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men of advanced years who have been hauled before the courts.

Decriminalisation would require amending the Act in such a way as to allow for possession of small amounts for personal private use by adults.

The Drug Court Act

The Drug Court (Treatment and Rehabilitation of Offenders) Act, consistent with the *1988 Convention*, adopts a health-related, rather than a punitive approach to drug use. It provides for the establishment of a Drug Court aimed at facilitating treatment and rehabilitation of drug offenders. It comprises a Resident Magistrate and two Justices of the Peace, one of whom must be a woman, specially appointed by the Minister.

Those brought before the Drug Court must be persons who appear to be dependent on the use of drugs but are of sound mind.

Where ganja is concerned, the Drug Court will hear cases involving smoking or otherwise using the substance, possession of utensils in connection with smoking, and possession of up to eight ounces of the matter. An approved treatment provider will provide the Court with an assessment of the person charged and pleaded guilty, in order to enable the Court to decide whether to order a prescribed treatment. On successful completion of the treatment he will be discharged and the offence not form part of his criminal record, unless convicted more than twice. Failure to comply or to complete the prescribed programme would result in the imposition of sentencing.

If the *Dangerous Drugs Act* were to be amended as indicated above, in order to provide for adult, private use of ganja, the *Drug Court Act* would have to be similarly amended. Provisions could be made to allow entry into the treatment and rehabilitation programme of persons who voluntarily seek such, or who have been referred by a competent authority, such as parents in the case of minors, or medical personnel, where it can be established that ganja is the cause of acts inimical to the safety of others.

But would such amendments be possible without breaching the *1961 Single Convention* and the *1988 Convention*?

1961 Single Convention

The *1961 Convention*, Article 4, is explicit on the general obligations of the parties:

The parties shall take such legislative and administrative measures as may be necessary:

a. To give effect to and carry out the provisions of this Convention within their own territories:
b. To co-operate with other States in the execution of the provisions ofthis Convention; and
c. Subject to the provisions of this Convention, to limit exclusively to medical and scientific purposes the production, manufacture, export, import, distribution of, trade in, use and possession of drugs.

Under Article 4(c), the use and possession of cannabis, one of the Scheduled substances, is limited to medical and scientific purposes. And again, under Article 28(3), which speaks specifically to the Control of Cannabis, "The Parties shall adopt such measures as may be necessary to prevent the misuse of, and illicit traffic in, the leaves of the cannabis plant"

But it is Article 36, on Penal Provisions, specifically paragraphs 1 (a) and 1 (b), and Article

38, on Measures Against the Abuse of Drugs, that frame in greater detail the obligations of Parties. Article 36, paragraph 1 (a) reads:

Subject to its constitutional limitations, each Party shall adopt such measures as will ensure that cultivation, production, manufacture, extraction, preparation, possession, offering, offering for sale, distribution, purchase, sale, delivery on any terms whatsoever, brokerage, dispatch, dispatch in transit, transport, importation and exportation of drugs contrary to the provisions of this Convention, and any other action which in the opinion of such Party may be contrary to the provisions of the Convention, shall be punishable offences when committed intentionally, and that serious offences shall be liable to adequate punishment particularly by imprisonment or other penalties of deprivation of liberty.

Use is not mentioned here as an offence, thus in theory it could be thought of as being excluded, making it possible to decriminalise use without contravening the Convention.

Paragraph 1 (b) of the Article presents the Parties the choice of conviction and punishment or treatment and rehabilitation. This is followed in greater detail in Article 38, where preventive measures, education, treatment and after-care, and training of personnel are called for.

Legal Expertise

The Commission sought the advice of international law expert, Dr Stephen Vasciannie of the University of the West Indies, and in a well-researched and thorough brief, this is what he wrote relative to the *1961 Single Convention*.

"[W]hen Articles 36 (1) (a) and (b) are read together, the legal situation seems to be as follows: (a) the Single Narcotics Convention requires States to subject certain activities concerning marijuana to criminal sanctions (including the cultivation, production, manufacture, possession, exportation and importation of that drug); (b) the Convention does not require States to prohibit the use (or consumption) of marijuana *per se*; and (c) in the event that an abuser of marijuana has committed an offence that would require criminal sanctions when committed by a non-abuser of the drug, it is open to the State to forego the application of criminal sanctions against the abuser.

On this reading of the Single Narcotics Convention, it would be possible for Jamaica to amend its national legislation in order to decriminalise marijuana use, and make its private use legal, without necessarily placing the country in breach of its obligations under the Convention."

But, notes Dr Vasciannie, the difficulty that would arise from such a step would be the contradiction whereby ganja use would be legal but its procurement illegal. In his opinion, "[t]his seems quite unworkable." However, the Commission has before it the experience of the Dutch, who, without being cited as breaching any of the Conventions, have adopted a contradictory, if pragmatic policy, giving restricted decriminalised status to cannabis distribution and consumption of small quantities, while applying penal sanction to its production, importation and trafficking.

According to *A Guide to Dutch Policy* put out by the Foreign Information Division of The Netherlands Ministry of Foreign Affairs, in cooperation with the Ministries of Health, Welfare and Sport, Justice, and Interior and Kingdom Relations, "[t]he use of drugs is not an offence under international agreements. Nor is it an offence in Germany, Italy, Denmark

or, indeed, most countries of the European Union" (2000, p. 6). The Government sees itself in compliance with the *UN Conventions of 1961, 1971 and 1988*, not to mention other bilateral and multilateral agreements on drugs. The policy is based on the "principle of expediency", whereby authorities are given "discretion to decide, on the grounds of the public interest, not to bring criminal action in a given case." High priority is given to suppressing the sale of hard drugs and trafficking of large quantities of drugs, hard and soft, while low priority is given to curbing the sale and possession of soft drugs for personal use. In this context "soft drugs" refer to cannabis and its derivatives.

Thus, notwithstanding the evident contradiction of decriminalising personal use while suppressing the sale and trafficking, a half-way position, which some would reject, is nonetheless possible under the *1961 Single Convention*, which does not explicitly prohibit use. Noted retired Solicitor General, Dr Kenneth Rattray, in verbal communication with the Chairman of the Commission, argues that the omission of sanctions against personal consumption was not an oversight by the Parties to the Convention, but rather an attempt to set a threshold beyond which actions of the State could be deemed to be in breach of certain fundamental human rights. In this regard, there are three principles of human rights that governed and have governed this and other similar Conventions: the principles of the right to personal privacy, and the right to religious freedom, and the principle of proportionality, by which the sanction should be proportionate to the offence. That the Parties to the Convention would have been mindful of these constraints is clearly evident in the interpretations given the Convention by the Secretary-General's *Commentary* on the Convention and by the International Narcotics Control Board, according to both of which the Single Convention intends the criminalisation of possession for the purposes of illicit trafficking and not for personal use.

Although Dr Vasciannie argues that had the negotiating Parties intended to limit possession to illicit traffic they would have said so, and therefore "[t]he fact that they did not must carry considerable significance in directing us to interpret Article 36(1) in keeping with the plain meaning of its text," Dr Rattray, with considerable experience in international law, emphasises the contextual and interpretive framework of negotiated agreements and treaties. He is therefore of the opinion that the interpretation of the International Narcotics Control Board carries weight.

In addition, Dr Rattray argues, the interpretation of the Conventions must be done in the context of the obligations assumed under International Human Rights Conventions, which have been long recognised as an aid to interpretation, particularly in cases of uncertainty or ambiguity.

He further contends that there is a growing body of international jurisprudence, which recognises that International Human Rights Conventions are of a superior order to obligations under other Conventions, and that in case of a conflict or inconsistency between such obligations, the obligation under the Human Rights Conventions must prevail.

Since Jamaica is a Party to the International Convention on Civil and Political Rights, which protects against invasion of privacy as well as protects freedom of religion, those obligations would have to be considered in the determination as to whether any obligations under the Drug Conventions must yield to Jamaica's obligations under the International Convention on Civil and Political Rights.

In sum, therefore, decriminalisation of possession for personal use and of use itself does not breach the *1961 Single Convention*.

1988 Convention

The *1988 Convention* also does not explicitly criminalise personal consumption, but by bringing under the purview of the criminal justice system cultivation, purchase and possession for personal use, it goes further than the *1961 Single Convention*. The relevant article is Article 3, paragraph 2, which reads:

"Subject to its constitutional principles and the basic concepts of its legal system, each Party shall adopt such measures as may be necessary to establish as a criminal offence under its domestic law, when committed intentionally, the possession, purchase or cultivation of narcotic drugs or psychotropic substances for personal consumption contrary to the provisions of the 1961 Convention, the 1961 Convention as amended or the 1971 Convention."

Translated into practice, it would have to be argued that by the strict letter of the law, the possession of an unlit spliff would constitute a criminal offence, but the smoking of it not. According to Dr Vasciannie, the same contradictions noted in respect of the *1961 Convention* would also apply, for

"Article 3 (2) would mean that all important stages preceding consumption, but not consumption itself, must be subject to the criminal law: the cultivator, the purchaser and the person in possession are all guilty of criminal offences in the perspective of the 1988 Convention. For parties to this Convention, therefore, decriminalisation for personal consumption would appear to be a position possible in form but implausible in practice."

He examines other legal options available to Jamaica. Amendment as a possible route would require the Secretary-General to notify the Council and all the Parties of the amended text. A decision may be taken on the basis of the comments of the Parties, or the Council may convene a conference, whether or not objections are raised. If the amendment is not rejected within eighteen months of its circulation, it enters into force. Given the fact that so many countries have seen it fit to ratify the Conventions (157 in the case of the *1961 Single Convention*, 154 in the case of the *1988 Convention*), and given also the relatively recent adoption of the *1988 Convention*, it is hardly likely, Dr Vasciannie believes, that Jamaica could muster enough support to carry such an amendment.

The other legal option for which provision is made is denunciation. By denunciation, the Secretary-General is advised by written instrument of the withdrawal of consent, which would then take effect the year following its submission. Legally, this is open to Jamaica to do, but, opines Dr Vasciannie, from a geo-political perspective it would make little sense. The Commission agrees.

The Commission does not, however, agree with his conclusion that while "the main drug conventions...do not in themselves require Jamaica to subject criminal sanctions to marijuana use...this does not necessarily permit decriminalisation in a manner that would be workable in Jamaica", and that therefore "the *status quo*, with all its deficiences, ought to be recommended."

Given the clear intent of the Convention not to violate certain fundamental human rights, a workable if untidy arrangement is possible, which would seek no significant change in the *status quo* at present other than relief to the thousands who annually are brought before the court for personal use. The suppression of the growing, large scale trafficking and export of ganja would and must continue, not least to guard against decertification by the United States. The suppression of public use would also continue. What would cease is the prosecution of adults for the possession of small amounts for private use.

By itself that would not be enough, if we are to allay the fears of our partners that we are reneging on our international obligations or to reduce the abuse of ganja, not to mention

other substances. It would require, also, a sustained education campaign, to deepen the work already going on at community levels and in the schools. Such an approach is actually quite consistent with both the letter and spirit of Article 38 of the *1961 Single Convention*, on Measures Against the Abuse of Drugs.

1. The Parties shall give special attention to and take practicable measures for the prevention of abuse of drugs and for the early identification, treatment, education, after-care, rehabilitation and social reintegration fo thepersons involved and shall co-ordinate their efforts to these ends.
2. The Parties shall as far as possible promote the training of personnel in the treatment, after care, rehabilitation and social reintegration of abusers of drugs.
3. The Parties shall take all practicable measures to assist persons whose work so requires to gain an understanding of the problems of abuse of drugs and of its prevention, and shall also promote such understanding among the general public if there is a risk that abuse of drugs will become widespread.

In the context of Jamaica, given the place of ganja in social and cultural life, decriminalisation represents the first step towards prevention, early identification, treatment and education. This is the unanimous position of all those working in the area of drug abuse. In the words of the Chief Medical Officer of Health, decriminalisation becomes a platform–one might say the only realistic platform, for demand reduction.

A realistic education campaign would seek to present in as balanced a way as possible the available experience and scientific knowledge of ganja, treating it as distinctly separate from all other substances, legal and illegal. It would continue to target, but now with greater confidence of success, young males who now needing no longer to fear condemnation and ostracism would be more ready to discuss it openly.

Decriminalisation will also require diplomatic efforts to join ranks with a growing number of Parties who unilaterally are taking measures to ameliorate their own anti-marijuana practices with respect to possession and use, our aim being to get the international community appropriately to amend the Conventions. In the Caribbean, where, according to a report by the Caribbean drug control Coordination Mechanism on 1999/2000 drug trends in the region, cannabis "is, in fact, the drug of choice" and "[u]nlike crack cocaine or cocaine…is, to a large extent, socially acceptable," diplomatic intiatives to get CARICOM to adopt a single position will undoubtedly strengthen Jamaica's ability to exert greater influence at the international level.

It will require, finally, practical proof that the country remains committed to the suppression of all drugs. Police interdiction of cocaine trafficking and use would need to be stepped up, which, if the Member of Parliament who appeared before the Commission is to be believed, is a matter of will.

The Commission has good reason to believe that it is the failure to do this that will threaten the country's certification status with the United States, and not the decriminalisation of personal possession and use of ganja. Were even a single cocaine trafficker to be caught, tried and sentenced, it would enhance the country's standing. The decriminalisation being recommended would free up more of Jamaica's human and financial resources to focus on the trafficking of cocaine. According to a well-informed source, this is where the Americans are frustrated with Jamaica.

Human Rights

Decriminalising on the basis that the Conventions do not prohibit use does not constitute the only justifiable rationale. There may be a better way. The Commission is grateful to

Lord Anthony Gifford for opening up the following consideration.

All the relevant articles of the Conventions are prefaced by constitutional limitations, variously phrased. For example, Paragraph 1 (a) of Article 36 of the *1961 Single Convention on Narcotic Drugs*, is qualified by the clause: "Subject to its constitutional limitations, each Party shall adopt such measures as will ensure etc."

Paragraph 2 of Article 3 of the *1988 Convention Against Illicit Traffic* is similarly prefaced: "Subject to its constitutional principles and the basic concepts of its legal system, each Party shall adopt such measures etc." In other words the Conventions pay due regard to the peculiarities of each country, such as would be reflected in its supreme law, the Constitution.

The Constitutional guarantees to individual rights and freedoms could normally have been invoked to allow personal use of ganja, as an expression of religious freedom or of the right to privacy, or other ri ht, without breaching international obligations. Unfortunately, such a loophole would not now apply to Jamaica, because of a saving clause which allows the Jamaican Constitution to be superseded by any statute in existence prior to the appointed day when the Constitution came into effect. In the case of *Dennis Forsythe v. the Director of Public Prosecutions and the Attorney General*, in which Forsythe argued that his constitutional right to freedom of religion as a Rastafarian who used ganja for sacramental purposes, and his right to the privacy of his home were violated when he was charged with possession of the prohibited substance, the Supreme Court handed down judgment which included among other reasons the fact that Section 26 (8) of the Constitution plainly declared that "any law in force immediately before the appointed day shall not be held to be inconsistent with any of the provisions" of Chapter III of the Constitution which sets out the Rights and Freedoms of the Jamaican citizen. *The Dangerous Drugs Act* being in force prior to the appointed day was judged by the Supreme Court to be not inconsistent with the Constitution, and so Dr Forsythe's motion was dismissed. Thus, Jamaica cannot at the present time make use of the constitutional limitation clause allowed by the Conventions.

However, the *Charter of Rights* being debated for adoption by Parliament were it to take effect, would replace the existing chapter of the Constitution, override the saving clause of Section 26 (8) of the Constitution and pave the way for Jamaica to take advantage of the Constitutional Limitation clause. There are two Drafts, one by the governing People's National Party, the other by the Opposition Jamaica Labour Party.

The Government's Draft at Section 13 (2) reads:

Save only for laws that are required for the governance of the State in periods of public emergency, or as may be demonstrably justified in a free and democratic society, Parliament shall pass no law and no public authority or any essential entity shall take any action which abrogates, abridges or infringes--

(b) the right to freedom of conscience, belief and observance of religious and political doctrines;

(l) the right to protection for privacy of home and other property; enjoyment and beneficial ownership of property.

The Opposition Draft at Section 14 (1) reads:

Save only for laws that are required for the governance of the State in periods of public emergency or public disaster or as may be demonstrably justified in a free and democratic

society, Parliament shall pass no law and no organ of the State shall take any action which abrogates, abridges or infringes:

(c)the right to freedom of conscience, belief and observance of religious and political doctrines;

(k) the right to enjoyment and beneficial ownership of property;

(l)the right to respect for private and family life, privacy of the home and of communication.

Ganja could be decriminalised for personal use and justified under the constitutionally protected right of enjoyment of the privacy of one's home, and possession in limited quantities for such private use likewise decriminalised. Also to be decriminalised in like manner would be the possession and use of ganja in pursuit of the right to freedom to manifest religious doctrines.

As Lord Gifford points out in his written submission, in effect supporting the above point of Dr Rattray, international human rights conventions as well as recent judicial decisions in other jurisdictions add some weight to the argument.

The rights to privacy and to the freedom to manifest one's religion as contained in both Drafts of the Charter of Rights are consistent with Articles 17 and 18 of the International Covenant of Civil and Political Rights, and Articles 11.2 and 12.1 of the American Convention on Human Rights. These rights are not absolute, and both Drafts include provisions to override them, although the Opposition Draft Section 19 of the Opposition's Draft goes so far as to make void any law or rule of law if:
(a) it requires or authorizes anything to be done in contravention of any provision of this chapter [i.e. the *Charter*];
(a) it prohibits the exercise of any right or freedom protected by this chapter; or
(b) if it restricts the exercise of any such right or freedom in a manner not authorized by this chapter.

The overriding provisions are, in the first place, those contained in the qualifier "Save only for laws, etc.", which cover emergency situations or such laws "as may be demonstrably justified in a free and democratic society." It is hard to see what kind of emergency could make it necessary to ban the private use of ganja, and equally how, given its cultural entrenchment and medical status, the criminalisation of ganja possession for personal use and the use itself could be "demonstrably justified in a free and democratic society." But the Constitutional Court would be called on to judge.

But secondly–and this is spelt out in the Government's Draft, the private possession and use of ganja would be subject to any law "which is reasonably required–

(a)in the interests of defence, public safety, public order, public morality, public health...;
(d)for the purpose of protecting the rights or freedoms of other persons."

It is conceivable that ganja use, even in private, could be challenged as being against public morality and public health, or for infringing the rights and freedoms of others. But here again the issue would be subject to argument before the Constitutional Court.

Recent decisions in the United States and Canada also strengthen the case for decriminalisation. We quote extensively from Lord Gifford's written submission:
In *US v Bauer and others*, cited as 1996 WL 264776 (9th Cir. [Mont]), the United States Federal Court of Appeal had to consider a plea from Defendants charged with trafficking and possession of marijuana, that they had the right to a 'religious use' defence. They relied on the Religious Freedom Restoration Act, a U.S. statue which guaranteed freedom of religion. The District Court had held that the relevant marijuana law 'substantially burdened the free exercise of the Rastafarian religion', but decided that 'the Government had an overriding interest in regulating marijuana.' The Court of Appeal reversed the District Court's decision. The court held that if the freedom of a person's exercise of religion is substantially burdened, the Government had to meet two tests: (a) a 'compelling governmental interest; and (b) that the application of the law is 'the least restrictive means of furthering that compelling governmental interest.' The Court found that the Government had not shown that a universal law against marijuana was the 'least restrictive means' of preventing the distribution of marijuana. Accordingly the defendants who were charged with simple possession would be re-tried, and they would have a defence if they could show that the use of marijuana was part of their religious practice as Rastafarians. The defendants charged with trafficking would have no such defence, since religious freedom was not involved.

The conclusion drawn by Lord Gifford is that "even in the United States, the possession of marijuana may be found to be legal by the courts if it is associated with the exercise of a fundamental right such as religious freedom."

In the Canadian case of *R v Terrance Parker* (Docket C28372, decided on 31st July 2000), the issue concerned the use of ganja for medical purposes. The Ontario Court of Appeal considered the evidence concerning the harmful as well as the therapeutic effects of ganja, and in making its ruling applied Section 7 of the Charter of Rights, according to which only by virtue of 'the principles of fundamental justice' may the right to liberty and security of the person be infringed.

The Court found that "the marijuana laws did infringe Parker's security in preventing him from undertaking a safe medical treatment for his condition of epilepsy. It held that a blanket prohibition did breach the 'principles of fundamental justice'", and so permitted the possession of marijuana for medical use. Significantly, the Court of Appeal took note of the fact that the United Nations *1988 Convention* had, as the Convention stipulated, to be subject to Canada's constitutional principles and basic concepts of its legal system.

A year later, Canada became the first state to pass legislation making "medical marijuana" legal.

Clearly, then, a strong legal case for the decriminalisation of ganja for personal, private use exists once both Government and Opposition are agreed on the terms of the *Charter*, and it becomes law by Act of Parliament. Once it becomes law, the decriminalisation of ganja for personal use, based on the right of privacy of the home, and its decriminalisation for religious use, based on the right of observance of religious doctrines, could then be covered by the Constitutional limitation respected by the United Nations Conventions.
Decriminalisation would not remove the patent contradiction exposed by Dr Vasciannie above, but it would be the more satisfactory of the two options in providing a sounder legal basis.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

The National Commission on Ganja accepts that ganja is not entirely safe. Despite its proven folk medicinal qualities, its use can be injurious to health. There is evidence that for those who smoke it the inhalation of tar and other compounds can affect the lungs; that users can experience short term memory loss and delayed reaction time; and that among young people it can retard the learning process. There is also documented evidence that the substance can produce in some people a mentally disturbed state of ganja psychosis.

Notwithstanding these and other ill effects, the Commission is of the view that many, if not most, persons who use ganja in moderation suffer no apparent short or long term debility. Not only that, but its reputation among the people as a panacea and a spiritually enhancing substance is so strong that it is must be regarded as culturally entrenched. As a result, the practice of criminalising the users of small quantities does far more harm than good to the society as a whole. The Commission is mindful also that there are legally available substances that have been shown to have physiological and psychological ill-effects that, based on current evidence, are more injurious than those of ganja. Such is the case with alcohol and tobacco.

It is the view of the Commission that the punitive sanctions administered by the justice system to users of small quantities is not only unjust but is a major source of disrespect and contempt for the legal system as a whole. Moreover, the punishment meted out to such offenders has not had and is not likely to have the desired effect of a deterrent. Administering the present laws as they apply to possession and use of small quantities of ganja not only puts an unbearable strain on the relationship of the police with the communities, in particular the male youth, but also ties up the justice system and the work of the police, who could use their time to much greater advantage in the relentless pursuit of crack/cocaine trafficking.

Accordingly the Commission recommends as follows:

1. that the relevant laws be amended so that ganja be decriminalised for the private, personal use of small quantities by adults;
2. that decriminalisation for personal use should exclude smoking by juveniles or by anyone in premises accessible to the public;
3. that ganja should be decriminalised for use as a sacrament for religious purposes;
4. that a sustained all-media, all-schools education programme aimed at demand reduction accompany the process of decriminalisation, and that its target should be, in the main, young people;
5. that the security forces intensify their interdiction of large cultivation of ganja and trafficking of all illegal drugs, in particular crack/cocaine;
6. that, in order that Jamaica be not left behind, a Cannabis Research Agency be set up, in collaboration with other countries, to coordinate research into all aspects of cannabis, including its epidemiological and psychological effects, and importantly as well its pharmacological and economic potential, such as is being done by many other countries, not least including some of the most vigorous in its suppression; and
7. that as a matter of great urgency Jamaica embark on diplomatic initiatives with its CARICOM partners and other countries outside the Region, in particular members of the European Union, with a view (a) to elicit support for its internal position, and (b) to influence the international community to re-examine the status of cannabis.

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An Analysis of Marijuana Policy

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ANALYSIS OF THE MARIJUANA POLICY

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An Analysis of Marijuana Policy

Committee on Substance Abuse and Habitual Behavior

Commission on Behavioral and Social Sciences and Education

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Commission on Behavioral and Social Sciences and Education

National Research Council

2101 Constitution Avenue, N.W.

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NATIONAL RESEARCH COUNCIL

2101 Constitution Avenue Washington D. C. 20418

Office of the Chairman

June 21, 1982

Dr. William Pollin, Director

National Institute on Drug Abuse

Parkiawn Building

Room 10-05

5600 Fishers Lane

Rockville, Maryland 20857

Dear Dr. Pollin:

I transmit, herewith, a report of the National Research Council's Committee on Substance Abuse and Habitual Behavior:

"An Analysis of Marijuana Policy" prepared at the request of the National Institute on Drug Abuse.

The Committee on Substance Abuse and Habitual Behavior, composed of 18 experts in the several relevant disciplines, has weighed carefully the available data regarding the costs, risks, and benefits of the major policy alternatives regarding the control of marijuana use and supply. The Committee is clear in pointing to the deficiencies of this body of evidence and cautions about the hazards of formulating policy recommendations based solely or in part thereon. In this regard, I call your attention to the following statement by Louis Lasagna and Gardner Lindzey contained in the Preface to the report:

The Committee wishes to make clear what it regards as the limits of this report for the selection of policy alternatives. Scientific judgment can estimate the prevalence of different kinds of use, risks to health, economic costs, and the like under current policies and try to project such estimates for new policies. It can come to some conclusions based on those estimates. But selection of an alternative is always a value-governed choice, which can ultimately be made only by the political process.

This caveat notwithstanding, the Committee has derived from its examination of the scientific data a conclusion about the major policy choices facing the nation with respect to

marijuana: complete prohibition, prohibition of supply only, and regulatory approaches. Specifically, the Committee concurs with the judgment of the National Commission on Marijuana and Drug Abuse, rendered in 1971, that a policy of prohibition of supply only is preferable to a policy of complete prohibition of supply and use.

THE NATIONAL RESEARCH COUNCIL , THE PRINCIPAL OPERATING ACENCY OF THE NATIONAL ACADEMY OF SCIENCES AND THE NATIONAL ACADEMY OF EGINEERING

Dr. Willian. Pollin

June 21, 1982

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What must be understood by the public, the media, and all who read the Committee's report is that its decision to endorse a policy change was not fashioned from scientific information--old or new--alone. Rather it was the analysis of a combination of factors which affect policy decisions, including the cost and efficacy of enforcement practices. Values were necessarily involved in balancing these factors and there are those within the membership 'and governing bodies of the Academies and the National Research Council who might not have come to the same policy conclusions, after reviewing the same data.

My own view is that the data available to the Committee were insufficient to justify on scientific or analytical grounds changes in current policies dealing with the use of marijuana. In this respect I am concerned that the Committee may have gone beyond its charge in stating a judgment so value-laden, that it should have been left to the political process.

I have one further concern that cannot go unaddressed. I fear that this report, coming as it does from a well-known and well-respected scientific organization, will be misunderstood by the media and the public to imply that new scientific data are suddenly available that justify changes in public attitudes on the use of marijuana. This would be unfortunate at a time when daily use trends by high school students are down significantly. As the Committee's discussion of marijuana's behavioral and health-related effects clearly demonstrates, there is no new scientific information exonerating marijuana. In fact, the review by our Institute of Medicine, published a few months ago, reevaluated existing scientific evidence and concluded, as have others, that marijuana is a harmful drug whose use justifies serious national concern.

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I wish to remind you that this is a committee report; the only position that can be inferred with respect to the National Research Council on the issue of marijuana policy is that the National Research Council is satisfied that the Committee was competent to examine the issue and diligent in carrying out its task. Despite my personal disagreement, I believe that the Committee has performed a useful service by illuminating many of the complex issues surrounding this highly controversial subject.

Yours sincerely,

Frank Press Chairman

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An Analysis of Marijuana Policy

National Research Council of the National Academy of Science, 1982

PREFACE

In 1978 the Committee on Substance Abuse and Habitual Behavior began a study of marijuana policy at the request and with the support of the National Institute on Drug Abuse. Sharp increases in marijuana use along with suggestions for reform of existing marijuana laws from scientists and policy makers prompted a renewed look at those laws. In addition, the National Commission on Marijuana and Drug Abuse, in its 1973 final report, Drug Use in America: Problem in Perspective, had recommended that a follow-up commission be appointed to review possible changes in the situation four years later. That recommendation was not implemented, so the Committee took as a framework for its task the assessment that the Commission recommended, especially the assessment of new evidence regarding the effects of recent changes in state marijuana policies.

The Committee conducted its study with awareness of the intensity of past controversies about marijuana use in U.S. society. In the four years since the Committee began its work, there has been an increase in visible concern among many parents about marijuana use among youth, its potential risks to the health of children, and the possibility that heavy use by some young people may seriously threaten their education. Parents who have experienced problems with their own children, or observed those of others, have organized to make marijuana policies a major item on current political agendas. In comparison with the situation at the inception of this study, there is today greater rancor in public discussion, press reports, legislative hearings, and policy-oriented technical meetings related to marijuana use.

This is the context in which the Committee completed its review of the evidence and arguments of earlier studies and weighed the significance of subsequent evidence for the major policy alternatives. Every policy has potentially good and potentially bad effects, and policy choices involve difficult comparisons of such effects. It is important to recognize that to allow the inertia developed by existing policies to prevent change is itself a choice.

The Committee is aware that analyzing a topic that is the subject of heated social debate has its hazards. Many of those participating in the marijuana debate have already selected what they take to be the admissible terms of the discussion and look with disfavor on anyone's insistence on a wider set of considerations. For example, some would settle the issue on physiological grounds alone: whether cannabis products, in the dose ranges customarily used by most people, cause tissue damage. Defenders of marijuana use may seize on the ambiguity or absence of evidence for such damage and ignore any other effects on education or safety; those opposed to marijuana use may emphasize the possibility of

chronic disease that is suggested by some laboratory findings and ignore the social, political, and economic costs of fighting a well-established custom.

This report does not review and analyze every conceivable policy nuance or option. It addresses the major choices--both because these families of alternative policies subsume many variants and because the choice among these major options must be discussed before specific, perhaps new, policy instruments can be designed.

The Committee wishes to make clear what it regards as the limits of this report for the selection of policy alternatives. Scientific judgment can estimate the prevalence of different kinds of use, risks to health, economic costs, and the like under current policies and can try to project such estimates for new policies. It can come to some conclusions based on those estimates. But selection of an alternative is always a value-governed choice, which can ultimately be made only by the political process. The role of scientific evidence in this process is not inconsiderable, even though, at times, the strongest evidence may be pushed aside and the wildest speculation prevail. But the weight of the evidence is only one factor in the process of policy formation; ultimately, that process involves value choices.

In completing its report, the Committee has benefited from many people in formulating, revising, and updating the analyses and data. A very early version of this report was discussed at the Committee's annual conference in 1979, and subsequent versions benefited from comments by staff of the National Institute on Drug Abuse and of the National Research Council. The final draft received close and constructive attention by members of the National Research Council's Commission on Behavioral and Social Sciences and Education, the Institute of Medicine, and the Report Review Committee of the National Academy of Sciences.

We have also maintained a close liaison with the staff and members of the Institute of Medicine's Committee to Study the Health-Related Effects of Cannabis and Its Derivatives, on which three members of our Committee also served, and whose recently published report, Marijuana and Health, significantly contributed to our work.

Two former Committee members, Troy Duster and Michael Agar, assisted in the early preparation of the report. At later stages we were very ably assisted by the staff of the Commission on Behavioral and Social Sciences and Education, in particular David Goslin, executive director, and Eugenia Grohman, associate director for reports. Without their help, it is doubtful that we could have completed this task. Finally, we are indebted to the staff and members of the Committee, for their diligence, patience, and commitment to a difficult assignment.

Louis Lasagna, Chair

Gardner Lindzey, Chair, 1977-1980

Committee on Substance Abuse and Habitual Behavior

An Analysis of Marijuana Policy

National Research Council of the National Academy of Science, 1982

INTRODUCTION

Since the early 1960s the use of marijuana as an intoxicant by a growing proportion of the American population has been an issue of major national concern. Despite repeated warnings of possible adverse health consequences and persistent efforts by law enforcement agencies to restrict the supply and use of marijuana. available data indicate that experimentation with or regular use of the drug is no longer restricted to a small minority of Americans. In 1979, for example, 68 percent of young adults between the ages of 18 and 25 reported having tried marijuana; 35.4 percent reported having used marijuana in the last month. Among adults over age 26, the proportion having ever used marijuana has more than doubled since 1971) from 9.2 percent to 19.6 percent (Fishburne et al., 1980; see Table I, below).

Although "the marijuana problem" may be viewed as of recent origin, marijuana is not a new drug. The cannabis plant has been cultivated and used both for its intoxicating properties and for its fiber (hemp) throughout the world for more than 10,000 years (Abel, 1980). At various times and places attempts have been made to restrict its use as an intoxicant; at other times and places its virtues have been extolled for medical purposes, and it has played a significant role in religious ritual. Because cannabis is easily grown--indeed, it is one of the hardiest of all plant species--its resin has been used for centuries along with tobacco, fermented distillates of grains and fruits (alcohol), and opium derivatives as one means of relieving stresses associated with daily life.

Despite its long history) the use of cannabis as an intoxicant was relatively unknown in the United States until the latter part of the nineteenth century) and even then its use as a drug was restricted to a tiny fraction of the population) primarily immigrants from Mexico. The first efforts to restrict its use in this country did not occur until 1911) when Congress) which at that time was considering proposals for federal antinarcotics legislation) listened to arguments that cannabis should be included in the list of illegal drugs. That effort failed) but during the next two decades a number of state legislatures moved to prohibit the possession of marijuana unless prescribed by a physician. It was not until 1937, when the Marijuana Tax Law was enacted) that the federal government became involved in the attempt to control its use. Even this law recognized the industrial uses of hemp and also exempted the seeds of the plant) which were then being sold as bird feed. In 1956, Congress included marijuana in the Narcotics Act of that year and, in 1961, the United Nations adopted the Single Convention on Narcotic Drugs, the terms of which state that each participating country could "adopt such measures as may be necessary to prevent misuse of, and illicit traffic in) the leaves of the cannabis plant." Congress approved participation in the convention in 1967 and three years later passed the Comprehensive Drug Abuse Prevention and Control Act, which provides the basis for current federal prohibitions regarding marijuana use.

Despite this history it was not until the 1960s that most Americans became aware of marijuana. The political and cultural protests of that period focused public attention on young people, their life-styles, and their use of drugs, including marijuana. That period created the context in which public policies regarding marijuana use have been debated since the early 1970s. As Abel (1980) points Out, for the first time marijuana use was not restricted to minority groups and fringe elements of society: many of the new users were native-born, middle-class, white college students. Without doubt, the political and cultural context in which marijuana emerged as an issue of national concern has strongly influenced the subsequent policy debate about its use.

The policy debate about marijuana use has also brought into sharp focus two conflicting but deeply held beliefs of large and overlapping segments of the American population. To many, the use of drugs of any kind solely for the purpose of producing states of intoxication is abhorrent, entirely apart from any presumed health effects. At the same time, many people strongly defend the right of individuals to privately indulge their desires, so long as others are not adversely affected. Adding to the complexity of the issues are continuing uncertainties about the health and developmental consequences of marijuana use, concern over the growing number of adolescent users, the social consequences of prosecuting otherwise law-abiding citizens for possession and use of marijuana, the relationship between the distribution of marijuana and that of other illegal drugs, the costs of enforcement of current laws, and the economic implications of the persistence of very large illegal markets.

The next section of this report presents a brief summary of existing evidence regarding the health consequences of marijuana use, drawing heavily on the recently completed study by the Institute of Medicine. The third section summarizes existing federal and state laws relating to the supply and use of marijuana. The fourth section of the report reviews the conclusions of the report of the National Commission on Marijuana and Drug Abuse (1972). The next two sections deal, respectively, with policies regarding the use and the supply of marijuana. The two final sections present a summary of the committee's conclusions regarding major policy options and recommendations for research needed to more adequately assess those options.

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THE DANGERS OF MARIJUANA

Marijuana is not a harmless drug. Although available evidence suggests that marijuana may be less likely than opiates, barbiturates, or alcohol to induce psychological and physical

dependence in its users, it has the capacity to reduce the effective functioning of individuals under its influence, and prolonged or excessive use may cause serious harmful biological and social effects in many users.

The recent report, and Health, of the Institute of Medicine in the appendix concludes:

The scientific evidence published to date indicates that marijuana has a broad range of psychological and biological effects, some of which, at least under certain conditions, are harmful to human health. Unfortunately, the available information does not tell us how serious this risk may be.

Overall, the report concludes (p. 5):

[W]hat little we know for certain about the effects of marijuana on human health--and all that we have reason to suspect--justifies serious national concern.

The complete summary of the Institute of Medicine report appears as the appendix to this report.

Over the past 40 years, marijuana has been accused of causing an array of antisocial effects, including: in the 1930s, provoking crime and violence; in the early 1950s, leading to heroin addiction; and in the late1960s, making people passive, lowering motivation and productivity, and destroying the American work ethic in young people. Although beliefs in these effects persist among many people, they have not been substantiated by scientific evidence.

Concerns about how marijuana affects citizenship, motivation, and job performance have become less salient in recent years as marijuana has moved more into the mainstream of society and has become less exclusively associated with radicals, hippies, or disadvantaged minorities Though there is still widespread belief that heavy marijuana use may be incompatible with a responsible, productive life, evidence that marijuana has not adversely affected either the productivity or the sense of social responsibility of some groups of users (see, e.g., Hochman and Brill, 1973) has tempered earlier fears of a widespread "motivation syndrome." Research that correlates marijuana use with undesirable behavior, such as alienation or inattention to school studies, has not established the direction of causality or ruled out spurious associations (see, e.g., Beachy et al., 1979). This issue, however, continues to be the subject of lively controversy and the Institute of Medicine report (1982:125) concludes that "it appears likely that both self-selection and authentic drug effects contribute to the 'motivational' problems seen in some chronic marijuana users."

Recently, a body of literature has accumulated that reports on links between marijuana use and such health impairments as lung disease, chromosome damage, reduced reproductive function, and brain dysfunction (summarized in Institute of Medicine, 1982, and National Institute on Drug Abuse, 1980). In some areas--for example, effects on the nervous system and behavior and on the cardiovascular and respiratory systems--there is clear evidence that marijuana produces acute short-term effects (Institute of Medicine, 1982:2,3):

With a severity directly related to dose, marijuana impairs motor coordination and affects tracking ability and sensory and perceptual functions important for safe driving and the operation of other machine8. . . . [It also] increase8 the work of the heart, usually by raising the heart rate and, in some persons, by raising blood pressure.

There is as yet no such clear evidence on the possible long-term effects in these areas, or of other potential health consequences of marijuana use; further research is needed. In

addition) most studies on human populations have been laboratory studies of young, healthy adult males. Differential effects of marijuana use on the elderly, on pregnant women, on groups that are psychiatrically vulnerable or at risk for disease or dysfunction, and particularly on adolescents have not been studied systematically

In our view, the most troublesome aspects of marijuana use are its potential effects on the development of adolescents. Parents as well as a number of clinicians and researchers are concerned that the social and intellectual development of teenagers may be harmed by chronic marijuana use. There is good evidence that intoxication may seriously impair such important skills as comprehension and retention of newly presented educational materials (Institute of Medicine, 1982). Rapidly growing tissues have been shown to be particularly vulnerable to some, although by no means all, toxic agents, and there is at least a possibility that toxic effects may be subtle and not clearly manifest until adulthood. Scientifically, these are difficult relationships to identify, and the research to date is still insufficient to strongly support any relationship.

Perhaps more significant than any lasting biological effect is the effect of the drug in different patterns of use on emotional development, on the formation of habits, and on the acquisition of coping skills for stress situations. Indeed, although the many issues raised by the use of intoxicants to escape stressful challenge have not been systematically studied, the evident attractiveness of marijuana to many adolescents, and its possible dose-related interference with the study and hard work needed for intellectual development in the crucial high school years, make this a special matter for concern. This is particularly so in light of the fact that, unlike alcohol, marijuana is used by many adolescents during school hours. Finally, reports of the effects of marijuana use on automobile driving skills are worrisome.

This Committee has reviewed the scientific literature surveys of marijuana effects on health and behavior, including the major recent study conducted by the Institute of Medicine (1982) and those by the National Institute on Drug Abuse (1979; 1980), Tashkin et al. (1978), Nahas (1977), and Fried (1977). We agree with the conclusion of the Institute of Medicine report that it is likely that long-term heavy marijuana use will be shown to result in measurable damage to health, just as long-term chronic tobacco and alcohol use have proven to cause such damage. It is evident that the full impact of marijuana use on human health will not be clear without careful epidemiological studies involving substantial populations of users--a matter of some decades--even though it is predictable that this drug--like all others--will cause harm in some of its users, particularly in its heaviest users, and among these, in its heaviest adolescent users. At this time, however, our judgment as to behavioral and health-related hazards is that the research has not established a danger both large and grave enough to override all other factors affecting a policy decision.

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OVERVIEW OF CURRENT MARIJUANA POLICIES

Current federal and state marijuana laws are in part governed by international treaty. The major federal law relevant to marijuana is the Comprehensive Drug Abuse Prevention and Control Act of 1970, which repealed all prior federal legislation and reduced federal penalties for possession and sale. Although marijuana possession and sale are still prohibited, possession has been reduced from a felony to a misdemeanor offense; the maximum penalty for a first offense is $5,000 and one year's imprisonment. The Act also provides for conditional discharge, by which first offenders found guilty of simple possession or casual transfer (which is treated as simple possession) may be placed on probation for up to one year (Congressional Digest, 1979).

The Uniform Controlled Substance Act of 1970, drafted by the National Conference of Commissioners on Uniform State Laws, was designed to make state laws more compatible with the new federal law. Like the federal act, the Uniform Act reclassified marijuana as a hallucinogen rather than a narcotic and reduced the penalty for p05session from the felony to the misdemeanor level; a majority of the states have adopted the Uniform Act. Eleven states have withdrawn the criminal sanction from possession for personal use. In these states, arrest has been replaced with a traffic-ticket type of citation, and a small fine is the sole allowable penalty. About 30 states include some provision for conditional discharge of first offenders, and about a dozen of them provide for all records of the offense to be expunged. The Alaska Supreme Court ruled in 1975 that possession for personal use by adults at home was protected by the constitutional right to privacy and hence was not subject to any penalty (Rosenthal, 1979).

State penalties for second-offense possession and for selling marijuana are extremely variable. (See National Organization for the Reform of Marijuana Laws and Center for Study of Non-Medical Drug Use, 1979, for summary tables of state marijuana laws.) Sale is almost always a felony, with maximum sentences ranging from two years to life, although casual transfer, or "accommodation," is sometimes exempt from felony treatment. All but 15 jurisdictions punish cultivation as heavily as they do sale; the Uniform Act includes the two in the same classification (manufacture), with the same penalty provisions.

Federal prohibition of small-scale possession is virtually unenforced. At the March 1977 House of Representatives hearings on decriminalization, the chief of the criminal division of the Department of Justice testified that the federal government no longer effectively prosecutes the use of marijuana, "nor do we, under any conceivable way, in the Federal Government have the resources to do so" (Select Committee on Narcotics Abuse and Control, 1977:13). In terms of its effects from a law enforcement point of view, the present official federal policy of complete prohibition does not differ in fact from a policy of prohibition of supply only. Complete prohibition is the federal law, but partial prohibition is the practice. However, the law, even though partly unenforced, has probably had a restraining influence on the willingness of states to adopt policies of less than complete prohibition. The states traditionally have followed the federal lead in drug abuse legislation, although they are not legally required to do so (see the testimony of Jay Miller, American Civil Liberties Union, to the Select Committee on Narcotics Abuse and Control, 1977). In summary, in most states and according to federal law, U.S. marijuana policy is one of complete prohibition--that is, prohibition of both supply and use

Major alternatives to complete prohibition include prohibition of supply only--called partial prohibition--and regulation.* Prohibition of supply only means having no or only civil penalties) for use, possession, or, sometimes, "casual transfer" of small quantities of marijuana, while having criminal penalties for manufacture, importation, or commercial sale of marijuana. Regulation means not only eliminating penalties for use but also allowing controlled production and distribution.

Within each of the three broad policy options--complete prohibition, prohibition of supply only, and regulation--numerous subsidiary policy choices exist. For example, a policy of complete prohibition necessitates decisions about the resources to be devoted to enforcement, the appropriate penalties to be imposed for violations, and whether marijuana should be made available for any medical uses. Under a policy of prohibition of supply only, decisions must still be made about penalties and permitted medical uses. In addition, one must also determine how to distinguish between users and suppliers; whether cultivation should be permitted; how stronger preparations of the cannabis plant, such as hashish, should be treated; whether to criminalize small-scale casual transfers, made with or without payment; and what should be done about certain specific behaviors, such as the public use of marijuana and the operation of motor vehicles under the influence of the drug. Under a policy of regulation, some of the issues to be decided are the type of control system (e.g., state monopoly or licensed sale), the rules as to potency and quality, and appropriate penalties for violation of the system's rules.

*In this discussion, we use the terms "complete prohibition," and "prohibition of supply and use" interchangeably. We also use the terms "partial prohibition," "prohibition of supply only," and "decriminalization" as equivalent. We generally prefer the terms "partial prohibition," or "prohibition of supply only" since many people seem to regard decriminalization as the equivalent of legalization or regulation--which it most certainly is not. (The policy of partial prohibition has also been called the vice model.) Finally, we use "regulation" and "legalization" as equivalent terms.

The variety of choices within each of the broad policy options suggests that none can be characterized in a monolithic way. Some regulatory systems could be so stringent as to have results similar to prohibitory laws: e.g., a regulatory system that raised the price drastically above what the illegal market charges. Similarly, lack of enforcement could strongly reduce the impact of a prohibitory option. As we have already noted, this latter effect has already occurred in some jurisdictions in which the law provide8 for complete prohibition but users are not in fact prosecuted.

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A REVIEW OF THE REPORT OF THE NATIONAL COMMISSION ON MARIJUANA AND DRUG ABUSE

An attempt to describe a full array of policy options together with associated benefits and detriments of each of them was made by the National Coumission on Marijuana and Drug Abuse in its 1972 report, Marijuana: A Signal of Misunderstanding. With respect to the major policy choices, the Commission did a thorough job. The members and staff recognized the limited knowledge base for their deliberations and subsequently recommended that a second commission be appointed to review the situation four years later. Such a follow-up commission was never appointed. It seems appropriate, then, that this Committee reappraise the Commission's work in light of subsequent research findings, especially those relating to recent changes in marijuana policies.

The Commission examined the spectrum of social policies available to control marijuana use and the benefits and detriments of implementing each policy. The legal alternatives presented included those identified above:

complete prohibition; prohibition of supply only; and

regulatory approaches. The Commission emphasized that choosing among the three approaches requires consideration of the social milieu, cultural values, and practicalities of implementation. The Commission considered such social conditions particularly important in examining marijuana controls because both use of the drug and the laws prohibiting supply and use had symbolic importance, representing a clash of values between a dominant culture that opposed marijuana use and a large minority that either used marijuana or condoned its use. The probable effects of the various policies considered by the Commission include changes in use patterns, enforcement costs, and influence on related social concerns such as the marketing of other illicit drugs and general respect for law.

The Commission commented on all three broad policy options. It suggested first that total prohibition has resulted in costly enforcement, alienation of the young, discrimination through selective enforcement, some deterrence of supply (especially to middle-aged and middle-class potential users), but minimal deterrence of use by those with access to the drug. Second, the Commission stated its belief that prohibition of supply only would support the official policy of discouraging use, but at the same time would recognize the practical difficulties of attempting to eliminate use. The report listed a number of choices that might be made under a system of partial prohibition and described some of the practical problems they might entail (e.g., the need to distinguish between casual and commercial distributors). Finally, the Commission described regulation as a policy that only mildly disapproved of occasional use and that concentrated on controlling excessive use, but was mostly designed to lower the costs of prohibiting the drug. The Commission argued that marijuana consumption would increase considerably if complete prohibition were replaced by regulation. In addition, the Commission considered a major drawback of any regulatory system to be that its elimination of the main symbol of society's disapproval--criminal sanctions--would cause resentment among the nonuser majority of the population. Marijuana was described as being symbolic of countercultural lifestyles: "the drug's symbolism creates a risk of strong political reaction to any liberalization of the present laws by older members of the society" (National Commission on Marijuana and Drug Abuse. 1972, Appendix Volume 11:1149).

On balance, the Commission concluded that, since the threat of punishment had not apparently deterred the millions of people who had already used marijuana, the replacement

of complete by partial prohibition would not produce a significant increase in marijuana use. Consequently, the Commission recommended that individual marijuana users should not be subject to criminal prosecution for their private use or possession of small amounts of the drug, and that, on balance, the best policy was one of prohibition of supply only. In accordance with this view, the Commission recommended that federal and state laws should be amended to achieve partial prohibition. In the decade since the Commission report, a number of states have changed their laws in varying ways. These legal changes can be viewed as natural experiments, and one can use the data from them to reassess the Commission's conclusions regarding these policies.

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THE USE OF MARIJUANA: COMPARING COMPLETE AND PARTIAL PROHIBITION

To compare the two types of marijuana control policies presently used in the United States--prohibition of supply and use and prohibition of supply only--we need to consider only the one particular in which they differ:

the application of criminal sanctions against marijuana users. To compare the effects of the two policies, we can examine the effects of the prohibition of use and determine whether prohibition results in more costs than benefits or vice versa.

In recent years the prohibition of marijuana use has come under increasing criticism. Many students of the U.S. marijuana situation, including the National Commission on Marijuana and Drug Abuse, members of Congress, political analysts, and legal experts, have suggested that existing laws prohibiting marijuana use be repealed. These suggestions have been prompted by the failure of current policies to deter large numbers of users, the consequent criminalization of large numbers of young Americans, and the high social costs of such law enforcement. A number of professional associations and agencies have also gone on record in support of the removal of all criminal penalties for the private possession and use of marijuana as a means of reducing the economic costs of law enforcement and the social costs of arrest or imprisonment (criminalization) of young people who are otherwise not criminally involved or labeled. The organizations and agencies that have expressed this view include the American Medical Association, the American Bar Association, the American Public Health Association, the Canadian Commission of Inquiry into the Non-Medical Use of Drugs, the National Council of Churches, the National Advisory Commission on Criminal Justice Standards and Goals, the National Commission on Marijuana and Drug

Abuse, among others. Eleven states, with one-third of the nation ls population, have adopted some version of partial prohibition or 'decriminalization." (In Oregon, Alaska, Maine, Colorado, California, Ohio, Minnesota, Mississippi, New York, North Carolina, and Nebraska, citations and small fines have replaced arrests and incarceration for use-only marijuana-related offenses.)

At first glance, criminalizing the selling of marijuana might appear inconsistent with failing to punish its purchase. But in the drafting of laws, a line is often drawn between legal and illegal conduct so that the maximum reduction in the proscribed behavior can be gained at minimum social cost. Frequently it turns out that laws aimed solely at suppressing sales are more cost-effective in reducing both the possession and use of a substance than are laws that attempt to suppress possession directly. There are several reasons for this. First, there are fever sellers than buyers; this permits a concentration of law enforcement efforts where they do the most good. Second, juries are likely to be more sympathetic to a "mere" user, who may be ill-advised, than to a dealer making a profit from the weaknesses of other.. Offenses treated under the vice model (partial prohibition) range from gambling--the person who takes illegal bets is guilty of a crime while the person who places them is not--to the offense of selling new automobiles not equipped with seat belts--the seller, not the buyer, is guilty of an offense. Even Prohibition in 1919 never criminalized the possession or use of alcohol, only its manufacture and sale.

Effects of Partial Prohibition

Probably the most important fact about a policy of prohibition of supply only is that where it has been adopted it has apparently not led to appreciably higher levels of marijuana use than would have existed if use were also prohibited. The National Commission on Marijuana and Drug Abuse's speculations about the lack of change in use patterns resulting from repeal of prohibitions on use have been confirmed by data since 1972. Reports from California, Oregon, and Maine indicate no appreciable increase in use following decriminalization of use, at least in the short term.

Oregon, the first state to repeal prohibition of use (in October 1973) has been studied in a series of Drug Abuse Council surveys (National Governors' Conference, 1977). Surveys in 1974 and 1975 showed no major increase following decriminalization. While the percentage of adults who were current users had increased by January 1977 (from 20 to 24 percent), use had increased similarly nationwide in the same period, suggesting that the causes for the adult increase in Oregon were the same as those for increases in the rest of the country rather than the result of changes in the law. Indeed, the percentage of adult ever-users in Oregon in 1976 (24 percent) was lower than the average percentage of adult ever-users in the western United States (28 percent) in 1975-1976, although higher than the national average (21.3 percent). (It should be noted that aggregate use rates in the western United States are heavily weighted by use rates in California, the largest western state, which had relatively high rates even prior to the state repeal of prohibition of use.) That the increase in use in Oregon from 1973 to 1976 was probably not due to the new law is suggested by other survey data. Only a small proportion of non-users said fear of legal prosecution was a reason for nonuse in 1974, 1975, and 1976 (National Governors' Conference, 1977). On the question of the fear of health dangers) Drug Abuse Council survey data show that such fear decreased significantly over those years but has increased since 1976.

The state of Maine, which repealed criminal penalties for marijuana use in May 1976, surveyed the effects of legislation in July and August 1978 (State of Maine Department of Human Services, 1979). Its study concluded that the change from criminal to civil penalties has not caused a large increase in marijuana use: less than 1 percent of all adults and 3.1 percent of all high school students reported any increase in their use as a result of the new

law; 3.5 percent of adult regular users and 7 percent of high school regular users reported any increase in their use directly attributable to the change in the law. There is also preliminary evidence, based on a nationwide study of high school students between 1975 and 1979, that "any increase in marijuana use in the decriminalized states, taken as a group, was equal to or less than the increases being observed in the rest of the country where decriminalization was not taking place" (Johnston, 1980:5). It could be argued that because de facto repeal of prohibition of use has been taking place throughout the country, one should not expect to see larger increases in use in states that legally decriminalize than in others. Even if this is true, however, the important point is that the legal change to decriminalization does not, in itself, appear to lead to increases in use.

This lack of change is not particularly surprising. The statistical chance that any person would be apprehended for his or her use is, in fact, extremely low throughout the United States (though, as we note below, the large number of users is sufficient to generate a substantial volume of arrests in states that do prohibit use). As a result, it is hard to imagine that the deterrent effect of prohibition laws on any given user would be very great.

It has been suggested that repeal of government prohibitions might change attitudes related to health or morals, perhaps symbolizing that health officials certify marijuana use to be safe. The absence of large increases in marijuana use in repeal states, however, indicates that either the change in policy has not had such a symbolic effect, or that, if it has, its causal significance is not appreciable--though it must be acknowledged that changes of this type might take generations to occur.

Costs of Prohibition of Use

The costs of policies directed at the user are not negligible, although actual savings in law enforcement costs attributable to repeal of prohibition of use per se are difficult to estimate. The difficulty arises in part because marijuana arrests have decreased nationally in recent years, reflecting the overall tendency to relax enforcement of marijuana laws, and that change could lead to inaccurate estimates of the impact of repeal. Nevertheless, reduced law enforcement activities seem to have led to substantial savings in states that have repealed laws that prohibit use.

California made a careful study of the economic impact of its law repealing prohibition of use, which went into effect in January 1976 (State Office of Narcotics and Drug Abuse, 1977). The law reduced the penalty for personal possession of one ounce or less of marijuana from a possible felony to a citable misdemeanor, punishable as an infraction with a maximum fine of $100 without regard to prior possession offenses. Criminal custody, booking, and pretrial incarceration procedures were eliminated. Possession of more than one ounce was also made a misdemeanor, with a maximum fine of $500, six months in jail, or both. According to the study, these changes resulted in a 74 percent reduction in what the state had been spending yearly to enforce its marijuana laws. (Estimates of what the state had been spending ranged from $35 million to more than $100 million yearly; see National Governors' Conference, 1977.)

In addition to its economic benefits, repealing prohibition of use saves the social costs of criminalizing the marijuana user. In recent years, close to 400,000 people have been arrested each year for marijuana-related offenses despite the general nonenforcement of criminal sanctions for use (Federal Bureau of Investigation, 1980). Only a small fraction of the arrests are made under federal law, largely for importation of marijuana. About 85 percent of all marijuana-related arrests are for possession, usually of one ounce or less (see, e.g., State Office of Narcotics and Drug Abuse, 1977).

A study by the National Commission on Marijuana and Drug Abuse of a sample

consisting of some 3,000 of the people arrested for marijuana-related offenses in 1970 indicated that the marijuana arrest was usually the arrestee's first experience with the criminal justice system, particularly among juveniles (National Commission on Marijuana and Drug Abuse, 1972). Yet, "it is standard practice for law enforcement agencies to report such offenses to prospective employers, licensing agencies, and other authorities as 'narcotic drug arrests'" (testimony of Jay Miller, American Civil Liberties Union to the Select Committee on Narcotics Abuse and Control, 1977). Thus young users, who are often otherwise law-abiding people, are subject to an arrest record, or even a prison term, with implications extending into many aspects of their lives.

Alienation from the rule of law in democratic society may be the most serious cost of current marijuana laws. The National Commission on Marijuana and Drug Abuse was concerned that young people who see no rational basis for the legal distinction between alcohol and marijuana may become cynical about America's political institutions and democratic process. The American Bar Association report (printed in Select Committee on Narcotics and Drug Abuse, 1977) concurs in the view that marijuana laws that criminalize the millions of Americans who have used marijuana engender disrespect for the law.

Public Attitudes Toward Partial Prohibition

Although the National Commission on Marijuana and Drug Abuse concluded that prohibition of supply only would be a better policy than prohibition of supply and use, it felt that a serious disadvantage of such a course would be the upset and moral outrage 8uch a policy would engender. Hindsight now shows that the Commission was mistaken in predicting a strong uniform public reaction to the adoption of partial prohibition policies. Experience since 1973 has shown that repeal of criminal penalties for use of marijuana has not been accompanied by massive public protest in the states in which it occurred and, in fact, has had the approval of the majority of citizens in those states (National Governors' Conference, 1977).

Nationally, attitude trends are consistent with the experience of the repeal states. Roffman (1978) reports that public opinion surveys indicate a slowly increasing preference for a reduction in penalties for marijuana offenses; a 1975 national survey (National Institute on Drug Abuse, 1975-1976) found that 52 percent of American adults favored only a fine or probation for small marijuana offenses; and a 1977 Gallup poll showed that 28 percent of the public favored legalization, compared with 12 percent in 1969.

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THE SUPPLY OF MARIJUANA: COMPARING PROHIBITED AND REGULATED MARKETS

Policy implementation does not occur in an ideal world. Prohibition of supply has not, in practice, meant that no one has had access to marijuana--though this may have been the intent of those who framed that law. Similarly, regulation of supply does not mean that everyone who uses marijuana will use it moderately, minimizing its harm. Prohibition of supply does make marijuana less accessible than it might otherwise be to a large number of Americans, and thus it almost certainly reduces the total amount of the drug used and the number of users. Such reduction is the purpose of a partial prohibition policy and to some extent it is accomplished. Arguments for a regulated, legal supply of marijuana are largely based on the social costs and incomplete effectiveness of prohibition of supply and on the belief that regulating rather than prohibiting the supply would not lead to an unacceptably large increase in use.

Under a regulatory policy, the cultivation, importation, manufacture, distribution, retailing, and, of course, use of marijuana would no longer be illegal per se. Within this broad category, specific policy options range from a virtual withdrawal of the government from marijuana control (allowing the drug to be freely produced, advertised, and sold, very much as coffee is today--but protecting the consumer against harmful adulterants), to a carefully controlled system of licensing, to a government monopoly on retail sales, wholesale distribution, or manufacture of marijuana. Thus, controls might be placed on such factors as quality, potency, amount purchased, time and place of sales, age of buyers, etc. If marijuana were regulated as is alcohol, restrictions would derive from federal, state, or local statutes, with the majority of them not at the federal level. Regulations might also include legally fixed prices--as in state-controlled alcohol beverage retailing or as a consequence of the levying of excise taxes.

The specific form and content of any proposed regulatory system are very important for those faced with the decision as to whether and under what conditions to remove penalties for the distribution of marijuana, but such details are beyond the scope of this report.

The advantages of a policy of regulation include the disappearance of most illegal market activity, the savings in economic and social costs of law enforcement directed against illegal supply systems, better controls over the quality and safety of the product, and, possibly, increased credibility for warnings about risks. The major disadvantages are a consequence of increased marijuana use--increases in harm to physical health and to individual development and behavior.

Costs of Prohibition of Supply

The number of arrests for violations related to supply is much lower than for those related to use. But enforcement of prohibition of supply is far more costly per arrest. Long undercover investigations, the purchase of expensive hardware, and the major consumption of trial and correctional resources are largely attributable to the prohibition of supply

The National Institute on Drug Abuse (1975) estimated that in 1974 costs for enforcement of marijuana laws totaled $600 million for state and local agencies. If we extrapolate from the California data (State Office of Narcotics and Drug Abuse, 1977), about three-fourths of the total is spent enforcing the law against marijuana supply. The total federal drug abuse law enforcement budget was more than $400 million in 1979, about half of which was the budget for the Drug Enforcement Administration. At the federal level, authorities do not

break down their expenditures on enforcement between marijuana and other drugs; virtually all of the federal resources that are allocated to marijuana are spent in attempting to enforce the laws against supply.

The task of attempting to make the prohibition of supply effective is, of course, formidable. In 1969 Operation Intercept demonstrated the practical difficulty of sealing off the Mexican border. In the weeks the operation lasted, hundreds of thousands of vehicles and passengers were searched every day; ensuing traffic jams caused expenditures by U.S. tourists and commuters to Mexico to drop 50-70 percent below normal (Kaplan, 1971). The situation was intolerable and the program was halted. However, the federal government has continued efforts to improve border surveillance and to penetrate trafficking networks. The White House Strategy Council on Drug Abuse (1979) notes that more than 5.6 million pounds of marijuana was seized at the Mexican border over a 12-month period in 1977-1978; a large increase over the 1.5 million pounds seized during the previous 12 months, "but a fraction of marijuana entering the country." Recently, the Council has suggested strengthening border surveillance by cooperative efforts of the Drug Enforcement Administration, the Customs Service, the Coast Guard, and the Department of State and by the use of the detection capabilities of the armed forces as well.

In our view, the prospects for major success in these ventures are not great. Nor is there much likelihood that some recently suggested measures against marijuana production outside the U.S. would make future prohibition of supply more effective. For example, the White House Strategy Council on Drug Abuse has supported crop eradication programs, provided that the proposed method of eradication is evaluated for possible health and environmental consequences and that a readily distinguishable marker is added to any chemical herbicides that are used, but the political obstacles to this course would be significant. Entirely apart from the views of producer nations, which are likely to be quite negative, the public is unlikely to support the use of chemicals of unknown toxicity on an import product, legal or not, that may be used by large numbers of Americans. And irrespective of the degree of success of controlling imports) the problem of domestic production under a policy of partial prohibition remains. Although the illegal domestic industry is thought to account for only about 15 percent of American marijuana consumption, marijuana grows easily in many parts of the United States. The National Commission on Marijuana and Drug Abuse cited a Department of Agriculture estimate that in 1972 there were S million acres containing wild marijuana in the United States and an undetermined but obviously growing number of acres under cultivation.

Law enforcement costs are by no means the only costs of prohibition of supply. There are large amounts of money being made in marijuana--which, like any illegal business, carries with it the likelihood of corruption of public officials and the loss of tax dollars. Violence is also a cost of attempting to prohibit marijuana supply; this problem is not confined to illegal marijuana production abroad. There has been violence in marijuana-growing regions in the United States. The extent of such violence is not known with any precision, but there have been popular press reports of kidnappings, assaults, burglaries, and homicides known to be connected with the marijuana business in northern California and elsewhere.

Another major cost of attempts to prohibit the supply of marijuana is related to the fact that many illegal sellers of marijuana also sell other illegal drugs, e.g., PCP, amphetamine, and barbiturates (Blum, 1971). It is likely, therefore, that prohibition of the supply of marijuana increases access to and use of other illegal drugs through the creation of an illegal marketing system for all drugs. Little is known about the structures and activities of illicit drug markets. It is clear, however, that there are many small-scale marijuana dealers) that many sellers service only their friends and acquaintances, and that those who sell marijuana are thereby more likely to come into contact with users and sellers of more dangerous

drugs, to use such drugs, and to make them available to their clientele (Blum, 1971). Moreover, there is reason to believe that marijuana sellers may become socialized into other illegal activities.

TABLE 1 Lifetime Prevalence and Use in Past Month of Marijuana, 1971-1979, by Category of User (percentage)

Category of User	1971	1972	1974	1976	1977	1979
Youth: Ages 12-17						
Ever used	14.0	14.0	23.0	22.4	28.0	30.9
Used in past month	6.0	7.0	12.0	12.3	16.6	16.7
Young Adults: Ages 18-25						
Ever used	39.3	47.9	52.7	52.9	59.9	68.2
Used in past month	17.3	27.8	25.2	25.0	27.4	35.4
Older Adults: Ages 26+						
Ever used	9.2	7.4	9.9	12.9	15.3	19.6
Used in past month	1.3	2.5	2.0	3.5	3.3	6.0
(Number)	(3,186)	(3,265)	(4,022)	(3,576)	(4,594)	(7,224)

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Costs of Regulating Supply

The wide availability and use of marijuana are not only major factors in the cost of attempts to prohibit the supply of the drug, they also have implications for the likely magnitude of increases in use that could be expected under a regulatory policy. Greater use of marijuana under a regulatory policy is regarded as the most significant cost of such a policy. In an analysis of this potential cost, however, it is important to note that under the present policy of prohibition, prevalence and frequency of marijuana use are substantial and have increased in recent years.*

*The data indicating rates of use are based on self-reports; as such, their reliability and validity may be questioned. Nevertheless, as Radosevich et al. (1979) indicate, studies of questions on drug use have consistently demonstrated reliable responses within the same instrument and over time. Furthermore, there are indications that most drug surveys do not have serious validity problems (see Whitehead and Smart and Abelson and Atkinson, both cited in Radosevich et al., 1979; Johnston et al., 1982).

A National Institute on Drug Abuse general household survey (Fishburne et al., 1980) shows that 35.4 percent of the 18-25-year-olds in the United States report having used marijuana in the month preceding the survey. Yearly surveys show a steady increase from 1971 to 1979 in the percentage of people who report having ever used marijuana as well as in the percentage of people who report being current users (see Table 1). These survey results (Fishburne et al., 1980) also indicate that between 1976 and 1977, the percentage of current users among 12-17-year-olds increased from 12.3 to 16.6 percent; this trend had leveled off by 1979 and has since shown a decline. In an annual survey of national samples of some 17,000 high school seniors, Johnston et al. (1982) found that 7.0 percent of the class of 1981 reported daily marijuana use, compared with 6.0 percent in 1975 and 10.7 percent in 1978, the peak year (see Table 2). There has been a similar trend in initial use at younger ages.

TABLE 2 Trends in Prevalence of Marijuana Use by High School Seniors (percentage)

Class							
Prevalence	1975	1976	1977	1978	1979	1980	1981
Ever used	47.3	52.8	56.4	59.2	60.4	60.3	59.5
Used in last							

12 months 40.0 44.5 47.6 50.2 50.8 48.8 46.1
Used in last
30 days 27.1 32.2 35.4 37.1 36.5 33.7 31.6
Used daily in
last 30 days 6.0 8.2 9.1 10.7 10.3 9.1 7.0
51)Daily use defined as using marijuana on 20 or more occasions in the last 30 days.

Although the present policy of prohibition of supply is not preventing the current levels of marijuana use, including use among the very young, it is probable that most strategies under a regulatory policy would result in an overall increase in use. Even more important than overall use rates, however, are likely changes in consumption patterns; such patterns are the most difficult changes to predict. The smallest increases in numbers of users can be expected to occur among those to whom marijuana is now most readily available--the young. Johnston et al. (1982) found that close to 90 percent of the high school seniors in their national sample survey report that marijuana is "fairly easy" or "very ea8y for them to get. This percentage remained relatively stable over the seven years, 1975-1981. At the same time, the reported availability of most other illegal drugs (except cocaine) declined considerably. For example, while 46.2 percent of the 1975 high school seniors said that LSD would be "fairly easy" or "very easy" to get, only 32.2 percent of the class of 1978 gave those responses. It would appear, therefore, that the reports of easy availability are not due to a tendency of adolescents to report any illegal drug as easy to get, but reflect their actual access to the drug. It might also be noted that only 13.9 percent of the class of 1978 reported having no friends who smoke marijuana; thus it is reasonable to expect that at least 86 percent have a factual basis for estimating the availability of the drug.

Other survey data corroborate these findings. Radosevich et al. (1979) report that a 1975 national survey by the Drug Abuse Council found that at least 70 percent of the high school students in their sample reported marijuana "easy to get, and O'Donnell et al. (1976) found similar results. There are no contrary reports for recent years. In sum, one can be reasonably confident that, at least with respect to older adolescents, the prohibition against supply does not succeed in suppressing access to marijuana. (The effect on price is discussed below.)

Regulation could be expected to provide the greatest increase in availability to those to whom the drug is now least available, i.e., older adults who are not in contact with marijuana sellers or a drug-using subculture and who are most likely to avoid illegal "connections."

It has been argued that a serious cost of the adoption of a regulatory policy for marijuana is the likelihood that such a change might delude many people into believing that the drug is safe. As noted above, there is no indication that the elimination of penalties for marijuana use has caused the drug to be regarded as any less dangerous. Moreover, alcohol and tobacco are almost universally regarded as involving risks to health, and these drugs are already made available under regulatory systems.

To the extent that marijuana use causes harm, one is necessarily concerned about policy changes that will lead to increases in use. As we have noted, however, it is a fact that marijuana is already widely available despite the legal prohibition of supply and that, despite the best efforts of government under any foreseeable set of conditions, it will continue to be. Though a regulatory policy would increase the availability of the drug, estimates of the size of these increases, and associated increases in harm, must be weighed against estimates of the costs and weaknesses of continuing prohibitions of supply. In pragmatic terms, the issue is whether more harm would be done, overall, by retaining the partly effective, costly prohibition of supply or by moving to a system of legalized regulated sales--wherein

presumably more people would use more marijuana, but some of the costs imposed by prohibition of supply would be removed.

Regulatory Systems: Some Concrete Aspects

To this point, a policy of regulation has been discussed rather abstractly in contrast with the more concrete discussion of prohibition policies. Experimentation with varying systems of regulation followed by adjustment and readjustment based on experience would be necessary before those most appropriate for particular circumstances could be developed. This can be a complex matter. For instance, U.S. alcohol policy, developed with the repeal of Prohibition, consists of an umbrella of national policy and a wide variety of supporting state and local regulation. The national policy umbrella includes controls on importation, taxation) potency) packaging, labeling, advertising, use in federal jurisdictions (e.g., parks, military installations), and use in Systems regulated by the federal government (e.g., air transportation); it also provides funds and guidelines for the treatment of casualties of excessive use. Under the umbrella policy, states and local jurisdictions regulate taxes, retail sales, hours of availability, age limits, and the like, where supply is legal, or prohibit sales entirely. Some states have monopoly systems for package sales, others use licensed private stores. Historically, under this system, the strictness of controls has reflected local sentiment about the consumption of alcohol. Although few "dry" jurisdictions exist today, various degrees of local "dryness" were quite widespread until very recently (National Research Council, 1981).

Controlling Use

A regulated system of marijuana sale might attempt to moderate use by inhibiting the frequency of use and the amounts used as well as by prescribing conditions of purchase and use. However, it is likely that under a regulatory system consumption would in great part be controlled by informal social norms--as it is today.

Manipulating the price of the drug is an obvious means of inhibiting use. It has been argued that most adults would be willing to pay a higher price for legal marijuana than they currently pay for illegal supplies in return for not having to seek out "connections" and being relieved of the feeling that they may be supporting organized crime. A high price would be comparatively more restrictive for young people--precisely those whom one would most want to discourage from use--since, though they seem affluent compared with young people in previous times, their budgets are in fact more constrained than those of adults. The possibility of illegal markets selling to young people remains, but today's kind of illegal market for marijuana would probably shrink greatly under a regulatory system in the same way that illegal alcohol distribution systems have become so scarce. Young users would be much more likely to gain access to marijuana by diversion from the legal market--as they do today for alcohol--or from homegrown plants than from a wholly illegal chain of distributors. Such a development would make marijuana selling a less profitable and status-producing occupation among the young.

It has been suggested that if legal limits were imposed on the potency of legally available marijuana, a substantial illegal market for high-potency forms of the drug, including hashish, would still exist. Since it is likely that there would continue to be some users who prefer high-potency forms of cannabis, this is a reasonable concern. But there is no compelling a priori reason to believe that a legal structure for retail marijuana sales, which includes limits on potency, would result in any increase in the availability and use of high-potency products.

Home Cultivation

Cultivation of marijuana by users is another issue that would have to be confronted in

devising a regulatory system. Growing marijuana without payment of a tax might be treated as a revenue offense. Without criminal penalties or vigorous enforcement, however, deterrent effects would be minimal since marijuana can be grown indoors anywhere in the United States using artificial light--and at comparatively little expense. A recent British study of options for marijuana control (Logan, 1979) suggests that, from a law enforcement perspective, it is not feasible to attempt to control home cultivation. Whether users would take the trouble to grow their own marijuana would depend in part on the legal price. The relatively high prices that might be charged in order to discourage use and to increase revenues would also tend to encourage home cultivation. Whatever its disadvantages, however, the use of homegrown marijuana at least would not bring users into contact with those who illegally sell the drug. With respect to young people, moreover, marijuana under cultivation is much harder for children to hide from parents than is the purchased prepared drug, and cultivation by juveniles could remain illegal if age limits on use were imposed. Nonetheless, the treatment of home cultivation represents a major issue for the design of a regulatory system.

Public Education

Excessive use may be discouraged by policies aimed at public education and at the use of the media, including a ban on commercial advertising. Although information on how to use drugs, on drug hazards, and on the attributes of drugs is passed along most effectively through informal channels (see, e.g., Hanneman, 1972), media and education programs can make such information far more readily available.

Research on the communication of messages to the public has identified source credibility as a major factor contributing to the persuasive power of a message (McGuire, 1969). It appears that the public is now extremely wary of some government information programs that attempt to influence health behaviors. The credibility of the federal government may be especially suspect when it issues health warnings about an illegal substance that it is clearly trying to prohibit. Rosenthal (1979) asserts that distrust of the government and the medical establishment has grown because of past exaggerations and distortions of the effects of some mind-altering drugs.

Informal Social Controls

In an assessment of possibilities for governmental controls under a regulatory system, the operation of informal norms for controlling substance use practices must be taken into account (Maloff et al., 1980). National experience with alcohol use, for example, provides evidence that there are informal rituals and sanctions that generally encourage moderation in the use of recreational drugs. Moreover, moderation is encouraged when a drug is introduced gradually, that is, to a growing population of users, like marijuana in the 1960s and early 1970s. One might expect that when a new drug is introduced into a society, governmental control would be particularly important since no informal controls for teaching people appropriate rules for use would have developed. If a potent drug is made widely available precipitously and very cheaply to a novice population, severe societal disruptions may occur: for example, the gin epidemics of early eighteenth-century England (see Clark, 1976). Because in the past two decades informal norms for controlling marijuana use have spread in the United States under conditions of greatly increased availability of marijuana, there is reason to believe that widespread uncontrolled use would not occur under regulation. Indeed, regulation might facilitate patterns of controlled use by diminishing the "forbidden fruit" aspect of the drug and perhaps increasing the likelihood that an adolescent would be introduced to the drug through families and friends who practice moderate use, rather than through their heaviest-using, most drug-involved peers.

Relations Among States

As has historically been the case with respect to alcohol, state governments differ in their approaches to marijuana. So long as present federal law continues to prohibit cultivation and distribution of marijuana, states cannot adopt a regulatory system, although they are legally free to reduce or eliminate their own penalties for sale and are not compelled to enforce federal laws. If federal law were changed, however, the institution of a regulatory system in one state would have reverberations in other states. Residents of states that continued to prohibit marijuana could be expected to cross state lines to purchase the drug in a state with a regulated system, thus further compromising the ability of states to enforce prohibition of supply among its residents. Furthermore, states that attempted to curtail consumption by raising prices might find their populations turning to lower-cost marijuana from neighboring states with lower prices. This is a familiar situation. Large numbers of both cigarettes and guns are smuggled illegally into New York from other states. Moreover, New Yorkers may travel to New Jersey to gamble in a casino, or Virginians to the District of Columbia to buy cheaper liquor. It is difficult to see how state prohibitions could remain effective if the number of states with regulatory systems grew very large unless the changes occurred in only one region of the country. However, there may be advantages in permitting a state-by-state approach. Conditions governing the costs and benefits both of partial prohibition and of regulation vary among the states. In this area of uncertainty, we may learn from experiment. If one regulatory system proved successful, other states would be more likely to adopt similar systems; similarly, if it worked poorly in one state, other states would be less inclined to adopt a regulatory policy.

Effects on Foreign Relations

The 1961 Single Convention on Narcotic Drugs, which now obligates the U.S. government to prevent the importation of marijuana and to prohibit the adoption of a licensing system by any state is a serious (although not an insurmountable) obstacle to the adoption of a federal regulatory policy and the development of state licensing. The treaty allows a signatory to terminate its adherence to the agreement at any time after two years from the date of the convention. Of course the general impact of any move to withdraw from the convention includes a broad foreign policy context, which is beyond the expertise of this Committee to judge.

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CONCLUSIONS

For the last decade, concern with health hazards attributable to marijuana has been rising. The hearts, lungs, reproductive functions, and mental abilities of children have been reported to be threatened by marijuana, and such threats are not to be taken lightly. Heavy use by anyone or any use by growing children should be discouraged. Although conclusive evidence is lacking of major, long-term public health problems caused by marijuana, they are worrisome possibilities, and both the reports and the a priori likelihood of developmental damage to some young users makes marijuana use a cause for extreme concern

At the same time, the effectiveness of the present federal policy of complete prohibition falls far short of its goal--preventing use. An estimated 55 million Americans have tried marijuana, federal enforcement of prohibition of use is virtually nonexistent, and 11 states have repealed criminal penalties for private possession of small amounts and for private use. It can no longer be argued that use would be much more widespread and the problematic effects greater today if the policy of complete prohibition did not exist: The existing evidence on policies of partial prohibition indicates that partial prohibition has been as effective in controlling consumption as complete prohibition and has entailed considerably smaller social, legal, and economic costs. On balance, therefore, we believe that a policy of partial prohibition is clearly preferable to a policy of complete prohibition of supply and use.

We believe, further that current policies directed at controlling the supply of marijuana should be seriously reconsidered. The demonstrated ineffectiveness of control of use through prohibition of supply and the high costs of implementing such a policy make it very unlikely that any kind of partial prohibition policy will be effective in reducing marijuana use significantly below present levels. Moreover, it seems likely to us that removal of criminal sanctions will be given serious consideration by the federal government and by the states in the foreseeable future. Hence, a variety of alternative policies should be considered.

At this time, the form of specific alternatives to current policies and their probable effect on patterns of use cannot be determined with confidence. It is possible that, after careful study, all alternatives will turn out to have so many disadvantages that none could command public consensus. To maximize the likelihood of sound policy for the long run, however, further research should be conducted on the biological, behavioral, developmental, and social consequences of marijuana use, on the structure and operation of drug markets, and on the relations of various conditions of availability to patterns of use.

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RECOMMENDATIONS FOR RESEARCH

Health and Behavior

The persistent concern about the health-related effects of marijuana requires both an immediate and a continuing response. First, as the report of the Institute of Medicine (1982:5) recommends, there should be "a greatly intensified and more comprehensive program of research into the effects of marijuana on the health of the American people." An important goal of this research program should be the identification of subgroups at high risk for physiological and psychological damage in relation to patterns of use and doses of marijuana. The report presents a detailed agenda of needed research. Second to the extent that potential health hazards are identified, policy research should address possible safeguards and precautions to protect the user.

If marijuana use can be scientifically shown to entail grave risks--to the brain, the cardiovascular and respiratory systems, or to reproductive functions, for example--that are currently not known, it can be argued that, as was the case with cigarette smoking, knowledge of those effects will be more effective than criminal enforcement as a deterrent to use.

Drug Markets

Research on the price elasticity of demand in legal and illegal markets is a clear priority. The result of such research will be important in determining the likelihood of controlling heavy use through price mechanisms and in computing the amount of money--if any--that could be realized in taxation of marijuana.

Present knowledge of the structure and activities of drug markets and networks is insufficient to allow prediction of the effects of policy changes on them. Research in this area is difficult but the questions are important. If many dealers who sell cocaine, PCP, amphetamines, and barbiturates as well as marijuana would be put out of business if marijuana were available through legal channels, it might result in a curtailed market for a variety of other drugs. On the other hand, it is also possible that the market structure is so loosely organized, and dealers so transiently involved, that removing marijuana from the illegal markets would have little effect. To be sure, much research on some of these questions could not be conducted unless a regulatory system were in place in some state. Nonetheless, some research, particularly ethnographic and economic studies, should be undertaken now to discover the importance of marijuana profits to drug-dealing networks; the transiency, size, and nature of such networks; etc. It is essential for research in this area to be supported by appropriate government agencies.

Effects on Use

Although many questions remain to be answered before the most informed choices can be made between prohibiting and regulating supply, there are many things that cannot be known unless some jurisdiction tries a regulatory policy. Although adoption of a regulatory policy is likely to result in increased use, little is known about changes in patterns of use that are likely to result. If federal laws prohibiting supply are changed to allow states to

license marijuana sales, epidemiological research programs must be ready to monitor any changes in use and their consequences. To do so, research should be organized and operating well in advance of any such policy changes in order to determine rates of use before the change. Although the shift in the law from complete to partial prohibition in 11 states has apparently had little effect on consumption patterns there, we do not know the degree to which legally available marijuana would attract a larger market. The impact on use of educational campaigns, health warnings, and informal social controls under a regulatory system should be investigated.

In the absence of the opportunity for states to adopt regulatory policies, there can only be educated guesses about which age groups are likely to increase use or whether individuals who now use marijuana will use more, etc. Meanwhile, every bit of analysis to predict the answers to these questions, by surveying public attitudes, assessing past experiences with the spread of drug use in society (e.g., alcohol use following the repeal of Prohibition), and critically reviewing the experience of other societies in which marijuana is more readily available, will be valuable.

Marijuana regulation would permit systematic provision of comprehensive, clearly communicated health warnings on package inserts or covers, in public health education, by medical practitioners, and by public health interest groups as well as by the government. The extent to which such warnings would have more credibility for users than current health warnings, generated in an atmosphere of prohibition, is an important subject for research. Despite widespread pessimism about the failures of drug education campaigns, there are encouraging results in educational approaches based on the Stanford Heart Disease Prevention Program experience. With appropriate, research-based models and techniques, public health education may be an attractive means for limiting excessive use (see, e.g., Maccoby, 1979).

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APPENDIX: SUMMARY OF MARIJUANA AND HEALTH

The Institute of Medicine (IOM) of the National Academy of Sciences has conducted a 15-month study of the health-related effects of marijuana, at the request of the Secretary of Health and Human Services and the Director of the National Institutes of Health. The IOM appointed a 22-member committee to:

analyze existing scientific evidence bearing on the possible hazards to the health and safety of users of marijuana;

analyze data concerning the possible therapeutic value and health benefits of marijuana;

assess federal research programs in marijuana;

identify promising new research directions, and make suggestions to improve the quality and usefulness of future research; and draw conclusions from this review that would accurately assess the limits of present knowledge and thereby provide a factual, scientific basis for the development of future government policy.

This assessment of knowledge of the health-related effects of marijuana is important and timely because marijuana is now the most widely used of all the illicit drugs available in the United States. In 1979, more than 50 million persons had tried it at least once. There has been a steep rise in its use during the past decade, particularly among adolescents and young adults, although there has been a leveling-off in its overall use among high school seniors in the past 2 or 3 years and a small decline in the percentage of seniors who use it frequently. Although substantially more high school students have used alcohol than have ever used marijuana, more high school seniors use marijuana on a daily or near-daily basis (9 percent) than alcohol (6 percent) Much of the heavy use of marijuana, unlike alcohol,

takes place in school, where effects on behavior, cognition, and psychomotor performance can be particularly disturbing. Unlike alcohol, which is rapidly metabolized and eliminated from the body, the psychoactive components of marijuana persist in the body for a long time. Similar to alcohol, continued use of marijuana may cause tolerance and dependence. For all these reasons, it is imperative that we have reliable and detailed information about the effects of marijuana use on health, both in the long and short term.

What, then, did we learn from our review of the published scientific literature? Numerous acute effects have been described in animals, in isolated cells and tissues, and in studies of human volunteers; clinical and epidemiological observations also have been reported. This information is briefly summarized in the following paragraphs.

EFFECTS ON THE NERVOUS SYSTEM AND ON BEHAVIOR

We can say with confidence that marijuana produces acute effects on the brain, including chemical and electrophysiological changes. Its most clearly established acute effects are on mental functions and behavior. With a severity directly related to dose, marijuana impairs motor coordination and affects tracking ability and sensory and perceptual functions important for safe driving and the operation of other machines; it also impairs short-term memory and slows learning. Other acute effects include feelings of euphoria and other mood changes, but there also are disturbing mental phenomena, such as brief periods of anxiety, confusion, or psychosis.

There is not yet any conclusive evidence as to whether prolonged use of marijuana causes permanent changes in the nervous system or sustained impairment of brain function and behavior in human beings. In a few unconfirmed studies in experimental animals, impairment of learning and changes in electrical brain-wave recordings have been observed several months after the cessation of chronic administration of marijuana. In the judgment of the committee, widely cited studies purporting to demonstrate that marijuana affects the gross and microscopic structure of the human or monkey brain are not convincing; much more work is needed to settle this important point.

Chronic relatively heavy use of marijuana is associated with behavioral dysfunction and mental disorders in human beings, but available evidence does not establish if marijuana use under these circumstances is a cause or a result of the mental condition. There are similar problems in interpreting the evidence linking the use of marijuana to subsequent use of other illicit drugs, such as heroin or cocaine. Association does not prove a causal relation, and the use of marijuana may merely be symptomatic of an underlying disposition to use psychoactive drugs rather than a "stepping stone" to involvement with more dangerous substances. It is also difficult to sort Out the relationship between use of marijuana and the complex symptoms known as the motivational syndrome. Self-selection and effects of the drug are probably both contributing to the motivational problems seen in some chronic users of marijuana.

Thus, the long-term effects of marijuana on the human brain and on human behavior remain to be defined. Although we have no convincing evidence thus far of any effects persisting in human beings after cessation of drug use, there may well be subtle but important physical and psychological consequences that have not been recognized.

EFFECTS ON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

There is good evidence that the smoking of marijuana usually causes acute changes in the heart and circulation that are characteristic of stress, but there is no evidence to indicate that

a permanently deleterious effect on the normal cardiovascular system occurs. There is good evidence to show that marijuana increases the work of the heart, usually by raising heart rate and, in some persons, by raising blood pressure. This rise in workload poses a threat to patients with hypertension, cerebrovascular disease, and coronary atherosclerosis.

Acute exposure to marijuana smoke generally elicits broncho-dilation; chronic heavy smoking of marijuana causes inflammation and pre-neoplastic changes in the airways, similar to those produced by smoking of tobacco. Marijuana smoke is a complex mixture that not only has many chemical components (including carbon monoxide and "tar") and biological effects similar to those of tobacco smoke, but also some unique ingredients. This suggests the strong possibility that prolonged heavy smoking of marijuana, like tobacco, will lead to cancer of the respiratory tract and to serious impairment of lung function. Although there is evidence of impaired lung function in chronic smokers, no direct confirmation of the likelihood of cancer has yet been provided, possibly because marijuana has been widely smoked in this country for only about 20 years, and data have not been collected systematically in other countries with a much longer history of heavy marijuana use.

EFFECTS ON THE REPRODUCTIVE SYSTEM AND ON CHROMOSOMES

Although studies in animals have shown that delta-9-THC (the major psychoactive constituent of marijuana) lowers the concentration in blood serum of pituitary hormones (gonadotropins) that control reproductive functions, it is not known if there is a direct effect on reproductive tissues. Delta-9-THC appears to have a modest reversible suppressive effect on sperm production in men, but there is no proof that it has a deleterious effect on male fertility. Effects on human female hormonal function have been reported, but the evidence is not convincing. However, there is convincing evidence that marijuana interferes with ovulation in female monkeys. No satisfactory studies of the relation between use of marijuana and female fertility and child-bearing have been carried out. Although delta-9-THC is known to cross the placenta readily and to cause birth defects when administered in large doses to experimental animals, no adequate clinical studies have been carried out to determine if marijuana use can harm the human fetus. There is no conclusive evidence of teratogenicity in human offspring, but a slowly developing or low-level effect might be undetected by the studies done so far. The effects of marijuana on reproductive function and on the fetus are unclear; they may prove to be negligible, but further research to establish or rule out such effects would be of great importance.

Extracts from marijuana smoke particulates ("tar") have been found to produce dose-related mutations in bacteria; however, delta-9-THC, by itself, is not mutagenic. Marijuana and delta-9-THC do not appear to break chromosomes, but marijuana may affect chromosome segregation during cell division, resulting in an abnormal number of chromosomes in daughter cells. Although these results are of concern, their clinical significance is unknown.

THE IMMUNE SYSTEM

Similar limitations exist in our understanding of the effects of marijuana on other body systems. For example, some studies of the immune system demonstrate a mild, immunosuppressant effect on human beings, but other studies show no effect.

THERAPEUTIC POTENTIAL

The committee also has examined the evidence on the therapeutic effects of marijuana in a variety of medical disorders. Preliminary studies suggest that marijuana and its derivatives or analogues might be useful in the treatment of the raised intraocular pressure of glaucoma,

in the control of the severe nausea and vomiting caused by cancer chemotherapy, and in the treatment of asthma. There also is some preliminary evidence that a marijuana constituent (cannabidiol) might be helpful in the treatment of certain types of epileptic seizures, as well as for spastic disorders and other nervous system diseases. But, in these and all other conditions, much more work is needed. Because marijuana and delta-9-THC often produce troublesome psychotropic or cardiovascular side-effects that limit their therapeutic usefulness, particularly in older patients, the greatest therapeutic potential probably lies in the use of synthetic analogues of marijuana derivatives with higher ratios of therapeutic to undesirable effects.

THE NEED FOR MORE RESEARCH ON MARIJUANA

The explanation for all of these unanswered questions is insufficient research. We need to know much more about the metabolism of the various marijuana chemical compounds and their biologic effects. This will require many more studies in animals, with particular emphasis on subhuman primates. Basic pharmacologic information obtained in animal experiments will ultimately have to be tested in clinical studies on human beings.

Until 10 or 15 years ago, there was virtually no systematic, rigorously controlled research on the human health-related effects of marijuana and its major constituents. Even now, when standardized marijuana and pure synthetic cannabinoids are available for experimental studies, and good qualitative methods exist for the measurement of delta-9-THC and its metabolites in body fluids, well-designed. studies on human beings are relatively few. There are difficulties in studying the clinical effects of marijuana in human beings, particularly the effects of long-term use. And yet, without such studies the debate about the safety or hazard of marijuana will remain unresolved. Prospective cohort studies, as well as retrospective case-control studies, would be useful in identifying long-term behavioral and biological consequences of marijuana use.

The federal investment in research on the health-related effects of marijuana has been small, both in relation to the expenditure on other illicit drugs and in absolute terms. The committee considers the research particularly inadequate when viewed in light of the extent of marijuana use in this country, especially by young people. We believe there should be a greater investment in research on marijuana, and that investigator-initiated research grants should be the primary vehicle of support

The committee considers all of the areas of research on marijuana that are supported by the National Institute on Drug Abuse to be important, but we did not judge the appropriateness of the allocation of resources among those areas, other than to conclude that there should be increased emphasis on studies in human beings and other primates. Recommendations for future research are presented at the end of Chapters 1-7 of this report.

CONCLUSIONS

The scientific evidence published to date indicates that marijuana has a broad range of psychological and biological effects, some of which, at least under certain conditions, are harmful to human health. Unfortunately, the available information does not tell us how serious this risk may be.

The major conclusion is that what little we know for certain about the effects of marijuana on human health--and all that we have reason to suspect--justifies serious national concern. Of no less concern is the extent of our ignorance about many of the most basic and important questions about the drug. Our major recommendation is that there be a greatly intensified and more comprehensive program of research into the effects of marijuana on the health of the American people.

Cannabis 1988 Old Drug, New Dangers The Potency Question

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The story of the new, allegedly stronger and more dangerous marijuana was rebirthed in January 1986 by the late Sidney Cohen, M.D., Professor of Psychiatry at UCLA: ``. . . material ten or more times potent than the product smoked ten years ago is being used, and the intoxicated state is more intense and lasts longer." In addition, Cohen (1986) asserted that ``the amount of THC [tetrahydrocannabinol] in confiscated street samples averaged 4.1 percent THC during 1984.

The sinsemilla varieties were about 7 percent with some samples reaching 14 percent. . . . all marijuana research to date has been done on 1 or 2 percent THC material and we may be underestimating present day smoking practices."

The average potency of marijuana samples seized by the Drug Enforcement Administration (DEA) increased from 0.5 percent THC in 1974 to 3.5 percent in 1985-1986, with sinsemilla (seedless marijuana) at 6.5 to 12 percent, announced Dr. Richard Hawks of NIDA later that year (Kerr 1986: 1). ``Parents who experimented in their youth are not aware that the potency is much higher," added Donald M. Delzer, Chairman of the National Federation of Parents for Drug Free Youth (Kerr 1986: 18).

``Now perceived as a hard drug, marijuana has increased 1,400 percent in potency since 1970," proclaimed the flyer of a national conference on marijuana (Henry Ohlhoff Outpatient Programs 1986). Drug abuse treatment professionals soon elaborated on the outcry. Tennant (1986) asserted that the drug of the 1970's contained one to three percent THC, while that of the 1980's contained five to 15 percent. Furthermore, the brain registers the difference exponentially, so the difference between one percent and 10 percent THC was not nine percent, but more like 900 percent (Garcia 1986: 3). Smith (1987) stated that Cohen ``taught us that marijuana was a lot more dangerous than we originally thought, particularly with the use of more potent preparations by young people." Inaba (1987) added that ``this new, stronger marijuana has a more disruptive effect on brain chemistry and body physiology than we had imagined previously," and mentioned heretofore

undescribed side effects among athletes: ``Baseball players who get beaned a lot admit to smoking marijuana. It impairs their ability to follow the ball."

In a column for drug abuse counselors, Meyers (1987) advised ``supportive therapy" for the effects of the ``new" marijuana, which were described as ``depersonalization, disorientation, derealization, changes in perception, and alterations in body image . . . acute brain syndromes with temporary clouding of mental processes . . . a change of time sense---where minutes seem like hours---slowed thinking, and feared perception of brain damage." Schick Shadel Health Services drug abuse treatment clinics (Unsigned 1987) now advertise that ``marijuana has increased THC content from one percent THC in 1975 to six to fourteen percent THC in 1985 due to hybridization techniques. . . .

For those who have become addicted to marijuana, whether it was years ago, or recently, treatment is necessary---even more critical today."

Despite the respectability of these authorities, none of these alarming claims are new, and neither is the potency issue. There are several claims intertwined: (1) that the marijuana available today is much stronger than that available previously, particularly since the early 1970's; (2) that the effects of this so-called new marijuana are different from effects known earlier; and (3) that all previous marijuana research has been done with weak material and is therefore irrelevant. Before leaping on the bandwagon, one should examine the validity of these assertions.

HISTORICAL PERSPECTIVE

Extremely potent marijuana has been described for 150 years by Western scientists and (with the possible exception of the bean-ball syndrome) so have the effects of the new marijuana. There has been a great deal of research on high-potency cannabis in many countries.

In the paper that introduced cannabis to Western medicine, O'Shaughnessy (1839) discussed the widespread social and medical uses of ganja (sinsemilla) in India and noted symptoms of ``delirium which the incautious use of the Hemp preparations often occasions, especially among young men first commencing the practice." Cannabis tinctures soon appeared in Europe and America (Robertson 1847; Savory 1843) and Fitz Hugh Ludlow (1857) described florid psychedelic trips after their oral ingestion, including all the symptoms mentioned by Meyers (1987). The Ohio State Medical Society (McMeens 1860) reviewed some 15 years of clinical experience with the drug and acknowledged the intense but physiologically benign mental effects caused by high doses or idiosyncratic sensitivity.

Wood (1869) reported the subjective effects of a tincture made from North American marijuana, experiencing a distortion in time sense, convulsions and memory loss, but no adverse aftereffects. He reported considerable success with it in the treatment of severe neuralgia. However, 15 years later Wood and Smith (1884) commented on the variable potency of cannabis and outlined appropriate treatment for overdoses in medical practice.

Early investigators (McMeens 1860; Bell 1857) attributed this variability to ``defective pharmaceutic processes" employed in foreign countries, and recommended that extracts prepared at home would be preferable. However, extreme variations in locally manufactured preparations were soon recognized in the Dispensatory of the United States (Wood & Bache 1868: 379-382). A practical bioassay technique was gradually perfected starting from the systematic observations of Hare (1887), followed by Evans (1894) and Marshall (1898), to compensate for batch-to-batch potency variations.

Pragmatically, the solution to the overdose/potency problem in both the United States (Wood & Bache 1868: 382) and England was to titrate the dose. In London, a patient who signed a letter to the editors of Lancet, W.W. (1890) reported a typical case: W.W. had inadvertently been given an overdose of cannabis

for treatment of neuralgia by his doctor and had suffered perceptual distortion, agitation, mood swings, and fear of death. Sir J. Russell Reynolds, M.D., F.R.S., physician to Queen Victoria's household, responded with a recommendation based on 30 years of experience with the drug (Reynolds 1890), stating "that Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess. . . . a minimum dose should be given to begin with, and . . . the dose should be very gradually and cautiously increased."

During the nineteenth century, social and scientific research on marijuana, as well as tinctures, were conducted with much stronger material than is available on the illicit market today. For example, the Indian Hemp Drugs Commission of 1893-1894 investigated the social, religious and medical uses of bhang (marijuana), ganja (sinsemilla) and charas (hashish). The potencies of varieties from different parts of the subcontinent were evaluated by government chemists and botanists (Evans 1894; Hooper 1894), using the "acknowledged superiority" of Bengal ganja as the standard. The Commission found that the moderate use of even highly potent marijuana caused no significant physical, mental or moral damage (Kaplan 1969; Mikuriya 1968).

In the 1890's, at the peak of medical interest in the drug, British chemists (Wood, Spivey & Easterfield 1899) isolated an impure active principle, cannabinol, using a "red oil" distilled from Indian cannabis as a starting point, which was considered to be the active ingredient until the 1930's (Work, Bergel & Todd 1939; Cahn 1931). In 1909, Marshall demonstrated that oxidation during storage was the primary cause of the drug's variable potency. With this advance the pharmaceutical industry shifted its attention to the production of standard extracts that could be used to assay medicinal compounds (Colson 1920). Because it had long been known that ganja and charas produced the most reliable extracts (Wallich 1883; Robertson 1847), in practical terms this meant the European and American producers had to learn how to grow ganja.

Sinsemilla cultivation by the Indian technique of culling male plants from the fields before female plants could set seeds---the very process to which recent researchers attribute the potency of the new marijuana---was exhaustively described by the British government in India (Kaplan 1969: 59-84; Prain 1893; Kerr 1877). In an effort to promote Bengali ganja, the British Raj imposed an export duty on inferior Bombay ganja at the turn of the century, and pharmacognosists in Europe and the U.S. began learning sinsemilla cultivation (Mair 1900).

Holmes (1900) discussed the potencies of Calcutta and Bombay ganja and recommended that the former be used for pharmaceutical preparations, either by home cultivation of ganja according to the Bengal methods he outlined (Holmes 1902a) or by extracting it immediately in Bengal and shipping it in tightly closed containers (Holmes 1902b). Comparing the potency of cannabis from Uganda, France and India, Holmes (1905) urged that only Indian sinsemilla preparations be admitted to the British Pharmacopoeia.

Likewise, Whineray (1909) and Hooper (1908) described ganja cultivation and manufacture, pointing out that cannabis grown in North America by the Indian methods could be as fully potent as Indian hemp. The National Standard Dispensatory of 1909, which included medicines from the pharmacopoeias of the U.S., Britain and Germany, gave the details of sinsemilla cultivation and featured a drawing of a perfect Calcutta ganja flower top (see Figure 1) as an example to be emulated by Western cultivators (Hare, Caspari & Rusby 1909: 374).

In the U.S., Hamilton and his colleagues (Hamilton 1918; Hamilton 1915; Hamilton, Lescohier & Perkins 1913; Houghton & Hamilton 1908) demonstrated that if care was exercised in cultivating and processing the plant for extraction, American-grown ganja and its extracts were as reliable as those from India and would not deteriorate significantly if stored properly. Information on cultivation of extremely potent seedless marijuana was thus widely disseminated to Western pharmaceutical producers during the first two decades of the twentieth century.

The U.S. government ignored these sensimilla cultivation techniques at the first federal marijuana farm established in 1904 on the Potomac Flats (where the Pentagon now sits) in Washington, D.C. (Silver 1979: 262-263), and as a result the 10-foot marijuana plants grown there and elsewhere in America proved to be much less potent than good samples of Indian hemp (Eckler & Miller 1912). However, private pharmaceutical firms were more successful. The Eli Lilly and Parke-Davis companies ran a cooperative venture at Parkedale (Parke-Davis's farm near Rochester, Michigan) from 1913 until 1938 to develop cannabis extracts for medical use, at first from Cannabis indica, but later standardized on a highly potent strain they developed that they called Cannabis Americana (Wheeler 1968).

Pharmaceutical companies were marketing cannabis extracts that were uniformly effective at 10 mg dose levels (Parke-Davis & Company 1930: 82) 11 years before its official removal from medicinal availability.

In 1941, cannabis was removed from the United States Pharmacopoeia (USP) at the behest of the Federal Bureau of Narcotics, which suddenly claimed that marijuana had no medical uses (Mikuriya 1973: xx). Yet even the removal of cannabis from the USP did not end scientific and social research on highly potent forms of cannabis, ranging from the red-dirt marijuana of the Midwest to the red oil of the laboratories. Adams, Pease and Clark (1940) described improved procedures for preparing purified red oil from Minnesota wild hemp, and comparison of the potencies of Minnesota marijuana and red oil was of significant interest to Loewe, pharmacological director of the LaGuardia Committee (Mayor's Committee on Marihuana 1944: 186ff). Red oil concentrates were used along with marijuana in the LaGuardia

Committee's experiments on prisoners, under Loewe's personal direction (Mayor's Committee on Marihuana 1944: 32); for a subjective account see Mezzrow and Wolfe (1946: 317ff). In the 1940's, Adams and Loewe in the U.S. and Todd in England isolated other cannabinoids, including THC, which Adams (1940) postulated as the active principle.

Such isolates were the mainstay of marijuana research during the 1940's and 1950's. A potent marijuana oil created as a truth drug for interrogation purposes by the Office of Strategic Services during World War II (Lee & Shlain 1985: 3-5) was the forerunner of later clandestine experiments conducted by the CIA and the Department of Defense at the Edgewood Arsenal in Maryland from the 1950's to the 1970's (Mikuriya 1973: xxii). Experiments with the designer drug synhexyl, a potent analog of delta3-THC, were conducted from the 1940's (Adams et al. 1941) until the mid-1970's (Lemberger 1976; Pars & Razdan 1976), but were abandoned before its potential was fully explored.

In the 1960's, the identification of pure delta9-THC as the active principle in cannabis (Gaoni & Mechoulam 1964) made it possible to assay the relative potencies of cannabinoids directly in human subjects (Isbell et al. 1967). Although Weil, Zinberg and Nelsen (1968) demonstrated the safety of human marijuana research, much of the U.S. research of the 1970's was conducted with low-potency marijuana because the government would not approve human research with high-potency strains. Indeed, in one early study (Jones & Stone 1970), a THC concentrate was removed from Mexican marijuana and then redistributed back into the bulk marijuana to return its potency to 0.9 percent THC. Outside the U.S., these strictures did not apply: The fact that cannabidiol interferes with the effects of delta9-THC was discovered in Brazil, using both purified cannabinoids on humans (Karniol et al. 1974).

The 1960's and 1970's saw a worldwide flowering of cannabis research, including its social, psychological, chemical, botanical and legal aspects as well as covering an enormous range of potencies and dosages. Major botanical work involved potency questions: observing phenotypes at the University of Mississippi (Etterman et al. 1971) and in Canada (Small 1979); establishing a lectotype for Cannabis sativa L. (Stearn 1974); distinguishing C. sativa from C. indica and C. ruderalis (Schultes et al. 1974); and cultivation techniques for increased THC production (Clarke 1981; Frank & Rosenthal 1978).

Thus the claim by Cohen (1986) that "all marijuana research to date has been done on 1 or 2 percent THC materiai" is not accurate for the 1970's or for any other decade going back to 1839. It ignores much of the laboratory research in the U.S. that was summarized by Cohen himself (Cohen & Stillman 1976), Hollister (1986) and the National Academy of Sciences (1982), and all of the social research on high-potency marijuana in Jamaica (Rubin & Comitas 1975; Bowman & Pihl 1973), Costa Rica (Carter & Doughty 1976), Greece (Fink et al. 1976) and Africa (DuToit 1980). It is difficult to think of any country in which the claim is true.

RECENT ESTIMATES OF POTENCY

Since the advent of quantitative analysis technology, there has been sporadic reportage of the percentage of delta9-THC and other cannabinoids in natural and semisynthetic cannabis products. Notwithstanding the psychophysical effects of other cannabinoids, the amount of THC present in a marijuana sample is believed to determine the drug's potency (National Commission on Marihuana and Drug Abuse 1972: 50), and potency is usually expressed in percent THC by weight. The results of quantitative analyses performed on street samples of marijuana have been published since the late 1960's. These results are generally higher than the alleged 0.5 percent THC content of marijuana cited for the early 1970's.

Lerner and Zeffert (1968) described the development of quantitative analysis for the determination of THC content, and noted much variation among samples of marijuana, hashish, and red oil (still being used experimentally in the 1960's). The THC content of confiscated Mexican marijuana was 0.8 to 1.4 percent, hashish averaged eight percent and red oil 31 percent in 1968.

Quantitative analyses of street samples of marijuana and hashish conducted by Canadian laboratories in 1971 for the Commission of Inquiry into the Non-Medical Use of Drugs (1972: 28-29) showed a range of 0.02 to 3.46 percent THC (median=0.93%) for marijuana, with hashish ranging from 1.0 to 14.3 percent THC (median=4.82%). Samples seized in police raids were less potent: marijuana was 0.05 to 1.65 percent THC (median=0.21%), while hashish was 0.0 to 8.6 percent THC (median=1.3%). The reported difference between confiscated police seizures and street samples submitted to laboratories for analysis may be due to the voluntary samples being submitted precisely because of their extraordinary potency, or that storage conditions in police evidence lockers are hardly optimal for potency stability.

This has a bearing on the potency question because the low potency cited by both Cohen (1986) and Hawks (see Kerr 1986) referred to samples confiscated by the DEA. It has been known since the early days of its isolation (Wollner et al. 1942) that THC oxidizes to cannabinol rapidly in samples stored at room temperature (24oC). Lerner (1963) reported that the concentration of THC in marijuana decreased at a rate of three to five percent under normal room conditions, and Razdan (1970) reported a rate of 10 percent per month.

The influence of temperature, light and age on potency was addressed by Starks (1977: 13-15). The low-baseline percentage of THC reported for the early 1970's may be due to this deterioration in confiscated, stored samples. In any case, the low baseline makes the difference in the THC content of later-reported samples appear much greater than it may have been in actuality, assuming that the marijuana smoked by consumers was fresher than stored police seizures.

For a short while in the early 1970's, PharmChem Laboratories in Palo Alto, California, tested and reported the percent of the THC content in anonymously submitted marijuana samples. For 1973, PharmChem reported an average THC content of 1.62 percent in marijuana, compared with hashish at 4.6 percent and hash oil (a refined extract of hashish) at 13.5 percent (Ratcliffe 1974).

In 1974, the DEA published guidelines that no longer allowed laboratories to provide quantitative results

directly to the sample donors. This, in effect, restricted public access to analysis information to whatever government officials wished to reveal. However, nonspecific summaries of THC percentage ranges were allowed to be published (Unsigned 1974).

The results of an independent examination of gas-liquid chromatographs of street samples of marijuana from California that were submitted to PharmChem during 1973 and 1974 are shown in Table I.

Seeded varieties ranged in THC from an average of 2.2 percent (Mexican) to 4.9 percent (Panama Red), while sinsemilla averaged 2.8 percent for Big Sur ``Holy Weed" to above six percent for Thai Sticks and Hawaiian ``Maui Wowie." This would appear to be a much more representative sample of the types of marijuana available in California in 1973-1974 than the half-percent grade cited by Cohen (1986) and Hawks (see Kerr 1986), or the one to three percent grade cited by Tennant (1986).

A retrospective summary of street-drug analysis trends from 1969 through 1975 published by PharmChem (Perry 1977) confirms the fact that quite potent forms of cannabis were available on the illicit U.S. market by 1975: ``Early quantitative work showed a range of 1.0-2.5 percent THC for average marijuana. In 1975, the range was 1.0-2.5 percent; samples in the range of 5.0-10.0 percent were not uncommon, and some contained as much as 14.0 percent THC. . . . Hash oil (concentrated from hash, usually amber or red in color) and grass oil (from marijuana, dark green or black in color) . . . vary greatly in potency, some samples [containing] up to 40 percent THC." Abundant information on the comparative potencies of cannabis grown in the U.S. and other countries in the mid-1970's was summarized by Starks (1977: 41-87).

In the spring of another election year, 1980, Cohen and DuPont launched a similar campaign, stating that confiscated marijuana in 1975 contained only 0.4 percent THC, while in 1979 the average was four percent, a 10-fold increase (Brody 1980: C1). This data conflicts directly with that published by PharmChem for 1975 street samples (Perry 1977) and that shown in Table I. Perhaps one should be thankful that, according to these estimates, marijuana potency dropped from four percent THC in 1979 to 3.5 percent THC in 1986 (Kerr 1986).

The most recent comparison of cannabis potencies was compiled from published sources from 1972 through 1981 by the National Academy of Sciences (1982: 16), and is summarized in Table II. It again demonstrates the great range of products available legally (i.e., NIDA samples) and illegally during that decade, and may in fact underestimate some potencies. For example, the 2.8 percent THC content cited for Jamaican ganja (Marshman, Popham & Yawney 1976) is slightly lower than the mean 2.96 percent THC material studied by Rubin and Comitas in 1970 through 1972 (Unsigned 1973), and significantly lower than the four to eight percent THC Jamaican ganja cited by the National Commission on Marihuana and Drug Abuse (1972: 50).

The government ``research harvests" in Table II (Rosenkrantz 1981) are considerably less potent than the sinsemilla samples that averaged three to 11 percent THC (Turner 1981, 1980). Perhaps this is because cultivators at the government marijuana farm at the University of Mississippi, like their predecessors in 1904, never learned proper sinsemilla cultivation (Turner et al. 1979), while illicit cultivators in California and Hawaii were making it standard for the industry (Frank & Rosenthal 1978: 258-259). If so, this alone could explain the wide discrepancies between the potency of marijuana reported by government sources and that actually being grown in the U.S. during the 1970's and 1980's.

SELF-ADJUSTMENT OF DOSE

An important consideration in regard to the potency issue is autotitration, the adjustment of dose by the individual user to obtain optimal effects and avoid unpleasant ones. As noted above, cautious titration of dose was standard practice when cannabis preparations were used in medicine. Smoking marijuana, customary in present social use of the drug, requires knowledge of when to stop in order to avoid symptoms

of overdose. The smoked route gives rapid feedback to the user with regard to levels of effect because the drug goes directly to the brain from the lungs, unimpeded by the gut or the liver.

Researchers for the Mayor's Committee on Marihuana (1944: 13) were among the first to notice that experienced marijuana smokers in the "tea-pads" of Harlem routinely practiced autotitration. The confirmed user, they noted, "appears to be quite conscious of the quantity he requires to reach the effect called 'high.' Once the desired effect is obtained he cannot be persuaded to consume more. He knows when he has had enough . . . and is ever-conscious of preventing himself from becoming 'too high.'" Similarly the Commission of Inquiry into the Non-Medical Use of Drugs (1972: 48) observed that "great variations in potency are usually accommodated by the experienced user through a 'titration' of dose (intake is reduced or stopped when the smoker reaches the preferred level of intoxication)." For U.S. users, the National Commission on Marihuana and Drug Abuse (1972: 166) commented: ". . . whatever the potency of the drug used, individuals tend to smoke only the amount necessary to achieve the desired effect."

SUMMARY AND CONCLUSIONS

Observation of the real world of social marijuana use, where autotitration is the norm, renders the scare tactics of the new marijuana proponents not only inaccurate but irrelevant. There is much published evidence about the availability of highly potent varieties of cannabis from the nineteenth century through the present day. The effects attributed to the new marijuana are the same ones debated for centuries in many different cultures. The assertion that "all marijuana research to date has been done on 1 or 2 percent THC material" (Cohen 1968) ignores several thousand years of human experience with the drug. The old medical cannabis extracts were stronger than most of the forms now available, though the potency of illicit hash oils by the mid-1970's was approaching the level of medicinal preparations available before their removal from the USP.

While it may be true that sinsemilla is more widely available than 10 or 15 years ago, its potency has not changed significantly from the 2.4 to 9.5 percent THC materials available in 1973-1974 (see Table I), or the five to 14 percent sinsemilla of 1975 (Perry 1977).

The range of potencies available then (marijuana at 0.1% to 7.8% THC, averaging 2.0% to 5.0% THC by 1975) was approximately the same as that reported now. With such a range, the evidence simply cannot support the argument by Cohen (1986) that marijuana is "ten or more times more potent than the product smoked ten years ago." And to say that marijuana potency has increased 1,400 percent since any date in history is patent nonsense.

It is not legitimate to imply that average low potencies represent the full range of potencies available in reality. Neither is it valid to cite the low end of the range then as a baseline to compare with the high end of the range now. The claimed baseline for THC content in the early 1970's would appear to be too low, probably because confiscated, stored police samples were utilized; and this low baseline makes the claimed difference in potency appear to be greater than it has been in reality.

In sum, the new marijuana is not new and neither is the hyperbole surrounding this issue. The implications of the new disinformation campaign are serious. Many people, particularly the experienced users of the 1960's and their children, will once again shrug off the warnings of drug experts and not heed more reasonable admonishments about more dangerous drugs. This is not only abusive to those who look to science, the medical profession, and government for intelligent leadership, but will sully the reputations of drug educators who wittingly cry wolf, and will inevitably diminish the credibility of drug abuse treatment professionals who pass on such flawed reports.

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INVITED REVIEW

Cannabis and the brain

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Summary

The active compound in herbal cannabis, Δ^9-tetrahydrocannabinol, exerts all of its known central effects through the CB_1 cannabinoid receptor. Research on cannabinoid mechanisms has been facilitated by the availability of selective antagonists acting at CB_1 receptors and the generation of CB_1 receptor knockout mice. Particularly important classes of neurons that express high levels of CB_1 receptors are GABAergic interneurons in hippocampus, amygdala and cerebral cortex, which also contain the neuropeptides cholecystokinin. Activation of CB_1 receptors leads to inhibition of the release of amino acid and monoamine neurotransmitters. The lipid derivatives anandamide and 2-arachidonylglycerol act as endogenous ligands for CB_1 receptors (endocannabinoids). They may act as retrograde synaptic mediators of the phenomena of depolarization-induced suppression of inhibition or excitation in hippocampus and cerebellum. Central effects of cannabinoids include disruption of psychomotor behaviour, short-term memory impairment, intoxication, stimulation of appetite, antinociceptive actions (particularly against pain of neuropathic origin) and anti-emetic effects. Although there are signs of mild cognitive impairment in chronic cannabis users there is little evidence that such impairments are irreversible, or that they are accompanied by drug-induced neuropathology. A proportion of regular users of cannabis develop tolerance and dependence on the drug. Some studies have linked chronic use of cannabis with an increased risk of psychiatric illness, but there is little evidence for any causal link. The potential medical applications of cannabis in the treatment of painful muscle spasms and other symptoms of multiple sclerosis are currently being tested in clinical trials. Medicines based on drugs that enhance the function of endocannabinoids may offer novel therapeutic approaches in the future.

Keywords: cannabinoid CB_1 receptor; Δ^9-tetrahydrocannabinol; rimonabant (SR141716A); anandamide; 2-arachidonylglycerol

Abbreviations: 2-AG = 2-arachidonylglycerol; DSI = depolarization-induced suppression of inhibition; FAAH = fatty acid amide hydrolase; Gi/o = G-proteins negatively linked to adenylate cyclase or to inositol phosphates; LTD = long-term depression; LTP = long-term potentiation; mGlu = metabotropic glutamate; NMDA = *N*-methyl-D-aspartate; THC = Δ^9-tetrahydrocannabinol

Introduction

A large literature exists on the effects of cannabis, with many of the earlier studies conducted in human subjects (Mendelson *et al.*, 1976; Jones, 1978; Hollister, 1986). Unfortunately, much of this research would now be regarded as inadequately controlled and poorly designed. However, research on cannabis has been stimulated in recent years by the recognition that specific receptors exist in the brain that recognize cannabinoids, and by the discovery of a series of endogenous cannabinoids that act as ligands for these receptors. As was the case with opiate research in the 1970s, research on a psychoactive drug of plant origin has revealed a hitherto unknown physiological control mechanism. This review will focus mainly on the more recent literature in this field.

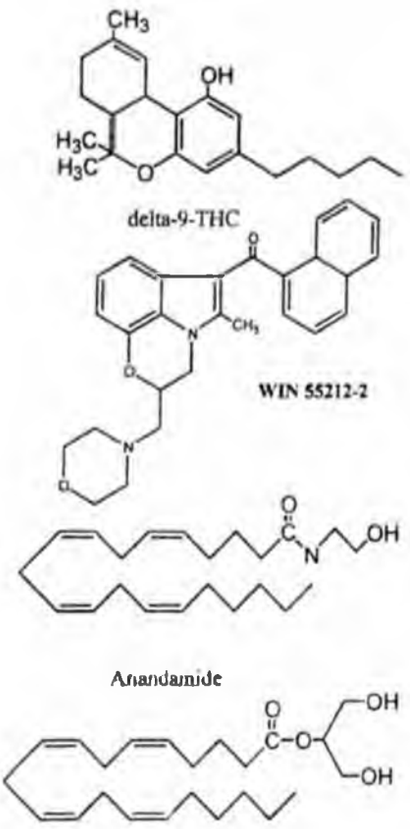

Fig. 1 Chemical structures of THC, the synthetic CB_1 receptor agonist WIN 55,2122 and the endocannabinoids.

The cannabinoid system in brain

Exogenous cannabinoids and their receptors

The principal active component in the complex mixture of cannabinoids present in extracts of the plant *Cannabis sativa* is Δ^9-tetrahydrocannabinol (THC) (Mechoulam, 1970) (Fig. 1). THC is a sticky resin that is not soluble in water. Smoking remains the most efficient means of delivering the drug and experienced users can titrate the dose by adjusting the frequency and depth of inhalation (Iversen, 2000). THC or cannabis extracts can also be taken orally in fat-containing foods or dissolved in a suitable pharmaceutical oil, but absorption is delayed and variable (Iversen, 2000). A series of man-made synthetic cannabinoids, some of which are more potent and more water soluble than THC, is also available (Pertwee, 1999) (Fig. 1). All of these compounds act as agonists at the CB_1 cannabinoid receptor (Matsuda *et al.*, 1990), which is the only one known to be expressed in the brain. A second cannabinoid receptor, CB_2, is expressed only in peripheral tissues, principally in the immune system (Munro *et al.*, 1993; Felder and Glass, 1998; Pertwee, 1999). THC and

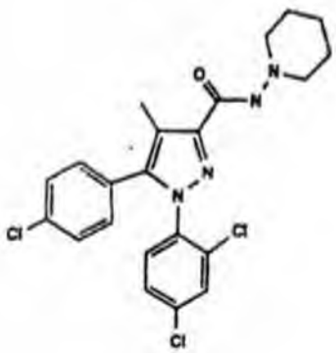

Fig. 2 Chemical structure of the CB_1 selective antagonist drug rimonabant (SR141716A).

the synthetic cannabinoids also act to some extent as agonists at the CB_2 receptor. Both cannabinoid receptors are members of the G-protein coupled class, and their activation is linked to inhibition of adenylate cyclase activity (Howlett *et al.*, 1988). A series of synthetic drugs is also now available that act as specific antagonists at CB_1 or CB_2 receptors (D'Souza and Kosten, 2001). One of these compounds, rimonabant(SR141716A), which acts selectively to block CB_1 receptors (Rinaldi-Carmona *et al.*, 1994; Compton *et al.*, 1996), has been widely used in studies of the actions of cannabinoids in the CNS (Fig. 2).

Endogenous cannabinoids

Following the discovery of specific cannabinoid receptors, a search was made for naturally occurring ligands of these receptors in mammalian tissues. This led to the discovery of a series of arachidonic acid derivatives with potent actions at cannabinoid receptors. These are: anandamide (*N*-arachidonyl-ethanolamine; Devane *et al.*, 1992), 2-arachidonylglycerol (2-AG; Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995; Stella *et al.*, 1997) and 2-arachidonylglyceryl ether (Hanuš *et al.*, 2001) (Fig. 1). Of these, anandamide is the ligand that has been most extensively studied so far. The endogenous cannabinoids known as 'endocannabinoids' are present only in small amounts in the brain or other tissues. Like other lipid mediators (e.g. prostaglandins) they appear to be synthesized and released locally on demand (see below). Anandamide and the other endogenous cannabinoids are rapidly inactivated by a combination of a transporter mechanism and by the enzyme fatty acid amide hydrolase (FAAH) (Di Marzo *et al.*, 1994; Piomelli *et al.*, 1998; Giuffrida *et al.*, 2001). Genetically engineered mice lacking FAAH displayed elevated levels of anandamide in brain and were supersensitive to the biological actions of anandamide (Cravatt *et al.*, 2001). The discovery of agents that could interfere with the inactivation of endogenous cannabinoids may provide a novel means of pharmaco-

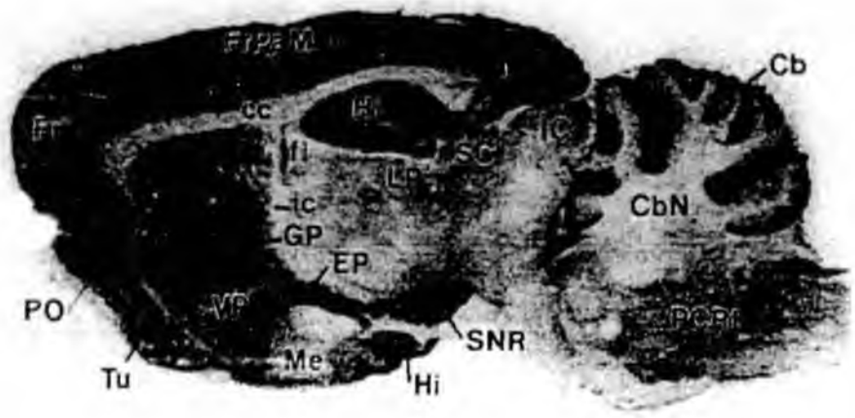

Fig. 3 Distribution of cannabinoid CB_1 receptors in rat brain revealed by an autoradiograph of the binding of radioactively labeled CP-55940 (a high affinity agonist ligand) to a sagittal brain section. The brain regions labelled are: Cb = cerebellum; CbN = deep cerebellar nucleus; cc = corpus callosum; EP = entopeduncular nucleus; fi = fimbria hippocampus; Fr = frontal cortex; FrPaM = frontoparietal cortex motor area; GP = globus pallidus; Hi = hippocampus; IC = inferior colliculus; LP = lateral posterior thalamus; Me = medial amygdaloid nucleus; PO = primary olfactory cortex; PCRt = parvocellular reticular nucleus; SNR = substantia nigra reticulate; Tu = olfactory tubercle; VP = ventroposterior thalamus. Photograph kindly supplied by Dr Miles Herkenham, National Institute of Mental Health, USA.

logically modifying cannabinoid function in the brain (Piomelli *et al.*, 2000).

Neuroanatomical distribution of CB_1 receptors in brain

The distribution of cannabinoid receptors was first mapped in rat brain in autoradiographic studies, using the radioligand [H^3]CP-55,940, which binds with high affinity to CB_1 sites (Herkenham *et al.*, 1991) (Fig. 3). The validity of using this radioligand was confirmed by autoradiographic studies in CB_1 receptor knockout mice, in which no detectable [H^3]CP-55,940 binding sites were observed (Zimmer *et al.*, 1999). More recently, antibodies that target the C- or N-terminal regions of the CB_1 receptor protein have been used for immunohistochemical mapping studies (Egertová *et al.*, 1998; Pettit *et al.*, 1998; Egertová and Elphick, 2000). Immunohistochemistry provides a superior degree of spatial resolution to autoradiography, but the overall pattern of distribution of CB_1 receptors revealed by the two approaches is very similar (Elphick and Egertová, 2001).

The mapping studies in rat brain showed that CB_1 receptors are mainly localized to axons and nerve terminals and are largely absent from the neuronal soma or dendrites. The finding that cannabinoid receptors are predominantly presynaptic rather than postsynaptic is consistent with the postulated role of cannabinoids in modulating neurotransmitter release (see below).

In both animals and man the cerebral cortex, particularly frontal regions, contains high densities of CB_1 receptors. There are also very high densities in the basal ganglia and in the cerebellum (Fig. 3). In the limbic forebrain CB_1 receptors are found particularly in the hypothalamus and in the anterior cingulate cortex. The hippocampus also contains a high density of CB_1 receptors. The relative absence of the cannabinoid receptors from brainstem nuclei may account for the low toxicity of cannabinoids when given in overdose.

The regional distribution of the CB_1 receptor in brain correlates only poorly with the levels of anandamide and other endocannabinoids in different brain regions (Felder *et al.*, 1996; Bisogno *et al.*, 1999). However, measurements of endocannabinoids have yielded variable results, and a strict correlation would not be expected for ligands that are only produced on demand. There is a better correlation between the regional distribution of CB_1 receptors and the enzyme FAAH. FAAH is widely distributed in CNS and other tissues, suggesting that its role is not confined to inactivating endogenous cannabinoids. Nevertheless, particularly high levels of FAAH were found in brain regions that are enriched in CB_1 receptors, and immunohistochemical staining suggested a complementary relationship between FAAH and CB_1 receptors at the synaptic level (Egertová *et al.*, 1998; Elphick and Egertová, 2001). In cerebellum, hippocampus and neocortex FAAH was expressed at high levels in the somato-dendritic regions of neurons that were postsynaptic to CB_1-positive axon terminals. The close and complementary relationship between CB_1 receptors and FAAH led to the hypothesis that FAAH may participate in the inactivation of endogenous cannabinoids released locally at synapses

(Elphick and Egertová, 2001). These authors postulated a retrograde cannabinoid signalling mechanism, whereby endogenous cannabinoids are released in response to synaptic activation, feedback to presynaptic receptors on these axon terminals, and are subsequently inactivated by FAAH after their uptake into the postsynaptic compartment. This hypothesis has been supported independently by neurophysiological findings, as described below.

Effects of cannabinoids on synaptic function

Inhibition of neurotransmitter release

The presynaptic localization of CB_1 receptors suggests a role for cannabinoids in modulating the release of neurotransmitters from axon terminals, and this has been confirmed by a substantial body of experimental data. Early reports (Gill *et al.*, 1970; Roth, 1978) showed that THC inhibited acetylcholine release from electrically stimulated guinea pig ileum. Similar inhibitory effects of THC and other cannabinoids on the release of a variety of neurotransmitters from CNS neurons have been observed in many subsequent studies (Schlicker and Kathmann, 2001). The neurotransmitters involved include L-glutamate, GABA, noradrenaline, dopamine, 5-HT and acetylcholine. The brain regions most often studied *in vitro*, usually in tissue slice preparations, have been cerebellum, hippocampus or neocortex. Neurotransmitter release has been studied directly in superfused preparations, and indirectly by measuring postsynaptic currents. Although most of these studies involved rat or mouse brain, a few studies have shown similar results using human brain tissue (Katona *et al.*, 2000; Schlicker and Kathmann, 2001). Because THC is only poorly water soluble, the more soluble synthetic CB_1 receptor agonists WIN552123, HU210 or CP55-2940 were used in these *in vitro* studies. The specificity of the cannabinoid effects were confirmed by demonstrating that the inhibitory effects of the agonists were completely blocked by the CB_1-selective antagonist rimonabant.

The cellular mechanisms involved in the inhibition of neurotransmitter release by cannabinoids remain unclear. Some have suggested that there is a direct inhibitory effect of CB_1 receptor activation on N-type Ca^{2+} currents (Caulfield and Brown, 1992; MacKie and Hill, 1992). However, the effect appears more likely to involve sites downstream of voltage-dependent Ca^{2+} channels, since a number of studies have shown that cannabinoids reduce the frequencies of miniature excitatory or inhibitory synaptic currents, which are Ca^{2+} independent, rather than altering their amplitude, which is Ca^{2+} sensitive (Schlicker and Kathmann, 2001). Deadwyler *et al.* (1995) suggested that the inhibitory effect of CB_1 receptor activation on adenylate cyclase activity causes a decreased phosphorylation of A-type K^+ channels by the cAMP-dependent enzyme protein kinase A. This, in turn, would activate the A-type K^+ channels and cause a shortening of the duration of presynaptic action potentials as they invade axon terminals.

Biosynthesis of endocannabinoids

Despite their similar chemical structures, the endocannabinoids are produced through distinct biochemical pathways. The formation of anandamide is thought to result from the hydrolysis of the precursor *N*-arachidonoyl phophatidylethanolamine, catalysed by the phosphodiesterase enzyme phospholipase D (Di Marzo *et al.*, 1994; Cadas *et al.*, 1997). 2-AG, on the other hand, is produced by cleavage of an inositol-1,2-diacylglycerol, catalysed by phospholipase C. Although both anandamide and 2-AG can activate CB_1 receptors, it is not clear whether both function as endocannabinoids, and whether their synthesis and release are independently controlled. The levels of 2-AG found in brain (2–10 nmol/g) are 50–1000 times higher than those of anandamide (10–50 pmol/g). There is some evidence for separate control of their biosynthesis. Stimulation of glutamate release from Schaffer collaterals in rat hippocampal slices increased levels of 2-AG, but not anandamide (Stella *et al.*, 1997). On the other hand, another study using *in vivo* microdialysis probes showed that local administration of the dopamine D2 receptor agonist quinpirole caused an increased release of anandamide from rat striatum without affecting levels of 2-AG (Giuffrida *et al.*, 1999). Indeed, despite the much higher tissue levels of 2-AG relative to anandamide and the availability of a very sensitive assay, no 2-AG could be detected at all in the striatal dialysate samples. In cultured rat cortical neurons activation of Ca^{2+} influx by stimulation of glutamate *N*-methyl-D-aspartate (NMDA) receptors caused an increase in 2-AG formation but not anandamide (Stella and Piomelli, 2001). However, if NMDA activation was combined with a cholinergic agonist (carbachol) the formation of both endocannabinoids was increased. In both cases Ca^{2+} influx was required for endocannabinoid synthesis. It is clear that much remains to be learned about the relative roles played by the different endocannabinoids. The biosynthesis of the most recently discovered third endocannabinoid, 2-arachidonylglyceryl ether, remains to be characterized.

Endogenous cannabinoids act as retrograde signal molecules at synapses

Important new insights into the physiological role of cannabinoids has emerged from neurophysiological studies published independently by three different research groups in 2001. A phenomenon known as depolarization-induced suppression of inhibition (DSI) has been known to neurophysiologists for some years (Alger and Pitler, 1995). It is a form of fast retrograde signalling from postsynaptic neurons back to inhibitory cells that innervate them, and is particularly prominent in the hippocampus and cerebellum. Three prop-

erties of DSI suggested to Wilson and Nicoll (2001) that a cannabinoid mechanism might be involved. First DSI, like endocannabinoid synthesis, requires Ca^{2+} influx into the postsynaptic neuron (Lenz *et al.*, 1998). Secondly, DSI is probably presynaptic, since the sensitivity of the postsynaptic cell to GABA is unaffected (Pitler and Alger, 1992). Finally, DSI is blocked by pertussin toxin, which interacts with the Gi-proteins negatively linked to adenylate cyclase or to inositol phosphates (Gi/o) protein to which the CB_1 receptor is coupled (Pitler and Alger, 1994). Wilson and Nicoll (2001) used slice preparations of rat hippocampus and induced DSI by brief depolarizing steps in the holding potential of voltage clamped CA1 pyramidal neurons. They found that DSI was completely blocked by the cannabinoid CB_1 receptor antagonists AM251 or rimonabant and could be mimicked by application of the CB_1 receptor agonist WIN55,2122, but the continued presence of the agonist prevented DSI by occlusion. Wilson and Nicoll (2001) were also able to show by recording from pairs of nearby CA1 neurons that depolarizing one of these neurons caused DSI to spread and affect adjacent neurons up to 20 µm away. They suggested that the small, lipid-soluble, freely diffusible endocannabinoids act as retrograde synaptic signals that can affect axon terminals in sphere of influence some 40 µm in diameter.

Ohno-Shosaku *et al.* (2001) came to a similar conclusion using a different experimental paradigm. They recorded from pairs of cultured hippocampal neurons with inhibitory synaptic connections. They found that depolarization of the postsynaptic neurons lead to DSI in approximately two-thirds of the neuron pairs, and showed that this was due to inhibition of GABA release. Those that exhibited DSI, but not the others, proved to be sensitive to the CB_1 receptor agonist WIN55,2122, which mimicked the inhibitory effect of DSI. Both DSI and the cannabinoid effect could be blocked by the CB_1 receptor antagonists AM-281 or rimonabant.

Further support for the conclusion that a cannabinoid-mediated mechanism underlies DSI came from Varma *et al.* (2001), who found that DSI was completely absent in hippocampal slices prepared from CB_1 receptor knockout mice (Ledent *et al.*, 1999). Varma *et al.* (2001) also reported that agonists which stimulate metabotropic glutamate (mGlu) receptors enhanced DSI, whereas the broad-spectrum antagonist of mGlu receptors, LY341495, tended to reduce DSI, suggesting that glutamate may also be involved. Interestingly, Varma *et al.* (2001) found that mGlu agonists failed to have any effect on DSI in the CB_1 knockout animals, suggesting that glutamate acts to enhance the endocannabinoid signal.

Retrograde signalling by endocannabinoids is not restricted to the inhibitory inputs to postsynaptic neurons. Kreitzer and Regehr (2001*a*) showed that depolarization of rat cerebellar Purkinje cells leads to a transient inhibition of excitatory inputs from parallel fibre and climbing fibre inputs, a phenomenon described as depolarization-induced suppression of excitation (DSE). They found that DSE was triggered by Ca^{2+} influx into the Purkinje cells, and could be completely blocked by the CB_1 antagonist AM-251, and mimicked and occluded by the CB_1 receptor agonist WIN55,2122. Kreitzer and Regehr (2001*b*) went on to show that inhibitory inputs to rat cerebellar Purkinje cells from basket cells and stellate cells were subject to DSI, and that this was also blocked by AM-251 and occluded by WIN55,2122. The DSE phenomenon in the cerebellum is also linked to mGlu receptors. Maejima *et al.* (2001) reported that mGlu agonists acting on mouse Purkinje cells mimicked DSE, and the effects could be blocked by CB_1 antagonists.

These findings suggest that endocannabinoids are involved in the rapid modulation of synaptic transmission in CNS by a retrograde signalling system that can influence synapses in a local region of some 40 µm diameter, causing inhibitory effects on both excitatory and inhibitory neurotransmitter release that persist for tens of seconds. This may play an important role in the control of neural circuits, particularly in cerebellum and hippocampus (see below). Exogenously administered THC or other cannabinoids cannot mimic the physiological effects of locally released endocannabinoids. Since they cause long-lasting activation of CB_1 receptors in all brain regions, their overall effect is to cause a persistent inhibition of neurotransmitter release from those nerve terminals that express CB_1 receptors, and as a consequence they temporarily occlude and prevent the phenomena of DSI and DSE.

Effects of cannabinoids on CNS function

Psychomotor control

CB_1 receptors are expressed at particularly high densities in the basal ganglia and cerebellum, so it is not surprising that cannabinoids have complex effects on psychomotor function (reviewed by Rodríguez de Fonseca *et al.*, 1998). One of the earliest reports of the effects of cannabis extracts in experimental animals described the awkward swaying and rolling gait caused by the drug in dogs, with periods of intense activity provoked by tactile or auditory stimuli, and followed eventually by catalepsy and sleep (Dixon, 1899). In rodents cannabinoids tend to have a triphasic effect. Thus in rats low doses of THC (0.2 mg/kg) decreased locomotor activity, while higher doses (1–2 mg/kg) stimulated movements, and catalepsy emerged at doses of 2.5 mg/kg (Sañudo-Peña *et al.*, 2000). Similarly in mice, Adams and Martin (1996) described a 'popcorn effect' in animals treated with THC. Groups of mice are sedated by the drug, but will jump in response to auditory or tactile stimuli, as they fall into other animals these in turn jump, resembling corn popping in a popcorn machine. Interestingly, the CB_1 receptor antagonist rimonabant stimulated locomotor activity in mice, suggesting that there is tonic activity in the endocannabinoid system that contributes to the control of spontaneous levels of activity (Compton *et al.*, 1996).

These effects of cannabinoids may be due, in part, to actions at cerebellar or striatal receptors. Patel and Hillard (2001) used tests of specific cerebellar functions to show that

cannabinoids caused increased gait width and the number of slips on a bar cross test. DeSanty and Dar (2001) observed rotorod impairments in mice after direct injection of synthetic cannabinoids into the cerebellum. These defects were no longer seen in animals pretreated with cerebellar injections of an antisense oligonucleotide directed to a sequence in the CB_1 receptor.

In human subjects it is also possible to demonstrate that cannabis causes impaired performance in test of balance (Greenberg *et al.*, 1994), or in tests that require fine psychomotor control, for example tracking a moving point of light on a screen (Manno *et al.*, 1970). Human cannabis users may also seek isolation and remain immobile for long periods.

A number of authors have attempted to combine what is known of the neuroanatomical distribution of the cannabinoid system and the results of behavioural and electrophysiological studies to speculate on the mechanisms underlying cannabinoid modulation of psychomotor function (Breivogel and Childers, 1998; Sañudo-Peña *et al.*, 1999; Giuffrida *et al.*, 2000; Elphick and Egertová, 2001). The CB_1 receptor is expressed particularly by striatal GABAergic medium-spiny projection neurons, and is abundant in regions contaning the axon terminals of these cells (globus pallidus, entopeduncular nucleus and substantia nigra reticulata, and in axon collaterals feeding back to medium-spiny projection neurons in striatum). CB_1 receptors are also abundant on the terminals of glutamatergic projection neurons from the subthalamic nucleus to globus pallidus, entopeduncular nucleus and substantia nigra reticulata. Cannabinoids might thus be expected to inhibit GABA release in striatum and GABA and glutamate release in the other nuclei. Sañudo-Peña *et al.* (1999) suggested that the primary role of the endocannabinoid system may be to inhibit tonic release of glutamate in the substantia nigra, regulating levels of basal motor activity. Exogenous cannabinoids also lead to decreased GABA release in substantia nigra, which could lead to a disinhibition of the inhibitory nigral input to the thalamocortical pathway, resulting in inhibition of movement. To what extent the effects of cannabinoids on motor function are due to actions in the cerebellum remains unclear, although as described above it is likely that effects on posture and balance are mediated in this brain region. As described previously, CB_1 receptors are known to occur abundantly on nearly all of the principal excitatory (glutamatergic) and inhibitory (GABAergic) inputs to cerebellar Purkinje cells.

The results of eliminating the expression of CB_1 receptors in knockout mice have yielded conflicting results. The knockout animals studied by Zimmer *et al.* (1999) displayed reduced levels of basal activity, in support of the hypothesis put forward by Sañudo-Peña *et al.* (1999), suggesting that tonic activation of CB_1 receptors promotes movement. However, the CB_1 knockout animals studied by Ledent *et al.* (1999) showed no change in spontaneous activity, and in some tests they exhibited increased motor activity. This is in line also with the observations of Compton *et al.* (1996) that the CB_1 antagonist SR141716 caused an increase in locomotor activity. The reasons for the discrepant findings in different strains of CB_1 knockout mice are unknown. Clearly, there is as yet only a poor understanding of the actions of cannabinoids in the basal ganglia and cerebellum. Interactions with other chemical signalling systems in the brain are likely to be important. Giuffrida *et al.* (1999) showed, for example, that dopamine D2 receptor agonists caused an increase in anandamide synthesis and release in striatum. Deadwyler *et al.* (1995) described the convergence of multiple presynaptic controls on the terminals of granule cells in cerebellum. In addition to the CB_1 receptor, these terminals also express high densities of kappa opioid, adenosine A_1 and GABA-B receptors, all of which are coupled through a similar Gi/o type G-protein to inhibit adenylate cyclase and are capable of inhibiting glutamate release. Such complexities are likely to prove the norm.

There is anecdotal evidence that cannabis can relieve muscle pain and spasticity in patients suffering from multiple sclerosis (Consroe *et al.*, 1996). Experimental data obtained by Baker *et al.* (2000) in an animal model of multiple sclerosis appears to support such claims. Mice immunized with myelin antigens develop spasticity and tremor. Both symptoms were ameliorated by administration of cannabinoids, and the symptoms were exacerbated by rimonabant, suggesting the involvement of CB_1 receptors and tonic activity in the endocannabinoid system. Controlled clinical trials of cannabis-based medicines for the treatment of multiple sclerosis are currently under way.

Cannabinoid mechanisms in the hippocampus and effects on memory

One of the well established effects of acute intoxication with cannabis in man is an impairment of short-term memory (the extensive literature on human studies is reviewed by Jones, 1978; Miller and Branconnier, 1983; Solowij, 1998; Earleywine, 2002). Many studies have shown significant effects on short-term memory, particularly when tests were used that depend heavily on attention (Abel, 1971; Mendelson *et al.*, 1976). Animal studies have also found that THC, synthetic cannabinoids and anandamide cause deficits in short-term memory in spatial learning tasks (for a review see Hampson and Deadwyler, 1999). These include delayed matching or non-matching tests in rodents (Mallet and Beninger, 1998; Hampson and Deadwyler, 1999), performance in a radial arm maze (Stiglick and Kalant, 1985; Lichtman and Martin, 1996), and a fixed ratio food acquisition task in squirrel monkeys (Nakamura-Palacios *et al.*, 2000). The effects of both cannabinoids (Lichtman and Martin, 1996) and anandamide (Mallet and Beninger, 1998) were reversed by rimonabant, indicating that they are mediated by the CB_1 receptor.

A probable site for these effects is the hippocampus. Hampson and Deadwyler (1999) claimed that the effects of the treatment of rats with cannabinoids on short-term memory in a delayed non-matching to sample test were equivalent to the effects seen after surgical removal of the hippocampus. In each case the animals were unable to segregate information between trials in the task because of disruptions to the processing of sensory information in hippocampal circuits. CB_1 receptors are expressed at high densities in the hippocampus. They are particularly abundant on the terminals of a sub-set of GABAergic basket cell interneurons, which also contain the neuropeptide cholecystokinin (Katona *et al.*, 1999), and this is also the case in human hippocampus (Katona *et al.*, 2000). These are presumably the GABAergic neurons involved in the endocannabinoid-mediated DSI phenomenon described above. The terminals of these cells surround large pyramidal neuron somata in the CA1–CA4 fields. GABAergic neurons in the dentate gyrus also express CB_1 receptors, with terminals concentrated at the boundary of the molecular and granule cell layers (Egertová and Elphick, 2000). In addition CB_1 receptors are expressed, at a lower level, in the glutamatergic pyramidal cells and their terminals. Cannabinoids can thus inhibit both the release of GABA and glutamate in hippocampal circuits.

The mechanisms underlying synaptic plasticity have been studied more intensely in the hippocampus than in any other brain region. In particular, the electrophysiological phenomena of long-term potentiation (LTP) and long-term depression (LTD) are thought to be involved in memory formation at glutamatergic synapses in the hippocampus. A number of studies have shown clearly that cannabinoids inhibit the induction of both LTP and LTD (for review see Elphick and Egertová, 2001). Cannabinoids appear to work by reducing glutamate release below the level needed to activate NMDA receptors, a requirement for LTP and LTD (Shen *et al.*, 1996; Misner and Sullivan, 1999). Although the actions of cannabinoids in reducing GABA release from hippocampal interneurons might have been expected to increase the level of excitability of hippocampal pyramidal cells, it seems that the cannabinoid-induced reduction in glutamate release predominates. The administration of exogenous cannabinoids is, of course, wholly unphysiological and cannot mimic the effects of endocabinnoids that are released in discrete local regions in response to particular patterns of afferent inputs. CB_1 receptors are capable of regulating both inhibitory and excitatory neurotransmitter release in the hippocampus and are thus capable of subtle control of synaptic plasticity. The CB_1-containing GABergic interneurons are thought to control oscillatory electrical activity in the hippocampus in the theta and gamma frequencies, which plays a role in synchronizing pyramidal cell activity (Hoffman and Lupica, 2000). CB_1 agonists decrease the power of such oscillations in hippocampal slices (Hájos *et al.*, 2000) and may thus influence the synchronous activity of pyramidal cells. The physiological importance of cannabinoid-mediated DSI may be to decrease GABAergic inhibition of these cells and thus facilitate learning when hippocampal inputs are active (Wilson and Nicoll, 2001).

One approach to answering the question of what role the tonic release of endocannabinoids may play in hippocampal function has been to examine the effects of CB_1 receptor knockout or of selective CB_1 receptor antagonists. Unfortunately, these studies have so far yielded conflicting results. Bohme *et al.* (2000) reported a significant enhancement of LTP in CB_1 knockout mice, and Reibaud *et al.* (1999) found a significant enhancement of memory in such animals. However, tests with the CB_1 antagonist rimonabant showed no effects on LTP (Terranova *et al.*, 1995) or on learning and memory in a spatial learning task (Mallet and Beninger, 1998), although Terranova *et al.* (1996) reported that rimonabant enhanced memory in a short-term olfactory memory test in rats (social recognition test).

Cannabinoids and the neocortex

Like other intoxicant drugs cannabis causes profound changes in a variety of higher brain functions. The literature on the acute effects of the drug in human subjects is large, and can only be summarized here (for reviews see Jones, 1978; Solowij, 1998; Iversen, 2000; Earleywine, 2002). The distribution of CB_1 receptors in the neocortex has been described in detail (Herkenham *et al.*, 1991; Egertová and Elphick, 2000). As in the hippocampus, the majority of cortical interneurons expressing high levels of CB_1 receptor are GABAergic cells, which also express cholecystokinin (Marsicano and Lutz, 1999). CB_1-positive terminals are concentrated in layers II–III and layers V–VI, with few in layers I or IV. Despite the obvious importance of the abundant CB_1 receptors in the neocortex there have so far been few electrophysiological studies of their effects on neural activity.

The earlier literature, however, contains several reports of the effects of acute and chronic cannabis use on EEG activity, both in man and animals (reviewed by Adams and Martin, 1996; Solowij, 1998). Most studies in man have observed changes consistent with a state of drowsiness, with increases in relative and absolute α power particularly in frontal regions of cortex. In contrast, the CB_1 antagonist rimonabant was shown to induce EEG changes characteristic of arousal in rats, and increased the time spent in wakefulness as opposed to sleep (Santucci *et al.*, 1996). Mechoulam *et al.* (1997) have suggested that anandamide may play a role in the control of the sleep–waking cycle.

Studies of the effects of cannabis on perceptual abilities have yielded a variety of often conflicting results. While users often report a subjective enhancement of visual and auditory perception, sometimes with synesthesia (sounds take on visual colourful qualities), laboratory studies have usually not shown marked changes in visual or auditory perception. One subjective effect that has been confirmed is the sensation that cannabis users experience time as passing more quickly relative to real time. In laboratory tests subjects overestimate

the amount of elapsed time when asked to estimate, or produce shorter than required intervals when asked to signal a period of elapsed time (Hicks *et al.*, 1984; Mathew *et al.*, 1998). This curious effect can also be seen in rats trained to respond for food reward using a fixed interval schedule. When treated with THC or WIN55,2122 the animals shortened their response interval, whereas the antagonist rimonabant lengthened this interval (Han and Robinson, 2001).

There have been many studies of the acute and chronic effects of cannabis on human cognitive function (Jones, 1978; Solowij, 1998; Earleywine, 2002). Performance on a variety of tests of cognitive function is impaired by the drug, but by comparison with alcohol the effects of cannabis are subtle. Whereas even moderate doses of alcohol, for example, impair reaction time, most studies with cannabis have failed to show consistent effects on measures of simple reaction time. Thus the drug's ability to disrupt cognitive function cannot be due to an inability to respond promptly. Among the impairments of cognitive function that have been observed in many, but not all, human studies are: decreased ability to inhibit responses, decreased vigilance, especially for long and boring tasks, decreased ability to perform complex mental arithmetic and impairments in tests of complex reaction times. On the other hand, intoxicated subjects can perform simple arithmetic, learn simple lists of words and recall memories laid down earlier.

Other studies have addressed the question of whether more severe deficits in cognitive function might develop in chronic heavy users of cannabis, or in animals treated for prolonged periods with the drug. The human studies are fraught with difficulties, as described in detail by Earleywine (2002). Among the confounding factors in human studies are that comparisons have to be made between groups of drug users versus non-users, but it is usually impossible to compare the baseline performance of these groups prior to cannabis use to see if they are properly matched. Statistical analysis of such data has often been poor, common errors being the use of so many different tests that the likelihood of finding some significant differences is increased, or the use of inadequate sample sizes. Other drug use can also confound the data. Results have been very variable. Some studies in long-term very heavy users of cannabis (10–20 joints per day for more than 10 years) in Jamaica (Bowman and Pihl, 1973) and Costa Rica (Satz *et al.*, 1976) failed to show any significant difference between users versus non-users using a battery of test assessments of cognitive function, and similar negative results were reported in some studies of US college students (Earleywine, 2002). However, most reports have shown that there are deficits in the performance of complex cognitive tasks in long-term cannabis users, although there is little evidence that these are qualitatively or quantitatively more severe than those seen after acute use of the drug (Earleywine, 2002).

Even more controversial is the question of whether long-term cannabis use can cause irreversible deficits in higher brain function that persists after drug use stops. Many studies have suffered from poor design. It is not sufficient to identify a group of cannabis users and simply to test them after stopping cannabis use. Pope *et al.* (2001), for example, recruited 63 current heavy users, who had smoked cannabis at least 5000 times in their lives, and 72 control subjects. Subjects underwent a 28-day washout from cannabis use, monitored by urine assays. At days 0, 1 and 7 the heavy users scored significantly below control subjects on a battery of neuropsychological tests, particularly in recall of word lists. However, by day 28 there were virtually no differences between the groups on any of the test results, and no significant association between cumulative lifetime cannabis use and test scores. The fact that drug-induced effects on cognitive performance can persist for up to a week after stopping the drug (perhaps because of the persistence of THC in the body, or because of a subtle withdrawal syndrome) means that many earlier studies that did not allow a sufficiently long washout period may be invalid. On the other hand, some well designed studies have shown subtle persistent cognitive deficits in ex-cannabis users. Solowij (1998) recruited a group of people who had used cannabis regularly for at least 5 years but who had stopped on average 2 years before the experiment. The subjects were given a very difficult task. They had to listen to a series of tones, some in the right ear some in the left; the tones were long or short (but differing by only 51 ms) and high or low pitch (but differing very little). Participants had to press a button as fast as possible in response to longer tones of a specified pitch in the correct ear. Previous research using this paradigm showed that current regular cannabis users had difficulty in discriminating between the tones. Measurements of event-related potentials also revealed small but significant abnormalities in the P300 wave (Solowij, 1998). The ex-users continued to make significant errors in the discrimination task, but they showed normal P300 waves. The conclusion of these and many other studies in ex-users seems to be that regular cannabis use can cause small but significant impairments in cognitive function that may persist after drug use stops. Such impairments appear to be associated with long-term heavy use of the drug and are unlikely to affect most recreational users.

Effects of cannabinoids on hypothalamic control of appetite

Many subjective reports suggest that cannabis intoxication is associated with an increased appetite, particularly for sweet foods, even in subjects who were previously satiated. This effect can be confirmed under laboratory conditions (Hollister, 1971; Mattes *et al.*, 1994), although results from studies in human subjects have tended to be variable, perhaps because the increased appetite is focused on certain types of food. Nevertheless, controlled clinical trials showed that THC (dronabinol) had significant beneficial effects in counteracting the loss of appetite and reduction in body weight in patients suffering from the AIDS-related wasting syndrome (Beal *et al.*, 1995), and this is one of the medical indications for which the drug has official approval in the USA.

THC also stimulates food intake in experimental animals, and again the effect is specific for high-fat or sweet high-fat diets, and is not seen in animals offered standard rat chow (Koch, 2001). The endocannabinoid anandamide also stimulates food intake in rats, and the effect is blocked by rimonabant (Williams and Kirkham, 1999). Conversely the CB_1 antagonist rimonabant given on its own suppressed food intake and led to reduced body weight in adult non-obese rats (Colombo *et al.*, 1998). These results suggest that cannabinoids may play a role in the regulation of food intake and body weight (Mechoulam and Fride, 2001). A possible reciprocal link between endocannabinoid mechanisms and the appetite-suppressing hormone leptin was suggested by Di Marzo *et al.* (2001*a*). They found that food-deprived CB_1 receptor knockout mice eat less than their wild-type litter mates, and the CB_1 antagonist rimonabant reduced food intake in the wild-type animals but not in the knockouts. Animals with defective leptin signalling (obese db/db or ob/ob mice and Zucker rats) exhibited elevated hypothalamic levels of anandamide and 2-AG. On the other hand, treatment of normal rats or ob/ob (leptin deficient) mice with leptin caused decreases in hypothalamic levels of the endocannabinoids. These findings suggest that hypothalamic endocannabinoids may play an important role in mediating the appetite-suppressant effects of leptin. At some stages during development these effects of endocannabinoids may be of critical importance. Fride *et al.* (2001) found that administration of the CB_1 antagonist rimonabant to new-born mouse pups had a devastating effect in decreasing milk ingestion and growth, continuing treatment with the antagonist led to death within 4–8 days. The effect of rimonabant could be almost fully reversed by co-administering THC.

Cannabinoids as anti-emetic agents

The ability of THC and the synthetic cannabinoid nabilone to control the nausea and vomiting associated with cancer chemotherapy is one of the few well documented medical applications for these drugs (for reviews of the controlled clinical trials see Vincent *et al.*, 1983; British Medical Association, 1997; Joy *et al.*, 1999; and the meta-analysis reported by Tramèr *et al.*, 2001). THC (dronabinol) and nabilone were approved for medical use in the USA, although neither drug has found much utility. The narrow window between the anti-emetic dose and that causing unwanted psychic effects made these drugs difficult to use. The advent of serotonin 5-HT_3 receptor antagonists as new and more powerful anti-emetic drugs that were free of unwanted psychic effects during the 1980s also made the cannabinoids less attractive.

Studies in experimental animals have confirmed that the anti-emetic effects of cannabinoids are mediated through CB_1 receptors (Darmani, 2002), and in some susceptible species (e.g. the least shrew) the CB_1 antagonist rimonabant is emetic, an effect that can be blocked by THC or WIN55,2122 (Darmani, 2001).

Cannabinoids and pain

Cannabis was widely used in 19th century medicine for pain relief and there is renewed interest in cannabis-based medicines, with pain as one of the key therapeutic targets (British Medical Association, 1997; Joy *et al.*, 1999). Endogenous cannabinoids and cannabinoid receptors exist at various levels in the pain pathways, from peripheral sensory nerve endings to spinal cord and supraspinal centres, in a system that is parallel to but distinct from that involving endorphins and opiate receptors.

Systemically administered THC and synthetic cannabinoids have anti-nociceptive and anti-hyperalgesic effects in a variety of animal models of acute and inflammatory pain (for reviews see Pertwee, 2001; Iversen and Chapman, 2002). Since cannabinoids inhibit motor activity this could prevent animals from exhibiting the normal behavioural reactions in analgesic tests; however, a number of studies have also shown that cannabinoids suppress electrophysiological responses of spinal cord neurons to noxious stimulation, and block spinal c-fos expression in response to such stimulation (Walker *et al.*, 1999; Pertwee, 2001; Iversen and Chapman, 2002). Cannabinoids and anandamide also exert anti-nociceptive effects in animal models of inflammatory pain when injected directly into spinal cord, brain stem or thalamus (Pertwee, 2001). Behavioural studies have shown that cannabinoids reduce thermal and mechanical allodynia in rat models of neuropathic pain (Herzberg *et al.*, 1997; Fox *et al.*, 2001; Iversen and Chapman, 2002). Furthermore, noxious stimulation evoked an increased release of anandamide in the periaqueductal grey region of brainstem, a key site for modulating nociceptive information (Walker *et al.*, 1999). The anti-nociceptive effects of cannabinoids are blocked by the CB_1 antagonist rimonabant, but the antagonist itself does not alter basal pain thresholds, suggesting that these are not controlled by tonic activity in the endocannabinoid system (Compton *et al.*, 1996).

Results obtained with CB_1 receptor knockout mice, however, suggest that not all of the anti-nociceptive effects of THC or anandamide are mediated via CB_1 receptors. Thus, although Di Marzo *et al.* (2000) found that the anti-nociceptive effects of THC were virtually absent in the knockout animals, anandamide continued to show analgesic activity in the hot-plate test. It is possible that the analgesic effects of anandamide are mediated in part through an action at other as yet ill-defined cannabinoid receptors (Breivogel *et al.*, 2001; Hájos *et al.*, 2001). Alternatively, it has been proposed that the effects of anandamide might be mediated through its ability to bind to the vanilloid VR1 receptor, which is present in primary afferent neurons and known to play an important role in nociceptive responses (Di Marzo *et al.*, 2001*b*). To complicate matters further, Zimmer *et al.* (1999), in a different strain of CB_1 receptor knockout mice, found that THC continued to exert some anti-nociceptive actions in hot-plate and formalin tests in the knockout animals. The reasons for the discrepant results obtained

with different strains of CB_1 receptor knockout mice are unknown.

There is evidence for an interaction between cannabinoid and opioid mechanisms. In tests of acute pain (Fuentes *et al.*, 1999) and chronic inflammatory pain (Welch and Stevens, 1992; Smith *et al.*, 1998) THC and morphine acted synergically—one potentiated the anti-nociceptive actions of the other. This potentiation could be blocked by either rimonabant or by naloxone, indicating that both CB_1 and opiate receptors were involved (Fuentes *et al.*, 1999). Meng *et al.* (1998) showed that temporary inactivation of neural activity in the rostral ventromedial medulla (RVM) in rat brainstem prevented the analgesic effects of systemically administered cannabinoids, while leaving their effects on motor activity unaffected. An electrophysiological analysis of the effects of cannabinoids on single cell firing patterns in RVM revealed that the effects of cannabinoids were similar to those elicited by morphine. The authors concluded that cannabinoids may produce analgesia through activation of a brainstem circuit that is also required for opiate analgesia, although the two mechanisms are pharmacologically distinct.

Basic research into the role of cannabinoids and endocannabinoids in pain mechanisms is progressing rapidly. Clinical progress, however, has been slow. A meta-analysis of clinical trials of cannabinoids as analgesics concluded that there was not enough evidence to justify their use in this indication (Campbell *et al.*, 2001). However, this may merely reflect the paucity of data from adequately sized controlled clinical trials, and cannabis-based medicines may yet find genuine medical applications in this field.

Cannabis as an intoxicant and drug of dependence

Cannabis intoxication

Despite being illegal, cannabis is one of the most widely used intoxicants; almost half of all 18 year olds in the USA and in most European countries admit to having tried it at least once, and ~10% of that age group are regular users (Iversen, 2000). There have been many subjective accounts of the cannabis 'high' (see Iversen, 2000; Earleywine, 2002). The experience is highly variable, depending on the dose of drug, the environment and the experience and expectations of the drug user. A typical 'high' is preceded initially by a transient stage of tingling sensations felt in the body and head accompanied by a feeling of dizziness or lightheadedness. The 'high' is a complex experience, characterized by a quickening of mental associations and a sharpened sense of humour, sometimes described as a state of 'fatuous euphoria'. The user feels relaxed and calm, in a dreamlike state disconnected from real world. The intoxicated subject often has difficulty in carrying on a coherent conversation, and may drift into daydreams and fantasies. Drowsiness and sleep may eventually ensue. The feelings of heightened perception, increased appetite and distortion of the sense of time have already been referred to. A survey of 1333 young British cannabis users (Atha and Blanchard, 1997) reported that the most common positive benefits reported were relaxation and relief from stress (25.6%), insight/personal development (8.7%) and euphoria (4.9%); more than half reported some positive benefits. But 21% of the users also attributed some adverse effects to cannabis use, including impaired memory (6.1%), paranoia (5.6%) and amotivation/laziness (4.8%).

As with other intoxicant drugs, little is known about the brain mechanisms that underlie the cannabis 'high'. The intoxicant effects are clearly mediated via CB_1 receptors. Huestis *et al.* (2001) carried out a well controlled study in 63 healthy cannabis users, who received either rimonabant or placebo and smoked either a THC-containing or placebo marijuana cigarette. The CB_1 antagonist blocked the acute psychological effects of the active cigarettes. Interestingly rimonabant itself when given alone (with placebo cigarette) produced no significant psychological effects. Mathew *et al.* (1997) used $H_2{}^{15}O$ and PET to measure changes in regional cerebral blood flow in a double blinded study in 32 volunteers comparing THC with placebo. Self ratings of cannabis intoxication correlated most markedly with increased blood flow in the right frontal region.

Endocannabinoids and CB_1 receptors are present in many regions of the limbic forebrain. For example, Katona *et al.* (2001) reported that CB_1 receptors were expressed in high densities in lateral and basal nuclei in the rat amygdala. As in hippocampus, the CB_1 receptors in these regions were located presynaptically on the terminals of cholecystokinin-containing GABAergic interneurons. Electrophysiological experiments showed that cannabinoids modulated GABAergic synaptic transmission. The authors suggested that such effects might underlie some of the actions of cannabinoids on emotional behaviour. Other experiments have revealed that, in common with other euphoriant drugs, THC selectively activates dopaminergic neurons in the ventral tegmental area. In an electrophysiological study French *et al.* (1997) reported that low doses of THC increased the firing of these cells. Tanda *et al.* (1997) used microdialysis probes to show that low doses of THC (0.15 mg/kg intravenously) caused an increased release of dopamine from the shell region of the nucleus accumbens, an effect that is also seen after administration of heroin, cocaine, d-amphetamine and nicotine. Tanda *et al.* (1997) found that the increased release of dopamine provoked by THC could be blocked by administration of the μ-opiate receptor antagonist naloxonazine, suggesting the involvement of an opioid mechanism.

Tolerance and dependence

Many animal studies have shown that tolerance develops to most of the behavioural and physiological effects of THC (for review see Pertwee, 1991). The earlier clinical literature suggested that tolerance also occurs after repeated administration of THC in man, although many of these studies were poorly controlled (for reviews see Jones, 1978, 1987;

Hollister, 1986). But for many years cannabis was not considered to be a drug of addiction. Withdrawal of the drug did not lead to any obvious physical withdrawal symptoms either in people or in animals, and animals failed to self-administer the drug, a behaviour usually associated with drugs of addiction.

Attitudes have changed markedly in recent years. The DSM-IV (American Psychiatric Association, 1994) defines 'substance dependence' and 'substance abuse' rather than 'addiction'. When the DSM-IV criteria are applied to populations of regular cannabis users surprisingly high proportions appear to be positive by these definitions. Swift *et al.* (2001) undertook a survey of 10 641 Australians aged 18 years and older. They reported that almost one-third of regular cannabis users fell within the definitions of 'substance abuse' (10.7%) or 'substance dependence' (21%). In the USA, Anthony *et al.* (1994) reported the results obtained from a large scale survey which indicated that some 46% of those interviewed had ever used cannabis and 9% of users became dependent. More carefully controlled studies have also shown that a reliable and clinically significant withdrawal syndrome does occur in human cannabis users when the drug is withdrawn. The symptoms include craving for cannabis, decreased appetite, sleep difficulty and weight loss, and may sometimes be accompanied by anger, aggression, increased irritability, restlessness and strange dreams (Budney *et al.*, 2001).

The existence of dependence on cannabinoids in animals is also much more clearly observable because of the availability of CB_1 receptor antagonist drugs that can be used to precipitate withdrawal. Thus, Aceto *et al.* (1996) described a behavioural withdrawal syndrome precipitated by rimonabant in rats treated for only 4 days with doses of THC as low as 0.5–4.0 mg/kg per day. The syndrome included scratching, face rubbing, licking, wet dog shakes, arched back and ptosis—many of the same signs are seen in rats undergoing opiate withdrawal. Similar withdrawal signs could be elicited by rimonabant in rats treated chronically with the synthetic cannabinoids CP-55,940 (Rubino *et al.*, 1998) or WIN55,2122 (Aceto *et al.*, 2001). Rimonabant-induced withdrawal after 2 weeks of treatment of rats with the cannabinoid HU-120 was accompanied by marked elevations of release of the stress-related neuropeptide corticotropin-releasing factor in the amygdala, a result also seen in animals undergoing heroin withdrawal (Rodriguez de Fonseca *et al.*, 1997). An electrophysiological study showed that precipitated withdrawal was also associated with reduced firing of dopamine neurons in the ventral tegmental area of rat brain (Diana *et al.*, 1998). These data indicate clearly that chronic administration of cannabinoids leads to adaptive changes in the brain, some of which are similar to those seen with other drugs of dependence. The ability of THC to cause a selective release of dopamine from the nucleus accumbens (Tanda *et al.*, 1997) also suggests some similarity between THC and other drugs in this category.

Furthermore, although many earlier attempts to obtain reliable self-administration behaviour with THC were unsuccessful (Pertwee, 1991), some success has been achieved recently. Squirrel monkeys were trained to self-administer low doses of THC (2 μg/kg per injection), but only after the animals had first been trained to self-administer cocaine (Tanda *et al.*, 2000). THC is difficult to administer intravenously and these authors succeeded perhaps in part because they succeeded in delivering the drug intravenously in doses comparable to those to which human cannabis users are exposed. The potent synthetic cannabinoids are far more water soluble than THC, which makes intravenous administration easier. Mice could be trained to self-administer intravenous WIN55,2122, but CB_1 receptor knockout animals failed to exhibit this behaviour (Ledent *et al.*, 1999). Another way of demonstrating the rewarding effects of drugs in animals is the conditioned place preference paradigm, in which an animal learns to approach an environment in which it had previously received a rewarding stimulus. Rats demonstrated a positive THC place preference after doses as low as 1 mg/kg (Lepore *et al.*, 1995).

A number of studies have suggested that there may be links between the development of dependence to cannabinoids and to opiates (Manzanares *et al.*, 1999). Some of the behavioural signs of rimonabant-induced withdrawal in THC treated rats can be mimicked by administration of the opiate antagonist naloxone (Kaymakçalan *et al.*, 1977). Conversely, the withdrawal syndrome precipitated by naloxone in morphine-dependent mice can be partly relieved by administration of THC (Hine *et al.*, 1975) or by endocannabinoids (Yamaguchi *et al.*, 2001). Rats treated chronically with the cannabinoid WIN55,2122 became sensitized to the behavioural effects of heroin (Pontieri *et al.*, 2001). Such interactions can also be demonstrated acutely. A synergy between cannabinoids and opiate analgesics has already been described above. THC also facilitated the anti-nociceptive effects of RB 101, an inhibitor of enkephalin inactivation (Valverde *et al.*, 2001). These authors found that acute administration of THC caused an increased release of Met-enkephalin into microdialysis probes placed into the rat nucleus accumbens.

The availability of receptor knockout animals has also helped to illustrate cannabinoid–opioid interactions. CB_1 receptor knockout mice exhibited greatly reduced morphine self-administration behaviour and less severe naloxone-induced withdrawal signs than in wild-type animals, although the anti-nociceptive actions of morphine were unaffected in the knockout animals (Ledent *et al.*, 1999). The rimonabant-precipitated withdrawal syndrome in THC-treated mice was significantly attenuated in animals with knockout of the pro-enkephalin gene (Valverde *et al.*, 2000). Knockout of the μ-opioid receptor also reduced rimonabant-induced withdrawal signs in THC-treated mice, and there was an attenuated naloxone withdrawal syndrome in morphine dependent CB_1 knockout mice (Lichtman *et al.*, 2001*a*, *b*).

These findings point clearly to interactions between the endogenous cannabinoid and opioid systems in CNS, although the neural circuitry involved remains unknown. Whether this relationship is relevant to the so-called 'gateway' theory is unclear. The US National Household survey of Drug Abuse (US Department of Health and Human Services,

1999) indicated that respondents aged 22 years or older who had started cannabis use before the age of 21 years were 24 times more likely than non-cannabis users to initiate use of hard drugs. But the proportion of cannabis users who progress in this way remains very small (~1% or less), and mathematical modelling using the Monte Carlo method suggested that the association between cannabis use and hard drug use need not be causal but could relate to some common predisposing factor, e.g. 'drug-use propensity' (Morral *et al.*, 2002).

Adverse effects of cannabis on the CNS

Is cannabis neurotoxic?

Although there have been claims that chronic cannabis use may permanently damage the brain, there is little scientific evidence to support these claims (for reviews see Dornbush *et al.*, 1976; Hollister, 1986, 1998; Zimmer and Morgan, 1997). As described above, some studies have revealed a modestly impaired ability to focus attention and filter out irrelevant information in ex-cannabis users (Solowij, 1998), but other studies failed to find any impairments in cognitive function (Pope *et al.*, 2001). There is little evidence that cannabis use impairs work performance or leads to an 'amotivational syndrome' (Dornbush *et al.*, 1976; Hollister, 1986; Abood and Martin, 1992), nor is there any convincing evidence for neuropathological changes in the brains of cannabis users (Hollister, 1986). The earlier studies have been complemented by the application of powerful modern neuroimaging methods. For example, an MRI study compared 18 current, frequent, young adult cannabis users with 13 comparable non-users and found no evidence of cerebral atrophy or regional changes in tissue volumes (Block *et al.*, 2000).

Animal studies have yielded conflicting results. Treatment of rats with high doses of THC given orally for 3 months (Scallet *et al.*, 1987) or subcutaneously for 8 months (Landfield *et al.*, 1988) was reported to lead to neural damage in the hippocampal CA3 zone, with shrunken neurons, reduced synaptic density and loss of cells. However, in another study the potent synthetic cannabinoid WIN55,2122 was administered twice daily (2 mg/kg) to rats and led to an apparent increase in hippocampal granule cell density, and increased dendritic length in the CA3 zone. In perhaps the most severe test of all, rats and mice were treated with THC 5 days each week for 2 years and no histopathological changes were observed in brain, even after 50 mg/kg/day (rats) or 250 mg/kg/day (mice) (Chan *et al.*, 1996). Although claims were made that exposure of a small number of rhesus monkeys to cannabis smoke led to ultrastructural changes in septum and hippocampus (Harper *et al.*, 1977; Heath *et al.*, 1980), subsequent larger scale studies failed to show any cannabis-induced histopathology in monkey brain (Scallet, 1991).

Studies of the effects of cannabinoids on neurons *in vitro* have also yielded inconsistent results. Exposure of rat cortical neurons to THC was reported to decrease their survival, with twice as many cells dead after 2 h exposure to 5 μM THC than in control cultures (Downer *et al.*, 2001). Concentrations of THC as low as 0.1 μM had a significant effect. The effects of THC were accompanied by release of cytochrome *c*, activation of caspase-3 and DNA fragmentation, suggesting an apoptotic mechanism. All of the effects of THC could be blocked by the antagonist AM-251 or by pertussis toxin, suggesting that they were mediated through CB_1 receptors. Toxic effects of THC have also been reported on hippocampal neurons in culture, with 50% cell death after 2 h exposure to 10 μM THC or after 5 days exposure to 1 μM drug (Chan *et al.*, 1998). The antagonist rimonabant blocked these effects, but not pertussis toxin. The authors proposed a toxic mechanism involving arachidonic acid release and formation of free radicals. However, other authors failed to observe any damage in rat cortical neurons exposed for up to 15 days to 1 μM THC, although they found that this concentration of THC killed rat C6 glioma cells, or human astrocytoma U373MG and mouse neuroblastoma N18TG12 cells (Sánchez *et al.*, 1998). In a remarkable study injections of THC into solid tumours of C6 glioma in rodent brain led to increased survival times, and a complete eradication of the tumours was evident in 20–35% of the treated animals (Galve-Roperh *et al.*, 2000). The anti-proliferative effects of cannabinoids has suggested a potential utility for such drugs in cancer treatment (Guzmán *et al.*, 2001).

Some studies have reported neuroprotective actions of cannabinoids. Administration of WIN55,2122 was found to reduce cerebral damage in rat hippocampus or cerebral cortex after global ischaemia or focal ischaemia models *in vivo* (Nagayama *et al.*, 1999). The endocannabinoid 2-AG protected against damage elicited by closed head injury in mouse brain, and the protective effects were blocked by rimonabant (Panikashvili *et al.*, 2001). THC had a similar effect *in vivo* in protecting against damage elicited by ouabain (Van der Stelt *et al.*, 2001). Rat hippocampal neurons in tissue culture were protected against glutamate-mediated damage by low concentrations of WIN55,2122 or CP-55,940 and these effects were mediated through CB_1 receptors (Shen and Thayer, 1998). But not all of these effects seem to require mediation via cannabinoid receptors. Nagayama *et al.* (1999) reported protective effects of WIN55,2122 that did not require either cannabinoid receptor in cortical neurons exposed to hypoxia, and similar findings were reported for the protective actions of anandamide and 2-AG in cortical neuron cultures (Sinor *et al.*, 2000). Both THC and cannabidiol, which is not active on cannabinoid receptors, protected rat cortical neurons against glutamate toxicity (Hampson *et al.*, 1998) and these effects, were also independent of CB_1 receptors. The authors suggested that the protective effects of THC in their studies might be due to the antioxidant properties of these polyphenolic molecules, which have redox potentials higher than those of known antioxidants (e.g. ascorbic acid).

The mixed reports of neurotoxic and neuroprotective effects of cannabinoids are confusing. While it may be possible to demonstrate neurotoxic actions after exposure of neurons to high concentrations of cannabinoids *in vitro*, there is little evidence for any significant neural damage *in vivo* after the administration of pharmacologically relevant doses of these drugs.

Cannabis and psychiatric illness

A temporary form of drug-induced psychosis can occur in some cannabis users. In some of the psychiatric literature this is referred to as 'cannabis psychosis' (or 'marijuana psychosis'). Research psychiatrists, particularly in Britain (Thomas, 1993; Hall and Degenhardt, 2000; Johns, 2001), have studied this condition carefully. It nearly always results from taking large doses of the drug, often in food or drink, and the condition may persist for some time, perhaps as the accumulated body load of THC is washed out. The acute toxic psychosis that is sometimes caused by cannabis can be sufficiently serious to lead to the subject being admitted to hospital, and the initial diagnosis can be confused with schizophrenia, since the patients may display some of the characteristic symptoms of schizophrenic illness. These include delusions of control (being under the control of some outside being or force), grandiose identity, persecution, thought insertion, auditory hallucinations (hearing sounds, usually non-verbal in nature), changed perception and blunting of the emotions. Not all symptoms will be seen in every patient, but there is a considerable similarity to paranoid schizophrenia. This has led some to propose a 'cannabinoid hypothesis of schizophrenia', suggesting that the symptoms of schizophrenic illness might be caused by an abnormal over-activity of endogenous cannabinoid mechanisms in the brain (Emrich *et al.*, 1997).

A number of studies have addressed the more contentious question of whether cannabis use can precipitate long-term psychiatric illness. The strongest evidence seemed to come from a study in Sweden that involved taking detailed medical records and information about the social background and drug-taking habits of 45 570 conscripts on entry to the Swedish army at age 18 years and following up of their subsequent medical history over a 15-year period (Andreasson *et al.*, 1987). A total of 4293 of the conscripts admitted having taken cannabis at least once, but the cannabis users accounted for a disproportionate number of the 246 cases of schizophrenic illness diagnosed in the overall group on follow-up. The relative risk of schizophrenia in those who had used cannabis was 2.4 times greater than in the non-users. In the small number of heavy users (who had taken the drug on more than 50 occasions) the relative risk of schizophrenia increased to 6.0. The authors concluded that cannabis was an independent risk factor for schizophrenia. There have been other similar reports (Mathers and Godse, 1992; Hall and Degenhardt, 2000; Johns, 2001). Hambrecht and Hafner (2000), for example, studied 232 patients in Germany with first-episode schizophrenia. They found that 13% of these had a history of cannabis use, a rate twice that of matched normal controls. At first viewing these findings seem convincing, but they do not prove any cause-and-effect relationship with cannabis. It may simply be that both cannabis use and schizophrenia are related to some common predisposing factor, such as personality. Indeed some psychologists and psychiatrists believe that they can identify psychological traits that are described as 'schizotypy' and which may predict an increased risk of developing clinical psychosis. Some studies in healthy adults have reported that those subjects who used cannabis scored higher on schizotypy scales than non-users (Williams *et al.*, 1996; Skosnik and Spatz, 2001). Half of the cannabis-using subjects in the original Swedish study had used cannabis more than 10 times and subsequently developed schizophrenia had also taken amphetamine, a drug known to be capable of inducing a schizophrenia-like psychosis. The cannabis users also came from deprived social backgrounds, another known risk factor of schizophrenia. More detailed follow-ups of some of the original Swedish cohort, however, claimed to have answered some of these criticisms (Andreasson *et al.*, 1989; Zammit *et al.*, 2002). In addition, further reports from New Zealand (Arseneault *et al.*, 2002; Fergusson *et al.*, 2003), Australia (Patton *et al.*, 2002) and France (Verdoux *et al.*, 2003) add weight to the hypothesis that the development of cannabis dependence in young people is associated with increased rates of psychiatric symptoms, both of psychosis and depression and anxiety (Patton *et al.*, 2002).

Nevertheless, the existence of a causative relationship between cannabis use and long-term psychotic illness remains unproven. If cannabis use did precipitate schizophrenia one might expect to have seen a large increase in the numbers of sufferers from this illness as cannabis use became more common in the West during the past 30 years. However, a detailed review of the epidemiological evidence up to 1990 appeared to show that this has not been the case (Thornicroft, 1990).

On the other hand, it is clear that cannabis can exacerbate the symptoms of existing psychotic illness. While schizophrenic patients seem to use cannabis and other psychoactive drugs as a form of 'self-medication', cannabis can make the key symptoms of delusions and hallucinations worse and it tends to counteract the anti-psychotic effects of the drugs used to treat the illness (Negrete *et al.*, 1986; Linzen *et al.*, 1994). On the other hand, one Swedish study reported that cannabis use made schizophrenic patients less withdrawn and more likely to speak (Peralta and Cuesta, 1992). It would seem prudent, nevertheless, to discourage the use of cannabis in patients with existing psychotic illness.

Conclusion

The discovery of the endocannabinoids and the availability of new pharmacological tools, together with the development of strains of genetically engineered knockout mice that lack

functional cannabinoid receptors, has revitalized the field of cannabis research in the past few years. The effects of administering THC or other cannabinoids can never simulate the highly localized function of the endocannabinoids, which appear to act as a fine control system to regulate neurotransmitter release at the synaptic level. There has been renewed interest in the potential therapeutic applications of cannabis-based medicines (British Medical Association, 1997; Joy *et al.*, 1999; Robson, 2001). THC or other cannabinoid agonists all suffer from the problem of a narrow therapeutic window between the desired clinical benefits and the unwanted psychic side-effects. It is possible that the pharmacological manipulation of the endocannabinoid system, boosting function, for example by drugs that inhibited the inactivation of the endocannabinoids, may offer a safer and more subtle approach to cannabis-based medicines in the future (Piomelli *et al.*, 2000).

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CANNABIS: OUR POSITION FOR A CANADIAN PUBLIC POLICY

REPORT OF THE SENATE SPECIAL COMMITTEE ON ILLEGAL DRUGS

SUMMARY

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SEPTEMBER 2002

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Glossary of key terms

Abuse

Vague term with a variety of meanings depending on the social, medical and legal contexts. Some equate any use of illicit drugs to abuse: for example, the international conventions consider that any use of drugs other than for medical or scientific purposes is abuse. The Diagnosis and Statistical Manual of the American Psychiatric Association defines abuse as a maladaptive pattern of substance use leading to clinically significant impairment or distress as defined by one or more of four criteria (see Chapter 7). In the Report we prefer the term excessive use (or harmful use).

Acute effects

Refers to effects resulting from the administration of any drug and specifically to its short term effects. These effects are distinguished between central (cerebral functions) and peripheral (nervous system). Effects are dose-related.

Addiction

General term referring to the concepts of tolerance and dependency. According to WHO addiction is the repeated use of a psychoactive substance to the extent that the user is periodically or chronically intoxicated, shows a compulsion to take the preferred substance, has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain the substance by almost any means. Some authors prefer the term addiction to dependence, because the former also refers to the evolutive process preceding dependence.

Agonist

A substance that acts on receptor sites to produce certain responses.

Anandamide

Agonist neurotransmitter of the endogenous cannabinoid system. Although not yet fully understood in research, these neurotransmitters seem to act as modulators as THC increases, the liberation of dopamine in nucleus accumbens and in the cerebral cortex.

At-risk use

Use behaviour which makes users at risk of developing dependence to the substance.

Cannabinoids

Endogenous receptors of the active cannabis molecules, particularly Delta 9-THC. Two endogenous receptors have been identified: CB1 densely concentrated in the hippacampus, basal ganglia, cerebellum and cerebral cortex, and CB2, particularly abundant in the immune system. The central effects of cannabis appear to be related only to CB1.

Cannabis

Three varieties of the cannabis plant exist: *cannabis sativa*, *cannabis indica*, and *cannabis ruredalis*. *Cannabis sativa* is the most commonly found, growing in almost any soil condition. The cannabis plant has been known in China for about 6000 years. The flowering tops and leaves are used to produce the smoked cannabis. Common terms used to refer to cannabis are pot, marijuana, dope, ganja, hemp. Hashish is produced from the extracted resin. Classified as a psychotropic drug, cannabis is a modulator of the central nervous system. It contains over 460 known chemicals, of which 60 are cannabinoids. Delta-9-tétrahydrocannabinol, referred to as THC, is the principal active ingredient of cannabis. Other components such delta-8-tétrahydrocannabinol, cannabinol and cannabidiol are present in smaller quantities and have no significant impacts on behaviour or perception. However, they may modulate the overall effects of the substance.

Commission on narcotic drugs (CND)

The Commission on Narcotic Drugs (CND) was established in 1946 by the Economic and Social Council of the United Nations. It is the central policy-making body within the UN system for dealing with all drug-related matters. The Commission analyses the world drug abuse situation and develops proposals to strengthen international drug control.

Chronic effects

Refers to effects which are delayed or develop after repeated use. In the report we prefer to use the term consequences of repeated use rather than chronic effects.

Decriminalization

Removal of a behaviour or activity from the scope of the criminal justice system. A distinction is usually made between *de jure* decriminalization, which entails an amendment to criminal legislation, and *de facto* decriminalization, which involves an administrative decision not to prosecute acts that nonetheless remain against the law. Decriminalization