

Cannabis and Health — A Review

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In spite of the publication of some 7,000 scientific articles on cannabis, doubt and confusion about the effects of cannabis still exist. These are largely due to the fact that the drugs obtained from the cannabis plant are very complex and variable substances and this variability is often either not understood or neglected. The failure to take account of this variability often devalues the result of investigations into the pharmacological and toxicological effects of the drug. Meaningful experiments must take the nature of the drug into account.

A number of drug preparations can be obtained from the cannabis plant. The three main drugs are:—

1. *Herbal Cannabis*: a tobacco-like material consisting of the dried small leaves and flowering parts of the plant. This is referred to as “marihuana”, “grass”, “pot” or “weed”. Marihuana usually contains 1-2 per cent of psycho-active material and is the main product in the U.S.A.
2. *Cannabis resin*: a pleasant smelling soft to hard solid squeezed from the cannabis plant. It is referred to as “Hashish” or “Hash”. Hashish such as Lebanese gold or Pakistani black usually contains 5-10 per cent of psychoactive material. Resin is the product most widely used in Ireland, although in more recent years a significant amount of Irish-grown herbal cannabis has been available (Corrigan, 1980).
3. *Cannabis oil*: prepared by extraction of the plant material and subsequent distillation of the extract. This is known as hash oil and contains 11-28 per cent active material.

The term “psychoactive material” refers to one of the 421 known chemicals which have been isolated from cannabis (Turner et al., 1980a). The interactions of these chemicals should be taken into account when assessing cannabis but this rarely happens. Biological data obtained with single components are of value but do not provide data for the crude drug.

The characteristic components of cannabis are a group of 60 nitrogen-free compounds called cannabinoids. These compounds exist in the plant as acids which slowly change into neutral forms after the plant is harvested. This conversion becomes almost instantaneous when the material is heated.

The major cannabinoid is called Delta 9 Tetrahydrocannabinol or THC. It is generally held that cannabis preparations can be evaluated on the basis of the THC content with the result that pharmacological data for pure THC are wrongly taken as the same as data for cannabis: This has given the impression that marihuana and hash are similar and uniform in their composition, when in fact the reverse is true. Cannabis drugs contain varying proportions of other cannabinoids such as cannabidiol (CBD) which has sedative effects, and cannabinol (CBN) which has only one-tenth the activity of THC. These other ingredients may be important in modifying the effects of THC as well as causing effects of their own. Thus, some of the reports based on THC may be only partially relevant to the effects of the plant material.

Potency of Drugs

The potency of these drugs is usually based on the THC content, which influences the level of both desired and undesired effects. Most of the confusion about the effects of cannabis can be attributed to the difficulty of knowing how much THC is transferred from the crude drug to the cells of the user. This difficulty arises partly from the way the drug is used and partly from the variability of the plant material. This latter arises in a number of ways:—

1. *Type of cannabis plant:* A distinction has been made between two types of cannabis, the fibre type with little or no THC and the drug type with high THC. The existence of intermediate strains complicates the situation further (Turner et al., 1979).
2. *The plant part used:* The highest content of THC is found in the small leaves surrounding the flowers with lesser amounts found in larger leaves and virtually none in the stems, roots and seeds (Fetterman et al., 1971). Therefore, carefully sifted material will be far more potent than material with a large proportion of seeds and stems. Obviously, hashish and hash oil, with their higher THC content, will be more potent than marihuana.
3. *Storage conditions:* Cannabinoids are extremely unstable in air and light. These two factors cause the breakdown of THC into inactive CBN or polymers (Fairbairn et al., 1976).

Thus, no two cannabis products, however carefully prepared, will be identical (Turner, 1980b). It must be stated, however, that overall the potency of 'street' cannabis is increasing; for example, in 1974, Mexican marihuana was found to have a THC content of 0.2 per cent; in 1979 this had risen to 2 per cent, while the more popular (in the U.S.A.) Colombian marihuana had a THC content of 4 per cent (Marihuana and Health report, 1980).

Amount of THC

In addition to the inherent variability of the plant material, there are a number of 'Pharmaceutical' factors which affect the amount of THC which enters the body. These include:

1. *The route of administration:* Cannabis products may be eaten but are more usually smoked in cigarettes called 'reefers' or 'joints' or in special ornamental pipes. Inhalation of the smoke is the most efficient route of administration as the acidic components are then rapidly converted into the neutral cannabinoids. THC is four times more psychoactive when inhaled and exerts its effects within minutes. When eaten, the onset of action is delayed for up to two hours.
2. *The dosage:* A 'grass' cigarette normally weighs from 0.5 gm to 1 gm and contains from 5 to 20 mg of THC. A dose equivalent to this would be obtained from approximately 60 mg of resin but I have come across 'joints' with over 200 mg of resin with consequent impact on the dose of THC. The THC content of 'joints' in England has been shown to vary from 0.15 mg of THC to 41 mg THC (Fairbairn et al., 1974).
3. *The experience of the user:* The amount of THC which reaches the cells of the smoker depends firstly on the temperature reached in the cigarette, secondly on whether the smoke is deeply inhaled and thirdly on the length of time the smoke is held in contact with the lungs (Manno et al., 1970). In general, about 50 per cent of the available THC enters the body after smoking (Rosenkrantz, 1974).

The effect of smoking on the cannabinoids and other chemicals is not completely known because workers have tended to focus on the 2 per cent of THC which reaches the brain from the lung while ignoring the effect of the remaining THC and smoke components. It is known that there are at least 150 compounds in cannabis smoke and that many of them are novel cannabinoid-type molecules whose biological activity is unknown (Salemink, 1976).

The complexity and variability of cannabis preparations is such that anecdotal comments on the effects of unstandardised preparations must be treated with the utmost caution. The value of experiments with standard cannabis is also doubtful without evidence of

the resulting blood levels of THC. The methodology for the determination of such levels has only recently become available and has made it possible to design experiments which accurately reflect THC levels found in human users.

Metabolism

After absorption, THC undergoes a very rapid transformation in the body, giving rise to about 75 psychoactive and inactive metabolites (Aguirell et al., 1976). Because THC is fat soluble, it disappears very rapidly from the blood stream into the fatty tissues where it has a half-life of eight days. THC and its metabolites are mainly excreted in the faeces. Repeated administration of cannabinoids at intervals of less than 8 to 10 days cause an accumulation of cannabinoids in tissues including the brain.

Effects of Cannabis

(a) *Desired effects:* The desired effect of a 'normal' dose of THC (i.e. 5-20 mg) is a state of euphoria called the 'high' which is characterised by CNS effects such as easy laughing, elation, heightened awareness and relaxation.

(b) *Undesired effects:* These normal doses also cause a significant impairment of learning ability, short-term memory and on psychomotor performance. It is generally accepted that normal cannabis use impairs thinking, reading comprehension (dark et al., 1970) and the ability to cope with verbal and arithmetic problems (Manno et al., 1970). The more complex the task, the greater the degree of disruption produced by intoxication. Most of this impairment, which has direct significance for learning ability in students who use cannabis frequently, is related to interference by cannabis with short-term memory storage (Tinklenberg et al., 1975). If one relates this to the large numbers of American students who smoke marihuana daily (12 per cent of High School students), then it is likely that there is a detrimental effect on class-room functioning (Marihuana and Health 1980, p. 11). Indirect support for this comes from a school in Atlanta where a parents' pressure group, in collaboration with the teachers, has drastically curtailed marihuana use in the school and as a result participation in the school's sporting activities has doubled, tardiness has fallen from 5,000 per day to 50 per day and enrolment in physics and chemistry classes has trebled (Frazer, 1980). Kelly has stated that a sudden drop in academic achievement and a lessening of interest in sport is a strong indicator of cannabis use in school children.

Cannabis and driving: Experimental studies have shown that THC causes impairment of driving ability, and it was concluded that the use of cannabis would increase the probability of driving accidents (Klonoff, 1974). At present there are few published figures on cannabinoid levels in persons involved in accidents. This is because it is very difficult to identify THC in the body by means of a simple technique, similar to the breathalyser, and until recently it was difficult to quantify levels of THC in the body.

The information available at present shows that the problem of cannabis and driving is a real one. American studies indicate that about 20 per cent of all traffic accidents are cannabis related (Marihuana and Health 1980). In the U.K. a limited survey of 66 post-mortem blood samples from traffic accident fatalities showed that 9 per cent of the samples had detectable levels of cannabinoids (Teale et al., 1977). A major problem with regard to the driving impairment is that it may last for several hours after the 'high' and users may be unaware of the impairment. These effects, associated with 'normal' levels of cannabis intoxication, have serious implications but are often ignored in any discussion of the hazards or otherwise of the drug (Tylden, 1975).

Toxicology of Cannabis

(a) *Acute toxicity:* The lethal dose of cannabis has not been determined in humans, which suggests that users are unlikely to die from an overdose. Larger than normal doses do cause signs of acute toxicity. Doses of 30-35 mg of THC can cause nausea, disorientation, anxiety, depersonalisation and paranoid-like states.

The acute anxiety reaction, which is the most usual adverse psychological reaction, appears to be more common in inexperienced users, although higher doses of the drug can cause such a reaction in experienced users (Halikas, 1974). It is generally conceded that anxiety and mild paranoid reactions are more likely if the user is initially anxious about the experience. The panic reaction generally responds to reassurance. Spontaneous recurrences of the drug experience, i.e. 'flash backs', have been reported and are not necessarily related to prior use of LSD, although those with a history of 'bad trips' are advised to avoid cannabis (Abruzzi, 1977; Staunton et al., 1976). There has been a noticeable increase in adverse reactions to cannabis in the U.S.A. (Marihuana and Health 1980, P. 24).

Unstable individuals or those under stress are more likely to have adverse reactions (Naditch, 1974) and some psychiatrists believe that cannabis should not be used by persons prone to mental illness which might be triggered or worsened by cannabis (Treffert, 1978).

(b) *Chronic toxicity:* Many workers have demonstrated the inhibitory effect of cannabinoids on the synthesis of macromolecules and the consequent disruption of cellular metabolism, DNA formation and cell division (Blevins and Regan, 1976). These cellular effects raised the possibility that chronic use of cannabis might affect sperm formation and impair reproductive function.

Cannabis and Reproduction

Impairment of sperm formation was first demonstrated in rats and mice exposed to cannabis smoke, cannabis extract and THC (Zimmerman, 1979). Changes in sperm numbers, motility and increased abnormalities were noted. Subsequent work in New York with young volunteers demonstrated similar effects after unrestricted smoking for four weeks (Hembree, 1979). Cannabinoids also affect the male reproductive system by causing a transient decrease in Testosterone levels through the inhibition of gonadotrophin production in the hypothalamo-hypophyseal area (Harclerode et al., 1979).

The production of abnormal sperm raises the possibility of a genetically transmitted abnormality if such a damaged sperm fertilised an ovum. Such a possibility can only be resolved by epidemiological studies performed on children born to chronic cannabis users. There are no published reports of abnormal offspring of fathers who have used large amounts of cannabis.

There is conflicting evidence that cannabis has teratogenic effects in animals. Some studies report an increase in birth defects while others do not (Fournier et al., 1976). A number of workers believe that cannabis is embryotoxic rather than teratogenic. An unequivocal effect has been demonstrated in rodents with a reduction in pregnancy rates and an increase in the resorption of litters (Rosenkrantz, 1979). This effect has been demonstrated with both THC and cannabis products at dose levels relevant to heavy chronic marihuana use in humans.

Similar reproductive losses have been seen in rhesus monkeys where 42 per cent of pregnant monkeys treated with THC lost the product of conception either through resorptions, spontaneous abortions or neonatal deaths. In the case of untreated monkeys, the birth loss was only 12 per cent (Sassenrath et al., 1979).

The embryotoxicity could be due to an effect on the foeto-placental circulation, to a suppression of hormones necessary to support a normal pregnancy (Rosenkrantz, 1980) or to the effect of carbon monoxide from the burning of the cannabis (Astrupetal, 1972).

When animals born to monkeys exposed to THC were observed over their first year, they were found to be physically normal but showed enhanced responses to external stimuli, were hyperactive and lacked appropriate caution in novel situations (Sassenrath et al., 1979). The effect on long-term development of exposure of the foetus to cannabinoids, which pass through the placenta (Vardaris, 1976), is unknown, as is the effect of THC transferred during lactation (Chao et al., 1976). Abel (1980) has criticised methodological shortcomings in experimental design which, he states, do not allow any conclusions to be drawn as to whether the effects on the embryo are directly due to the action of the cannabinoids or are indirectly due to drug-induced changes in the mother.

It is notoriously difficult to apply animal findings to humans. It is also clinically and morally difficult to design meaningful experiments to investigate adverse reproductive effects in human females. One survey of 26 'street-users' who smoked marijuana at least three times per week for at least six months showed that the user group had three times more abnormal menstrual cycles when compared to a matched non-using group (Bauman et al., 1980).

These adverse effects on both male and female reproductive systems may be of greater importance for those marginally fertile, or for the developing adolescent, than for the mature healthy adult. There is a need, however, for additional information regarding the possibility that increased reproductive problems may be associated with human exposure to cannabis. It seems advisable that young women should be warned to avoid cannabis (Graham, 1977).

Pulmonary effects

The effect of cannabis on cells also show up in the respiratory system. Cannabis cigarettes produce more tar than high tar tobacco cigarettes and benzopyrene, a known carcinogen, is 70 per cent more abundant in marijuana smoke than in tobacco smoke (Novotny et al., 1976). Cannabis tar has been shown to be carcinogenic when applied to the skin of experimental animals (Hoffman et al., 1975). Cannabis smoke has been shown to be cytotoxic, indicating that it may be carcinogenic in much the same way as tobacco smoke. This is of particular significance because in marijuana smoking a larger volume of smoke enters the lungs and is held there longer than in tobacco smoking; also the 'joint' is unfiltered and almost entirely consumed (Cohen et al., 1976). In a study comparing cannabis and cigarette smokers, it was found that smoking less than 1 joint per day decreased the vital capacity as much as smoking 16 tobacco cigarettes (Tashkin et al., 1978).

Studies in rats show that the long-term effects of cannabis smoke on the lungs are similar to those of tobacco smoke with irreversible inflammation and lesions seen after 90 days' exposure. The effects were more intense than those caused by tobacco or placebo cigarettes and are caused not only by carbon monoxide, tar and particulate matter but also by the cannabinoids (Rosenkrantz and Fleischman, 1979). Other studies have shown that the antibacterial defence system provided by pulmonary alveolar macrophages is significantly more impaired by cannabis smoke than tobacco smoke (Huber et al., 1979). There is as yet no direct evidence that smoking marijuana causes lung cancer because experience in the West with the drug is too recent, but daily use of marijuana is considered likely to lead to lung damage similar to that resulting from heavy tobacco smoking. Since both drugs are often used together, a study of the effects of the combined drugs on the lung is required.

Cardiovascular effects

Cannabis increases the heart rate and precipitates angina attacks in those with impaired cardiac function more rapidly and following less effort than tobacco. A warning to such patients not to use cannabis seems justified (Prakash and Aranow, 1976).

Effects on the brain

Changes in brain activity and brain damage have been found in monkeys following exposure to cannabis. These effects have been confirmed by both EEG evidence and histological changes and are linked to the use of 1 joint daily for 6 months (Heath et al., 1979). Brain damage has also been noted in some humans but the experimental basis of this finding has been hotly disputed (Campbell et al., 1971).

The question of the effect of cannabis on the brain and on personality is the area of greatest controversy in the debates concerning the effects of cannabis, mainly due to the difficulty of assessing brain damage and changes in personality. A Scottish study indicates that increased involvement with cannabis is associated with (a) increased levels of anxiety, neuroticism and psychoticism, (b) increased difficulties with personal relationships, (c) employment problems and (d) an increasing emphasis on alcohol consumption. The authors believe that cannabis use presages psychological malfunction rather than acting as a major causal agent (Wells and Stacey, 1976).

A number of workers (Mendelson, 1974; Souif, 1975; Chopra, 1976; Knight, 1976) have pointed out the existence of an amotivational ('dropout') syndrome in groups of chronic users. It has been found difficult to confirm this in the U.S. where it is believed that the 'syndrome' may be part of a rejection of establishment values and the 'work-ethic' (Negrete, 1973).

Studies involving American College students have shown no evidence for the syndrome (Hochman and Brill, 1973) but the value of these findings is limited because College dropouts were not included in the survey (Marihuana and Health 1980, p. 26). A majority of studies indicate that chronic use causes enduring effects on memory and intellectual functioning. A number of studies of chronic users in Jamaica (Beaubrun and Knight, 1973) and Costa Rica (Dornbush et al., 1976) have shown no evidence of serious mental pathology but the quality of all studies on chronic use reported so far leaves much to be desired. The controversy over the relationship between chronic cannabis use and mental ill-health will only be solved by means of carefully controlled longitudinal studies.

Dependence, Tolerance and Progression to Heroin

It is usually accepted that physical dependence of the opiate or alcohol/ barbiturate type does not develop with cannabis. Recent research indicates that cannabis satisfies the criteria for an addictive drug (Paton, 1979) in that physical symptoms follow the withdrawal of the drug after heavy dosage. These symptoms include irritability, restlessness, decreased appetite, sleep disturbance, nausea, vomiting and diarrhoea. These symptoms are all the more remarkable when one considers the slow rate of elimination of the drug from the body. In addition, considerable tolerance to the effects of cannabis occurs (Hollister, 1979). It is claimed that this tolerance gives a physiological basis to the necessity for the frequent smoker to increase dosage or to seek more potent psychotropic drugs (Nahas, 1977). There is little evidence to support a causal relationship between the use of cannabis and progression to such drugs as LSD, heroin and barbiturates. There is, however, some evidence that regular heavy users of cannabis are more likely to use more dangerous drugs (Goode, 1974).

Interactions with other drugs

There is only limited evidence concerning the effects of the combination of marijuana and other drugs. In general, THC interacts with other psychotropic drugs by increasing their depressant effects or reducing their stimulating effects. The most widely used combination is that of cannabis and alcohol, the combined effect of which in animals is greater than the two drugs alone (Siemens et al., 1974). Limited human results are consistent with the animal studies showing reduced reaction time and coordination (Belgrave et al., 1979).

Cannabis as a source of new drugs

Cannabis is not only used as a social or recreational drug, but it has also been used in medicine for a variety of complaints. THC and other cannabinoids are being evaluated at present as new drugs in the treatment of a number of conditions. For example, THC is known to reduce intra-ocular pressure, thus indicating potential benefits in glaucoma (Hepler and Frank, 1971). There have been a number of reports about its beneficial use, but clinical trials using cigarettes and THC eyedrops have had variable results. Combinations with other pressure-reducing drugs have been more successful than THC alone.

The ability of the drug to cause bronchodilation indicated potential benefits in asthma but the pulmonary effects already noted seem to offset this benefit. Cannabis smoking has also been recommended as a method of preventing the nausea and vomiting associated with radiation treatment and cancer chemotherapy (Sallen et al, 1975). This appears to be the most promising application as consistently good reports have been obtained in trials when THC dissolved in sesame seed oil was administered as capsules and compared with conventional anti-emetics (Lucas and Laszlo, 1980). A number of reports have shown side-effects and one promising synthetic cannabinoid has been withdrawn from clinical trial because of adverse reactions (Sweet, 1980).

Cannabidiol has impressive anti-convulsant properties and, because it has little euphorogenic activity, it may be useful clinically. On the other hand, THC can induce attacks of epilepsy by causing hyperexcitability after withdrawal. This suggests that the use of marijuana may jeopardise the control of seizures in epileptics and epileptics should, accordingly, be warned not to use cannabis (Feeney, 1979).

The adverse CNS effects of THC will probably prevent the clinical use of THC and cannabis except as an anti-emetic in cancer therapy. It is expected that specific drugs against glaucoma, asthma and anxiety, based on the natural cannabinoids, will become available in the next few years.

The disputed question of the safety or otherwise of chronic cannabis use is unlikely to be answered definitively within the next 20 to 30 years (Nahas, 1977). This is roughly comparable to the time it has taken to establish the health effects of tobacco in man. Whatever the ultimate evidence about more serious consequences of chronic use, there is no doubt that acute cannabis intoxication interferes with immediate intellectual functioning as well as with driving. Thus marijuana is not harmless.

It is recognised that there are at present a number of groups at particular risk from cannabis. These include: epileptics, women of child-bearing age, those with cardiac trouble, those prone to mental illness and those with a previous history of bad drug trips. Adolescents are a very vulnerable group, both in relation to the effects on their neurohormonal systems and with regard to the effect on their psychological maturity. It is widely held that regular use of marijuana by young people is undesirable as it inhibits maturity and prolongs adolescence (Rosenthal, 1980).

Any attempt to alter the liberal Irish laws in relation to cannabis must be critically examined against a background of international knowledge combined with local information

on the groups at risk and the extent of that risk. A rational discussion of the implications of cannabis use in Ireland requires information on:

1. the numbers using the drug
2. the frequency of use
3. the numbers using the drug daily
4. the age of first use
5. the types and potency of cannabis on the market
6. the numbers driving under the influence of the drug
7. the number of adverse reactions to the drug.

We do not have this knowledge.

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A more detailed bibliography is available on request from the author at: Department of Pharmacognosy, School of Pharmacy, 18 Shrewsbury Road, Dublin 4.