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MARIHUANA*

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THE facts on marihuana which I shall present to you this evening comprise the results of the coöperative efforts of three laboratories—the chemical investigations at the University of Illinois, the pharmacology at Cornell Medical College under the direction of Dr. S. Loewe, and the clinical experiments at Welfare Island Hospital under the auspices of the Mayor's Committee on Marihuana and under the immediate direction of Dr. Samuel Allentuck. All three laboratories acquired their supplies of raw materials from Dr. H. J. Wollner of the Narcotics Laboratory of the Treasury Department, and received much encouragement and stimulation from him. Dr. J. R. Matchett of the same laboratory contributed significantly to the general problem by devising a method whereby a fraction of the red oil of hemp, containing a very high concentration of the active principle, could be obtained.

Cannabis sativa, more commonly called hemp, is of peculiar interest. It has been known for thousands of years as a product of commerce; the fiber of the plant for clothing and rope, the seeds for the oil they

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contain. The presence of an intoxicating principle in the resin of the plant has also long been recognized, since the physiological action of hemp preparations is mentioned in some of the earliest records available and is described in the first medical treatises. In the last two thousand years over four hundred articles have been published describing its intoxicating characteristics and the effects on humans.[1]

The preparation of the hemp for consumption as an intoxicant varies in different countries and consequently several names, such as marihuana, charas, ganja, hashish, and others, have been adopted, each in a definite locality. It is significant that the same characteristic phenomenon from any of these products is observed in man when the doses are equated.

The clarification of the chemical and medical aspects of hemp extracts has been extraordinarily slow for a material known as long and used as frequently as marihuana. The reasons have been several—the failure of chemists to isolate a pure active principle, the unsuccessful attempts of the pharmacologist to find an animal test which paralleled the activity in humans, and finally the lack of controlled clinical experiments.

The recorded medical literature is most confusing. The reports are contradictory, and the description of the drug varies from one which is habit-forming and which with constant use is as harmful to the system as morphine, to one which is almost completely innocuous with a stimulation not far remote from that of alcohol. Spread of the use of marihuana in the United States has been due in part to its ready availability, since hemp grows wild in countless places all over the country. Newspaper articles have described marihuana smoking among school children, and magazine articles have carried vivid accounts of activities encountered in tea-pads—dens where marihuana is enjoyed by devotees. Marihuana has been accredited with precipitating premeditated criminal acts, of lowering morals and releasing inhibitions, and of serving as a stepping-stone to other drug addictions such as the use of heroin. Furthermore, the claim has been made that continued use of marihuana produces mental deterioration. A "Marihuana Bill" was passed by the United States Congress in 1934. For purposes of administration marihuana is defined essentially as any part of the hemp plant or extract therefrom which induces somatic and psychic changes in man. The regulations and penalties in the bill for use and distribution

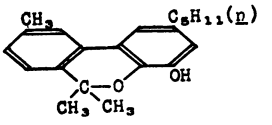
of marihuana are as rigid as those imposed for the use and sale of morphine.

In the investigations which are to be described this evening, more quantitative data on the chemistry, pharmacology, and clinical aspects of marihuana have been gathered than hitherto have been available and present a foundation for the eventual complete understanding of this interesting natural product. The chemical investigations, an excellent résumé of which up to 1938 has been published by Blatt,[2] will be discussed first. Practically all of the chemical experiments which have been reported were performed on the resin present in hemp from various sources and the same general procedure for isolating the resin has been used by all investigators in this field. After extraction with an organic solvent, filtration of the solution thus obtained, removal of the solvent and vacuum distillation of the residue, a highly viscous, physiologically active oil results, red in color and boiling over a wide range. Fractionation of the oil leads to the concentration of the active components in the portion boiling from 180-190° (1 mm.) which is commonly known as "purified red oil." This purified red oil usually used in the chemical studies has been shown definitely to be a welter of closely related substances which are very difficult to separate from each other and which occur in varying proportions dependent on the source of the hemp.

Between 1840 and 1895, most of the chemical investigations consisted in attempts to discover tests which would provide means of identifying a hemp extract. Numerous color reactions were reported, only one of which has received frequent application and until recently general acceptance. This is the so-called alkaline Beam test which is the purple color produced by treatment of a hemp extract with 5 per cent methanolic potassium hydroxide.[3] From our chemical results and from an extensive investigation of agronomic varieties of hemp by Dr. Matchett[4] it can be concluded that this test is not indicative of a substance with marihuana activity.

In 1895 Wood, Spivey, and Easterfield[5] were able to isolate from "purified red oil" by means of a treatment with acetic anhydride, a crystalline acetate, which was removed from the residual oil and which could be purified in the normal way. Hydrolysis of this pure acetate resulted in a homogeneous viscous oil which these investigators called cannabinol. Until about a decade ago, when the fact was shown to be erroneous, cannabinol was accepted as the active principle of hemp.

CHART I



(Cannabinol, Cahn)

Cannabinol	M.P. °C.	Cannabidiol	M.P. °C.
$C_{21}H_{26}O_2$	75–76	$C_{21}H_{30}O_2$	66–67
p-Nitrobenzoate	165–166	*bis*-3,5-Dinitrobenzoate	106–107
m-Nitrobenzenesulfonate	127–129	*bis*-*m*-Nitrobenzenesulfonate	119–120
Acetate	76–77	Oil	
3,5-Dinitrophenylurethan	220–222	Oil	
Optically inactive		$[\alpha]^{27}D$—125° (ethanol)	
No alkaline Beam test		Superb alkaline Beam test	
No marihuana activity		No marihuana activity	

These same investigators performed preliminary experiments on the structure of the cannabinol molecule. Further work on its chemistry was impeded by the fact that in spite of many attempts in different laboratories the isolation of cannabinol was not repeated until 1932. At that time Cahn[6], an English chemist, again obtained this compound and completed a series of brilliant researches from the results of which he was able to establish the skeleton and the substituents in the molecule but was unsuccessful in determining the orientation of all the groups.

It was with this background that the chemical experiments were begun at the University of Illinois.* Attempts to isolate cannabinol from the purified red oil of Minnesota wild hemp by the procedure described by Cahn failed. Consequently, attention was turned to attempts to isolate a phenolic product, the presence of which was established by qualitative tests. Of the numerous reagents employed, 3,5-dinitrobenzoyl chloride reacted to give a crystalline compound which was readily removed from the residual oil and purified. It proved to be a *bis*-ester, the hydrolysis of which by an appropriate method gave a new substance which was termed "cannabidiol" because of the presence of two phenolic groups.[7] It was isolated first as an oil but eventually was obtained as a crystalline solid. By developing a new procedure as a substitute for Cahn's method the isolation of cannabinol from this same oil was also accomplished, and for the first time cannabinol was induced to crystal-

* The experimental work of the series of researches at the University of Illinois was performed by the following students: B. R. Baker, C. K. Cain, J. H. Clark, Madison Hunt, Charles F. Jelinek, W. D. McPhee, D. C. Pease, C. M. Smith, R. B. Wearn and Hans Wolff.

lize.[8]* The properties of cannabinol and cannabidiol are compared in Chart I. Cahn's proposed formula for cannabinol is shown; his evidence for this structure was conclusive except for the positions of the hydroxyl and *n*-amyl groups.

The similarity in the empirical formulas of these two compounds is striking and led to the belief that these two sister substances must have structural formulas not too unrelated. The optical activity of cannabidiol suggested immediately the probability of partial hydrogenation of one aromatic nucleus in cannabinol and indeed the left one, since cannabidiol contains phenolic groups.

Although cannabidiol, like cannabinol, is physiologically inactive, the study of its structure and its reactions was most revealing. The results served to determine completely the structure of cannabinol and led to the formation of tetrahydrocannabinols, products of high marihuana potency which are probably active principles in the red oil of hemp.

The complicated and extensive chemical investigations on the structure of cannabidiol, on the synthesis of cannabinol, and on the preparation of tetrahydrocannabinol and synthetic analogs, will be presented in very brief form and only the more significant facts will be mentioned. The structure of cannabidiol[10] will be considered first with the pertinent reactions given in logical rather than chronological order.

Typical color tests indicated a phenol group, and formation of *bis*-esters and ethers the probable presence of two such groups. Catalytic reduction resulted in the absorption of two moles of hydrogen with formation of a molecule which still retained the two phenolic groups, thus leading to the deduction that two aliphatic double bonds were present. Pyrolysis of cannabidiol with pyridine hydrochloride caused cleavage into *p*-cymene and olivetol (1,3-dihydroxy-5-*n*-amylbenzene) both of which were identified by comparison with authentic samples. This is convincing evidence that cannabidiol is composed of dihydrocymyl and olivetol residues. The positions of the linkage between these residues were determined next. Cannabidiol was first reduced to tetrahydrocannabidiol and then oxidized; menthane carboxylic acid was isolated, identical with a specimen obtained by synthesis from l-menthol,

* Cannabidiol and cannabinol are the only pure compounds related by structure to the active constituents which have been isolated from hemp extracts. Claims have been made for the isolation of other compounds or their derivatives, but no detailed information is available and the results require confirmation.[9]

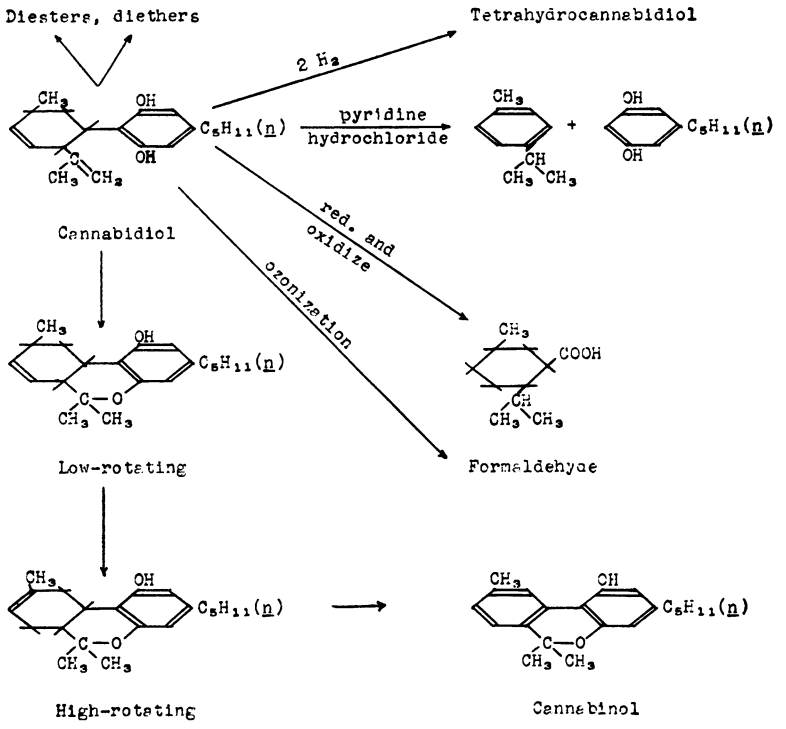


CHART II

thus demonstrating that the attachment of the dihydrocymyl residue was adjacent to the isopropyl grouping. From a comparison of the absorption spectra of various amyl resorcinols and of cannabidiol and its reduction product, the dihydrocymyl was postulated as being attached to the olivetol between the hydroxyl groups. Direct chemical proof of this was accomplished by conversion of cannabidiol with acidic reagents to tetrahydrocannabinol which, upon dehydrogenation, gave cannabinol. Cannabinol was shown to contain the linkage between the hydroxyls by synthesis of this molecule by an unequivocal method.

The structure of the cannabidiol molecule was thus established except for the orientation of the two aliphatic double bonds in the dihydrocymyl residue. One of these proved to be terminal, since ozonization of cannabidiol gave formaldehyde. This information, along with the fact that tetrahydrocannabinol was produced from cannabidiol through closure of a pyran ring, left no doubt that this terminal double

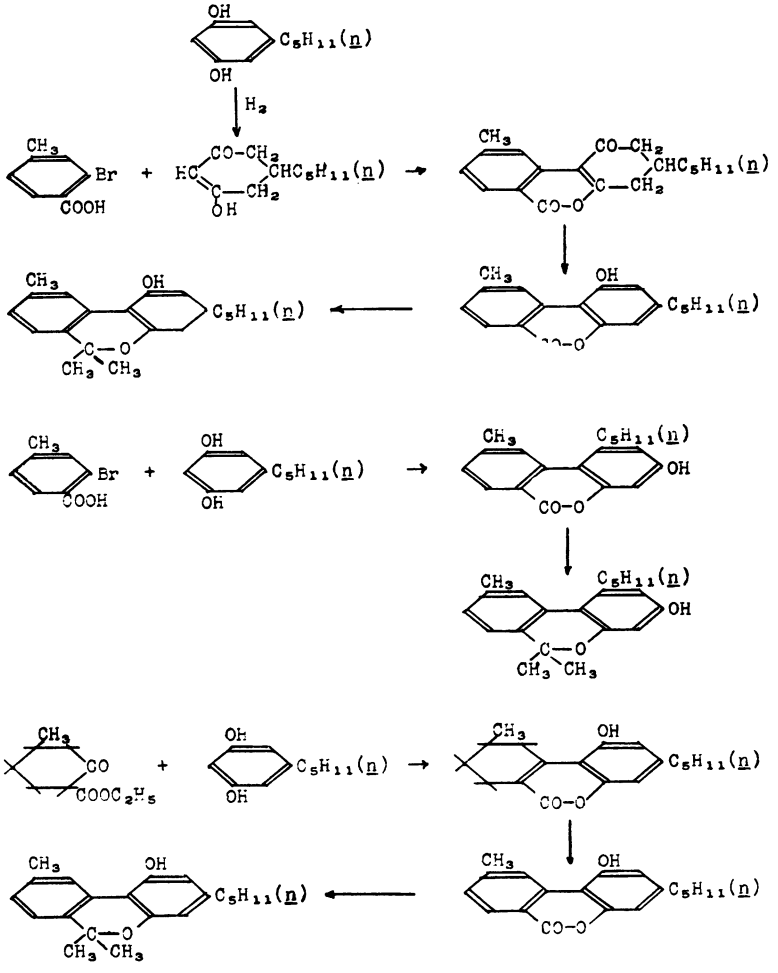


CHART III

bond must be present as an isopropenyl group. The location of the second double bond was determined only by indirect means. Since the arguments are rather involved, they will be omitted here and merely the positions assigned for the double bonds will be given. The tetrahydrocannabinol obtained in the isomerization of cannabidiol, varied in rotation dependent on the reagent used. Apparently two forms exist which were isolated as low-rotating and high-rotating isomers. In the low-rotating tetrahydrocannabinol, which presumably has the double bond in the same position as in cannabidiol, the double bond was deduced

to be in the γ,δ-position between the unsubstituted carbons; in the high-rotating isomer, the double bond is probably substituted in the γ,δ-position which includes the ring carbon holding the methyl group.

The establishment of olivetol as a cleavage product of cannabidiol revealed the probable orientation of the hydroxyl and *n*-amyl groups in cannabinol. This supposition was proven correct by the synthesis of cannabinol by two different methods[11] as shown in Chart III. The syntheses served also to prove that the position of the linkage of the two benzene rings is between the hydroxyl groups and thus confirmed a similar attachment of the rings in cannabidiol.

2-Bromo-4-methylbenzoic acid and dihydroolivetol condensed in the presence of alkali and a copper salt to 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone; dehydrogenation gave 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone which, with excess of methylmagnesium iodide, gave cannabinol, (1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran). An analogous condensation of 2-bromo-4-methylbenzoic acid with olivetol, followed by treatment with methylmagnesium iodide, gave the isomeric cannabinol with the linkage between an hydroxyl and the *n*-amyl group. The second method consisted in condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol in the presence of phosphorous oxychloride to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone. Dehydrogenation to the corresponding 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone followed by treatment with methylmagnesium iodide gave cannabinol.

The disappointment accompanying the discovery that cannabidiol had no marihuana activity was more than compensated by the observation that both the low-rotating and high-rotating tetrahydrocannabinols possess very marked marihuana potency.[12] These two substances, which were high-boiling oils, have not yet been induced to crystallize. All attempts to isolate solid crystalline derivatives have failed. The isomerization of cannabidiol required intensive study before procedures were found which resulted in products of constant rotation. Apparently, without very specific conditions, mixtures of low- and high-rotating forms are obtained which cannot be converted readily to a product of maximum rotation. Tetrahydrocannabinol of constant rotation $[\alpha]^{27}$ D$-265°$ can be produced conveniently from cannabidiol merely by heating the latter in benzene solution with a little toluene sulfonic acid until the reaction mixture exhibits no alkaline Beam test. This product was the

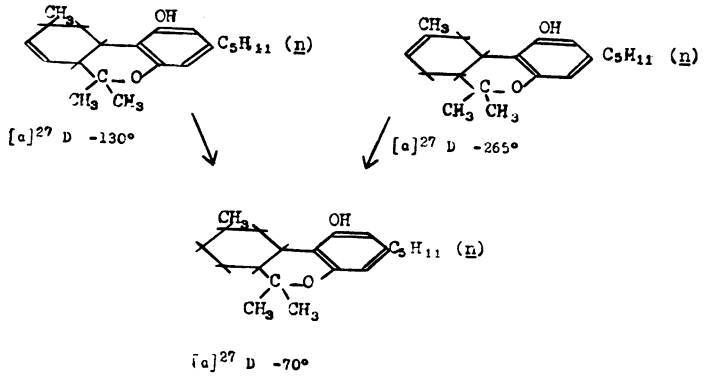


CHART IV

principal one selected for pharmacological and clinical investigation.

The acetates of these tetrahydrocannabinols also had marihuana potency though less than that of the unacetylated compounds. By catalytic reduction all of the tetrahydrocannabinols of varying optical activity gave a hexahydrocannabinol of essentially the same optical activity. This product was physiologically active though less so than any of the tetrahydrocannabinols from which it was derived.

The typical marihuana activity manifested by the isomeric tetrahydrocannabinols constitutes ponderable evidence that the activity of the plant itself, and of extracts prepared therefrom, is due in large part to one or the other of these compounds, or both, and possibly also to their stereoisomers, of which a number are possible. Confirmation of this supposition is available from an investigation by Wollner, Matchett, Levine and Loewe,[13] the results of which were published just recently. These authors have described the isolation from acetylated red oil of a tetrahydrocannabinol acetate of potency greater than that of either of the tetrahydrocannabinols prepared by isomerization of cannabidiol. Partition of the acetylated red oil was accomplished by selective adsorption. Silica gel removed cannabidiol diacetate and unknown material from a benzene solution of the mixture; alumina adsorbed substances of lower rotation by two passages, first in carbon tetrachloride, then in pentane solution. The product was judged to be stereochemically homogeneous by failure to effect further separation through selective adsorption or by careful fractional distillation in a specially designed high-vacuum fractionating column. Hydrolysis of the acetate yielded a tetrahydro-

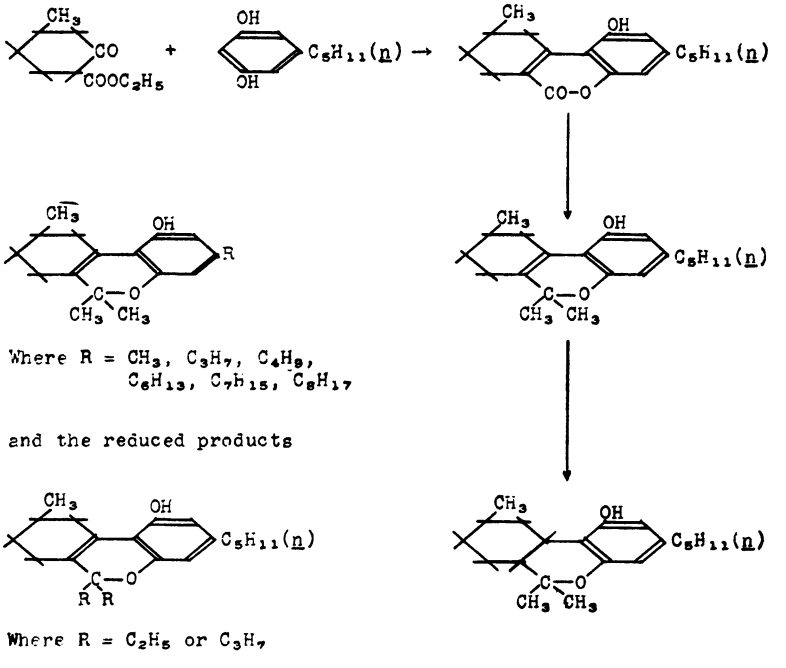


CHART V

cannabinol whose structure was identified through analysis and dehydrogenation to cannabinol. Its potency was similar to the products prepared by isomerization of cannabidiol. It would appear that rearrangement occurred during hydrolysis, since reacetylation failed to restore either the optical rotation or physiological potency to the original value.

With the discovery of the character of substances which possess marihuana activity, attention was directed next to attempts to synthesize compounds of similar activity. A very satisfactory procedure was devised for obtaining an isomer of the natural tetrahydrocannabinol with the double bond conjugated to the benzene ring. It consisted in the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone which, with excess methylmagnesium iodide, yielded 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.[14] The product proved to have marihuana activity though only about one-tenth that of its isomer, natural tetrahydrocannabinol. A series of several closely related synthetic compounds was then prepared by the same

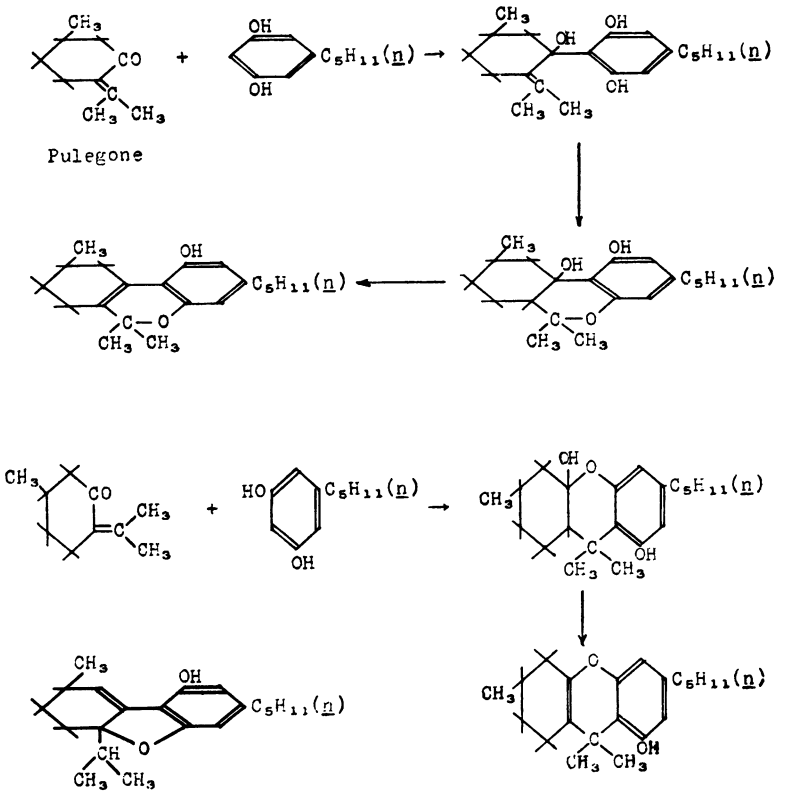


CHART VI

Homologs were prepared in which the *n*-amyl group was substituted by C_3H_7, C_4H_9, C_6H_{13}, C_7H_{15}, C_8H_{17}, C_9H_{19}; the reduction product of each was also synthesized.

procedure using the same keto ester but homologs of olivetol.[15] All of these products were reduced to the corresponding hexahydro compounds.[16] The synthetic tetrahydrocannabinol was also modified by replacing the 6-methyl groups by ethyl and propyl groups.[17] (Chart V.)

A provisional synthesis designed to obtain an optically active tetrahydrocannabinol was sought in the condensation of pulegone and olivetol.[17,18] In the presence of phosphorous oxychloride, a product which analyzes for, and has the properties of tetrahydrocannabinol is formed. A possible mechanism by which such a reaction might take place is shown in Chart VI. The purity of the final product is by no means established. There is a possibility of contaminants formed by condensation of the two reactants to give a partially hydrogenated xanthane

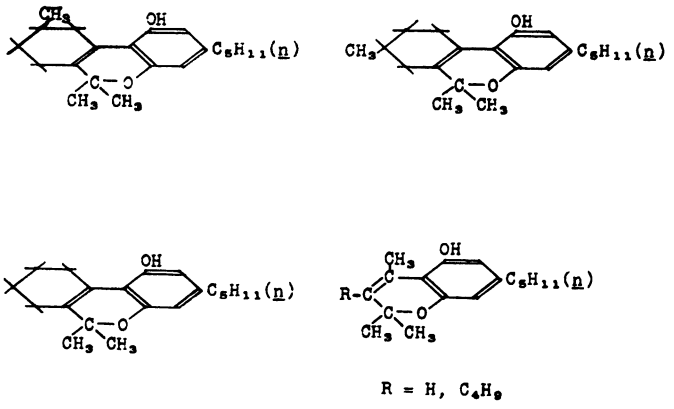


CHART VII

or a tetrahydrodibenzofuran, isomeric with tetrahydrocannabinol. Homologs in which the olivetol portion was substituted by other 1,3-dihydroxy-5-alkylbenzenes were synthesized.[16] The reduction product of each was prepared.

Finally in Chart VII are shown molecules in which the left-hand ring has been modified by removal or by change in the position of the methyl group.[17]

The pharmacological studies on hemp extracts have been equally as meager as the chemical investigations and in the long history of *Cannabis* preparations only three tests have been reported. Liataud[19] in 1844 observed that motor incoördination in the dog was a characteristic effect induced by marihuana preparations; Fraenkel[20] in 1903 interpreted this incoördination as a cataleptic condition. This was followed in 1928 by the observations of Gayer[21] that in various animals such as cats, rabbits, or dogs, intravenous injection of marihuana preparations in acetone solution induced corneal anesthesia which was characteristic of active fractions of the resin. In 1937, Munch and Mantz[22] reported no unequivocal effects when *Cannabis* preparations were administered to albino mice. On the other hand, Loewe[23] noted a definite increased depressant action when treated mice were given a hypnotic of the barbiturate series. Pernocton, butyl-bromoallyl barbituric acid, gave the greatest enhancement of any of the drugs tested.

The Gayer corneal anesthesia test was developed further by Marx and Eckhardt[24] but neither these investigators nor Gayer himself went further than to designate that the corneal reflex was normal or abnor-

mal. The corneal response was ascertained by tapping with von Frey hairs. Walton[25] took steps in a quantitative direction by counting the number of responses occasioned by tapping the cornea a given number of times and by plotting the results over the whole duration of the effect. By thus locating a definite maximum in the areflexia-versus-time curve of each experiment, quantitative comparisons were made possible by determining the ratios of doses producing equal maxima in different animals. Loewe[26] developed this procedure further by application of his method of "Bioassay by Approximation" to overcome as far as possible the large intra-individual and the large group variabilities which seem to be inherent in the reaction of all types of animals to marihuana preparations. His study of the Gayer test applied to the behavior of rabbits as test animals showed not only great inter-individual variations in sensitivity but also enormous intra-individual variations in the same animal. Using the same animal repeatedly, this investigator found a consistent decrease in sensitivity to one and the same dose. Therefore, even though the method of approximation was applied, the values of potency obtained by this method are not suitable for anything but qualitative purposes. Moreover, they do not parallel the dog-ataxia potencies of the same preparations, the divergence sometimes being tenfold. This indicates either that the Gayer test is not conclusive for quantitative measurements or else that an active principle other than that disclosed by the dog-ataxia test is present in red oil.

The "mouse sleep prolongation test" may be dismissed with merely a brief discussion. The *Cannabis* preparations, usually red oil, were administered by stomach tube. After a definite time, pernocton was injected intravenously at a level just above the threshold of hypnotic action. The synergistic effect of the *Cannabis* was measured by the period of suppression of the righting reflex averaged over all the animals of a single-dose group. This effect, though typical of red oil, could not be duplicated with the natural or synthetic tetrahydrocannabinols which had been shown definitely to have physiological activity in man. Pure cannabidiol, which is devoid of the marihuana effect upon man, showed the highest potency in this test and consequently the action from the red oil probably is due to its cannabidiol content.

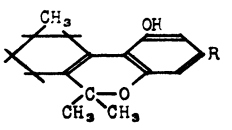
The determination of the cataleptic condition in dogs reported by Fraenkel, as accepted in former editions of the United States Pharmacopoeia for bioassay of *Cannabis* extracts, was developed further by

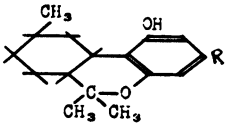
Walton[25] to attempt to make the effect the basis of a quantitative test. Six arbitrary stages of intensity of effects were recognized; first a slight depression; second, a barely detectable ataxia; third, an obvious ataxia; fourth, a marked ataxia in which the animal frequently pitches forward and barely catches itself; fifth, inability to stand alone; sixth, inability to rise and plunge about. The ataxia is chiefly a static one and is manifested particularly by swaying movements. Intravenous doses of red oil dissolved in acetone always acted within half an hour. A similar intensity of effect by oral administration required five to seven times the dose. Walton employed for evaluating potency the procedure used in most bioassay methods, the comparison of test and standard doses of equal intensity of effect. By comparing the results at various levels of dosage and by repeating the procedure a considerable number of times, he obtained more accurate results than had hitherto been reported. About eight trials with the unknown on the same dog, calibrated in about six trials with the standard, were used. A single assay required about three weeks or more for completion.

Loewe applied his principle of "Bioassay by Approximation" to the ataxia test and has thus been able to obtain a more decisive method for comparison of active products. The procedure aims at obtaining from each one of an adequate number of calibrated dogs, several figures of comparison of a test dose with the calibration doses. These figures represent ratios of doses, the response to which is not quantitatively the same. They are used to approximate the true potency value from both sides. At the same time the degree of overlapping marks the range of variation and gives an idea of the inherent inaccuracy. An entire assay may in this way be performed in a single day and highly consistent results may be obtained. The maximum order of accuracy is 10 per cent since this is the minimum of variation in the response of the same animal at different times. Since parallelism between the results of the dog-ataxia tests and the effects of the different preparations on humans has been established, it may be concluded that the ataxia method as developed by Loewe represents a reliable index of potency.

Using this procedure as just outlined, the comparison of results on the various natural and synthetic products will be presented in charts. Each value given represents the result obtained by the use of several dogs; three or four in the case of low potency materials, ten to twenty or more for substances of higher potency.

CHART VIII





R=*n*-alkyl	Potency Tetrahydro	Hexahydro
CH_3	0.16 ± 0.03	below 0.04
C_3H_7	.40 ± .08	0.26 ± .04
C_4H_9	.37 ± .12	.37 ± .06
C_5H_{11}	standard 1.00	.51 ± .08
C_6H_{13}	1.82 ± 0.40	1.86 ± .37
C_7H_{15}	1.05 ± .15	0.83 ± .13
C_8H_{17}	0.66 ± .13	.24 ± .06

Tetrahydrocannabinol $[\alpha]^{27}D$	Parke, Davis and Company	
−265° 7.3 ± 0.89	Fluid Extract	0.060
−260° 7.8 ± .78	American Fluid Extracts	
−240° 7.6 ± 1.1	thirty to forty different	
−165° 9.3 ± 2.9	samples varied in	
−160° 8.23 ± 2.17	potency	.003–0.130
−126° 6.5 ± 0.65	majority varied	.019– .052
Hexahydrocannabinol	Purified red oil	1.24
−70° 3.0 ± 0.43	Highly purified red oil	
	(Matchett)	4.33

In Chart VIII is shown a comparison of the potencies of the series of products analogous to synthetic tetrahydrocannabinol. The latter was adopted as a standard. The corresponding hexahydro derivatives were also tested. It is observed that the modification of the alkyl group results in a gradual increase in activity with increase in size until a maximum is reached at the *n*-hexyl derivative. The point of maximum potency is the same in the hexahydro compounds, though all, with the exception of the *n*-hexyl, exhibit a decreased effect. There is also presented the potencies of tetrahydrocannabinols of different optical rotations all derived from cannabidiol, the potency of an average purified red oil and of a highly active portion of red oil obtained from it by extraordinarily careful fractionation. The increased activity of the optically active natural tetrahydrocannabinols is striking. The commercial cannabis fluid extracts are of very low and variable potency.

In Chart IX, the potency of products of questionable purity produced from pulegone and various olivetol homologs, together with their hy-

CHART IX

Pulegone Condensation Products

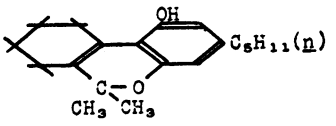
R = *n*-alkyl	Potency: Original products	Potency: Reduced products
C_3H_7	below 0.23	< 0.20
C_4H_9	0.25 ± .10	< .15
C_5H_{11}	.58 ± .12	.64 ± 0.10
C_6H_{13}	1.22 ± .12	.78 ± .22
C_7H_{15}	1.15 ± .15	.83 ± .17
C_8H_{17}	1.37 ± .25	below .25
C_9H_{19}	below .20	.....

drogenated derivatives are shown. The maximum potency appears in the *n*-octyl molecule, and the values for the *n*-heptyl and *n*-octyl derivatives exceed those of the corresponding products synthesized by an unequivocal procedure.

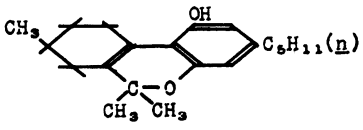
Finally in Chart X, the activities of other analogs are shown. Each has an activity less than that of the molecule possessing methyl groups in the 6,6,9-positions.

Recognizing that the indulgence in marihuana in New York City has constituted a growing problem of major consequence involving psychiatric, medical, legal, sociological and civic aspects, a clinical study was undertaken by a committee appointed by Mayor LaGuardia and supported by funds allotted by several foundations. The primary objectives were the determination of the mental and physical actions of marihuana on the kind of person resorting to its use and the consequent social implications. Dr. Samuel Allentuck directed the clinical studies in a unit of the Welfare Island Hospital and the facts I am presenting have been summarized from his report on the results.

An orientation group, the members of which were subjected to numerous and varied procedures, was used to determine precisely which tests would best lend themselves to the solution of the specific problems. From the results a program was established which consisted in a systematic study of a group of seventy-seven subjects ranging in age from 21 to 45 years and from borderline to superior in intelligence, all of them voluntary recruits from one prison population. About half had used marihuana previously. After a physical, neurological, and psychiatric examination, they were placed in one or more of five categories as to personality types—normal, antisocial, autistic, cyclothymic and epileptic. Each individual before and during the period of action of



0.126±0.05



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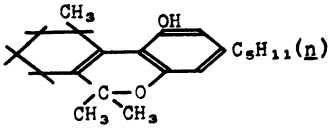

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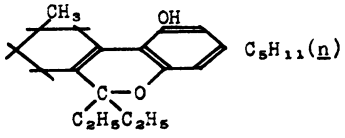
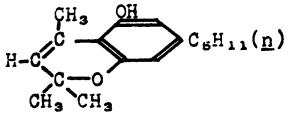


0.12±0.024

$(C_3H_7)(C_3H_7)$

0.04±0.01



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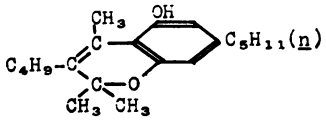

0.04±0.01

CHART X

marihuana was interviewed at regular intervals throughout the day by various members of the staff. Possible subjective and objective phenomena resulting from use of the drug were discussed and elaborated upon in detail. Introspective reports were obtained in the absence of the drug, under pseudo-stimulation with placebos and during intoxication with marihuana or allied synthetics; analysis of the data was based on the most frequently mentioned phenomena. The patients were also subjected to periodic tests for blood pressure or pulse changes, pupillary changes, urinalyses, blood chemistries, hematological surveys, basal metabolic rates, electrocardiograms, arterial and venous pressure tracings and vital capacities. In addition, psychological examinations before and during the intoxication periods were carried out, including a wide variety of psychophysical, psychomotor and clinical tests.

The marihuana was supplied in the form of a fluid concentrate which was desolvated and administered in the form of pills. Pure tetrahydrocannabinol was diluted with a little olive oil and placed in gelatin cap-

sules, holding 15 mg. of drug, the equivalent in physiological potency to one pill containing 300 mg. of crude solids from hemp. The 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran and its 3-*n*-hexyl homolog were administered in a similar manner using the equivalent doses which produced similar activity, namely, 120 mg. per capsule of the former and 60 mg. per capsule of the latter. It is significant that these relative amounts are practically identical with those observed by Loewe for obtaining identical effects in dog-ataxia tests.

The patients were started on two marihuana pills or on equated doses of tetrahydrocannabinol or the two synthetic analogs. The dose was increased by two pills at a time at intervals of two days unless toxic symptoms supervened. At the appearance of toxicity, the patient was returned to the physiological dose and this was increased one pill at a time. Thus the maximum tolerated dose for each individual was determined and at the same time approximately the threshold at which psychotic changes first appeared. Tetrahydrocannabinol and the synthetic compounds dissolved in olive oil were in some cases administered by intramuscular injection. Other clinical tests were made which involved intoxication from smoking marihuana cigarettes.

Barbiturates, cold showers and sweet candies were found to be efficacious in ameliorating any alarming physical or psychotic symptoms which developed following marihuana overdosage.

The detailed results of this carefully planned and executed clinical investigation, the first of its kind on record, must be left to the complete report when it is published. Merely the more significant findings which may prove of maximum value will be presented here. The crude drug in the form of concentrated marihuana extract, tetrahydrocannabinol derived from cannabidiol, and the two purely synthetic compounds, 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran and the corresponding 3-*n*-hexyl derivative elicited similar clinical and psychiatric phenomena upon the same subjects. The pharmacological action of these drugs somewhat resembles atropine and the psychiatric portrait, alcohol. The effects of marihuana do not vary qualitatively with the route of administration, whether ingested, injected or inhaled. By inhalation, however, they are more prompt in their appearance and disappearance; by ingestion they appear within one-half to one and one-half hours, reach their maximum in from three and one-half to five hours and disappear within seven hours.

The observed physical effects, one or more of which occur in each patient, are (a) elevation of the pulse rate, the increase being directly proportionate to the degree of intoxication; (b) elevation of the blood pressure; this varies with the individual and usually rises in direct proportion to the pulse; (c) injection of the conjunctival blood vessels which varies with the dose; (d) dilation of the pupils and sluggish reaction to light and in accommodation; vision for proximity, distance and color changes slightly; (e) circum oral tremors; tremulousness of the protruded tongue and the extremities; (f) dryness of the oral and pharyngeal mucous membranes; (g) increased frequency with decreased amplitude of thoracic respiratory movements; (h) ataxia; (i) hyperreflexia. The observed psychiatric effects are (a) apprehension and anxiety, (b) euphoria, (c) loquaciousness, (d) lowering of inhibitions, (e) hunger and thirst, (f) feeling of being "high," (g) uncontrollable bursts of laughter or giggles, (h) drowsiness, languor, lassitude and a pleasant feeling of fatigue.

Clinical tests revealed that marihuana produces no significant changes in basal metabolic rates, blood chemistry, hematological picture, liver function, kidney function or cardiac electrical conduction. Marihuana delays somewhat gastric and intestinal motility as gauged by the Carlson apparatus and x-ray studies; it produces definite increase in the frequency of the alpha wave in electroencephalographic recordings thus indicating increased relaxation.

Other observations of a more general character were recorded. Tolerance for marihuana may be produced by repeated administration of subtoxic doses over a prolonged period of time. Thus the same dose elicited progressively fewer and milder symptoms. Marihuana is unlike opium derivatives in that it does not give rise to a biological dependence accompanied by withdrawal symptoms. Neither does it establish a strong craving as exists in tobacco smoking or in alcoholic indulgence. Follow-up of the subjects has failed to establish existence of any craving for the product. Many of the unpleasant physical symptoms previously mentioned appear only as a result of the administration of excessive doses of drug. It is no more of an aphrodisiac than alcohol.

Since all the clinical experiments at Welfare Island were conducted on volunteer prisoners, it was desirable for completeness or perhaps to satisfy my curiosity to obtain some results on subjects in another social class. As a consequence, I have conducted a dozen or more experiments

using as test individuals chemists among whom were two members of the National Academy of Sciences and two high-ranking and very successful industrial chemists. In all cases very small doses, 15 mg. or 30 mg. of tetrahydrocannabinol, were administered about one hour before dinner. Each individual reacted differently with the possible exception of the observed stimulation of the appetite. They all recognized an intoxication which they described as in general like, but in detail different from that induced by alcohol. Thus, one industrial chemist who shows no outward change under the influence of alcohol, reported essentially no effect from 15 mg. except a mild stimulation of his desire for food. A 30 mg.-dose, however, to this same individual had a pronounced effect. Though he noticed no particular craving for food before dinner, as soon as he started eating he became particularly hungry and consumed a very large meal. He felt intoxicated and dissociated from his normal self, had a feeling of heaviness in his head and legs and reported a fogginess which he described as the inability to focus his eyes on more than a single object at a time. Since this man desired to get the effect of distorted time and space which is recorded as a frequent phenomenon associated with the marihuana user, he tried it a third time, taking 45 mg. The result was a ravenous hunger which was not satisfied after eating the equivalent of two hearty meals. A marked hypergeusia was also noted. The same fogginess appeared and heaviness in head and legs. During the conversation which took place among his five associates at the dinner table, he was able to comprehend a question but by the time the answer was given, which was immediately, he couldn't remember the question. In spite of the intoxication with the resulting phenomena, this subject had no difficulty in holding his own and then some in a poker game composed of expert players.

A second industrialist took 15 mg. at 5:00 o'clock in the afternoon and felt the first effects about 6:30 when he lost coördination in his fingers to the extent that he had to stop playing the violin, which he was doing at the time. Shortly thereafter he developed a tremendous appetite which was, if anything, sharpened by eating an enormous dinner and popcorn all through the evening. He had a mild lift about like a cocktail or two on an empty stomach and this and the hunger left about 11:00 o'clock.

A chemistry professor who took 30 mg. had a mildly increased appetite and reported feeling a bit fuzzy during his dinner, which resulted

in difficulty in comprehending what his associates were saying. This was followed by sleepiness and lassitude until the effects of the drug disappeared two hours afterwards. The stimulation was only slight, which paralleled the effect of alcohol upon this man.

A fourth subject of high standing in university circles wrote me in detail concerning his experience. I am quoting from his letter received two days after the experiment.

"This is to report to you on the outcome of my trip conducted under the powerful guidance of the marihuana drops. I would be interested some time to know just how much of what specific material you gave me, but there is no question but that it gave me a most terrific wallop. In brief:

"5:20 P.M. Took two capsules, went for short swim, had a highball and began to feel something beyond the mild glow from the drink about 6:15. By 6:30 felt bouncy in the knees, a little gay and foolish.

"6:00-8:30 P.M. Very much in the fog. Had alternate waves of hilarity and depression. Sat in smoking compartment looking at myself in the mirror, writing notes on the experiment, and feeling very silly and stupid. Would feel the onset of a surge of hilarity and then break into a raucous, rippling laugh. This gayety was not particularly pleasant, however, for throughout I felt wholly dissociated from myself, knew that I was at the mercy of the drug, and greatly resented this lack of control. The feeling was very different from that of being at one or another stage of intoxication, for I looked perfectly clear and normal and I could stand erect without swaying and execute motions with considerable precision. I could not, to my annoyance and as I was well aware, speak or write or think coherently. This bothered me particularly in the waves of depression, when my lips would feel very parched and salty and I would long to break the spell and regain my own consciousness. A very pressing and persistent sensation was that of extreme hunger, but I had sense enough to wait until the laughing spells were under control before going into the diner.

"Here are a few excerpts from the log: '7:20. Not so good; for a few minutes I sat and looked at myself in a silly way. . . . This is *me* again. I very suddenly snapped out of it and am struggling back to normal. Lips are very dry. Maybe I'm not *quite* out of it. . . . The above is true. I am writing here in a serious vein—but quick, I must write that a minute or two ago I was sitting here in the men's lounge giggling at

myself in the mirror and saying: This stuff does make you feel pretty gay (gay in the neese). Isn't that the damndest thing? [I knew the spelling was wrong but couldn't right it.] . . . 7:42. Yes, snapping out again. I just had a most jubilant laugh and feel another coming along. 7:45, not feeling laughy, feel like hell. This is really awful stuff. . . . 8:03. I feel like a fool. Lips bad. Want water, but I am terribly hungry and wish the experiment were over. I am thinking very much of eating, for I am very hungry. . . . 8:09. Nearly came out of it. It is awful. Helpless, awful feeling. Over, over, when will it be over? When can I eat? . . . 8:13. A fellow just came in to shave. Why now? Why not at this time of the evening EAT. . . . ha, ha. Now I have been silly. Looked silly. . . . ha, ha. Of all places to have this—the train. Bad, bad. Oh I feel like hell, salty lips . . .'

"At 8:30 I devoured an enormous steak dinner with great rapidity and thoroughness, and left no trace of any of the fixings, even though I ordinarily do not eat ripe olives or salad, and although ordinary delicacy would keep me somewhat below the ten crackers I had with my cheese. The food tasted no better or worse than usual, and I had a dissociated feeling that my mouth was a purely mechanical guide for all that came its way, and wondered if mine was not very much the same as the 'appetite' of a cat.

"At 9:00 I felt myself coming out of the spell, and again at 9:15 I felt sane for a minute or two. A little later the sane periods began to predominate, and by 10 P.M. I was back again in control and could sit down and write out the details of a new natural product synthesis.

"Thus ended the trip. I didn't sleep too well or too poorly, and the next morning I felt O.K. and had no hang-over.

"It was an interesting experiment, but I can't write too enthusiastic an endorsement for this drug you fellows are synthesizing. The feeling of well-being would not, in my estimation, equal that from about three highballs, and the penalty seemed to me to be pretty severe. The outstanding impressions were the feeling of detachment from myself and the extreme hunger. Are these both associated with the same part of the molecule? If not, you might hydrogenate out some of the bad effects and thereby obtain a wonderful aperitif."

After the Welfare Island study of every phase of the action of marihuana and the synthetic drugs and after finding no discernible evidence of any permanent deleterious effects, either mental or physical, Dr. Al-

lentuck considered the question of the possible therapeutic value of these substances. The potential availability of pure synthetics of standard potency invites such a study, for hitherto merely hemp extracts were accessible, the clinical activity of which must be determined for each batch of extracted material. Since the outstanding manifestation of the marihuana action is the euphoria which makes its user feel "high," consideration was given to its possible employment as a drug for individuals in various stages of mental depression as cyclothymics, involutionals, reactives, or those with organic conditions in which dysphoria is a dominant factor. The invariable characteristic of the drugs to stimulate the appetite, suggests they might be applicable in psychoneurosis in which a lack of desire for food exists. Many subjects show an alcohol-like picture of intoxication following the use of marihuana. The idea of using these drugs in the treatment of chronic alcoholic addiction was considered and preliminary experiments by Dr. Allentuck on private patients and colleagues were sufficiently encouraging to merit investigation on a larger scale and over a longer period of time.

The euphoria produced by marihuana is in many ways comparable to that achieved by the use of opium derivatives. This suggested the possibility of use in the treatment of opiate derivative addictions to eliminate or ameliorate the withdrawal symptoms commonly experienced during previously attempted so-called "cures." To clarify this question Dr. Allentuck selected a series of cases among drug addicts undergoing treatment. One group of thirteen received 15 mg. of tetrahydrocannabinol orally three times daily at 5:00 A.M., 2:00 P.M. and 10:00 P.M. and a sterile hypodermic injection; another group of fourteen received the same treatment without the sterile injection. Subjective and objective findings were recorded. In general the consensus of subjective opinions favored the new treatment as compared to previous cures and the established routine taken by some of these patients. They felt happier, had a better appetite and wanted to return to activity sooner. These results served as a basis for further study of fifty cases in which quantitative criteria were employed.

Two groups of twenty subjects were selected, one group receiving the tetrahydrocannabinol treatment up to a maximum of ten days and the others receiving none. Members of each group were observed throughout the day. Each morning they were interviewed and any complaints recorded on a chart. Thus an attempt was made to arrive

at a quantitative comparison of the withdrawal symptoms. It was found that the tetrahydrocannabinol treatment was useful in alleviation or elimination of withdrawal symptoms and in diminishing or eliminating the accompanying discomfort which follows cessation of narcotic indulgence. Any withdrawal symptoms under the tetrahydrocannabinol treatment were of a mild character and occurred within the first three or four days following which the patients began to feel much better. The chief complaints were restlessness, headache and dryness of the throat. They had an increased appetite and desire for food which diminished or eliminated such withdrawal symptoms as nausea, diarrhea and perspiration. They felt physically stronger and showed psychomotor activity. The feeling of euphoria produced by the tetrahydrocannabinol helped in rehabilitating the physical condition and in facilitating social reorientation. An outstanding result is a subjective feeling of relaxation. The sleep induced by the drug likewise contributes to the general improvement in the patients' health. These results are in contrast to those from the use of Magendie's solution which produces in the patients contentment for the first three or four days, after which signs of marked discomfort or withdrawal effects appear. The patients after this treatment, upon their discharge were shaky and generally in poor physical condition. These preliminary results with tetrahydrocannabinol justify a more exhaustive study of its possibilities as a means of relieving the withdrawal symptoms in narcotic addicts.

With this brief picture of the results of the coöperative program before you, I may conclude by adding a few remarks about what may be expected from a continuation of the investigations under way. In the chemical field, repeated attempts to synthesize a tetrahydrocannabinol with a double bond in the γ, δ-position have failed. Just recently, however, a new approach has appeared and the results have progressed to the point where I am convinced it is merely a matter of time before the goal is reached. The physiological reaction of this product will allow a conclusion in regard to the relative importance of the position of the double bond in the alicyclic ring and of the optical activity in the tetrahydrocannabinol molecule. Other synthetic molecules of a similar character, which are soluble in aqueous acids or bases and, therefore, perhaps suitable for intravenous injection, are being prepared. It is hoped also to clarify the significant groups and their orientation which induce marihuana activity. Thorough investigation of the constituents

in red oil is necessary to complete the understanding of hemp extracts.

In pharmacology, there is still much to be done in coöperation with the chemist to elucidate in more detail relationship between activity and molecular structure. With pure chemical substances of marihuana activity, it will now be possible to determine experimentally what actions are exerted upon body functions other than those which have hitherto attracted attention. The relationship between the mechanism of ataxia action in the dog and the psychic action in man should be clarified. It has not yet been established that the structural differences between the various marihuana-active substances do not result in a relative prevalence toward ataxia effectiveness by some, psychic effectiveness by others.

In the clinical field, the practical application of these substances must be awaited with the usual necessary patience. The initial experiments of Dr. Allentuck make it appear likely that some use of this interesting drug or its synthetic equivalents will be discovered.

In all phases of this work just completed, the groundwork has been laid so that a wider interest should ensue, and significant contributions may be anticipated in the chemistry, pharmacology and clinical aspects of this class of substances.

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