Pharmacokinetics and Metabolism of \(\Delta^1\)-Tetrahydrocannabinol and Other Cannabinoids with Emphasis on Man*

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I. Introduction

This review will summarize the pharmacokinetic properties of \(\Delta^1\)-tetrahydrocannabinol (\(\Delta^1\)-THC, \(\Delta\), fig. 1) mainly in man, since only limited information is available in experimental animals. We will also review the metabolites of \(\Delta^1\)-THC, with particular emphasis on those metabolites which have either psychotomimetic properties similar to \(\Delta^1\)-THC or which are eliminated in man.

Metabolic transformations have mainly been elucidated in various in vitro systems and in experimental animals. Only recently, more extensive information on the metabolism of \(\Delta^1\)-THC in man has become available. The pharmacokinetics of the isomer of \(\Delta^1\)-THC, viz. \(\Delta^8\)-THC (2), will be dealt with very briefly, because it only represents a minute constituent of marihuana. Two other major cannabinoids (fig. 1), cannabinol (CBN, 3) and cannabidiol (CBD, 4), will also only be briefly reviewed, because available data for these compounds is somewhat limited. We will review only more significant and recent results, since an extensive survey of all published material in the area would be too voluminous. Thus, much of the early literature not directly related to pharmacokinetics and metabolism is referred to in review articles and in proceedings of symposia.

Unfortunately, two almost equally popular numbering systems are in use today. The biogenetically based monoterpenoid system (\(\Delta^1\)-THC) is used in this survey since it is applicable to both \(\Delta^1\)-THC, CBD, and CBN. The dibenzopyran (\(\Delta^8\)-THC) system which is also shown cannot be used for CBD but has lately been adopted by Chemical Abstracts. The use of these two systems has caused even more confusion when dealing with the metabolites.

The chemistry of cannabinoids has been reviewed re-
to obtain Δ1-THC involves the use of (±)-p-mentha-2,8-
dien-1-ol and olivetol (5-pentyl-resorcinol) in a one step
synthesis. Also (+)-Δ1-THC (unnatural series), CBD, and
CBN have been synthesized (72).

Appropriately modified procedures have been used to
allow the introduction of deuterium, tritium, or carbon-
14 labels in the cannabinoid molecule. The use of a tracer
in metabolic studies has been essential since the meta-
brolic transformation products occur in large numbers but
in small amounts. The early pharmacokinetic studies
were also carried out with radiolabeled Δ1-THC, since no
alternative analytical methods were available at the time
(63). Δ14C label can be introduced either into the benzene
ring, into the side chain, or into the 7-position, but all
procedures are comparatively tedious (42). Tritium or
deuterium can more easily be introduced into the olivetol
side chain by reduction of an unsaturated bond or a
ketone intermediate. Such syntheses have been described
by Pitt et al. (89) and Ohlsson et al. (82), while other
methods have recently been reviewed by Harvey (42).

B. Influence of Route of Administration

Smoking. Cannabis preparations, particularly of the
marihuana type, are usually smoked, which from the
pharmacokinetic analysis point of view introduces nu-
erous uncontrollable factors. One factor concerns the
composition of the drug itself: Δ1-THC is present in a
concentration range from about 0.3% to more than 3%
in hashish up to 10%. It may occur as such, but in
 crude materials Δ1-THC is usually present as monoca-
 rboxylic acids (1 with a single carboxyl group in either
position in the benzene ring). Δ1-THC is also mixed in
the preparation with other cannabinoids, mainly CBD
and CBN, which probably influence the pharmacoki-
etics of Δ1-THC to a limited extent, as discussed later
in this review. In some studies, pure Δ1-THC has been
mixed with placebo marihuana cigarettes, but in most
pharmacokinetic and other studies, the Δ1-THC content
has been calculated as the sum of Δ1-THC and the
 corresponding acids. The latter readily decarboxylate on
heating to yield Δ1-THC (39, 72). Although we know of
no direct comparison, our results might suggest that Δ1-
THC plasma levels are in the same range, independent
of whether pure Δ1-THC or Δ1-THC in the form of crude
marihuana is smoked (2).

Thus, not only the dose of Δ1-THC smoked is im-
portant, but also the time used for smoking. In our
studies, we asked the subjects to smoke the marihuana cigarette
during a period of 3 to 5 min, which is faster than the
usual practice, but advantageous for kinetic analysis (2,
7). Other groups have used 10, 15, or 20 min, which is
similar to actual practice, but causes the dose to be
delivered over those periods of time in approximately 20
fractions (2). Furthermore, the puff duration, volume
inhaled, and the holding of the breath after inhalation
are of importance for the transfer of Δ1-THC (24, 86).
However, the humidity of the cigarette (humidification

II. Pharmacokinetics of Δ1-THC

A. Chemical Aspects of Δ1-THC

The cannabinoids (1 to 4) and many of their metabo-
lites are highly lipid soluble compounds. Δ1-THC can be
dissolved in aqueous solution only in the range of a few
μg/ml or less depending upon conditions (31). The oc-
tanol/water partition ratio of Δ1-THC at neutral pH is
in the order of 6000 (72). Thus, Δ1-THC is a resinsoluble,
especially water-insoluble oil with a pKa value of 10.6
(31). In contrast to almost all other psychotropic agents,
it lacks a nitrogen. Δ1-THC in aqueous solutions readily
binds to glass surfaces, but this can be prevented by the
use of silylated glassware (31). Δ1-THC also rapidly
diffuses into plastic containers and membranes, expe-
tially those containing plasticizers. It is a photolabile
compound, susceptible to heat, acid, and oxidation by
oxygen and can be partly oxidized to CBN (72). However
Δ1-THC handled correctly is a stable compound and can
be stored for months at −20°C at low concentrations,
dissolved in ethanol.

Natural (−)-Δ1-THC (and CBD) has two chiral centers
at C-3 and C-4 in the trans-configuration. This asym-
metry is obviously a problem when nonlabeled, and even
more so when labeled, (−)-Δ1-THC has to be synthesized
as the pure drug. Several stereospecific syntheses have
been described using optically active monoterpenes as
starting materials (39, 42, 72). One convenient scheme

FIG. 1. Structural formulas of Δ1-THC and the monoterpene num-
bering (Δ1-THC) and dibenzopyran (Δ2 numbering systems. The
structural formulas and numbering systems of two other major canna-
binoinds, viz. cannabinol (CBN) and cannabidiol (CBD) are also shown.
The structure of a minor component of cannabis, Δ2-THC (Δ2-THC
dibenzopyran system) is included.
is frequently used to decrease harshness upon smoking) or type of cigarette paper used appear to have no influence on the percentage of transfer of Δ1-THC (86). In addition to these confounding factors, one has to add the smokers' individual preferences in selecting their own level of intoxication.

A number of years ago, we found that about 20% of the Δ1-THC present in a marihuana cigarette (45% with a pipe) was transferred via the main stream smoke when a group of cannabis users smoked in their usual fashion (4). We have found (5) that there is no obvious difference in the amount of Δ1-THC transferred, whether the cigarette is smoked as a tobacco or a marihuana cigarette, with deep inhalations (5). The latter may, however, be important for the amount of Δ1-THC absorbed by the lung (5). CBD and CBN were also transferred to a similar degree as Δ1-THC (4).

Davis et al. (24) have recently published a detailed study of the smoking characteristics of marihuana cigarettes under smoking-machine conditions which simulate puff duration and puff volume of many marihuana smokers. Under these conditions, they found that 16 to 19% of the Δ1-THC in the marihuana cigarette was found in the main stream smoke condensate. When the whole cigarette was consumed in a single puff, yielding little side stream smoke, 69% of the Δ1-THC was recovered in the main stream smoke. One might then assume that about 30% of the Δ1-THC (less of CBN) was destroyed by pyrolysis. A computer-based smoking dynamic system has also been developed that permits a more detailed evaluation of the smoking behavior (55).

The effect of smoking on the cannabinoids and other compounds present in cannabis preparations has recently been reviewed by Harvey (42). Apart from quantitative decarboxylation of cannabinoid acids, the ratios of cannabinoids in the smoke and in the crude drug seem to be similar, but numerous pyrolytic products are formed (4, 42). In many respects, tobacco and marihuana smoke are quite similar, apart from nicotine being obviously present in tobacco while Δ1-THC, CBD, and CBN are present in the marihuana smoke condensate (42).

Other routes of administration. Cannabis preparations are sometimes ingested p.o., in which case the acid of the stomach can be expected to degrade Δ1-THC. Several competing reactions occur at low pH. One is the isomerization of Δ1-THC to the thermodynamically more stable Δ2-THC (31). In addition to isomerization, the oxygen in the pyran ring is also protonated, causing ring cleavage to substituted CBDs (31, 42).

Δ1-THC (5 mg), CBD, and CBN (20 mg) can also be given safely and reproducibly by the i.v. route in man if administered as a solution in 2 ml of ethanol into the injection port of a rapidly flowing i.v. solution of saline over a period of 2 min (83). In most animal experiments, i.v. formulations consist of emulsions of Δ1-THC in Tween 80 or albumin (90).

Systemic absorption of Δ1-THC in the rabbit after ophthalmic administration is slow and variable (19) but may be substantial. Similarly, we have found that i.p. administration of Δ1-THC in the rat yields slowly increasing and not readily reproducible plasma levels.

C. Measurement of Cannabinoids and Biological Fluids

Most of the analytical development during the past decade has focused on Δ1-THC, the important pharmacologically active constituent of marihuana (33, 42, 49). The development of the highly sensitive analytical methods needed to measure the blood or plasma levels of Δ1-THC has, however, been somewhat disappointing. There are several reasons for this. Foremost is the high potency of Δ1-THC. In man, doses above 10 μg of Δ1-THC per kg consumed from smoking marihuana (calculated as absorbed Δ1-THC) are sufficient to cause a “high.”

Another complicating factor is the difficulty in separating ng amounts of Δ1-THC from endogenous lipids. Consequently, only highly sensitive and selective assay methods are applicable, such as electron capture-gas chromatography (EC-GC), high-performance liquid chromatography (HPLC) with sensitive detectors or post-column derivatization, radioimmunoassays (RIA), combined with purification steps, or gas chromatography-mass spectrometry (GC-MS). Methods to adequately measure urinary metabolites for forensic analysis are also difficult and outside the scope of this review.

Clean-up methods [wet columns, derivatization, thin-layer chromatography (TLC)] are necessary to achieve partial purification of the Δ1-THC in the blood plasma from interfering lipids and metabolites prior to assay. Thus, Garrett and Hunt (32) found that an EC-GC method to assay Δ1-THC in dog plasma had a sensitivity of 0.5 to 1 ng/ml in the fasted dog, whereas the sensitivity decreased 10-fold in the nonfasted animal. The sensitivity of analytical methods for Δ1-THC seems also to vary with species. For instance, Harvey developed a very sensitive method using a double-focusing mass spectrometer tuned to a metastable ion in the spectrum of Δ1-THC for quantitating the cannabinoid in rabbit plasma (down to 5 pg/ml). The sensitivity in human plasma was, unfortunately, much less (42). EC-GC procedures using pentafluorobenzoate seem not to be sufficiently sensitive to measure Δ1-THC levels in man, except for the first hour or two after smoking (32). Also, neither currently available HPLC, nor TLC methods are adequate (42).

Three methods seem to be in regular use to measure Δ1-THC in human blood plasma. One is based upon our original GC-MS method, in which deuterated Δ1-THC is added to the plasma sample as internal standard (3). A clean-up is achieved using a Sephadex LH-20 column, and a TMS-derivative provides increased sensitivity (down to 0.05 to 0.3 ng/ml) in the GC-MS assay (78). A similar GC-MS procedure employing chemical ionization is used by Foltz et al. (27). Cross-reactivity with other cannabinoids and their metabolites is a major drawback.
of RIAs. However, several groups have developed reasonably specific assays for both Δ⁠₁-THC and its major metabolite 7-hydroxy-Δ⁠₁-THC in human blood plasma (22, 49). The limit of sensitivity appears to be around 2 ng of Δ⁠₁-THC per ml in human blood plasma. CBD and CBN can be measured with high sensitivity (0.1 to 0.3 ng/ml) using GC-MS essentially as described above for Δ⁠₁-THC (1). For more extensive discussions on the analysis of cannabinoids in body fluids, we refer to recent reviews (42, 49).

**D. Plasma Levels of Δ⁠₁-THC in Man after Smoking, p.o., and i.v. Administration**

Lemberger et al. were the first to study the blood levels of Δ⁠₁-THC in man (63). They showed that radiolabeled THC given i.v. disappeared faster from the blood plasma of chronic marihuana smokers (half-life, 28 h) than from the plasma of nonusers (half-life, 57 h). There were no differences in the volume of distribution. The analytical techniques used in this study have, however, been questioned (23). Lemberger et al. also discovered that a metabolite of Δ⁠₁-THC, 7-hydroxy-Δ⁠₁-THC (11-hydroxy-Δ⁠₈-THC), was quickly formed in man and present in blood, urine, and feces (63). Since the metabolite is psychoactive, this finding raised the question of whether Δ⁠₁-THC was active per se or only (or partly) after metabolic transformation to 7-hydroxy-Δ⁠₁-THC. Lemberger et al. also studied the temporal correlation between the peak plasma levels of radiolabeled Δ⁠₁-THC and its metabolites and the psychological “high” (64). The discovery that the psychological effects of both p.o.-administered and inhaled Δ⁠₁-THC were temporally correlated with plasma levels of the metabolite was taken as support for a hypothesis that the metabolite, indeed, is the active compound. This “active metabolite hypothesis” is discussed later in this review.

With availability of adequate RIA and GC-MS assay methods for Δ⁠₁-THC in blood plasma, knowledge about the pharmacokinetics of Δ⁠₁-THC in man has increased rapidly during the last few years.

Fig. 2 A shows the average plasma levels of Δ⁠₁-THC after i.v. administration of 5.0 mg of Δ⁠₁-THC during a 2-min injection period. The Δ⁠₁-THC concentrations were followed for 4 h using a GC-MS procedure (83). Δ⁠₁-THC levels were about 200 ng/ml at 3 min postinfusion and declined rapidly to about 15 ng/ml at 1 h and about 3 ng/ml at 4 h. In this study, the psychological “high” had essentially disappeared by 3 h (83).

From a pharmacokinetic point of view, it is advantageous to assess the kinetics of Δ⁠₁-THC after i.v. administration compared to smoking. The latter route delivers Δ⁠₁-THC in approximately 15 to 25 fractions or “puffs” at irregular intervals over 5 to 20 min. It is obviously difficult to obtain enough representative plasma samples during the actual smoking of Δ⁠₁-THC, although plasma levels probably fluctuate less than one would expect (10; fig. 6). Further, since the plasma levels drop so rapidly, the influence of the first 20 min is large on the total area under the plasma curve (AUC) used to determine the systemic availability after smoking. Hence, errors in determining Δ⁠₁-THC in the early plasma samples will influence certain kinetic parameters significantly.

Smoking a marihuana cigarette containing 19.0 mg of Δ⁠₁-THC over a period of 5 to 7 min in order to achieve each individual subject’s desired “high” yielded the plasma levels shown in fig. 2 B. Essentially, the smoking curve is parallel to the i.v. curve at about half the concentration. It should be noted that the average amount of Δ⁠₁-THC smoked (amount of Δ⁠₁-THC originally in the cigarette less the amount remaining in the butt) was 13.0 mg with a range of 11.6 to 15.6 mg. The curves in fig. 2, A and B, are average plasma curves. The interindividual variation is less after i.v. administration than after smoking. The curves in fig. 2, A and B, would suggest a biphasic disappearance of Δ⁠₁-THC, but this does not include a final elimination phase.

Administration of 20 mg of Δ⁠₁-THC p.o. in a chocolate cookie was also studied in the same subjects (83). The average plasma curve (fig. 2 C) indicates a slow increase in Δ⁠₁-THC levels to 6 ng/ml at 1 h followed by a steady decline. The mean curve, however, is typical of few subjects; Δ⁠₁-THC seems to be slowly and unreliably absorbed from the gut after p.o. administration, as studied in the present formulation. Some subjects showed two plasma peaks; some did not show maximum plasma concentrations until 4 to 6 h after administration, but most subjects had plasma peaks between 1 and 2 h. The low plasma levels are not due to a poor absorption of Δ⁠₁-THC or its possible breakdown products (see section II A) as 90% of the total radioactivity was absorbed after the p.o. administration of radiolabeled Δ⁠₁-THC (64).

In order to study the terminal half-life of Δ⁠₁-THC, it is necessary to follow the plasma levels for 48 h or more after administration. Fig. 3 A show the average plasma levels over 48 h in a group of heavy and in a group of light marihuana users after smoking 10.0 mg of Δ⁠₁-THC-d₈ (84). The deuterium-labeled analogue was used, since heavy users may have difficulties in abstaining from the drug for 48 to 72 h. The results after i.v. administration of 5.0 mg of Δ⁠₁-THC-d₈ are shown in fig. 3 B. There is little difference between the two groups, although, as in a previous larger study (66), there was a trend for heavy users to obtain lower plasma levels of Δ⁠₁-THC than light users. Part of this difference could be explained by a higher average body-weight in heavy users.

It is also clear from fig. 3, A and B, that heavy users achieved higher plasma levels of Δ⁠₁-THC than light users smoking the same amount. This can be attributed to a more efficient smoking technique (83, 84). From fig. 3, it is evident that Δ⁠₁-THC levels are in the 0.1 to 1 ng/ml range 6 h after smoking 10 mg of Δ⁠₁-THC. It also appears that there is little difference (between heavy and light users) in the terminal half-life of Δ⁠₁-THC.
The kinetics of Δ⁠₁-THC in man have also been investigated in men and women by Wall et al. (99). Fig. 4 shows average plasma levels after 2.2 mg of Δ⁠₁-THC by slow infusion and 15 mg p.o. in women. In general, the results of this study suggested no obvious kinetic differences between men and women. The plasma Δ⁠₁-THC levels after i.v. dosing are clearly higher in this study (99) than in ours (83, 84) or observed at 6 h by Hunt and Jones (54). Whether this is due to differences in analytical techniques (GC-MS versus tritium label), in the formulation used for the i.v. administration (ethanol solution versus microsuspension in albumin), or something else is not clear, although we suspect it is the formulation. Studies in rats (26), where plasma levels of Δ⁠₁-THC were compared after i.v. infusion of radiolabeled Δ⁠₁-THC dissolved either in polyethylene glycol or premixed in plasma, suggest that higher Δ⁠₁-THC concentrations may be caused by the protein formulation. The plasma levels (fig. 5) after p.o. dosing using an oil formulation are in the same range as ours (83). The disposition of Δ⁠₁-THC in man has also been studied by Hunt and Jones (54). The plasma levels of Δ⁠₁-THC they recorded during approximately 30 h after a 2-min infusion of a 2-mg ¹⁴C-Δ⁠₁-THC dose agree very closely with our findings that Δ⁠₁-THC levels decreased to less than 1 ng/ml 3 h after dosing (84).

Plasma Δ⁠₁-THC levels during the smoking process have probably been best studied by Barnett et al., although information is quite limited (10). Their six subjects, who were male or female smokers, were asked to smoke one marihuana cigarette containing about 9 mg of Δ⁠₁-THC at their usual pace (average, 10- to 11-min smoking time). Two h later, they were asked to smoke a second cigarette. The plasma Δ⁠₁-THC concentrations versus time are shown in fig. 6 and indicate that smoking is most intense during the first few minutes. All subjects
reached maximum Δ1-THC plasma levels before the end of smoking (10). However, the authors could not fully rule out that the time to maximum concentrations might have been an artifact of the blood sampling.

There is very little dose-response information with respect to Δ1-THC or marihuana. However, Perez-Reyes and coworkers carried out a study that covered the dose range of 9.7 to 16.0 mg of Δ1-THC by smoking (86). Although the subjects were asked to smoke until their usual “high,” it was found that the higher potency of the marihuana, the more Δ1-THC was smoked. They further found a direct correlation between the peak plasma Δ1-THC level and the Δ1-THC content of the cigarette, whereas the relation of the AUC was less straightforward. The relation of dose to pharmacological response (“high”) was also reasonable (86).

E. Pharmacokinetic Parameters in Man

Plasma Δ1-THC levels in man decay in a fashion which can be interpreted using 3-, 4-, or 5-compartment models (10, 25, 54). Although the use of compartmental models is controversial, in our experience the terminal half-life is long in both heavy and light users (half-life > 20 h) (84). Hunt and Jones also found a similar average half-life in man, about 19 h (range, 13.8 to 26.0 h), independent of whether the subjects were relatively moderate users or exposed to heavy p.o. Δ1-THC doses for about 2 weeks (54). Similarly, Lemberger et al. found a half-life for Δ1-THC in chronic users of 28 h, whereas it was found to be longer (half-life = 57 h) in naive users (63). Wall et al. likewise suggested a terminal half-life of 25 to 36 h for both men and women (99).

In fig. 7, we show the slow elimination of Δ1-THC in a very heavy marihuana smoker after discontinuation of the drug. To control for interference from illicit use of marihuana after discontinuation, the subject received Δ1-THC-d2 before abstinence. The steady, parallel decline of both curves from day 1 to day 8 after discontinuation
suggests a terminal half-life of 20 h with possibly a tendency to become longer (2).

Thus, the terminal half-life of Δ1-THC is in the order of 20 to 30 h and is in the same range as many psychotropic drugs such as amitriptyline, imipramine, haloperidol, and nitrazepam. Little is known about interindividual differences in half-lives. We feel, however, that the present estimates of half-life for Δ1-THC are based on somewhat uncertain data and should be strengthened by more long-term elimination studies using more precise assay methods.

The systemic availability ("bioavailability") of Δ1-THC has been assessed by comparing the area under plasma concentration versus time curve (AUCs) after i.v. and p.o. administration or smoking. During smoking, the bioavailability of Δ1-THC is limited by pyrolysis, loss through side stream smoke, inefficient absorption in the lung and, possibly, to a small extent by metabolism in the lung before entering the systemic circulation (36, 102). After p.o. administration, the availability of Δ1-THC is limited by the sensitivity of Δ1-THC to acidic gastric juice (see section II A) and also by presystemic elimination in gut and liver, the "first pass elimination." In table 1, we have recorded the systemic availability of Δ1-THC, as evident from published data. We have assumed that Δ1-THC kinetics are not dose dependent.

Thus, partly depending upon the experience of the user, the systemic availability of smoked Δ1-THC is usually in the range of 10 to 25%. The lowest systemic availability we have recorded of smoked Δ1-THC is 2% and the highest, 56%. Fig. 8 illustrates individual values of areas under the plasma concentrations versus 0- to 240-min time curves after smoking and i.v. administration of Δ1-THC in heavy and light users of marijuana. The interindividual variation is considerable after both smoking and i.v. infusion of Δ1-THC, and there is considerable overlap between the two groups (66). Hardly
any data on intraindividual differences are available, but our scanty information would indicate consistency in the same individual. Furthermore, the study of Barnett et al. (10) provides some evidence for this assumption.

The volume of distribution of Δ^1-THC in man has been estimated by several authors to be about 10 L/kg, typical of a lipophilic drug (54, 84, 99). As such, it also shows a high plasma clearance value of 760 to 1190 ml/min in one study (84) and about 800 ml/min in another (54), close to the hepatic plasma flow of about 800 ml/min.

Limited information is available on the protein binding of Δ^1-THC and its blood/plasma distribution ratio (32, 42, 100), as conventional techniques are not readily applicable (32). In vitro experiments suggest that only 10 to 20% of Δ^1-THC in blood is bound to the red blood cells (32, 100). The remainder exists in plasma, at least 97% bound to proteins. It would appear that Δ^1-THC is mainly bound to lipoproteins, but the metabolite 7-hydroxy-Δ^1-THC is also bound to albumin (100).

F. Tolerance to Δ^1-THC—Functional Tolerance or Induced Metabolism?

Development of tolerance to both pharmacological and psychological effects of Δ^1-THC after prolonged administration is well established in both man and animals (88b, 54, 51). Two hypotheses have been suggested: (a) functional tolerance due to adaptation to drug concentrations or (b) dispositional tolerance as a result of either increased metabolism or other pharmacokinetic changes. Indeed, the early study of Lemberger et al. suggested that the half-life of Δ^1-THC in chronic users was clearly shorter than in nonusers, although these results have not been collaborated by later studies (63). Interpretation of the effects of an induction of metabolism is not simple, as one could also postulate that a more rapid formation of the psychoactive metabolite 7-hydroxy-Δ^1-THC could lead to an increased sensitivity rather than tolerance, provided that the further metabolism of 7-hydroxy-Δ^1-THC was less facilitated.

Hunt and Jones studied the influence of prolonged p.o. Δ^1-THC administration on the pharmacokinetics and metabolism of Δ^1-THC in man (54). They evaluated possible changes based on plasma levels of unchanged ^1^C^-Δ^1^-THC after i.v. administration before and after a 2-week Δ^1^-THC administration (fig. 5). Minor changes, such as an increase in plasma clearance, were caused by the previous exposure to Δ^1^-THC, but the volume of distribution and most other pharmacokinetic parameters were unchanged. Consequently, they concluded that the development of tolerance to the cardiovascular and psychological effects of Δ^1^-THC could not be explained by changes in drug disposition. This is also evident from fig. 5. Whether the amount of exposure was enough to cause pronounced tolerance is, however, not clear.

In two studies, we compared differences in some pharmacokinetic parameters between heavy and light cannabis users (66, 84). As discussed elsewhere, the definition of “heavy user” may be crucial—our group of heavy users could be considered as moderate (at least one marihuana cigarette per day) to heavy (10 or more per day) users. In both the study (84) shown in fig. 3 and another larger study (66) of similar design, we found limited differences in plasma levels and rate of disappearance of a Δ^1^-THC i.v. dose between the two groups, although there was a nonsignificant tendency for heavy users to have lower plasma levels. The average Δ^1^-THC plasma levels after smoking were, in both studies, about twice as high in heavy as in light users. This difference is probably explained by the more efficient smoking of the experienced users. Although one has to remember that there are several types of effects and mechanisms towards which tolerance can develop, such as “high,” tachycardia (β-adrenergic mediation), and anticholinergic effects, it is likely that the tolerance which develops is mainly functional. There are, however, indications that very frequent marihuana smoking is needed to develop tolerance (65, 88b).

G. Relations between Plasma Levels and Effects

As early as 1972, Galanter et al. found indications in a group of marihuana users (after smoking radiolabeled Δ^1^-THC during a period of 10 min) that the plasma levels of Δ^1^-THC peaked within 15 min, accompanied by a parallel increase in pulse rate (30). Both plasma Δ^1^-THC concentration and pulse rate declined rapidly, whereas the subjective “high” increased more slowly but was maintained longer. In another study, Borg et al. found a significant dose-response effect, both on pulse rate and impaired performance, from increasing doses of smoked Δ^1^-THC (14b). Since then, many investigators, using
appropriate assay methods for Δ1-THC and occasionally also for the metabolite 7-hydroxy-Δ1-THC, have tried to correlate plasma levels of Δ1-THC with subjective psychological effects ("high"), pulse rate, memory, and performance tests.

In one extensive study, we attempted to correlate plasma concentrations of Δ1-THC with self-rating of degree of intoxication, with pulse rate and with conjunctival injection after i.v., p.o., and smoke administration of Δ1-THC (53). Before taking each blood sample from the 11 subjects, they rated their "high" on a scale from 0 to 10. Fig. 9 shows the relations between plasma Δ1-THC concentration and "high" after i.v. administration of Δ1-THC. There is a relation, although modest, between Δ1-THC level and intoxication. After p.o. administration, the correlation was slightly better ($r = 0.42$), and after smoking, still somewhat better ($r = 0.53$). Equally obvious, however, was the large number of subjects experiencing only a little "high" in spite of high Δ1-THC levels, while other subjects experienced a pronounced "high" at very low Δ1-THC levels (53). This partial lack of correlation can be understood from fig. 10 A, where both average Δ1-THC levels and average degree of "high" are plotted over time. After i.v. administration, the peak Δ1-THC levels are obviously reached in the first plasma samples, but the peak "high" is not reached until 15 min after injection. Plasma Δ1-THC levels also decline more rapidly than the psychological effects. Since it was observed that some subjects experienced only a little "high" in spite of high Δ1-THC plasma levels during the initial distribution phase—when the drug might still not have been able to efficiently pass the blood-brain barrier—we attempted to evaluate correlations between Δ1-THC plasma levels and "high" at different times and after different routes of administration. Correlations were slightly better for smoking from 10 to 120 min after administration but were not highly significant for any time period or any route (53).

The relation between the degree on "high" and the recorded plasma concentration (about 250 assessments) for all routes of administration is shown in table 2. The individual variability is considerable.

In fig. 10 C, we have shown the time course of the "highs" after all three modes of administration. The time courses after i.v. administration and smoking are quite similar, just as the plasma curves in the same subjects (fig. 2, A and B) after these routes of administration are similar. The time course of "high" after p.o. administration of 20 mg of Δ1-THC (fig. 10 B) peaks decidedly later and at a lower maximum. However, considering the low average peak level of Δ1-THC in these subjects (6 ng/ml; fig. 10 B), the magnitude of the "high" is still remarkable. As discussed later in this section, this can be partially attributed to the psychoactive effects of increased production of the active metabolite 7-hydroxy-Δ1-THC after p.o. administration of Δ1-THC. Thus, this study showed that, although there is a moderate correlation between plasma Δ1-THC values and "high," there is also a wide variation in individual values (53). A clear-cut relationship between plasma concentrations of Δ1-THC and degree of intoxication (evaluated by subjective "high"), as has been shown for alcohol, could not be demonstrated.

Conjunctival injection in relation to plasma Δ1-THC concentration has also been assessed (53). It was found to be maximal 10 min after both smoking and i.v. administration and, thereafter, it decreased. After p.o. administration, the maximum conjunctival injection coincided with the Δ1-THC plasma peak (fig. 2 C). The effect was variable but, in general, the reddening of the conjunctivae was present as long as plasma Δ1-THC levels were above 5 ng/ml.

Another highly reliable sign of cannabis effect is the increase in pulse rate. After a 5-mg i.v. dose of Δ1-THC, increases of 25 to 100 beats (average, +40 beats/min) at a Δ1-THC plasma level of about 100 ng/ml were recorded (53). After smoking about 13 mg of Δ1-THC, the maximum average increase in pulse rate was 34 at plasma levels of about 45 ng/ml. The pulse rate response occurs

![Fig. 9. Relation between log concentration of plasma Δ1-THC and "high" after i.v. administration of 5.0 mg of Δ1-THC. From ref. 53.](image-url)
Fig. 10. Time course of average "high" versus plasma Δ^1^-THC levels after i.v. administration (A) and after p.o. administration (B). C, time course of "high" ratings after three routes (i.v., smoking, p.o.) of administration of Δ^1^-THC. Redrawn from ref. 53.

The relationship between plasma Δ^1^-THC levels after marihuana smoking and pharmacological effects (tachycardia and "high") in man has also been studied by Cocchetto et al. (21). Using hysteresis' plots, they found that both heart rate and subjective "high" were present in a "deep compartment" relative to the plasma compartment. Their finding that the time course of tachycardia as well as "high" both lagged behind the plasma concentration peak of Δ^1^-THC is congruent with the findings from our group (53, 66), Wall and Perez-Reyes (98), Galanter et al. (30), and others. Cocchetto et al. (21) also suggested that plasma Δ^1^-THC concentrations are poor predictors of simultaneous psychological and physiological effects. This is also in agreement with our previous study (53). Incidentally, Domino et al. have combined data from several of our studies and formulated an interesting mode. Based on certain assumptions, these workers suggested that the time course for an average subjective marihuana high might be predicted from plasma Δ^1^-THC levels (25).

Miller et al. have explored more deeply the relationships in man between Δ^1^-THC plasma concentrations and various effects (73). They also investigated relations to factors in the Linear Mood Scale. Although certain mood factors in the scale such as disturbed/weird and sensitive/aware correlated better with kinetic parameters than others, they concluded that a global subjective "high" rating was still the most reliable index. They also found the temporal dissociation between "high" and plasma concentrations noted by others (21, 30, 53).

The effects of Δ^8^-THC seem, in general, to be very similar to those of Δ^1^-THC (6). Assessment of performance by critical flicker fusion (CFF) or reaction time indicated that the lowest performance levels were obtained well after the peak in plasma level. The effect on heart rate was better correlated with plasma Δ^8^-THC levels. The effect on heart rate appears to be independent of the psychological effects, since heart rate acceleration can be blocked by i.v. propranolol without altering the "high" (6).

The conclusion from a number of studies in man on relations between pharmacokinetic parameters of Δ^1^-THC and psychological ("high") or physiological (pulse rate) effects is quite clear. There is a reasonable corre-
lation between plasma $\Delta^1$-THC level and effects on pulse rate and the even greater dissociation for the subjective “high.” The mechanism for this is not understood. The lag time between peak plasma level and peak “high” cannot readily be explained by the slow formation of an active metabolite. The reason for the lag is not known, but one possible explanation—not well supported by experimental results—is that the lag could be due to a somewhat slower transformation of $\Delta^1$-THC into the brain (85). Such a delaying process could be further influenced by the time required to start the biochemical events or, speculatively, to penetrate to the receptor, or displace a possible endogenous ligand in order to yield the desired psychological “high.” Other theoretically possible explanations for the limited relations between pharmacokinetic and pharmacodynamic parameters are the presence of a bell-shaped dose-response curve or the possibility that the “high” is a net result of two counteracting dose-response curves with different shapes. Neither of these two latter explanations has any experimental support at present.

Active metabolite theory. The discovery of the active metabolite 7-hydroxy-$\Delta^1$-THC, has led to the suggestion that rate of onset of activity following $\Delta^1$-THC could, to a great extent, depend on its slow transformation to the active metabolite. The delay in onset of “high” and other effects could then be theoretically accounted for by the comparatively slow formation of the active compound, 7-hydroxy-$\Delta^1$-THC (64). This hypothesis, however, does not seem plausible, since the marihuana-like psychological “high” appears at about the same “slow” rate after i.v. dose of both $\Delta^1$-THC and 7-hydroxy-$\Delta^1$-THC in man. The latter compound does not provide an “instant high” but has a pharmacological profile identical to $\Delta^1$-THC itself (62, 88a).

Other experiments in man have shown that, after both i.v. administration of $\Delta^1$-THC (99) and smoking (98), the levels of 7-hydroxy-$\Delta^1$-THC are so low (about $\frac{1}{50}$ of $\Delta^1$-THC) that it would seem unlikely that the metabolite could make an important contribution to the effects of $\Delta^1$-THC per se. Other findings, using sensitive methods, suggest, however, that, after equal i.v. doses of $\Delta^1$-THC and 7-hydroxy-$\Delta^1$-THC in man, the plasma levels of $\Delta^1$-THC are about 3 times higher than those of the metabolite (98). The same 3-fold difference in plasma levels from similar doses has also been obtained in animal experiments (91). Further experiments have shown that the comparative brain levels of the isomeric 7-hydroxy-$\Delta^1$-THC were about 3 times higher than those of $\Delta^1$-THC (85). Thus, plasma levels of 7-hydroxy-$\Delta^1$-THC in man $\frac{1}{50}$ of the levels of $\Delta^1$-THC, by extrapolation, would indicate an amount of 7-hydroxy-$\Delta^1$-THC about $\frac{1}{4}$ that of $\Delta^1$-THC in the body. Further, the two compounds are about equipotent in man (88a). To summarize, present evidence indicates that it is unlikely that 7-hydroxy-$\Delta^1$-THC contributes considerably to the effects of $\Delta^1$-THC after smoking or i.v. injection.

After p.o. administration of $\Delta^1$-THC to man, however, plasma levels of 7-hydroxy-$\Delta^1$-THC are almost equal to those of $\Delta^1$-THC (98, 99) at all sampling time periods from 1 to 6 h after administration. Based upon the relative plasma/brain levels of $\Delta^1$-THC and 7-hydroxy-$\Delta^1$-THC, as discussed above, one would assume that the total amount of the metabolite 7-hydroxy-$\Delta^1$-THC in the body would be at least twice the amount of $\Delta^1$-THC itself after p.o. administration of $\Delta^1$-THC. It is known that, per mg administered i.v., 7-hydroxy-$\Delta^1$-THC is equally potent in producing a “high” as $\Delta^1$-THC (88a). One might then speculate that, after p.o. dosing of $\Delta^1$-THC, the metabolite 7-hydroxy-$\Delta^1$-THC contributes more than $\Delta^1$-THC per se to the psychological “high.”

As discussed later (section V C), 7-hydroxy-$\Delta^1$-THC is the only metabolite that is active enough and abundant enough in man to be able to contribute to the effects of $\Delta^1$-THC. It is true that there is a better correlation in man between the occurrence of more polar metabolites, such as $\Delta^1$-THC-7-oic acid (24), and psychological “high” (98). Since this acid, and presumably all other polar metabolites, is inactive (98), this covariation between effect and total plasma metabolite levels seems fortuitous.

Our present views on the “active metabolite theory” may be summarized as follows. In man it is unlikely that any active metabolite, such as 7-hydroxy-$\Delta^1$-THC, contributes in an important way to the effects of $\Delta^1$-THC after smoking or i.v. administration. After p.o. administration, however, we assume that 7-hydroxy-$\Delta^1$-THC contributes at least as much as $\Delta^1$-THC itself.

III. Pharmacokinetics and Distribution of $\Delta^1$-THC in Animals

The pharmacokinetics of $\Delta^1$-THC has been studied in detail only in the dog by Garrett and Hunt (32). They estimated a terminal half-life of approximately 8 days. Harvey (42) found a terminal half-life in the rabbit of 2 to 4 days. In both these studies, the plasma $\Delta^1$-THC levels were followed for more than 1 week. The plasma levels in other studies where $\Delta^1$-THC has been administered to animals have usually been quite short, and the rapid decline mainly reflects uptake by the tissues. Hunt and Jones calculated that about 70% of a $\Delta^1$-THC dose administered i.v. to an animal would be taken up by the tissues and that some 30% would be metabolized (54). After 6 h, the rate-limiting step for elimination of unmetabolized $\Delta^1$-THC is the return to plasma of $\Delta^1$-THC sequestered in tissues. This assumption is supported by the results in the rat of Kreuz and Axelrod (60), who found a half-life of 5 days for $\Delta^1$-THC when determined from $\Delta^1$-THC present in fat. If the terminal half-life is controlled by the return from tissues, one would expect that the half-life would be, as generally found in human studies (section II E), quite insensitive to changes in
metabolic clearance due to induction or inhibition of Δ<sup>1</sup>-THC metabolizing enzymes. The amount of fat in the body in man may, however, theoretically make a difference in half-life between lean and obese individuals, although this has not been tested (21).

The distribution of Δ<sup>1</sup>-THC and its metabolites has been studied quite extensively in mice and other animals. Whole-body autoradiography of Δ<sup>1</sup>-THC, combined with analysis of Δ<sup>1</sup>-THC and its metabolites present in the tissues, showed that the distribution pattern in mice changes with time (91). Earlier studies in rabbits revealed similar changes with high levels of Δ<sup>1</sup>-THC found in kidneys and lungs 2 h after an i.v. administration (102). After 3 days, however, spleen and bone fat showed the highest levels of Δ<sup>1</sup>-THC. High, sustained fat levels of Δ<sup>1</sup>-THC have also been found by others (42). Long-chain fatty acid conjugates of Δ<sup>1</sup>-THC metabolites may possibly be retained in the tissues (61).

The nature of the material in the tissues has been partly identified in the mouse (91). Surprisingly enough, the brain contained very low concentrations of both Δ<sup>1</sup>-THC and metabolites. 7-Hydroxy-Δ<sup>1</sup>-THC was produced rapidly, and the brain concentrations of this metabolite after i.v. administration of Δ<sup>1</sup>-THC remained parallel with Δ<sup>1</sup>-THC at about half the concentration of Δ<sup>1</sup>-THC itself. Furthermore, in the lung, heart, kidney, and spleen, the concentration of Δ<sup>1</sup>-THC were higher than those of 7-hydroxy-Δ<sup>1</sup>-THC. In the liver, the situation was reversed, with the 7-hydroxy metabolite levels being higher than the Δ<sup>1</sup>-THC levels throughout the 5-min to 96-h analyses. The levels of more polar metabolites were consistently higher (3 to 10 times) than those of Δ<sup>1</sup>-THC itself, particularly in spleen and liver, but less so in brain. The blood levels of 7-hydroxy-Δ<sup>1</sup>-THC remained at about 1/6 of those of Δ<sup>1</sup>-THC.

Low levels of Δ<sup>1</sup>-THC in the brain have been reported in three other studies (42, 57, 85) in amounts which correspond at most to 1% of the administered dose at peak concentration. If we assume that a similar distribution exists in man, one would expect that a pronounced "high" in man will be caused by the presence of as little as 10 μg of Δ<sup>1</sup>-THC in the brain, immediately after smoking a marihuana cigarette.

The concentration of radiolabel in the brain from 14C-labeled Δ<sup>1</sup>-THC was distributed in the caudate nucleus, putamen, thalamus, pons, hippocampus, and the frontal and parietal cortex, but there was no dramatic uptake at any particular site (42). The patterns of distribution for Δ<sup>1</sup>-THC, CBN, and CBD were similar (9) in the brain.

The route of administration and the formulation of Δ<sup>1</sup>-THC are important for its absorption and distribution (94).

**IV. Pharmacokinetics of CBD and CBN in Man**

CBD is one of the major constituents in most cannabis preparations but has no psychotomimetic effect in man (50). The compound, however, has anticonvulsant activ-
Cannabinoids and metabolism of Δ⁠¹⁠⁻⁠tetrahydrocannabinol

Cannabinoids with Δ⁠¹⁠⁻⁠THC as the primary metabolite of Δ⁠¹⁠⁻⁠THC in man. Some of the reasons for this slow development are: the high potency of Δ⁠¹⁠⁻⁠THC (a single mg absorbed is enough to produce psychoactive effects in man); the very diverse metabolism of cannabinoids (approximately 80 metabolites of Δ⁠¹⁠⁻⁠THC are known today); the difficulties in the separation and isolation of the metabolites; and perhaps also problems in obtaining necessary legal and ethics committee approvals for the appropriate human studies. Studies on the metabolism of Δ⁠¹⁠⁻⁠THC have been carried out in the mouse, rat, guinea-pig, rabbit, dog, monkey, and man using both in vitro and in vivo methods. In this

V. Metabolism of Δ⁠¹⁠⁻⁠THC

It has taken more than a decade of metabolic studies to progress from the early identification of 7-hydroxy-Δ⁠¹⁠⁻⁠THC as the primary Δ⁠¹⁠⁻⁠THC metabolite (72, 39, 42) to the elucidation of the chemical structures of the urinary metabolites of Δ⁠¹⁠⁻⁠THC in man. Some of the reasons for this slow development are: the high potency of Δ⁠¹⁠⁻⁠THC (a single mg absorbed is enough to produce psychoactive effects in man); the very diverse metabolism of cannabinoids (approximately 80 metabolites of Δ⁠¹⁠⁻⁠THC are known today); the difficulties in the separation and isolation of the metabolites; and perhaps also problems in obtaining necessary legal and ethics committee approvals for the appropriate human studies. Studies on the metabolism of Δ⁠¹⁠⁻⁠THC have been carried out in the mouse, rat, guinea-pig, rabbit, dog, monkey, and man using both in vitro and in vivo methods. In this

summary, the material has been separated into primary metabolites and metabolites eliminated in feces and urine.

A. Isolation and Identification of Metabolites

The isolation of primary metabolites of Δ⁠¹⁠⁻⁠THC from metabolic studies using human liver (38) is, in principle, similar to the techniques used to isolate urinary metabolites with the modifications necessary due to the ubiquitous presence of carboxylic functions in urinary Δ⁠¹⁠⁻⁠THC metabolites (34, 35). Fig. 13 shows the procedures for isolation of acidic metabolites of Δ⁠¹⁠⁻⁠THC from the urine of man. Although these procedures are indeed tedious, they have allowed the isolation of a large number of metabolites in a reasonably pure form, the structures of which have been determined unequivocally by nuclear magnetic resonance (NMR) analysis (75, 76). Certain of these structural assignments have later been confirmed by synthesis.

Wall et al (97) have isolated metabolites using somewhat different methods. Extensive isolation schemes have been utilized by Kanter and Hollister for the separation and identification of urinary metabolites of Δ⁠¹⁠⁻⁠THC (58, 59). Finally, Harvey and Paton have used limited isolation procedures and relied heavily on combined GC-MS for the structural assignments (47). Mass spectrometry is particularly useful, and Binder et al. could predict the position of side chain hydroxylation from mass spectrometry (MS) data (14a). The mass spectrometric fragmentations of cannabinoids and the mechanisms have been extensively investigated by Harvey (47, 40, 41, 48) and by Binder (13, 14a), using derivatization techniques. A wealth of information of the structural assignment, particularly based on MS data, is available in the subsequently quoted papers.

Gudzinowicz et al. have in their extensive review of
assay and metabolism of cannabinoids cited numerous experimental procedures (33).

B. Primary Metabolites

The experimental procedures in metabolic studies have obviously differed, depending upon the goals of the various investigations. Thus, in addition to conventional in vivo studies, certain in vitro metabolic techniques have been used mainly for two purposes: (a) to allow the formation of sufficient metabolites or using large amounts of “10,000 x g supernatant” from human or animal liver to enable a partial purification or actual isolation for the identification of the chemical structures of primary metabolites, or (b) to study enzymes, mechanisms, and interactions in the biotransformation of cannabinoids under more optimal conditions.

The compounds designated as “primary metabolites” have, in general, been isolated from in vitro experiments and have undergone one or two metabolic reactions, usually equivalent to the introduction of two hydroxyl groups. Excreted metabolites, particularly those in urine, have often undergone several metabolic reactions, although many exceptions are known; e.g., Δ⁰-THC is eliminated in the urine to a small extent as the ether glucuronide (75, 37).

All the early isolated and structurally identified metabolites of Δ⁰-THC (and also of CBD and CBN) were obtained from in vitro studies using liver preparations. The reason for this is that the major in vitro metabolites are only mono- or dihydroxylated compounds, and, since they are present in comparatively large amounts, they are more readily recognized.

7-Hydroxy-Δ⁰-THC (5) was the first metabolite to be isolated, and its structure was proven by NMR and MS in 1970 by Nilsson et al. (74) and Wall et al. (96). The analogous hydroxylation of Δ⁶-THC to 7-hydroxy-Δ⁶-THC was shown by Burstein et al. (16) and Foltz et al. (28). The structure of 7-hydroxy-Δ¹-THC (5) is found in table 3. Approximately 80 metabolites of Δ¹-THC are now known, but table 3 only shows the structures of mono- and dioxygenated compounds, the structures of urinary metabolites identified in man, and some unusual metabolites (42). The conversion of Δ¹-THC to hydroxylated species is known to be microsomal and requires NADPH and molecular oxygen. The reaction is inhibited by carbon monoxide, indicating the involvement of cytochrome P-450 (15). Hydroxylation in the 7-position is the major initial reaction in all species except the dog. The unnatural isomer (+)-Δ¹-THC is also metabolized in the mouse in the same ways as (−)-Δ¹-THC, with (+)-7-hydroxy-Δ¹-THC being the major metabolite (56). This experiment invalidated the speculation that the apparent inactivity of (+)-Δ¹-THC in behavioral tests might be due to a lack of bioactivation. It was quickly found that (−)-7-hydroxy-Δ¹-THC was about equipotent with (−)-Δ¹-THC, even in man (96, 88a, 98, 62). This finding greatly stimulated further studies on the metabolism of Δ¹-THC and on the psychoactivity of Δ¹-THC metabolites.
Hydroxylations occur most readily in positions allylic to the double bond, as evidenced by the facile formation of 7-hydroxy-Δ1-THC and also of the 6α- and 6β-hydroxy (7) compounds (table 3). The two epimers are usually formed in roughly equal amounts; otherwise, the α-epimer dominates. Both the 6α- and the 6β-hydroxy groups can be further oxidized (43, 18, 57) to the ketone, Δ1-THC-6-one (21). So far, no metabolite carrying a hydroxyl group in the allylic 3-position has been found. This may, however, be a position which is not readily accessible to metabolic reactions.

All major cannabinoids carry a pentyl side-chain which can be attacked by metabolizing enzymes. The first side-chain-hydroxylated metabolites, the 1"- and 3"-hydroxy metabolites, were discovered by Maynard et al. in the Δ6-THC series as minor products of a dog liver supernatant (71). Since then, we and others (45, 102, 46) have found four side-chain-monohydroxylated compounds in the Δ1-THC-series: 1"-hydroxy- (8); 2"-hydroxy- (9); 3"-hydroxy- (10); and 4"-hydroxy-Δ1-THC (11, table 3).

5"-Hydroxy-Δ1-THC has not yet been identified, neither as a monooxygenated metabolite nor as a further hydroxylated species. The identification of Δ1-THC-5",7-dioic acid as a metabolite of Δ1-THC in rabbit (76) also indicates that the 5"-position of Δ1-THC is prone to be metabolized. As discussed later, considerable species and tissue variations occur with respect to side-chain hydroxylation but, in general, it seems to be a minor pathway where 3"- and 4"-position oxygenation is favored. The occurrence of major urinary metabolites in man (section V E) with a shortened side-chain can be taken as circumstantial evidence that side-chain hydroxylations may be an initial or early reaction in the formation of these metabolites.

The stereochemistry (R and S) of the introduction of the hydroxyl group in the side-chain is not known. Harvey et al. have, however, observed by GC of the trimethylsilyl derivates that 1"-hydroxy-Δ1-THC was present as diastereoisomers in unequal quantities in the livers of Δ1-THC-treated guinea-pigs (46).

A number of dihydroxylated Δ1-THC metabolites are shown in table 3. In essence, all the possibilities suggested by the monooxygenated metabolites are encountered: hydroxylation of the 7-position combined with hydroxylation of 6α- or 6β- or 1"- to 4"-positions in the side-chain; 6β-hydroxylation combined with side-chain hydroxylation; or two side-chain hydroxylations in the same metabolite. Only one example (20, table 3) of trioxynated Δ1-THC metabolites is shown, but several other metabolites of this type have been identified, representing the same pattern of hydroxylation as in compounds 12 to 19. The occurrence of a keto function, as in Δ1-THC-6-one (21), in combination with a hydroxy or a carboxyl group is quite common.

The presence of the allylic double bond would indicate the possibility of an epoxidation, and the expected product 1α,2α-epoxyhexahydrocannabinol (22), or its 7-hydroxy derivative, has been identified in rabbit (12), dog (45), and man (38). Δ1-THC and other cannabinoids are rapidly oxidized by the hepatic mixed-function oxidases. Other tissues, such as intestines (cf. 42) and lung (102, 36), also have some capacity for metabolic activity. Of considerable interest is the finding in the dog (102), rat, and guinea-pig (36) that biotransformation of Δ1-THC in lung tissues showed a quite different quantitative pattern from the liver. Dog liver (102) predominantly formed 6α- and 6β-hydroxylated Δ1-THC metabolites, whereas the lung produced 3"- and 4"-hydroxy-Δ1-THC. The perfused lungs of rats and guinea-pigs (36) converted Δ1-THC mainly to 4"-hydroxy-Δ1-THC, whereas the livers gave 7-hydroxy-Δ1-THC as the major product.

Species differences of a quantitative nature can also be found. In the mouse, 6α-hydroxylation is dominant over β-hydroxylation (42), whereas in man and guinea-pig, the reverse is true. Side-chain hydroxylation occurs widely in many species but is less important in man. Thus, one has to be aware of species and tissue differences in metabolism, but on the whole, these are usually of minor importance.

Primary metabolites found in man. Primary metabolites of Δ1-THC in man have been isolated as products of 10,000 x g supernatant of induced (antiepileptic drug treatment) and noninduced human livers (38). The metabolic patterns were similar in the livers, with 7-hydroxy-Δ1-THC as the most abundant metabolite. They all formed compounds oxygenated in the 6-position, but side-chain oxygenation was most pronounced in the induced liver. Trace amounts of an epoxide were formed. Table 4 shows the relative proportions of mono- and dihydroxylated metabolites.

The results in table 4 are based on quite limited material, but they indicate only quantitative differences in the metabolism of Δ1-THC (38). Hydroxylation in the 7-position of Δ1-THC is by far the dominating metabolic reaction.

Wall and his group (97, 98, 96) and Lemberger et al. (63) have investigated the occurrence of primary metabolites in plasma after p.o. and i.v. administration of radiolabeled Δ1-THC in man. Following i.v. infusion (98), the levels of 7-hydroxy-Δ1-THC and 6β-hydroxy-Δ1-THC in plasma are quite similar and at about 1/10 of the level of Δ1-THC itself. The amounts of 6α-hydroxy-Δ1-THC and 6,7-dihydroxy-Δ1-THC are less than 1/2 of the 6β-hydroxy compound. Other more polar metabolites occur much more abundantly. After p.o. administration, the amount of 7-hydroxy-Δ1-THC in plasma is about equal to that of Δ1-THC itself (98). The relative proportion of dihydroxylated Δ1-THC is also increased after p.o. ingestion of Δ1-THC.

The findings of both the in vivo and in vitro experiments in man are congruent. Hydroxylation to 7-hydroxy-Δ1-THC is the major initial metabolic reaction.
TABLE 3
Chemical structures of some Δ⁵-THC metabolites. The metabolites with the prevus H have been identified as metabolites in humans. Structures 24 to 43 have been isolated as urinary excretion products.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Ref.</th>
</tr>
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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>35, 46, 74, 96, 97</td>
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<tr>
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<td>α-OH</td>
<td>H</td>
<td>H</td>
<td>20, 38, 97, 102</td>
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<tr>
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<td>β-OH</td>
<td>H</td>
<td>H</td>
<td>38, 45, 97, 102</td>
</tr>
<tr>
<td>H 8 1'-OH-Δ⁵-THC</td>
<td>CH₃</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>45, 46</td>
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<td>CH₃</td>
<td>OH</td>
<td>H</td>
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</tr>
<tr>
<td>H 10 5'-OH-Δ⁵-THC</td>
<td>CH₃</td>
<td>OH</td>
<td>H</td>
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<td>36, 45, 102</td>
</tr>
<tr>
<td>H 11 4'-OH-Δ⁵-THC</td>
<td>CH₃</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>13, 36, 102</td>
</tr>
<tr>
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<td>α-OH</td>
<td>H</td>
<td>H</td>
<td>12, 38, 45, 46, 97</td>
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<td>CH₃COOH</td>
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<td>Gluc</td>
<td>H</td>
<td>H</td>
<td>59, 103</td>
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</table>

* Epoxy group in C-1 and C-2 position.
† Glucuronide.
decreased the activity and 1'-hydroxylation essentially abolished the activity (77). In the mouse cataleptic test, Δ⁶-THC, 7-hydroxy-Δ⁸-THC, 3'-hydroxy-Δ⁸-THC, and 1α,2α-epoxyhexahydrocannabinol were equipotent with Δ⁸-THC (85). 5'-Hydroxy-, 4'-hydroxy-, 2'-hydroxy-, and 1'-hydroxy-Δ⁸-THC were less active. It was also found in this study that structural factors rather than distribution to the brain were important in determining the cataleptic/psychotomimetic effects, although all monohydroxylated compounds reached the brain more quickly and to a larger extent than Δ⁶-THC.

Martín et al. (68) have recently reviewed the pharmacological activity of Δ⁹-THC metabolites and concluded that 3'-hydroxy-Δ⁹-THC is more potent (2 to 3 times) than Δ⁹-THC. Hydroxylation in the 3'- or 7-position retained or enhanced the activity of Δ⁹-THC, but the combination 3'-, 7-dihydroxy-Δ¹-THC clearly reduced the activity.

D. Routes and Rates of Excretion

If one makes a rough estimate of the elimination rate of Δ¹-THC in man, one finds that about 1/3 of the dose is excreted in feces and about 1/3 in the urine, all as metabolites (34, 35, 98). The elimination is quite slow, with about 50% of the dose being excreted in 4 to 5 days. A similar slow elimination rate is found in the dog, rabbit, and rat. Studies on the fate of Δ¹-THC in various animals appear to be roughly similar: viz., rapid disappearance of Δ¹-THC after i.v. administration; rapid formation of high levels of metabolites; sequestration of Δ¹-THC into various tissues; hepatic recycling of metabolites; and preferential elimination of metabolites (usually more than 1/3) via feces (26, 39). Neither Δ¹-THC nor CBD is excreted in the urine in unmetabolized form, but traces of CBN may occur (97, 98). Some Δ¹-THC may be excreted in feces (98), presumably as a hydrolysis product after elimination as the glucuronide in the bile (37, 103). More of the metabolites are excreted in the urine of rabbits (8) than of rats and mice (91, 92). The slow elimination in man indicates that the metabolites are also retained in the body and that enterohepatic circulation of Δ¹-THC metabolites is important (47, 97, 98). The conjugated fraction of metabolites in feces is small in contrast to urine, which may be the result of gastrointestinal hydrolysis of metabolites eliminated as conjugates. Free 7-hydroxy-Δ¹-THC seems to be the major fecal constituent in man, together with Δ¹-THC-7-oic acid (97, 98).

E. Metabolites in Urine and Feces

The first two urinary metabolites to be identified were metabolites 26 and 27 (table 3). They were tentatively identified by Burstein et al. as urinary metabolites of Δ¹-THC in rabbits (17). These two compounds possess a carboxyl function at the 7-position and additional hydroxyl groups at the 1'- and 2'-positions in the side-chain. Since oxidation at C-7 was previously established as a major route of metabolism, the finding that this position was further oxidized to a carboxyl group in

| Metabolite Structure with an additional hydroxyl group in 7-position. |
|---------------------|---------------------|---------------------|---------------------|
| 6α-Hydroxy-Δ¹-THC 6 | 7α-Hydroxy-Δ¹-THC 7 | Trace 1            |
| 6β-Hydroxy-Δ¹-THC 6 | 7β-Hydroxy-Δ¹-THC 7 | Trace 1            |
| 2'-Hydroxy-Δ¹-THC 9 | 7'-Hydroxy-Δ¹-THC 7 | Trace 1            |
urinary metabolites was to be expected. Indeed, most of the over 30 acidic metabolites so far isolated carry a carboxylic function in this position.

The further transformation of 7-hydroxy-\(\Delta^1\)-THC (5) would presumably occur via the aldehyde 7-oxo-\(\Delta^1\)-THC (23), a metabolite which was identified in small amounts as an incubation product of \(\Delta^1\)-THC with rat liver microsomes (11).

\(\Delta^1\)-THC-7-oic acid (24) has been identified as a metabolite in the guinea-pig, mouse, rabbit, rat, and man (97, 98, 42). Some of the acid is found in free form, but most of it is apparently conjugated as an ester glucuronide and perhaps also as the ether glucuronide (98, 103). The acid 24 is also referred to as 11-nor-\(\Delta^9\)-THC-9-COOH, 11-carboxy-\(\Delta^9\)-THC (98), or \(\Delta^9\)-THC-11-oic acid (42).

A series of unsubstituted monocarboxylic acids (e.g., 25), carrying the carboxylic function in positions 1" to 4" in the side-chain, have been identified in the guinea-pig (46). The major acid (25), containing a 3-carboxy group, has also been identified in the mouse, rabbit, rat, and man.

It has also been assumed that shortening of the side-chain may be due to \(\beta\)-oxidation (46), and the occurrence of metabolite 41 may indirectly support this. On the other hand, Wall and Perez-Reyes have shown that \(\Delta^1\)-THC-7-oic acid, administered i.v., is essentially eliminated without further metabolism, except for possible conjugation (98). Thus, acids may be eliminated efficiently.

The structures of 19 urinary metabolites of \(\Delta^1\)-THC in the rabbit were established by Nordqvist et al. (75, 76). This represents only about 20\% of the metabolites of \(\Delta^1\)-THC present in the rabbit urine. The main compound isolated was 4", 5"-bisnor-\(\Delta^1\)-THC-7-, 3"-dioic acid (39) which was later found to be a main metabolite of \(\Delta^1\)-THC in urine of man (34). Allylic hydroxylation at C-7 was found to be a major metabolic route, followed by oxidation of C-1" and C-3". Only two monocarboxylic acids were identified (24, 25). Two other isolated structures are shown as metabolites 28 and 29. Later, a large number of acidic metabolites were identified by Harvey et al., after extraction of tissues from animals administered \(\Delta^1\)-THC (46). A number of urinary \(\Delta^1\)-THC metabolites are also shown in table 3. The diversity encountered among the primary metabolites of \(\Delta^1\)-THC is also amply illustrated for urinary metabolites, the only difference being further oxidation to acids and, sometimes, shortening of the side-chain. Several urinary glucuronides have been identified so far; e.g., the glucuronide of \(\Delta^1\)-THC itself (37, 75) and the ester glucuronide of \(\Delta^1\)-THC-7-oic acid (76, 98, 59, 103, 37). A further and unusual glucuronide, the 4"-C-glucuronide of \(\Delta^6\)-THC, has been identified as a metabolic product of \(\Delta^6\)-THC in vitro (65). Moreover, the glucuronides of 7-hydroxy-\(\Delta^1\)-THC and 5"-hydroxy-\(\Delta^1\)-THC have been identified in vitro experiments (72). Most of the conjugates (ester-type glucuronides) are readily hydrolyzed by chemical (34, 35), and less readily by enzymatic, means (34, 35, 98). At present, it seems to be unclear how much of the acid 24 that exists is in conjugated or unconjugated form. As is the case for the \(\beta\)-glucuronide of furosemide, which is unstable at urinary pH and readily transformed to isomeric glucuronides resistant to \(\beta\)-glucuronidase (93), we expect the ester glucuronide of \(\Delta^1\)-THC-7-oic acid to be unstable.

Metabolites excreted in man. All metabolites of \(\Delta^1\)-THC identified in the urine of man or animals are of acidic nature. Fecal excretion is the major excretion route for \(\Delta^1\)-THC metabolites in man, approximately 35\% being eliminated by this route within 72 h. About 15\% are excreted in the urine during this same period of time (98, 34, 35). The metabolites in feces are diverse with both neural, acidic, and acidic polar compounds present (98). The elimination of metabolites in man is slow, and recent data based upon RIA methods suggest that urinary \(\Delta^1\)-THC metabolites may be eliminated for several weeks after the cessation of marihuana use (23).

The major metabolites in feces are 7-hydroxy-\(\Delta^1\)-THC and \(\Delta^1\)-THC-7-oic acid (98).

The metabolite pattern in urine is more complex, and fig. 14 shows the structures of \(\Delta^1\)-THC and 18 nonconjugated metabolites isolated from human urine after p.o. administration of \(\Delta^1\)-THC (34, 35). All compounds except 24 are oxidized in the side-chain. It appears likely that most of these acids were at least partly eliminated as ester glucuronides, since the original urine sample was subjected to mild base treatment to hydrolyze ester glucuronides.

![Fig. 14. Structures of \(\Delta^1\)-THC metabolites isolated from human urine. The compound numbering system is the same as in table 3.](http://example.com/fig14.png)
About ⅔ of the metabolites (34, 35) in human urine were identified and, in addition to the compounds shown in fig. 14, the ether glucuronide of Δ⁹-THC (35) was also identified (table 3, 42, R₃ = glucuronate). Δ¹-THC-7-oic acid (24) was the most abundant metabolite (27% of the urinary metabolites), followed by the diacid 39 (8%), the 4"-hydroxy acid 29 (5%), and the acids 41, 31, 30, 32, 33, and 27 in decreasing abundance from 3 to 1% of the total amount of urinary metabolites. The remainder (fig. 14) are present within the range of 1% to trace amounts (34, 35).

The consistent occurrence of side-chain oxidation in all metabolites except 24 indicates that side-chain hydroxylation may channel the further metabolism to a compound excreted via the kidneys.

VI. Metabolism of CBD and CBN
Since Δ¹-THC is the main psychoactive principle of cannabis, metabolic and other studies have heavily focused on this compound. CBD and CBN are two other major cannabinoids and, as discussed elsewhere, there is conflicting evidence whether they interfere with the actions or kinetics of Δ¹-THC (1, 39, 72).

CBD was readily converted to a number of metabolites (table 5). 7-Hydroxy-CBD was by far the main metabolite in the rat liver, followed by Ga- and 6β-hydroxy-CBD (70). Hydroxylation was also found in all positions of the side-chain. A large number of dihydroxylated CBD-metabolites were also identified (67). The monohydroxylated metabolites and some dihydroxylated metabolites are shown in table 5, together with the major urinary CBD acid in man. The metabolite pattern is similar to that of Δ¹-THC (table 3). Almost 90% of the dioxygenated material was present as 7-hydroxylated metabolites. Side-chain hydroxylation occurred mainly at C-4" and to a lesser degree at C-3". The metabolism of CBD in vivo in the mouse (69) is unusually diverse, with metabolites showing a simple glucuronidation of CBD (44, R₃ = glucuronate), CBD-7-oic acid (56), partial loss of side-chain (57), and more complex metabolites.

In man, CBD seems to be metabolized in a similar way as in animals, although the information is limited (97). Monohydroxylated CBD metabolites are quickly formed, primarily 7-hydroxy-CBD. One major metabolite in both plasma and urine is CBD-7-oic acid, but the amount of more polar metabolites formed seems larger than for Δ¹-THC. After i.v. administration, some CBD is eliminated in the urine in the conjugated form. Free CBD, in large amounts, is excreted in the feces. The excretion rate of metabolites in human urine is similar (16% in 72 h) to that of Δ¹-THC in man (97).

The metabolic patterns for CBN are less diverse, since one more ring is aromatic in nature. The major metabolite is 7-hydroxy-CBN (101); otherwise, all positions in the side-chain are available for metabolic oxidation (table 6), which can lead to numerous but expected end products, analogous with Δ¹-THC and CBD (101, 44, 104, 29, 106, 105). Monohydroxylated metabolites have also been identified as esters of long chain fatty acids (104).

CBN is metabolized in man (97) to large amounts of monohydroxy-CBN, as revealed by analysis of feces after i.v. administration. The level in plasma of 7-hydroxy-CBN is about ⅓ of the CBN concentration. Dihydroxy-CBN, CBN-7-oic acid, and more polar metabolites are

---

**TABLE 5**

*Structures of some metabolites of CBD*

<table>
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<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>R₇</th>
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<td>H</td>
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<td>H</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>C₅H₁₁COOH</td>
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</table>

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also formed. Only about 8% of the CBN dose was found to be excreted in urine within 72 h, whereas 35% was excreted in the feces over this same time period.

VII. Conclusions

Plasma Δ1-THC profiles were found to be similar after i.v. injection and smoking of Δ1-THC. Immediately after smoking 10 to 20 mg of Δ1-THC, as a marihuana cigarette, plasma Δ1-THC levels of about 100 ng/ml were estimated; at 1 h, they were in the range of 10 ng/ml; at 4 h, about 1 ng/ml; and about 0.1 ng/ml at 24 to 72 h, indicating a slow terminal elimination. Most investigators estimate the terminal half-life of Δ1-THC to be in the range of 20 to 36 h.

The systemic availability of smoked Δ1-THC (comparison of AUC for smoked versus i.v. Δ1-THC) was higher (23 ± 16%) in a group of heavy marihuana users compared to a group of light users (10 ± 7%). The variation in availability was 10-fold within each group. Administration of Δ1-THC p.o. yields slow and erratic absorption (systemic availability, 6 ± 3%)

The average plasma clearance values are high (950 ml/min) for both heavy and light users and approach total hepatic blood flow. Other studies suggest limited variation in pharmacokinetic parameters between heavy and light users, indicating that the development of tolerance to behavioral and pharmacological effects in THC users is most likely functional and not dispositional.

Δ1-THC is initially metabolized in man in a way similar to that in most animals, i.e., by preferential allylic oxidation to 7-hydroxy-Δ1-THC. In addition, 6β-hydroxylation is favored over 6α-hydroxylation, whereas side-chain hydroxylation and epoxidation appear to be marginal pathways in man. Side-chain hydroxylation may preferentially lead to elimination via urine. 7-Hydroxy-Δ1-THC will probably only contribute to a small degree to the effects of Δ1-THC per se when smoked, whereas it could be approximately equal in effect to Δ1-THC after p.o. administration.

Δ1-THC-7-oic acid (as the ester glucuronide) is the major urinary Δ1-THC metabolite in man. Almost all other identified urinary Δ1-THC metabolites (10 to 15% of dose in 48 h) show a side-chain containing either a hydroxyl group or a carboxylic function.

The relations of plasma Δ1-THC levels to psychological and physiological effects of Δ1-THC are complex. A temporal dissociation between plasma concentrations and effects is evident and may possibly be explained by a somewhat slow penetration of the blood-brain barrier, slow distribution within the brain, and a lag-time in biochemical reactions.

The pharmacokinetics and metabolism of CBD and CBN in man and animals follow the pattern similar to that of Δ1-THC.

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