkeys maintained opiate-dependent by injecting morphine every 6 h. Cannabinoids were not effective in suppressing the withdrawal symptomatology seen in these opiate-dependent monkeys. Hine and his colleagues (124) demonstrated that intraperitoneal doses of 2, 5, or 10 mg/kg of Δ^9-THC did not induce withdrawal in morphine-dependent mice. These results suggest that the cannabinoid does not have opiate antagonist properties. However, the injection of these doses of Δ^9-THC, but not CBD, did block the appearance of some of the signs of opiate withdrawal including wet-dog shakes, escapes, diarrhea, and increased defecation which were induced by naloxone. In these experiments, Δ^9-THC was given 1 h prior to the administration of 4 mg/kg of naloxone. The authors concluded that the cannabinoid might be useful as a treatment of opiate detoxification (124). A similar conclusion was reached by Bhargava (12) who reported that Δ^9-THC attenuated a number of the opiate withdrawal characteristics induced by naloxone. Thus far, however, there is little supporting evidence that cannabinoids and opiates work through similar systems.

Ferraro and Grilly (92) did not see a change in behavior which would indicate a withdrawal syndrome following the end of the daily administration of 4 mg/kg of Δ^9-THC for 42 days in chimpanzees. Mature rats did not show residual effects of daily treatments with cannabis

containing 20 mg/kg of Δ^9-THC for 3 m when tested 1 to 4 mo later (263). A number of residual effects were observed when a similar chronic experiment was carried out in immature rats (91, 262, 264). These authors did not describe any withdrawal symptomatology at the end of this long term treatment.

Although some of the reports discussed above would suggest that physical dependence occurs with chronic administration of cannabinoids, the evidence is not convincing. There are many reports of alterations of behavior in animals and man following the abrupt cessation of chronic administration of drugs which alter central nervous system function. The most accepted criteria for physical dependence is the elimination of this behavioral syndrome when the drug is readministered. This has not been observed consistently in experiments with cannabinoids. The discovery of a specific antagonist for cannabinoids such as the opiate antagonists would be important since it could be used to determine whether withdrawal can be induced following chronic exposure to cannabinoids.

X. Neurochemistry

The effects of cannabinoids on a number of brain neurochemical systems were reviewed by us in 1977 (116). We concluded from the data reviewed at that time that the cannabinoids did not alter the basal level of norepinephrine or dopamine in rodent brain, but did increase synthesis of both catecholamines in mice and rats. The effects of the cannabinoids on the cholinergic system were less clear than those on brain catecholamine systems. In this review, I will not repeat all the information from the earlier chapter, but will discuss certain aspects of the earlier findings as they have an impact on subsequent studies which have contributed to our current knowledge of the effects of cannabinoids on brain neurochemical systems.

A. Biogenic Amine Systems

Maitre and his colleagues (174) reported that the injection of doses of 10–100 mg/kg of Δ^9-THC did not alter the content of endogenous norepinephrine or the uptake of tritiated norepinephrine in the heart. These investigators also showed that Δ^9-THC had no effect on brain levels of norepinephrine and dopamine. The synthesis rate of norepinephrine and dopamine from tritiated tyrosine was enhanced following the administration of Δ^9-THC. Later, studies by Bloom and his colleagues (22, 23) showed that doses of Δ^9-THC as low as 1 to 16 mg/kg given intravenously caused an increase in whole mouse brain synthesis rates of dopamine and norepinephrine.

The daily intravenous administration of 2 mg/kg of Δ^9-THC to rats did not alter the endogenous levels of norepinephrine or dopamine in the brain nor epinephrine or norepinephrine in the adrenal gland. However, this chronic treatment did result in a significant increase in the synthesis of tritiated catecholamines in the brain and adrenals (189). Ho and his colleagues (125) reported that rats who inhaled Δ^9-THC also had an increased turnover rate of catecholamines compared to controls. The increase in the synthesis of brain catecholamines has been shown to be a direct effect of Δ^9-THC on the neurons and not an indirect effect such as the result of the hypothermia induced by the cannabinoid (23). This direct effect of Δ^9-THC on catecholamine neurons was confirmed when it was demonstrated that the cannabinoid could increase the synthesis of catecholamines in an *in vitro* synaptosomal preparation (19).

In spite of the fact that most authors have reported no change in brain levels of catecholamines, it has been reported that Δ^9-THC caused changes in the levels of catecholamines in specific rat brain areas and that these changes were associated with changes in behavior (15). Bhattacharyya and colleagues (7) reported that an initial decrease in levels of dopamine in the diencephalon and caudate nucleus along with an increase in levels of serotonin in the diencephalon and medulla pons were associated with an initial behavioral depression. A stimulatory phase followed which was associated with an increase in dopamine and a decrease in serotonin in the respective brain areas. As depression returned, the levels of biogenic amines returned to near normal levels. This triphasic behavioral effect has not been reported extensively in the literature. A stimulatory phase has often been reported prior to the depression phase, but not between two phases of depression. However, this same group of investigators also have reported that neurochemical changes in specific brain areas were correlated with behavioral changes observed following repeated administrations of cannabinoids. These results would be strengthened by confirmation from other laboratories.

Patel and colleagues (216) reported that the daily subcutaneous injection of 3 mg/kg of Δ^9-THC for 25 days produced alterations in catecholamine levels in the preoptic area, the mediobasal hypothalamus, and plasma. Norepinephrine levels were decreased in all three areas, epinephrine was reduced in the plasma and the mediobasal hypothalamus, while the levels of dopamine and dihydroxyphenylacetic acid were increased in the mediobasal hypothalamus. The major difference in these experiments, as opposed to those reported previously, is that the catecholamines were quantitated using high pressure liquid chromatography with electrochemical detection, rather than the fluorescence techniques used for many years. Certainly, one would not propose that a change in analytical technique should alter the effects of a drug on brain chemistry. Both techniques are valid and widely used.

Δ^9-THC produced a concentration-related decrease in the uptake of [^{14}C]dopamine in mouse brain crude synaptosomal preparations. Similarly, Δ^9-THC also increased the release of preloaded [^{14}C]dopamine. This latter effect was additive to that of amphetamine (136).

Maclean and Littleton in 1977 (173) suggested that alterations in striatal dopamine metabolism could be related to some of the behavioral effects induced by cannabinoids to rats under stressful conditions. The behavioral changes seen in these rats included hypothermia, immobility, and hyper-reactivity.

Osgood and Howes (215) concluded that Δ^9-THC altered interneuronal dopamine distribution without affecting the enzymes involved in its metabolism. This hypothesis was based upon the observation that Δ^9-THC increased striatal levels of homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in 3,4-dihydroxyphenylalanine (*l*-DOPA)-treated animals but did not alter levels of these catecholamine metabolites in controls (215).

Concentrations of Δ^9-THC of 560 nM and 14 μM significantly reduced the efflux of tritium in rat vas deferens incubated with tritiated noradrenaline. This decrease in tritiated norepinephrine release by Δ^9-THC was hypothesized to be a part of the mechanism of its antihypertensive effects. That is, the authors proposed that Δ^9-THC has adrenergic blocking activity, as evidenced by its inhibition of release of tritiated norepinephrine induced by electrical stimulation (113).

The intraperitoneal injection of 40 but not 20 mg/kg of Δ^9-THC produced a significant reduction in brain and vas deferens levels of noradrenaline in the rat. The level of adrenaline in the adrenal gland was decreased significantly until 90 min after administration. The effect on noradrenaline levels in the brain and vas deferens occurred 40 min after cannabinoid injection. Concentrations of Δ^9-THC of 10^{-8} to 10^{-6} M showed a biphasic effect on the uptake of noradrenaline into the isolated hypogastric-vas deferens preparation of the rat. After 10 to 20 min, Δ^9-THC produced a significant increase in the uptake of *dl*-noradrenaline in these tissues. However, at times greater than 30 min, a reduction in uptake was observed. Finally, these authors showed that a concentration of 10^{-8} M Δ^9-THC did not alter release of tritiated noradrenaline induced by nerve stimulation (10). These biphasic and multiple effects of cannabinoids on brain and peripheral organ stores of catecholamines may contribute to the complex behavioral effects of these compounds.

The intravenous injection of Δ^9-THC produced a decrease in electrically induced ganglionic transmission. Doses below threshold for blocking transmission potentiated the inhibitory action of exogenous catecholamines. The authors proposed that the effects of Δ^9-THC in their system could be used as a model for the effects of the cannabinoid in the brain. They further proposed that the facilitation of the effects of norepinephrine in this model resembles a mechanism of the proposed antidepressant effects of the cannabinoids (112).

The oral administration of 20 mg/kg of Δ^9-THC did not alter whole brain levels of norepinephrine, dopamine, nor serotonin in rats. Similarly the levels were not altered in the neostriatum, hypothalamus plus midbrain, thalamus, cerebellum, or medulla-pons areas of the brain. The administration of 60 mg/kg of Δ^9-THC 2 h prior to the injection of α-methyltyrosine did not cause an alteration in the disappearance of norepinephrine or dopamine in whole brain, neostriatum, hypothalamus plus midbrain, thalamus, or medulla-pons area. These authors concluded that it was unlikely that the behavioral effects produced in rats by acute injections of Δ^9-THC could be due to an alteration in norepinephrine or dopamine (29).

Carlini and Carlini (42) proposed in an early study that intraneuronal ribonucleic acid was the site of neuronal changes required for learning and retention of a learned task. However, the intraperitoneal injection of 10 mg/kg of cannabis extract daily for 6 days did not induce a change in the ribonucleic acid content of rat brain. The authors indicated that the dose of cannabis used was 10 times greater than that necessary to improve performance, yet it did not alter brain RNA (42). Musty and his colleagues (209) have proposed that cannabinoids sensitized the central dopamine system, which in turn inhibited the norepinephrine system. The interaction of the catecholamines in the brain produced an increase in aggressiveness. It also has been reported that one can decrease aggressive behavior induced by cannabis extract in REM-sleep-deprived rats by the injection of a very large dose, that is, 50 to 100 mg/kg of atropine sulfate. Scopolamine at a dose of 20 mg/kg also decreased the aggressive behavior. The quaternary atropine analog, atropine methyl nitrate, did not alter the fighting behavior of these animals, supporting the hypothesis that this is a central effect. These authors suggested that their evidence supported the hypothesis that the cholinergic system was responsible for the decrease in aggressive behavior induced by cannabis extract in these animals. They also suggested the possibility that the high doses of these anticholinergic drugs had a nonspecific inhibiting effect on dopaminergic systems which had been suggested to be important for aggressive behavior in rats (72).

Banerjee and his colleagues (9) have demonstrated that Δ^9-THC and a number of its analogs inhibit the uptake of norepinephrine and serotonin into synaptosomes generated from the hypothalamus. These compounds were also potent in inhibiting the uptake of dopamine into synaptosomes from the striatum. These compounds inhibited the uptake of γ-aminobutyric acid (GABA) into synaptosomes from the cortex. The effect of the cannabinoids on uptake of these neurotransmitters was noncompetitive. Even though there were a multiplicity of effects of various cannabinoids on the uptake of one or more neurotransmitters into synaptosomes generated from some brain regions, these data did not give convincing evidence to the mechanism of action of any of the behavioral effects of cannabinoids. However, it also

has been reported that the intravenous injection of low doses of Δ^9-THC (1 to 10 mg/kg) increased the uptake of catecholamines in synaptosomes from the cortex and striatum (121).

A larger series of cannabinoids were shown to inhibit the high affinity uptake of serotonin into a synaptosome-enriched homogenate of rat forebrain. Inhibition of uptake was in the micromolar range for most cannabinoids and the effect was dose-related. It was not possible to correlate the effects of the cannabinoids on inhibition of serotonin uptake with a pharmacological effect of the cannabinoid in the whole animal. It is doubtful that any one neurochemical effect of the cannabinoids would explain the complex behavioral syndrome in animals most similar to the psychotomimetic effect of these compounds in man. THC, like other drugs that alter behavior, disrupts the homeostatic control of numerous neurochemical mechanisms. The alteration of synaptosomal uptake of serotonin by cannabinoids is believed to be one of the mechanisms contributing to the complex behavioral effects of these compounds (140). The work of Gallager et al. (108) indicates that doses of Δ^9-THC that produce pronounced behavioral changes in rats do not alter cerebral serotonergic systems. The literature is less clear on the effects of Δ^9-THC or other cannabinoids on the turnover rate of brain serotonin. A number of investigators have reported a cannabinoid-induced decrease in serotonin turnover (225, 239, 252) while others have reported no change (108, 267, 297).

Δ^9-THC has been shown to inhibit the accumulation of tritiated leucine and tritiated norepinephrine, as well as tritiated serotonin in a rat forebrain synaptosomal preparation. Somewhat less of an effect was seen on the release of tritiated norepinephrine and serotonin from preloaded synaptosomes. Δ^9-THC did not alter the release of tritiated leucine, thereby showing some specificity on this system. An 18-h pretreatment with reserpine inhibited the Δ^9-THC-induced release of tritiated serotonin. The inhibition of uptake of tritiated serotonin by Δ^9-THC was accompanied by a reduction in the conversion of serotonin to 5-hydroxyindoleacetic acid. There was no change in the metabolism of serotonin seen at the concentrations of Δ^9-THC which facilitated the uptake of serotonin. Taken together, all these data suggest the involvement of both synaptic vesicle and neuronal membranes in the site of action for Δ^9-THC (142).

The Δ^9-THC analog, 9-nor-9β-hexahydrocannabinol (B-HHC) was found to be much more potent than Δ^9-THC and equally potent to morphine in the mouse tail-flick test. This cannabinoid analog, like morphine, produced a dose-dependent increase in the accumulation of newly synthesized dopamine and norepinephrine. All of these effects were blocked by pretreatment with naloxone; however, cross-tolerance between β-HHC and morphine did not exist in regard to either the antinociceptive activity as quantitated by the tail-flick test or the increase in catecholamine synthesis. These results indicate that some similarities exist between cannabinoids and opiates in producing antinociception. They also indicate that catecholamine-containing neurons are involved in the central effect of cannabinoids and opiates on tail-flick response (21).

Taken all together, it is clear that cannabinoids produce dose-related effects on central biogenic amine systems. The most consistently observed effect is an increase in catecholamine synthesis. The biological significance of changes in levels of one or another biogenic amine in specific brain regions cannot be determined without additional experimentation. The most sensitive subcellular site of the neuron to cannabinoid insult has not been elucidated.

B. Cholinergic Systems

Δ^8- and Δ^9-THC induced the conversion of ^{3}H-choline to ^{3}H-acetylcholine in rat striatal, hypothalamic, and cortical slices. CBD did not alter the synthesis of acetylcholine in these experiments (104). Revuelta and colleagues (232) reported that doses of 0.2 to 10 mg/kg of Δ^9-THC produced a dose-related decrease in acetylcholine turnover in the hippocampus. CBD was without effect at doses as high as 20 mg/kg. Both 5 mg/kg of Δ^9-THC and 20 mg/kg of CBD produced a decrease in turnover in striatum, but were inactive in parietal cortex. We have tested a large series of cannabinoids, metabolites, and analogs for their effect on acetylcholine turnover rate in six mouse brain areas. The hippocampus was the only area in which a dose-related decrease in acetylcholine turnover was observed at reasonable doses of Δ^9-THC. However, this effect could not be associated with psychotomimetic activity since when the doses of the nonpsychoactive compounds were increased to the point where they produced marked behavioral depression, the decrease in hippocampal acetylcholine turnover was observed. It was our conclusion, therefore, that the decrease in acetylcholine in the hippocampus was best correlated with generalized CNS depression (272).

Domino and his colleagues (85) reported that doses of 3.2 and 10 mg/kg increased the utilization of acetylcholine in the rat hippocampus, but did not alter it in the thalamus, caudate, or hypothalamus. These authors suggested that these changes in hippocampal cholinergic function could be linked to the perception changes and memory losses associated with cannabinoids.

The interperitoneal injection of 6 mg/kg of Δ^9-THC produced an increase in brain levels of acetylcholine in the striatum and amygdala, but not in the cortex, diencephalon, or brainstem of rats. This increase in acetylcholine level was not accompanied by a decrease in the activity of acetylcholine esterase. The possibility was presented that the increase in acetylcholine levels seen without a concomitant decrease in acetylcholinesterase could be due to a decrease in the release of acetylcholine in these tissues (299). This type of effect of Δ^9-THC was

demonstrated by Gill and his colleagues (111) when they showed that Δ^9-THC inibited the electrically induced twitch responses in the guinea pig ileum.

Gascon and Peres (109) have reported that ∇^8- and Δ^9-THC have a biphasic effect on acetylcholine-induced contractions of the guinea pig vas deferens. The cannabinoids produced a transient potentiation which was followed by a longer lasting inhibition. The authors suggest that since Δ^9-THC did not alter cholinesterase activity, it might be potentiating the effects of acetylcholine by altering release. This suggestion that Δ^9-THC potentiates release of acetylcholine is in direct contrast to a number of other reports in the literature.

It is clear that the hippocampus is the area of the brain most sensitive to cannabinoid-induced changes in cholinergic functions. The most pronounced effect of cannabinoids on cholinergic function is a decrease in acetylcholine synthesis and a decrease in acetylcholine release.

XI. Neurophysiology

Turkanis and Karler (279–281) have written a number of reviews on this aspect of cannabinoid research. Neurophysiological experiments have been utilized to define some of the more subtle effects of the cannabinoids and to identify their molecular mechanisms of action. It is clear from the work of many laboratories that, on a neurophysiological level, the cannabinoids produce both CNS excitation and CNS depression, just as in overt behavioral studies (149, 217, 275, 281). Low doses of psychoactive cannabinoids produced stimulatory effects as characterized by high voltage synchronous activity in the EEG and enhanced sensory evoked potentials. The diversity of these effects may be best exemplified by the observations that the cannabinoids can both cause convulsions and also act as anticonvulsants (48, 278). A considerable number of electrophysiological studies have appeared describing the effects of the cannabinoids on the hippocampus (100, 283, 297, 293) an area of the brain which plays an important role in various cognitive processes, including memory (134, 176, 266). Δ^9-THC increased the amplitude of hippocampal population excitatory postsynaptic potentials and spikes (287). These stimulatory effects were generally observed at low doses of Δ^9-THC whereas higher doses produced depression of these responses (100).

Cannabinoids have been studied extensively for their effects on the EEG of laboratory animals and man (290). Cannabinoids including marihuana extract, Δ^9-THC and Δ^8-THC, and a number of analogs have been shown to produce a flattening of hippocampal and cortical EEGs as well as high voltage bursts in a number of species (120, 188, 205, 238). Δ^8-THC at reasonable doses of 2.5 and 5 mg/kg and marihuana extract produced abnormal rhythmic discharges of the EEG which could override REM sleep episodes in rats. These EEG changes occurred after either acute or chronic treatment with the cannabinoids (188). Buonamici and colleagues (34) reported that the use of EEG power spectral analysis as opposed to spontaneous EEG activity, enables them to show quantitative and qualitative changes induced by cannabinoids in REM sleep episodes. They concluded that these changes were related to alterations in the state of consciousness induced by the cannabinoids. There was a greater effect of cannabinoids on EEG as measured at subcortical electrodes in experimental animals than was observed utilizing cortical electrodes (28, 49, 125, 133, 259). The EEG changes induced by cannabinoids as measured by surface electrodes in man were not pronounced (94, 95, 132, 144, 158, 172, 233).

A current hypothesis proposed by Turkanis and Karler (280) states that the CNS depressant effects of Δ^9-THC are due to an increase in the firing threshold and a decrease in the magnitude of the action potential in the soma. The action potential in the axon is unaltered. Wilkison (294) suggested that a generalized depression of sensory integration at both cortical and subcortical levels was involved in the depression of visual information arriving at the cortex. Δ^9-THC produced a dose-related (0.25 to 4 mg/kg) slowing of the cortical primary response to stimulation of the ipsilateral ventralis posterolaterals or the contralateral radial nerve. THC also decreased the secondary cortical responses induced by stimulation of the radial nerve. Dimethylheptylpyran, an analog of Δ^9-THC, produced similar effects in these procedures (295). Hosko and colleagues (135) demonstrated that the caudal brainstem was the primary central site for the effects of Δ^9-THC which were manifested in changes in the autonomic nervous system.

Low doses (0.125 mg/kg and higher) of Δ^9-THC have been shown to augment both the early and late evoked responses in frontal lobe polysensory areas of the brain. Δ^9-THC also augmented late repetitive activity. These effects were shown to be similar to those of mescaline and a number of convulsants but not similar to those of depressants, such as pentobarbital, chlorpromazine, or ethanol, or other agents, such as phencyclidine (PCP), lysergic acid diethylamide (LSD), strychnine, or amphetamine (27). This effect of cannabinoids might shed light on the stimulatory characteristics of the predominantly depressant effects of these agents.

A dose-response decrease in time occupied by high voltage activity was observed in the EEG of cats. Doses of Δ^9-THC from 1 to 4 mg/kg caused mydriasis which persisted for at least 2 h in each cat tested. Each of the doses also produced vomiting, defecation, and a decrease in locomotor activity. The dissociated EEG pattern seen after Δ^9-THC is similar to that seen after other hallucinogenic drugs such as psylocybin and ditran (126).

As mentioned earlier, the oral administration of marihuana extract distillate containing 20 mg/kg of Δ^9-THC showed a significant decrease in the intergrated EEG which was maximal after one or two daily doses. "Spindle-like" activity also was observed. The effects decreased

gradually on repeated daily administration. Tolerance developed to the effects on the EEG and to some but not all of the behavioral effects in these rats (224).

Δ^9-THC at a dose of 100 to 300 μg inhibited the firing rate of lateral geniculate neurons which were light sensitive. However, these neurons which were inhibited by light either remained unchanged or increased the rate of firing following Δ^9-THC. This differential effect of Δ^9-THC on the lateral geniculate neurons has been suggested to be due to an effect of the cannabinoid on the modulation of these neurons by monominergic systems in the midbrain (16). The multiple effects of cannabinoids on brain monoaminergic systems have been reviewed in the previous section.

Lapa and colleagues (163) reported that doses of 0.6 and 1 mg/kg of Δ^9-THC depressed polysynaptic reflexes in the cat. They recorded potentials from the superior sensory nucleus of the trigeminal nerve and on the nerve itself, following stimulation of the lower eyelid. The presynaptic potential was also depressed. In this preparation, the predominamt effect on THC was probably a depression of conduction along the presynaptic axon. The authors suggest that inhibition of synaptic transmission at other sites in the brain could be responsible for the neural effects of cannabinoids.

Δ^8-THC at doses of 2.5 and 5.0 mg/kg and marihuana extract produced abnormal rhythmic polyspike discharges of the EEG which could override REM sleep episodes in rats. This occurred after either acute or chronic treatment with the cannabinoids (188).

XII. Drug Interactions

There have been several studies in which the effects of cannabinoids have been attenuated by other drugs. In many cases, the drugs which attenuate the cannabinoid effects have been central nervous stimulants which probably represent an indirect interaction rather than a specific antagonism. Kudrin and Davydova (159) generated considerable interest when they reported that phenitrone would antagonize many of the behavioral effects of cannabinoids. Berger and Krantz (11) reported that phenitrone did not block the behavioral effects of Δ^9-THC in mice or dogs. Lomax and Campbell (171) reported that phenitrone potentiated rather than antagonized the hypothermia induced by the intraperitoneal injection of 20 mg/kg of Δ^9-THC in rats. We found that phenitrone did not block the pharmacological effects of cannabinoids in either dogs or pigeons. Phenitrone did, however, block the modest activity seen with Δ^9-THC in the mouse tail-flick test but did not block the hypothermia induced by either a single or five daily injections of Δ^9-THC in mice (256).

Since the predominant effects of Δ^9-THC and other cannabinoids on the central nervous system are depressant in nature, it is reasonable to expect that the effects of the cannabinoids would at least be additive and possibly synergistic with other central nervous system depressants. It is well known that people often abuse different drugs at the same time. Many abused drugs produce depression of the central nervous system. Synergistic depressive effects could produce toxic effects or even lethality. A review of the interaction of cannabis and other drugs appeared in 1981 (58). At least an additive effect of two CNS depressants has been shown when ethanol and a cannabinoid are administered to rodents. For instance, it has been shown that the effects of these drugs on body temperature, performance measures, and anticonvulsant activity are greater when given together than when either drug is given alone (90, 99, 103, 145, 169, 228, 246, 253).

As described in Section VII, "Tolerance," cross-tolerance has been reported between ethyl alcohol and Δ^9-THC in rodents. This cross-tolerance could suggest similarity in their actions and possibly in their mechanism of action. In at least some instances, the cross-tolerance to these effects was observed in both directions. That is, fewer effects were observed when an active dose of ethyl alcohol was given to Δ^9-THC-tolerant animals as well as when an active dose of Δ^9-THC was given to ethanol-tolerant animals (211). The suggestion that these two drugs, which are both depressants of the central nervous system are working through similar mechanisms is not supported by the differences in their acute effects on behavior. The stimulatory component of the depressant syndrome is not seen after alcohol administration. Similarly, the acute effects of cannabinoids differ from those of the benzodiazepines, yet it has been shown that Δ^9-THC and other cannabinoids potentiate the anticonvulsant activity of diazepam (156). As one might expect, certain components of the depressant effects of a drug may be potentiated by a drug from another class without an alteration in each aspect of the entire behavioral symptomotology.

Δ^9-THC and morphine were both shown to decrease spontaneous activity in rats. The effects of morphine in these animals was reversed by naloxone; however, naloxone was ineffective in reversing the depression induced by Δ^9-THC. These results suggest that these two drugs are producing this effect through different mechanisms. When animals were treated chronically with these two drugs, tolerance developed to the effects of THC and significant tolerance developed to the locomotor depressive activities of morphine. Some cross-tolerance was observed. Naloxone had a slight depressant effect on locomotor activity of animals given THC chronically but caused an increase in motor activity of animals given morphine (276). This portion of the experiments indicates that a withdrawal syndrome can be induced by naloxone following chronic morphine but not following chronic Δ^9-THC. However, Kumar et al. (161) reported that chronic Δ^9-THC treatment caused an increase in endogenous opioid peptide levels in the plasma and medial hypothalamus but not in the preoptic area of rats.

These results indicate the possibility that endogenous opioid systems may be involved in the pharmacological actions of Δ^9-THC. Considerably, more evidence is needed before this hypothesis will be widely accepted by the scientific community.

Pyror and his colleagues (227) have reported that an active dose of Δ^9-THC will potentiate the phencyclidine-induced decrease in response rate under a fixed-ratio schedule of food presentation in rats. Recently, Thompson and Winsauer (271) confirmed and expanded these studies to show that Δ^9-THC potentiated the disruptive effects of phencyclidine in monkeys.

A number of studies have been reported in the literature which demonstrate an interaction between reserpine and Δ^9-THC (5, 89, 252). Many of these interactions, especially those in which the cannabinoid inhibits or attenuates the effects of reserpine, may be due to the ability of the cannabinoid to alter the normal subcellular distribution of reserpine (141). Preincubation of brain tissue with Δ^9-THC altered the distribution of reserpine in brain fragments. There was a marked increase in the level of reserpine in the myelin membrane fragment of the mitochondrial fractions. The data from these experiments supported the hypothesis that Δ^9-THC retards the action of reserpine by altering the neuronal distribution of reserpine in various membrane components of the cell (141). Reserpine-induced hypokinesias were potentiated by Δ^9-THC (206) and levonantradol (204). The site of action was shown to be the extrapyramidal system and was hypothesized to be due to an interaction of the cannabinoids with a nicotinic site (204). Additional work is needed to suggest this hypothesis. The cannabinoids have not been shown to have pronounced effects on either central or peripheral nicotinic systems.

The interaction of the many active constituents contained in the marihuana plant have been exceedingly interesting (56, 64, 150). It has been shown, for instance, that CBD potentiates the analgesic effect and the inhibitory effect of Δ^9-THC in rat pole-climbing experiments. On the other hand, it also will antagonize the depressant effects of Δ^9-THC in the mouse catatonia test and the corneal areflexia test in rabbits. The increased defecation and decreased aggressiveness caused by Δ^9-THC in REM-sleep-deprived animals is also potentiated by CBD. These results were used to suggest that CBD either antagonizes the stimulatory effects of Δ^9-THC or potentiates the depressant properties of the cannabinoid (150). This suggestion presents a number of problems since each of the behaviors mentioned in this experiment is depressed by Δ^9-THC. CBD, on the other hand, reduced the magnitude and the duration of the hypothermic effects of Δ^9-THC in rats (25). CBD also reduced the effects of Δ^9-THC on heart rate, respiration, and body temperature in rabbits (25) and blocked the Δ^9-THC induced convulsions in a genetically unique strain of rabbits (56). CBD also antagonized the decrease in response rate induced by Δ^9-THC in rats and pigeons (67) and monkeys (30). Inactive doses of cannabichrome produced a potentiation of the lethality of Δ^9-THC but did not potentiate its effects on body temperature or its ability to prolong barbiturate-induced hypnosis (118). Cannabichrome was also shown to potentiate the analgesic activity of Δ^9-THC but did not alter the impairment induced by Δ^9-THC on the conditioned avoidance response (68). Additional evidence that other constitutents of marihuana may attenuate the effects of Δ^9-THC is generated from experiments in which a dose of Δ^9-THC is shown to produce a greater effect than a dose of marihuana extract which contains an even higher dose of Δ^9-THC (26). A review of the interactions of Δ^9-THC and other centrally acting drugs has appeared (76).

XIII. Search for a Therapeutic Agent

The results of many pharmacological studies of the effects of cannabinoids in laboratory animals have been useful in predicting possible psychic side effects as well as defining therapeutic potential for metabolites and synthetic analogs of the cannabinoids. Razdan and Howes (231) and Lemberger (165) have written excellent reviews of the therapeutic potential of cannabinoids. In our own search for a specific acting cannabinoid, we reported that the substitution of a heterocyclic atom, such as nitrogen or sulfur in the C-ring, gave compounds with pharmacological profiles of activity similar to those of their paired natural constituents of marihuana, that is, Δ^8- and Δ^9-THC. These heterocyclic analogs produced static ataxia in mongrel dogs, potentiated the pressor response to epinephrine and norepinephrine in anesthetized rodents and dogs, and caused the depression of spontaneous activity and induced hyperexcitability and at higher doses a loss of righting reflex in mice (73). Since that time, many other heterocyclic cannabinoids have been synthesized, and certain of these have been tested for various therapeutic potentials in man. Two of these compounds have been studied in great detail in laboratory animals and also have been studied in man. These compounds are nabilone and levonantradol. Stark and Dews (260) reported that nabilone had certain behavioral pharmacological characteristics similar to those of chlordiazepoxide and others similar to those of Δ^9-THC. Although some differences were observed, the effects of nabilone and Δ^9-THC on the cardiovascular system of a number of species were somewhat similar (261). Levonantradol, on the other hand, was developed as a more potent analgesic than the natural cannabinoids (156, 203). Both nabilone and levonantradol as well as a number of other cannabinoids have been shown to be active in a number of clinical settings (165, 231, 273). A more detailed description of the search for a therapeutic agent in this series is presented in the review by Razdan (230a) in this series. What is attempted in the rest of this review is a description of the results of animal pharmacological investigations which have led to the

hypothesis of a specific therapeutic potential for a compound in this series. An attempt is also made to elucidate the mechanism of specific action of the cannabinoids which would have therapeutic activity. The clinical pharmacology of these compounds is described in the review by Hollister (129a) in this series and that information will not be repeated here.

XIV. Cardiovascular

The effects of cannabinoids on the cardiovascular system were reviewed in 1981 (58). It was clear at that time, and little more has been published which could change those conclusions, that the effects of cannabinoids on the cardiovascular system are varied depending on the species used, the drug administered, the vehicle used, and the frequency of administration. A number of studies are described below which will give an indication of the varied responses which have been observed. One concludes from the literature that the effects of the cannabinoids on the cardiovascular system in humans are less robust than those seen in animals. This is due for the most part to the fact that lower doses of cannabinoids have been given to humans.

Cavero et al. (45) reported in 1973 that the hypotensive effects of Δ^9-THC in anesthetized dogs was not due to an alteration of peripheral adrenergic and/or cholinergic function. The results of these experiments and those of their earlier cross-circulation experiments indicated to them that the hypotensive effect of Δ^9-THC in this species was due primarily to a central effect of the cannabinoids.

In 1973, Kochar and Hosko (155) reported that only two of seven healthy male volunteers showed electrocardiographic changes after the oral administration of 0.2 mg/kg of Δ^9-THC. Six of the seven young men showed increased heart rate following an oral dose of 0.3 mg/kg of THC in the same study. These authors concluded that Δ^9-THC may have direct effects on the heart and that a cummulative effect on this organ might occur with repeated exposure.

Δ^9-THC at the subcutaneous dose of 20 mg/kg caused a significant lowering of blood pressure in naive rats and in rats that were stressed by immobilization. Δ^9-THC also blocked the increase in blood pressure induced by the immobilization process (296). Studies such as this supported the hypothesis that cannabinoids might be useful in stress-induced hypertension. Their depressant effects on the central nervous system would be an advantage in such therapy. Of course, the depressant effects on the brain might be involved in the mechanism of the antihypertensive effects of the cannabinoids.

Cavero and his colleagues (44) demonstrated in 1972 that an intravenous dose of 5 mg/kg of Δ^9-THC produced hyperpnea and hypoxemia in dogs. Hypotension peaked at 15 min. This hypotensive effect of the cannabinoids was seen only in animals who were maintained at their normal pO_2 level, whereas animals spontaneously breathing did not show the hypotensive effect. Bradycardia was seen in all dogs after Δ^9-THC.

In adrenal-regenerated hypertensive rats 3 mg/kg of Δ^9-THC given intraperitoneally significantly lowered blood pressure. The acute effect on blood pressure disappeared following daily administration of this same dose. A more delayed fall in blood pressure was observed following subsequent daily injections (17). This differential tolerance development indicates that a different mechanism exists for the initial and delayed effects on blood pressure.

The intravenous administration of 0.5 mg/kg of Δ^9-THC produced bradycardia in anesthetized dogs which was not completely blocked by vagotomy. The decrease in cardiac output induced by Δ^9-THC in intact dogs was lessened to some extent in vagotomized animals. These investigators also reported that Δ^9-THC produced an increase in pulmonary resistance without altering blood gases or pulmonary compliance (32). Concentrations of 1 to 100 μM Δ^9-THC, Δ^8-THC, CBN, and CBD all depressed contra-activity in the isolated rat heart. Δ^9-THC and CBN both produced tachycardia in these experiments and CBN produced bradycardia. Δ^8-THC did not alter heart rate in these experiments (247).

The subcutaneous injection of 10 mg/kg of Δ^9-THC caused a prolonged and significant decrease in heart rate in unanesthetized rats. Bradycardia per se was not observed on the 16th day of daily administration of this dose of the cannabinoid. These results led the authors to suggest that tolerance did not develop to this cardiovascular effect of Δ^9-THC (154). However, an alternate hypothesis deserves mention. That is, the heart rate prior to the injection of Δ^9-THC on day 16 was approximately the same as that seen on day 1 at the time of peak bradycardia. It is possible that Δ^9-THC cannot reduce heart rate beyond this level in the unanesthetized rat. Higher doses of drug were not investigated in these experiments. Bradycardia and hypotension were both observed in rats when 10 mg/kg of Δ^9-THC was given by the intravenous route of administration (2).

The intraperitoneal administration of 6 mg/kg of Δ^9-THC to unanesthetized rats once a day for 10 days caused an initial bradycardia and pressor response. The decrease in heart rate was not seen following the injection of the cannabinoid on the 5th day and an increase in heart rate was observed on day 10. The pressor response increased throughout the experiment (151). These results indicate that the effects of the cannabinoid on these two parameters of cardiovascular function are distinctly different.

The intravenous administration of Δ^8- or Δ^9-THC produced a dose-related transient increase in blood pressure followed by a more prolonged hypotensive effect and bradycardia in anesthetized rats. When these compounds were administered intra-arterially into the perfused hind quarter of the rat, they both produced an increase in perfusion pressure which indicated a vascular

constriction. The constriction produced by Δ^9-THC was reduced by 90% by pretreatment with phentolamine. Reserpine pretreatment significantly reduced the constrictor effects of intra-arterially administered tyramine or Δ^9-THC. Taken altogether, these data suggest that the cannabinoids produce vasoconstrictor activity in the rat which may be mediated at least in part through a tyramine-like action on adrenergic nerve terminals (3).

(−)-9-Nor-9β-hydroxy-hexahydrocannabinol is a cannabinoid which has many of the pharmacological properties of Δ^9-THC inducing hypotension and bradycardia in anesthetized dogs (183). As mentioned earlier, abnormal Δ^8-THC and abnormal CBD were studied for their effects on the cardiovascular system of anesthetized dogs. It is interesting to note that abnormal CBD contained potent hypotensive activity without the psychotomimetic effects produced by Δ^8-THC in these animals. These data suggest that structural modifications in this series can lead to the separation of different pharmacological effects of the cannabinoids. Also they suggest to us that abnormal CBD should be investigated further as a drug which will alter cardiovascular function at doses which do not produce pronounced effects on the brain. If this lead were to stand up, it would be one of the first instances of separating these activities of a cannabinoid (4).

Doherty and colleagues (84) reported that N-methyl-levonantradol was 10 times more potent than nabilone and 100 times more potent than Δ^9-THC in producing equal respiratory depressant effects as measured by an elevation of the resting concentration of resting CO_2 in expired air. The effects of these three drugs on the cardiovascular system of anesthetized cats were response-limited whereas the respiratory depressant effects continued on to death. These authors reported that the respiratory frequency was decreased in both intact and vagotomized cats. They concluded that the multiple effects of the cannabinoids on the respiratory and cardiovascular systems were due to an upward shift in the carbon dioxide set point of the chemorespiratory "detector," a depression of the respiratory center in the lower medulla, depression of the vasomotor center, and a cardioaccelerator action on the heart.

The studies referred to above, those reviewed by us previously (116), and those recently reviewed by Jones (143) all show that cannabinoids produce much different effects on the cardiovascular system of experimental animals and man. Bradycardia is most often seen in anesthetized animals, whereas tachycardia is the predominant effect in humans. One often observes a decrease in blood pressure due to the administration of cannabinoids to anesthetized animals. Cannabinoids do not have a pronounced effect on blood pressure in humans.

XV. Reproduction

It is quite well established that Δ^9-THC and a number of THC analogs have pronounced effects throughout the male and female reproductive systems. In essence, the majority of the evidence shows that Δ^9-THC causes a decrease in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion and a reduction in the size of the testis and a regression of the Leydig cells in many species (82, 83, 180, 212, 236, 248). The administration of exogenous luteinizing hormone-release hormone (LHRH) brought the LH levels back to normal, indicating that the effect of the cannabinoid was at the hypothalamus (249, 284).

Δ^9-THC increased levels of LHRH and met-enkephalin in the mediobasal hypothalamic tract of ovariectomized rats. The ability of Δ^9-THC to inhibit the release of LHRH from the medial basal hypothalamus was reversed by naloxone; therefore, an endogenous opioid system was implicated. Δ^9-THC at doses of 2, 15, or 30 mg/kg in male intact rats decreased LHRH levels in the anterior hypothalamus and the medial basal hypothalamus in a dose-related fashion. An increase in serum testosterone levels was not observed which led the authors to conclude that Δ^9-THC decreased biosynthesis of LHRH rather than increasing its release (160).

The effects of Δ^9-THC on the male reproductive system of rats was not blocked by the administration of testosterone (229). Chronic Δ^9-THC also was shown to cause a decrease in body weight and accessory sex organ weights. The continuous treatment with exogenous androgen blocked both of these effects of Δ^9-THC (105). In another study, Δ^9-THC produced a decrease in testosterone levels as well as a decrease in LH in rats. Both of these effects appeared to be temporary since the levels of the hormones returned to control values during chronic treatment with the cannabinoid (115). Husain and his colleagues (137) as well as others have reported that cannabinoids cause functional disruptions of gonadal functions (137). Their results caused them to suggest that alterations in glucose metabolism in the rat testicular tissue may be the cause of these changes (137). Some reports hvae shown that Δ^9-THC and other cannabinoids are estrogenic in females, while others show that they are anti-estrogenic. The results of experiments in the males are more clear-cut and straightforward than those in the females.

Merari and colleagues (201) studied the effect of Δ^9-THC on copulation in male rats. They found that doses in the range of 2 to 3 mg/kg of Δ^9-THC increased latency to the first mount, latency to the first mount following ejaculation, and latency to ejaculation. They did not find changes in the number of insertions or mounts and concluded that the decrease in sexual performance was due to decreased motivation caused by Δ^9-THC. Dalterio (62) reported that Δ^9-THC and CBN at the relatively high dose of 50 mg/kg orally produced changes in reproductive function of male mice. This dose of cannabinoids given to pregnant and lactating mothers produced alterations in reproductive function in male offspring. Studies

at lower doses are needed to determine the relevance of these effects seen in mice to the possible effects in man.

Δ^9-THC was shown to be a weak but yet significant competitor for binding of estrodiol to cystoplasmic estrogen receptors. This binding of Δ^9-THC to the estrogen receptor caused the authors to suggest that Δ^9-THC produced a primary estrogenic effect rather than this being an indirect or secondary phenomenon (230). As mentioned earlier, some controversy exists as to the estrogenic properties of cannabinoids. The intraperitoneal injection of 1, 2.5, or 10 mg/kg of Δ^9-THC to ovariectomized rats produced a significant uterotrophic effect. This increase in uterine weight in ovariectomized animals supports the suggestion of estrogenic activity for Δ^9-THC (225). However, Okey and Bondy (214) have reported that Δ^9-THC does not have estrogenic activity as defined by competitive binding studies with tritiated estradiol-17-β for specific high affinity binding sites in uterine cytosol. These latter authors subsequently reported that Δ^9-THC did not compete with 17-β-estradiol for binding in uterine or mammary cytosols in mice (213).

Timed pregnant rats were intubated with increasing doses of Δ^9-THC from 5 to 50 mg/kg/day from day 1 to day 5 of gestation. Half of the treated rats were given 50 mg/kg/day and the other half were given 100 mg/kg/day from day 6 until day 21 of gestation. No viable litters were born to the rats in the high dose group. The lower dose produced a reduction in weight gain during pregnancy and a decrease in pup body weight at birth. This lower dose did not produce an effect on litter size or on body weight of the pups at 21 days of age. Additionally, pups from the low dose group were not different from pups whose mothers had been given vehicle throughout pregnancy when tested at 21 days of age in a number of behavioral tests (1).

The chronic medication of mice with 5 mg/kg/day of Δ^9-THC produced a significantly higher incidence of abnormal ova following injection of human chorionic gonadotropin (212). Dalterio et al. (63) reported that a single prenatal exposure of CBN or CBD or Δ^9-THC to mice caused the F_1 offspring to have reduced fertility and testicular abnormalities. The dose of cannabinoid used in these studies was considerably higher than that consumed by man but well below acutely toxic doses in mice.

The distribution of radioactivity in the brains of mothers and fetuses was studied following the intravenous injection of 0.5 mg/kg of tritiated Δ^9-THC to pregnant dogs. The brain level of radioactivity was 3 times higher in the maternal brain than in the fetal brain. Generally, the distribution within the brain was similar in both the mother and fetus. One major difference that was observed was in the subcellular distribution of radioactivity in the fetal brain as compared to that in the maternal whole brain homogenate. The distribution in each appeared to be related directly to the phospholipid content of the subcellular fractions (185).

There is no question that Δ^9-THC and other cannabinoids have been shown to have pronounced effects on the reproductive system of many animal species. The doses of the cannabinoid used in most of these experiments are higher than those ingested by man. Tolerance has been shown to develop to most of these effects, thus reducing the probability of long term, severe effects of repeated use of cannabinoids on the reproductive system of humans. It is important to point out, however, that effects on the reproductive system should be evaluated extensively in the pharmacological and toxicological workup of a cannabinoid destined for any therapeutic use. Obviously, effects on the reproductive system should be monitored closely in cases of overdose of cannabinoids. It is reasonable to expect that any drug that alters brain function will have effects on the neuroendocrine and neuroreproductive systems with the expected alterations of function. The experimental results discussed above and in other reviews show that cannabinoids are not an exception to this rule. The effects of cannabinoids on neuroendocrine and reproductive function has been reviewed recently by Rosenkrantz (234) who concludes that definitive evidence exists to implicate the cannabinoids in many aberrations of sexual function and other endocrine functions. Additional chronic experiments at low doses of cannabinoids and across species are needed before we will be able to determine if the effects of cannabinoids on the reproductive system should limit the development of these agents for therapeutic purposes.

XVI. Endocrine

There have not been an extensive number of studies on the effects of cannabinoids on the endocrine glands. As stated in the beginning of this review, there is little evidence that cannabinoids have direct effects on peripheral organs, including the endocrine glands. A few of the studies which have appeared are included here as an example of what has been done. In each of these cases, the changes quantitated may be the result of an effect of the cannabinoid on the brain which is expressed as a change in hormonal levels. In 1970, we reported that Δ^9-THC was a potent stimulator of ACTH secretion. Δ^9-THC differed from other drugs which cause a stimulation of ACTH secretion in that it was inactive in causing ACTH secretion in pentobarbital-anesthetized rats. Δ^9-THC also differed from morphine and many other compounds which caused stimulation of ACTH secretion in that it did not block the secretion induced by epinephrine. Tolerance was not observed to the effect of Δ^9-THC on ACTH secretion following five daily doses of Δ^9-THC (180). These results have been confirmed and extended by others who have also suggested that the primary effect is in the brain.

The intraperitoneal injection of 3 mg/kg of Δ^9-THC reduced serum thyrotropin levels by 90%. The peak time for this effect was approximately 1 h after injection. Triiodothyroxine and thryroxine were also decreased by

a single injection of Δ^9-THC with a maximal inhibition occurring 6 h after injection. This effect of cannabinoids on thyroid hormones was thought not to be due to an effect on the pituitary or the thyroid since Δ^9-THC at the same dose did not alter the effect of TRH in these animals (122).

Kumar et al. (161) reported that although acute injections of Δ^9-THC produced an increase in plasma prolactin levels, chronic exposure caused a decrease in plasma prolactin levels. Their experiments did not rule out the possibility that Δ^9-THC produces a biphasic effect, i.e., initial increase followed by a suppression of plasma prolactin levels. This biphasic effect of Δ^9-THC on prolactin is similar to its effect on behavior stimulation followed by generalized depression of activity.

XVII. Food Intake

There is considerable information in the anecodotal literature about the effects of marihuana on food intake. One of the most frequent comments has to do with an increased craving for sweets after the ingestion of marihuana. Few reports have appeared in the scientific literature which deal with the effects of cannabinoids on food intake. The interperitoneal administration of 2.5 or 5 mg/kg of Δ^9-THC caused a dose-related decrease in food intake when the food was presented 2 h after drug administration. The daily administration of 2.5 mg/kg of Δ^9-THC for 9 days also caused a significant reduction in food intake. The animals gained weight less rapidly than control rats in these experiments. However, if the Δ^9-THC was given 16 h before eating instead of immediately before eating, there was little effect (251). It is well known that Δ^9-THC and active metabolites are still in the brain at 16 h. A decrease in food intake in rats given behaviorally effective doses of Δ^9-THC on a daily basis has also been reported (175). Taylor and Yap (269) found that twice daily intravenous injections of doses from 2 to 6 mg/kg of Δ^8- or Δ^9-THC caused a decrease in both food intake and body weight. Similarly, Verberne and colleagues (289) reported that Δ^9-THC given intravenously at doses from 2 to 6 mg/kg twice a day caused a reduction in food intake and body weight. The reduction in food intake was seen on each day of the 11-day treatment schedule, but the magnitude of the decrease was less on subsequent days, suggesting that tolerance developed to this effect. Tolerance to the reduction in food intake was not as evident as tolerance to the effect on body weight. These few studies all indicate that cannabinoids decrease and not increase food intake in laboratory animals. Thus, another discrepancy between the effects of cannabinoids in a laboratory animal experiment and in man. The effect of cannabinoids on the gastrointestinal tract has not been investigated in any detail. In one study, Δ^8- and Δ^9-THC were less potent than morphine in blocking propulsion in the gastrointestinal tract as measured by the charcoal meal test (74). Additional studies into the effect of cannabinoids on gastrointestinal function are needed. The results of these studies might shed light on the discrepancy in the effects of cannabinoids on food intake in animals and man.

XVIII. Antinociception

Early reports indicated that Δ^9-THC and certain other psychoactive cannabinoids were as potent as morphine in the tail-flick and other biological assays used to quantitate antinociception in laboratory animals. For instance, Buxbaum (37) reported that Δ^9-THC was equally potent to morphine in the rat tail-flick and hot-plate tests, but when these two substances were compared for their analgesic activity in the mouse, morphine was found to be more potent than Δ^9-THC. Yet, the cannabinoid showed significant analgesia as measured in these tests systems. Other laboratories found the cannabinoids to be less potent than morphine in both species. After considerable investigation, the most widely held view was that the cannabinoids did not possess potent antinociceptive activity in spite of the fact that they had some moderate activity in such tests as the phenylquinone-induced writhing test. These effects were not antagonizable by naloxone and therefore were felt to be non-opiate in nature. Many reports have appeared which are similar to that of Bhargava and Matwyshyn (14) who showed minimal analgesic activity for Δ^9-THC. Naloxone did not antagonize this activity of Δ^9-THC in the tail-flick tst. However, in this experiment, Δ^9-THC by itself did not produce significant activity. Milne et al. (203) reported that Δ^9-THC was 10 times less potent than morphine in the abdominal stretching test and approximately 18 times less potent than morphine in the mouse tail-flick test. Various analogs of Δ^9-THC, most notably levonantradol, were found to be much more potent than morphine in these procedures (156).

Although a number of previous studies had shown that Δ^9-THC had only weak activity in the tail-flick test, Martin (182) recently has demonstrated that intravenous injection of Δ^9-THC was 45 times more potent in this procedure than when the drug was administered subcutaneously. When given by the intravenous route of administration, Δ^9-THC was 3 times more potent than morphine given by the same route of administration. However, when Δ^9-THC was administered subcutaneously, it was much less potent than morphine in this procedure. Other cannabinoids including the 11-hydroxylated metabolite of Δ^9-THC were also potent as quantitated by the tail-flick test when administered by the intravenous route of administration. There are very few examples in the literature of a compound which is active in a particular test system by one route of administration but not by another route. It is intriguing that the intravenous injection of a reasonable amount of Δ^9-THC would cause an effect which is identical to that of morphine; yet, much higher doses given by a different peripheral route of administration do not produce a similar effect.

There are no reports in which the authors suggest that CBN, CBD, or other constituents of marihuana other than Δ^8- and Δ^9-THC are active in one or another analgesic tests in animals or man.

XIX. Anti-inflammatory

Considerable discrepancy exists in the literature as to the activity of cannabinoids in a number of animal assays for anti-inflammatory, mild analgesic, and antipyretic activity. Sofia and his colleagues (254) reported that Δ^9-THC was 20 times as potent as aspirin and approximately twice as potent as hydrocortisone in the carrageenan edema test in rats. These results were not confirmed in the study of Kosersky et al. (157) who reported that orally administered Δ^9-THC was inactive in blocking the carrageenan-induced edema in the rat paw model. These two groups of investigators also disagreed as to the activity of Δ^9-THC as an antipyretic and as a mild analgesic. Kosersky and his colleagues reported antipyretic but not analgesic activity, while Sofia and his colleagues reported analgesic but not antipyretic activity for Δ^9-THC. Similar doses were used by the two groups of investigators, but they did use different vehicles to suspend the Δ^9-THC. Sofia and his colleagues suspended the cannabinoid in undiluted propylene glycol whereas Kosersky and his colleagues bound the Δ^9-THC to fatty acid-poor serum albumin. If Δ^9-THC had been inactive in all assays when bound to serum albumin, the binding to the albumin could be the cause for the lack of activity. However, the antipyretic activity was seen only in those experiments in which Δ^9-THC was given in serum albumin.

XX. Antiemetic

In man, orally administered Δ^9-THC can prevent nausea and vomiting in patients being treated with anticancer drugs. Since the side effects are often disturbing to geriatric patients, it is particularly useful in younger patients (200). Δ^9-THC was found to be an active antiemetic agent when administered to cats by the oral or intramuscular route of administration, but its antiemetic activity was not predictable when given intravenously. Doses of Δ^9-THC that caused behavioral impairment when given intravenously were not predictable in terms of antiemetic activity (190). It is a very rare occurrence for the intravenous route of administration to be less predictable than other peripheral routes of administration.

Δ^9-THC, nabilone, and the phenothiazine, prochlorperazine, were all able to attenuate the taste aversion induced in mice by cyclophosphamide (162). Levonantradol, another cannabinoid-related antiemetic in man (60, 81), was not active in this test procedure. These results indicate that this paradigm can be used to screen compounds for possible antiemetic activity *versus* the cancer chemotherapy-induced emesis. The levonantradol data indicate that false-negatives exist using this procedure.

Another aspect of cannabinoid pharmacology that would be a useful adjunct to the antiemetic effect has to do with reports that the cannabinoids have some utility in retarding the growth of certain tumors. For instance, Δ^9-THC, Δ^8-THC, and CBN, but not CBD, retarded Lewis lung adenocarcinoma growth and extended survival time in mice. Although these responses were dose-related, it took doses which were considerably higher than those which are necessary to produce central nervous system effects (208). Ideally, a cannabinoid analog could be found that would have antagonized the emetic side effect and potentiate the retardation of tumor growth induced by an anticancer agent.

XXI. Anticonvulsant

It is quite clear that cannabinoids, particularly Δ^9-THC and CBD, are active in a number of animal models for anticonvulsant activity. The metabolite of Δ^9-THC, 11-OH-Δ^9-THC, and the synthetic analog dimethylheptylpyran (DMHP) are more potent than the parent compound (146). Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC have been shown to delay the onset of pentylenetetrazol-induced seizures. The two metabolites, but not the parent compound, potentiated the effect of pentobarbital in this procedure. Δ^8-THC and 11-oxo-Δ^8-THC also had a significant protective effect against the lethal effects of pentylenetetrazole (298). Although the exact mechanism of the anticonvulsant effect of cannabinoids is not known, Karler, Turkanis, and their colleagues have reported that Δ^9-THC can depress neuronal transmission between the two cerebral cortices (282). They have also found that the cannabinoids can depress certain epileptic foci (278). Although there are some similarities in the anticonvulsant properties of Δ^9-THC and CBD, there also are a number of clear distinctions. CBD, but not Δ^9-THC, is efficacious *versus* pentylenetetrazol-induced maximal seizures (277). Koe and his colleagues (156) have reported that Δ^9-THC and a number of structurally related cannabimimetics, including the potent compound levonantradol, significantly potentiated the activity of diazepam versus pentylenetetrazol-induced seizures. They also demonstrated a good correlation between the potency of these compounds to potentiate diazepam and their potency to inhibit flunitrazepam binding to mouse brain. Chesher and Jackson (47) reported that Δ^9-THC was without effect in protecting mice against chemoshock-induced seizures. It was effective *versus* electroshock only at the very high doses of 160 to 200 mg/kg. These investigators found that CBD and CBN were without effect in either test system.

It has been reported that CBD inhibited the clonic and tonic convulsions induced by the GABA inhibitors, 3-mercaptoproprionic acid, picrotoxin, isonicotinic acid, hydrazine, pentylenetetrazol, and bicuculline. However, CBD did not block the convulsions induced by strychnine

which is a glycine antagonist. These authors interpreted these results to suggest that the effects of CBD as an anticonvulsant were to inhibit seizure spread by an action on GABA mechanisms rather than on glycine mechanisms (52). CBD does not appear to have the excitatory behavioral component observed with Δ^9-THC. The work of a number of investigators has led to the hypothesis that CBD has better potential as an anticonvulsant than Δ^9-THC (138, 139, 147, 282). Tolerance develops to the anticonvulsant properties of Δ^9-THC more readily than it does to those of CBD. This lower propensity for tolerance and the lack of an excitatory component for CBD suggest that it would be a better candidate as an antiepileptic drug in humans. This suggestion is further supported by the observation of hyperexcitability seen after the withdrawal of repeated administrations of Δ^9-THC, but not after cessation of chronic doses of CBD (148). Interestingly, both the (+)- and (−)-isomers of CBD have been shown to be active anticonvulsants (198). The two isomers of DMHP are also equipotent. The comparative total anticonvulsant profiles for CBD, Δ^9-THC, and phenytoin indicate that CBD is more similar to phenytoin than it is to its analog Δ^9-THC. Yet, CBD has a profile of anticonvulsant properties which differs from that of prototype drugs in this class such as phenytoin and phenobarbital (149). For instance, the potency of CBD differs from species to species more than the potency of the other two prototype drugs.

It is interesting to note that Consroe and his colleagues (53, 57) have shown that in a strain of genetically unique rabbits, Δ^9-THC and other cannabinoids produce convulsions. The severity of the convulsions which are seen at doses of Δ^9-THC equivalent to those consumed by humans (53, 54) is dose-related (187), and only those cannabinoids that produce psychotomimetic effects in man produce convulsions in these rabbits (54, 55, 57). Pretreatment with CBD blocks the Δ^9-THC-induced convulsions (56). Δ^9-THC has been shown to have convulsant properties in other species (48, 278).

XXII. Summary

The pharmacology of the cannabinoids is characterized by at least two very provocative phenomena. First, the multiplicity of effects. As I have mentioned throughout this review, most of these effects are due to actions on the central nervous system. The major problem in the search for a therapeutic agent in this series has been due to the inability to find a cannabinoid with the therapeutic action at doses below those that produce side effects. The high lipid solubility of the cannabinoids allows them to be distributed throughout the brain at reasonable doses. The second aspect of their pharmacology worthy of special mention is their low toxicity. Throughout this review, I have indicated that the minimal effective dose of Δ^9-THC for a particular pharmacological effect in animals was higher than that usually consumed by man. Yet, in almost all cases, it was much lower than the dose which produced toxic effects in the same species. These two characteristics of the animal pharmacology of cannabinoids carry over to humans. For instance, each of the cannabinoids tested in man causes many side effects at active doses and lethal effects of overdose by humans are nonexistent or rare. Toxicity following chronic use may be a different issue.

A great deal of work has been carried out in an attempt to characterize the pharmacological effects of cannabinoids. It is clear from the material reviewed in this article that most if not all of the predominant effects of cannabinoids in whole animals are due to the direct effects of these compounds on the central nervous system. Our state of knowledge is too limited to rule out the possibility that they also produce effects on certain peripheral organs. It is expected that the majority of these effects will be shown to be due to the interaction of the cannabinoids with the neuronal innervation of the organ rather than directly with the organ tissue itself. Very high doses of cannabinoids just like all active drugs have an effect on many organ systems. These are toxicologic not pharmacologic and are nonspecific. The effects of cannabinoids at the molecular level have been reviewed by Martin (182a) in this series. This type of research is expected to elucidate the mechanism of action of cannabinoids at the cellular level.

It is clear that the cannabinoids produce a unique behavioral syndrome in laboratory animals and in man. The extensive neurochemical and neurophysiological experiments have given us suggestions but not conclusive evidence for the mechanism of either the stimulatory or depressant component of this unique behavioral syndrome. The reinforcement properties of cannabinoids might be the least well defined. The physicochemical characteristics of these compounds have limited self-administration studies in animals. It is obvious that the reinforcing properties of the cannabinoids has led to the widespread abuse of marihuana.

Although very limited, there are some reports in the literature which suggest some similarities between the effects of cannabinoids and drugs in other CNS-active drug classes. It is tempting to speculate about the possible role of endogenous opiates in the action of cannabinoids due to similarities with morphine. Slightly more acceptable might be the speculation that an endogenous cannabinoid exists in brain. There is little or no evidence for this now, but there was not an endogenous opiate known to us 15 years ago.

The therapeutic potentials for cannabinoids have been reviewed by Hollister (129a) in this series. It is surprising how little evidence can be extrapolated from the animal literature to support the potential therapeutic usefulness of these compounds. They are not unique in this respect. The therapeutic utility of many compounds has been defined in man. The recent approval of Δ^9-THC and nabilone as antiemetic agents *versus* emesis induced by

cancer chemotherapeutic agents should enhance the development of other therapeutically useful cannabinoids.

Acknowledgments. The author is grateful to Dr. Billy R. Martin and Ms. Susan Anderson for helpful suggestions on the preparation of this manuscript. He is also most appreciative of the excellent work of Ms. LaVerne Brown in typing the many drafts of this paper.

REFERENCES

1. ABEL, E. L.: Effects of Δ^9-THC on pregnancy and offspring in rats. Neurobehav. Toxicol. Teratol. **6:** 29–32, 1984.
2. ADAMS, M. D., CHAIT, L. D., AND EARNHARDT, J. T.: Tolerance to the cardiovascular effects of Δ^9-tetrahydrocannabinol in the rat. Br. J. Pharmacol. **56:** 43–48, 1976.
3. ADAMS, M. D., EARNHARDT, J. T., DEWEY, W. L., AND HARRIS, L. S.: Vasocontrictor actions of Δ^8- and Δ^9-tetrahydrocannabinol in the rat. J. Pharmacol. Exp. Ther. **196:** 649–656, 1976.
4. ADAMS, M. D., EARNHARDT, J. T., MARTIN, B. R., HARRIS, L. S., DEWEY, W. L., AND RAZDAN, R. K.: A cannabinoid with cardiovascular activity but no overt behavioral effects. Separatum Experientia **33:** 1204, 1977.
5. ADAMS, P. M., AND BARRATT, E. S.: Role of biogenic amines in the effects of marijuana on EEG patterns in cats. Electroencephalogi. Clin. Neurophysiol. **39:** 621–625, 1976.

5a. AGURELL, S., HALLDIN, M., LINDGREN, J., OHLSSON, A., WIDMAN, M., GILLESPIE, H., AND HOLLISTER, L.: Pharmacokinetics and metabolism of Δ^1tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol. Rev. **38:** 21–43, 1986.

6. ALVES, C. N., GOYOS, A. C., AND CARLINI, E. A.: Aggressiveness induced by marihuana and other psychotropic drugs in REM sleep deprived rats. Pharmacol. Biochem. Behav. **1:** 183–189, 1973.
7. AULAKH, C. S., BHATTACHARYYA, A. K., HOUSSAIN, M. A., AND PRADHAN, S. N.: Behavioral and neurochemical effects of repeated administration of Δ^9-tetrahydrocannabinol in rats. Neuropharmacology **19:** 97–102, 1980.
8. BALSTER, R. L., AND FORD, R. D.: The discriminative stimulus properties of cannabinoids: a review. *In* Drug Discrimination and State Dependent Learning, ed. by B. T. Ho, D. W. Richards III, and D. L. Chute, pp. 131–147, Academic Press, New York, 1978.
9. BANERJEE, S. P., SYNDER, S. H., AND MECHOULAM, R.: Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J. Pharmacol. Exp. Ther. **194:** 74–81, 1975.
10. BENSEMANA, D., AND GASCON, A. L.: Effect of Δ^9-THC on the distribution, uptake and release of catecholamine in rats. Rev. Can. Biol. **33:** 269–278, 1974.
11. BERGER, H. J., AND KRANTZ, J. C.: Phenitrone: ineffective blockade of (−)-*trans*-Δ^9-tetrahydrocannabinol in mice and dogs. J. Pharm. Pharmacol. **24:** 492–493, 1972.
12. BHARGAVA, H. N.: Time course of the effects of naturally occurring cannabinoids on morphine abstinence syndrome. Pharmacol. Biochem. Behav. **8:** 7–11, 1978.
13. BHARGAVA, H. N.: The effects of thyrotropin-releasing hormone and histidyl-proline diketopiperazine on Δ^9-tetrahydrocannabinol-induced hypothermia. Life Sci **26:** 845–850, 1980.
14. BHARGAVA, H. N., AND MATWYSHYN, G. A.: Influence of thyrotropin releasing hormone and histidyl-proline diketopiperazien on spontaneous activity and analgesia induced by Δ^9-tetrahydrocannabinol in the mouse. Eur. J. Pharmacol. **68:** 147–154, 1980.
15. BHATTACHARYYA, A. K., AULAKH, C. S., PRADHAM, S., GHOSH, P., AND PRADHAM, S. N.: Behavioral and neurochemical effects of Δ^9-tetrahydrocannabinol in rats. Neuropharmacology **19:** 87–95, 1980.
16. BIEGER, D., AND HOCKMAN, C. H.: Differential effects produced by delta-1-tetrahydrocannabinol on lateral geniculate neurones. Neuropharmacology **12:** 269–273, 1973.
17. BIRMINGHAM, M. K.: Reduction by Δ^9-tetrahydrocannabinol in the blood pressure of hypertensive rats bearing regenerated adrenal glands. Br. J. Pharmacol. **48:** 169–171, 1973.
18. BLACK, M. B., WOODS, J. H., AND DOMINO, E. F.: Some effects of (−)-Δ^9-trans-tetrahydrocannabinol and other cannabis derivatives on schedule-controlled behavior. Pharmacologist **12:** 258, 1970.
19. BLOOM, A. S.: Effect of Δ^9-tetrahydrocannabinol on the synthesis of dopamine and norepinephrine in mouse brain synaptosomes. J. Pharmacol. Exp. Ther. **221:** 97–103, 1982.
20. BLOOM, A. S., AND DEWEY, W. L.: A comparison of some pharmacological actions of morphine and Δ^9-tetrahydrocannabinol in the mouse. Psychopharmacology **57:** 243–248, 1978.
21. BLOOM, A. S., DEWEY, W. L., HARRIS, L. S., AND BROSIUS, K. K.: 9-*nor*-9β-Hydroxyhexahydrocannabinol, a cannabinoid with potent antinociceptive activity: Comparison with morphine. J. Pharmacol. Exp. Ther. **200:** 263–270, 1977.
22. BLOOM, A. S., JOHNSON, K. M., AND DEWEY, W. L.: The effects of cannabinoids on body temperature and brain catecholamine synthesis. Res. Commun. Chem. Pathol. Pharmacol. **20:** 51–57, 1978.
23. BLOOM, A. S., AND KIERNAN, C. J.: Interaction of ambient temperature with the effects of Δ^9-tetrahydrocannabinol on brain catecholamine synthesis and plasma corticosterone levels. Psychopharmacology **67:** 215–219, 1980.
24. BORGEN, L. A., AND DAVIS, W. M.: Vehicle and route of administration as parameters affecting operant behavior effects of Δ^9-tetrahydrocannabinol. J. Pharm. Sci. **62:** 479–480, 1973.
25. BORGEN, L. A., AND DAVIS, W. M.: Cannabidiol interaction with Δ^9-tetrahydrocannabinol. Res. Commun. Chem. Pathol. Pharmacol. **7:** 663–670, 1974.
26. BORGEN, L. A., LOTT, G. C., AND DAVIS, W. M.: Cannabis-induced hypothermia: a dose-effect comparison of crude marijuana extract and synthetic Δ^9-tetrahydrocannabinol in male and female rats. Res. Commun. Chem. Pathol. Pharmacol. **5:** 621–626, 1973.
27. BOYD, E. S., BOYD, E. H., AND BROWN, L. E.: The effects of some drugs on an evoked response sensitive to tetrahydrocannabinols. J. Pharmacol. Exp. Ther. **189:** 748–758, 1973.
28. BOYD, E. S., AND MERITT, D. A.: Effects of barbiturates and a tetrahydrocannabinol derivative on recovery cycles of medial lemniscus, thalamus and reticular formation in the cat. J. Pharmacol. Exp. Ther. **151:** 376–384, 1966.
29. BRACS, B., JACKSON, D. M., AND CHESHER, G. B.: The effect of Δ^9-tetrahydrocannabinol on brain amine concentration and turnover in whole rat brain and in various regions of the brain. J. Pharm. Pharmacol. **27:** 713–715, 1975.
30. BRADY, K. T., AND BALSTER, R. L.: The effects of Δ^9-tetrahydrocannabinol alone and in combination with cannabidiol on fixed-interval performance in rhesus monkeys. Psychopharmacology **72:** 21–26, 1980.
31. BRANCH, M. N., DEARING, M. E., AND LEE, D. M.: Acute and chronic effects of Δ^9-tetrahydrocannabinol on complex behavior of squirrel monkeys. Psychopharmacology **71:** 247–254, 1980.
32. BRIGHT, T. P., FARBER, M. O., BROWN, D. J., AND FORNEY, R. B.: Cardiopulmonary toxicity of Δ^9-tetrahydrocannabinol in the anesthetized dog. Toxicol. Appl. Pharmacol. **31:** 100–106, 1975.
33. BROWNE, R. G., AND WEISSMAN, A.: Discriminative stimulus properties of Δ^9-tetrahydrocannabinol: mechanistic studies. J. Clin. Pharmacol. **21:** 2275–2345, 1981.
34. BUONAMICI, M., YOUNG, G. A., AND KHAZAN, N.: Effects of acute Δ^9-THC administration of EEG and EEG power spectra in the rat. Neuropharmacology **21:** 825–829, 1982.
35. BURGESS, J. W., WITT, P. N., PHOEBUS, E., AND WEISBARD, C.: The spacing of rhesus monkey troops changes when a few group members receive Δ^9-THC of *d*-amphetamine. Pharmacol. Biochem. Behav. **13:** 121–124, 1980.
36. BURSTEIN, S.: A survey of metabolic transformations of Δ^1-tetrahydrocannabinol. *In* Cannabinoid Analysis in Physiological Fluids, ed. by J. Vinson, pp. 1–12, American Chemical Society, Washington, DC, 1979.
37. BUXBAUM, D. M.: Analgesic activity Δ^9-tetrahydrocannabinol in the rat and mouse. Psychopharmacology **25:** 275–280, 1972.
38. Cannabis and Health Hazards—Proceedings of an ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use, ed. by K. O. Fehr and H. Kalant. Addiction Research Foundation, Toronto, 1983.
39. CARLINI, E. A.: Tolerance to chronic administration of cannabis sativa (marihuana) in rats. Pharmacology **1:** 135–142, 1968.
40. CARLINI, E. A., HAMAOUI, A., AND MARTZ, R. M. W.: Factors influencing the aggressiveness elicited by marihuana in food-deprived rats. Br. J. Pharmacol. **44:** 794–804, 1972.
41. CARLINI, E. A., AND LINDSEY, C. J.: Effect of sertonergic drugs on the aggressiveness induced by Δ^9-tetrahydrocannabinol in REM-sleep-deprived rats. Braz. J. Med. Biol. Res. **15:** 281–283, 1982.
42. CARLINI, G. R. S., AND CARLINI, E. A.: Effects of strychnine and cannabis sativa (marihuana) on the nucleic acid content in brain of the rat. Med. Pharmacol. Exp. **12:** 21–26, 1965.
43. CARNEY, J. M., BALSTER, R. L., MARTIN, B. R., AND HARRIS, L. S.: Effects of systemic and intraventricular administration cannabinoids on schedule-controlled responding in the squirrel monkey. J. Pharmacol. Exp. Ther. **210:** 399–404, 1979.
44. CAVERO, I., KUBENA, R. K., DZIAK, J., BUCKLEY, J. P., AND JANDHYALA, B. S.: Certain observations on interrelationships between respiratory and cardiovascular effects of (−)-Δ^9-trans-tetrahydrocannabinol. Res. Commun. Chem. Pathol. Pharmacol. **3:** 483–492, 1972.
45. CAVERO, I., SOLOMON, T., BUCKLEY, J. P., AND JANDHYALA, B. S.: Studies on the hypotensive activity of (−)-Δ^9-transtetrahydrocannabinol in anesthetized dogs. Res. Commun. Chem. Pathol. Pharmacol. **6:** 527–540, 1973.
46. CHEREK, D. R., THOMPSON, T., AND KELLY, T.: Chronic Δ^9-tetrahydrocannabinol administration and schedule-induced aggression. Pharmacol. Biochem. Behav. **12:** 305–309, 1980.
47. CHESHER, L. B., AND JACKSON, D. M.: Anticonvulant effects of cannabinoids in mice: Drug interactions within cannabinoids and cannabinoid interactions with phenytoin. Psychopharmacology **37:** 255–264, 1974.
48. CHIU, P., OLSEN, D. M., BORYS, H. K., KARLER, R., AND TURKANIS, S. A.: The influence of Δ^9-tetrahydrocannabinol on cobalt epilepsy in rats. Epilepsia **20:** 365–375, 1979.
49. CHRISTENSEN, C. W., BEST, J. B., AND HERIN, R. A.: Changes seen in the

electroencephalogram and heart rate in the rat after administration of marijuana intravenously. Fed. Proc. **30:** 375, 1971.
50. CHRISTENSEN, H. D., FREUDENTHAL, R. J., GRIDLEY, J. T., ROSENFELD, R., BOEGLI, G., TESTINO, L., BRINE, D. R., PITT, C. B., AND WALL, M. E.: Activity of Δ^9-tetrahydrocannabinol and related compounds in the mouse. Science (Wash. DC) **172:** 165–167, 1971.
51. CONRAD, D. G., ELSMORE, T. F., AND SODETZ, F. J.: Δ^9-Tetrahydrocannabinol: dose-related effects on timing behavior in chimpanzee. Science (Wash. DC) **175:** 547–550, 1972.
52. CONSROE, P., BENEDITO, M. A. C., LEITE, J. R., CARLINI, E. A., AND MECHOULAM, R.: Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. Eur. J. Pharmacol. **83:** 293–298, 1982.
53. CONSROE, P., AND FISH, B. S.: Behavioral pharmacology of tetrahydrocannabinol convulsions in rabbits. Commun. Psychopharmacol. **4:** 287–291, 1980.
54. CONSROE, P., AND FISH, B. S.: Rabbit behavioral model of marijuana psychoactivity in humans. Med. Hypotheses **7:** 1079–1090, 1981.
55. CONSROE, P., JONES, B. C., AND CHIN, L.: Δ^9-Tetrahydrocannabinol, EEG and behavior: the importance of adaptation to the testing milieu. Pharmacol. Biochem. Behav. **3:** 173–177, 1975.
56. CONSROE, P., MARTIN, P., AND EISENSTEIN, D.: Anticonvulsant drug antagonism of Δ^9-tetrahydrocannabinol-induced seizures in rabbits. Res. Commun. Chem. Pathol. Pharmacol. **16:** 1–13, 1977.
57. CONSROE, P., MARTIN, A. R., AND FISH, B. S.: Use of a potential rabbit model for structure-behavioral activity studies of cannabinoids. J. Med. Chem. **25:** 596–599, 1982.
58. COPER, H.: Pharmacology and toxicology of cannabis. *In* Handbook of Experimental Pharmacology, ed. by F. Hoffmeister and G. Stille, vol. 55, pp. 135–158, Springer Verlag, Berlin, 1981.
59. CRADOCK, J. C., DAVIGNON, J. P., LITTERST, C. L., AND GUARINO, A. M.: An intravenous formulation of Δ^9-tetrahydrocannabinol using a non-ionic surfactant. J. Pharm. Pharmacol. **25:** 345, 1973.
60. CRONIN, C. M., SALLAN, S. E., GELBER, R., LUCAS, V. S., AND LASZLO, J.: Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy. J. Clin. Pharmacol. **21:** 435–505, 1981.
61. CUTLER, M. G., AND MACKINTOSH, J. H.: Cannabis and Δ^9-tetrahydrocannabinol. Effects on elements of social behavior in mice. Neuropharmacology **23:** 1091–1097, 1984.
62. DALTERIO, S. L.: Perinatal or adult exposure to cannabinoids alters male reproductive functions in mice. Pharmacol. Biochem. Behav. **12:** 143–153, 1980.
63. DALTERIO, S. L., STEGER, R. W., AND BARTKE, A.: Maternal or paternal exposure to cannabinoids affects central neurotransmitter levels and reproductive function in male offspring. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Agents, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 411–425, Academic Press, New York, 1984.
64. DALTON, W. S., MARTZ, R., LEMBERGER, L., RODDA, B. E., AND FORNEY, R. B.: Influence of cannabidiol on Δ^9-tetrahydrocannabinol effects. Clin. Pharmacol. Ther. **19:** 300–309, 1976.
65. DARLEY, C. F., AND TINKLENBERG, J. R.: Marihuana and memory. *In* Marijuana Effects on Human Behavior, ed. by L. L. Miller, pp. 73–102, Academic Press, New York, 1974.
66. DAVIES, A., AND GRAHAM, J. D. P.: The mechanism of action of Δ^9-tetrahydrocannabinol on body temperature in mice. Psychopharmacology **69:** 299–305, 1980.
67. DAVIS, W., AND BORGEN, L.: Effects of cannabidiol and Δ^9-tetrahydrocannabinol on operant behavior. Res. Commun. Chem. Pathol. Pharmacol. **9:** 453–462, 1974.
68. DAVIS, W. M., AND HATOUM, N. S.: Neurobehavioral actions of cannabichromene and interactions with Δ^9-tetrahydrocannabinol. Gen. Pharmacol. **14:** 247–252, 1983.
69. DAVIS, W. M., MORETON, J. E., KING, W. T., AND PACE, H. B.: Marihuana on locomotor activity: biphasic effect and tolerance development. Res. Commun. Chem. Pathol. Pharmacol. **3:** 29–35, 1972.
70. DE LONG, F. L., AND LEVY, B. I.: A model of attention describing the cognitive effects of marihuana. *In* Marihuana Effects on Human Behavior, ed. by L. L. Miller, pp. 103–120, Academic Press, New York, 1974.
71. DENEAU, G. A., AND KAYMAKCALAN, S.: Physiological and psychological dependence to synthetic Δ^9-tetrahydrocannabinol (THC) in rhesus monkeys. Pharmacologist **13:** 246, 1971.
72. DE SOUZA, AND NETO, J. P.: Effects of anti-acetylcholine drugs on aggressive behavior induced by cannabis sativa in REM sleep-deprived rats. J. Pharm. Pharmacol. **30:** 591–592, 1978.
73. DEWEY, W. L., HARRIS, L. S., HOWES, J. F., KENNEDY, J. S., GRANCHELLI, F. E., PARS, H. G., AND RAZDAN, R. K.: Pharmacology of some marijuana constituents and two heterocyclic analogues. Nature (Lond.) **226:** 1265–1267, 1970.
74. DEWEY, W. L., HARRIS, L. S., AND KENNEDY, J. S.: Some pharmacological and toxicological effects of 1-trans-Δ^8- and 1-trans-Δ^9-tetrahydrocannabinol in laboratory rodents. Arch. Int. Pharmacol. Ther. **196:** 133–145, 1972.
75. DEWEY, W. L., JENKINS, J., O'ROURKE, T., AND HARRIS, L. S.: The effects of chronic administration of trans-Δ^9-tetrahydrocannabinol on behavior and the cardiovascular system of dogs. Arch. Int. Pharmacol. Ther. **198:** 118–131, 1972.
76. DEWEY, W. L., JOHNSON, K. M., AND BLOOM, A. S.: Interactions of active constituents of marijuana with other drugs in the neuron. Ann. NY Acad. Sci. **281:** 190–197, 1976.
77. DEWEY, W. L., MARTIN, B. R., BECKNER, J. S., AND HARRIS, L. S.: A comparison of the subcellular distribution of cannabinoids in the brains of tolerant and nontolerant dogs, rats and mice following the injection of radiolabelled Δ^9-THC. *In* Marihuana: Chemistry, Biochemistry, and Cellular Effects, ed. by G. G. Nahas, pp. 349–365, Springer-Verlag, New York, 1976.
78. DEWEY, W. L., MARTIN, B. R., AND MAY, E. L.: Cannabinoid stereoisomers: pharmacological effects. *In* Handbook of Stereoisomers: Drugs in Psychopharmacology, ed. by D. F. Smith, pp. 317–326, CRC Press, Boca Raton, FL, 1984.
79. DEWEY, W. L., MCMILLAN, D. E., HARRIS, L. S., AND TURK, R. F.: Distribution of radioactivity in brain of tolerant and nontolerant pigeons treated with ^{3}H-Δ^9-tetrahydrocannabinol. Biochem. Pharmacol. **22:** 399–404, 1973.
80. DEWEY, W. L., PENG, T.-C., AND HARRIS, L. S.: The effect of 1-trans-Δ^9-tetrahydrocannabinol on the hypothalamo-hypophyseal-adrenal axis of rats. Eur. J. Pharmacol. **12:** 382–384, 1970.
81. DIASIO, R. B., ETLINGER, D. S., AND SATTERWHITE, B. E.: Oral levonantradol in the treatment of chemotherapy-induced emesis: Preliminary observations. J. Clin. Pharmacol. **21:** 815–835, 1981.
82. DIXIT, V. P., AND LOHIYA, N. K.: Effects of cannabis extract in the response of accessory sex organs of adult male mice to testosterone. Indian J. Physiol. Pharmacol. **19:** 98–100, 1975.
83. DIXIT, V. P., SHARMA, V. N., AND LOHIYA, N. K.: The effects of chronically administered cannabis extract on the testicular function of mice. Eur. J. Pharmacol. **26:** 111–114, 1974.
84. DOHERTY, P. A., MCCARTHY, L. E., AND BORISON, H. L.: Respiratory and cardiovascular depressant effects of nabilone, N-methyllevonantradol and Δ^9-tetrahydrocannabinol in anesthetized cats. J. Pharmacol. Exp. Ther. **227:** 508–516, 1983.
85. DOMINO, E. F., DONELSON, A. C., AND TUTTLE, T.: Effects of Δ^9-tetrahydrocannabinol on regional brain acetylcholine. *In* Cholinergic Mechanisms and Psychopharmacology, ed. by D. J. Jenden, pp. 673–678, Plenum Publishing Company, New York, 1978.
86. EDERY, H.: Models to predict cannabinoid-induced disturbances. Arch. Toxicol. Suppl. **6:** 91–103, 1983.
87. EDERY, H., GREENFELD, Y., PORATH, G., BEN-ZRI, Z., SHANI, A., AND MECHOULAM, R.: Structure activity relationships in the tetrahydrocannabinol species. Arzneim. Forsch. **22:** 1995–2003, 1972.
88. ELSMORE, T. F., AND FLETCHER, G. V.: Δ^9-Tetrahydrocannabinol: aversive effects in rat at high doses. Science (Wash. DC) **175:** 911–912, 1971.
89. ENGLERT, L. F., HO, B. T., AND TAYLOR, D.: Effects of Δ^9-tetrahydrocannabinol on reserpine-induced hypothermia in rats. Br. J. Pharmacol. **49:** 243–250, 1973.
90. ESPLIN, B., AND CAPEK, R.: Quantitative characterization of THC and ethanol interaction. Res. Commun. Chem. Pathol. Pharmacol. **15:** 199–202, 1976.
91. FEHR, K., KALANT, H., AND LEBLANC, A. E.: Residual learning deficit after heavy exposure to cannabis or alcohol in rats. Science (Wash. DC) **193:** 1249–1251, 1976.
92. FERRARO, D. P., AND GRILLY, D. M.: Lack of tolerance to Δ^9-tetrahydrocannabinol in chimpanzees. Science (Wash. DC) **179:** 490–492, 1972.
93. FERRARO, D. P., AND GRISHAM, M. G.: Tolerance to the behavioral effects of marijuana in chimpanzees. Physiol. Behav. **9:** 49–54, 1972.
94. FINK, M.: Effects of acute and chronic inhalation of hashish, marijuana and Δ^9-tetrahydrocannabinol on brain electrical activity in man: evidence for tissue tolerance. Ann. NY Acad. Sci. **282:** 387–398, 1976.
95. FINK, M., VOLAVKA, J., PANAGIOTOPOULOS, C. P., AND STEFANIS, C.: Quantitative EEG studies of marihuana, Δ^9-THC and hashish in man. *In* Pharmacology in Marihuana, ed. by M. C. Braude and S. Szara, pp. 383–391, Raven Press, New York, 1976.
96. FISHBURNE, P. M., ABELSON, H. L., AND CISIN, I.: Natural Survey on Drug Abuse: Main Findings 1979. National Institute on Drug Abuse, Rockville, MD, 1980.
97. FORD, R. D., BALSTER, R. L., DEWEY, W. L., AND BECKNER, J. S.: Δ^9-THC and 11-OH-Δ^9-THC: behavioral effects and relationship to plasma and brain levels. Life Sci. **20:** 1993–2004, 1977.
98. FORD, R. D., BALSTER, R. L., DEWEY, W. L., ROSECRANS, J. A., AND HARRIS, L. S.: The discriminative stimulus properties of Δ^9-tetrahydrocannabinol: generalization to some metabolites and congeners. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and W. E. Willette, pp. 545–561, Academic Press, New York, 1984.
99. FORNEY, R. B., AND KIPLINGER, G. F.: Toxicology and pharmacology of marijuana. Ann NY Acad. Sci. **191:** 74–82, 1971.
100. FOY, M. R., TEYLER, T. J., AND VARDARIS, R. M.: Δ^9-THC and 17β-estradiol in hippocampus. Brain Res. Bull. **8:** 341–345, 1982.
101. FREDERICKS, A. B., AND BENOWITZ, N. L.: An abstinence syndrome following chronic administration of Δ^9-tetrahydrocannabinol in rhesus monkeys. Psychopharmacology **71:** 201–202, 1980.

102. FRIED, P. A., AND HUSBAND, C. A.: Depth perception in rats following acute or chronic injections of DL-Δ^9-tetrahydrocannabinol. Life Sci. **12:** 289–295, 1973.
103. FRIEDMAN, E., AND GERSHON, S.: Effects of Δ^8-THC on alcohol-induced sleeping time in the rat. Psychopharmacology **39:** 193–198, 1974.
104. FRIEDMAN, E., HANIN, I., AND GERSHON, S.: Effect of tetrahydrocannabinols on ^{3}H-acetylcholine biosynthesis in various rat brain slices. J. Pharmacol. Exp. Ther. **196:** 339–345, 1976.
105. FUJIMOTO, G. I., KREY, L. C., AND MACEDONIA, L.: Effect of chronic cannabinoid treatment on androgenic stimulation of male accessory sex organs in the rat. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 401–410, Academic Press, New York, 1984.
106. FUJIWARA, M., IBII, N., KATAOKA, Y., AND UEKI, S.: Effects of psychotropic drugs on Δ^9-tetrahydrocannabinol-induced long-lasting muricide. Psychopharmacology **68:** 7–13, 1980.
107. FUJIWARA, M., AND UEKI, S.: The course of aggressive behavior induced by a single injection of Δ^9-tetrahydrocannabinol and its characteristics. Physiol. Behav. **22:** 535–539, 1979.
108. GALLAGER, D. W., SANDERS-BUSH, E., AND SULSER, F.: Dissociation between behavioral effects and changes in metabolism of cerebral serotonin following Δ^9-tetrahydrocannabinol. Psychopharmacology **26:** 337–345, 1972.
109. GASCON, A. L., AND PERES, M. T.: Effect of Δ^9- and Δ^8-tetrahydrocannabiol on the peripheral autonomic nervous system *in vitro*. Can. J. Physiol. Pharmacol. **51:** 12–21, 1973.
110. GAYER, H.: Pharmakological wertbestimmung von orientalischern haschisch und herba cannabis indicae. Arch. Exp. Pathol. Pharmacol. **129:** 312–318, 1929.
111. GILL, E. W., PATON, W. D. M., AND PERTWEE, R. G.: Preliminary experiments on the chemistry and pharmacology of cannabis. Nature (Lond.) **228:** 135–137, 1970.
112. GOLDSTEIN, F. J., VERNOT, E. T., AND STRAHLENDORF, H. K.: Potentiation of catecholamine inhibition of ganglionic transmission by Δ^9-tetrahydrocannabinol. Neuropharmacology **16:** 71–72, 1977.
113. GRAHAM, J. D. P., LEWIS, M. J., AND LI, D. M. F.: The effect of Δ^1-tetrahydrocannabinol on the release of ^{3}H-(−)-noradrenaline from the isolated vas deferens of the rat. Br. J. Pharmacol. **52:** 233–236, 1974.
114. GRUNFELD, Y., AND EDERY, H.: Psychopharmacological activity of the active constituents of hashish and some related cannabinoids. Psychopharmacology **14:** 200–210, 1969.
115. HARCLERODE, J., BIRD, L., SAWYER, H., BERGER, W., MOONEY, R., AND SMITH, R.: Sex hormone levels in adult rats injected with Δ^9-tetrahydrocannabinol and phencyclidine. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 441–452, Academic Press, New York, 1984.
116. HARRIS, L. S., DEWEY, W. L., AND RAZDAN, R. K.: Handbook of experimental Pharmacology, vol. 45, Cannabis, Its Chemistry, Pharmacology and Toxicology, ed. by W. R. Martin, pp. 371–429, Springer-Verlag, Berlin, 1977.
117. HARRIS, R. T., WATERS, W. H., AND MCLENDON, D.: Evaluation of reinforcing capability of Δ^9-tetrahydrocannabinol. Psychopharmacology **37:** 23–29, 1974.
118. HATOUM, N. S., DAVIS, W. M., ELSOHLY, M. A., AND TURNER, C. E.: Cannabichromene and Δ^9-tetrahydrocannabinol: interactions relative to lethality, hypothermia, and hexobarbital hypnosis. Gen. Pharmacol. **12:** 357–362, 1981.
119. Health Consequences of Acute and Chronic Marihuana Use, ed. by M. O. Maykut, Pergamon Press, New York, 1984.
120. HEATH, R. E., FITZJARRELL, A. T., FONTANA, C. J., AND CAREY, R. E.: *Cannabis sativa*: effects on brain function and ultrastructure in rhesus monkeys. Biol. Psychiatry **15:** 657–690, 1980.
121. HERSHKOWITZ, M., AND SZECHTMAN, H.: Pretreatment with Δ^1-tetrahydrocannabinol and psychoactive drugs: effects on uptake of biogenic amines and on behavior. Eur. J. Pharmacol. **59:** 267–276, 1979.
122. HILLARD, C. J., FARBER, N. E., HAGEN, T. C., AND BLOOM, A. S.: The effects of Δ^9-tetrahydrocannabinol on serum thyrotropin levels in the rat. Pharmacol. Biochem. Behav. **20:** 547–550, 1984.
123. HINE, B.: Morphine and Δ^9-tetrahydrocannabinol: two-way cross tolerance for antinociceptive and heart-rate responses in the rat. Psychopharmacology **87:** 34–38, 1985.
124. HINE, B., FRIEDMAN, E., TORRELIO, M., AND GERSHON, S.: Morphine-dependent rats: blockade of precipitated abstinence by tetrahydrocannabinol. Science (Wash, DC) **187:** 443–445, 1974.
125. HO, B. T., TAYLOR, D., ENGLERT, L. F., AND MCISAAC, W. M.: Neurochemical effects of L-Δ^9-tetrahydrocannabinol in rats following repeated inhalation. Brain Res. **31:** 233–236, 1971.
126. HOCKMAN, C. H., PERRIN, R. G., AND KALANT, H.: Electroencephalographic and behavioral alterations produced by Δ^1-tetrahydrocannabinol. Science (Wash. DC) **172:** 968–970, 1971.
127. HOLLISTER, L. E.: Clinical pharmacology of marihuana. *In* Research Advances in Alcohol and Drug Problems, ed. by R. J. Gibbons, Y. Israel, H. Kalant, R. E. Popham, W. Schmidt, and R. C. Smart, vol. 1, pp. 243–266, John Wiley and Sons, New York, 1974.
128. HOLLISTER, L. E.: Marihuana in man: three years later. Science (Wash. DC) **172:** 21–29, 1971.
129. HOLLISTER, L. E.: Structure-activity relationships in man of cannabis constituents and homologues and metabolites of Δ^9-tetrahydrocannabinol. Pharmacology (Basel) **11:** 3–11, 1974.
129a. HOLLISTER, L. E.: Health aspects of cannabis. Pharmacol. Rev. **38:** 1–20, 1986.
130. HOLLISTER, L. E., AND GILLESPIE, B. A.: Action of Δ^9-tetrahydrocannabinol: an approach to the active metabolite hypothesis. Clin. Pharmacol. Ther. **18:** 714–719, 1975.
131. HOLLISTER, L. E., RICHARDS, R. K., AND GILLESPIE, H. K.: Comparison of tetrahydrocannabinol and synhexyl in man. Clin. Pharmacol. Ther. **9:** 783, 1968.
132. HOLLISTER, L. E., SHERWOOD, S. L., AND CAVASINO, A.: Marihuana and the human electroencephalogram. Pharmacol. Res. Commun. **2:** 305–308, 1970.
133. HOLTZMAN, D., LOVELL, R. A., JAFFE, J. H., AND FRIEDMAN, D. X.: 1-Δ^9-Tetrahydrocannabinol: neurochemical and behavioral effects in the mouse. Science (Wash. DC) **163:** 1464–1467, 1969.
134. HONIG, W. K.: Working memory and the temporal map. *In* Information Processing in Animals: Memory Mechanisms, ed. by N. E. Spear and R. R. Miller, pp. 167–197, Erlbaum Assoc., New Jersey, 1981.
135. HOSKO, M. J., SCHNELING, W. T., AND HARDMAN, H. F.: Δ^9-Tetrahydrocannabinol: site of action for autonomic effects. *In* The Cannabinoids: Chemical Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 635–648, Academic Press, New York, 1984.
136. HOWES, J., AND OSGOOD, P.: The effect of Δ^9-tetrahydrocannabinol on the uptake and release of ^{14}C-dopamine from crude striatal synaptosomal preparations. Neuropharmacology **43:** 1109–1114, 1974.
137. HUSAIN, S., AND LAMB, M. W.: Possible mechanism for the cellular effects of marijuana on male reproductive function. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 453–470, Academic Press, New York, 1984.
138. IZQUIERDO, I., AND NASELLO, A. G.: Effects of cannabidiol and of diphenylhydantoin on the hippocampus and on learning. Psychopharmacology **31:** 167–175, 1973.
139. IZQUIERDO, I., ORSINGER, O. A., AND BERARDI, A. C.: Effects of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. Psychopharmacology **28:** 95–102, 1973.
140. JOHNSON, K. M., DEWEY, W. L., AND HARRIS, L. S.: Some structural requirements for inhibition of high-affinity synaptosomal serotonin uptake by cannabinoids. Mol. Pharmacol. **12:** 345–352, 1976.
141. JOHNSON, K. M., DEWEY, W. L., AND HO, B. T.: *In vitro* alteration of the subcellular distribution of ^{3}H-reserpine in the rat forebrain by Δ^9-tetrahydrocannabinol. Res. Commun. Chem. Pathol. Pharmacol. **15:** 665–671, 1976.
142. JOHNSON, K. M., HO, B. T., AND DEWEY, W. L.: Effects of Δ^9-tetrahydrocannabinol on neurotransmitter accumulation and release mechanisms in rat forebrain synaptosomes. Life Sci. **19:** 347–356, 1976.
143. JONES, R. T.: Cardiovascular effects of cannabinoids. *In* Marihuana '84, ed. by D. J. Harvey, pp. 325–334, IRL Press, Oxford, 1985.
144. JONES, R. T., AND STONE, G. R.: Psychological studies of marijuana and alcohol in man. Psychopharmacology **18:** 108–117, 1970.
145. KALANT, H., AND LEBLANC, A. E.: Effect of acute and chronic pretreatment with Δ^1-tetrahydrocannabinol on motor impairment by ethanol in the rat. Can. J. Physiol. Pharmacol. **52:** 291–297, 1974.
146. KARLER, R., CELY, W., AND TURKANIS, S. A.: Anticonvulsant properties of Δ^9-tetrahydrocannabinol and other cannabinoids. Life Sci **15:** 931–947, 1974.
147. KARLER, R., AND TURKANIS, S. A.: Cannabis and epilepsy. *In* Marijuana: Biological Effects, ed. by G. G. Nahas and W. D. M. Paton, pp. 619–641, Pergamon Press, Oxford, 1979.
148. KARLER, R., AND TURKANIS, S. A.: Subacute cannabinoid treatment: anticonvulsant activity and withdrawal excitability in mice. Br. J. Pharmacol. **68:** 479–484, 1980.
149. KARLER, R., AND TURKANIS, S. A.: The cannabinoids as potential antiepileptics. J. Clin. Pharmacol. **21:** 437S–448S, 1981.
150. KARNIOL, I. G., AND CARLINI, E. A.: Pharmacological interaction between cannabidiol and Δ^9-tetrahydrocannabinol. Psychopharmacology **33:** 53–70, 1973.
151. KAWASAKI, H., WATANABE, S., AND UEKI, S.: Effects of chronic administration of Δ^9-tetrahydrocannabinol on the cardiovascular system and pressor and behavioral responses to brain stimulation in freely-moving rats. Eur. J. Pharmacol. **65:** 63–70, 1980.
152. KAYMAKCALAN, S.: Nine physiological and psychological dependence on THC in rhesus monkeys. *In* Cannabis and Its Derivatives, ed. by W. D. M. Paton and J. Crown, pp. 142–149, Oxford University Press, London, 1972.
153. KAYMAKCALAN, S., AYHAN, I. H., AND TULUNAY, F. C.: Naloxone-induced or postwithdrawal abstinence signs in Δ^9-tetrahydrocannabinol-tolerant rats. Psychopharmacology **55:** 243–249, 1977.
154. KAYMAKCALAN, S., AND SIVIL, S.: Lack of tolerance to the bradycardic effect of Δ^9-tetrahydrocannabinol. Pharmacology (Basel) **12:** 290–295, 1974.

155. KOCHAR, M. S., AND HOSKO, M. J.: Electrocardiographic effects of marihuana. J. Am. Med. Assoc. **225:** 25–27, 1973.
156. KOE, B. K., MILNE, G. M., WEISSMAN, A., JOHNSON, M. R., AND MELVIN, L. S.: Enhancement of brain ^{3}H-flunitrazepam binding and analgesic activity of synthetic cannabimimetics. Eur. J. Pharmacol. **109:** 201–212, 1985.
157. KOSERSKY, D. S., DEWEY, W. L., AND HARRIS, L. S.: Antipyretic, analgesic and anti-inflammatory effects of Δ^9-tetrahydrocannabinol in the rat. Eur. J. Pharmacol. **24:** 1–7, 1973.
158. KOUKKOU, M., AND LEHMANN, D.: Human EEG spectra before and during cannabis hallucinations. Biol. Psychiatry **11:** 663–677, 1976.
159. KUDRIN, A. N., AND DAVYDOA, O. N.: Elimination of hashish intoxication with phenitrone in dogs. Farmakol. Toksikol. (Mosc.) **31:** 549–552, 1968.
160. KUMAR, M. S. A., AND CHEN, C. L.: Effect of an acute dose of Δ^9-THC on hypothalamic luteinizing hormone releasing hormone and met-enkephalin content and serum levels of testosterone and corticosterone in rats. Subst. Alcohol Actions/Misuse **4:** 37–43, 1983.
161. KUMAR, M. S. A., PATEL, V., AND MILLARD, W. J.: Effect of chronic administration of Δ^9-tetrahydrocannabinol on the endogenous opioid peptide and catecholamine levels in the diencephalon and plasma of the rat. Subst. Alcohol Actions/Misuse **5:** 201–210, 1984.
162. LANDAUER, M. R., BALSTER, R. L., AND HARRIS, L. S.: Attenuation of cyclophosphamide-induced taste aversions in mice by prochlorperazine, Δ^9-tetrahydrocannabinol, nabilone, and levonantradol. Pharmacol. Biochem. Behav. **23:** 259–266, 1985.
163. LAPA, A. J., SAMPAIO, C. A. M., TIMO-IARIA, C., AND VALLE, J. R.: Blocking action of tetrahydrocannabinol on transmission in the trigeminal system of the cat. J. Pharm. Pharmacol. **20:** 192–193, 1968.
164. LEITE, J. R., AND CARLINI, E. A.: Failure to obtain "cannabis directed behavior" and abstinence syndrome in rats chronically treated with cannabis sativa extracts. Psychopharmacology **36:** 133–145, 1974.
165. LEMBERGER, L.: Clinical evaluation of cannabinoids in the treatment of disease. *In* Marihuana '84, ed. by D. J. Harvey, pp. 673–680, IRL Press, Oxford, 1985.
166. LEMBERGER, L.: Potential therapeutic usefulness of marihuana. Annu. Rev. Pharmacol. Toxicol. **20:** 151–172, 1980.
167. LEMBERGER, L., MCMAHON, R., AND ARCHER, R.: The role of metabolic conversion on the mechanisms of actions of cannabinoids. *In* Pharmacology of Marihuana, ed. by M. C. Braude, and S. Szara, vol. 1, pp. 125–133, Raven Press, New York, 1976.
168. LEMBERGER, L, AND RUBIN, A.: The physiological disposition of marihuana in man. Life Sci. **17:** 1637–1642, 1974.
169. LEWIS, E. G., DUSTMAN, R. E., PETERS, B. A., STRAIGHT, R. C., AND BECK, E. C.: The effects of varying doses of Δ^9-tetrahydrocannabinol on the human visual and somatosensory evoked response. Electroencephalogr. Clin. Neurophysiol. **35:** 347–354, 1973.
170. LOEWE, S.: The chemical basis of marihuana activity. J. Pharmacol. Exp. Ther. **84:** 78–81, 1945.
171. LOMAX, P., AND CAMPBELL, C.: Phenitrone and marihuana induced hypothermia. Experientia (Basel) **27:** 1191–1192, 1971.
172. LOW, M. D., KLONOFF, H., AND MARCUS, A.: The neurophysiological basis of marijuana experience. Can. Med. Assoc. J. **108:** 157–165, 1973.
173. MACLEAN, K. I., AND LITTLETON, J. M.: Environmental stress as a factor in the response of rat brain catecholamine metabolism to Δ^8-tetrahydrocannabinol. Eur. J. Pharmacol. **41:** 171–182, 1977.
174. MAITRE, L., STAEHELIN, M., AND BEIN, H. J.: Effect of an extract of cannabis and of some cannabinols on catecholamine metabolism in rat brain and heart. Agents Actions **1:** 136–143, 1970.
175. MANNING, F. J., MCDONOUGH, J. H., JR., ELSMORE, T. F., SALLER, C., AND SODETZ, F. J.: Inhibition of normal growth by chronic administration of Δ^9-tetrahydrocannabinol. Science (Wash. DC) **174:** 424–426, 1971.
176. MANNO, J. E., MANNO, B. R., KIPLINGER, G. F., AND FORNEY, R. B.: Motor and mental performance with marihuana: relationship to administered dose of Δ^9-tetrahydrocannabinol and its interaction with alcohol. *In* Marihuana: Effects on Human Behavior, ed. by L. L. Miller, Academic Press, New York, 1974.
177. Marihuana and Health, Institute of Medicine, National Academy of Sciences, National Academy Press, 1982.
178. Marihuana Effects on the Endocrine and Reproductive Systems, ed . by M. C. Braude and J. P. Ludford, National Institute of Drug Abuse Research Monograph 44, Rockville, MD, 1984.
179. Marihuana in Science and Medicine, ed by G. C. Nahas, Raven Press, New York, 1984.
180. MARKS, B. H.: Δ^9-Tetrahydrocannabinol and leuteinizing hormone secretion. Prog. Brain Res. **39:** 331–338, 1973.
181. MARTIN, B. R.: Characterization of the antinociceptive activity of intravenously administered Δ^9-tetrahydrocannabinol in mice. *In* Marihuana '84, ed. by D. J. Harvey, pp. 685–692, IRL Press, Oxford, 1985.
182. MARTIN, B. R.: Structural requirements for cannabinoid-induced antinociceptive activity in mice. Life Sci. **36:** 1523–1530, 1985.
182a. MARTIN, B. R.: Cellular effects of cannabinoids. Pharmacol. Rev. **38:** 45–74, 1986.
183. MARTIN, B. R., DEWEY, W. L., ACETO, M. D., ADAMS, M. D., EARNHARDT, J. T., AND CARNEY, J. M.: A potent antinociceptive cannabinoid which lacks opiate substitution properties in monkeys. Res. Commun. Chem. Pathol. Pharmacol. **16:** 187–190, 1977.
184. MARTIN, B. R., DEWEY, W. L., HARRIS, L. S., AND BECKNER, J. S.: ^{3}H-Δ^9-tetrahydrocannabinol tissue and subcellular distribution in the central nervous system and tissue distribution in peripheral organs of tolerant and nontolerant dogs. J. Pharmacol. Exp. Ther. **196:** 128–144, 1976.
185. MARTIN, B. R., DEWEY, W. L., HARRIS, L. S., AND BECKNER, J. S.: ^{3}H-Δ^9-tetrahydrocannabinol distribution in pregnant dogs and their fetuses. Res. Commun. Chem. Pathol. Pharmacol. **17:** 457–470, 1977.
186. MARTIN, B. R., HARRIS, L. S., AND DEWEY, W. L.: Pharmacological activity of Δ^9-THC metabolites and analogs of CBD, Δ^9-THC and Δ^9-THC. *In* The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 523–544, Academic Press, New York, 1984.
187. MARTIN, P., AND CONSROE, P.: Cannabinoid induced behavioral convulsions in rabbits. Science (Wash. DC) **194:** 965–967, 1976.
188. MASUR, J., AND KHAZAN, N.: Induction by cannabis sativa (marihuana) of rhythmic spike discharges overriding REM sleep electrocortiogram in the rat. Life Sci. **9:** 1275–1280, 1970.
189. MAZURKIEWIEZ-KWILECKI, I. M., AND FILEZEWSKI, M.: The effects of chronic treatment with Δ^9-tetrahydrocannabinol on catecholamine synthesis in the rat. Psychopharmacology **33:** 71–79, 1973.
190. MCCARTHY, L. E., FLORA, K. P., AND VISHNUVAJJALA, B. R.: Disparities in the antiemetic and behavioral actions of Δ^9-tetrahydrocannabinol and its 11-hydroxy metabolite in the cat. Res. Commun. Subst. Abuse **5:** 103–114, 1984.
191. MCMILLAN, D. E.: Behavioral pharmacology of the tetrahydrocannabinols. *In* Advances in Behavioral Pharmacology, ed. by T. Thompson and P. B. Dews, vol. 1, pp. 1–34, Academic Press, New York, 1977.
192. MCMILLAN, D. E., AND DEWEY, W. L.: On the mechanism of tolerance to Δ^9-THC. *In* Current Research in Marijuana, ed. by M. F. Lewis, pp. 97–114, Academic Press, New York, 1972.
193. MCMILLAN, D. E., DEWEY, W. L., AND HARRIS, L. S.: Characteristics of tetrahydrocannabinol tolerance. Ann. NY Acad. Sci. **191:** 83–99, 1971.
194. MCMILLAN, D. E., DEWEY, W. L., TURK, R. F., HARRIS, L. S., AND MCNEIL, J. H., JR.: Blood levels of ^{3}H-Δ^9-tetrahydrocannabinol and its metabolites in tolerant and nontolerant pigeons. Biochem. Pharmacol. **22:** 383–397, 1973.
195. MCMILLAN, D. E., FORD, R. D., FRANKENBIEM, J. M., HARRIS, R. A., AND HARRIS, L. S.: Tolerance to active constituents of marihuana. Arch. Int. Pharmacodyn. Ther. **198:** 132–144, 1972.
196. MCMILLAN, D. E., HARRIS, L. S., FRANKENBEIM, J. M., AND KENNEDY, J. S.: *l*-Δ^9-Tetrahydrocannabinol in pigeons. Science (Wash. DC) **169:** 501–503, 1970.
197. MECHOULAM, R., AND EDERY, H.: Structure-activity relationships in the cannabinoid series. *In* Marihuana Chemistry, Pharmacology, Metabolism and Clinical Effects, ed. by R. Mechoulam, pp. 101–136, Academic Press, New York, 1973.
198. MECHOULAM, R., LANDER, N., SREBNIK, M., ZAMIR, I., BREUER, A., SHALITA, B., DIKSTEIN, S., CARLINI, E. A., LEITE, J. R., EDERY, H., AND PORATH, G.: Recent advances in the use of cannabinoids as therapeutic agents. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 777–793, Academic Press, New York, 1984.
199. MECHOULAM, R., MCCALLUM, N. K., AND BURSTEIN, S.: Recent advances in the chemistry and biochemistry of cannabis. Chem. Rev. **76:** 75–112, 1976.
200. Medical Letter report on Synthetic marijuana for nausea and vomiting due to cancer chemotherapy. **27:** 97–98, 1985.
201. MERARI, A., BARAK, A., AND PLAVES, M.: Effects of Δ-1,2-tetrahydrocannabinol on copulation in the male rat. Psychopharmacology **28:** 243–246, 1973.
202. MILLER, L. L., DREW, W. G., AND JOYCE, P.: Δ^9-THC: effect on acquisition and retention of a one-trial passive avoidance response. Behav. Biol. **8:** 421–426, 1973.
203. MILNE, G. M., KOE, B. K., AND JOHNSON, M. R.: Stereospecific and potent analgesic activity for nantradol. A structurally novel, cannabinoid-related analgesic. *In* Problems of Drug Dependence, 1979, ed. by L. S. Harris, pp. 84–92, National Institute of Drug Abuse Research Monograph 27, Rockville, MD, 1979.
204. MONTGOMERY, S. P., MOSS, D. E., AND MANDERSCHEID, P. Z: Tetrahydrocannabinol and levonantradol effects on extrapyramidal motor behavior: neuroanatomical location and hypothesis of mechanism. *In* Marihuana '84, ed. by D. J. Harvey, pp. 295–302, IRL Press, Oxford, 1985.
205. MORETON, J., AND DAVIS, W. M.: Electroencephalographic study of effects of tetrahydrocannabinol on sleep in the rat. Neuropharmacology **12:** 897–907, 1973.
206. MOSS, D. E., MCMASTER, S. B., AND ROGERS, J.: Tetrahydrocannabinol potentiates reserpine-induced hypokinesia. Pharmacol. Biochem. Behav. **15:** 779–783, 1981.
207. MUNSON, A. E., AND FEHR, K. O.: Immunological effects of cannabis. *In* Adverse Health and Behavioral Consequences of Cannabis Use, ed. by K. O. Fehr and H. Kalant, pp. 257–353, Addiction Research Foundation, Toronto, 1983.
208. MUNSON, A. E., HARRIS, L. S., FRIEDMAN, M. A., DEWEY, W. L., AND

CARCHMAN, R. A.: Antineoplastic activity of cannabinoids. J. Natl. Cancer Inst. **55:** 597–602, 1975.
209. MUSTY, R. E., LINDSEY, C. J., AND CARLINI, E. A.: 6-Hydroxydopamine and the aggressive behavior induced by marihuana in REM sleep-deprived rats. Psychopharmacology **48:** 175–179, 1976.
210. Deleted in proof.
211. NEWMAN, L. M., LUTZ, M. P., GOULD, M. H., AND DOMINO, E. F.: Δ^9-Tetrahydrocannabinol and ethyl alcohol evidence for cross-tolerance in the rat. Science (Wash. DC) **175:** 1022–1023, 1971.
212. NOGAWA, T., SHINOHARA, O., HENRICH, R. T., AND MORISHIMA, A.: The effects of chronic administration of Δ^9-tetrahydrocannabinol on the early embryonic development of mice. *In* The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 345–357, Academic Press, New York, 1984.
213. OKEY, A. B., AND BONDY, G. P.: Δ^9-Tetrahydrocannabinol and 17-β-estradiol bind to different macromolecules in estrogen target tissues. Science (Wash. DC) **200:** 312–314, 1978.
214. OKEY, A., BONDY, G. P., SOLOMON, J., AND COCCHITA, M. A.: Is Δ^9-tetrahydrocannabinol estrogenic? Science (Wash. DC) **195:** 904–906, 1976.
215. OSGOOD, P., AND HOWES, J.: Cannabinoid induced changes in mouse striatal homovanillic acid and dihydroxyphenylacetic acid: the effects of amphetamine and L-DOPA. Res. Commun. Chem. Pathol. Pharmacol. **9:** 621–631, 1974.
216. PATEL, V., BORYSENKO, M., AND KUMAR, M. S. A.: Effect of Δ^9-THC on brain and plasma catecholamine levels as measured by HPLC. Brain Res. Bull. **14:** 85–90, 1985.
217. PATON, W. D. M.: Pharmacology of marijuana. Annu. Rev. Pharmacol. **15:** 191–220, 1975.
218. PATON, W. D. M., AND PERTWEE, R. G.: Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. Br. J. Pharmacol. **44:** 250–261, 1972.
219. PATON, W. D. M., AND PERTWEE, R. G.: The pharmacology of cannabis in animals. *In* Marihuana Chemistry, Pharmacology, Metabolism and Clinical Effects. ed. by R. Mechoulam, pp. 191–285, Academic Press, New York, 1973.
220. PERTWEE, R. G.: The ring test: a quantitative method for assessing the cataleptic effect of cannabis in mice. Br. J. Pharmacol. **46:** 753–763, 1972.
221. PERTWEE, R. G.: Effects of cannabinoids on thermoregulation: a brief review. *In* Marihuana '84, ed. by D. J. Harvey, pp. 263–277, IRL Press, Oxford, 1985.
222. PERTWEE, R. G., MOOCHHALA, S., NYEMITEI-ADDO, I., AND TODD, D. A.: The effects of intrahypothalamic injection on Δ^9-tetrahydrocannabinol, dopamine and prostaglandin E_2 on behavioral thermoregulation in mice. *In* Environmental Drugs Thermoregulation, 5th International Symposium on Pharmacological Thermoregulation, Saint-Paul-de-Vence, ed. by P. Lomax and E. Schönbaum, pp. 82–85, Karger, Basel, 1983.
223. PIRCH, J. H., COHN, R. A., BARNES, P. R., AND BARRATT, E. S.: Effects of acute and chronic administration of marihuana extract on the rat electrocorticogram. Neuropharmacology **11:** 231–240, 1972.
224. PIRCH, J. H., COHN, R. A., BARNES, P. R., AND BARRATT, E. S.: Tolerance to EEG and behavior effects of marijuana in rats. Drug Addict. Exp. Pharmacol. **1:** 133–144, 1972.
225. PODDAR, M. K., BISWAS, B., AND GHOSH, J. J.: Δ^9-Tetrahydrocannabinol and brain biogenic amines. *In* Drugs and Central Synaptic Transmission, ed. by P. B. Bradley and B. N. Dhawan, pp. 193–199, Macmillan, London, 1976.
226. PRADHAM, S. N., GHOSH, B., AULAKH, C. S., AND BHATTACHARYYA, A. K.: Effects of Δ^9-tetrahydrocannabinol on foot-shock-induced aggression in rats. Psychopharmacology **4:** 27–34, 1980.
227. PRYOR, G. T., HUSAIN, S., LARSEN, F., MCKINZIE, C. E., CARR, J. D., AND BRAUDE, M. C.: Interactions between Δ^9-tetrahydrocannabinol and phencyclidine hydrochloride in rats. Pharmacol. Biochem. Behav. **6:** 123–126, 1977.
228. PRYOR, G. T., LARSON, F. F., CARR, J. D., AND BRAUDE, M. C.: Interactions of Δ^9-tetrahydrocannabinol with phenobarbital, ethanol and chlordiazepoxide. Pharmacol. Biochem. Behav. **7:** 331–345, 1977.
229. PUROHIT, V., SINGH, H. H., AND AHLUWALIA, B. S.: Evidence that the effects of methadone and marijuana on male reproductive organs are mediated at different sites in rats. Biol. Reprod. **20:** 1039, 1979.
230. RAWITCH, A. B., SCHULTZ, G. S., EBNER, K. E., AND VARDARIS, R. M.: Competition of Δ^9-tetrahydrocannabinol with estrogen in rat uterine estrogen receptor binding. Science (Wash. DC) **197:** 1189–1191, 1977.
230a. RAZDAN, R. K.: Structure-activity relationships in cannabinoids. Pharmacol. Rev. **38:** 75–150, 1986.
231. RAZDAN, R. K., AND HOWES, J. F.: Drugs related to tetrahydrocannabinol. Medicinal Res. Rev. **3:** 119–146, 1983.
232. REVUELTA, A. V., MORONI, F., CHENEY, D. L., AND COSTA, E.: Effect of cannabinoids on the turnover rate of acetylcholine in rat hippocampus, striatum and cortex. Naunyn-Schmiedeberg's Arch. Pharmacol. **304:** 107–110, 1978.
233. RODIN, E. A., DOMINO, E. F., AND PORZAK, J. P.: The marijuana-induced "social high." J. Am. Med. Assoc. **213:** 1300–1302, 1970.
234. ROSENKRANTZ, H.: Cannabis Components and responses of neuroendocrine-reproductive targets: an overview. *In* marihuana '84, ed. by D. J. Harvey, IRL Press, pp. 457–505, Oxford, 1986.
235. ROSENKRANTZ, H.: Cannabis, marihuana and cannabinoid toxicological manifestations in male and animals. *In* Adverse Health and Behavioral Consequences in Cannabis Use, ed. by K. O. Fehr and H. Kalant, pp. 91–175, Addiciton Research Foundation, Toronto, 1983.
236. ROSENKRANTZ, H., AND BRAUDE, M. C.: Comparative chronic toxicities of Δ^9-tetrahydrocannabinol administered orally or by inhalation in rat. *In* The Pharmacology of Marihuana, ed. by M. C. Braude and S. Szara, pp. 571–584, Raven Press, New York, 1976.
237. SASSENRATH, E. N.: Assessment of acute versus long-term effects of Δ^9-tetrahydrocannabinol on social behavior and adaptability in group-living macaques. *In* Ethopharmacology: Primate Models of Neuropsychiatric Disorders, pp. 277–291, Alan R. Liss, Inc., New York, 1983.
238. SEGAL, M.: Central implantation of cannabinoids: induction of epileptiform discharges. Eur. J. Pharmacol. **27:** 40–45, 1974.
239. SEGAWA, T., BANDO, S., AND HOSOKAWA, M.: Brain serotonin metabolism and Δ^9-tetrahydrocannabinol-induced muricide behavior in rats. Jpn. J. Pharmacol. **27:** 581–582, 1977.
240. SEMJONOW, A., AND BINDER, M.: Generalization of the discriminative stimulus properties of Δ^9-THC to Δ^9,11-THC in rats. Psychopharmacology **85:** 178–183, 1985.
241. SIEBER, B., FRISCHKNECHT, H., AND WASER, P. G.: Behavioral effects of hashish in mice. IV. Social dominance, food dominance, and sexual behavior within a group of males. Psychopharmacology **73:** 142–146, 1981.
242. SIEGEL, R. K.: Effects of cannabis sativa and lysergic acid diethylamide on a visual discrimination task in pigeons. Psychopharmacology **15:** 1–8, 1969.
243. SIEMENS, A. J.: Cross-tolerance between ethanol and Δ^9-tetrahydrocannabinol: the contribution of changes in drug disposition. Fed. Proc. **37:** 318, 1978.
244. SIEMENS, A. J., CHANG, T. B., DOYLE, O. L., AND GEORGE, P.: Influence of Δ^9-tetrahydrocannabinol (THC) on development of ethanol tolerance and dependence. Phamacologist **21:** 205, 1979.
245. SIEMENS, A. J., AND DOYLE, O. L.: Cross-tolerance between Δ^9-tetrahydrocannabinol and ethanol: the role of drug disposition. Pharmacol. Biochem. Behav. **10:** 49–55, 1979.
246. SIEMENS, A., AND KALANT, H.: Metabolism of Δ^1-tetrahydrocannabinol by rats tolerant to cannabis. Can. J. Physiol. Pharmacol. **52:** 1154–1166, 1974.
247. SMILEY, K. A., KARLER, R., AND TURKANIS, S. A.: Effects of cannabinoids on the perfused rat heart. Res. Commun. Chem. Pathol. Pharmacol. **14:** 659–675, 1976.
248. SMITH, C. G., BESCH, N. F., SMITH, R. G., AND BESCH, P. K.: Effect of tetrahydrocannabinol on the hypothalamic-pituitary axis in the ovariectomized rhesus monkey. Fertil. Steril. **31:** 335–339, 1979.
249. SMITH, C. G., SMITH, M. T., BESCH, N. F., SMITH, R. G., AND ASCH, R. H.: Effect of Δ^9-tetrahydrocannabinol (THC) on female reproductive function. *In* Marihuana—Biological Effects, ed. by G. G. Nahas and W. D. M. Paton, pp. 449–467, Pergamon Press, Oxford, 1979.
250. SNYDER, E. W., LEWIS, E. G., DUSTMAN, R., AND BECK, E. C.: Sustained ingestion of Δ^9-tetrahydrocannabinol and the operant behavior of stumptailed maraques. Pharmacol. Behav. **3:** 1129–1132, 1975.
251. SOFIA, R. D., AND BARRY, H.: Acute and chronic effects of Δ^9-tetrahydrocannabinol on food intake by rats. Psychopharmacology **39:** 213–222, 1974.
252. SOFIA, R. D., DIXIT, B. N., AND BARRY, H.: The effect of Δ^1-tetrahydrocannabinol on serotonin metabolism in the rat brain. Life Sci. **10:** 425–437, 1971.
253. SOFIA, R. D., AND KNOBLOCH, L. C.: The interaction of Δ^9-tetrahydrocannabinol pretreatment with various sedative-hypnotic drugs. Psychopharmacology **30:** 185–194, 1973.
254. SOFIA, R. D., NALEPA, S. D., HARAKAL, J. J., AND VASSAR, H. B.: J. Pharmacol. Exp. Ther. **186:** 646–655, 1973.
255. SOLOMON, J., COCCHIA, M. A., GRAY, R., SHATTUCK, D., AND VOSSMER, A.: Uterotrophic effect of Δ^9-tetrahydrocannabinol in ovariectomized rats. Science (Wash. DC) **192:** 559–561, 1976.
256. SPAULDING, T. C., FORD, R. D., DEWEY, W. L., MCMILLAN, D. E., AND HARRIS, L. S.: Some pharmacological effects of phenitrone and its interaction with Δ^9-THC. Eur. J. Pharmacol. **19:** 310–317, 1972.
257. SPRAGUE, G. L., AND CRAIGMILL, A. L.: Effects of two cannabinoids upon abstinence signs in ethanol-dependent mice. Pharmacol. Biochem. Behav. **9:** 11–15, 1978.
258. SPRAGUE, G. L., AND CRAIGMILL, A. L.: Ethanol and Δ^9-tetrahydrocannabinol: mechanism for cross-tolerance in mice. Pharmacol. Biochem. Behav. **5:** 409–415, 1976.
259. STADNICKI, S. W., SCHAEPPI, E., ROSENKRANTZ, H., AND BRAUDE, M. C.: Crude-marijuana extract: EEG and behavioral effects of chronic oral administration in rhesus monkeys. Psychopharmacology **37:** 225–233, 1974.
260. STARK, P., AND DEWS, P. B.: Cannabinoids. I. Behavioral effects. J. Pharmacol. Exp. Ther. **214:** 124–130, 1980.
261. STARK, P., AND DEWS, P. B.: Cannabinoids. II. Cardiovascular effects. J. Pharmacol. Exp. Ther. **214:** 131–138, 1980.

262. Stiglick, A., and Kalant, H.: Learning impairment in the radial-arm maze following prolonged cannabis treatment in rats. Psychopharmacology **77:** 117–123, 1982.
263. Stiglick, A., and Kalant, H.: Residual effects of chronic cannabis treatment on behavior in mature rats. Psychopharmacology **85:** 436–439, 1985.
264. Stiglick, A., and Kalant, H.: Residual effects of prolonged cannabis administration on exploration and DRL performance in rats. Psychopharmacology **77:** 124–128, 1982.
265. Stone, C. J., and Forney, R. B.: The effects of phencyclidine on ethanol and sodium hexobarbital in mice. Toxicol. Appl. Pharmacol. **40:** 177–183, 1977.
266. Swanson, L. W., Teyler, T. J., and Thompson, R. F.: Hippocampal long-term potentiation: mechanisms and implications for memory. Neurosci. Res. Prog. Bull. **20:** 613–769, 1982.
267. Taylor, D. A., and Fennessy, M. R.: The effect of Δ^9-tetrahydrocannabinol (Δ^9-THC) on the turnover rate of brain sertonin of the rat. Clin. Exp. Pharmacol. Physiol. **6:** 327–334, 1979.
268. Taylor, D. A., and Fennessy, M. R.: Time-course of the effects of chronic Δ^9-tetrahydrocannabinol on behavior, body temperature, brain amines and withdrawal-like behavior in the rat. J. Pharm. Pharmacol. **34:** 240–245, 1981.
269. Taylor, D. A., and Yap, C. Y.: Effect of chronic Δ^9-THC and Δ^9-THC administration in the rat. *In* Marihuana '84, ed. by D. J. Harvey, pp. 279–286, IRL Press, Oxford, 1985.
270. Ten Ham, M., and Van Noordwijk, J.: Lack of tolerance to the effect of two tetrahydrocannabinol on aggressiveness. Psychopharmacology **29:** 171–176, 1973.
271. Thompson, D. M., and Winsauer, P. J.: Δ^9-Tetrahydrocannabinol potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Pharmacol. Biochem. Behav. **23:** 1051–1057, 1985.
272. Tripathi, H. L., Vocci, F. J., and Dewey, W. L.: Effect of cannabinoids on cholinergic systems in various regions of the mouse brain. Fed. Proc. **38:** 590, 1979.
273. Trounce, J. R.: Marihuana '84. Summary of the session on clinical and therapeutic aspects. *In* Marihuana '84, ed. by D. J. Harvey, pp. 729–731, IRL Press, Oxford, 1985.
274. Trouve, R., and Nahas, G.: Effects and interactions of natural cannabinoids on the isolated heart. *In* Marihuana '84, ed. by D. J. Harvey, pp. 347–358, IRL Press, Oxford, 1985.
275. Truitt, E. B., Jr., and Braude, M. C.: Preclinical pharmacology of marijuana. *In* Research Advances in Alcohol and Drug Problems, ed. by R. J. Gibbins, V. Israel, H. Kalant, R. E. Popham, W. Schmidt, and R. G. Smart, vol. 1, pp. 199–242, John Wiley and Sons, New York, 1974.
276. Tulunay, F. C., Ayhan, I. H., and Sparber, S. G.: The effects of morphine and Δ^9-tetrahydrocannabinol on motor activity in rats. Psychopharmacology **78:** 358–360, 1982.
277. Turkanis, S. A., Cely, W., Olsen, D. M., and Karler, R.: Anticonvulsant properties of cannabidiol. Res. Commun. Chem. Pathol. Pharmacol. **8:** 231–246, 1974.
278. Turkanis, S. A., and Karler, R.: Central excitatory properties of Δ^9-tetrahydrocannabinol and its metabolites in iron-induced epileptic rats. Neuropharmacology **21:** 7–13, 1982.
279. Turkanis, S. A., and Karler, R.: Electrophysiological mechanisms of Δ^9-tetrahydrocannabinol's convulsant actions. *In* The Cannabinoids: Chemical Pharmacologic and Therapeutic Aspects, ed. by S. Agurell, W. L. Dewey, and R. E. Willette, pp. 233–244, Academic Press, New York, 1984.
280. Turkanis, S. A., and Karler, R.: Electrophysiological mechanisms and loci of Δ^9-tetrahydrocannabinol caused CNS depression. *In* Marihuana '84, ed. by D. J. Harvey, pp. 233–244, IRL Press, Oxford, 1985.
281. Turkanis, S. A., and Karler, R.: Electrophysiologic properties of the cannabinoids. J. Clin. Pharmacol. **21:** 4495–4615, 1981.
282. Turkanis, S. A., and Karler, R.: Excitatory and depressant effects of Δ^9-tetrahydrocannabinol and cannabidiol on cortical evoked responses in the conscious rat. Psychopharmacology **75:** 294–298, 1981.
283. Turner, C. E.: Marihuana and cannabis: research why the conflict? *In* Marihuana '84, ed. by D. J. Harvey, pp. 31–36, IRL Press, Oxford, 1985.
284. Tyrey, L.: Δ^9-Tetrahydrocannabinol suppression of episodic leuteinizing hormone secretion in the ovariectomized rat. Endocrinology **102:** 1808–1814, 1978.
285. Ueki, S.: Abnormal behavior induced by Δ^9-tetrahydrocannabinol and its pharmacological characteristics. Trends Pharmacol. Sci. **1:** 126–129, 1980.
286. Valle, J. R. D., Souza, J. A., and Hyppolito, N.: Rabbit reactivity to cannabis preparations, parahexyl and tetrahydrocannabinol. J. Pharm. Pharmacol. **18:** 476–478, 1966.
287. Vardaris, R. M., Teyler, T. J., and Weisz, D. J.: Δ^9-THC and the hippocampus: effects of CA1 field potentials in rats. Brain Res. Bull. **2:** 181–187, 1977.
288. Verberne, A. J. M., Taylor, D. A., and Fennessy, M. R.: Attenuation of Δ^9-tetrahydrocannabinol-induced withdrawal-like behavior by Δ^9-tetrahydrocannabinol. Psychopharmacology **73:** 97–98, 1981.
289. Verberne, A. J. M., Taylor, D. A., and Fennessy, M. R.: Withdrawal-like behavior induced by inhibitors of biogenic amine reuptake in rats treated chronically with Δ^9-tetrahydrocannabinol. Psychopharmacology **68:** 261–267, 1980.
290. Volvaka, J., Dornbush, R., Filstein, S., Clare, G., Zaks, A., Fink, M., and Freedman, A. M.: Marijuana, EEG, and behavior. Ann New York Acad. Sci. **191:** 206–215, 1971.
291. Walton, R. P., Martin, L. F., and Keller, J. H.: The relative activity of various purified products obtained from American grown hashish. J. Pharmacol. Exp. Ther. **62:** 239–251, 1938.
292. Weil, A. T., Zinberg, N. E., and Nelsen, J. M.: Clinical psychological effects of marihuana in man. Science (Wash. DC) **162:** 1234–1242, 1968.
293. Weisz, D. J., Gunnel, D., Teyler, T. J., and Vardaris, R. M.: Changes in CA1 population spikes following administration of Δ^9-THC. Brain Res. Bull. **8:** 155–162, 1982.
294. Wilkison, D. M.: Electrophysiological effects of THC on cortical sensory evoked activity. *In* Marihuana '84, ed. by D. J. Harvey, pp. 621–633, IRL Press, Oxford, 1985.
295. Wilkison, D. M., Pontzer, N. J., and Hosko, M. J.: Slowing of cortical somatosensory evoked activity of Δ^9-THC and dimethylheptylpyran in alpha-chloralase anesthetized cats. Neuropharmacology **21:** 705–709, 1982.
296. Williams, R. B., NG, L. K. Y., Lamprecht, F., Roth, K., and Kopin, I. J.: Δ^9-Tetrahydrocannabinol: a hypotensive effect in rats. Psychopharmacology **28:** 269–274, 1973.
297. Yagiela, J. A., McCarthy, K. D., and Gibb, J. W.: The effect of hypothermic doses of *l*-Δ^9-tetrahydrocannabinol on biogenic amine metabolism in selected parts of rat brain. Life Sci. **14:** 2361–2378, 1974.
298. Yamamoto, I., Watanabe, K., Oguri, K., and Yoshimura, H.: Anticonvulsant activity of 11-hydroxy-Δ^8-tetrahydrocannabinol and 11-oxo-Δ^8-tetrahydrocannabinol against pentylenetetrazol-induced seizures in the mouse. Res. Commun. Subst. Abuse **1:** 287–298, 1980.
299. Yoshimura, H., Fujiwara, M., and Ueki, S.: Biochemical correlates in mouse-killing behavior of the rat: brain acetylcholine and acetylcholinesterase after administration of Δ^9-tetrahydrocannabinol. Brain Res. **81:** 567–570, 1974.
300. Zitko, B. A., Howes, J. F., Razdan, R. K., Dalzell, B. C., Dazell, H. C., Sheehan, J. C., Pars, H. G., Dewey, W. L., and Harris, L. S.: Water-soluble derivatives of delta-1-tetrahydrocannabinol. Science (Wash. DC) **177:** 442–444, 1972.