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# PHARMACOLOGY OF MARIJUANA

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This review is concerned primarily with the papers that have appeared since the end of 1972 subsequent to the material in the book by Nahas (1) and the review volumes edited by Mechoulam (2) and by Gibbins et al (3). The main new developments have been in the biochemistry of cannabis metabolites, in cellular and toxicological effects, and in a widening of human studies.

## CHEMICAL ASPECTS

### *Structure-Action Relationships (4, 5, 6)*

Variations in potency among cannabinoids by a factor of over 2000 are now recorded, which allow considerable scope for structure-action studies. But estimates of relative potency remain difficult to make because of the variability among subjects (whether animals or humans). At a deeper level, little work has been done to assess how far variations in potency reflect differences in pharmacokinetics or in metabolism (with possible formation both of active and inactive metabolites), as against differences in effect at the ultimate site(s) of action. In addition, many of the structures involved have several isomers and are usually tested as mixtures. Finally, pharmacological study has not been sufficiently detailed to exclude major differences in *type* of action between the various substances. This may be important, since trial of 1,1-dimethylheptyl-$\Delta^3$-THC (DMHP) in man showed that, while it produces pronounced tachycardia and hypotension in man, it has no psychic effect (7). The same may be true of other compounds tested only in animals.

Subject to these qualifications, the following provisional generalizations may be made, characterizing the tetrahydrocannabinol (THC) molecule as possessing three rings, terpenoid, pyran, and aromatic and using the terpenoid nomenclature.

1. Lengthening the aliphatic chain on the aromatic ring to heptyl increases activity considerably, particularly if there is methyl substitution in the 1" position; this is further augmented by a second 1"- or 2"-methyl group. Unsaturation in the chain does not impair activity. The three most active derivatives so far obtained

appear to be DMHP (1000 X pyrahexyl); 1,2-dimethylheptyl-$\Delta^3$-THC (500 X); and the latter structure with a 1,2 double bond (500 X). It is interesting that under these conditions $\Delta^3$ derivatives are more potent than $\Delta^1$ or $\Delta^6$ derivatives. Replacement of the first carbon atom in the alkyl chain by oxygen only reduces activity slightly.

2. In the aromatic ring, the phenolic group is critical, and activity is lost if it is absent or masked with other than a labile group such as acetate. It need not be at C3'; in the dimethylheptyl $\Delta^3$ series, considerable activity was retained with 4'-DMH and 5'-OH. Electronegative groups at C6' or C4' abolish activity.
3. In the pyran ring, the gem dimethyl group is critical. Substitution by carbonyl, or by diethyl or higher aliphatic groups, drastically reduces or abolishes activity. Opening of the ring or substituting N for O also removes activity; substitution of $-CH_2-$ for O has not been tested.
4. In the terpenoid ring, more variation is possible. Considerable activity is retained after replacement of the C7 methyl group by hydrogen or ethyl, or hydroxylation at C7 (yielding the first metabolite), or hydroxylation at C6, or alkyl substitution at 2, 5, and 6; but methyl substitution at C6 in the dimethylheptyl series greatly reduces activity. Hitherto it has been thought that a generally planar structure for the whole molecule was required for cannabinoid activity. A recent paper (8) describes a series of benzoxacins and benzoxonins in which the terpenoid ring must be at a substantial angle with the rest of the molecule; some of the compounds were considerably more active than $\Delta^1$-THC, by a behavioral test in rats.

The general requirement, therefore, appears to be that of a 5–7 C atom chain attached to a benzpyran nucleus (or equivalent) carrying a phenolic group, joined in turn to a rather variable alicyclic, not necessarily coplanar, structure, which may be hydroxylated. Certain particular findings require mention. One is the observation that desmethyl-$\Delta^6$-THC retains activity (9); because this cannot form a C7-OH metabolite, such a metabolite cannot be essential for cannabinoid action. Second, in addition to the variations of activity with structure mentioned, stereospecificity occurs (pp. 109, 118 in reference 6). In a detailed study of (+) $\Delta^1$-THC (10) it has been shown that its low potency in animals, about one thirteenth that of (–) $\Delta^1$-THC,

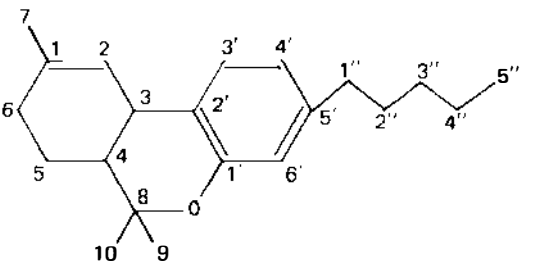


*Figure 1* Basic features of $\Delta^1$-THC molecule, with carbon atoms numbered according to the terpenoid system. $\Delta^1$ refers to the double bond between C1 and C2; in $\Delta^3$ compounds it is between C3 and C4. $\Delta^1$-THC also has 3'-OH.

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cannot be attributed to failure of uptake by the brain or to abnormally fast metabolism. Theories of cannabinoid action must therefore allow for a considerable degree of not only structural but also stereoisomeric specificity at the site of action.

## COMPOSITION OF CANNABIS AND CANNABIS SMOKE

Cannabis plants are now generally allotted to a single species, *Cannabis sativa.* But there are considerable variations seen in pattern and content of resin and fiber, and it is uncertain whether these differences are attributable to genetically distinct varieties, or to environmental influences (chemovars, cultivars, phenotypic variants). Consistent variations in pattern of cannabinoid composition with the region of origin are familiar to analysts (17). Up to five phenotypes could be proposed on the basis of cannabinoid analysis (11–16), characterized respectively by a high THC to cannabidiol (CBD) ratio, THC/CBD $\triangleq$ 1, a low THC to CBD ratio, presence of cannabigerol monomethyl ether [found in Japanese samples (12)], and presence of propyl-THC in more than trace amounts (apparently associated with Nepalese material). The view that tropical and subtropical climates are required for high production of THC has proved erroneous; plants with high THC content have been grown in temperate climates (12, 18) and additional radiation did not alter yield (18). These results, however, have been only over one generation; and evidence from the Phytotron in Paris (19)—in which cross-fertilization by local strains can be prevented—suggests that in subsequent generations the cannabinoid production by a plant drifts towards the pattern normally associated with its particular climate of the moment. For practical purposes it must be assumed that the cannabis consumed by the drug user, whether imported or home-grown, will continue to be a highly variable material.

In connection with medical or epidemiological studies it should be noted that in North America, cannabis is usually smoked alone, but elsewhere with tobacco. As regards dose rates in practice, an interesting British study, including analysis of reefers actually used (20), recorded rates of THC consumption ranging from 0.1 mg/day (casual user) to 199 mg/day (habitual user) endorsing the similar range of figures collated by the World Health Organization (WHO) (21). In estimating cannabinoid intake, analysis of $\Delta^1$-tetrahydrocannabinolic acid, for which techniques now exist (22), may become important (23). This acid is rapidly decarboxylated to $\Delta^1$-THC by heat and will be recognized as THC both by the smoker and by gas-liquid chromatography (GLC). If taken by mouth, however, the acid may not be decomposed. The presence of tobacco also may alter THC availability; for while it appears that CBD does not cyclize to form THC when cannabis alone is smoked, this can occur in the more acid environment of burning tobacco (24). Transfer of THC from cigarette to mainstream smoke in the mouth can range from 10–60% according to efficiency of smoking and size of butt ("roach") discarded (25–28). Absorption of smoke once inhaled seems virtually complete, although how far this is bronchial, how far alveolar, has not been analyzed.

The full role of cannabinoids other than THC is not yet clear. The presence of CBD, with its capacity to inhibit microsomal enzymes (29) and hence to modify the metabolism of $\Delta^1$-THC (30), is only one factor. An assay in man, rabbits, mice, and

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rats of three marijuana samples indicated that two were more active than expected from their content of $\Delta^1$-THC (31); these lacked cannabidiol, but methyl or propyl derivatives of THC, cannabinol, and other cannabinoids may have contributed.

## DETECTION

Forensic techniques exist for detecting cannabinoids on fingers, in mouthwashings, or in room air (32, 33). The odor of marijuana is largely due to $\alpha$- and $\beta$-pinene, myrcene, and limonene (34). Quantitative measurement of cannabinoids and their metabolites in body fluids remains difficult. Mass fragmentography (35) has enabled Agurell et al (36) to measure $\Delta^1$-THC in blood after smoking a cigarette containing 10 mg: peak levels of 19–26 ng/ml were obtained within 10 min, falling to about half by 45 min and to 5 ng/ml or less within 2 hr. McCallum (37), using gas chromatography, flame photometry, and phosphate ester derivatization, however, did not detect $\Delta^1$-THC, but high levels of cannabinol (CBN). Some progress towards immunoassay has been made (38, 39), but specificity and sensitivity in practical use remain to be established. A promising report has recently been published by Teale et al (266). Other papers involve pyrolysis of CBD (39a), isolation of cannabicitran (40), cannabinol methyl ether (41), long-chain hydrocarbons (42), non-cannabinoid phenols (43), alkaloids (44), a brief note on use of mass spectrometry (45), and an account of Argentine marijuana (46).

## DISTRIBUTION OF $\Delta^1$-THC AND ITS METABOLITES

$\Delta^1$-THC binds strongly to plasma proteins, $\alpha$- and $\beta$-lipoproteins chiefly, but also to albumen (27a, 47, 48); albumen binding is minimal except with high concentrations. The 7-OH metabolite is bound chiefly to albumen, slightly less to $\alpha$-lipoprotein and only a little to $\beta$-lipoprotein; 95–99% of drug is bound (49). The concentration of free active cannabinoid in plasma must therefore be very low (perhaps only 1% of plasma content). This raises the question whether it reaches the tissues in free form, or as a protein-bound or micellar complex.

Affinity of the drug for its excipient is an experimental problem: there is now evidence that $\Delta^1$-THC injected intravenously after mixing with serum or Cremophor®, or given in sesame oil orally, is less readily available than in ethanol or polyethylene glycol intravenously or Tween® 80 orally (27a, 50, 51). For intraperitoneal injection, $\Delta^1$-THC was most effective in delaying convulsions when given in a propylene glycol/Tween 80 mixture, fairly effective in polyvinylpyrrolidone (PVP), and almost ineffective in bovine serum albumen or saline/Tween 80 (52). There must, therefore, be a complex equilibrium between the various retaining or uptake sites provided by the excipients, plasma proteins, chylomicra, and tissues, all competing for the drug. This may well account for persistence of the drug at site of injection (53). The situation will be further complicated if more than one drug is present as illustrated by the evidence for competition at binding sites in vivo between $\Delta^1$-THC and 7–OH–THC (54). After intravenous injection of labeled THC, autoradiography reveals small discrete spots of radioactivity in lungs and spleen;

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because these are not seen after oral administration, they are probably microdroplets or micellar complexes of drug (55) and reflect in yet another way the hydrophobic nature of the drug, as well as providing a complication to intravenous administration.

Low free plasma concentration implies that tissue uptake will initially be limited by tissue blood flow; only with sustained exposure would the influence of lipid content of a tissue show itself fully (56). Studies of tissue distribution conform roughly to this pattern (50, 55, 57, 58). In acute experiments with injection of labeled drug, activity is very high to high in lung, liver, and kidney; high to moderate in heart, salivary gland, Harderian gland, gastric mucosa, spleen, bone marrow, placenta, brown fat, adrenal cortex, thyroid (follicular epithelium), pituitary, mammary gland, corpora lutea; moderate to low in brain, fetus, epididymis, and testis. THC and its metabolites appear in ewe's milk (59). In the brain, label appears primarily in gray matter, particularly in caudate nucleus, putamen, pons, thalamus, amygdala, hippocampus, frontal and parietal cortex, and septum. If allowance is made for the factor of blood flow, there is no pronounced localization of drug, although the data are fully compatible with cannabinoid action on extrapyramidal or limbic areas.

With continued exposure to drug, so that blood flow is no longer rate limiting, affinity for fat appears. Kreusz & Axelrod (60) found, with injection of 100 $\mu$g/kg 3H-$\Delta^1$-THC on alternate days, that levels of $\Delta^1$-THC in fat were still rising after 28 days. Similar cumulation occurred (in descending order of content) in liver, lung, and brain. After a single dose of THC, the approximate half-life of THC in fat was 5 days.

At the cellular level, $\Delta^1$-THC is strongly concentrated in particulate fractions of brain homogenates; tissue/medium ratios of about 600 are found for synaptosomes and mitochondria, with THC concentrations of $3 \times 10^{-7}$ to $10^{-5}$ *M*. Polar metabolites appear in the supernatant. The accumulation of THC was not significantly different at 4° and 37°C, nor affected by ouabain or dinitrophenol (61). Partition coefficients between buffer and synaptosome membrane lie between 100 and 500, and for red cell ghosts between 800 and 40; the coefficient falling as free THC concentration increased from $4 \times 10^{-6}$ to $4 \times 10^{-5}$ *M* (62). Tissue/medium concentration for brain cortex slices in vitro of about 100 had been reported earlier (63). These results conform with the in vitro octanol/water partition coefficient for $\Delta^1$-THC of 6000 and of 7-OH-$\Delta^1$-THC of 3500 (64). At the subcellular level, local concentration with respect to tissue water must therefore be expected at membranes and other hydrophobic sites. But this may not always show itself fully in simple tissue/blood ratios; tissues vary in lipid content and composition, and blood has a considerable capacity for uptake by virtue of its cells, proteins, and lipids.

## METABOLISM

The salient features of cannabinoid metabolism are reviewed by Burstein (65); these are (*a*) allylic hydroxylation, primarily at C7 but also at C6, yielding the primary metabolite, 7–OH–THC, 6$\alpha$ and $\beta$ OH-$\Delta^1$-THC, and 6,7,-dihydroxy-$\Delta^1$-THC;

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(*b*) hydroxylation of the pentyl side chain at C1" or C2"; (*c*) further oxidation to 7-oic acid, and to other acids (an interesting recent finding (66) is the dicarboxylic acid, 7-oic and 3"-COOH); and (*d*) conjugation, the full pattern of which is far from clear.

The rhesus monkey has been found to resemble man more closely than squirrel monkey or baboon in the timing and proportion of urinary (as opposed to fecal) elimination (67, 68). Studies of DMHP indicate that it is handled similarly to $\Delta^1$-THC in the rat, but much more slowly in rabbit (69); the first metabolite of DMHP has not been identified and will be of interest because the $\Delta^3$ structure does not offer allylic attack. Many more metabolites remain to be identified. The formation of the epoxide 1,2-epoxy-$\Delta^1$-THC (70) should be noted as an example of a possibly reactive species. Metabolite formation is rapid; 7-OH-$\Delta^1$-THC is detectable in blood 0.5 min after injection of $\Delta^1$-THC in a mouse (50, 71). With repeated dosage, cumulation of 7–OH– and 6,7-di-OH-$\Delta^1$-THC occurs in the tissues, as does THC itself, though at lower levels. Cumulation of the di–OH compound in fat is particularly noteworthy (60).

After a single injection of $\Delta^1$-THC, blood levels of $\Delta^1$-THC decline biphasically, first with a short half-time, ranging from about 15 min in mouse (50) to about 30 min in man (72), then more slowly with a half-time of the order of days. The pattern is similar for the metabolites. The level of $\Delta^1$-THC in blood is higher than that of 7-OH-$\Delta^1$-THC, and that of the total unidentified other metabolites higher still (50, 72–74). Metabolism of CBD and of injected 7-OH-$\Delta^6$-THC follows a similar pattern (75–77).

Considerable interest has been taken in the possibility that $\Delta^1$-THC effects are all mediated by 7–OH–THC. Relevant data are (*a*) the metabolite appears to produce all the effects of the parent compound; (*b*) it is at least as potent, possibly slightly more so in humans (5, 74, 75, 75a,
the levels of 7-OH-$\Delta^1$-THC in blood after $\Delta^1$-THC injection are low; (*d*) the effect of the metabolite is similar in speed of onset but with an earlier peak than that of the parent (5, 74, 75); (*e*) analysis correlating brain levels with cataleptic response in mice, after injection either of $\Delta^1$-THC or 7-OH-$\Delta^1$-THC, indicates that both drugs contribute to the effect (78); (*f*) the maximum hypothermic effect of 7-OH-$\Delta^1$-THC is considerably less than that of $\Delta^1$-THC (79, 80); (*g*) a twofold rise in level of metabolite in the brains of mice, as a result of giving CBD with $\Delta^1$-THC, did not increase the immobility effect of $\Delta^1$-THC (81).

The role of the liver in metabolism has been further explored. Since 60–70% of a dose of $\Delta^1$-THC is eliminated in 6 hr in a rat with a biliary cannula (82), there must be a prolonged enterohepatic circulation to account for the delayed elimination in the normal animal. Although the half-time of $\Delta^1$-THC in the blood in marijuana users is about 60% of that in naive subjects (72), tests to determine whether $\Delta^1$-THC can induce microsomal activity in the liver (83), using direct (84) or indirect methods [shortening of hexobarbital sleeping time (85)], have yielded negative results. In rats, smoke from cannabis or placebo cigarettes induced aryl hydrocarbon hydroxylase in lung but not in liver (86); large oral doses of crude resin induced such activity in liver and lung, but pure $\Delta^1$-THC in lung only (87); $\Delta^1$-THC itself cannot account

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for the phenomena. The active substance in the resin or in smoke has not been identified; benzo [α] pyrene is present only in small amounts (11 ng/mg resin) (88).

There is general agreement that CBD is mainly responsible for the prolongation by cannabis of barbiturate sleeping time, by microsomal inhibition (29, 89, 90). In studies on microsomal systems, spectral and inhibitor dissociation constants have been obtained with various systems, for CBD, $\Delta^1$-THC, propyl-THC, $\Delta^6$-THC, and CBN. In general, they are all similar, except for CBD which has dissociation constants 3–4 times lower (84, 89, 91). The cannabinoids inhibit Type I microsomal binding (as in demethylation of aminopyrine or morphine, or hexobarbitone side chain oxidation), but not Type II (e.g. aniline hydroxylation) (92). The aryl hydrocarbon hydroxylase induced by phenobarbitone is inhibited by $\Delta^1$-THC, but that induced by methylcholanthrene (a simple autosomal dominant trait) is resistant (92). $\Delta^1$-THC has been shown to prolong antipyrine metabolism in humans (93).

Induction of other enzymes has been noted. Berman et al (94) found that 2 hr after 5 mg/kg $\Delta^1$-THC, liver dechlorinase activity increased fourfold; there was no increase in liver weight or microsomal protein. Higher doses, however, did not increase dechlorinase activity, but loss of weight by the animal complicated the experiment. THC also induces liver tryptophan pyrollase and tyrosine α-ketoglutarate transaminase, and CBD potentiates this action (94a).

Potentially important is the finding by Greene et al (95) that human jejunal biopsy samples can metabolize $\Delta^1$-THC (probably to 7-OH-$\Delta^1$-THC) and that in the rat, after jejunal instillation of labeled THC, half the label in the portal blood is already polar. It was also found that little THC was absorbed via the lymphatics and the thoracic duct.

## CELLULAR ACTIONS (CELL BIOCHEMISTRY AND PATHOLOGY) AND TOXICITY

There is some difficulty in dividing up this field because a particular action may be of interest chiefly as regards mechanism in one context and toxicology in another. It will be considered by beginning with subcellular effects and ending with gross toxicity.

### *Liver Mitochondria*

It has been shown (96, 97) that THC in vitro will uncouple state IV respiration, decrease respiratory control, produce swelling of mitochondria and release of matrix enzymes (much potentiated by $Mg^{2+}$), disrupt mitochondrial structure, and accentuate flocculation of phospholipid micelles. Increase of oxygen uptake reaches a maximum at 15 μg $\Delta^1$-THC per mg mitochondrial protein; the effect was abolished by amounts of about 50 μg/mg protein. Similar stimulation of $O_2$ consumption has now (98) been obtained in tissue taken from animals receiving prior injections in vivo, and DL-amphetamine (but not pentobarbital) shared the action.

A related effect is the action of THC on fresh bull sperm, by which oxygen uptake is increased (0.03 m*M* or above), motility distorted or impaired, and unstable swelling of the mitochondrial helix produced (0.2 m*M* or above) (99).

In W I human diploid lung fibroblasts, $\Delta^1$-THC (from 0.32 $\mu M$ upwards) antagonized the effect of prostaglandin $E_1$ ($PGE_1$) and adrenaline in raising cyclic AMP levels. In contrast, it did not affect isolated adipocytes (100).

With rat liver lysosomes, $\Delta^1$-THC and CBD at 2 $\mu M$ slightly diminished acid phosphatase release in hypo-osmotic media, but at 20 $\mu M$ or above greatly accentuated release and damaged the lysosomes. Such an action is shared by other fat-soluble substances and may be important in respect of liver damage (101, 102).

Stabilization of the red cell and inhibition of its ATPase by $\Delta^1$-THC at 0.02–0.1 m$M$ had been described earlier. Inhibition of $K^+$ influx (more pronounced at pH 6 than pH 7) is now reported at 10 $\mu M$ $\Delta^1$-THC and above; 1% (20.8 m$M$) ethanol did not reproduce the effect (103).

Leucocyte migration in vitro was impaired by $\Delta^1$-THC at 20 $\mu$g/ml upwards and by marijuana extracts more than expected from their THC content. Leucocytes from marijuana smokers and nonsmokers were affected similarly. The cells were not killed (as judged by trypan blue exclusion). At 200 $\mu$g/ml extract, over 90% inhibition occurred (104).

Bacterial chemotaxis (studied with *Pseudomonas fluorescens*) was inhibited by $\Delta^1$-THC (10 $\mu$g/ml) but not by cannabinol, cannabidiol, or cannabigerol (105).

Regeneration of the planarian worm *Dugesia tigrina* is reduced by $\Delta^1$-THC at 0.6 $\mu M$ upwards; $\Delta^6$-THC was slightly less, CBD considerably less active (106).

Lymphocyte blastogenesis, stimulated by phytohaemagglutinin, and measured by uptake of labeled thymidine, was impaired by $\Delta^1$-THC at 3 $\mu M$ or more (107); this result was obtained both with rat and human cells. Related to this is the inhibition of cell-mediated immunity in marijuana smokers reported by the same group (108). Blastogenic responses in lymphocytes taken from marijuana smokers were about 60% that of normal controls and at a level comparable with that of patients in uremia or under immunosuppressant therapy. It may be noted that similar tests in cigarette smokers (109) did not produce evidence of decrease in immune responsiveness.

A number of studies have concerned the cell nucleus and chromosomes. In a series of papers, the Leuchtenbergers and their colleagues have reported that smoke from marijuana cigarettes passed over cultures of human lung explant produces, in addition to some initial cytotoxicity, abnormalities of mitosis and impairment of contact inhibition, with considerably increased variation of DNA content and chromosome number. In young cultures, 1–4 days after exposure to smoke, the frequency of mitotic abnormality was 20–30%, compared to control values of 0–3%. Ordinary cigarette smoke produced similar changes (110–112). Marijuana and cigarette smoke are also alike in producing a tar that elicits neoplastic changes (113) and the more rapidly detectable squamous metaplasia and acanthosis of sebaceous glands (114) in mouse skin. Two studies provide further evidence that THC itself may not induce chromosome abnormalities. Human leucocytes cultured in presence of $\Delta^1$-THC, and leucocytes taken from hamsters injected with marijuana distillate (17.1% $\Delta^1$-THC), did not show any significant increase in breaks, although mitosis was abolished at 100 $\mu$g/ml $\Delta^1$-THC in the culture medium (115, 116). A similar result was obtained, both as to lack of abnormalities and arrest of mitosis,

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in experiments with a crude Jamaican resin. In studies of chromosomes from marijuana users, however, Stenchever and his colleagues (117) found an average of 3.4% chromosome breaks, against controls of 1.2%; the study was carefully controlled, with 100 cells examined for each subject (49 users, 20 controls), and "blind" scoring. Another study from Jamaica (118) (9–25 cells analyzed per subject, 18 users, 15 controls, blind scoring not specified) found no difference, but binomial calculation shows that because of the limited number of cells studied, an effect of the order of magnitude reported by Stenchever et al is not excluded. It is not clear, if these chromosomal changes are substantiated, whether they should be regarded as reflecting a *direct* interaction of the drug with nuclear material or as secondary results of an interference with cell division.

The observation that $\Delta^1$-THC inhibits biosynthesis of proteins and nucleic acids in brain (63) has prompted further studies. Acute exposure of infant rats to $\Delta^1$-THC causes a reduction of nuclear membrane-attached ribosomes in brain; 7-OH-$\Delta^1$-THC was more active, and cannabidiol, cannabigerol, cannabinol, and $\Delta^6$-THC less so (119). Brain chromatin from rats treated with $\Delta^1$-THC has been found to have a lower capacity to promote RNA synthesis (in the presence of *Escherichia coli* DNA-dependent RNA polymerase) (120).

Impairment of bone marrow leucopoiesis has been found after six daily intravenous injections of a large dose of THC (50 mg/kg) in the rat (121); the proportion of metamyelocytes was reduced, and the proportion of mature lymphocytes was increased; a reduction of erythrocytic cells was not significant. Complete arrest of spermatogenesis was produced in mice after daily administration of 2 mg/kg THC for 45 days (122); degenerating forms of spermatids and fragmented sperm were seen, with regression of Leydig cell tissue and accessory sex glands. Complete recovery of spermatogenesis and Leydig's cells was found 63 days after treatment. A negative effect in the rat of THC injection on accessory sex organ and testis weights and on testosterone uptake may have been due to the limited period of treatment (4 days) (123).

In earlier studies on the effect of cannabis on fetal development (see 124, pp. 238–40, 270) crude extracts had proved teratogenic in tests on rabbits, hamsters, and rats, but $\Delta^1$-THC itself lacked that action, only producing some stunting and neonatal mortality with failure of maternal lactation. The result with $\Delta^1$-THC has been confirmed (125), treatment of rats on days 10–12 of pregnancy producing a higher proportion of abnormal births and a fall in birth weight, but no deformity; in addition there was no impairment in behavioral tests of the progeny at the age of 16 and 20 days. In a test using a crude cannabis extract on days 8–11 of pregnancy in rats, again no deformity was seen, and there was a modest reduction in litter size; but at 65 days, learning by the offspring in a Lashley maze was impaired (126). Studies of maternal and fetal heart rate and EEG in guinea pigs during exposure of the mother to marijuana smoke showed considerable changes, but are hard to interpret in the absence of blood gas studies (126a).

Full results of a series of toxicity tests sponsored by the National Institute of Mental Health have been published, of which preliminary reports had appeared (127, 127a). The tests were made with $\Delta^1$-THC, $\Delta^6$-THC and a concentrated mari-

juana extract (CME) containing 25–32% $\Delta^1$-THC, 2% $\Delta^6$-THC, 2.9% cannabidiol, 3.5% cannabinol, and 4% ethanol. The acute oral $LD_{50}$ in rats ranged from 860–1910 mg/kg for $\Delta^1$, 860–1980 for $\Delta^6$, and 1380–3300 for CME; females were more sensitive, and deaths were characteristically delayed up to 3 days (127). A further study in rats gave an intravenous $LD_{50}$ for $\Delta^1$-THC of 36–40 mg/kg and a similar value for drug given by inhalation if correction is made for loss in nasal passages. The oral $LD_{50}$ was 800 mg/kg if an aqueous emulsion was used and 1270 mg/kg with sesame oil (128). Single oral doses up to 3000 mg/kg of $\Delta^1$ and $\Delta^6$ in beagles or rhesus monkeys were not lethal (apart from two deaths from aspiration of drug by beagles) (127).

The acute toxicity of $\Delta^1$-THC in rats is increased by liver damage, or by treatment with SKF 525A, and decreased by phenobarbital pretreatment (129). In mice, toxicity is higher if they are aggregated than if isolated; the effect is similar to but smaller than that seen with D-amphetamine (twofold increase against sixfold for amphetamine) (130).

With chronic oral administration in rats (131), an $LD_{50}$ of about 450 mg/kg was obtained with all three substances, most deaths again being within 3 days. An interesting feature with doses of 50 mg/kg upwards, after about 7 days, was the onset of hyperactivity progressing to irritability, fighting resulting in wounding, with some convulsions; at higher dosage, there was less fighting and more convulsions. There was a striking loss of fat especially in females (from 3422 to 143 mg/100 g body weight), and a 10–15% loss in exsanguinable blood volume. Growth rates were impaired by 50 mg/kg daily; food and water consumption declined but later rose to match that of controls; urine volume increased considerably with time. Relative organ weights declined for uterus, prostate, ovary, and spleen and increased for adrenal; absolute organ weights decreased for testis, liver, and kidney. Among histological changes, lymphopenia in the spleen, spermatogonial degeneration in testis, and vacuolization and necrosis in adrenal were noteworthy.

In the rhesus monkey both intravenous and oral chronic toxicity of $\Delta^1$-THC were tested (132). By the intravenous route, 45 mg/kg a day killed 2 of 4 monkeys (days 8 and 19). The oral chronic toxicity tests revealed the following results: single dose of 9000 mg/kg not lethal; 50 mg/kg daily, 1 death out of 6 (day 16); 250 mg/kg, no deaths out of 6; 500 mg/kg, 2 deaths out of 8 (days 10 and 14). The studies on intravenous toxicity reflect the problems of studying the toxicity of a highly hydrophobic substance; although the controls receiving the vehicle used (sonicated sesame oil and Tween 80) showed no lesions, those that died after $\Delta^1$-THC showed hemorrhagic pneumonia and ulceration and necrosis of the injection sites. Pathological changes in the oral tests, to which perhaps more significance may be attached, included atrophy of the pancreas, ulcerative colitis, myeloid hyperplasia of the bone marrow, vacuolar nephrosis, thymus atrophy, and enlarged adrenal glands. Liver tended to increase in weight, testis and heart to diminish; prostate, ovary, pituitary, spleen, lung, and thyroid weights were generally unaffected. As with rats, tolerance developed to the initial behavioral effects of the drug, but subsequently hyperactivity was seen only in some animals and did not always persist.

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A separate study has been made of the effect on liver glycogen (133). Significant falls of 40% or more occurred in monkeys receiving 4 mg/kg $\Delta^1$-THC iv, in rabbits with 15 mg/kg sc, and in rats given a single exposure to the smoke from material containing 34 mg/kg $\Delta^1$-THC. Changes in glycogen content were independent of changes in body weight or liver weight; in monkey and rabbit, there was no change in blood glucose. A neurochemical analysis was also made of brains from the rat chronic toxicity trial (134). Significant decreases in protein, RNA, acetylcholinesterase and monoamine oxidase were found,but no change in brain weight, total lipid, or cholesterol concentrations, compared to controls. A fall in glycolipids was noted in the male animals.

The effect in dogs of three months smoking of marijuana cigarettes has been reported (135); assuming 50% delivery of the $\Delta^1$-THC in the cigarettes, the daily dose would have been about 5 mg/kg per day. Growth of body weight was reduced (about 50% of the increase in untreated and in tobacco cigarette controls), although food intake was higher. In contrast, with tobacco cigarettes food intake was reduced, but weight gain was normal. A significant tachycardia developed (32% increase), and an elevation in the ST segment of the electrocardiogram was sometimes seen. Blood analyses showed a slight normochromic polycythemia with reduction in mean corpuscular volume and a relative lymphopenia for both types of cigarettes. The loss of weight in the marijuana group was attributed to malabsorption or to gastrointestinal disturbance. Water intake was not studied, although another study suggests that this may be critical (136). In rats receiving 2.5 mg/kg $\Delta^1$-THC daily, the usual failure to gain weight was observed, and food intake fell within normal limits, but water intake was depressed throughout the 22 day experiment.

The cellular and toxicological effects of cannabis in animals deserve attention, now that it is being recognized that some human users take relatively high doses. So long as human pathological study is lacking, animal effects provide for the time being the only guide. A review of these actions reveals two consistent themes: 1. there is a generally depressant effect on normal cell function and on cell division. This shows itself in such effects as the uncoupling of oxidative phosphorylation, the reduction of $K^+$ influx in the red cell, the impairment of chemotaxis, the interference with lymphocyte blastogenesis and spermatogenesis, and the damage to fetal development. 2. There is a tendency for the effects to be cumulative. If one measures this tendency by the ratio of the amount required to produce a given lethality in a single dose to the daily dose required to produce the same effect, and collates these data with earlier findings, the cumulation ratio is about 10 for mice [sc or ip injection of crude cannabis (56)], about 4 for rats (oral $\Delta^1$-THC or marijuana extract), and at least 10, possibly much higher, for rhesus monkeys. These characteristics are, of course, typical of any highly lipophilic molecule.

But it is difficult to interpret fully much of the data. This is partly because many of the responses could be secondary to, or influenced by, other actions of cannabis. Thus its hypothermic action in small animals is rarely controlled, yet a fall in body temperature, or the physiological response to it, could have far-reaching effects. Reduction in food or water intake could have an equally radical influence. The

presentation to metabolic pathways of a lipophile, with resultant activation or inhibition, for instance of liver microsomes, could involve many complex interactions with both exogenous and endogenous substances. The ability of cannabis to stimulate secretion of adrenal cortical hormones may also underlie a number of effects; also, the recent finding that plasma testosterone is reduced in users suggests that other endocrinological changes remain to be discovered. Finally with in vitro work, there is a special point; tissue/medium ratios of $\Delta^1$-THC are so high (up to 600) that nominal medium concentrations of THC may well be in error, as a result of drug uptake into the tissue concerned.

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## NEUROPHYSIOLOGY

$\Delta^1$-THC has been tested in isolated nerve preparations. On squid giant axon (137), $\Delta^1$-THC was ineffective at 3 m$M$ concentration, but the 11-OH metabolite reduced the action potential at concentrations from $10^{-8}M$ upwards; conduction velocity also declined, and spontaneous discharge occurred in deeply blocked nerve. Similar depression but not the spontaneous activity could be obtained with $0.3M$ ethanol. With unmyelinated, desheathed, rabbit vagus nerve fibers (138), $\Delta^1$-THC depressed the compound action potential; the difference from the squid axon may be a species difference, or due to the adjuvant effect of 0.2% ethanol in the $\Delta^1$-THC solution in the rabbit experiments. The sodium pump (as assessed by the hyperpolarization after a tetanus) was not affected; replacement of $Cl^-$ in Ringer's solution by isethionate greatly reduced the effect of $\Delta^1$-THC. $\Delta^1$-THC has also been found to reduce the excitability of Auerbach's plexus in guinea pig ileum, to abolish the twitch response to field stimulation, and to depress acetylcholine output (15, 56).

In experiments on the lateral geniculate body of the rat under urethane anesthesia, $\Delta^1$-THC inhibited the discharge of light-sensitive cells, but either had no action or increased discharge rate of dark-firing cells (139); 5-HTP had some antagonistic effect, and it was suggested that $\Delta^1$-THC might alter a monoaminergic modulation of the lateral geniculate principal cell and its recurrent collateral inhibitory feedback. In a test (140) of the effect on stimulation of various nociceptive sites in rats, $\Delta^1$-THC in large doses had little effect on the escape response to electrical shock to the foot, greatly reduced that to medial lemniscal and (to a lesser extent) hippocampal stimulation, and had little effect on ventrodorsal thalamic, ventral tectal, or lateral hypothalamic stimulation; it is suggested that lemniscal stimulation is sensitive because it involves, as well as nociceptive fibers, other fibers that may be involved in "gating" the pain sense. Cannabinoids will inhibit the production of seizure discharges in the hippocampus in response to stimulation of the fornix; CBD and CBN are more active than $\Delta^1$ and $\Delta^6$-THC (141). The directly evoked hippocampal response was not affected. In a comparison of DMHP, $\Delta^1$-THC and CBD as antagonists of maximal electric shock convulsions, potency was in the order DMHP $>$ $\Delta^1$-THC $>$ CBD, but only with CBD was the anticonvulsant dose below the toxic dose as assessed by performance on a rotating bar (142). $\Delta^1$-THC can also inhibit convulsions aroused by stimulation of anterior limbic cortex or the amygdala. Tolerance developed to this action, as well as to the suppression of $\theta$ activity

in the hippocampus, vocalization on touching and ataxia; between 9 and 42 daily injections were required (142a). With audiogenic seizures in mice (primed by exposure to 105 d$B$ for 1 min at 19 days age and tested at 28 days), $\Delta^1$-THC reduced the incidence of seizures both when given before the test and when given before priming—an action not shared by LSD, mescaline, and certain other drugs; this may reflect its anesthetic-like aspect (143).

A number of studies have involved the hypothalamus. In rats, $\Delta^1$-THC (like mescaline) reduces self-stimulation by bipolar electrodes in posterior lateral hypothalamus (144). Full tolerance to THC develops in about 7 days, but there is no cross-tolerance with mescaline (amphetamine and cocaine increase self-stimulation, morphine reduces it, pentobarbital and meprobamate may do either according to dose). $\Delta^1$-THC also reduces water consumption in water-deprived rats, antagonizes the dipsogenic effect of carbachol placed in the lateral hypothalamus, and if injected itself into the hypothalamus (30 $\mu$g) reduces drinking (145). Although stimulation of the lateral hypothalamus will induce rats to increase their oral consumption of alcohol solutions, it does not do so with hashish suspensions (146).

A consistent picture is now emerging from records of electrical activity in various areas of the brain with the following characteristics: (*a*) sometimes an initial period of arousal, (*b*) a reduction of overall cortical electrical activity, (*c*) a tendency to cycle more or less abruptly between fast and slow rhythm, (*d*) the appearance of high amplitude waves at various sites, and (*e*) a reduction in hippocampal theta activity (147, 148). An interesting study by Heath (149) points to the septal area as particularly important in monkeys exposed to marijuana smoke, with a consistent appearance of 5–10 sec bursts of high voltage $\delta$ activity (3–4 Hz) every 20–30 sec. These were sometimes also seen in mesencephalic reticulum and in posteroventral lateral thalamus. In addition, high amplitude spindle bursts (16 Hz) occurred in septum, temporal cortex, and also in deep cerebellar nuclei, orbital cortex, and hippocampus. Tobacco smoke, alcohol, or smoke from low THC material did not reproduce these actions. Relating these results to other work, Heath suggests the action on the septum is related to the euphoria, and on the cerebellum and thalamus to somatosensory effects of cannabis. Martinez et al (150), using intravenous dosage from 0.05 mg/kg $\Delta^1$-THC upwards, observed high amplitude bursts in basolateral amygdala and superior cerebellar peduncles at all doses, in parietal cortex and fastigial nuclei at high doses, in dorsal hippocampus rarely, and frontal cortex never. Pirch et al (151) in the rat found an overall reduction in integrated cortical voltage. With continued treatment, tolerance to this effect developed after 5–12 doses, but high voltage spindle bursts began to appear at 3–5 days and persisted throughout treatment. On withdrawal of the drug, after complete tolerance was achieved, a rebound increase in cortical activity appeared on the second day. Tolerance did not develop to one dose a week.

Interest thus focuses on the deeper structures of the brain, particularly the limbic system and the septal area. Although the electrophysiological data do not point to a primary hippocampal role, a valuable theoretical paper by Drew & Miller (152) analyzes the attractive possibility that cholinergic mechanisms in the hippocampus are particularly significant for the action of $\Delta^1$-THC on cognitive function. More

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generally, the consistent appearance of high amplitude bursts and spindling is interesting; taking the simple view that high voltage waves imply abnormal synchrony of discharge by substantial groups of cells, and that the normal differentiation in neuronal activity depends on, among other things, inhibitory mechanisms, one can envisage that THC has a particular effect in depressing inhibitory activity in some way.

## EXPERIMENTAL PSYCHOLOGY

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Three interesting new responses have been studied. First is the "vocalization" in rats induced by THC, when the animal squeals in response to gentle handling, a puff of air (153). With 5 mg/kg THC the response is elicited for about 3 hr. It is also produced by Ditran®, Sernyl®, psilocybin, cocaine, amphetamine, and yohimbine, but not amitriptyline; it is antagonized by morphine, chlorpromazine, diazepam, and tetrahydroacridine but not by phenitrone or salicylate. The response is probably to be viewed as one of distress rather than pain, and may be an operationally simple model for dysphoric effects of drugs.

Second are the studies on labor division in rats (154, 155), using pairs of rats in which one (worker) animal does most of the lever pressing and the other (nonworker) receives most of the food reward. If the worker rat was given THC, inversion of roles took place in 7 of 12 pairs. Labor division in animals trained under a CRF (continuous reinforcement) schedule was more sensitive to drugs than under a VI (variable interval) schedule; chlorpromazine, but not amylobarbital, could also produce the effect. Apart from the intriguing social analogies, the authors argue that the continued interest of the ex-worker rats in the reward shows that the reduction of work is not "amotivational," but rather a deconditioning due to a change in perception. A simple reduction of "motivation," to below the level required for work but above that required to take food, would also explain it.

Third are studies on discrimination (156). $\Delta^1$-THC orally in a dose of 1 mg/kg did not impair monkeys' ability to learn to perform first on a nondifferential reinforcement schedule and then on a green/white light discrimination schedule. When, however, the discrimination was reversed, the drug-treated animals tended to perseverate with the previously correct response and took longer to acquire the new response. Because earlier work indicates that $\Delta^1$-THC does not interfere with extinction of a response to a previously rewarding stimulus, the authors suggest that the drug impairs the acquiring of the new response, perhaps by increasing the aversiveness of negative discriminative stimuli—initially leading to active avoidance of what has become a positive stimulus when discrimination is reversed. The experiments also illustrate the greater sensitivity to $\Delta^1$-THC of more complex tasks.

Other studies throw light on what may loosely be called stimulant effects of $\Delta^1$-THC. Thus bar pressing by rats for water is slightly increased by low oral doses, but depressed by higher doses (157), and similar results have been obtained with adjunctive drinking (158). The effect of $\Delta^1$-THC varies with the test used; thus pit avoidance may be reduced, shuttle avoidance enhanced, and passive avoidance unaffected (159). $\Delta^1$-THC potentiates the impairment by ethanol of a motor task in rats, but with high doses of the drug, the impairment lessens, suggesting the appear-

ance of a stimulant action (160). There is an analogous finding with rats tested in a Y-maze: $\Delta^1$-THC, LSD, and hyoscine were all found to reduce entries and alternation, but $\Delta^1$-THC became less effective as the dose increased (161). In an extensive study, cannabidiol was found to antagonize the effect of $\Delta^1$-THC in producing catatonia in mice, corneal areflexia in rabbits, defecation and reduced ambulation in rats under chronic dosage, and aggression in sleep-deprived rats, but potentiated its effects on pain sense and rope climbing (162); it is suggested that CBD blocks excitant effects of $\Delta^1$-THC, and augments depressant effects. Another new study has tested the effect of $\Delta^1$-THC on rat locomotor behavior on an activity wheel; it was found to reduce activity in rats not habituated to the wheel, but to increase it in those habituated (and correspondingly inactive); the drug, in its role as a novel stimulus, was probably dishabituating (163). In the Sidman avoidance test, $\Delta^1$-THC in lower doses increases the number of responses, but efficiency declined, both premature and late responses increasing (164). Such experiments ram home both the inadequacy of terms such as stimulant and depressant, and the complexity of the neural systems underlying behavior.

Other studies include evidence that $\Delta^1$-THC does not reduce fighting in rats elicited by electric shock to the feet (165); that it does not alter depth perception in rats (166); and that $\Delta^1$-THC is about twice as active as $\Delta^6$ on rats' rope climbing and on mouse catatonia and motor activity, equiactive on rabbit corneal areflexia, and twice as active in man (28). Carlini has reviewed the acute and chronic behavioral effects of cannabis (167).

Efforts to find a neurochemical basis for these behavioral effects continue (See Reference 2, pp. 226–28, 273–74), although decisive findings are still lacking. Chronic treatment of mice with $\Delta^1$-THC was found to reduce the level of pyridoxyl- and pyridoxamine-5'-phosphate up to 30%, and to increase pyridoxal 2–3-fold, in brain and liver (168); noradrenaline content of peripheral tissues, but not brain, rose 20–30%. Daily intravenous dosage for a week in rats produced increased synthesis of $H^3$-catecholamines in brain and adrenals, although endogenous NAD and dopamine in brain, adrenaline and NAD in adrenals, and NAD in heart, did not alter (169); it was also noted that adrenal weight increased and heart weight decreased. Minor transient changes in brain monoamine oxidase and tryptophan hydroxylase, and an inhibition of the rise of brain 5-HT with age are reported (170). In aggressive rats with a high defecation index, chronic dosage reduced 5-HT in cerebrum, midbrain, and hypothalamus, but not cerebellum and medulla (171). *p*-chlorophenylalanine (PCPA) and dopa treatment enhance the aggressiveness of cannabis-treated partially starved rats (172) supporting the general notion that catecholamine might mediate and 5-HT repress the aggression. Finally, phenitrone, once claimed to be a hashish antagonist, has been itself found to have mescaline-like and other effects in cats (173).

## TOLERANCE AND WITHDRAWAL EFFECTS

The development of tolerance continues to be reported for most effects of cannabis and $\Delta^1$-THC: these involve performance of rats on a rotating rod or a balance beam (174), shock avoidance in rats (175), analgesia (176), reduction of body weight (177),

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pigeon pecking for food reward (178, 179), effects in the frog (179a), catalepsy in mice (180), effects on sleep in rats (181), elevation of blood corticosterone levels in mice (180), rat bar pressing for food (182), and DRL (differential reinforcement of low rates) schedules in monkeys (183, 184). Neurophysiological responses to which tolerance occurs include the anticonvulsant effect and depression of $\theta$ waves in the hippocampus (142a), and the reduction in the integrated electrocorticogram of rat (177). The latter study is the first to report full dose-response curves to $\Delta^1$-THC before and after the development of tolerance; a tolerance dose ratio of eightfold was found, the dose-response curves being approximately parallel, although there was a suggestion that the maximum reduction of the electrocorticogram was reduced in the tolerant state. There are three examples of absence of tolerance, in respect of inhibition of isolated mouse or hamster aggression (185), impairment by $\Delta^1$-THC of a delayed-matching-to-sample task in chimpanzees (186), and the ability of monkeys to discriminate between THC and its vehicle (187) or another drug (morphine) (188).

An interesting finding (174) is that if immature rats are given THC, tolerance to the drug develops more rapidly than normal when they are given it again in later life. Heart and brain weights were reduced in immature animals chronically treated with THC; others have also observed such reductions in older animals (169, 190). Another curious observation in the pigeon was that after tolerance had developed (within a few days) to the impairment of pecking for a food reward, there was a temporary enhancement of response for some days (179). The same authors found that the route of administration (oral, intramuscular, or intravenous) made little difference in tolerance development.

Cross-tolerance in the rat has been found between $\Delta^1$-THC and ethanol and pentobarbital (175) and on pigeon pecking between $\Delta^1$-THC and its 11-OH metabolite (178), but not with morphine or chlorpromazine (175, 188). A further difference from morphine is that cannabinoid inhibition of intestinal motility is not antagonized by nalophine (189).

One extensive study has failed to find withdrawal phenomena, using behavior and sensitivity to convulsants as tests (190). Other work has, however, revealed such changes. The best studied is rebound in the integrated electrocorticogram of the rat (177), an effect reaching its maximum 2–6 days after cessation of drug, and returning to normal in 12–17 days. In addition, a performance decrement (but no other abstinence signs) has been noted in chimpanzees on DRL or delayed matching schedules (184, 186). Rebound rapid eye movement (REM) sleep is mentioned in a later section. Kaymakcalan & Deneau had earlier described abstinence phenomena in monkeys which, with human experience has been reviewed elsewhere (124, p. 356; 203). A disconcerting study reports that naloxone induced an abstinence syndrome after THC administration, marked by diarrhea and weight loss, teeth chattering, wet dog shakes, salivation, and ptosis (188).

A good many mechanisms for tolerance have been suggested. One possibility is induction of metabolizing enzymes (originally suggested as an explanation for reverse tolerance through formation of an active metabolite); this received some support from the finding that the half-time of $\Delta^1$-THC in the blood of human

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subjects was about 40% shorter in marijuana users than in non-users. There is, however, little direct evidence of such induction, and certainly not enough to account for the degrees of tolerance observed; in pigeons the blood levels achieved after injection of $\Delta^1$-THC were the same in tolerant and nontolerant birds (190a). A similar result with tolerance to hypothermia in mice has been obtained by Lawrence & Pertwee (267). Another possibility, similar to an early suggestion for morphine, is that the drug possesses two partly opposed actions and that one of these increases with continued administration. A further metabolic theory (185) is that initially an active metabolite is formed, but that its formation is impaired by continued THC administration—although THC levels themselves would rise; if some effects (e.g. hypothermia or catalepsy) were produced by the metabolite, while others (e.g. impairment of aggression) were due to THC, it would explain many findings. The main difficulty with this approach is that, so far, $\Delta^1$-THC and 11-OH-$\Delta^1$-THC appear to be very similar in properties. Because $\Delta^1$-THC depresses transmitter output from Auerbach's plexus, and this may be its type of action in general, a surfeit theory of tolerance can be proposed (191). A recurrent theory is that tolerance in behavior tests is due to learning by the animal to compensate for any deficit. An interesting pointer to this (183) was found with monkeys on a DRL schedule: it was noticed that when the test started 3 hr after an oral dose of $\Delta^1$-THC, performance improved in the fourth hour over the third hour; this might, of course, have been due to a waning of THC action. But if the testing was delayed to the fourth hour, a precisely similar contrast appeared between fourth and fifth test hours. This strongly suggests that the animal learns, *during* a test session, to adapt to the impairment of performance, and hence a similar adaptation *between* successive sessions could be envisaged. The further suggestion has been made (186) that failure of tolerance arises when no appropriate compensatory response is available. Such ideas link readily with human experience (192).

Nevertheless, it is hard to see how learning can contribute to tolerance (for instance) to electroencephalographic changes. Because there is cross-tolerance with ethanol and barbiturates, it seems likely that some kind of cellular tolerance also occurs. It may be noted that the existence of tolerance may be missed if sufficient time (up to 20–30 days) is not allowed for its development, if a period of cumulation of THC masks its development, or if doses having supramaximal effects are employed. It seems likely that any given situation is complex, and that the roles of metabolism, learning, and cellular effects varying with different neuronal systems all should be considered on their merits.

## HUMAN STUDIES

Studies on potency and type of action of $\Delta^1$-THC, 7-OH-$\Delta^1$-THC and a number of congeners have been mentioned earlier (5, 7, 28, 31, 74, 75, 75a, 75b).

### *Perceptual and Cognitive*

Although fine ataxia is known to be produced by cannabis, vestibular function has only recently been tested (193). A dose of 15 mg $\Delta^1$-THC smoked had no effect on

gaze nystagmus, pendulum tracking, spontaneous nystagmus, positional nystagmus or torsion swing nystagmus during the subsequent 4 hr. On the other hand, a rise in flicker fusion frequency (mean 1.33 cps) (194) and a lowering of threshold to electrical stimulation of the fingers (195) have been reported. This evidence of sharpening of perceptual acuity (for which there is little other direct evidence) may correspond to the hypersensitivity after cannabis noted by many animal workers. $\Delta^1$-THC (together with psilocybin) has also been tested psychophysically (196) for its effect on the parameters of the power function $R = kS^n$ (where $R$ is the response, a visual or tactile estimate of size with reference to a standard; $S$ is the size of object presented; $k$ and $n$ are constants). Neither drug altered the linear relationship between log $R$ and log $S$, but $\Delta^1$-THC tended to increase $n$ for visual comparisons, and to lower $k$; psilocybin had the opposite effect. If the theory is adopted that $n$ is proportional to the ratio $G_p/G_e$ ($G_p$ = perceptual channel capacity, and $G_e$ = cognitive channel capacity), the result appears compatible with other knowledge. The effect, in general, is that in perceptual comparisons with some standard, differences are exaggerated.

The main effects of cannabis on memory are becoming clearer. There is agreement that it does not interfere with entry of information into the sensory register. Further, material learned before smoking cannabis can be retrieved after smoking as if smoking had not intervened (197); retrieval mechanisms are, therefore, apparently not affected [although this has been questioned (198)]. But recall or recognition of material learned and tested under cannabis is impaired for anything other than intervals of a few seconds. It has also been found that habitual users, tested while not under the influence of the drug, when compared to nonusers showed impairment for a verbal memory task (recall required over 2 or more minutes) but not in an arithmetic task (information storage of only a few seconds required) (199). Impairment of short-term memory correlates both with impairment of attention and with depersonalization and change of temporal sense (200). A feature worth noting is that the change consists of both failure to recall correct information and an increase of inaccurate recall ("inclusion error").

Discussion of the phenomena depends on the theoretical model chosen, in which memory itself does not always take first place. (*a*) A psychological theory (199) is that the cannabis user changes his pattern of learning, and comes to attend more to internal than to external stimuli. (*b*) Another proposal is that cannabis alters the initial coding of new information so that the individual under the influence of cannabis carries more associations than normal into the limited short-term store, thus diminishing its effective capacity (201). (*c*) A third approach suggests that there is a primary defect in ability to pay attention, leading to lack of concentration and hence of rehearsal of material, and thus, as a result of memory impairment, to loss of time sense and ego identity (200). The fact that cannabis, at least in low dose, increases the contingent negative variation (CNV) suggests, if the present interpretation of CNV is correct, that attention is not impaired (meaning by attention, that state when the subject warned by a light flash is waiting to press a button on hearing a tone 2–3 seconds later) (202). The position is complex, however, because with a CNV discrimination test, where the correct tone must also be identified, and a signal

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follows the response indicating whether or not this was done, CNV *before* the response dwindles, and *after* the response is increased (202). (*d*) Some observers feel the primary effect to be reduction of motivation; capacity to pay attention (and hence memory) could depend on this. Distortion of time sense has also been suggested as primary, because memory requires a time scale (152). (*e*) Alternatively one can consider as primary a process of sensory disinhibition, which impairs the inhibitory selective processes involved in handling both internal and external stimuli; this could lead to a perceptual flooding which, as well as leading to hypersynchronous electrical activity, would interfere with memory storage, increase the duration of felt time, and complicate psychomotor function (203). (*f*) Finally, there might be a quite specific effect on neuronal networks such that more repetitions (rehearsals) of a stimulus are required to produce a trace of given permanence. On analysis the various approaches overlap considerably; the main uncertainty is in identifying a "primary" effect (if there is one), with psychosocial conditioning, amotivation, and change in sensory mechanism as favorite candidates.

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### *Psychomotor Effects*

In tests on simulated car driving, both cannabis and alcohol increased the time required to brake or start; alcohol increased, while cannabis decreased the number of gear changes (204). Cannabis had a greater effect than alcohol on estimation of time and distance (205). In a tracking task (which may be compared to steering), cannabis increased errors, whether drug was given orally (206) or smoked (207). Low doses of $\Delta^1$-THC impaired performance in a divided attention task which required response to signals at the center of the visual field and simultaneous alertness to signals in the periphery (208). Stability of stance, measured by a "wobble-board," is very sensitive to cannabis (as the La Guardia report noted); a dose-related effect can be obtained (207) down to 3 μg/kg THC (delivered in smoke). A dose-related impairment of a wide range of dynamic and static psychomotor tests (198) and a reduction in maximum speed of tapping, but no change in preferred speed of tapping, have been reported (209). The relation of such findings to driving performance under cannabis is complex and has been reviewed together with statistical data (210). For the moment it appears that cannabis in social doses can impair driving performance, like alcohol, but that it differs in the detail of the impairment.

### *Control by the User*

The ability of the user to "come down" and to titrate his intake of drug has now been tested. The failure in recent studies to find material differences between experienced and naive subjects in cognitive tests or in rating of material against placebo, which has been confirmed (211), had suggested that subject-control had been overestimated. It has now been found that the user can, if motivated, lessen the cannabis effect on time sense, but not on short-term memory. It was interesting that the subjective estimate of the "high" was not impaired by the attempt; tachycardia was also unaffected (212). In experiments on self-titration, smokers were asked to achieve a standard high, using material varying fourfold (0.2–0.8%) in $\Delta^1$-THC content; the mean consumption of the most potent material was, however, only 27%

lower than that of the least, so that THC consumption actually rose threefold (11 mg against 3.8 mg) (213). Various explanations may be offered, but two factors should be borne in mind which would make control less accurate: the rather flat dose-response curve (214) and the slow kinetics of cannabis. To these must be added the well-known effects of expectation and the placebo action, which dilute out dose-related effects. In a different study, 30 users were asked to smoke as much as they could take (up to maximum of 70 mg), the dose achieved being used in subsequent tests (215). The mean amount taken under these conditions was 19.5 mg (highest 31 mg), equivalent to 10 mg absorbed, if 50% loss in smoking is assumed. (Two subjects had panic reactions; a third became stuporous on 30 mg, although a fourth individual very experienced with marijuana could still play a guitar after 31 mg).

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### *Effect on Plasma Testosterone*

Potentially important is a preliminary study showing a fall of about 45% in plasma testosterone in a group of 20 cannabis users compared to matched nonuser controls (216). Levels rose again if use was stopped. Response to stimulation by human chorionic gonadotrophin was within normal limits. Six of 17 men showed oligospermia, and 2 were impotent. Earlier reports of gynecomastia, however, were not confirmed, nor evidence obtained of raised prolactin levels. The results may be related to the impairment of sexual performance in male rats after single doses of $\Delta^1$-THC (217), and to the abolition of the surge of secretion of luteinizing hormone and ovulation in the female rat (217a). More generally, another important finding in rats is that $\Delta^1$-THC can interfere selectively with corticosterone uptake by hippocampus and septum (218).

### *Actions with Therapeutic Possibilities*

The availability of a new series of chemical structures in pure form has revived interest in the therapeutic possibilities of tetrahydrocannabinols. $\Delta^1$-THC has been considered as a hypnotic. Sedation or sleep in the latter part of its action is well known. Analysis in animals has shown that it and $\Delta^6$-THC may suppress or reduce the incidence of paradoxical (REM) sleep (181, 219). Subsequent rebound increase in paradoxical sleep was not seen in rats, although it occurs in cats. Tolerance to the effect developed quite quickly in rats and was still present 13 days after withdrawing the drug. $\Delta^1$-THC can block the increase in paradoxical sleep in animals previously deprived of it, producing a modified type of sleep marked by a continued $\theta$ rhythm in hippocampus, lack of muscle activity, and cortical spindling without the normal phasic activity (181). Sleep deprivation constitutes a form of stress, and $\Delta^1$-THC in animals so treated has been found (as with other forms of stress) to produce aggression and irritability rather than depression (220). In trials of $\Delta^1$-THC in man (221), doses of 10–30 mg orally significantly shortened time to fall asleep, and there was a reduction in awakenings in the first half of the night. The side effects constituted the usual actions of cannabis of which only racing of thoughts after getting into bed bothered the subjects. More serious was the hangover, being "stoned" for up to 24 hr after 30 mg. Residual effects the following day even after

doses of 9 mg (= 4.5 mg absorbed) have been noted in about 20% of subjects (214). During sleep after $\Delta^1$-THC, the amount of time in the REM phase is reduced (222, 223); after 4–5 consecutive nights of use, mild insomnia occurred, but no marked REM rebound.

A preliminary report of use as an adjunct to anesthesia (224) showed that massive doses do not induce anesthesia in man, but produce considerable tachycardia with occasional arrhythmias and panic reaction in some subjects. Use for clinical sedation, analgesia, and amnesia must be further explored. This result conforms with the suggestion that THC is a partial anesthetic (56) due to some disparity between its physicochemical properties and those of the neural membranes critical for anesthesia, leading to a pharmacological cut-off. Evidence that it is additive with general anesthetics had been confirmed in mice with ketamine, thiopentone, and althesin (225) and with halothane and cyclopropane in man (225a, 225b).

The analgesic potency is known (see reference 124, pp. 220, 274, 294) to vary considerably with the test used. With electrical stimulation of the tooth in the dog, a peak increase of threshold stimulus of fivefold was found; tolerance to the analgesic effect developed in 8 days (176). Hyperalgesia may, however, be produced, perhaps related to dose; with electrical stimulation of the fingers, inhalation by human subjects of marijuana smoke (about 12 mg of $\Delta^1$-THC) produced a fall in the thresholds for any sensation, for sensation of pain, and for tolerance of the pain (195). In this connection the aspirin-like properties of $\Delta^1$-THC may be considered (56). Burstein and his colleagues (226, 227) have shown that $\Delta^1$-THC can inhibit prostaglandin $E_1$ synthesis from arachidonic acid. They went on to find, however, that of the natural cannabinoids, cannabinol was the most active ($ID_{50}$ $7 \times 10^{-5} M$, against indomethacin $8.4 \times 10^{-7} M$) and that olivetol itself is active at $10^{-4} M$. There is therefore a poor correlation with psychoactive properties, but it may still be significant for other actions of cannabis. $\Delta^1$-THC has also been found to have anti-inflammatory action (by the carrageen-edema and adjuvant-induced arthritis tests) (228); because this activity was abolished in adrenalectomized and almost abolished in hypophysectomized animals, and because $\Delta^1$-THC actually decreased survival time after adrenalectomy, the molecule must itself lack corticosteroid action, and the anti-inflammatory effect be due to the known corticoid release. Although tolerance can occur to this (180) it could contribute to clinical analgesia.

Use in psychiatry, for instance in treatment of depression, had earlier been found unpromising. A double-blind trial has revealed a high incidence of dysphoric reactions (229); one type of depressed patient appears particularly prone to such reaction. High incidences of dysphoric reactions have also been recorded in laboratory tests and in users (214, 230). An interesting aspect is the report of severe depression being induced by physostigmine (eserine) in two marijuana-intoxicated individuals; not only was the high removed, but weeping and suicidal feelings developed; atropine reversed this action (231). At first sight this seems contradictory to a study in mice (232); in this, depression of motor activity by $\Delta^1$ and $\Delta^6$-THC and eserine was potentiated by tacrine, while a stimulant effect of Ditran and scopolamine was antagonized, leading the authors to attribute to $\Delta^1$-THC an anticholinesterase-like effect. Both studies agree, however, in finding that $\Delta^1$ THC and an anticholinesterase

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jointly led to a profound depression. A study (233) of the behavior of sensitivity groups receiving marijuana, placebos or no drug, also failed to point to a use for marijuana in group or antidepressant therapy. It should be noted that marijuana can distort the usual pattern of a manic psychiatric state, producing a schizophreniform phase (234).

The suggestion that $\Delta^1$-THC might be of use as a hypotensive agent arises chiefly from work on anesthetized animals. The earlier evidence that the drug reduced sympathetic tone has been confirmed (235, 236), and a reduction in impulse discharge rate in the inferior cardiac nerve recorded. The bradycardia produced by an acute dose of $\Delta^1$-THC in animals is mediated partly by vagal activity, partly by reduction of sympathetic activity. The afferent pathway involved in the bradycardia is not clear; it is produced in cats by injection of $\Delta^1$-THC into cerebral ventricles and in dogs both by injection into the donor circulation of a cross-perfusion of the head and by injection into the recipient (235, 236). In humans, and in animals under chronic dosage, however, tachycardia occurs. A new finding is that $\Delta^1$-THC reduced venous tone (237). No effect of acute doses (up to 2.5 mg/kg iv in the dog) on myocardial contractility was found (237); but a limited antiarrhythmic effect occurs, delaying the onset of ventricular extrasystoles after ouabain, but not early arrhythmias or lethality (238) Also relevant is that $\Delta^1$-THC prevents the rise in blood pressure in immobilized rats (239). An interesting study on serum dopamine-$\beta$-hydroxylase in rats showed that both $\Delta^1$-THC and ethanol reduced it (as expected from the drugs' effect on sympathetic activity), but that $\Delta^1$-THC potentiated the rise produced by immobilization, while alcohol inhibited this (240). That the drugs differed is not surprising in view of the curious hypersensitivity to handling of rats that $\Delta^1$-THC produces, and the work by Carlini's group on the interactions between THC and stress procedures. Similarly, $\Delta^1$-THC potentiates the immobilization-induced rise of tyrosine hydroxylase and dopamine $\beta$-hydroxylase in the rat adrenal (241). It is not yet clear how the evidence for reduction of sympathetic tone is to be reconciled with these evidences for increase in activity of sympathetic biosynthetic enzymes; experimental conditions do, however, vary considerably. It must be remembered that the anesthetized animal is of limited use in testing for a central hypotensive action, because anesthesia greatly potentiates this (cf hydroxydione, 242); in unanesthetized animals and in man, the hypotension is usually absent. At the same time, limb blood flow may increase, and vasoconstrictor reflexes may be impaired; also, postural hypotension in humans has been repeatedly noted (242a–244, and see reference 2, p. 322). The existence of postural hypotension, although the heart rate still accelerates, when a subject is tilted, may appear paradoxical; but it is typical of the effect of a small dose of ganglion-blocking agent (245) and probably reflects no more than the effect of a modest reduction of sympathetic tone on two different pathways. For practical use, the tachycardia produced in man, the development of tolerance to the hypotensive effect recorded in animals (245a), and the reports of electrocardiographic changes (in the S-T segment, in the T-wave, and ventricular extrasystoles) (246, 247) are discouraging. A more interesting candidate might be DMHP or a derivative (7); a dose of 200 $\mu$g iv in man gave a substantial fall in systolic blood pressure lasting over 6 hr, with little psychological effect; there

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was, however, a considerable tachycardia and marked postural hypotension, and the roles of cumulation and tolerance with repeated doses remain unknown.

Studies in connection with asthma and glaucoma have been more fruitful. Both smoked and oral $\Delta^1$-THC reduce airway resistance in normals and in asthmatics; there was no alteration in functional residual air or in carbon dioxide sensitivity (248, 249). The effect is not produced by the respiratory technique of marijuana smoking. Although it correlated with the tachycardia developed, unlike the latter (244, 250) it was not blocked by propranolol (251). These were acute studies, and the evidence of pulmonary pathology in chronic cannabis smokers must be borne in mind (252–254).

As regards glaucoma, two studies have shown that smoking cannabis can lead to a significant fall in intraocular pressure (IOP) in man (255, 256). This finding prompted an interesting investigation in the rabbit (257), in which the reduction of IOP was confirmed; it was accompanied by a doubling of protein concentration in aqueous humor, a transient increase in heart rate, but no consistent change in blood pressure. In further experiments on an isolated ciliary body preparation, $\Delta^1$-THC was found to reduce secretion of fluids at zero pressure gradient and to increase passive permeability; there was also a fall in short-circuit current and in membrane resistance. The authors themselves suggest that an ocular vasoconstriction produced by THC (corresponding to the tachycardia) is the most likely cause, despite the fact that the drug produces conjunctival vasodilation. Another factor in man might be pupillary constriction, which has been found, rather than mydriasis, to follow cannabis smoking (215, 255), along with a narrowing of the palpebral fissure, reduction in tear secretion, and conjunctival hyperemia.

### *Acute and Chronic Adverse Reactions and Sociological Studies*

Brief mention may be made of a study of adverse reactions and recurrences (surprisingly frequent) after cannabis use (230): a case of accidental poisoning (258) by the bursting of a swallowed rubber balloon containing contrabrand hashish oil (assuming the oil contained 30% THC, this implies an alimentary dose of about 30 mg/kg) produced drowsiness, lethargy, tachycardia, and anisocoria, followed by recovery in 48 hr; reports on clinical features of cannabis use (254, 259); a psychiatric study of toxic effects of chronic use, and the pattern and extent of recovery after giving up the drug (260); analyses of personality correlates of marijuana use (261), of the role of peer influence in adolescent drug use (262), and of risk taking in women student users and nonusers (263); and an attempt to measure the strength of a drug habit by the verbal association with drug-related words (264). There has been no further clinical study on the question of cerebral atrophy as shown by enlargement of the cerebral ventricles (265), although loss of brain weight has been noted in animals (169, 174, 190).

## GENERAL CONCLUSIONS

Underlying much of the pharmacology of cannabis is the high lipophilicity of its active principles which is responsible for the slowness of its kinetics, its cumulation,

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its persistence, and the difficulty of experimental work on it. The biotransformations encountered are also typical. The general pharmacology overlaps in many ways, both neuropharmacologically and in general cellular effects, with the other lipophiles such as the general anesthetics and the industrial solvents. Yet it differs from classical anesthetics in a number of ways, e.g. in effect on time sense at one level or on mitochondrial respiration at another. Indeed, a searching question is "Why cannot $\Delta^1$-THC itself produce surgical anesthesia, considering its fat-solubility?".

This question, together with the curious limit to the effect of $\Delta^1$-THC on microsomes, prompted the suggestion that it shows the phenomenon of pharmacological cut-off (56), illustrated by Ferguson (268) in discussion of the toxicity of long-chain alcohols. Considering the strongly hydrophobic character of $\Delta^1$-THC, it is possible that there is too great a physicochemical disparity between it and biological membranes into which it is inserted for a volume fraction to be achieved sufficient to produce the phenomena of full anesthesia. As Ferguson pointed out, such a cut-off can give rise to a sort of pseudo-specificity, dictated by the properties of the systems studied. Such a partial anesthetic property of $\Delta^1$-THC could thus account for some of its specific features. But other factors probably are at least partially responsible. The slowness of kinetics means that some of the patterns of response may simply represent variations in blood flow in different structures—the most rapidly perfused allowing the most rapid uptake of a drug present only in low concentration in free form. Varying safety factors of different neural systems will also give some apparent specificity of effect. Finally, the fact that activity varies in compounds differing only in optical activity, indicated in earlier studies, and now established as between (+) and (–) $\Delta^1$-THC, means that some specificity exists at the receptor site, even if it is only that of the conformations possible of spaces in a lipid membrane, and even though this might not show itself with a smaller molecule or one with other characteristic features. With such arguments one can for the moment hold together both the likenesses and the disparities between $\Delta^1$-THC and other lipophiles.

It is interesting that no specific neurotransmitter effect has been unequivocally identified. This may reflect the complexity of neurochemical interactions in the brain, with so many possibilities for reciprocal modulation between transmitters and between neural systems. But it might also reflect a more elementary mode of action, namely a general impairment limited to the most vulnerable regions, i.e. the most delicately poised transmissions, the smallest nerve fibers, and the finest details of dendritic function. Consideration of the toxicity data, particularly the changes in organ weights, which, because they do not correspond to those seen in starvation, cannot simply be attributed to reduction of food intake, also suggest that particular peripheral tissues may also be preferentially affected.

On this approach, the general pattern of action of $\Delta^1$-THC reflects, because of its limited action, a sieving-out of those processes in the body which are rate limiting or have low safety factors, and are susceptible to lipophilic attack. If this is the case, it should be possible to generalize the pattern to other lipophiles showing cut-off and to the chronic effects of anesthetics and solvents at lower dose levels.

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