ALASKA LEGISLATURE COMMITTEE FILES, 2005-2006 8672
11799 SENATE HEALTH,EDUCATION & SOCIAL SERVICES

Unlike alcohol where psychomotor impairment is correlated with blood alcohol level, there is no simple relationship between levels of THC (or its metabolites) in blood and impairment (18, 26). This is for two reasons: the delay between experiencing the subjective high and the appearance of THC in the blood; and large variations between different people in the level of intoxication experienced at the same blood level of THC. A consensus conference of forensic toxicologists concluded that there was not sufficient evidence for blood concentrations of THC to define a legal basis for driving a motor vehicle while under the influence of cannabis (27).

2.6 Two special concerns

2.6.1 Storage of THC

There is good evidence that with repeated dosing of cannabis at frequent intervals, THC can accumulate in fatty tissues in the human body where it may remain for considerable periods of time (Ashton (18) and see above). The storage of cannabinoids *would* be serious cause for concern if THC were a highly toxic substance which remained physiologically active while stored. THC is not a highly toxic substance and it is unlikely to have active effects while stored in body fat because it acts in receptors that are not present in body fat. One *potential* health implication of THC storage is that the release of stored cannabinoids into blood may produce unexpected symptoms of cannabis intoxication. The release of stored THC has been suggested as an explanation of 'flashback experiences' (e.g. Negrete (28); Thomas (29)). Such experiences have been rarely reported by cannabis users (e.g. Edwards (30)), and their significance is complicated by the fact that those who have reported these experiences have often used other hallucinogenic drugs.

2.6.2 Increases in the potency of cannabis

Cohen (31) claimed that research underestimates the adverse health effects of cannabis because it was largely based upon studies conducted when cannabis users used less potent forms of cannabis (0.5% to 1.0% THC) than later became available in the USA in the 1980s (3.5% THC in 1985–1986). This claim has been repeated often in the popular and scientific media (18, 32), usually asserted rather than shown and often supported by anecdotal reports of samples of cannabis containing high percentages of THC. An alleged 'thirty-fold' increase in potency has contributed to recent concerns about the health effects of cannabis in Australia (7).

There are two different interpretations of this claim: (i) that the average THC content of cannabis plants has increased; and (ii) that the average THC content of cannabis products consumed by users has increased by 10–30 times (7).

The USA is the only country that has regularly collected data on the THC content of cannabis plants over the past several decades. Claims that this data indicated that the THC content of cannabis in the USA had increased between three to seven fold from the early 1970s to the mid 1980s have been challenged by data from independent laboratories, and because such claims relied on the assumption that the samples from the middle 1970s were representative of cannabis consumed at that time. More recent data have failed to show a 10–30 fold increase in the THC content of seizures between 1984

and 1998. At most this series shows a small increase in THC content from 3.3% in 1980 to 4.4% in 1998 (6, 33). Recent data published on the THC content of cannabis seized in New Zealand over the past 20 years has not shown any increase in average THC content (34).

2.7 Cannabinoid biology

Research during the 1990s has clarified the ways in which cannabinoids act in the human body and brain (35, 36). This research has identified 'cannabinoid receptors' and 'endogenous cannabinoids'. Cannabinoid receptors are the molecular sites in the brain and body at which the active components of cannabis, such as THC, act (36). Endogenous cannabinoids are substances that naturally occur in the human brain and body that, like THC, act on cannabinoid receptors in the brain. These include anandamide (37) and 2 arachidonyl-glycerol (2AG) (38, 39).

Two types of cannabinoid receptors, CB_1 and CB_2 have been identified. The CB_1 receptor that is found primarily in the brain is responsible for the psychological effects of THC (40). The CB_2 receptor is found in the immune system but its precise role remains unclear. CB_1 and CB_2 receptors belong to a large group of receptors found in the membranes of nerve cells that are involved in chemical signalling between nerve cells. Cannabinoid receptors have been found in the nervous system of lower vertebrates, including chickens, turtles and trout (41). This suggests that these receptors were present early in evolution, and their conservation implies that they serve an important biological function in many species including mammals (2).

The distribution of CB_1 and CB_2 receptors in the brain, immune and reproductive tissues is consistent with many of their therapeutic and recreational effects (38, 39). CB_1 cannabinoid receptors in the brain are most concentrated in brain systems that are involved in controlling mood, motor function, memory formation, food intake, pain modulation, immune, and reproductive functions (39).

Cannabis disrupts short-term memory in humans (see Chapter 4). This effect is consistent with an abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory (3, 39). A high density of CB_1 receptors in the basal ganglia and cerebellum is consistent with the observation that cannabinoids interfere with coordinated movement (2). Cannabis has very little acute effect on respiratory function in humans (42, 43), which is consistent with the observation that the lower brainstem area has few cannabinoid receptors. The absence of cannabinoid receptors in the lower brainstem also explains why high doses of THC are rarely lethal (3).

2.8 Summary

Cannabis is derived from the *cannabis sativa* plant. THC is the constituent of cannabis that produces the psychoactive effects sought by recreational users. Different forms of cannabis (marijuana, heads, hash and hash oil) vary in their potency. Cannabis is

predominantly smoked in a joint or in a water pipe because this is the most efficient way to deliver THC quickly to the bloodstream and brain. THC and its metabolites can be detected in blood and urine but there is no simple relationship between these levels in blood or urine and the degree of intoxication or psychomotor impairment. THC acts on brain receptors ('cannabinoid receptors') that are also acted upon by substances that occur naturally in the brain ('endogenous cannabinoids'). Cannabinoid receptors are found in brain regions involved in control of mood, memory, and motor performance, all of which are affected by cannabis.

2.9 References

1. Gaoni, Y. & Mechoulam, R. (1964) Isolation, structure and partial synthesis of an active constituent of hashish, *Journal of the American Chemistry Society*, 86, 1646–1647.
2. Martin, B. & Cone, E. (1999) Chemistry and pharmacology of cannabis, in: Kalant, H., Corrigal, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 19–68 (Toronto, Addiction Research Foundation).
3. Iversen, L. (2000) *The Science of Marijuana* (Oxford, Oxford University Press).
4. Abood, A. & Martin, B. (1992) Neurobiology of marijuana abuse, *Trends in Pharmacological Science*, 13, 201–206.
5. Clarke, R. C. & Watson, D. P. (2000) The botany of natural cannabis medicines, in: Russo, E. (Ed.) *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential* (New York, Haworth Press).
6. ElSohly, M. A., Ross, S. A., Mehmedic, Z., Arafat, R., Yi, B. & Banahan, B. F., 3rd (2000) Potency trends of delta-9-THC and other cannabinoids in confiscated marijuana from 1980–1997, *Journal of Forensic Sciences*, 45, 24–30.
7. Hall, W. & Swift, W. (2000) The THC content of cannabis in Australia: Evidence and implications, *Australian and New Zealand Journal of Public Health*, 24, 503–508.
8. Adams, I. & Martin, B. (1996) Cannabis: Pharmacology and toxicology in animals and humans, *Addiction*, 91, 1585–1614.
9. Hawks, R. (1982) The constituents of cannabis and the disposition and metabolism of cannabinoids, in: Hawks, R. (Ed.) *The Analysis of Cannabinoids in Biological Fluids. National Institute on Drug Abuse Research Monograph No. 42*, pp. 125–137 (Rockville, MD, US Department of Health and Human Services).
10. Ohlsson, A., Lindgren, J.-E., Wahlen, A., Agurell, S., Hollister, L. & Gillespie, H. (1980) Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking, *Clinical Pharmacology and Therapeutics*, 28, 409–416.
11. Ghodse, A. (1986) Cannabis psychosis, *British Journal of Addiction*, 81, 473–487.
12. Barnett, G., Licko, V. & Thompson, T. (1985) Behavioral pharmacokinetics of marijuana, *Psychopharmacology*, 85, 51–56.

13. Perez-Reyes, M., Di Guiseppi, S., Davis, K., Schindler, V. & Cook, C. (1982) Comparison of effects of marihuana cigarettes of three different potencies, *Clinical Pharmacology and Therapeutics*, 31, 617–624.

14. Fehr, K. & Kalant, H. (1983) *Cannabis and Health Hazards* (Toronto: Addiction Research Foundation).

15. Jones, R. (1987) Drug of abuse profile: cannabis, *Clinical Chemistry*, 33, 72B–81B.

16. Johansson, E., Agurell, S., Hollister, L. & Halldin, M. (1988) Prolonged apparent half-life of delta-9-tetrahydrocannabinol in plasma of chronic marijuana users, *Journal of Pharmacy and Pharmacology*, 40, 374–375.

17. Kelly, P. & Jones, R. (1992) Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users, *Journal of Analytical Toxicology*, 16, 228–235.

18. Ashton, H. (2001) Pharmacology and effects of cannabis: A brief review, *British Journal of Psychiatry*, 178, 101–106.

19. Hunt, C. & Jones, R. (1980) Tolerance and disposition of tetrahydrocannabinol in man, *Journal of Pharmacology and Experimental Therapeutics*, 215, 35–44.

20. Dackis, C., Pottash, A., Annitto, W. & Gold, M. (1982) Persistence of urinary marijuana levels after supervised abstinence, *American Journal of Psychiatry*, 139, 1196–1198.

21. Ellis, G., Mann, M., Judson, B., Schramm, N. & Tashchian, A. (1985) Excretion patterns of cannabinoid metabolites after last use in a group of chronic users, *Clinical Pharmacology and Therapeutics*, 38, 572–578.

22. Johansson, E., Sjovall, J., Noren, K., Agurell, S., Hollister, L. & Halldin, M. (1987) Analysis of delta-9-tetrahydrocannabinol (delta-9-T HC) in human plasma and fat after smoking, in: Chaesher, G., Consroe, P. & Musty, R. (Eds.) *Marijuana: An International Research Report*, pp. 291–296 (Canberra, Australian Government Publishing Service).

23. Gross, S., Worthy, T., Nerder, L., Zimmerman, E., Soares, J. & Lomax, P. (1985) The detection of recent cannabis use by saliva delta-9 THC radioimmune quantitation, *Journal of Analytical Toxicology*, 2, 98–100.

24. Thompson, L. & Cone, E. (1987) Determination of delta-9-hydrocann... ...ol in human blood and saliva by high-performance liquid chromotography with amperometric detection, *Journal of Chromotography*, 421, 91–97.

25. Menkes, D., Howard, R., Spears, G. & Cairns, E. (1991) Salivary THC following cannabis smoking correlates with subjective intoxication and heart rate, *Psychopharmacology*, 103, 277–279.

26. Agurell, S., Halldin, M., Lindgren, J., Ohlsson, A., Widman, M., Gillespie, H. & Hollister, L. (1986) Pharmacokinetics and metabolism of delta-9-tetrahydrocannabinol and other cannabinoids with emphasis on man, *Pharmacological Reviews*, 38, 21–43.

27. Consensus Report CDP Research Technology Branch NIDA (1985) Drug concentrations and driving impairment, *Journal of the American Medical Association*, 254, 2618–2621.

28. Negrete, J. (1988) What's happened to the cannabis debate?, *British Journal of Addiction*, 83, 359–372.

29. Thomas, H. (1993) Psychiatric symptoms in cannabis users, *British Journal of Psychiatry*, 163, 141–149.

30. Edwards, G. (1983) Psychopathology of a drug experience, *British Journal of Psychiatry*, 143, 139–142.

31. Cohen, S. (1986) Marijuana research: Selected recent findings, *Drug Abuse and Alcoholism Newsletter*, 15, 1–3.

32. Gold, M. S. (1991) Marijuana, in: Miller, N. S. (Ed.) *Comprehensive Handbook of Alcohol and Drug Addiction*, pp. 353–376 (New York, Dekker).

33. ElSohly, M. A. & Ross, S. A. (1999) Quarterly report: Potency monitoring project. Report 69: January 1, 1999 – March 31, 1999 (Mississippi, National Center for Development of Natural Products, University of Mississippi).

34. Poulsen, H. & Sutherland, G. (2000) The potency of cannabis in New Zealand from 1976 to 1996, *Science and Justice*, 40, 171–176.

35. Institute of Medicine (1999) *Marijuana and Medicine: Assessing the Science Base* (Washington, DC, National Academy Press).

36. Ameri, A. (1999) The effects of cannabinoids on the brain, *Progress in Neurobiology*, 58, 315–348.

37. Devane, W., Hanus, L., Breuer, A., Pertwee, R., Stevenson, L., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A. & Mechoulam, R. (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor, *Science*, 258, 1946–1949.

38. Felder, C. & Glass, M. (1998) Cannabinoid receptors and their endogenous agonists, *Annual Review of Pharmacology and Toxicology*, 38, 179–200.

39. Pertwee, R. (1999) Cannabinoid receptors and their ligands in brain and other tissues, in: Nahas, G., Sutin, K., Harvey, D. & Agurell, S. (Eds.) *Marijuana and Medicine*, pp. 177–185 (Totowa, NJ, Humana Press).

40. Heustis, M., Goelick, D. A., Heishman, S. J., Preston, K. L., Nelson, R. A., Moolchan, E. T. & Frank, R. A. (2001) Blockade of effects of smoked marijuana by the CB1-Selective Cannabinoid Receptor Antagonist SR141716, *Archives of General Psychiatry*, 58, 322–328.

41. Howlett, A., Bidaut-Russell, M., Devane, W., Melvin, L., Johnson, M. & Herkenham, M. (1990) The cannabinoid receptor: biochemical, anatomical and behavioral characterization, *Trends in Neuroscience*, 13, 420–423.

42. Hollister, L. (1986) Health aspects of cannabis, *Pharmacological Reviews*, 38, 1–20.

43. Chesher, G. & Hall, W. (1999) Effects of cannabis on the cardiovascular and gastrointestinal systems, in: Kalant, H., Corrigall, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 435–458 (Toronto, Canada, Centre for Addiction and Mental Health).

3 Patterns of cannabis use

3.1 Measuring cannabis use

Most information about cannabis use is collected by surveying the general population and high school and university students. These surveys typically ask each person whether he or she has used cannabis: at any time in their lives (lifetime use), in the past year (past year use), and in the past month. Rates of weekly and daily cannabis use are low in most populations, so surveys typically only report whether the person has used cannabis in his or her lifetime or in the past year.

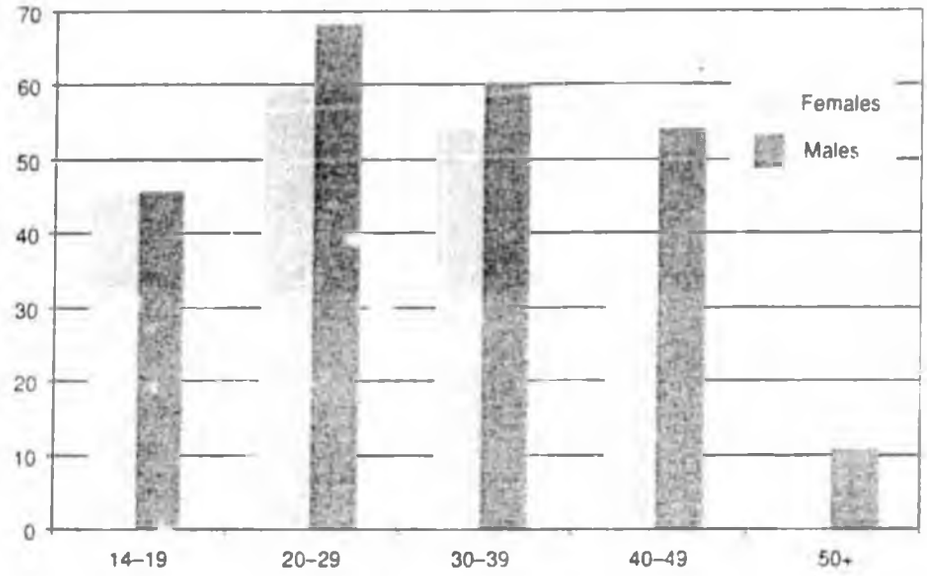
There is good evidence that carefully designed surveys provide valid information on self-reported cannabis use. O'Malley, Bachman, and Johnston (1), for example, showed that self-reported drug use in three waves of interviews of high school seniors was as reliable as self-reports of other behaviour. They have also shown that although some older adults later under-report drug use in adolescence and early adult life, under-reporting of cannabis use is quite low (2, 3). Most importantly, any small biases in self-reported cannabis use are fairly constant over time, meaning that we can be reasonably confident about *trends* in drug use from surveys (4, 5).

3.2 Cannabis use in Australia

Cannabis is the most widely used illicit drug in Australia. In 1998 39% of adults aged 15 and older reported that they had used cannabis at some time in their lives (6). Men were more likely to have used cannabis than women at all ages (44% of males vs. 35% of females) (7). Rates of cannabis use were highest among young adults: 45% of 14–19 year olds and 64% of 20 to 24 years olds reported lifetime cannabis use. Rates declined steadily with age (see Figure 1). The low rates of lifetime cannabis use among adults over the age of 50 years reflects the beginning of widespread cannabis use among young Australian adults in the early 1970s (7).

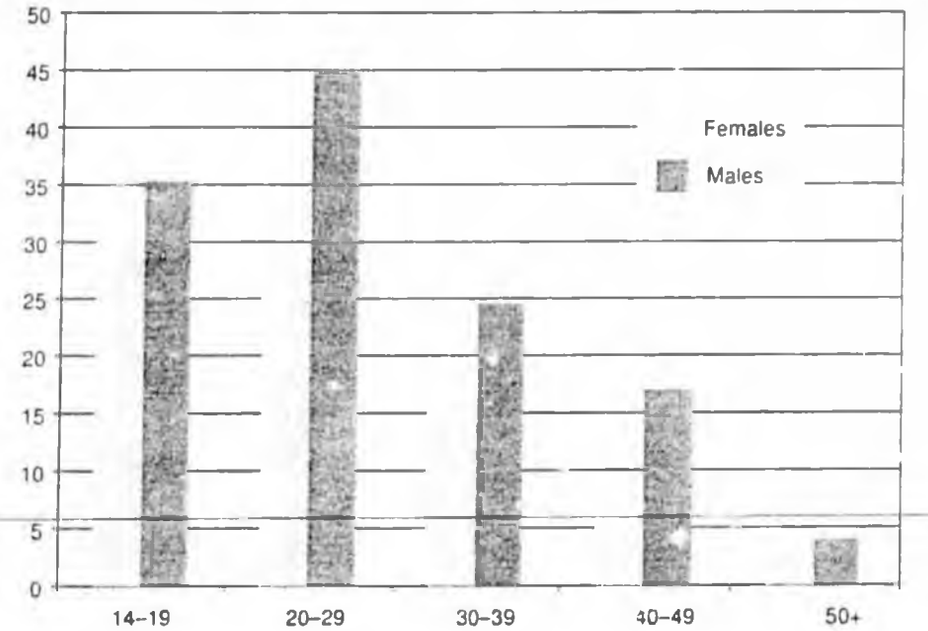
Most cannabis use is not regular. In the 1998 survey, three quarters of women and two thirds of men who had ever used cannabis either had not used in the past year or had used less than weekly (6). The proportion of users who became weekly users was 7% of women and 15% of men. Weekly cannabis use was most common among those aged 20 to 24 years, declining steeply thereafter (8).

Figure 1: Prevalence of lifetime cannabis use by age and gender, 1998 NDS survey



The rate of cannabis use in the past 12 months was 18% in the 1998 NDS. This was an increase on rates of use in previous household surveys, which found rates of 12 to 13% (9). Current use of cannabis was more common among males (21%) than females (15%) (Figure 2) but there was no difference in the youngest age group. The prevalence of current cannabis use was highest among 14–19 year olds (35%) and 20–29 year olds (37%). This is consistent with previous NDS surveys (8).

Figure 2: Prevalence of 12-month cannabis use by age and gender, 1998 NDS survey



The 1996 Australian School Student's Alcohol and Drugs Survey found that 36% of students aged 12–17 had used cannabis (10). Earlier studies of drug use among school aged youth in various Australian states conducted in the early 1990's reported rates of cannabis use between 25 to 30% (8). The 1996 school survey results suggest that there was an increase in the use of cannabis among youth during the 1990s, a finding that is supported by the NDS household surveys. The most recent national school survey found a small decline in rates of recent cannabis use among school students between 1996 and 1999 (11).

Australian cannabis users were more often males, who were under 35 years of age and more likely to be unemployed than non-users. While persons with higher education levels are more likely to have tried cannabis at some time in their lives, persons with lower levels of education are more likely to be regular users (9). Current cigarette smokers are more likely to smoke cannabis than non-smokers, and regular drinkers are more likely than occasional or non-drinkers, to be regular users of cannabis (12). Cannabis in Australia is mo... typically smoked, and the types of cannabis most commonly used are heads and leaf (9). The preferred mode of administration among younger users is a bong and to a lesser extent, a pipe; older users are more likely to smoke joints (13).

Surveys of drug use in the general population were not conducted in Australia until the mid 1980s. However, throughout the 1970s some market research companies included questions on cannabis use in other surveys (14). These show an increase in cannabis use in all age groups between 1973 and 1984. Among 20 to 29 year olds, for example, 23% reported having used cannabis in 1973 while the figure increased to 39% in 1984. The sharp increase in the rates of cannabis use between the 1984 market research survey and the 1985 national household survey may reflect greater anonymity given to respondents in the 1985 survey, and the different settings in which these questions were asked (in an 'omnibus' survey of consumer attitudes in 1984 and a special purpose survey about drug use and drug-related issues in 1985). There has been an increase in the percentage of Australians who report having ever tried cannabis in the NDS household surveys from 28% in 1985 to 39% in 1998.

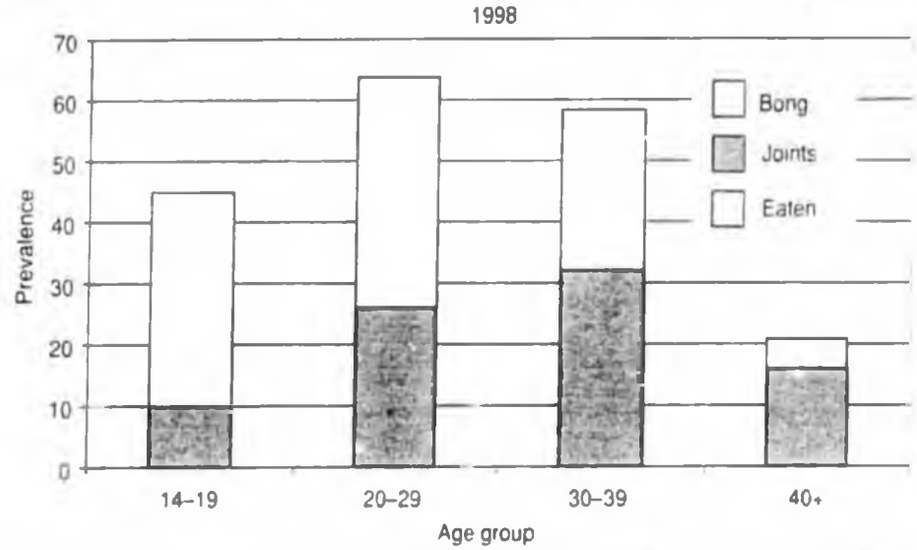
3.2.1 Changing patterns of cannabis use

Younger cannabis users now use more potent forms of cannabis at an earlier age. The 1998 NDS data show a decline in the age of initiation among younger cannabis users. One in five cannabis users (21%) born between 1940 and 1949 had initiated cannabis use by age 18, compared to 43% of those born in 1950–59, 66% of those born 1960–69 and 78% of those born in 1970–79 (15).

Earlier initiation of cannabis use increases the chances that these users will become daily or nearly daily cannabis users (16, 17). This, in turn, increases the risks of becoming dependent on cannabis and experiencing problems as a result of their use (16, 18). Levels of consumption among some adolescent cannabis users can be very high. For example, 40% of a sample of NSW juvenile offenders reported smoking 40 or more 'cones' of cannabis a week (19).

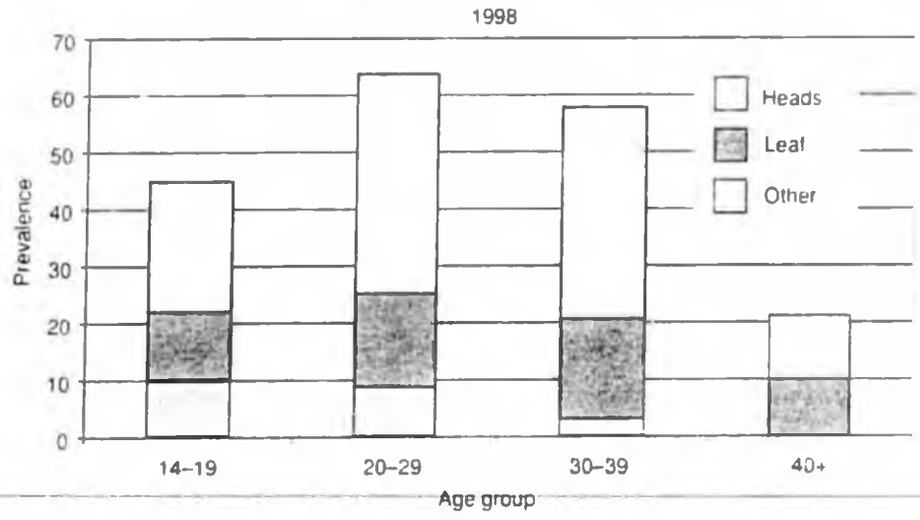
The greater expense of cannabis heads also encourages regular users to smoke them in waterpipes or 'bongs' in the belief that this maximises the delivery of THC. In the 1998 NDS Survey just over half of all persons who had used cannabis in the last year smoked 'heads' (57%) using bongs (56%). Younger users were more likely than older users to prefer bongs or pipes to joints (Figure 3) and heads to leaf, with the opposite trend in older users (Figure 4).

Figure 3: Prevalence of preference for different methods of using cannabis by age group



Source: National Drug Strategy Household Survey, 1998; Social Science Data Archives

Figure 4: Prevalence of preference of use of cannabis products according to age group



Source: National Drug Strategy Household Survey, 1998; Social Science Data Archives

All these changes in patterns of use—earlier initiation of cannabis use, greater use of more potent cannabis products such as heads, and the use of waterpipes—have probably increased the amount of THC consumed by regular cannabis users, while the concentration of THC in cannabis products has increased only marginally.

3.3 Cannabis use in the United States

In the United States two major surveys of illicit drug use have been undertaken since the early 1970s. The National Household Survey on Drug Abuse (sponsored by the National Institute on Drug Abuse) has surveyed household samples of adults throughout the U.S. since 1972. Since 1975, the 'Monitoring The Future' project has surveyed nation-wide samples of high school seniors, college students and young adults each year (2, 3).

3.3.1 NIDA Household Survey

NIDA has surveyed approximately 9000 persons aged 12 years and older in randomly selected households throughout the U.S. every two to three years since 1972. Since 1991, the survey has been conducted annually with a sample of over 30,000 participants (20).

In 1999, one third (35%) of the national sample reported that they had used cannabis, 9% had used in the past year, and 5% reported that they were current users (Table 1) (21). Lifetime use increased from 11% among those aged 12 to 17 years to 59% among those aged 26 to 34 years before declining to 25% among those over the age of 35 years. Rates of discontinuation of use were high: more than two thirds of men and three quarters of women who had use cannabis at some time in their lives had not used it in the last year. Monthly cannabis use was uncommon. It was more common among men (9%) than women (6%) and most common among those aged 12 to 17 years (11%).

The NIDA Household survey series from 1974 to 1990 showed that rates of cannabis use increased throughout the 1970s, peaked in 1979, declined steadily throughout the 1980s to reach their lowest level in 1990, before increasing again in 1992.

Table 1: Prevalence of cannabis use (US National Household Survey on Drug Abuse, 1999)

	Lifetime	Past 12 months	Past month
12–17 years	18.7	14.4	7.7
18–25 years	46.8	24.8	14.8
26 + years	34.7	5.4	3.0
Total	34.6	8.9	5.1

Table 2: Trends in past month cannabis use (US National Household Survey on Drug Abuse 1974–1999)

Age	1974	1976	1977	1979	1985	1988	1990	1992	1995	1996	1999
12–17	12.0	12.3	16.6	16.3	13.2	8.1	7.1	5.3	10.9	9.0	7.7
18–25	25.2	25.0	27.4	38.0	25.3	17.9	15.0	13.1	14.2	15.6	14.8
26+	2.0	3.5	3.3								3.0
26–34				20.8	23.1	14.7	10.9	11.4	8.3	8.4	
35+				2.8	3.9	2.3	3.1	2.5	2.8	2.9	

3.3.2 The Monitoring The Future project

In this series of surveys, the prevalence of cannabis use has been estimated among secondary school students, college students and young adults. Since 1975 approximately 15,000 high school seniors have been surveyed. The college students and young adults who are surveyed each year represent a sample of those who were originally surveyed as high school seniors (about 14%) and have been followed up every two years. Since 1991 national samples of 8th and 10th grade students have also been annually surveyed.

In the 1999 survey, lifetime cannabis use increased with each higher age group but use in the past year reached a plateau in the 18 (last year of high school) to 28 year age group (Table 3). Daily use peaked at age 18, with 6% of high school seniors and 4.4% of 19 to 28 year olds reporting daily cannabis use. This is much lower than the 11% of high school seniors in the peak year of 1978 who used cannabis.

Table 3: Prevalence of cannabis use in the 1999 US Monitoring the Future Survey

	Lifetime use	12 month use	Past month use	Past month daily use
8th grade (14 years)	22.0	16.5	9.7	1.4
10th grade (16 years)	40.9	32.1	19.4	3.8
12th grade (18 years)	49.7	37.8	23.1	6.0
College	50.8	35.2	20.7	4.0
19–28 years	54.6	27.6	15.6	4.4

Because of high rates of daily cannabis use in the late 1970s, in 1982 more questions were asked about the duration of daily use. In 1982, 21% of the 12th graders reported that they had smoked cannabis daily for a month a more. This fell to 8% by 1992. Daily use has been consistently higher among males than females, and among those not planning to attend college. More than half of those who were daily users by age 18 began this pattern of heavy use by age 16. In 1993, 3% of all American 12th graders surveyed reported that they had smoked cannabis daily for two years or more on a continuous basis.

There have been rises and falls in cannabis use among American adolescents since 1975. Among 18 year olds, lifetime prevalence peaked at 65% in 1980, then fell by nearly half by the early 1990s. Use in the past year peaked at 51% in 1979 and fell to 22% by 1992. The rate of discontinuing use increased among those who had ever used cannabis (Table 4, third column), with less change in rates of discontinuation among those who had used

it 10 or more times. Most of those who ceased cannabis use had not had a great deal of experience with cannabis. The time trends in cannabis use were different from those of other drugs, suggesting that the changes in cannabis use reflected factors specific to that drug. Although most users of other illicit drugs also had used cannabis, trends in the use of other illicit drugs were independent of the cannabis-use trends.

Table 4: Trends in cannabis use among those in Year 12 (US Monitoring the Future Study, 1999)

	Lifetime use	12 month use	Discontinuation rate among those who had used cannabis	
			Ever	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	45	36	20	8
1995	42	35	17	5

After more than a decade of declining rates of cannabis use among American secondary students, the 1992 and 1993 surveys reported that cannabis use rose sharply among 8th, 10th and 12th graders, and to a lesser extent among college students and young adults. There was an increasing initiation rate and a higher rate of continued use.

Johnston and colleagues have argued that changes in beliefs about the risks of cannabis use were responsible for the reduction in use between 1979 and 1991 and for the rise in use since 1992. They reported a strong negative correlation over time between the rates of cannabis use and the perceived risk of using cannabis and peer disapproval of use (e.g. (2, 3, 22). Between 1992 and 1996, a decrease in perceived risk, and a smaller decrease in personal disapproval of cannabis use, preceded an increase in rates of use (23).

3.3.3 The natural history of cannabis use

Bachman et al (24) have examined patterns of cannabis use from adolescence into adulthood in the Monitoring the Future data. They analysed data from 14 successive cohorts of high school seniors and college students who were followed from age 18 to 35 to assess the effect of major life transitions (such as entering college, entering full time employment, marrying and having children) on rates of use of cannabis in the past 30 days.

They found a steady decline in cannabis use from the early and mid 20s to the early 30s. The pattern for cannabis was similar to that for alcohol; it differed from tobacco use which was much more persistent. Major role transitions explained a substantial part of these changes. Use increased among those entering college but their use only caught up

with that of students who did not enter college (who used cannabis more often in high school than those who went on to college). Bigger decreases in use were seen in males and females on marriage and during pregnancy. Entering the military had a large impact on cannabis use, probably reflecting drug-testing before entry to service (24).

These findings have been confirmed in a detailed study of a single cohort of high school students that was followed from early adolescence into the middle adulthood (25, 26). This study also found that cannabis use peaked in the early 20s and declined steadily through the 20s and into the 30s. The decline was explained by the increasing societal responsibilities of marriage, children and employment. Use persisted in those who: did not enter conventional marriage (e.g. remained single or cohabited); did not enter college; and who were unemployed (see Chapter 8 below).

3.4 Cannabis use in Canada

A national telephone survey was conducted in Canada in 1994 by Health and Welfare Canada on 12,155 persons aged 15 years and older (27). Overall, 28% of the sample reported that they had used cannabis at some time in their lives, with males more likely to have used cannabis than females in all age groups. Rates of use in the past year declined with age from a high of 26% among those aged 15 to 17 years to 1.4% among those aged 45 to 54 years and 1% among those aged 55 to 64 years. Most users discontinued their use.

There have been school surveys conducted in a number of Canadian provinces since the early 1970s. Adlaf and Smart (28) reviewed survey results in six of the ten provinces where surveys had been conducted between the early 1970s and the late 1980s. The most consistent trend was an increase in the prevalence of cannabis use during the 1970s followed by a sharp decline during the 1980s.

Since 1977 Ontario has conducted a series of surveys of students in grades 7, 9, 11 and 13 (corresponding to ages 10 through 19 years old) with sample sizes of between three and five thousand. The prevalence of cannabis use during the previous 12 months declined from 32% in 1979 to 14% in 1989. Declines were also reported for nine other drug types including tobacco and alcohol. Rates of illicit drug use were lower in Ontario than in the neighbouring United States. The size of the decline in rates of annual cannabis use was greater than for other substances (28). The Ontario surveys also found, like the U.S. surveys, that the perceived health risks of cannabis use increased as rates of use declined (28). Since the beginning of the 1990s there has been an increase in rates of cannabis use in the past year among Ontario high school students, from 12% in 1991 to 29% in 1999 (29). Comparison of trends in cannabis use in Canada has found the same pattern as reported in the USA, namely, a decline throughout the 1980s, followed by an increase in the early 1990s (30).

3.5 Cannabis use in Europe

Few European countries have undertaken regular community or high school surveys of cannabis and other illicit drug use. Those that have done so (e.g. Denmark, France, the Netherlands, Switzerland, and the United Kingdom) all reported increases in rates of cannabis use in the early 1990s (31). In all cases, the prevalence of current use was substantially less than lifetime use, indicating that most users stopped their use. Rates of current use were highest among those aged 15 to 24 years.

The Pompidou Group (32) examined illicit drug use among high school students in Belgium, France, Greece, Italy, Netherlands, Portugal, and Sweden (using a sample from the USA as the comparison). The study found that the rates of use of almost all illicit drugs were two or more times higher in the US sample. In the European samples, cannabis had been used at least once by between 10% and 36% of the older student population, and had been used in the past 30 days by between 3% and 14% of the European students as against 19% of the US students. Cannabis was used on a near daily basis by 1% or less of European samples compared with 3% in the US.

In 1992 in the Netherlands, a large national survey of drug use was undertaken involving over 10,000 students aged 10–18 years (33). About one third of males and one fifth of females had used cannabis at some time in their lives. Data from three national school surveys in 1984, 1988 and 1992 showed large increases in use between 1988 and 1992, particularly among males.

In 1997 the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) reported rates of lifetime cannabis use among adults and adolescents in household surveys in 9 countries and among high school students in 14 countries (34). Rates of lifetime use among adults varied from a high of 31.3% in Denmark to a low of 3.6% in a German mail survey. Rates among young adults varied between a high of 43% in Denmark to a low of 6% in Germany. Rates of use in the past year were available in fewer countries because of the low prevalence of this pattern of use, with rates varying between 1% in Sweden (for all illicit drugs combined) to a high of 21% in the United Kingdom (34). The school surveys showed higher rates of lifetime use, with a range between 41% in the United Kingdom and a low of 3% in Spain (34).

Smart and Ogborne (35) have recently analysed survey data on illicit drug use among students in 36 countries circa 1995. Most of these countries were European and developed industrialised societies. The highest rates of lifetime use of cannabis were in Britain. The rate was 53% in Scotland, followed by 41% in the United Kingdom and 33% in Wales. Then followed the USA (32%), Australia (31%) and the Netherlands (22%). Table 5 shows estimates produced by the EMCDDA in 2000.

Table 5: Prevalence of cannabis use in recent surveys in European countries

	Lifetime use (young adults)	12-month use (young adults)	Lifetime use (all adults)	12-month use (all adults)
Belgium	9.2	3.6	5.8	1.5
Denmark	43.0	6.0	31.3	3.3
Finland	17.5	6.3	9.7	2.5
France	25.7	8.9	16.0	4.7
E Germany	7.8	4.5	4.2	2.3
W Germany	20.1	7.8	13.4	4.5
Greece	19.7	8.8	13.1	4.4
Ireland	-	-	6.4	-
Netherlands	27.3	9.8	18.1	5.2
Spain	31.8	14.2	22.2	7.6
Sweden	16.0	2.0	13.0	1.0
United Kingdom	42.0	23.0	25.0	9.0

Taken from EMCDDA (2000)

These data suggest that, with the exception of the United Kingdom and Denmark, rates of cannabis use by young people in Europe is probably much lower than that in the USA. This has been confirmed in the recent European School Survey Project on Alcohol and Drugs (EPSAD) (36) which used the Monitoring the Future instrument to survey drug use in 95,000 year 10 school students in 30 participating countries. It found that the average rate of lifetime cannabis use in Europe was much lower (17%) than in the USA (41%). Rates in individual countries ranged between 1% in Romania and 35% in the Czech Republic, France and the United Kingdom (36).

3.6 Cannabis use in other regions

There is limited survey data on rates of cannabis use in other parts of the world (37). Surveys have been reported from different countries but their results have often been reported in ways that make it difficult to compare rates. In many cases these data provide only crude rates of cannabis use, survey methods are poorly reported, and it is sometimes unclear whether rates are lifetime or recent cannabis use (37). The limited data from developing countries in Africa, the Caribbean, Asia and South America suggest that rates of cannabis use are much lower in these countries than in Europe and English-speaking countries (37).

3.7 Correlates of cannabis use

Age: First use of cannabis typically begins in the teens and the heaviest rates of use occur in the early 20s. Rates of cannabis use remain relatively high during the early 20s but declines thereafter. Chen and Kandel (26) found that the majority of young adults who experimented with cannabis had done so by age 18 and Bachman *et al* (24) have found that rates of use decline steadily from the mid 20s into the early 30s.

Gender: Rates of cannabis use in the lifetime, the past year and past week are consistently higher among males than females (2, 3, 8, 28). Daily use and long-term daily use are much more common among males (2, 3).

Income: A positive relationship has been found between income in adolescence and early adult life and cannabis use (9), with those earning more money more likely to report cannabis use. In the United States, Johnston (22) also reported that daily cannabis use correlated positively with income and hours worked on a paid job.

Socioeconomic Status: The relationship between cannabis use and socioeconomic status (SES) is weak. Higher rates of cannabis use are sometimes found among lower SES individuals but in the past two decades there has been no relationship between parent's education and cannabis use among 12th grade students in the United States, with the exception that the group with lowest parental education had slightly lower cannabis use than the others (2, 3). That difference may be better explained by differences in income during adolescence rather than by social class.

Ethnicity: Information on the relationship between ethnicity and cannabis use is limited. Ethnic differences in one country may not generalise to others and small sample sizes often make ethnic comparisons unreliable. Even in the very large Monitoring the Future survey, samples from several years have to be combined to make reliable comparisons between the three largest ethnic groups (2, 3, 38). These show that African-American students have lower rates of use in all grades than White or Hispanic students. Hispanics, on the other hand, tend to have the highest rates of use in the early grades, before the rates of school drop-out increase.

Availability: In general, and all other things being equal, the more freely available a drug is, the higher its use in the population. This hypothesis has been broadly supported in the case of alcohol consumption, where the larger the number of licensed outlets and the longer the hours of trading, the higher the levels of community alcohol consumption and alcohol-related problems (39, 40). There is very little evidence to rigorously test this hypothesis in the case of cannabis use. Self-reports from surveys on how easy it is to obtain cannabis (2, 3) have shown very little change over long periods of time for cannabis in the USA.

3.8 Summary

Patterns of cannabis use have been most extensively studied in developed societies such as the USA, Canada, Australia and some European countries. The limited data in Europe shows lower rates of use than in Australia, Canada and the USA. The highest rates are in the United Kingdom, Denmark and France. The limited data from developing countries suggest that Africa, the Caribbean, Asia and South America have much lower rates of cannabis use than Europe and English-speaking countries.

The USA, which has systematically collected survey data on cannabis and other drug use since 1975, has documented long waves of cannabis consumption among young people. Rates of cannabis use increased through the 1970s in the USA, peaked in 1979 and

declined throughout the 1980s until 1991. Rates of use increased sharply in 1992 and have continued to increase throughout the 1990s with a leveling out in the late 1990s. A rising trend in cannabis use during the early 1990s has been reported in Australia, Canada, the Netherlands, Norway and Sweden. The 'natural history' of cannabis use in studies conducted in the USA is for use to start in the mid to late teens, reach its maximum in the early 20s and decline in the mid to late 20s. A minority of cannabis users continue to use into their 30s. Marrying and having children substantially reduce rates of cannabis use.

A substantial minority of young people in Europe, North America and Australia (and during some periods in the USA and Australia, the majority) have tried cannabis at least once in their lives. Rates of regular cannabis use are much lower. Most cannabis users discontinue their use. Lifetime and recent cannabis use are higher among males than females, and highest among young adults in their early 20s.

3.9 References

1. O'Malley, P., Bachman, J. & Johnston, L. (1983) Reliability and consistency of self-reports of drug use, *International Journal of the Addictions*, 18, 805–824.
2. Johnston, L. D., O'Malley, P. M. & Bachman, J. G. (1994) *National Survey Results on Drug Use from the Monitoring the Future Study, 1975–1993, Secondary School Students* (Rockville, MD, National Institute on Drug Abuse).
3. Johnston, L. D., O'Malley, P. M. & Bachman, J. G. (1994) *National Survey Results on Drug Use from the Monitoring the Future Study, 1975–1993, College Students and Young Adults* (Rockville, MD, National Institute on Drug Abuse).
4. Johnston, L. D., O'Malley, P. M. & Bachman, J. G. (2000) *National Survey Results on Drug Use from the Monitoring the Future Study, 1975–1999, Secondary School Students* (Rockville, MD, National Institute on Drug Abuse).
5. Johnston, L. D., O'Malley, P. M. & Bachman, J. G. (2000) *National Survey Results on Drug Use from the Monitoring the Future Study, 1975–1999, College Students and Young Adults Ages 19–40* (Rockville, MD, National Institute on Drug Abuse).
6. Australian Institute of Health and Welfare (1999) 1998 National Drug Strategy Household Survey: First results (Canberra, Australian Institute of Health and Welfare (Drug Statistics Series)).
7. Makkai, T. & McAllister, I. (1998) *Patterns of drug use in Australia, 1985–1995* (Canberra, Australian Government Publishing Service).
8. Donnelly, N. & Hall, W. (1994) Patterns of cannabis use in Australia, NCADA Monograph Series No. 27 (Canberra, Australian Government Publishing Service).
9. Makkai, T. & McAllister, I. (1997) *Marijuana use in Australia: Patterns and Attitudes* (Canberra, Australian Government Publishing Service).
10. Lynskey, M., White, V., Hill, D., Letcher, T. & Hall, W. (1999) Prevalence of illicit drug use among youth: Results from the Australian school students' alcohol and drugs survey, *Australian and New Zealand Journal of Public Health*, 23, 519–524.

11. White, V. (2000) Australian secondary school students' use of over-the-counter and illicit substances in 1999 (unpublished report) (Melbourne, Centre for behavioural Research in Cancer, Anti-Cancer Council of Victoria).

12. Lynskey, M. & Hall, W. (1999) Cannabis use among Australian youth: prevalence and correlates of use. NDARC Technical Report No. 66 (Sydney, National Drug and Alcohol Research Centre, UNSW).

13. Hall, W. & Swift, W. (2000) The THC content of cannabis in Australia: Evidence and implications, *Australian and New Zealand Journal of Public Health*, 24, 503–508.

14. McAllister, I. & Makkai, T. (1991) Whatever happened to marijuana? Patterns of marijuana use in Australia, 1985–1988, *International Journal of the Addictions*, 26, 491–504.

15. Degenhardt, L., Lynskey, M. & Hall, W. (2000) Cohort trends in the age of initiation of drug use in Australia, *Australian and New Zealand Journal of Public Health*, 24, 421–426.

16. Fergusson, D. M. & Horwood, L. J. (1997) Early onset cannabis use and psychosocial adjustment in young adults, *Addiction*, 92, 279–296.

17. Kandel, D. B., Davies, M., Karus, D. & Yamaguchi, K. (1986) The consequences in young adulthood of adolescent drug involvement. An overview, *Archives of General Psychiatry*, 43, 746–54.

18. Hall, W., Solowij, N. & Lemon, J. (1994) The health and psychological consequences of cannabis use (Canberra, Australian Government Publishing Service).

19. Salmelainen, P. (1995) The correlates of offending frequency: A study of juvenile theft offenders in detention (Sydney, New South Wales Bureau of Crime Statistics and Research).

20. National Institute on Drug Abuse (1992) National Survey of Drug Abuse: Population Estimates 1991—Revised November 20, 1992 (Rockville, MD, National Institute on Drug Abuse).

21. Substance Abuse and Mental Health Services Administration (1999) National Household Survey on Drug Abuse, 1999 (Rockville, MD, Department of Health and Human Services).

22. Johnston, L. D. (1981) Frequent marijuana use: Correlates, possible effects, and reasons for using and quitting, in: deSilva, R., Dupont, R. & Russell, R. (Eds.) *Treating the marijuana dependent person*, pp. 8–14 (New York, American Council on Marijuana and Other Psychoactive Drugs, Inc).

23. Bachman, J. G., Johnston, L. D. & O'Malley, P. M. (1998) Explaining recent increases in students' marijuana use: impacts of perceived risks and disapproval, 1976 through 1996, *American Journal of Public Health*, 88, 887–892.

24. Bachman, J. G., Wadsworth, K. N., O'Malley, P., Johnston, L. & Schulenberg, J. (1997) *Smoking, drinking and drug use in young adulthood: The impacts of new freedoms and responsibilities* (Mahwah, NJ, Lawrence Erlbaum).

25. Chen, K. & Kandel, D. B. (1998) Predictors of cessation of marijuana use: An event history analysis, *Drug and Alcohol Dependence*, 50, 109–21.

26. Chen, K. & Kandel, D. B. (1995) The natural history of drug use from adolescence to the mid-thirties in a general population sample, *American Journal of Public Health*, 85, 41–7.

27. Williams, B., Chang, K. & Van Truong, M. (1992) *Canadian Profile: Alcohol and Other Drugs 1992* (Canada, Addiction Research Foundation Publications).

28. Adlaf, E. M. & Smart, R. G. (1991) Drug use among adolescent students in Canada and Ontario: The past, present and future, *Journal of Drug Issues*, 21, 59–72.

29. Adlaf, E. M., Paglia, A., Ivis, F. J. & Ialomiteanu, A. (2000) Nonmedical drug use among adolescent students: Highlights from the 1999 Ontario Student Drug Use Survey, *Canadian Medical Association Journal*, 162, 1677–1680.

30. Ivis, F. J. & Adlaf, E. M. (1999) A comparison of trends in drug use among students in the USA and Ontario, Canada: 1975–1997, *Drugs, Education Prevention and Policy*, 6, 17–27.

31. Harkin, A., Anderson, P. & Goos, P. (1997) Smoking, Drinking and Drug Taking in the European Region (Copenhagen, WHO Regional Office for Europe).

32. Johnston, L., Driessen, F. & Kokkevu, A. (1994) Surveying Student Drug Misuse: A Six-Country Pilot Study (Strasbourg, France, Cooperation Group to Combat Drug Abuse and Illicit Trafficking in Drugs (Pompidou Group), Council of Europe).

33. DeZwat, W., Mensink, C. & Kuipers, S. (1994) Key Data: Smoking, Drinking, Drug Use and Gambling Among Pupils Aged 10 Years and Older—The 3rd Sentinel Station Survey with Regard to High Risk Substances (Utrecht, Netherlands Institute on Alcohol and Other Drugs).

34. European Monitoring Centre for Drugs and Drug Addiction (1998) Annual Report on the State of the Drugs Problem in the European Union, 1998 (Lisbon, EMCDDA).

35. Smart, R. G. & Ogborne, A. C. (2000) Drug use and drinking among students in 36 countries, *Addictive Behaviors*, 25, 455–460.

36. Hibell, B. (2001) European School Survey Project on Alcohol and Drugs *Press release* (Stockholm,).

37. Hall, W., Johnston, L. & Donnelly, N. (1999) Epidemiology of cannabis use and its consequences, in: Kalant, H., Corrigall, W. Hall, W. & Smart, R. (Eds.) *The health effects of cannabis*, pp. 71–125 (Toronto, Can Centre for Addiction and Mental Health).

38. Bachman, J. G., Wallace, J., O'Malley, P., Johnston, L., Kurth, C. & Neighbors, H. (1991) Racial/ethnic differences in smoking, drinking and illicit drug use among American high school seniors, 1976–1989, *American Journal of Public Health*, 81, 372–377.

39. Bruun, K., Edwards, G., Lumio, M., Makela, K., Pan, L., Popham, R., Room, R., Schmidt, W., Skog, O., Sulkenen, P. & Osterberg, E. (1975) *Alcohol Control Policies in Public Health Perspective, Volume 25* (Helsinki, Finnish Foundation for Alcohol Studies).

40. Edwards, G., Anderson, P., Babor, T., Casswell, S., Ferrence, R., Giesbrecht, N., Godfrey, C., Holder, H., Lemmens, P., Makela, K., Midanik, L., Norstrom, T., Osterberg, E., Romelsjo, A., Room, R., Simpura, J. & Skog, O. (1994) *Alcohol policy and the public good* (Oxford, Oxford University Press).

4 The acute effects of cannabis

4.1 Psychological effects

The effects of cannabis depend upon the dose received, the mode of administration, the user's prior experience with cannabis, any concurrent drug use, and the 'set and setting'—the user's expectations, attitudes towards the effects of cannabis, their mood state, and the social setting in which it is used (1). The main reason why most young people use cannabis is to experience a 'high': mild euphoria, relaxation and perceptual alterations, including time distortion, and the intensification of ordinary experiences, such as eating, watching films, listening to music, and engaging in sex (1, 2). When used in a social setting, the 'high' may be accompanied by infectious laughter, talkativeness, and increased sociability.

Cognitive changes include impaired short-term memory and attention. These make it easy for the user to become lost in pleasant reverie and difficult to sustain goal-directed mental activity (3, 4). Motor skills, reaction time, motor coordination and many forms of skilled psychomotor activity are impaired while the user is intoxicated (1, 4).

Some users report unpleasant experiences after using cannabis. These include anxiety, panic, a fear of going mad, and depression (5–7). These are often reported by users who are unfamiliar with the effects of cannabis (7), and by some patients given THC for therapeutic reasons (8). More experienced users may report these effects after swallowing cannabis because its effects may be more pronounced and of longer duration than they usually experience after smoking. These effects can be prevented by preparation of users about the effects they may experience and they can be managed by reassurance and support (5, 7). Psychotic symptoms, such as delusions and hallucinations, are very rare experiences that may occur at very high doses of THC, and perhaps in susceptible individuals at lower doses (5–7) (see Chapter 10 below).

4.2 Physical effects

The most immediate effect of smoking cannabis is to increase the heart rate by 20% to 50% within a few minutes to a quarter of an hour of smoking cannabis (9–11). Changes in blood pressure also occur. These depend upon posture: blood pressure is increased while the person is sitting, and decreases while they are standing. A sudden change from lying down to standing up may produce postural hypotension and a feeling of 'light-headedness' and faintness that is often the earliest indication of intoxication in naive users (12). In healthy young users these cardiovascular effects are unlikely to be of any clinical significance (11). They may amplify anxiety if the cannabis-induced palpitations and feeling faint are misinterpreted as symptoms of serious misadventure.

4.2.1 Toxic dose levels

THC is the component of cannabis that has the highest toxicity in animals. The cause of death is cessation of breathing or the heart, if breathing is assisted (13). Because tolerance develops to its effects, the toxic dose of THC depends upon the amount by which a dose exceeds the customary dose (14). Laboratory studies in humans of daily dosing of high levels of THC over weeks have demonstrated tolerance to mood effects, heart rate changes, decrease in skin temperature, increased body temperature, and impaired performance on psychomotor tests (15).

There are no reported cases of human deaths attributed to cannabis toxicity (16, 17). With many drugs the toxic dose gets smaller as one moves from mice, rats, monkeys and dogs to humans. With THC, by contrast, humans are probably much *less* susceptible to the acute toxicity of THC than animals. For example, the dose of THC which kills 50% of animals when administered intravenously is 40 mg/kg in the rat but it is 130 mg/kg in the dog and monkey (13). Extrapolation from the animal evidence suggests that the lethal human dose of THC is at least as high as, and probably higher than, that observed in the monkey. This means that the estimated toxic dose of THC in humans is so large, e.g. 4000 mg (18), that it is unlikely to be easily achieved by recreational users.

4.3 Psychomotor effects

A major societal concern about cannabis intoxication is that it may impair the psychomotor performance of automobile drivers, increasing the risk of accidents in cannabis users who drive a car while intoxicated. Individuals who drive while intoxicated with alcohol are dangerous to others in proportion to how intoxicated they are (19). It has been more difficult to decide whether cannabis intoxication impairs psychomotor performance in a similar way to alcohol.

4.3.1 Effects of cannabis on psychomotor tasks

Simple reaction time is not reliably affected by cannabis (20, 21). In choice reaction time tasks, in which the response is conditional upon the occurrence of a stimulus in the presence of another discriminant stimulus (such as the pitch of a tone), reaction time is usually slower after using cannabis (22, 23).

The performance of concurrent tasks is almost always adversely affected by cannabis, although the effects on the component tasks are not always consistent (24–28). In studies of concurrent tasks subjects are asked to do one task which requires continuous attention, typically tracking, while discriminating between significant stimuli that occur sporadically and non-significant stimuli that occur more frequently.

4.3.2 Effects of cannabis on simulated driving and flying

In simulated driving tasks subjects use skills similar to those involved in driving a car under laboratory conditions which have been designed to emulate the performance characteristics of a car. These simulations have two major advantages (29): cannabis users can be tested after taking large doses of cannabis, and they can be placed in simulated emergency situations which test their level of impairment. It would be unethical to do either of these things on the road. The difficulty with simulator studies lies in achieving fidelity to the conditions of on-road driving.

Smiley (29, 30) who critically reviewed research on the effects of cannabis on simulated driving has argued that the early studies which showed fewer effects than later studies suffered because of their unrealistic car dynamics. Later studies that used more realistic driving simulators have shown impairments of lane control after cannabis use. Some of the studies have also shown reductions in risk-taking as manifested in slower speeds, and maintenance of a larger distance from the car in front in following tasks (30).

A smaller number of simulator studies have been done on the effects of cannabis on flying skills. Janowsky et al (31) found substantial increases in errors in keeping the plane at the proper altitude and heading during a simulated flight after pilots had taken cannabis. Yesavage et al (32) originally reported that a simulated flying task was impaired up to 24 hours after smoking cannabis but this study did not include a control group. A later study with a control group (33) failed to replicate this result and only found an effect 1 to 4 hours after smoking. A third study that also included a control group (34) failed to show impairments in performance up to 24 hours after smoking cannabis. Although much has been made of the original findings (despite the failure to replicate them), the effects were very small and of uncertain significance for flying safety. Jones (35) has argued that the use of cannabis by pilots 24 hours before flying may be more an indicator of poor judgement than a risk because of residual psychomotor effects of cannabis.

4.3.3 Effects of cannabis on driving on road courses

A number of studies have been done on the effects of cannabis on driving cars around off road courses. These studies have found that cannabis has modest effects by comparison with alcohol. An early study by Hansteen et al (36) showed that a moderate dose of alcohol (approximately 0.07 BAC) or THC (5.9 mg) impaired driving on a traffic-free course, with driving speed decreased after using cannabis but not alcohol. Smiley et al (37), using a different type of course, found that reaction time to signal stimuli was increased by a combination of cannabis and alcohol. Klonoff (38) studied driving on a closed course, and in city traffic, after a placebo and two doses of smoked cannabis (4.9 and 8.4 mg THC). Driving on the closed course was impaired by both doses. Driving in traffic, however, was not significantly affected. Sutton (39) also found that cannabis had little effect on actual driving performance.

Peck et al (40) recorded performance on a range of driving tasks on a closed circuit on four occasions after the administration of placebo, up to 19 mg of smoked THC, 0.84 g/kg of alcohol, and the combination of both drugs. On most individual and derived composite measures, cannabis impaired performance. The effects of cannabis on driving performance were less than those of alcohol.

A recent series of on road studies by Robbe and colleagues (41, 42) found modest impairment of driving skills after cannabis on actual driving on either a driving course without traffic, on a highway or in urban traffic. They found that drivers were aware of their intoxication after using cannabis and took steps to minimise its impact on their driving by slowing down (41).

The effects of cannabis use on on-road driving have been smaller than the effects of intoxicating doses of alcohol (29, 30). Cannabis use has consistently made drivers slow down (30). This contrasts with the typical increase in speed when drivers are intoxicated

by alcohol. The compensatory behaviour of cannabis users may explain the comparatively small effects of cannabis intoxication in on road driving studies. For ethical reasons on road studies have not been able to test the response of cannabis-intoxicated drivers to emergency situations in which there is less opportunity to compensate for impairment. The few studies which have simulated this situation (e.g. by measuring reaction to other tasks while driving) have shown that cannabis use impairs emergency decision-making (29, 30).

4.3.4 Studies of cannabis use and accident risk

It is unclear whether cannabis use increases the risk of being involved in motor vehicle accidents. Surveys (42, 43) have found that the majority of cannabis users have driven after using cannabis, despite being aware of impairment (38, 44). But epidemiological studies of accident fatalities and injuries have not definitively shown that cannabis users are more likely to be involved in motor vehicle or other accidents. This contrasts with the role of alcohol intoxication in accidents where case-control studies have shown that persons with blood alcohol levels indicating intoxication are over-represented among accident victims by comparison to drivers who are not involved in accidents (45). The lack of the evidence in the case of cannabis reflects major difficulties in obtaining the necessary evidence to assess its role (19).

There are a substantial number of studies of the prevalence of cannabinoids in the blood of drivers who have been involved in motor vehicle accidents (see Chesher (19) and McBay (46) for reviews). Studies of accident fatalities tested post-mortem have found that 4% to 37% of blood samples contained cannabinoids, most often in combination with blood alcohol levels (BAC) indicative of intoxication (e.g. (47–49). An Australian study of 1045 fatalities (50, 51) found cannabinoids in the blood of 11% of drivers, 35% of whom also had BACs indicative of intoxicating doses of alcohol. Similar findings have been reported in studies of Californian motorists tested on suspicion of impairment by the Highway patrol (52) and in a prospective study of trauma patients (53).

These findings are difficult to evaluate for a number of reasons. First, it is not clear that drivers with cannabinoids are over-represented among accident victims because we do not know how many drivers who have not been involved in accidents have cannabinoids in their blood (54). Finding a rate of 35% of accident victims with cannabinoids in their blood may seem high but so is the rate of cannabis use among young males, the group who are most likely to be involved in motor vehicle accidents (53). Second, the presence of cannabinoids in blood levels does not necessarily mean that a driver was intoxicated by cannabis at the time of an accident (55) (see Chapter 2 above). Third, it is difficult to attribute an accident to cannabis when drivers with cannabinoids in their blood also have high blood alcohol levels (19, 46).

'Culpability analysis' has been developed to address these issues (54). In these analyses, a researcher decides which driver was 'culpable' for an accident using information about the circumstances of the fatal crash but excluding information on their alcohol and drug use. Drivers with no alcohol or other drugs in their blood are used as the control group to see whether cannabis and other drugs increase driver culpability. A common problem with these analyses is that the culpability of drug-free drivers is often high. This makes it difficult to detect an increase in culpability among drivers with alcohol, cannabis and other drugs in their blood.

Most culpability analyses have shown increased culpability among drivers with intoxicating levels of alcohol in their blood (19, 56). Drivers who have only had cannabis present have been in the minority because most also have intoxicating doses of alcohol (19, 56). There has been no evidence of an additive effect of alcohol and cannabis in these analyses despite the fact that laboratory studies suggest that the impairments produced by alcohol and cannabis are additive (19). These findings have been replicated in two Australian studies that used culpability analysis to examine the role of cannabis in fatal (51) and non-fatal motor accidents (50, 57, 58). There was a strong relationship between alcohol level and culpability in each study but neither study found any relationship between THC and culpability.

A different approach has been used by Gieringer (59), who estimated the proportion of drivers who might be expected to have blood and urine samples positive for cannabinoids from US household surveys. He estimated that cannabis users were 2 to 4 times more likely to be accident victims than non-cannabis users. Cannabis users who also used alcohol were even more likely to be over-represented among the victims of motor vehicle accidents.

4.3.5 Other epidemiological data on accidental injury

There is other suggestive evidence that cannabis use may increase the risk of accidents. Two surveys of self-reported accidents among adolescent drug users found a relationship between self-reported cannabis use and involvement in accidents. Cannabis smokers were approximately twice as likely to report being involved in accidents than non-cannabis smokers (60, 61).

Two studies of deaths among cannabis users provide suggestive evidence of an association between cannabis use and accidents (62, 63). Andreasson and Allebeck reported mortality over 15 years among 50,465 Swedish military conscripts. They found that men who had smoked cannabis 50 or more times by the age of 18 had an increased risk of premature death (Relative Risk (RR) = 4.6). Motor vehicle accidents accounted for 26% of these deaths and 7% were other accidents (e.g. drownings and falls). The increased risk was no longer statistically significant after statistical adjustment for antisocial behaviour and alcohol and other drug use in adolescence (62).

Polen et al (63) compared health service use by 450 people who did not use cannabis, and 450 persons who were daily smokers of cannabis only, who were screened by Kaiser Permanente Medical Centers between July, 1979 and December, 1985. They found an increased use of medical care by cannabis-only smokers for accidental injury over one to two years of follow-up, with cannabis users who were the heaviest alcohol users showing the highest rates of use. Sidney et al (64) reported death rates after 10-years among 65,171 members of the Kaiser Permanente Medical Care Program aged between 15 and 49. The sample comprised 38% who had never used cannabis, 20% who had used less than six times, 20% who were former users, and 22% who were current users. Regular cannabis users had a slightly increased rate of premature death (RR = 1.33) but this was explained by increased deaths caused by AIDS in men, probably because cannabis use was more common among male homosexuals than male heterosexuals.

4.4 Summary

The major adverse acute effects of cannabis use are anxiety and dysphoric experiences in a substantial minority of cannabis users. The risks of fatal overdose are very small, with no deaths reported in the medical literature.

Cannabis adversely affects the performance of a number of psychomotor tasks in a way that is related to dose and the difficulty of the task. The acute effects on psychomotor performance of cannabis in doses used recreationally are similar to but smaller than those of intoxicating doses of alcohol. Alcohol and cannabis also differ in their effects on user's willingness to take risks when driving. Persons intoxicated by cannabis engage in less risky behaviour than persons intoxicated by alcohol because they seem to be more aware of their impairment.

It has been difficult for technical and ethical reasons to decide whether the impairment produced by cannabis intoxication increases the risk of motor vehicle accidents. There is reasonable evidence from studies of cannabinoid levels in accident victims, and the few epidemiological studies, to suggest that driving after using cannabis probably increases the risk of motor vehicle accidents. The increased risk may be of the order of 2 to 4 times but it is difficult to rule out the possibility that it is the result of the combined use of cannabis and alcohol.

4.5 References

1. Jaffe, J. (1985) Drug addiction and drug abuse, in: Gilman, A., Goodman, L. & Murad, F. (Eds.) *The Pharmacological Basis of Therapeutics* (USA, Macmillan).
2. Tart, C. (1970) Marijuana intoxication: Common experiences, *Nature*, 226, 701–704.
3. Solowij, N. (1998) Cannabis and cognitive functioning, *Cambridge, England UK: Cambridge University Press.*
4. Beardsley, P. & Kelly, T. (1999) Acute effects of cannabis on human behavior and central nervous system functions, in: Kalant, H., Corrigall, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 127–170 (Toronto, Centre for Addiction and Mental Health).
5. Smith, D. E. (1968) Acute and chronic toxicity of marijuana, *Journal of Psychedelic Drugs*, 2, 37–47.
6. Thomas, H. (1993) Psychiatric symptoms in cannabis users, *British Journal of Psychiatry*, 163, 141–149.
7. Weil, A. (1970) Adverse reactions to marihuana, *New England Journal of Medicine*, 282, 997–1000.
8. Institute of Medicine (1999) *Marijuana and Medicine: Assessing the Science Base* (Washington, DC, National Academy Press).

9. Jones, R. (1984) Cardiovasc effects of cannabinoids, in: Harvey, D. J., Paton, W. & Nahas, G. (Eds.) *Mar ana '84: Proceedings of the Oxford Symposium on Cannabis*, pp. 325–334 (Oxford, IRL Press).

10. Huber, G., Griffith, D. & Langsjoen, P. (1988) The effects of marihuana on the respiratory and cardiovascular systems, in: Chesher, G., Consroe, P. & Musty, R. (Eds.) *Marijuana: An International Research Report. NCADA Monograph No. 7*, pp. 19–24 (Canberra, Australian Government Publishing Service).

11. Chesher, G. & Hall, W. (1999) Effects of cannabis on the cardiovascular and gastrointestinal systems, in: Kalant, H., Corrigall, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 435–458 (Toronto, Canada, Centre for Addiction and Mental Health).

12. Maykut, M. (1984) *Health Consequences of Acute and Chronic Marihuana Use* (Oxford, Pergamon Press).

13. Rosencrantz, H. (1983) Cannabis, marihuana and cannabinoid toxicological manifestations in man and animals, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 91–176 (Toronto, Addiction Research Foundation).

14. Compton, D., Dewey, W. & Martin, B. (1990) Cannabis dependence and tolerance production, *Advances in Alcohol and Substance Abuse*, 9, 128–147.

15. Jones, R. & Benowitz, N. (1976) The 30-day trip—Clinical studies of cannabis tolerance and dependence, in: Braude, M. & Szara, S. (Eds.) *Pharmacology of Marijuana, Volume 2*, pp. 627–642 (New York, Academic Press).

16. Blum, K. (1984) *Handbook of Abusable Drugs* (New York, Gardner Press).

17. Nahas, G. (1984) Toxicology and pharmacology, in: Nahas, G. (Ed.) *Marihuana in Science and Medicine* pp. 109–246 (New York, Raven Press).

18. Gable, R. S. (1993) Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically, *American Journal of Drug and Alcohol Abuse*, 19, 263–281.

19. Chesher, G. (1995) Cannabis and road safety: An outline of research studies to examine the effects of cannabis on driving skills and actual driving performance, in: Road Safety Committee Parliament of Victoria (Ed.) *The Effects of Drugs (Other than Alcohol) on Road Safety*, pp. 67–96 (Melbourne, Road Safety Committee, Parliament of Victoria).

20. Borg, J., Gershon, S. & Alpert, M. (1975) Dose effects of smoked marihuana on human cognitive and motor functions, *Psychopharmacologia*, 42, 211–8.

21. Dornbush, R., Fink, M. & Freedman, A. (1971) Marijuana, memory, and perception, *American Journal of Psychiatry*, 128, 194–197.

22. Block, R. & Wittenborn, J. (1986) Marijuana effects on the speed of memory retrieval in letter-matching task, *International Journal of Addiction*, 21, 281–285.

23. Block, R. & Wittenborn, J. (1984) Marijuana effects on semantic memory: Verification of common and uncommon category members, *Psychological Reports*, 55, 503–512.

24. MacAvoy, M. & Marks, D. (1975) Divided attention performance of cannabis users and non-users following cannabis and alcohol use, *Psychopharmacologia*, 44, 147–152.

25. Marks, D. & MacAvoy, M. (1989) Divided attention performance in cannabis users and non-users following alcohol and cannabis separately and in combination, *Psychopharmacology*, 99, 397–401.

26. Casswell, S. & Marks, D. (1973) Cannabis induced impairment of performance of a divided attention task, *Nature*, 241, 60–1.

27. Chait, L. D. (1990) Subjective and behavioral effects of marijuana the morning after smoking, *Psychopharmacology*, 100, 328–333.

28. Perez-Reyes, M., Hicks, R., Bumberry, J., Jeffcoat, A. & Cook, C. (1988) Interaction between marihuana and ethanol: Effects on psychomotor performance, *Alcoholism*, 12, 268–276.

29. Smiley, A. (1986) Marijuana: On-road and driving simulator studies, *Alcohol, Drugs and Driving*, 2, 121–134.

30. Smiley, A. (1999) Marijuana: On road and driving simulator studies, in: Kalant, H., Corrigall, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 171–193 (Toronto, Addiction Research Foundation).

31. Janowsky, D., Meacham, M., Blaine, J., Schoor, M. & Bozzetti, L. (1976) Marijuana effects on simulated flying ability, *American Journal of Psychiatry*, 133, 384–388.

32. Yesavage, J., Leirer, v.-O., Denari, M. & Hollister, L. (1985) Carry-over effects of marijuana intoxication on aircraft pilot perfromance: A preliminary report, *American Journal of Psychiatry*, 142, 1325–1329.

33. Leirer, v.-O., Yesavage, J. & Morrow, D. G. (1989) Marijuana, aging and task difficulty effects on pilot performance, *Aviation, Space and Environmental Medicine*, 60, 1145–1152.

34. Leirer, v.-O., Yesavage, J. & Morrow, D. G. (1991) Marijuana carry-over effects on aircraft pilot performance, *Aviation, Space and Environmental Medicine*, 62, 221–227.

35. Jones, R. (1987) Drug of abuse profile: cannabis, *Clinical Chemistry*, 33, 72B–81B.

36. Hansteen, R., Miller, R., Lonero, L., Reid, L. & Jones, B. (1976) Effects of cannabis and alcohol on automobile driving and psychomotor tracking, *Annals of the New York Academy of Science*, 282, 240–256.

37. Smiley, A., LeBlanc, A., French, I. & Burford, R. (1975) The combined effects of alcohol and common psychoactive drugs: 11 field studies with an instrumented automobile, in: Israelstram, S. & Lambert, S. (Eds.) *Alcohol, Drugs and Traffic Safety. Proceedings of the 6th International Conference on Alcohol, Drugs and Traffic Safety*, pp. 433–438 (Toronto, Addiction Research Foundation).

38. Klonoff, H. (1974) Marijuana and driving in real-life situations, *Science*, 186, 317–324.

39. Sutton, L. (1983) The effects of alcohol, marijuana and their combination on driving ability, *Journal of Studies on Alcohol*, 44, 438–445.

40. Peck, R., Biasotti, A., Boland, P., Mallory, C. & Reeve, V. (1986) The effects of marijuana and alcohol on actual driving performance, *Alcohol: Drugs and Driving*, 2, 135–154.

41. Robbe, H. W. J. (1994) *Influence of Marijuana on Driving* (Maastricht, Institute for Human Psychopharmacology, University of Limberg).

42. Robbe, H. W. J. & O'Hanlon, J. (1993) Marijuana's effect on actual driving: Summary of a 3-year experimental program, in: Utzelmann, H., Berghaus, G. & Kroj, G. (Eds.) *Alcohol, Durgs and Traffic Safety*, pp. 603–611 (Koln, Verlag TUV Rheinland).

43. Dalton, W., Martz, R., Lemberger, L., Rodda, B. & Forney, R. (1975) Effects of marijuana combined with secobarbitol, *Clinical Pharmacology and Therapeutics*, 14, 298–304.

44. Didcott, P., Reilly, D., Swift, W. & Hall, W. (1997) Long Term Cannabis Users on the New South Wales North Coast. NDARC Monograph No. 30 (Sydney, National Drug and Alcohol Research Centre, UNSW).

45. English, D., Holman, C., Milne, E., Winter, M., Hulse, G., Codde, S., Corti, B., Dawes, V., De Klerk, N., Knuiman, M., Kurinczuk, J., Lewin, G. & Ryan, G. (1995) *The quantification of drug caused morbidity and mortality in Australia, 1995* (Canberra, Commonwealth Department of Human Services and Health).

46. McBay, A. (1986) Drug concentrations and traffic safety, *Alcohol, Drugs and Driving*, 2, 51–59.

47. Cimbura, G., Lucas, D., Bennet, R., Warren, R. & Simpson, H. (1982) Incidence and toxicological aspects of drugs detected in 484 fatally injured drivers and pedestrians in Ontario, *Journal of Forensic Science*, 27, 855–867.

48. Mason, A. P. & McBay, A. J. (1984) Ethanol, marijuana, and other drug use in 600 drivers killed in single-vehicle crashes in North Carolina, 1978–1981, *Journal of Forensic Sciences*, 29, 987–1026.

49. Williams, A., Peat, M., Crouch, D., Wells, J. & Finkle, B. (1985) Drugs in fatally injured young male drivers, *Public Health Reports*, 100, 19–25.

50. Drummer, O. H. (1998) Involvement of drugs in accident causation (Canberra, Federal Office of Road Safety).

51. Drummer, O. H. (1994) Drugs in drivers killed in Australian road traffic accidents: the use of responsibility analysis to investigate the contribution of drugs to fatal accidents (Melbourne, Victorian Institute of Forensic Pathology).

52. Zimmerman, E., Yaeger, E., Soares, J., Hollister, L. & Reeve, V. (1983) Measurement of delta-9-tetrahydrocannabinol (THC) in whole blood samples from impaired motorists, *Journal of Forensic Sciences*, 28, 957–962.

53. Soderstrom, C., Triffilis, A., Chankar, B., Clark, W. & Cowley, R. (1988) Marijuana and alcohol use among 1023 trauma patients, *Archives of Surgery*, 123, 733–737.

54. Terhune, K. (1986) Problems and methods in studying drug crash effects, *Alcohol, Drugs and Driving*, 2, 1–13.

55. Consensus Report CDP Research Technology Branch NIDA (1985) Drug concentrations and driving impairment, *Journal of the American Medical Association*, 254, 2618–2621.

56. Terhune, K. W., Ippolito, C. A., Hendricks, D. L., Michalovic, J. G., Bogema, S. C., Saninga, P., Blomberg, R. & Preusser, D. F. (1992) The incidence and role of drugs in fatally injured drivers (Washington, DC, US Department of Transportation).

57. Longo, M. C., Hunter, C. E., Lokan, R. J., White, J. M. & White, M. A. (2000) The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: Part I: The prevalence of drug use in drivers, and characteristics of the drug-positive group, *Accident Analysis and Prevention*, 32, 613–622.

58. Longo, M. C., Hunter, C. E., Lokan, R. J., White, J. M. & White, M. A. (2000) The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: Part II, *Accident Analysis and Prevention*, 32, 623–632.

59. Gieringer, D. H. (1988) Marijuana, driving and accident safety, *Journal of Psychoactive Drugs*, 20, 93–101.

60. Hingson, R., Heeren, T., Mangione, T., Morelock, S. & Mucatel, M. (1982) Teenage driving after using marijuana or drinking and traffic accident involvement, *Journal of Safety Research*, 13, 33–37.

61. Smart, R. & Fejer, D. (1976) Drug use and driving among high school students, *Accident Analysis and Prevention*, 8, 33–38.

62. Andreasson, S. & Allebeck, P. (1990) Cannabis and mortality among young men: A longitudinal study of Swedish conscripts, *Scandinavian Journal of Social Medicine*, 18, 9–15.

63. Polen, M., Sidney, S., Tekawa, I., Sadler, M. & Friedman, G. (1993) Health care use by frequent marijuana smokers who do not smoke tobacco, *Western Journal of Medicine*, 158, 596–601.

64. Sidney, S., Beck, J. E., Tekawa, I. S., Quesenberry, C. P., Jr. & Friedman, G. D. (1997) Marijuana use and mortality, *American Journal of Public Health*, 87, 585–590.

5 Cellular and immunological effects of cannabis use

5.1 Is cannabis a potential cause of cancer?

Cannabis could be a cause of cancer if the cannabinoids it contains (or substances produced when it is burnt) produce genetic mutations in the user's somatic cells (such as those in the lung) (1). There is only weak evidence that THC is 'mutagenic' in this sense. THC can produce changes in cellular processes in animal cells in the test tube (2) but these changes probably delay or stop cell division rather than produce cellular changes that may lead to cancer (1).

There is no evidence that THC and other cannabinoids produce mutations in microbial tests of mutagenicity, such as the Ames test (1, 3). There is inconsistent evidence on whether cannabinoids produce breaks in chromosomes (3) but if they do, these changes are unlikely to cause cancers (1) because chromosomal abnormalities are more likely to kill the affected cell than to produce malignant transformation and proliferation (1). A recent study in rats and mice found no evidence that THC caused cancer (4).

Cannabis ***smoke*** is mutagenic in the test tube, and hence is potentially a cause of cancer (i.e. carcinogenic) (1, 3, 5). Cannabis smoke produces chromosomal aberrations, is mutagenic in the Ames test (6) and causes cancers in the mouse skin test (1). The fact that it is cannabis *smoke* that is carcinogenic (6) suggests that any cancers caused by cannabis smoking are most likely to occur in organs that receive long term exposure to cannabis smoke and the tars it contains, such as the lung, the upper aerodigestive tract (mouth, tongue, oesophagus) and the bladder (1).

5.2 Is cannabis smoking a cause of aerodigestive tract cancers?

There are good reasons for suspecting that cannabis may cause cancers of the lung and the aerodigestive tract (the oropharynx, nasal and sinus epithelium, and the larynx). First, tobacco is a cause of respiratory cancer (7) and cannabis smoke contains many of the same cancer-causing substances as tobacco smoke (8). Second, chronic cannabis smokers show many of the pathological changes in lung cells that precede the development of cancer in tobacco smokers (9, 10).

Third, cancers of the upper aerodigestive tract have been reported in young adults who have been chronic cannabis smokers (11–15). In many cases these were also cigarette smokers and alcohol consumers but Caplan and Brigham reported two cases of cancer of the tongue in men aged 37 and 52 years (12), neither of whom smoked tobacco or consumed alcohol. A history of long-term daily cannabis use was their only shared risk factor. These reports raise a suspicion but provide limited support for the hypothesis that

cannabis use is a cause of upper respiratory tract cancers. They do not compare rates of cannabis use in cases and controls, cannabis exposure has been assessed retrospectively and in the knowledge that the user has cancer; and they do not control for confounding factors such as alcohol and tobacco use.

Two recent controlled studies have produced inconsistent results. Sidney et al (16) studied cancer incidence during an 8.6 year follow up of 64,855 members of the Kaiser Permanente Medical Care Program (KPMCP). Study participants were asked about cannabis use during medical screening between 1979 and 1985. Their average age at entry was 33 years and they were followed until: death, a diagnosis of cancer or HIV/AIDS, exit from the KPMCP or 31 December 1993 (a mean of 8.6 years). At study entry 38% had never used cannabis, 20% had used it less than 6 times, 20% were former users, and 22% were current cannabis users. Data were collected from a cancer registry and the California mortality data system.

There were no more cases of cancer among those who had ever used cannabis or who were current cannabis users than among those who had not used cannabis at study entry. There were more tobacco-related cancers among tobacco smokers (regardless of cannabis use) but no more among cannabis smokers. Males who had ever smoked cannabis had an increased risk of prostate cancer (RR = 3.1) and so did males who were current cannabis smokers (RR = 4.7) (16).

Zhang et al (17) compared rates of cannabis use among 173 persons with primary squamous cell carcinoma of the head and neck and 176 controls who were blood donors matched on age and sex from the same hospital. Cases were more likely to have used cannabis than controls (14% and 10% respectively), with an odds ratio for cannabis smoking of 2.6 after adjusting for cigarette smoking, alcohol use and other known risk factors. The cases with cancer smoked cannabis more often and for longer than the controls. The relationship between cannabis smoking and these cancers was stronger among adults under the age of 55 years (Odds Ratio (OR) = 3.1). There was a suggestion that cancer cases were more likely to smoke both tobacco and cannabis than controls (17).

How do we reconcile the negative findings of the Sidney et al study with that of Zhang et al? The persons studied by Sidney et al were too young (average age of 43 at follow up) to see many excess cases of cancer attributable to cannabis smoking. The chance of Sidney et al finding cancers was further reduced because only 22% were cannabis users at study entry.

There is as yet no evidence that regular cannabis smoking causes cancers of the lungs and lower respiratory tract of the type caused by cigarette smoking (10). Studies of respiratory cancers would be timely since cannabis users in the post-War birth cohorts are reaching the age of 60 years when the incidence of all cancers steeply increases. A longer follow-up of the Sidney et al cohort may reveal whether cannabis smoking causes respiratory cancers.

5.3 The public health impact of cancers caused by cannabis smoking

On *current patterns of use*, cannabis smoking will cause very few respiratory cancers, even if the risks of *daily* cannabis smoking are comparable to those of daily tobacco smoking (18). This is because in Western societies there are many more daily tobacco (25–30%) than daily cannabis smokers (1–3%) (19), most cannabis smokers stop in their mid to late twenties (20), and the 1% or less who smoke cannabis daily over decades typically smoke 1 to 3 cannabis cigarettes per day rather than 10 to 30 tobacco cigarettes a day (21). Among this minority of users, prolonged use of cannabis into the fourth and later decades may increase the risk of respiratory cancer, especially among tobacco smokers who also smoke cannabis.

5.4 Is cannabis smoking during pregnancy a cause of childhood cancers?

Cannabis smoking has also been linked to cancers in children born to mothers who used cannabis during their pregnancy. Three case control studies have examined cannabis use as a risk factor for childhood cancers, along with a range of other risk factors. There was no prior reason to expect cannabis use to be related to these cancers, as there was with respiratory cancers.

Maternal cannabis use and childhood cancer were associated in a case-control study of Acute Nonlymphoblastic Leukemia (ANLL), a rare form of childhood cancer (22, 23). The study was designed to assess the relationship between this childhood cancer and maternal and paternal environmental exposures to petrochemicals, pesticides and radiation. Maternal cannabis use was assessed before and during pregnancy as one of many variables to be statistically controlled when analyzing the relationship between ANLL and maternal and paternal environmental exposures.

A strong association was found between maternal cannabis use and ANLL. The mothers of cases were 11 times more likely to have used cannabis before and during their pregnancy than mothers of controls. The relationship persisted after statistical adjustment for other risk factors. An alternative explanation is that because reports of cannabis use were obtained after the diagnosis of the ANLL, mothers of children with ANLL may have been more likely to report cannabis use than were mothers of controls. The authors did find that the rate of cannabis use among the controls in this study was much lower than among controls in other studies. When the rate of cannabis use among controls was adjusted upwards there was a reduced but still significant three-fold increase in risk.

Two other case-control studies have reported an increased risk of rhabdomyosarcoma (24) and astrocytomas (25) in children born to women who reported using cannabis during their pregnancies. Neither planned to study the association between childhood cancer and maternal cannabis use. In each case, cannabis use was one of a large number of variables that were to be controlled for in statistical analyses of the relationship between the exposure of principal interest and the childhood cancer.

Trends in the rates of these cancers suggest that these studies may have produced chance results. There was no increase in the rate of any of these cancers between 1979 and 1995 (26). The rate of ANLL, for example, remained steady during this period (27). The same was true of soft-tissue sarcomas (which include rhabdomyosarcomas) (28). Cancers of the brain (about 52% of which are astrocytomas) did increase in incidence between 1979 and 1995 (29) but in a way that is more likely to reflect improved diagnosis than maternal cannabis use. The rate of these cancers increased abruptly in 1985, after Magnetic Resonance Imaging became widely available in the USA, and remained stable thereafter (29).

5.5 Immunological effects

Tobacco smoking suppresses humoral and cell-mediated immunity so it is reasonable, given the similarities between cigarette and cannabis smoke (30), to expect that cannabis smoke suppresses immunity (2). Cannabinoid receptors are also expressed in some immune cells (Kamminski, 1998) so THC may influence the immune system. If cannabinoids have immunosuppressive effects then their therapeutic use may be limited in patients with impaired immune systems. This could preclude their use as anti-emetic agents in cancer chemotherapy and as appetite stimulants and mood enhancers in patients with AIDS.

There are difficulties in deciding whether cannabis impairs the immune system in humans. First, most studies have been conducted on whole animals and in animal and human cell cultures that have been exposed to cannabis smoke or cannabinoids. The relevance of these studies to humans is limited by the fact that they used very high oral doses of THC (31). Second, there have been very few epidemiological studies of immune system functioning and disease susceptibility in heavy chronic cannabis users (31).

5.5.1 Effects of cannabinoids on humoral immunity

The effect of cannabinoids on humoral immunity has been assessed by measuring their effect on animal and human B-cell responses to sheep red blood cells. Cannabinoids do not consistently alter B-cell functioning (32). While cannabinoids consistently impair the B-cell responses in mice, no such effects have been observed in humans, and the few positive studies have produced results that are within the normal range (32).

Antibodies have been formed to THC in animals (31) and there are clinical reports in humans that cannabinoids exacerbate allergies and that allergy to cannabinoids can develop in humans (31). Hollister (33), however, has argued that although a few persons may become truly allergic to cannabinoids it is more likely that these are rare allergic reactions that are due to contaminants (e.g. bacteria, fungi, moulds, parasites, worms, chemical) found in cannabis.

5.5.2 Effects of cannabinoids on cell-mediated immunity

Studies of the effects of cannabinoids on T-cells and macrophage numbers have been mixed, with some showing reductions (2) while others have not (34). The evidence is also mixed on the effect of cannabinoids on T-cell functioning. A number of the earliest

studies suggested that T-cells from chronic cannabis users were less responsive but later laboratory studies of chronic heavy dosing in humans (35) have failed to replicate these results. Studies exposing human T-cells to cannabinoids have also produced mixed results while animal studies have showed a decreased T-cell response (32).
In a review of the literature published in this field in the 1990s, Klein (31) concluded that THC affected the function of immune cells including lymphocytes, macrophages, and polynuclear cells in the test tube but relatively high drug concentrations were required, the effects were not related to psychoactivity, and they were reversible.

5.5.3 Effects of cannabinoids on host resistance

Studies in mice and guinea pigs have suggested that high doses (200 mg/kg) of THC reduce resistance to infection (36–39). A consistent finding in humans has been that exposure to cannabis ***smoke*** adversely affects alveolar macrophages, the immune cells in the respiratory system that comprise the first line of defence against micro-organisms which enter the body through the lungs (5). Studies of these cells in cannabis smokers have shown abnormalities (40), and exposure of alveolar macrophages to cannabis smoke impairs their ability to inactivate bacteria (5, 32), and a fungus (41). It is the noncannabinoid components of cannabis smoke that produce these effects (5).

5.5.4 The human significance of the immunological effects of cannabinoids

The animal evidence is reasonably consistent that cannabinoids impair cell-mediated and humoral immunity and several animal studies have found decreased resistance to a bacteria and virus. However, the doses required to produce these immunological effects in animals are much higher than the doses used by humans (1). Human users may also develop tolerance to any immunological effects of cannabinoids, which may reduce the small effects projected from animal studies. Given the large number of cannabinoid effects to which tolerance has been shown to develop it would not be surprising if this were also true of its immunological effects.

The limited human evidence is mixed. A small number of studies that suggest that cannabis use impairs immunity have not been replicated by others. Munson and Fehr (32) concluded that there was 'no conclusive evidence' that cannabinoids impaired functioning of T-lymphocytes, B-lymphocytes or macrophages, or reduced immunoglobulin levels in humans. There was 'suggestive evidence' of impaired T-lymphocyte functioning reflected in an impaired reaction to mitogens and allogenic lymphocytes (32). More recently, Wallace et al (42, 43) failed to find impairment of lymphocyte function in alveolar macrophages in cannabis smokers although they did find it in tobacco smokers.

The significance of these immunological impairments in chronic cannabis users is uncertain. There have been sporadic reports of ill health among chronic heavy cannabis users in Asia and Africa (32) but these reports are difficult to evaluate because of the confounding effects of poor living conditions and nutritional status (32). Three field studies of the effects of chronic cannabis use in Costa Rica (44), Greece (45), and Jamaica (46), failed to find any evidence of increased susceptibility to infectious diseases among chronic cannabis users. But less than 100 users were studied, a number which is too small to detect a small increase in the incidence of common infectious and bacterial diseases.

A recent study by Polen et al (47) compared health service utilisation by non-smokers and daily cannabis-only smokers enrolled in a health maintenance organisation. Their results provided suggestive evidence of an increased rate of treatment for respiratory conditions among cannabis-only smokers, although its significance is uncertain because infectious and non-infectious respiratory conditions were not separated. Further studies of this type may better assess how serious a risk chronic heavy cannabis smoking poses to the immune and respiratory systems (31).

5.6 Effects of cannabis on immunity in immunocompromised persons

Cannabis has been used by young adults in Western societies for over 30 years so the absence of epidemic infectious disease among these users makes it unlikely that cannabis smoking produces *major* impairments in the immune systems of users. The absence of such epidemics does not rule out the possibility that heavy cannabis use may impair immunity in ways that produce small increases in rates of common bacterial and viral illnesses (32). This could have escaped the notice of clinical observers.

Studies of the effects of cannabis use on patients with immune systems compromised by AIDS provide one way of detecting immunological effects of cannabis. If there were no effects in patients with compromised immune systems, it would be a reasonable to infer that there was little risk of immunological effects in recreational users.

A number of epidemiological studies of HIV positive homosexual men have examined the effects of cannabis and other drug use on progression to AIDS. Kaslow et al (48) studied progression to AIDS among 4,954 homosexual and bisexual men and found that HIV-positive cannabis users were *not* more likely to progress to AIDS and cannabis use was not related to immunological functioning. There was no relationship between cannabis use and progression to AIDS over six years in 451 HIV-positive men in the San Francisco Men's Health Study (49). The only study which found an association between cannabis and progression to AIDS was the Sydney AIDS Project in which 386 gay men were followed up over 12 months (50). This result may be at odds with the others because the study had a short follow up and many of the HIV positive cases may already have had AIDS (30).

A study of deaths in 64,855 HMO patients in California (51) did find an association between cannabis use and premature death from AIDS. Unmarried men had much higher rates of cannabis use than married men but in this study cannabis use was probably a marker for high-risk sexual behaviour rather than an independent risk factor.

5.7 Summary

Cannabis *smoke* is mutagenic (capable of inducing genetic mutation) and carcinogenic in animal tests and it contains many of the same carcinogens as tobacco smoke. It is therefore a potential cause of cancer in body cells that are chronically exposed to it, such as those of the aerodigestive and respiratory tracts.

There are case reports of aerodigestive tract cancers among relatively young adults who have been daily cannabis users. A case control study found an association between cannabis smoking and head and neck cancer but a large prospective study did not. The youth of the participants and the low rate of regular cannabis use in this prospective study reduced its ability to detect an increase in these cancers. Further follow-up and case control studies are needed to clarify the issue.

There is weaker evidence for an increased risk of cancers among children born to women who smoked cannabis during pregnancy. Three studies of very different types of cancer have reported an association with maternal cannabis use but none of these was a planned study of the role of cannabis use in these cancers so replication of their results is required. There is no evidence that the rate of any of these cancers has increased over the past few decades.

In animals THC in high doses can impair cell-mediated and humoral immunity and reduce resistance to infection by bacteria and viruses. The relevance of these findings to human health is uncertain because the doses that produce these effects in animals are very high, and tolerance probably develops to the effects on the immune system in human users. The limited evidence on the immune effects of cannabis in humans is conflicting; the small number of studies that have produced adverse effects have not been replicated. The studies that have produced evidence of adverse effects have reported small changes that are within the normal range.

There has not been any increase in rates of infectious disease among chronic heavy cannabis users. Given the duration of large-scale cannabis use by young adults in Western societies, the absence of such epidemics makes it unlikely that cannabis smoking produces ***major*** impairments in the immune system. It is more difficult to exclude the possibility that chronic heavy cannabis use produces minor impairments in immunity.

There are three prospective studies of HIV-positive homosexual men two of which indicated that continued cannabis use did ***not*** increase rates of progression to AIDS and one of which suggested that it did. A recent epidemiological study which compared health service utilisation by nonsmokers and daily cannabis smokers provided suggestive evidence of an increased rate of medical care use for respiratory conditions among cannabis smokers. The most sensitive test of any small immunological effects of cannabis may come from studies of the therapeutic usefulness of cannabinoids in immunologically compromised patients, such as those undergoing cancer chemotherapy, or those with AIDS.

5.8 References

1. MacPhee, D. (1999) Effects of marijuana on cell nuclei: A review of the literature relating to the genotoxicity of cannabis, in: Kalant, H., Corrigal, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 293–309 (Toronto, Centre for Addiction and Mental Health).
2. Nahas, G. (1984) Toxicology and pharmacology, in: Nahas, G. (Ed.) *Marihuana in Science and Medicine*, pp. 109–246 (New York, Raven Press).
3. Marselos, M. & Karamanakos, P. (1999) Mutagenicity, developmental toxicity and carcinogenicity of cannabis, *Addiction Biology*, 4, 5–12.
4. Chan, P., Sills, R., Braun, A., Haseman, J. & Bucher, J. (1996) Toxicity and carcinogenicity of delta-9-tetrahydrocannabinol in Fischer rats and B6C2F1 mice, *Fundamental and Applied Toxicology*, 30, 109–117.
5. Leuchtenberger, C. (1983) Effects of marihuana (cannabis) smoke on cellular biochemistry of *in vitro* test systems, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 177–224 (Toronto, Addiction Research Foundation).
6. Bloch, E. (1983) Effects of marijuana and cannabinoids on reproduction, endocrine function, development and chromosomes, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 355–432 (Toronto, Addiction Research Foundation).
7. International Agency on Cancer (1990) *Cancer: Causes, Occurrence and Control* (Lyon, International Agency on Cancer).
8. National Academy of Science (1982) *Marijuana and Health* (Washington, DC, National Academy Press).
9. Fligiel, S., Beals, T., Venkat, H., Stuth, S., Gong, H. & Tashkin, D. (1988) Pulmonary pathology in marijuana smokers, in: Chesher, G., Consroe, P. & Musty, R. (Eds.) *Marijuana: An International Research Report. NCADA Monograph No. 7*, pp. 43–48 (Canberra, Australian Government Publishing Service).
10. Tashkin, D. (1999) Effects of cannabis on the respiratory system, in: Kalant, H., Corrigall, W., Hall, W., & Smart, R., *The Health Effects of Cannabis* pp. 311–346 (Toronto, Addiction Research Foundation).
11. Donald, P. (1991) Advanced malignancy in the young marijuana smoker, in: Freidman, H., Specter, S. & Klein, T. (Eds.) *Drugs of Abuse, Immunity and Immunodeficiency* (London, Plenum Press).
12. Caplan, G. A. & Brigham, B. A. (1990) Marijuana smoking and carcinoma of the tongue. Is there an association?, *Cancer*, 66, 1005–6.
13. Endicott, J. N., Skipper, P. & Hernandez, L. (1993) Marijuana and head and neck cancer, *Advances in Experimental Medicine and Biology*, 335, 107–13.
14. Nahas, G. & Latour, C. (1992) The human toxicity of marjiuana, *Medical Journal of Australia*, 156, 495–497.

15. Taylor, I. F. (1988) Marijuana as a potential respiratory tract carcinogen: A retrospective analysis of a community hospital population, *Southern Medical Journal*, 81, 1213–1216.

16. Sidney, S., Quesenberry, C. P., Friedman, G. D. & Tekawa, I. S. (1997) Marijuana use and cancer incidence (California, United States), *Cancer Causes and Control*, 8, 722–728.

17. Zhang, Z.-F., Morgenstern, H., Spitz, M., Tashkin, D., Yu, G.-P., Marshall, J., Hsu, T. & Schantz, S. (1999) Marijuana use and increased risk of squamous cell carcinoma of the head and neck, *Cancer Epidemiology, Biomarkers and Prevention*, 8, 1071–1078.

18. Hall, W. (1998) The respiratory risks of cannabis smoking, *Addiction*, 93, 1461–1463.

19. Hall, W. (1995) The public health implications of cannabis use, *Australian Journal of Public Health*, 19, 235–242.

20. Bachman, J. G., Wadsworth, K. N., O'Malley, P., Johnston, L. & Schulenberg, J. (1997) *Smoking, drinking and drug use in young adulthood: The impacts of new freedoms and responsibilities* (Mahwah, NJ, Lawrence Erlbaum).

21. Didcott, P., Reilly, D., Swift, W. & Hall, W. (1997) Long Term Cannabis Users on the New South Wales North Coast. NDARC Monograph No. 30 (Sydney, National Drug and Alcohol Research Centre, UNSW).

22. Neglia, J., Buckley, J. & Robinson, L. (1991) Maternal marijuana and leukemia in offspring, in: Nahas, G. & Latour, C. (Eds.) *Physiopathology of Illicit Drugs: Cannabis, Cocaine, Opiates* (Oxford, Pergamon Press).

23. Robinson, L., Buckley, J., Daigle, A., Wells, R., Benjamin, D., Arthur, D. & Hammond, G. (1989) Maternal drug use and the risk of childhood nonlymphoblastic leukemia among offspring: An epidemiologic investigation implicating marijuana, *Cancer*, 63, 1904–1911.

24. Gruffenman, S. Schwartz, A. G., Ruymann, F. B. & Maurer, H. M. (1993) Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children, *Cancer Causes and Control*, 4, 217–24.

25. Kuijten, R., Bunin, G., Nass, C. & Meadows, A. (1992) Parental occupation and childhood astrocytoma, *Cancer Research*, 52, 782–786.

26. Reis, L., Eisner, M., Kosary, C., Hankey, B., Miller, B., Clegg, L. & Edwards, B. (2000) *SEER Cancer Statistics Review, 1973–1997* (Bethesda, MD, National Cancer Institute).

27. Smith, M. A., Gloekler, Reis, J., Gurney, J. & Ross, J. (2000) Leukemia, in: Reis, L., Eisner, M., Kosary, C. *et al.* (Eds.) *SEER Cancer Statistics Review, 1973–1997*, pp. 17–34 (Bethesda, MD, National Cancer Institute).

28. Gurney, J., Young, J., Roffers, S., Smith, M. A. & Bunin, C. (2000) Soft-tissue sarcomas, in: Reis, L., Eisner, M., Kosary, C. *et al.* (Eds.) *SEER Cancer Statistics Review, 1973–1997*, pp. 111–123 (Bethesda, MD, National Cancer Institute).

29. Gurney, J., Smith, M. A. & Bunin, C. (2000) CNS and miscellaneous intracranial and intraspinal neoplasms, in: Reis, L., Eisner, M., Kosary, C. *et al.* (Eds.) *SEER Cancer Statistics Review, 1973–1997*, pp. 51–63 (Bethesda, MD, National Cancer Institute).

30. Institute of Medicine (1999) *Marijuana and Medicine: Assessing the Science Base* (Washington, DC, National Academy Press).

31. Klein, T. (1999) Cannabis and immunity, in: Kalant, H., Corrigal, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis* pp. 347–374 (Toronto, Centre for Addiction and Mental Health).

32. Munson, A. & Fehr, K. (1983) Immunological effects of cannabis, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 257–354 (Toronto, Addiction Research Foundation).

33. Hollister, L. (1992) Marijuana and immunity, *Journal of Psychoactive Drugs*, 24, 159–164.

34. Dax, E., Pilotte, N., Adler, W., Nagel, J. & Lange, W. (1989) The effects of 9-ENE-tetrahydrocannabinol on hormone release and immune function, *Journal of Steroid Biochemistry*, 34, 263–270.

35. Lau, R., Tubergen, D., Barr, M., Domino, F., Benowitz, N. & Jones, R. (1976) Phytohemagglutinin-induced lymphocyte transformation in humans receiving delta-9-tetrahydrocannabinol, *Science*, 192, 805–087.

36. Friedman, H. (1991) Cannabis and immunity, in: Nahas, G. & Latour, C. (Eds.) *Physiopathology of Illicit Drugs: Cannabis, Cocaine, Opiates*, pp. 79–90 (Oxford, Pergamon Press).

37. Morahan, P., Klykken, P., Smith, S., Harris, L. & Munson, A. (1979) Effects of cannabinoids on host resistance to *Listeria monocytogenes* and Herpes Simplex Virus, *Infection and Immunity*, 23, 670–674.

38. Mishkin, E. & Cabral, G. (1985) Delta-9-tetrahydrocannabinol decreases host resistance to herpes simplex virus 2 vaginal infection in the B6C3F1 mouse, *Journal of General Virology*, 66, 2539–2549.

39. Cabral, G., Mishkin, E., Marciano-Cabral, F., Coleman, P., Harris, L. & Munson, A. (1986) Effect of delta-9-tetrahydrocannabinol on Herpes Simplex Virus Type 2 Vaginal Infection in the guinea pig (42325), *Proceedings of the Society for Experimental Biology and Medicine*, 182, 181–186.

40. Tennant, F. S., Jr. (1980) Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers, *Substance and Alcohol Actions/Misuse*, 1, 93–100.

41. Sherman, M. P., Aeberhard, E. E., Wong, V. Z., Simmons, M. S., Roth, M. D. & Tashkin, D. P. (1995) Effects of smoking marijuana, tobacco or cocaine alone or in combination on DNA damage in human alveolar macrophages, *Life Sciences*, 56, 2201–2207.

42. Wallace, J., Tashkin, D., Oishi, J. & Barbers, R. (1988) Peripheral blood lymphocyte subpopulations and mitogen responsiveness in tobacco and marijuana smokers, *Journal of Psychoactive Drugs*, 20, 9–14.

43. Wallace, J. M., Oishi, J. S., Barbers, R. G., Simmons, M. S. & Tashkin, D. P. (1994) Lymphocytic subpopulation profiles in bronchoalveolar lavage fluid and peripheral blood from tobacco and marijuana smokers, *Chest*, 105, 847–52.

44. Carter, W., Coggins, W. & Doughty, P. (1980) Cannabis in Costa Rica: A study of chronic marihuana use *Philadelphia* (Institute for the Study of Human Issues,).

45. Stefanis, C., Dornbush, R. & Fink, M. (1977) *Hashish: Studies of Long-Term Use* (New York, Raven Press).

46. Rubin, V. & Comitas, L. (1975) *Ganja in Jamaica: A Medical Anthropological Study of Chronic Marihuana Use* (The Hague, Mouton).

47. Polen, M., Sidney, S., Tekawa, I., Sadler, M. & Friedman, G. (1993) Health care use by frequent marijuana smokers who do not smoke tobacco, *Western Journal of Medicine*, 158, 596–601.

48. Kaslow, R., Blackwelder, W., Ostrow, D., Yerg, D., Palenick, J., Coulson, A. & Valdiserri, R. (1989) No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals: A report from the Multicenter AIDS Cohort Study, *Journal of the American Medical Association*, 261, 3424–3429.

49. DiFranco, M., Sheppard, H., Hunter, D., Tosteson, T. & Ascher, M. (1996) The lack of association of marijuana and other recreational drugs with progression to AIDS in the San Francisco Men's Health Study, *Annals of Epidemiology*, 6, 283–289.

50. Tindall, B. (1988) The Sydney AIDS project, *Australian and New Zealand Journal of Medicine*, 18, 8–15.

51. Sidney, S., Beck, J. E., Tekawa, I. S., Quesenberry, C. P., Jr. & Friedman, G. D. (1997) Marijuana use and mortality, *American Journal of Public Health*, 87, 585–590.

6 The reproductive effects of cannabis use

Studies conducted in the mid-1970s showed that animals given large doses of cannabis or THC during pregnancy had lower levels of the gonadal hormones (testosterone and oestrogen) that control reproduction (1–5). There were also case reports of breast development in young men who had a history of heavy cannabis use (6). A study by Kolodny et al (7) found that chronic male cannabis users had lower levels of testosterone, a lower sperm count and motility, and more abnormal sperm than controls. These observations raised concerns that the use of cannabis by young adults during the 1970s and 1980s would impair fertility in men and adversely affect pregnancy outcomes in women. Cannabinoid receptors are expressed by cells in the hypothalamus and pituitary that regulate sex hormone production (8) so it is possible that THC can affect the functioning of the reproductive system.

6.1 Effects on the male reproductive system

Male animals given large doses of cannabis, crude cannabis extracts, THC and other cannabinoids showed lowered testosterone levels, retarded sperm maturation, reduced sperm count and sperm motility, and increased rates of abnormal sperm (1, 5, 9, 10). Although the mechanisms for these effects were uncertain, it was likely that they were a direct effect of THC on the testis, and an indirect effect on the hypothalamic hormones that stimulate the testis to produce testosterone (5).

Human studies of the effects of cannabis on male reproductive function produced mixed results (9). The study by Kolodny et al (7), which reported reduced testosterone, sperm production, and sperm motility and increased abnormalities in sperm, was not replicated in a larger, better controlled study of chronic cannabis users. This study failed to find any difference in testosterone level at study entry, or after three weeks of daily cannabis use (11). The significance of the animal findings for human cannabis users are uncertain (2) because testosterone levels in human cannabis users have generally been within the normal range (12).

6.2 Effects on the female reproductive system

In animal studies cannabis and THC interfere with the hormones controlled by the hypothalamic-pituitary-gonadal axis in non-pregnant female animals (1), delaying oestrous and ovulation (9). There have been very few human studies of the effects of cannabis on the female reproductive system because of fears that cannabis use may produce birth effects in women of childbearing age (13). An unpublished study by Bauman (1980 cited by Nahas (3)) compared the menstrual cycles of 26 cannabis smokers with those of 17 controls and found a higher rate of anovulatory cycles among the cannabis users. Mendelson and Mello (14) failed to find that cannabis use affected the female sex hormones, or the duration of the cycle. Mueller, Daling, Weiss and Moore (15) reported a modest association (OR = 1.7) between cannabis use and

infertility in a case-control study of 150 women with primary anovulatory infertility and 150 controls. The relationship was strongest in women who had used cannabis *less* frequently. In the absence of any other human evidence, Bloch (1), the Institute of Medicine (2) and Murphy (9) have argued that the animal evidence suggests that cannabis use probably inhibits human female reproductive function but it is uncertain how large these effects are.

6.3 Foetal development and birth defects

The possibility that cannabis use during pregnancy may adversely affect pregnancy outcomes is raised by evidence that THC crosses the placenta in animals (1) and humans (16). This makes it possible that THC, and other cannabinoids, may interfere with the development of the foetus, that is, may act as teratogens.

In mice, rats, rabbits, and hamsters large doses of cannabis or THC can produce foetal resorption, growth retardation, and malformations (1). Growth resorption and growth retardation have been more consistently reported than birth malformations (17) and the doses that produce malformations have been very high (17). Birth malformations have been observed more often after the administration of crude cannabis extract rather than pure THC, suggesting that other cannabinoids may produce any teratogenic effects. It is also unclear whether these teratogenic effects can be attributed to THC or to reduced food intake caused by the large doses of cannabis that have been used (1, 17). Bloch (1) concluded that THC was unlikely to be teratogenic in humans and was, at most, 'weakly teratogenic' in rodents and rats.

6.3.1 Human studies

Epidemiological studies of the effects of cannabis use on human reproduction have produced mixed results for a number of reasons. First, adverse reproductive outcomes and heavy cannabis use during pregnancy are relatively rare. This means that unless cannabis use produces a large increase in the risk of abnormalities, very large sample sizes will be required to detect adverse effects of cannabis use on foetal development. Many of the studies that have been conducted to date have been too small to detect effects of this size (18–20).

Second, societal disapproval of illicit drug use during pregnancy may discourage honest reporting when women are asked about drug use during their pregnancy (21). If a substantial proportion of cannabis users are misclassified as non-users, any relationship between cannabis use and adverse outcomes will be attenuated, requiring even larger samples to detect it (22).

Third, women who use cannabis during their pregnancies differ from those who do not in a variety of ways that may affect the outcome of their pregnancies. Cannabis users are, for example, more likely to smoke tobacco and use alcohol and illicit drugs during their pregnancy. They are also likely to have lower income, poorer education levels and poorer nutrition, all of which predict an increased risk of poorer pregnancy outcomes (10, 20, 23). These make it difficult to confidently attribute any poor birth outcomes to cannabis use rather than to other drug use, or to poor maternal nutrition and prenatal care.

Given these difficulties, there is reasonable consistency (although not unanimity) in the finding that cannabis use in pregnancy is associated with slightly reduced birth weight (24–26), and length at birth (23). This relationship has been found in the best-controlled studies, and it has persisted after statistically controlling for potential confounding variables (24, 25). A recent meta-analysis of these studies found that regular cannabis smoking during pregnancy possibly reduced birth weight but results varied considerably between studies (27). The mean weight reduction of 48 g (for any cannabis use vs no cannabis use during pregnancy) was much smaller than that associated with tobacco smoking during pregnancy, namely, 200 g (27).

The relationship between cannabis use and birth abnormalities is less certain. Milman (28) reported several cases of children with features similar to the Foetal Alcohol Syndrome (FAS) born to women who smoked cannabis during pregnancy but did not use alcohol. Epidemiological studies have largely not reported an increased rate of congenital abnormalities among children born to women who used cannabis during pregnancy (23, 25, 26, 29).

One study reported a five-fold increase in the rate of children with FAS-like features born to women who reported using cannabis (29). This finding was puzzling because there was *no* relationship between self-reported alcohol use and the 'foetal alcohol syndrome'. An additional study reported an increase in the crude rate of birth abnormalities among children born to women who reported using cannabis but this result was no longer statistically significant after adjustment for confounders (30). The study by Zuckerman et al is the most convincing study that failed to find an effect. A large sample of women was studied, among which a substantial proportion reported cannabis use that was verified by urinalysis. There was a low rate of birth abnormalities among the cannabis users, and no suggestion that their rate was higher than that in the controls.

6.4 Post-natal development

The most extensive research on the effects of cannabis use during pregnancy on the post-natal development of the child comes from the Ontario Prospective Prenatal Study (OPPS). This study assessed developmental and behavioural abnormalities in children born to women who reported using cannabis during pregnancy (31–39). A sample of 698 mothers were asked about their drug use during pregnancy and their children were measured on the Brazelton scales after birth and neurologically assessed at one month. In subsequent studies, these children were assessed using standardised scales at six and twelve months and throughout their childhood and into their adolescence (31).

The initial OPPS studies reported a developmental delay shortly after birth in the infants' visual system, and an increased rate of tremors and startle among the children born to cannabis users (31). The effects found at birth faded by one month, and there were no differences in performance on standardised tests of ability at six and twelve months. Small effects were again reported at 36 and 48 month follow ups (40) but these were not found at 60 and 72 months (41). These results are suggestive of a transient developmental impairment occurring among children who had experienced a shorter gestation and prematurity. It seems unlikely that the tests used in later follow-ups were

insensitive to the effects of prenatal cannabis exposure because they showed adverse effects of tobacco smoking during pregnancy on behavioural development at 60 and 72 months (40, 41).

The results of studies that have attempted to replicate the OPPS findings have been mixed. Tennes et al (23) conducted a prospective study of the relationship between cannabis use during pregnancy and postnatal development in 756 women, a third of whom reported using cannabis during their pregnancy. The children were assessed shortly after birth using the same measures as Fried (20) and a subset were assessed at one year of age. There were no differences in behavioural development after birth between the children of women who did and did not use cannabis and there were no differences at one year. More recently, Day et al (42), have followed up children at age three born to 655 women who were asked about their substance use during pregnancy. They found a relationship between the mothers' cannabis use during pregnancy and the children's performances on memory and verbal scales of the Stanford-Binet Intelligence Scale at age three. A later follow up at age six did replicate the OPPS findings of increased impulsivity and impaired attention among children whose mothers had smoked cannabis during their pregnancy (43).

Fried and Smith (31) concluded after reviewing the literature that the effects of 'prenatal exposure to marihuana are subtle' and 'considerably moderated by other risk factors'. There were 'limited (if any) effects upon foetal growth and central nervous system functioning' and little evidence of effects on growth and behaviour during the toddler stage. They argued that there was suggestive evidence for subtle effects after the age of three in impulsivity, attention and problem solving, the significance of which needed to be clarified by further research.

A more sceptical view was expressed in a recent meta-analytic review of the effects on foetal development of maternal use of cocaine, a drug with a much greater reputation for foetal toxicity than cannabis (44). Frank et al concluded that, after controlling for exposure to tobacco and alcohol, there were no effects of prenatal cocaine use on physical of behavioural development to age six.

6.5 Summary

High doses of THC use disrupt the male and female reproductive systems in animals. THC interferes with hormones controlling reproduction, reducing testosterone secretion, sperm production, motility, and viability in males, and interfering with the ovulatory cycle in females. It is uncertain whether these effects occur in humans, given the high doses used in animal studies, the inconsistency of findings in studies of human males, and the fact that the effects observed in the positive human studies are still within the normal range.

Cannabis use during pregnancy probably leads to lower birthweight, although the decrease is much smaller than that produced by tobacco use. Cannabis use during pregnancy is unlikely to be a *major* cause of birth defects but it is possible that cannabis use during pregnancy produces a small increase in the risk of birth defects as a result of

exposure of the foetus in utero. There is suggestive evidence that infants whose mothers smoke cannabis during their pregnancy may experience behavioural and developmental effects during the first few months after birth and possibly in the longer term. These effects, if they exist, are likely to be smaller than comparable effects of alcohol use and tobacco smoking during pregnancy.

6.6 References

1. Bloch, E. (1983) Effects of marijuana and cannabinoids on reproduction, endocrine function, development and chromosomes, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 355–432 (Toronto, Addiction Research Foundation).
2. Institute of Medicine (1982) *Marijuana and Health* (Washington, DC, National Academy Press).
3. Nahas, G. (1984) Toxicology and pharmacology, in: Nahas, G. (Ed.) *Marihuana in Science and Medicine*, pp. 109–246 (New York, Raven Press).
4. Nahas, G. & Frick, H. (1987) Developmental effects of cannabis, *Neurotoxicology*, 7, 381–395.
5. Wenger, T., Croix, D., Tramu, G. & Leonardeli, J. (1992) Effects of delta-9-tetrahydrocannabinol on pregnancy, puberty, and the neuroendocrine system, in: Murphy, L. & Bartke, A. (Eds.) *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*, pp. 539–560 (Boca Raton, CRC Press).
6. Harmon, J. & Aliapoulios, M. (1972) Gynecomastia in marihuana users, *New England Journal of Medicine*, 287, 936.
7. Kolodny, R., Masters, W., Kolodner, R. & Toro, G. (1974) Depression of plasma testosterone levels after chronic intensive marihuana use, *New England Journal of Medicine*, 290, 872–874.
8. Wenger, T., Toth, B., Juaneda, C., Leonardelli, J. & Tramu, G. (1999) The effects of cannabinoids on the regulation of reproduction, *Life Sciences*, 65, 695–701.
9. Murphy, L. (1999) Cannabis effects on endocrine and reproductive function, in: Kalant, H., Corrigal, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 293–309 (Toronto, Centre for Addiction and Mental Health).
10. National Academy of Science (1982) *Marijuana and Health* (Washington, DC, National Academy Press).
11. Mendelson, J., Kuehnle, J., Ellingboe, J. & Babor, T. (1974) Plasma testosterone levels before, during and after chronic marihuana smoking, *New England Journal of Medicine*, 291, 1051–1055.
12. Hollister, L. (1986) Health aspects of cannabis, *Pharmacological Reviews*, 38, 1–20.

13. Rosenkrantz, J. (1985) Cannabis components and responses of neuroendocrine - reproductive targets: An overview, in: Harvey, D., Paton, W. & Nahas, G. (Eds.) *Marihuana '84: Proceedings of the Oxford Symposium on Cannabis* pp. 457–505 (Oxford, IRL Press).

14. Mendelson, J. & Mello, K. (1984) Effects of marijuana on neuroendocrine hormones in human males and females, in: Braude, M. & Ludford, J. (Eds.) *Marijuana Effects on the Endocrine and Reproductive Systems*, pp. 97–113 (Rockville, MD, National Institute on Drug Abuse).

15. Mueller, B. A., Daling, J. R., Weiss, N. S. & Moore, D. E. (1990) Recreational drug use and the risk of primary infertility, *Epidemiology*, 1, 195–200.

16. Blackard, C. & Tennes, K. (1984) Human placental transfer of cannabinoids, *New England Journal of Medicine*, 311, 797.

17. Abel, E. (1985) Effects of prenatal exposure to cannabinoids, in: Pinkert, T. (Ed.) *Current Research on the Consequences of Maternal Drug Abuse. NIDA Research Monograph No. 59*, pp. 20–35 (Rockville, MD, US Department of Health and Human Services).

18. Greenland, S., STaisch, K., Brown, N. & Gross, S. (1982) The effects of marijuana use during pregnancy. I. A preliminary epidemiologic study, *American Journal of Obstetrics and Gynaecology*, 143, 408–413.

19. Greenland, S., Staisch, K., Brown, N. & Gross, S. (1982) The effects of marijuana use on human pregnancy, labor and delivery, *Neurobehavioural Toxicology and Teratology*, 4, 447–450.

20. Fried, P. A. (1980) Marihuana use by pregnant women: neurobehavioral effects in neonates, *Drug and Alcohol Dependence*, 6, 415–24.

21. Day, N. L., Wagener, D. & Taylor, P. (1985) Measurement of substance use during pregnancy: Methodologic issues, in: Pinkert, T. (Ed.) *Current Research on the Consequences of Maternal Drug Abuse. NIDA Research Monograph No. 59*, pp. 36–47 (US Department of Health and Human Services).

22. Zuckerman, B. (1985) Developmental consequences of maternal drug use during pregnancy, in: Pinkert, T. (Ed.) *Current Research on the Consequences of Maternal Drug Abuse. NIDA Research Monograph No. 59* pp. 96–106 (Rockville, MD, US Department of Health and Human Services).

23. Tennes, K., Aritable, N., Blackard, C., BCyles, C., Hasoun, B., Holmes, L. & Kreye, M. (1985) Marihuana: prenatal and postnantal exposure in the human, in: Pinkert, T. (Ed.) *Current Research on the Consequences of Maternal Drug Abuse. NIDA Research Monograph No. 59*, pp. 48–60 (Rockville, MD, US Department of Health and Human Services).

24. Hatch, E. & Bracken, M. (1986) Effect of marijuana use in pregnancy on fetal growth, *American Journal of Epidemiology*, 124, 986–993.

25. Zuckerman, B., Frank, D., Hingson, R., Amaro, H., Levenson, S., Kayne, H., Parker, S., Vinci, R., Aboagye, K., Fried, L., Cabral, H., Timperi, R. & Bauchner, H. (1989) Effects of maternal marijuana and cocaine use on fetal growth, *New England Journal of Medicine*, 320, 762–768.

26. Gibson, G., Baghurst, P. & Colley, D. (1983) Maternal alcohol, tobacco and cannabis consumption and the outcome of pre ncy, *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 23, 1. ,9.

27. English, D., Hulse, G., Milne, E., Holman, C. & Bower, C. (1997) Maternal cannabis use and birth weight: A meta-analysis, *Addiction*, 92, 1553–1560.

28. Milman, D. (1982) Psychological effects of cannabis in adolescence, in: National Institute on Drug Abuse (Ed.) *Marijuana and Youth: Clinical Observations on Motivation and Learning*, pp. 27–37 (Rockville, MD, National Institute on Drug Abuse).

29. Hingson, R., Alpert, J., Day, N., Dooling, E., Kayne, H., Morelock, S., Oppenheimer, E. & Zuckerman, B. (1982) Effects of maternal drinking and marijuana use on fetal growth and development, *Pediatrics*, 70, 539–546.

30. Linn, S., Schoenbaum, S., Monson, R., Rosnber, R., Stubblefield, P. & Ryan, K. (1983) The association of marijuana use with the outcome of pregnancy, *American Journal of Public Health*, 73, 1161–1164.

31. Fried, P. A. & Smith, A. M. (2001) A literature review of the consequences of prenatal marihuana exposure: An emerging theme of a deficiency in aspects of executive function, *Neurotoxicology and Teratology*, 23, 1–11.

32. Fried, P. A. & Watkinson, B. (2000) Visuoperceptual functioning differs in 9- to 12-year olds prenatally exposed to cigarettes and marihuana, *Neurotoxicology & Teratology*, 22, 11–20.

33. Fried, P. A. & Watkinson, B. (2000) Erratum: Visuoperceptual functioning differs in 9- to 12-year olds prenatally exposed to cigarettes and marihuana (Neurotoxicology and Teratology 22 (2000) (11–20)), *Neurotoxicology & Teratology*, 22, 267.

34. Fried, P. A., Watkinson, B. & Gray, R. (1999) Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana, *Neurotoxicology & Teratology*, 21, 513–25.

35. Fried, P. A., Watkinson, B. & Gray, R. (1998) Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana, *Neurotoxicology & Teratology*, 20, 293–306.

36. Fried, P. A. (1996) Behavioral outcomes in preschool and school-age children exposed prenatally to marijuana: A review and speculative interpretation. NIDA Research Monograph 164, pp. 242–60 (Rockville, MD, US Department of Health and Human Services).

37. Fried, P. A., Watkinson, B. & Siegel, L. S. (1997) Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana, *Neurotoxicology and Teratology*, 19, 171–183.

38. Fried, P. A. (1995) The Ottawa Prenatal Prospective Study (OPPS): Methodological issues and findings—It's easy to throw the baby out with the bath water, *Life Sciences*, 56, 2159–2168.

39. Fried, P. A. (1995) Prenatal exposure to marihuana and tobacco during infancy, early and middle childhood: Effects and an attempt at synthesis, *Archives of Toxicology. Supplement*, 17, 233–60.

40. Fried, P. A. & Watkinson, B. (1990) 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol, *Journal of Developmental & Behavioral Pediatrics*, 11, 49–58.

41. Fried, P. A., O'Connell, C. M. & Watkinson, B. (1992) 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: Cognitive and language assessment, *Journal of Developmental and Behavioral Pediatrics*, 13, 383–91.

42. Day, N. L., Richardson, G. A., Goldschmidt, L., Robles, N., Taylor, P. M., Stoffer, D. S., Cornelius, M. D. & Geva, D. (1994) Effect of prenatal marijuana exposure on the cognitive development of offspring at age three, *Neurotoxicology & Teratology*, 16, 169–175.

43. Leech, S. L., Richardson, G. A., Goldschmidt, L. & Day, N. L. (1999) Prenatal substance exposure: effects on attention and impulsivity of 6-year-olds, *Neurotoxicology & Teratology*, 21, 109–18.

44. Frank, D. A., Augustyn, M., Knight, W. G., Pell, T. & Zuckerman, B. (2001) Growth, development, and behavior in early childhood following prenatal cocaine exposure: A systematic review, *Journal of the American Medical Association*, 285, 1613–1625.

7 Cardiovascular, respiratory and gastrointestinal effects

7.1 Cardiovascular effects of cannabis

One of the most consistent effects of cannabis in humans and animals is to increase heart rate (1–3). This change parallels the subjectively experienced 'high' and is related to the amount of THC in the blood (3, 4). Healthy young adults are only mildly stressed by these cardiovascular effects of cannabis (5).

An increased heart rate is most obvious in occasional cannabis users because regular users become tolerant to this and other effects of THC (4). Tolerance occurs within 24 hours in laboratory studies and even large amounts of cannabis may have little effect on heart rate (1, 2, 6–9). Tolerance to these effects has also been observed in field studies of chronic heavy cannabis users in Costa Rica (10), Greece (11), and Jamaica (12). These studies failed to find any adverse effects of cannabis on heart function.

7.1.1 Effects on patients with cardiovascular disease

Patients with ischaemic heart disease, hypertension, and cerebrovascular disease who use cannabis (13, 14) may experience cardiac arrhythmias, chest pain, and myocardial infarction (or heart attack). Because THC has analgesic effects it may mask chest pain, delaying treatment. Cannabis smoking also increases the level of carboxyhaemoglobin in the blood, decreases oxygen delivery to the heart and increases the work of the heart (4). Patients with cerebrovascular disease may experience strokes caused by changes in blood pressure and patients with hypertension may experience exacerbations of their disease for the same reason.

A number of laboratory studies have found that smoking cannabis cigarettes adversely affects patients with heart disease. Aronow and Cassidy (15) compared the effect of smoking a cannabis and a placebo cigarette on heart rate and the time required to induce chest pain in an exercise tolerance test. Heart rate increased by 43%, and the time taken to produce chest pain halved after smoking a cannabis cigarette. Aronow and Cassidy (16) compared the effects of smoking a single cannabis cigarette and a high nicotine cigarette in 10 men with heart disease, all of whom were cigarette smokers. Smoking cannabis produced a 42% increase in heart rate, compared with a 21% increase after smoking the tobacco cigarette. Exercise tolerance time was halved after smoking a cannabis cigarette by comparison with a tobacco cigarette. These findings have been confirmed by Gottschalk and colleagues (17).

7.1.2 Significance of cardiovascular effects

It seems unlikely that healthy young adults who occasionally smoke cannabis develop heart disease as a result of their cannabis smoking. Most of these cannabis users discontinue their use by their late 20s (18, 19). A recent study (20) provides support for predictions that adverse cardiovascular effects may occur in a minority of chron

cannabis users who continue to use cannabis into their late 40s and early 50s, the age of highest risk for heart disease (21).

Mittleman et al reported a case-crossover study of the possible role that smoking cannabis may play in triggering an acute myocardial infarction (heart attack) (20). They asked 3882 patients who had had a myocardial infarction in the previous 4 days about their use of marijuana in the hour before it occurred, and compared this with their typical frequency of use. Only 3.5% of all patients, and 12.5% of those under the age of 44 years, had smoked cannabis in the previous year but it increased the risk of a myocardial infarction 4.8 times in the hour after use. The risk dropped rapidly after the first hour, as expected from the effects that THC and carbon monoxide from smoking have on heart function. The effect of smoking cannabis was smaller than the effect of cocaine use observed in earlier studies (a 24 fold increase). Mitteleman et al estimated that a 44-year-old adult who used cannabis daily would increase their annual risk of an acute cardiovascular event by 1.5% to 3%. They concluded that: 'smoking marijuana is a rare trigger of acute myocardial infarction' that 'may pose a health risks to patients with coronary heart disease and perhaps to individuals with multiple coronary risk factors' (p. 2808). The significance of this contribution may rise as the proportion of older adults who smoke cannabis increases.

7.2 Effects on the respiratory system

It is likely that regular cannabis smoking adversely affects the respiratory system (22). Cannabis smoke is similar to tobacco smoke, and contains a higher proportion of particulate matter and more of some carcinogens (e.g. benzpyrene) than tobacco smoke (22, 23). The inhalation of cannabis smoke therefore deposits carcinogenic substances on lung surfaces. Cigarette smoking is a cause of bronchitis, emphysema, and cancers of the lung, oral cavity, trachea, and oesophagus (24). Although tobacco smokers smoke many more cigarettes than cannabis smokers, cannabis smokers typically inhale more deeply, and hold their breath for longer, thereby depositing more particulate matter in the lung (22).

7.2.1 Chronic bronchitis and obstructive pulmonary disease

Convincing evidence that chronic cannabis use may impair lung function and cause symptoms of respiratory disease comes from a series of studies conducted by Tashkin and his colleagues since the mid 1970s (22). One of their early studies evaluated the effects of heavy daily cannabis smoking on respiratory function. The subjects were young male cannabis smokers who were studied in a closed hospital ward where they were allowed free access to cannabis for 47 to 59 days. There was a significant decrease in the function of large and medium-sized airways during the study and the degree of impairment was related to the number of cannabis cigarettes smoked, suggesting that the quantity of inhaled irritants was the important factor.

Tashkin and his colleagues (25) subsequently studied cannabis only smokers (MS, n = 144), cannabis and tobacco smokers (MTS, n = 135), tobacco only smokers (TS, n = 70), and non-smoking controls (NS, n = 97). These subjects were followed to study changes in lung function, signs and symptoms of respiratory disease, and histopathological changes that precede the development of cancer.

At baseline Tashkin et al (25) found more symptoms of bronchitis (such as cough, bronchitic sputum production, wheeze and shortness of breath) in all types of smokers (MS, MTS, TS) than non-smokers. Cannabis and tobacco smokers did not differ in the rates of these symptoms. Lung function tests showed poorer functioning and greater abnormalities in small airways among tobacco smokers whereas cannabis smokers had poorer large airways function than non-cannabis smokers.

Follow up studies of this cohort have shown different effects of cannabis and tobacco smoking on lung function (26). The first follow up study two to three years after the baseline study retested almost half of these subjects, most of whom were in the same smoking categories as at baseline. At both baseline and follow up, cough, sputum, and wheeze were more common in smokers than among nonsmokers. There was no significant change in the respiratory status of any of the smoking groups over time when those individuals who ceased smoking were excluded. The same was found when the subjects were followed up 3 to 4 years after first assessment. In addition, the group that smoked both cannabis and tobacco showed both types of damage found in those who only smoked cannabis or tobacco.

Tashkin and colleagues (27, 28) studied the histopathology of the lungs in a sample of their cohort. Fligiel et al (27) compared the bronchial morphology of 30 males who were heavy smokers of cannabis-only with those of 17 cannabis and tobacco smokers, 15 tobacco only smokers and 11 nonsmoking controls. All subjects who smoked had more severe abnormalities than nonsmokers. Many of these were more common in cannabis smokers, and they were most marked in men who smoked cannabis and tobacco. These abnormalities occurred at a younger age in cannabis than tobacco smokers, despite the fact that the cannabis smokers smoked less than a quarter as many 'joints' as the tobacco smokers smoked cigarettes.

Additional research (29, 30) suggests a number of reasons why cannabis smoking may be more toxic to the respiratory system than tobacco smoking. Laboratory studies show that cannabis smokers inhale a larger volume of smoke than tobacco smokers (40% to 54% more). They also inhaled more deeply and held their breath about four to five times longer than tobacco smokers. As a result, they retained more particulate matter, and absorbed three times more carbon monoxide, than tobacco smokers (29).

Other studies have replicated some of the findings of Tashkin and colleagues. Bloom et al (31) examined the relationship between smoking 'nontobacco' cigarettes and respiratory symptoms and respiratory function in the general population. Their sample comprised 990 individuals aged under 40 years who were followed up in a prospective community study of obstructive airways disease. The proportion who said that they had ever smoked a 'non-tobacco' cigarette was 14% (the same as the rate of cannabis smoking in general population surveys at the time), 9% were current and 5% ex-smokers of 'non-tobacco' cigarettes. On average non-tobacco cigarettes were smoked 7 times per week for 9 years. Non-tobacco smokers were more likely to have smoked tobacco and they inhaled more deeply than tobacco only smokers.

Non-tobacco smokers reported more cough, phlegm, and wheeze, regardless of whether they smoked tobacco or not. They also had poorer respiratory function. Those who had never smoked had the best functioning, followed in order of decreasing function by

current cigarette smokers, current non-tobacco smokers, and current smokers of tobacco and non-tobacco cigarettes. Non-tobacco smoking alone had a bigger effect on respiratory function than tobacco smoking alone, and the effects of both types of smoking on respiratory function was additive.

Sherril et al (32) have reported follow up data on respiratory symptoms and respiratory function in this sample. Rates of non-tobacco use declined over time, as did the quantity of cannabis that was smoked per week. At each follow-up non-tobacco smokers were twice as likely to report chronic cough, chronic phlegm and wheeze than non-smokers. The rate of reported symptoms increased with the number of non-tobacco cigarettes smoked per week and with the length of time that non-tobacco cigarettes were smoked. Non-tobacco smokers showed impairment on all indices of respiratory function.

Taylor et al (33) studied symptoms of respiratory disease and respiratory function in 1037 young New Zealand adults who were followed from birth until age 21. They compared symptoms of respiratory disease and respiratory function in those who were: cannabis dependent, cigarette smokers and non-smokers of tobacco and cannabis. Tobacco smokers had a higher rate of chronic bronchitis, wheeze and cough than non-tobacco smokers and the rate of these symptoms increased with the number of cigarettes smoked per day. Cannabis dependent subjects had higher rates of wheezing, shortness of breath, chest tightness and morning sputum production than non-smokers, after taking account of tobacco use. Among cannabis dependent subjects the effects in cannabis users were similar to those in tobacco smokers of 1–10 cigarettes/day. A higher proportion of cannabis dependent subjects had impaired respiratory function and the adverse effects of tobacco and cannabis smoking on respiratory function were additive.

7.2.2 Respiratory cancers

As discussed in detail in Chapter 5, there is evidence that cannabis *smoke* is mutagenic and carcinogenic and a potential cause of cancer in body cells that are regularly exposed to it, such as those of the aerodigestive and respiratory tracts. There are case reports of aerodigestive tract cancers among relatively young adults who have been daily cannabis users. A case control study has found an association between cannabis smoking and head and neck cancer (34). The only prospective cohort study to date has not found evidence of increased incidence of head and neck or respiratory cancers, although it found evidence of increased rates of prostate cancer. The relative youth of the participants and the low prevalence of regular cannabis use in the latter study reduced its ability to detect an increase in respiratory cancers. There is also evidence that the lungs of chronic cannabis smokers show changes in gene expression that appear to be precursors of cancer in tobacco smokers (35). Further follow ups of the Sidney et al cohort (36), and additional case control studies, are needed to clarify the issue (see Chapter 5).

7.3 Effects on the gastrointestinal system

Studies in experimental animals have not found any evidence that THC causes liver damage (37–39). Liver weight was reduced but this may have been caused by reduced food consumption because very high doses of THC were used. There is no human evidence that the chronic use of cannabis disturbs liver function (4).

Anecdotal evidence suggests that cannabis increases appetite ('the munchies' or 'hash hungries') (40–42). Cannabinoids reduce food and water intake in animals (4) but experimental studies in humans provide some support for the anecdotal reports (43–45). THC in the synthetic form of dronabinol (Marinol) has been shown to produce weight gain when used to treat nausea and vomiting caused by cancer chemotherapy. A similar weight gain was reported when used in patients with HIV infection. There are now objective data to support these anecdotal reports, and these suggest that THC has a potential therapeutic use as an appetite stimulant.

7.4 Summary

Smoking cannabis increases heart rate and affects blood pressure but there is no evidence that these effects have a permanently deleterious effect on the normal cardiovascular system. These effects are less benign in patients with hypertension, cerebrovascular disease and coronary atherosclerosis in whom THC may increase the work of the heart. The seriousness of these effects in persons with cardiovascular disease will be determined as persons who initiated cannabis use in the late 1960s enter the risk period for cardiovascular disease.

Cannabis smoking causes chronic bronchitis and impairs functioning of the large airways and produces pathological changes in lung tissues that may be precursors of lung cancer. Case studies and a case-control study suggest that cannabis may cause cancers of the aerodigestive tract. Additional studies of these cancers are a high priority.

There appears to be little or no human or animal evidence that cannabinoids affect liver function. The most interesting gastrointestinal effect of cannabis is its therapeutic use in reducing nausea and stimulating appetite in cancer and AIDS patients.

7.5 References

1. Beaconsfield, P., Ginsburg, J. & Rainsbury, R. (1972) Marihuana smoking: Cardiovascular effects in man and possible mechanisms, *New England Journal of Medicine*, 287, 209–212.
2. Johnson, S. & Domino, E. (1971) Some cardiovascular effects of marihuana smoking in normal volunteers, *Clinical Pharmacology and Therapeutics*, 12, 172–176.
3. Perez-Reyes, M. (1990) Marijuana smoking: Factors that influence the bioavailability of tetrahydrocannabinol, in: Chiang, N. & Hawks, R. (Eds.) *Research Findings on Smoking of Abused Substances. NIDA Monograph No. 99*, pp. 42–62 (Rockville, MD, National Institute on Drug Abuse).
4. Chesher, G. & Hall, W. (1999) Effects of cannabis on the cardiovascular and gastrointestinal systems, in: Kalant, H., Corrigall, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 435–458 (Toronto, Canada, Centre for Addiction and Mental Health).

5. Tennant, F. S., Jr. (1983) Clinical toxicology of cannabis use, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 69–90 (Toronto, Addiction Research Foundation).

6. Benowitz, N. & Jones, R. (1975) Cardiovascular effects of prolonged delta–9-tetrahydrocannabinol ingestion, *Clinical Pharmacology and Therapeutics*, 18, 287–297.

7. Benowitz, N., Rosenberg, J., Rogers, W., Bachman, J. & Jones, R. (1979) Cardiovascular effects of intravenous delta-9-tetrahydrocannabinol: Autonomic nervous mechanisms, *Clinical Pharmacology and Therapeutics*, 25, 440–446.

8. Hollister, L., Richards, R. & Gillespie, H. (1968) Comparison of tetrahydrocannabinol and synhexyl in man, *Clinical Pharmacology and Therapeutics*, 9, 783–791.

9. Weiss, J., Watanabe, A., Lemberger, L., Tamarkin, N. & Cardon, P. (1972) Cardiovascular effects of delta-9-tetrahydrocannabinol in man, *Clinical Pharmacology and Therapeutics*, 13, 671–684.

10. Carter, W., Coggins, W. & Doughty, P. (1980) Cannabis in Costa Rica: A study of chronic marihuana use (Philadelphia, Institute for the Study of Human Issues).

11. Stefanis, C., Dornbush, R. & Fink, M. (1977) *Hashish: Studies of Long-Term Use* (New York, Raven Press).

12. Rubin, V. & Comitas, L. (1975) *Ganja in Jamaica: A Medical Anthropological Study of Chronic Marihuana Use* (The Hague, Mouton).

13. Institute of Medicine (1982) *Marijuana and Health* (Washington, DC, National Academy Press).

14. Jones, R. (1984) Cardiovascular effects of cannabinoids, in: Harvey, D. J., Paton, W. & Nahas, G. (Eds.) *Marihuana '84: Proceedings of the Oxford Symposium on Cannabis*, pp. 325–334 (Oxford, IRL Press).

15. Aronow, W. & Cassidy, J. (1974) Effect of marihuana and placebo marihuana smoking on angina pectoris, *New England Journal of Medicine*, 291, 65–67.

16. Aronow, W. & Cassidy, J. (1975) Effect of smoking marihuana and of a high nicotine cigarette on angina pectoris, *Clinical Pharmacology and Therapeutics*, 17, 549–554.

17. Gottschalk, L., Aronow, W. & Prakash, R. (1977) Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological and cardiovascular functioning in angina patients, *Biological Psychiatry*, 12, 255–266.

18. Kandel, D. B. (1984) Marijuana users in young adulthood, *Archives of General Psychiatry*, 41, 200–209.

19. Bachman, J. G., Wadsworth, K. N., O'Malley, P., Johnston, L. & Schulenberg, J. (1997) *Smoking, drinking and drug use in young adulthood: The impacts of new freedoms and responsibilities* (Mahwah, NJ, Lawrence Erlbaum).

20. Mittleman, M. A., Lewis, R. A., Maclure, M., Sherwood, J. B. & Muller, J. E. (2001) Triggering myocardial infarction by marijuana, *Circulation*, 103, 2805–2809.

21. Institute of Medicine (1999) *Marijuana and Medicine: Assessing the Science Base* (Washington, DC, National Academy Press).

22. Tashkin, D. (1999) Effects of cannabis on the respiratory system, in: Kalant, H., Corrigall, W., Hall, W. & Smart, R. (Eds.) *The Health Effects of Cannabis*, pp. 311–346 (Toronto, Addiction Research Foundation).

23. Leuchtenberger, C. (1983) Effects of marihuana (cannabis) smoke on cellular biochemistry of *in vitro* test systems, in: Fehr, K. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 177–224 (Toronto, Addiction Research Foundation).

24. English, D., Holman, C., Milne, E., Winter, M., Hulse, G., Codde, S., Corti, B., Dawes, V., De Klerk, N., Knuiman, M., Kurinczuk, J., Lewin, G. & Ryan, G. (1995) *The quantification of drug caused morbidity and mortality in Australia, 1995* (Canberra, Commonwealth Department of Human Services and Health).

25. Tashkin, D. P., Coulson, A. H., Clark, V. A., Simmons, M., Bourque, L., Duann, S., Spivey, G. & Gong, H., Jr. (1987) Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers, *American Review of Respiratory Diseases*, 135, 209–216.

26. Tashkin, D., Fligiel, S., Wu, T., Gong, H., Barbers, R., Coulson, A., Simmons, M. & Beals, T. (1990) Effects of habitual use of marijuana and/or cocaine on the lung, in: Chang, C. & Hawks, R. (Eds.) *Research Findings on Smoking of Abused Substances. NIDA Monograph No. 99*, pp. 63–87 (Rockville, MD, National Institute on Drug Abuse).

27. Fligiel, S., Beals, T., Venkat, H., Stuth, S., Gong, H. & Tashkin, D. (1988) Pulmonary pathology in marijuana smokers, in: Chesher, G., Consroe, P. & Musty, R. (Eds.) *Marijuana: An International Research Report. NCADA Monograph No. 7*, pp. 43–48 (Canberra, Australian Government Publishing Service).

28. Gong, H., Fligiel, S., Tashkin, D. P. & Barbers, R. (1987) Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco, *American Review of Respiratory Disease*, 136, 142–149.

29. Wu, T., Tashkin, D., Djahed, B. & Rose, E. (1988) Pulmonary hazards of smoking marijuana as compared with tobacco, *New England Journal of Medicine*, 318, 347–351.

30. Tashkin, D. (1988) Summary of the session on pulmonary effects, in: Chesher, G., Consroe, P. & Musty, R. (Eds.) *Marijuana: An International Research Report. NCADA Monograph No. 7*, pp. 49–54 (Canberra, Australian Government Publishing Service).

31. Bloom, J., Kaltenborn, W., Paoletti, P., Camilli, A. & Lebowitz, M. (1987) Respiratory effects of non-tobacco cigarettes, *British Medical Journal*, 295, 1516–1518.

32. Sherrill, D. L., Krzyzanowski, J. W., Bloom, J. W. & Lebowitz, M. D. (1991) Respiratory effects of non-tobacco cigarettes: A longitudinal study in general population, *International Journal of Epidemiology*, 20, 132–137.

33. Taylor, D. R., Poulton, R., Moffitt, T., Ramankutty, P. & Sears, M. (2000) The respiratory effects of cannabis dependence in young adults, *Addiction*, 95, 1669–1677.

34. Zhang, Z.-F., Morgenstern, H., Spitz, M., Tashkin, D., Yu, G.-P., Marshall, J., Hsu, T. & Schantz, S. (1999) Marijuana use and increased risk of squamous cell carcinoma of the head and neck, *Cancer Epidemiology, Biomarkers and Prevention*, 8, 1071–1078.

35. Barsky, S. H., Roth, M. D., Kleerup, E. C., Simmons, M. & Tashkin, D. P. (1998) Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco, *Journal of the National Cancer Institute*, 90, 1198–1205.

36. Sidney, S., Quesenberry, C. P., Friedman, G. D. & Tekawa, I. S. (1997) Marijuana use and cancer incidence (California, United States), *Cancer Causes and Control*, 8, 722–728.

37. Ham, M. & DeJon, J. (1975) Effects of delta-9-tatrahydrocannabinol and cannabidiol on blood glucose concentrations in rabbits and rats, *Pharmaceutisch Weekblad*, 110, 1157–1161.

38. Lukas, M. & Temple, D. (1974) Some effects of chronic cannabis treatment, *Australian Journal of Pharmaceutical Sciences*, NA3, 20–22.

39. Sprague, R., Rosenkrantz, H. & Braude, M. (1973) Cannabinoid effects on liver glucogen stores, *Life Sciences*, 12, 409–416.

40. Tart, C. (1970) Marijuana intoxication: Common experiences, *Nature*, 226, 701–704.

41. Siler, J., Sheep, W. & Bates, L. (1933) Marijuana smoking in Panama, *Military Surgery*, 73, 269–280.

42. Snyder, S. (1970) *Use of Marijuana* (New York, Oxford University Press).

43. Abel, E. (1971) Changes in anxiety feelings following marihuana smoking, *British Journal of Addiction*, 66, 185–187.

44. Hollister, L. (1971) Hunger and appetite after single doses of marijuana, alcohol and dextroamphetamine, *Clinical Pharmacology and Therapeutics*, 12, 44–49.

45. Mendelson, J. & Mello, K. (1984) Effects of marijuana on neuroendocrine hormones in human males and females, in: Braude, M. & Ludford, J. (Eds.) *Marijuana Effects on the Endocrine and Reproductive Systems*, pp. 97–113 (Rockville, MD, National Institute on Drug Abuse).

8 Effects on motivation and the risk of dependence

8.1 Motivational effects

Chronic daily cannabis use has been reported to impair motivation in users in Egypt and the Caribbean (1). Young cannabis users in the USA in the early 1970s who were apathetic, withdrawn, lethargic and unmotivated (2, 3) were said to suffer from an 'amotivational syndrome' (3, 4). It is difficult in these cases to disentangle the effects of chronic cannabis use from those of poverty, poor education and pre-existing psychiatric disorders (5–7).

The effects of cannabis use on motivation were assessed in a number of field studies of chronic cannabis users in Costa Rica (8), Jamaica (9) and the USA (10). Rubin and Comitas (9), for example, found that Jamaican farmers who regularly smoked cannabis worked harder but less efficiently after using cannabis. A study of Costa Rican cannabis smokers produced mixed evidence on the effect of chronic cannabis use on job performance. Carter et al (8) compared 41 heavy cannabis users (10 cannabis cigarettes per day for ten or more years) with 41 nonusers of cannabis matched on age, marital status, education, occupation, and alcohol and tobacco use. The nonusers were more likely: to have a stable employment history, to have been promoted and given pay rises, and to be in full-time employment. Users spent more of their incomes on cannabis and were more likely to be in debt. Among users, however, those who had steady jobs or who were self-employed smoked twice as many cannabis cigarettes per day as those with more frequent job changes, or those who were chronically unemployed.

A follow up study of long-term cannabis users in the USA suggests that the amotivational syndrome is rare among long-term cannabis users. Halikas et al (10) assessed symptoms of the amotivational syndrome in 100 regular cannabis users six to eight years after they were first studied. Only three individuals had ever experienced amotivational symptoms in the absence of depression and their use did not differ from that of other cannabis users.

Laboratory studies of long-term heavy cannabis use have also failed to clearly show that cannabis impairs motivation (5). Early studies conducted by the LaGuardia Commission (11) reported deterioration in behaviour among prisoners given daily doses of cannabis over a period of some weeks but these reports were based upon uncontrolled observation. A study using standardised measures of performance failed to observe such effects (11). In this study 10 casual and 10 heavy cannabis smokers were observed in a laboratory over a 31-day study period. For 21 of these days subjects were given access to as many cannabis cigarettes as they earned by performing a simple task. All subjects earned the maximum number of points allowed per day throughout the study and their output was not affected by cannabis use. Providing similar access to alcohol in heavy drinking subjects in the same setting profoundly disrupted performance. Similar results were reported in a study by Campbell (12) in which young cannabis users were given

high doses of cannabis. They showed no gross behavioural changes, no social deterioration, and no alterations in intellectual functioning but their productivity was reduced when they were given 30 mg of THC per day, a dose that many subjects found unpleasant.

Schwenk (13) has recently reviewed evidence on the relationship between cannabis use and job performance in laboratory studies, surveys, observational studies, anthropological studies and studies of drug testing. He concluded that the associations between cannabis use and poor job performance in laboratory studies and surveys were small. Schwenk argued that these results were more consistent with the hypothesis that there was a relationship between the characteristics of cannabis users and poor job performance rather than with the hypothesis that cannabis use was a cause of poor job performance.

The amotivational syndrome remains contentious because of differences of opinion about the value of clinical observations and controlled studies. Those who accept the existence of the syndrome appeal to the small number of cases fitting the description of an 'amotivational syndrome' (14). Sceptics are more impressed by the unsupportive field and laboratory studies. If there is an amotivational syndrome, it is a relatively uncommon consequence of prolonged heavy cannabis use. Research suggests that the features of the 'amotivational syndrome' can be better explained as symptoms of chronic cannabis intoxication in cannabis dependent users, thereby obviating the need to invent a new psychiatric syndrome (5).

8.2 Is there a cannabis dependence syndrome?

For much of the 1960s and 1970s cannabis was not regarded as a drug of dependence because it did not seem to produce tolerance or a withdrawal syndrome like that seen in alcohol and opioid dependence. Views changed in the late 1970s and early 1980s with the adoption of a broader conception of drug dependence (15). This new conception reduced the emphasis on tolerance and withdrawal and placed more emphasis on the compulsion to use, a narrowing of the drug using repertoire, rapid reinstatement of dependence after abstinence, and the high salience of drug use in the user's life. It was reflected in the Third and Fourth Revised Editions of the Diagnostic and Statistical Manual (DSM-III-R and DSM-IV) of the American Psychiatric Association (16, 17).

8.2.1 Drug dependence in DSM-IV

'The essential feature of Substance Dependence is a cluster of cognitive, behavioral and physiologic symptoms indicating that the individual continues use of the substance despite significant substance-related problems' (p.176) (16). A diagnosis of Substance Dependence is made if *three or more* of the following criteria occur at any time in the same 12-month period:

'1. tolerance, as defined by either of the following:

   a. need for markedly increased amounts of the substance to achieve intoxication or desired effect

   b. markedly diminished effect with continued use of the same amount of the substance

2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance
   b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended;
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors, driving long distances), use the substance (e.g. chain smoking), or recover from its effects;
6. important social, occupational, or recreational activities are given up or reduced because of substance use;
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.' (16).

8.2.1 Cannabis tolerance and withdrawal: experimental evidence

Cannabis users can develop tolerance to the effects of THC and they can experience withdrawal symptoms under certain conditions. Tolerance to many of the behavioural and physiological effects of THC has been demonstrated in humans and animals (18–23). The precise mechanisms are unknown but they probably involve changes in cannabinoid receptor function (20, 24).

Jones and Benowitz (25) studied the effects of 210 mg dose of oral THC per day given in a fixed dosing schedule to healthy male volunteers with extensive histories of cannabis use. Over the 30-day study, the positive effects of intoxication declined and there was a recovery in social, cognitive and psychomotor performance. Georgotas and Zeidenberg (19) also reported tolerance to the subjective effects of cannabis in humans.

Early case reports of cannabis withdrawal symptoms in humans have been supported by abstinence symptoms in laboratory studies (18, 21, 26). Studies in clinical and non-clinical samples of long-term cannabis users have reported withdrawal symptoms, such as anxiety, insomnia, appetite disturbance and depression (27–30).

Jones and Benowitz (25) abruptly withdrew regular cannabis users after two weeks on high doses of oral THC. Within six hours, they complained of 'inner unrest' and after 12 hours they reported 'irritability, insomnia, and restlessness' that were also observed by staff. These symptoms were correlated with THC dose and frequency of use, and were reduced after using cannabis (22). Georgotas and Zeidenberg (19) reported similar symptoms during the first week of abstinence in subjects who had received 210 mg of smoked cannabis a day for four weeks. Recent laboratory studies by Haney et al (31, 32) have reported withdrawal symptoms at much lower doses of THC given orally and by smoking. The most common symptoms were anxiety, depression and irritability.

Kouri and Pope (33) reported a controlled prospective study of withdrawal symptoms among chronic cannabis users who were assessed daily on various withdrawal symptoms while in a hospital ward for 28 days. Their ratings of mood, anxiety, depression and irritability were compared to those of two control groups of abstinent former heavy cannabis users and non-users of cannabis. During the course of the 28 days the chronic cannabis users showed decreases in mood and appetite and increases in irritability, anxiety, physical tension, and physical symptoms, and their scores on the Hamilton Depression and Anxiety scales increased. These appeared within 24 hours and were most marked in the first 10 days although the increase in irritability and physical tension persisted throughout the 28-day observation period.

Research using the cannabinoid antagonist SR 141716A (which immediately reverses the effects of THC) has shown that a withdrawal syndrome can be produced in rats, mice and dogs that have been maintained on THC (34, 35). The antagonist produces compressed and accentuated symptoms that are much more dramatic than the milder and more prolonged symptoms that occur under usual conditions of human use (36). The relatively long half-life and complex metabolism of cannabis may also result in a less intense withdrawal syndrome than drugs such as opiates (24).

8.2.2 Epidemiological studies of cannabis dependence

The Epidemiological Catchment Area (ECA) study estimated the rates of cannabis abuse and dependence in US population in the early 1980s (37). It found that 4.4% of the US population had a diagnosis of cannabis abuse or dependence according to DSM-III criteria. A third of those with lifetime cannabis abuse or dependence (38%) reported problems with cannabis use in the last year. Men had a higher risk of cannabis dependence than women, with the highest risk among 18 to 29 year olds. (38).

The most common symptoms reported by those who were cannabis dependent were: requiring larger amounts (21%), having psychological (21%) or social (17%) problems attributed to cannabis, and inability to reduce use (8%). Few reported health problems (5%) or withdrawal sickness (3%) (39). Surveys using similar methods to the ECA have produced similar estimates of the rate of cannabis dependence in Canada and New Zealand (40–42).

The National Comorbidity Survey (NCS) conducted in the USA between 1990 and 1992 (43) found that 4.2% of adults met DSM-III-R criteria for cannabis dependence at some time in their lives. The proportion of people who had ever used cannabis who met criteria for cannabis dependence was 9%. This compared to 32% of nicotine, 23% of heroin, 17% of cocaine, 15% of alcohol and 11% of stimulant users who met criteria for dependence.

The Australian National Survey of Mental Health and Well-being (44) found that 1.7% of Australian adults met the International Classification of Diseases (ICD-10) (45) criteria for a diagnosis of cannabis dependence, and 0.1% met criteria for harmful use in the previous year. One in four (23%) of those who had used cannabis more than five times in the last year met criteria for cannabis dependence or harmful use.

8.2.3 Studies of long-term cannabis users

Studies of long-term cannabis users in Egypt (46), India (47), Germany (2), Greece (48), Costa Rica (8) and Jamaica (9) did not study symptoms of dependence other than withdrawal, which then defined dependence. Stereotyped use patterns, persistent desire to quit, tolerance, chronic intoxication, mild withdrawal and continued use despite problems were reported in the Egyptian, Indian and Jamaican studies but there were no withdrawal symptoms reported in the Costa Rican, Jamaican or Greek studies.

Kandel and Davies (49) described problems reported by a subset of daily cannabis users (aged 28–29 years) who were recruited in a large prospective study of 1,222 adolescents. The major adverse consequences of cannabis use reported were: cognitive deficits, reduced energy, depression, and, among males, problems with their spouse.

Recent Australian surveys of long-term cannabis users diagnosed a substantial proportion as cannabis dependent. Among 243 rural cannabis users, who had used cannabis several times a week for 19 years, 57% qualified for lifetime DSM-III-R and ICD-10 cannabis dependence diagnoses (30). The most common symptoms reported were: frequent intoxication during daily activities (73%) and a strong urge to use cannabis (75%). Few reported withdrawal symptoms (5%) or using cannabis to relieve withdrawal symptoms (20%), although 54% reported tolerance. Only 26% believed they had a problem with cannabis and only 9% had sought help to cut down or stop.

Among 200 young Sydney adults who had used cannabis at least weekly for 11 years, 92% met criteria for a DSM-III-R lifetime diagnosis of dependence and 40% were classified as severely dependent (29). Tolerance and withdrawal were reported by 78% and 76% respectively and use to relieve withdrawal symptoms by 39%. Most met criteria for cannabis dependence in the past year according to DSM-III-R (77%) and ICD-10 (72%) criteria. A follow-up of these users found that cannabis use and dependence symptoms were stable over a year (50). The majority (81%) of the follow-up sample met criteria for a dependence diagnosis during the last year on three measures of dependence.

8.2.4 Clinical populations

Cannabis dependent persons seek help with cannabis-related problems in Australia, the United States and Europe. The National Census of Clients of Australian Treatment Service Agencies (51, 52) found that the proportion of cases in whom cannabis was the *main* drug problem increased from 4% in 1990 to 7% in 1995. Between 1994 and 1998 cannabis was the primary drug of abuse for between 11% and 26% of clients of treatment agencies in the United States (53, 54). Cannabis was the primary drug problem for between 2% and 16% of clients attending treatment agencies in the European Union in 1998 (55).

A Swedish treatment program (56) reported that its clients typically complained of: unsuccessful attempts to stop or moderate use and frequent (often daily) intoxication, despite suffering adverse effects connected with their cannabis use. These included sleeplessness, depression, impaired concentration and memory, and blunting of emotions.

Stephens and colleagues (57) described the symptoms reported by 382 persons who sought help to cease cannabis use. These included: an inability to stop using (93%), feeling bad about using cannabis (87%), procrastinating (86%), loss of self-confidence (76%), memory loss (67%) and withdrawal symptoms (51%). Similar experiences have been reported among users in recent US (28, 58) and Australian studies of interventions for problem cannabis use (27). In the Australian study, among 180 long-term cannabis users seeking help, the most common symptoms were withdrawal and use to relieve withdrawal.

8.2.5 The risk of cannabis dependence

People who use cannabis daily over weeks to months are most likely to become dependent. Kandel and Davis (49) estimated that one in three daily cannabis users met DSM-III criteria for dependence. The risk of dependence among less frequent users of cannabis is lower (59). In the ECA study, 17% of those who used cannabis more than 5 times met DSM-III criteria for dependence at sometime in their lives (38). In the National Comorbidity Study (NCS), Anthony et al (43) estimated that the proportion of persons who had ever used alcohol, amphetamines, cannabis, cocaine, heroin, nicotine and sedatives who met DSM-III-R criteria for dependence on each drug at some time in their lives were: 32% for nicotine, 23% for heroin, 15% for alcohol and cocaine and 9% for cannabis.

These estimates suggest the following rules of thumb about the risks of cannabis dependence. For those who have ever used cannabis the risks of developing dependence is probably of the order of one chance in ten. Among those who use the drug more than a few times the risk of developing dependence is in the range of from one in five to one in three. As a rule, the more often cannabis has been used, and the longer it has been used, the higher the risk of dependence.

The following factors also predict a higher risk of regular involvement with cannabis: poor academic achievement, deviant behaviour in childhood and adolescence, nonconfornity and rebelliousness, personal distress and maladjustment, poor parental relationships, earlier use, and a parental history of drug and alcohol problems (49, 60–62).

8.2.6 The consequences of cannabis dependence

The large gap between the ECA estimates of cannabis abuse and dependence in the community and the number of cannabis users who seek treatment suggests that many of these cases remit without treatment, as is true of alcohol abuse and dependence (63). Kandel and Davies (49) found that by age 28 to 29, less than 15% of daily cannabis users were still using daily, and Bachman et al have found that most regular cannabis users discontinued their use during the mid to late twenties (64).

Among the minority of regular cannabis users who are sufficiently troubled to seek help the major complaints are: a loss of control over their cannabis use, cognitive and motivational impairments which may interfere with work performance, lowered self-esteem and depression, and complaints by spouses and partners about their frequent

intoxication (see above). There is no doubt that some dependent cannabis users report impaired performance and a reduced quality of everyday life but more research is necessary to decide how common this is, and how impaired cannabis dependent persons are.

8.2.7 The treatment of cannabis dependence

Little research has been done on the sort of assistance that should be given to cannabis users who seek help to stop using cannabis (65). Although many users may succeed in quitting without professional help we need to assist those who are unable to stop on their own. It is not clear what type of treatment should be provided for dependent cannabis users who have repeatedly failed to stop using cannabis and seek help.

Roffman et al (66) reported one of the few randomised controlled trials comparing group based relapse prevention and social support. Subjects were 120 men and women (aged 32 with 16 years of cannabis use) who answered advertisements for help to stop using cannabis. One-month after treatment only 30% of their patients were still abstinent and by the end of a year only 17% were abstinent.

Stephens et al (67) recently reported another study of behavioural treatment for cannabis dependence in 291 subjects. Subjects were randomly assigned to one of three treatments: (1) a 14 session group based relapse prevention intervention (RPSG) similar to their earlier study but with more sessions; (2) an individualised advice (IAI) two session intervention using principles of motivational interviewing adapted from Miller's Drinker's Check-up; and (3) a delayed treatment condition (DTC) in which participants did not receive any treatment for four months.

At the four month follow up all three groups had reduced their cannabis use but the two treatment groups showed the largest reduction and did not differ from each another. In the treatment groups 37% were abstinent compared with only 9% in the delayed treatment group. The amount of cannabis use also declined by 70% in the treatment groups and by 30% in the delayed treatment groups. Abstinence rates declined over time but the two treatments did not differ at 7, 13 and 16 months after treatment. Twenty-two percent of participants were abstinent throughout the 16 month study and their abstinence was corroborated by partners and family members.

Budney, Higgins, Radinovich and Novy (68) reported a controlled comparison of three treatments for 60 cannabis dependent patients. They compared three treatments: motivational enhancement to quit (M), motivational enhancement plus behavioural coping skills (MBT), and MBT plus incentives to remain abstinent (MBTV). In the latter, vouchers for retail items were exchanged for urine samples that were negative for cannabinoids. The MBTV group had a longer period of continuous abstinence than the other two groups which did not differ from each other. By 14 weeks post-treatment fewer than 10% of participants had been continuously abstinent from cannabis.

Copeland, Swift, Roffman and Stephens (69) replicated the study by Stephens et al (67) in an Australian sample. They randomly assigned 229 cannabis dependent adults to three treatments: a six session cognitive behavioural intervention; a single session cognitive

behavioural treatment, and a delayed treatment control group who were offered treatment four months after the other two groups. Only 6.5% of all subjects (n = 11) were continuously abstinent during the 8-month follow up period and all of these were in the treatment groups. There were greater reductions in cannabis related problems and in dependence symptoms in the two treatment groups.

So far rates of continuous abstinence from cannabis have been low in the treatments tested, although there have been substantial reductions in rates of use and problems related to use. Nonetheless, much more research is needed before sensible advice can be given about the best ways to achieve abstinence from cannabis. In the absence of better evidence of treatment effectiveness, people offering treatment for cannabis dependence should avoid replicating experience in the treatment of alcohol dependence where inpatient treatment has been widely adopted in the absence of any evidence that it is more effective than outpatient forms of treatment (70, 71).

8.3 Summary

There is no compelling evidence for an amotivational syndrome among chronic cannabis users. Some heavy users do complain of impaired motivation but this pattern of behaviour is better explained as a symptom of chronic intoxication among persons who are cannabis dependent.

There is good evidence that a cannabis dependence syndrome can develop in some chronic cannabis users. These users develop tolerance, experience withdrawal symptoms on cessation of use, have problems controlling their cannabis use, and continue to use despite the experience of adverse personal consequences of use. Cannabis dependence is the most common form of drug dependence after alcohol and tobacco in the USA and Australia. The risk of developing dependence is about:: one in ten among those who ever use the drug; between one in five and one in three among those who use cannabis more than a few times; and around one in two among those who become daily users. Few cannabis dependent persons seek treatment, probably because many disorders remit without treatment. It is not clear as yet what advice should be given to the minority of dependent cannabis users who seek help to stop their use.

8.4 References

1. Brill, H. & Nahas, G. (1984) Cannabis intoxication and mental illness, in: Nahas, G. (Ed.) *Marihuana in Science and Medicine*, pp. 263–305 (New York, Raven Press).
2. Tennant, F. & Groesbeck, C. (1972) Psychiatric effects of hashish, *Archives of General Psychiatry*, 33, 383–386.
3. McGlothlin, W. & West, L. (1968) The marijuana problem: An overview, *American Journal of Psychiatry*, 125, 370–378.
4. Smith, D. E. (1968) Acute and chronic toxicity of marijuana, *Journal of Psychedelic Drugs*, 2, 37–47.

5. Edwards, G. (1976) Cannabis and the psychiatric position, in: Graham, J. (Ed.) *Cannabis and Health*, pp. 321–342 (London, Academic Press).

National Academy of Science (1982) *Marijuana and Health* (Washington, DC, National Academy Press).

7. Negrete, J. (1983) Psychiatric aspects of cannabis use, in: Fehr, O. & Kalant, H. (Eds.) *Cannabis and Health Hazards*, pp. 577–616 (Toronto, Addiction Research Foundation).

8. Carter, W., Coggins, W. & Doughty, P. (1980) *Cannabis in Costa Rica: A study of chronic marihuana use* (Philadelphia, Institute for the Study of Human Issues).

9. Rubin, V. & Comitas, L. (1975) *Ganja in Jamaica: A Medical Anthropological Study of Chronic Marihuana Use* (The Hague, Mouton).

10. Halikas, J., Weller, R., Morse, C. & Shapiro, T. (1982) Incidence and characteristics of motivational syndrome, including associated findings, among chronic marjiuana users, in: National Institute on Drug Abuse (Ed.) *Marijuana and Youth: Clinical Observations on Motivation and Learning*, pp. 11–26 (Rockville, MD, National Institute on Drug Abuse).

11. Mendelson, J., Rossi, A. & Meyer, R. (1974) *The Use of Marihuana: A Psychological and Physiological Inquiry* (New York, Plenum Press).

12. Campbell, I. (1976) The amotivational syndrome and cannabis use with emphasis on the Canadian scene, *Annals of the New York Academy of Sciences*, 282, 33–36.

13. Schwenk, C. R. (1998) Marijuana and job performance: Comparing the major streams of research, *Journal of Drug Issues*, 28, 941–970.

14. Cohen, S. (1986) Marijuana research: Selected recent findings, *Drug Abuse and Alcoholism Newsletter*, 15, 1–3.

15. Edwards, G., Arif, A. & Hodgson, R. (1981) Nomenclature and classification of drug and alcohol related problems: A WHO memorandum, *Bulletin of the World Health Organization*, 59, 225–242.

16. American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* (Washington, DC, American Psychiatric Association)

17. American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders, Third Edition- revised* (Washington, DC, American Psychiatric Association).

18. Jones, R. (1983) Cannabis tolerance and dependence, in: Fehr, O. & Kalant, H. (Eds.) *Cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use*, pp. 617–689 (Toronto, Addiction Research Foundation).

19. Georgotas, A. & Zeidenberg, P. (1979) Observations on the effects of four weeks of heavy marijuana smoking on group interaction and individual behavior, *Comprehensive Psychiatry*, 20, 427–432.

20. Adams, I. & Martin, B. (1996) Cannabis: Pharmacology and toxicology in animals and humans, *Addiction*, 91, 1585–1614.

21. Compton, D., Dewey, W. & Martin, B. (1990) Cannabis dependence and tolerance production, *Advances in Alcohol and Substance Abuse*, 9, 128–147.

22. Jones, R., Benowitz, N. & Herning, R. (1981) The clinical relevance of cannabis tolerance and dependence, *Journal of Clinical Pharmacology*, 21, 143S–152S.

23 Hollister, L. (1986) Health aspects of cannabis, *Pharmacological Reviews*, 38, 1–20.

24. Childers, S. & Breivogel, C. (1998) Cannabis and endogenous cannabinoid systems, *Drug and Alcohol Dependence*, 51, 173–187.

25. Jones, R. & Benowitz, N. (1976) The 30-day trip—Clinical studies of cannabis tolerance and dependence, in: Braude, M. & Szara, S. (Eds.) *Pharmacology of Marijuana, Volume 2*, pp. 627–642 (New York, Academic Press).

26. Wikler, A. (1976) Aspects of tolerance to and dependence on cannabis, *Annals of the New York Academy of Sciences*, 282.

27. Rees, V., Copeland, J. & Swift, W. (1998) Brief cognitive behavioural interventions for cannabis dependence, in: Dillon, P., Topp, L. & Swift, W. (Eds.) *Illicit Drugs: Current issues and responses. Proceedings from the Eleventh National Drug and Alcohol Research Centre Annual Symposium. Monograph No. 37*, pp. 111–124 (Sydney, National Drug and Alcohol Research Centre, UNSW).

28. Stephens, R., Roffman, R. & Simpson, E. (1994) Treating adult marijuana dependence: A test of the relapse prevention model, *Journal of Consulting and Clinical Psychology*, 62, 92–99.

29. Swift, W., Hall, W. & Copeland, J. (1998) Characteristics of long-term cannabis users in Sydney, Australia, *European Addiction Research*, 4, 190–197.

30. Swift, W., Hall, W., Didcott, P. & Reilly, D. (1998) Patterns and correlates of cannabis dependence among long-term users in an Australian rural area, *Addiction*, 93, 1149–1160.

31. Haney, M., Ward, A. S., Comer, S. D., Foltin, R. W. & Fischman, M. W. (1999) Abstinence symptoms following oral THC administration to humans, *Psychopharmacology*, 141, 385–94.

32. Haney, M., Ward, A. S., Comer, S. D., Foltin, R. W. & Fischman, M. W. (1999) Abstinence symptoms following smoked marijuana in humans, *Psychopharmacology*, 141, 395–404.

33. Kouri, E. M. & Pope, H. G. (2000) Abstinence symptoms during withdrawal from chronic marijuana use, *Experimental and Clinical Psychopharmacology*, 8, 483–492.

34. Aceto, M., Scates, S., Lowe, A. & Martin, B. (1996) Dependence studies on delta-9-tetrahydrocannabinol: Studies on precipitated and abrupt withdrawal, *Journal of Pharmacology and Experimental Therapeutics*, 278, 1290–1295.

35. Cook, S., Lowe, J. & Martin, B. (1998) CB1 receptor antagonist precipitates withdrawal in mice exposed to delta-9-tetrahydrocannabinol, *Journal of Pharmacology and Experimental Therapeutics*, 285, 1150–1156.

36. Swan, N. (1995) Marijuana antagonist reveals evidence of THC dependence in rats. *NIDA Notes*, 10, 1–6.

37. Robins, L. N. & Regier, D. A. (1991) *Psychiatric disorders in America: The Epidemiological Catchment Area study* (New York, The Free Press).

38. Anthony, J. & Helzer, J. (1991) Syndromes of drug abuse and dependence, in: Robins, L. & Regier, D. (Eds.) *Psychiatric Disorders in America* pp. 116–154 (New York, Macmillan Free Press).

39. Anthony, J. & Trinkoff, A. (1989) United States epidemiological data on drug use and abuse: How are they relevant to testing abuse liability on drugs?, in: Fischman, M. & Mello, N. (Eds.) *Testing for abuse liability of drugs in humans. Research Monograph No. 92*, pp. 241–266 (Rockville, MD, National Institute on Drug Abuse).

40. Wells, J., Bushnell, J., Joyce, P., Oakley-Browne, M. & Hornblow, A. (1992) Problems with alcohol, drugs and gambling in Christchurch, New Zealand, in: Abbot, M. & Evans, K. (Eds.) *Alcohol and drug dependence and disorders of impulse control*, pp. 3–13 (Auckland, NZ, Alcohol Liquor Advisory Council).

41. Russell, J., Newman, S. & Bland, R. (1994) Drug abuse and dependence, *Acta Psychiatric Scandinavica*, Supplement 376, 54–62.

42. Hwu, H.-G. & Compton, W. (1994) Comparison of major epidemiological surveys using the Diagnostic Interview Schedule, *International Review of Psychiatry*, 6, 309–327.

43. Anthony, J. C., Warner, L. & Kessler, R. (1994) Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology*, 2, 244–268.

44. Hall, W., Teesson, M., Lynskey, M. & Degenhardt, L. (1999) The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: Findings from the National Survey of Mental Health and Well-Being, *Addiction*, 94, 1541–1550.

45. World Health Organisation (1993) *The ICD-10 Classification of Mental and Behavioural Disorders—Diagnostic Criteria for Research* (Geneva, World Health Organization).

46. Soueif, M. (1967) Hashish consumption in Egypt, with special reference to psychosocial aspects, *Bulletin on Narcotics*, 19, 1–11.

47. Chopra, G. & Jandu, B. (1976) Psychoclinical effects of long-term marijuana use in 275 Indian chronic users. A comparative assessment of effects in Indian and USA users, *Annals of the New York Academy of Sciences*, 282, 95–108.

48. Stefanis, C., Dornbush, R. & Fink, M. (1977) *Hashish: Studies of Long-Term Use* (New York, Raven Press).

49. Kandel, D. & Davies, M. (1992) Progression to regular marijuana involvement: Phenomenology and risk factors for near daily use, in: Glantz, M. & Pickens, R. (Eds.) *Vulnerability to Drug Abuse*, pp. 211–253 (Washington, DC, American Psychological Association).

50. Swift, W., Hall, W. & Copeland, J. (2000) One year follow-up of cannabis dependence among long-term users in Sydney, Australia, *Drug and Alcohol Dependence*, 59, 309–318.

51. Torres, M., Mattick, R., Chen, R. & Baillie, A. (1995) *Clients of treatment service agencies: March 1995 Census findings* (Canberra, Commonwealth Department of Human Services and Health).

52. Webster, P., Mattick, R. & Baillie, A. (1992) Characteristics of clients receiving treatment in Australian drug and alcohol agencies: A national census, *Drug and Alcohol Review*, 11, 111–119.

53. United States Office of National Drug Control Policy (1994) Pulse Check: national trends in drug abuse. December 1994 (Washington, DC, Office of National Drug Control Policy).

54. United States Office of National Drug Control Policy (1998) Pulse Check: national trends in drug abuse. Winter 1998 (Washington, DC, Office of National Drug Control Policy).

55. European Monitoring Centre for Drugs and Drug Addiction (1998) Annual Report on the State of the Drugs Problem in the European Union, 1998 (Lisbon, EMCDDA).

56. Tunving, K., Lundquist, T. & Erikkson, D. (1988) 'A way out of the fog': An outpatient program for cannabis users, in: Chesher, G., Consroe, P. & Musty, R. (Eds.) *Marijuana: An International Research Report*, pp. 207–212 (Canberra, Australian Government Publishing Service).

57. Stephens, R., Roffman, R. & Simpson, E. (1993) Adult marijuana users seeking treatment, *Journal of Consulting and Clinical Psychology*, 61, 1100–1104.

58. Budney, A. J., Radonovich, K. J., Higgins, S. T. & Wong, C. J. (1998) Adults seeking treatment for marijuana dependence: A comparison with cocaine-dependent treatment seekers, *Experimental & Clinical Psychopharmacology*, 6, 419–426.

59. Hall, W., Solowij, N. & Lemon, J. (1994) The health and psychological consequences of cannabis use (Canberra, Australian Government Publishing Service).

60. Brook, J., Cohen, P., Whiteman, M. & Gordon, A. (1992) Psychosocial risk factors in the transition from moderate to heavy use or abuse of drugs, in: Glantz, M. & Pickens, R. (Eds.) *Vulnerability to Drug Abuse*, pp. 359–388 (Washington, American Psychological Association).

61. Newcomb, M. (1992) Understanding the multidimensional nature of drug use and abuse: The role of consumption, risk factors and protective factors, in: Glantz, M. & Pickens, R. (Eds.) *Vulnerability to Drug Abuse*, pp. 255–296 (Washington, American Psychological Association).

62. Shedler, J. & Block, J. (1990) Adolescent drug use and psychological health: A longitudinal inquiry, *American Psychologist*, 45, 612–630.

63. Helzer, J., Burnham, A. & McEvoy, L. (1991) Alcohol abuse and dependence, in: Robins, L. & Regier, D. (Eds.) *Psychiatric Disorders in America*, pp. 81–115 (New York, Free Press, Macmillan).

64. Bachman, J. G., Wadsworth, K. N., O'Malley, P., Johnston, L. & Schulenberg, J. (1997) *Smoking, drinking and drug use in young adulthood: The impacts of new freedoms and responsibilities* (Mahwah, NJ, Lawrence Erlbaum).

65. Kleber, H. (1989) Treatment of drug dependence: What works?, *International Review of Psychiatry*, 1, 81–100.

66. Roffman, R. A., Stephens, R. S., Simpson, E. E. & Whitaker, D. L. (1988) Treatment of marijuana dependence: Preliminary results, *Journal of Psychoactive Drugs*, 20, 129–137.

67. Stephens, R., Roffman, R. & Curtin, L. (2000) Comparison of extended versus brief interventions for marjiuana, *Journal of Consulting and Clinical Psychology*, 68, 898–908.

68. Budney, A. J., Higgins, S. T., Radinovich, K. J. & Novy, P. L. (2000) Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence, *Journal of Consulting and Clinical Psychology*, 68, 1051–1061.

69. Copeland, J., Swift, W., Roffman, R. & Stephens, R. (in press) A randomised controlled trial of brief interventions for cannabis use disorder, *Journal of Substance Abuse Treatment*.

70. Miller, W. & Hester, R. (1986) The effectiveness of alcoholism treatment: What research reveals, in: Miller, W. & Heather, N. (Eds.) *Treating Addictive Behaviors: Processes of Change*, pp. 121–174 (New York, Plenum Press).

71. Heather, N. & Tebbutt, J. (1989) *An Overview of the Effectiveness of Treatment for Drug and Alcohol Problems. NCADA Monograph Series No. 11* (Canberra, Australian Government Publishing Service).

9 The effects of cannabis use on cognitive functioning

Cannabis acutely impairs cognitive performance, so there is an understandable concern that its chronic use may cause longer lasting impairment of cognitive functioning. This possibility seemed to be supported by clinical observers in the USA during the early 1970s (e.g. Kolansky and Moore, (1, 2)) who reported that young adults who had used cannabis weekly or more often had 'poor attention span, poor concentration, confusion' (2). More recently, some long-term cannabis users seeking help to stop using cannabis have complained that their memory and thinking is impaired (3). The difficulty with these reports has been in ruling out alternative explanations, namely, that cognitive impairment preceded cannabis use or was the result of other drug use.

9.1 Cross-cultural studies

One research strategy has been to examine cognitive performance in heavy cannabis users in cultures with a tradition of heavy use. An early report by Soueif (4) illustrates the problems with this strategy. Soueif studied Egyptian male prisoners of whom 850 were hashish smokers and 839 controls. The hashish users performed more poorly than the controls on ten of sixteen measures of perceptual speed and accuracy, distance and time estimation, immediate memory, reaction time and visual-motor abilities (4–7). The findings were weakened because the two groups also differed in ways that may have affected cognitive performance, namely, the hashish users were less well educated and more likely to use opiates and alcohol (8).

In the late 1960s the National Institute on Drug Abuse (NIDA) commissioned three cross-cultural studies in Jamaica, Greece and Costa Rica to assess the effects of chronic cannabis use on cognitive functioning (among other things). It was assumed that any cognitive effects of chronic daily cannabis use should be apparent in users with a long-history of heavy cannabis use, a pattern of use that was common in these cultures.

Bowman and Pihl (9) reported two field studies of cannabis users in Jamaica who had been daily cannabis users for a minimum of 10 years (23 joints per day) while controls had no experience with cannabis. No differences were found between the users and nonusers in either study or when rural and urban samples were combined. Rubin and Comitas (10) reported similar findings in a study of 30 Jamaican cannabis users who had used for 17.5 years and 30 nonusers.

The Greek study (11, 12) compared 47 daily hashish users (who used for 23 years) with 40 controls matched for age, sex, education, demographic region, socioeconomic status and alcohol consumption. The groups did not differ in total IQ score on either the WAIS or Raven's Progressive Matrices but the controls obtained a higher verbal IQ score than hashish users and the users performed worse than controls on all but one of the subtests of the WAIS (13). Since subjects did not abstain from hashish before testing, it was not clear whether these differences were due to long-term hashish use, or the acute effects of the drug at the time of testing.

In the Costa Rican study (14), researchers compared 41 males who had used 10 cannabis joints per day for 17 years with matched controls on a test battery that assessed neuropsychological, intellectual and personality variables. The Costa Rican users did not differ significantly from controls on any test. Page, Fletcher and True (15) followed up this sample after 10 years, by which time they had used cannabis for around 30 years. No differences were detected on any of the original tests but there were significant differences on three new tests of sustained attention and short-term memory. They emphasised that these differences were 'quite subtle' and 'subclinical', with only a small number of subjects clinically impaired. It was also difficult to exclude the possibility that the differences were due to recent cannabis use, since 24 hour abstinence was requested but not verified.

A number of studies of long term Indian cannabis users have also reported cognitive impairment. Agarwal et al (16) studied forty subjects who had used bhang daily for about 5 years. A comparison of their scores with normative data found that 18% had memory impairment, 28% showed mild intellectual impairment (IQs less than 90), and 20% showed substantial cognitive disturbances on the Bender-Gestalt Visuo-Motor Test. Wig and Varma (17) substantially replicated these results and Mendhiratta, Wig and Verma's (18) found that 50 heavy cannabis users reacted more slowly and had poorer concentration and time estimation than 50 matched controls.

The cross-cultural studies of long-term heavy cannabis users provide equivocal evidence of cognitive impairment among long-term cannabis users. They have either failed to find any differences or have found modest cognitive impairment in persons with a long history of heavy cannabis use. Their negative results cannot be attributed to short duration or low intensity of cannabis use because these subjects had used cannabis for between 17 and 23 years, and the amount of THC consumed per day ranged from 20–90 mg in the Jamaican study to 120–200 mg in the Greek sample. The differences that were observed are difficult to interpret because users often had higher rates of polydrug use, poorer nutrition, poorer medical care, and higher rates of illiteracy than controls, all factors which may have biased these studies towards finding poorer performance among cannabis users. Many of these studies also failed to ensure that subjects were not intoxicated by cannabis at the time of testing.

9.2 Studies of Western cannabis users

Studies of the cognitive performance of North American cannabis users have generally been on college students with much shorter histories of cannabis use than the chronic users in the cross cultural studies (19). It is therefore unsurprising that most of these studies have failed to find evidence of cognitive impairment in cannabis users (19). One study to which these criticisms do not apply is that of Schaeffer et al (20) who studied cognitive impairment in 10 heavy cannabis users in the United States who used cannabis daily for religious reasons. All were Caucasian and all had been born and educated in the USA. All had smoked between 30 and 60 gms of cannabis a day for over 7 years and they had *not* used alcohol or any other psychoactive substances. At the time of testing, all subjects had evidence of recent heavy cannabis use in their urine. Overall, their scores on the WAIS IQ test were in the superior to very superior range, and their scores on all other tests were within normal limits but with only 10 subjects the study had a limited capacity to detect cognitive impairment.

9.3 Laboratory studies of daily cannabis use

Another strategy for investigating the cognitive effects of chronic cannabis use has been to study the cognitive performance of persons who use cannabis daily over periods of weeks. These studies have controlled the quantity, frequency, and duration of cannabis use, as well as nutrition and other drug use, by observing subjects in a hospital ward while they use cannabis. All such studies have used pre- and post-drug observation periods. The sample sizes in these studies have been small and cannabis has been used from 21 to 64 days.

Dornbush et al (21) administered cannabis containing 14 mg THC to 5 regular cannabis users for 21 days. They were tested before and 60 minutes after using cannabis on short-term memory and digit symbol substitution. Performance on the short-term memory test decreased on the first day of drug administration but gradually improved until by the last day of the study it had returned to baseline. Performance on the digit symbol substitution test was unaffected by cannabis but improved with time as a result of practice.

Mendelson, Rossi and Meyer (22) studied the effects of 21 days of cannabis use on 20 healthy, young male subjects who smoked as much cannabis as they wanted to. Short-term memory was impaired during intoxication but there was no impairment of performance before or after cannabis smoking. Similar failures to detect cognitive effects have been reported in three other studies (23–25).

9.4 Controlled laboratory studies of chronic cannabis users

Research studies in the late 1980s and 1990s improved upon the earlier studies of chronic cannabis users by using control groups, verifying abstinence from cannabis before testing, and quantifying the quantity, frequency and duration of cannabis use (Solowij, 1998). More effort was also made to relate specific cognitive processes to quantity, frequency and duration of cannabis use.

A study by Block and colleagues (26) addressed the concern that cannabis users had poorer cognitive ability than controls *before* they started using cannabis. Block et al matched their user and nonuser samples in their scores on the Iowa Tests of Basic Skills collected in the fourth grade of high school, ensuring that the two groups did not differ in intellectual abilities before they began using cannabis. Block and colleagues compared 144 cannabis users, 64 of whom were light users (less than 4 times per week for 5.5 years) and 80 heavy users (5 or more times per week for 6.0 years) with 72 controls aged 18-42. Twenty-four hours of abstinence was required prior to testing. The results showed that heavy cannabis users performed more poorly on tests of verbal expression and mathematical skills on the 12th grade Iowa test.

Solowij et al (27–29) studied the effects of long-term cannabis user's ability to exclude irrelevant stimuli when concentrating their attention on a task. Solowij assessed attentional processes in long-term cannabis users using a combination of performance

and brain event-related potential (ERP) measures as markers of underlying cognitive processes. She measured the amplitude and latency of ERP components that have been shown to reflect various stages of information processing.

Solowij et al (27) studied 9 cannabis users aged 19–40 who had used cannabis for 11 years for an average of 5 days per week. They were matched on age, sex, years of education and alcohol consumption with 9 controls who had either never used or had used cannabis fewer than 15 times in their lives. Subjects were excluded if they had a history of head injury, neurological or psychiatric illness, had used other drugs, or had high levels of alcohol consumption. The groups did not differ in premorbid IQ estimated by the NART score (30). Cannabis users were asked to abstain from cannabis and alcohol for 24 hours prior to testing and were urine tested to ensure that they did so.

Subjects performed an auditory selective attention task in which random sequences of tones varying in location, pitch and duration were presented through headphones while brain electrical activity (EEG) was recorded. They were asked to attend to a particular pitch presented in particular ear, and to respond to long duration tones by pressing a button. Cannabis users performed significantly more poorly than controls, with fewer correct detections, more errors and longer reaction times. They were less able than controls to filter out irrelevant information, suggesting that long-term cannabis use impaired the ability to efficiently process information.

In a second study Solowij et al (28, 29) assessed relationships between degree of impairment and the frequency and duration of cannabis use. Thirty-two cannabis users were divided into four groups of equal size (N = 8) defined by frequency (light: 2 or fewer times per week versus heavy: more than 3 times per week) and duration (short: 4 or fewer years of use versus long: 5 or more years of cannabis use). Subjects were matched to a group of nonuser controls (N = 16). The cannabis users performed worse than the controls and the greatest impairment was in the heavy user group. The long duration user group found it harder to ignore irrelevant stimuli than the short duration users and controls who did not differ. This impairment increased with the number of years of use but it was not related to frequency of use. There were no differences between groups defined on frequency of use on this measure. Speed of information processing was related to frequency of cannabis use but not to duration of use.

Solowij (31) assessed whether these ERP changes in long-term cannabis users persisted after extended abstinence from cannabis. She studied 32 former users who had used cannabis for a mean of 9 years and who had been abstinent for a mean of 2 years. She found some partial recovery of functioning: the speed of information processing was not reduced in the ex-users but their ability to ignore irrelevant stimuli remained impaired. The degree of impairment increased with the length of cannabis use and was unrelated to the length of abstinence.

Supportive evidence was provided by a NIDA funded study by Struve and colleagues of CNS changes in chronic cannabis users. This research found evidence of larger changes in EEG frequency, primarily in frontal-central cortex, in daily cannabis users of up to 30 years duration compared to short term users and nonusers (32). The results also

suggested that the EEG changes increased with the number of years of daily cannabis use. The major limitation of this research is that changes in frequency of EEG spectra have not been shown to be related to cognitive functioning.

This research group also assessed cognitive functioning (33–35) in subjects screened for current or past psychiatric and medical disorders and CNS injury. Daily cannabis users who had at least 3 years of use were compared to a group who had used daily for 6-14 years, a group who had used on a daily basis for 15 years or more, and a nonuser control group. Sample sizes averaged 15 per group. They reported a dose-response relationship between test performance and intensity of cannabis use, with controls performing best, followed by short term daily cannabis users, with the poorest performance in the very long-term group (33–35).

Pope and Yurgelun-Todd (36) compared the cognitive performance of heavy and light cannabis using college students. The heavy users (n = 65) had used for at least 2 years, on 28 of the past 30 days, and had cannabinoids in their urine. The light users (n = 64) had used no more than 3 days in the past month and had no cannabinoids in their urine. The authors used this design because they argued that infrequent users would 'differ less from heavy users on some possible confounding variables than would control subjects who had never used cannabis at all, while still differing sharply from heavy users on ... extent of recent cannabis use' (p 521).

Subjects were admitted overnight to a hospital ward to ensure that they were abstinent from cannabis at least 19 hours before being tested. The two groups did not differ on any social or demographic variables, except that heavy users came from more affluent families and scored more poorly on Verbal IQ and self-reported Scholastic Aptitude Tests. These differences were statistically adjusted for when comparing the two groups on the neuropsychological tests. The groups did not differ on tests of digit span, auditory sequential processing, the Stroop Test or the Wechsler Memory Scale. They differed on tests of attention (the Wisconsin test, the Benton VFT, and the CLVT) and these differences persisted when adjusted for differences in verbal IQ, self-reported SAT score and other drug use.

9.5 Epidemiological evidence

Lyketsos et al (37) reported a large-scale prospective epidemiological study of the effect of cannabis use on cognitive functioning. They followed up 1318 adults 11.5 years after they were assessed on the Mini Mental State Exam (MMSE) and assessed cognitive decline on the MMSE. They also inquired about use of cannabis, alcohol and tobacco. Their study came close to meeting the criteria for an optimum study specified by Pope et al (38), namely, it was a longitudinal study using a large sample of people from the general population who were assessed on cognitive performance and on cannabis and other drug use. Lyketsos et al found that the mean MMSE score declined by 1.2 points over 11.5 years and the decline was greater among older participants. There was, however, no relationship between cannabis use and the decline in MMSE score, and this lack of relationship persisted when adjustments were made for age, sex, education, minority status and use of alcohol and tobacco.

The Lyketsos et al study supports other evidence that cannabis use does not produce *gross* impairment of cognitive function but for a number of reasons it does not exclude the possibility that cannabis use causes more subtle cognitive impairment. First, only 57% of those initially interviewed were followed up and those lost to follow up had poorer MMSE scores at first assessment. Second, the MMSE is a screening test for gross cognitive impairment; it is not sensitive to small changes in cognitive functioning (39). Third, more than two weeks daily use at any of the three assessments qualified as 'heavy cannabis use'. Since cannabis use declines steeply with age (40) very few of this sample were likely to be daily cannabis users for any length of time.

9.6 Studies of neurotoxicity

Human studies of brain anatomy have generally failed to find signs of gross 'brain damage' after chronic use of cannabis (19, 41). The human studies of cognitive functioning suggest that cannabis may produce more subtle changes in brain function that existing methods of brain imaging are not sufficiently sensitive to detect (19). Wert and Raulin (41) proposed, that on the available evidence 'there are no gross structural or neurological deficits in marijuana-using subjects, although subtle neurological features may be present' (p.624).

9.7 Summary

The evidence suggests that long term heavy use of cannabis does not produce severe impairment of cognitive function like that observed in heavy alcohol users. There is some evidence that daily cannabis use over many years may produce more subtle impairment in memory, attention and the organisation and integration of complex information. This evidence suggests that these forms of cognitive impairment increase with the duration of cannabis use. It remains to be seen whether the impairment can be reversed by an extended period of abstinence.

Well controlled studies using sophisticated methods of investigation have failed to demonstrate gross structural change in the brains of heavy, long term cannabis users. These negative results are consistent with the evidence that any cognitive effects of chronic cannabis use are subtle, and hence unlikely to be manifest as gross structural changes in the brain.

9.8 References

1. Kolansky, H. & Moore, W. (1972) Toxic effects of chronic marihuana use, *Journal of the American Medical Association*, 222, 35–41.

2. Kolansky, H. & Moore, W. (1971) Effects of marihuana on adolescents and young adults, *Journal of the American Medical Association*, 216, 486–492.

3. Stephens, R., Roffman, R. & Curtin, L. (2000) Comparison of extended versus brief interventions for marjiuana, *Journal of Consulting and Clinical Psychology*, 68 898–908.

4. Soueif, M. (1971) The use of cannabis in Egypt: A behavioural study, *Bulletin on Narcotics*, 23, 17–28.

5. Soueif, M. (1975) Chronic cannabis users: Further analysis of objective test results, *Bulletin on Narcotics*, 27, 1–26.

6. Soueif, M. I. (1976) Differential association between chronic cannabis use and brain function deficits, *Annals of the New York Academy of Sciences*, 282, 323–43.

7. Soueif, M. I. (1976) Some determinants of psychological deficits associated with chronic cannabis consumption, *Bulletin on Narcotics*, 28, 25–42.

8. Carlin, A. (1986) Neuropsychological consequences of drug abuse, in: Grant, I. & Adams, K. (Eds.) *Neuropsychological Assessment of Neuropsychiatric Disorders*, pp. 478–497 (New York, Oxford University Press).

9. Bowman, M. & Pihl, R. (1973) Cannabis: Psychological effects of chronic heavy use. A controlled study of intellectual functioning in chronic users of high potency cannabis, *Psychopharmacologia*, 29, 159–170.

10. Rubin, V. & Comitas, L. (1975) *Ganja in Jamaica: A Medical Anthropological Study of Chronic Marihuana Use* (The Hague, Mouton).

11. Stefanis, C., Dornbush, R. & Fink, M. (1977) *Hashish: Studies of Long-Term Use* (New York, Raven Press).

12. Stefanis, C., Boulougouris, J. & Liakos, A. (1976) Clinical and psychophysiological effects of cannabis in long term users, in: Braude, M. & Szara, S. (Eds.) *Pharmacology of Marihuana*, pp. 659–665 (New York, Raven Press).

13. Kokkevi, A. & Dornbush, R. (1977) Psychological test characteristics of long term hashish users, in: Stefanis, C., Dornbush, R. & Fink, M. (Eds.) *Hashish: Studies of Long-Term Use*, pp. 43–48 (New York, Raven Press).

14. Satz, P., Fletcher, J. & Sutker, L. (1976) Neuropsychologic, intellectual and personality correlates of chronic marijuana use in native Costa Ricans, *Annals of the New York Acedemy of Sciences*, 282, 266–306.

15. Page, J., Fletcher, J. & True, W. (1988) Psychosociocultural perspectives on chronic cannabis use: The Costa Rican follow-up, *Journal of Psychoactive Drugs*, 20, 57–65.

16. Agarwal, A., Sethi, B. & Gupta, S. (1975) Physical and cognitive effects of chronic bhang (cannabis) intake, *Indian Journal of Psychiatry*, 17, 1–7.

17. Wig, N. N. & Varma, V. K. (1977) Patterns of long-term heavy cannabis use in north India and its effects on cognitive functions: a preliminary report, *Drug and Alcohol Dependence*, 2, 211–9.

18. Mendhiratta, S., Wig, N. & Varma, S. (1978) Some psychological correlates of long-term heavy marihuana users, *British Journal of Psychiatry*, 132, 482–486.

19. Solowij, N. (1998) *Cannabis and cognitive functioning*, (Cambridge, Cambridge University Press).

20. Schaeffer, J., Andrysiak, T. & Ungerleider, J. T. (1981) Cognition and long-term use of ganja (cannabis), *Science*, 213, 465–466.

21. Dornbush, R., Clare, G., Zaks, A., Crown, P., Volavka, J. & Fink, M. (1972) Twenty-one day administration of marijuana in male volunteers, in: Lewis, M. (Ed.) *Current Research in Marihuana*, pp. 115–127 (New York, Academic Press).

22. Mendelson, J., Rossi, A. & Meyer, R. (1974) *The Use of Marihuana: A Psychological and Physiological Inquiry* (New York, Plenum Press).

23. Frank, I., Lessin, P., Tyrell, E., Hahn, P. & Szara, S. (1976) Acute and cumulative effects of marihuana smoking in hospitalised subjects: A 36 day study, in: Braude, M. & Szara, S. (Eds.) *Pharmacology of Marihuana, Volume 2* (New York, Raven Press).

24. Harshman, R., Crawford, H. & Hecht, E. (1976) Marihuana, cognitive style, and lateralised hemisphere, in: Cohen, S. & Stillman, R. (Eds.) *The Therapeutic Potential of Marihuana*, pp. 205–254 (New York, Plenum Press).

25. Cohen, S. (1976) The 94-day cannabis study, *Annals of the New York Academy of Sciences*, 282, 211–220.

26. Block, R. I., Farnham, S., Braverman, K., Noyes Jr, R. & Ghoneim, M. M. (1990) Long-term marijuana use and subsequent effects on learning and cognitive functions related to school achievement: Preliminary study *NIDA Research Monograph*, pp. 96–111 .

27. Solowij, N., Mitchie, P. & Fox, A. (1991) Effects of long-term cannabis use on selective attention: An event-related potential study, *Pharmacology, Biochemistry and Behavior*, 40, 683–688.

28. Solowij, N., Mitchie, P. & Fox, A. (1992) Frequency and duration of cannabis use differentially affect brain function in a selective attention task, Paper presented at the *Paper presented at the 10th International Australiasian Winter Conference on Brain Research (AWCBR), Queenstown, New Zealand, 16–21 August 1992; and at the National Drug and Alcohol Research Centre Fifth Anniversary Annual Symposium on the Correlates and Consequences of Excessive Drug Use, Sydney, Australia, 4 December 1992.*

29. Solowij, N., Mitchie, P. & Fot, A. (1993) Differential impairments of selective attention due to frequency and duration of cannabis use, *Paper presented at the International Cannabis Research Society Annual Meeting, Satellite to the 55th Annual Scientific Meeting of the College on Problems of Drug Dependence, Toronto, Canada, 10–17 June 1993.*

30. Nelson, N. (1984) The National Adult Reading Test (NFER).

31. Solowij, N. (1995) Do cognitive impairments recover following cessation of cannabis use?, *Life Sciences*, 56, 2119–2126.

32. Struve, F., Straumanis, J., Patrick, G., Norris, G., Nixon, F., FitzGerald, M., Manno, J., Leavitt, J. & Webb, P. (1993) Topographic quantitative EEG sequelae of chronic cumulative THC exposure: Recent and continuing studies *Paper presented at the International Cannabis Research Society Annual Meeting, Satellite to the 55th Annual Scientific Meeting of the College on Problems of Drug Dependence, Toronto, Canada, 10–17 June 1993.*.

33. Leavitt, J., Webb, P., Norris, G., Struve, F., Straumanis, J., G., P., FitzGerald, J. & Nixon, F. (1991) Differences in complex reaction time between chronic heavy THC users and non-users controls, *Poster presented at the 53rd Annual Scientific Meeting of the College on Problems of Drug Dependence, Palm Beach, Florida, 10–17 June.*

34. Leavitt, J., Webb, P., Norris, G., Struve, F., Straumanis, J., FitzGerald, J., Nixon, F., Patrick, G. & Manno, J. (1992) Performance of chronic daily marijuana users on neuropsychological tests, Paper presented at the *Poster presented at the 54th Annual Scientific Meeting of the College on Problems of Drug Dependence, Keystone, Colorad, 20–25 June.*

35. Leavitt, J., Webb, P., Norris, G., Struve, F., G., P., FitzGerald, J. & Nixon, F. (1993) Performance of long-term THC users on tests of reaction time using Sternberg's procedure, Paper presented at the *Poster presented at the 55th Annual Scientific Meeting of the College on Problems of Drug Dependence, Toronto, Canada, 12–17 June.*

36. Pope, H. G. & Yurgelun-Todd, D. (1996) The residual cognitive effects of heavy marijuana use in college students, *Journal of the American Medical Association*, 275, 521–527.

37. Lyketsos, C. G., Garrett, E., Liang, K. Y. & Anthony, J. C. (1999) Cannabis use and cognitive decline in persons under 65 years of age, *American Journal of Epidemiology*, 149, 794–800.

38. Pope, H. G., Gruber, A. J. & Yurgelun-Todd, D. (1995) The residual neuropsychological effects of cannabis: The current status of research, *Drug and Alcohol Dependence*, 38, 25–34.

39. Bowie, P., Branton, T. & Holmes, J. (1999) Should the Mini Mental State Examination be used to monitor dementia treatments?, *Lancet*, 354, 1527–1528.

40. Bachman, J. G., Wadsworth, K. N., O'Malley, P., Johnston, L. & Schulenberg, J. (1997) *Smoking, drinking and drug use in young adulthood: The impacts of new freedoms and responsibilities* (Mahwah, NJ, Lawrence Erlbaum).

41. Wert, R. & Raulin, M. (1986) The chronic cerebral effects of cannabis use I. Methodological issues and neurological findings, *The International Journal of the Addictions*, 21, 605–628.

10 Cannabis use and psychotic disorders

There is reason to suspect that cannabis use may be a cause of psychotic disorders, i.e. mental illnesses in which sufferers experience hallucinations and delusions and show impaired reality testing. THC produces symptoms found in some psychotic disorders, namely, euphoria, distorted time perception, and cognitive and memory impairments (1, 2). In laboratory studies normal volunteers given high doses of THC have reported visual and auditory hallucinations, delusional ideas, thought disorder, and symptoms of hypomania (3, 4). A 'cannabis psychosis' has been reported by clinical observers in countries with a long history of heavy cannabis use, such as India and Egypt (1, 5).

We need to distinguish two hypotheses about possible relationships between cannabis use and psychosis (6). The strongest causal hypothesis is that heavy cannabis use can cause a 'cannabis psychosis', that is, a psychosis would not occur in the absence of cannabis use and in which the causal role of cannabis can be inferred from the symptoms and their relationship to cannabis use (being preceded by heavy cannabis use and remitting after abstinence).

A second hypothesis is that cannabis use can precipitate an episode of schizophrenia. According to this hypothesis, cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that bring about schizophrenia, a psychotic disorder which becomes chronic in a substantial proportion of those who develop it.

If cannabis use can precipitate schizophrenia it is also likely that it can exacerbate the symptoms of the disorder. Even if cannabis use does not precipitate schizophrenia, its use may exacerbate symptoms of schizophrenia either directly, by affecting the dopaminergic system in the brain, or indirectly, by reducing compliance with, or interfering with the effects of, the neuroleptic drugs used to treat its symptoms.

In order to infer that cannabis use is a cause of psychosis in any of these ways we need evidence: that cannabis use and psychosis are associated; that chance is an unlikely explanation of the association; that cannabis use preceded the psychosis; and that plausible alternative explanations of the association can be excluded (7). As we will see, there is evidence that cannabis use and psychosis are associated, that chance is an unlikely explanation of the association, and that cannabis use often precedes psychoses. The most difficult task is excluding the hypothesis that the relationship between cannabis use and psychosis is due to other factors (e.g. other drug use, or a genetic predisposition both to develop schizophrenia and use cannabis).

10.1 'A cannabis psychosis'

Case reports of 'cannabis psychoses' (8–11) describe individuals who develop psychotic symptoms or disorders after using cannabis. Chopra and Smith (9), for example, described 200 patients who were admitted to a psychiatric hospital in Calcutta between