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PROGRAMME ON SUBSTANCE ABUSE

Cannabis: a health perspective and research agenda

DIVISION OF MENTAL HEALTH AND
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Abstract

The use of cannabis, a psychoactive substance under international control, is widespread throughout the world. Reliable information on the actual and potential health consequences of cannabis use is thus an important input into health policy analysis and for the development of national and international drug control strategies.

The last WHO report on this topic was issued jointly with the Addiction Research Foundation of Ontario in 1981 (*ARF/WHO Scientific Meeting on Adverse Health and Behavioural Consequences of Cannabis Use*). In the intervening years, there have been many requests for an updated WHO report on the health consequences of cannabis use.

In response to these requests, WHO convened a group of scientific experts on cannabis in Geneva in November 1993. The present report is the end-product of a review and update process which started at that meeting. This report provides a review and summary of current knowledge about cannabis use and health effects, and is likely to be relevant for policy makers, public health officials, educators, and others concerned with health promotion.

Epidemiological studies from Australia, Canada, Europe, and the USA have indicated an increase in the prevalence of cannabis use by young people over the last decade. In other regions, mostly in developing countries, data available is more scarce, making it difficult to draw any conclusions about the general levels of cannabis use in these countries.

There have been significant advances in research over the last 15 years. These include: basic research on the mechanism of action of cannabinoids (of which Δ-9-tetrahydrocannabinol or THC is the most potent), the molecular structure needed for such action, the discovery of a specific receptor molecule to which the cannabinoid molecule attaches in brain cells and other tissue sites, the discovery of a natural chemical substance in the brain that normally acts on those receptor sites, and the mapping of the receptor sites in various parts of the brain and elsewhere in the body. Cannabis acutely impairs cognitive development and psychomotor performance, which increases the risk of motor vehicle accidents among those who drive intoxicated by cannabis. There has also been substantial progress in understanding the chronic effects of cannabis on the respiratory system and on various types of cells in the body's immune system. Chronically, there are selective impairments of cognitive functioning, and a dependence syndrome may develop. Chronic cannabis use may also exacerbate schizophrenia in affected individuals. On the other hand, several studies have demonstrated therapeutic effects of THC for nausea and vomiting in advanced stages of cancer and AIDS and studies on other therapeutic uses are underway.

There is a clear need for both epidemiological and applied research on cannabis and its derivatives. There are important gaps in knowledge about the health consequences of cannabis use which need to be addressed by well-controlled studies, including data on the patterns and consequences of cannabis use in developing countries, the chronic adverse effects of cannabis use and on the relative effectiveness of cannabinoids for medical use.

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Acknowledgements

Many individuals have assisted the Programme on Substance Abuse (PSA) in the preparation of this document. The contribution of the members of the WHO Expert Working Group on the Health Effects of Cannabis Use (see Annex 1) and the authors of the background documents for the Working Group meeting in May 1995 (see Annex 2) is gratefully acknowledged.

Based on the deliberation of the Working Group meeting, an editorial group consisting of Drs Harold Kalant, William Corrigall and Reginald Smart prepared a summary report which has served as the basis for this document. Their contribution was substantial and much appreciated. Subsequent drafts were reviewed by over 100 external reviewers, including selected scientists of the WHO Expert Advisory Panel on Drug Dependence and Alcohol Problems, and all WHO Collaborating Centres in the field of substance abuse. We wish to specifically acknowledge their input, as well as the contribution of Dr Wayne Hall and of the various experts at the US National Institute on Drug Abuse (NIDA) who have commented on various drafts of this report. Several helpful comments and suggestions were also made by the United Nations International Drug Control Programme (UNDCP).

1. Why this report now ?

1.1 Need for the report

The goal of the World Health Organization (WHO) is to promote the highest possible level of health for all peoples of the world. Psychoactive substances are a major cause of disease and injury in all regions of the world and a significant impediment to progress of 'health for all' strategies.

The use of cannabis, a psychoactive substance under international control, is widespread throughout the world. Reliable information of the actual and potential health consequences of cannabis use, including the costs and benefits of different interventions, is thus an important input into health policy analysis and for the development of national and international drug control strategies.

The last WHO report on this topic was issued jointly with the Addiction Research Foundation of Ontario in 1981 (*ARF/WHO Scientific Meeting on Adverse Health and Behavioural Consequences of Cannabis Use*). In the intervening years, there have been many requests for an updated WHO report on the health consequences of cannabis use.

In response to these requests, WHO convened a group of scientific experts on cannabis in Geneva in November 1993. The participants at this meeting (listed in Annex 1) agreed that an updated report on the health consequences of cannabis use should be prepared, and adopted a two-stage plan to produce such a report. First, scientists were commissioned to produce extensive literature reviews in the form of background papers on various topics, and these were reviewed by other experts. The authors and titles of the background documents are listed in Annex 2. Second, based on these reviews, a summary report was drafted by the original group of experts during a second meeting held in Geneva from 22-24 May 1995.

The draft summary report was then circulated to selected scientists of the WHO Expert Advisory Panel for Drug Dependence and Alcohol Problems, WHO Collaborating Centres, as well as other scientists and various technical units within WHO. Subsequently, the report was revised on the basis of these comments and in collaboration with the authors of the relevant sections of the summary report. The present report is thus a collaborative review based on inputs from scientists and public health specialists in all regions of the world.

1.2 Purpose and content of the report

This report provides a review and summary of current knowledge about cannabis use and health effects, and is likely to be relevant for policy makers, public health officials, educators, and others concerned with health promotion. The report is intended less for the use of research scientists and clinical experts, who usually have access to detailed information and studies through specialty journals and monographs, and computerized bibliographic services. In preparing this report, an effort has been made to summarize knowledge without using excessively technical language where possible, or with only essential bibliographic documentation, and with an emphasis on the major changes in knowledge in the past fifteen years and their potential implications.

There have indeed been significant advances in some areas in the last fifteen years. These include: basic research on the mechanism of action of cannabinoids, the molecular structure needed for such action, the discovery of a specific receptor molecule to which the cannabinoid molecule attaches in brain cells and other tissue sites, the discovery of a natural chemical substance in the brain that normally acts on those receptor sites, and the mapping of the receptor sites in various parts of the brain and elsewhere in the body. There has also been substantial progress in understanding the effects of cannabis on the respiratory system and on various types of cells in the body's immune system. Issues such as the link between cannabis use and schizophrenia, and the nature of cannabis dependence, have been substantially clarified. In contrast, in a number of other areas there has been no fundamental change in understanding. All of these matters are developed in greater depth in the body of this report.

1.3 Other sources of recent information

The background papers that served as the basis of this summary report contain much more detailed information and more complete lists of bibliographic references on the individual topics which they cover (see Annex 2 for a complete list).

In addition, a number of major reviews of the cannabis literature have appeared during the past few years (e.g. Arif & Westermeyer, 1988; Hall et al., 1994; Kandel, 1993; Mechoulam et al., 1994; Musty et al., 1991; Adams & Martin, 1996), and these have been taken into account when preparing this report. More detail on various issues discussed in this report can be found in these reviews.

2. Cannabis and health: some issues about inference

The approach to assessing the health effects of cannabis use followed in this report is the same as has been adopted by WHO/PSA to assess the health effects of the use of alcohol, tobacco and other psychoactive substances, namely that a reasonable standard of scientific proof is required to arrive at conclusions about the probable adverse health effects of cannabis. Some of these issues involved in assessing whether scientific evidence does indeed constitute causality are outlined below.

2.1 Making causal inferences

Causal inferences require, among other things, evidence of an association between cannabis use and an adverse health outcome; evidence that cannabis use preceded the health outcome; evidence that chance is an unlikely explanation of the association; and the exclusion of plausible alternative explanations of the association.

Reasonable evidence of an association between cannabis use and a health outcome is provided by the observation of such a relationship in case-control, cross-sectional, cohort, or experimental studies.

If cannabis use is the cause of an adverse health effect then there should be good evidence that cannabis use precedes the health effect. The strongest such evidence is provided by an observational cohort study or an experiment. In the case of cannabis, such studies are difficult to conduct due to the fact that cannabis is an internationally controlled psychoactive substance.

Chance can be ruled out if proper statistical evaluation indicates that the likelihood that the result may have occurred by chance is very small.

The alternative explanation that is much harder to exclude is that any relationship between cannabis use and a health outcome is due to an unmeasured variable which causes both cannabis use and the adverse health effect, i.e. a 'confounding' factor or factors. Experimental evidence provides the 'gold standard' for ruling out such explanations. This would require the random assignment of persons to use or not use cannabis, so as to ensure that users and non-users were equivalent in all relevant respects prior to their cannabis exposure. However, such random assignment is unethical, except in studies of innocuous health effects, because of the unacceptable risks imposed on volunteer subjects, quite apart from legal considerations in the case of cannabis.

Experiments using laboratory animals permit random assignment of subjects to cannabis or placebo exposure. There may be, however, considerable problems in extrapolating results across species. These may be minimized by proper attention to the importance of different routes of administration (e.g. oral, intravenous), different forms of cannabis (e.g. pure cannabinoids versus smoked cannabis plant material), and the question of equivalence of doses in different species (e.g. rat versus human).

When an appropriate animal model does not exist, or when human experiments are unethical, observational studies are necessary and provided they are properly conducted, non-causal factors can be controlled. If the relationship persists after such statistical adjustment, then the probability is increased that the health outcome is due to the effect of the exposure, in this case cannabis use.

Causal inferences can be drawn from research findings by judging the extent to which the evidence meets widely accepted criteria. These include: strength of association, consistency of association, specificity, dose-response, biological plausibility, and coherence with other knowledge. These criteria are not sufficient to show that an association is causal but the more that are met, the more likely it is that the association **is** causal.

2.2 Acute and chronic health effects

Any attempt to summarize the health effects of cannabis, or of any other psychoactive substance, runs the risk of oversimplification. The health effects experienced by a user will depend not only on the fact that cannabis was used, but also on a host of other factors. Acute drug effects, for example, will be influenced by the dose, the mode of administration, the user's prior experience with the drug, concurrent drug use, and the user's expectation, mood state and attitudes towards substance use, as well as environmental, biological and genetic factors.

The acute health effects of any psychoactive substance are conceptually easier to appraise than its chronic health effects: the temporal order of substance use and effect is clear; drug use and its effects typically occur closely together in time; and if the effects are not life-threatening or otherwise dangerous, they can be reliably reproduced by administering the psychoactive substance experimentally under controlled conditions. However, in such studies, the possibility of controlling for blood levels of THC (▵-9- tetrahydrocannabinol, the main active principle of cannabis) would allow stronger causal inferences between effects and THC levels as there is a great variability in bioavailability (amount of a substance which is available after absorption by any route) according to the route of administration. It is more difficult to attribute relatively rare acute adverse experiences (e.g. flashbacks, psychotic symptoms) to substance use. It is difficult to decide whether these are: rare events that are coincidental with substance intake; the effects of other psychoactive substances which are often taken together with cannabis; rare consequences of substance use that only occur at very high doses; manifestations of unusual forms of personal vulnerability; or the results of interactions between different substances.

Causal inferences about the long-term effects of chronic cannabis use become more difficult the longer the interval between use and the occurrence of the ill effects; the longer the interval, the more numerous the alternative explanations that need to be excluded. With continued chronic use this interval does not exist although it is still difficult to make causal inferences due to concurrent factors. The most rigorous evidence of chronic health effects is provided by laboratory studies of experimental animals in which well controlled doses are administered over a substantial period of the animals lives. However, a great many assumptions have to be made in extrapolating from health effects observed in laboratory animals to the probable health effects of equivalent doses and patterns of use in humans. In addition, there may be problems in extrapolating from studies with pure THC to human experience with crude cannabis preparations. The plant material contains many other compounds, both cannabinoid and non-cannabinoid in nature, and the possibility must always be considered that differences between experimental and clinical observations may be due in part to the effects of these other substances. Ideally, as bioavailability following the smoking route varies considerably between and within subjects, the measurement of blood levels of tetrahydrocannabinols should be included in any study design.

Epidemiological studies of the relationship between cannabis use and disease in humans are clearly relevant for public health policy, but they are less rigorous in assessing the degree of exposure to cannabis and in excluding alternative explanations of observed associations. There is consequently uncertainty about the interpretation of both 'positive' and 'negative' human epidemiological evidence. In the case of positive findings, cannabis use is often correlated with the use of other psychoactive substances (e.g. alcohol and tobacco) which are known to affect health adversely. This makes it difficult to confidently attribute (or exclude) some of these adverse health effects to cannabis use. When epidemiological studies fail to find adverse health effects of chronic cannabis use, it is

nonetheless uncertain whether the substance has indeed few, if any, chronic effects in humans, or whether we have not used sufficiently sensitive methods or procedures (e.g. cohort size) to reliably detect such effects. Studies on cannabis-related impairments conducted in cultures with traditional, social use of cannabis, might be helpful in distinguishing between the effects of cannabis use *per se* and those of a lifestyle often associated with illicit substance use.

3. Epidemiology of cannabis use

3.1 Methodological aspects of assessing cannabis use

The earlier literature on patterns of cannabis use is largely based on studies in developed countries, reflecting the emergence of widespread cannabis use among adolescents and young adults in these countries, and the health, legal and social concerns that this has led to. However, an increasing number of studies (for example, Smart et al., 1980; Carlini et al., 1990; Adelekan, 1989; Kramer, 1990) have been carried out in developing countries (in this case, Bahamas, Brazil, Nigeria and Venezuela, respectively), which provide some insight into cannabis use in developing countries as well.

Because cannabis is an illegal psychoactive substance, (cannabis and cannabis resin and extracts and tinctures of cannabis are included in Schedule I of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol), data on the levels and patterns of its use are much less widely available than on the use of alcohol and tobacco. Moreover, the illegality of cannabis gives rise to a number of potential biases that operate to underestimate the prevalence of its use. First, illicit substance users are likely to be under-sampled in household surveys, and those who are contacted may be reluctant to participate in a survey. Second, even if users agree to participate they may be less inclined to give truthful responses. Despite these biases there is sufficient evidence for the validity of self-reported substance-use in carefully designed studies to permit inferences about trends in illicit substance use.

No attempt has been made to estimate global figures on the prevalence of cannabis use, given the different methods of data collection, analysis, definitions and periods when surveys have been carried out. However, the United Nations Drug Control Programme has estimated the number of cannabis 'abusers' (annual prevalence) in the 1990s at 141 million people, i.e. 2.45 per cent of the world's population, based on figures given by Member States (UNDCP, 1997).

3.2 North America

3.2.1 United States of America

The United States have regularly undertaken surveys of illicit substance use over the last 15 to 20 years; these include the National Household Survey on Drug Abuse, conducted throughout the US on a regular basis by the National Institute on Drug Abuse (NIDA) since 1972 (NIDA, 1992); and the 'Monitoring the Future' nationwide surveys of samples of high school seniors, college students and young adults, conducted annually since 1975 (Johnston et al., 1997).

The NIDA national household survey originally covered approximately 9000 persons aged 12 years and older in randomly selected households throughout the US every two to three years. Since 1991, the survey has been conducted annually on over 30 000 participants.

In 1992, one-third of the national household sample reported that they had tried cannabis, 9 per cent had used it in the past year, and 4 per cent reported that they were current users. Lifetime use ranged from 11 per cent among those aged 12 to 17 years to 59 per cent among those aged 26 to 34 years, while 25 per cent of those over the age of 35 years reported some use. Rates of discontinuation of use were high, with over two-thirds of men and three-quarters

of women who were ever users not having used cannabis in the last year. Weekly cannabis use was uncommon: it was higher among men than women (9 per cent of men and 6 per cent of women), with a peak prevalence of 21 per cent among those aged 12 to 17 years who had ever used cannabis. Time series data from 1974 to 1990 showed that the prevalence of cannabis use increased throughout the 1970s, peaked in 1979, and declined steadily throughout the 1980s to levels lower than those reported in 1974.

The 'Monitoring the Future' surveys (Johnston et al., 1997) show wide fluctuations since 1975 in cannabis use among American adolescents in secondary school; lifetime prevalence among twelfth-graders (ages 16 to 18 years) peaked at 65 per cent in 1980 and had fallen by nearly half by the early 1990s; use in the last year peaked at 51 per cent in 1979 and fell by more than 60 per cent by 1992. The rate of noncontinuation also rose considerably (Table 1). While most users of other illicit substances had also used cannabis, trends in the use of those substances were independent of trends in cannabis use.

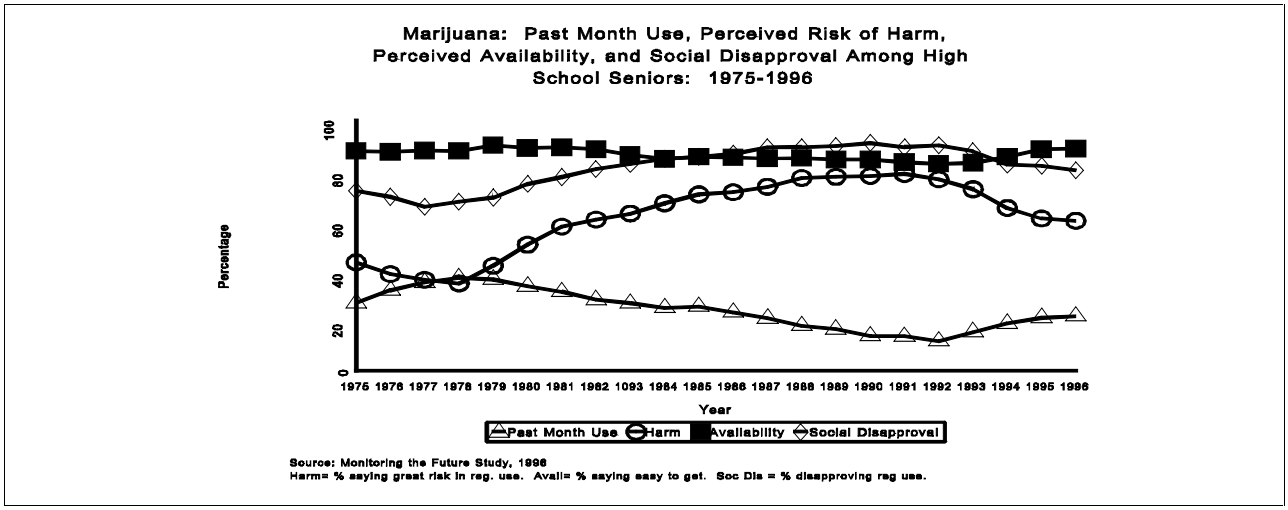
Table 1. Trends in Cannabis Use among Twelfth-Graders in the USA

	% Any Lifetime Use	% Any Use in Past 12 Months	% Noncontinuation Rates*	
			Used Any	Used 10+ Times
1975	47	40	15	4
1980	60	49	19	5
1985	54	41	25	8
1990	41	27	34	12
1992	33	22	33	11
1993	35	26	26	8
1994	38	31		
1995	42	35		
1996	45	36		

Source: Johnston et al., 1997

* This variable is defined as the percentages of those who ever used the drug (or used it 10 or more times) but did not use it in the past year. To avoid the implication of confirmed permanent cessation of use, which logically cannot be inferred from the survey, the investigators used the term 'noncontinuation' rather than 'discontinuation'.

After more than a decade of steady decline in cannabis use, the 1992 survey of eighth-graders (ages 14 to 16) and the 1993 and 1994 surveys of eighth-, tenth- and twelfth-graders showed an abrupt rise in all three grades, and a smaller rise among college students and young adults. There were increases in both the initiation rate and prevalence of continued use (Johnston et al., 1997).



Johnston and his colleagues have marshalled considerable evidence that changes in attitudes and beliefs about cannabis use explained the steady decrease during the 1980s, and the more recent increase in use. They report that an increased perception of the risks of cannabis use was strongly correlated with decreased rates of use over time, while in the most recent years, there was a significant decline in perceived dangers of cannabis use (Johnston, 1995).

3.2.2 Canada

A national telephone survey was conducted in Canada in 1994 by Health Canada of 12 155 persons aged 15 years and older. Overall, 28.2 per cent of the sample reported that they had ever used cannabis, but only 7.4 per cent has used cannabis in the past year. Rates of use were twice as high among males than females. Prevalence of current use declined with age from a high of 26.1 per cent among those aged 15 to 17 years to 1.4 per cent among those aged 45 to 54 years and 0.7 per cent among those aged 55 to 64 years. Rates of discontinuation were substantial, with only 26 per cent of those who had ever used cannabis having done so in the past year.

There have been a number of school surveys conducted in various provinces throughout Canada since the mid-1970s. The most consistent trend has been an increase in prevalence through the 1970s, then a sharp decline through the 1980s. Rates of illicit drug use were lower in Ontario than in the neighbouring United States of America. The size of the decline in rates of annual cannabis use was greater than for other substances. Among cannabis users, frequency of use has also declined since 1979 (Adlaf et al., 1995). However, there have been some more recent increases in overall rates of cannabis use within the last few years.

3.3 Australia and New Zealand

Cannabis continues to be the most widely used illicit psychoactive substance in Australia, with approximately one third of adults reporting that they had used the substance, and 72 per cent of all young adults between the ages of 20 and 24 at some point in their lives having used cannabis (de Zwart et al., 1994). In a national household survey of adults conducted in 1993, the prevalence of use was related to gender and age. Men were more likely to have used than women, and adults over the age of 45 years were much less likely to have used than younger adults. This reflects the initiation of widespread cannabis use among young Australian adults in the early 1970s (Donnelly & Hall, 1994).

More than half of those who had ever used cannabis in Australia had discontinued their use, or continued to use less than weekly. Seven per cent of women and 15 per cent of men became weekly users. Weekly cannabis use was most common among younger age groups, and highest among those aged 20 to 24 years, declining steeply thereafter. The use of cannabis has increased dramatically over the past 20 years, with the proportion reporting ever having used the substance increasing from 12 per cent of adults in 1973, to 28 per cent in 1985, and then to 34 per cent in 1993

(Donelly & Hall, 1994). The 'Omnibus' household surveys that were conducted throughout the 1970s by market research companies also showed that there has been an increase in the prevalence of cannabis use for all age groups between 1973 and 1984 (McAllister et al., 1991).

In New Zealand, a 1990 survey showed that 12 per cent of New Zealanders between 15 and 45 years of age had used cannabis in the previous 12 months (Black & Casswell, 1991) . Forty-three per cent of New Zealanders in the age group report lifetime cannabis use. In 1991, a study of 949, 13 to 14 year old children showed that by the age of 15 years, approximately 10 per cent had used cannabis on one or more occasions, and 2.2 per cent reported using cannabis on more than ten occasions (Fergusson et al., 1993).

3.4 Europe

The WHO Regional Office for Europe has collected results from a series of surveys in the European region on drug use among the general population. In 21 countries that were surveyed in the western part of the WHO European Region, cannabis has been reported as the most used illicit drug in the general population. In Denmark, in 1994, approximately 37 per cent of those between the ages of 16 and 44 have indicated they had used cannabis at least once. Using survey data through the mail, approximately 40 per cent of the same cohort had said they had used cannabis, indicating a slight rise in use in Denmark. In 1991 in Switzerland, 17 per cent of adults aged 17 to 45 reported ever use of cannabis. In a 1994 survey, 50 per cent of youth by the age of 20 said they had tried cannabis at least once, a considerable increase. However, this may be due in part to the young age of the cohort. In Germany, a 1994 survey of 18 to 59 year olds indicated that 13.6 per cent of those in the western part of the country had ever used cannabis, as opposed to 2.8 per cent of those in the eastern part of the country. The prevalence of ever use in the United Kingdom in 1992 was 14 per cent among 12 to 59 year olds (Harkin et al., 1997).

For all of the countries participating in the survey, current use, as expected, was much lower than ever use, indicating that cessation of use is very common. In the broad adult population, no more than 6 per cent in all of the countries for which data are available were using cannabis in the month prior to the survey. Among those in the age group 16 to 19 years, current use is generally higher. In the UK in 1991, 23 per cent of males and 13 per cent of females in this age group had used cannabis in the previous year, while among the 20 to 24 year age group, 18 per cent of males and 11 per cent of females had used cannabis during the last year. In Denmark, two 1994 surveys found that 14 per cent and 10 per cent of those aged 16 to 19, and 12 per cent, and 20 per cent of those 20 to 24 years of age, had used cannabis during the previous year (Harkin et al., 1997).

Seven of the eight Western European countries which participated in a survey on trends in cannabis use indicated that current use was increasing. These include France, where drug use generally has increased among young people since 1978, and the UK, where in school surveys the percentages of 13 and 14 year-olds who have ever used cannabis more than doubled from 1989 to 1993; and the percentage at ages 15 and 16 increased sixfold over the same period. Luxembourg reported that cannabis use had increased by about 20 to 25 per cent in the last ten years (Harkin et al., 1997).

The Pompidou Group (Johnston et al., 1994) has undertaken a study of the feasibility and validity of using high school surveys to monitor illicit substance use among high school students in Belgium, France, Greece, Italy, the Netherlands, Portugal and Sweden (using a sample from the USA for comparison). The study showed that it was possible to obtain valid data on illicit substance use. It found that the prevalence rates of almost all illicit psychoactive substances were generally higher in the USA sample. In the European samples, cannabis had been used at least once by 10 per cent to 36 per cent of the older student population, and had been used in the past 30 days by between 3 per cent and 14 per cent of the European students as against 19 per cent of the USA students. Cannabis was used on a near daily basis by 1 per cent or less of the European samples compared to 3 per cent in the USA.

In the Netherlands, a large national survey of substance use among more than 10 000 high school students aged 10 to 18 years old was conducted in 1992. About one-third of males and one-fifth of females had ever used cannabis

(de Zwart et al., 1994). Data from three national school surveys in 1984, 1988 and 1992, showed large increases in use between 1988 and 1992, particularly among older males. In the UK, a survey of 3258 randomly selected household residents found that the lifetime prevalence of illicit substance use was 6.9 per cent, with the most commonly used substance being cannabis (Russell et al., 1994).

Taken together, these data suggest that there has been an increase in the prevalence of cannabis use by young people over the last decade in Europe, as well as in Australia, Canada and the USA.

3.5 Cannabis use in other regions

For over ten centuries, opium and cannabis have been used as therapeutic agents in the treatment of a wide variety of ailments, or as part of celebrations or as a spice in food in African and Asian countries (UNDCP, 1997). There are, however limited survey data on trends in cannabis and other illicit substance use in these countries and other parts of the world. Occasional surveys are reported from specific countries but in most cases these data only provide a crude indication of levels of cannabis use. Survey methods are rarely reported, and results are often published only in summary form. It is often unclear whether reported rates of use refer to ever having used or to more frequent use, and there are rarely any data on rates of use in different age groups and for men and women. Often only an overall rate of cannabis use is reported for all adults which understates rates of cannabis use among young adults who are the heaviest users.

The lack of standardized methods for sampling and surveys, the limited data reported, and the absence of detailed age and sex-specific rates from most of these countries indicates the urgent need for promoting comparable data collection among countries. In this respect, WHO has recently completed guidelines on the use of standardized survey methods for use by countries to promote comparable data collection and to more accurately assess cross-cultural differences in rates and patterns of cannabis use.[1] With these caveats, the data are briefly described below.

3.5.1 Africa

African tribes also made considerable use of cannabis - in Tanzania, the drug found its way into the diet of the Southern Highlands where cannabis leaves and seeds were used as a spice in the preparation of special dishes. Traditional healers in Tanzania have also been known to use an extract from the cannabis plant for the treatment of ear-ache (Kilonzo & Kaaya, 1994).

Cannabis is a traditional psychoactive substance in sub-Saharan Africa, mainly used for ritualistic or medical purposes, but to a varying degree also accepted as an intoxicant (DuToit, 1980). A few studies on psychoactive substance use among secondary school students have been conducted in some sub-Saharan countries, mainly in Nigeria and Kenya (Adelekan, 1989; Dhadphale et al., 1982), showing the existence of experimentation and use of various substances among adolescents, although prevalence was generally lower than in Europe.
In 1990 and 1994, two large surveys were conducted among secondary school students in Zimbabwe (Eide & Acuda, 1995; 1996). In 1990, the prevalence of lifetime use of cannabis among 12 to 14 year old students varied between 5.5 per cent for boys and 1.0 per cent for girls, while among 17 to 18 year old students it varied between 12.7 per

[1] WHO Manual on Substance Abuse Epidemiology (in draft). Available from the WHO Programme on Substance Abuse, Geneva 1997.

cent for boys and 3.2 per cent for girls. Cannabis use was more prevalent among males of lower socioeconomic strata living in high-density urban areas, possibly reflecting its comparatively low price.

The data from 1994 indicated a trend towards an increase in lifetime use of cannabis among private school students, suggesting a diffusion from lower to higher socioeconomic strata. This trend needs to be further investigated. Cannabis use during the last 30 days also slightly increased among male students in the 1994 survey.

Low rates of ever having used cannabis have been reported in small surveys in Namibia and Nigeria. A 1991 survey of 600 Namibian school children and their parents reported that 8.2 per cent of parents had ever used cannabis, and 3.3 per cent were daily users. Among the school children 7.0 per cent had ever used cannabis, 3.7 per cent were occasional users and 0.7 per cent were daily users. In Ilorin, Nigeria, a self-administered survey of 1041 secondary school students in 1988, indicated that use of cigarettes and cannabis occurred significantly more in males, while no sex differences were noted for any other psychoactive substance surveyed. In Lagos State, Nigeria, a 1991 survey reported that 5 per cent of the sample had ever used cannabis.

In South Africa, a survey was conducted in 1990 of over 3000 individuals aged 14 years or older on their current use of psychoactive substances. It was found that 13 per cent of all adult males in urban areas reported current use of cannabis, compared to 9 per cent in towns, 22 per cent in squatter communities and 5 per cent for tribal areas (Rocha-Silva, 1991). An epidemiological study carried out in 1991 of 7340 students from 16 different schools in the Cape Peninsula reported that 7.5 per cent of the total sample had ever smoked cannabis. More males than females had ever smoked cannabis, and there was a trend of increased lifetime use with increased grade level in school (Flisher, 1993). Another study focusing on African youth in both rural and urban areas, aged 10 to 21 years old, had reported that cannabis use was predominantly found amongst urban males, with 5.5 per cent indicating that they were current users (Rocha-Silva et al., 1996).

3.5.2 Latin America and the Caribbean

In Brazil, three large national school-based surveys conducted in 1987, 1989 and 1993 found that the percentage of the surveyed population who had ever used cannabis was 2.9 per cent in 1987, 3.4 per cent in 1989 and 5.0 per cent in 1993. The highest prevalence of use was in Brasilia (5.6 per cent in 1987, 4.0 per cent in 1989 and 5.3 per cent in 1993) and São Paulo (3.5 per cent in 1987, 4.7 per cent in 1989 and 5.7 per cent in 1993). Although in 1993, Porto Alegre had 8.0 per cent of reported lifetime use of cannabis (Carlini et al., 1990; Galduroz et al., 1994).

A number of surveys of drug use have been conducted in Colombia. Torres de Gelvis & Murelle (1990), reported the findings of a 1987 survey of 2500 residents in four urban centres in Colombia. Respondents were aged between 12 and 64 years. Two per cent of males and 0.3 per cent of females had used cannabis during the previous year. Rates were low for all age groups with the highest level of 3 per cent for the 20-24 year age group. In terms of lifetime rates, 10 per cent of males and 3 per cent of females had ever used cannabis.

A 1992 National Household Survey on Drug Abuse in Colombia (Ospina et al., 1993) found that 5.3 per cent of adults reported having used cannabis at least once (10.4 per cent of males and 1.7 per cent of females). Usage was highest among those aged 18-24, with 1.5 per cent having used during the previous year. Only 0.5 per cent of 12 to 17 year olds had used during the past 12 months.

A Mexican household survey of psychoactive substance use in 1988 among respondents 12 to 65 years of age found an overall rate of lifetime cannabis use of 3 per cent. Cannabis use was higher among males than females (7.6 per cent versus 2.2 per cent) and more prevalent among younger age groups. The highest rates of use were in the North West region where 15.4 per cent of respondents aged 12 to 34 years of age reported ever having used cannabis, 7.9 per cent reported having used during the past year, and 4.0 per cent reported having used during the past month (Centros de Integracion Juvenil, 1992). Cannabis has been the most reported drug of initiation in the past 3 years in Mexico (Tapia-Conyer et al., 1994).

Alfaro-Murillo (1990) reviewed a series of surveys of drug use in Costa Rica conducted over the period of 1983-97. The most recent and representative of these was a 1987 multi-staged survey of 2700 respondents aged from 14 to 60 years of age. Only 3 per cent of the sample reported having ever used cannabis. The same author reported summary results from a school survey in 1985 of 818 high school students of whom under 5 per cent reported ever use of cannabis.

A cross national analysis of psychoactive substance use in Latin American and Caribbean countries, including Bolivia, Colombia, the Dominican Republic, Ecuador, Guatemala, Haiti, Jamaica, Panama, Paraguay, and Peru (Jutkowitz & Eu, 1994) indicated that Jamaica had the highest lifetime prevalence of cannabis use, at 29 per cent, of all countries studied. In other countries, less than 10 per cent of respondents had ever used cannabis. Lifetime prevalence levels were similar in most of those countries: 7.3 per cent in Guatemala, 6.5 per cent in Colombia, 6.1 per cent in Panama, and 8.3 per cent in Peru. Paraguay had a lifetime prevalence of 1.4 per cent and the Dominican Republic 2 per cent.

The same study reported that in all countries except Haiti, men were more likely than women to have ever used and to currently use cannabis. In high prevalence countries such as Guatemala and Panama, cannabis use starts as early as alcohol and tobacco (15 and earlier), and a substantial proportion of lifetime users currently use the substance (average 40 per cent). In low prevalence countries such as Haiti and Dominican Republic, cannabis use occurs at an older age on average (in the twenties) than alcohol and tobacco use (Jutkowitz & Eu, 1994).

Smart & Patterson (1990) reported the findings of surveys of drug use among students and delinquents in the Bahamas. In student samples aged 11 years and over, 8 per cent had ever used cannabis.

3.5.3 Asia

India has a long tradition of cannabis use from Vedic times as part of various religious traditions. In some Asian countries cannabis is also added to food as a condiment and used in herbal medicines. The extent of such use has not been well-documented.

With respect to use for psychoactive effects, only recently have limited survey data been collected on patterns or trends in cannabis use in some regions. Generalization is difficult because of regional differences in patterns of use. Surveys in three Northern Indian states in 1989 and 1991 (Indian Council of Medical Research, 1993) found a lifetime prevalence rate of 3 per cent and a prevalence of current use of 1 per cent, with no evidence of any increase between 1989 and 1991. In Varanasi, a study of 4326 college students revealed that overall cannabis use among them was 4.5 per cent. This decline in prevalence, from 10.2 per cent in 1976, was mainly in occasional users and the proportion of regular users had actually increased, with a significant increase among women students (Reddy et al., 1993). In Southern India, a lifetime prevalence of use of 7 per cent has been reported, with 2.5 per cent current users. Higher prevalence figures of 10 per cent and 27 per cent have been reported in surveys of students (presumably ever use) (Indian Council of Medical Research, 1993).

Household surveys conducted in a rural area of India, an urban slum area and in a city among persons aged 10 years and older found the following prevalence of ever use of cannabis: 3.2 per cent in the rural area; 3.2 per cent in the slum area; and 2.7 per cent in the city (Machado, 1994). Cannabis use in the rural area was predominantly for religious purposes whereas in the other two regions its use was mainly recreational. Cannabis use was not perceived as a problem behaviour in the rural area given the socioreligious context of use, but it was seen as such in the urban areas where it was perceived as a deviant form of behaviour (Machado, 1994).

No survey results were available to WHO on cannabis use in any other countries from the Asian region.

4. Chemistry and pharmacology

4.1 Terminology

Cannabis is a generic term used to denote the several psychoactive preparations of the plant *Cannabis sativa*. The major psychoactive constituent in cannabis is Δ-9-tetrahydrocannabinol (THC). Compounds which are structurally similar to THC are referred to as cannabinoids. In addition, a number of recently identified compounds that differ structurally from cannabinoids nevertheless share many of their pharmacological properties. The Mexican term 'marijuana' is frequently used in referring to cannabis leaves or other crude plant material in many countries. The unpollinated female plants are referred to as *sinsemilla*. The resin from the flowering tops of cannabis plants is called *hashish*. Cannabis oil (hashish oil) is a concentrate of cannabinoids obtained by solvent extraction of the crude plant material or of the resin.

4.2 Cannabis and various preparations

Cannabis contains at least 60 cannabinoids, several of which are biologically active. The primary compound of interest is (-)-trans-Δ-9-tetrahydrocannabinol (hereafter referred to only as THC, unless otherwise specified) which is the most potent cannabinoid in the plant. Cannabinoids also occur in the plant in the form of carboxylic acid derivatives, e.g. tetrahydrocannabinolic acid. The THC content and the cannabinoid composition are known to vary widely depending upon the variety and growing conditions. The THC content in cannabis is typically in the range of 0.5 to 4 per cent (Huestis et al., 1992). Cannabis oil, hashish and sinsemilla all contain concentrations of THC exceeding that in the average plant material. Sinsemilla may have THC concentrations of 7 to 14 per cent. THC content in hashish generally ranges from 2-8 per cent, although it may be as high as 10 to 20 per cent. The concentration of THC in cannabis oil varies between 15 to 50 per cent. Concerns regarding THC content in cannabis have been renewed because of recent developments in indoor hydroponic cultivation techniques. For example, these efforts have enhanced the THC content in Dutch hemp, so-called 'Netherweed', to concentrations as high as 20 per cent .

Dosage

A typical joint contains between 0.5 and 1.0 g of cannabis plant matter which may vary in THC content between 5 and 150 mg (i.e. typically between 1 per cent and 15 per cent). The actual amount of THC delivered in the smoke has been estimated at 20 to 70 per cent, the rest being lost through combustion or sidestream smoke. The bioavailability of THC (the fraction of THC in the cigarette which reaches the bloodstream) from marijuana cigarettes in human subjects has been reported from 5 per cent to 24 per cent. Given all of these variables, the actual dose of THC absorbed when smoked is not easily quantified.

In general, only a small amount of cannabis (e.g. 2 to 3 mg of available THC) is required to produce a brief pleasurable high for the occasional user, and a single joint may be sufficient for two or three individuals. A heavy smoker may consume five or more joints per day, while heavy users in Jamaica, for example, may consume up to 420 mg THC per day. In clinical trials designed to assess the therapeutic potential of THC, single doses have ranged up to 20 mg in capsule form. In human experimental research, THC doses of 10, 20 and 25 mg have been administered as slow, medium and high doses.

The pharmacological and toxicological consequences of cannabis exposure are likely due to numerous constituents in the plant. In addition, smoking cannabis results in the formation of a large number of pyrolysis products. The vapour phase consists of nitrogen oxides, carbon monoxide, hydrogen cyanide and nitrosamines, and the particulate phase contains many known carcinogens including phenols, cresols and polynuclear aromatic hydrocarbons. During smoking, tetrahydrocannabinolic acid, which lacks psychoactivity, is converted to THC, thus adding to cannabis potency.

4.3 Synthetic cannabinoids

In order to investigate the mechanism by which cannabinoids produce their effects in the central nervous system, numerous structural changes have been made in the THC molecule. Minor structural changes to THC profoundly

alter its psychoactive potency; this indicates a highly specific mechanism of action. Furthermore, systematic structural modifications have resulted in the development of novel cannabinoids that are considerably more potent than THC. Notable examples include the bicyclic analogue CP 55,940[2] and 11-hydroxy-dimethylheptyl-△-8-THC, the latter being several hundredfold more potent than THC itself. In addition to enhancement of potency, these syntheses led to the development of some cannabinoids with structures distinctly different from that of THC. Despite the development of structural diversity and enhanced potency, all of these analogues produce the full complement of THC behavioural effects.

4.4 Receptors

Recognition of the structural requirements for the cannabinoid analogues prompted the search for a cannabinoid receptor in the brain (Howlett et al., 1990). Using a radio labelled form of a potent bicyclic cannabinoid, Devane et al. (1988) were able to characterize a binding site that exhibited three key features: cannabinoid agonists bound with high affinity, non-cannabinoids did not bind, and that this site was present in very high abundance in the brain. Moreover, Compton et al. (1993) demonstrated a very high correlation between receptor affinity and biological potency of the various compounds, a necessary criterion for a receptor-based mechanism of action.

This receptor is distributed differentially in the various regions of the brain, in a pattern that is similar throughout a variety of mammalian species, including humans. Most of the receptors are in the basal ganglia, cerebellum, cerebral cortex and hippocampus. A rough correlation appears to exist between this distribution and some of the effects of cannabis. For example, binding sites in the hippocampus and cortex may be linked to the subtle effects of cannabis on cognitive function, while those in the basal ganglia and cerebellum may be associated with cannabis-produced ataxia.

In addition to the cannabinoid receptor in the brain, a peripheral receptor has been identified in macrophages in the spleen. The peripheral receptor is structurally different from the brain receptor. This observation is important because it suggests the possibility that other receptor subtypes with entirely unique functional roles may exist.

4.5 Endogenous ligands and an endogenous cannabinoid system

An endogenous ligand for the cannabinoid receptor has recently been identified (Devane et al., 1988, and 1992). Known as anandamide, it appears to have actions which are similar to those of cannabis in several pharmacological assays, although it is considerably less potent than △-9-THC and has a shorter duration of action.

In order for anandamide to act as a neurotransmitter or neuromodulator, there must be appropriate synthetic and metabolic pathways. Synthesis has been demonstrated to occur in homogenates of rat brain. Anandamide can be degraded by a variety of tissues including brain, liver, kidney and lung. Evidence is emerging that a family of anandamide-type compounds may exist.

Although the recent progress in neuroscience suggests the existence of a cannabinoid neurochemical system, its role in the brain and its relationship to other neurochemical systems remain to be clarified (Mechoulam et al., 1994). There is so far no direct evidence for a primary functional role; it may be, therefore, that the endogenous cannabinoid system is largely neuromodulatory in function. The consequences of manipulating the cannabinoid system can be only conjectural at this time. Based upon receptor localization in the brain and the pharmacological effects of cannabinoids, it is reasonable to foresee roles in cognition, memory, reward, pain perception and motor coordination,

[2] The chemical name of this compound is (-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)-cyclohexanol.

to name a few. At present it remains to be determined whether, and to what extent, use of cannabis will alter processes which regulate the endogenous cannabinoid system.

4.6 Antagonist

An experimental compound which acts as an antagonist on the brain cannabinoid receptor has been identified (Rinaldi-Carmona et al., 1994). This compound prevents or reverses the pharmacological effects of cannabinoids. It appears to be highly selective for the cannabinoid receptor, and does not bind to a variety of other brain receptors. The discovery of this antagonist provides a valuable tool for investigating the functional role of the cannabinoids in the central nervous system.

4.7 Pharmacokinetics

THC is absorbed more quickly when delivered by smoking than after oral ingestion. Each puff represents a small bolus of the drug that is delivered to the circulatory system via the capillary bed surrounding the alveolar sacs of the lungs. Huestis et al. (1992) reported measuring detectable amounts of THC (7 to 18 mg/ml) following a single puff of cannabis smoke in individuals smoking cannabis cigarettes (1.75 per cent and 3.55 per cent THC content). When experienced users smoked cannabis cigarettes containing 1.32, 1.97 and 2.54 per cent THC, peak concentrations developed in excess of 100 mg/ml (Ohlsson et al., 1980; Perez-Reyes et al., 1982; Huestis et al., 1992), although there was considerable intersubject variability. Obviously, the dynamics of smoking substantially influences how much of the drug is absorbed. The number of puffs, spacing, hold time, and lung capacity, contribute to this variance.

When cannabis is smoked by non-tolerant individuals, physiological and behavioural effects appear rapidly. Huestis et al. (1992) found that peak effects occurred at 17.4 ± 4.8 and 13.8 ± 4.2 minutes after initiation of smoking of a low (1.75 per cent) or high (3.55 per cent) dose cigarette. Maximum effects were recorded within 4 to 6 minutes after the last puff of cannabis smoke.

Plasma levels of THC fall rapidly as the drug redistributes into fatty tissue in accordance with its high lipid solubility. The delay between peak blood concentrations and peak drug effects are likely related to delays in penetration in the central nervous system, and to subsequent redistribution of THC following rapid uptake by adipose tissues (Barnett et al., 1982; Barnett et al., 1985).

Generally, behavioural and physiological effects return to baseline levels 4 to 6 hours after usage. Blood concentrations of THC peak prior to drug-induced effects, leading to a dissociation between blood concentrations of THC and pharmacological effects. This time discordance has led investigators to improve the technology for measuring THC and its metabolites in biological fluids and tissues (Cook, 1986; King et al., 1987; Gjerde, 1991), and to develop pharmacokinetic/pharmacodynamic models that establish a relationship between concentrations of THC and the physiological, behavioural and performance changes produced by cannabis (Chiang & Barnett, 1984).

4.8 Research gaps

It will be important to identify the various neurochemical processes (such as synthesis, release, inactivation, storage, etc.) which constitute the functioning of an endogenous cannabinoid system, and to discover the physiological roles of this system. This knowledge will be the basis for understanding whether and how the use of cannabis modifies the endogenous system. Another priority is the development of a range of potent cannabinoid agonists and antagonists with diverse structural features. These are needed to explore the development of potential therapeutic cannabinoid agents. Continued efforts should be made to clarify the relationship between blood cannabinoid levels and behavioural effects, and to better understand the pharmacokinetics of chronic use, and fetal metabolism following *in utero* exposure.

5. Effects on the brain and behaviour

5.1 Acute effects on central nervous system functions and behaviour

The acute effects of cannabis use have been recognized for many years, and features such as mild euphoria, relaxation, increased sociability, heightened sensory perception and increased appetite have been described in earlier reports. The acute effects of higher doses, including perceptual changes, depersonalization and panic have also been well described previously (ARF/WHO, 1981). Research conducted since the last WHO report has focused mainly on quantifiable effects such as those on memory, psychomotor performance and appetite; however, some work has also been done on the acute psychotropic effects of cannabis. A recent report done by Mathew et al. (1993), showed that cannabis smoking was associated with significant depersonalization that was maximal 30 minutes after smoking. Other behavioural changes associated with cannabis intoxication included loss of time sense, sensation of 'high', anxiety, tension and confusion (Mathew et al., 1993).

Recent studies have confirmed and extended earlier findings that cannabis can affect memory in various ways. Free recall of previously learned items is often impaired when cannabis is present both during the learning and the recall; the major impairment is often reflected by intrusions and novel items. In a study done by Block et al. (1992), the acute effects on human cognition of cannabis were assessed. It was found that cannabis impaired all capabilities of learning, including associative processes, and psychomotor performance. The only areas that were not affected were those of abstraction and vocabulary. It was also found that cannabis use altered associative processes, thereby making uncommon associations more pervasive (Block et al., 1992). Recall of prose material is generally impaired by cannabis, but its effects upon recall of series of numbers (the digit-span test), recognition, and paired-associates tasks (arbitrary word pairings) have been inconsistent. Generally, material learned in the absence of cannabis can be recalled even if cannabis is present in the blood. Although the acute effects of cannabis on memory appear to be modest, the possibility must be considered that chronic use by an adolescent might result in a cumulative developmental impairment.

A substantial number of recent studies have confirmed that cannabis use consistently increases the consumption of food, especially of high carbohydrate foods. In contrast, cannabis has not shown consistent effects upon the users' subjective reports of appetite. The reason for this apparent dissociation between appetite and food consumption is not known (Mattes et al., 1994).

Several studies have shown that cannabis appears to increase the perceived rate of the passage of time. Consistent with earlier observations, numerous studies in the past ten years have confirmed that cannabis impairs psychomotor performance in a wide variety of tasks, such as handwriting, tests of motor coordination, divided-attention, digit-symbol substitution, and operant tasks of various types (Solowij et al., 1991). The consistency of results is probably attributable to improved experimental technique, as reflected by greater attention to the importance of task complexity, standardization of THC administration, studies of dose-effect relationships, and of sharper definition of acute versus residual effects.
A number of studies have examined the acute effects of alcohol and cannabis on various performance tasks, but the results have been quite varied. In almost all cases the combination had a greater detrimental effect than that of either drug alone, but in some cases the effects were fully additive, in other cases incompletely additive, and in a few instances apparently antagonistic. This is an important area for further research.

Cannabis has been shown in a variety of ways to function reliably as a reinforcing agent[3] and the degree of reinforcement is proportional to the THC content (Gardner & Lewinson, 1991).

[3] reinforcing agent - substance intake leads to repeated use of the same substance

Relatively few studies have examined the effects of cannabis on a variety of social behaviours, including verbal and aggressive behaviours. A somewhat inconsistent pattern of changes has been reported following cannabis use, and the behavioural effects of cannabis can be influenced by the social context of use.

Finally, residual effects of cannabis administration and effects of cannabis and other licit and illicit drugs are poorly defined and require more research. Cannabis is often used concurrently with other psychoactive substances. The resultant effects on human behaviour have received less attention and yet the impact polysubstance use has on health and safety may be substantial.

5.1.1 Dose-effect relationships

Some investigators have attempted to identify a range of THC concentrations in blood or other body fluids which can be related to behavioural changes, as can be done for alcohol. For THC the relationship of effect to dose is complicated by the wide individual variability observed in responses from subjects undergoing performance testing. This variability can be due to factors related to dose, mode of administration, physiological and pharmacological differences, complexity of performance tasks, situational demand during testing, and the prior drug experience of the subject.

Once equilibrium between brain and blood concentrations is established (approximately 45 minutes after use), a linear relationship between blood concentrations and pharmacological effects appears (Chiang & Barnett, 1984). Recently developed mathematical models may clarify the relationship between THC and metabolite concentrations in blood on one hand and drug-induced effects on the other, and provide estimates of time elapses since last cannabis use (Huestis et al., 1992).

5.2 Effects on driving

Behaviours for which the acute effects of cannabis might be expected to be particularly important include the operation of dangerous machinery and driving a motor vehicle. There is sufficient consistency and coherence in the evidence from experimental studies and studies of cannabinoid levels among accident victims (Smiley et al., 1981; Stein et al., 1983; McBay, 1986; Soderstrom et al., 1988) to conclude that there is an increased risk of motor vehicle accidents among persons who drive when intoxicated with cannabis. Impairment of various performance measures related to driving skills has been demonstrated immediately following cannabis use and up to 24 hours thereafter. Simpson (1986) has also shown that cannabis is present in the blood, indicating use within the last few hours, in 7 to 10 per cent of samples of persons involved in traffic accidents. Williams et al. (1985) in a study of young male fatalities in California, found a rate of 37 per cent samples positive for cannabis. This risk is magnified when cannabis is combined with intoxicating doses of alcohol. Simpson (1986) also found that 80 per cent of the time, when cannabis was present, alcohol was also present in the samples.

The relatively small number of experimental studies carried out since the previous WHO report have confirmed that cannabis can impair various components of driving behaviour, such as braking time, starting time, and reaction to red lights or other danger signals. However, persons under the influence of cannabis may perceive that they are impaired, and where they can compensate, they may do so (Stein et al., 1983; Smiley et al., 1981). For example, they may tend not to attempt to pass the vehicle ahead, to slow down, and focus their attention on the driving task when they know a response will be required. However, such compensation is not possible when they are presented with unexpected events, or where the task requires continuous attention, and hence the risk of accidents remains higher following cannabis use. The effects on driving behaviour are still present for an hour after smoking, but do not continue for extended periods at the doses used in these studies.

On the other hand, a study carried out on the carry over effects of cannabis on aircraft pilot performance showed that cannabis use impaired flight performance at 0.25, 4, 8 and 24 hours after smoking. These results suggest that human performance while using complex machinery can be impaired as long as 24 hours after smoking as little as 20 mg of THC, and that the user may be unaware of the drug's influence (Leirer et al., 1991).

Available data are not yet sufficient to quantify the effects of cannabis use as an accident risk. There is uncertainty about the role of cannabis in motor vehicle accidents in part because blood levels of cannabinoids not only indicates recent use and do not indicate whether a driver or pedestrian was intoxicated with cannabis at the time of an accident (Consensus Development Panel, 1985). In addition, more than 75 per cent of drivers with cannabinoids in their blood have also been found to be intoxicated with alcohol (Gieringer, 1988; McBay, 1986).

A number of these studies have compared the effects of various doses of alcohol and cannabis. In many respects the effects of these substances are similar, but in others there appear to be differences (Smiley, 1986). For example, both drugs impaired accuracy of lane control, and increased reaction time to subsidiary stimuli. However, they produced different effects on patterns of visual search during simulated driving. The influence of personality variables on these responses may require further study.

5.3 Long-term effects of cannabis on the central nervous system

5.3.1 Cognitive functions

A number of studies carried out in Costa Rica, Greece, Jamaica and other countries in the 1970s appeared to show little or no effect of chronic cannabis use on cognitive function in groups of adult subjects. These studies assessed cognitive functions by neuropsychological tests, many of which were originally developed for use in North America and may have been inappropriate for use in other cultures. However, more recent studies (Fletcher et al., 1996) making use of improved test procedures and electrophysiological methods, have shown that the long-term use of cannabis leads to subtle and selective impairments of cognitive functioning. These include the organization and integration of complex information involving various mechanisms of attention and memory processes, including verbal learning, card sorting, auditory attention, tone discrimination, and the filtering out of irrelevant information. Prolonged use may lead to progressively greater impairment, which may not recover with cessation of use for at least 24 hours (Pope & Yurgelum-Todd, 1995), or 6 weeks (Solowij et al., 1991, Solowij et al., 1995), and which could potentially affect functioning in daily life.

Not all individuals are equally effected. The basis for individual differences needs to be identified and examined. There has also been insufficient research to address the impact of long term cannabis use on cognitive functioning in adolescents and young adults, and on age and gender differences.

5.3.2 Brain function and neurotoxicity

The review of effects of long-term cannabis use on cognitive function, referred to above, has revealed the existence of subtle signs of disturbances of brain function. However, these could be interpreted either as evidence of persisting intoxication with cannabis (a 'withdrawal effect') or as indications of permanent structural or functional damage to neurons. Evidence to date does not permit a clear conclusion with respect to these two possibilities.

The early claims of gross anatomical changes in the brains of chronic cannabis users have not been substantiated by later studies with high resolution computerized tomography, in either humans or primates (Rimbaugh et al., 1980; Hannerz & Hindmarsh, 1983). On the basis of histological and electron microscopic examinations, however, other animal studies have suggested that chronic cannabis use produces morphological changes in synapses as well as hippocampal neuronal loss (Landfield et al., 1988; Eldridge et al., 1992), although others failed to find any abnormalities (Slikker et al., 1992). More subtle functional changes may possibly be detected by imaging techniques such as positron emission tomography (PET), single photon emission computerized tomography (SPECT), and magnetic resonance imaging (MRI) as these become more widely applied to the study of chronic cannabis users (Volkow et al., 1991).

There have been a few investigations of the long-term effects of cannabis on cerebral regional blood flow (CBF). Tunving et al. (1986) demonstrated globally reduced resting levels of CBF in chronic heavy users of 10 years compared to nonuser controls, but no regional flow differences were observed. Levels of CBF returned to normal values with abstinence. However, this study was flawed in that some subjects were given benzodiazepines, which are known to lower CBF, prior to the first measurement. Mathew and colleagues (1986) in another study did not find any differences in CBF levels between users and non-user controls.

Therefore one must still rely largely on the persistence of functional disturbances as a means of exploring possible cell toxicity. If such functional changes last long after the disappearance of cannabis from the body, they might be interpreted as evidence of permanent damage. Several studies for example, have shown learning and memory deficits months after the end of chronic cannabis administration to rats. Similarly other studies have shown receptor down-regulation or neurotransmitter changes (Oviedo et al., 1993). However, they did not include actual measurement of residual cannabis levels in brain at the time of testing.

In view of the possible impact of chronic cannabis use at critical stages of development, such as during adolescence, the re-examination of these questions, with due consideration of the methodological issues, is clearly required.

5.4 Adolescent development

There has been a predictable sequence of initiation into the use of illicit drugs among adolescents throughout the 1970s and into the 1990s in which experimentation with cannabis preceded the use of hallucinogens, benzodiazepines, amphetamines, various sedatives, cocaine, and heroin. Generally, the earlier the age of initiation into cannabis use, and the greater the involvement with it, the greater the likelihood of progression to the use of other illicit drugs (Kandel, 1984; Kandel, 1988).

However, the causal role of cannabis in this sequence of illicit drug use remains controversial (Kandel & Johnson, 1992). The hypothesis does *not* imply that a high proportion of those who experiment with cannabis will go on to use heroin, for example. The overwhelming majority of cannabis users do not use other illicit psychoactive substances. First, cannabis is largely a behaviour of adolescence and early adulthood (in countries where there is no traditional use of the substance). Second, a more plausible explanation is that it reflects a combination of the selective recruitment into cannabis use of non-conforming and deviant adolescents who have a propensity to use illicit drugs, and the socialization of cannabis users within an illicit drug using subculture which increases the opportunity and encouragement to use other illicit drugs (Newcombe & Bentler, 1988; Osgood et al., 1988).

There has been some support for the hypothesis that adolescent use of cannabis impairs educational performance in cross-sectional studies (e.g. Kandel, 1984). Cannabis use appears to increase the risk of high-school drop-out and of job instability in young adulthood, but the apparent strength of these relationships may have been exaggerated as there was no control over differences between groups before initiation of cannabis use (Newcombe & Bentler, 1988).

There is suggestive evidence that cannabis use has adverse effects upon family formation, mental health, and involvement in drug-related crime (Kandel, 1984; Newcombe & Bentler, 1988). In the case of each of these outcomes, the apparently strong associations revealed in cross-sectional data are much more modest in longitudinal studies after statistically controlling for associations between cannabis use and other variables which predict these adverse outcomes.

5.5 Psychiatric disorders due to cannabis use

The major psychiatric syndromes and behavioural disorders that have been putatively linked to cannabis use are: an amotivational syndrome, a dependence syndrome, cannabis induced psychoses, and the initiation and exacerbation of schizophrenia (Basu et al., 1994).

5.5.1 Amotivational syndrome and cannabis psychoses

The state of the evidence on amotivational syndrome and cannabis induced psychoses has not substantively changed since the 1981 WHO report. In both cases, the existence of the hypothesized disorders still depends upon uncontrolled clinical observations. Although there is reasonable self-report evidence that heavy cannabis use can impair motivation, an amotivational syndrome has not been clearly defined nor have its central features been clearly distinguished from the effects of chronic intoxication in chronic heavy cannabis users.

The existence of putative 'cannabis psychoses' also largely depends upon clinical observations of individuals developing acute organic and functional psychotic disorders following heavy cannabis use, with the disorders remitting within days of abstinence from cannabis. There are also a limited number of case-control studies comparing the clinical symptoms and course of psychotic disorders in individuals who do and do not have cannabinoids in their urine. The occurrence of an acute organic disorder with a brief and self-limiting course has met with some agreement, even in more recent studies (Chaudry et al., 1991; Thomas, 1993). However, it remains true that the phenomenology of 'cannabis psychoses' has not been clearly defined nor have these putative disorders been distinguished from schizophrenia and other psychotic problems that occur among cannabis users (Andreasson et al., 1989; Mathers & Ghodse, 1992). The confirmation of such disorders needs more research evidence.

5.5.2 Cannabis dependence syndrome

Clinical and epidemiological research has clarified the status of the cannabis dependence syndrome. A reduced emphasis on the importance formerly attached to tolerance and withdrawal symptoms in diagnostic criteria for dependence has removed a major reason for scepticism about the existence of a cannabis dependence syndrome. Clinical and epidemiological research using standardised diagnostic criteria has produced good evidence for a cannabis dependence syndrome that is characterized by impairment, or loss of control over use of the substance, cognitive and motivational handicaps which interfere with occupational performance and are due to cannabis use, and other related problems such as lowered self-esteem and depression particularly in long-term heavy users (Anthony & Helzer, 1991). As with other psychoactive substances, the risk of developing dependence is highest among those with a history of daily cannabis use. It is estimated that about half of those who use cannabis daily will become dependent (Anthony & Helzer, 1991). Cannabis dependence treatment programmes are not widespread and the outcome of the treatment often relies on the substance user having a greater sense of economic security and a lower inclination to drop out of the programme, with those staying in the programme having the greatest success rates of quitting cannabis smoking (Stephens et al., 1993; Roffman et al., 1993). The large discrepancy between population prevalence estimates and the small numbers of cannabis users seeking treatment suggests that there is a high rate of remission in the absence of treatment, while a lack of motivation to seek treatment and to stop use cannot be ruled out.

Since tolerance and withdrawal symptoms are still widely regarded as diagnostic criteria of substance dependence, it is worth noting that there is abundant experimental evidence of tolerance to many of the effects of cannabis. There is not yet universal agreement about the production of a withdrawal syndrome. Although a recent study has demonstrated that long term administration of cannabinoid to rats alters the central nervous system in a manner similar to that observed with other drugs of abuse and also, induces neuroadaptive processes which correspond to a cannabis withdrawal syndrome (de Fonseca et al., 1997). However, withdrawal signs have been described in animals treated chronically with cannabinoids and then given one of the new receptor antagonists (Aceto et al., 1995; Tsou et al., 1995).

5.5.3 Cannabis use and schizophrenia

Epidemiological research has produced clear evidence from case-control, cross-sectional and prospective studies of an association between cannabis use and schizophrenia. The prospective study of Andreasson et al. (1987), has shown a dose-response relationship between the frequency with which cannabis had been used by age 18 and the risks over the subsequent 15 years of being diagnosed as schizophrenic. The association is not in doubt but its

significance remains controversial because it is unclear whether it reflects the precipitation of schizophrenia by cannabis use or the increased use of cannabis and other drugs as a consequence of schizophrenia (Williams et al., 1996). In a more recent study (Allebeck et al., 1993), out of 229 people in Stockholm County with a diagnosis of cannabis dependence and psychosis, 112 fulfilled DSM III-R criteria for schizophrenia. In most cases, regular cannabis use preceded onset of psychosis by at least one year, which supports the argument that cannabis is a risk factor for schizophrenia. Further supportive evidence has been provided by the WHO international prospective study of schizophrenia (Jablensky et al., 1991).

5.5.4 Other disorders

A number of other psychiatric disorders have been linked with cannabis use. These include: an amnesic syndrome, persistent depersonalisation, and flashbacks. There is no evidence to support the existence of an amnesic syndrome comparable to the Wernicke-Korsakov syndrome that occurs in chronic heavy alcohol users. There is some evidence (reviewed in the chapter on cognitive effects) that chronic heavy cannabis use may produce more subtle cognitive impairments. The other two disorders are only supported by a small number of case histories and, in the case of flashbacks, there is considerable uncertainty as to whether these effects were attributable to cannabis or other drug use.

5.6 Priorities for future research

A better understanding of the effects of chronic cannabis use is required. This includes research which explores the effects on cognitive functioning, especially during critical developmental phases such as adolescence. In addition, the question of cannabis-produced brain damage can be answered only by ascertaining if there are morphological changes in the brain that correlate with functional deficits which outlast the duration of cannabis in the brain; these studies will require use of newer neuroscience techniques in experimental animals as well as in humans.

The major psychiatric research priorities are: better delineation of the clinical features of cannabis dependence, including its responsiveness to interventions to assist users to stop; and intervention studies with schizophrenic individuals who use cannabis, to see whether cessation of such use improves outcomes.

6. Effects on the respiratory system

Worldwide, after tobacco, cannabis is probably the most commonly smoked substance. With the exception of nicotine in tobacco and over 60 cannabinoids in cannabis, the smoke from these two compounds share many of the same respiratory irritants and carcinogens. In fact, the tar phase of the smoke of marijuana has about 50 per cent more of some of the carcinogens than a comparable quantity of unfiltered tobacco (Leutchtenberger, 1983; Institute of Medicine, 1982).

6.1 Histopathology

Early animal studies indicated that a prolonged high dose exposure to cannabis smoke could result in parenchymal lung injury (Fleischman et al., 1979; Rosenkrantz & Fleischman, 1979). The findings of later experimental studies suggest that high dose cannabis exposure is associated with the development of chronic obstructive bronchitis, and carries the risk of invasive malignancy such as that produced by tobacco smoke. In a longitudinal study done on the respiratory effects of cannabis, a total of 1802 subjects who smoked cannabis were followed for six years. The study found an increased risk for 'chronic cough' (RR of 1.73) and of 'wheezing' (RR of 2.01), after adjusting for age, tobacco smoking and occurrence of the symptom in a preceding survey. There was also a significant reduction in pulmonary function, with exposure as low as the consumption of less than one cannabis cigarette per day for one year or more (Sherrill et al., 1991). The histopathological changes occurred mainly in the distal airways and included acute and chronic inflammation, fibrosis, and alveolar cell hyperplasia (Rosenkrantz & Fleishman, 1979).

Later prospective investigations undertaken on primates found changes such as bronchiolar squamous metaplasia, and peribronchiolar/interstitial fibrosis. The severity of these small airway changes was related to the dose and duration of cannabis exposure with higher doses and longer exposure to smoke leading to greater changes, while atypical cell hyperplasia with focal atypia were also found (Tashkin et al., 1987).

In human studies, it has been shown that the principal respiratory damage caused by long term cannabis smoking is an epithelial injury of the trachea and major bronchi. In a study undertaken in Germany, it was found that the number of T-cell lymphocyte counts were lower in chronic cannabis smokers, thereby increasing their chances of developing squamous cell carcinoma of the oral cavity and pharynx (Wengen, 1993). The difference between the findings in animal and human studies is probably due to the fact that observations in humans are limited to those which can be made by bronchoscopy. Human bronchoscopic studies undertaken on young adults who had no respiratory symptoms found evidence of histological changes in the upper airways among heavy cannabis smokers. These changes included basal cell hyperplasia, stratification, goblet cell metaplasia, and basement membrane thickening (Roby et al., 1991; Tashkin et al., 1987). The few studies that have been undertaken generally show that there is no additive effect between cannabis and tobacco (Gil et al., 1995; Sherill et al., 1991; Tashkin et al., 1987), although one study, the Tucson study, did show an additive effect (Bloom et al., 1987). However, in a follow-up survey the same additive effect was not found (Sherman et al., 1991). Whether or not there is an additive effect between tobacco and cannabis smoking remains uncertain, and more research needs to be done to further explore this issue. The histological abnormalities resulting from cannabis consumption were more severe per cigarette smoked than for tobacco (Wu et al., 1988).

Autopsies undertaken on cannabis smokers who had no respiratory symptomatology at the time of death also found changes in the form of focal infiltration by pigmented macrophages around bronchioles and within alveolar spaces, and focal fibrosis within alveolar walls. In this study, the relative contribution of tobacco to these changes could not be ascertained with certainty except in one case though the person did not smoke tobacco (Fligiel et al., 1991).

6.2 Immune defence

The alveolar macrophage, the key cell in the lung's defence against infection, has been shown to be impaired by cannabis smoke in both animal and human studies. While animal studies failed to demonstrate a change in macrophage numbers following cannabis smoke exposure, subsequent investigations in humans, comparing non-smokers to cannabis and tobacco smokers, suggested an increase in the number of macrophages in habitual cannabis smokers (Wallace et al., 1994; Barbers et al., 1987; Barbers et al., 1991). This probably reflects an immunological response to any lung injury induced by cannabis smoke. The effect is independent of tobacco consumption (Wallace et al., 1994).

Macrophage cells harvested in these human studies have alterations to their morphology, possibly reflecting an impairment in cell function. Residual particles from cannabis smoke in the form of intra cytoplasmic inclusions have been found to be cycled between subsequent generations of macrophages as part of the process of cellular turnover (Davis et al., 1979). While there is a suggestion in human studies that cannabis smoking did not alter phagocytosis or respiratory burst, it possibly did impair destruction of ingested organisms (Lopez-Cepero et al., 1986). The mechanism of macrophage impairment has not been fully elucidated and requires further investigation. These studies suggest that regular cannabis consumption reduces the respiratory immune response to invading organisms. Further, serious invasive fungal infections as a result of cannabis contamination have been reported among individuals who are immunocompromised, including a series of patients who were affected by AIDS (Denning et al., 1991).

These findings suggest that persistent cannabis consumption over prolonged periods can cause airway injury, lung inflammation, and impaired pulmonary defence against infection. Epidemiological studies that have adjusted for sex, age, race, education, and alcohol consumption suggest that daily cannabis smokers have a slightly elevated risk of respiratory illness compared to nonsmokers.

6.3 Lung physiology

Several studies on humans have demonstrated an acute bronchodilator effect of both smoked cannabis and oral THC. These findings have been replicated in both healthy and asthmatic populations (Boulougouris et al., 1976). However, the potential therapeutic use of cannabis and synthetic cannabinoids as bronchodilators has been largely discounted.

Two recent studies in relatively young populations compared respiratory symptoms and lung function in nonsmokers and long-term smokers of both cannabis and tobacco (Bloom et al., 1987; Tashkin et al., 1988). In both studies, heavy habitual cannabis consumption, with or without tobacco, was associated with a higher prevalence of symptoms of chronic bronchitis and a higher incidence of acute bronchitis than in the nonsmoking group.

However, the studies disagreed about effects on peripheral airway resistance. One longitudinal study indicated that cannabis consumption was associated with increased large airway resistance but not with the development of chronic obstructive bronco-pulmonary disease or emphysema (Gil et al., 1995; Tashkin et al., 1988). The other study found a significant deleterious effect on the ventilatory function of small airways and alveoli among habitual cannabis smokers. The effect was at least as great as the effect of tobacco consumption (Bloom et al.,1987). Recent studies have also failed to agree on whether any impairment in pulmonary function is additive to the effects of tobacco consumption. Both the site of impairment and potential interaction between cannabis and tobacco require further investigation.

While the pulmonary absorption of carbon monoxide from cannabis smoke is relatively high compared to that from tobacco smoke, the impact of this on heavy habitual consumers is modest. This probably reflects the short half-life for clearance of carbon monoxide, and the relatively longer intervals between occasions of cannabis use. However, the carboxyhaemoglobin levels in cannabis smokers are higher than in nonsmokers; this may result in a slight interference with tissue oxygenation (Tashkin et al., 1988).

Ventilatory responses to rebreathing carbon dioxide have been shown by different studies to decrease (Bellville et al., 1975), increase (Zwillich et al., 1978), or remain unchanged (Vachon et al., 1973) immediately after smoking cannabis. A recent, more detailed study of control of breathing responses to smoking cannabis of varying potency has failed to reveal any acute effect of cannabis on central or peripheral ventilatory drive or on metabolic rate in habitual cannabis smokers (Wu et al., 1992).

6.4 Carcinogenesis

Cases of cancers of the aerodigestive tract have been reported in young adults with a history of cannabis use (Taylor, 1988; Fergusson et al., 1989; Donald, 1991). Attribution of causality has been hindered because many of the cases also used alcohol and tobacco (Polen et al., 1993). However, these cases are of particular concern because such cancers are rare in adults under the age of 60, even among those who smoke tobacco and drink alcohol. Case-control and experimental studies of such cancers should be a high priority for research on the possible adverse health effects of chronic cannabis use.

7. Effects on endocrine and reproductive systems

Studies of the effects of cannabis on male and female reproductive systems have examined: the pituitary hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which are responsible for the synthesis of the sex hormones (estrogen and testosterone) and the normal functioning of the sex organs; the pituitary hormone prolactin which alters LH and FSH levels; the levels of estrogen and testosterone; and the physiological status of the sex organs.

7.1 Male reproductive hormones

Although there is general agreement that THC treatment lowers plasma levels of LH and testosterone in male laboratory animals (Symons et al., 1976; Chakravarty et al., 1982; Puder et al., 1985; Fernandez-Ruiz et al., 1992), the effects in the human male are not as clear. Early studies reported that cannabis exposure produced either a transient reduction (Schaefer et al., 1975; Cohen, 1976) or no effect in levels of plasma LH and testosterone in human males (Cushman, 1975; Mendelson et al., 1978). However, the findings that chronic cannabis exposure does affect human reproductive function (Kolodny et al., 1974; Hembree et al., 1979; Issidorides, 1979) suggests that cannabinoids do alter the reproductive hormones that control testicular function and have some effect on testicular parameters.

Subsequent studies have largely confirmed that plasma LH levels were unchanged after smoking one to two cannabis cigarettes containing 2.8 per cent THC (Cone et al., 1986). Daily exposure to either oral THC or cannabis smoking had no effect on plasma levels of either LH or testosterone in men who were prior cannabis users. Similarly, circulating levels of LH, FSH, prolactin and testosterone were not found to be clinically different between cannabis users and non-users (Markinanos & Stefanis, 1982; Dax et al., 1989; Block et al., 1991).

The conflicting results in these human studies could reflect differences in experimental procedures and the possible effect of previous cannabis exposure (i.e. tolerance) and other drugs in test subjects, effects which can be carefully controlled in animal studies.

7.2 Female reproductive hormones

$\triangle$-9-THC alters pituitary secretion of LH, FSH, and prolactin when administered either acutely or repeatedly to both intact and ovariectomized experimental animals (Steger et al., 1980, 1981). In addition to suppressing normal circulating levels of LH in female rats, THC also inhibits the surges of LH and FSH which are essential for ovulation. As a consequence, THC blocks ovulation in intact rats and monkeys (Smith et al., 1979). Moreover, the occurrence of the first ovulation in the maturing female rat is delayed following peripubertal administration of THC (Field & Tyrey, 1986). Tonic prolactin levels are significantly decreased following acute or repeated THC treatment in both intact and ovariectomized female rats (Hughes et al., 1981). In addition, prolactin surge occurring under a variety of situations is blocked by THC administration (Steger et al., 1983). THC treatment also disrupts the normal rhythm of menstrual cycles in monkeys (Asch et al., 1981).

Cannabis smokers have shorter menstrual cycles due to an inadequate luteal phase. When the acute effects of cannabis smoking on plasma LH, prolactin and sex steroid hormones were evaluated during the follicular and luteal phases of the menstrual cycle in groups of adult females, it was found that during the luteal phase of the menstrual cycle, plasma LH and prolactin were suppressed, thereby shortening their cycles (Mendelson et al., 1985, 1986). However, self-reported chronic cannabis users were not found to have any changes in circulating levels of LH, FSH and prolactin when compared to non users (Block et al., 1991). It appears that the hormonal response to cannabis exposure depends on the stage of the menstrual cycle.

7.3 Target organs

In addition to the aforementioned hormonal alterations, animal studies show that cannabinoid exposure reduces testicular, seminal vesicle and prostate weights, decreases ovarian weight and increases pituitary and adrenal weights. These cannabinoid effects have been attributed to actions at both peripheral and brain sites.

7.4 Other hormones

There is considerable evidence that cannabinoid exposure can affect the hypothalamic-pituitary-adrenal axis. Early animal studies have demonstrated that THC is a potent stimulator of adrenocorticotropin (ACTH) release in male rats. Acute THC administration also elevates plasma corticosterone levels in male and female rats. Anandamide, the endogenous ligand for the cannabinoid receptor, produces some effects similar to those of THC.

Landfield et al. (1988) observed that THC administration induced aging-like degenerative changes in rat brain tissue similar to those resulting from elevated corticosterone. These investigators have also demonstrated that THC administration alters the corticosterone receptor in brain. It seems possible that the corticoid and anandamide systems could be mutually regulatory. Additional evidence will be needed if such a relationship is to be established. However, it should be noted that men who were heavy cannabis users did not exhibit alterations in cortisol level (Block et al., 1991) or impaired adrenocortical reactivity to ACTH.

In early studies, it was shown that THC inhibited growth hormone secretion in male rats. However, other studies have demonstrated either no change or an increase in growth hormone in male rats treated with THC. More recently it has been shown that infusion of THC directly into brains of adult male rats suppresses growth hormone secretion. Although differences in animal models, and route and doses of THC administration may explain these variable growth hormone responses to THC, more studies are warranted to determine conclusively the effects of cannabis exposure on growth hormone in both males and females.

Few other endocrine systems have been studied. Circulating thyroxine levels have been shown to be reduced following acute or chronic THC administration in male rats and rhesus monkeys. THC treatment may also affect the release of the posterior pituitary hormone oxytocin (Tyrey & Murphy, 1988).

7.5 Implications for hormonal alterations

Early experimental studies reported decreased sexual activity, including copulatory behaviour, in male rats exposed to THC. To date, controlled studies investigating the effects of cannabis exposure on copulatory behaviour of the adult female have not been reported.

There is very little literature concerning the effects of cannabis on fertility *per se*. The findings that cannabinoids interfere with normal hypothalamic-pituitary-gonadal function (Murphy et al., 1990) and can disrupt ovulation and sperm production suggest that fertility could be affected. However, there is no epidemiological evidence on the issue.

Cannabis-induced reductions in testosterone and spermatogenesis observed in some studies are probably of little consequence in adults. This action of cannabis might be of importance in the prepubertal male or in individuals whose fertility is already impaired for other reasons; however, at present this is purely conjecture.

7.6 Future directions

Although there is no compelling evidence for an alteration in fertility by cannabinoids, further research is needed considering the comparatively high prevalence of cannabis use during the early reproductive years. Future research should examine interactions between the endogenous cannabinoids and glucocorticoids.

8. Effects on intrauterine and postnatal development

8.1 Background

Knowledge of how much active substance is delivered to biological tissues is basic to an understanding of the pharmacology and toxicity of a compound. Nearly all of the developmental studies on animals have investigated only pure THC and have allowed the measurement of amounts of drug actually delivered to the placenta and foetus. In

contrast, human reproductive studies have typically investigated the effects of smoked cannabis of uncertain THC content resulting in unknown concentrations of active drug in the fetal-placental unit. These issues complicate the interpretation of research on the effects of cannabis use on pre- and postnatal development.

8.2 Animal studies

Abel (1985) has pointed out the serious methodological and interpretational flaws that characterized the early literature of animal studies on the developmental toxicity of THC. Adverse effects observed in offspring may not have been produced by direct drug effects on the embryo and foetus but may have been secondary to poor maternal nutrition and dehydration. THC can also disrupt normal maternal care at parturition and, through hormonal effects, inhibit milk production and release, all having possible adverse consequences for the development of the offspring (Hutchings, 1985).

In studies using appropriate controls for maternal nutrition and fostering, several dose-related effects have been found in rat offspring following administration of THC to the pregnant dam. At birth, a dose-related increase in the male: female ratio of live offspring was consistently found, suggesting that female foetuses have a greater susceptibility to THC lethality (Hutchings et al., 1987; Morgan et al., 1988). During the postnatal period, a dose-related inhibition of both somatic growth and brain protein synthesis was found. These effects were transitory, however, and the THC-exposed animals caught up to the controls by the time of weaning (Hutchings et al., 1987). Hutchings found no evidence of neurobehavioural deficits in the offspring, independent of maternal toxicity; these findings are consistent with those of other well-controlled animal studies (Abel, 1985).

8.3 Human studies

8.3.1 Epidemiological studies

Epidemiological studies of the prevalence of drug use in pregnant women are often complicated by sampling procedures of uncertain validity. Human studies should be based on representative samples of the whole population of pregnant females. In many studies, however, the samples are selectively biased toward drug users. There is also uncertain comparability of self-reports of drug use gathered before birth (i.e. prospectively) with those obtained after birth (i.e. retrospectively). Exact doses and patterns of use are usually difficult to quantify. The effects of other drug use and socioeconomic factors are often difficult to assess by case control methods. No objective markers of cannabis use are yet available, although some new methodologies are being developed to identify and quantify *in utero* cannabis exposure, i.e. hair analysis, meconium analysis.

Despite these problems there is reasonable evidence that cannabis use during pregnancy impairs fetal development, leading to a reduction in birth weight, perhaps as a consequence of shorter gestation, and probably by the same mechanism as cigarette smoking, namely, fetal hypoxia. In a case study done on the effects of prenatal cannabis use on offspring growth from birth through to three years of age, prenatal cannabis exposure was associated only with decreased length at birth. Neither tobacco nor cannabis use predicted gestational age or morphological abnormalities (Day et al., 1992). Young maternal age also seemed to increase the negative effects from prenatal tobacco and cannabis exposure (Cornelius et al., 1995). Prenatal exposure to cannabis was also associated with disturbed nocturnal sleep patterns at three years of age, with more arousals and lower sleep efficiency (Dahl et al., 1995). There were no effects present of prenatal cannabis exposure on growth when the children reached age six (Day et al., 1994a). There is uncertainty about whether cannabis use during pregnancy produces any increase in the risk of birth defects by direct toxicity *in utero*. The limited number of human studies have not consistently shown any increased rate of birth defects.

There is little evidence that cannabis use can produce chromosomal or genetic abnormalities in either parent which could be transmitted to their offspring. Such animal and *in vitro* evidence as exists suggests that the mutagenic capacities of cannabis smoke are greater than those of THC, and are probably of greater relevance to the risk of users developing cancer than to the transmission of genetic defects to the offspring. There are a few case-control studies

which suggest that there is an increased risk of several rare cancers (childhood non-lymphoblastic leukaemia, rhabdomyosarcoma, and astrocytoma) among children born to women who used cannabis prior to conception or during pregnancy (Neglia et al., 1991; Robinson et al., 1989, Kuijten et al., 1990). Further exploration of these claims is warranted as reporting bias may have been an alternative explanation to the findings.

8.3.2 Neurobehavioural studies

The results of a large-scale prospective study, the Ottawa Prenatal Prospective Study of maternal cannabis use (Fried, 1980; Fried, 1995), suggest that any long-term consequences of prenatal exposure to the child are very subtle. In the newborn and neonate, there appears to be an association between nervous system function and prenatal exposure. Between 6 months and 3 years of age, no neurobehavioural consequences of maternal cannabis use were found (Frief & Watkinson, 1988; and 1990). However, at 4 years, offspring of regular cannabis users showed reduced verbal ability and memory. Similar deficits were seen in school-aged children as well (Day et al., 1994a; Fried, 1995), and were accompanied by decreased attention and by increased impulsiveness in the children of those mothers who had been the heaviest users of cannabis during pregnancy. These results suggest that *in utero* exposure to cannabis can affect to some degree the mental development of the growing child (Day et al., 1994b). Given the important implications of such a relationship, future research should address this possibility.

Finally, knowledge on fetal metabolism of cannabis and its components is limited, although this would be important to determine the effects of *in utero* drug exposure. New methodologies are being developed to identify and quantify *in utero* drug exposures, i.e. hair analysis, meconium analysis. More appropriate and objective markers of *in utero* cannabis exposure have not yet been developed and the existent drug anolytes (tetrahydrocannabinol and/or 11-nor-$\triangle$-9-tetrahydrocannabinol) are not adequate to monitor.

9. Effects on cell nuclei

Most information on interactions of cannabis with cell nuclei deals with four types of effects; (1) those on macromolecular synthesis, (2) chromosomal aberrations, (3) mutagenicity, and (4) carcinogenicity. In assessing this evidence it is important to bear in mind that the effects of pure cannabinoids, such as THC, will almost certainly be different from those of complex mixtures of large numbers of known and unknown compounds that make up cannabis smoke. Differences in the material examined may account for some of the contradictory findings in the literature.

Cannabinoids can interfere with the normal cell cycle (Zimmerman & McClean, 1973) and can also decrease synthesis of DNA, RNA and protein (Blevins & Regan, 1976). More recently, Tahir & Zimmerman (1992) have shown that THC can disrupt the formation of microtubules and microfilaments in rat cells in culture and hence may interfere with such diverse cellular processes as cell division, cell migration and neuron differentiation. Another recent study (Mailleux et al., 1994) showed a significant increase was produced in expression of the gene coding for the growth factor pleiotropin and could be detected in the adult rat forebrain following a single intra peritoneal injection of THC (5 mg/kg), a finding which needs further investigation.

Regarding the possibility of cannabinoids to induce chromosome aberrations, including chromosomal breaks, deletions, and other errors in chromosomal separation, the literature is still inconclusive and has shown contradictory results (Zimmerman & Zimmerman, 1990-91; Chiesara et al., 1983; Piatti et al., 1989; Behnke & Eyler, 1993). There is general consensus that both cannabis use (as judged by findings in users or animals exposed to marijuana smoke) and exposure to certain constituents of cannabis preparations (or in some cases cannabis smoke condensates) may indeed have mutagenic effects in the Ames assay for mutagenicity (Busch et al., 1979; Wehner et al., 1980; Sparacino et al., 1990). On the other hand, pure THC as such has been found to have no mutagenic effects (Zimmerman et al., 1978; Generoso et al., 1985; Berryman et al., 1992).

The demonstrated mutagenicity of cannabis smoke would predict some risk of carcinogenicity. Most of the new evidence, however, consists of case reports of upper respiratory or oropharyngeal cancers in cannabis smokers (Wengen, 1993) and no full-scale epidemiological studies have been conducted.

Future research in this area should focus on the following areas: systematic comparisons of cannabis smoke condensates, smoke fractions and pure cannabinoids in the same experimental systems for studying production of chromosome aberrations, especially in cultured human cells; systematic comparisons of the mutagenicity of cannabis and tobacco smoke; additional studies on the carcinogenicity of cannabis preparations in a variety of animal models; and epidemiological studies of the risks of cancer related to cannabis smoke as compared to tobacco smoke.

10. Effects on immune system

Many research studies on cannabis and immune system functions in whole animals and tissue culture systems have been published in the past 10 years (e.g. Hollister, 1988; Friedman et al., 1994). Cannabinoids, especially THC, have been found to modify the function of a variety of immune cells, increasing some responses and decreasing others. This variation in drug effects depends upon experimental factors such as drug concentration, timing of drug delivery, and the type of cell function analysed. The range of cell types and functions studied is very broad, including such diverse phenomena as morphology, biochemistry and phagocytic activities of macrophages from humans and other species, both *in vitro* and *in vivo*; production and release of cytokines, prostaglandins, and other mediators of immune responses; B and T lymphocyte responses *in vivo* and *in vitro*; antibody formation; and resistance to infections, in both experimental models and human disease, especially in AIDS patients.

The results of all of these investigations indicate that cannabinoids are immunomodulators, i.e. capable of perturbing immune system homeostasis when administered to the living subject or when added to cell cultures. However, it is also clear that the immune system is relatively resistant to these drugs. Many of their effects appear to be relatively small, totally reversible after removal of the cannabinoids, and produced only at concentrations or doses higher than those required for psychoactivity (more than 10μM *in vitro*, or more than 5mg/kg *in vivo*). Moreover, immunomodulatory effects can be produced by some cannabinoids which do not induce psychoactive effects. These findings suggest that cannabinoid effects on immune cells may not be exclusively mediated by the recently described cannabinoid receptors, even though such receptors have been demonstrated in these cells. However, the existence of a cannabinoid receptor on macrophages, that differs significantly from the cannabinoid receptor in the brain, suggests that the possible role of receptor-mediated actions in immunomodulation by cannabinoids requires further study.

Unfortunately, the health impact of any immune effects of cannabis smoking is still unclear. Many studies have clearly established that THC can act as an immunomodulator. However, relatively few of them have employed animal paradigms or human subjects in studies designed to test the effects of cannabis exposure on host resistance to microbes, viruses and tumours. Several animal studies have demonstrated impairment of resistance to bacterial or viral infections in mice exposed to cannabis smoke or THC, but the results have not been entirely consistent. Moreover, most studies have used cannabinoid doses that are difficult to relate to levels self-administered by humans. It is clear that well designed studies of this topic are needed, and that they will require the cooperation of immunologists, infectious disease specialists, oncologists and pharmacologists in their design, execution and interpretation.

11. Effects on other organ systems

11.1 Cardiovascular effects of cannabis

The most consistent and reproducible of the human effects of cannabis is dose dependent tachycardia, i.e. an increase in heart rate that correlates with the subjective ratings of 'high'. Both sympathetic and parasympathetic mechanisms seem to be involved in this cannabis-induced tachycardia.

Increases in heart rate lead to increases in cardiac output but the extent of the effect on blood pressure depends on peripheral resistance. The cannabis-induced increase in heart rate may increase cardiac output as much as 30 per cent, yet increases in supine blood pressure are usually less than 10 per cent. Postural hypotension can be exaggerated. Cannabis has been shown to increase blood flow in the limbs.

Acute cardiovascular effects of cannabis are less likely in adolescents and young adults, among whom prevalence of use is highest; however, a few reports of myocardial infarction in young cannabis smokers deserve closer examination (Choi & Pearl, 1989; Podczeck et al., 1990).

The possibility remains that chronic heavy cannabis smoking may have more subtle effects on the cardiovascular system, analogous to the long-term cardiotoxic effects of tobacco smoking, because the cardiovascular effects of THC and nicotine are similar. Moreover, since many cannabis smokers are also cigarette smokers, there is the possibility that there may be adverse interactions between nicotine and cannabinoids in their effects on the cardiovascular system. This requires further research.

The cardiovascular effects of cannabis may be hazardous for patients with hypertension, cerebrovascular disease and coronary atherosclerosis for whom marijuana poses a threat by increasing the work of the heart. The severity and prevalence of this threat remain to be determined as the cohort of chronic cannabis users of the late 1960s and early 1970s enters the age of maximum risk for various cardiovascular complications.

11.2 Effects of cannabinoids on the liver and gastrointestinal tract

There appears to be little or no human or animal evidence that acute or chronic use of cannabinoids affects liver function. There is reasonable animal evidence that cannabinoids decrease intestinal motility and delay gastric emptying. There is no evidence of significant symptoms of constipation as a consequence, and, as typically used, cannabis has minimal effects on the absorption of alcohol.

The most interesting aspects of the gastrointestinal effects of cannabis are theoretical and therapeutic. The sites of action of the antinauseant and antiemetic effects, and also of the stimulant effects of the cannabinoids on food intake, remain to be identified. As with studies of the opioids, the isolated intestine preparation may serve as a useful model for the study of cannabinoid receptors, and may provide the opportunity to differentiate between central and peripheral receptors.

12. Therapeutic uses

12.1 Background

The broad range of potential therapeutic applications of cannabinoids reflects the wide distribution of cannabinoid receptors throughout the brain and other parts of the body. The possibility of distinct subtypes of cannabinoid receptors and the probable development of new compounds to bind selectively to these receptors, as either agonists or blockers, may well open the door to the selective treatment of a number of disorders. In time, some of these compounds may be targeted specifically to one function or another of the endogenous cannabinoid system.

Despite the positive appraisal of the therapeutic potential of cannabinoids as an antiemetic and antiglaucoma agent, they have not been widely used and the clinical research undertaken is limited. Other therapeutic uses for

cannabinoids warrant further basic pharmacological and experimental investigation and clinical research into their effectiveness.

12.2 Utility as an anti-emetic agent in cancer chemotherapy

The moderate efficacy and safety of THC in the control of nausea induced by cancer chemotherapy was established in experiments in the late 1970s and early 1980s. Since then, dronabinol (International Nonproprietary Name (INN) for THC), has proved its clinical utility in a few countries as an adjunct therapy for that indication (Grunberg & Hesketh, 1993). Some of the early problems with unwanted side effects of oral dosages of THC have been remedied through the availability of dronabinol capsules with half the dosage of the earlier formulation.

12.3 Stimulation of food intake in AIDS wasting syndrome

In the USA, approximately 16 per cent (about 14 000 people) of the total AIDS population suffer from the progressive anorexia and weight loss known as AIDS wasting syndrome. Dronabinol has been approved by the US Food and Drug Administration as a food intake stimulant for AIDS patients suffering from wasting syndrome, based on a well-controlled double-blind, randomized clinical study with AIDS patients (Plasse et al., 1991). Another controlled, double-blind, randomized trial is currently being conducted to compare the efficacy of dronabinol and megestrol acetate, a synthetic hormone, in treating the wasting syndrome.

12.4 Other areas of therapeutic potential

While THC has long been known to reduce the increased intra ocular pressure of glaucoma, it has not been fully studied therapeutically for this indication. This has been because of concern over the long-term ocular and systemic effects of THC use, especially in older individuals who are the most frequent victims of glaucoma.

Early studies had shown that cannabinoids were no more effective than other drugs used as analgesics and that relief of pain was achieved only at doses that induced severe side effects in animals. Some newly synthesized cannabinoids are extremely potent analgesics; however, separation of the analgesic and side effects in humans remains to be demonstrated. Further experiments with these compounds may illuminate not only their mechanisms of action, but also the body's multiple mechanisms of pain reception and blockade.

Animal studies have suggested other possible therapeutic applications of THC or other cannabinoids in various disorders. In studies with human subjects, however, cannabinoids have not yet been proven useful in the treatment of convulsant or movement disorders or in treating multiple sclerosis or asthma. There are also reports of an antidepressant effect, and some patients may indeed use cannabis to 'self-treat' depressive symptoms (Gruber et al., 1997), but these need to be better evaluated.

12.5 Therapeutic potential for cannabis

The therapeutic uses of THC described above have led to discussions about the therapeutic potential of cannabis itself, although little research exists in this area and satisfactory clinical studies have not been conducted. In order to explore possible therapeutic uses of cannabis, several scientific issues need to be considered, including the standardization of cannabis preparations required for some types of clinical and pre-clinical studies, the difficulties inherent in the study of smoking as the mode of administration of a substance, the need for a comparable placebo 'cigarette' which would not be easily identified by experimental subjects and patients in controlled trials, the large number of patients which would be needed to study the comparative efficacy of smoking cannabis compared with other cannabinoids and other therapeutic agents, and the possibility of using alternative delivery systems which could avoid cannabis smoking and the other components of such a smokable form. In addition, the broader implications of such research on cannabis control policies would need to be carefully considered.

13. Comparing cannabis with other drugs

The group of experts who prepared the review of the current knowledge about cannabis in 1995 included a section in the draft report which attempted to compare what is known about the health effects of cannabis to the health hazards of a variety of licit and illicit drugs with psychoactive effects such as alcohol, tobacco and opiates.

However, the reliability and public health significance of such comparisons are doubtful. Users of one drug are more likely to be users of one or more other drugs, and the risks of combined use are not necessarily identical to, or the sum of, the risks associated with the use of the individual drugs. Moreover, the hazards linked to the use of any drug are strongly influenced by such factors as the social and cultural context of drug use in the community, the political and economic context, availability of various psychoactive substances, preparation and dose, route of administration, frequency of use, and associated life style. The quantitative risks of cannabis use are largely unknown in the absence of reliable epidemiological studies, and therefore such comparisons tend to be more speculative than scientific.

In addition, since the proportion of the population that uses cannabis regularly over a period of years is currently much smaller than the proportions that use alcohol or tobacco in a comparable way, the magnitude of the public health hazard based purely on such exposure considerations is likely to be lower than that posed by alcohol or tobacco. However, it must be emphasized that most users of cannabis also use other drugs. There is no *a priori* reason to reject the likelihood that the risks of multiple drug use are additive. From a public health perspective, therefore, it may be more useful to assess the total risk resulting from all drug use, including that of cannabis.

Additionally, the public health significance of cannabis use in developing societies is even less well understood, given the lack of research, as indeed are the hazards of alcohol and tobacco. Comparisons of the health effects of psychoactive substance use in these populations are likely to be of limited validity.

14. Summary

Acute health effects of cannabis use

The acute effects of cannabis use have been recognized for many years, and recent studies have confirmed and extended earlier findings. These may be summarized as follows:

- cannabis impairs cognitive development (capabilities of learning), including associative processes; free recall of previously learned items is often impaired when cannabis is used both during learning and recall periods;

- cannabis impairs psychomotor performance in a wide variety of tasks, such as motor coordination, divided attention, and operative tasks of many types; human performance on complex machinery can be impaired for as long as 24 hours after smoking as little as 20mg of THC in cannabis; there is an increased risk of motor vehicle accidents among persons who drive when intoxicated by cannabis

Chronic health effects of cannabis use

The chronic use of cannabis produces additional health hazards including:

- selective impairments of cognitive functioning which include the organization and integration of complex information involving various mechanisms of attention and memory processes;

- prolonged use may lead to greater impairment, which may not recover with cessation of use, and which could affect daily life functions;

- development of a cannabis dependence syndrome characterized by a loss of control over cannabis use is likely in chronic users;

- cannabis use can exacerbate schizophrenia in affected individuals;

- epithelial injury of the trachea and major bronchi is caused by long-term cannabis smoking;

- airway injury, lung inflammation, and impaired pulmonary defence against infection from persistent cannabis consumption over prolonged periods;

- heavy cannabis consumption is associated with a higher prevalence of symptoms of chronic bronchitis and a higher incidence of acute bronchitis than in the non-smoking cohort;

- cannabis use during pregnancy is associated with impairment in fetal development leading to a reduction in birth weight.

- cannabis use during pregnancy may lead to postnatal risk of rare forms of cancer although more research is needed in this area.

The health consequences of cannabis use in developing countries are largely unknown because of limited and non-systematic research, but there is no reason *a priori* to expect that biological effects on individuals in these populations would be substantially different to what has been observed in developed countries. However, other consequences might be different given the cultural and social differences between countries.

Therapeutic uses of cannabinoids

Several studies have demonstrated the therapeutic effects of cannabinoids for nausea and vomiting in the advanced stages of illnesses such as cancer and AIDS. Dronabinol (tetrahydrocannabinol) has been available by prescription for more than a decade in the USA. Other therapeutic uses of cannabinoids are being demonstrated by controlled studies, including treatment of asthma and glaucoma, as an antidepressant, appetite stimulant, anticonvulsant and antispasmodic, research in this area should continue. For example, more basic research on the central and peripheral mechanisms of the effects of cannabinoids on gastrointestinal function may improve the ability to alleviate nausea and emesis. More research is needed on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents can be found.

15. Recommendations for future research

Information on the effects of cannabis on physical and psychological functioning has increased greatly as has knowledge of the extent and patterns of use. However there is still a need for further research in several important areas including clinical and epidemiological research on human health effects, chemistry and pharmacology, and research into the therapeutic uses of cannabinoids. Moreover, there are important gaps in knowledge about the health consequences of cannabis use. The most pressing issues for further research are summarized below.

15.1 Clinical and epidemiological research

There is a need for more data on the patterns of cannabis use and resulting problems particularly in developing countries. Such research would benefit from greater use of simplified and comparable methods of gathering data in these countries, so that information collected in different countries can be compared. Few countries have cohort studies of cannabis use patterns which are important in order to assess the natural history of cannabis use and the

reasons for starting and stopping cannabis use at all levels of consumption. There is also a need for case-control studies comparing those experiencing cannabis problems, with people who have, and do not have, alcohol and other psychoactive substance use problems.

There is a need for controlled studies investigating the relationships between cannabis use, schizophrenia and other serious mental disorders. In particular, there is a need for intervention studies of schizophrenic persons to see whether stopping cannabis use improves their outcomes in treatment.

Insufficient research has been undertaken on the 'amotivational' syndrome which may or may not result from heavy cannabis use. It is not clear that such a syndrome exists, even though heavy cannabis use is sometimes associated with reduced motivation to succeed in school and at work. Also, new research is needed to show whether the reduced motivation seen in some cannabis users is due to other psychoactive substance use and whether it precedes cannabis use. How reduced motivation relates to psychological problems is still unknown and requires further research.

Research on chronic and residual cannabis effects is also needed. The pharmacokinetics of chronic cannabis use in humans are poorly described and this lack of knowledge restricts the ability of researchers to relate drug concentrations in blood or other fluids and observed effects.

The prevalence and consequences of dependence on cannabis is a major area requiring further research. There is a need for better delineation of the clinical features of cannabis dependence and for studies of its responsiveness to interventions aimed at assisting users to stop.

Further studies are required on fertility effects in cannabis users, in view of the high rate of use during the early reproductive years. Researchers investigating infertility should be encouraged to study the effects of cannabis use. In addition, given the importance of the issue of *in utero* exposure, more research on fetal metabolism, especially of premature infants, is needed. Another priority would be replication of the case-control studies of maternal cannabis use and childhood cancers.

Further clinical and epidemiological research is required on the effects of cannabis on respiratory function and respiratory diseases. More studies are needed to show whether cannabis affects the risk of lung malignancies and at what level of use that may occur. In addition, more studies are needed to clarify the rather different results of pulmonary histopathological studies in animals and man.

More clinical and experimental research is needed on the effects of cannabis on the immunological function. Future studies should be aimed at establishing the relationship between cannabinoid-induced immunomodulation and altered host resistance to microbes and tumours, and exploring the role of cannabinoid receptors on host immunity and in the regulation of the normal immune response. More clarity should also be sought concerning the molecular mechanisms responsible for immune effects, including both cannabinoid receptor and non-receptor events.

The possibility that chronic cannabis use has adverse effects on the cardiovascular system should have a priority in epidemiological research. There is evidence from laboratory studies that cannabinoids have pronounced acute effects on cardiovascular functioning and it is known that cannabis smoke is qualitatively similar to tobacco smoke which is a known serious hazard for cardiovascular diseases. The fact that the cohort of cannabis users who initiated use in the early 1970s are now entering the period of maximum risk for cardiovascular disease suggests that it would be timely to conduct case-control studies of cardiovascular disease and cannabis use.

Frequently the risks of cannabis use are compared with those of other drugs such as alcohol and tobacco. However, the science to evaluate health risks of cannabis use is much less extensive and much less conclusive than the voluminous research that has been conducted on these psychoactive substances. In addition, there is insufficient research on cannabis-related mortality from accidents and other causes to permit proper comparisons. More comparative epidemiological studies of cannabis and other drugs are needed to assess their relative mortality and morbidity risks at different levels of use.

15.2 Chemistry, pharmacology and physiology

Certain approaches to the planning and design of research would improve an understanding of cannabis effects in a number of areas. For example pharmacological research is needed to understand to what extent the varieties of cannabis preparations affect humans and animals differently. Attention needs to be given to elucidating dose-response relationships rather than simply examining the effects of a single dose. More information is needed on how dose-response relationships for most effects vary for different species. Further research is needed on what animal dose for a given type of toxicity corresponds to what human dose in order to ensure comparability in the two types of studies.

Several important research issues remain ambiguous with regard to the effects of cannabis on human physiology. For example the sites of action for appetite stimulants and the antiemetic effects of cannabis are unknown. Another high priority is to identify the physiological roles of the endogenous cannabinoid system. Also, some future research should be directed towards establishing whether a specific interaction occurs between the endogenous cannabinoid and glucocorticoids. This will require multifaceted efforts by chemists, neurochemists and molecular biologists. Strategies include the identification of additional endogenous cannabinoids, syntheses of analogues with selected pharmacological profiles and development of genetically-altered experimental animals which are devoid of cannabinoid receptors. It is imperative to determine whether the endogenous cannabinoid system meets all the requirements for a neurotransmittal system.

Some effort has been made to determine the relationship between THC concentrations in blood and other fluids and the degree of behavioural impairment produced. Although this task is difficult, efforts should continue with the goal of defining a concentration-effect relationship as clearly as has been done for alcohol.

Further development of cognitive and psychomotor tests for controlled studies that are sensitive to the performance effects of cannabis use and that reflect the complexity of specific daily functions (i.e. driving, learning, reasoning) also need additional research.

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Annex 1

**EXPERT WORKING GROUP ON
HEALTH EFFECTS OF CANNABIS USE**

Geneva, 22-24 May 1995

List of Participants

Dr Robert Ali, Treatment Services, Drug and Alcohol Services Council, Adelaide, Australia
Dr S. M. Channabasavanna, National Institute of Mental Health and Neurosciences, Bangalore, India

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Annex 2

EXPERT WORKING GROUP ON HEALTH EFFECTS OF CANNABIS USE

Geneva, 22-24 May 1995

Background papers

Beardsley PM, Kelly TH *Acute effects of cannabis on human behaviour and CNS function: update of experimental studies*

Channabasavana SM, Paes M, Hall W *Mental and behavioural disorders due to cannabis use*

Chesher G, Hall W *The effects of cannabis on the cardiovascular and gastrointestinal systems*

Hall, W *Assessing the health and psychological effects of cannabis use*

Hall W, Johnston L Donnelly N *Epidemiological evidence on patterns of cannabis use and their health consequences*

Hall W, Room R *A comparative appraisal of the health and psychological consequences of alcohol, cannabis, nicotine and opiate use*

Hartel CR *Medical uses of marijuana*

Hutchings DE, Fried PA *Cannabis during pregnancy: neurobehavioural effects in animals and humans*

Klein TW *Cannabis and Immunity*

MacPhee DG *Effects of marijuana on cell nuclei: a review of the literature*

Martin BR, Cone EJ *Chemistry and Pharmacology*

Murphy LL *Cannabis effects on endocrine and reproductive function*

Smiley A *Marijuana: on road and driving simulator studies*

Solowij N *The long term effects of cannabis on the central nervous system I. Brain function and neurotoxicity*

Solowij N *The long term effects of cannabis on the central nervous system II. Cognitive functioning*

Tashkin DP *Cannabis effects on the respiratory system: review of the literature*

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