

CANNABIS

A General Survey of its Harmful Effects

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Cannabis: Introduction and General Facts

Cannabis sativa grows well in tropical and temperate climates. Marijuana consists of the dried plant parts, Hashish is the resin secreted by glandular hairs all over the plant mainly round the flowers, protecting the plant from water loss. Sinsemilla is the dried material from the tops of the female plants. Hashish oil (up to 60% THC), is obtained by extraction but rarely used in the UK.

Cannabis contains some 400 chemical substances. These vary with the habitat and are often contaminated with microbes, fungi or pesticides (Jenike 1993, BMA 1997). More than 60 cannabinoids, substances unique to the plant have been identified. The most psychoactive of these and the main cause of many of the other harmful pharmacological effects is THC (delta-9-tetrahydrocannabinol) (Ranstrom 2003). Other natural cannabinoids are delta-8-THC, cannabinol and cannabidiol (BMA 1998).

Brain signals pass along nerve cells in the form of electrical impulses, and chemicals called neurotransmitters carry the messages between cells. These dozens of neurotransmitters are released at the end of one neuron (nerve cell) and fit into receptor sites by shape on the next cell. Transmission of nerve signals takes a fraction of a second. The psychoactive THC mimics a neurotransmitter called anandamide and so affects its receptor sites (Devane et al, 1992).

Two types of receptor site have been identified, CB1 receptors are distributed in the brain in the areas concerned with motor activity and control of posture (cerebellum and basal ganglia), emotion (amygdala and hippocampus), memory, cognition, the “high”, distortion of the sense of time, sound, colour and taste, the alteration of the ability to concentrate and the production of a dreamlike state (cerebral cortex and hippocampus), and sensory perception (thalamus). No CB1 receptors are present in the brain stem so the drug does not affect basal bodily functions including respiration. This explains the lack of deaths by overdosing with cannabis (Harkenham et al, 1991, 1992, BMA 1997). CB2 receptors were discovered in 1994 by Lynn and Harkenham. They were outside the brain on specific components of the immune system. Binding of cannabinoids was also seen in the heart, lungs, endocrine and reproductive systems, so all these systems are affected.

Cannabinoids are absorbed rapidly into the body after inhalation from smoked cannabis preparations. The effects become noticeable in a matter of minutes. They are then rapidly distributed all over the body and maximum brain concentrations are reached within 15 minutes. The psychological effects can last for 2 to 4 hours then slowly decline over the next 12 hours. When taken orally, THC absorption is much slower and more variable and the onset of its effects are delayed by 30 minutes to 2 hours. The duration of its effects are prolonged, 5 to 6 hours due to continued absorption from the gut and some cognitive and motor skills are impaired for much longer e.g. driving. (Huestis et al 1992, BMA 1997). Cannabis can cross the placenta, enter the circulation of the foetus and pass into breast milk.

Cannabinoids are highly lipid-soluble and so rapidly accumulate in the fatty tissues, being slowly released back into other body tissues and organs including the brain and bloodstream. Elimination of a single dose can take 30 days, unlike water-soluble alcohol which is removed at the rate of one unit per hour, and appears in the faeces and urine. Repeated doses will therefore accumulate in the body and affect the brain over long periods of time (BMA 1997). Cannabis is a multi-faceted drug. The inhibitory effects of THC on the release of a variety of neurotransmitters in the central nervous system has also been observed in several studies (Schliker and Kathmann, 2001, Katona et al 2000). Blood levels of THC drop rapidly after smoking due to its conversion into metabolites and sequestration into fatty tissues (Grotenhermen 2003).

Since 1971 when drugs were classified and cannabis was consigned to class B, the amount of THC in the plant in some varieties of Cannabis sativa has changed considerably. At that time the content of THC in marijuana was around 0.5 – 3% (Ranstrom 2003). Smokers in the late 80s and 90s had access to sensemilla (7 to 11% THC, Schwartz 1991). Hashish has consistently had a THC content of 4 to 5%. However, selective breeding of the plant, especially in Holland, has produced varieties such as Netherweed and Skunk with THC contents up to and over 20% (Jenike, 1993, BMA 1998). These stronger types, now commonly grown in the UK are favoured by today’s users, the lower levels being much less common

(Ranstrom 2003). An article in The Guardian on 29th August 2006 reported that “Analysis of recent home-grown hauls detected THC levels as high as 20%, nearly 7 times higher than samples of imported resin, which used to be the predominant form of the drug on the streets, and typically contained around 3% THC” Detective Inspector Neil Hutchison said, “A decade ago 11% of the cannabis sold on the street was grown in the UK. Now more than 60% is produced in Britain ...”. The Forensic Science Service, Drugs Intelligence Unit confirmed this figure (10/10/06) and said that between 30 and 40% of the rest is imported resin, some imported herbal cannabis is still seen as well.

It should be mentioned that cannabis research is still very young. In 1996 the total number of scientific papers did not exceed 10,000 and today probably stands between 14 and 15,000. This is in contrast to research on tobacco with about 140,000 studies to date (Ranstrom 2003). The total collection of scientific papers on cannabis is held in the library of The University of Mississippi.

In 1981, the WHO Report on Cannabis Use said, “It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, “risk factors” have been freely identified, although full causality has not yet been established. Nevertheless such risk factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is often not applied to cannabis”. “To provide rigid proof of causality in such investigations is logically and theoretically impossible , and to demand it is unreasonable”.

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Cannabis and the Cardiovascular system

Comparatively little research has been done in this area, but there are sufficient published scientific papers to raise concern.

At first the intoxication produced by cannabis causes an increase in heart rate of between 20 and 50% (Huber et al 1988, Jones 1984). A rise in blood pressure occurs if the person is sitting or lying, but on standing up the pressure drops, in some cases causing the person to faint (Maykut 1984). A new and naive smoker may be concerned about these effects (Sidney 2002), but someone with a healthy heart is not thought to be at risk.

Cannabis affects the cardiovascular system in other ways as well. THC increases the production of chemicals called catecholamines which stimulate the heart, it also has analgesic properties which may lessen any chest pain and delay the seeking of treatment and the level of carboxyhaemoglobin is raised, decreasing the supply of oxygen to the heart, placing it under greater strain (Jones 1982 and 1984).

Older field studies involving chronic cannabis users in Costa Rica (Carter et al 1980), Greece (Stefanis et al 1977) and Jamaica (Rubin and Comitas 1975), found no evidence of cardiac toxicity even in subjects with existing heart disease. And electrocardiographic studies in both acute and prolonged administration have rarely revealed pathological changes (Benowitz and Jones 1975, Jones 1984). So again it was concluded that young healthy adults using cannabis intermittently ran no major risk of a life-threatening cardiovascular event as may occur with a drug like cocaine. (Gawin, Ellinwood 1988).

However tolerance quickly develops to the acute cardiovascular effects of cannabis (Benowitz and Jones 1975, Jones and Benowitz 1976, Nowlan and Cohen 1977). And Jones (1984) showed that in people receiving daily high doses by mouth, tolerance develops in 7 to 10 days. This could possibly help to explain why toxic effects are sometimes not seen.

More recently though, there have been a number of papers documenting myocardial infarction and angina pectoris among young people using cannabis.

Podczeck and others 1990 reported 2 cases of myocardial infarction in very young healthy people and Choi and Perl 1989 and Perl and Choi 1992 found the same in young men, heavy users, with no history of heart disease. In 2000 Kosior and others wrote about 2 cases of cardiac arrhythmia (one of atrial fibrillation and one of recurrent paroxysmal tachycardia) in youngsters. Jones in 2002 reported transient ischaemic attacks and strokes in young and older people as well as deaths in young people from myocardial infarction.

Three teenagers, 15, 16 and 17, who “binge smoked” cannabis suffered strokes, two died and one was left paralysed. In the two who died the stroke appeared to have been triggered by a clot in the brain or a constriction of the blood vessels over a wide area (Geller et al 2004). Professor John Henry of Imperial College said it was very disturbing, “I have seen cases of stroke due to cannabis use but fortunately none of my patients have died. One woman had all the signs of a stroke with paralysis down one side but fortunately recovered after several days”.

A 36 year-old man suffered strokes on three separate occasions, at almost yearly intervals, shortly after smoking a large amount of cannabis. He had been an occasional cannabis user, did not use other drugs and drank only occasionally. He had no known risk factors for stroke and no narrowing or hardening of the arteries which may lead to strokes or heart attacks. Mateo et al in 2005 said, “...even if the side effect is rare, it is a serious one”

An item in The Crawley News (Trinity Mirror PLC) on 12/07/06 reported that a 23-year-old sales manager had collapsed and died from a brain haemorrhage. He was a fit, healthy man with no hardening of the brain arteries but had a history of cannabis abuse and had been complaining of headaches for some time. At the inquest, Dr Colin Hunter-Craig said, “He died of a brain haemorrhage due to cannabis abuse... This is incredibly rare in young people, but in old people we would recognise this as a stroke”.

Research in 2001 by Herning et al using Transcranial Doppler Sonography (Sound waves to measure cerebral artery blood flow resistance) found that prolonged marijuana use in 18 to 30 year olds increased the resistance in these arteries so restricting blood flow to the brain. 16 long-term male users were compared with 19 non-users. The deficit persisted for 4 weeks after abstinence. They compared the results to that of the brain of a 60 year old. Advancing age increases the chance of a stroke.

Mittleman and others in 2001 interviewed 3882 patients with heart attacks. He concluded that the risk of onset of myocardial infarction rose by almost 5 times in the hour following the smoking of a joint.

In January 2004 an article in Neurologist by Moussouttas reviewed all reported cases of presumed cannabis related cerebral ischemic events in the medical literature, as well as pertinent human and animal experimental studies on the cardiovascular and cerebrovascular effects of cannabis. His conclusion was "Cannabis use seems to have been causally related to several instances of cerebral ischemia and infarction. Proposed etiologic mechanisms have included cerebral vasospasm, cardio-embolization and systematic hypotension with impaired cerebral auto-regulation, but most of the available data points to a vaso-spastic process. The exact relation to cerebro-vascular disease remains to be determined".

We still do not know the long term effects of exposure to cannabis smoke on the cardiovascular system over several years but our experiences with the problems of tobacco smoke should make us very cautious. Jones (1984) suggested that, "after years of repeated exposure, there may be lasting, perhaps even permanent alterations of the cardiovascular system function". He says, "There are enough similarities between THC and nicotine's cardiovascular effects to make the possibility plausible".

One paper in 2004 involving a study on genetically modified mice found that THC helped prevent atherosclerosis, a "furring up" of the arteries caused by plaques of protein and other material. The study was headed by Francois Mach a cardiologist, and published in Nature. He warned that smoking cannabis would not be the answer as oxygen levels are reduced and THC increases the heart rate and interferes with blood pressure as previously described. He called for THC (already available as a medicine, Nabilone) or other cannabinoid derivatives to be investigated for this role. This is in line with all licensed medicines that must be pure single chemicals and subjected to standard clinical testing. This request was repeated in another paper by Mach and Steffens in January 2006.

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Cannabis and its Effects on the Immune System

Since crude cannabis often contains various species of pathogenic fungi and bacteria it is important to establish the effects of cannabis smoking on the immune system.

The immune system exhibits a complex array of responses. Innate responses involve macrophages, important in engulfing and destroying foreign matter and natural killer cells, morphologically like lymphocytes, they bind to target cells and insert destructive granules into them.

Acquired immunity consists of lymphocytes.

B cells are responsible for the production of antibodies in “humoral immunity”. T cells carry out “cell-mediated immunity”. Activated T-lymphocytes act as cytotoxic cells and/or release substances which activate monocytes (the forerunners of macrophages) and macrophages.

Early research into the immune system was documented in the 1981/82 WHO Report into the adverse effects of cannabis.

Experimental animals consistently produced evidence that THC or marijuana administered parenterally or by inhalation resulted in immunological defects in mice and rats, rats being the more sensitive (Munson and Fehr 1982). These defects included decreased antibody responses and reduced lymphocyte proliferation. The cell-mediated immune suppression in mice was measured by a reduced response to bacteria, skin grafts and foreign cells, it also decreased lymphocyte proliferation. These results were obtained by THC doses which produced very little behaviour effects in the mice. However Smith and others in 1978 suggested that cannabinoids other than THC may contribute to the immuno-suppressive effects. Rosenkrantz in 1976, experimenting on rats found that THC significantly inhibits humoral (related to the production of antibodies) and cell-mediated (dependent on the presence of activated T-lymphocytes) immunity in the immune response of rats in a dose-related manner. A similar response was obtained by marijuana smoke from an automatic inhaler (controlled by THC-absent smoke). Doses equivalent to human consumption were used.

At that time Munson and Fehr found the evidence as to whether THC or marijuana can perturb monocyte or macrophage function to be mixed. It appeared that the effects were more pronounced if the cannabinoids were given in the early phase of antibody production (Luthra et al 1980) and were even more pronounced in young animals (Pruess and Lefkowitz 1978). Also up till 1981/82 there was no definite proof of immune dysfunction in human users of cannabis. Evidence was very contradictory (Munson and Fehr 1982). They had looked at the numbers and functions of T and B-lymphocytes and macrophages. Serum immunoglobulin levels had also been investigated.

One study reported that the phagocytic ability of polymorphonuclear white blood cells was impaired (Petersen et al 1975) and another that there were biochemical and ultrastructural changes in the white blood cells of chronic hashish users (Stefanis and Issidorides 1976, Issidorides 1979).

Another approach to investigating a possible impairment of the immune system is to test the resistance of living organisms to infection. Cannabis-treated mice have shown a decreased resistance to infection by *Listeria monocytogenes* and Herpes simplex (Morahan and others 1979). In humans with dormant genital herpes, infections have been reactivated shortly after cannabis use (Juel-Jensen 1972). Other drugs which suppress the immune responses in mice also do the same in humans (WHO 1982).

A publication from the National Academy of Sciences, Institute of Medicine 1999, *Marijuana and Medicine: Assessing the Science Base*, gave an explanation of the problems encountered by human study researchers.

Blood leucocytes (white blood cells), isolated from people who have been smoking marijuana, used to evaluate the immune response in vitro almost always failed as the process involved high speed centrifugation and washing. This removed the cannabinoids (Kaklamani et al 1978, Lau et al 1976, Rachelefsky et al 1976 and White et al 1975).

Blood leucocytes from non-users can be used to test the effect of THC on their ability to proliferate in response to stimulation *in vitro*. The problem here is that marijuana smoke consists of many distinct cannabinoids, not just THC. At least one of the others, CBN (cannabinol) has greater activity on the immune system than on the CNS (Central Nervous System) (Herring and others 1998).

Another approach is to study human-derived cell lines. These lines can be treated with cannabis *in vitro* to test the responses to various stimuli. However subsequent cells may not be the same as the original one, eg not have the same number of cannabis receptors.

The late eighties saw a resurgence in research on cannabis and the immune system, probably prompted by the spread of AIDS.

RH Schwartz in an article in *The Journal of Hospital and Community Psychiatry* 1987 wrote that marijuana use is a factor in preparing the ground for HIV infection.

In 1988 Hamadeh and his associates warned that “Invasive *Aspergillus* (a fungus) has become a significant cause of death in immuno-suppressed patients. Physicians should be aware of this potentially lethal complication of marijuana use in compromised hosts such as patients with AIDS or malignancies”. Serious invasive fungal infections as a result of cannabis contamination have been reported among immunocompromised individuals including some with AIDS (Denning et al 1991).

In the same year, 1988, Tindall and others said that HIV positive marijuana smokers have an increased incidence of bacterial pneumonia compared to non-marijuana smokers, and added that marijuana smoking increases the progression to full-blown AIDS in HIV positive persons.

The fact that genital warts do not respond to systemic recombinant interferon alfa-2 treatment during cannabis consumption was discovered by Gross and others in 1991, and in 1994, Caiaffa and colleagues confirmed Tindall’s findings that marijuana smoking increases the incidence of bacterial pneumonias in AIDS patients.

A more recent study discovered that THC suppresses the immune function and enhances HIV replication in the hu PBL-SCID mouse. Exposure to THC *in vivo* can suppress the immune function, increase HIV co-receptor expression and act as a co-factor to significantly enhance HIV replication (Roth et al 2005).

Some hospital patients who had smoked 12 marijuana cigarettes a day for 4 days were found to have decreased antibody production in one type (IgG), Two other types of antibody were normal (IgA and IgM), and IgE was actually elevated (Nahas et al 1991).

Human mononuclear phagocyte cultures were treated with THC *in vitro*. There was a suppression of phagocyte function and also the spreading ability of macrophages. A metabolite of THC, 11-OH-THC, was found to reduce natural killer cell activity (Specter and Lantz 1991).

Cabral and others in 1991 carried out some experiments on rhesus monkeys. They subjected them to marijuana smoke in various groups for over a year then gave them a 7-month rest period. “High-dose” animals were given one marijuana cigarette a day, “low-dose” ones 1 marijuana cigarette for two consecutive days at weekends. Both groups had altered morphology of alveolar macrophages and protein expression. The cell surfaces were irregular and there was increased vacuolarization. Hosts thus affected could be at increased risk of infection.

THC is able to interfere with the functioning of white blood cells taken from humans. Both neutrophils which fight bacterial infection and mononuclear cells of the immune system which fight viruses were suppressed by various concentrations of THC (Djeu et al, Watzl et al, 1991).

In 1992 Cabral and Vasquez discovered that THC inhibited extrinsic but not intrinsic anti-herpes activity in a dose-dependent manner. This means that THC had no effect on the capacity of macrophage-like cells to take up the virus and no replication of the virus occurred inside the macrophage cells. However there was

an inhibition of the macrophages to suppress viral replication in infected virus-susceptible cells. The action was reversible on removal of the drug.

In the same year Kaminski and others found that cannabis receptors CB2 on spleen cells, when activated by THC, suppress the system whereby a secondary messenger substance is released in the cells. This results in the suppressed system reducing the functioning of the spleen cells involved in the immune response.

Laboratory experiments exposing human and rodent cells to THC or other marijuana ingredients resulted in the inhibition of the normal disease-preventing reactions of many key types of immune cells (Adams and Martin 1996).

T-cell proliferation was found to be normal in a group of marijuana smokers but when examined more closely there was an increase in one sub-set and a decrease in another (Wallace et al 1988, Whitfield et al 1997). Intermittent disturbances in T and B cell function were found but the magnitude was small and other measures were frequently normal (Klein et al 1998).

Professor Guy Cabral of The Department of Microbiology and Immunology, Virginia Commonwealth University, in the last 20 years has written over 50 papers on the subject of marijuana and the immune system.

In 1998 Cabral and Pettit wrote a review paper on the subject of cannabis and immunity. “This substance (*THC*) has been shown to be immunosuppressive and to decrease host resistance to bacteria, protozoan and viral infections. Macrophages, T-lymphocytes and natural killer cells appear to be major targets of the immunosuppressive effects of THC. Definitive data which directly links marijuana use to increased susceptibility to infection in humans is currently unavailable, however the fact that current literature reports indicate that THC alters resistance to infection in vitro in a variety of experiments on animals supports the hypothesis that a similar effect occurs in humans.

Cabral wrote another review of the literature in 1999 in *Marijuana and Medicine* (Nahas and Latour eds). “Marijuana has been shown to decrease host resistance to bacterial, protozoan and viral infections in experimental animal models and in vitro systems. Recent immuno-epidemiological studies suggest that marijuana may also influence the outcome of viral infections in humans. . . . Delta-9-THC alters the functioning of an array of immune cells including lymphocytes, natural killer cells and macrophages, thereby affecting their capacity to exert anti-microbial activities. . . . At sites such as the lung. . . THC may alter cellular membranes because of its highly lipophilic nature. . . , at sites distal to the lung, THC, at relatively low concentrations may exert its suppressive effects on immune cells by interacting with cannabinoid receptors CB1 and CB2”.

A Columbia study in 1999 by Dr James Dobson found a control group smoking a single marijuana cigarette every other day for a year had a white blood cell count 39% below the normal. He said, “ Marijuana can cause great harm”.

Apoptosis is the key mechanism programmed by the genetic code which regulates the life and death of a cell. It is the “programmed cell death” of all mammalian cells. Apoptosis relates to the destruction of the DNA formation by the cell itself. Professor Gabriel Nahas, interviewed for an Italian newspaper, Italy Daily Roma in 2000 said the process accounted for the findings more than twenty-five years (1973) before of the damaging effects of marijuana and THC on lymphocytes. THC induces apoptosis of the cells. Because of the long-term storage of THC in body fat, the “death signals” from the THC remain in the body and act on the cells for weeks.

Cultures of immune cells from mice, splenocytes and peritoneal macrophages were treated with THC and the DNA fragmentation preceded membrane damage, indicating that THC induced apoptosis rather than necrosis (Zhu et al 1998).

Mice exposed to THC or related substances were more likely to develop bacterial infections and tumours than unexposed mice (Zhu et al 2000).

Friedman and his colleagues produced a review paper in 2003. It covered several drugs of abuse and their effects on immunomodulation. He said, "Recent studies of the effects of opiates or marijuana on the immune system have demonstrated that they are receptor mediated, occurring both directly via specific receptors on immune cells and indirectly through similar receptors on cells of the nervous system.

Another deleterious effect of cannabis on the immune system was found by Tohyama and others in 2006. Cannabis can cause some white blood cells to lose the ability to migrate to sites of infection and inflammation. The cells seemed to lose their ability to develop a front/rear polarity needed to migrate to these sites.

The immune system has a part to play in the development of cancer through the activity of alveolar macrophages. The following paragraph is also included in my section on cannabis and cancer.

Alveolar macrophages protect the lungs from infection, they also kill tumour cells. Marijuana and tobacco smokers produce two or three times as many of these cells as non-smokers. The effects of smoking both being additive (Barbers et al 1987). The macrophages in both tobacco and marijuana smokers were larger and had more inclusions, probably due to the ingestion of smoke particles (Beals et al 1989). A more recent paper by Baldwin and others in 1997 found significant impairment of the macrophage cells of both tobacco and marijuana smokers. These cells have been shown to have cannabis receptors (Bouaboula et al 1993). Anti-tumour immunity depends on antigen-presenting dendritic cells being able to stimulate the proliferation of T lymphocytes that identify and destroy tumour cells. The in-vitro studies in which dendritic cells and T lymphocytes were incubated with or without THC, the THC suppressed the T cell proliferation in a dose-dependent manner (Roth et al 1997). Two earlier papers were written on this subject in 1975 by Petersen et al and Nahas et al.

DNA alterations have been seen in the lymphocytes of pregnant marijuana smokers and their newborns. This study is particularly important as tobacco smokers were excluded (Ammenheuser et al 1998). Cannabis smoking also depressed pro-inflammatory cytokine production. Cytokines regulate macrophage function so this may account for the impairment of their ability to kill tumour cells (Baldwin et al 1997).

Low levels of THC inhibited the tumour necrosis factor, thereby weakening the killing activity of lymphocytes against tumour cells (Kusher et al 1994).

Zhu and colleagues in 2000 showed that THC suppresses host immune reactivity against lung cancer. In two different lung cancer models in mice, intermittent administration of THC led to accelerated growth of tumour implants. He said, "Our findings suggest that THC promotes tumour growth by inhibiting anti-tumour immunity by a CB2 receptor-mediated pathway".

Pacifici and others in 2003 found cannabis smokers had fewer natural immune-enhancing killer cells and lymphocytes and higher levels of a protein that may promote tumour growth called interleukin-10. These changes can dampen the immune system's responses to infection, increasing susceptibility to infection and promoting tumour growth.

"The inability of alveolar macrophages from habitual marijuana smokers without apparent disease to destroy fungus, bacteria and tumour cells, and to release pro-inflammatory cytokines, suggests that marijuana might be an immunosuppressant with clinically significant effects on host defence. Therefore the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with pre-existing immune deficits – including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients)" (National Academy of Sciences *Marijuana and Medicine* 1999).

There have been a few papers putting forward the idea that cannabinoids or their metabolites may prove useful in the treatment of some cancers.

The administration of THC and a synthetic cannabinoid agonist into the tumour induced a considerable regression of malignant gliomas in rats and in mice. No substantial neurotoxic effect was produced by the cannabinoid treatment in the conditions employed.

Two glioma cell lines in culture demonstrated that the cannabinoids signalled apoptosis in the cells. It was suggested that these results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas (Galve-Roperph et al 2000).

A metabolite of THC is 11-COOH-THC, and ajulemic acid (AJA) is a synthetic analogue of it. In cell cultures AJA proved to be approximately one half as potent as THC in inhibiting tumour growth against a variety of tumour cell lines. However its effects lasted longer. The conclusion was that AJA produced significant anti-tumour activity and effected its actions primarily through CB2 receptors (Recht et al 2001).

Casanova and colleagues in 2001 showed that both CB1 and CB2 receptors are present in hair follicles and skin. The synthetic cannabinoid WIN55, 212-2 induced a decrease in the viability of several mouse skin cancer cell lines, non-cancer lines being unaffected. This occurred through the process of apoptosis. CB1 and CB2 receptors were involved.

Providing that purified single extracts of cannabinoids or synthetic equivalents are subjected to the rigorous clinical testing required by law, there should be no objection to these proposals. Crude cannabis is not a candidate for medical use.

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Cannabis, Depression, Aggression, Violence and Suicide

The association between cannabis use and depression has received much less attention than that between cannabis use and psychosis. It may be that depressed people are less likely to seek treatment than those with psychosis (Degenhardt et al,2001).

Thomas reported in a review article in 1993, that it was not possible to find scientific proof that cannabis causes a depression of clinical proportions. However he said there was a large body of clinical observations showing that short-lived dysphoric episodes can be provoked by the use of cannabis.

In Andreasson and Allbeck's study of 45,000 Swedish conscripts (1990) exploring relationships between cannabis, schizophrenia and suicide, they concluded that the cannabis indirectly increases the risk of suicide as a result of its ability to precipitate, exacerbate and cause depression and psychosis. In other words, the increasing frequency of suicides in large scale users was thought to reflect the increased frequency of depression in cannabis abusers.

Weller (1989) compared abusers, users and non-users in outpatients. Fifty-five per cent of the abusers had clinical depression according to the DSM III. Rowe (1995) found an association with marijuana and depression in women. However both these studies have many confounding factors known to be responsible for causing depression e.g. use of alcohol and sedatives, family background with significantly higher levels of drug abuse, criminal activity and suicide. So a causal connection was impossible to establish.

Data from The US National longitudinal Alcohol Epidemiologic Survey indicated a diagnosis of cannabis use or dependency in the last year was associated with a 6.4 fold increased chance of receiving a diagnosis for major depression in that time (Grant 1995).

More recently though, the questions of whether cannabis is a risk factor for causing depression, or depressed people use cannabis to self-medicate has been tackled by Bovasso in 2001. Based on data from 1980, he examined 1920 people in 1995.

"In participants with no baseline depressive symptoms, those with a diagnosis of cannabis abuse at baseline were four times more likely than those with no cannabis abuse diagnosis to have depressive symptoms at the follow-up assessment, after adjusting for age, gender, antisocial symptoms, and other baseline covariates. These symptoms mostly took the form of suicidal thoughts. Among the participants who had no diagnosis of cannabis abuse at baseline, depressive symptoms at baseline failed to significantly predict cannabis abuse at the follow-up assessment". This last finding was also reported by Kandel et al in 1984 and in 2000 by Kandel et al and McGee et al. In 2005, Hallfors et al also concluded that "Engaging in sex and drug behaviours places adolescents, and especially girls, at risk for future depression".

JS Brook and others in 2001 published a longitudinal study on over 2000 Colombian adolescents. A clear connection was found between marijuana use and raised levels of anxiety and depression. A prediction can be made of later distress in adolescence if marijuana is used at an early age.

DW Brook and others in 2002 in another longitudinal study found that early marijuana use in childhood and adolescence increased the risk of major depression by 17%. Again the warnings were given of the implications for psychiatric problems later in life because of early use.

Patton and others (2002) followed the progress of 1600 young people, male and female from the age of 14/15 in 1997/8, starting by and large before they had any mental problems or had used drugs. He studied them at 14/15 and again at 21/22. Daily use of cannabis in young women but not men, was linked with an increased risk of between 4 and 5 times in the odds of reporting a state of depression after adjustment for co-founding factors. Weekly use was associated with around a twofold greater risk for depression and the prevalence of the condition increased with higher usage of the drug. They also showed that depression in teenagers did not give rise to an increased cannabis use in early adulthood.

Chen and others (2002) on re-analysing the US National Co-morbidity Survey (NCS), found that those dependent on cannabis at some time in their lives was associated with a 3.4 times greater risk of major

depression. And also in 2002 in Australian adolescents a moderate connection was discovered between cannabis use and depression after taking account of other drug use, age and gender. The correlation was most marked in those who had used once or more in the last month (Rey et al, 2002).

Degenhardt et al (2003) reviewed the literature on this subject and produced the following results. "There was a modest association between heavy or problematic cannabis use and depression in cohort studies and well-designed cross-sectional studies in the general population. Little evidence was found for an association between depression and infrequent cannabis use. A number of studies found a modest association between early-onset, regular cannabis use and later depression, which persisted after controlling for potential confounding variables. There was little evidence of an increased risk of later cannabis use among people with depression and hence little support for the self-medication hypothesis. There have been a limited number of studies that have controlled for potential confounding variables in the association between heavy cannabis use and depression. These have found that the risk is much reduced by statistical control but a modest relationship remains".

Another review was conducted in 2004 by Rey and others. Their results were very similar. "There is growing evidence that early and regular marijuana use is associated with later increases in depression, suicidal behaviour and psychotic illness, and may bring forward the onset of schizophrenia. Most of the recent data reject the view that marijuana is used to self-medicate psychotic or depressive symptoms".

In a study of 600 same-sex twins, only one of whom was cannabis dependent, it was found that the risk of major depressive disorder was greater in the cannabis dependent twin of fraternal twins; this was not borne out in identical twins (Lynskey et al, 2004).

Other papers indicating a significant association between cannabis use and depressive orders include: Kelder et al (2000), Winokur et al (1998), Troisi et al (1998) and Miller et al (1996).

It is very difficult to determine whether cannabis is associated with violence due to the use of cannabis, withdrawal from the drug, a personality predisposition to violence or indeed because of the illegality. Disputes often arise between drug dealers, users and peers (Arsenault et al 2000). Professor Heather Ashton says in her 1999 review article, Adverse effects of cannabis and cannabinoids that "cannabis in most recreational settings decreases aggressive feelings in humans and increases sociability. However, occasional predisposed individuals, especially if under stress, become aggressive after taking cannabis. Violent behaviour may also be associated with acute paranoid or manic psychosis induced by cannabis intoxication".

Dyer (1996) wrote in the BMJ that, "Drug or alcohol misuse combined with a mental disorder could treble or quadruple the risk of violence".

Two studies by Kouri and others (1999 and 2002) investigated aggression during withdrawal from cannabis. The Harvard Study in 1999 compared 17 long-term heavy users with 20 infrequent or former smokers. All abstained from the use of cannabis and all other drugs for the duration of the experiment. They were not told that they were being monitored for aggression - temperature and heart rates were measured, so data were not gathered by "self-reporting". The heavy users showed much more aggression than the controls especially in the first week of abstinence. By day 28 this behaviour had faded.

In the 2002 study they monitored 30 current users and 30 controls (16 former heavy users and 14 light users). There was no difference between the groups to start with except in the ability to concentrate which was worse in the current users. The subjects reported an increase in irritability, anxiety, tension and physical symptoms peaking 7 to 10 days after abstinence. Thus from the 2 studies it can be argued that "aggressive responses of current cannabis users are due to marijuana withdrawal rather than a mere history of marijuana use".

Fergusson and others during The Christchurch Cohort Study in 1997 when the subjects were aged 16, assessed them for cannabis and violence (assault, fighting, weapon use, threats of violence against another). There was a dose-response relationship with higher cannabis use and an increasing number of violent offences which persisted after controlling for other drug use and peer criminal behaviour, suggesting that

deviant peer affiliations are not responsible. In a follow-up at the age of 21 (2002), they found the same association. The link was especially strong in those who had started using early, between 14 and 15 and were regular users (weekly or monthly). An increased frequency in incidents of property or violent crime, depression, suicidal ideation and suicide attempts was observed. The authors pointed out that there was a possibility that pre-existing psychosocial problems may have encouraged cannabis use rather than the other way around so caution must be applied and the results may not indicate a causal explanation for cannabis.

Spunt et al (1994) interviewed 268 people in prison for murder in New York State in 1984. 73 had been under the influence of cannabis at the time and 18 said that the use of cannabis was linked to their crime. When asked, 4 of them said it made them violent and aggressive, one said that when he was high he lost control and another that he doubted he would have done it had he not been under its influence. Four were of the opinion that it lowered their inhibitions and 2 said it made them paranoid. Some who were under the influence of both cannabis and alcohol at the time said the combined effect made them lose self-control.

Twelve cases of aggravated violent crime were looked at in Geneva between 1996 and 2000 (Niveau and Dang, 2003). All the perpetrators were under the influence of only cannabis at the time. Others were discarded because of poly-drug use. Five were previously known to have a personality disorder and three others had psychiatric disorders. All twelve suffered from severe negative effects of cannabis use. Four had an acute psychotic condition, one a relapse into or exacerbation of chronic paranoid psychosis, another 3 had intense anxiety and 3 delirium. The remaining one had a “mood” disorder. There is a growing interest in “dual diagnosis”, ie cannabis use is included as one of the disorders. There is also growing concern about the combination of alcohol and cannabis.

Serious problems of fighting with weapons, window breaking and theft in males and aggressive acts, violent quarrels with teachers, openly cursing or being sent to see the school head in females were all predictors for early cannabis initiation (Pederson et al 2001). Hall JA and others (2003) said that users of cannabis at an early age are at greatest risk of delinquency and violence. They are also most likely to engage in such behaviours before beginning to use cannabis.

Arsenault and others in their “Dunedin Study 2000”, discovered that alcohol dependent individuals were almost twice, marijuana-dependents almost 4 times, and those suffering from schizophrenia spectrum disorder, two and a half times more likely than controls to be violent (Arsenault et al, 2002).

A more recent investigation among 5,500 Dutch adolescents between 12 and 16, found that criminality and aggression increased with increasing use of cannabis. No link was discovered between internalising problems, withdrawal and behaviour. Social factors, regular tobacco smoking and alcohol use were all taken into account. Significant associations were only found in those who had used the drug recently (Monshouwer, 2006)

In a Welsh study of 740 identical and non-identical twins, it was found that, while the environment played a part in the development of cannabis use disorder in those with conduct disorder, genetics had a significant influence. Therefore the absence/presence of a conduct disorder in a twin pair is a good predictor of cannabis use. The findings suggest that cannabis use and violence to some extent co-occur due to personality tendencies (Miles et al, 2002).

Other researchers to find a connection between cannabis and violent behaviour are: Resnick et al, 1997, Dornbusch et al, 1999, Friedman, 1996 and White, 1998.

A 1995 (Fugelstad et al) Swedish study looked at suicides. In a study of 53 people who jumped from a great height, 11% were under the influence of cannabis, a disproportionate number. They calculated that a cannabis smoker is 18.7 times more likely to take his own life by jumping than a non-smoker. The number of cannabis-related suicides, in comparison with suicides related to the use of other drugs, users of heroin, amphetamines or alcohol, was much higher and none of them jumped from high places or committed murder before taking their own lives. No homicides were carried out by the users of other drugs who committed suicide.

Beautrais et al (1999) found only a very limited independent association between cannabis and suicide but indicated the indirect link by way of psychosis and depression, both of which can increase suicide rates.

The Australian News on November 25th 2002 reported a “Marijuana suicide epidemic” among the Aborigines in The Northern territories. In one community of 650 people, 30 suicide attempts related to cannabis were made in one year, in one month period, 3 succeeded. It appeared that they were buying marijuana, mixing it with alcohol and becoming paranoid.

Research was carried out in the Caribbean island of Trinidad where there is an established use of cannabis and high suicide rates. “Depression and psychotic experiences were common findings in adolescent cannabis users with a significant preponderance of depressive experiences. Our findings suggest that there is a convincing relationship between suicidal behaviour and cannabis use”(Maharajh and Konings, 2005).

There have been numerous reports in the press linking cannabis with violent incidents and suicide. These are a few examples:

A wealthy 52 year-old music producer was attacked in her home by a 20 year-old family friend made psychotic by the drug. She had to have 11 operations to rebuild her face. At the time doctors warned she would likely die (The Times 5/02/06). A judge attacked the use of cannabis after a 25 year-old professional golfer with a history of cannabis smoking killed his grandmother and aunt in a frenzied attack (Daily Mail 25/11/03). A coroner blamed cannabis for 2 deaths after a long-running feud over a hedge. A 52 year-old man grew his own supplies in his attic and had become addicted after smoking between 5 and 10 cannabis cigarettes a day. He shot his 66 year-old neighbour then committed suicide a week later in prison (Daily Mail 16/01/04). A teenager stabbed himself to death in the chest with scissors in front of his helpless father, he thought he was invincible. He had previously threatened his sister and girlfriend (Daily Mail 28/02/02). Then there was the well-publicised case of Luke Mitchell, 16 who slashed and killed his 14 year-old girl friend Jodi Jones in Scotland. He told his psychiatrist he smoked 600 joints a week (Daily Mail 12/02/05).

Britain’s most senior coroner, Hamish Turner, issued warnings in various papers in November 2003 that hundreds of young people are dying because of prolonged use of cannabis. He claimed that, over the last year, of the 100 deaths he had dealt with, 10% had a significant link to the drug (Daily Mail 3/11/03).

A 22 year-old nurse smoked cannabis for 5 years, became very depressed and hung himself in his bedroom (Daily Mail 12/06/05). A student hung himself after developing a mental illness induced by the use of cannabis. He left a suicide note which read, “Cannabis has ruined my life” (The Times 9/09/03). James Taylor hanged himself in his Torquay flat after smoking cannabis since he was 15. He suffered mental health problems and depression (Daily Mail 3/11/03).

I recently met a nurse from a GP Practice. She said, “If only people could come in and look at the records. The number of our young patients they would see who have as their priority condition: “Marijuana-induced depression, Marijuana-induced psychosis or Marijuana-induced schizophrenia, would really bring the problem home to them. They would not believe it. This is a huge problem”.

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Cannabis and Driving

Tests of car-driving on tracks free of other vehicles by Klonoff 1974, Hansteen 1976 and Attwood 1981, using low or even very low doses of THC, found slight to moderate impairment of driving ability.

Cannabis intoxication affects mental functions in the same way, whether the user is just starting, or is a regular smoker. Moscowitz, a leading researcher in this field, reported in 1985 that, even in *moderate doses*, cannabis use impairs the functions of co-ordination, tracking (following a randomly moving obstacle with an instrument), perception and vigilance. He proceeded to test drivers on car simulators and confirmed his findings. Moscowitz, Miller and Branconnier (1983) all recorded a deterioration of the ability to assess time accurately and an impairment of short-term memory. Although probably not of prime importance in driving cars, these deficiencies would be of vital significance in an airline pilot. Smiley (1986) using higher doses, suddenly placed an obstacle in the path of drivers on simulators and found several were unable to avoid a crash.

In an experiment on reaction times, Wilson and others in 1993 demonstrated that a clear association exists between the dose of cannabis (15-35mg) and reaction times.

In 1994, WHJ Robbe, of The University of Limburg in Maastricht, studied drivers who had taken 20 milligrams of THC - a very low dose. A single one-gram cigarette today can contain anything up to 200 milligrams. He found a significant deterioration in driving ability, especially keeping the car steady in the middle of a lane and a constant distance from the verge. He also discovered that, comparing the 20mg cannabis dose to a blood alcohol level of 1g/litre of blood (just over the legal limit) in identical studies, the results were very close as regards the deterioration in each variable.

Several researchers, including Robbe and Capel and Pliner 1973, have found on doing these kinds of experiments that, if strongly motivated, drivers can, barring distractions or unexpected complications, compensate for some of the impairments. The dangers posed by cannabis in a *real* situation, may therefore be underestimated.

And in 1995 Cheshier tested car driving ability in placebo-controlled studies in real traffic situations and dose-related performance decrements *were* recorded. An American study in 1988 by Carl Soderstrom et al, reported that, although 9 to 10 times as many people in the United States drink alcohol, cannabis is implicated in a similar number of accidents.

Janowsky used experienced airline pilots on flight simulators to investigate the problem. In 1976, despite the low dose (eight milligram) involved, the subsequent deterioration in short-term memory caused them to make mistakes. Confirmation came in 1991 in a well-publicised study by Leirer et al of Stanford, California. Using a dose of 20 milligrams THC, in a double-blind experiment, they found that the performance was worse in all aspects of flying, even up to and beyond 24 hours after consumption, and the pilots were totally unaware of a problem. Someone taking a joint today *should not* be driving tomorrow.

Tests on driving were carried out by a BBC team for a Five Live Report, "The Drug Drivers" on 30th December 2001. Radar equipment linked to satellites monitored the driving skills of a 32-year-old woman before and after she smoked a joint. There was a marked decline of her reaction times and in her overall competence. At 66 mph, she took on average of 4.6 seconds to come to a halt over 270 feet. After a joint her time increased to 5.35 seconds and the stopping distance to 308.5 feet. A sobriety test was failed almost an hour later.

Analysing blood samples from accident victims is an approach that some researchers have used. In 1988, Dr Dale Gieringer found that "Significant blood levels of THC occur 3 to 5 times more frequently in fatally injured drivers than in the normal population".

In 1980 Warren et al, researching in Ontario, found that those who drove under the influence of cannabis were almost twice as likely to be involved in an accident.

In 1990 this information was up-dated by Cimbura and others. He found that, of 1169 fatally injured drivers and 225 pedestrians between 1982 and 1984 in Ontario, THC was present in the blood of 10.9% of the drivers and 7.6% of the pedestrians, ethanol in 57.1% of drivers and 53.3% of pedestrians. This is a threefold increase in blood THC levels since the 1980 study.

1999 saw a report in The Canadian Journal of Public Health by Walsh et al, stating that cannabis is the most frequent illicit drug found in drivers killed or injured in motor vehicle collisions in Ontario, with 22.8% of drivers admitting driving under its influence.

Nearer home in Scotland in the same year, 1999, in a four-year period from 1995 to 1998, the Department of Forensic Medicine and Science (Seymour and Oliver) received 752 samples from drivers suspected of driving under the influence of drink or drugs in the Strathclyde region. Drugs were detected in 68% and 90% of blood and urine samples respectively.

Cannabis was the most frequent occurring in 39% of all positive blood samples.

Analysis of blood to quantify the amount of the drug “needed” to make driving hazardous was carried out in 1993 in a study of truck driver fatalities by Crouch and others. They concluded that marijuana use was a factor in all cases where the delta-9-THC content exceeded 1.0ng/ml of blood and alcohol where the blood/alcohol concentration was 0.04% wt/vol or greater. In 50 of 56 cases where psychoactive drugs or alcohol were found, impairment due to substance abuse contributed to the fatal accident.

Ramaekers et al in 2004 using more modern techniques for blood analysis, found an ever stronger link between cannabis consumption before or during driving and an increased risk of accidents than previously thought. He found that drivers under the influence were 3 to 7 times more likely to be the cause of accidents in which they were involved.

Researchers have repeatedly warned that, since alcohol affects the psychomotor functions fairly quickly, and cannabis the cognitive ones, the combination will undoubtedly be extremely dangerous, especially in a complex traffic situation. In 2002 Ramaekers team carried out a study and showed that moderate amounts of alcohol and moderate amounts of cannabis can together cause a very strong increase in the risk of making a driving error.

Differences in countries are apparent in this respect. In a 1986 USA survey by McBay, 75% of a sample of drivers involved in accidents had cannabinoids and alcohol in their blood. In Australia only 50% of the surviving drivers of dangerous or fatal collisions had this combination (Road Safety 1995) and in Norway (Gjerde 1991) 56% of drug impaired drivers were negative for alcohol but positive for THC.

In their 1997 report on cannabis the WHO said that cannabis increases the risk of motor vehicle accidents and the risk is much higher with a combination of cannabis and alcohol.

A French study in 2003 by Mura et al took blood from 900 injured road traffic accident victims and compared it with blood from 900 controls at the same A and E departments but not for traffic accidents. The most common drug detected was alcohol but for cannabis alone (no other drug in the system) 10% of drivers tested positive and only 5% of the controls.

The BMJ in December 2005 carried a paper by French scientists led by Bernard Laumon. From 10,748 fatal car crashes between 2001 and 2003 they investigated the 6766 drivers held to be responsible for the accident. The controls were 3006 of the other drivers. Taking into account the age of the vehicle and age of driver, the researchers concluded that cannabis caused a significant number of the fatalities. 681(7%) tested positive for cannabis and 2096 (21.4%) for alcohol. Cannabis was deemed directly responsible for 2.5% and alcohol 29% of the crashes. A combination of cannabis and alcohol was held to be 16 times more risky than either drug alone.

Another factor to consider is that, cannabis users erroneously think they have “sobered up” long before they really have, so they may well drive before they should. In a survey at Glasgow University, at the beginning of 2001, it was reported that one in 10 young people between 17 and 39 regularly drove under the influence of drugs, 75% after smoking cannabis. They were also quite happy to take a lift from friends who had just

taken drugs. A huge six-fold increase in road crash victims found with illegal drugs in their systems sparked off this study of 1000 drivers. One “spliff” is thought by some experts to have the same effect as the amount of alcohol needed to just exceed the drink-drive limit. The biggest problem was among men between the ages of 20 and 24. There are now increased calls for reliable roadside testing for drugs to be introduced. The difficulty here, is to ascertain when the drug was actually taken. In the case of cannabis, the consumption of a joint only once a month or even less frequently, will give consistently positive results. Blood levels of THC may prove useful in this respect.

A month later, an Internet study was conducted for ‘Max Power’ a motoring magazine for young people, especially aimed at men between 17 and 24. This revealed an even more alarming 27% of youngsters regularly driving at least once a week while under the influence of drugs; most of them boasting that their driving skills actually improved, 36% confessed to a monthly occurrence. Cannabis was, by far, the commonest drug taken. The Daily Mail reported on 23rd April 2006 that another survey for “Max Power” had revealed a huge increase in these figures. Nearly half of the 447 youngsters interviewed admitted to driving regularly after having taken drugs like ecstasy or cocaine, one in five said it was a daily occurrence. They were confident of escaping detection because of the lack of roadside tests which are not due to be in use for about 2 years.

An analysis of the 2003 Monitoring the Future and Census Bureau data in the USA showed the following results: Out of nearly 4 million high school seniors in America, it was estimated that approximately one in six i.e. 600,000 drove under the influence of marijuana, nearly the same as for alcohol, 640,000. An estimated 38,000 reported they had crashed while under its influence in 2001, 46,000 while affected by alcohol.

Many youngsters seemed totally ignorant of the law, they were not aware that it is an offence to drive under the influence of drugs, as it is with alcohol.

In 2002 a paper from New South Wales (O’Kane et al) in Australia reported, “ The incidence of driving while affected by cannabis is rising in parallel with increasing cannabis use in the community. Young drivers are at particular risk. Improvements in research, methodology, technical and laboratory testing methods have occurred in the last 10 years. ...Studies now show that cannabis has a significant impairing effect on driving when used alone and that this effect is exaggerated when combined with alcohol. Of particular concern is the presence of cannabis as sole psychiatric drug in an increasing number of road fatalities”.

An Economic and Social research Council team led by Dr Philip Terry of Birmingham University released a study on 27th January 2004. Most regular cannabis users admitted to driving under the influence of the drug in spite of being aware that it impairs their performance. 74% had taken a car or motorbike on the road while feeling stoned, 70% believed it had a bad effect on their driving, but 41% felt their actions were acceptable. 100 frequent users (4 to 7 times a week) and 90 casual users (no more than 4 days a month) were questioned. One third of the frequent users were willing to drive even when they considered themselves to be “very high”. Nearly 80% said roadside testing would be a deterrent although one in eight had been stopped while under its influence and none had been tested for intoxication by the drug or charged for being under its influence.

A bulletin from The New South Wales Bureau of Crime Statistics and Research Number 87 in September 2005 by Jones et al, concluded that “Random drug testing appears to act as a more effective deterrent against drug-driving than an increase in the severity of sanctions or providing factual information about the risks associated and the behaviour”.

The Monash University Accident Research Centre in Australia produced a report in 2004 reviewing the epidemiological, driving performance and drug screening literature as it relates to cannabis and road safety. Data for fatally injured drivers between 1997 and 1999 show that 8.5% of those tested were positive for THC, the psychoactive component. They were found to be significantly more culpable than drug-free drivers, even more so when the cannabis was combined with alcohol. They reported, “Recent on-road and simulator studies have set the bench mark for cannabis and driving research. There is no doubt that recent research is continuing to show that cannabis, both alone and with alcohol, impairs a range of measures of

driving performance. The predominant form of impairment observed after smoking cannabis alone is an increase in lane-weaving behaviour...also... increased variability in headway to a lead vehicle. This is an important finding because it is commonly interpreted as reflecting the ability to perceive changes in the relative velocities of other vehicles and ability to adjust own speed accordingly, and is suggestive of impaired perceptual abilities. When cannabis is combined with alcohol, variability of headway is again increased, and variability in lane-weaving behaviour is increased to a greater extent than for cannabis alone. This is again indicative of impaired performance. Furthermore drivers with both cannabis and alcohol take significantly longer to react to changes in the speed of other vehicles. The frequency of visual search for traffic at intersections has been found to be similar for placebo, alcohol alone and cannabis alone, but reduced significantly when alcohol and cannabis are combined.drivers are less able to respond to peripheral traffic while maintaining performance on the central driving task”.

The increasing toll of accidents caused by drugged drivers is well publicised in the press. Recent reports include the death of a four-year old girl by a driver who had earlier smoked 2 cannabis joints. Barnaby Pearce 19, driving at almost 80 mph in a 60 mph zone, smashed into the side of a car driven by the girl’s grandfather (Daily Mail 19/8/05). Another 19 year old, Mitch Treliving killed himself and 7 other people in a head-on crash after driving at 100mph and losing control. His airborne BMW landed on a Land Rover on the opposite carriageway. A pathologist said there were trace amounts of alcohol in his blood but more significant levels of cannabis (Daily Mail 14/4/05). And David Whitnall 26, a self-confessed user of skunk, almost daily since his teens, ploughed into the back of a Fiat at 120mph while steering his sports car with his knees. He killed a woman and severely injured her husband. He was given 6 years in prison and a 10-year ban. Skunk was found in his possession (Times 3/2/06).

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Cannabis and Cancer

There are several problems associated with the investigation of possible links between cannabis use and any carcinogenic effects it may have on human cells.

There are now some 140,000 or so scientific research papers on tobacco, while those on cannabis still amount only to about a tenth of that number. It is a relatively young science and, like tobacco, its side effects are usually not apparent for decades.

Cannabis smoking has only been widespread in Western society since the early 1970s and there would presumably be a 20 to 30 year latency period between the initiation of smoking and the development of cancer as is the case with tobacco.

Cannabis smokers often mix tobacco with their cannabis so they run all the well-documented risks of developing cancer associated with tobacco smoke. Relatively few of them smoke cannabis alone so any consequences and therefore causes are almost impossible to separate out. Marijuana smokers are more likely to under report their smoking, if they report it at all.

Large samples are required for case-control studies to take place. It is very difficult to get reliable information about an illegal substance from a large number of people. Questions about cannabis smoking are rarely asked of lung cancer patients.

On the other hand the similarities between tobacco and cannabis are many, the main difference being the presence of nicotine in tobacco and the 60 or so cannabinoids in cannabis (Hoffman et al 1975, Tashkin et al 1997, BMA 1997). So similar side effects may be expected.

Although the number of cannabis "cigarettes" consumed in a day would generally be much fewer than the daily total of tobacco cigarettes, the technique is different. Cannabis smoke is usually inhaled more deeply, held in the lungs for longer and smoked right down to the butt to get full money value. Cannabis cigarettes generally lack filters. (Wu et al 1988). More tar is inhaled from the cannabis butt than from its tip (Tashkin et al 1999).

Cannabis smoke contains 4 to 5 times as much tar as tobacco smoke so the amount of tar deposited in the lungs daily in a cannabis smoker is comparable to that of a tobacco smoker with a 20 a day habit (Benson et al, 1995).

Also the tar from cannabis contains 50% more of some of the carcinogens found in tobacco, notably benzpyrene, a potent carcinogen and a key factor in the promotion of lung cancer (Hoffman et al 1997, Tashkin et al 1997, Novotny et al 1976, Leuchtenberger et al 1983).

For lung cells to become cancerous, a particular combination of cell-growth regulating genes (oncogenes) must become activated or undergo mutation (suppressor genes of tumours).

Marijuana smoke has been reported to produce chromosome aberrations in bacteria as demonstrated by the Ames test (Busch et al 1979 and Wehner et al 1980).

Biopsies of bronchial mucosa have yielded interesting results. Abnormal proliferation of cells (goblet and reserve), transformation of normal ciliated cells to squamous metaplasia (skin-like cells), accumulation of inflammatory cells and abnormal cell nuclei have all been observed (Gong et al 1987, Fliegel et al 1997, Barsky et al 1998). A much higher proportion of these abnormalities was seen in marijuana smokers compared to non-smokers, the number was similar to that of tobacco smokers. Smokers of both tobacco and marijuana exhibited the highest number of all, suggesting the two have an additive effect. Precursors of the development of lung cancer in tobacco smokers include squamous metaplasia and abnormal nuclei (Auerbach et al 1961). Confirmation of these observations also came in 1980 from FS Tennant when he examined US servicemen who were heavy hashish smokers. The mutagenic properties of cannabis smoke

were previously recorded in papers in the seventies (Magus and Harris 1971 and Hoffman et al 1975). Human lung explants, exposed to marijuana smoke resulted in DNA and chromosomal alterations (Van Hoozen et al 1997).

Oncogenes and tumour suppressive genes, when mutated, produce proteins which cause cells to multiply rapidly and uncontrollably, resulting in tumours. Two of these proteins were found to be markedly increased in cannabis smokers compared to tobacco or non-smokers, the effects of tobacco and cannabis being additive (Roth et al 1998).

The mutagenic effects of marijuana smoke have also been observed by Chiesara and Rizzi 1983, Gilmore et al 1971, Herha and Obe 1974 and Stenchever et al 1974.

Benzpyrene can cause alteration of a gene, P53, one of the commonest tumour suppressor genes if acted on by a chemical particle, CYP1A1. THC has been shown to increase production of this particle so making possible the development of respiratory cancer. P53 is thought to play a part in 75% of lung cancers and it is expressed in 11% of cannabis and tobacco smokers (Dinissenko et al 1996, Marques-Magallanes et al 1997).

The immune system has a role to play in the development of cancer. Alveolar macrophages protect the lungs from infection, they also kill tumour cells. Marijuana and tobacco smokers produce two or three times as many of these cells as non-smokers. The effects of smoking both being additive (Barbers et al 1987). The macrophages in both tobacco and marijuana smokers were larger and had more inclusions, probably due to the ingestion of smoke particles (Beals et al 1989). A more recent paper by Baldwin et al in 1997 found significant impairment of the macrophage cells of both tobacco and marijuana smokers. These cells have been shown to have cannabis receptors (Bouaboula et al 1993). Anti-tumour immunity depends on antigen-presenting dendritic cells being able to stimulate the proliferation of T lymphocytes that identify and destroy tumour cells. In in-vitro studies in which dendritic cells and T lymphocytes were incubated with or without THC, the THC suppressed the T cell proliferation in a dose-dependent manner (Roth et al 1997). Two earlier papers on this subject were written in 1975, Peterson et al and Nahas et al. DNA alterations have been seen in the lymphocytes of pregnant marijuana smokers and their newborns. This study is particularly important as tobacco smokers were excluded (Ammenheuser et al 1998). Cannabis smoking also depressed pro-inflammatory cytokine production. Cytokines regulate macrophage function so this may account for the impairment of their ability to kill tumour cells (Baldwin et al 1997).

Experiments on animals have yielded confirmatory evidence for many of the previous observations. In 1979 Rosenkranz and Fleischman found changes in the bronchial epithelia of rats after they had inhaled marijuana smoke for several months. These changes were consistent with precancerous alterations in cells. In the same year Fried and Charlebois administered cannabis smoke to rats during pregnancy and discovered impaired development in the F2 generation, so not only was damage caused to the first but also the second generation. In 1997 Zhu and others treated mice for 2 weeks with THC prior to the implantation of Lewis lung cancer cells. Larger faster-growing tumours resulted suggesting that the THC impairs the development of anti-tumour immunity in vivo. Dubinett et al in 2000 also found that mice injected with THC had reduced capability to fight the growth of tumours.

Painting tar from marijuana smoke on the skins of mice produced lesions correlated with malignancies (Cottrell 1973).

There are a significant number of reports of human cancers which may be linked to the smoking of marijuana. FM Taylor in 1988 examined adults with upper respiratory tract cancer over a period of 4 years. Of 6 men and 4 women, average age 33.5 years, nine had carcinomas of the lungs tongue or larynx, five were heavy cannabis smokers, two smoked it regularly, one had possibly used other drugs and two were non cannabis smokers. It was complicated by the fact that six were heavy alcohol users and six were smokers of tobacco. He concluded that regular marijuana use was a potent factor especially in the presence of other risk factors. He conceded that alcohol and tobacco may have played a part, but pointed out that the peak incidence for cancers due to tobacco or alcohol is in the seventh decade of life. All of these victims were much younger.

In 1989 Caplan and Brigham reported two cases of tongue cancer. One was a man of 37 the other a man of 52. Both were heavy cannabis users, neither smoked tobacco or drank alcohol. Endicott and Skipper in

1991 conducted a 2-centre USA retrospective study. Twenty-six patients of age 41 or less were diagnosed with throat or head tumours. The normal average age for tumours of this type is 57. All 26 were current or former marijuana smokers.

PJ Donald in 1993 examined patients with cancer of the head and throat over a 20-year period. He found 22 patients of age 40 or under on diagnosis, with squamous cell cancer. Their average age was 26. Nineteen of them were cannabis smokers, 16 being heavy users. In 13 the tumour was in the tongue or elsewhere in the oral cavity. Only half of them smoked tobacco.

110 private patients with lung cancer were studied. Nineteen (17%) of them were under 45. Thirteen of these had smoked marijuana of whom 12 reported current tobacco use. No tobacco-only smoking patients under 45 were noted (Sridhar et al 1994).

An epidemiological study to examine a possible association between cancer and marijuana was published in 1997 by Sidney and colleagues. 65,000 health plan members aged between 15 and 49 in 1979 to 1985 were followed for the development of new cancers till 1993. 182 tobacco-related cancers were detected, of which 97 were in the lungs. The study revealed no risk factors for cancers for lifetime or current use of marijuana.

The major limitation in this exercise is that those who were heavy or long-term users of cannabis were not followed up for long enough to detect cancers. Another criticism is that there may not have been sufficient of these long-term or heavy users to make the study effective. It must be remembered that most marijuana users quit before the level of exposure is sufficient to initiate the development of cancer and cannabis smoking has only been widespread in the USA since the 70s.

Zhang et al in 1999 studied 173 patients with carcinoma of the head and neck and compared them with 176 cancer-free controls. Age, sex, race, education, alcohol consumption and exposure to cigarette smoke either actively or passively, were all controlled for. Marijuana smoking increased the risk of squamous cell carcinoma of the head or neck, and a further increased risk was suggested with rising doses. Among people who smoked once a day the risk factor was 2.1 times compared with non-smokers, with those using it more than once a day the risk factor rose to 4.9. With patients who smoked cannabis and tobacco the risk was 36 times that for non-smokers.

It was reported in the press in January 2000 that a leading cardio-thoracic surgeon, Mr Alan Kirk of Glasgow's Western Infirmary was treating 12 patients aged 27 to 35 for lung cancer. Ten of them admitted they were regular cannabis smokers. Lung cancer normally develops in much older patients. All of them had also used tobacco but Mr Kirk said he thought it likely that cannabis had accelerated the process. He now routinely asks all his younger lung cancer patients whether they have smoked the drug. He has called for large scientific studies to be done.

The most prominent name and authority on cannabis and diseases of the respiratory system is that of Dr Donald Tashkin. He has researched the topic since the early seventies.

In 1993 he listed the factors suggesting that cannabis smoking may be associated with an increased risk of respiratory tract cancers.

1. Cannabis smoke has 50% more of certain carcinogens than tobacco smoke, especially the highly carcinogenic benz-pyrene.
2. Four times as much tar is produced by a cannabis cigarette than a tobacco one.
3. Experiments on animals have shown that cannabis smoke or tar from it is carcinogenic.
4. Heavy cannabis consumers have significantly higher numbers of cellular changes consistent with the preliminary stages of cancer.
5. There have been several reports of young cannabis-using people exhibiting the development of cancer. Tumours have appeared 10 to 30 years earlier than those who smoked tobacco alone.

In a review paper in 2002 he added that examination of the mucous membranes in long-term smokers suggests that THC weakens the immune defences against tumour cells.

In November 2002 the British Lung Foundation produced a paper "A Smoking Gun? The Impact of Cannabis Smoking on Respiratory Health". One of their recommendations was: "The British Lung Foundation recommends a public health education campaign aimed at young people to ensure that they are fully aware of the increased risk of pulmonary infections and respiratory cancers associated with cannabis smoking".

In September 2003 The Thoracic Society of Australia and New Zealand produced a position paper in The Internal Medicine Journal on the respiratory health effects of cannabis (Taylor and Hall). They also called for a campaign. "Public Health Education should dispel the myth that cannabis smoking is relatively safe by highlighting that the adverse respiratory effects of smoking cannabis are similar to those of smoking tobacco...that the respiratory hazards of smoking cannabis are significant...almost all studies indicate that the effects of cannabis and tobacco smoking are additive and independent".

Gardner and others in 2003 found that a cannabinoid, methanandamide, resulted in an increased rate of tumour growth in murine lung cancer.

The death rate from lung cancer in Maori people is 3 times higher than in non-Maoris. In fact they have the highest lung-cancer death rate in the world. The average age of death is lower, 63 compared to 70 years. There is also a high incidence of tobacco smoking in these people, but equivalent rates are seen in areas of Asia and Europe where fewer succumb to cancer of the lung. A high rate of heavy marijuana use among the Maoris has led scientists to suggest that this may be a contributory factor. Research has shown that cannabis use has reached epidemic proportions and is rising (Harwood et al 2004). The Sydney Morning Herald on July 27th 2006 reported that, of the 142,144 people treated by Australia's drug and alcohol treatment agencies in 2004-2005, 13,666 or almost 10% were Aboriginal or Torres Strait Islanders, amounting to nearly 5 times the proportion of indigenous people in the population. Among these people, 21% of males between 10 and 19 years were treated compared to 11% of other Australian males of the same age. With indigenous 10 to 19 year-old females the figures were 19% compared to 11% of the others. Cannabis was the commonest illicit drug for which treatment was sought.

Sarafian et al in 2005 suggested that THC contributes to DNA damage, inflammation and alterations in apoptosis (programmed cell death) in tracheo-bronchial epithelium and concluded that, "THC delivered as a component of marijuana smoke, may induce a profile of gene expression that contributes to the pulmonary pathology associated with marijuana use".

In June 2005 Roth and Tashkin of UCLA, the two leading authors of many papers linking cannabis and cancer for over 10 years, described an epidemiological study at the meeting of the International Cannabinoid Research Society in Tampa, Florida. This paper has yet to appear on the ICRS website. Tashkin reported that they had failed to substantiate the link. Needless to say the press immediately issued banner headlines like "Marijuana is safer than tobacco". However it has emerged that the study lacked statistical power. Tashkin and Roth explained that they had very few patients smoking more than 6 joints a day, a very mild level of consumption. They said that had they had more moderate and heavy smokers, their outcomes would almost certainly have been different. The study was originally designed to have 3 controls for each cancer case, in reality the ratio was around 0.7. Statistics are powerful but not powerful enough to account for gross flaws in sampling errors and study design.

Tashkin also in June 2005, reviewed the literature on lung injury caused by smoking marijuana. He concluded, "Regular marijuana smoking produces a number of long-term pulmonary consequences including chronic cough and sputum, histopathologic evidence of widespread airway inflammation and injury and immunohistochemical evidence of dysregulated growth of respiratory epithelial cells that may be pre-cursors of cancer.....Habitual use of marijuana is also associated with abnormalities in structure and function of alveolar macrophages including impairment in microbial phagocytosis and killing that is associated with defective production of immunostimulatory cytokines and nitric oxide thereby potentially predisposing to pulmonary infection".

Dr Martha Terris et al, of Georgia's Medical College and the Veterans Affairs Medical Centre Augusta, writing in Urology January 2006 reported that, of 52 men between 44 and 60 with transitional cell bladder cancer, 88.5% had a history of marijuana smoking. Almost 31% were still using the drug. 104 controls

were seekers of urological care other than bladder cancer. Tobacco smoking is the major risk for bladder cancer but is only common in the over 60s. Since marijuana metabolites have a half-life in urine about 5 times greater than tobacco metabolites, they warned that, "Marijuana smoking may be an even more potent stimulant of malignant transformation in transitional epithelium than tobacco smoking".

A systematic review of 19 studies into the impact of marijuana smoking on the development of pre-malignant lung changes and lung cancer was carried out by Mehra et al in 2006. Deficiencies in the methodology of some of the studies were noted. The conclusion was as follows: "Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions".

In 1981 the WHO report on cannabis use said, "It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, "risk factors" have been freely identified, although full causality has not yet been established. Nevertheless such risk factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is often not applied to cannabis"... "To provide rigid proof of causality in such investigations is logically and theoretically impossible, and to demand it is unreasonable".

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Cannabis and Dependence

Drug abuse: Individuals cause harm to themselves (physical, mental or social) or to others through use of the drug. There is a degree of control, use is not constant and they can abstain.

Dependence: A compulsive need for the drug. All harm (physical, mental and social) is ignored as are all other everyday interests. Obtaining the drug becomes all-consuming.

Physical dependence: produces tolerance where more of the drug is needed to get the same effect. Changes take place in the brain. Also observed are **withdrawal symptoms** when use of the drug is stopped. (Because of the long-term persistence of THC in brain cells, the withdrawal symptoms are ameliorated unlike the more dramatic symptoms of heroin withdrawal which is metabolised quickly. Heroin users need a “fix” about every 4 hours).

Psychological dependence: A strong desire or craving for the drug. The drugged state is preferred to normality. It is the more difficult to treat.

Almost all addictive drugs stimulate a part of the brain, the mesolimbic **dopamine system** which is the Central nervous System’s Reward Pathway. Cannabis receptors are found here. When stimulated, these receptors begin the cycle of reward which can lead people on to take more. This circuit is shared with animals. (Koob GF 1992).

Some early experiments on dependence failed to prove anything as the doses given to experimental subjects were unrealistically low and the timescale was too short (e.g. Hollister 1986). However in 1983, Jones et al had given higher and more frequent doses for 3 weeks. Their subjects rapidly developed tolerance and showed withdrawal symptoms. And before that, in 1979 Georgotas and Zeidenberg gave daily doses of 210mg THC, equivalent to a single 1g cigarette today. After 4 weeks the subjects found the marijuana “much weaker” In the first week of abstinence they were irritable, unco-operative, resistant and “hostile”, suffered from insomnia and were hungry. The symptoms took 3 weeks to disappear.

After 1986, a substantial number of studies and observations have supported these findings, ie that dependence develops in association with long-term use. (e.g. Miller and Gold 1989, Gable 1993 and Stephens et al 1993).

It was also generally agreed that tolerance develops (Compton et al 1990, Oviedo et al 1993, De Fonseca et al 1994).

Haney et al 1999, researching oral cannabis, THC and cigarettes with 1.8-3.1% THC, described in particular the tolerance to the “high” sought by users.

This tolerance results in a rise in dosage or increased use observed in experiments and in studies of users (Swift et al 2001, Coffey et al 2000, Von Sydow et al 2001)

Compton also described the withdrawal symptoms he found: sleeplessness, anxiety, irritability, sweating, trembling, nausea and weight loss. The severity of these symptoms increased with a longer time, a greater frequency and a larger dosage.

Withdrawal symptoms were also found by Duffy and Milin 1996, Hutcheson et al 1998, Haney et al 1999, Kouri et al 1999 and Johns 2001) The prevalence of withdrawal symptoms in chronic cannabis usage was estimated at 16 to 29% (Thomas 1996 and Wiesbeck et al 1996).

More serious withdrawal symptoms, psychiatric problems and aggression, were reported by Teitel 1971, Rohr et al 1989, and Kouri et al 1999.

People using cannabis therapeutically reported uncomfortable feelings on cessation of use (BMA 1997).

Crowley et al in 1997 looked at University-based adolescents in treatment programmes for substance abuse. They involved males and females. 78.6% met the standard criteria for cannabis dependence. Two thirds (over 80% of men and over 60% of women) reported withdrawal symptoms. The progress from first use to regular use was as rapid as tobacco progression and more rapid than alcohol, suggesting cannabis is a reinforcer. All the patients said that cannabis had clearly caused serious trouble in their lives.

Experimental animals had brain changes similar to those resulting from opiate, alcohol and cocaine withdrawal (De Fonseca et al 1997). Laboratory animals (squirrel monkeys) will self-administer doses of THC equivalent to those used by humans. Self-administration by animals has long been considered a model for human drug-seeking behaviour characteristic of virtually all abused and addictive drugs. The drug-seeking behaviour was comparable in intensity to that maintained by cocaine under identical conditions therefore suggesting that marijuana has as much potential for abuse as drugs like heroin and cocaine. (Goldberg et al 2000).

As a result of these findings, cannabis dependence (but not yet “withdrawal conditions following cannabis use” due to continuing disagreement among researchers) was included as a diagnostic unit in the DSM IV (Diagnostic and Statistical Manual of Mental Disorders 1994) and ICD-10, WHO 1992.

The European Description of The ICD-10 Classification of Mental and Behavioural Disorders, WHO, Geneva, 1992 Diagnosis of Cannabinoid Dependence Syndrome, is as follows:

Diagnostic Guidelines

A definite diagnosis of dependence should be made only if three or more of the following have been experienced or exhibited at some time during the previous year.

- (a) a strong desire or sense of compulsion to take cannabinoid;*
- (b) difficulties in controlling cannabinoid-taking behaviour in terms of its onset, termination or levels of use;*
- (c) a physiological withdrawal state when cannabinoid use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for cannabinoid; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;*
- (d) evidence of tolerance, such that increased doses of cannabinoid are required in order to achieve effects originally produced by lower doses;*
- (e) progressive neglect of alternative pleasures or interests because of cannabinoid use, increased amount of time necessary to obtain or take the substance or to recover from its effects;*
- (f) persisting with cannabinoid use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.*

Narrowing of the personal repertoire of patterns of cannabinoid use has also been described as a characteristic feature.

It is an essential characteristic of the dependence syndrome that either cannabinoid taking or a desire to take cannabinoid should be present, the subjective awareness of compulsion to use drugs is most commonly seen during attempts to stop or control substance use.

Morgenstern et al in 1994 found the DSM concept at least as valid as those for dependence found in opiates, alcohol, stimulants and sedatives.

Jan Ramstrom who wrote “Adverse Health Consequences of cannabis Use”, A Survey of Scientific Studies published up to and including the Autumn of 2003 said, “...there is now general agreement on the issue of cannabis and dependence including the importance of withdrawal symptoms”.

One recent paper seems to buck the trend of the general acceptance of cannabis addiction and the fact that it is a recognised diagnosable condition. In 2002, NT Smith published a review paper in “Addiction”. “This review highlights the methodological weaknesses in some of the literature on this subject ie variable levels of drug dose administration in laboratory conditions, lack of controlled studies and absence of definitions of the withdrawal syndrome. It concludes that more controlled research might uncover a diagnosis of withdrawal symptoms in human users and may be a precedent for the introduction of a cannabis-withdrawal syndrome before the exact root is known”.

Coffey et al in 2003 reported that weekly use of cannabis marks the threshold for an increased risk of later cannabis dependency with selection of cannabis in preference to alcohol possibly indicating an early addiction process. She found that 30% of teenagers smoking more than one a week became addicted by their early twenties, those between 14 and 17 were 20 times more likely. Those starting between 14 and 15 progressed to the most harmful use. Almost 66% of teenagers smoke cannabis and about 7% show signs of dependence. The more they smoke, the higher the risk. Interestingly, dependent cannabis users reported compulsive and out-of-control use more frequently than dependent alcohol users, withdrawal to a similar extent and tolerance considerably less often.

Chambers and others in a paper in 2003 on the development of the adolescent brain, warned of their increased vulnerability to addiction compared to adults. He suggested that drug addiction should be thought of as a development disorder in the brains of teenagers, as the changing brain circuitry leaves them especially vulnerable to the effects of drugs and alcohol. This brain circuitry is centred on the chemical (neurotransmitter) dopamine. Parts of the brain changing rapidly during adolescence are stimulated by addictive drugs. The circuitry that releases chemicals that associate novel experiences with motivation to repeat them develops far more quickly in adolescence than the mechanisms that inhibit urges and impulses. Drugs tapping into this neural imbalance may underlie a teenager’s affinity for impulsive and risky behaviour. They are more likely to experiment with drugs but the experience will have more profound effects, sometimes permanent, on the brain. “You have a situation where the motivational brain areas are particularly active”, he said, “and the part of the brain that is supposed to inhibit impulses is not working well, because it is sort of under construction. The parts of the frontal cortex that are activated by adults when they weigh risks and rewards lag developmentally”.

A definitive review of the addictive propensity of cannabis was undertaken in 2003 by Eliot L Gardner. He reviewed 224 scientific papers, 75 of which were published in the 1970s and 80s and the other 149 after 1989. He concluded that “cannabinoids act on the brain reward processes and reward-related behaviours in strikingly similar fashion to other addictive drugs”.

And a review of papers (55 references) dealing with withdrawal symptoms was published in 2004 by Budney, Hughes and others. “Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol.The onset and time course of these symptoms appear similar to those of other substances withdrawal symptoms. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance”.

Continuing their work, Budney and Hughes have just (2006) contributed again to our knowledge of the withdrawal syndrome in cannabis. In their “Purpose of review” they say, “The demand for treatment for cannabis dependence has grown dramatically. The majority of the people who enter treatment have difficulty in achieving and maintaining abstinence from cannabis”. Among their findings are, “The neurological basis for cannabis withdrawal has been established via discovery of an endogenous cannabinoid system, identification of cannabinoid receptors, and demonstrations of precipitated withdrawal with cannabinoid receptor antagonists. Laboratory studies have established the reliability, validity and time course of a cannabis withdrawal syndrome and have begun to explore the effect of various medications on such withdrawal. Reports from clinical samples indicate that the syndrome is common among treatment seekers”.

Several papers have been written on the extent and prevalence of cannabis dependence.

Young Americans were followed for 13 years from the 7th 8th or 9th grade in school. At 27 to 29 years old just under 24% abused cannabis and just over a quarter of them were addicted, ie 8% of the total population (Newcomb 1992).

A North American population study of 20,000 people reported that, of the 4.4% who abused cannabis roughly 60% were dependent on it. That is about 2.6% of the population (Hall et al 1994) And in a letter to The Lancet in 1998 Hall and Solowij wrote that, of those who ever start using cannabis, 10% will become daily users and 20 to 30% will use it weekly.

In 2003 Fergusson et al, following up 1265 children born in Christchurch, New Zealand for 21 years, concluded that, for the majority of users, cannabis did not lead to problems of dependence. Nonetheless, nearly 10% of the cohort showed clear signs of cannabis dependence by age 21, especially males who were prone to other forms of risk-taking behaviour.

On Sunday June 13th 2004 The Observer carried a story that increasing numbers of people were becoming dependent on the drug. Department of Health figures recorded 9% of attendees at clinics cited cannabis as their problem drug, twice the number ten years before. Research from the United States showed that cannabis is the commonest reason for 12 to 17 year olds to be placed in treatment centres – 60% of all cases. Treatment for cannabis dependence or habitual usage among youngsters had risen 142% in a decade.

Dr Romeo Ashruf, a Dutch addiction specialist and Director of the Parnassia Clinic in The Hague, told Network 2's Bijou's This TV programme on March 20th 2006 that Dutch children as young as 12 were addicted to cannabis. The powerful home-grown nederwiet they are using is up to 20 times stronger in its THC content than imported varieties. Referrals used to be for young people between 16 and 21, but are now for 14 to 19 year olds. He warned parents of the difference in strength of the drug today.

Cambridge University Press has recently (2006) published a book "Cannabis Dependence: Its Nature, Consequences and Treatment in the series: *International Research Monographs in the Addictions*, which "Breaks through the controversial politics of cannabis use to give a clear, scientific synthesis of all the Health-related issues relating to cannabis use".

"Reviews and assesses all the interventions applied to both adult and adolescent users".

"Gives the criteria for diagnosis and scope of cannabis dependence".

It should be pointed out that most people in Northern Europe smoke cannabis with tobacco. Addiction to nicotine, according to some experts is one of the most difficult to treat and certainly many smokers seem to find it almost impossible to give up. This "double addiction" would significantly exacerbate the problems of giving up cannabis.

James Langton smoked cannabis for 30 years. He said, "When I was smoking cannabis it was the most important thing in my life. More important than my family, my friends, my relationships or my job. When I was without it, I was irritable, anxious and could concentrate on little else until I was stoned again...if you had asked me at any time over that long period whether I was addicted to the stuff, I would have laughed in your face and denied it. I knew, as everyone knew at the time, that cannabis wasn't addictive."....Apart from denial, fear is the other factor that reinforces cannabis addiction...I was terrified of physical withdrawal.disrupted sleep, night sweats, cramps, nausea and loss of appetite. Other symptoms are closer to nicotine withdrawal such as mood swings, irritability and depression".

He has now set up "Clearhead", a new privately funded organisation offering support and information to those seeking to make positive changes in their lives regarding their use of cannabis. He has a website and runs weekend workshops.

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Cannabis and the Gateway Effect

The question as to whether cannabis “encourages” the use of other drugs has occupied the minds of researchers for the last 30 years or so. It is a very important one since if true, the use of cannabis would be much more dangerous than the effects of the cannabis use alone.

Tobacco and/or alcohol use in teenagers makes the use of other drugs more likely (Merrill et al, 1994) and the same is true of cannabis. A MORI poll in 1991 found that 50% of smokers had tried an illegal drug compared to only 2% of non-smokers and Califano (2003) concluded that young cigarette smokers were 14 times more likely to try pot. Cigarette smoking was discovered to be an important predictor of both the initiation and persistence of cannabis use.

Professor Denise Kandel and her team in America have researched this subject for many years. Early in her work she found a series of graded steps that most of her subjects followed. There were four: 1. Beer and wine 2. Cigarettes and spirits 3. Marijuana 4. Other illegal drugs (Kandel, 1989). The younger they started, the further they progressed and the more intense the abuse at any age the greater the risk of progression to the next stage. Of those who had used cannabis more than 1000 times, 90% moved on to other drugs. Between 100 and 1000 it was 79%, dropping to 51% between 10 and 100 times. Even 1 to 9 times usage saw 16% follow this path. Of non-users, only 6% eventually used drugs other than cannabis. (Kandel, 1986).

Among other researchers to discover a link between use of cannabis and use of other drugs are: Aas and Pederson, 1993, Von Sydow, et al 2001 and Brook, et al 1989 (The East Harlem Study of African-American and Puerto Rican 14 year old adolescents). In a large longitudinal study, 36% of a group of 27 to 29 year-olds were found to be dependent on both marijuana and cocaine (Newcomb, 1992). Kleber (1995) said that 60% of young Americans using marijuana before the age of 15 will use cocaine later in life, and those between 12 and 17 who use cannabis are 85 times more likely to use cocaine than non-smokers of the same age.

“The statistical association between the intensity of cannabis consumption and the likelihood of using hard drugs strengthens the case for assuming that there is a causal connection between cannabis smoking and progression to harder drugs, but it does not constitute proof of such a causal link. The general impression, then, has been that the imperative role of cannabis in the “stepping stone” model has resisted all attempts to prove it scientifically. On the other hand, a large body of circumstantial evidence has been gathered. It is found time and again that cannabis is a central component of the network of influencing factors that leads to the abuse of hard drugs” (Ramstrom, 2003).

To sum up, support for the gateway effect is as follows: 1. Marijuana users are many times more likely than non-users to progress to hard drug use. 2. Almost all who have used marijuana and hard drugs have used marijuana first (Yamaguchi and Kandel, 1984) 3. The greater the frequency of marijuana use, the greater the likelihood of using marijuana later.

Explanations for the gateway effect include the following:

1. Changes in brain chemistry that may make young people more susceptible.
2. Experiences with cannabis may encourage experimentation with other drugs.
3. Common factors in personality or background.
4. Cannabis use is illegal so supplies come from the illegal market, bringing exposure of young people to drug dealers.

Dr Patrick Dixon in his book *The Truth About Drugs* (1998), says, “Common sense tells us there is a link. We know that once teenagers start smoking tobacco it is easier for them to cross the next step and

smoke cannabis". My pupils used to tell me, "Find a smoker and you will find a cannabis user". The smoking technique has been learned. Dr Dixon also said, ".....once someone starts using cannabis it is easier for them to try something else, and for the following reasons:

Desensitisation: "It was a big step at first, but cannabis didn't kill me – actually I can't see what all the fuss is about so why not try some other things?"

Targeting by dealer: "My mate offered me some free dope and also had some other stuff he was giving away so I tried both"

Knowledge of supply: "I was thinking about trying something else and I already knew who to ask".

Drug-taking part of social life: "My friends do things together. We all smoke dope. Someone had something else so for a bit of a laugh we all tried it"

"It is dangerous nonsense therefore to suggest that cannabis use does not significantly increase the risk of a serious drug addiction later on" (Dixon, 1998).

Exactly the same sentiments were expressed to me by an ex-pupil, an ex-user. "Cannabis didn't seem to have much effect and didn't harm us so we looked for a bigger and better high. We tried more or less everything that was going except heroin". (Crack cocaine was not around at the time).

The "personality and background predisposition hypothesis" was explored by Degenhardt and others in 2001. They looked at 201 15 to 16 year olds who had used cannabis at least 40 times. They found 3 "clusters" of heavy users. There was a small group with anti-social behaviour, another with low self-esteem and poor relationships with their parents and friends, the third group were "ordinary". This last group were the least likely to use other illicit drugs.

Information from 44624 individuals of between 12 and 25 was gathered. These people did not seek out drugs but were "exposed" to the opportunity of taking them at a party or friend's home. Users of tobacco and alcohol were more likely than non-users to have the opportunity to try marijuana and indeed were more likely to take it. Opportunities to try cocaine were associated with prior marijuana smoking. Among the young people who had a cocaine "opportunity", those who had used marijuana were more likely to use cocaine than those with no previous history of using cannabis. They also found that by the age of 21, half the teenagers who had smoked marijuana had a chance to try a hallucinogenic drug, LSD, mescaline, PCP or mixed-stimulant-hallucinogens, compared to only 1 in 16 of non-users. Within one year of "exposure" two-thirds of the cannabis-users had tried it, but only 1 in 6 of those who had never smoked cannabis (Wagner and Anthony, 2002).

Two separate twin studies explored the "family environment/genetic influence".

In 2003, Lynskey and others examined 311 same-sex twins (identical and non-identical) in Australia. They were discordant for cannabis use before the age of 17. The twin using cannabis before 17 had odds of other drug use, alcohol dependence and drug use/dependence that were 2.1 to 5.2 times higher than their co-twin who was a non-user of cannabis prior to the age of 17. No significant differences were found between mono- and di-zygotic twins. Controlling for early alcohol or tobacco use, parental conflict/separation, childhood sex abuse, conduct disorder, major depression and social anxiety had negligible effects of the outcome. So common environmental and genetic influences seemed not to be predisposition factors. Association with different peers and the social contexts in which cannabis was used may have some bearing on the results.

In 2006 Lynskey, again with a team, conducted research into twins this time of Dutch nationality, 219 same-sex pairs, discordant for cannabis use before 18 were used. Covariants were adjusted. The rates of lifetime party drug use, use of hard drugs, but not regular cannabis use, were significantly higher in the pre-18 using twin. Again this suggested that the progression seen is not explained by common familial risk factors, genetic or environmental. Different friends or social experiences obviously could play a part.

Professor David Fergusson and his teams have conducted a long-term longitudinal study in New Zealand, The Christchurch Health and Development Study. It has followed 1265 children from birth in the middle of 1977. They have been regularly assessed till the age of 21 with an 80% follow-up (Fergusson et al, 1997, 2000, 2002).

At the age of 18, the associations for the “gateway question” did not appear to be very strong when all other factors were taken into account. However at 21, more data were available and methods of analysis were more advanced. For young 14 to 15 year old heavy consumers a very strong association existed even after controlling for other suspected or known causal factors. It was the first time such a strong connection had been seen (Fergusson et al, 2002). By the age of 21 nearly 70% of the cohort had used cannabis and 26% other drugs. In all but 3 cases, cannabis use came first. Those using cannabis on 750 occasions/year had hazards of other illicit drug use 59.2 times higher than non-users. After adjustments for co-variants, childhood, family and adolescent lifestyle factors, the association was still remarkably strong. Fergusson points out that, “...findings support the view that cannabis may act as a gateway drug that encourages other forms of illicit drug use. Nonetheless the possibility remains that the association is non-causal and reflects factors that were not adequately controlled in the analysis”.

In April 2006 Ferguson updated his results. The sequence of events he said could suggest a cause and effect relationship where the use of cannabis encourages the use of other illicit drugs. He points out that it has often been suggested that associations between cannabis and other illicit drug use arise from common factors that predispose young people to using cannabis and other drugs. However, he says, this study applied complex statistical methods and controls and still found a clear tendency for those using cannabis to have higher rates of usage of other illegal drugs. It was most evident for regular users and more marked in adolescents than young adults.

Looking for a neurophysiological explanation rather than a psychosocial mechanism, the phenomenon of sensitisation, an “inverse tolerance effect” was suggested as long ago as 1999 by Torngren. This is the process by which an addictive substance increases a person’s sensitivity to the exhilarating effects of that substance. This process exists in humans and has been shown in animals. Exposure to one substance e.g. cannabis, should be able to make a person more sensitive to another substance like heroin (cross-sensitisation). At the moment, he said, this remains hypothetical reasoning.

Professor Heather Ashton, Emeritus Professor of Clinical Psychopharmacology at The University of Newcastle-on-Tyne, puts forward mechanisms for the association which may favour a causal role for cannabis. They are:

1. Tolerance to the “high” leading users to seek more potent drugs.
2. Withdrawal symptoms being alleviated by the use of other drugs.
3. Interaction of cannabinoids with the endogenous opioid systems which have been shown in animals to increase the rewarding properties of opioids such as heroin.

(Ashton 2002)

Professor Robin Murray of The Institute of Psychiatry in London commented (The Daily Telegraph 18/06/05), “ Clearly it needs to be replicated but there is already evidence that, in animals, cannabis and amphetamine show cross-tolerance. So that rodents given THC, the active ingredient of cannabis, show greater effects when given amphetamine”.

A 2006 paper by Maldonado, Valverde and Berrendero has shown that the endocannabinoid system (neurotransmitters mimicked by THC) is involved in the common neurobiological mechanism underlying drug addiction in three ways.

1. The system participates in the primary rewarding effects of nicotine, alcohol, opioids and cannabinoids through the release of endocannabinoids in one part of the brain (the ventral tegmental area).
2. Endocannabinoids are also involved with motivation to seek drugs through a dopamine-independent mechanism (this has been demonstrated for psychostimulants and opioids).
3. The common mechanisms responsible for relapse into drug-taking behaviour also include the participation of endocannabinoids. This is done by mediation of the motivational effects of drug-related stimuli in the environment and exposure to drugs.

Professor Yasmin Hurd (2006) warns that the human brain is not fully developed till around the age of 25. Chronic periodic use of cannabis can interfere with the development of rat brains. She says, “The developing brain is definitely more sensitive”. After training rats to self-administer heroin by pushing a lever, rats exposed to THC took more heroin than those not previously exposed to it. They were more sensitive to lower concentrations of heroin and took more in response to stress. Her conclusion reads: The current findings support the gateway hypothesis demonstrating that adolescence cannabis exposure has an enduring impact on hedonic processing resulting in enhanced opiate intake, possibly as a consequence of alterations in limbic opioid neuronal populations”.

In the light of all the evidence, it is obvious that every effort must be made to try to prevent vulnerable children from ever starting to use cannabis, not least because of the potential damage done by cannabis itself.

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Effects of Cannabis Use on the Reproductive system, Pregnancy and Development of Children

In the mid-seventies animal experiments suggested that cannabis adversely affects the secretion of gonadal hormones in both males and females, and the foetal development of animals given THC during pregnancy (Bloch 1983, Nahas 1984, Nahas and Frick 1987, Wenger et al 1992).

Research was triggered by the reporting of gynecomastia (breast development) in 3 young men (23 to 26) all heavy cannabis users (Harmon 1972). These findings are now in doubt as a small case-controlled study failed to find a relationship in 11 cases and controls (Cates and Pope 1977), and Mendelson (1984) said there would surely be more cases as the number of young men using cannabis was high.

Kolodny and others investigated men who were chronic cannabis users in 1972. They had reduced plasma concentrations of testosterone, sperm count and motility, with an increased number of abnormal sperm. Bloch 1983, Wenger 1992, and The National Academy of Science 1982, gave support to all his findings with experiments on animals.

Wenger said they were either due to the action of THC on the testes and/or the brain hormones that stimulate sperm production.

Kolodny's results were contradicted by Mendelson and others in 1974 in a large well-controlled study of heavy users. Other studies have produced positive and negative findings of the effect of THC on testosterone.

Although the reductions in testosterone and sperm numbers observed in some studies may not be of great significance in healthy adults, Hollister (1986) argued that they could pose problems in pre-pubertal males. A boy of 16, smoking cannabis since the age of 11, suffered from retarded development of the secondary sexual characteristics and growth. Partial recovery was attained 3 months after stopping (Copeland et al 1980). Also men with already impaired fertility may be at risk.

Dr Lani Burkman of Buffalo University Medical School, New York, reported to the annual meeting of The American Society of Reproductive Medicine in San Antonio, Texas on October 13th 2003. She had looked at the sperm of 22 frequent cannabis users (14 times a week for at least 5 years) and compared it with that of 59 men, non-users who had children. She found that the sperm were moving too fast, too soon. They would "burn out" before they reached the egg and would be unable to fertilise it. She suggested this may be a cause of infertility. She also found the users produced fewer sperm.

Studies on female fertility have also produced conflicting results. Bloch found that on exposing non-pregnant animals to THC, there was interference with the hormones concerned in reproduction produced in the brain. Oestrus was delayed, as was ovulation by a reduction of luteinising hormone and an increase in prolactin secretion. Rozenkrantz (1985) said exposure of pregnant women to THC was too risky as it may damage the foetus. Conflicting results have also been obtained on the cycling of sex hormones and duration of menstrual cycles in women.

The blastocyst stage of the embryo has to be implanted in the uterus wall for its continued development. Anandamide, the neurotransmitter mimicked by THC is produced at a high level in the uterus before implantation and then down-regulated at the time of implantation. High levels of anandamide induce spontaneous pregnancy loss in women. The use of cannabis at this crucial time during pregnancy may have the same effect (Paria et al 2001, Wang et al 2003).

A paper in 2006 (Klonoff-Cohen et al) on the effects of marijuana use on the outcomes of IVF (In Vitro Fertilisation) and GIFT (Gamete Intra-Fallopian Transfer) fertility treatments found that the prospect of a good outcome is reduced if either of the partners uses marijuana. Females produced fewer eggs and the child had a significantly lower birth weight, the more recent the use, the worse the effects. Male marijuana use was also associated with lower birth weight. Both timing and amount of the drug used negatively affected IVF and GIFT.

The risk of miscarriage or ectopic pregnancy of women smoking cannabis in the early stages of pregnancy was highlighted in recent research by Dey and others in 2006. Anandamide controls the development of the embryo so the level of the neurotransmitter is crucial. THC by mimicking anandamide disrupts the correct signaling process. The embryos of mice treated with THC had more cell abnormalities than the controls and the embryos failed to travel to the uterus.

THC passes through the placenta in animals and humans, so it could potentially damage the embryo (Bloch 1983, Blackard and Tennes 1984). It is also passed in breast milk (Astley and Little 1990).

Experiments on animals have shown a number of very serious effects on gestation of offspring born to females given THC during pregnancy. These results must lead to a consideration of the possibility of similar effects occurring in humans (Abel 1985).

There is now consistent evidence to show that habitual cannabis smoking during pregnancy is associated with a lower than average birth weight (Hatch and Bracken 1986, Zuckerman et al 1989) and height (Zuckerman et al 1989 and Tennes 1985) the relationship persists after control for confounding variables. Gibson and his colleagues in 1983 looked at the cases of 36 women, using cannabis 2 or more times/week. Twenty five per cent of them had premature births.

Earlier experiments before the mid-eighties, not surprisingly produced inconsistent results as they were often conducted with insufficient care.

In 1995 Shiono and others failed to find any significant association between marijuana smoking and birth weight, however when the mothers blood was tested a clear tendency towards lower birth weight was apparent.

An analysis of 10 different studies into the effects of cigarette smoking in 1997, 7 of which involved cannabis use, displayed only a weak association between cannabis use and birth weight. For any use of the drug the average reduction was 48g. Use 4 times a day averaged 131g loss of weight. They concluded that the difference was small compared to the effects on birth weight of tobacco smoking, and that there is inadequate evidence that cannabis at the amount typically consumed by pregnant women, causes low birth weight (English et al 1997).

There are enormous problems in conducting surveys of this type. Heavy use of cannabis during pregnancy is rare, many samples are too small (Greenland et al 1982a/b, Fried 1980). Because of its illegality, many women are unwilling to be honest about their drug taking so lots of them will be classed as non-drug users (Zuckerman et al 1989). They are also likely to use alcohol, tobacco and other illegal drugs and tend to belong to a different social class (Fried, 1980, 1982, Tennes 1985). But the greatest problem is small numbers.

In 2002 the Avon Longitudinal Study of Parents and Children team in Bristol (Fergusson et al) looked at 12000 mothers expecting single babies. On average the babies were 216g lighter for women smoking once a week, they were significantly shorter and had smaller heads. When other factors were taken into consideration the average reduction in weight dropped to 90g. They equated the effect of a weekly joint to that of 15 cigarettes.

In animals very high doses of marijuana were needed to increase the rate of malformations occurring in the offspring. And indeed some experiments found this association (Linn et al 1983). Bloch (1983) found that in sufficient dosage, re-absorption, growth retardation and other malformations occurred in rats, rabbits mice and hamsters. But most of the best-designed studies failed to confirm these findings. Zuckerman et al in 1989 discovered among 202 infants, pre-natally exposed to marijuana, a rate of malformations no higher than in a control group of non-using mothers. Gibson et al 1983, Hingson et al 1982 and Tennes et al 1985, uncovered no increase in the rate of major congenital abnormalities in children born to marijuana-using mothers.

Abel (1985) and Bloch (1983) suggested the malformations may be due to reduced nutrition due to the very

high doses of the drug. Hollister (1986) added that “Virtually every drug that has ever been studied for dysmorphogenic effects has been found to produce these if the dose is high enough, enough species are tested or the treatment is prolonged”.

However many of the papers that exonerate cannabis use were conducted using marijuana and not THC at the start of the eighties when the THC content of the marijuana widely used was very low. And Hall and others warned in 1994 that, “It would be unwise to exclude cannabis as a cause of malformation until larger and better-controlled studies have been carried out”.

Malformations could of course be caused by chromosome damage. It has not been possible to show that THC can produce effects on specific genes which can cause abnormalities (Hall 1994, Hollister 1986). Cannabis smoke on the other hand is mutagenic (Bloch 1983). Hollister (1986) and The Institute of Medicine (1982) both discounted evidence that cannabinoids may cause mutations.

Three studies in the late eighties and early nineties linked cannabis use to an 11-fold increase in the cases of one form of leukaemia, ANNL (Acute Nonlymphoblastic Leukaemia) born to mothers using cannabis during pregnancy and increases in two other forms of childhood cancer, rhabdosarcoma and astrocytomas (Robison et al, 1989 Neglia al 1991, Grufferman et al 1993). The children with ANNL were younger than children with the disease born to non-using mothers and had cell differences which the researchers said made it unlikely that the relationship was due to chance.

There is little literature on the subject of the development of children whose mothers had smoked cannabis while pregnant. One study, unique in its longevity, The Ottawa Prenatal Prospective Study has been carried out from 1978 to the present day by Dr Peter Fried and his team. The children were examined neurologically immediately after birth and again several times in their first year. Tests for cognitive and psychomotor functioning were then executed yearly. At first, signs of neurological development deficiencies were detected, a delay in the development of the visual system and an increased rate of tremors and startle, as were withdrawal symptoms. These disappeared and nothing was reported till the age of four when memory and verbal ability were found to be deficient. At 5 and 6 these seemed to have gone but the six year olds had impaired ability to sustain attention. From 6 to 9, several deficits in cognitive functions were noted and the parents reported behavioural problems. Between 9 and 12, there was a reduced ability as “regards memory in connection with visual stimuli, analytical ability and integrative ability”. Again attention maintenance was a problem. The same pattern emerged from 13 to 16 (Fried 2003).

Fried said that the damage inflicted by cannabis at the foetal stage would not be noticed until the child needed to use his or her “executive” functions (for problem-solving and planning) at the age of four. Leavitt et al (1994) and Lundqvist (1995) found similar deficits in adult cannabis users. Fried also warns that the marijuana in 1978 when his investigation began had a much lower average THC content, so the risks may now be higher. On 15th July 2006 Dr Fried is due to give a talk at The 13th World Conference on Tobacco OR Health in Washington DC. As part of his long running study, he will say that children of mothers who smoked marijuana while pregnant are more than twice as likely to take up the habit when they reach adolescence.

Dahl (1995) had found sleeping problems in 3 year olds and Day (1994) lower intelligence scores also at the age of 3. These findings support those of Fried.

Another long-term study has been published. Goldschmidt and others in 2002 gathered data from over 250 women who used cannabis while pregnant. Reports from parents and teachers were used and at age 6 the teachers reported problems with delinquent behaviour. At 10, questionnaires were distributed and interviews conducted. A clear relationship between exposure to cannabis and delinquency was established, manifested by attention deficits, impulsiveness and hyperactivity.

Tennes and others in 1985 studied over 200 women who had used cannabis during pregnancy. The children were monitored after birth and again at one year old. They failed to find any differences between them and the controls.

An Italian research team under Vincenzo Cuomo (2003) injected pregnant rats with a low dose of artificial cannabinoid. The offspring were hyperactive. This disappeared at adulthood but was replaced by learning and memory retention problems. Because rats do not have confounding factors like tobacco smoking, standard of living or alcohol use, the results can be very useful. Fried said this showed great consistency with his study on humans.

The most recent study on the effects of pre-natal marijuana exposure (Day et al September 2006) has concluded that, "Prenatal exposure to marijuana, in addition to other factors, is a significant predictor of marijuana use at age 14". Other variables controlled for were: the child's current alcohol and tobacco abuse, pubertal stage, sexual activity, peer drug use, delinquency, family history of drug abuse and parental depression, current drug use, strictness and levels of supervision.

In 2002, Nahas and others reported that THC damages the formation of DNA in the dividing cells of testes and has been shown to impair the development of sperm cells in man. Marijuana or THC produces an early apoptosis of these fast-dividing cells and THC-induced apoptosis has also been found to occur in cells of the immune system (Zhu et al, 1998). Apoptosis is the "programmed cell death" of all our cells as they grow older, it is an irreversible biological process.

THC accumulates in fatty tissues and there are huge reserves of fat in the body for THC storage. With regular marijuana smoking the THC will build up quickly and take about 30 days to be completely eliminated. There will thus be a constant slow release of THC that will affect any processes going on in the body. Nahas concluded, "During chronic exposure to THC the pharmacokinetic molecular mechanisms which limit the storage of THC in the brain and testes are not sufficient to prevent a persistent deregulation of membrane signalling and the induction of functional and morphological changes which reflect a premature apoptosis of spermatogenic cells. Long-term longitudinal epidemiological studies have reported decreased spermatogenesis in healthy fertile adults".

Referring to 25-year old research findings on cannabis and the reproductive process detailed in his book *Marijuana and Medicine* 1999, Nahas said, "The latest studies in molecular biology have demonstrated that THC, the active ingredient in marijuana, damages the earliest stages of reproductive function. Thus marijuana is gametotoxic (toxic to embryos and sperm). It kills the reproductive cells of seven animal species, produces damage to the embryo, and retards foetal development. All of these destructive effects of marijuana on sperm cells, embryonic cells or lymphocytes have now been related to the early production of "apoptosis", the programmed death of the cell".

Frequent maternal marijuana use may be a weak risk factor for Sudden Infant Death Syndrome, SIDS (Scragg et al 2001).

In 2002 in The Princess Royal Maternity Hospital in Glasgow, drug tests (from the first stools) were carried out on 400 newly born babies. One in eight was found to have been exposed to cannabis in the womb. The study was carried out by forensic scientists from Glasgow University (Dr Ghada Abd-El-Azzim and Dr Robert Anderson), paediatric consultants (Lesley Jackson and Charles Skeoch) and senior registrar Scott Williamson. About 130 babies every year are treated at the hospital for drug dependency. Treatment can take days, weeks or months. According to the *Forensic Science International Journal*, more than 75% of babies exposed in this way will have medical problems later in childhood compared to 27% of the unexposed infants (Sunday Post 15/12/02).

A review article was written in 2006 (Huizink and Mulder). They came to the conclusion; that pre-natal exposure to either maternal smoking, alcohol or cannabis use is related to some common neurobehavioural and cognitive outcomes, including symptoms of ADHD (inattention, impulsivity), increased externalising behaviour, decreased general cognitive functioning, and deficits in learning and memory tasks.

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Effects of Cannabis on cognitive functioning, personality and educational performance.

In 1986 two wide-ranging review studies were carried out of all the papers into cognitive functioning and cannabis up to that time. The results were inconclusive. However it was suggested that the differential impairment observed in subjects - some users suffered damage while others did not under identical conditions, may be because of a differential vulnerability of the subjects: for example, some may be more susceptible to cerebral impairment (Wert and Raulin 1986). This suggestion has now been accepted in general for many illnesses. It should be pointed out that, the American market was at that time still dominated by weaker preparations of cannabis.

Since then, testing methods have become more sensitive and cannabis damage has been found to be subtler than expected and of a different type from that caused by alcohol.

Renewed testing of some of the older studies, with more sophisticated techniques, found definite differences between users and non-users especially in the fields of sustained attention and short-term memory (Page et al 1988).

The following experiments were normally carried out at least 24 hours after abstinence from cannabis to get rid of the intoxicating effects.

Block and others (1990) found that intense prolonged use of cannabis impairs the ability to express oneself verbally and to solve maths problems.

Schwartz et al (1989) in a study of teenagers using 7% THC long-term (It was already in the USA in the late eighties), showed significant impairment of short-term memory, persisting for at least 6 weeks after stopping. Unfortunately the money then ran out.

Prolonged use of marijuana lessens the ability to focus attention and screen out irrelevant information (Solowij 1991, 1995a, 1995b) In 1999 she reported that this held true even after abstinence for 2 years. She also found a direct relationship between the degree of impairment and length of time of abuse.

Sixty-five heavy users of cannabis (smoking every day) male and female, were compared with sixty-four "light" users (median of one/day in the last 30 days). After abstinence for a minimum of 19 hours, the heavy users had significantly greater impairment than the light ones on attention and executive functions (decreasing mental flexibility and reduced learning ability) after adjustment for confounding factors (Pope et al 1996).

Hall and others (1994), Lundqvist (1995), Leavitt et al and various other researchers all reported that long-term cannabis produces the following effects:

*“impaired ability to carry out complex thought operations and impaired ability to screen out distracting impressions;
reduced ability to process information;
no effect on long-term memory but impaired short-term memory, particularly with regard to information which is of a kind unfamiliar to the individual or which is complex in nature;
difficulty in carrying out tasks which require intellectual flexibility, long-term strategic planning and the ability to learn from experience;
no effect on the ability to deal with the routine, familiar demands of everyday life, but problems when faced with the task of expressing oneself verbally in a new, unfamiliar situation or in a situation where old ways of thinking and old knowledge are inadequate”* (in Ramstrom 2003).

Dr Thomas Lundqvist of Lund University Hospital, Sweden, is one of the researchers who has contributed most to this aspect of cannabis use. In his PhD thesis in 1995 he studied the cognitive damage acquired by

some 400 of the long-term cannabis abusers who had sought treatment at his outpatient clinic. His clinical observations provide a wealth of information about the various effects of cannabis. He divided the cognitive functions impaired into 7 different categories.

A summary of his findings can be found in “*Adverse Health Consequences of Cannabis Use: A Survey of Scientific Studies Published up to and including the Autumn of 2003*” by Jan Ramstrom as follows:

Verbal Ability

Having a vocabulary that corresponds to one’s age, finding the words for what one wants to say, understanding others and having the ability for abstract thought.

Logical-analytical ability

Ability to analyse and draw logical conclusions. Ability to understand causal connections and ability to judge oneself in a critical/logical manner.

Psychomotility

Ability to maintain attention and to vary the degree and focus of attention. Ability to understand other points of view and to change one’s own point of view. Some degree of general flexibility with regard to different ways of looking at and interpreting societal phenomena.

Memory

Short-term memory/working memory: *Ability to remember what has just happened or been communicated, which is a prerequisite not only for the integration of what has just been communicated but also for the integration and organisation of a whole range of cognitive processes, as well as a precondition for a reasonably adequate temporal perception*

Long-term memory: *This consists of both “episodic memory”, which makes it possible to remember events and their temporal context. And “semantic memory”, which has more to do with what we call “knowledge”, e. g. different facts and the inter-relationships between different phenomena.*

Analytical and synthetic ability

Based on the ability to combine the other functions. Makes it possible to synthesise, sort out and organise mental material.

Psychospatial ability

Makes it possible to orientate oneself, other people and various phenomena in time and space, which is a precondition for temporal organisation as well as one of the prerequisites for social orientation.

Gestalt memory (holistic memory)

Enables us to understand and form patterns – not only to understand that there is a connection, but also to understand its nature and structure. For example, enables us to make and maintain the connection between a person, a name and a social role.

He found more or less pronounced weaknesses in all categories for all 400 subjects. Lundqvist also described a personality profile which he said was typical of cannabis users:

Have difficulty in finding the words to express what they really mean.

Have a limited ability to be amused by or enjoy literature, film, theatre or the like.

Have a feeling of boredom and emptiness in everyday life, along with feelings of loneliness and of not being understood.

Externalise problems and are unable to take criticism.

Are convinced that they are functioning adequately.

Are unable to examine their own behaviour self-critically.

Feel that they have low capacity and are unsuccessful.

Are unable to carry on a dialogue.

Experience difficulty in concentrating and paying attention.

Have rigid (fixed) opinions and answers to questions.

Make statements such as “I’m different, other people don’t understand me, I don’t belong to society”.

Do not plan their day.

Think they are active because they have many on-going projects - which they seldom see through to completion.

Have no daily or weekly routines.

Ten former cannabis abusers were interviewed between 2 and 10 months after they had stopped concerning any changes they had experienced. All said their way of thinking and their perception of the world had

changed. Most importantly they said their verbal ability, logical analytical ability and psychomotility had got better.

Nearly 10 years before, Hendin and others (1987) had asked 150 white long-term (6 days/week for at least 2 years) cannabis users subjective questions regarding their habit and its effects on them. No alcohol or other drugs were used by them, nor were they socially disadvantaged or marginalised in any way. Two thirds felt their main problem was one of memory impairment. Just under half said their ability to concentrate on a complex task had worsened and the same number couldn't finish jobs. Just over 40% considered their ability to think was less clear and 36% were less ambitious.

Cannabis users often claim that the drug gives them insight, increases self-awareness and gives them a deeper understanding of life. Many of the researchers were struck by the consistency of exactly the opposite results. Introspection was inhibited, thoughts and feelings were separated and individuals were less able to distinguish what is reality.

Obviously a reduction in memory capability will impact on learning ability and should be cause for concern especially with regard to our children. Exposure to drugs and vulnerability from them is at its highest in the teenage years. A paper on the development of the brain by Giedd (1999) points out that the brain is still maturing into the mid-twenties and Chambers and others (2003) say that the motivation/risk taking areas of the brain develop faster than the parts responsible for inhibition. Charles Nelson, a child psychologist from The University of Minnesota said, "Adolescents are capable of very strong emotions and very strong passions but their pre-frontal cortex hasn't caught up with them yet. It's as though they don't have the brakes that allow them to slow these emotions down".

Adolescents are minors and their decisions to use or not use drugs are not conventionally regarded as being as free and informed as in the case of choice for adults (Kleiman1989). If a child uses cannabis regularly during the transition period from childhood to adulthood, then educational achievement, becoming independent from parents, relationships including marriage and career choice, all these processes may be expected to be affected (Baumrind and Moselle 1985, Polich, Ellickson, Reuter and Kahan, 1984). The possible exalating use of cannabis and progression to the use of other drugs, not to mention the risk of accidents especially while driving should all be causes for concern (Kleiman 1989, Polich, Ellickson, Reuter and Kahan, 1984).

A clinic in Sweden, The Maria Ungdomsmottagning in Stockholm, finds it often easier to give help to young people dependent on heroin than to firmly addicted cannabis users (Ramstrom 2003). Parents' associations in Sweden and the USA, campaigning against drugs, take a very strong anti-cannabis position as they have witnessed numerous cases of the development of teenagers come to an abrupt stop because of its use (Ramstrom 2003).

Baumrind and Moselle (1985) said the forging of a personal identity is central to the maturing of children and Ramstrom in 1991 emphasised the importance of social integration to develop identity in the later teenage years. The ability for abstract thought is also crucial for forging an identity (Baumrind and Moselle 1985, Ramstrom 1991 and Steingart 1969).

The ability to perform formal thought operations is the basis of the ability for abstract thought – the vision of a world differing from reality. This skill also provides the foundation for long-term planning of the development of one's own personality. For example a child may say, "When I grow up I'll be a doctor". This should be replaced by a statement reflecting an increasingly maturing adolescent, "If I work hard, choose the right subjects and get good grades, I will be able to apply to medical school"(Lundqvist 1995).

Ramstrom (2003) said, "If the development of identity does not progress, the teenager remains at a childish level of development characterised by both a lack of independence and a deficient integration in the adult world". He also said, " Deterioration of short-term memory obviously makes learning more difficult, but it also has a negative effect on the individual's ability to make plans, to establish new relationships and to make realistic assessments of the world around him or her".

Kerstin Tunving wrote in an article in 1987, “To sum up, the impression is, based on clinical observations, that teenagers who abuse cannabis “sleep away” their teens. They often do not develop at the same pace as youth of the same age, but stay childish and dependent”.

In recent years, researchers have found associations between cannabis use and mental and social problems in the late teens and early adulthood, psychosis (Arsenault 2002) depression and suicidal thoughts (Bovassa 2001 and Patton et al 2002), crime and unemployment (Fergusson and Horwood 1997, Fergusson et al 2000, 2002).

Detailed descriptions of the long-term effects of cannabis use on teenagers is present in textbooks, Heinemann 1984, Ranstrom 1987, Lunqvist report 1995, and in a paper by Kolansky and Moore 1971.

Holmberg (1981) studied over 1000 Swedish 15 to 16 year olds, with a follow up 11 years later. The following results were found:

Mortality rates were 5 to 8 times higher among the original abusers. They also had experienced more medical and social problems, 10% had had a psychotic episode during the time and the 2.4% who were heavy users were more likely to have become properly addicted.

A very extensive longitudinal in-depth study of young cannabis users was carried out by Newcombe and Bentler in 1988. It focused on the transition to adulthood. Not surprisingly the risk of impairment to mental functions increased, they were less able to make careful plans, had negative psychosocial factors in the teenage years and were more likely to drop out of school or training courses. They found it harder to hold down a job, experienced more divorces and had worse social networks.

Confirmation of these findings came from Fergusson and his co-workers in 1997, 2000 and 2002 (Christchurch Study). They said, “Cannabis use, and particularly regular or heavy use, was associated with increased rates of a range of adjustment problems in adolescence/young adulthood – other illicit drug use, crime, depression, and suicidal behaviours – with these adverse effects being most evident for school aged regular users”.

It has already been mentioned that cannabis use can impair memory, attention and therefore learning (Baumrind and Moselle 1985), thus potentially increasing the risk of high school failure and possible drop-out. These findings were supported in cross-sectional studies by Kandel (1984), Robins and others 1970, and Hawkins and others in 1992. They all found a positive relationship with cannabis use as an adult and the risk of dropout from school.

Longitudinal studies by Kandel in 1986 and Newcombe and Bentler 1988, however, gave mixed support for the idea. Kandel looked at her cross-sectional study again and reported that the connection all but disappeared as the dropout students using cannabis had lower aspirations than the controls. Newcombe and Bentler found only a negative effect of *hard drugs* in adolescence and completion of high school.

More recently, Lynskey and Hall conducted a review of papers on educational attainment in 2000. They concluded that cannabis use significantly increases the risk of poor school performance and early school leaving.

To quote, “Cross-sectional studies have revealed significant associations between cannabis use and a range of measures of educational performance including lower grade point average, less satisfaction with school, negative attitudes towards school, increased rates of absenteeism and poor school performance..... A number of prospective longitudinal studies have indicated that early cannabis use may signify increased risks of subsequent poor performance and in particular, early school leaving. This association has remained after control for a wide range of prospectively assessed co-variables.....In particular , early cannabis use appears to be associated with the adoption of an anti-conventional lifestyle characterised by affiliations with delinquents and substance-using peers, and the precocious adoption of adult roles including early school leaving, leaving the parental home and early parenthood”.

The survey proposed that the link between early cannabis use and educational attainment arises because of the social context within which cannabis is used and not because cannabis use causes impairment. However Solowij (1998) concluded there is evidence that long-term cannabis use (daily or near-daily for 10 years or

more), was associated with the impairment of selective attention. Few adolescents will have used cannabis intensively or for long enough to produce the effects seen in adults.

Hall added that this does not mean that acute cognitive impairment is irrelevant in adolescents, only that cognitive impairment found in those who use cannabis is more likely to be the results of acute intoxication than the effects of long-term use. If adolescents used regularly then school performance would suffer especially if they were poor or average to start with.

Solowij also said (1998) in her book “Cannabis and Cognitive Functioning”, “Use more often than twice per week for even a short period of time, or use for 5 years or more at the level of even once per month, may each lead to a compromised ability to function to their full mental capacity, and could possibly result in lasting impairments (this does not imply that use below these levels may be considered safe)”.

I can certainly concur with these findings. I have seen the performance of a few of my students, bright grammar school boys, slowly deteriorate. They fail to achieve the grades they deserve and some miss out on the university of their choice. They will never admit to using cannabis, the information often comes from their peers, and some parents simply do not want to know.

In another paper in 2001 Hall said that it is clear that heavy cannabis use may compromise educational attainment and thus future achievement.

Two papers in 2002 added to the evidence. One by Solowij et al examined the effects of the duration of cannabis use on specified areas of cognitive functioning among users seeking treatment for cannabis dependence. Their results confirmed that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use. And Bolla and colleagues also found heavy cannabis use to be associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. They said it was unclear if these decrements would resolve with continued abstinence or grow progressively worse with continued heavy marijuana use.

The preliminary results of a longitudinal study into the effects of marijuana use on IQ in The Canadian Medical Association Journal (2002), reported that current use of the drug had a negative effect on global IQ scores only in subjects who smoked 5 or more joints a week. It was not found in previously heavy users who had now given up so did not have a long-term impact. IQs were tested in 9 to 12 year olds and again when they reached 17 to 20. The drop was around 4 points.

In 2003 Pope and others found early-onset cannabis users exhibiting poorer cognitive performance than late-onset users or control subjects especially in verbal IQ, but they could not determine the cause of this difference from their data.

Fergusson, Horwood and Beautrais in 2003 found an increased cannabis use to be associated with an increase in school leaving, qualifications, failure to enter university and failure to obtain a university degree. This connection persisted after control for confounding factors. There was no evidence to suggest the presence of reverse causal pathways, i.e. that lower educational achievement lead to increased cannabis use. The findings support the view that cannabis use may act to decrease educational achievements in young people. It is likely that this reflects the effects of the social context within which cannabis is used rather than any direct effect of cannabis use on cognitive ability or motivation.

Lynskey and others in 2003 published the results of another study of high school completion. They concluded: “Early regular cannabis use (weekly use at age 15), is associated with an increased risk of leaving school early”. And Bray and others in 2000 said a teenage marijuana user’s odds of dropping out are more than twice that of a non-user.

The National Household Survey on Drug Abuse in America in 2002 reported that marijuana use is linked to poorer grades. A teenager with an average “D” grade is 4 times more likely to have used marijuana than a teenager with an average “A” grade.

Professor Robin Murray, Director of The Institute of Psychiatry in London, was quoted in The Times on Saturday 12th February 2005, “ One of the reasons why some young people who smoke cannabis start performing badly at school or university is that they are cognitively impaired by the cannabis lingering in their brain. A young person who smokes cannabis every day, or even 3 times a week, can be in a state of low-grade intoxication most of the time. However, if you stop, these adverse cognitive effects also stop”.

The most recent evidence on cannabis and cognitive functioning comes from Greece and a study by Messinis and some of his colleagues (March 2006). They concluded that long-term marijuana use is linked to “subtle deficits in specific neuropsychological domains”. Those who smoked at least 4 joints a week for several years performed significantly worse than non-users. In particular, verbal learning (the ability to remember previously learned words) and executive functioning (organising and coordinating simple tasks), were among the worst affected.

Wadsworth and others in January 2006 aimed to examine whether an association existed between cannabis use, cognitive performance, mood, and human error at work. There was a positive relation between cannabis use and impairment of cognitive functioning and mood. No more errors were reported in the workplace than in the controls. There was also a positive correlation with lower alertness and a slower response in organising things. Memory problems were evident at the start of the week and psychomotor slowing and poorer recall of episodes at the end of the week.

In contrast to other research findings, Dr Igor Grant, editor of the Journal of The International Neuropsychological Society which he founded, wrote in the July 2003 edition that marijuana smoking has only a marginally harmful long-term effect on learning and memory. No effect at all was seen on other functions including reaction times, attention, language, reasoning ability and perceptual and motor skills. Dr Grant said he found the findings to be of particular significance since several states are considering whether to make it available as a medicinal drug. The paper was sponsored by a state-supported programme to oversee research into the use of cannabis to treat certain diseases. (Dr Grant is Director of The University of California Center for Medicinal Cannabis Research).

Dr Thomas Lundqvist in a review of the cognitive consequences of cannabis use in 2005 documented studies into the subject using brain-imaging techniques to try to reveal any neurotoxic effects of cannabis. Neuro-imaging data has been extracted from studies on acute and chronic abusers of marijuana in resting and in challenging cognitive situations.

Several studies at rest, using different techniques CBF, PET, SPECT, fMRI showed sub-normal cerebral blood flow or lower cerebellar metabolism in long-term users assessed within one week of abstinence. Marijuana users showed 9% lower values of average whole brain activity compared with controls. Also at rest, acute exposure to marijuana gave rise to increases in dose-related CBF (Cerebral Blood Flow) in experienced users in some areas of the brain but not others e.g. those that are memory related.

When given a cognitive challenge, the controls showed significant activation in the pre-frontal cortex. Heavy smokers 24 hour to 28 days after washout, displayed diminished activity in this region but increased activity in another (the cingulate) which was not seen in the controls. There is thus a differential of cortical activity in subjects with a history of heavy cannabis use. CBF was decreased in areas associated with attention and attentional moderation of sensory processing.

In one study using PET scans, following a 25 day abstinence, heavy users had no deficit in their executive functioning, at the same time as showing hypo-activity in some of the areas responsible for executive functioning and hyperactivity in others. This suggests there may be an alternative neural network employed as compensation i.e. they “work harder” to meet the demands of the task.

Lundqvist concluded that neuropsychological and brain-imaging techniques point to deficits in attention, memory and executive functioning.

He also suggested that studies failing to detect cognitive decline associated with cannabis use may reflect insufficient heavy or chronic use of cannabis in the sample or use of insensitive assessment instruments.

Herning and others (2005) also proposed a “blood flow theory” to account for the deficits in cognitive functioning among users of cannabis. Using Transcranial Doppler Sonography they recorded blood flow velocity in the cerebral arteries of heavy, moderate and light users, 3 days after admission to an in-patient research unit and after 28 to 30 days of monitored abstinence. The conclusion was that “Chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated in part, in blood vessels or in the brain parenchyma. These findings might provide a partial explanation for the cognitive deficits observed in a similar group of marijuana users”.

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Cannabis and Mental Illness (Psychosis/schizophrenia)

Although I welcomed the comments about cannabis made by Tony Blair just before the election, and his recognition of the dangers it poses, I was angered to hear him say to John Humphrys on the Today programme (May 4th 2005), in reference to the down-classification debacle, “It was worth seeing what happened”. Was this just some huge experiment conducted primarily on our vulnerable young people? How many of them would, prior to down-classification, ever have been tempted to try the drug but given the “green light” by this government, now find themselves with a psychiatric problem, perhaps for life. We shall never know.

There is much talk about whether cannabis actually *causes* psychosis or schizophrenia. There are 2 points about this argument.

Firstly, to quote from the Report of an ARF (Addiction Research Foundation)/WHO scientific meeting in Toronto as long ago as 1981 on adverse health and behavioural consequences of cannabis use. “It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, “risk-factors” have been freely identified, although full causality has not yet been established. Nevertheless such risk-factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is not often applied to cannabis”. “To provide rigid proof of causality in such investigations is logically and theoretically impossible, and to demand it is unreasonable”.

And in March 2006, Harrison Pope, a professor of psychiatry at Harvard Medical School, said that in most aspects of science, the only way to answer a question once and for all is to do a randomized, controlled trial of 100 people or more. But since giving people marijuana in a clinical setting poses a rather formidable dilemma he and other psychiatrists must fall back on messy methodology.

Secondly, there is ample undisputed evidence that cannabis exacerbates the course of schizophrenia and triggers it at an earlier age than would have been the case. It also causes a toxic psychosis recognized as a diagnostic unit in the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders.

When you have young people suffering from a psychiatric illness, that would never have manifested itself if he or she had not taken the drug, then cannabis is certainly a contributing factor, whether or not they may have had a genetic predisposition. As new studies emerge, the evidence that cannabis may actually *cause* schizophrenia becomes ever stronger, see the last 3 papers in the updated section at the end of the paper.

Robin Murray and John Witton of The Institute of Psychiatry, London, in their paper, “Reefer madness revisited: cannabis and psychosis” March 2004, said, “The public health message is clear. Some cases of psychotic disorder could be prevented by discouraging cannabis use, particularly among psychologically vulnerable youths, with the youngest cannabis users most at risk.....action is needed to avoid a further burden on already over-stretched mental health services”.

When BSE became a problem, in spite of the fact that the government had no real idea how the disease was transmitted, beef-on-the-bone was banned. “We must err on the side of caution”, said a spokesman at the time. Indeed we must. Why were they so incautious in the case of cannabis classification?

It is ironic that the USA whose drug tsar John Walters’ strong prevention messages are seeing a consistent year-by-year drop in drug use, invited a British scientist, Professor Neil McKeganey, Professor of Drug Misuse Research, Glasgow University, to speak at a conference on May 3rd 2005, when our previous Home Secretary, David Blunkett, before down-classification, consistently refused to see a group of 6 eminent British scientists, all experts in the field of drugs.

In 2004 I was asked to speak to a group of parents, all of whom had children who were psychotic or schizophrenic. All the youngsters had previously used cannabis. There was no doubt whatsoever in the minds of these parents what had caused their children to become ill. They were incensed that no one had

ever warned them of the dangers of this harmful drug. They kept me talking and answering questions for 3 hours. I think it was one of the most emotional and disturbing evenings I have ever spent.

There has been a 22% increase in the number of hospital admissions of cannabis users with mental illness since down-classification in the UK. In the year April 2003-04, the number of admissions was 710, up from 580 in each of the two previous years. In the same period, admissions caused by the abuse of other drugs including heroin and alcohol fell. The exception was cocaine which rose by 16%. I thought that one of the reasons for down-grading cannabis was to free up police time to combat the harder drugs.

On January 23rd 2005, The Herald (Scotland) reported that numbers of hospital discharges after treatment for cannabis-related problems had more than trebled in The Lothians and doubled in the Greater Glasgow Health Board Area. According to police figures, the number of under-16s at the end of 2004 charged with supply or possession of drugs had risen by 13%. Some were only 10 years old.

Professor Peter Jones of Cambridge University, one of Britain's leading psychiatrists and an expert in schizophrenia, addressing an Institute of Psychiatry (London) Conference on 28th November 2005 said, "Cannabis is a huge issue for psychiatric services at this moment. I work in a first-contact schizophrenia service and it might as well be a Cannabis Dependency Unit". He warned that children of 10 or 11 who start smoking the drug could be trebling their risk of schizophrenia. He said that 80% of first episode psychiatric disorders, schizophrenia or schizophrenia-like illnesses occurred in either heavy users of cannabis or cannabis dependents. "I think this is an iceberg effect", he said, "If you were able to measure the toll on GCSE results, A level results, training and social development, we would have a much bigger number of deleterious effects".

Professor Robin Murray of the Institute of Psychiatry in London, who has done so much to draw attention to the links between cannabis and mental illness, took part in a Radio 4 You and Yours programme on 30th December 2004. When asked if he would say that cannabis is one of the biggest problems facing psychiatric wards, replied, "I've been saying it for some time. It's worse now, it's *very* difficult to convince patients that cannabis is causing their problems. They say that's not what the *government* says. Their general understanding is that it is safe".

He ended the programme by saying that Mental Health Services are overwhelmed. People are arriving with cannabis psychosis. They don't get good treatment, nor do these with problems unrelated to cannabis. Mental Health Services in big cities cannot cope. He had recently talked to 100 psychiatrists and asked whether any of them would invite relatives or friends in to see their units. Only *one* would be prepared to do this. "We are awash with mental health problems" he said, "and cannabis is a big contributor".

In a letter to The Guardian 19th January 2006, Professor Murray said, "The mistake was that in its 2002 report, The Advisory Council on the Misuse of Drugs denied that cannabis was a contributory cause of schizophrenia, continued to deny this for the next two years and thus mislead ministers into repeatedly stating that there was no causal link between cannabis and psychosis". On 8th October 2006, he said, "Five years ago, 95% of psychiatrists would have said that cannabis doesn't cause psychosis. Now, I would estimate that 95% say it does. It's a quiet epidemic".

I have therefore attempted to make a list of scientific studies on cannabis and psychosis and to make it available to anyone with an interest in this important subject.

The following list is not in any way meant to be comprehensive. As I researched this subject more and more thoroughly I uncovered literally dozens of other publications. I think I have mentioned all of the most important ones, apologies to the authors of those I have not included but the literature and messages are there for anyone to access.

In the last few years increasing concern has been expressed about the association of cannabis with mental illness. The number of cannabis users is going up. In the USA in some age groups, almost as many people are smoking cannabis as cigarettes. Children are starting to use the drug at an increasingly early age, more and more studies are emerging which link cannabis use with psychological and social problems, demand for treatment for cannabis users is rising and there is a change in the THC content of some cannabis

varieties. Selectively bred strains such as skunk and nederwied (netherweed) have much greater percentages of THC than did the marijuana of the sixties and seventies.

Jan Ramstrom, the Swedish psychiatrist and expert on substance abuse who wrote *Adverse Health Consequences of Cannabis Use* (2003) said, "At present we find ourselves in a curious situation where researchers and clinicians are becoming even more concerned, while the general public, not least in Europe, seems to grow less concerned".

He also said, "It is worth mentioning that the opiates (heroin etc), apart only from the development of dependence, produce far fewer toxic psychiatric complications than do cannabis preparations"

Two fundamentally different psychotic manifestations are involved.

Toxic psychosis: Cannabis-induced psychotic disorder, recognized as a diagnostic unit in the DSM IV (Diagnostic and Statistical Manual of Mental Disorders) is caused by the toxic effects of the drug and involves a group of brain damage syndromes. The symptoms are caused by cannabis consumption and subside when drug use ceases. The use of anti-psychotic medicines to eliminate any residual symptoms means most patients make a full recovery unless he or she resumes the taking of cannabis or indeed other drugs. Symptoms of delirium often dominate, i.e. bewilderment and memory disturbance. Paranoia, hallucinations and aggression alternating with euphoria also occur. There is usually an absence of any heredity factor.

Functional psychosis: "Functional" in this sense applies to the absence of organic damage. Cullberg 2000, said that there probably is some organic damage, possibly taking the form of some subtle vulnerability as yet unknown. This category covers schizophrenia and schizophrenia-like psychosis which usually runs a chronic course. Symptoms of delirium are absent and there is often a feeling of outside interference with thought. Often the person has a "premorbid personality" with extreme reserve, loss of interest and bizarre suspicious ideas.

To quote Jan Ramstrom again, "...what we are dealing with here are the most profound disturbances known to psychiatry; even when they are short-lived, such disturbances can leave marks on those affected and on their families which may remain for many years or even be of life-long duration.....there is both an abuse condition and a serious mental disorder. These "dual disorders" are among the most difficult to assess in the whole of psychiatry. Moreover, conditions of this type not rarely make demands on the most costly resources available in the field of psychiatric care".

Early Studies.

Papers as early as the 1970s saw researchers connecting cannabis consumption with psychosis.

1972. Tennant and Groesbeck studied American soldiers in Europe and found large numbers abusing drugs mostly hashish. Between 1968 and 1971, the number of acute psychotic reactions, not necessarily leading to schizophrenia increased from 16 in 1968 to 77 in 1971, an almost 5-fold increase in 4 years. They concluded that hashish smoking was the major contributor.

1974. Chopra and Smith described 200 patients admitted to a Calcutta psychiatric hospital between 1963 and 1968 with psychotic symptoms following cannabis use. Most cases were preceded by the ingestion of large quantities. One third had no previous psychiatric history and the symptoms were the same regardless of their history. The most potent cannabis preparations resulted in psychotic reactions in the shortest period of time.

1974. DA Treffert allowed 4 schizophrenic patients, all on anti-psychotic medicine to act as their own controls. Having been warned not to, all of them smoked cannabis occasionally. All of them experienced deterioration in their condition, sometimes with very serious consequences. This clearly demonstrated that there was a direct association between relapses into pot smoking and serious deterioration in the schizophrenia condition.

1974. Breakey and others pointed to some sort of association between drug use, including cannabis, and the

onset of schizophrenic illness. He considered that cannabis and other drugs could precipitate latent schizophrenia, but also thought that cannabis could do this in cases where the illness would not occur otherwise. They based this conclusion on the fact that the drug induces schizophrenia on average 4 years earlier than the onset in other types of schizophrenia. The onset was also more sudden, and the premorbid personality always better than a comparative group of non-drug using schizophrenics.

1976. Thacore and Shukla made a clear attempt to demonstrate the occurrence of a specific cannabis-provoked functional psychosis.

Other papers around this time, giving support to the findings include, Talbott and Teague 1969, Weil 1970, Bernardson and Gunne 1972 and Harding and Knight 1973.

So even as long ago as the early seventies some researchers were trying to ring alarm bells about the possible psychological problems of cannabis use.

The eighties brought another crop of papers on the subject.

1981. MB Holmberg found that 10% of 16 year-old consumers of large quantities of drugs, almost exclusively cannabis, by the age of 27, would have a record of psychosis. This was much higher than the 3% in the normal population.

1985. Bier and Haastrup looked at psychological admissions over one year in a Copenhagen hospital. Thirty patients had cannabis-provoked psychosis. They then estimated that 15 in a population of 100,000 would be admitted each year with psychosis either precipitated or caused by cannabis.

1986. Negrette and others concluded that interaction between cannabis smoking and schizophrenia had the following characteristics. Cannabis smokers have more relapses, more hospital visits, the positive symptoms of schizophrenia are more dramatic and the patients are less susceptible to neuroleptic medication.

1986. Ghodse said there was clear evidence from countries where heavy cannabis use is common, that cannabis causes a short-term toxic psychosis. This was supported by laboratory experiments.

Among the large body of reports from researchers and clinicians at this time are the following: Palsson, Thulin and Tunving 1982, Rottamburg et al 1982, Tsuang et al 1982, Carney 1984, Brook 1984, Tunving 1985 and Hollister 1986.

However the most important publication at this time was the large study of Swedish conscripts by Andreasson, Allebeck et al in 1987.

Forty-five thousand conscripts had their drug-taking details taken at entry, aged 18 or 19. The levels of schizophrenia were then recorded over the next 15 years. Those on admission who claim to have taken cannabis on more than 50 occasions were found to be 6 times more likely to be diagnosed with schizophrenia in the following 15 years than those who had never consumed the drug. When confounding factors were taken into account, the risk became smaller but remained statistically significant.

Although the study attracted some criticisms, Negrette, the doyen in this field judged the connection to be reasonable taking other previous studies into account, while accepting there were some weaknesses. Andreasson in 1989 and Allebeck in 1993 strengthened their position by further research. They examined the medical records of 112 cannabis-dependent and schizophrenic patients. The findings in all significant respects confirmed the original study.

Further support came from the analysis of records of 100 schizophrenic patients between 1973 and 1977 randomly chosen by Dalman et al in 2002. A large measure of consistency was established with respect to regions, hospitals and timescale as well as the diagnostic criteria for schizophrenia, DSM-IV.

Over twenty years later in 2002, Zammit and others re-analysed the results. In the light of new research into

the development of schizophrenia, they were able to discount more of the original objections.

Research continued in the nineties.

1990. Tien and Anthony conducted an epidemiological analysis of drug and alcohol use and concluded that there was an association between cannabis use and psychosis. Daily use over a year suggested a 2.4 times greater risk than non-users, any use related to a risk of 1.3 times. The daily risk figure remained significant after adjustment for other substance abuse and baseline psychiatric diagnosis.

1991. Chaudry et al studied cannabis psychosis following bhang ingestion. Bhang drinkers in Pakistan were found to have mania and paranoid features. Treated with anti-psychotic medicines, the majority recovered completely in 5 days. None had residual symptoms.

1991. Johnson, from his own long experience and a review of the current literature, estimated that 10% of all of those who had used cannabis more than once, experienced either delirium or psychosis. Later estimates confirmed this figure, notably Thomas in 1996 who sent questionnaires to young New Zealanders. Johns as recently as 2001 supported this claim.

1995. Wylie observed a group of British consumers of Dutch cannabis with a high THC content. He recorded a “wave of psychosis and confusional states”. The risk therefore becomes greater the more often cannabis is used and the greater its strength.

1998. Hall concluded that cannabis can cause psychotic like symptoms during intoxication, can lead to a “cannabis psychosis” to increase the relative risk of schizophrenia, and affect the clinical course of established schizophrenia.

Other studies which deserve mention are: Thornicroft 1990, Eikmeir et al 1991, Mathers et al 1991, Rolfe et al 1993, Kristensen 1994, McBride and Thomas 1995, Castle and Ames 1996, Hambrecht and Hafner 1996 and Fowler 1998.

A paper by J Giedd et al in 1999 on development of the adolescent brain must be mentioned here. They conclude that the brain does not finish its development till the mid twenties or beyond. So the warning is that drug abuse could alter the normal course of the maturing of the brain in the teenage years. Research by Giedd on this subject is on-going.

Since the year 2000 there has been a flood of publications.

2002. Louise Arseneault et al assessed 1100 New Zealand children at 11, 15, 18 and 26. Young adults smoking cannabis at the age of 15 were at a greater risk of developing schizophrenia or a schizophrenia-like illness by the age of 26. The risk was 10% times compared to 3% for non-users. Use at 15 was a stronger risk factor for schizophreniform disorder than use by the age of 18.

2002. The Nemesis Study by Van Os et al studied 4045 psychosis-free Dutch people and 59 who had a psychotic disorder, taken at random from 60 localities. They concluded that it must be considered proven that smoking cannabis can provoke a functional (non-toxic) schizophrenia-like psychosis. They replicated the Swedish study of Andreasson. It was of shorter duration and had fewer participants, but not the weaknesses. There was a baseline assessment and 2 follow up sessions, after 1 and 3 years, by questionnaire and clinical interviews. The study showed that individuals using cannabis at baseline were almost 3 times more likely to manifest psychotic symptoms at follow up. After confounding factors were taken into account the risk remained significant. A dose-response relationship was also found. The risk factor for the heaviest users rose to 6.8.

They concluded: “cannabis use is an independent risk factor for the emergence of psychosis in psychosis-free persons and that those with an established vulnerability to psychotic disorders are particularly sensitive to its effects, resulting in poor outcome”.

2002. Nunez and Gurpegui compared 26 patients with cannabis-induced psychosis to 35 with acute schizophrenia. All used cannabis, they were repeatedly urine tested. They concluded that cannabis when

continuously and heavily used can induce a psychotic disorder distinct from acute schizophrenia.

2002. Hiroshi Ujike found genetic abnormalities in the genes for the cannabinoid receptors on the brain cells of schizophrenics compared to non-schizophrenics. This implies a potential malfunction of their marijuana-linked circuitry, perhaps making them more vulnerable to schizophrenia.

Many people have argued and it seems logical that if the use of cannabis has increased then so must the incidence of schizophrenia.

2003. Boydell et al found that there was indeed a continuous and statistically significant rise in the incidence of schizophrenia between 1965 and 1997. It had doubled over the last 3 decades. The increase was greatest in people under 35.

2003. The Christchurch Health and Development Study. Fergusson et al looked at 1200 children from birth to the age of 21. The cannabis-dependent youngsters developed psychotic symptoms more often than those who were non-dependent. Individuals with cannabis-dependence disorder at 18 had a 3.7-fold increased risk of psychosis than those with no dependence disorder. At 21 the risk fell to 2.3 times. They conclude that: "the findings are clearly consistent with the view that heavy cannabis use may make a causal contribution to the development of psychotic symptoms since they show that, independently of pre-existing psychotic symptoms and a wide range of social and contextual factors, young people who develop cannabis dependence show an elevated rate of psychotic symptoms".

Another paper on the development of the brain appeared at this time.

2003. Chambers et al reviewed literature regarding the neurocircuitry underlying motivation, impulsivity and addiction. They focused on studies investigating adolescent neurodevelopment. They found that adolescent neurodevelopment occurs in brain regions associated with motivation, impulsivity and addiction. These developmental processes may advantageously promote learning drives for adaptation to adult roles but may also confer greater vulnerability to the addictive actions of drugs. This has significant implications for understanding adolescent behaviour, addiction vulnerability and the prevention of addiction in adolescence and adulthood.

2004. Veen et al. One hundred and thirty-three Dutch patients with schizophrenia were interviewed. There was a strong association between the use of cannabis and an earlier age of first psychotic episode in male schizophrenics. On average they were 6.9 years younger than non-using patients.

2004. D'Souza et al. Various doses of THC were administered to 22 healthy subjects, screened for any vulnerability to schizophrenia. Some of them developed symptoms resembling schizophrenia for 30 minutes to 1 hour. There were no side effects after 1, 3 and 6 months. The study findings go along with several other lines of evidence that suggest a contribution of cannabis and/or abnormalities in the brain cannabinoid receptor system to the pathophysiology of schizophrenia.

2004. Arendt et al. Findings: 1439 heavy cannabis users seeking treatment for abuse problems in Denmark were compared to 9122 abusers of other substances. Conclusion: Co-morbid psychiatric disorders are common among heavy cannabis users seeking treatment. Some psychiatric disorders occur more frequently in this group compared to users of other substances.

2005. Isaac and Holloway did their research in PICUs (Psychiatric Intensive Care Units). There was a high rate of cannabis abuse (71.3%) among the PICU population. Patients with cannabis abuse spent longer as their psychosis was more severe. They were also younger at first hospital admission. The conclusion was that cannabis abusers have more severe psychotic illness especially in schizophrenia. There are additional problems of weight gain.

2004. Frischer et al from Keele University monitored 3% of the population of England and Wales. The number of people using drugs and having mental illness rose by 62% between 1993 and 1998. (230 GP practices were looked at). Men accounted for 79% and women 44%. The average age affected fell from 38 to 34. The number of cases of 25 to 34 year olds more than doubled.

Drug abuse and psychosis were up by 147%, paranoia by 144% and schizophrenia by 128%. They said, “A long-term, well funded, innovative campaign aimed at publicising the real mental health risks associated with drugs including cannabis needs to be in place as soon as possible”.

2004. Stephanis et al looked at 3500 19-year olds in Greece.

Conclusions: These results add credence to the hypothesis that cannabis contributes to the population level of expression of psychosis. In particular, exposure early in adolescence may increase the risk for the sub-clinical positive and negative dimensions of psychosis, but not for depression.

2005. Favrat et al. Clinical trials of THC on psychomotor function and driving performance were conducted on 8 occasional cannabis users with no history of psychosis. Low doses were used. Two young men reacted badly. One 22 year-old showed severe anxiety and psychotic symptoms 90 minutes later, and was unable to do the tests. The other, also 22, was unable to do the tests for several hours, and experienced very unpleasant symptoms.

The doses were administered under clinical conditions and were much lower than would normally be found in a modern joint. The importance of this research is that oral administration of the THC caused significant psychotic reactions. Oral medicines are becoming increasingly available and doctors should be aware of these findings.

2005. Ferdinand. The “Zuid Holland” Study, a 14 year follow up study of 1580, initially 4 to 16 year olds, drawn randomly from the Dutch population. (Because cannabis use is generally condoned in Holland, false negative reports of cannabis use may occur less frequently. This adds to the value of this study). Findings: Cannabis use in individuals who did not have psychotic symptoms before they began using cannabis, predicted future psychotic symptoms, the risk was almost 3 times greater. Also psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use.

Conclusion: The results either imply a common vulnerability with varying order of onset or a bi-directional causal relationship between cannabis use and psychosis.

2005. Van Os et al. Nearly 2500 young people between the ages of 14 and 24, with or without predisposition to psychosis were studied. Adjustment was done for confounding factors such as alcohol, cigarettes and other drugs.

There was a dose-response relationship with increasingly frequent use of cannabis.

Conclusions: Cannabis use in young people moderately increased the risk of developing psychotic symptoms. The risk for onset of symptoms was much higher in young people with a predisposition for psychosis. Predisposition psychosis at baseline did not predict cannabis use at follow up. This rejects the self-medication hypothesis i.e. that psychotic patients take drugs to relieve the symptoms of the illness.

An Australian study in 2006 tracked 81 young people mostly male in their early 20s, single, unemployed and who were addicted to cannabis. All of them had developed a psychotic mental illness in the previous 6 months. Dr Leanne Hides said, “ We found that cannabis use contributes to a relapse in psychotic episodes and then as a result of that they are more likely to use cannabis. Basically they’re going around in circles and they can’t really win”.

2005. Fergusson et al. This was a 25 year longitudinal study of 1055 New Zealand children from birth.

Conclusions: “Even when all factors were taken into account, there was a clear increase in rates of psychotic symptoms after the start of regular use, with daily users of cannabis having rates that were over 150% those of non-users. These findings add to a growing body of evidence from different sources, all of which suggest that heavy use of cannabis may lead to increased risks of psychotic symptoms and illness in susceptible individuals”.

2005. Caspi et al. have found variants in a gene (COMT) which is involved in dopamine transmission. It was found to moderate the influence of adolescent cannabis use on the development of adult psychosis. One in four people carries this gene.

The research was carried out on 803 men and women born in Dunedin, New Zealand in 1972 and 1973. They were enrolled at birth. The gene comes in 2 variants, methionine and valine, and everyone has two copies of the gene.

If a person inherits 2 methionine types, the rate of psychotic illness is 3%, the normal rate for non-users. However if a person has 2 valine variants, the rate rises to 15% for those who have used cannabis in their teens. Dr Caspi said, "Research has shown that the valine gene variant and cannabis affect the brain's dopamine system in similar fashion, suggesting that they deliver a "double dose" that can be damaging".

Several review articles have also appeared in the last few years.

2001. Johns. Conclusion: "Heavy cannabis misuse leads to the risk of psychotic episodes and aggravates the symptoms and course of schizophrenia. For any psychiatric patient, risk management and care planning is incomplete without a thorough assessment of substance abuse".

2003. Degenhardt and Hall. Conclusion: "Cannabis use does not appear to be causally related to the incidence of schizophrenia but its use may precipitate disorders in persons who are vulnerable to develop psychosis and worsen the course of the disorder among those who have already developed it".

2004. Arsenaault et al. A review of 5 papers was undertaken:
The Swedish Conscript cohort, Andreasson 1987 and Zammit et al 2002.
The Dutch Nemesis Sample, Van Os 2002.
The Christchurch Study, Fergusson et al 2003.
The Dunedin Study, Arsenaault 2002.
The overall conclusion: "A twofold increase in the relative risk for later schizophrenia. At the population level, elimination of cannabis smoking would reduce the incidence of schizophrenia by around 8% assuming a causal relationship. Cannabis is a component cause for psychosis, part of a complex constellation of factors".

2004. Rey et al. Conclusion: The weight of evidence points in the direction of early and regular use of cannabis having substantial negative effects on psychosocial functioning and psychopathology.

2004. Drewe et al. This article appeared in response to the potential legalization of cannabis in Switzerland. Conclusion: "An increase in consumption would be expected therefore there would probably be an increase in the prevalence of psychosis, not only acute toxic but also chronic psychosis. Schizophrenic psychoses would be expected to be triggered at an earlier age so there could be deleterious consequences not only for many currently healthy individuals but for disablement pensions".

2004. Raphael and Wooding. Conclusion: "Of primary importance is the fact that cannabis use does have a number of significant associated harms. It is not a soft or safe option and its notable co-morbidity with psychotic and non-psychotic illnesses make it a significant and growing public health issue – a fact increasingly reflected in both the national and international scientific literature".

Other reviews deserving mention include: Leweke et al 2004, Witton and Murray 2004, John Macleod et al 2004 and Smit et al 2004.

In 2004 Marijuana and Madness was published by Cambridge University Press. The editors were, Professor David Castle of The Mental Health Research Unit, Melbourne, and Professor Robin Murray of The Institute of Psychiatry in London.

Twenty-nine contributors to 13 chapters are listed. Many of them have been mentioned in this article. The review from the journal "Addiction" says:

"Each chapter is well written and well presented... There is little doubt that the chapters are expertly written... Marijuana and madness illustrates clearly the benefits of a multi-disciplinary perspective in providing the tools for answering a complex question".

Professor Robin Murray of the Institute of Psychiatry, London, drew attention to the fact in 2003 that recent evidence had demonstrated that THC increases the release of dopamine, thus increasing its level in the brain. Psychotic symptoms in conditions like schizophrenia are mediated by dopamine.

In November 2005 a study by Dr Andrew Campbell of the NSW Mental Health Review Tribunal, and a lecturer in psychology at the University of Sydney, found that 4 out of every 5 incurable schizophrenics had used cannabis regularly between the ages of 12 and 21. He studied schizophrenics committed to institutions or ordered to undergo compulsory treatment in NSW over a 5 year period. He warned that it was an epidemic to which we are blind and quoted figures from Britain and the Netherlands showing a base rate of schizophrenia 11 per 100,000 in Wales compared with London and Amsterdam of 60-70 per 100,000. He attributed the difference to the higher rate of cannabis use in these cities by 12 to 21 year olds.

A Danish study just published in The British Journal of Psychiatry, November 2005, by a team from Aarhus Psychiatric Hospital led by Mikkel Arendt, found that almost half (44.5%) of 535 patients taken from the Danish Psychiatric Central Register and treated for cannabis-induced psychotic symptoms, went on to develop a schizophrenic illness, a third developing paranoid schizophrenia. The signs of schizophrenic illness appeared earlier in cannabis users than others with the condition. Only one in six needed no further treatment. They were compared with 2721 people treated for schizophrenia-spectrum disorders who had no history of cannabis-induced illness. Symptoms appeared in male cannabis users at average age 24.6 years compared with 30.7 in the comparison group, with females it was 28.9 compared with 33.1 years,

On November 30th 2005 researchers from Zucker Hillside Hospital, New York, led by Mazar Ashtari and Sanjiv Kumra presented evidence to The Radiological Society of North America (RSNA) at their annual meeting. They used Diffusion Tensor Imaging (DTI), a sophisticated technique measuring the motion of water molecules in the brain to reveal microscopic abnormalities. They found similar abnormalities in the brains of daily adolescent cannabis users to adolescents with schizophrenia. These defects were in a part of the brain still developing during adolescence and associated with the higher aspects of language and auditory functions. Their findings also suggested that heavy use of marijuana may lead to earlier onset schizophrenia in adolescents genetically predisposed to the disorder.

The 21st January 2006 edition of the BMJ carried a paper by Fergusson DM et al entitled "Cannabis and Psychosis". It reviewed and brought together the 2 lines of research on this subject, the epidemiological and neuroscientific studies. The summary points were as follows: -

Epidemiological evidence suggests a persistent association between cannabis use and psychosis that is robust to methodological challenges.

Neuroscientific studies show that cannabis may lead to psychosis through effects on the processing of dopamine in the brain.

Taken together this evidence suggests a causal relation in which frequent use of cannabis leads to a greater risk of psychotic symptoms.

The latest review of the evidence linking cannabis to psychosis was published in August 2006 by Degenhardt and Hall. From 6 longitudinal studies in 5 countries they found that regular use of cannabis predicts an increased risk of a schizophrenia diagnosis or report of symptoms of psychosis. These relations persist after control for confounding factors and don't seem to result from the use of cannabis to self-medicate the symptoms of psychosis. A contributory causal relation is biologically plausible because psychological disorders involve disturbances in the dopamine neurotransmitter system with which the cannabinoid system interacts.

Skosnik and others in October 2006 researching neural synchronization in cannabis users concluded that, "These data provide evidence for neural synchronization and early-stage sensory processing deficits in cannabis use. This finding, along with the observed increased rates of schizotypy in cannabis users, adds support for a cannabinoid link to schizophrenia spectrum disorders".

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Summary of papers on the damaging effects of cannabis

General facts about cannabis

The plant Cannabis sativa is the source of the drug. Marijuana refers to the dried plant parts, hashish the resin, sinsemilla the dried tops of the female plant and the very potent hashish oil can be extracted.

Cannabis contains around 400 chemicals, 60 of which are cannabinoids. The most psychoactive and cause of most damage in the body is delta-9- tetrahydrocannabinol (THC). THC occupies the receptor sites of the natural brain chemical anandamide. CB1 receptors are found all over the brain, CB2 on other cells of the body, especially cells of the immune system, so many body systems are affected. Being fat-soluble, the THC remains for weeks in the cell membranes, continually affecting the brain and body.

Smoked cannabis is quickly absorbed. The “high” lasts 2 to 4 hours. Consumed orally, the effects are delayed but prolonged. THC enters the placenta, the foetus and breast milk. Some very strong types of cannabis like Skunk and Netherweed are now common with a THC level of up to and over 20%. Grown and increasingly used in the UK they account for more than 60% of the market. Cannabis research is still a very young science.

Effects on the cardiovascular system

Comparatively little research has been done on this subject but enough exists to raise concerns.

Cannabis intoxication raises heart rates. If a person is sitting down or lying, the blood pressure rises but on standing up, it falls. People with healthy hearts should not be at risk. Tolerance to acute cardiovascular effects of cannabis can develop in a few days therefore, particularly in older research, often no evidence of cardiac toxicity was found. However more recently a number of papers have reported myocardial infarction (heart attacks) and angina pectoris in young people. Two teenagers actually died after “bingeing” on cannabis. They had suffered strokes, another was left paralysed. Prolonged use in young people causes blood flow to the brain to become restricted, and the risk of a heart attack in the hour following the smoking of a joint rises 5-fold especially in middle aged and older people.

A 2004 review article concluded, “Cannabis use seems to have been causally related to several instances of cerebral ischemia (strokes) and infarction”.

The long-term effects of smoking cannabis on the cardiovascular system are still unknown but Jones in 1984 suggested that, “after years of repeated exposure, there may be lasting, perhaps even permanent alterations of the cardiovascular system function. There are enough similarities between THC and nicotine’s cardiovascular effects to make the possibility plausible”.

Effects on the immune System

Cannabis is often contaminated with pathogenic fungi and bacteria so it is essential to find out whether cannabis use affects the body’s defence mechanisms.

The immune system is complex. Macrophages engulf and destroy foreign matter, natural killer cells bind to target cells and destroy them. B-lymphocytes produce antibodies against infective organisms and T-lymphocytes kill cells or activate macrophages or their forerunners, monocytes.

Early research on animals in the 70s and early eighties produced consistent evidence of immunological defects. These included decreased antibody response and lymphocyte proliferation and reduced response to foreign cells eg bacteria and skin grafts. Research on humans at that time provided contradictory results due

mainly to technical deficiencies. The ability of animals to resist infection was also tested. Cannabis-tested mice showed decreased resistance to *Listeria monocytogenes* and Herpes simplex. Zhu and others in 2000 confirmed these findings. Dormant genital herpes in humans was reactivated after cannabis consumption.

In the late eighties several studies focused on marijuana and AIDS. Consistently HIV+ patients using cannabis were found to have severe fungal infections, an increased incidence of bacterial pneumonia compared to non-users, faster replication of the HIV virus and progression to full-blown AIDS.

Research in the nineties added to the evidence that smoking marijuana leads to suppression of the immune system and in 1999, Professor Guy Cabral, one of the foremost scientists working in this field, carried out reviews of the literature and said, "Marijuana has been shown to decrease host resistance to bacterial, protozoan and viral infections in experimental animal models and in vitro systems. Recent immunological studies suggest that marijuana may also influence the outcome of viral infections in humans.Delta-9-THC alters the functioning of an array of immune cells including lymphocytes, natural killer cells and macrophages, thereby affecting their capacity to exert anti-microbial activities".

In the late nineties it was discovered that THC induces apoptosis (programmed cell death) of lymphocytes.

Alveolar macrophages protect the lungs from infection and kill tumour cells. Marijuana significantly impairs these macrophage cells. The proliferation of lymphocytes which also kill tumour cells is also suppressed.

The National Academy of Sciences said, "...the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with pre-existing immune deficits – including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients)".

Depressive, aggressive, violent and suicidal effects

Studies investigating links between cannabis and depression have found that the likely increased risk of developing depression varied between 3 and 6.4 times. Consistently the "theory of self-medication" (that depressed people turn to cannabis for relief) has been disproved. Two reviews were carried out in 2003 and 2004. Their conclusions were very similar. Rey and others in 2004 said, "There is growing evidence that early and regular marijuana use is associated with later increases in depression, suicidal behaviour and psychotic illness, and may bring forward the onset of schizophrenia. Most of the recent data reject the view that marijuana is used to self-medicate psychotic or depressive symptoms".

Louise Arseneault et al in 2002 in their "Dunedin Study" reported that alcohol-dependent individuals were almost twice, marijuana-dependent almost 4 times, and those suffering from schizophrenia-spectrum disorder 2.5 times more likely to be violent than controls.

It is very difficult to determine whether cannabis is associated with violence due to the use of the drug, withdrawal from the drug, a personal predisposition to violence or indeed the illegality of the situation. Professor Heather Ashton in her 1999 review said, "cannabis in most recreational settings decreases aggressive feelings in humans and increases sociability. However occasional predisposed individuals, especially if under stress, become aggressive after taking cannabis. Violent behaviour may also be associated with acute paranoid or manic psychosis induced by cannabis intoxication".

At least two studies have shown that cannabis users can become aggressive during the withdrawal period especially in the first week. Fergusson and others in their "Christchurch Cohort Study" suggested that deviant peer associations were not responsible, and several papers show evidence for violence being due to a pre-existing personality disorder. One study of identical and non-identical twins found the presence/absence of a conduct disorder in a twin pair is a good predictor of cannabis use suggesting that cannabis use and violence to some extent co-occur due to personality tendencies.

A Swedish investigation into suicides discovered cannabis users to be 18.7 times more likely to commit suicide by jumping from a high place than a non-user. The link between cannabis use and suicide may well

be an indirect one by way of depression and psychosis. Hamish Turner, Britain's most senior coroner said in 2003 that he had dealt with 100 deaths in the last year and 10% of them had a significant link to cannabis.

Effects on driving

Cannabis intoxication affects mental functions in the same way whether a person is a regular user or just starting. There is a clear association between cannabis dose and reaction times, the greater the dose, the slower the reactions.

From experiments in the seventies till the present day cannabis has been shown to have a detrimental effect on driving ability whether the experiments are conducted on tracks free from other vehicles, simulators or in real-life driving conditions. A low 20mg dose of THC, a single cigarette today can contain up to 200mg, produces deterioration in driving ability similar to that displayed by a driver just over the legal alcohol limit. Several researchers have found that, barring distractions or unexpected complications, strongly motivated drivers can compensate for some of the impairments.

Tests on airline pilots using flight simulators showed them to be unable to land their planes properly even up to 24 hours after consumption and were completely unaware of a problem.

Another approach to the problem is to analyse the blood taken from accident victims. In several studies cannabis was the most frequently found illicit drug in the blood of drivers killed or injured in vehicle accidents and in 2004, Ramaekers and others said that drivers under the influence of cannabis were 3 to 7 times more likely to have caused the accident in which they were involved.

A combination of alcohol and THC greatly increases the likelihood of making an error while driving, one researcher put this increased risk at 16 times compared with the use of cannabis or alcohol alone. Scientists have for many years warned that, since alcohol quickly affects psychomotor function and cannabis cognitive processes, the combination would undoubtedly be extremely dangerous, especially in a complex traffic situation.

Many young drivers consider that they have "sobered up" long before they actually have so they drive again before they should. Many, mostly young men of 20 to 24, have a very casual attitude towards driving under the influence and are quite happy to accept lifts from friends who have had a joint. Some even boast their driving skills improve. In 2001 27% of young men, aged 17 to 24, admitted in a magazine survey to driving at least once a week under the influence of drugs, mainly cannabis. By 2006 the same magazine found the number had risen to almost 50%, 20% said it was a daily occurrence.

Generally they thought that drug testing would act as an efficient deterrent.

Cannabis and cancer

As with tobacco, cancers caused by cannabis will not quickly become apparent, there is a latency period of 20 to 30 years, and unlike tobacco, cannabis use in the West has only been widespread since the seventies. Also the number of scientific papers on tobacco outnumber those on cannabis by 10 to 1, it is a young science. Other limiting factors for cannabis research are that cannabis and tobacco are often mixed, large samples are required for case-control studies and people are reluctant to confess to their illegal activities. However the two plants have very similar constituents, the main difference being the nicotine in tobacco and cannabinoids in cannabis, so similar side effects must be expected. Cannabis contains about 50% more benzo[a]pyrene, a potent carcinogen, than tobacco and deposits 4 to 5 times more tar in the airways and lungs.

For cancers to occur, the DNA of some genes needs to be affected. Cell abnormalities have been detected in many papers on cannabis, akin to the numbers observed in tobacco smokers, a combination of the two results in an additive effect, and produces the highest total.

Cells of the immune system play a part. Alveolar macrophages help protect the lungs from infection and kill tumour cells, significant impairment of these has been seen in marijuana and tobacco smokers.

Likewise the proliferation of T-lymphocytes that destroy tumours is suppressed. Experiments on animals have provided confirmation of the impact on the immune system and tar from marijuana smoke painted on the skins of mice produced lesions correlated with malignancies.

There is much documentation of the occurrence of cancers particularly of the head and neck in smokers of cannabis. The average age for cancers of these types in tobacco smokers is around 60. The ages of the marijuana users was much less, one study averaged 26 years and in another none was over 41. One piece of research put the odds of developing head or neck cancer in cannabis smokers at 2.1 compared with non-smokers at a consumption of one a day, 4.9 for use more than once, and 36 for a combination with tobacco. Recently cannabis smoking has been linked with bladder cancer.

Cannabis and Dependence

Dependence involves a compulsive need for the drug. Both physical and psychological addictions occur with cannabis. Physical addiction produces tolerance and withdrawal symptoms, psychological addiction is a strong craving for the drug. Almost all addictive drugs including cannabis, stimulate the dopamine-producing system in the brain. This is the Reward Pathway of the Central Nervous System, cannabis receptors are present, the cycle of reward begins leading people on to take more.

Numerous papers have supported the findings that dependence develops with long-term use, and that tolerance is established. This tolerance results in a rise in dosage or increased use, observed both in experiments on animals and in studies of users. The presence of withdrawal symptoms has also been seen in many studies varying from mild anxiety, irritability and nausea to more severe psychiatric problems and aggression. The severity increased with a longer time, greater frequency and larger dosage. The progress from first to regular use was as rapid as tobacco and more rapid than alcohol.

Cannabis dependence was included as a diagnostic unit in the DSM IV (Diagnostic and Statistical Manual of Mental Disorders 1994) and ICD-10, WHO 1992. Morgenstern and others in 1994 found the DSM concept at least as valid as those for dependence found in opiates, alcohol, stimulants and sedatives.

Adolescents are particularly vulnerable to addiction as the brain reaches full development only at the age of 25 or so. The dopamine system in the motivational part develops ahead of the inhibitory area so there is an imbalance encouraging impulsive and risky behaviour. Chambers and others in 2003 warned that teenagers are more likely to experiment with drugs but the experience will have more profound effects, sometimes permanent on the brain.

Two reviews of the literature were carried out in 2003 and 2004. Eliot L Gardner in 2003 looked at 224 studies from the seventies onwards and concluded, “cannabinoids act on the brain reward processes and reward-related behaviours in strikingly similar fashion to other addictive drugs”. Budney and colleagues 2004, reviewing 55 papers on withdrawal symptoms, said, “Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol The onset and time course of these symptoms appear similar to those of other substances withdrawal symptoms. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance”.

A 1998 letter in *The Lancet* reported that 10% of those who ever try cannabis will become daily and 20 to 30% weekly users of cannabis. This was confirmed in 2003 by Fergusson. Of the 1265 children in his Christchurch study, 10% showed clear signs of dependency by the age of 21. This was especially true of males. Demand for treatment for cannabis dependence has grown dramatically. Research from the USA shows that cannabis is the commonest reason for 12 to 17 year olds to be placed in treatment centres, 60% of all cases, a rise of 142% in a decade.

Cannabis and the Gateway Effect

Tobacco and/or alcohol use in teenagers makes the use of other drugs more likely and the same is true of cannabis. Given the opportunity to try marijuana at the house of a friend or a party, users of tobacco and alcohol were more likely to accept. Likewise marijuana smokers were more likely to take cocaine if the chance arose, and within a year of exposure to one of the hallucinogenic drugs, LSD mescaline etc, two-thirds of cannabis smokers had tried it compared to only one in six non-users.

Professor Denise Kandel and her team found that most subjects followed a series of graded steps: beer and wine; cigarettes and spirits; marijuana; other illegal drugs. The younger they started the further they progressed and the more intense the use at any age, the greater the risk of progression to the next stage. Many studies have confirmed that this progression exists. One reported that 60% of young Americans using marijuana before the age of 15 will later in life use cocaine. Almost all who have used marijuana and hard drugs have used marijuana first. Ramstrom said in 2003, "It is found time and again that cannabis is a central component of the network of influencing factors that leads to the abuse of hard drugs".

Explanations for the gateway effect include: Changes in brain chemistry that may make youngsters more susceptible; experiences with cannabis may encourage experimentation with other drugs; common factors in personality or background; exposure of young people to drug-dealers.

A possible family environment/genetic link was explored in 2 studies of same-sex twins, only one of which used cannabis, in one case before the age of 17 and the other, 18. Discounting all the confounding factors, the odds of the "using" twin progressing to other drugs varied between 2.1 and 5.2 times that of the non-using twin. Common environmental and genetic influences would not appear to be a factor.

The "personality and background predisposition hypothesis" was investigated in a study of 3 groups of heavy-using teenagers. One group had low self-esteem and poor relationships, one anti-social behaviour and another "ordinary". The last group were least likely to progress to other drugs.

Fergusson, 2006, in his latest update of the Christchurch study, said that after complex statistical controls for all confounding factors, there still remained a clear tendency for cannabis users to have higher rates of use of other illegal drugs, most evident in regular users and adolescents. So some researchers have sought a neurophysiological explanation.

In 1999 Torngren suggested that exposure to cannabis should make a person more sensitive to another substance, a phenomenon seen in animals. Professor Heather Ashton 2002, proposed mechanisms to identify cannabis in a causal role: Tolerance of the "high" leading user to seek more potent drugs. Alleviation of withdrawal symptoms by using other drugs; Interaction of cannabinoids with the endogenous opioid systems, already shown in animals to increase the rewarding properties of heroin.

Professor Yasmin Hurd has just published the results of a study involving rats (July 5th 2006). She has found that exposure to cannabis during adolescence primes the system. Young rats exposed to cannabis later took much larger doses of opium when trained to self-administer compared to the unexposed controls and were more sensitive to lower concentrations. She concluded, "The current findings support the gateway hypothesis demonstrating that adolescence cannabis exposure has an enduring impact on hedonic processing resulting in enhanced opiate uptake, possibly as a consequence of alterations in limbic opioid neuronal populations".

Cannabis, the reproductive system and babies

Early research into the effects of THC on testosterone, sperm abnormalities and numbers in the seventies and eighties produced conflicting results but Hollister 1986 argued that although the findings may not be of significance in healthy adults, problems may arise in pre-pubertal males and men with impaired fertility. However recent research by Burkman in 2003 has again shown a reduced sperm count in heavy users. She

also found that sperm would “burn out” before reaching the egg as they were moving too fast, too soon, potentially causing infertility.

Likewise early research on female fertility, in particularly the hormone system has been inconclusive. An interesting paper in 2006 looked at the outcomes of IVF and GIFT if marijuana was used by either partner. Females produced fewer eggs and lighter babies, male users also fathered babies who weighed less. High levels of anandamide in the uterus prevent implantation of the embryo. Using cannabis at this crucial time would have a similar effect.

THC passes through the placenta and appears in breast milk. There is now consistent and clear evidence that babies born to cannabis-using mothers are smaller. In this respect a weekly joint is the equivalent of 15 tobacco cigarettes.

Very high doses of marijuana were needed to increase the rate of malformations in the offspring of animals. And again conflicting evidence was obtained. However studies in the eighties were conducted using low-strength marijuana and not THC. Hall and others warned in 1994, “It would be unwise to exclude cannabis as a cause of malformation until larger and better-controlled studies have been carried out”.

One paper linked cannabis smoking with an 11-fold increase in the incidence of one type of leukaemia, and others reported increases in 2 other childhood cancers.

A unique study begun in 1978 by Peter Fried in Canada into the effects on offspring whose mothers had used cannabis while pregnant is still continuing. A few neurological deficiencies were noted at first but had disappeared by the end of the first year. At the age of 4, memory and verbal ability were deficient, and by 5 to 6 they had impaired ability to sustain attention. Behavioural problems and deficits in cognitive functioning became apparent from 6 to 9 and from 9 to 16 memory problems and attention maintenance were reported. Fried said that it is the “executive” functions of children that are noticeably affected, they don’t emerge till about the age of 4 and involve problem solving, planning etc. Support for his findings comes from several researchers, in particular, delinquent behaviour in 6 year olds. In 2003 similar results were found in rats. This is particularly useful since rats don’t have lots of confounding factors like tobacco smoking, alcohol use or standards of living.

In 2002 Nahas and others discovered that THC induces apoptosis (programmed cell death) in fast-dividing cells in the body like the sperm-producing cells in the testes and cells of the immune system. It damages the formation of DNA. This finding also relates to embryo damage and foetal development retardation seen in pregnant cannabis smokers.

Of 400 babies born in a Glasgow maternity hospital in 2002 one in eight had been exposed to cannabis in the womb.

A review article in 2006 concluded that pre-natal exposure to either maternal smoking, alcohol or cannabis use is related to some common neuro-behavioural and cognitive outcomes, including symptoms of ADHD, increased externalising behaviour, decreased general cognitive functioning and deficits in learning and memory tasks.

Effects on Cognitive functioning, personality and educational performance

Cannabis use has in numerous studies been associated with short-term memory problems persisting even 6 weeks after abstinence. Other consequences include: inability to solve maths problems, focus attention, find words to express oneself, and screen out irrelevant information up to two years after stopping. On this last point, Solowij found the degree of impairment and the length of abuse time were correlated. Executive functioning is badly affected. This encompasses mental flexibility, complex thought operations, the processing of information, drawing logical conclusions, planning, learning from experience and abstract thought.

Thomas Lundqvist, having researched this subject for over a decade has added: the inability to be self-critical, understand connections, understand another’s viewpoint and be able to change one’s own. He finds

users lonely, bored, empty and with the feeling they are misunderstood. They have rigid opinions, fixed answers to questions, can't plan their day and have no proper routine.

Users responses to questions confirm they find memory problems worst, followed by trouble in concentrating, thinking clearly and lacking any ambition.

Of particular concern must be children with their still-developing brains. Learning and memory deficits impinge on academic performance. Educational achievement independence, relationships including marriage and career choices are all affected. The normal development of teenagers seems to come to an abrupt halt. Many drop out of school, find it hard to hold down a job, have more divorces, worse social networks, higher mortality rates and more medical and social problems. Social integration and the development of an identity fail to progress. They "sleep away their teens....but stay childish and dependent". Books containing accounts of the long-term effects of cannabis on teenagers include Heinemann 1984, Ranstrom 1987, Hendin 1987 and Newcomb and Bentler 1988.

Solowij said in 1998, "Use more often than twice per week for even a short period of time, or use for 5 years or more at a level of even once per month, may each lead to a compromised ability to function to their full mental capacity, and could possibly result in lasting impairments".

In an effort to find an explanation for all these harms, several researchers have looked for changes in blood flow in the brain. CBF, PET, SPECT and fMRI scans showed sub-normal cerebral blood flow or lower cerebellar metabolism in long-term users assessed within a week of abstinence. Lundqvist concluded that neuropsychological and brain-imaging techniques point to deficits in attention, memory and executive functioning. Another study discovered increased resistance to blood flow in the cerebral arteries of users.

Cannabis and mental illness

This is arguably the aspect of cannabis use that causes most concern and with every justification. The number of cannabis users with mental illness is rising. These are lives needlessly ruined for ever. The cost of treatment for mental illness is enormous.

Professor Robin Murray of The Institute of Psychiatry in London said, "The public health message is clear. Some cases of psychotic disorder could be prevented by discouraging cannabis use, particularly among psychologically vulnerable youths, with the youngest cannabis users most at risk.action is needed to avoid a further burden on our already-overstretched mental health services".

And Professor Peter Jones of Cambridge University, a leading psychiatrist and expert in schizophrenia said that 80% of first episode psychiatric disorders, schizophrenia or schizophrenia-like illnesses, occurred in either heavy users or cannabis dependents. His unit, he said, might as well be called a "Cannabis Dependency Unit".

The Swedish psychiatrist Jan Ranstrom said in 2003, "It is worth mentioning that the opiates (heroin etc) apart only from the development of dependence, produce far less toxic psychiatric complications than do cannabis preparations".

Cannabis-induced psychotic disorder is recognised as a diagnostic unit in the DSM IV (Diagnostic Manual of Mental Disorders). Most patients make a full recovery providing they don't resume their habit. Hereditary factors are usually absent. Schizophrenia or schizophrenia-like psychosis usually runs a chronic course.

As far back as the seventies researchers were connecting cannabis use with psychosis and schizophrenia. They found that some subjects using hashish and large quantities of cannabis experienced psychotic symptoms. The more potent the cannabis preparation, the faster they developed, and many had no psychiatric history. They also discovered that cannabis smoking caused schizophrenic conditions to worsen considerably.

Many papers in the eighties confirmed these findings. One of the most important studies, a large investigation into Swedish conscripts was carried out in 1987. Those on admission who had taken cannabis on more than 50 occasions were more than 6 times more likely to develop schizophrenia in the next 15

years than non-users. When confounding factors were taken into consideration the risk became smaller but was still significant. Again confirmation of this study came from several other researchers.

In the nineties another set of papers added weight to the previous conclusions and a figure emerged that of all those who had used cannabis more than once, 10% experienced either delirium or psychosis. Two other researchers agreed with this figure in later years.

A warning was given during this time of the vulnerability of the adolescent brain which does not complete development till the mid-twenties.

Since 2000 a flood of literature has emerged. Many new and confirmatory findings were made and I will attempt to list them:

The risk of developing schizophrenia or a schizophrenia-like illness for a 15-year old is normally 3% by the age of 26. For cannabis users it is 10%, and the younger they start, the higher the risk. The Swedish conscript study was repeated and the results confirmed, indicating the heavier the use the greater the risk. There was a statistically significant rise in cases of schizophrenia between 1965 and 1997: the number had doubled, the highest risk being among the under-thirty-fives. Cannabis-dependent youngsters at 18 had a 3 to 7 fold increased risk of psychosis. In patients with schizophrenia, the ones who had used cannabis had developed their illness on average 6.9 years earlier in one paper and 5 to 6 years earlier in another. One study found administration of THC by an oral route particularly liable to result in a psychotic episode even with a low dosage. Several studies rejected the "self-medication hypothesis" i.e. that people with psychosis take cannabis to alleviate the symptoms. One review concluded there was a 2-fold rise in the relative risk for later schizophrenia. A Danish study in 2005 reported almost half of patients treated for cannabis-induced psychosis eventually developed a schizophrenia-like illness, one third became full-blown paranoid schizophrenics; only one in six needed no further treatment. A gene involved in dopamine transmission in the brain has been found to have a variant carried by one in four of the population. If two copies of this variant are inherited then the chance of developing schizophrenia rises from 3% to 15% if cannabis is consumed during the teenage years. No problem is experienced for those who don't use the drug. It is thought that a double dose of dopamine is delivered to the brain. People with schizophrenia have an excess of dopamine in the brain. Scans of the brains of adolescents with schizophrenia have brain abnormalities similar to those of adolescent daily cannabis users.

Early in 2006, Fergusson brought together the 2 lines of research, epidemiological and neuroscientific studies in this subject in the BMJ. He concluded:

1. Epidemiological evidence suggests a persistent association between cannabis use and psychosis that is robust to methodological challenges.
2. Neuroscientific studies show that cannabis may lead to psychosis through effects on the processing of dopamine in the brain.
3. Taken together this evidence suggests a causal relation in which frequent use of cannabis leads to a greater risk of psychotic symptoms.