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Cannabis: Pharmacology and Interpretation of Effects

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ABSTRACT: A selective introductory review of the *Cannabis* literature is presented. Subjects reviewed include the relative psychoactivities of *Cannabis* constituents, the disposition and distribution of THC and its metabolites, the relative psychoactivities of THC metabolites, and the use of cannabinoid concentrations in physiological fluids in interpretations of the significance of *Cannabis*-induced effects. The pharmacology of cannabinoids in humans is emphasized.

KEYWORDS: toxicology, marijuana

Marijuana and other *Cannabis* products are used by a significant proportion of people in our society. When smoked or ingested, these substances produce perceptual, cognitive, affective, and behavioral changes in the user. The *Cannabis* constituent that is responsible for the production of the majority of this psychoactive response is (−)-trans-delta-9-tetrahydrocannabinol or THC [*1*]. There has been great concern that the psychoactive response experienced by marijuana users has a detrimental effect on the performance of complex coordinated psychomotor skills. Naturally, the impairment of performance would be of greatest concern in those individuals with direct responsibility for the health and safety of others and in individuals whose impaired actions could potentially be dangerous to themselves or to others near them. Motor vehicle operators, pilots, air traffic controllers, law enforcement or emergency aid personnel, military personnel, and industrial workers are all good examples of people whose impaired performance could potentially be dangerous.

During the last decade, remarkable progress has been made in the ability to analyze biological samples for cannabinoid compounds. This ability was developed as a prerequisite for, and was instrumental in the acquisition of data concerning the pharmacology, pharmacokinetics, metabolism, behavioral effects, and toxicology of *Cannabis* constituents. These analytical methods and the knowledge derived from their use in basic research on cannabinoids are now being used in attempts to interpret the significances of cannabinoid concentrations found in forensic science specimens. The frequency with which these analytical methods are used and the frequency with which forensic scientists are required to provide estimates of the probable significances of *Cannabis*-induced effects or the degree of impairment experienced by a *Cannabis* user based on cannabinoid concentrations in biological specimens are both expected to increase. Use of these methods and in-

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terpretive skills will be especially important in cases where *Cannabis*-induced impairment is suspected and where this impairment is believed to have made the *Cannabis* user responsible or culpable for death or serious injury.

This selective introductory review was compiled to facilitate interpretation of *Cannabis*-induced effects, while recognizing the analytical, pharmacological, and methodological limitations inherently associated with their production. Interpretations of *Cannabis*-induced effects must be based on specifically determined THC and THC metabolite concentrations in blood or plasma specimens. Taken alone, THC concentrations may not be useful for correlation with behavioral changes if specimens are obtained more than 1 h after smoking *Cannabis*, because of the low THC concentrations present [*2*]. Finally, the major problem limiting the ability to interpret effects based on cannabinoid concentrations is the failure of forensic scientists, behavioral pharmacologists, and toxicologists to compile a comprehensive concentration-effects data base upon which interpretations can be based. Significant improvements in analytical methods and in the quality and scope of the requisite data base for interpretation will only occur or be acquired from continuing research. As such, the acquisition and implementation of these advances will occur comparatively slowly. However, the basic dispositional and distributional properties and behaviors of THC are known and will be largely unaltered by further research. Therefore, it is appropriate that the pharmacological properties of THC be used to suggest approaches to solving the methodological problems associated with the interpretation of *Cannabis*-induced effects.

This review is intended to be a compilation of THC pharmacology in human biological systems, with emphasis placed on THC and THC metabolites detected in blood and plasma following administration of THC in *Cannabis* by smoking or oral ingestion. The THC metabolities not yet detected in biological sources of human origin, as well as the psychoactivities of cannabinoids in nonhuman systems, have not been emphasized.

The Relative Psychoactivities of Cannabis Constituents and Their Pyrolysis

As of 30 June 1978, 421 different compounds had been isolated from *Cannabis* and reported in the chemical literature [*3*]. The compounds classified as "cannabinoids" have been described as being "the class of compounds containing 21 carbon atoms that are typical of *Cannabis sativa L.*, their (natural) carboxylic acids, analogues, and transformation products" [*4*]. Sixty-one natural cannabinoids, apparently unique to *Cannabis*, have been identified so far [*3*]. Some of the cannabinoids found in *Cannabis* are shown in Fig. 1. Of these compounds, (−)-trans-delta-9-tetrahydrocannabinol or THC, which is present in *Cannabis* along with its 2- and 4-carboxylic acids, is the only compound that is both highly psychoactive and present in relatively high amounts, usually 1 to 5% by weight. There are at least two other compounds found in *Cannabis* that are known to be psychoactive in humans: an isomer of THC, delta-8-tetrahydrocannabinol (delta-8-THC), and the propyl homologue of THC, delta-9-tetrahydrocannabivarin (delta-9-THCV). Delta-8-THC has been shown to be 75 [*5*] and 67% [*6*] as potent at THC when both drugs were administered to humans by intravenous injection, while delta-9-THCV was found to be roughly 25% as active as THC [*5*]. Both compounds produced the same qualitative pattern of psychological and physiological effects as THC [*5*], and the same potency ratios were determined when these compounds were administered orally [*5,6*]. However, these two compounds probably do not contribute substantially to the effects produced by the use of marijuana. Delta-8-THC is a degradative product of THC [*3*], and it is not present in fresh marijuana. Only small and variable amounts of delta-8-THC are commonly found in *Cannabis* products [*7–10*]. Delta-9-THCV is a natural product of marijuana [*3*], but the amount of delta-9-THCV in marijuana was found to be minor when compared to the amount of THC present [*11*].

One other cannabinoid, cannabinol (CBN), could potentially contribute to the psychoactivity produced by the use of marijuana. CBN is a degradative product of THC. It is not found in

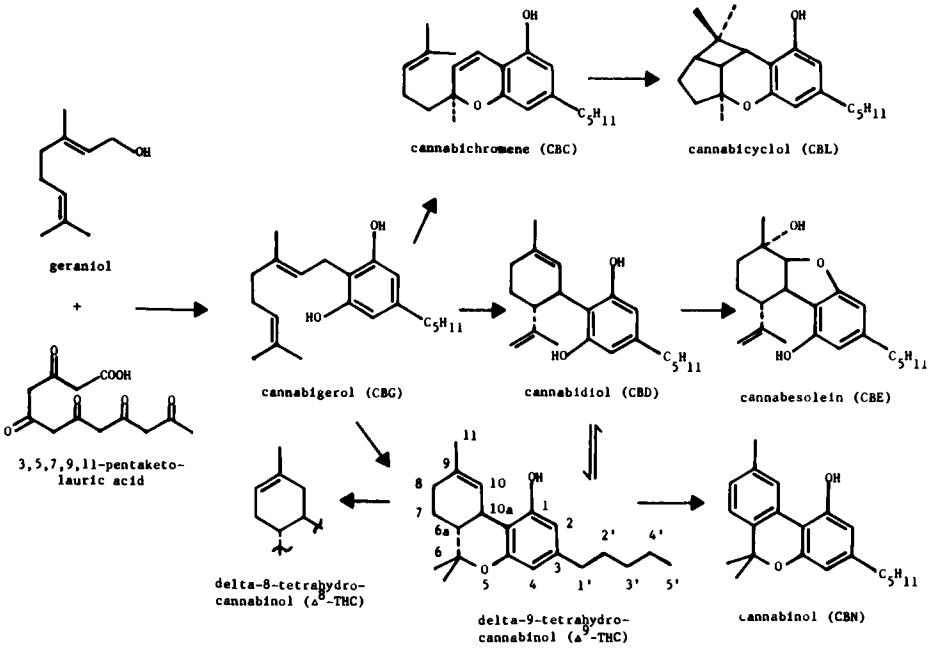

FIG. 1—*Natural products of* Cannabis. *The dibenzopryan numbering system has been used for all cannabinoids. Natural cannabinoids are synthesized either as neutral compounds or as carboxylic acids, with the acidic substituent at positions analogous to the 2- or 4-positions of delta-9-THC. Those acids may be decarboxylated to yield neutral cannabinoids.*

fresh marijuana [*12–14*]. Its formation from THC via epoxide intermediates [*15*] and via free-radical mechanisms [*16*] has been reported. Intermediate dienes generated during the formation of CBN have been trapped and isolated using the dienophile *N*-phenylmaleimide [*17*]. Although its concentration in marijuana is usually quite low, CBN may sometimes be present in an amount equivalent to or greater than the amount of THC present [*18*]. However, the intrinsic psychoactivity of CBN is comparatively poor relative to that of THC. To produce perceivable subjective psychological effects or equivalent cardioacceleratory effects in humans, ten times more CBN had to be administered at a rate six times the intravenous infusion rate used for THC [*19*]. The authors concluded that while CBN produced a spectrum of effects similar to those produced by THC, its relative psychoactivity was "several orders of magnitude" less than that of THC. In another instance, intravenous infusion of 18 mg of CBN into human subjects produced a very mild yet "definite high" [*20*]. However, in other studies, oral doses up to 400 mg of CBN produced no subjective psychological effects [*5,21*]. CBN has also been reported to be a potentiator of the effects of THC when large doses of each are concurrently administered [*22–24*]. CBN was not a significant metabolite of THC administered by intravenous injection [*25,26*].

Cannabidiol (CBD) is another major cannabinoid found in *Cannabis*. It is not psychoactive in humans when large doses are administered orally [*5,21*] or intravenously [*5,19,20*]. It has been reported that large doses of CBD decrease the effects produced by concurrently administered doses of THC to humans [*27–29*]. However, a recent study demonstrated that plasma concentrations of THC were not significantly altered by concurrent oral administration of either CBN or CBD [*24*]. None of the other major *Cannabis* constituents have been reported to be psychoactive. Therefore, although several of the cannabinoids found in *Cannabis* may con-

tribute to or modify the psychoactive effects experienced by users of marijuana, it would seem that THC is responsible for the production of the large majority of those effects.

When *Cannabis* is smoked, the natural 2- and 4-carboxylic acids of THC are quantitatively decarboxylated to form THC [*13,30–33*]. Other than decarboxylation reactions, there seems to be very little interconversion or isomerization of cannabinoids during pyrolysis [*30,31,34–37*]. Estimates of total THC survival during pyrolysis range from 32 [*35*] to 50% [*30,34*] to a maximum of 62% [*37*]. An analysis of the dynamics of marijuana smoking has been published [*38*]. When marijuana smoke is inhaled, THC is absorbed in a process that can be described by first-order kinetics. For each inhalation, the half-life of the absorption process is about 1 min [*39*].

Systemic bioavailability of THC administered by smoking has been reported to be 18 ± 6% [*40*]. Two other studies have reported the systemic bioavailability of THC smoked in marijuana to be 23 ± 16% and 10 ± 7% in heavy and light users, respectively [*41*], and 27 ± 10% and 14 ± 1% in heavy and light users, respectively [*42*].

The Plasma Protein Binding of THC

In blood, THC is nonspecifically, nonsaturably, and almost completely bound to plasma proteins, lipoproteins, and albumins [*43–45*]. This high protein binding is a result of its low solubility in aqueous systems (0.77 mg/L in isotonic saline or 2.8 mg/L in distilled water, both at 23°C [*46*]) and its high lipophilicity. The Hansch constant for THC, or the log of the concentration ratio determined after partitioning between octanol and water, was 5.78 [*47*]. A similar calculation of this constant for partitioning between purified rat synaptosomal membranes and isotonic phosphate buffer was 5.1 and was constant between 10^{-8} and $10^{-6}M$ THC (3.1 to 310 μg/L) [*47*]. The extensive protein binding of THC and its poor distribution into red blood cells when in the presence of plasma proteins [*44,46*] make plasma the favored specimen for THC analysis. A comparison of hemolyzed blood and plasma concentrations from split specimens showed that the average ratio of the determined THC concentrations—0.46 [*2*]—matched the expected ratio of erythrocyte to whole blood volumes, that is, the hematocrit—0.45 [*48*]. In effect, the plasma concentrations were diluted by the volume of the red blood cells.

The Distribution and Metabolism of THC and the Relative Psychoactivities of THC Metabolites

When administered to humans, THC is rapidly distributed [*39,49*] from the central compartment to peripheral tissues with high lipid contents. It is also rapidly metabolized [*49*]. In fact, it is nearly completely metabolized before it is finally excreted as metabolites in urine and feces [*20,33,50–52*]. A very large number of THC metabolites have been isolated from human sources both in vitro [*53–55*] and in vivo [*20,25,26,33,52–54,56–58*]. Some of the more important metabolites of THC are shown in Fig. 2. Undoubtedly, the two most important THC metabolites found in plasma or blood are 11-hydroxy-delta-9-tetrahydrocannabinol (11-hydroxy-THC), and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC). They are both constituents of the major catabolic pathway of THC. THC undergoes allylic hydroxylation at the 11-position primarily in the liver, in a cytochrome P-450 oxygenase mediated process [*59–66*]. Presumably, the carboxylic acid metabolite is formed from 11-hydroxy-THC via oxidation to the α,β-unsaturated aldehyde, 11-oxo-THC, followed by further oxidation to the acid. The metabolic conversion from the hydroxide to the aldehyde and then to the carboxylic acid has been directly observed using delta-9-THC in vitro with mouse liver microsomes [*67*], using delta-8-THC [*68*] in vitro with rabbit liver microsomes, and using delta-8-THC in vivo in mice [*69*].

The compound 11-hydroxy-THC is approximately as psychoactive or even slightly more psychoactive than THC, and produces the same somatic and psychological effects as THC [*5,70–72*]. However, it probably does not contribute significantly to the effects produced by marijuana smoking. Plasma concentrations of 11-hydroxy-THC were found to be only about

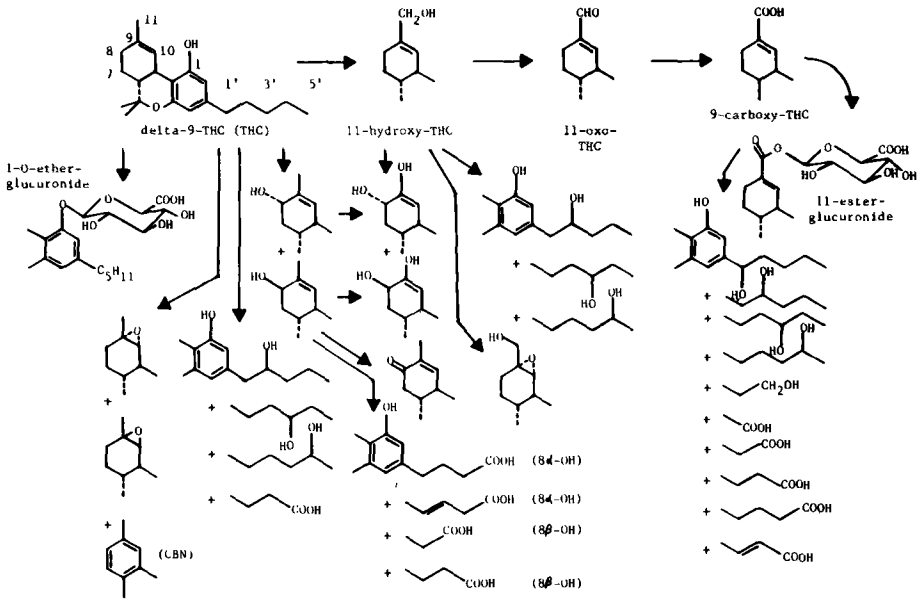

FIG. 2—*Known human metabolites of delta-9-tetrahydrocannabinol, (Δ^9-THC), isolated from either in-vivo or in-vitro sources.*

1/10 to 1/20 of THC plasma concentrations after marijuana smoking [*33*]. Given the poor capacity of rat brain tissue to metabolize THC in vivo [*73*], it is unlikely that significant amounts of 11-hydroxy-THC or other psychoactive metabolites are produced from THC in the brain. After oral administration, however, THC is absorbed by humans slowly and erratically, and the extent of absorption is highly dependent on the vehicle used for administration [*74*]. Systemic bioavailability of THC administered on chocolate cookies was only 6 ± 3% [*40*]. Plasma concentrations of orally administered THC are usually much lower than those found after smoking and reach a peak at a later time, while the onset of effects is delayed and the effects last longer [*40, 52, 75*]. Because of an extensive first-pass effect, 11-hydroxy-THC concentrations may be equivalent to or greater than THC concentrations [*33, 52, 76*]. Therefore, after oral ingestion of marijuana, 11-hydroxy-THC may be responsible for a significant fraction of the effects produced. However, THC is administered by smoking far more often than it is orally. The other major metabolite found in blood, 9-carboxy-THC, is nonpsychoactive [*51*]. It may be present in concentrations far exceeding those of THC, especially in plasma specimens taken more than about 30 min or so after smoking begins [*77*].

There are several other metabolites of THC that may be found in human plasma, including the 8α- and 8β-hydroxy metabolites, and the 8α, 11-dihydroxy and 8β, 11-dihydroxy metabolites [*20, 52, 54*]. The 8β-hydroxy metabolite was found to be about 38% as psychoactive as THC when administered to humans by intravenous infusion [*72*] but was only about 20% as active as THC when administered as a bolus [*5*]. The 8α-hydroxy metabolite was determined to be inactive when administered by infusion [*72*] but was about 28% as active as THC when injected as a bolus [*5*]. Plasma concentrations of these two metabolites were found to be roughly equivalent to the concentration of 11-hydroxy-THC produced by an injection of THC [*52*]. Because only low concentrations of these two metabolites would be expected to be found after smoking, and because of their relatively poor psychoactivity, these two monohydroxylated metabolites probably do not contribute significantly to the psychoactive effects produced by marijuana smoking. The dihydroxy-THC metabolites are inactive in mice at doses up

to 10 mg/kg [53,62]. So far, the only other THC metabolites detected in human plasma are "polar acids," whose exact structures have not yet been determined [20,33,52]. It has been suggested that one component of these polar acids might be the β-ester glucuronide of 9-carboxy-THC [52]. This compound was found to be by far the most prevalent THC metabolite found in urine [78,79]. Another recent report showed that a cross-reacting cannabinoid compound found in urine is eluted during high-pressure liquid chromatography before either 9-carboxy-THC or its β-ester glucuronide [80]. These polar acids are probably a mixture of the β-ester glucuronide of 9-carboxy-THC and other polar cannabinoid metabolites that are present in urine [56–58].

The Correlation of THC Concentrations in Physiological Fluids and Subjective Self-Reported Psychological Effects

Blood or plasma are the only specimens that can be used to correlate experimentally determined THC concentrations and the resultant effects, because they are the only easily obtainable specimens that can be analyzed to provide concentrations of cannabinoids that are potentially relatable to the concentrations of psychoactive cannabinoids at "active sites" or "receptors" in the central nervous systems (CNS). The major liability associated with the analysis of blood and plasma specimens is that invasive techniques are required to obtain them. Urine testing has become very popular because simple and fast screening methods have become available and because urine collection is noninvasive. However, the results from urine tests can only be used to determine whether or not a person has either smoked or ingested *Cannabis*; they cannot be used to indicate the presence of any effects or impairment. This limitation is caused by the excretory patterns exhibited by THC and its metabolites. Very little or no unmetabolized THC is excreted in urine [49,50,74,81–83]. Instead, it is excreted in urine as a wide variety of oxidized cannabinoids including 9-carboxy-THC and its β-ester glucuronide, 11- or 8-hydroxylated cannabinoids with alkylcarboxy side chains five carbons long or less, and other metabolites where 9-carboxy-THC has been hydroxylated on the side chain [56]. Five other dicarboxylic acid metabolites have been detected where 9-carboxy-THC compounds bear alkylcarboxy side chains of varying lengths [57]. Recently, a second glucuronide, the phenolic 1-0-ether glucuronide of THC, was detected in human urine [58].

The clearance rate of these metabolites is limited by a slow deep compartment return of sequestered THC and by slow urinary elimination of the metabolic transformation products [49]. Roughly 80 to 90% of an intravenously administered dose of THC is excreted during the first five days following the dose, with about 20% excreted in the urine and the remainder in the feces [49]. Urinary excretion patterns of cannabinoid metabolites vary considerably between subjects and have been reported to exhibit a temporal variation within subjects, with a shift towards increasing proportions of conjugated materials with increasing time since administration [84,85]. However, other authors have reported that the majority of the 9-carboxy-THC excreted is conjugated regardless of the elapsed time since administration [20,33,52,79].

Depending on the sensitivity of the analytical method used, cannabinoid metabolites may be detected in urine for four to ten days after a single use and for up to twenty days following chronic marijuana smoking [86,87]. Another recent report showed that cannabinoids were detected for 14 to 36 days ($n = 7$, mean = 24 days) in the urine of chronic marijuana smokers undergoing supervised abstinence [88]. Low concentrations of cannabinoids may sometimes be detected in urine specimens from subjects who have been passively exposed to high concentrations of marijuana smoke on several consecutive days [89]. The excretion of cannabinoid metabolites in urine is also modified by many factors not related to drug use, such as hydration. For these reasons, it is not uncommon to find high concentrations of THC metabolites in the urine of subjects when no THC-induced subjective psychological effects are present. Therefore, high urinary concentrations of cannabinoids may indicate relatively recent marijuana use (in the last several days), but they cannot be used to indicate the presence of any effects of im-

pairment. Some of the problems associated with the analysis of cannabinoids in urine have recently been reviewed [*90, 91*].

The testing of saliva [*92*], breath [*93*], and eluate specimens from mouth swabs [*94*] or hand swabs [*95*] are prone to similar problems. After intravenous injections of radiolabelled THC, no radioactivity could be detected in saliva samples. Therefore, neither THC nor any of its metabolites could have diffused from blood into saliva or breath [*92*]. The cannabinoids detected in the oral cavity after smoking are present only because they were entrapped there during the smoking process. Although saliva, breath, or mouth swab tests could be used to indicate that marijuana was smoked within the last several hours, it will be impossible to develop quantitative impairment correlations based on tests of these specimens [*92*]. THC or its metabolites could not be detected in vitreous humor specimens from 34 fatally injured drivers, 9 of whom had detectable THC concentrations (up to 5 μg/L) in their bloods [*96*].

Before considering the temporal relationships between THC or 9-carboxy-THC concentrations and the effects produced by marijuana smoking, it would be helpful to examine their individual temporal distributions. Figure 3 contains these data, which were obtained from an experiment where six subjects each smoked two marijuana cigarettes provided by the National Institute on Drug Abuse (NIDA), each containing 8.8 mg of THC. The second cigarette was smoked 2 h after the first [*38, 39, 97*]. It should be noted that the general patterns exhibited in these distributions have been observed in many other studies [*40–42, 49, 75, 77*]. Many of these papers also contain pharmacokinetic analyses of THC and THC metabolite concentrations.

The THC concentration-time curve (Fig. 3) consists of two apparently triphasic (including absorption) parallel curves that rise to their respective peaks very quickly and then fall to about 10% of their peak concentrations within the first hour. The THC concentration-time curve then continues an apparently asymptotic approach to zero concentration. The distribution of 9-carboxy-THC concentrations is characterized by a slower increase than that exhibited by THC, by lower peak concentration values at greater times, and by much less of a decrease in concentration immediately after the peak [*77*]. Subjective effects usually begin immediately after the initiation of smoking, reach their peak between 20 and 40 min, and usually last up to about 4 h [*38, 75, 77, 97*].

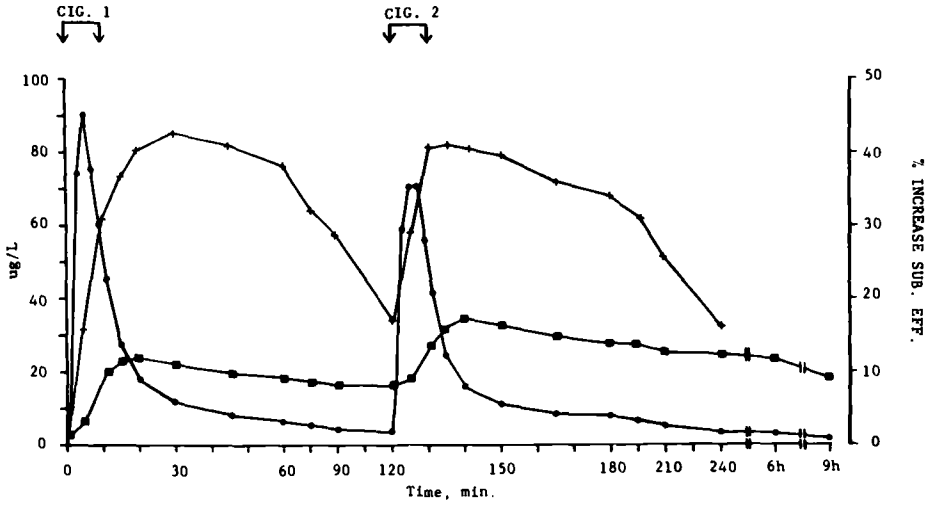

FIG. 3—*Average plasma concentrations of THC (●) and 9-carboxy-THC (■) and average subjective effects (+) in six subjects after smoking two NIDA marijuana cigarettes, each containing 8.8 mg of THC (1%).*

After marijuana smoking, the magnitudes of the peak concentrations of THC and 9-carboxy-THC and the magnitude of the peak subjective effects are proportionally related to the dose delivered [*77*]. This work confirmed earlier reports suggesting that above a threshold dose for activity [*98*], increasing doses of THC produced linear dose-dependent decreases in mental and physical performance such as stance and hand stabilities, increases in heart rate and conjunctival reddening, and increases in scores on sensation and mood questionnaires [*99*]. Furthermore, the time of occurrence of either peak effects or peak concentrations of THC and 9-carboxy-THC were also independent of the dose [*77*]. Moderate interindividual variability was noted in the magnitudes of the peak concentrations and peak effects at any given dose [*77*].

The major factor preventing the correlation of THC concentrations and subjective effects is the temporal noncoincidence of their peak values. Maximal THC plasma concentrations occur within 3 to 7 or 6 to 9 min after the initiation of smoking, long before smoking stopped (between 10 and 15 min, respectively) [*39, 77*]. The progressive decrease in the rate at which THC was absorbed could not be related to any change in the way the subjects smoked [*38*]. Maximal effects were noted to occur between 18 and 28 min [*77*]. Therefore, it is evident that THC plasma concentrations decline long before and while peak effects are experienced (see Fig. 3). After the peak, subjective effects decline in a roughly linear fashion [*39*], while the low μg/L THC concentrations decrease very slowly. Therefore, either significant, minimal, or no effects may be noted when THC concentrations are farily low.

The factors responsible for the noncorrelation of THC concentrations and effects are distributive by nature. This is intuitively reasonable because concentration measurements are performed in a tissue (blood) distal to the site where activity is elicited, the CNS. A certain time lag, attributable to the time required for transport to and distribution into the CNS, could be expected. Cocchetto et al [*97*] stated that the THC concentration-time profile was "out of phase with, and lagged behind" the temporal distribution of effects. Furthermore, the effects were elicited from a compartment that was "deep with respect to the reference plasma compartment" [*97*]. The potential influence of THC redistribution on effects was also noted by Ohlsson et al. [*100*], who demonstrated that THC plasma concentrations in the mouse fell while brain concentrations increased or remained constant.

Given these problems, it is not surprising that the correlation between THC plasma concentrations after smoking and subjective self-reported psychological effects is not strong [*38, 40, 75, 77, 97, 101*]. Linear regression correlation coefficients ranging from 0.53 to 0.56 have been reported during clinical experiments [*40, 75, 101*]. The ability to extrapolate from THC plasma concentrations to effects would be even poorer in forensic science situations. THC plasma concentrations up to 2.2 μg/L have been produced in the absence of any effects by passive inhalation of marijuana smoke [*89, 102*]. It is also widely believed that chronic marijuana smokers may accumulate significant "residual" plasma concentrations of THC that have little or no effects on the subjects. After chronic administration of THC, tolerance develops to both the somatic and psychological effects of THC [*41, 49, 103, 104*]. The advent of tolerance was not accompanied by significant changes in THC plasma concentrations versus nontolerant individuals [*49*]. The pharmacokinetic changes noted (increases in the average total metabolic clearance and initial volume of distribution) were not large enough to account for the changes in effects produced by the advent of tolerance [*49*]. For these reasons, it will be very difficult if not impossible to establish any "cutoff concentration" of THC in plasma that is presumptive of significant effects.

The Use of Marijuana and Induced Decrements in the Performance of Skills Such as Driving

The effect of marijuana use on the performance of tasks associated with driving and on performance during driving tests on driving simulators, on closed courses, and on test tracks has been extensively reviewed [*105–109*]. The authors of these studies present detailed descriptions of the difficulties encountered in the design and execution of these studies and the interpreta-

tion of their results. The latter three publications also review epidemiological or incidence studies that concern potential marijuana-induced performance impairment. Reviews of some of the more important early studies and of some recent studies are presented below.

Whether or not meaningful decrements in performance abilities in complex psychomotor tasks are produced by marijuana use is still not clear. A recent study used performance in tests of compensatory cursor tracking abilities on a video screen as an impairment indicator [*110*]. Although marijuana use did impair tracking ability, the magnitude of the effect was so slight that it was not directly observable. Higher doses of THC did impair performance in some driving tasks associated with visual search and recognition [*111*]. However, 25 other indices of driver performance were not affected in these same studies. A more recent closed-course driving study determined that the effects of marijuana use on driver performance could be differentiated from placebo effects only by using complex multivariate analyses of responses from sensitive transducers monitoring the driver [*112*]. The effects of marijuana were not easily discernible by direct observation. This study also showed that the performance decrements produced by concurrently administered ethanol and marijuana were produced in an additive manner [*112*].

Double-blind driving studies have been performed using dual-control vehicles [*113*]. Increased objective impairment, measured using the number of cones hit by the test-track drivers, was noted after subjects smoked 8.4 mg of THC in marijuana cigarettes, but not after they smoked 4.9 mg of THC. Subjective impairment, measured by observers in vehicles driven on city streets, was noted in three of eleven categories: judgment, care, and concentration. However, in both the subjective and objective tests, many of the subjects showed either no performance impairment or their performances improved. In another notable driving study, observers either placed in the vehicle or stationed along 10.6-km (6.6-mile) course were unable to determine that the performance of drivers who had smoked marijuana (6.2 mg of THC per 70-kg body weight) was in any way impaired [*114*]. However, these drivers did show a 27% increase in scores of objectively measured impairment (number of cones hit) over the control (placebo marijuana) group.

There have been several notable epidemiological or incidence studies that have attempted to determine if marijuana use is overrepresented in various "at-risk" driver populations, and therefore if marijuana use is detrimental to the safe operation of a motor vehicle. These studies have all been hampered by the lack of data concerning incidence rates for marijuana use in various control populations. In an early study [*115*], THC was detected in blood specimens taken from 6 of 66 fatally injured drivers killed in Great Britain. The concentrations detected were all very low (less than 3.4 μg/L) and all but one of the six drivers had a high blood ethanol concentration. The authors suggest that there was a considerable bias in the selection of these specimens. Later, Reeve et al [*116*] reported that blood specimens from 285 of 1792 (15.9%) drivers arrested for impaired driving contained more than 5 μg/L THC. However, the specimen population selected was strongly biased towards the inclusion of intoxicated drivers with low blood ethanol concentrations. As such, the population selected is not representative of either impaired drivers or of any control population. No concentration data were reported, and the documentation required to establish the characteristics of the assay was inadequate. It is doubtful that this study provides any useful data concerning marijuana-induced impairment.

A Canadian study [*96*] reported the incidence of detection of many different drugs, including THC, which was detected in only 15 of 401 (3.7%) fatally injured drivers. All of the THC blood concentrations were less than 5 μg/L and 8 of the 15 drivers had blood ethanol concentrations above 1.0 g/L. These THC concentrations are too low to presume that they had any effects on the drivers' abilities. A recent study of THC concentrations in drivers killed in single-vehicle crashes in North Carolina [*109, 117, 118*] reported that 47 of 600 (7.8) drivers had THC blood concentrations above 3.0 μg/L. Only ten drivers had THC blood concentrations above 10.0 μg/L. The authors concluded that there was probably only one driver who could have experienced a significant adverse effect because of the use of *Cannabis* alone [*109*]. The great ma-

jority (32 of 47 or 68.1%) of the drivers with detectable THC blood concentrations had ethanol concentrations greater than 1.0 g/L. In a summary of major epidemiological studies, McBay and Owens [*108*] stated that "Sparse as the reports may be, they tend to show that if there are drivers who are unsafe because of marijuana, their numbers are small and most are also influenced by alcohol."

Correlation of THC serum concentrations and objectively measured impairment have been examined in a recent study [*119*] of 59 subjects who smoked marijuana ad libitum and were tested by using a series of 3 physical performance test tasks (Romberg test, finger-nose test, and one-foot-standing-steadiness test). It was reported that 94 and 60% of the subjects failed one of the three tests when they were administered 90 and 150 min, respectively, after smoking. It was also reported that if the THC concentrations and performance test results determined 5 min after smoking stopped were ignored, then failure in one of the three tests was "inevitably" associated with THC serum concentrations above 25 to 30 μg/L. However, the value of this study's conclusions are limited by many factors. The dose administered was not controlled and no control subjects (smoking placebo marijuana) were used. Objective evaluation of the subjects' performances was not possible because the study was not double-blind in nature. The tests administered measured performance in selected motor skills, but not necessarily in skills used while driving. Only "results that showed either the clear presence or absence of impairment were used" to evaluate the impairment-concentration relationship. Therefore, only some (32, 47, and 70%, respectively) of the results from the three component tests were reported. Considered individually, the three tests do not reliably detect THC-induced motor impairment, since roughly 20, 18, and 50%, respectively of the three tests administered resulted in failure. Independent evaluation of the use of these tests as a battery is not possible because no attempt was made to compile and present the results from the tests with respect to either the subject or the time of blood sampling or performance testing. Therefore, the presumption of physical impairment at THC serum concentrations greater than 25 to 30 μg/L cannot be substantiated from the data presented.

A report to the U.S. Congress on the effects of marijuana on highway safety [*120*] summarizes the current state of knowledge concerning marijuana-induced performance impairment:

> Experimental research, taken as a whole, indicates that certain dose levels of marijuana can impair tracking and perceptual functions involved in driving [*105*]. Perception and other complex mental functions appear to be more affected than simple motor or sensory tasks that demand little processing of information. The few studies involving actual car handling on closed courses support the implications of laboratory tests that marijuana use by drivers, especially in higher doses, can increase the likelihood of traffic crashes. However, whether the differences found in laboratory are large enough to have impact in an actual driving situation is unknown [*120*].

In other words, the relationships between testing procedures and real-life situations and the potential effects that decrements in performance measured by those procedures have on the performance of complex integrated and coordinated psychomotor tasks outside the laboratory are not known.

From the preceding discussion, it is apparent that plasma concentrations of THC cannot be used by themselves to predict either effects or performance decrements in either clinical or forensic science situations. Could plasma concentrations of other cannabinoids be used for this purpose? Although peak plasma concentrations of 9-carboxy-THC and maximal subjective effects showed good temporal correlation [*52, 77*] it is unlikely that this metabolite could effectively be used alone as a psychoactivity index, for several reasons. First, being a nonpsychoactive compound, there is no direct causal relationship between concentration and effects. Second, attempts to correlate 9-carboxy-THC concentrations and subjective effects will be influenced by the same types of factors limiting the correlation of effects with urinary concentrations of cannabinoid metabolites. That is, relatively high concentrations of 9-carboxy-THC can be detected in plasma for many hours after marijuana smoking [*77*] (see Fig. 3), and these

concentrations will not necessarily be associated with any effects. This may be particularly true for chornic marijuana smokers. Concentrations of 9-carboxy-THC could potentially be used to infer a relationship with effects if the relationship were exact and specific, but it is neither.

The Use of THC and 9-Carboxy-THC Concentrations in the Interpretation of Effects Produced by Marijuana Smoking

Although neither THC nor 9-carboxy-THC concentrations can be used alone to predict effects, the determination of both THC and 9-carboxy-THC concentrations in a forensic science blood specimen does have two important functions. First, although the two analyses are not mutually confirmatory, they are mutually supportive. The absence of either compound in the presence of the other indicates either that the concentrations are very low and no effects could be induced, or failure of the analysis. Secondly, Fig. 3 shows that THC concentrations fall below 9-carboxy-THC concentrations within about 15 min after smoking began. In several other reports, this occurred roughly 30 min after smoking began [*20,33,52,77,121*]. In all of these reports, near-maximal effects were experienced when THC and 9-carboxy-THC plasma concentrations were equivalent. Therefore, the relative amounts of these two compounds can be used to determine if a subject has not yet, is now, or has already experienced peak effects.

Relative amounts of THC and 9-carboxy-THC in blood or plasma specimens have been used to estimate the effects experienced by drivers killed in single-vehicle accidents [*109,117,118*]; they have also been used in a proposed method to distinguish between actively exposed *Cannabis* smokers and persons passively exposed to marijuana smoke [*102*]. More exact methods for estimating the effects produced by marijuana use will probably depend on the development of mathematical normalization schemes that use THC and 9-carboxy-THC plasma concentrations to estimate the elapsed time since the most recent use. Preliminary investigations of the use of these normalization schemes to predict the time since marijuana smoking [*122*] and *Cannabis* resin ingestion [*123*] have been presented.

Summary and Conclusions

The data base for interpretations of the relationship between cannabinoid concentration and effects is woefully inadequate. At present, interpretations of effects based solely on cannabinoid concentrations are not supportable in adversarial proceedings. These interpretations will be supportable only when THC and 9-carboxy-THC concentrations in plasma or blood are determined by specific fully validated analytical methods when the analytical results are supported by results from appropriate independent confirmatory procedures, when the correlations between cannabinoid concentrations and induced decrements in the performance of relevant skills can be demonstrated to be both significant and beyond reasonable reproach, and when the presumption of impairment is supported by independently obtained corroborative evidence. Data to support imposition of any "per se" concentration of THC or cannabinoids in plasma or blood that is indicative of significant effects or impairment has not been reported in the *Cannabis* literature. Retrograde temporal extrapolation or "back-calculation" of concentrations of any cannabinoid in any human physiological fluid or tissue are not supportable, and thus interpretations of effects based on back-calculated concentrations are not scientifically defensible.

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