"ON THE DANGERS OF CANNABIS"

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". . . this weed, messenger of a false happiness, panderer to a treacherous love . . . which makes him sick—morally more than physically—and changes thousands of persons into nothing more than human scum. It is this weed . . . of the brutal crime and the burning hell . . . which sets free the spiritual and the bestial, and makes the rabble bespatted pages with blood."

Wolff (1949).

Introduction

A tall, robust, dioecious annual which grows from 3 to 15 feet high, *Cannabis sativa* is perhaps one of the oldest of man's cultivated useful plants. It has served a three-fold economic purpose; man has obtained fibre from its stems, oil from its seed and drug from its resin. Knowledge of the use of cannabis by man goes back at least 6000 years. Archaeological specimens have been found in an Egyptian site of 3000 to 4000 years of age. Coarse hempen cloth estimated to be 6000 years old has been found in Europe.

A very early and detailed description of medicinal and economic use of cannabis appeared in The Herbal, a pharmacopoeia prepared by the Chinese Emperor Shen Nung in about 2737 B.C. Shen Nung encouraged the cultivation of the plant for fibre and suggested that it be used medicinally for "female weakness, gout, malaria, constipation and absent mindedness" (Schofield, 1971). This latter is particularly interesting as one of the striking effects of acute intoxication with cannabis is an impairment of immediate memory.

The use of cannabis as an intoxicant apparently originated in China, spread to India and thence to North Africa. It seems that its introduction as an intoxicant to Europe was as late as the seventeenth or eighteenth century. Some have suggested it to be as late as the return to Europe of Napoleon's troops, who learned of the drug's effect in North Africa.

Preparations of cannabis for therapeutic purposes were available commercially in the United States until 1937. Parke Davis, Eli Lilly and Squibb promoted preparations of cannabis extract for asthma, tension and pain. Walton (1937) reviewed the therapeutic application of marihuana; Douthwaite in 1947 considered that Extractum cannabis BPC is the preparation of choice for the treatment of duodenal ulcer.

In 1957 the WHO estimated that throughout the world, there were approximately 200 million marihuana users. Within the last decade there has been "an explosive increase in the use of marihuana in the United States" (Jaffe, 1970), and similar terms might be used to describe the usage in Australia.

It is against this background of "clinical" knowledge of considerable human usage of the drug that we must view the status of our "scientific" knowledge of the pharmacology and toxicology of the active substances.

The active constituents

The psychoactive principles of cannabis are found in a gummy resin secreted by the leaves and flowering tops of the plant. The potency of the various preparations of cannabis depends not only upon the concentration of the resin in the various preparations but also on the composition of the resin.

The various preparations of cannabis are known under very many names, usually depending upon the origin of the material. However, in general terms they may be considered under two groups according to the content of resin.

A) Marihuana*, Bhang, grass, weed, pot, tea, maryjane, boo: a preparation mainly of leaves and perhaps stem and containing only about 5 to 10% resin. Potency varies according to the composition of the resin.

B) Hashish*, ganja: a concentrated preparation of the resin containing perhaps 40% resin. In India, charas is a preparation which is said to be pure resin.

There is an abundant literature on the chemistry of cannabis resin, much of the research having been carried out for forensic purposes. The resin contains a group of compounds, the cannabinols, of which about 30 have been described, though only a few of them have been shown to possess significant biological activity. The most active are the tetrahydrocannabinols (THC) of which two isomers occur naturally. In terms of concentration, the major constituents of cannabis resin are cannabidiol, the tetrahydrocannabinols and cannabinol. However, the relative concentration of the different cannabinols, and particularly the concentration of THC varies considerably in different plants and preparations obtained from them. Furthermore, it is highly likely that the proportions of the cannabinols in one preparation may change in time upon storage. In this regard it is interesting to note the findings of Korte (1970) that THC is not to be found in the growing plant, but rather it appears, perhaps as a degradation product, after the plant has dried. It is also likely that on further storage and ageing, the unstable THC is slowly degraded to less active constituents.

Plants growing in a hot, dry climate are considered to produce a resin with a greater potency of psychoactive constituents. Contrary to earlier reports, both male and female plants exude psychoactive resins of approximately equal potency.

* To avoid confusion the term cannabis will be used as a generic term to indicate all preparations of the plant. When it is necessary to distinguish between preparations A & B above, the terms marihuana and hashish will be used.

In view of the tremendous variability in the composition of the resin, it is very difficult to evaluate earlier studies of the pharmacology and toxicology of cannabis when in these studies no information is available to indicate the concentration of the active principles employed. Indeed we still find ourselves in a similar position of ignorance. Whilst one can now relate dosage of extracts in proportion of their known ingredients, there is still the possibility that other, yet unidentified constituents are pharmacologically active. Klein *et al.* (1971) and Gill *et al.* (1970) have recently described several alkaloids, one of which has atropine-like properties. Atropine in sufficient dosage is hallucinogenic. In addition the possibility of interactions between the different cannabinols should be considered. Experienced smokers believe there to be a qualitative difference between different samples of cannabis. This suggests that there might be more than one active substance responsible for the characteristic intoxication.

Effects: desired and undesirable

The evidence and information on the toxicity of drugs is obtained from two sources. First, it is obtained from the deliberate intoxication of experimental animals with known and controlled doses of the drug, and secondly, from clinical use of the drug. Assessment in these cases is always difficult and a full report of the case history is essential because in isolated cases one can never be sure of the cause-effect relationship. However, two important considerations are:

(a) when successive reports from different districts and observers describe similar signs and symptoms, the evidence for a cause-effect relationship becomes increasingly strong, and

(b) if this is the case it then becomes important to estimate the incidence of the reaction in the treated population. Obviously, it is only when accurate information of the number of people using the drug (and the extent of their use) is available that one can assess the proportion of this total who are suffering an adverse reaction. As cannabis is an illegal substance, it is particularly difficult to assess the incidence of adverse reactions; the extent of the user population is just not known. It is of great importance to have accurate and continuous estimates of the user population.

As most of the adverse reactions to cannabis are associated with its desired and sought-after effects, it is as well to describe briefly what these are.

Effects of cannabis

In most common usage the drug is smoked. By this method, absorption is rapid and effects are usually evident within 10 to 20 minutes. In view of this rapid absorption, the experienced user is able to "titrate" the dosage. When a suitable degree of intoxication has been reached, no further drug is taken. In contrast, when taken by mouth, the dose is usually larger because absorption is much slower, erratic and incomplete. Effects are not apparent until up to one hour after the

drug has been taken and if the effect is too severe, very little can be done about it. It is also claimed that the same sample of cannabis taken orally produces a qualitatively different response from when it is smoked.

The effects of acute intoxication should be considered under the two headings:

(a) Physiological or physical effects and

(b) Psychological or mental effects.

The literature on cannabis is replete with descriptions of both categories of cannabis intoxication. From the literary descriptions of Baudelaire, Dumas, Rabelais to more objective and controlled experimental studies by Hollister (1970, 1971), Weil *et al.* (1968), Adams (1942) and the reports of the British Indian Hemp Commission (1894), the Mayor La Guardia report (1944) and that of Williams *et al.* (1946), it cannot be said that the gross effects of cannabis in man have not been thoroughly described. A recent paper by Tart (1970) describes almost *ad nauseam* the subjective experiences of a group of cannabis users. Information that is lacking is a closer and more detailed knowledge of the effects of each active principle alone and in combination on physiological and biochemical mechanisms. And in particular, it is imperative that we should know more of the long-term effects on health of the continued, chronic administration of the drug.

(a) **Physiological effects**

Effects usually include an increase in heart rate, a drying of the throat and mouth, a reddening of the eyes due to dilation of the blood vessels of the conjunctiva. Appetite is usually stimulated, especially for sweet foods and there may be an increased frequency of urination. Less commonly nausea and vomiting may occur as might dizziness, ataxia and tremor. The effects usually last 2 to 4 hours and, unlike alcohol intoxication, there is no "hangover".

Some previously reported effects associated with cannabis intoxication have not been substantiated in properly controlled clinical experiments. It was commonly stated for example, that the individual acutely intoxicated with cannabis had widely diluted pupils and had a lowered blood sugar level.

(b) **Psychological effects**

Of greater consequence are the effects of the drug on mental processes. As with any psychotropic drug, the effects can vary not only from patient to patient, but also in the same patient on different occasions. The attitudes, mood, motivation and expectation of the individual at the time of taking the drug can all modify the reaction to its effects. Similarly the immediate environment in which the drug is taken can influence the response. If the environment or the drug taker's companions are threatening or are disliked, the drug is more likely to accentuate these conflicts and result in a psychologically adverse reaction.

The initial effects of cannabis intoxication are often stimulating (like those of

alcohol) though in some may induce a state of anxiety. Users describe a feeling of enhanced interpersonal relationship and communication. Also described is a state of greater introspection and tranquillity. The psychological effects which are typically reported may be categorised under three headings:

1. An apparent enhancement (distortion?) of sensory perception.
2. A distortion of space-time perception.
3. An interference with immediate memory.

1. Effect on sensory perception

The following statements selected from Tart (1970) describe subjectively this phenomenon:

"I can see patterns, forms, figures, meaningful designs in visual materials that does not have any particular form when I'm straight . . ."

"I can hear more subtle changes in sounds . . ."

"My sense of touch is more exciting, more sensual."

". . . taste sensations take on new qualities."

"Smells become richer and more unique."

Experimentally, cannabis-induced increases in response amplitude to evoked stimuli in the polysensory areas of the cortex of the squirrel monkey have been reported by Boyd *et al.* (1971). The electrocorticogram of these animals showed spiking and sometimes spike and wave pattern due to cannabis which differed strikingly from the pentobarbitone-induced flattening of the wave pattern. These results may or may not be an experimental correlate of the described effects of enhanced sensory perception.

2. Effect on space-time perception.

". . . awareness of time and space become confused. Things seem to take an unearthly long time although, sometimes, much less often, things which should take a long time seem to have zipped by in an instant. Zipping slips by in an instant. Unzipping seems to take forever."

The effect on space-time perception has been confirmed by experimental procedures in man by Hollister (1970), Weil (1968).

3. Memory functioning

"My memory span for conversations is somewhat shortened, so that I may forget what the conversation is about even before it has ended." The information however can be recalled with special effort.

This effect has been confirmed in experiments with volunteers. Abel (1970). Weil *et al.* (1968).

The adverse effects of cannabis

The dependence-producing drugs can exert effects which are a danger to the physical and mental health of the individual. In addition, drugs can produce effects in the individual which adversely affect his role in society to such an extent that he may become a threat to society. The adverse reactions to cannabis will be considered along these lines.

Under the heading "What are the special risks for young users?" a pamphlet on marihuana issued by the U.S. Department of Health, Education and Welfare states:

"Breaking the laws dealing with marihuana can have serious effects on the lives of young people. They may find their education interrupted and their future shadowed or altered by having a police record. An arrest or conviction can complicate their life and plans at many turns. For example, in many States, a person with a police record must meet special conditions to obtain or renew a driver's licence. Conviction can prevent a person from entering such professions as medicine, law or teaching. It can make it difficult for him to get a responsible position in business or industry. Special hearings are necessary before he can hold a government job. Before a student tries marihuana, he should be aware of the social and legal realities about getting involved with the drug."

This surely must be counted amongst the adverse effects of cannabis. It might very well be its most serious adverse effect.

A. **Danger to physical health**

(i) **The lethal dose**

The lethal dose of cannabis in man is unknown. There is no satisfactory documented evidence to attribute death directly to cannabis. A report of two cases from India where death was attributed to a gross overdosage of cannabis taken orally was cited by Walton in 1938. Hughes *et al.* (1970) comment upon the similarity of signs and symptoms of these and they report a case of a 21-year-old man who suffered a diabetic ketoacidosis following the ingestion of marihuana over a three-day period. This patient, who had a family history of diabetes, responded satisfactorily to insulin therapy. The authors speculate that the deaths cited by Walton might have been due to an untreated ketoacidosis precipitated by the eating of a large quantity of cannabis. One other fatality was cited in the Wootten report (1968) and was reportedly caused by gross overeating under the acute influence of cannabis.

A report headed "Toxicological study of a fatal intoxication by man due to cannabis smoking" by Heyndrick *et al.* (1969) concerns a case of a 23-year-old man who was found dead. The association of his death with cannabis rests upon the identification of cannabis in his possession and of cannabinol in a sample of urine.

The lethal dose of cannabis in experimental animals has not been satisfactorily determined. Joachimoglu (1965) compared the LD_{50} in mice of hashish extract with that of its sublimate obtained in a cigarette smoking machine to precipitate the material in the smoke. The LD_{50} of the hashish extract (of unstated potency of cannabinols) was 940 mg/Kg, whilst that of the sublimate was 3,200 mg/Kg.

Lomax (1970) quotes figures of LD_{50} for the THC in mice of 1,500 mg/Kg and of marihuana in the dog, to be 10,000 mg/Kg.

The therapeutic index, an estimate of the safety margin of a drug, is defined as the ratio between the median toxic dose (LD_{50}) and the median effective dose (ED_{50}). The therapeutic index for cannabis has been estimated as 40,000. This compares with a value of 10 for alcohol.

(ii) The acute intravenous administration of cannabis in man

The acute intravenous administration of aqueous extracts of marihuana has been reported by several authors. In all, seven cases are recorded and all have survived. [Henderson & Pugsly (1968), 1 case; King & Cowen (1969), 2 cases; Garry & Keylon (1970), 1 case; King, Pechet & Pechet (1970), 3 cases.] Effects described in these cases included body tremor, hypotension, and collapse, tachycardia and a fall in blood platelet level. Two patients showed a glucosuria, a finding comparable with those associated with the ingestion of large amounts of marihuana referred to earlier.

(iii) Cannabis smoking and respiratory disease

As the most common method of taking cannabis is by smoking it, and in view of the association of tobacco cigarette smoking with lung cancer, bronchitis and other diseases, it is important to investigate the possibility that these conditions might also be induced by smoking cannabis.

However, a meaningful comparison will be difficult to make because of the differences in the frequency of smoking of the two substances. The average daily consumption of a cigarette smoker is far in excess of that of even the heavy cannabis users. Nevertheless, the practice of deep and prolonged inhalation of the smoke by cannabis users might present a danger of respiratory complications. Waldman (1970) reports a case of a patient who had been smoking five to six marihuana cigarettes per day for some years who presented with "marked bronchitis, the symptoms of which were of recent origin".

It appears that cannabis smoke does contain carcinogenic substances (Magus & Harris, 1971) and that the concentration of these substances in a marihuana cigarette is less than half of that of a tobacco cigarette. In view of the lower frequency of smoking by marihuana users it might be predicted that marihuana smoking could produce cancer though the incidence would be lower than that associated with cigarette smoking.

(iv) **Other physical effects of cannabis**

Experimental evidence using animals suggests that cannabis extracts inhibit pituitary-thyroid function (Lomax, 1970) and activate pituitary-adrenal function (Kubena, 1971). Both of these effects are believed to be associated with an effect of THC on the hypothalamus. Effects of this nature associated with cannabis have not yet been described in man.

An apparent lowering of the convulsive threshold in an epileptic patient was reported by Keeler & Reifler (1967). This is an effect similar to alcohol and other sedatives. Whilst a clear pharmacological classification for cannabis has yet to be determined, it appears that it does share many of the properties of the hypnotic-sedative group of drugs (Meyers, 1970). This suggests that, like alcohol, cannabis should be used with extreme caution by the epileptic.

(v) **Teratogenicity**

Two reports have described congenital malformations of infants born to mothers who had taken cannabis during their pregnancy (Hecht *et al.* 1970; Persaud and Ellington, 1967). However, these cases must be interpreted with great caution because in both cases other drugs, including LSD, were also taken during pregnancy. In neither case was there any evidence of chromosomal abnormalities. Studies conducted *in vitro* of the effects of cannabis extracts on chromosomes have revealed no deleterious effects. (Neu *et al.* 1970; Martin, 1969). The incidence of idiopathic foetal abnormalities is such that the frequency of reports of this nature cannot permit an interpretation of a cause-effect relationship.

Laboratory studies in experimental animals have shown an association between cannabis intake and foetal abnormalities in rats (Persaud & Ellington, 1968) and in hamsters (Geber & Schramm, 1969). Foetal abnormalities could not be produced in mice (Persaud & Ellington, 1968) or in rabbits (Geber & Schramm, 1969) although in these species there was an increased incidence of foetal resorptions and stunted progeny.

Persaud & Ellington refer to their material as cannabis resin and the actual dosage given is difficult to extrapolate. Geber & Schramm do indicate the method of preparation of their sample from crude marihuana and it is possible to extrapolate their findings in terms of the crude plant material, although the potency in terms of the cannabinols is unknown. On this basis it has been calculated by Hasleton (1971) that the lowest dose which produced foetal abnormalities in hamsters would be equivalent to about 8 gm of crude marihuana taken by a 140 lb female, over the crucial period of early pregnancy. Whilst it is a heavy consumption, this level might be achieved by some users. Geber & Schramm conclude that on the basis of their data, "the teratogenicity of marihuana resin in animals, is, by comparison on a milligram per kilogram basis with other psychotomimetic agents previously reported, relatively low."

It is important to remember that cannabis does not present a molecule new to man. Various preparations have been used extensively for some thousands of years and it would be expected that if foetal abnormalities are induced by the drug, the incidence is unlikely to be high. Nevertheless, with the current information as to the possible teratogenicity of *any* drug it is always wise for women to avoid taking any drug during pregnancy, especially within the first trimester.

B. Dangers to mental health

"After considering the literature and reviewing clinical material, it becomes clear that the term 'adverse marihuana reaction' is a complex one and includes value judgements as well as clinical observation. As a label it seems to have little aetiological significance and practically no prognostic value. Because use of marihuana currently is an emotionally charged issue with considerable polarisation, it is particularly important to clarify clinical data and understand the application of judgemental terms when they are used. Clearly we need to know more about the properties of marihuana, more about the personality of the people using it, and a detailed description of the setting before, during, and after use before we can attach value judgements to its use." Bialos (1970).

To date it has not been possible, with the data available, confidently to classify cannabis pharmacologically into any of the presently known groups of drugs. Some of its properties suggest that it is a mild hallucinogen, resembling an attenuated LSD (Isbell *et al.* 1967) whilst others suggest it is a sedative-hypnotic and related to the barbiturates, the minor tranquillisers and to alcohol (Meyers, 1970; Grinspoon, 1970; Lindsmith, 1969; Boyd & Meritt, 1966). It is not a narcotic.

Isbell *et al.* (1967) administered synthetic THC to a group of former opiate-dependent subjects who were familiar with the effects of cannabis. Given orally (120 μg/Kg), or smoked (50 μg/Kg), the subjects reported subjective effects similar to those of cannabis use. The subjects also exhibited the physical signs of cannabis intoxication of increased heart rate and reddening of the eyes. At doses 5 to 10 times higher (200-250 μg/Kg smoked or 300-480 μg/Kg orally) subjects reported effects similar to those of LSD. However, the mechanism of action of THC and LSD appears to be different as there was no cross-tolerance in this study between the two drugs.

It is difficult at this stage to determine the intake of THC by a user smoking cannabis to achieve a satisfactory degree of intoxication. Losses of active material by burning and the proportion of the smoke which is not absorbed and that which is simply lost to the atmosphere are not known. Hollister (1971) has estimated the intake to be approximately 40 μg/Kg whilst extrapolating from Weil *et al.* (1968) about 250 μg/Kg produced a "good average high" in experienced users. In another study (Lemberger *et al.* 1971) experienced users claimed they could detect subjective effects following the intravenous injection of 0.5 mg THC, i.e. about 7 μg/Kg.

Incidence of acute adverse reactions

With only inaccurate estimates of the number of people using cannabis and even less knowledge of the frequency and extent of their usage, it is difficult to determine the incidence of the reported adverse reactions. A study by Keup (1970) of admissions to a mental hospital (Brooklyn State Hospital) gives some indications that the incidence in Brooklyn is very low indeed. During a twelve-month period in which there were 2126 admissions, cannabis was considered to be a direct cause in only two patients (0.09%) and a contributing cause in another four patients (0.19%). Pillard (1970) mentions an informal survey of the Boston University Student Health Service, which cares for a student population of 20,000 which revealed that only five to seven patients with cannabis-associated anxiety reactions are being seen yearly. The author comments that doubtless more occur but are not reported to physicians.

In view of the estimates of the widespread use of cannabis it is perhaps surprising that the clinical literature reporting adverse effects is relatively small. Reports of case histories of acute reactions derived from a literature search compiled by the National Library of Medicine, U.S.A. (Medlars) for the last 4 years and up to February, 1971, listed 39 references. A study of these cases indicated that cannabis, depending upon the dose, the personality of the subject and the setting in which the drug is taken, can precipitate acute panic-anxiety reactions and an acute toxic psychosis (acute brain syndrome). There is evidence for a spontaneous recurrence of hallucinatory symptoms without further exposure to the drug and in patients with a previous history of personality disorder (pre-psychotic?) it is claimed that cannabis can precipitate a frank psychosis. Long-term use of cannabis is claimed to be associated with an effect on motivation and ambition of the individual, an effect which has been termed the "amotivational syndrome" or the "drop-out" phenomenon. Most of the clinical reports of adverse reactions to cannabis are classified by the authors as "marihuana psychoses". Under this broad terminology it is clear that quite varied reactions, with different symptoms, history and prognosis have been included. For a clearer understanding and interpretation of these reactions it is necessary to attempt a more specifically defined classification of these phenomena.

Critical examination and classification of the psychiatric consequences of cannabis use have been made by Weil (1970); Bialos (1970); Keup (1970) and Smith & Mehl (1970). For the present review these reactions will be discussed under the following classifications:

1. The acute panic-anxiety reaction.
2. The toxic psychosis.
3. Precipitation of psychotic reaction.
4. Recurrence of hallucinatory symptoms.
5. The "amotivational syndrome".

1. The acute panic-anxiety reaction

This reaction is an acute anxiety state in which the patient finds the physical and psychological effects of the drug alarming. The intensity of the reaction depends to a great extent upon the personality and expectations of the patient. The incidence of the reaction is predominantly in those using the drug for the first time and within a peer group whose experience with the drug is limited.

The acute panic reaction is considered by Weil (1970) to constitute the majority of all adverse responses to cannabis. He suggests that reassurance is all the treatment necessary. Nevertheless the reaction can be of frightening intensity as the following case history will suggest:

. . . a 37-year-old New York housewife was persuaded by her 15-year-old daughter to "turn-on" by eating candy made with hashish. She had never tried cannabis before and agreed to do so out of "curiosity" although she was very apprehensive. The daughter ate three times as much candy as the patient and became "pleasantly high" for about six hours. The patient, one hour after ingesting the candy, felt her heart racing and thought she was going to have a heart attack. She became panicky and lay down without telling her daughter what was wrong. Shortly afterward she felt "flushed and dizzy" and became convinced that she was poisoned. Finally, she got the daughter to call a family physician, who persuaded the patient to take a taxi-cab to a nearby emergency ward. When the physician arrived at the hospital he found her in a state of nervous collapse with a regular heart rate of 140. He ordered an intramuscular injection of chlorpromazine and had her admitted to a psychiatric bed. She remained agitated and depressed for four days and was discharged on the fifth day with no after-effects. The daughter who had taken three times the dose of hashish, had a "good time" that lasted about six hours. (Weil, 1970.)

This reaction is directly comparable to the reaction of a naive subject to his first exposure to excessive alcohol consumption. However, the reaction in this case is attenuated by the consideration that in Western society alcohol is (a) legal, and there is consequently little fear of arrest (b) an accepted and even desirable intoxicant (c) except in fringe circumstances, there is no emotional and irrational association that the drug might lead to insanity (d) the peer group is more likely to be able to cope with the situation because of greater familiarity with the drug.

2. Toxic psychosis

Weil (1970) defines toxic psychosis as a temporary malfunction of the cerebral cortex due to the presence of toxins in the body. The symptoms disappear when the toxins disappear. The reaction is a non-specific one and one that can occur to overdoses of many drugs including cannabis.

In contrast to the anxiety reactions, patients suffering a toxic psychosis are confused, disoriented and commonly are hallucinating.

The following case history reported in Weil's paper illustrates the characteristics of this syndrome.

". . . A 24-year-old law student who smoked marihuana daily and 'never had any difficulty with it' read that Baudelaire had obtained hallucinatory experiences by drinking suspensions of powdered hashish in coffee. Accordingly, he obtained a '½-inch cube' of hashish, powdered it, suspended it in coffee, and drank it on an empty stomach early in the evening. He described his subsequent experiences as follows: 'I didn't feel anything for about 40 minutes. Then I gradually started feeling high, and the feeling intensified over the next 20 minutes. About 1 hour after I had finished the coffee, I suddenly felt higher than I ever had after smoking hashish, and I also began to feel sick. Then everything became very confusing. I couldn't make sense of what people were saying or what was happening. I don't remember very well what happened next. I think I went to bed and just lay in misery for about 6 hours. The only thing I can compare it to is what I remember it was like to have measles as a child, when I had a temperature of 105°F. I know I saw crawling patterns on the walls and heard very unpleasant voices calling me. I couldn't recognise or talk to people who came into the room to find out how I was. I fell into a fitful sleep sometime after midnight and had horrible nightmares. In the morning I felt exhausted and washed out, but the worst of it was over. I ached all over and had a headache and hangover for a day and a half.' "

3. "Precipitated" psychoses

As distinct from the toxic psychoses which are directly the result of the toxic effect of a drug on the cortex, the reactions classified as precipitated psychoses are significantly associated with non-drug factors. Most commonly these include a basic, pre-existing personality disorder and/or an environment that is abnormal and hostile. Cannabis dosage in most of the reported cases has been excessive (Colbach & Crowe's case No. 3 claimed he was smoking 20 Vietnamese marihuana cigarettes daily), though in some cases 'social' doses only were involved (e.g. Klee 1970; George 1970).

In these cases, Smith & Mehl (1970) point out "the psychosis is characteristic of the personality structure of the user, not of the drug. The drug intoxication merely triggers the psychosis, as happens with a variety of other drugs, including alcohol, amphetamine and LSD."

Reactions to cannabis which would be classified in this category have been reported by Grossman (1969); George (1970); Perna (1969); Klee (1969); Colbach & Crowe (1970).

Overall, the incidence of cannabis psychosis appears to be very low and "a reflection of very special personality difficulties in the subjects involved or exceptional dose levels" (Le Dain Report 1971).

On the other hand, in India and other Eastern countries there has been a long-standing belief of an association of cannabis and the psychotic reaction (Benabud

1957). However, McGlothlin & West (1968) have pointed out that Western authorities have questioned both the methodology of the studies and the adequacy of the diagnoses. "Although part of the difference may be due to the fact that much larger amounts of the drug are used in the East, it is doubtful that this could reasonably account for the wide discrepancy in the findings." Another factor in interpreting data derived from Eastern countries is a consideration of the nature of the preparations of cannabis used. In the Middle East and Far East cannabis is often mixed with other substances, including opium and *Datura stramonium*, both of which are psychoactive substances (Le Dain Report 1970).

4. **Recurrence of hallucinatory symptoms**

The recurrence of the intoxicating effects of the hallucinogenic drug LSD whilst the patient is in the drug-free state has been widely reported in the literature: (Frosch *et al.* 1965; Rosenthal 1964; Louria 1968). The subject was reviewed by Smart & Bateman (1967) and Barber (1970). A similar recurrence of symptoms from a previous experience with hallucinatory drugs is believed to have been precipitated by cannabis (Favazza & Domino 1969; Weil 1970). The phenomenon has also been reported to occur in patients who had used no other drug but cannabis (Keeler *et al.* 1968; Smith & Mehl 1968).

It is hard to estimate the incidence of this reaction. On the one hand Keeler *et al.* (1968) suggest that it may be relatively common and "may often be accompanied by a degree of anxiety sufficient to constitute a psychiatric emergency". On the other hand, Smith & Mehl (who report that in a two-year period at the Haight-Ashbury Medical Clinic of San Francisco 40,000 patients were treated) state that they "are inclined to the view that 'flashback' effects, though real, are quite rare".

The mechanism involved in this reaction is unknown. At the time they occur one assumes that the drug has long since been excreted. Whether a long-lasting biochemical change has been produced by the drug has yet to be shown.

5. **The "amotivational syndrome"**

Apart from the possibility of the precipitation of a psychotic reaction in a predisposed individual, the adverse effects of cannabis discussed so far have been acute, temporary and reversible. Of more concern is the possibility that the continued consumption of cannabis over a long period may lead to personality and behavioural changes. Early reports of such changes came from India (Chopra & Chopra 1939) and in recent years concern on the subject has been expressed by West 1955; McGlothlin & West 1968; West 1970; and by Baker & Lucas 1969, in Britain. The term "amotivational syndrome" was applied to the phenomenon by McGlothlin & West, and is described as a progressive personality change involving a diminished ambition and motivation together with an apparent loss of certain intellectual skills. West's description of these changes, which he believes may be associated with continuous heavy cannabis use of some years' duration was first published in 1955.

"There are a great many young people, including some of the brightest and some of the best, who have been using marihuana now more or less regularly for three to four years. Addiction or even habituation is denied. The smoking is said to be simply for pleasure. Untoward effects are usually, although not always, denied. But the experienced clinician observes in many of these individuals personality changes that seem to grow subtly over long periods of time: diminished drive, lessened ambition, decreased motivation, apathy, shortened attention span, distractibility, poor judgement, impaired communication skills, loss of effectiveness, introversion, magical thinking, derealisation and depersonalisation, diminished capacity to carry out complex plans or prepare realistically for the future, a peculiar fragmentation in the flow of thought, habit deterioration, and progressive loss of insight."

Referring to this statement fifteen years later, West (1970) said, "There is a clinical impression of organicity in this syndrome which I simply cannot shake off or explain in any other fashion."

A direct cause-and-effect relationship of cannabis with the personality changes described has yet to be established. Indeed, West stresses that this is only a clinical impression. It is difficult to imagine the standards by which even an experienced clinician would assess subtle changes over long periods in such parameters as "judgement", "effectiveness" and "insight". Also it is difficult to understand how a drug can be directly responsible for a change in the attitudes of an individual. It is quite likely that individuals who hold certain attitudes are attracted to cannabis, rather than there be a cause-effect relationship.

A study by Suchman (1968) suggests that there is an association of the use of cannabis by certain individuals or groups and of certain personality traits and attitudes that he describes with the term "hang-loose ethic". Adherents of this ethic question the values of established order, including the traditional values of religion, pre-marital chastity, ambition, competition and the accumulation of material wealth. In Suchman's study, the more strongly the individual embraced the ethic the more favourable were his attitudes towards the use of cannabis. Suchman suggests that cannabis is part of this behaviour pattern rather than the cause of it.

A study of attitudes and behaviour patterns of a group of students attending the University of Sydney also suggests that the use of cannabis as a social drug attracts students that do conform to a similar ethic as that described by Suchman. The cannabis users in Hasleton's study tended to be social and political radicals, intellectual, theoretical and "open minded". In line with this, subjects tended to be disinterested in traditional religious affiliations and were more likely to be living away from home with other students than were their non-using peers.

However, it is the progressive nature of the "amotivational syndrome" and its association with heavy cannabis use that does suggest a cause-effect relationship. Recent research into the metabolism, distribution and excretion of THC has

revealed information which suggests the possibility of an accumulation of the drug with repeated doses. Two studies utilising radio-actively labelled THC have shown that after a small dose given intravenously to human volunteers metabolites of the drug were excreted predominantly in the faeces within four days. However, radio-active metabolites were still appearing in the urine and faeces for as long as eight days after the initial dose. Similar results have been reported from experiments in rats (Miras 1965; Ho *et al.* 1970) and in rabbits (Agurell 1970; Agurell *et al.* 1970). Hollister (1971) reported that cannabis metabolites are detectable in the urine two weeks after the last dose. *In vitro* experiments have shown that THC is bound to plasma proteins to the extent of 80 to 95 per cent (Agurell 1970).

These results suggest that THC, which is a water-insoluble, fat-soluble substance, is stored in the body. It is quite feasible to suppose therefore that with repeated exposure to the drug, and with a rate of intake which exceeds the rate of excretion, there should be a build-up of the levels of stored THC in the tissues. The question then arises: is this stored drug biologically active? If the answer to this question is shown to be in the affirmative, a correlation between this phenomenon and certain aspects of "amotivational syndrome" should seriously be considered.

C. Danger to the community

Drugs can affect the order of society in a number of ways. Firstly, they can pose an economic burden on society by being a danger to the health and productivity of the individual. Secondly, the direct effect of drugs may be such as to produce anti-social behaviour in the individual whilst he is intoxicated. This behaviour may be unpleasant, aggressive or even violent. Or the intoxication may impair psycho-motor performance such that the subject loses efficiency and become a danger if in control of complex machinery, e.g. a motor vehicle. Thirdly, associated with drugs of strong dependence-producing capability (the availability of which has been legally restricted) is an increased incidence of crime.

The association of cannabis with each of these factors will now be discussed.

1. Health hazard to the individual

The current evidence of the acute toxicity of cannabis has been reviewed above. When one considers the nature of the acute reactions and their prognosis, together with an estimate of their incidence in the user population, the drug does not present a serious threat to health. In terms of chronic effects, we must be cautious in our judgement. The possibility that heavy use may lead to an "amotivational syndrome" needs to be carefully studied.

Cannabis, inasmuch as it is an intoxicant and euphoriant and is used in a social setting as a relaxant, resembles alcohol. Comparisons of the toxicity of the two drugs therefore are frequently made.

It is true that on presently available information cannabis appears to be of similar or lower toxicity than alcohol, which is capable of producing transient

psychiatric episodes, acute hallucinosis and Korsakoff's psychosis and delirium tremens. These conditions are associated with the excessive use of alcohol. It seems reasonable to compare the severity and prognosis of these reactions to alcohol with that of the "amotivational syndrome" and the precipitated psychoses which might be associated with excessive cannabis use.

2. **Anti-social behaviour of the cannabis-intoxicated individual**

Anslinger & Tompkins (1953) have asserted that, "In the earliest stages of intoxication the will-power is destroyed and inhibitions and restraints are released; the moral barricades are broken down and often debauchery and sexuality result."

It is difficult to establish the origin of this assertion because there is no evidence to substantiate it. Benabud (1957), in a report which cannot be said to be sympathetic towards cannabis, stated that, although the drug has the reputation of being an aphrodisiac, this is not upheld by the facts.

Lindsmith (1966) records that cannabis rather tends to cause the user to lose interest in sex, and expresses this in these terms: "Venus, herself, could not tempt them (cannabis users) when they are under the influence of the drug". Pharmacologically, Lindsmith's suggestion is more feasible than that of Anslinger and Tompkins since the report by Gill, Paton & Pertwee (1970) of an atropine-like substance in extracts of cannabis. Atropine and like compounds count impotence amongst their side effects. However, most users of cannabis contend that, whilst it is not an aphrodisiac, it does increase the pleasure and sensuality of the sexual experience.

Cannabis and driving skills

Crancer and colleagues from the Department of Motor Vehicles of Washington State, U.S.A., compared the effects of alcohol and cannabis on driving skill, using a driving simulator. Thirty-six subjects, all experienced cannabis users, were tested under the three conditions of no drug, cannabis and alcohol. The cannabis was smoked to a degree of intoxication subjectively assessed as a "normal social high", and alcohol taken to a predicted blood level of 0.1 per cent. Total scores involving errors of speedometer, acceleration, steering, braking and signalling were compared for the three treatments. Score totals of errors for the cannabis treatment did not differ significantly from the scores with no drug, whilst significantly more errors were committed under the influence of alcohol. However, one must be cautious in interpreting these results. The level of intoxication with cannabis is notoriously difficult to control and, although the authors stated that they used a minimum of 1.7 gm of marihuana containing 1.3 per cent THC, there is no way of adequately determining the amount absorbed, nor is there a way of biologically assessing the degree of intoxication. In addition, the alcohol intake appeared to be inadequately monitored; Frank (1970) considered that according to the amount given the blood levels produced would have been nearer to 0.18 per cent, hardly a "normal social high".

It is quite clear that acute cannabis intoxication in the naive subject does impair the performance of psychomotor tasks (Weil *et al.* 1968; Hollister 1970). Furthermore, most experienced users consider that when under the influence of the drug their driving competence is impaired (McGlothlin & West 1968; Hollister 1971). As is the case with alcohol it is highly likely that individuals will drive whilst intoxicated with cannabis and this intoxication is liable to present a similar hazard. Forensic difficulties to be encountered here rest with the lack of a sensitive and reliable test for cannabis intoxication. There are methods for detecting cannabis metabolites in urine (Christiansen & Rafaelsen 1969). However, these are complicated by the fact that these metabolites are detectable in the urine long after the intoxicating effects of the drug have dissipated. Hollister (1971) states that he has detected these metabolites two weeks after the last dose of cannabis.

Is cannabis a drug of addiction?

The World Health Organisation Expert Committee on Drug Dependence in its sixteenth report (1969) recommended that the terms "addiction" and "habituation" be replaced by the term "Drug dependence", with a modifying phrase linking it to a particular drug type to differentiate the characteristics of one class of drugs to another. On this concept, drug dependence of the cannabis type is defined:

1. Desire (or need) for repeated administration of the drug on account of its subjective effects, including the feeling of enhanced capabilities.
2. Little or no tendency to increase the dose, since there is little or no development of tolerance.
3. A psychic dependence on the effects of the drug related to subjective and individual appreciation of those effects.
4. Absence of physical dependence so that there is no definite and characteristic abstinence syndrome when the drug is discontinued.

The Brain Committee (H.M. Stationery Office, 1961) considered that cannabis is not a drug of addiction but an intoxicant. Allentuck & Bowman (1942) say that "the psychic habituation to marihuana is not as strong as to tobacco or alcohol". Freedman and Rockmore (1946), in a study of 310 users with an average of seven years of cannabis use, reported that most of them had refrained from using the drug for long periods without reduction in efficiency or need for medical care.

The subject has been reviewed by Watt (1965), who concludes, "It seems clear therefore that cannabis by itself induces neither dependence nor addiction". "The Expert Committee (World Health Organisation) has defined drug dependence of cannabis type very clearly as habit forming". "The habit is gregarious and is easily abandoned."

The progression from cannabis to narcotics

Although it is generally conceded that cannabis is not "addicting", there are still some who contend that use of it will lead to the use of narcotics. The only

way to test this hypothesis is to compare directly over a period of time the total population of cannabis users (or a representative sample of them) and determine the proportion of this population who become users of narcotics. A study of this nature has not been done. Rather, the evidence presented is based upon a study of the drug use history of presently known narcotic users. In these populations the proportion who have used cannabis is high, as also is their use of tobacco and alcohol. On this subject the United States Task Force Report (1967) concludes:

"The charge that marihuana 'leads to the use of addicting drugs' needs to be critically examined. There is evidence that a majority of the heroin users who come to the attention of public authorities have, in fact, had some prior experience with marihuana. But this does not mean that one leads to the other in the sense that marihuana has an intrinsic quality that creates a heroin liability. There are too many marihuana users who do not graduate to heroin, and too many heroin addicts with no known prior marihuana use, to support such a theory. Moreover there is no scientific basis for such a theory.

"The most reasonable hypothesis here is that some people who are predisposed to marihuana are also predisposed to heroin use. It may also be the case that through the use of marihuana a person forms the personal associations that later expose him to heroin."

On the same subject, the Wootten report similarly concludes, ". . . we have concluded that a risk of progression to heroin from cannabis is not a reason for retaining the control over this drug (cannabis)."

Nevertheless the progression hypothesis still has a distinguished proponent in Paton (1968), who has correlated the increase in the incidence in abuse of both cannabis and heroin and claims there to be a direct relationship. However, the strongest criticism of this work is that of the source of Paton's data. He has drawn his information for heroin from the Home Office lists of registered addicts. This list is probably a near-complete record of heroin users in Britain. Cannabis figures are those for convictions for cannabis possession or use and not by any means a true estimate of cannabis users. Furthermore, those convicted are not typical of the group of cannabis users.

A comprehensive discussion of the "progression" hypothesis and a criticism of Paton's conclusions are given by Schofield (1971).

The concept of progression was expressed earlier to describe a link between tobacco and cannabis (Rowell 1939).

"Slowly, insidiously, for over three hundred years, Lady Nicotine was setting the stage for a grand climax. The long years of tobacco using were but an introduction and training for marihuana use. Tobacco, which was first smoked in a pipe, then as a cigar, and at last as a cigarette, demanded more and more of itself until its supposed pleasures palled, and some of the tobacco victims looked about for something stronger. Tobacco was no longer potent enough."

Cannabis and crime

Many reports claim a casual relationship between cannabis use and crime. Similar comments apply in this regard as were applied to the determination of the "progression" hypothesis inasmuch as the evidence for the association of cannabis and crime has been derived from statistics of criminal populations. The fact that criminals use cannabis is no proof that the drug is the determining factor in the commission of the crime. Bromberg (1934, 1939) has made an extensive study of the use of cannabis and reported that whilst the incidence of the drug in the criminal population was high, "no positive correlation could be found between violent crime and marihuana". Similarly, Andrade (1964) studied 120 cannabis-using criminals and could show no relationship between cannabis and their criminal activities.

However, like alcohol, cannabis is an intoxicant, and in a user with criminal tendencies the drug might be used as a means of "fortification" in preparation for criminal activity. Pharmacologically, amphetamines or alcohol seem to be better suited to this purpose, as McGlothlin and West point out, "the passive reaction to marihuana use tends to inhibit rather than cause crime, whereas alcohol consumption is more likely to release aggressive behaviour." Similar comments have been made by Chopra & Chopra (1939). The Wootten Report (1968) states that, "In the United Kingdom the taking of cannabis has not so far been regarded, even by the severest critics, as a direct cause of serious crime. The evidence of a link with violent crime is far stronger with alcohol than with the smoking of cannabis."

Summary

1. A review of the literature concerning the dangers to health of the use of preparations from the plant *Cannabis sativa* has been made.
2. The acute physical effects most commonly experienced are bloodshot eyes, dry mouth, increased pulse rate and muscle weakness (lethargy).
3. Acute mental effects such as perceptual changes, disorientation of time and space and effects on short-term memory may be considered by some who take the drug as desirable, by others as adverse. Whether these actions are interpreted as adverse depends upon attitudes and expectations of the individual as well as the nature of the external circumstances. "Acute panic reactions" are considered to constitute the bulk of cases of adverse reactions to cannabis.
4. The incidence of acute psychotic reactions apparently precipitated by cannabis appears to be low. This reaction also is dependent upon non-drug factors such as a previous history of psychiatric illness, or personality disorder, and/or an unfavourable environmental setting.
5. There is no evidence to show with certainty a cause-effect relationship of cannabis with foetal deformities or chromosomal abnormalities.
6. Adverse effects on physical health following the long-term use of cannabis

have not been satisfactorily demonstrated. An association with asthma, bronchitis and other respiratory conditions has been claimed. Cancer-producing substances occur in cannabis smoke, but in a concentration less than half that of tobacco smoke.

7. Further research is necessary to determine if the chronic use of cannabis constitutes a danger to mental health. An "amotivational syndrome" has been described as being associated with the prolonged, heavy use of cannabis.
8. Cannabis is not considered to be a "drug of addiction".
9. It is generally conceded that there is no truth in the contention that cannabis use leads to the use of narcotic drugs.
10. There is no evidence to show any direct association between cannabis and crime.

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A report by Campbell *et al.* which appeared since this review was completed is of considerable importance and should be mentioned briefly here. These authors describe ten cases in which cerebral atrophy was demonstrated. The technique of air encephalography was used and dilatation of cerebral ventricles as the evidence for cerebral atrophy. All cases presented with symptoms of personality disorder and a history of regular heavy cannabis use over a range of 3 to 11 years (mean of 5.5 years). The measurement of ventricular dilatation in these cases was significantly different from normal for their age (18 to 28 years, mean of 22.8 years).

Factors which remain to be determined are: (a) if a true cause-effect relationship with cannabis exists in these cases, or whether the neurological condition (leading to atrophy) preceded, and was itself a determining factor of the patients' drug abuse. In this regard it is important to cite the studies of Lönnum of 100 patients with ventricular enlargement similar to that described by Campbell *et al.* Lönnum's patients covered a wider age distribution, but 97% of them showed intellectual deterioration and 71% had no history of drug abuse.

(b) Similar encephalographic studies should therefore be made of patients within the same age groups as those of Campbell *et al.*, with personality disorders and who have not been using cannabis.

(c) Experiments should be conducted to determine if similar neurological changes can be effected by the chronic administration of cannabis to experimental animals.

It is important to mention that other conditions may also be associated with ventricular enlargement. This point is discussed by the authors, and also in an editorial in the *Lancet:* "Such changes are also to be found after head injuries and in patients who have personality disorders without epilepsy, or with attacks that are thought to be hysterical or are brought on by overbreathing. As Dr. Campbell and his colleagues point out, alcoholism, too, may be accompanied by ventricular dilatation and by personality changes. There also the argument can be advanced that alcoholism is the effect rather than the cause, but at least it seems to be accepted that complete abstinence may secure arrest or reversal of the mental changes, though this is less likely if ventricular enlargement is present. It is perhaps appropriate to mention that the better knowledge of alcoholic encephalopathy does not deter millions of normal people from using alcohol."

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