The human toxicity of marijuana

Gabriel Nahas and Colette Latour

The pathophysiological effects of marijuana smoke and its constituent cannabinoids were reported first from in-vitro and in-vivo experimental studies. Marijuana smoke is mutagenic in the Ames test and in tissue culture and cannabinoids inhibit biosynthesis of macromolecules. In animals, marijuana or Δ^9-tetrahydrocannabinol (THC), the intoxicating material it contains, produces symptoms of neurobehavioural toxicity, disrupts all phases of gonadal or reproductive function, and is fetotoxic. Smoking marijuana can lead to symptoms of airway obstruction as well as squamous metaplasia. Clinical manifestations of pathophysiology due to marijuana smoking are now being reported. These include: long-term impairment of memory in adolescents; prolonged impairment of psychomotor performance; a sixfold increase in the incidence of schizophrenia; cancer of mouth, jaw, tongue and lung in 19–30 year olds; fetotoxicity; and non-lymphoblastic leukaemia in children of marijuana-smoking mothers.

(Med J Aust 1992; 156: 495-497)

The recreational smoking of products derived from *Cannabis sativa*, mainly its resin (hashish) or the chopped flowering tops of the plant (marijuana), has become trivialised in Western industrialised countries since 1960. The immediate effect of this drug is the creation of a pleasant, dreamy state, with impairment of attention, cognitive and psychomotor performance, which appears to the subject to be reversible. Because of its lack of acute life-threatening effects, cannabis has been called a "soft drug", no more damaging than coffee or tobacco.[1] However, this designation should be revised in view of the drug's prolonged impairing effects on memory and learning and its long-term toxic effects on the lung and on immune defences, brain and reproductive function, which have only recently been reported[2] and which confirm experimental observations.[3]

Products extracted from *Cannabis sativa* for the purpose of smoking originate from a variety of the plant which grows in subtropical climes of Africa, South America, South-East Asia, Australia and New Zealand. The flowering tops of cannabis contain the intoxicating material Δ^9-tetrahydrocannabinol (THC), which may make up 1%–6% of the total weight of this part of the plant. In contrast, the fibre variety of cannabis, which grows in temperate climes and is used for the manufacture of rope and twine, contains very little THC. In addition to THC, more than 60 other cannabinoids have been identified in cannabis. It also contains eight other classes of compounds, as reviewed by Turner,[4] including 421 compounds, which are for the most part xenobiotics — substances foreign to the body, not used for food or fuel. Among them are alkaloid derivatives of spermidine, sterols, terpenes and flavanoid glucosides.

Cannabis material which is smoked recreationally consists of three preparations — marijuana, hashish and hash oil. Marijuana or "grass" consists of the chopped flowering tops of the female plant and is smoked like a tobacco cigarette. It contains 1%–5% THC. Hashish is the dried resin of the plant, contains 6%–10% THC and is smoked in a pipe. Hash oil, which is an oily extract of the flowering tops of the female plant, contains 30%–60% THC.

Under the influence of heat, cannabinoids rapidly decarboxylate. At 200°C–400°C aromatisation of the cannabinoids occurs. Some 150 polycyclic aromatic hydrocarbons have been identified in marijuana smoke and the proportions of the higher molecular weight compounds, particularly the carcinogen benzo[a]pyrene, are greater in marijuana than in tobacco smoke. The most likely sources of these hydrocarbons are the cannabinoids. Other constituents of marijuana smoke include phenols, phytosterols, acids and terpenes. In other respects the smoke of tobacco and marijuana is similar. Toxic substances such as carbon monoxide, hydrogen cyanide, and nitrosamines are present in equivalent concentrations in both smokes and the "tar" yield is also similar.

THC and other cannabinoids are very fat-soluble and have a half-life of eight days in fat. It therefore takes one month to completely eliminate a single dose of THC, which is stored in liver, lung, spleen and fat. Less than 1% reaches the brain or the testis. Consumption of cannabis more often than once a week will result in storage of THC in the body. THC is a polar compound which is slowly metabolised into more water-soluble, non-psychoactive metabolites, of which 80 have been identified to date. The bioavailability of THC is 20% when inhaled and 6% when ingested. Excretion of metabolites is via the liver and intestine (80%), with enterohepatic recirculation; urinary excretion does not exceed 20%. In addition, THC and its metabolites cross the placental barrier and are transferred to maternal milk.

Cannabis extracts are mutagenic in standard in-vitro and in-vivo tests.[5] THC and other cannabinoids also impair DNA and RNA synthesis in cell cultures[6] and inhibit the primary immune response and resistance to herpes simplex virus in rodents.[7] Such properties account for the toxicity which has now been reported in man.

Pulmonary toxicity and carcinogenicity of the aerodigestive tract

Symptoms of airway obstruction have been clinically documented in controlled experiments performed in young people who smoke marijuana every day.[8] These symptoms are surprising because acute exposure to THC dilates the bronchi. Microscopic examinations of bronchial biopsies taken from heavy users of hashish 20–26 years of age showed squamous cell hyperplasia.[9] The finding of carcinogens in marijuana smoke, experimental evidence of the immunodepressive effects of THC and the presence of epithelial abnormalities known to be precursors of lung cancer in tobacco smokers suggested that chronic marijuana smokers would develop cancer of the upper aerodigestive tract. This has now been documented.

Donald reported 12 cases of advanced head and neck cancer in young patients with an average age of 26 years (range 19–38 years).[10] All had been daily marijuana or hashish smokers since high school, but did not smoke tobacco or use much alcohol. Their cancers were mostly squamous cell tumours of the tongue or jaw with local lymph node involvement, which Donald had seen before only among subjects 60 years of age or older who had been heavy drinkers and tobacco smokers for decades. Endicott and Skipper[11] reported similar observations in 20 young marijuana smokers who had developed tumours of the mouth, larynx and upper jaw and Taylor[12] reported that, of 10 patients under 40 years of age with cancer of the respiratory tract, seven had a history of daily marijuana use. Taylor concluded that regular marijuana use appeared to be an additional significant risk factor for the development of cancer of the upper airways. Ferguson et al. described a 27-year-old man who died of metastatic lung carcinoma.[13] He had smoked marijuana heavily and steadily since the age of 11 years. Cases of cancer of the tongue have also been reported in marijuana smokers.[14]

Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, NY 10032; and INSERM, Hôpital Fernand Widal, Paris.
Gabriel Nahas, MD, PhD, Professor of Anesthesiology.
Laboratoire de Pharmacologie et Toxicologie Cellulaires, INSERM, Hôpital Fernand Widal, Paris.
Colette Latour, PhD, Associate Director.
Reprints and correspondence: Professor G Nahas, INSERM, Hôpital Fernand Widal, 200 rue du Fbg St Denis, 75010 Paris.

Marijuana and leukaemia

The mutagenic and carcinogenic potential of marijuana is corroborated by the study of Robison.[15] This investigation was undertaken to assess in-utero exposure to different medications in children who had developed non-lymphoblastic leukaemia. In a case–control study of 204 pairs of children, maternal use of medications and drugs in the year preceding pregnancy and during gestation was analysed. The study showed there was a tenfold increased risk of leukaemia in the offspring of mothers who had smoked marijuana just before or during pregnancy. No other drug use during pregnancy (including tobacco, alcohol, and pain-killers) could be associated with such a risk. Children exposed to marijuana *in utero* developed the disease at a younger age compared with the controls (at a mean age of 19 months compared with 93 months) and showed clonal abnormalities.

Damaging effects of marijuana on human fetal development

In the 1970s, Rosenkrantz[16] and others reported that marijuana products were toxic to fetal development in all species studied: fish, birds, rodents, hamsters, rabbits, dogs and monkeys. Offspring also displayed retarded development and behavioural anomalies.[17] Then in the 1980s, anomalies in newborn babies exposed to marijuana during gestation were reported by several investigators. Quasi et al.[18] and Hingson et al.[19] described deficits (lower weight and head circumference) in babies born to marijuana-smoking mothers. These studies illustrating the damaging effects of cannabis on the developing human fetus were later confirmed by three independent groups of investigators: in 1986 by Hatch and Bracken,[20] in 1987 by Lester and Dreher[21] and in 1989 by Zuckerman et al.[22] Lester and Dreher used high-speed computer voice analysis to assess the maturity of newborn infants. The cries of infants born to marijuana-smoking mothers in Jamaica showed a much higher frequency of voice anomalies than did cries of infants from non-smokers, suggesting possible impairment of fetal brain development. Zuckerman et al. reported a long-term study of 1226 mothers who were studied during pregnancy. Marijuana use was documented by urinalysis in 16% of the prospective mothers. Infants born to these marijuana-smoking mothers were shorter, weighed less and had smaller head circumferences at birth. Long-term developmental and behavioural effects which could result from intrauterine cannabis exposure remain to be assessed in man.

Marijuana and the brain

The acute impairment of mental performance by marijuana in man is well recognised. Soueif observed that this impairment was present well beyond the period of acute intoxication.[23] For example, a Costa Rican study by Fletcher, reported in 1973, found that heavy marijuana users scored as well as non-users on several tests of learning and memory.[24] However, in 1988 a follow-up study, performed by the same group on the same cohort of Latin American marijuana users and on non-using controls, showed selective impairment of short-term memory skills in cannabis users, contradicting the results obtained 10 years earlier.[25] In 1988, Varma et al. also reported short-term memory impairment in heavy marijuana smokers studied in India.[26] In 1989, Schwartz et al. reported the results of an exceptionally well-controlled study which showed persistent short-term memory impairment in a group of middle-class American adolescents who used marijuana.[27] Their median age was 16 years and they had at least eight years of formal education. Their performance was compared with that of a group of controls matched for age and intelligence. When initially tested, the boys and girls formerly dependent on cannabis did much worse on short-term memory tests than the control group, and after six weeks of supervised abstention from intoxicants they still had short-term memory deficits. The study of Schwartz et al. proves the specific lasting property of marijuana to impair memory storage, an essential part of the learning process, and to adversely affect psychomotor performance.

The disruption of selective aspects of short-term memory by THC is similar to that found in patients with brain damage presenting with memory disorders. These memory deficits caused by disease, trauma or THC have been traced to impairment of the hippocampus, the relay centre which receives information during memory consolidation and which codes spatial and temporal stimuli and responses. Herkenham et al. reported that THC binds to the hippocampus of rat, dog, monkey and man.[28] Impaired mental performance due to marijuana has been related to impaired turnover of acetycholine. Studies on man using positron emission tomography (PET) showed that THC significantly alters glucose metabolism in the frontal and parietal lobes and cerebellum for several hours.[29] Such metabolic changes in areas of the brain which control memory and information processing are associated with impairment in the performance of complex tasks.

The most striking evidence of the lingering effects of marijuana on memory and coordination was reported by Leirer and Yesavage[30] who studied 10 experienced private pilots in a double-blind experiment. The subjects were trained for eight hours on a computerised flight simulator. The test started one morning with a control "flight", after which each subject smoked either a marijuana cigarette containing 19 mg of THC or a placebo cigarette from which the THC had been removed. The simulated landing was repeated one, four and 24 hours later. In every case, the worst performance occurred one hour after THC inhalation. But 24 hours later, those pilots who had smoked marijuana still experienced significant difficulty in aligning the computerised landing simulator and in landing the "plane" at the centre of the runway. However, the pilots themselves reported no awareness of any marijuana after-effects on their performance, mood or alertness. It is not known exactly for how long beyond 24 hours a single marijuana cigarette will disrupt the fine brain mechanisms controlling memory. The pilot of the commercial aircraft in a 1983 crash at Newark, New Jersey, which involved landing misjudgement, was found to have smoked marijuana 24 hours before the accident. It is known that traces of THC are still present in the brain 24-hours after administration. More down-to-earth tasks, such as operating complicated equipment or trains, may also be susceptible to "day-after" marijuana effects.

Marijuana and road accidents

Chesher et al. reported in 1985 that THC was 4000 times more potent than alcohol in producing decrements in performance of subjects studied under controlled conditions.[31] Since then, several major railroad accidents have illustrated the impairing effects of marijuana on the performance of complex tasks. In January 1987, a freight train rammed at full speed into the Metroliner travelling from Washington to New York at full speed, killing 16 passengers and injuring forty-eight. The conductor of the train had ignored three red signals before the crash. Cannabinoids were detected in his body fluids. A year later, marijuana was detected in a 30-year-old switchman who had fled his post in a control tower after a train derailment in Chester, Pennsylvania. He had failed to take an incoming train off a stretch of track undergoing maintenance. In the ensuing crash, 25 people were injured.

A report issued in February, 1990 by the United States National Transportation Safety Board has provided the most extensive evidence linking fatal accidents among truck drivers to cannabis.[32] The report covered 182 accidents, involving 86 trucks, in which 210 people were killed. One-third of the victims whose bodies were examined had recently used alcohol or drugs: 12.8% had used marijuana, 12.5% had used alcohol and 8.5% had used cocaine.

Marijuana and schizophrenia

It is well established that marijuana smoking can trigger an acute psychotic episode in schizophrenics.[33] However, Andreasson et al., in a 15-year prospective study of 55 000 Swedish military conscripts, showed that the relative risk of developing schizophrenia among those who were heavy consumers of cannabis (use on more than 50 occasions) was six times greater than in non-users.[34]

The ability of cannabis to induce long-lasting mental disturbances in Western man, now epidemiologically documented, confirms older anecdotal reports from mediaeval Islamic countries (1396), India (1878–1972), Egypt

(1843–1925), Brazil (1955), the Bahamas (1970) and Jamaica (1976).[35] The existence of cannabis-induced psychosis provides evidence that the repetitive disturbance of brain neurotransmission by THC can permanently impair the basic biochemical neural mechanisms which control coherent behaviour.

In conclusion, the results of standard in-vitro and in-vivo toxicological tests performed in the 1970s on animal preparations to which marijuana extracts were administered have proved to be good predictors of the long-term pathophysiological manifestations observed 20 years later in chronic marijuana smokers. These manifestations also confirm anecdotal accounts reported throughout history of the damaging effects of cannabis.

Acknowledgements

This work was supported by a grant from the City of Paris and the Lounsbery Foundation.

References

1. Hollister LE. Health aspects of cannabis. *Pharmacol Rev* 1986; 38: 1-32.
2. Nahas G, Latour C, editors. Cannabis. In: First International Colloquium on Illicit Drugs. Advances in the biosciences. Oxford: Pergamon Press, 1991: 3-126.
3. Nahas GG, Cannabis: toxicological properties and epidemiological aspects. *Med J Aust* 1986; 145: 82-87.
4. Turner CE, Elsohly MA, Boeren EG. Constituents of *Cannabis sativa L.* XVII. A review of the natural constituents. *J Nat Prod* 1980; 43: 169-234.
5. Busch FW, Seid DA, Wei ET. Mutagenic activity of marihuana smoke condensates. *Cancer Lett* 1979; 6: 319-324.
6. Leuchtenberger C, Leuchtenberger R, Ritter U, et al. Effects of marijuana and tobacco smoke on DNA and chromosomal complement in human lung explants. *Nature* 1973; 242: 403-404.
7. Cabral GA, Vasquez R. Marijuana decreases macrophage antiviral and antitumor activities. In: Nahas GG, Latour C, editors. First International Colloquium on Illicit Drugs. Advances in the biosciences. Oxford: Pergamon Press, 1991; 93-105.
8. Tashkin DP, Calvarese BM, Simmons MS, Shapiro BJ. Respiratory status of seventy-four habitual marihuana smokers. *Chest* 1980; 78: 699-706.
9. Tennant FS, Guerry RL, Henderson RL. Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. *Subst Alcohol Actions Misuse* 1980; 1: 93-100.
10. Donald PJ. Marijuana and upper aerodigestive tract malignancy in young patients. In: Nahas GG, Latour C, editors. First International Colloquium on Illicit Drugs. Advances in the biosciences. Oxford: Pergamon Press, 1991: 39-54.
11. Endicott J, Skipper P. Marihuana and the upper aerodigestive tract malignancy in young subjects. In: *Internationales Symposium gegen Drogen in der Schweiz.* Zurich: VPM, 1991; 547-552.
12. Taylor FM 3d. Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population. *South Med J* 1988; 81: 1213-1216.
13. Ferguson RP, Hasson J, Walker S. Metastatic lung cancer in a young marijuana smoker [letter]. *JAMA* 1989; 261: 41-42.
14. Caplan GA, Brigham BA. Marijuana smoking and carcinoma of the tongue. Is there an association? *Cancer* 1990; 66: 1005-1006.
15. Robison LL, Buckley JD, Daigle AE, et al. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). *Cancer* 1989; 63: 1904-1910.
16. Rosenkrantz H. Effects of cannabis on fetal development of rodents. In: Nahas GG, Paton WDM, editors. Marihuana, biological effects. Oxford: Pergamon Press, 1979: 479-499.
17. Dalterio S, Bartke A, Mayfield D. Prenatal exposure to cannabinoids and sexual behavior of offspring. *Science* 1981; 216: 581-582.
18. Quasi QH, Mariano E, Milman DH, et al. Abnormalities in offspring associated with prenatal marihuana exposure. *Dev Pharmacol Ther* 1985; 8: 141-148.
19. Hingson R, Alpert JJ, Day N, et al. Effects of maternal drinking and marihuana use on fetal growth and development. *Pediatrics* 1982; 70: 539-546.
20. Hatch EE, Bracken MB. Effect of marijuana use in pregnancy on fetal growth. *Am J Epidemiol* 1986; 124: 986-993.
21. Lester BM, Dreher M. Effects of marijuana use during pregnancy on newborn cry. *Child Dev* 1989; 60: 765-771.
22. Zuckerman B, Frank DA. Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; 320: 762-768.
23. Soueif MI. Differential association between chronic cannabis use and brain function deficits. *Ann N Y Acad Sci* 1976; 282: 323-343.
24. Satz P, Fletcher JM, Sutker LS. Neuropsychologic, intellectual, and personality correlates of chronic marijuana use in native Costa Ricans. *Ann N Y Acad Sci* 1976; 282: 266-306.
25. Page JB, Fletcher J, True WR. Psychosociocultural perspectives on chronic cannabis use: the Costa Rican follow-up. *J Psychoactive Drugs* 1988; 20: 57-65.
26. Varma VK, Malhotra AK, Dang R, et al. Cannabis and cognitive functions: a prospective study. *Drug Alcohol Depend* 1988; 21: 147-152.
27. Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P. Short-term memory impairment in cannabis-dependent adolescents. *Am J Dis Child* 1989; 143: 1214-1219.
28. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A* 1990; 87: 1932-1990.
29. Volkow ND, Gillepsi H, Mullani N, et al. Use of positron emission tomography to investigate the action of marihuana in the human brain. In: Nahas GG, Latour C, editors. First International Colloquium on Illicit Drugs. Advances in the biosciences. Oxford: Pergamon Press, 1991: 3-11.
30. Leirer VO, Yesavage JA. Marihuana carry-over effects on aircraft pilot performance. *Aviat Space Environ Med* 1991; 62: 221-227.
31. Chesher GB, Bird KD, Stramarcos A, Nikias M. A comparative study of the dose response relationship of alcohol and cannabis on human skills performance. In: Harvey DJ, editor. Marihuana nineteen eighty-four: proceedings of the Oxford Symposium on Cannabis; Third International Cannabis Symposium, Ninth International Congress of Pharmacology. Oxford: IRL Press, 1985: 621-627.
32. Department of Transportation, Washington. National Transportation Safety Board report. Washington: Department of Transportation, 1990.
33. Negrete JC. Cannabis and schizophrenia [editorial]. *Br J Addict* 1989; 84: 349-351.
34. Andréasson S, Allebeck P, Engström A, Rydberg V. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* 1987; 2: 1483-1485.
35. Brill M, Nahas GG. Cannabis intoxication and mental illness. In: Nahas GG, editor. Marihuana in science and medicine. New York: Raven Press, 1985; 228-279.

PERSPECTIVE

Marijuana as medicine

In a field in Tasmania, a crop of marijuana is springing up. But, unlike most marijuana crops, its produce is destined not for the illegal drug market but for the manufacture of paper. Under the monitoring of the Tasmanian Departments of Health and Primary Industry, the Hemp for Paper Consortium, a private concern, is cultivating the plant with the hope of showing that it can be successfully grown in Tasmania and that making paper from its fibre will prove financially viable. Similar projects are under way elsewhere in Tasmania and in New South Wales.

Despite the facts that the use of the fibre of the cannabis plant for making paper, rope and fabric is not new and that the variety of the plant grown for such uses contains very low levels of psychoactive substances, the Hemp for Paper Consortium faced considerable suspicion from local authorities.

Similarly, marijuana has a long history of use as a therapeutic drug, but there is an argument that its illegal status has hampered research in this direction. Indeed, tincture of cannabis was used in "mixtures" in Australia until the mid-1960s when it was declared a prohibited drug.[1] Since then there has been little clinical experience with the drug in this country.

However, the active compounds in marijuana, the cannabinoids, of which the most important is Δ^9-tetrahydrocannabinol (THC), represent a distinct pharmacological class of drugs which are not widely exploited in orthodox medicine but which have been claimed to be effective in a range of disorders. Marijuana has been used mainly for its antispasmodic, analgesic and hypnosedative effects, but it has diverse properties and has also been used in the treatment of epilepsy, asthma, nausea, hypertension, glaucoma and various movement disorders.

One of the better known therapeutic uses of marijuana is in the treatment of nausea in patients receiving cancer chemotherapy, and this is also the subject of one of the few pieces of Australian research done on the drug. In a study reported in the Journal in 1979, researchers at the Royal Children's Hospital, Melbourne, conducted a double-blind trial of THC, placebo and the then-current treatments of nausea in children receiving chemotherapy (oral metoclopramide and prochlorperazine).[2] They found that THC was an effective antiemetic agent, although it was not successful in all patients and commonly produced drowsiness.

When marijuana is used therapeutically, the "high" sought by recreational users is regarded as a side effect. However, tolerance of the "high" is variable and younger patients and those who have used marijuana previously tend to tolerate it better.[3] In fact, the Melbourne researchers found it was unusual for the children to report a "high" although they conceded that the younger children may have been incapable of describing the experience.

This variability in response to the psychoactive effects of marijuana was also demonstrated in a New Zealand study conducted around the