

June 1998

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The Use of Cannabis and its Derivatives for Medical and Recreational Purposes

This document is a joint submission by the Royal Society and the Academy of Medical Sciences to the current House of Lords Science and Technology Select Committee enquiry into the science behind the arguments over the use of cannabis and its derivatives for medical and recreational purposes. It was prepared by a working group chaired by Professor P.J. Lachmann. The other members were Professor J.G. Edwards, Dr R.G. Pertwee, Professor T.W. Robbins, Dr A.S.C. Rice, Sir Richard Sykes, Professor P.D. Wall and Dr E. Fellman (Secretary). It has been endorsed by the Council of the Royal Society and by the Council of the Academy of Medical Sciences.

Introduction

In formulating this response, we considered questions posed by the House of Lords Science and Technology Select Committee. This document is a summary of the evidence; the full scientific answers to these questions are available as a separate technical annex which may be obtained from the Science Advice Section of the Royal Society.

There is much anecdotal evidence regarding the therapeutic effects of cannabis, and a clear distinction needs to be drawn between evidence from these sources and evidence from controlled clinical trials and laboratory testing. In this response, we have based our arguments as far as possible on the latter.

The physiological effects of taking cannabis

The plant, *Cannabis sativa*, contains more than 60 aromatic hydrocarbon compounds called cannabinoids. Among these, delta-9-tetrahydrocannabinol (THC) is the most studied component, and synthetic compounds based on it have been produced. THC is widely accepted as being the major psychoactive component as well as being responsible for many of the pharmacological effects.

In order to have an effect a compound needs to interact with a specific receptor in the body. Two receptors, CB1 and CB2, have been identified as interacting with THC and other cannabinoids (this is discussed fully in the separately available technical annex) although the mode of action of cannabis and its derivatives is not fully understood. Physiological effects of the cannabinoids are dependent upon whether administration is acute or chronic as well as the dose and type of administration.

Physiological effects associated with cannabis use include: reductions in psychomotor coordination, performance and motor function; tachycardia (raised pulse rate); lowered blood pressure on standing (at higher doses); alterations in thermoregulation, in endocrine and reproductive function and in gut motility; inhibition of neurotransmitter release; analgesia; enhanced appetite and bronchodilation.

The psychological effects of taking cannabis

Psychological effects, as with physiological effects, will vary with dose and whether use is acute or chronic. A sense of euphoria is felt by regular cannabis users, intermittent users tend not to feel euphoric, but lose co-ordination instead. Higher doses of cannabis produce loss of concentration and drowsiness, and cause perceptual changes that may result in dysphoria.

Cannabis can have a marked, but short-term, effect on psychomotor performance (for example, on driving-related tasks such as reaction time). It can also affect attention and short-term memory performance (and perhaps therefore impair learning).

There is evidence for some long-term adverse effects on cognition but these are subtle and occur against a backdrop of little sign of major impairment across most of the cognitive domains investigated.

Cannabis can induce dose-related, short-term mental disturbances; effects include anxiety, panic, paranoid delusions, feelings of unreality, and distortions in perception. In the majority of instances, these disturbances are quickly recovered from and not repeated.

There is no firm evidence that long-term cannabis use induces psychiatric disturbance. Cannabis exposure has been reported to be a risk factor for schizophrenia, but causal links between the two have not been established with certainty.

Variation of effects with methods of preparation and administration

Cannabis is usually smoked or taken orally. Smoke from herbal cannabis contains similar toxic constituents to cigarette smoke. Oral doses give unpredictable effects due to variations between patients in absorption from the gastro-intestinal tract. More reliable formulations and modes of administration are needed; nothing approaching a pharmaceutical grade resin has ever been defined and the very large number of constituents could present major difficulties.

The dependence and tolerance potential of cannabis

Cannabis has a dependence potential, and evidence suggests that tolerance to both the physical and subjective effects of cannabis can occur. (One should be aware that other potentially addictive drugs with medical benefits are currently available, and these include the opioids and benzodiazepines).

Cannabis use as predisposition to later use of heroin: Suggestions are sometimes heard that cannabis may in a causal sense lead on to the taking of heroin. That in the UK a strong statistical relationship exists between prior use of cannabis and later use of heroin is undoubted, but the first drug used by people who go on to heroin is nearly always alcohol or nicotine, rather than cannabis. There is no plausible biological mechanism to support the idea of cannabis as a gateway to opiates. The dealer from whom cannabis is bought is unlikely also to be offering heroin so there is no strong explanation for linkage to be found at the social level. Thus although the idea that cannabis use can predispose to later use of heroin is difficult to disprove there is no convincing evidence to support this hypothesis.

Evidence for valuable medicinal actions

The active ingredient of cannabis, THC, and other cannabinoid compounds are being used to treat a variety of disorders. Drugs which selectively activate CB1 or CB2 receptors have already been developed.

Emesis: Dronabinol (synthetic THC in sesame oil) was approved in the US for the treatment of nausea induced by treatments such as cancer chemotherapy. In the UK, nabilone, a synthetic analogue of THC, is licensed for similar use.

Pain: Many currently available analgesic drugs have serious side effects and are not always effective in the treatment of pain, particularly neuropathic pain, which is resistant to the analgesic effects of opioids. Hence, there is a clinical need for the development of novel

analgesic drugs. Various cannabinoids produce inhibition of pain responses. At present, there is laboratory evidence which supports an analgesic effect of cannabinoids, but there is no reliable human clinical evidence to support or refute claims of cannabinoid induced analgesia. Limited trials and anecdotal evidence suggest further clinical and laboratory study is needed. Recent work has shown that some of the analgesic effects of cannabinoids may be related to CB1 and CB2 receptors located outside the central nervous system. With further research, this could result in the development of cannabinoid analgesics which have no central nervous system side effects.

Spasticity: Spasticity is commonly seen in patients with multiple sclerosis, stroke, cerebral palsy or spinal injury. Animal experiments have shown that cannabinoids suppress spinal reflexes. The use of cannabinoids for multiple sclerosis and spinal injury is promising; THC significantly reduced spasticity in patients not presenting with cerebellar disease. There is much anecdotal evidence and also some limited data from controlled clinical trials that cannabinoids can reduce the intensity of some of the symptoms of multiple sclerosis and spinal injury. However, better designed more extensive clinical trials are now needed to test these uses more conclusively.

Glaucoma: Raised intra-ocular pressure (glaucoma) can produce irreversible damage to the optic nerve and can cause blindness. There is good evidence that cannabinoids can lower intra-ocular pressure, although the site and optimal administration route are not yet established.

Bronchial asthma: Cannabinoids show promise for the treatment of the early phase response of asthma, the phase in which the small tubules in the lungs (bronchioles) narrow as a result of exposure to certain allergens. Cannabinoids can significantly dilate the bronchioles of both healthy and asthmatic subjects and seem to be no less effective than conventional drug treatments. Further studies are required to improve cannabinoid formulation for administration as an aerosol.

Appetite: Dronabinol can be prescribed in the US as an appetite stimulant in cancer patients and to treat weight loss in AIDS patients.

The strength of the scientific evidence in favour of permitting medical use

While there is evidence to suggest beneficial therapeutic effects from taking cannabis in relieving spasticity (particularly in multiple sclerosis), as an analgesic, as an anti-emetic, an appetite stimulant and as a bronchodilator, there is a dearth of data from randomised clinical trials. The risks and benefits of using cannabis for these various indications need to be properly evaluated for cannabis itself and for the individual cannabinoids to establish whether they have a useful role in clinical practise. Until such studies have been made, there is no persuasive case for the non-experimental medical use of cannabis.

The strength of the scientific evidence in favour of maintaining prohibition of recreational use

Our concern is only to show how science can illuminate discussion of this question rather than to put forward any particular view.

We are confident that evidence exists that cannabis use can give rise to various types of physical and psychological problems. Most individual risks, whether acute or chronic, are likely to have a dose-response relationship with level of cannabis use. Population levels of use for cannabis are likely to have a bearing on public health. Removing the prohibition on cannabis would have uncertain effects, although some harm and some added costs would undoubtedly result. The size of the impact on the nation's health cannot be inferred from reference to existing scientific evidence. It is for government to decide whether there are sufficient societal advantages to balance the risks of removing prohibition.

Conclusions

In any debate, we believe that the issues of clinical use of cannabis and its derivatives should be uncoupled from the issues of recreational use.

There is substantial anecdotal as well as a limited amount of more objective evidence that cannabinoids are clinically effective in certain conditions e.g. pain, spasticity and emesis. However, the effects of cannabis in various disease states may not be straightforward. Several components of cannabis might be required to reproduce the effects seen with the whole drug.

We do not consider that the current medical data on efficacy and safety from randomised controlled trials are sufficient to support the medical prescribing of cannabis as yet. This is due to the psychoactive and physiological side-effects and the evidence that tolerance and mild dependence can occur (dronabinol and nabilone, which are currently used clinically, are both psychotropic cannabinoids that probably induce tolerance and dependence). Furthermore, we do not support the notion of smoking cannabis for medical purposes; smoke from herbal cannabis contains toxic substances similar to those from cigarette smoke. We suggest that further controlled clinical trials and laboratory research be conducted with cannabinoids under carefully defined circumstances (in whatever forms or routes of administration) and should include isolated single components of cannabis (e.g. THC), extracts of herbal cannabis, as well as selective CB1 and CB2 compounds. A thorough comparison of the resulting data would help to define the role of individual compounds and receptors, help to improve modes of administration and formulation, and possibly aid in the development of safer, more specific therapies for conditions that are currently poorly treated.

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ANNEX A

Membership of working group

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ANNEX B

SCIENTIFIC EVIDENCE

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1. What are the physiological effects of taking cannabis in its various forms?

Detailed reviews of the physiological effects have been carried out by Paton and Pertwee (1973a, 1973b) and Pertwee (1988, 1997a).

1.1 The plant *Cannabis sativa* is the unique source of a set of more than sixty oxygen-containing aromatic hydrocarbon compounds called cannabinoids. Among these is D^9 -tetrahydrocannabinol to which most of the known pharmacological properties of cannabis can be attributed. It is now known that the main effects of D^9 -tetrahydrocannabinol are mediated by specific cannabinoid receptors, two types of which have so far been identified. These are CB1 receptors, discovered in 1990, and CB2 receptors, discovered in 1993. Both of these receptor types are coupled to their effector systems through $G_{i/o}$ proteins. CB1 receptors are present in the central nervous system as well as in certain neuronal and nonneuronal peripheral tissues whereas CB2 receptors are found mainly in cells of the immune system. The possibility that mammalian tissues express additional cannabinoid receptor types of physiological significance cannot be excluded. Indeed, preliminary pharmacological evidence that supports this possibility already exists. Another important recent discovery has been that mammalian tissues also produce compounds that can activate cannabinoid receptors, the most important being arachidonylethanolamide (anandamide) and 2-arachidonoyl glycerol. These "endogenous cannabinoids" and their receptors constitute the "endogenous cannabinoid system". Further details about the pharmacology of cannabinoids and their receptors can be found in a recent review (Pertwee, 1997a).

1.2 The distribution pattern of CB1 receptors within the central nervous system is heterogeneous, unlike that for any other receptor type and consistent with the known ability of cannabinoid receptor agonists to impair cognition and memory, to alter motor function and movement and to relieve pain (see below). The highest concentrations of cannabinoid binding sites in the brain are in the basal ganglia (substantia nigra pars reticulata, the entopeduncular nucleus, the globus pallidus and the lateral caudate-putamen). Other areas of the brain quite rich in cannabinoid binding sites include the hippocampus, cerebral cortex, intrabulbar anterior commissure, nucleus accumbens, septum, olfactory bulb and molecular layer of the cerebellum. Among areas of the brain less densely populated with cannabinoid binding sites are the central gray substance, the area postrema, the caudal nucleus of the solitary tract, the amygdala, thalamus, habenula, preoptic area and hypothalamus, and much of the brain stem. Regions of the spinal cord that are richest in cannabinoid binding sites are lamina X and the substantia gelatinosa.

1.3 Some CB1 receptors occur at central and peripheral nerve terminals and these are known to reduce transmitter release when activated. Hence one of the physiological roles of these receptors is probably to modulate the release of central and peripheral neurotransmitters in certain pathways.

1.4 Little is yet known about the physiological role(s) of the more recently discovered CB2 receptor although it seems likely that this will prove to involve modulation of immune function in health and/or disease. It is vital that further research is funded to elucidate the physiological and pathophysiological role(s) of this receptor type as this may well reveal important new clinical

applications for cannabinoid receptor agonists or antagonists. Additional research is also urgently needed to establish the mechanisms underlying effects of cannabinoids of known or potential therapeutic value: it is noteworthy that almost nothing is known even about the mechanisms underlying the two effects of cannabinoids that it already is permissible to exploit for therapeutic purposes in the UK or USA: antiemesis and appetite stimulation (see below).

1.5 The effects of cannabis that make up a 'high' consist essentially of changes in perception, mood, emotion and cognition. Thus, after cannabis has been taken there are reports that colours seem brighter and music more pleasant and that 'felt time' passes more slowly than 'clock time'. Effects on mood and emotion vary. Usually there is some euphoria. Sometimes, however, particularly in the inexperienced, mood may be unaffected or there may be dysphoria or anxiety. More serious adverse psychopharmacological responses may occur, in particular panic reactions and psychoses. Signs of changed cognitive functions include difficulty in concentrating and thinking and impairment of memory. The 'high' is usually followed by a period of drowsiness.

1.6 Associated with the 'high' are reductions in psychomotor coordination, performance and motor function and changes in autonomic processes. The most prominent autonomic changes are cardiovascular, in particular tachycardia, postural hypotension, supine hypertension and conjunctival hyperaemia. There is now also evidence that endothelium derived hyperpolarizing factor may be an endogenous cannabinoid - i.e. that one physiological role of endogenous cannabinoids may be to regulate blood flow through resistance vessels. Other changes in autonomic function that can be caused by cannabis or psychoactive cannabinoids include alterations in thermoregulation, in endocrine and reproductive function and in gut motility. More detailed descriptions of the pharmacological effects of cannabis and cannabinoids, both *in vivo* and *in vitro*, are to be found elsewhere (Paton & Pertwee, 1973a, 1973b; Pertwee, 1988, 1997a).

1.7 The part played by cannabinoid receptors in the production of some of the effects of cannabis/cannabinoids in the whole organism remains to be established. Among the effects of cannabinoids already known from animal experiments to be mediated by CB1 receptors are antinociception (analgesia) and changes in memory, motor function (hypokinesia and catalepsy), thermoregulation (hypothermia), memory, gut motility (inhibition) and transmitter release (inhibition).

1.8 On repeated administration to animals or man, cannabis can give rise to tolerance and dependence. The tolerance seems to be mainly pharmacodynamic in nature, resulting far more from adaptive changes within the brain than from changes in cannabinoid disposition or metabolism. There is evidence to suggest that it stems at least in part from a decrease in cannabinoid receptor density. Cannabinoid tolerance and dependence are discussed in greater detail in section 4.

2. What are the psychological effects of taking cannabis in its various forms?

Psychological (cognitive) effects of cannabis

2.1 Acute effects

2.1.1 Subjective and behavioural

Behavioural effects include increased tendencies to hyperactivity and laughter and talkativeness in social situations, although the discourse may not always make sense, Appetite for food and

drink is enhanced. These effects are often experienced in a relatively calm, relaxed, or even dream-like subjective state, although they can be opposed by anxiety and restlessness. Sensory effects include feelings of 'lightheadedness', floating sensations, hyperacuity of visual and auditory perception, visual illusions and a marked perception of the slowing of the passage of time (Tart 1971; Grinspoon, 1977). These effects are generally dose-related and produced by the active constituent delta-⁹-tetrahydrocannabinol. Higher doses can lead to strong feelings of panic or anxiety, paranoid reactions, and at very high doses, a state of delirium (Hollister 1986). However, the concept of a cannabis-induced state of psychosis is controversial (Thomas, 1993).

2.1.2 Experimental investigations of cognitive function

Cannabis can have marked deleterious effects on psychomotor performance, for example in driving, flying aeroplanes, and the operation of heavy machinery. Even experienced users are impaired with intermediate and high doses on difficult driving-related tasks such as tracking, reaction time, and divided attention (Barnett, Licko and Thompson, 1985). Substantial deficits were seen on all measures and performance was not restored to normal levels until about 10-12 hrs after smoking a single standardized marijuana cigarette. However, it is unlikely that cannabis at present is a major risk factor in car accidents (Gieringer 1988).

Acute cannabis has been reported to impair attentional and memory performance, when administered to cannabis experienced volunteers in the form of a standard marijuana cigarette containing delta-9-tetrahydrocannabinol (THC, 1.2%, by weight) (Hooker and Jones, 1987). Placebo cigarettes contained no THC but were otherwise identical, so THC can be assumed to have been the active constituent. Retrieval of lists of words in verbal free recall tasks was particularly affected by increased interference from incorrect items. The Stroop interference test of selective attention was also impaired. However, sustained attention, retrieval from semantic memory and the speed of reading and naming colours was unaffected.

There is some evidence for tolerance to acute effects on cognition in heavy cannabis smokers (Cohen and Rickles, 1974).

2.2 Chronic effects

2.2.1 Experimental investigations of cognitive function

Users may consume cannabis on daily basis for many years. There is evidence for some long term adverse effects but these are subtle and occur against a backdrop of little sign of major impairment across most of the cognitive domains investigated (for considered reviews, see Pope et al, 1995; Wert and Raulin, 1986). In one well-executed study, Block and Ghoneim (1993) did demonstrate that heavy marijuana use (>7 times per week for an average of 6 years) in young (predominantly male) adults produced small but significant impairments in memory retrieval (Bushke test), verbal expression and mathematical ability, compared with a well-matched group of non-users. However, they also reported some small **improvements** in a test of concept formation at an intermediate dose. Differences in alcohol use or other, illicit drugs between these two groups were shown not to have contributed to these effects. It is possible, though unlikely, that the effects arose from residual effects of cannabis outlasting the enforced period of abstinence (24h). Solowij (1995) has shown deficits in selective attention and evoked potentials in ex-cannabis users, abstinent from periods of 6 months to 3 years. Fletcher, Page and Francis (1996) also report long-term deficits in older cannabis users on certain tests of attention, involving divided or selective attention, and on short term ('working') memory tasks.

They emphasise that the deficits are much more subtle than those found, for example, in dementing or amnesic disorders.

In these controlled studies there has not been much information on individual differences, or gender and age-related modulation of these effects. Nor has there been systematic analysis of the effects of modes of preparation and administration of cannabis, and its various constituents.

2.2.2 Relationship to brain cannabinoid receptors

The pattern of cognitive impairment described does not relate especially clearly to the distribution of cannabinoid receptors in the brain, but is by no means inconsistent with it. There has not yet been any study of the effects of the new cannabinoid receptor antagonists on cognitive function in man, although these are being developed as appetite suppressant and cognitive enhancing compounds, presumably for the treatment of dementia.

An extensive study by Kalant and colleagues (e.g. Stiglick and Kalant, 1982) on effects of chronic exposure to marijuana extract in rats for 90 or 180 days showed evidence of impaired spatial learning, impaired timing behaviour, hyperactivity, but enhanced avoidance learning- all symptoms associated with damage to the hippocampal formation, where cannabinoid receptor densities are high.

2.3 Other psychological effects (non-cognitive)

2.3.1 Cannabis is likely to produce euphoria, relaxation, a feeling of being "spaced out" and a keener appreciation of the sensory environment, and it is for those reasons that it is taken (WHO 1997). Rather easily these wanted experiences mix with or shade over toward feelings of anxiety, dysphoria and suspiciousness (WHO 1977). A few mildly bad experiences are unlikely to put the cannabis taker off continued use, but more flagrant bad experience may be a reason for quitting.

Short-term psychiatric mental disturbance

Cannabis can induce mental disturbance lasting between, say, a few hours and 36 hours,. Such episodes are likely to be distressing and will for this period put the user more or less out of touch with reality: the clinical picture will typically include anxiety or panic, paranoid delusions, feelings of unreality, and distortions in perception (Chopra 1974, Rottanburg 1982, Ghodse 1986, Chaudry et al 1991). Recovery is likely to be complete other than perhaps for later transient experience of flashbacks (Edwards 1983). The existence of this syndrome is well authenticated and although it is not possible to put a precise figure on the frequency of its occurrence, it is not uncommon in any country where cannabis is widely used: psychiatrists working on an emergency admission service will be alert to the existence of this syndrome (Mathers et al 1991). The condition is probably dose-related, but there may also be idiosyncratic vulnerability.

A question then arises as to the level of social concern which should attach to the potential of this drug to produce this kind of short-lived adverse event. On the one hand it should be noted that in the great majority of instances the disturbance is quickly recoverable and without sequelae. On the other hand loss of contact with reality must in principle be expected to carry some small but uncertain risk for the user and other people, and a demand on health service resources is created. To the extent that such reactions are dose-related, the dissemination of techniques of inhalation such as the "hot knives" technique which involves massive inhalation of cannabis through a funnel may carry added danger.

The possibility of somewhat longer term cannabis-induced psychiatric disturbance

With chronic heavy use of this potentially cumulative drug a chronic intoxication may be induced and it is not unreasonable to expect that continuing psychotic disturbance might be an accompaniment, with the symptoms clearing only some time after the drug is stopped and while cannabis cleared from the system (Ghodse 1986). The existence of this syndrome is however only conjectural.

Cannabis and schizophrenia

A Swedish study (Andreasson et al 1997) showed that at a 15 year follow-up of a cohort of young males, those who were frequent users of cannabis at base point later experienced a six-fold increase in relative risk of developing schizophrenia compared with the earlier non-users. That is a statistically significant finding, but other obvious explanations besides causality can be envisaged. The evidence that cannabis can destabilise pre-existing and otherwise successfully treated schizophrenia is more persuasive (Negrete et al 1986, Cleghorn et al 1991), and can be a matter of clinical concern for those who treat this condition.

3. How do the effects vary with particular methods of preparation and administration

3.1 Cannabis is usually smoked or taken by mouth (as dried plant material or using the sticky resin that is secreted by the plant). Cannabis leaves or cannabis resin are sometimes taken orally in cakes or fudge or as a drink. Tincture of cannabis (a solvent extract of cannabis that it was permissible to prescribe in the UK until 1971), was of course also taken orally. The licensed medicines, D⁹-tetrahydrocannabinol (dronabinol) and nabilone (see section 3), are both taken by mouth.

3.2 As far as the clinical use of cannabinoids is concerned, there is a need for better formulations and modes of administration (Pertwee, 1997b). Thus when taken orally, D⁹-tetrahydrocannabinol seems to undergo somewhat variable absorption from the gastrointestinal tract and to have a rather narrow "therapeutic window" (dose range in which it is effective without producing significant unwanted effects) (Pertwee, 1997b). For example, in a clinical study with two multiple sclerosis patients, D⁹-tetrahydrocannabinol was effective in one of the patients at an oral dose of 5 mg whilst in the second patient it was effective only when the dose was raised to 15 mg (both 5 mg and 10 mg D⁹-tetrahydrocannabinol were ineffective in this patient). In another clinical study in which eight multiple sclerosis patients were given D⁹-tetrahydrocannabinol or placebo by mouth, both 2.5 and 5 mg D⁹-tetrahydrocannabinol were ineffective in relieving spasticity, 7.5 mg was effective and 10 mg was intolerable to some of the patients (narrow 'therapeutic window'). The existence of a large inter-patient variation in the oral dose level of D⁹-tetrahydrocannabinol that is effective combined with a very narrow "therapeutic window" for oral D⁹-tetrahydrocannabinol makes it difficult to predict an oral dose of this drug that will be both effective and tolerable to a patient.

3.3 Possible alternative modes of cannabinoid administration are by rectal suppository (Brenneisen et al., 1996), by skin patch, by direct application to the eye (for glaucoma) or by aerosol inhalation (see also Sections 5.4 and 5.5).

4. To what extent is cannabis addictive? To what extent do users develop tolerance to cannabis?

4.1 There is evidence that tolerance to both physiological and subjective effects of cannabis can occur in the human subject (Georgotas and Zeidenburg 1979, Compton et al 1990), and a withdrawal syndrome has been described (Jones and Benowitz 1976). Although those findings are of interest, neither induction of tolerance nor the occurrence of withdrawal symptoms are by

themselves sufficient criteria to conclude that a drug has significant dependence potential in a meaningful, clinical sense. Within the present-day concept of dependence (Edwards et al 1981, American Psychiatric Association 1994), the essential question which has to be asked is whether cannabis use can lead to a strong habit, a drug-centredness, and a difficulty in giving up despite a wish so to do. That common-sense approach has then to be operationalised for purpose of research (Anthony and Hezler 1991). Seen within that kind of perspective there is now strong evidence that a clinical syndrome of cannabis dependence exists and that something between 5-10% of long term cannabis users will develop dependence (see Hall et al 1994 for a review), but that figure will be influenced by dosage levels and patterns of use within any given study population. That prevalence figure is probably at rather the same level as life time prevalence of alcohol dependence among people who drink alcohol (Edwards et al 1994), but with heavier per capita use of cannabis a higher prevalence of dependence might be expected.

4.2 The practical significance of the conclusion that cannabis has a dependence potential needs to be considered critically. Dependence is not itself intrinsically harmful but it may carry with it certain risks or problems:-

People who are dependent on cannabis are likely to achieve and maintain higher levels of use than non dependent subjects: if risk attaches to that kind of use, dependent subjects will be at enhanced risk (Troisi et al 1998).

The drive toward drug-taking motivated by the dependence will mean that dependent subjects will tend to ignore or play down adverse consequences, educative input, informal pressures from friends or family, and formal social controls.

People who become dependent may however eventually not like the state that they find themselves in and the feeling of loss of personal control which is intrinsic to this state. They may then seek professional help with consequent health service costs. So salient has this issue become that the National Institute of Drug Addiction (NIDA) in the USA is currently funding a multi-centre trial on treatment of cannabis dependence, while recent data from the UK's regional drug data bases (Home Office 1998) shows that 6% of individuals attending drug agencies in this country today identify cannabis as their primary drug of misuse (1836 new agency contacts over a six month period). Reports on people seeking help for their cannabis dependence have come from Australia (Didcott et al 1988), Sweden (Tunving et al 1998) and the USA (Jones 1984).

In sum we conclude under this heading that dependence on cannabis is a clinical reality and one with personal and social implications.

5. What is the evidence that cannabis in its various forms has valuable medical actions? In the treatment of which diseases? How rigorous is the evidence? Is there a case for promoting clinical trials even if the current level of control is maintained?

Medical uses are also summarized in: Hollister, 1986; British Medical Association, 1997; Pertwee, 1997b.

5.1 As well as having physiological importance, the discovery of the endogenous cannabinoid system has significant pharmacological and therapeutic implications. Indeed, drugs that selectively activate CB1 or CB2 receptors (agonists) or selectively block one or other of these receptor types (antagonists) have already been developed. Moreover, one cannabinoid receptor agonist, nabilone (Cesamet ®), is currently used clinically in the UK. This drug, a synthetic analogue of D⁹-tetrahydrocannabinol, is licensed for use as a suppressant of nausea

and vomiting provoked by anticancer drugs. In the USA, D⁹-tetrahydrocannabinol itself is prescribed for this purpose and also to boost the appetite of AIDS patients and so reduce or reverse loss of body weight. The formulation used, D⁹-tetrahydrocannabinol in sesame oil, is called dronabinol (Marinol ®). The introduction into the clinic of D⁹-tetrahydrocannabinol and nabilone as antiemetics preceded the development of ondansetron and no clinical studies directed at comparing the efficacy of this excellent new anti-emetic with that of D⁹-tetrahydrocannabinol or nabilone have yet been carried out. The licensed use of cannabinoids as antiemetics/appetite stimulants will not be discussed further in this document as it is presumably not a contentious issue.

5.2 As detailed elsewhere (Hollister, 1986; British Medical Association, 1997; Pertwee, 1997b), additional therapeutic uses of cannabinoid receptor agonists may include the suppression of some symptoms associated with multiple sclerosis, with spinal injury and with certain other movement disorders (e.g. muscle spasticity/spasm) and the management of glaucoma, bronchial asthma, pain and inflammatory disorders. The CB1 receptor antagonist, SR141716A, may also have therapeutic potential, for example in reducing memory deficits associated with ageing or neurological diseases (Pertwee, 1997a). The evidence supporting the use of cannabinoids for multiple sclerosis and spinal injury, for pain, for primary open-angle glaucoma and for bronchial asthma is particularly promising and is therefore discussed further below.

5.3 The evidence that cannabinoids would be effective in relieving spasticity, tremor and pain caused by multiple sclerosis or spinal injury is based on preclinical, anecdotal and clinical data (see Pertwee, 1997b for references). More specifically, animal experiments have shown that cannabinoid receptor agonists suppress spinal reflexes, produce marked behavioural changes in motor function, for example hypokinesia and catalepsy, and have significant efficacy in standard tests of antinociception (see also section 5.11-5.13). The effects on motor function are no doubt mediated at least in part by the large populations of cannabinoid CB1 receptors that are present in the basal ganglia of the brain (see para 1.2). Whether cannabinoids produce their putative antispasticity effect by acting at these brain sites remains to be established. There is also good evidence that cannabinoid-induced antinociception is centrally mediated, in this case at sites within both brain and spinal cord (see also section 5.11-5.13). In addition, experiments with rats and guinea-pigs have shown that tetrahydrocannabinol can delay the onset and reduce the intensity of the clinical signs of experimental autoimmune encephalomyelitis, a putative animal model of multiple sclerosis. Also relevant is a report that the synthetic cannabinoid receptor agonist, WIN55212-2, can decrease the severity of dystonia in mutant Syrian hamsters with primary generalized dystonia. As to the anecdotal data, these are to be found in numerous newspaper reports and also in responses to a recent questionnaire we distributed to multiple sclerosis patients who self-medicate with cannabis (Consroe et al., 1997). Of the 112 subjects in this survey who were experiencing the following symptoms, the percentage reporting improvement after taking cannabis was 96.5% for spasticity at sleep onset, 95.1% for pain in muscles, 93.2% for spasticity when waking at night, 92.3% for pain in the legs at night, 90.7% for tremor of arms/head and 90.6% for depression. The numbers of subjects reporting these symptoms were respectively 86, 61, 59, 52, 43 and 74. Because this survey targeted multiple sclerosis patients who self-medicate with cannabis, the data it generated cannot be used to predict the proportion of all multiple sclerosis patients who might benefit from cannabis. The clinical data supporting the use of cannabinoids for multiple sclerosis or spinal injury come from seven clinical trials, albeit with rather small numbers of patients. These indicate that cannabis, D⁹-tetrahydrocannabinol or nabilone can reduce the intensity of at least some signs and symptoms of multiple sclerosis or spinal injury, particularly spasticity, pain, tremor and nocturia.

Additional clinical evidence that cannabinoids are analgesic is described by section 5.11-5.13. Better designed, more extensive clinical trials are now needed that will test the efficacy of cannabis or individual cannabinoids against signs and symptoms of multiple sclerosis and spinal injury more conclusively.

5.4 Raised intraocular pressure (glaucoma), if not checked, will produce irreversible damage to the optic nerve that will eventually lead to blindness. The most common form of this disorder is primary open-angle glaucoma, also known as chronic simple glaucoma. This is characterized by a gradual loss of both visual acuity and peripheral vision, by a blurring of vision and by the appearance of coloured haloes around bright objects. There is good evidence from experiments with animals, healthy human subjects and patients with primary open-angle glaucoma that cannabinoids can lower intra-ocular pressure (Green, 1998). The site and mode of action of cannabinoids for depression of intra-ocular pressure remain to be established as does the question of the optimal route of cannabinoid administration for glaucoma. Cannabinoids can reduce intra-ocular pressure when applied directly to the eye. However, one practical limitation when this route is used is the lack of a suitable drug vehicle. (Vehicles that have been used in experiments induce copious tear production in human subjects) (Green, 1998). Another potential problem is cannabinoid tolerance as the need for intra-ocular pressure to be kept within safe limits at all times dictates that glaucoma patients be continuously exposed to effective concentrations of their treatment drug.

5.5 Bronchial asthma is often characterized by early and late phase responses. In the early phase response, there is a narrowing of the small tubules in the lungs called bronchioles. This bronchospasm, which produces a marked increase in airflow resistance, may be caused by allergens such as pollen or house dust or by other kinds of stimuli, for example cold air, infections of the respiratory tract or emotional stress. In the late phase response, there is an acute bronchial inflammatory reaction leading to the production of mucus. Cannabinoids show promise for the treatment of the early phase response of asthma. Thus they can significantly dilate the bronchioles of both healthy and asthmatic subjects and seem to be no less effective than conventional drug treatments of asthma (Hollister, 1986; British Medical Association, 1997). Both cannabis and individual cannabinoids are active when taken orally or when inhaled, either in smoke or in an aerosol produced by a nebulizer or Ventolin inhaler (Williams et al., 1976; Tashkin et al., 1977; Hollister, 1986; British Medical Association, 1997). It is noteworthy that in one study (Tashkin et al., 1977), Δ^9 tetrahydrocannabinol administered as an aerosol induced bronchoconstriction, coughing and chest discomfort in 2 out of 5 asthmatic subjects. The mechanisms underlying the bronchodilator effect of cannabinoids remain to be established. However, only cannabinoids with psychotropic properties have so far been found to produce bronchodilation (Hollister, 1986), indicating that the effect may be cannabinoid receptor-mediated. One important priority for any further studies is the development of an improved cannabinoid formulation for administration as an aerosol.

5.6 Like all other drugs, cannabis and cannabinoids can give rise to unwanted effects. However, the known adverse effects of cannabinoids seem to be no worse than those of some accepted therapeutic agents. In one clinical trial with 34 cancer patients (see Pertwee, 1997b), the most commonly reported unwanted symptoms produced by Δ^9 -tetrahydrocannabinol were dizziness, sedation and dry mouth (more than 75% of subjects), blurred vision (65% of subjects), mental clouding (53% of subjects) and ataxia, numbness, disorientation, disconnected thought, slurred speech, muscle twitching and impaired memory (27 to 44% of subjects). In addition, cannabis may sometimes induce transient confusion, panic attacks, depersonalization, paranoid delusions and/or hallucinations (Paton & Pertwee, 1973b; Paton et al., 1973; Chopra & Smith, 1974;

Tennant & Groesbeck, 1977; Chaudry et al., 1991). Cannabis has also been reported to produce a subtle impairment of postural control (see Pertwee, 1997b).

5.7 Some individuals may be more at risk from the adverse effects of cannabinoids than others (Hollister, 1986; Pertwee, 1997b). For example, cannabis may aggravate existing psychoses and can elevate heart rate. Consequently it would be unwise to give psychotropic cannabinoids to patients with schizophrenia (overt or latent), coronary arteriosclerosis or congestive heart failure. The clinical significance of the ability of cannabinoids to retard foetal development, to induce foetal resorption in animals or to suppress immune function remains to be established.

5.8 Because of the tars and gases produced during the combustion process, smoked cannabis is toxic to airway tissue and probably also carcinogenic (Hollister, 1986; British Medical Association, 1997; Roth et al., 1998). However cannabis is also active orally (see section 2).

5.9 Centrally active CB1 receptor agonists have the disadvantage of maximizing the incidence of adverse effects by producing indiscriminate activation of all CB1 receptors. One solution could be to develop drugs that activate the endogenous cannabinoid system indirectly by selectively inhibiting the tissue uptake or metabolism of endogenous cannabinoids so as to increase their concentrations at cannabinoid receptors. This strategy relies on the likelihood that such drugs will not affect all parts of the endogenous cannabinoid system at one time but rather produce effects only at sites where there is on-going production of endogenous cannabinoids. Drugs that inhibit one or other of the processes responsible for the removal of endogenous cannabinoids from the extracellular space already exist (Pertwee, 1998a). This and other possible strategies for improving the benefit to risk ratio of cannabinoids are detailed elsewhere (Pertwee 1996, 1998a,b).

5.10 In conclusion, there is sufficient evidence to warrant additional clinical studies with cannabinoids for the management of several disorders, including multiple sclerosis, spinal injury, glaucoma, bronchial asthma and pain. These studies should be directed at providing objective and conclusive answers to the following questions. First, do cannabinoids have efficacy against selected symptoms that is of clinical significance and, if so, do the benefits outweigh the known risks? Second, does cannabis (or a mixture of two or more cannabinoids) have any therapeutic advantages over individual cannabinoids such as D⁹-tetrahydrocannabinol? Third, is there a significant need for additional drug treatments to manage any of the disorders against which cannabinoids may prove to be effective? Additionally, it will be important to search for better cannabinoid formulations and modes of administration. To succeed, clinical studies with cannabinoids will require adequate funding, the availability of appropriate outcome measures and the committed involvement of scientists and physicians with appropriate cannabinoid and clinical expertise.

5.11 Analgesic effects

5.12 Laboratory evidence of cannabinoid-induced analgesia.

There is a substantial body of evidence from laboratory research which suggests that various cannabinoids possess analgesic effects. However, much of this evidence is based on experiments which examined the responses of laboratory animals to ephemeral noxious stimuli (e.g. the tail flick test). Whilst of physiological interest, and heavily utilised in the pharmaceutical industry, these tests are unsatisfactory as models of clinical pain. The results of experiments which employed clinically relevant models of inflammatory (Mazzari et al 1996, Richardson et al 1998, Jagger et al 1998, Tsou et al 1996) or neuropathic (neuralgic)(Herzberg et al, 1997) pain are now appearing and generally support the concept of cannabinoid-induced analgesia.

Whilst most of the studies of cannabinoid analgesia have examined the neuronal (CB1) receptor, it is now becoming clear that the CB2 receptor may also play a role in analgesia.

CB2 receptors are located on cells of immune origin, including mast cells, which are pivotal in the development of the hyperalgesia (tenderness) which develops around an area of tissue injury. Endogenous CB2 agonists attenuate the development of inflammatory hyperalgesia by participating in the process of "autacoid local inflammation antagonism" (Mazzari et al 1996, Jagger et al 1998, Levi-Montalcini et al 1996).

An intriguing body of evidence is emerging which suggest that a proportion of the analgesic effects of the cannabinoids may be mediated by CB1 and CB2 receptors located without the central nervous system (Mazzari et al 1996, Richardson et al 1998, Jagger et al 1998). Exploitation of this effect could conceivably result in the development of cannabinoid analgesics devoid of central nervous system side-effects, but further research is required.

Recent advances in cannabinoid pharmacology (including the discovery and cloning of CB1 and CB2 receptors, the development of specific receptor antagonists and the engineering of genetically modified mice in which the genes encoding cannabinoid receptors are disrupted) have provided tools which will allow further elucidation of the analgesic effects of cannabinoids in the laboratory.

More laboratory research is required to fully elucidate the mechanism of cannabinoid- induced analgesia. The experimental tools required to achieve this are now becoming available.

5.13 Clinical evidence for an analgesic effects of cannabinoids (British Medical Association, 1997).

For doctors, the current choice of analgesic drugs is essentially restricted to paracetamol, or derivatives of aspirin (non-steroidal analgesics) or morphine (opioids). These drugs are all associated with serious side-effects and are not always effective for the treatment of pain. This is particularly so for neuropathic pain (neuralgia), which is peculiarly resistant to the analgesic effects of opioids. Paracetamol and non-steroidal analgesics exhibit a "ceiling of analgesia" and are therefore only effective in the treatment of pain of moderate intensity. There is thus a clinical need for the development of novel analgesic drugs.

There are numerous anecdotal claims of cannabinoid-induced analgesia. Whilst of some interest, these reports require substantiation, by means of randomised controlled trials in different clinical pain models, before clinical evidence of cannabinoid analgesia can be assumed. There are only 6 controlled trials reported in the literature (examining cancer, post-operative and neuropathic pain) (British Medical Association, 1997), these are of poor quality and low power. These studies examined D⁹ tetrahydrocannabinol, cannabidiol or levonantradol and four out of the six reported an analgesic effect. Any analgesic effect appears to be similar to that afforded by codeine. Thus, there is currently no reliable human clinical evidence to support nor to refute claims of cannabinoid- induced analgesia. Nevertheless, the data from these anecdotal reports and limited trials does provide some vindication for further clinical study.

The conduct of randomised controlled trials of sufficient power and sophistication, in appropriate clinical models, is warranted to answer the above questions. Such trials are justified by the merging evidence from laboratory study and very limited clinical data. Such trials should examine both analgesic efficacy and side-effects. The precise mechanism of cannabinoid-induced analgesia is unknown and it is presently unclear whether the single molecule approach provided by selective cannabinoid agonists or the synergy of the multiplicity of compounds in

herbal cannabis will provide the optimal analgesia. Therefore, both extracts of herbal cannabis (of predictable potency) and the selective cannabinoid receptor agonists should be compared to placebo in appropriately designed clinical trials. The safety of cannabinoids should be assessed before they are used for clinical trials.

6. How strong is the scientific evidence in favour of maintaining prohibition of recreational use?

6.1 Under this heading our concern is only to show how science can illuminate discussion of the questions rather than ourselves push any particular view. We believe that science can indeed throw light on how this question can be rationally approached and would like to see current public debate much better informed than is at present the case. However, we would at the end of the day expect any such decision to be determined by social and political considerations and that is not territory which we wish to enter. In terms of the strictly scientific input to the debate we wish to identify five relevant postulates:-

6.2 There is scientific evidence to support the postulate that the recreational use of cannabis is not harm-free. We are confident that evidence exists that cannabis can give rise to various types of physical and psychological problems. The confidence with which this assertion can be made will vary with the type of problem being considered and there is room for variation in scientific interpretation. Here is a listing with each potential item bracketed within terms of our own judgement for strength of the evidence for a causal association between cannabis use and that problem on a 5-point scale (5 = very strong, 1 = very weak). In reaching these conclusions we have been much helped by material set out in two recent reviews (Hall et al 1994, WHO 1997). The informal and provisional nature of these ratings needs to be stressed, but this approach may perhaps aid debate, even if others would give different scores. The scientific evidence on psychological problems has been reviewed in an earlier section of this paper, while for recent authoritative reviews on physical and social pathologies, we would refer to WHO (1998) and Hall et al (1994).

Psychological problems

Acute interference with psychomotor function other cognitive function	5
Acute interference with short term memory and other cognitive function	5
Residual deficit in complex cognitive functioning after cessation of use	3
Short-term psychotic disturbance	5
Medium-term psychotic disturbance resulting from continued heavy use	1
Causation of schizophrenia	1
Destabilisation of treated schizophrenia	3
Existence of a clinically significant cannabis dependence syndrome	5

Physical problems

Chronic bronchitis resulting from smoked cannabis	4
Cancers of the bronchus and upper airway resulting from smoking cannabis	2
Impairment of immune system	2
Impairment of foetal development, with small birthright	3

Social costs and problems

Cost to mental health services relating to treatment of acute psychosis and dependence and to physical health services due to illness and accident-related trauma	5
Impairment in school-age scholastic performance	2
Impairment in adult work performance	2
Contribution to motor vehicle accidents	5

We would expect the list and attached ratings to look very different in, say, five years' time and the pace of research in some but not all of these areas is impressive. We cannot rule out the possibility either of some of what today appear to be adverse consequences later being eliminated from the list, nor the possibility of the evidence strengthening or new problems coming to light.

6.3 Most individual risks, whether acute or chronic, are likely to have a dose-response relationship with level of cannabis use. As regards acute effects on psychological and psychomotor functioning of kinds which can be examined in the laboratory, dose-response effects are well established. Although there is good reason to expect that in relation to the list of potential chronic pathologies higher levels of exposure will carry greater risk, these may be risk curves of different shapes or accelerations for different problems and on this type of question there are at present no clear answers. With alcohol it is evident that the risk relationship between drinking and cirrhosis is exponential, for some cancers more or less a straight line, and for coronary heart disease J-shaped (Edwards et al 1994). We do not however know whether doubling an individual's level of exposure to cannabis would less than double or more than double their risk of any of the pathologies set out in the check-list above.

6.4 Population level exposure of cannabis-related harm will be related to population levels of cannabis use. Research on population alcohol consumption suggests that across Europe a 1 litre per capita increase in alcohol consumption will cause a 1% increase in overall population mortality (Her and Rehm, 1998). We also have a fairly good knowledge of how an overall increase in alcohol consumption is shared out among the drinking population: for an X% overall per capita increase in consumption there will be a greater than X% increase in heavy drinkers however defined, and a more than X% increase in mortality from a pathology such as cirrhosis where the risk function is exponential (Edwards 1994). No parallel knowledge of an exact kind is available on how cannabis use is likely to be shared out among a using population if the supply is increased, but it is reasonable to assume that an X% increase in overall use would result in not less than an X% increase in heavy use with increase in different problem rates according to the shape of problem-specific risk curve. Population levels of use for this drug are thus likely to have a bearing on public health.

6.5 Price and access are likely to have an impact on population levels of drug use. We do not want to go too far in the social science direction, but are aware that considerable econometric research exists on the price elasticity and income elasticity of alcohol (Edwards et al 1994). While similar work on illicit drugs is at a far earlier stage and there is uncertainty as to how the fact of dependence may distort relationships (Bickel and Madden 1998, Bickel et al 1998, Reuter 1998), we would however expect that any cheapening of cannabis would lead to increased levels of use, increased persistence of use, and increased numbers of users. On analogy with research conducted with legislative controls on alcohol (Edwards et al 1994), we

would expect weakening of controls over cannabis to result in increased use levels but this is an empirical question on which research at present is not conclusive (Reuter 1998).

6.6 Within the perspective of what the health sciences have to tell, removal of prohibition on cannabis would have to be described as a voyage into the unknown.

Some added harm and some added costs would undoubtedly result. Whether the impact on the nation's health and safety would be relatively small or whether the consequences would be a damaging endemic of multiple and costly harms or something between these two extremes, is in our view a question which cannot be resolved by reference to existing scientific evidence. It is up to society and government to decide whether there are imperatives that make that risk worth taking, but risky it would be.

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