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MARIHUANA

By Professor ROGER ADAMS

UNIVERSITY OF ILLINOIS

THE term "marihuana" is commonly used to represent any part of the hemp plant or extract therefrom which induces somatic and psychic changes in man.

The hemp plant has been known since remote antiquity, having originated in central Asia and spread into practically all countries of the world. For centuries, the fiber of the plant has been used for clothing and rope; the seed have been pressed for oil. The oldest known reference to the hemp plant is in a Chinese treatise, "Rh-ya," written in the fifteenth century B.C. That hemp contains an intoxicating principle has also been known for centuries and records of this fact date back to 1000 to 1500 B.C. The medicinal action is mentioned in Sanscrit, Hindu and Chinese medical treatises published about the beginning of the Christian era. Hundreds of other references during the past nineteen hundred years discuss the physiological action of this plant.

Hemp is an herbaceous annual growing three to eighteen feet in height, depending on soil and climate. Botanically it belongs to the genus *Cannabis,* of which there is only a single species, *Cannabis sativa,* occurring in a few varieties; *Cannabis indica* is one of these. When the female plant is about to flower, the tops, which have large quantities of hairs, become covered with a multitude of pluricellular glandulose hairs. These appear as minute glistening points and are so numerous that the tops appear to be shining with dew. The tops are very sticky and when pressed emit a strong mint-like smell. The resin often spreads to the surface of the leaves or branches. It is largest in amount when flowers begin to appear and continues

to form until the seeds are mature—it ceases when the seeds are ripe. Botanists have suggested that the resin is formed as a varnish to protect the seed while the sap is providing the fertilized ovules with the elements necessary for maturation. The amount of resin depends almost entirely on the climate, the largest, as might be expected, in hot dry climates such as Chinese Turkestan and smallest in temperate climates where there is plenty of moisture. The morphological characteristics of *Cannabis* are modified very easily—one variety to another—merely by change in climatic conditions. The resin appears to contain most of the intoxicating principle of the plant. The male plant during flowering also exudes a certain amount of resin but much less than that produced by the female plant.

In the far East the resin (called charas) was in the early days collected from the uncut plant in several ways. Men wearing leather coats walked through the hemp and the resin stuck to the leather from which it was scraped. Sometimes sticks with leather strips attached to the end were drawn over the flowering tops. The tops were sometimes rolled in the hands and the resin scraped from the hands onto a receptacle. From cut plants, the tops were pressed between cloths or rubbed between fine mattings. By any of these procedures, a dark resinous mass was obtained, which was purified somewhat by kneading with a little water to remove dirt and extraneous material and then stored in a dry atmosphere, since it deteriorates when damp.

The modern method, such as is used at the present time in Chinese Turkestan, consists in cutting and drying the female flower heads, crushing in the hands to a powder and sieving so that it attains the fineness and consistency of sand or sawdust. This powder is stored in rawhide bags for four or five months during the winter. With the onset of hot weather the material is taken out and exposed to the sun for a short time, sufficient to allow the resin to melt. It is stored again in hide bags of ten-pound to fourteen-pound capacity. After a few days the agglutinated mass is again taken out and kneaded well by means of wooden rods so that a certain amount of oily matter appears on its surface. The process of kneading is continued until each bag yields about one or two pounds of oil. At this stage the charas is transferred to fresh bags and is ready for sale. The product consists of a greenish-black mass with a peculiar and characteristic odor.

Another commonly used East Indian hemp product called bhang consists of the specially dried leaves and flowering shoots, chiefly of the female plant. The process is merely to cut and dry the plants and to separate therefrom the leaves by striking against a block of wood.

Another product is ganja. In Eastern Bengal at the present time hemp is cultivated for the production of this material. As the female plants begin to form the resin, all the large leaves on the stems and branches are removed. The smaller leaves and the brackets of inflorescence become agglutinated into a resinous mass. The plants are then cut about six inches from the ground and exposed to the rays of the sun for a few hours. The redundant portions of the stem which do not bear flowering heads are then cut off and those bearing flowering heads are arranged in a circle with the heads directed toward the center and overlapping each other. Treading and kneading is commenced. While holding the plant tight with the left foot, the laborers press down and trample with the right foot. The process is continued until the narcotic resin is pressed firmly among the flowers in the desired form. Fresh bundles are placed over those which have been already pressed and the treading is repeated. This goes on until the ring is about a foot in height after which the flowering twigs are removed. The resulting flat resinous mass is known as flat ganja.

Ganja and charas, admixed with tobacco, are generally smoked, while bhang is usually taken by mouth in the form of a beverage or confection. In northern Africa, the hemp tops and leaves are often mascerated with water to a fluid paste and swallowed whole. Frequently they are extracted with alcohol and the residues from the solvent admixed with jams. The powdered tops and leaves sometimes are mixed with crushed nuts as a stuffing for dates, Turkish paste or in cakes; or mixed with nuts, spices, oil and chocolate to a thick paste, which is chewed.

In the United States and in several other countries, the tops of the flowering plants are cut and dried, the coarse material removed and the product chopped to the proper particle size for incorporation in cigarettes. This is the form of hemp most commonly observed in illicit distribution in this country.

The names for hemp preparations are very numerous. In addition to those already cited, should be mentioned in particular the term, hashish, which is in common usage.

There is no satisfactory bioassay method for determining the potency of marihuana. The best procedure in animal testing is administration to certain types of dogs, after which the character and degree of the incoordination, particularly of the hind legs, are observed. This very subjective method gives information as to the intoxicating power of the test sample but furnishes no indication as to the active principle content. Decerebrated cats are not affected; it thus may be concluded that marihuana affects the cerebral hemispheres and therefore poisons the intellect.

The most careful study of the effect of marihuana upon humans has been made upon educated Europeans. An extensive survey of marihuana addicts

among native North Africans and East Indians also has been reported. The general effect of marihuana is to weaken the individual's will, the faculty which controls, sorts out groups and correlates according to logical laws. Thus, in the case of the intoxicated subject, memory and imagination predominate, he becomes entirely absorbed in the past and the future and loses sight of the realities of the moment. *Cannabis* affects the mind most powerfully.

There are several successive phases to intoxication by hemp. The subject first feels himself strong, agile, elegant, capable of extraordinary feats of prowess. He experiences an intense desire to move about. Walking, jumping, dancing seem desirable, though he usually abstains from such action. Gradually his mind becomes filled with ideas foreign to the subject on which he is endeavoring to fix his attention. Suddenly he is overcome by absurd and irresistible laughter caused by any trifling incident, which very often is not amusing even to the slightest degree. Simultaneously, the addict needs conversation and talks excitedly. The conversation becomes more and more incoherent as the will loses its power to direct thought. Ideas well up incessantly in addicts, especially those with some education; they whirl through the brain, becoming ever more lively and striking, and are associated together in the most unexpected ways.

Gradually, as the action of the drug progresses, exact notion of persons and neighboring objects is lost, the emotions are extremely exaggerated and paradoxical. Mental confusion increases and moments of lucidity become shorter and shorter. Finally, the subject reaches the stage of a sensation of moral and physical lassitude; he wants complete silence; the least effort becomes an almost impossible exertion; the mind allows itself to be lulled into a state of apathy, indifference and complete calm. The Mohammedans called this "kif."

This state is marked by a complete change in notion of time. It appears infinitely slow, owing to the number and variety of impressions which rapidly enter the mind. These ideas, particularly those half-formed, seem innumerable, and since time is measured only by the memory of them it seems infinitely long.

The notion of space also is wholly impaired. The distance between the subject and a person standing quite near him appears tremendous. The hand seems to be separated by an enormous space from the glass it attempts to seize. Objects are seen through a mist so that outlines are indistinct and shapes are blurred. Sight and hearing are extremely acute, but the perceptions are distorted and the distortions are constantly varying. This is the stage of great suggestibility. Any impressions made on the senses immediately give rise to imaginary perceptions, illusions and hallucinations.

Succeeding this is a deep and heavy sleep. The subject upon awakening, in general, remembers what he experienced during his intoxication. Apparently a subconscious condition prevails, but the persistence of memory indicates that consciousness still subsists.

The order and the intensity of the various phenomena differ in each individual and depend frequently on the influence of outward circumstances at the moment. In most cases, an exaltation of the most common thoughts of the individual may be noted. Thus, it acts like most cerebral stimulants, including alcohol. The most intimate and secret thoughts of the marihuana subject are revealed by unconscious movements, acts, illusions and hallucinations, as well as by words.

Marihuana intoxication is accompanied frequently by disagreeable symptoms. Especially with an overdosage, and dependent on the environment, the subject before he reaches the euphoria stage may suffer excruciating pains in the head and neck and a feeling of torture. He may even imagine he is going to die and, in general, may go through a period of great anxiety. If he has an aversion to any one, his antipathy is transformed into a fierce hatred; he is convinced that he now has everything to fear from his enemies and that they are hatching some odious plot against him. There is only one step from the belief that danger is imminent. The addict often reaches this stage and becomes a prey to sudden fits of terror and irresistible criminal impulses. This accounts for certain violent reactions, sometimes murder of friends and relatives, committed under influence of the drug.

All these observations have been based, for the most part, on tests with educated Europeans who had ingested preparations through the mouth. An intensive study of North African native addicts has indicated some differences in effect from those just mentioned; thus, during the period of euphoria, a rapid sequence of amusing and witty ideas is replaced in the native by a flow of absurdities, coarse jokes and obscenities; the phase of motor excitation is little marked, possibly because of the fact that the native who desires complete intoxication always smokes reclining on cushions or mats.

The phenomena observed during hashish intoxication vary widely according to whether *Cannabis* is smoked or *Cannabis* preparations are ingested. If the resin content is approximately the same, the effects are more rapid (after fifteen minutes) when hemp is smoked than when it is swallowed (one to two hours or even longer).

The North African natives generally are smokers and usually smoke to excess. Under these conditions the reactions are prolonged and after the final sleep the subject awakens in a stupor. The use of marihuana finally leads to loss of fitness for work and

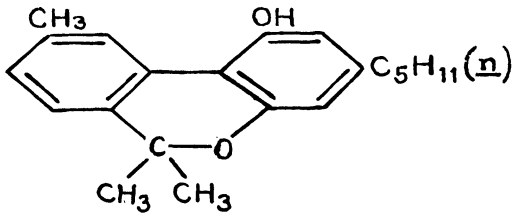
resistance to fatigue. Later, the subject is prone to headaches, loss of appetite and general degradation of the body. There is the factor of individual resistance, but the rapidity of degeneration depends on the quantity of the drug consumed.

The physiological action of marihuana may be described in most general terms as the release of inhibitions in the subject. As a consequence, an individual with natural criminal tendencies, which he controls under ordinary conditions, will commit crimes when under the influence of the drug. It is pretty securely established that this drug itself is not an aphrodisiac. It is impossible to predict the reactions in any particular subject. An exact knowledge of the intoxication of marihuana and its deleterious effects will have to await carefully controlled clinical experiments.

Ordinarily marihuana is not considered an addiction drug in the same sense as morphine, since the sudden cessation of the use of hemp does not give rise usually to the disquieting phenomena that accompany privation in the case of other narcotics. Its consumption in the United States, which had for several years increased, has recently been effectively checked.

The chemistry of marihuana is complicated and very confusing. Between 1840 and 1895 most of the chemical work consisted in rather unsuccessful attempts to find tests which would provide a means of identifying the presence of marihuana or an extract. In 1896, Wood, Spivey and Easterfield extracted hemp with petroleum ether and distilled from the extract a high-boiling fraction which apparently contained most of the active principle. This they called "red oil" because of its appearance. They were able to isolate from this oil by means of acetic anhydride a pure crystalline acetate from which by hydrolysis a straw-colored oil resulted, called by them cannabinol. For several decades, cannabinol was supposed to be the active principle of marihuana until finally it was proved otherwise. These early investigators contributed some facts toward the constitution of cannabinol but left the problem far from complete.

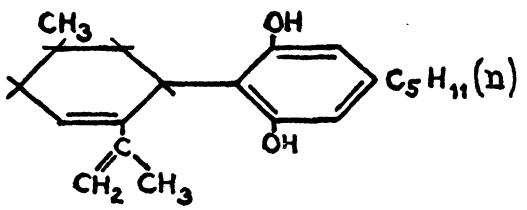
In spite of many attempts, no other investigators were successful in repeating the isolation of cannabinol until 1932, when Cahn again obtained this compound. He performed a series of brilliant researches from which he deduced a structure dubious in respect merely to the position of the hydroxyl and *n*-amyl groups. Just recently in the University of Illinois laboratories researches led to the postulation that the hydroxyl and *n*-amyl groups must occupy positions different from those suggested by Cahn. This new formula was demonstrated to be correct by an unequivocal method of synthesis. Cannabinol is 1-methyl-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran and has structure I.



I

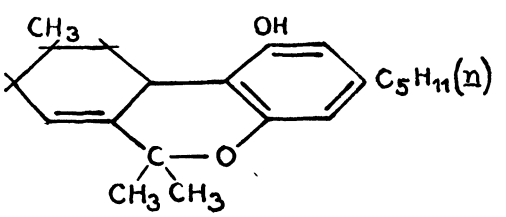
Most of the chemical work in the past has been done on charas. The experiments in the University of Illinois laboratories were performed with an extract from Minnesota wild hemp. From the red oil from this source, cannabinol has been isolated by a new procedure and also another pure compound, cannabidiol. Both substances were obtained in crystalline form. Cannabidiol composed about 45 per cent. of the red oil in hand and cannabinol about 15 per cent.

The study of the structure of cannabidiol is not yet complete, but the formula shown in II is doubtful only in respect to the position of the double bond in the left-hand ring. Cannabidiol, like cannabinol, is physiologically inactive.



II

Observation of structures I and II makes it appear likely that cannabidiol is a precursor of cannabinol. Thus, in the plant cannabidiol might isomerize readily to a tetrahydrocannabinol (III) which upon oxidation would be converted to cannabinol (I).



III

Such a series of reactions has now been consummated in the laboratory and thus confirms the probability that the plant reactions are similar.

Of peculiar interest and importance is the fact that the tetrahydrocannabinol formed by isomerization of the cannabidiol with various acidic reagents may be obtained in two forms depending on the reagent and physical conditions used in the reaction. One has a specific rotation fairly constant at about $-160°$ and the other at about $-240°$. The evidence is that the

structures of these differ merely in the position of the double bond or possibly stereochemically. The lower-rotating form has a very high marihuana activity, many-fold that of purified red oil. The higher-rotating form is less active than the lower-rotating. Both the tetrahydrocannabinols are hydrogenated to a single hexahydrocannabinol of specific rotation $-70°$, which is also physiologically active. It seems probable that the marihuana activity of red oil is due to one or more of these substances.

Several methods have been devised and successfully used for synthesis of tetrahydrocannabinols from simple starting materials. Homologs and analogs are also available through the new procedures. The possible marihuana activity of these compounds is now being tested.

Recently Todd has isolated from red oil in the form of a derivative a substance he calls cannibol. No information regarding its chemical characteristics is yet available.

Haagen-Smit and his coworkers reported a few weeks ago the isolation from red oil of a crystalline compound which has marked physiological activity. No information on the chemistry of the compound has yet been published.

Red oil is obviously a welter of closely related chemical substances very difficult to separate from each other. It is probable in view of the researches under way in the University of Illinois laboratories that one or perhaps more than one active principle exists and that they are tetrahydrocannabinols or closely related compounds. The probability is that the substances isolated by Todd and by Haagen-Smit will be found to be similar to these in character.

Hemp is readily identified when vegetative material is available for study. Tests are also available for identifying extracts of hemp. Reliable, scientific unequivocal methods for identifying one or more active constituents in red oil, however, must await the more extended study of the pure active compounds. Only then also will it be possible to perform quantitative clinical tests in order to obtain more accurate information on the physiological and psychological action of marihuana.

THE ROYAL SOCIETY OF CANADA

By Professor D. A. KEYS
McGILL UNIVERSITY

THIS year the fellows of the Royal Society of Canada were the guests of the University of Western Ontario in London, for their annual meeting from May 20 to 22. The attendance was not as large as last year, but representatives from all parts of Canada attended and presented papers. The university buildings, situated in beautiful spacious grounds outside the city, presented a peaceful contrast to the present conditions in Europe, that visibly affected all who attended the meeting.

The presidential address, "A Study of the Organization and Work of the Royal Society of Canada," was delivered by Dr. H. M. Tory, following a complimentary dinner tendered the fellows, their wives and guests, by the City of London on Monday night, May 20. The president stated that the Royal Society of Canada differed in one respect from the similar society in England, in that it included under its organization all the intellectual movements which were deemed worthy of recognition. Thus with the Natural Science Sections III, IV and V, were associated the Literary Sections, including philosophy, literature, history and economics. After outlining the various contributions of the older sciences and literary fields of knowledge to our present western society, the lecturer concluded with the suggestion that we should at our annual meeting each year have a major symposium dealing in some form with the relations existing between the various sections. Two typical topics suggested were "The Effect of Science upon Literature in the Last Hundred Years" and "The Present State of Controversy between Science and Philosophy."

On the following evening, Dr. R. W. Boyle received the Flavelle Medal of the Royal Society for distinction in scientific subjects, in recognition of his researches, particularly on the development of "Asdics" and his work on ultrasonics. The presentation of the medal was followed by a scholarly lecture delivered by Dr. F. Cyril James, principal of McGill University, on "Science and Society," in which he traced the changes in western society brought about in the four centuries between 1475 and 1875 due to the impact of scientific discovery. He pointed out that the primary function of the social sciences is the charting for society of a course that is most appropriate in the light of the existing fund of human knowledge. Apparently the impact of science on society has not been wholly beneficial; the ethos of western society has not responded to the changes in its material environment, but if we are willing to face the major problem of deciding upon our ideals, the forces that science has placed at our disposal are sufficient to make the attainment of those ideals a practical possibility.

Section III (Chemical, Mathematical and Physical