

CHAPTER 4

TOXIC EFFECTS OF CANNABIS AND CANNABINOIDS:

REVIEW OF THE EVIDENCE

4.1 The prohibition of the recreational use of cannabis, and some of the doubts about medical use, are based on the presumption that cannabis is harmful to individual and public health. We have tested the strength of that presumption, and this Chapter records what we have found. New research on this subject is constantly coming forward, so this cannot be said to be the last word on it. Although cannabis is not in the premier league of dangerous substances, new research tends to suggest that it may be more hazardous to health than might have been thought only a few years ago (Edwards QQ 21, 27).

4.2 In assessing the adverse effects associated with cannabis use, we have been assisted by a number of detailed recent reviews, including the recent WHO report Cannabis: a health perspective and research agenda (WHO/MSA/PSA/97.4); the Australian National Drug Strategy report The health and psychological consequences of cannabis use (1994) and other documents[9] submitted by Professor Wayne Hall, Executive Director of the Australian National Drug and Alcohol Research Centre in Sydney, and his colleagues; and the recent reviews noted above commissioned by the Department of Health. The evidence submitted to us by the Royal Society and the Royal College of Psychiatrists is also particularly relevant.

Acute (short-term) effects of cannabis

4.3 The acute toxicity of cannabis and the cannabinoids is very low; no-one has ever died as a direct and immediate consequence of recreational or medical use (DH QQ 219223). Official statistics record two deaths involving cannabis (and no other drug) in 1993, two in 1994 and one in 1995 (HC WA 533, 21 January 1998); but these were due to inhalation of vomit. Animal studies have shown a very large separation (by a factor of more than 10,000) between pharmacologically effective and lethal doses.

4.4 One minor toxic side-effect of taking cannabis which merits attention is the short-term effect on the heart and vascular system. This can lead to significant increases in heart rate and a lowering of the blood pressure (Pertwee Q 299). For this reason patients with a history of angina or other cardiovascular disease could be at risk and should probably be excluded from any clinical trials of cannabis-based medicines.

4.5 The most familiar short-term effect of cannabis is to give a "high" — a state of euphoric intoxication. This is, of course, precisely the effect sought by the recreational user, analogous to the effect of alcohol and sought for similar reasons. We have been told, however, that people who use cannabis for medical purposes regard it as an unwelcome side-effect (Hodges Q 97).

4.6 Intoxication with cannabis leads to a slight impairment of psychomotor and cognitive function, which is important for those driving a vehicle, flying an aircraft or operating machinery (DH Q 197). The Department of Health rate this as "the major concern from a public health perspective" raised by recreational use (p 46), and Professor Hall considers it the most serious possible short-term consequence of cannabis use, both for the user and for the public (p 222).

4.7 There is some disagreement about how long such impairments persist after taking cannabis: most assume that they last for only a few hours (e.g. Kendall p 266); but Professor Heather Ashton of the University of Newcastle-upon-Tyne, principal author of the BMA report, suggested that subtle cognitive impairments could persist for 24 or even 48 hours or more (Q 72), whereas the DETR say "probably 24 hours at most" (Press Notice 94/Transport, 11 February 1998). On the other hand the impairment in driving skills does not appear to be severe, even immediately after taking cannabis, when subjects are tested in a driving simulator. This may be because people intoxicated by cannabis appear to compensate for their impairment by taking fewer risks and driving more slowly, whereas alcohol tends to encourage people to take greater risks and drive more aggressively (POST note 113; cp DH p 240).

4.8 Analysis of blood samples from road traffic fatalities in 1996-97 (the results of the first 15 months of a three year DETR study—Press Notice 94/Transport, 11 February 1998) showed that 8 per cent of the victims were positive for cannabis, including 10 per cent of the victims who were driving. However, it is not clear what figures would have been obtained from a random sample of road users not involved in accidents (DH Q 211); and

some of those who tested positive may have taken the cannabis as much as 30 days before, so that the effects would have worn off long since (DH p 240). The interpretation of traffic accident data is further confounded by the fact that 22 per cent of the drivers found to be cannabispositive also had evidence of alcohol intake; proportions of alcoholpositives among cannabispositive drivers as high as 75 per cent have been reported in other countries in similar studies. Professor Hall considers cannabis's contribution to danger on the roads to be very small; in his view the major effect of cannabis use on driving may be in amplifying the impairments caused by alcohol (cp Keen Q 42). According to a survey of 1,333 regular cannabis users by the Independent Drug Monitoring Unit (IDMU) in 1994, users who drove reported a level of accidents no higher than the general population; those with the highest accident rates were more likely to be heavier poly-drug users.

4.9 It is difficult to see how cannabis intoxication could be monitored, if its use were permitted. There could be no equivalent of the breathalyser for alcohol, since small amounts of cannabis continue to be released from fat into the blood long after any short-term impairment has worn off (see paragraph 3.5 above).

4.10 A single dose of cannabis for an inexperienced user, or an overdose for an habitual user, can sometimes induce a variety of intensely unpleasant psychic effects including anxiety, panic, paranoia and feelings of impending doom (BMA p 9, RCPsych p 282). These adverse reactions are sometimes referred to as a "whitey" as the subject may become unusually pallid (Montgomery Q 577). These effects usually persist for only a few hours.

4.11 In some instances cannabis use may lead to a longer-lasting toxic psychosis involving delusions and hallucinations that can be misdiagnosed as schizophrenic illness (Strang Q 239, van der Laan Q 512). This is transient and clears up within a few days on termination of drug use; but the habitual user risks developing a more persistent psychosis, and potentially serious consequences (such as action under the Mental Health Acts and complications resulting from the administration of powerful neuroleptic drugs) may follow if an erroneous diagnosis of schizophrenia is made. It is also well established that cannabis can exacerbate the symptoms of those already suffering from schizophrenic illness (Q 239) and may worsen the course of the illness; but there is little evidence that cannabis use can precipitate schizophrenia or other mental illness in those not already predisposed to it (RCPsych p 283).

4.12 These relatively rare adverse psychological effects of cannabis are not considered to represent a serious limitation on the potential medical use

of the drug (Strang Q 244), save that patients suffering from schizophrenic illness or other psychoses should be excluded. However they do constitute an issue for public health. According to the Department of Health, cannabis contributes to the extra cost of acute psychiatric services imposed by drug misuse, though this cannot be separately costed (p 46; cp RCPsych p 282). The Royal College of Psychiatrists (p 284) believe that the proportion of users who experience acute adverse mental effects is "significant".

Chronic (long-term) toxicity

4.13 Cannabis can have untoward long-term effects on cognitive performance, i.e. the performance of the brain, particularly in heavy users. These have been reviewed for us by the Royal College of Psychiatrists and the Royal Society. While users may show little or no impairment in simple tests of short-term memory, they show significant impairments in tasks that require more complex manipulation of learned material (so-called "executive" brain functions) (Edwards Q 21). There is some evidence that some impairment in complex cognitive function may persist even after cannabis use is discontinued[10]; but such residual deficits if present are small, and their presence controversial (van Amsterdam Q 494, Hall Q 741). Dr Jan van Amsterdam of the Netherlands National Institute of Public Health and the Environment, who has reviewed the literature on long-term cognitive effects of prolonged heavy use and kindly came to Westminster to tell us his findings, pointed out the practical difficulties of assessing possible residual effects (Q 487). These include the impossibility of obtaining predrug baseline values (i.e. measures of the cognitive functioning of the subject before their first use of cannabis), the difficulty of estimating the drug dose taken, the need for a lengthy "washout" period after termination of use to allow for the slow elimination of residual cannabis from the body, and the possibility of confusing long-term deficits with withdrawal effects. He felt that many of the published reports on this subject had not taken adequate account of these problems.

4.14 The occurrence of an "amotivational syndrome" in long-term heavy cannabis users, with loss of energy and the will to work, has been postulated. However it is now generally discounted (van Amsterdam Q 503); it is thought to represent nothing more than ongoing intoxication in frequent users of the drug (RCPsych p 283).

4.15 Animal experiments have shown that cannabinoids cause alterations in both male and female sexual hormones; but there is no evidence that cannabis adversely affects human fertility, or that it causes chromosomal or genetic damage (WHO report ch.7). The consumption of cannabis by

pregnant women may, however, lead to significantly shorter gestation and lower birth-weight babies in mothers smoking cannabis six or more times a week (WHO report ch.8; DH p 47). These effects may be due to the inhalation of carbon monoxide in cannabis smoke, which lowers the ability of the blood to carry oxygen to the foetus, rather to any direct effect of cannabinoids. If so, they are comparable with the effects of smoking tobacco.

4.16 The NHS National Teratology [i.e. foetal abnormality] Information Service advise, "There are a few case reports of malformations following marijuana use in pregnancy. However, there is no conclusive evidence to suggest either an increase in the overall malformation rate or any specific pattern of malformations". Nevertheless, they warn: "We would not recommend the legalisation of cannabis because of the potential fetotoxicity that may occur if it is used in pregnancy" (p 280).

4.17 Most of our witnesses regard the consequences of smoking cannabis as the most important long-term risk associated with cannabis use [11]. Cannabis smoke contains all of the toxic chemicals present in tobacco smoke (apart from nicotine), with greater concentrations of carcinogenic benzenanthracenes and benzpyrenes. It has been estimated (BMA p 11) that smoking a cannabis cigarette (containing only herbal cannabis) results in approximately a fivefold greater increase in carboxyhaemoglobin concentration[12], a threefold greater increase in the amount of tar inhaled, and a retention in the respiratory tract of one third more tar, than smoking a tobacco cigarette. Cannabis resin, the most commonly used form of cannabis in the United Kingdom, is often smoked mixed with tobacco, thus adding the well-documented risks of exposure to tobacco smoke, while complicating the picture for the researcher.

4.18 Regular cannabis smokers suffer from an increased incidence of respiratory disorders, including cough, bronchitis and asthma. Microscopic examination of the cells lining the airways of cannabis smokers has revealed the presence of an inflammatory response and some evidence for what may be pre-cancerous changes. There is as yet no epidemiological evidence for an increased risk of lung cancer (DH p 46, Q 205); but, by analogy with tobacco smoking, such a link may take 25-30 years or more before it becomes evident, and the widespread use of smoked cannabis in Western societies dates only from the 1970s. There are some reports of an increased incidence of cancers of the mouth and throat in young cannabis users[13], but so far these involve only small numbers and no cause and effect relationship has been established. Nevertheless, Professor Hall considers it a "pretty reasonable bet" that heavy users incur a risk of cancer (Q 741); and the risk is considered by some of our witnesses to be sufficiently serious to rule out any approval of long-term medical use of smoked cannabis, and to justify the present prohibition on recreational use.

Tolerance to cannabis

4.19 Tolerance is the phenomenon whereby a regular user of a drug requires more each time to achieve the same effect. It is not an adverse effect in itself; but it may make medical use more difficult, and recreational use more damaging as the user's demand for the drug increases.

4.20 Dr Pertwee told us that both animal and human data show that tolerance can develop on repeated administration of high doses of cannabinoids; tolerance may develop more readily to some effects in animals (e.g. lowering of body temperature) than to others (Q 304). However Clare Hodges[14], a sufferer from MS, said that she had not experienced tolerance to the palliative effects of low doses of cannabis, and had been taking the same dose (9g of herbal cannabis per week, costing about £30 per week, usually smoked) for six years; neither had other medical users reported tolerance in their experience (QQ 117-119; cp LMMSG p 269).

4.21 Whether tolerance develops may therefore depend on how much drug is consumed, and how often. Neil Montgomery, a research journalist currently studying cannabis users through the Department of Social Anthropology at the University of Edinburgh, said that his observations of heavy cannabis users (using more than 28g of cannabis resin per week) suggested that they needed as much as eight times higher doses to achieve the same psychoactive effects as regular users consuming smaller doses of the drug (Q 570). Clear evidence of tolerance has also been reported in volunteers given large doses of THC under laboratory conditions (Pertwee Q 304).

4.22 This conforms with the evidence of Professor Wall, who compared the experience with morphine and related opiate pain-relieving agents during the past 20-30 years, pioneered by Dame Cicely Saunders and the Hospice movement. This has shown that tolerance (and addiction—see below) are not major problems in the medical use of these drugs, although in recreational use they may pose severe problems (Q 120).

Dependence on cannabis

4.23 The repeated use of cannabis or cannabinoids does not result in severe physical withdrawal symptoms when the drug is withdrawn; so many have argued that these drugs are not capable of inducing dependence. Dr Pertwee, and Dr David Kendall of the University of Nottingham (p 267), however, described new evidence from animal studies showing marked signs of withdrawal in animals treated repeatedly with large doses of cannabinoids and then challenged with a newly developed cannabinoid CB1 receptor antagonist (see Box 1) called SR141716A. This has provided the first real evidence for physical dependence and withdrawal symptoms in animals (QQ 308-310).

4.24 The BMA report says that withdrawal symptoms from cannabis in man are mild and shortlived; but in the light of the newer definitions of dependence noted in Box 2 this evidence is inconclusive. Professor Ashton indicated that she felt cannabis to be potentially addictive, and compared the withdrawal symptoms—tremor, restlessness and insomnia—to those experienced by users of alcohol, sleeping pills or tranquillisers. She had talked to students with quite severe cannabis withdrawal problems (Q 73).

BOX 2: DEFINITIONS OF DEPENDENCE

The consumption of any psychoactive drug, legal or illegal, can be thought of as comprising three stages: use, abuse, and addiction. Each stage is marked by higher levels of drug use and increasingly serious consequences.

Abuse and addiction have been defined and redefined by various organisations over the years. The most influential current system of diagnosis is that published by the American Psychiatric Association (DSM-IV, 1994). This uses the term substance dependence instead of addiction, and defines this as a cluster of symptoms indicating that the individual continues to use the substance despite significant substance-related problems. The symptoms may include tolerance (the need to take larger and larger doses of the substance to achieve the desired effect), and physical dependence (an altered physical state induced by the substance which produces physical withdrawal symptoms, such as nausea, vomiting, seizures and headache, when substance use is terminated); but neither of these is necessary or sufficient for the diagnosis of substance dependence. Using DSM-IV, dependence can be defined in some instances entirely in terms of psychological dependence; this differs from earlier thinking on these concepts, which tended to equate addiction with physical dependence.

The DSM-IV system also defines substance abuse as a less severe diagnosis, involving a pattern of repeated drug use with adverse consequences but falling short of the criteria for substance dependence.

4.25 Professor Griffith Edwards, a member of the Advisory Council on the Misuse of Drugs[15] (Q 27), said that, using internationally agreed criteria (DSM-IV—see Box 2), there seemed no doubt that some regular cannabis users become dependent, and that they suffer withdrawal symptoms on terminating drug use. According to the WHO report, cannabis dependence is characterised by a loss of control over drug use, cognitive and motivational impairments that interfere with work performance, lowered self-esteem and often depression. Professor Hall wrote, "By popular repute, cannabis is not a drug of dependence because it does not have a clearly defined withdrawal syndrome. There is, however, little doubt that some users who want to stop or cut down their cannabis use find it very difficult to do so, and continue to use cannabis despite the adverse effects that it has on their lives." In oral evidence he added that users who sought treatment for cannabis dependence had typically taken large amounts of cannabis every day for perhaps 15 years or more (Q 745).

4.26 The Institute for the Study of Drug Dependence likewise conclude that, while physical dependence is rare, "Regular users can come to feel a psychological need for the drug or may rely on it as a "social lubricant": it is not unknown for people to use cannabis so frequently that they are almost constantly under the influence" (p 263).

4.27 One measure of the significance of cannabis dependence is the proportion of users who become dependent. Since cannabis dependence is poorly defined, and the total number of users is unknown, this figure is elusive. Data from a recent study of 200 regular users in Australia[16] suggest that more than 50 per cent of such users may be classified as dependent, although many of these do not consider themselves as dependent. This corresponds with the finding of an American study of 1991, cited by the WHO report, that "about half of those who use cannabis daily will become dependent". According to Professor Hall, "Epidemiological studies suggest that cannabis dependence in the sense of impaired control over use is the most common form of drug dependence after tobacco and alcohol, affecting as many as one in ten of those who ever use the drug" (p 221).

4.28 Neil Montgomery estimates that approximately 5 per cent of regular cannabis users are heavy users, consuming as much as 28g of cannabis resin per week. "These are people who have become dependent on cannabis; they are psychologically addicted to the almost constant consumption of cannabis...Becoming stoned and remaining stoned throughout the day is their prime directive" (Q 554).

4.29 Another measure of the extent of cannabis dependence is the

number of people who seek treatment for it. Department of Health figures (1996) show that in 6 per cent of all contacts with regional drug clinics cannabis was the main drug of misuse (Q 27). A similar figure, that cannabis users constitute 7 per cent of all new admissions to drug treatment centres in Australia, was reported recently. Dr Philip Robson[17], who runs a Regional Drug Dependence Unit in Oxford, said that 4.9 per cent of those admitted to his unit cited cannabis as their main drug (Q 462). However he did not regard cannabis as an important drug of addiction: "The drug falls well below the threshold of what would be expected for a dependencyproducing drug which has clinical significance...I do not meet people who are prepared to knock over old ladies in the street or burglarise houses or commit other crimes to obtain cannabis". Professor Robbins estimated that at least 2 per cent of regular cannabis users (whom he defined as those using cannabis more than once a week) in the USA are dependent, on the basis of an estimate of 5m users and an official figure of 100,000 on specific treatment for cannabis dependency syndrome (Q 623).

4.30 It has been suggested that US figures may be inflated by people on compulsory treatment, for instance after testing positive at work, who may not in fact be dependent. According to Professor Hall, however, "In Australia ... drug testing is uncommon and there is no cannabis treatment industry. Yet treatment services...have seen an increase in the number of persons seeking help for cannabis" (p 221). He even suggests that the figures may be kept down by the widespread belief that it is not possible to be dependent on cannabis (Q 748).

4.31 Giving up cannabis is widely believed to be relatively easy: according to the Department of Health, "studies report that of those who had ever been daily users only 15 per cent persisted with daily use in their late twenties" (p 45). Most epidemiological studies in Britain and the United States have shown that the illicit use of cannabis mainly involves people in their late teens and twenties, with relatively few users over the age of 30.

4.32 It has been assumed that young cannabis users give up the habit when they enter their thirties; IDMU (p 236), however, suggest that this pattern may be changing. The British Crime Survey (1996) shows that although the prevalence of cannabis use falls after the age of 30, the greatest proportional increases in the period 1991-1996 were in older age groups, with incidence of past use doubling in the 40-44 age group (from 15 per cent to 30 per cent) and trebling in the 45-59 age group (from 3 per cent to 10 per cent). IDMU conclude that the current relatively low levels of cannabis use in the over-30 age group may reflect a generational and cultural divide, rather than substantial numbers of users giving up.

4.33 It is therefore clear that cannabis causes psychological dependence in some users, and may cause physical dependence in a few. The Department of Health sum up the position thus (p 45, cp Edwards Q 28): "Cannabis is a weakly addictive drug but does induce dependence in a significant minority of regular cannabis users."

9 Including Hall W, Room R and Bondy S, A comparison of the health effects of alcohol, cannabis, tobacco and opiates, in Kallant H, Corrigan W, Hall W and Smart R eds The Health Effects of Cannabis, Addiction Research Foundation, Toronto, 1998; and articles awaiting publication in Addiction (Respiratory risks of cannabis smoking, 1998, 93, 1461), Drug and Alcohol Review, and the Lancet Seminar series (14 November 1998).

10 N Solowij, Cannabis and Cognitive Functioning, Cambridge University Press, 1998.

11 See in particular DH p 46; papers kindly supplied by Professor Donald Tashkin, University of California Los Angeles School of Medicine, and Professor Hall; and Appendix 3, paragraph 8.

12 Carboxy-haemoglobin is formed by the action of carbon monoxide on haemoglobin in the blood. It interferes with the transport of oxygen around the body.

13 E.g. Taylor FM III, Marijuana as a potential respiratory carcinogen: a retrospective analysis of a community hospital population, South. Med. J. 1988, 81, 1213.

14 Miss Hodges is the founder-Director of the UK Alliance for Cannabis Therapeutics (ACT). "Clare Hodges" is a nom de guerre.

15 Professor Edwards is Professor Emeritus of Addiction Behaviour at the Institute of Psychiatry, University of London; past Chairman of the National Addiction Centre; and editor-in-chief of the journal Addiction. The ACMD is established under the Misuse of Drugs Act 1971, to advise the Government.

16 By Dr Wendy Swift, Australian National Drug and Alcohol Research Centre.

17 Consultant psychiatrist, Warneford Hospital; senior clinical lecturer, University of Oxford; author of one of the reviews for the Department of Health referred to in paragraph 1.4.