

The Active Principles of Cannabis and the Pharmacology of the Cannabinols

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Today's status of the pharmacology of Cannabis, to be reported here as it has emerged from a fourteen year investigation,* part of which is as yet unpublished, contrasts sharply with the textbook presentations which even now often deal with the subject on the level of a-quarter-of-a-century-old knowledge. In fact, the pharmacological spectrum of the cannabis drug, formerly derived in part from misinterpreted actions of crude preparations of either Oriental (hashish) or American hemp (marijuana), has been classified and re-evaluated; botanical relations between the various "species" of Cannabis have been revised by aid of determinations of their content in active principles; the SAR† of the cannabis-active substances has been elucidated; a new class of chemical agents, comprising products of laboratory synthesis as well as of plant origin, has been opened up; and, last but not least, experimental and clinical investigation of the pure substances has turned a subject of merely toxicological interest into a source of therapeutic potentialities.

* The status of the Cannabis problem immediately before the discovery of the active principles (1938) is best surveyed in Walton's book and Blatt's chemical review. The literature from then on to 1942 will be found in Roger Adams' lecture and in the review which the author in 1941, contributed, upon the La Guardia Committee's invitation, to that committee's book published in 1944.

† "SAR" (relationship between chemical structure and biological activity) has found entrance into the American literature as a concise symbol suggested (Fed. Meetings, 6 :352, 1947) for that phrase so difficult to compress into a brief expression, and will be used in that sense (Structure-Activity Relationship) hereinafter.

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**Chemistry of the
active principles
of hemp.**

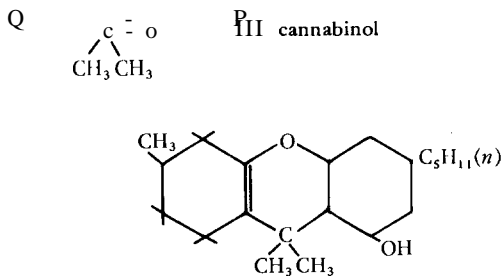
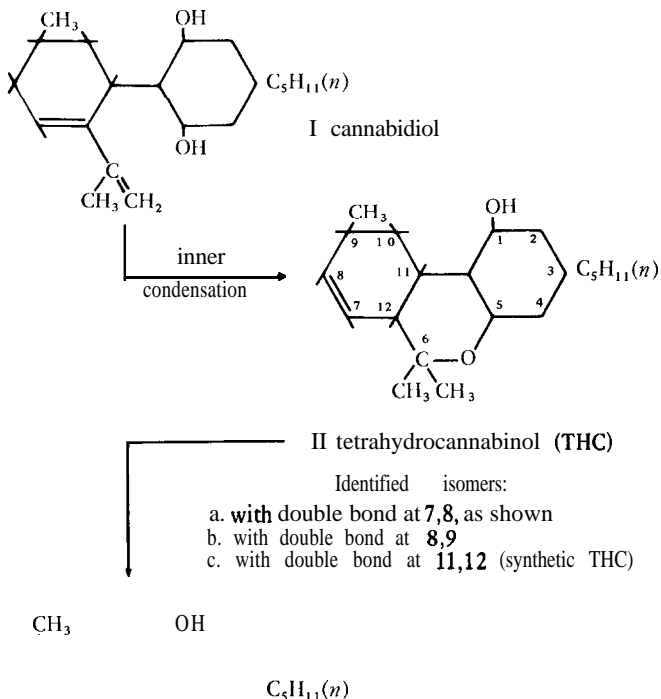
That the active substances are contained in the so-called "Red Oil," a high-vacuum distillate from cannabis extracts, had been known for many decades. Only in 1937 to 1942, however, was it ascertained by the work of an American research team* that the Red Oil consisted essentially of two inactive substances, cannabiol ($C_{21}H_{30}O$; III) and cannabidiol ($C_{21}H_{30}O$; I), and a varying mixture of tetrahydrocannabinols ($C_{21}H_{30}O$; THC; II a, b, and c), the representatives of "cannabis activity."† The conclusion of this first research phase was marked by a detailed description of the first and apparently maximally potent natural agent, a THC from Indian hemp resin, designated as charas tetrahydrocannabinol; its potency (P; cf. below) was 14.6.

Motor ataxia in the dog was the test reaction which served as a guide in the procedures to isolate the active compounds. It served to determine their content in the starting materials, to fractionate the crude oils, and to assay the potency of the purified substances. That the research plan resulted in success is due to two circumstances, namely, the choice of the right test response and its adaptability to quantitative purposes. It is now evident that motor ataxia is the one action in experimental animals which closely parallels psychic cannabis action in man; although this action is not accessible to evaluation by the customary biostatistical procedures because of the excessive variation of inter-individual sensitivity of the dog, a biostatistically adequate assay method could be developed by the introduction of a new principle of "intra-individual potency comparison."

The history of the discovery of the cannabis-active substances is characterized by the following paradox. On the one hand, those investigators who followed analytical procedures, by employing tons of starting material, large-scale molecular

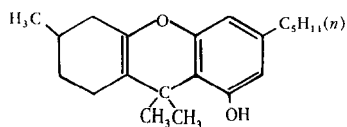
* H. J. Wollner, J. R. Matchett and J. Levine, Narcotics Laboratory, U.S. Treasury Department, Washington, D. C.; Roger Adams, et al., Department of Chemistry, University of Illinois; and this author.

† This is the term to be employed hereinafter for the characteristic psychic action and its equivalent in the animal experiment, which in some countries are designated as "hashish action," in others as "marijuana action."



IV pulegon condensation product (hypothetical tetrahydroxanthane structure)

* **Ed.** Note: In the current chemical structural nomenclature, these formulae would be considerably changed. As an example, the pulegon condensation product would be shown as:



The “ $-C_5H_{11}(n)$ ” is the normal amyl group, identical with “ $-(CH_2)_4 \cdot CH_3$ ” found in the following review.

distillation, and chromatographic and elution methods rapidly got hold of numerous, obviously chemically pure active substances but were unable to identify them structurally, particularly since even today they foil all attempts at crystallization. On the other hand, the discoverer of the two inactive by-products predicted the structure of the plant principles without going into an analysis of any one of the natural agents. As early as 1930-33, Cahn in England had obtained cannabinol as a major component of the hashish resin formed as a surface excretion on Oriental hemp, and had identified it correctly except for minor inaccuracies in the positions of the hydroxyl and the amyl group. In 1939, Adams demonstrated it to be a 1-hydroxy-3-n-amyl-6,6,9-trimethyl-6-dibenzopyran and at the same time prepared it synthetically. Cannabidiol, of which hashish resin contains only minimal quantities, was discovered in 1940 by Adams in extracts from freshly harvested North American hemp as a similarly considerable part (33 percent) of the crude oil, identified as menthadienylolivetol, and synthesized. The chemical relationship between the two substances, their inactivity, and the age differences of the raw materials gave rise to the ingenious hypothesis that cannabidiol signified the starting material and cannabinol the end-product of a phytochemical conversion process and that the intermediates on the way of this process, namely, hydroaromatic cannabidiol-isomeric precursors of cannabinol, may be the searched-for active principles.

This was confirmed on various avenues of approach: (1) Adams, by intramolecular condensation of cannabidiol, obtained—depending on the process of isomerization employed—two such semi-synthetic tetrahydrocannabinols (II b and c), both of which Loewe found to be very markedly cannabis-active; the two isomers differ in optical rotation, position of the double-bond, and potency (7.3 and 8.2). (2) At once, the oily substances which Wollner and Loewe and their associate? had isolated from hashish and American hemp and found to be highly potent could now be identified as THC. (3) Soon, Adams mastered the difficult synthesis of another THC (IIa) from 5-methylcyclohexanon-2-carboxylate and olivetol, the much lower potency of which was from then on employed as standard ($P = 1$). (4) Part of the presumable processes which in nature create the active

substances could be imitated *in vitro*; in an inactive cannabidiol synthesized by Adams, which had been irradiated with ultraviolet light, active substances could be demonstrated⁴ in an amount which indicated that about 2 percent had been converted to THC.²

Like the synthetic cannabidiols, the completely synthetic THC's are racemates, whereas the natural and the semisynthetic THC's are laevorotatory. In 1942, Adams and his associates dissolved the synthetic rac. THC into its two optical isomers (rot. +152 and -114, respectively), and here, too, the l-isomer (P = 1.66) turned out to be superior to the d-isomer (P = 0.38).⁸

Stereo- and optical isomerism make possible a large number of isomeric THC's which differ in the spatial arrangement of the 9-methyl group and of the planes of the hydroaromatic ring, and in the position of the double-bond in this ring. Probably all these isomers are cannabis-active, though they differ greatly in potency, and quite a number of them has been prepared from hemsps of different origin.⁴ The potency of fluid extracts from hemsps of different origins also varies quite markedly. Botanically, however, it is noteworthy that on the one hand fluid extracts from hemp cultivated in Rumania, Manchuria, Italy, Tunis and climatically very different parts of U.S.A. were cannabis-active (P: max. 0.52 in Tunisian hemp, min. 0.003 in an American hemp).⁴ On the other hand, a hemp grown from Oriental seeds on an experimental field near Washington, D.C., and re-seeded there for three subsequent years maintained its high potency.⁴ It is therefore quite possible that the composition of the active fraction constitutes the only difference between various varieties of Cannabis sativa. American hemp appears to be characterized by THC's of P 6.0 to 7.3 and 8.0 to 9.5, which may be identical with Adams's semisynthetic THC's from cannabidiol. In Oriental hemp, THC's of P 12.0 to 14.6 occur, in which the position of the double-bond in the hydroaromatic ring is as yet undefined and which have not yet been obtained from other hemsps. At closer analysis, the cannabinol component of the hemp plant proved also to be cannabis-active; completely synthetic as well as natural, frequently re-crystallized cannabinols had the same potency of 0.04⁹, which obviously is only of academic interest. The

hexahydrocannabinols are also active⁴ and so are presumably the dihydrocannabinols which can be assumed to be intermediate products in the conversion of THC to cannabinol; but none of these have as yet been demonstrated in hemp. In the plant, the cannabinols appear to occur in part as esters of aromatic acids.^{17c}

The content in active substances is not limited to the "flowering tops of the male plant," but occurs in many parts of the plant; for example, even seedlings of a few centimeters in height⁴ and seeds^{6b} yielded active extracts.

Synthetic cannabinoids and Structure-Activity Relationship (SAR)

According to the preceding data, cannabinol and all reduction products of its toluene ring can be considered to embody cannabis activity, and, in view of the activity of the parent substance, insignificant as it may be, it appears chemically and pharmacologically justified to designate the new class of chemicals as the class of cannabinols. After the gates had been opened by the disclosure of the natural agents and of synthetic procedures, the already mentioned representatives of the class were joined by many other compounds which served in our studies of SAR. Also to a team of British investigators^{3, 4} who had already for quite a time devoted themselves to the problem of the Cannabis drugs, that gate opened up a field of successful and, in part, independent chemical research whose results, unfortunately, for reasons to be discussed below did not become serviceable to the comparative study of cannabis activity in its proper sense.

Information on SAR of the class was largely obtained by measurements of the ataxia potencies. It was demonstrated that the I-hydroxyl group is an important component of the phenol ring of the THCs; its effective blockade greatly diminishes activity.^{3, 4} Also significant is the position of the substituents of this ring. For example, the 1-n-hexyl-3-hydroxy isomer of parahexyl, * the 3-n-hexyl homolog of the completely synthetic THC, has a P of only 0.05-t; i.e., only one-fortieth that of the substance of comparison. The role of the hydro-aromatic ring was studied in many analogs of the "synthetic THC" (P = 1). Lack of the 9-methyl group brings P down to 0.13 ; its substitution by ethyl, to 0.22 ; transfer to position 10, to 0.25; to position 8, to 0.14; an additional methyl group in position 7, to 0.75, but in position 8, to 0.11; replacement of the 6, 6-methyls by ethyls reduces P to

0.12, by propyls to 0.04. All such alterations at the cyclohexene ring, as well as opening of the ring so as to leave in its place a 6-*n*-butyl and an 11-methyl group ($P = 0.04$), reducing it to an 11-methyl group 0.033) or replacing it by cycloheptan (0.21) reduce but do not completely abolish activity.

Not until the significance of the 3-alkyl side chain was studied were increases in potency observed. The changes of P with changes in the length and arrangement of this side chain are presented in condensed form in Figure 1. Essential facts on SAR are as follows: (1) Shortening of the 3-*n*-amyl chain decreases potency.⁴ (2) Peak-effective, however, in the series of homologs of the "synth. THC" standard (Series A of Figure) is not this *n*-amyl compound, but its 3-*n*-hexyl homolog (parahexyl).⁴ which is about twice as potent (1.8), yet far inferior to the natural THCs. The same relation repeats itself in the other homologous series (C, D; cf. below) having an unbranched side chain. (3) Branching of the side chain can result in substances of far greater P , but in these series (E, F, and G¹²⁻¹⁵) peak potency is associated with a six- but not with a nine-C-atom side chain. (4) Optimum effectiveness was always found in side chains branched near to their "root"; for example, among the methyl-amyl isomers, P decreases consistently from the value 3.65 of the 1'-methylamyl-R (Series E) with transfer of the methyl group into position 2' (H; 1.58), into 3' (K; 1.25), and 4' (L; 1.14). (5) Methyl branching under otherwise equal conditions, appears to grant the greatest activity [compare in Series E 1'-methylamyl-R (3.65) with 1'-ethylbutyl-R (M; 1.68), and 1'-isopropyl-propyl-R (N; 3.18), and in Series G 1', 2'-dimethylbutyl-R (3.84) with 1'-ethyl-2'-methylpropyl-R (P; 3.40)]. (6) Double branching at the same C-atom appears not to offer any advantage over single branching (compare the two Series E and F). In contrast, two methyl branches at two adjoining positions 1' and 2' (Series G) result in representatives of outstanding potency which is only diminished by prolongation of the branched chain (Series P) or by addition of a third branch (Q).*

The role of the third (pyran) ring is illustrated by the observation that analogs of the hypothetical type IV, prepared from pulegon and appropriate resorcinol derivatives, are in tetra- as well as in hexa-hydrated form (Series C and D,

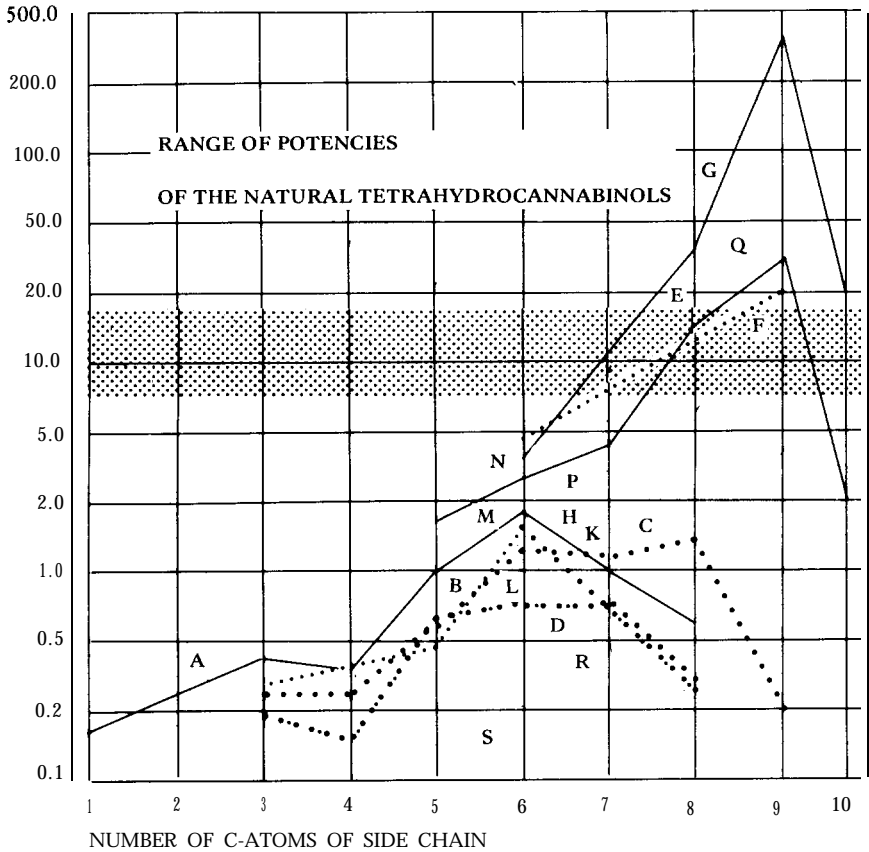


FIGURE I

Relationship between structure of the alkyl side chain and the ataxia potency of the cannabinoids. — The majority of the 47 synthetic cannabinoids represented in the figure are 1-hydroxy-3-alkyl isomers or homologs of synthetic tetrahydrocannabinol and these are designated, in the following legend, only by the structure of their 3-alkyl side chain. — A: ———, 3-*n*-alkyl. — B: ·····, 3-*n*-alkyl (homologs of synthetic hexahydrocannabinol). — C: ·····, 3-*n*-alkyl (tetrahydrogenated pulegon condensation products). — D: ·····, 3-*n*-alkyl (hexahydrogenated pulegon condensation products). — E: ———, 3-(1'-methylalkyl). — F: ·····, 3-(1',1'-dimethylalkyl). — G: ———, 3-(1',2'-dimethylalkyl). — H: ———, 3-(2'-methylamyl). — K: ———, 3-(3'-methylamyl). — L: ———, 3-(4'-methylamyl). — M: ———, 3-(1'-ethylbutyl). — N: ———, 3-(1'-isopropylpropyl). — P: ———, 3-(1'-ethyl-2'-methylpropyl). — Q: ———, 3-(1',2',4'-trimethylhexyl). — R: ———, 3-(1'-methylhexyl), tetrahydrogenated pulegon condensation product. — S: ———, 2-cyclohexyl-3-hydroxy. — For further details compare text.

respectively) approximately as potent as the corresponding cannabinols. These compounds may differ from the cannabinols in the mutual position of the two carbon-rings and in the structure of the heterocyclic ring. 1'-methylation appears not to increase potency in this series (cf. R).

Naturally, the problems of SAR are by no means consummated by the comparative bioassays of this scanty hundred of compounds hitherto studied. Many questions, among them that of the applicability of experiences in one series to other series, e.g., to homologs of the natural THCs, are still open. The role of the configuration of the 3-side-chain could certainly be further elucidated by the study of another hundred congeners; for example, substances have been synthesized in which the 3-alkyl chain is linked to the phenol ring by an ether linkage ^{16 - 17a}; if it were permissible to draw conclusions from the results of the Gayer test, a weak Cannabis activity would have to be ascribed to some of these ethers.^{17a}

Only recently, in a study of 2-cyclohexyl-3-hydroxyl-6, 6, 9-trimethyl-7, 8, 9, 10-tetrahydro-dibenzopyran,¹¹ we found that cyclic arrangement of the side chain is superior to a straight and unbranched side chain (compare S in Figure 1; potencies of the corresponding n-alkyls are below the frame of the graph)-a finding which points to new possibilities.

The substances of the cannabinol class are viscous oils, some solid at room temperature, and extremely poorly water-soluble. Even in the best solvents for cannabinols (acetone, ethanol, glycols), certain representatives with long side chain dissolve only slowly and yield only colloidal solutions. Accordingly, all cannabinols are difficultly absorbed; even after intravenous injection, thirty to sixty minutes and often more elapse until peak effect is attained, and the peak effect persists for hours-even for five days, as was observed after a single medium-sized intravenous dose of the 1'-methylonyl representative of Series E. Oral administration requires twenty to thirty times the intravenous dose, and subcutaneous administration hardly ever produces a demonstrable effect. Even after high doses, we were as yet unable to demonstrate urinary excretion of active substances." In the blood, however, 1.6 to 10.5 percent of

**Conditions of
action of the
Cannabinols**

parahexyl given by vein were found circulating after two to three hours and 2.4 percent after eleven hours; the lungs of a dog contained 0.9 percent of a dose injected twenty hours before.¹⁸ Probably because of these physicochemical characteristics of the compounds, the margin of safety is enormous; per kg body weight, the oral L.D., of Charas THC in the mouse is more than two hundred thousand times the intravenous threshold dose for ataxia in the dog and more than forty thousand times the oral threshold dose for psychic action in man.¹⁹

**The action
spectrum of the
cannabinols.**

Not all the actions of crude hemp preparations or oil redistillates reported in the literature could be reproduced with pure active substances. At that, many of them are of minor importance at the present state of the Cannabis problem. This holds true, for instance, for the effects upon heart rate, respiration and pupil. Therefore, the following discussion will be limited to those, in part newly revealed, sections of the large action spectrum, which have been studied with the aid of pure substances.

1. Psychic Actions. Analysis of the psychic actions in man, still more so in animals, is a task as yet unsolved. Even with pure substances, neither the host of experimental psychologists of the LaGuardia Committee" nor the effects with a "battery of psychological tests" both elsewhere** and in test persons in our department* were capable of disclosing more than a large range of variation of all phenomena tested. Thus, the availability of numerous pure substances of the class has not as yet given impetus to the analysis of the unique "pleasure action," but a few experiences have been collected which deserve to be mentioned partly as modest beginnings, partly with a view to therapeutic aspects. For instance, both parahexyl²² and compounds "RA 122" and "RA 125A"²¹ were found to have no effect upon the normal human EEG or upon musical appreciation.^{22b} Therapeutic effects of parahexyl have been reported in depressive states^{23a} but in consideration of the negative experiences of Pond^{23b} and of unpublished personal reports to the writer they are in urgent need of further verification. Charas THC has been extensively employed for "psychic relaxation" and is reported²⁴ to be equivalent to the customary barbiturates for purposes of narcoanalysis, narcocatharsis and

narcosuggestion. The idea, however, that Cannabis and morphine may be comparable in euphorizing effects has not proved fruitful in its application to morphine withdrawal; withdrawal symptoms were neither shortened nor abated by parahexyl treatment.^{25a} Noteworthy, though difficult to evaluate, are reports on psychiatric episodes, mostly in psychopaths, occurring in some instances under prolonged treatment with, and in other instances upon withdrawal of cannabis-active drugs.^{25 a - g}

2. Cataleptic Effects. They are never missing in the picture of the hemp "jag," always accompany the ataxia effects in the dog, and are produced by all ataxia-active pure substances.^{4,19} They can be seen in many species of animals, and a catalepsy test has been described¹⁹ which occasionally has been found quite serviceable.

3. Ataxia Action. This has gained ever-increasing prominence among all cannabis actions, as an experimental tool. It is not only highly serviceable,* but is closely correlated with psychic action. This has been confirmed for all those crude and pure products which have been both bioassayed by the writer and evaluated in man^{20,24}; particularly good agreement was found between ataxia and psychic potencies of four cannabinoids at the occasion of their especially careful and expert evaluation by Dr. L. Kubie. There are only vague notions about the locus and mechanism of the ataxia action.⁴ In view of its outspoken parallelity to the psychic action, a close correlation in the mechanisms of the two actions has to be considered seriously. As a matter of course, final proof of both identity in mechanism and the quantitative parallelity can only be expected from an evaluation in man of all the compounds available.

4. Central Stimulant Actions were observed with all substances of the class. From medium degrees of ataxia upward, dogs at times exhibit convulsive motor symptoms.^{4, 19} They are possibly related to the compensatory counteractions against the disturbance in coordination; their frequency varies with the dog's individuality and strain. Indisputable and unique convulsions appear consistently after doses greater than twenty times the threshold ataxia dose after intravenous administration of the high-potent "RA 122" and dominate the picture of action of lethal doses. Mice often become pugnacious after medium doses of cannabinoids.¹⁹

Vomiting occurs in dogs rather regularly and late, usually one to five hours after injection, following doses upward from a medium-effective intravenous dose. The emetic effect as well as the hyperexcitability of the scratch reflexes can probably be ascribed to a central stimulant action.^{4, 19}

5. Hypnotic **Activity**. Elements of central nervous stimulation among the actions of hemp are of interest in view of the question of its soporific action. Probably cataleptic symptoms in man have often been interpreted as signs of a sedative action. In the dog, concomitance of catalepsy with higher degrees of ataxia which prevent upright posture results in a syndrome which might impress a superficial observer as sleep. In experiments with combinations of aqueous hemp extracts and hypnotics, **Burgi** believed he had demonstrated a hypnotic component of Cannabis action.²⁷ We were able to duplicate his observation with fluid extracts of hemp; they prolonged sleep duration in mice after a pernocton dose which is just enough to suppress the righting reflex. Sleep prolongation, in our experiments, was significant indeed, but only for this one hypnotic; however, even the consideration prolongation by a large dose of Cannabis equals no more than the effect producible by an additional 10 to 20 percent of the pernocton dose employed. Above all, however, a study of pure substances gave proof that this action is due not to any one of the cannabis-active components, but to the otherwise inert cannabidiol.²⁸ * Moreover, the natural as well as the synthetic cannabis-active substances lack any other indications of central nervous depressant action. Even in states of severest hypomotility and impairment of attention, up into the terminal phases of lethal effect, the animals, quite contrary to those under the influence of hypnotics, still respond, with frustraneous movements to moderate acoustic, tactile, or pain stimuli. This is in accordance with the characteristic criterion of Cannabis action both in dog and in man, namely, that the drugged individual can readily be diverted by environmental stimuli.⁴

6. **Corneal Areflexia**. Abolition of the wink reflex in rabbits after administration of hemp extracts or crude oils was discovered in 1928 by Gayer in Straub's laboratory and considered to be a faithful expression of Cannabis activity.²⁹ First of all, at closer analysis this systemic action has proved inappropriate for quantitative purposes because of the great

variation in inter- and intraindividual susceptibility. Only after a tedious search in a large stock of animals by way of numerous **recalibrations** can one find a number of individuals suitable to yield conclusive data in strictly intraindividual potency **comparisons**^{4, 30} that there are two types of **areflexia** producing agents, namely, (a) ataxia-active **THCs** which lose neither in ataxia nor in areflexia activity by such oxidation, and (b) other extractives possessing little or no ataxia activity, but a marked areflexia activity which can be destroyed by oxidation. In the search for the as yet unidentified substances of this type (b), the Gayer test in its **present**³⁰ more complicated but more reliable form is thus the test reaction of its choice.

7. *Anticonvulsive Action.* It was only by the aid of the highly active synthetic cannabinol congeners and due to the methods elaborated in this laboratory by Goodman and Toman and associates³² that the antiepileptic activity of cannabinols could be disclosed and specified. All cannabinols tested were effective. Their activity is of the type of **anticonvulsant** activity of diphenylhydantoin. Like this drug, they abolish the tonic hind leg extensor component in the pattern of supermaximal electroshock in rats and **cats**³³ (and presumably also in **man**³⁴), whereas they prolong the duration of metrazol convulsions, modify their appearance and display a strong lethal synergism with **metrazol**.³³ The cannabinols differ from diphenylhydantoin and its congeners by exhibiting, in their maximum-potent representatives, much greater potency and, in reference to lethal effectiveness an incomparably greater margin of safety. When referred to psychic side effects, the therapeutic indices of the various agents vary considerably. In a preliminary **experiment**,³⁵ "RA 122" lacked the ability of diphenylhydantoin, discovered by Toman et al.,³⁶ to raise the threshold of the isolated nerve preparation for electrical stimulation and to prevent the repetitive discharge elicitable by immersion of the nerve in neutral isotonic phosphate solution; it is true that, in view of the minimal water-solubility of the cannabinols, the result is inconclusive.

Alteration of the electroshock pattern points to anti-grand mal activity, suppression of metrazol convulsions to anti-petit mal activity.³² Accordingly, clinical experiments were undertaken with some of the agents. A first series³⁷ in **diphenyl-**

hydantoin-refractory grand-mal epileptics proved noteworthy effectiveness and absence of psychic side effects when "RA 122" was given orally for several months in daily doses of one mg or less, or the weaker isomer, "RA 125A," in somewhat higher dosage. A second series³⁸ consisted of five institutionalized children with severe grand-n-al epilepsy and mental underdevelopment, in whom daily doses of 0.13 gm phenobarbital combined with 0.3 gm diphenylhydantoin or 0.2 gm Mesantoin had proved inadequate. "RA 122," in daily doses of 1.2 to 1.8 mg, was in three children "at least as effective" as prior therapy; the fourth became almost free from attacks and the fifth completely free. Following transfer to 4 mg of "RA 125A," the attacks remained infrequent in one patient, the other one suffered exacerbations. The first patient had a brief paranoid episode, similar to others he had repeatedly experienced prior to the cannabinol therapy. In contrast to their ineffectiveness upon the normal EEG the cannabinols normalized the EEG of grand-mal patients.

The protective activity of cannabinols against electroshock and grand-mal attacks is of theoretical interest in view of the apparent absence of structural relationship between the cannabinols and the antiepileptics from the classes of hydantoin, barbiturates and oxazolidinediones. The practical evaluation of cannabinols as antiepileptics, notwithstanding their superior potency and persistence of action, will largely depend upon the problems of their side effects which will be discussed below.

8 Analgesic Action. It was probably the conceivable tendency to compare every euphorizing drug with morphine regarding anodynic properties, which brought British investigators to take up anesthesia tests and to ascertain the intravenously injected hashish extracts were somewhat effective, and that some cannabinols of the 1-hydroxy-3-alkyl-R and one of the 2-alkyl-3-hydroxy-R type were considerably effective (see Table 1). Using a modification, introduced in this department by Nickerson, of the customary methods of rat-tail heat stimulation which had also been employed in the afore-mentioned studies, we observed an even greater effectiveness in two other cannabinols.

9 Lethal Action. As already mentioned, large doses are required for a lethal effect, which are not always available and are not easy to administer because of the poor solubility

of the substances. Data for quite a number of older preparations (previous to 1947) have been presented previously.¹⁹ Only some particularly illustrative observations need be reported here. The values of intravenous L.D.₅₀ in the mouse⁴ indicate that the lethal toxicity of pure substances is markedly lower than that of the crude preparations. The necessity of employing solvents such as propylene glycol, which are by no means indifferent, and the minimal water-solubility of the drugs are probably responsible for the poor reproducibility of the lethal-dose values. Such shortcomings are less important than the experience that the lethal mechanism of the same substance can be different with different routes of administration. The late death of dogs after oral administration of parahexyl is associated with profuse intestinal hemorrhage, after intravenous injection with severe pulmonary edema. In contrast, incomparably smaller intravenous doses of "RA 122," which is ataxia-effective even in doses of a few micrograms, cause death associated with convulsions within a few hours, obviously owing to some primary central nervous mechanism. This suggests the interpretation that the lethal effect of the lower-potent cannabis-active substances is due to non-specific mechanisms and that only that of the high-potent agents originates from a mechanism more closely related to the main activity, which in the low-potent substances is masked or outdone by non-specific toxicity.

10. Habituation. The clinical authors of the La Guardia Committee's report, on the basis of observations in chronically marihuana-smoking prisoners, deemed the danger of habituation negligible.²⁰ This has evoked a vehement controversy.⁴⁰ The most lucid answer to the problem of hemp habituation will be found with Goodman and Gilman.⁴¹ Conclusive animal experiments are not available. For its curiosity value, the "beginner's habituation" may be mentioned: The more than one hundred fifty dogs from the writer's twenty-six hundred bioassay experiments, some of which had been tested twice per week for many years, almost invariably exhibited a certain decrease in sensitivity during the period of the three to four initial experiments, and from then on maintained a rather constant susceptibility. This habituation was the more pronounced, the less the individual's postural behavior was dominated by tenseness. Accord-

ingly, the apparent decrease in susceptibility seems to be due to the "learning" of postural responses compensating for the ataxic incoordination, at the mercy of which the individual finds itself quite helpless during its first experiences in ataxia. All other intraindividual variations in susceptibility, as they developed over long periods, were completely irregular, varied in intensity, and consisted in increases as well as decreases; in bitches, they were not without relation to sex cycles and pregnancy, for which reason all assays were conducted in males.

**Interrelation
between different
cannabinol actions.**

It has been repeatedly emphasized above that up to now all observations have pointed to an even quantitatively close relation between the psychic and the ataxia activity. The ratio between psychic potency in man and ataxia potency in dogs of an individual substance is a constant which varies very little in the entire class. Contrariwise, it has been demonstrated above that neither of these two activities has a constant relationship to lethal activity.

That the corneal areflexia action is not correlated with the ataxia action, is evidenced by the fact that in crude hemp products the two activities can be dissociated by oxidation. It is true that not only the unknown cannabis-inactive substances disclosed by that procedure, but also ataxia-active cannabinol possess areflexia activity. However, the potency ratio between the two activities varies from substance in a wide range, as has been shown earlier⁴ for a series of cannabinols and is confirmed in Table 1 in nine, partly new substances. A similar inconstancy of the potency ratios is also evident when analgesia and ataxia activity are compared (Table 1, column 5).

The relation between antiepileptic (anti-electroshock) and ataxia activity is also marked by a certain though lesser inconstancy of the potency ratios (Table 1, column 4). Here, however, the results should be evaluated with greater reserve. For the electroshock experiments, for better comparability of the cannabinols with other antiepileptics, were performed after oral administration of aqueous, lecithin-homogenized emulsions of oily drug solutions, whereas the potency values for ataxia and all other actions were determined after intravenous administration. Since in these comparisons numerator and denominator of the potency ratio originate from

experiments with different routes of administration, it is possible that inequality of the ratios is due to differences in absorption, distribution and detoxification. A comparison of the E.D.₅₀ values for corneal areflexia of the British investigators with the writer's ataxia values indicates that in some cannabinols the areflexia dose is smaller than the ataxia dose. That makes it tempting to base all evaluation upon the Gayer test which, superficially judged, is more convenient than the ataxia test. For SAR studies and for the assay of cannabis activity of crude preparations and unknown mixtures, this must be urgently discouraged because the potency ratios are so inconstant. Quite inversely, the analgesic dose of all cannabinols and the anti-electroshock dose of some are high as compared with the ataxia dose. In such substances, each of the two therapeutic effects may be obtained only at the price of considerable psychic side effects. Were such an unfavorable potency ratio common to all cannabinols, the outlook would be small indeed that further search could reveal other substances of the class more devoid of these side effects. The inconstancy of the ratios leaves the possibility open that there are cannabinols of a greater therapeutic index both for analgesia and for epilepsy therapy. Actually, available experience already teaches that in clinically equieffective doses the only two cannabinols which have as yet undergone clinical examination are not equally liable to produce psychic side effects : "RA 122" not only exerted greater therapeutic action than "RA 125A" but also had a smaller incidence of psychic Cannabis effects. That the two substances differ clinically with regard to the risk of side effects agrees with the fact that the experimental potency ratios of different cannabinols differ; that "RA 122" has fewer side effects than "RA 125A" is contrary to what one would have expected according to the size of the two potency ratios and may thus indicate that ratios of experimental potency values which are obtained after administration by different routes are not the last word on this subject.

Theoretically, the dissociation between psychic activity on the one hand and analgesia, corneal areflexia and antiepileptic activity on the other hand, as demonstrated by the inconstancy of the respective potency ratios, is probably an indication that the actions compared must be ascribed to different reactive groups or, more generally expressed, to

different parts of the total configuration of the same drug molecule.

Summary.

1. This review attempts to present some evidence for the proemial statement that our knowledge of the cannabis drugs has undergone a striking change.

2. After a report on the isolation of the natural Cannabis agents and their identification as tetrahydrocannabinols, their subsequently studied synthetic isomers and analogs are surveyed and some data are reported on the structure-activity relationship in this new class of chemicals, the cannabinoids.

3. The pharmacology of the cannabis-active substances, as revised with the aid of a study of the pure substances, is briefly presented, and examples are given for the decisive elucidation obtained by the study of the most recent, highest-potent synthetic agents, the potency of which was found to be up to seventy times the average and up to thirty-five times the maximum potency of natural tetrahydrocannabinols.

4. Some details and therapeutic trials of the psychic cannabis action are reported.

5. The significance of the ataxia action in the dog, which appears to parallel closely the psychic action in man, for identification and bioassay of cannabis-active compounds is illustrated and, contrariwise, the corneal areflexia in the rabbit is discussed as a quite detached property of some of the hemp products and congeners, which is only of very limited usefulness.

6. The old question of the hypnotic activity of the Cannabis drugs is answered in the negative from a study of the pure substances; closest to hypnotic activity is the practically insignificant, very limited capability of crude preparations to prolong the hypnotic action of certain barbiturates, an activity which is absent in the pure cannabis-active substances and embodied only in an otherwise inert by-product, cannabidiol.

7. The analgesic activity of cannabinoids, only recently disclosed and not yet tested for its practical applicability, is briefly discussed.

8. In their anticonvulsant activity, also an only recently discovered property, the cannabinoids are demonstrated to be closely related to diphenyl-hydantoin, according to both

experimental criteria and clinical experiences; the most potent synthetic congener of the cannabinols appears to possess more than one hundred fifty times the anti-grand mal potency of diphenyl-hydantoin.

9. The problem of the therapeutic indices of the five major actions and that of their mutual relations in the roles of main and side actions are dealt with on the basis of experimental data; the potency ratios hitherto established do not preclude the possibility that continued search of the new class of compounds will lead to congeners having a still greater margin of antiepileptic effectiveness than the as yet best examined "RA 122," and perhaps also to congeners having an adequate therapeutic index of analgesic activity.

10. Contributions are presented to the problems of habituation and of the mechanism of the lethal action; as a menace of habituation, addiction and tolerance the cannabis-active drugs appear to rank lowest among the narcotics, and according to the margin of safety some of them rank uppermost among all drugs.

TABLE 1

1	2	3	4	5
	ataxia potency ^a	Potency Ratios P/P' ^b P': ataxia; P: corneal anticonvulsant areflexia potency analgesia		
<i>1-hydroxy-3-alkyls:</i>				
1. n-amyl (synth. THC)	1,4 ⁴	1.18		3.33
2. n-amyl (Charas-THC)	14,6 ⁵	0.15 ³⁰	0,08	0,41 ^d
3. n-hexyl (Parahexyl)	1,82 ⁴	1,0	1,0	1,0
4. 4'-methylamyl (iso-hexyl)	1,14 ¹³	0,16	—	—
5. n-heptyl	1,05 ⁴	1,73	—	—
6. 1'-methylheptyl	16,4 ¹³	1,33	—	0,067
7. 1',2'-dimethylheptyl (RA 125A)	60,0 ^e	—	1,67	—
8. 1',2'-dimethylheptyl (RA 122)	512,0 ¹⁴	—	0,40	—
<i>3-hydroxy-2-alkyls:</i>				
9. n-hexyl	0,028 ^e	8,6	—	71,4
10. n-heptyl	0,010 ^e	48,5	—	—
11. cyclohexyl	0,074 ^e	10,1	—	—
	Mean:	8,0	0,79	15,2
	s.e.:	15,6	0,70	28,0
	% s.e.f:	195%	89%	184%

* The details underlying the figures of the Table will be published separately; for the present purpose of demonstrating the inconstancy of the P/P'-ratios the details can be dispensed with. — a: All values referred to synth. THC. — b: All

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values referred to **Parahexyl**. - c: = Anti-electroshock potency, according to unpublished experiments of Dr. E. A. Swinyard. - d: This value results from the author's own experiments (analgesia comparisons after oral administration), whereas all other values of this column are calculated from the analgesia doses which **Avison c.s.**¹¹ determined after intravenous injection. Hence this value is not directly comparable with the other values of this column, but this is of no significance for the overall outcome. e: **Loewe**, unpublished. - f: **S.C.** as percentage of mean.

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