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Paper

Cannabis and Its Problems

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The approach to cannabis in this paper is essentially that of preventive medicine. It is already clear that a significant number of adolescents are requiring medical care of some sort as a result of taking cannabis. The full number affected can only be guessed; but due weight must be given to the individual and social loss of lives impaired in adolescence, as compared with (say) lung cancer in late middle age. One must note, too, that extensive cannabis use in a population with high expectation of life, health and wealth, is a new phenomenon; and that for the foreseeable future it will be not the pure active principle tetrahydrocannabinol (THC) but forms of the crude resin that are used. Pharmacological study is incomplete, therefore, if crude material is not used. A major difficulty in the whole field is the growth of multiple drug use, complicating enormously the analysis of the effects seen.

Fat Solubility: Distribution and Fate in the Body

The making of 'majoun' (O'Shaughnessy 1842) provides a vivid illustration of the lipophilic nature of cannabis, with the extraction of the psychically active principle into butter, a partition which then resists washing with water. More analytically, THC has a partition coefficient of 6000 (octanol:water); its metabolite, 7-OH-THC, has a coefficient of 3000, chloroform about 300, and ethyl alcohol about 0.1. For THC, this partition corresponds to about 1200:1 for biological membranes and agrees with uptake observed in brain slices (Jakubovič & McGeer 1972). This immediately implies that there will be strong binding in the blood (Wahlqvist *et al.* 1970) and a very low level of drug free in the plasma. In turn this means that uptake by the tissues will be limited by blood flow (Kety 1951). Autoradiographic and other studies with THC show that the tissues with high blood flow (lung, liver, kidney, spleen) take up the drug quickly. Adrenal cortex, corpora lutea, mammary gland, testis and hair follicles have considerable affinity. Grey matter takes it up faster than white (cf. the faster blood flow in grey matter: Wilkinson *et al.* 1969). In mice, at the peak of the cataleptic action of THC, 2 mg/kg, the brain contains about 0.5 μg/g THC and 0.1 μg/g of the first metabolite (Gill & Jones 1972). It penetrates the blastocyst and can be recognized in fœtal brain. Only with prolonged exposure does it accumulate in a slowly perfused, though lipophilic, tissue such as fat (Agurell *et al.* 1972, Harbison & Mantilla-Plata 1972, Freudenthal *et al.* 1972, Kennedy & Waddell 1972, Shannon & Fried 1972).

Affinity for lipid, by segregating the drug from the water-based mechanisms for elimination, prolongs the life in the body of a drug, whereas metabolism reduces it. THC is converted by liver microsomes to 7-OH-THC, itself psychically active, and then to further metabolites, excreted as conjugates in urine and fæces. The net result in man is a half-time of labelled THC in blood of about fifty-five hours in the naive subject, thirty-five hours in habitual users (Lemberger *et al.* 1970, 1971). Life-time in human brain and other relevant tissues is not known; it takes about six days for 70–80% of labelled THC to be excreted. There appear to be 20–30 metabolites which has made the determination of THC in the body by blood or urine analysis a formidable problem.

Toxicity

The fat-solubility of the active principle of cannabis implies that toxicity will be cumulative, and this is found to be the case, as judged by weight loss and lethality (Paton *et al.* 1972, Braude 1972). The toxicity of crude material is found in the petrol-ether-soluble fraction; THC appears to be the most toxic member of this fraction, but cannot account for the whole effect; propyl-THC, cannabinol and cannabidiol also contribute (Paton & Pertwee, unpublished). It appears that the harmful and the psychic effects of cannabis cannot be dissociated.

In experiments, primarily done to develop tolerance in animals without the stress of repeated injection or gavage, it has been found that mice and guinea-pigs offered petrol-ether extract of cannabis in milk as well as normal free access to water and food, will spontaneously take enough over a period of 7–20 days to kill some of the animals. All the animals lose weight, but some

are vulnerable, fail to make good the weight loss, and die; the others adapt in some way and recover, despite continuing cannabis consumption.

Doses in Mice and Men

Animal experiments with cannabis are sometimes discounted on grounds of the dosage used, but this is probably unwise. A typical psychic effect in man is produced by about 5 mg THC in a reefer, approximately 0.1 mg/kg body weight, corresponding to 100–500 mg crude material (2–10 mg/kg) at 1–5% THC content. But with the habitué, much higher rates occur, up to 10 mg/kg THC, particularly in the East (WHO 1971). In this country daily doses of 6–12 g in a mixture of marihuana and hashish have been reported (Hindmarch 1972); at 2% THC, this would yield 2–4 mg/kg THC daily. Since toxic effects, at least, are cumulative, the effective amount present in the body would be several times this (just as with, for instance, daily dosage of digoxin). Further, in comparisons with animals, the average dose of a range of drugs required varies more closely with surface area and metabolic rate than with body weight; and a mouse needs roughly 10–15 times more than a man does to produce an effect, just as it eats proportionately more (Spinks 1965, van Noordwijk 1964). Doses of the order of 50 mg/kg THC (and correspondingly more of crude material) in small animals are, therefore, not irrelevant to human experience.

Particular Actions of Cannabis and THC

Teratogenicity: Cannabis has been found to produce fœtal resorption and deformities of reduction type in rats, rabbits and hamsters; in mice only resorption was found (Persaud & Ellington 1968, Geber & Schramm 1969*a*, *b*). A dose of 4.2 mg/kg resin intraperitoneally on Days 1–6 of gestation was effective in rats; larger doses were used in other animals, and the effect was found to be dose-related. The doses used are a small fraction of the dose estimated to be lethal to the mother (cf. Robson & Sullivan's (1968) criterion). While cannabis can depress mitosis, there is no evidence that it directly produces chromosome abnormality; but since the volatile anæsthetics also impair cell division and produce fœtal deformity, explanation for these results should probably be looked for on the lines of a type of 'anæsthesia' of limb buds or other groups of rapidly dividing cells. THC itself has not been found teratogenic; it may cause stunting and neonatal death as a result of inhibiting maternal lactation (Borgen *et al.* 1971). It is not clear whether these effects are absent in the human, or that the drug is being avoided in pregnancy, or that unidentified cases are missed in the overall 1–2% of birth rate defects. Epidemiological study is needed.

Liver microsomes: The old observation that cannabis prolongs the action of barbiturates has been shown to be due to inhibition of liver microsomes; THC is active, but the effect of crude cannabis is mainly due to the much more active cannabidiol (Paton & Pertwee 1972). The habitual cannabis user is likely to metabolize a considerable range of drugs more slowly than normal.

Hypothermia and circulation: One can probably link together the ability of cannabis and THC to produce vasodilation (notably of conjunctivæ), impairment of thermoregulation leading to profound hypothermia in small animals, and a slight fall in blood pressure of central origin (sometimes preceded by an initial rise) as resulting from withdrawal of sympathetic tone. Postural hypotension may be the most important aspect of this. It should be noted that tachycardia is also a striking early effect of cannabis; the picture recalls that of partial ganglion block, in which tachycardia and postural hypotension may coexist. Cannabis is not, however, a ganglion-blocking agent. In addition cannabis and THC can lower body temperature raised by a pyrogen (Paton *et al.* 1972); since cannabis also has a mild analgesic action, an analogy with aspirin exists.

Cell pathology: The smoke from a reefer, like cigarette smoke, yields a tar carcinogenic when painted on mouse skin (Magus & Harris 1971). In lung epithelium explants, the smoke caused cell fusion, mitotic lag, and loss of contact inhibition (Leuchtenberger & Leuchtenberger 1971).

THC in low concentration resembles methylcholanthrene in generating malignancy in rat embryo cells incubated with a murine leukæmia virus, but is slower in action (Price *et al.* 1972). Crude cannabis inhibits mitosis. Reactivation of genital herpes by cannabis smoking has been described (Juel-Jensen 1972). THC uncouples oxidative phosphorylation (Mahoney & Harris 1972). These and other observations require extension and confirmation; the affinity of THC for membrane lipid may be an important factor.

Behavioural effects and neurophysiology: The effects of cannabis on behaviour are as varied as those of the personalities of the consumers. But a great deal of the phenomena can be seen as following from a 'dis-inhibiting' action: the euphoria (as well as the occasional dysphoria); the occasional release phenomena, uncontrollable laughter or movement; the flooding of sensory impressions and imagery, as though a selective gate were lifted; the impairment of concentration and selec-

tive attention; the impairment of transfer of information from short-term to long-term memory – a process known to be interfered with by increase in sensory input; the change in time sense, such that 'felt' time becomes longer than clock time (time sense is believed to depend on the number of sensory impressions received). From the difficulty with concentration and memory comes the impairment of mental tasks requiring these qualities; simple tasks are only affected by very high doses, but more realistic tasks requiring retention in the mind both of the working procedure and of the goal (e.g. Goal Directed Serial Alternation: Melges *et al.* 1970; or other tasks: Kiplinger *et al.* 1971) are affected by doses down to 12 μg/kg THC.

Such a dis-inhibitory effect may well also underly the main electro-encephalographic change seen (after possible initial arousal), namely a generation of hypersynchronous discharges, sometimes termed 'epileptiform', arising apparently from the deeper parts of the brain (Colasanti & Khazan 1971, Martinez *et al.* 1971, 1972, Pirch *et al.* 1971, Pirch *et al.* 1972, Segal & Kenney 1972). There is no evidence that cannabis is epileptogenic, and it has in fact a modest phenytoin-like action. But it does appear that, accompanying the psychological effects, there are signs of more than normally co-ordinated neuronal discharges.

As an exceedingly tentative working model, taking into account in addition the evidence that THC can reduce ACh output *in vitro* from the nerve network of the alimentary tract (*see* Paton *et al.* 1972), one may suggest that the action of the drug is to impair transmitter output particularly at inhibitory synapses, so that it reduces selective processing (which necessarily requires inhibition to exclude rejected material), and allows release phenomena and synchronous – possibly reverberatory – discharges. The actual pattern seen will depend, as discussed above, on the distribution of the drug.

Psychopathological phenomena: Although there is some controversy about cannabis 'psychosis', there is an extensive (though rarely cited) literature on the phenomena, with a large number of case histories. Distinctions need to be made between effects due simply to cannabis, exacerbation of a personality disorder, precipitation of psychosis, and exacerbation of pre-existing psychosis. The picture is characterized by cognitive impairment and fragmentation of thought, confusion and depersonalization, paranoid thinking, incongruity and flatness of affect, hallucinations or more commonly very free visual imagery, withdrawnness and preoccupation with the milieu interieur. Similar effects have been transiently produced in scores of experimental subjects. The changes in the habitual user persist, however, for a considerable time after giving up the drug – several months if previous use was prolonged; and the slow overall kinetics of cannabis action need to be stressed.

One particular pattern, the so-called 'amotivational syndrome', as it affects the adolescent, has drawn attention since it could well interfere with the individual's maturation. It can be suggested that the behaviour pattern reflects adoption of a particular 'life style', with cannabis as an incidental; but the way that, on giving up cannabis, behaviour gradually reverts to that before the drug was taken (e.g. Kolansky & Moore 1972) suggests that it is equally likely that cannabis can, through its psychic action, radically change patterns of life.

The observations by Campbell *et al.* (1971) are relevant here. They studied 10 subjects, aged 18–28, who had all smoked cannabis heavily for years. The first 4 patients had been referred for investigation of headache, memory loss or behaviour change. On air ventriculography no signs of brain tumour were found, but the ventricles were rounded and enlarged indicating loss of brain substance. For controls of comparable age (since ventricular size increases with age) 13 cases were found in their records, matched for age but not sex, who had neurological symptoms but in whom no neurological disease was found. In a later note (Campbell *et al.* 1972) references to criticisms made and a rejoinder may be found. The work clearly needs confirmation; but in view of the cumulative toxicity of cannabis, of the fact that the age-group concerned is also that in which persistence of the mental effects of cannabis is being noted, of the cellular effects of cannabis preparations, and of the serious implications the work could have for adolescent development, the work needs taking seriously. Unfortunately, air ventriculography is not a trivial procedure, and it is not at all clear how a satisfactory control group could be found.

Factors Predisposing to Continued or Increasing Use

Since it is the habitual user of cannabis who is most affected, and because of its cumulative characteristic, the nature of the forces predisposing to repeated or increasing consumption are vital. Among them must be the wish to recapture an effect when it has waned, the establishment of ordinary habit, and perhaps, when the effect of a given dose has become familiar, a wish to explore further. Beyond this, and more specifically, the drug may alter the subject's assessment of the consequences of its use. Further *tolerance* develops to a very wide range of cannabis effects in animals; and while it has not been properly

Table 1

Cannabis withdrawal effects

Animals:	*Reference*
Irritability (cats, rats)	Chopra & Chopra 1957
Irritability, depression, tremor, yawning (rhesus)	Deneau & Kaymakçalan 1971, Kaymakçalan 1972
Increase in integrated electro-corticogram (rat): Day 2	Pirch *et al.* 1972
Increase in motor activity (rat): Day 2	Davis *et al.* 1972
Man:	
Restlessness, anxiety, jerking movements, headache, suicidal fantasies	Marcovitz & Myers 1944
Irritability, excitement, violent outbursts, psychotic behaviour	Fraser 1949
Apathy, bad temper, depression	Tylden 1967
Restlessness, anxiety, cramps, sweating, aches	Bensusan 1971
Anxiety, depression, fine tremors, sweating, disturbed sleep	Kielholz & Ladewig 1970

mapped out in man, it is only necessary to compare the amount required to produce a 'mind-bending' effect in a naive subject with that taken by a habitué to conclude that it occurs in man too. Its development should be masked initially, as has been found in animals, by the results of cumulation. Finally, although withdrawal symptoms comparable to those after opiate or barbiturate withdrawal do not occur, a consistent *withdrawal syndrome* exists, marked particularly by sleeplessness, irritability and tremors (Table 1). In the rat, tolerance to the depression of integrated cortical potential by THC is followed, on withdrawal of drug, by a rebound increase; the increase was not seen until the second day of withdrawal, corresponding with the slow kinetics of the drug.

Conclusion

For medical practice, it is the habitual user of cannabis, in whom effects build up, who is likely to present the main problem. Unfortunately it is not yet possible to define what rate of consumption represents 'habitual' use. Possible impairment of liver microsomes prompts caution in drug dosage. The possibility of postural hypotension should be understood, as also the irritant effects of the smoke. The tachycardia has been insufficiently explored; since in resting subjects it may reach 160/minute, and is (anecdotally) stated to increase with exercise, study of habitual users under mild physical stress is desirable. In all studies of cannabis, the slowness of its kinetics must be taken into account; the characteristic changes take time to develop, and on ceasing to take the drug an equivalent time is required before visual effects, time sense, 'muddliness' and concentration return to normal. If it is desired to try to treat the habit, it is useful to suggest that the subject should try to abandon the drug just for a limited period; but the period should be 2–3 months.

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DISCUSSION

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Effects of Cannabis in Man

Professor Paton's review is admirable because of its range and depth. He has presented cumulative evidence showing that cannabis can cause adverse effects, and these are principally dose-related. As most of the data is based on animal experiments in laboratory settings, much caution is necessary in extrapolating these findings on to humans for at least three reasons. Animals and humans respond differently; impaired coordination, for example, is confirmed in man (Weil *et al.* 1968), gross ataxia is not (Clark & Nakashima 1968). Novices and habitual users respond differently to cannabis, but such group differences are difficult to establish in animals. Thirdly, and perhaps most important of all, humans selectively choose to use cannabis. The drug is used principally as a social solvent to change mood and perception, and we can observe and interpret these effects in humans with some degree of confidence. Animals in their natural environment, on the other hand, rarely, if ever, use cannabis through choice, and furthermore we are not equipped to interpret its effects on their mood and perception.

Factors Affecting Human Response

Amongst the more important ones that should be mentioned are: dose; whether or not the subject is a novice; his mental set (expectations of the user); and the setting in which he uses the drug. Kiplinger *et al.* (1971) have demonstrated that if the set and the setting are kept uniform the responses are dose-related, as judged by scores on Cornell Medical Index and Impaired Motor and Mental Performances. Tart (1970) also found that while at low and moderate dose level cannabis promotes social interaction, at higher dose level the result may be the opposite.

It is, however, pertinent to point out that cannabis is on the whole used at moderate dose level in cultures where the drug is socially accepted. Many workers have demonstrated that novices react more adversely to the use of cannabis than the habitual users – indicating that ability to contain and enjoy the effects of cannabis is probably a learnt behaviour. Setting, as well as the mental set, has an important influence on the effects of cannabis use (Wikler 1970, Waskow *et al.* 1970). In isolation and in austere setting the effect of cannabis is more sedative than euphoric. As to expectation, in the setting of users, smoking of placebos may produce a pleasurable intoxication.

Immediate Adverse Effects and Comparison with Alcohol

The most noticeable adverse effects are in the realm of depersonalization and derealization (Hollister & Gillespie 1970, Hollister *et al.* 1968). Higher mental functions such as coordination, attention and judgment, reaction time (e.g. braking time), immediate memory and learning ability are all impaired (Kalant 1969, Kiplinger *et al.* 1971, Melges *et al.* 1970). It has been demonstrated that cannabis and alcohol potentiate each other's effects. These findings have obvious implications for public safety. It has also been shown that 2.5–5 mg of $\triangle^9$THC is likely to be absorbed from one to two cigarettes of marihuana and can lead to impaired motor performance similar to that achieved by 50 mg/100 ml of blood alcohol level.

Against these adverse effects should be stressed the socializing, euphorogenic and relaxing effects of cannabis, and the fact that 'average' habitual users learn to control and contain both the dose and the effects of cannabis.

Effects of Long-term Use

This is an issue which has been debated for decades, and we are no further in our knowledge than were the Indian Hemp Commission in the 1890s and the Mayer's Commission in 1944. These two bodies declared that moderate use of cannabis over long periods, in persons not predisposed to mental illness, does not lead to psychosis or personality deterioration. On the other hand, sporadic and recurring reports (on the whole defective in methodology) have asserted otherwise. Now that we can estimate the $\triangle^9$THC content in samples of cannabis, it may be worth considering the establishment of a research facility which will receive all the cases diagnosed as of cannabis psychosis or of toxic reactions due to cannabis, and study them fully and scientifically. Space does not permit elaboration of how this can be accomplished, but I think it deserves serious consideration to further our understanding of adverse effects of cannabis in man.

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