

CANNABIS

A General Survey of its Harmful Effects

Submission to The Social Justice Policy Group

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Introduction

When I was asked to take charge of the Health Education Programme in my school about 20 years ago, I had limited knowledge of drugs and the damage they can do. Since cannabis was then, and still is, the most frequently used illegal drug I decided to find out as much as possible about it.

What I discovered all that time ago, shocked me, and ever since I have been trying to publicise the damage that this drug can do to the brains and bodies of its users.

Cannabis use has risen inexorably since 1981 when British Crime Survey data was first published. 1.75 million adults in Britain are estimated to have used cannabis in the last month. More worrying though is the 12% of 11 to 15 year olds who took it in the year 2004-2005, the year following down-classification. This was up by 1% (thousands more children) from the previous year.

Apart from the devastating consequences that mental illness brings to users and their families, many other harmful effects have been recorded. Various cancers, heart attacks and strokes, disruption to the reproductive processes, deficiencies in children born to cannabis-using mothers and impaired immune systems are all part of the sorry saga.

But what most concerned me as a teacher was the ruin of the careers of some of my pupils. Few children using cannabis even occasionally will achieve their full potential. Because the drug persists in the cell membranes literally for weeks, the functioning of the brain is permanently impaired even on one joint a month.

For all these reasons I have collected data on cannabis from many different sources and on many different aspects, including driving, the gateway theory and possible use in medicine. Well over 400 papers are referenced. There are many more. I hope this book will be useful to anyone, and especially those dealing with young children. The younger a child is when use starts, the more likely he or she is to develop a mental illness, become addicted or move on to other drugs. It is our duty as adults to protect them. They are our future.

Mary Brett

Foreword I

The very word cannabis arouses opinions and emotions. There are few substances which are surrounded by more controversy, and which have at the same time such important and potentially far-reaching public health implications. Most of the evidence concerning cannabis and different aspects of health is clear, but not definitive, as it takes time to accumulate the detail that makes it apparent to everyone what are the likely outcomes of using a particular substance. In other words, we know what is likely to happen, but it is a question of “watch this space”, before we know how it will affect society. For example, the excess mortality and healthcare costs associated with the use of tobacco and alcohol are well known, while those for cannabis remain largely unknown. Eventually there will be robust estimates which will aid healthcare workers and political decision-making, but for the moment we have to wait. This is especially true of cannabis because the baseline is difficult to establish – prevalence rates are changing, and so is the strength of the plant’s active ingredients. At the same time, this lack of definitive evidence concerning the population is certainly not to be taken as a lack of evidence of harm for individuals.

Mary Brett has done us all a great favour by putting together a large amount of data concerning cannabis, and anyone who is teaching, researching, learning or just plain curious will find here a wealth of detail covering the different kinds of damage that cannabis is capable of causing. Because she has been following up the subject for several years, she has been able to put together a wealth of detail as it has evolved, which can only serve to be a great benefit to anyone who is interested in or concerned about the health implications of cannabis.

Professor John Henry
Clinical Toxicologist
St Mary’s Hospital, Paddington, London.

Foreword II

The present renewed interest in cannabis is so great that anyone seeking to be well informed is likely to be overwhelmed by the burgeoning literature on the subject. Scarcely a week passes without a new publication on cannabis and cannabinoids and a new "revelation" in the media. Mary Brett is to be congratulated on providing an unbiased and comprehensive survey which encompasses most of the present knowledge of the harmful effects of cannabis and the issues that arise in education because of its widespread use, particularly in the young. She gives a clear, balanced and well referenced presentation of the published evidence, ranging from the effects of cannabis on cognitive function and educational performance, mental and physical health, to its effects on driving and its possible "gateway effect" into other recreational drugs. Writing from the perspective of a school science teacher, she contributes a well-argued chapter about drug education in UK schools which cogently refutes current "harm-reduction" approaches. This readable survey will be of value to all those interested in cannabis including users themselves and their parents, teachers, general practitioners and academics in search of a digest of recent references. The facts are presented in a form that is accessible both to specialists and to the general public.

Professor Heather Ashton
Honorary Consultant in Clinical Psychopharmacology
Newcastle University

The following have endorsed this submission:

Professor Heather Ashton, Emeritus Professor of Clinical Psychopharmacology, Newcastle University.

Professor Neil McKeganey, Professor of Drug Misuse Research, University of Glasgow.

Professor Eric Voth, MD, FACP, Chairman Institute on Global Drug Policy, Editor in chief, The Journal of Global Drug Policy and Practice.

Dr Ian Oliver, Former Chief Constable of both Central Scotland and Grampian Police, International Consultant on Drugs to the UN, Board member of the International Scientific and Medical Advisory Forum on Drug Abuse and an elected member of The Institute of Global Drug Policy.

Dr Michelle Tempest, Liaison Psychiatrist, Addenbrookes Hospital Cambridge.

Dr Hans-Christian Raabe, GP Manchester. Long-time Campaigner against Cannabis.

Dr Hans Koeppel MD, Psychiatrist, Swiss Doctors against Drugs. Chair of Scientific Board EURAD (Europe Against drugs).

Dr Anthony Seldon, Master, Wellington College, Berks.

Grainne Kenny, International President of EURAD (Europe Against Drugs). Trained Counsellor and Drug Educator.

Dennis Wrigley, Leader and co-founder, The Maranatha Community, Manchester. (The Maranatha Community has been deeply involved in helping young people with drug problems for over 25 years in many parts of the United Kingdom. Its thousands of members include doctors, scientists, teachers, social workers, counsellors, in addition to numerous voluntary workers).

Peter O'Loughlin, Director, The Eden Lodge Practice. Drug and Alcohol Recovery Specialist.

Debra Bell, Founder, Chair, 'Talking About Cannabis'.

Peter Walker, ex-Headteacher Abbey School, Faversham, Kent. Advisor to the Government on Drug Testing in Schools.

Dawn Lowe-Watson, Writer, Bereaved Parent.

Bill Cameron, President Drug-Free Scotland.

Quotes:

Professor Neil McKeganey: “I have found it to be a very useful summary of the evidence”.

Professor Eric Voth: “This paper is excellent and valid, It is an excellent addition to understanding of the marijuana problem”.

Professor Heather Ashton: “I use it as a reference all the time”.

Grainne Kenny: “This is a very valuable paper and a must-read for anyone involved in drug policy. Mary Brett’s documentation on scientific research into cannabis is much sought after throughout Europe. It is an ideal explanation and support for all of us who care about the future of our young people. The United Nations Convention (article 33) on the Rights of Children clearly states that, ‘We must Protect all Children from the use of and involvement with Narcotic Drugs’. Cannabis is a narcotic drug. We cannot afford to ignore her findings”.

Dr Hans Koppel: “This is a very valuable scientific-based paper, a good introduction and overview on cannabis and the consequences of its use. Cannabis is a narcotic drug in the sense of a psychoactive harmful substance with severe consequences to the brain function. This document is a very important help and enrichment for the difficult controversy on the cannabis problem. Congratulations!!”

Dr Ian Oliver: “A thoroughly accurate and well researched document which demonstrates beyond any argument to the contrary that cannabis is a dangerous drug”.

Dr Michelle Tempest: “I work on the front line and deal with all A and E admissions. This covers all psychiatric illness (ages 17 - 65) and will often include patients who have been abusing drugs, frequently cannabis which can exacerbate mental illness. I am often the one on the front line having to explain to parents and children about the dangers and consequences of cannabis use”.

Debra Bell: “Mary’s work on cannabis is an invaluable tool for anyone who wishes to educate themselves on the dangers of cannabis, especially on the young. I have recommended it to all concerned parents and carers who have contacted our organisation as being the most up to date and informative document you can find today. Mary Brett is quite simply a phenomenon”.

Dawn Lowe-Watson: “I am not a scientist and don't know whether it is possible or relevant for me as a parent to endorse Mary Brett's brave and brilliant work on the dangers of cannabis. I lost my eldest son to drugs. He died of heroin in 2000 and some of his last words to me were - "Don't ever smoke pot, mother dear!" This gifted man had been mentally ill for most of his adult life and locked in a secure ward for four of those. I said it was hardly likely. He always told me how the pot had made him paranoid and the pain turned him to heroin, cocaine and everything that eventually destroyed him”.

Dennis Wrigley: “I strongly endorse this excellent survey and pay tribute to the great work of Mary Brett to help our young people whose lives are threatened by the scourge of cannabis. Mary Brett is admired throughout the country for the accuracy of her scholarship as well as her compassion for those in need”.

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), sensory perception (thalamus), mood in general and sleep. No CB1 receptors are present in the brain stem so the drug does not affect basal bodily functions like 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. At a meeting of the Science and Technology Committee of the House of Commons on 22nd November 2006, Dr Brian Iddon MP said that 70% of the cannabis in the UK is home grown and is skunk. The discovery of a new high-potency hybrid known as “Colombian” in December 2006 in Mexico has sent alarm bells ringing. It can be planted at any time of year and matures in 2 months. Worse than that, it cannot be killed by pesticides. A plot the size of a football field yields as much as was formerly grown on a 10 to 12 acre plot (Associated Press, Mark Stevenson 20/12/06). A Home Office Cannabis Potency Study in 2008 found that seizures in early 2008 were 80.8% herbal and 15.3% resin, the rest (3.9%) were indeterminate or not cannabis. Over 97% of the herbal cannabis was sinsemilla, the remainder imported traditional. The mean potency of the sinsemilla was 16.2% (range 4.1 to 46%). The mean potency of the imported herb was 8.4% (range 0.3% to 22%) but accounted for very few samples. Mean potency of cannabis resin was 5.9%, similar to previous years.

On 25th April 2007, the ONDCP (Office National Drug Control Policy) and NIDA (National Institute on Drug Abuse) issued the latest analysis from the University of Mississippi’s Potency Monitoring Project that the highest ever levels of THC had been found since analysis began in the late 1970s. The average amount of THC in seized samples is 8.5%, up from 7% in 2003, in 1983 the average was under 4%. More than 60% of teens receiving treatment for drug abuse or dependence report marijuana as their primary drug of abuse. In 2005 the number of marijuana-related hospital emergency room admissions was 242,200 up from 215,000 in 2004. The highest concentration found in a sample was 32.3%. Roughly 60% of first-time marijuana users are under 18 in the USA.

Moir et al reported that cannabis smoke not only contains about 50 substances that can cause cancer but also 20 times more ammonia (linked to cancer) than tobacco smoke. Hydrogen cyanide (linked to heart disease), nitrogen oxides (linked to lung damage) and certain aromatic amines were at levels 3 to 5 times more.

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.

A new type of cannabis product was reported by Drug Watch International on 25th February 2008. It is called “Budder”. It is reported as being the purest cannabis product available at anywhere between 82 and 99.6% pure THC/CBD/CBN. One hit is equalled to 1 to 2 full cannabis joints and the “high” to be clearer and more long-lasting than average marijuana. Inhalation is the method of choice. A miniscule amount (head of pin) is applied to heated metal and inhaled. Major effects usually subside in 3 to 4 hours, others up to 8 hours. Hallucinations, paranoia, disconnection and hunger can all be felt. It is extremely potent and its effects can be delayed, leading some users to ‘over consume’ and be overwhelmed. It is made by whipping in air and freezing isomerized hash oil. The delta -9-THC is converted to delta-6-THC so normally inactive cannabinoids are activated.

A paper in 2005 by Pijlman and others found a considerable increase in the levels of THC in cannabis sold in Dutch coffee shops. In 2004, the average level of THC in home grown Dutch marijuana (Nederwiet) was 20.4%, significantly higher than that of imported marijuana at 7%. Dutch hashish (Nederhasi) contained 39.3% THC in 2004 compared with 18.2% in imported hashish. The average percentage of THC in Dutch marijuana, Dutch hashish and imported hashish had almost doubled since 1999. It had remained consistent in imported marijuana.

2010 Another report into concentrations of THC in Dutch marijuana was conducted for 2009 –2010 by The Netherlands Institute of Mental Health and Addiction (The Trimbos Institute). Random samples, sinsemilla (Nederwiet), imported marijuana, Dutch hash and hash from imported marijuana and the most potent herbal (202) were bought from Coffee shops. The average THC content of all samples was 16.7%, and 22% in the hash samples. Average THC of Nederwiet was 17.8% imported marijuana 7.8%. Hash from Dutch hemp had more (32.6%) than hash from foreign cannabis (19.0%). Average THC in Nederwiet was higher in 2010 than 2009 (17.8 cf 15.1%). THC in foreign marijuana was lower than year before (7.5% in 2010 and 9.9% in 2009). Average most potent 17.9%. Nederwiet had considerably less CBD than imported marijuana.

The average THC content of skunk (over 80% of the UK market now) is around 18%.

A new “form” of cannabis, SPICE (JWH-018), is being used by young people, and was legal in the UK. This is a synthetic psychoactive substance, created by an American academic purely for research purposes in 1995. According to The Royal Society of Chemists, it gives a “marijuana-like high” and is said to be 4 to 5 times stronger than THC. The chemical is added to packets of herbs, all legal. The structure of spice is quite different from THC but it has the same effects. It has already been banned in Holland, Austria, Germany and Switzerland. It was banned in the UK in December 2009.

In July 2010 Alexandra Datig found several very harmful fungi associated with marijuana. Black mould, *Stachybotrys*, exists on almost all building materials. The growth of cannabis indoors poses a great problem as it provides ideal conditions. Also the 3 most dangerous strains of *Aspergillus*, *fumigatus*, *flavus* and *niger* exist naturally on the plant. A deadly aflatoxin could be the result. A 1996 treatment study by Withenshaw Hospital, Manchester, on 10,000 patients with invasive *Aspergillosis* has shown \$633m in costs, average \$63,300/patient to treat not cure the disease.

In 2010, Arendt et al published mortality figures among 20,581 drug users over a 10 year period (1996-2006) in Denmark. 1441 deaths were recorded in follow-up (111,445 person years). Standardised Mortality Ratios (SMRs) for primary users of specific substances were, cannabis 4.9, cocaine 6.4, amphetamine 6.0, heroin 9.1 and other opioids 7.7. For ecstasy the crude mortality rate was 1.7/1000 person years.

March 2011 ASReece published ‘Chronic Toxicology of Cannabis.’ 5198 papers were screened by hand and preferentially include the most recent ones.

FINDINGS: There is evidence of psychiatric, respiratory, cardiovascular, and bone toxicity associated with chronic cannabis use. Cannabis has now been implicated in the etiology of many major long-term psychiatric conditions including depression, anxiety, psychosis, bipolar disorder, and an amotivational state. Respiratory conditions linked with cannabis include reduced lung density, lung cysts, and chronic bronchitis.

Cannabis has been linked in a dose-dependent manner with elevated rates of myocardial infarction and cardiac arrhythmias. It is known to affect bone metabolism and also has teratogenic effects on the developing brain following perinatal exposure. Cannabis has been linked to cancers at eight sites, including children after in utero maternal exposure, and multiple molecular pathways to oncogenesis exist.

CONCLUSION: Chronic cannabis use is associated with psychiatric, respiratory, cardiovascular, and bone effects. It also has oncogenic, teratogenic, and mutagenic effects all of which depend upon dose and duration of use.

2011 Accidental poisoning in children was reported in 4 cases in a care centre in Southern Spain by Croche Santander B et al. Paediatric accidental cannabis poisoning is an uncommon but life-threatening intoxication. Reduced level of consciousness, drowsiness, ataxia, tremble, apnea, hypotonia and seizures were all witnessed. THC was detected by urine screening. All recovered and were discharged within 24 hours. They concluded that the possibility of cannabis poisoning should be considered in unexplained acute onset of neurological findings in previously healthy children.

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”.

Updated information on THC concentration in weed, netherweed and hash in **Dutch coffee shops 2010 to 2011**. . Frans Koopmans, De Hoop Clinic, Dordrecht, Netherlands.

Since the nineteen seventies the policy on cannabis use in The Netherlands has substantially been different from that in many other countries. It is based on the idea that separating the markets for hard and soft drugs prevents cannabis users to resort to hard drug use. Over the years so-called coffeeshops emerged. Coffeeshops are alcohol free establishments where the selling and the use of soft drugs is not prosecuted, provided certain conditions are met. Many of the cannabis products sold in these coffeeshops originate

from Dutch-grown grass called 'nederwiet'. On behalf of the Ministry of Health, Welfare and Sports we investigate the potency of cannabis products as sold in coffeeshops in The Netherlands.

Δ^9 -Tetrahydrocannabinol (THC) is the main psychoactive compound in marihuana and hashish. The aim of this study is to investigate the concentration of THC in marihuana and hash (=cannabis resin) as sold in Dutch coffeeshops. In addition we examined whether there are differences between the cannabis products originating from Dutch grown hemp (nederwiet) and those derived from imported hemp. This is the twelfth consecutive year that this study has been performed. Apart from THC, the content of two other cannabinoids, cannabidiol (CBD) and cannabitol (CBN), are measured.

The names and addresses of 50 (out of a total of 666) Dutch coffeeshops were randomly selected. For the purpose of this study, 65 samples of nederwiet, 19 samples of imported marihuana, 9 samples of Dutch hash and 56 imported hash samples were anonymously bought in the selected coffeeshops. In addition, 49 samples of the most potent (herbal) marihuana product available were bought. As a rule samples of 1 gram were bought. Samples were bought anonymously.

Traditionally hash contains more THC than marijuana. The average THC-content of all the marihuana samples together was 15,3% and that of the hash-samples 16,5%. The average THC-content of nederwiet (16,5%) was significantly higher than that of the imported marihuana (6,6%). The average THC-percentage of the marihuana samples that were bought as most potent (17,0%) did not differ from that of the most popular varieties of nederwiet (16,5%). Hash derived from Dutch hemp contained more THC (29,6%) than hash originating from foreign cannabis (14,3%). The average THC-percentage of nederwiet was lower in 2011 than in 2010 (16,5 vs. 17,8%), but this difference was not statistically significant. The THC-percentage in imported hash was significantly lower than the year before (14,3% in 2011 versus 19,0% in 2010).

There is some evidence that not only THC-content is indicative for the effects and risks of cannabis, but that CBD might attenuate some of the negative effects of THC. This means that cannabis with a high CBD / THC ratio would have less negative health consequences than cannabis that has little or no CBD. Nederwiet has very low levels of CBD (median = 0,3%), whereas imported hash contained on average 6,7% CBD.

The ratio between CBN and THC can give an indication of the freshness of the preparation (Ross and Elsohly, 1997). Levels of CBN were higher in imported marihuana and hash compared to products derived from homegrown cannabis. Also the ratio of CBN/THC was significantly higher in the imported products. The ratio was higher in imported marijuana compared to nederwiet and in imported hashish as compared to hashish made from nederwiet. Prices that had to be paid for imported marihuana were lower than those for any of the other cannabis products. The prices of hash made from nederwiet were higher. The average price for a gram nederwiet increased from 2007 to 2009 (up to 50%), but since then prices remained the same. On average, a gram of nederwiet costs €8,30.

2012 Mason et al Treatment for cannabis addiction. Gabapentin, on the market to treat neuropathic pain and epilepsy, helps people to quit marijuana use. 50 treatment-seeking users taking gabapentin experienced fewer withdrawal symptoms, smoked less weed and scored higher on cognitive skills compared with those who had placebos. In the last 4 weeks of the study all gabapentin users were cannabis free.

2012 Crippal and others looked at medicines to reduce intoxication (euphoria, disturbed perception, giggling, red eyes, dry mouth, increased appetite, increased heart rate, misperception of time etc). A recent increase in the number of emergency room visits for marijuana intoxication prompted researchers to look for medical treatment. Propranolol used to treat cardiac conditions reduced several symptoms in well-done studies.

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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.

Podczek 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.

2002 *Clinical Cardiology* carried an article by McLeod L et al on myocardial infarction in a young man following the combined use of cannabis and viagra. Viagra is metabolised predominantly by cytochrome P450 3A4 isoenzyme. Cannabis is a known inhibitor of this isoenzyme. Caution is needed in prescribing viagra in cases where the person has cardiovascular disease because of the vasodilatory effects of viagra.

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.

In 2005 a letter to the editor of *The International Journal of Cardiology* was sent by Lindsay et al. It described 2 distinct cases giving cause for concern. In the first, “cannabis use precipitated a malignant arrhythmia in a patient with critical ischaemia from long-standing coronary artery disease. In the second, a young patient presented with an acute myocardial infarction that had started while smoking marijuana; subsequently diffuse coronary artery disease was found at angiography despite the patient’s low risk factor status”.

A case of paroxysmal atrial fibrillation (AF), a common condition usually triggered by alcohol use, was documented when a young female 22 year old presented herself. She had normal echocardiography but was a regular daily (1-2 joints) cannabis smoker. The author, Charbonney in 2005, warned that marijuana was a unusual trigger but should be checked for in young people after alcohol consumption had been ruled out.

The *Irish Examiner* on 3rd May 2007 reported the sudden death of a 21 year-old fit young father. Tiny traces of cannabis were found in his system. Assistant state pathologist, Dr Margaret Bolster said David Kelly died because the rhythmical electrical pulse in his heart misfired, causing it to stop. She pointed to a growing body of medical evidence which shows links between the triggering of similar heart conditions and the use of drugs like cannabis and cocaine. The individual may have had an underlying genetic cardiac problem, this happens in almost a quarter of such cases.

A study in February 2008 on atrial fibrillation and marijuana smoking by Korantzopoulos et al links atrial fibrillation with marijuana smoking. Only healthy young male smokers took part and it was found that “Compelling evidence is accumulating that cannabis has significant haemodynamic (change in blood pressure) and electrophysiological (tachycardia and atrial fibrillation) effects on the cardiovascular system”. The authors concluded that atrial fibrillation should be included in the cardiovascular complications of marijuana smoking. Its incidence in the general population is probably underestimated.

A 2008 paper by Mukamal et al found that marijuana use was associated with a 3-fold greater mortality after acute myocardial infarction. This suggests there may be particular risks for people with established cardiovascular disease.

2008 A possible connection between marijuana abuse and strokes or heart attacks was found in a paper in 2008 (May) by Jayanthi and others. Abnormalities in proteins caused by heavy marijuana use were investigated. A protein, apoC -111 (apolipoprotein C-111) showed significant increases in marijuana users. This is associated with increases in triglycerides. This may be one reason why some marijuana users have an increased risk of stroke and heart attack.

2010 Jouanjus et al looked at cannabis-related hospitalizations among 200 patients admitted to the public hospitals of the Toulouse area of France between Jan 2004 and Dec 2007. They found that one of the adverse events (AE) was lethal. Psychiatric disorders occurred in 57.7%, leading to 18.2% of AEs, central and peripheral nervous system disorders, 15.8%, acute intoxication 12.1%, respiratory system disorders 11.1%, and **cardiovascular disorders 9.5%**.

2011 April Wolff et al examined 48 consecutive young patients admitted for acute ischemic stroke. They found multifocal intracranial stenosis associated with cannabis use in 21% (10 patients), and concluded that multifocal angiopathy associated with cannabis consumption could be an important cause of ischemic stroke in young people.

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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 re-surgence 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.

Zhang et al in 2007 produced a paper showing that “the use of cannabinoids may place individuals at greater risk of the development and progression of Kaposi’s sarcoma. The herpesvirus associated with the development of Kaposi’s sarcoma, KSHV, is needed but insufficient for its development. Marijuana was investigated for its effect on this disease. “Our results indicate that delta 9 THC can enhance KSHV infection and replication and foster KSHV-mediated endothelium transformation. Thus, use of cannabinoids may place individuals at greater risk for the development and progression of Kaposi’s sarcoma”.

Cannabis has been shown to modulate mitochondrial function and induce cell death in a paper in 2007 by Athanasiou and others. Time-lapse microscopy of human lung cancer (H460) cells showed that anandamide (AEA), THC and a synthetic cannabinoid (HU210) all caused morphological changes characteristic of apoptosis. All 3 ligands caused significant decreases in oxygen consumption and mitochondrial membrane potential in rat heart mitochondria. THC and HU210 significantly increased the production of hydrogen peroxide, AEA had no significant effect. Further evidence was obtained of the damaging effects on mitochondria (the structures in cells which produce energy).

In 2007 a paper by Eisenstein et al found that both THC and anandamide directly inhibit cells of the immune system via CB2 receptors.

A paper by Chao et al in 2008 found that recreational drug use does not adversely affect CD4 cell counts. They wrote, “We did not find any clinically meaningful associations, adverse or otherwise, between use of marijuana, cocaine, poppers, or amphetamines and T-cell counts and percentages in either HIV-uninfected or HIV-infected men”. However in their conclusion they added, “although the circulating numbers of CD4 and CD8 T cells do not appear to be significantly affected by use of these substances, these findings do not preclude the possibility that substance use may adversely affect the functional properties of T cells”.

Ishida and others in January 2008 found that chronic marijuana use may increase fibrosis for Hepatitis C patients. Between 2001 and 2004, 204 patients with hepatitis C were interviewed for risk factors associated with HCV and use of alcohol and cannabis. Virologic testing and liver biopsies were carried out. Current daily cannabis use increased the odds of moderate to severe fibrosis by nearly 7-fold. This study confirms an earlier French one of 2004 which came to the same conclusion of an increase in fibrosis in daily users.

A paper in February 2008 (Thomson et al) found that cannabis smoking may be a risk factor for periodontal disease, independent of tobacco use. The Dunedin NZ Longitudinal Study supplied the data for this research. Three groups were determined, no exposure to cannabis, 293(32.3%), some exposure, 428(47.4%) and high exposure, 182(20.2%) .The incidence of Combined Attachment Loss (CAL), between 26 and 32 years of age, in the none group was 6.5%, some exposure 11.2% and high exposure 23.6%. After controlling for tobacco use, sex, irregular use of dental services and dental plaque, the relative risk estimates of the highest group were 1.6 for having 1 or more sites with 4mm or greater with CAL, 3.1 for having 1 or more sites with 5mm or greater CAL and 2.2 for having CAL compared with the “none” group.

Hegde et al, 2010 found that THC suppresses the immune system by massively expanding the number of myeloid-derived suppressor cells (MDSC) both in vivo and in vitro. These cells in the immune system have only recently been discovered. These cells have been known to increase in cancer patients so they may suppress the immune system against cancer chemotherapy, actually promoting cancer growth. The lead author, Dr Prakash Nagarkatti concluded, ‘Marijuana cannabinoids present us with a double-edged sword. On one hand due to their immuno-suppressive nature, they can cause increased susceptibility to cancer and infections. However, further research of these compounds could provide opportunities to treat a large number of clinical disorders where suppressing the immune system is actually beneficial’.

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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 cannabis 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).

Green and Ritter in 2000, in a large drug use survey of men born between 1944 and 1954 found that marijuana users who use the drug to cope with problems are more depressed than those who do not use it to cope with problems.

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).

2002, Vlahov D et al found that New Yorkers who increased their use of marijuana, tobacco or alcohol after September 11th had increased chances of developing Post Traumatic Symptoms. Marijuana increased both PTS symptoms and depression more than the other substances.

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).

Friedman et al in 2003 found that, for a conventional non-delinquent sub-group, a higher degree of significant relationship between degree of marijuana use and degree of violence occurred, compared to the degree of this type of relationship than was found for either cocaine/crack use, amphetamine use, or tranquilliser/sedative use. In a group that is high on delinquent behaviour, the effect of marijuana was less. Thus, this special disinhibition effect was found only for marijuana and not for the other drugs.

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)

A series of surveys by PRIDE (Parent Resources and Information on Drug Education USA) and ONDCP (Office of National Drug Control Policies) in 2006 added more evidence of the link between cannabis use and violence.

Of those students who reported carrying a gun to school during the 2005/6 school year, 63.9% had also used marijuana, 39.9% cocaine and 36.8% crystal meth in the past year. (PRIDE Surveys (2006) Questionnaire report for grades 6-12: 2006 National Summary 184).

Of those students who reported hurting others with a weapon at school, 68.4% had used marijuana, 48.3% cocaine and 44.1% crystal meth in the past year. (PRIDE surveys 2006 etc 197)

The incidences of youth physically attacking others, stealing, and destroying property increased in proportion to the number of days marijuana was smoked in the past year. Marijuana users were twice as likely as non-users to report they disobeyed school rules. (Office of National Drug Control Policy 2006 *Marijuana Myths and Facts: The Truth Behind 10 Popular Misperceptions 10*).

Of those students who reported threatening someone with a knife, gun or club, or threatening to hit, slap or kick someone in the school year 2005/6, 27% had used marijuana, 7.8% cocaine and 6.2% crystal meth in the past year (PRIDE surveys (2006) etc 194).

During the school year 2005/6, 39.6% of those in trouble with the police used marijuana, 12.2% cocaine and 9% crystal meth in the past year (PRIDE surveys (2006) etc 195).

PRIDE surveys are available: <http://www.pridesurveys.com/customercenter/us05ns.pdf>.

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).

Heavy cannabis use and depression were linked in a study on 3 Aboriginal communities in Arnhem Land in the Northern Territory in May 2008 by Lee and others. “After adjusting for other substance use (tobacco, alcohol and lifetime petrol sniffing) age and sex, heavy cannabis users were 4 times more likely than the remainder of the sample (106 individuals) to report severe depressive symptoms”.

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".

"Teens Drugs and Violence", a special report from the Office of National Drug Control Policy in the USA, in June 2007 concluded that "Early use of marijuana – the drug most widely used by teens – is a warning sign for later gang involvement" and "Teens who participate in gangs are more likely to be involved in violent acts and drug use". "Teens who report current and regular marijuana use are 9 times more likely than non-users to experiment with other illegal drugs or alcohol, and five times more likely to steal... Children who use marijuana are nearly four times more likely to join gangs. Being a member of a gang dramatically increases a teen's risk of being a victim of violence, not just a perpetrator".

A possible mechanism for cannabis-induced violence was found in a paper by Howard and Menkes in October 2007. Five habitual cannabis users were given a reefer containing 11mg of THC. An electrocortical measure of affective impulsivity, Go/No Go contingent negative variation was carried out during and after smoking. Slow brain potentials developed normally in both Go/No Go conditions before and during smoking but were severely disrupted 20 to 30 minutes later – peak intoxication! (The effects were said to resemble those occurring in patients with lateral prefrontal cortex lesions). Larger scale studies were called for.

In 2009 Dr Gabriella Gobbi found that teenage cannabis users have decreased serotonin transmission leading to mood disorders, and increased norepinephrine transmission which leads to greater long-term susceptibility to stress. She Said, "Our study is one of the first to focus on the neurobiological mechanisms at the root of this influence of cannabis on depression and anxiety in adolescents." It is also the first to demonstrate that cannabis causes more serious damage during adolescence than adulthood.

2010 Fazel and others conducted a study into bipolar disorder and violent crime. Participants were: individuals with 2 or more discharge diagnoses of bipolar disorder (n = 3743), general population controls (n = 37,429) and unaffected full siblings of individuals with bipolar disorder (n = 4059) 314 individuals with bipolar disorder (8.4%) committed violent crime compared to 1312 general population controls (3.5%). The risk was mostly confined to patients with substance abuse co-morbidity, and minimal in patients without substance use comorbidity. This was further attenuated when the unaffected full siblings were used as controls. They concluded, 'Although current guidelines for the management of individuals with bipolar disorder do not recommend routine risk assessment for violence, this assertion may have to be reviewed in patients with comorbid substance abuse'.

2011 Otten et al found that cannabis smoking increases the risk of depression in the case of genetic vulnerability. Data were collected over 5 years from 428 families and their 2 adolescent children in Holland. In young people with a variant of the gene 5-HTT cannabis use led to an increase in depressive symptoms. The effect was still 'robust' even accounting for alcohol use, smoking, upbringing, socio-economic status or personality.

Daily Mail Tuesday September 28th 2010 reported the case of a public schoolboy, hooked on cannabis, who stabbed his best friend 13 times and left him for dead. Harry Schick, 17, was locked up for 9 years. The boy, Gavin Doyle, was able to dial 999 and was rescued from woods by a helicopter with heat-seeking equipment. He is still experiencing problems from wounds to his hands. "Schick had no history of violence though his psychiatric report said that his heavy use of cannabis had led him to become distanced from reality".

2010 de Graaf et al looked at early cannabis use and depression. They concluded: The overall association was modest (controlled for sex and age), was statistically robust in 5 countries, and showed no sex difference. The association did not change appreciably with statistical adjustment for mental health problems, except for childhood

conduct problems, which reduced the association to nonsignificance. This study did not allow differentiation of levels of cannabis use; this issue deserves consideration in future research.

2012 August Fergusson et al looked at The Christchurch Health and Development Study (1265 NZ children born in 1977 and studied at 4 months, 1 year, then yearly till age of 16, then at 18, 21, 25 and 30). These research findings were presented at The Second national Cannabis Conference in Brisbane on September 20th 2012. Not only did cannabis use precipitate suicidal thoughts but the higher the frequency of regular use, the faster susceptible individuals became suicidal. If all males used cannabis less frequently than several times/week, suicidal ideation would be experienced by 15% of 18 year olds, 24% of 21 year olds and 30% of 30m year olds. If they had all started using cannabis several times a week from the age of 17, then all males would show an increase of 24% of 18s and 31% for 21s.

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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 Cimbara 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".

2004 Raemakers et al did a review of driving and dose-related risk of crashes after cannabis use. Surveys that established recent use of cannabis by direct measurement of THC in the blood showed that THC positives, particularly at high doses are about 3 to 7 times more likely to be responsible for the crash as compared to drivers with no alcohol or THC in the system. Together... recent use of cannabis may contribute to the crash where past use does not. ... similar findings concerning the combined use of alcohol and cannabis in traffic. Combined use of THC and alcohol produced severe impairment of cognitive, psychomotor, and actual driving performance in experimental studies and sharply increased the crash risk. Up to a dose of 300ug/kg THC the risk is found to be equivalent to risk at the legal driving limit for alcohol.

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”.

2005 Asbridge et al looked at adolescent Canadians and cannabis use before driving. ‘While the current findings cannot confirm whether DUIC (Driving Under the Influence of Cannabis) was directly responsible for a MVC (Major Vehicle Crashes), adolescents who used cannabis in the one hour prior to driving were more likely to be involved in MVCs. The risk was around double those who didn’t use cannabis.

Dr Katherine Papafotiou told a seminar at Swinburne University of Technology, Victoria, Australia on October 13th 2006 that while cannabis manifests itself differently to alcohol, it can be equally dangerous when used before driving. Cannabis users were more likely to lane-weave and stop too close to vehicles in front of them. She also found that driver errors occurred more often when alcohol and cannabis were both present. The 3-year study tested 80 Victorians between 21 and 35 who were either regular or irregular users.

2007, Khiabani HZ et al found that THC affects the cognitive and psychomotor skills of drivers. These effects could last longer than a measurable concentration of THC in the blood. Culpability studies have recently demonstrated an increased risk of becoming responsible in fatal or injurious traffic accidents even with low blood concentrations of THC. It has also been demonstrated that there is a correlation between the degree of impairment, the drug dose and the THC blood concentration.

Another Australian study in August 2007 by Ch’ng and others found that cannabis was the most frequently found drug in the systems of motor vehicle drivers presenting to an adult major trauma centre in Victoria. The blood of 436 victims was analysed, 46.7% contained metabolites of cannabis, 15.6% benzodiazepines, 11% opiates, 4.1% amphetamines, methadone 3% and cocaine 1.4%. THC was found almost exclusively in the 15 to 44 year old age group. “Drug usage found in this group of injured drivers was disturbingly high”.

NIDA (National Institute on Drug Abuse) in the USA funded a study on drugs, including alcohol, and driving published in November 2007. In 2006, 30% of high school seniors reported driving after drinking heavily or using drugs, or being a passenger in a car where the driver had been drinking heavily or using drugs, at least once in the previous 2 weeks. Although the numbers reduced between 2001 and 2003, declining from 35 to 31%, after 2004 it had leveled off. In 2006, 13% had driven after using marijuana. Vehicle accidents are the leading cause of death among those aged 15 to 20.

2008 The RAC Foundation reported the results of a survey of more than 2000 users of Facebook. It was looking at texting with a mobile phone while driving. 45% of UK drivers use SMS (Short message services) while driving. Particularly the young. They commissioned TRL (Transport Research Laboratory) to study the level of impairment caused by texting while driving. TRL driving simulator was used, as it had been previously for alcohol, cannabis and mobile phone conversations. 17 young people between 17 and 24 were used. Reaction times to trigger stimuli were 35% lower when texting, compared with alcohol, 12% lowering and cannabis 21%. Texters did reduce the speed but were more likely to stray into adjacent lanes and the speed slowdown didn’t help.

An EMCDDA report on drug use and driving December 2008 found that:

Cannabis can have a detrimental effect on driving ability as it impairs some cognitive and psychomotor skills necessary for driving.

Most of the effects increase in a dose-dependent manner.

Drivers are aware of the impairment but can only partially compensate.

Alcohol with cannabis causes additional impairment.

Chronic use can lead to performance deficiencies that last longer than intoxication and worsen with frequency and length of use.

There is an increased risk of being involved in an accident and this is worsened with the combination with alcohol. Use of either drug alone is less risky.

2008, Ronen and others assessed the effects of 2 (13mg and 17mg) doses of THC relative to alcohol (0.05% BAC) on driving performance, physiological strain, and subjective feelings. 14 healthy students, all recreational cannabis users took part. Both levels of THC cigarettes significantly affected the subjects in a dose-dependent manner. The moderate dose of alcohol and the low THC dose were equally detrimental to some of the driving abilities, with some differences between the 2 drugs. THC primarily caused elevation in physical effort and physical discomfort during the drive while alcohol tended to affect sleepiness levels. After the THC administration subjects drove significantly slower than in the control condition, while after alcohol ingestion, subjects drove significantly faster than the controls. No THC effects were observed after 24 hours on any of the measures.

2010 June 2nd Alan Crancer conducted a study into traffic deaths in California from the use of marijuana. He found that the largest increase in fatalities in fatal crashes where the driver tested positive for marijuana occurred over the 5 years following the establishment of the medical marijuana programme in January 2004. There were 1240 fatalities under these circumstances for the 5 years compared to 631 fatalities for the 5 years before, an increase of almost 100%. He suggested that the TC2010 (Regulate, Control and Tax Cannabis Act) initiative might triple the number of marijuana-related deaths on California's highways.

2010 Beirness and Beasley carried out a roadside survey of alcohol and drug use among drivers in British Columbia. 1533 vehicles were selected. 89% of drivers provided a breath sample and 78% a sample of oral fluid. They found: 10.4% tested positive for drugs, 8.1% had been drinking, 15.5% tested positive for alcohol, drugs or both. Cannabis and cocaine were the commonest drugs found. Conclusions: 'The finding that drug use is more common than alcohol use among drivers highlights the need for a unique and separate societal response to the use of drugs by drivers commensurate with the extent of safety risks posed to road users. The observed differences between driving after drug use and driving after drinking have implications for enforcement and prevention'.

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 Treiving 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). The driver of a speedboat that killed a 2 year-old British boy on a beach in the Bahamas in 2002 has tested positive for cannabis. Blood and urine samples were taken at the time but never tested. When a Metropolitan police team tested them much later, the facts came to light. He also was without a proper licence or insurance. James Bain has not yet been prosecuted over the death (Daily Mail 07/01/07). The pilot of a 1946 Piper J3 Cub in Walnut Ridge Little Rock in America was found to have enough marijuana in his system that may have contributed to an accident which killed himself and one passenger (Associated Press 2007, <http://www.todaysthv.com/printfullstory.aspx?storyid=41149>).

2011 Li and others looked at mandatory testing and aviation accidents in the USA. 'The odds of accident involvement for employees who tested positive for drugs was almost 3 times the odds for those who tested negative.

2011 June Romano et al found in the US that, of those who died in a crash, about 25% tested positive for drugs. The most common were marijuana and stimulants like cocaine and amphetamines. Of drivers simply randomly pulled over, 14% tested positive. This suggests that drugs do contribute to road deaths as the presence was almost twice as high among those killed. 44,000 fatally injured drivers in the USA were studied between 1998 and 2009. Stimulants were linked to all types of crashes – speeding, ignoring other laws, inattention or not using seatbelts. Marijuana linked with speeding and non belt use.

2011 Mu-Chen and others produced a review paper for vehicle crashes for users of marijuana. 9 epidemiologic studies were examined in the past 2 decades. They found that drivers who test positive for marijuana or drive within 3 hours of taking it are more than twice as likely to be involved in a crash than non-users. The greater the amount of marijuana compounds in the urine, also the more frequent self-reported marijuana use were both associated with a greater risk of a vehicle accident. 28% of drivers who

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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 benzyrene, 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.

Benzopyrene 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".

Other adverse respiratory effects are seen with cannabis smoking. In 2004 Moore et al looked at over 6500 adults aged 20 to 59. Current marijuana use was defined as 100+ lifetime use and at least one day of use in the past month. Self-reported respiratory symptoms included chronic bronchitis, frequent phlegm and wheezing, shortness of breath, pneumonia and chest sounds in the absence of a cold. They concluded that

efforts to reduce and prevent marijuana use may have substantial public health benefits associated with decreased respiratory health problem.

In 2006 the risk of lung cancer and past use of cannabis was studied in Tunisia by Berthiller et al. They found that the odds ratio for the past use of cannabis and lung cancer was 4.1 after adjustment for age, tobacco use and occupational exposures. No clear dose-response relationship was observed between the risk of lung cancer and the intensity or duration of cannabis use. "This study suggests that smoking cannabis may be a risk factor for lung cancer".

Bluhm and others in 2006 found that maternal use of recreational drugs increased the risk of neuroblastoma in offspring. 538 children with the cancer were studied, and compared with 504 age-matched controls. They concluded that maternal use of any illicit or recreational drug around pregnancy increased the risk of neuroblastoma in offspring, particularly marijuana use in the first trimester of pregnancy. Evaluation of other recreational drugs was limited by infrequent use.

A systematic review of 34 studies on pulmonary function and respiratory complications was carried out in 2007 by Tetrault et al. The summarized findings are as follows:

Short-term marijuana smoking was associated with improved airway response in 10 of 11 challenge studies (effects assessed immediately or shortly afterwards, 15 mins or 1 hour). However the results of the other one suggested a reversal of this effect after 1.5 to 2 months of marijuana smoking. Longer-term marijuana smoking was inconsistently associated with airflow obstruction. Results from pulmonary function tests were worse in marijuana smokers than in controls in 8 of 14 studies. Longer-term marijuana smoking was associated with an increased risk of various respiratory complications (cough, sputum production, wheezing, dyspnea, pharyngitis, worsening of asthma symptoms) in 14 of 14 studies. The overall quality of studies varied, many failed to control for tobacco smoking and none defined a standardized measure of marijuana dose.

A story in BBC News on 3rd June 2007 reported a case of emphysema in a 37-year-old woman who had smoked cannabis for 20 years when it was diagnosed at the age of 34. She had progressed from 2/day to up to 10/day. Dr Onn Min Kon of St Mary's Hospital London believes her cannabis smoking may be to blame for her condition. He has several other young cannabis-smoking patients who have lungs normally seen in 65 year-olds. The woman said, "If I don't stop smoking I won't be around much longer – there is no cure for emphysema, the holes in my lungs are getting bigger.... There should be adverts showing people like me". Dr Kon is planning a study to compare the lungs of cannabis smokers with those of tobacco-only users., he will use lung-function tests and CT scans.

Marijuana worsens breathing problems in current smokers with chronic obstructive pulmonary disease (COPD) according to a paper presented at The American Thoracic Society 2007 International Conference in May 2007. Among people of 40 and over, tobacco smokers were 2.5 times as likely to develop COPD as non-smokers, while smoking cigarettes and marijuana together the risk rose to 3.5 times. The odds of someone smoking tobacco and cannabis developing *any* respiratory symptoms were 18 times more than a person who used neither. The study involved 648 adults of 18 and over (Tan W 2007).

On March 26th 2007, Dr Sarah Aldington of The Medical Research Institute in Wellington presented a paper to The Thoracic Society conference in Auckland. She said that "Approximately 5% of lung cancer cases in those aged 55 and under may be attributable to cannabis, equating to 15 new cases a year. In 2002 306 people were diagnosed in New Zealand with lung cancer. "The younger someone starts smoking cannabis, the higher the risk of lung cancer", she said. The risk of developing the disease increased by about 8% per year for people whose cumulative exposure equated to smoking one joint a day, about the same as a person with a pack a day tobacco habit.

Aldington et al in Thorax 2007, in a study of 339 subjects, divided into 4 smoking groups, tobacco only, cannabis only, cannabis and tobacco and non-smokers of either substance. They concluded that, "Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast cannabis smoking was seldom associated with macroscopic emphysema. The 1:2.5 to 6 dose equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function is of major public health significance".

A connection between cannabis smoking and emphysema was described in a paper by Beshay and others in October 2007. It concluded, "In case of emphysema in young individuals, marijuana use has to be

considered in the differential diagnosis. The period of marijuana smoking seems to play an important role in the development of lung emphysema. This obviously quite frequent condition in young and so far asymptomatic patients will have medical, financial and ethical impact, as some of these patients may be severely handicapped or even become lung transplant candidates in the future”.

In 2008, Moir et al compared marijuana and tobacco smoke. Ammonia was present in mainstream marijuana smoke at up to 20 times that in tobacco smoke, hydrogen cyanide, NO, NOx, and some aromatic amines were 3 to 5 times greater. Sidestream marijuana smoke had more polycyclic aromatic hydrocarbons (PAHs) than sidestream tobacco smoke. ‘The confirmation of the presence, in both mainstream and sidestream smoke of marijuana cigarettes of known carcinogens and other chemicals implicated in respiratory diseases is important information for public health and communication of the risk related to exposure to such materials’.

Hii et al in January 2008 found that marijuana smokers face rapid lung destruction, approximately 20 years earlier than tobacco smokers. Bullous lung disease (bullae) is a condition where air trapped in the lungs causes an obstruction to breathing and eventual destruction of the lungs. The condition can often go undetected, not showing up on chest x-rays. The average age of marijuana smokers with lung problems is 41 compared with tobacco smokers at 65. One of the authors said, “ What is outstanding about this study is the relatively young ages of the lung disease patients, as well as the lack of abnormality on chest x-rays and lung functions in nearly half the patients we tested. Marijuana is inhaled as extremely hot fumes to the peak inspiration and held for as long as possible before slow exhalation. This predisposes to greater damage to the lungs and makes marijuana smokers more prone to bullous disease as compared to cigarette smokers”.

A comparison of the carcinogenic effects of cannabis versus tobacco was carried out in New Zealand by Aldington et al January 2008. They found that the lung cancer risk of one marijuana joint a day equals that of a daily packet of cigarettes. For every one joint/day smoked for a year the risk factor rose 8%. This association was similar to the 7% risk seen for a pack/day for a year of tobacco smoking.

Daling et al in 2009, found an association between marijuana smoking and testicular cancer. 369 men between 18 and 44 with testicular germ cell tumours were investigated in Washington State. Men who smoked the drug once a week or started long-term when they were adolescents were twice as likely to develop the particularly aggressive form, nonseminoma which accounts for about 40% of all cases. Current marijuana use was linked to a 70% increase for the disease.

Tan WC et al, 2009 (April) found that smoking marijuana and tobacco increases the risk of COPD. People over 40 who used both tobacco and marijuana were almost 3 times more likely to suffer from COPD. The use of marijuana alone was not linked to this increase in risk. It appears that the marijuana may act as a kind of “primer” in the airways, augmenting the effects of tobacco.

June 2009, Singh R et al found that cannabis use increases the risk of cancer. They unearthed “convincing evidence” that cannabis smoke damages DNA in ways that could potentially increase the risk of cancer in humans. They discovered that the smoking of 3 to 4 cannabis cigarettes/day would cause the same degree of damage to bronchial mucus membranes as 20 or more tobacco cigarettes/day. Cannabis smoke, because of its lower combustibility compared to tobacco, contains 50% more carcinogenic polycyclic aromatic hydrocarbons than tobacco smoke.

June 2009 The CIC (Carcinogen Identification Committee) of The OEHHA (Office of Environmental Health Hazard Assessment) of the California Environmental Protection Agency, determined that marijuana smoke was clearly shown, through scientifically validated testing, according to generally accepted principles, to cause cancer.

2012 Pletcher looked at the association between marijuana exposure and pulmonary function over 20 years. He concluded that ‘occasional and low cumulative marijuana use’ (2-3 joints/month) was not associated with adverse effects on pulmonary function’, but also that there was increasing evidence of lung trouble among smokers of 20 or more/month. However his research was widely criticised. The comparison was made with a tobacco smoker of 8-9cigarettes/day. They did not compare 2-3/month tobacco users with 2-3/month cannabis smokers, or heavy with heavy. They only looked at limited lung function parameters, FeV1 (Forced expiratory Volume) and FVC (Forced Vital Capacity). No microscopic analysis of tissue was carried out. No other area of potential damage was addressed. Marijuana smokers inhale more deeply than tobacco smokers and hold their breaths longer. This may stretch the lungs so resulting in larger volumes.

How much air you can force out of your lungs was the only measurement taken. Other studies have produced different results and can be read in this chapter:

Aldington S *Cannabis links to lung cancer*

Paper to The Thoracic Society Conference Auckland, New Zealand March 26th 2007.

Thorax 2007; 0:1-7. doi: 10.1136/thx.2006.077081

Aldington S et al, *Cannabis use and risk of lung cancer: a case-control study* European Respiratory Journal 2008; 31: 280-6.

Moir D, Rickert S, Levasseur G, Larose Y et al, *A Comparison of mainstream and Sidestram Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions* Chem. Res. Toxicol. 2008; 21: 494-502

Moore BA, Augustson EM, Moser RP, Budney AJ *Respiratory Effects of Marijuana and Tobacco Use in a US Sample* J Gen Intern Med 2004; 20: 33-37.

Hii SW, Tam JDC, Thompson BR, Naughton M, *Bullous lung disease due to marijuana* Respirology Jan 2008; 13 (1): 122-7.

2012 British Lung Foundation C.E.O. Dame Helena Shovelton said that cannabis smoking poses a 20 times greater risk of lung cancer per cigarette than tobacco smoking. Used by more than a third of young people under 24, but 88% believe it's less dangerous than tobacco. A third said it did not harm health. The average puff on a joint is two thirds longer and held in lungs for 4 times longer. So Cannabis smoker inhales 4 times as much tar and 5 times as much carbon monoxide. With each puff the smoke particles become more concentrated and harmful.

Lacson et al, Sep 2012 Looked at the possible increase of testicular cancer in marijuana users. Testicular cancer is the commonest cancer diagnosed in young men of 15-45 and is increasing. The self-reported recreational use among 163 young men with diagnosed testicular cancer and compared it with 292 healthy controls. Men with a history of marijuana use were twice as likely to have sub-types of testicular cancer called non-seminoma, and mixed germ cell tumours. These tumours carry a worse prognosis than the seminoma type

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 developmental 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". Another research report by Budney in *Addiction* 101 (suppl.1) 2006, found that "...cannabis dependence is much more similar to than different from other types of substance dependence, even with regard to withdrawal. The generic DSM-IV dependence criteria can be applied fairly well to cannabis, and yield findings similar to that observed with other substance dependence disorders....whether we can do better by developing more sophisticated generic criteria or using substance specific criteria".

In a paper still in press (2006), Budney et al say, "The demonstration of a dose-dependent suppression of cannabis withdrawal by oral THC provides additional support for validity of the cannabis withdrawal syndrome and its inclusion in the DSM".

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 Theis 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".

In 2006 Copersino et al looked at 104 non-treatment seeking adults, primarily cannabis users who had made at least one serious attempt to stop using the drug. "Study findings provide evidence for the clinical significance of a cannabis withdrawal syndrome, based on the high prevalence and co-occurrence of multiple symptoms that follow a consistent time course and that prompt action by the subjects to obtain relief, including serving as negative reinforcement for cannabis use" They said that these findings support the existence of a clinically significant cannabis withdrawal syndrome, which should be considered for inclusion in the DSM-V.

An article in The Ottawa Citizen on 24/11/06 reported that Psychiatrist Kathy Szirtes, speaking at a "Dazed and Confused" forum for teenagers in Rideau High School, said that adults may take 2 years to become addicted to marijuana while children can take only about 6 months as their brains are still not properly developed. Marijuana cravings she said were often mistaken for symptoms of ADHD. The forum was sponsored by the CAMC, Champlain Addiction Coordinating Body and Ottawa Integrated Drugs and Addictions Strategy.

CB1 gene variants may be linked with symptoms of marijuana dependence in adolescents. Hopfer and others found that 2 CB1 variants (present in 12% of the population) were significantly linked to the likelihood of the development of one or more dependent symptoms and another variant (present in 21% of the population) was linked to a lower risk of dependent symptoms developing. DNA samples were taken from 541 youths aged 17 or over who had recently used marijuana at least 5 times. 327 had one or more symptoms of dependence, the other 214 became the controls.

Chronic abuse of different drugs cause similar brain changes. Whether long-term users favour cocaine, cannabis or PCP, autopsies of their brains show a number of common gene changes consistent with diminished brain plasticity (ability to learn from new experiences and adapt to new situations). A paper by Lehrmann and others found that the anterior pre-frontal cortex (decision-making region) was dysfunctional in the brains of drug users. The brains of 42 deceased abusers were studied. Nearly 80% of them had similar alterations in genetic output compared to the controls. Genes involved in calcium signalling were turned down and those in lipid and cholesterol-related pathways were turned up. The abuser's ability to make sound decisions could be threatened.

2006: Nocon et al examined prospectively over 4 years, the profile of cannabis dependence and the risk of specific dependence criteria in a community sample of 2446 young people between 14 and 24. 30% were users of cannabis. 35% met at least one dependence criterion, withdrawal 17%, tolerance 15%, loss of

control 14%, and continued use despite a health problem 13%. Even 22% of low frequency users met one criterion, as did 81% of high frequency users. The occurrence of dependence could not be attributed to the concomitant use of other illicit drugs or dependence on alcohol or tobacco.

Over 2500 adult daily cannabis users completed an Internet survey. Fewer than half of daily cannabis users meet the DSM-IV-TR criteria for cannabis dependence. This study aimed to determine whether the negative aspects associated with use of cannabis can be explained by a proxy measure of dependence instead of by frequency of use. Comparing those who were dependent (N=1111) with those who were not (N=1770), the former consumed greater amounts of cannabis, various other drugs and alcohol. They also exhibited higher levels of depression and lower levels of happiness, motivation and satisfaction with life. The study concluded, “ Although all of our subjects reported daily use, only those meeting proxy criteria for cannabis dependence reported significant associated problems. Our data suggests that dependence need not arise from daily use, but consuming larger amounts of cannabis and other drugs undoubtedly increases problems” (Looby and Earleywine 2007).

A paper from STASH (Science Threads of Addiction, Substance Use and Health), January 2007, looked at the transition from drug use to dependence. Over 8000 participants were involved in the study (a report of 3 papers). The probabilities of initiation of drug use peaked at age 18 for alcohol and marijuana. The risk of developing dependence on these drugs also peaked in the teens. Male marijuana users were approximately twice as likely to become dependent in the 2 to 5 years after first use than female users.

A plant extract which may block cannabis addiction has been discovered. MLA (methyllycaconitine) from the seeds of *Delphinium brownie*, a plant in the buttercup family was given to rats. They lost their craving for a synthetic version of THC and a reward response to THC was blocked in the brain. By analysing fluid from the nucleus accumbens in the reward signalling area of the brain they found that release of dopamine was blocked by MLA. It is not known exactly how MLA works but no side-effects were reported. Dopamine levels were not reduced below the normal. (Goldberg S et al 2007).

A review paper on Marijuana Dependence and its Treatment by Budney and others was published in December 2007. They concluded that the “good news” was the increased recognition that cannabis can cause addiction. Significant negative consequences in a sub-set of users has resulted in specific marijuana-related treatments and interventions similar to those used for other substance disorders. More people are now seeking help as it is now perceived to be acceptable to do so. Rapid advances in the neurobiology associated with marijuana and the cannabinoid system bring hope for increasingly effective treatment options. More severe dependence may be prevented in some users and better contacts made with users who may benefit.

Vandrey et al compared withdrawal symptoms from cannabis and tobacco in a paper in January 2008. They concluded that, “Overall withdrawal severity associated with cannabis alone and tobacco alone was of a similar magnitude. Withdrawal during simultaneous cessation of both substances was more severe than for each substance alone, but these differences were of short duration and substantial individual differences were noted. These results are consistent with other evidence suggesting cannabis withdrawal is clinically important and warrants detailed description in the DSM-V and ICD-11”.

2007 Adult Psychiatric and Morbidity Study: The prevalence of drug dependence was 3.4% (4.5% of men, 2.3% of women). Most dependence was on cannabis only (2.5%), rather than other drugs (0.9%). Symptoms of dependence were most commonly reported by adults aged between 16 and 24 (13.3% of men, 7.0% of women in this age group).

In 2008 (May) Walden and Earleywine found that the quantity of cannabis used predicts future problems with dependence, social factors and respiratory health. Nearly 6,000 adults using at least once a month reported on levels of intoxication and quantity used. Quantity was found to be an important predictor of these 3 problems.

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.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) in their annual report in 2010 found that 'Factors specifically associated with progression to dependence include intensive or risky patterns of cannabis use, persistent use and early onset. Individuals who experience positive effects (e.g. laughter, happiness) of their early cannabis use (at age 14-15) had an increased risk of cannabis dependence later in life'.

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.

2011 Lopez-Larson et al looked at prefrontal and insular cortical thickness in adolescent users. 18 heavy users were compared with 18 non-users. 'Our results suggest that the age of regular use may be associated with altered prefrontal cortical gray matter development in adolescents. Furthermore reduced insular cortical thickness may be a biological marker for increased risk of drug dependence'.

2011 Vanderbilt Addiction Center researchers found that exercise can curb marijuana use and cravings. 12 participants, all cannabis-dependent (av 5.9 joints/day) and not willing to have treatment exercised by running on a treadmill. Their cravings for and use of cannabis were cut by more than 50% after exercising on the treadmill for 10 sessions of 30 minutes each over a fortnight. The maximum reduction occurred in the first week, and overall fell to 2.8 joints/day.

2011 November Levine et al looked at nicotine as a gateway drug. Epidemiological evidence has pointed to the fact that most illicit drug users report use of tobacco or alcohol prior to illicit drug use. The aim was to discover a possible biological mechanism by which nicotine exposure increases the vulnerability of people to illicit drug use. Mice exposed to nicotine in their drinking water for at least 7 days, showed an increased response to cocaine. The nicotine changes the DNA structure, re-programmes the expression pattern of specific genes especially the FosB gene that has been related to addiction and so ultimately alters the behavioural response to cocaine. The 2003 Nat Epidemiological Study of Alcohol-related consequences was examined. The rate of cocaine dependence was higher among cocaine users who smoked prior to cocaine use than those who tried cocaine first before smoking. 'Now that we have a mouse model of the actions of nicotine as a gateway drug, this will allow us to explore the molecular mechanisms by which alcohol and marijuana might act as gateway drugs' said Kandel, 'in particular if there is a single common mechanism'.

2012 Moghaddam compared the brain activity of adolescent and adult rats involved in an activity in which they expected a reward. Increased activity occurred in an unusual area in the adolescents – the Dorsal Striatum (DS) – a site associated with habit forming, decision-making, motivated learning. Adult rats did not show this. The nucleus accumbens, traditionally associated with reward, was similarly activated in adults and young. Electrodes were implanted into the brains. Reward expectancy is processed differently in adolescent brains but it can affect regions directly responsible for decision-making and action selection. 'Adolescence is a time when the symptoms of most mental illnesses – such as schizophrenia and bipolar and eating disorders – are first manifested, so we believe that this is a critical period for preventing these illnesses'.

2011 Allsop et al looked at the development of a 'Cannabis Withdrawal Scale'. Results showed that the scale had excellent psychometric properties. Nightmares and/or strange dreams was the most valid item but caused relatively little associated distress. Unlike intense angry outbursts which caused much associated distress. Inability to get to sleep caused significant distress. They concluded that 'The Cannabis Withdrawal scale can be used as a diagnostic instrument in clinical and research settings where regular monitoring of withdrawal symptoms is required'.

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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. A report published in December 2006 by the Canadian Centre on Substance Abuse “Risks Associated with Tobacco Use in Youth Aged 15-19”, an analysis of the data from the Canadian Addiction Survey, 2004, found that 91% of smoking youth reported using cannabis in the past year compared with 28.8% of non-smoking youth. And compared with 3.5% of non-smoking youth, 31% of smokers below 20 (including the 15 to 19 year olds) reported using cocaine, amphetamines, heroin, ecstasy or hallucinogens in the past year.

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 on 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.

2004 Agrawal et al looked at twins. They concluded: Early cannabis use is strongly associated with other illicit drug use and abuse/dependence. The relationship arises largely due to correlated genetic and environmental influences with persisting evidence for some causal influences.

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”.

The December 2006 edition of *Alcoholism: Clinical and Experimental Research* carried an article about smoking among adolescents and an increased risk of developing alcohol-use disorders. Results indicate that smoking “primes” the brain for subsequent addiction to alcohol and possibly other drugs. Almost 75,000 adolescents and young adults were randomly selected for the study by Grucza and Chen. Typically teenage smokers had a 50% higher risk of developing an alcohol-use disorder (a range of problems including alcohol abuse and alcohol dependency). Grucza said, “Addictive drugs all act on a part of the brain that is described as the central reward circuitry. Once this system is exposed to one drug, the brain may become more sensitive to the effects of other drugs, as demonstrated by a number of rodent studies. Our results are in line with an emerging literature that shows adolescence may be a unique window of vulnerability for addiction”.

In February 2007 a Swedish paper by Ellgren set out “to determine whether cannabis exposure during periods of active brain development alters reward-related behaviour and neurobiology for psycho-stimulant and opioid drugs by the use of animal models”. Results did not support the cannabis gateway hypothesis in relation to subsequent psycho-stimulant use but did support it in relation to opioids. The typical pattern of intermittent use by adolescents was mimicked and discrete opioid-related alterations were revealed in brain regions highly implicated in reward and hedonic processing. This was coupled to increased heroin intake in a self-administration paradigm, and increased morphine conditioned place preference, indicating altered sensitivity to the reinforcing properties of opioids. In the limbic region, there were pronounced alterations in endocannabinoid levels in cognitive brain areas even though alterations were also apparent in reward-related regions. Pre-natal exposure induced discrete opioid-related alterations within brain regions highly implicated in reward and hedonic processing.

They concluded, “Taken together, this thesis presents neurobiological support for the cannabis gateway hypothesis in terms of adult opiate, but not amphetamine abuse, with underlying long-term disturbances of discrete opioid-related systems within limbic brain regions”.

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.

October 23 2007 brought a report from The National Center on Addiction and Substance Abuse at Columbia University. (CASA), “Tobacco: The Smoking Gun”. They found that “Compared to 12 to 17 year olds that don’t smoke, those who do are more than 5 times likelier to drink and 13 times likelier to use tobacco than non-smokers. Those who begin smoking at age 12 or younger: More than three times likelier to binge drink; nearly 15 times likelier to smoke marijuana and nearly 7 times likelier to use other illegal drugs such as heroin and cocaine”. The nicotine poses as significant danger of chemical and structural changes in the developing brain. This can make a teenager more susceptible to alcohol and other drug addiction and mental illness.

A paper by Patton et al in 2007 found in a 10-year 8-wave cohort study of 1943 Victorian children, originally 14 to 15, that heavy (daily) teenage cannabis users tend to continue selectively with cannabis use. “Considering their poor young adult outcomes, regular adolescent users appear to be on a problematic trajectory.”

In 2008 (April) Fergusson et al updated their findings from The Christchurch Longitudinal Study. Their results showed that “Illicit drug use and abuse/dependence from ages 16 to 25 were significantly associated with a range of parental adjustment measures; exposure to abuse in childhood; individual factors; and measures of childhood and early adolescent adjustment. Analyses...suggested that parental illicit drug use, gender, novelty-seeking and childhood conduct disorder predicted later illicit drug use and abuse/dependence. Further analysis revealed that these pathways to illicit drug use and abuse/dependence were mediated via cannabis use, affiliation with substance-using peers, and alcohol use during ages 16-25”. In their conclusion they said, “the use of cannabis in late adolescence and early adulthood emerged as the strongest risk factor for later involvement in other illicit drug use”.

2010 June 2010 Melberg et al (Norwegian researchers) tested the “gateway” hypothesis. ‘The model they chose suggests two distinct groups; a smaller group of “troubled” youths for whom there is a statistically significant gateway effect that more than doubles the hazard of starting to use hard drugs, and a larger fraction of youths for whom previous cannabis use has less impact’.

2010 A study from Australia by Degenhardt et al found that occasional cannabis use in adolescence predicts later drug use and educational problems. Nearly 2000 secondary school pupils were followed from 14.9 to 24 years of age. Those who continued cannabis use into early adulthood had higher risks of later adult alcohol and tobacco dependency and illicit drug use, as well as being less likely to complete a post secondary qualification.

2011 (July) Swift et al found that quitting cannabis in your twenties cuts progression to other drugs. Use of cannabis declines among Australians throughout their twenties but Those who are still using are more likely to be weekly users or even more frequent. They have an increased risk compared with occasional users. Weekly users – risk of other illicit drugs – 2 to 3 times, daily – 6 times as likely to smoke tobacco and less likely to give up all others except cocaine. Nearly 2000 Victorian secondary school pupils followed for 13 years, from 1992. Six, six monthly intervals, then 20-21, 24-25, and 29. While overall decrease (age 20 – 58% to only 29% at 29) in cannabis use in young adults, number of those who use weekly/daily almost doubled. Among non-users, use of amphetamines, cocaine or ecstasy virtually non-existent.

2012 Mayet looked at the influence of cannabis use patterns on the probability of subsequent initiation with other illicit substances among French adolescents. 29,393 teenagers were studied. All possible pathways were modelled from initial abstinence to cannabis initiation, daily cannabis use and (other illicit drugs) initiation. The model was adjusted for tobacco and alcohol use. The risk for (other illicit drugs) initiation was 21 times more with experimenters, 124 times higher among daily users than non-users. Tobacco and alcohol were associated with a greater risk of moving on to cannabis.

2012 September. Agrawal looked at 3797 sets of twins in Australia and siblings between 21 and 46. to find out whether cigarette smokers were at increased likelihood of early opportunity to use cannabis and early onset of cannabis use. They found that regular users were more likely to report an earlier opportunity to use cannabis and early onset of cannabis use. Conclusion: These findings indicate that the well-known overlap in cannabis and cigarette smoking behaviours may evolve as early opportunity to use and extend through the course of the substance use trajectory.

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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). In another paper in 1985 Abel found that a combination of alcohol and marijuana caused 73% fetomortality (offspring deaths) in rats and 100% in mice.

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, Sherwood et al 1999) 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. An increased risk of prematurity was also found by Sherwood et al 1999.

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 et 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 et al in 1992 found that marijuana use increases the symptoms of ADHD in first grade children. Six year old children are more likely to show signs of this condition if their mothers smoked 6 or more marijuana cigarettes /week.

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 paper by Schuel et al in 2002 found evidence that anandamide signaling regulates human sperm functions required for fertilization. An analogue of AEA (anandamide) and also THC modulated capacitation and fertilizing potential of human sperm in vitro, sperm fertilizing capacity (in the Hemizona assay) was reduced by 50%. "These findings suggest that AEA-signaling may regulate sperm functions required for fertilization in human reproductive tracts, and imply that smoking of marijuana could impact these processes.

2002 Richardson and others looked at prenatal exposure to alcohol and marijuana and the effects on 10 year-old neuropsychological outcomes. At 10 over 500 children from a longitudinal study were tested for problem solving, learning, memory, mental flexibility, psychomotor speed, attention and impulsivity. Prenatal marijuana use had an effect on learning and memory as well as impulsivity.

2005 Gray et al looked at prenatal exposure and effects on depressive symptoms at age 10. 633 mother/child dyads were studied. Exposure to marijuana in the first and third trimesters predicted significantly increased levels of depressive symptoms (rather than a diagnosis of a major depressive disorder).

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.

Bluhm et al in 2006 found that maternal recreational use of drugs and marijuana during pregnancy were associated with increased risk of neuroblastoma in offspring.

Barros and colleagues, writing in *The Journal of Paediatrics* in January 2007 found that marijuana-exposed infants born to adolescent mothers scored differently on measures of arousal, regulation and excitability compared to non-exposed infants, they showed subtle behavior changes in the first few days of life, they cried more, startled more easily and were more jittery. The authors said this may interfere with mother-child bonding.

Harkany et al in a paper in January 2007 found that endocannabinoid signaling modulates CNS (Central Nervous System) patterning so that “pharmacological interference with endocannabinoid signals during foetal development leads to long-lasting modifications of synaptic structure and functioning. Marijuana abuse during pregnancy can impair social behaviours, cognition and motor functions in the offspring with the impact lasting into adulthood.

Another paper in May 2007 had similar findings. Endocannabinoids in the human body play a vital role in the development of a baby’s brain. They are responsible for controlling how the complex system of nerves develop in the embryonic brain. Dr Ann Rajnicek said “Smoking cannabis could interfere with the signals that are being used in the brain to wire it up correctly in the first place. As the brain develops further, there will be functional problems – potential brain damage” (Berghuis P et al 2007).

Forrester and Merz found selected birth defects with prenatal drug use in a study in Hawaii. December 2007. Cases were infants/fetuses with any one of 54 selected birth defects delivered during 1986-2002. Marijuana rates were significantly higher than expected for 21(39%) of the birth defects. These defects were associated with the CNS, cardiovascular system, oral clefts, limbs and the gastrointestinal system.

A paper in March 2008 by Goldschmidt et al found that intelligence test performance was adversely affected at the age of 6 in children born to cannabis-using mothers. 648 children were involved in the study. Women were questioned about their use of marijuana at 4 and 7 months of pregnancy and at delivery. The results were: ‘There was a significant nonlinear relationship between marijuana exposure and childhood intelligence. Heavy marijuana use (one or more cigarettes per day) during the first trimester was associated with lower verbal reasoning scores on the Stanford-Binet Intelligence scale. Heavy use during the second trimester predicted deficits in the composite, short-term memory and quantitative scores. Third trimester heavy use was negatively associated with the quantitative score. Other significant predictors of intelligence include maternal IQ, home environment and social support’. They concluded that, “These findings indicate that prenatal marijuana exposure has a significant effect on school-age intellectual development”.

I recently was in conversation with a midwife who had delivered babies of cannabis-using mothers. She said, “They are ravenous, chew their hands constantly, drink 3 times as much milk as non-affected babies, are promptly sick, then hungry again.

January 2010 El Marroun et al again found that maternal cannabis use even for a short period in pregnancy may be associated with lower birthweight and head circumference, and this this was more pronounced than the growth restriction seen in tobacco users. 7.5 thousand women were assessed.

2010 Gray et al: 86 pregnant women provided details of daily cannabis and tobacco use during pregnancy. Cannabis exposure was associated with decreased birth weight, reduced length and smaller head circumference, even after control for tobacco c-exposure.

2010 Campolongo et al looked at the developmental consequences of perinatal cannabis exposure - neuroendocrine and behavioural effects in adult rodents. Conclusions: ‘There is increasing evidence from animal studies showing that cannabinoid drugs are neuroteratogens which induce enduring neurobehavioral abnormalities in the exposed offspring. Several preclinical findings reviewed in this paper are in line with clinical studies reporting hyperactivity, cognitive impairments and altered emotionality in humans exposed in utero to cannabis. Conversely, genetic, environmental and social factors could also influence the neurobiological effects of early cannabis exposure in humans’.

2010 Willford et al looked at prenatal tobacco, alcohol and marijuana, and their effects on processing speed, visual-motor coordination, and interhemispheric transfer. 320, 16-year olds, taking part in a longitudinal study into effects of prenatal substance exposure on development outcomes were investigated.

No interactions were found between the 3 substances. Confounding factors were controlled for. There were significant and independent effects of the 3 on processing speed, and interhemispheric transfer of info. Tobacco and marijuana were implicated with deficits in visual-motor coordination.

2011 Day and others looked at the effects of prenatal marijuana exposure (PME) on delinquent behaviour. 580 mother/child dyads were used from the 4th prenatal month through 14 years. Offspring of heavier marijuana users were significantly more likely to report delinquent behaviour at age 14. The odds ratio for delinquency for those exposed to one or more joints per day during gestation was 1.76. PME significantly predicted child depressive symptoms and attention problems at 10, after controlling for other significant covariants. Child depressive symptoms and attention problems at 10 significantly predicted delinquency at 14 years. The association between PME and delinquent behaviour at 14 years was mediated by depressive symptoms and attention problems in the offspring at 10 years.

2011 Frank et al studied the impact of intrauterine exposure to substances on initiation of use by adolescents. 149 adolescents who had been exposed to cocaine in the uterus were followed from birth till the age of 16. Higher levels of IUCE (intrauterine cocaine exposure) were associated with a greater likelihood of initiation of any substance (licit or illicit) as well as marijuana and alcohol specifically. Those with lighter intrauterine marijuana exposure had a greater likelihood of initiation of any substance as well as of marijuana particularly. Time dependent higher levels of exposure to violence between ages 8 and 16 were also robustly associated with initiation of any illicit or licit use and of marijuana and alcohol particularly.

2011 April: Marroun and others found, using stats from over 4000 children that intrauterine exposure to cannabis is associated with behavioural problems in early childhood with an increased risk for aggressive behaviour and attention problems as early as 18 months in girls, but not boys. No association was found between cannabis use of the father and child behaviour problems.

2012 Jan, Goldschmidt and others found, in a longitudinal study from birth, that a significant negative relation was found between prenatal exposure to marijuana (PME) and 14 year old WIAT(Wechsler Individual Achievement Test) composite and reading scores. The deficit in school achievement was mediated by the effects of PME on intelligence test performance at 6, attention problems and depression symptoms at 10, and early initiation of marijuana use.

Psychoyos et al in 2012 August found that new high-potency marijuana can interfere with early brain development in developing fetuses. 'Some new high-potency strains, including some medicinal cannabis blends, contain up to 20 times more THC than did 'traditional marijuana from decades past' said Delphine Psychoyos, the co-author. 'Easy access to drugs via the internet or dispensaries makes the problem worse'. Harmful effects can begin as early as 2 weeks from conception. Exposure to today's marijuana in early pregnancy is associated with anencephaly, a devastating birth defect in which infants are born with large parts of the brain or skull missing.. Early pre-natal use was also tied up with ADHD, learning disabilities, memory problems in toddlers and 10 year olds as well as depression, aggression and anxiety in the teens.

Lacson and others in September 2012 found that marijuana use may increase the risk of developing subtypes of testicular cancer that tend to carry a worse prognosis. This result should be considered not only in people using cannabis recreationally but also when marijuana and its derivatives are used for therapeutic reasons in young male patients. 163 young men diagnosed with testicular cancer were compared with 292 healthy men of the same age and race/ethnicity. The marijuana-using men were twice as likely to have subtypes called non-seminoma and mixed germ cell tumours. These cancers usually occur in younger men and carry a worse prognosis than the seminoma type. These results confirm those of 2 previous studies of marijuana and testicle cancer.

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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". Another study into the effects of marijuana on morphological changes in the brain in 2000 (Wilson et al), found that the age at which marijuana exposure begins is important. Subjects who started to use marijuana before the age of 17 were compared with those who began later. The younger starters had smaller whole brain and percent cortical grey matter and larger percent white matter volumes, the males had significantly higher CBF (Cerebral Blood Flow) than other males. Both sexes who started younger were physically smaller in height and weight.

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 (Kleiman 1989).

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 escalating 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.

Ranganathan and D'Souza in 2006 reviewed the literature on the acute effects of cannabinoids on memory tasks in humans. Their conclusion suggested that cannabinoids impair all stages of memory including encoding, consolidation and retrieval.

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".

Marijuana's well-known effects on memory (short-term) according to neuroscientists, may be the result of misfiring brain cells. A paper published on 19th November 2006 by Robbe and others found that rats given THC experienced disruptions in the synchronous brain-cell firing that causes the formation of memories. There was a slowing of brain wave activity, principally theta and fast-ripple waves (believed to be involved in short-term memory formation) but also gamma waves (thought to help in moving memories into long-term storage). At very high doses the drug appeared to prevent learning altogether.

Chronic abuse of different drugs cause similar brain changes. Whether long-term users favour cocaine, cannabis or PCP, autopsies of their brains show a number of common gene changes consistent with diminished brain plasticity (ability to learn from new experiences and adapt to new situations). A paper by Lehrmann and others found that the anterior pre-frontal cortex (decision-making region) was dysfunctional in the brains of drug users. The brains of 42 deceased abusers were studied. Nearly 80% of them had similar alterations in genetic output compared to the controls. Genes involved in calcium signalling were turned down and those in lipid and cholesterol-related pathways were turned up. The abuser's ability to make sound decisions could be threatened.

An Australian study by George Patton et al 2007, on nearly 2000 Victorian high school 14 to 15 year olds since 1992 has found that, "while both alcohol and cannabis carried health risks, the overwhelming evidence was that cannabis was "the drug for life's future losers". Almost two thirds had tried cannabis before they were 18. They are more likely to suffer poor long-term mental health than drinkers, more likely to graduate to amphetamines, ecstasy and cocaine, and be less likely to be working, be qualified or in a relationship. They concluded, "Heavier teenage cannabis users tend to continue selectively with cannabis use. Considering their poor young adult outcomes, regular adolescent cannabis users appear to be on a problematic trajectory".

Jan Van Ours and Jenny Williams wrote a discussion paper in September 2007 about cannabis and educational attainment. People between 25 and 50 were interviewed. Those initiated into cannabis use earliest suffer the greatest adverse effects. Future earnings and prospects are both damaged. They concluded that, "1. Preventing cannabis uptake will improve the educational outcomes of youths, and 2. even if cannabis use cannot be prevented, delaying the age at which uptake occur will deliver educational benefits".

A paper in 2008 by Quinn et al found that adolescent rats were less averse to repeated doses of THC than adult rats but had greater residual cognitive deficits and changes in hippocampal protein expression. The dose mimicked that of heavy cannabis use in humans. The adults after 2 weeks avoided the region of the cage associated with injections but the youngsters didn't. Many more protein changes were found in the adolescents and they had trouble with short-term memory. It was pointed out that the brains of the young rats were not yet fully developed so they were more vulnerable.

In 2008 Fergusson updated his findings from the Christchurch Study. He found, "...increasing cannabis use in late adolescence and early adulthood is associated with a range of adverse outcomes later in life. High levels of cannabis use are related to poor educational outcomes, lower income, greater welfare dependence and unemployment and lower relationship and life satisfaction".

2008 Perkonig et al found that youth cannabis use commonly extends into adulthood. Over 3000 (14 to 24 years old) German young people were followed. Of those who had repeated use of cannabis at baseline, 56% were still using it 4 years later and 46% 10 years later.

2008 Caldeira et al found that first year college students show high rate of cannabis use disorders. In a group of students who had used cannabis more than 5 times in the past year, 1 in 10 met the criteria for dependence and 14.5% met the criteria for cannabis abuse. 474 participants had used cannabis more than 5 times and of those: 24.3% regularly put themselves in physical danger when under the influence; 10.6% continued to use despite problems with family or friends; 40.1% reported concentration problems and 13.9% said they missed classes.

2008 Jager and Ramsey looked at long-term consequences of adolescent marijuana use on the development of cognition, brain structure and function in an overview. They concluded: Over the last decade there has been a steady increase in the prevalence of frequent cannabis use among teenagers, accompanied by a decrease in age of first use. Evidence from both animal and human studies suggests that the severity of the effects of cannabis use on cognitive development is dependent on the age when cannabis use begins. One possible explanation is that those who begin cannabis use early in adolescence are more likely to become heavily dependent. It is plausible that chronic cannabis abuse will then interfere with educational and vocational training. From a more biological perspective, however, use of cannabis during critical developmental periods in the still maturing brain may induce persistent alterations in brain structure and brain function. Therefore, the effects of frequent cannabis use during adolescence could be different from and more serious than during adulthood, an issue increasingly recognized in the field of cannabis research. In this paper we review the relevant animal and human literature on long-term effects of frequent exposure

to cannabis during adolescence on the development of cognition, brain structure and function, and discuss implications, methodological and conceptual issues, and future prospects.

Yucei, Solowij et al 2008, performed high-resolution structural magnetic resonance imaging on 15 men (average age 39.8 years) who smoked more than 5 joints/day for 10 years, and compared them with images from 16 individuals (Average age 36.4 years) who were not cannabis users. The hippocampus (memory and emotion) and the amygdala (fear and aggression) tended to be lower in cannabis users, by 12% and 7.1% respectively. They concluded, “Although modest use may not lead to significant neurotoxic effects, these results suggest that heavy use might indeed be toxic to human brain tissue”.

Ashtari and others in 2009 discovered that the developing brains of teens may be disrupted by heavy marijuana use. They used DTI (Diffusion Tensor Imaging) in 14 heavy smokers (Averaging nearly 6 joints/day in the final year of their smoking (they had smoked from 13 to 18/19 years of age). Abnormalities were seen in areas connecting memory, decision-making, attention, language and executive functioning skills – exactly the critical areas which develop in late adolescence. The images suggested damage or an arrest in development of the myelin sheath (insulation) that surrounds brain fibres. This abnormal white matter development could slow down information transfer and affect cognitive functioning. Five of the subjects also had a history of alcohol abuse.

Gobbi et al 2009, discovered that daily consumption of cannabis in teens can cause depression and anxiety and have irreversible long-term effects on the brain. ‘Teenagers who are exposed to cannabis have decreased serotonin transmission which leads to mood disorders as well as increased norepinephrine transmission which leads to greater long-term susceptibility to stress’, she said. Damage caused is more serious during adolescence than adulthood.

2009 Hester et al in 2009, using brain-imaging technology showed that during a decision game, chronic marijuana users showed less activity in an error-processing part of the brain than peers who do not use. They did not make more mistakes than the controls but were significantly less likely to realise it they had done 91% compared with 77%. This deficit in awareness may contribute to their continued use of the drug.

2009 Rubino et al looked at changes in hippocampal morphology induced by adolescent HC treatment. THC Pretreated rats had a significantly lower total dendritic length and number than vehicles, as well as reduced spine density. Our data suggest that THC pretreated rats may establish less synaptic contacts and/or less efficient synaptic connections throughout the hippocampus and this could represent the molecular underpinning of the cognitive deficit induced by adolescent THC treatment.

2010 A study from Australia by Degenhardt et al found that occasional cannabis use in adolescence predicts later drug use and educational problems. Nearly 2000 secondary school pupils were followed from 14.9 to 24 years of age. Those who continued cannabis use into early adulthood had higher risks of later adult alcohol and tobacco dependency and illicit drug use., as well as being less likely to complete a post secondary qualification.

2010 Dumontheil and others found that lack of concentration in adolescents is to do with brain structure, their mental capacities are not the same as adults. They found an unexpected level of activity in the prefrontal cortex which is involved in multi-tasking and decision-making. This means it continues to do a lot of needless work when making decisions. This “chaos” continues till the late 20s. These chaotic thought patterns are a result of too much grey matter. As we age the amount of grey matter decreases.

2010 November Staci Ann Gruber, speaking at Neuroscience 2010, the annual meeting of The Society of Neuroscience reported that people who start using marijuana at a young age have greater cognitive shortfalls. Researchers also found that the more marijuana a person used corresponded to greater difficulties in focus and attention. (Teen’s brains are only about 80% developed and are not completed till the 20s or 30s).

2010 Demirakca T et al discovered diminished gray matter in the hippocampus of cannabis users. Chronic cannabis use has been associated with memory deficits and a reduction in volume of the hippocampus, but no study yet has accounted for the different effects of THC and CBD. Cannabis users showed lower GM (gray matter) volumes located in a cluster of the right anterior hippocampus. An inverse correlation of the ratio YHC/CBD with the volume of the right hippocampus was observed.

Conclusion: Lower volume in the right hippocampus in chronic cannabis users was corroborated. Higher THC and lower CBD were associated with this volume reduction indicating neurotoxic effects of THC and neuroprotective effects of CBD, confirming previous preclinical and clinical results.

2010 Hanson et al found that marijuana users demonstrated poorer verbal learning, verbal working memory and attention memory compared to controls. Improvements were seen in users on word list learning after 2 weeks of abstinence and on verbal working memory after 3 weeks. While attention processing speed was similar between groups, attention accuracy remained deficient throughout the 3 week abstinence period. These results implicate possible hippocampal, subcortical and prefrontal cortex abnormalities.

2010 Koskinen et al conducted a meta-analysis of the rate of cannabis use disorders (CUDs) in clinical samples of patients with schizophrenia. 35 studies were examined. The median current rate of CUDs was 16% (10 studies) and the median lifetime rate was 27.1% (28 studies). The median rate for CUDs was markedly higher in first episode vs long-term patients (current 28.6%/22.0%, lifetime 44.4%/12.2% respectively) and in studies where more than two thirds of the participants were male, than in the other studies (33.8%/13.2%). CUDs were also more common in younger samples than in the others (current 38.5%/16.0% lifetime 45.0%/17.9%). Conclusion: Approximately every 4th schizophrenia patient in our sample of studies had a diagnosis of CUDs. CUDs were especially common in younger and first-episode patient samples as well as in samples with a high proportion of males.

2011 Ali and others looked at the social contagion effect of marijuana use among adolescents. Their findings indicate that peer effects are important determinants of marijuana use even after controlling for potential biases. A 10% increase in the proportion of close friends and classmates that use cannabis increases the probability that an individual chooses to use marijuana by 5%.

2011 Buckner et al studied social anxiety and marijuana-related problems. The relationship between current (past 3 months) marijuana-related problems and 2 aspects of social anxiety (fear in social situations and social avoidance) among 102 current users was examined. Although both conditions were significantly correlated with marijuana-related problems, only social avoidance was uniquely related to marijuana problems after controlling for social fear, sex, negative affect, alcohol problems and marijuana use frequency. Sex moderated the relationship between social avoidance and marijuana related problems such that men with greater social avoidance exhibited the greatest severity of marijuana related problems. They conclude: Avoidance of social situations appears robustly related to marijuana-related problems.

2011 Feb, Solowij N and others studied verbal learning and memory in adolescent cannabis users, alcohol users and non-users aged 16 to 20. 181 adolescents took part. They found that cannabis users performed significantly worse than alcohol users and non-users on all performance indices. The degree of impairment was associated with the duration, quantity, frequency and age of onset of cannabis use, but unrelated to alcohol or any other drug use. The earlier the onset, the worse the memory performance. Conclusions: Despite relatively brief exposure, adolescent cannabis users relative to their age-matched counterparts demonstrated similar memory deficits to those reported in adult long-term heavy users. The results indicate that cannabis adversely affects the developing brain and reinforce concerns regarding the impact of early exposure.

2011 March Feinstein et al found that MS patients using marijuana to relieve pain were 'hurting' their thinking skills. The study used 25 patients and 25 controls. The users scored significantly lower on tests of attention, thinking speed and gauging space between objects. About 40 to 60% of people with MS have problems with decision making, thinking and reasoning. Pot smoking may be making this worse.

2011 June Fontes et al found that regular cannabis users, if they start before the age of 15 perform worse on brain tests than those who start later. 104 chronic cannabis users, of whom 49 had started before the age of 15, took part in a series of tests involving, executive functioning, attention, perseverance, ability to form abstract concepts, visual and motor skills and mental flexibility. There was no difference between the groups or controls in terms of IQ. The early onset group performed significantly worse on attention, impulse control and executive functioning.

Dr Maria Fontes said, 'We know that adolescence is a period in which the brain appears to be particularly vulnerable to the neurotoxic effects of cannabis'.

Gruber et al 2011 looked at age of onset of marijuana use and executive function. Age of onset, frequency, and magnitude of MJ use were all shown to impact cognitive performance. Findings suggest that earlier MJ onset is related to poorer cognitive function and increased frequency and magnitude of MJ use relative to later MJ onset. Exposure to MJ during a period of neurodevelopmental vulnerability, such as adolescence, may result in altered brain development and enduring neuropsychological changes.

2011 Crean and others conducted a review of executive functions and use of cannabis. These are the conclusions: The trajectory of effects of cannabis on executive functions follows an interesting pattern of recovery of some functions and persisting deficits in others. The acute effects of cannabis use are evident in attentional and information processing abilities with recovery of these functions likely after a month or more of abstinence. Decision-making and risk-taking problems aren't necessarily evident immediately after smoking; however, if cannabis use is heavy and chronic, impairments may emerge that do not remit with abstinence, particularly if heavy use was initiated in adolescence such that maturation of executive functions was not achieved. Acute cannabis use impairs inhibition and promotes impulsivity, and over a period of abstinence, these deficits are most evident in tasks that require concept formation, planning and sequencing abilities. Working memory is significantly impaired following acute exposure to cannabis; however, these deficits resolve with sustained abstinence. Evidence is less clear in regards to verbal fluency abilities; however, research suggests that chronic, heavy use may impact verbal fluency abilities even after long-term abstinence. The long-term effects of cannabis on executive function is most clearly demonstrated when studies use chronic, heavy cannabis users, as opposed to light, occasional users. Yet even occasional cannabis use can acutely impair attention, concentration, decision-making, inhibition, impulsivity and working memory.

2012 Kucewicz looked at the fact that brain activity becomes uncoordinated and inaccurate during altered states of mind leading to neurophysiological and behavioural impairments reminiscent of schizophrenia. This study tested whether the detrimental effects of cannabis on memory and cognition could be the result of 'disorchestrated' brain networks. An agonist of THC was used on rats and completely disrupted co-ordinated brain waves across the hippocampus and prefrontal cortex. (like 2 sections of an orchestra playing out of sync. The rats became unable to make decisions while navigating round a maze.

2012 March Han et al found that acute cannabinoids can impair the working memory (the ability to retain and use information over short periods of time). A previously unknown signalling mechanism between neurons and non-neuronal cells called astrocytes (always thought to be merely supporting and protecting cells of neurons) has been found. 'Our study provides compelling evidence that astrocytes control neurons and memory, the supporting actor has become the leading actor' said Zhang, one of the authors. It was discovered that THC weakened the synapses between neurons in the hippocampus, crucial for memory formation, and this was controlled by the previously undiscovered CB1 receptors on the astrocytes.

2012 August, Zalesky et al (Australia) Looked at the effect of long-term cannabis use on axonal fibre connectivity. 59 people who had been using marijuana for 15 years on average were compared with scans (MRI) of 33 people who had never used the drug. The white matter in brains (complex wiring system) continues to develop over a lifetime. Changes to the volume, strength and integrity of the white matter were measured. Dr Seal, the lead researcher said there was a reduction in the volume of white matter of more than 80% of the users studied. The average age of initiation was 16 but there were some who had started at 10 or 11 – they were more seriously affected. Dr Seal said, 'This is the first study to demonstrate the age at which regular cannabis use begins is a key factor in determining the severity of the brain damage..... We don't know if these changes are irreversible but we do know that these changes are quite significant..... These people can have trouble learning new things and they are going to have trouble remembering things'.

2012 August, Meir et al as part of the long-running Dunedin Study, found that the IQ of children hooked on cannabis in their teens, and continuing to take it, fell by an average of 8 points (equivalent to dropping from average IQ to the lower third of the population). More than 1,000 children were out through a battery of tests at ages 13, 14 and then 38. None had tried cannabis when the research started making it easier to observe the effects of cannabis. Interviews on cannabis use were conducted at 18, 21, 26, 32 and 38. Attention and memory were also harmed. Tests normally used to spot the early signs of Alzheimers were conducted and adolescent cannabis users fared worse. The effects on IQ could still be seen in those who

had not touched cannabis for a year. Small falls in IQs were seen in those who never or occasionally used the drug and those who had started to use it as an adult.

2012 September Long et al, 'The system of the brain responsible for mediating effects of cannabis, the endo-cannabinoid system, is most vulnerable to the drug during adolescence'. Dr Leonora Long said, 'During adolescence the endo-cannabinoid system in the brain undergoes a lot of change, and interfering with these changes by using cannabis could have consequences for the development of healthy brains in adults. Cannabis use is common among teens and adolescents, and adolescence is a time when adult behaviours and decision-making are developing, so this discovery is very significant. The endocannabinoid system is involved in appetite, pain sensation, mood and memory, and affects the way neurons in the brain communicate with each other.'

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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 most recent in the updated section at the end of the chapter.

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 April 25th 2008, in answer to a parliamentary question from Graham Brady MP, updated figures for admission to hospitals with mental illness were given. In 2003/4 40,763 people in England were admitted for primary or secondary diagnoses of schizophrenia, in 2006/7 it was 45,955, an increase of 12.7%. For psychosis, the increase was 20.8%, from 176,776 to 213,624. Since 2001, the year in which the intention to downclassify was suggested, the figures for schizophrenia have risen by 24% and those for psychosis by 42%.

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".

On November 4th 2006 The Manchester Evening News carried a report that "Cannabis raids help patients". Mark Holland, a senior health worker of 26 experience in the NHS as a consultant nurse and senior member of the Manchester Mental health and Social Care Trust, said, "I have definitely noticed a change in many of my clients. ...I tell them their symptoms seem a bit milder because they haven't had a joint". Across Manchester there has been a drop in the number of people needing hospital treatment for acute psychotic episodes – one of the first falls in several years. Greater Manchester Police have been taking part in Operation Keymer, set up to target hundreds of cannabis factories across the country, focusing particularly on the powerful "skunk" variety.

BBCNews carried a story on May 7th 2007 that admissions to mental health hospitals in England due to cannabis use had risen by 85% between 1996 and 2006. In 1996/7 there were 510 admissions, this rose to 946 in 2005/6. This was given in an answer to a parliamentary question from Andrew Lansley, Shadow Health Secretary. In the last 5 years alone, the rise was 65%. "This is the tip of the iceberg" said Professor Murray. He added that cannabis use was a contributory cause of up to 10% of cases of schizophrenia yet this was unrecognized.

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".

French psychiatrist, Moreau de Tours 1845, first reported acute psychotic reactions in himself, students and patients after taking cannabis. Some of these were short-lived, lasting a few hours but some up to a week.

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-1V.

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.

2000 Wilson et al looked at brain morphology and early marijuana use. *Results.* There are three primary findings related to age of first use of marijuana. Subjects who started using marijuana before age 17, compared to those who started later, had smaller whole brain and percent cortical gray matter and larger percent white matter volumes. Functionally, males who started using marijuana before 17 had significantly higher CBF than other males. Both males and females who started younger were physically smaller in height and weight, with the effects being greater in males. *Conclusions.* These findings suggest that the age at which exposure to marijuana begins is important. Early adolescence may be a critical period for effects that are not present when exposure begins later. These results are discussed in light of reported effects of marijuana on gonadal and pituitary hormones.

2002 Zammit et al followed up the Swedish Conscript study of 1969/70.

Abstract: *Objective.* An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these

uncertainties while extending the follow up period to identify additional cases. Design. Historical cohort study. *Setting*: 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20). *Participants*. 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics. *Main Outcome Measures*. Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage. Results. Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, $P < 0.001$), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, $p < 0.015$). the adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases. *Conclusions*. Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.

2002. Louise Arsenault 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.

2002. In a survey of 3142 prisoners, it was found that, first use of amphetamines or cocaine before the age of 16 and severe cannabis or cocaine dependence were related to an increased risk of psychosis. Severe dependence on heroin was associated with a reduced risk of this classification (Farrell et al 2002).

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 D'Souza and others, in a 3-day double blind randomized placebo-controlled study, injecting 2.5 mg and 5mg intravenous THC, studied the cognitive, motor, behavioural and endocrine effects in 13 stable, antipsychotic-treated schizophrenia patients and compared them with healthy subjects. They found that Delta-9-THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. No short or long-term adverse effects were found.

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.

2005. To investigate the overall effect size and consistency of the association between cannabis and psychosis, a meta-analysis from prospective studies was carried out. The pooled odds ratio was 2.1 and could not be explained by confounding or reverse causality. Evidence suggests that cannabis is a component cause in the development and prognosis of psychosis, in which mechanisms of gene-environment interaction are most likely to explain this association (Henquet et al).

2005 Henquet investigated the relation between cannabis use and psychotic symptoms in individuals with above average predisposition for psychosis who first used cannabis during adolescence. 2437 (14-24 years) with/without this predisposition were studied. They concluded that ‘Cannabis use moderately increased the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis’.

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”. A report in The Independent on 13th May 2007 said that experts from The Institute of Psychiatry in London had isolated the gene and hoped that a mouth-swab test as an early warning system for identifying vulnerable youngsters. Dr Marta Di Forti said screening could help parents worried about their children.

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. Arsenault 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, Arsenault 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.

“The Adolescent Brain: A Work in Progress” was published in June 2005 by The National Campaign to Prevent Teenage Pregnancy (USA), Weinberger DR et al. “In sum, a large and compelling body of scientific research on the neurological development of teens confirms a long-held, common-sense view: teenagers are not the same as adults in a variety of key areas such as the ability to make sound judgements when confronted by complex situations, the capacity to control impulses, and the ability to plan effectively. Such limitations reflect, in part, the fact that key areas of the adolescent brain, especially the pre-frontal cortex that controls many higher order skills, are not fully mature until the third decade of life”.

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.

2005 Semple et al found that: Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia.

In conclusion, the available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.

2006. Barnes et al studied 152 people recruited to the West London First-Episode Schizophrenia Study. Information on mental state, cognition (IQ, memory, executive functions), social function, age at onset of psychosis and self-reported data on drug and alcohol use were collected. Cannabis use and gender had independent effects on age at onset of psychosis, after adjusting for alcohol misuse and use of other drugs. They concluded that "The strong association between self-reported cannabis use and earlier onset of psychosis provides further evidence that schizophrenia may be precipitated by cannabis use and/or that the early onset of symptoms is a risk factor for cannabis use".

In February 2007, more evidence was obtained for structural abnormalities in the brain due to cannabis use. Szeszko et al investigated prefrontal grey and white matter regions in patients experiencing a first schizophrenia episode who also used, or were dependent on cannabis. Twenty of these patients were compared with 31 similar patients with no cannabis use, and 56 healthy volunteers. "Patients who used cannabis had less anterior cingulate anterior matter compared with both patients who did not use cannabis and healthy volunteers". They concluded, "A deficit in the anterior cingulate is associated with a history of cannabis use among patients experiencing a first episode of schizophrenia and could have a role in poor decision-making and in choosing more risky outcomes".

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.

They also asked the question, "What are the policy implications of the evidence on cannabis and psychosis?" They said, "The observational evidence and biological plausibility of the hypothesis that cannabis is a contributory cause of psychosis is at least as strong as evidence for causal relations between heavy alcohol and amphetamine use and psychosis. On public health grounds there is a good case for discouraging cannabis use among adolescents and young adults". In the conclusion they called for young adults to be informed of the mental health risks, especially early and frequent use. "We must exercise caution in liberalizing cannabis laws in ways that may increase young individuals' access to cannabis, decrease their age of first use, or increase their frequency of cannabis use. We should consider the feasibility of reducing the availability of high-potency cannabis products".

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".

A paper by Lehrmann and others in December 2006 found similar brain changes caused by different drugs of abuse. The brains of 42 deceased drug abusers were examined. The drugs involved were cocaine, marijuana and PCP. The researchers then measured the level of expression of more than 9000 individual genes in small tissue samples taken from the aPFC (anterior Prefrontal Cortex), a region important in decision-making. Nearly 80% of the drug abuse cases displayed similar alterations in genetic output compared with the controls. For example, genes involved in calcium signaling were turned down while genes involved in lipid and cholesterol-related pathways were turned up. "Our results show that cocaine, marijuana and PCP can alter the function of this critical brain area in similar ways, which could threaten the drug abuser's ability to make sound decisions".

An editorial in the Medical Journal of Australia at the beginning of January 2007 (Jorm and Lubman), announced the expenditure of \$21.6 million by The Australian Government for a campaign to get the message right to help the public reduce their risk of mental illness and warn of the link with illicit drugs.

Barkus in a review article in The Psychiatric Times, January 2007 concluded that, "There appears to be evidence of substance use (at least cannabis use) as a component cause for psychotic disorders. However it is still unclear whether substance use operates as a causal factor in the absence of underlying biologic vulnerability to psychosis and whether the expression of isolated psychotic symptoms is directly related to clinical psychotic disorders. The evidence for the causal relationship between substance use and psychotic disorders is primarily based on epidemiologic studies; further clinical studies are needed to determine how substance use operates as a risk factor for psychotic disorders. It is possible that this evidence will emerge from the growing numbers of early intervention services worldwide".

In March 2007, a paper by Dr Matthew Hickman and others warned that by 2010, up to 25% new cases of schizophrenia in Britons may be due to cannabis. In three English cities, Nottingham, Bristol and Southwark in London, the incidence of exposure to cannabis rose fourfold from 1972 to 2002. In the under-18s it rose 18-fold. The increase would be seen earlier particularly among young men. If cannabis use causes schizophrenia, these increases would lead to overall prevalence of 29% and 12% respectively between 1990 and 2010. They point out that up till now there is no *proof* that cannabis is a cause of the condition. Some answers would be forthcoming if the projected increase took place.

2007 Kristensen et al found that cannabis abuse for 'at risk' groups increased the risk of psychosis. 48 subjects, identified as at risk of psychosis (subsyndromal psychotic symptoms and/or family history) were examined. At one year follow-up, 6 had made the transition, of the 32 who had no/minimal use of cannabis, only 1 had progressed to psychosis. Of the 16 who had cannabis dependence, five converted to psychosis. Conclusion: The results showed a significant association between cannabis use and conversion to psychosis.

The April 2007 edition of NIDA (National Institute of Drug Abuse USA) Notes highlighted 2 papers on the brain development of adolescents by Galvan et al. "Children and adolescents both have an immature

prefrontal area, but only adolescents make risky decisions”, said Dr Galvan, “ We speculated that the adolescent brain must be unique in some way that promotes risk-taking”. They hypothesized that the nucleus accumbens (NAc) in the brain might play a complementary role to the OFC’s (Orbitofrontal Cortex) in adolescent risk taking. The NAc alerts and motivates people when there is an opportunity to get something desirable. The OFC moderates these impulses in the interests of safety and longer-term goals. Thus if NAc activity is highly sensitised when the OFC is weak, the drive to act would over-rule the cautious response and more risks would be taken. From their experiment with 13 children, 12 adolescents and 12 adults, they confirmed their hypothesis. The implications are, they concluded that “disproportionate contributions of subcortical systems relative to prefrontal regulatory systems may underlie poor decision-making that predisposes adolescents to drug use and ultimately addiction”.

A research note from Australia published on June 7th 2007, “Does cannabis use lead to mental-health problems?: findings from the research”, concluded that, “it is crucial that emerging evidence about the links between cannabis use and mental health problems is communicated clearly (particularly to those most at risk) and in a way that acknowledges the complexity of the issues involved without obscuring the level and gravity of the risks posed by cannabis use to vulnerable groups” (Buckmaster and Thomas).

An Australian study released in June 2007 indicates that continuous cannabis use increases psychotic symptom severity but not depression symptom severity in schizophrenic patients. 101 patients from 16 to 50 years of age with schizophrenia and related disorders were examined over a 10-month period. Degenhardt and others estimate that daily cannabis users will see an average 3.9 point increase in BPRS (Brief Psychiatric Rating scale) scores in the following month. This indicates a deterioration in their psychotic symptoms compared with patients not using cannabis. “There was no evidence that cannabis was used in response to increased psychotic or depressive symptoms”.

An article in Psychiatric News on July 6th 2007 highlighted a lecture by Dr Nora Volkow, director of NIDA entitled “The Neurobiology of Free Will” at APA (American psychiatric Association)’s annual meeting in San Diego in May. “Addiction and the progressive loss of control over behaviour that seems to accompany the addictive process are the result of changes in multiple regions of the brain. Changes occur initially as a result of the abnormal increase in dopamine that results from use of all drugs of addiction and eventually affect memory and attention, the regulation of impulsivity, and executive functioning”. She said, “ We have come to see addiction as a disease that involves the destruction of multiple systems in the brain that more or less are able to compensate for each other. When pathology erodes the various systems, you disrupt the ability to compensate, and the addictive disease erodes and destroys the life of the individual”.

In July 2007 a paper was published in The Lancet. It was a systematic review of 35 studies into possible links between cannabis and psychotic illness. It caused a great stir in the press coming the week after Gordon Brown had announced another review of the classification of cannabis. It found that cannabis users were 40% more likely to develop a psychotic illness than non-users, with heavy users being more than twice as likely to suffer from a mental illness. The authors, led by THM Moore and S Zammit predicted that 14% of psychotic outcomes in young British adults may be due to cannabis. Professor Robin Murray of The Institute of Psychiatry in London said this estimate may be too low as the cannabis available today is stronger than in the past. He said, “My own experience suggests to me that the risk with skunk is higher” (The Times 27/08/07). They concluded, “...there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life”.

A 2-year study by Yucel et al published in August 2007 found, using brain-imaging technology, that opiate-addicted individuals have to make enormous efforts to exercise control over their drug-taking behaviour in the face of adverse health consequences and are vulnerable to relapse. The frontal cortex was working inefficiently, brain cells in this region were less healthy.

September 2007 saw the publication of a paper, “Cannabinoids influence Lipid-Arachidonic Acid pathways in Schizophrenia” by Smesny et al. “Results demonstrate an impact of long-term cannabis use on lipid-arachidonic acid pathways. Considering pre-existing vulnerability of lipid metabolism in schizophrenia, observed effects of cannabis use support the notion of a gene x environment interaction”.

2007 Zammit et al found that their results did not support the presence of different effects of cannabis use on schizophrenia according to variation in the COMT gene.

A letter to the editor of The American Journal of Psychiatry in October 2007 from Bowers and Kantrowitz described elevated levels of plasma dopamine metabolites in cases of cannabis psychosis. Three groups

were studied in a small sample. Five cases of first admission cannabis-related psychosis showed significantly higher levels of homovanillic acid (24.8ng/ml) than 15 admitted for non-related cannabis psychosis (15.1ng/ml) and 17 non psychotic subjects (9.6ng/ml).

Professor Robin Murray gave a speech at a meeting, “Cannabis and children – complacency is not an option” organized by the group “Talking About Cannabis” (www.talkingaboutcannabis.com) in the Boothroyd Room, House of Commons on October 30th 2007. He said that if THC is injected intravenously into “normal volunteers” then after 10 minutes delusions and hallucinations would occur, returning to “normality” at about 200 minutes. Volunteers said, “...I thought I was God”, “I thought you were all trying to trick me” and “I felt you could read my mind, that’s why I didn’t answer...my mind was nude”. He said if enough THC were used, hallucinations and paranoia would result. Because the THC content in cannabis commonly used by children was much higher now (traditional was 3%, skunk is 14%THC), he said it was not acceptable that 13 year olds were using the equivalent of “a bottle of vodka a day”.

He also explained how the balance between two constituents of cannabis had changed in the development of skunk. THC causes hallucinations and paranoid ideas but CBD (cannabidiol) is not hallucinogenic, has anxiety-relieving properties and no adverse effect on cognition. In other words it acts as a balance to the THC. In the old herbal cannabis the two ingredients were more or less balanced. Now in the case of skunk, the THC content has been greatly increased and the CBD has not altered, so the relative amount of CBD compared to THC is much smaller. In a report by The Home Office in 2008 about cannabis potency, it was found that cannabis resin had a meanCBD content of 3.5% (Range 0.1 to 7.3%) but in nearly all cases the CBD content of herbal cannabis was less than 0.1%.

He made an important observation, “By accident the controversy over the reclassification of cannabis provided an opportunity for unofficial public education. This has resulted in a fall in use. What we need now is a proper education campaign aimed especially at children”.

A paper in April 2008 by Morgan and Curran took up this theme. Hair analysis was used to determine levels of THC and CBD in 140 drug users. 54 were positive for cannabis. 26 had both THC and CBD present and THC alone in 20 others. Among the 3 groups, THC alone, THC + CBD and no cannabinoid, the THC only group had significantly higher scores for psychosis proneness than the others. The THC+CBD group had significantly lower scores with social withdrawal than the no cannabinoid group. Delusional thinking also scored highly in the THC group and greater than no cannabinoid in the CBD+THC one. This research highlights the importance of distinguishing between different cannabinoids, and the debate over cannabis-psychosis links.

Cannabis use and adult ADHD symptoms were investigated in a paper by Fergusson and Boden in 2008. The conclusion was, ‘The current study suggested that the association between cannabis use and adult ADHD symptoms was mediated by other substance use that was associated with cannabis use. The results suggest that cannabis use leads to other drug use, which in turn leads to increased ADHD symptoms. However it should be noted that the potential influence of such factors as genetic predispositions may still be unaccounted for’.

Cannabis use and brain structural alterations were found in first-episode schizophrenia by Bangalore et al in January 2008. There was a decrease in gray matter density in the right posterior cingulate cortex. Cannabis use may be associated with altered brain structure in particular regions rich in CB1 receptors. A call was made for larger prospective studies.

2008 Feb Ashtari found that adolescents and young adults who are heavy users of cannabis are more likely to have disrupted brain development. These were found in the memory, attention, decision-making, language and executive functioning skills areas. Subjects had an average age of 19. DTI (Diffusion Tensor Imaging) found an arrest in the developing of the myelin sheath. This could slow signaling in the brain and affect cognitive functioning. Ashtari emphasized the preliminary nature and said it needed more research.

Excessive loss of brain volume was found in cannabis using first episode schizophrenia patients by Rais et al in April 2008. Gray matter volume in the cerebrum reduces over time in schizophrenics. A study involving 51 patients with recent onset schizophrenia were compared with 31 healthy subjects. 19 of the patients used cannabis, but no other illicit drug in the 5-year follow-up period, the other 32 used no drugs. By using MRI scans it was found that schizophrenia patients showed a larger gray matter decrease than the healthy controls, also larger increases in lateral and third ventricle volumes than healthy subjects and patients who did not use cannabis in the follow-up period. The decrement was considerably more

pronounced in the patients who continued to use cannabis. They concluded, “First episode schizophrenia patients who use cannabis show a more pronounced brain volume reduction over a five-year follow up than patients with schizophrenia who do not use cannabis”.

2008 Crebbin et al investigated drug and alcohol misuse in first-episode psychosis in the UK. Information on patients in Northumberland between 16 and 36 years of age was collected at first presentation and annual follow-up from 1998 till 2005. Hospitalisation was used as an outcome measure and violence rates were examined in retrospect. Drug misuse without alcohol was associated with a highly significant increase in hospital days. Alcohol problems with/without co-existing drug misuse was not predictive of increased hospital days. Drug and alcohol misuse together was associated with violence. They concluded that drug misuse may have a bigger impact than alcohol use on the outcome of first episode psychosis. (Drugs were, skunk, amphetamines and cocaine).

June 2008, in a paper by Miettunen and others, adolescents in Finland were found to have an association between cannabis use and prodromal symptoms of psychosis. 6330 children between 15 and 16 were investigated, the largest ever study of its type. Those who had tried cannabis (5.6% of the sample) were more likely to present 3 or more prodromal symptoms after controlling for confounding factors like behaviour. A dose-response effect was seen. “We conclude that cannabis use is associated with prodromal symptoms of psychosis in adolescence”.

Leweke 2008 found ‘recent replication studies indicate that frequent cannabis use doubles the risk for psychotic symptoms and schizophrenia’.

2008 June, Yucel and others found brain abnormalities in long-term (>10years) and heavy users (>5 joints/day) of cannabis, average age 39.8 years and mean duration 19.7 years, with no history of polydrug use or mental problems. Cannabis users had bilaterally reduced hippocampal and amygdale volumes. Conclusion: “These findings indicate that heavy daily cannabis users across protracted periods exerts harmful effects on brain tissue and mental health”.

2008 Zammit et al conducted a systematic review of the effects of cannabis use on the outcomes of psychotic disorders. Cannabis use was consistently associated with increased relapse and non-adherence, but some confounders particularly alcohol had not been accounted for in some studies. They concluded, “Confidence that most associations reported were specifically due to cannabis use is low. Despite clinical opinion, it remains important to establish whether cannabis is harmful, and what outcomes are particularly susceptible, and how such effects are mediated. Studies to examine this further are eminently feasible”. [Two co-authors had been co-opted on to the ACMD in their review of cannabis (PB Jones and TRE Barnes) and several had received fees for lectures, talks or consultancy work for pharmaceutical companies].

2008 Atakan Z. asked if the use of cannabis by people with severe mental illness was important. She said that cannabis use is more common among people with severe mental illness than in the general population. “It has detrimental effects on the course of the illness, physical health and social life of others, as well as being a financial burden on health services”. Her article seeks to find out why they continue to use it despite the effects on their condition.

2008 July Lewis et al found that alterations in a molecular pathway activated by marijuana may contribute to the cognitive symptoms of schizophrenia. Expression of the receptor CB1R (cannabinoid receptor in the brain) is significantly reduced in schizophrenics. This results in the transmission of GABA, a neurotransmitter involved with working memory being impaired. Activation of the receptor by THC will worsen this deficit.

August 2008 Spanish researchers have found a strong and independent link between cannabis use and earlier onset psychosis. Gonzalez-Pinto et al said it was not related to gender or the use of other drugs, but to the amount of cannabis used. They estimate that cannabis use accounts for 10% of psychosis cases. Compared with non-users age at onset was reduced by 7, 8.5, and 12 years among users, abusers, and dependents respectively.

2008 August Henquet et al researched gene-environment interplay between cannabis and psychosis. They said that cannabis use is considered a contributory cause of schizophrenia and psychotic illness, but only a small proportion of users develop psychosis. Amount of the drug, duration of using, strength of THC and age of first exposure are all factors. Genetic factors in particular are likely to play a part. “Evidence

suggests that mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. In this respect, multiple variations within multiple genes – rather than single genetic polymorphisms – together with other environmental factors (eg stress) may interact with cannabis to increase the risk of psychosis”.

2008 September 166 patients in Massachusetts, USA admitted to hospital with bipolar disorder 1 for average 4.7 years were investigated. Patients were more likely to experience a manic or hypomanic episode in the same or subsequent quarter (3 month period) as they had used cannabis than at other times. Baethge et al was the lead German researcher.

Two papers on brain function have been published by McGuire et al in 2008 and 2009. They involved the administration of THC and CBD. FunctionalMRI scanning and behavioural measures were used in healthy male volunteers. Each subject was scanned at monthly intervals on 3 occasions preceded by administration of either THC, CBD or a placebo. In the first paper in 2008 they found that THC reduced activation in the part of the pre-frontal cortex that is normally critical for inhibiting a response. In the second one in 2009, anxiety was tested using faces with fearful expressions. Normally these would provoke anxiety, activate the amygdala and increase skin conductance. CBD reduced the response of the amygdala to the faces and this was correlated with its effect on skin conductance.

2008 November Arendt et al “ People who have long-lasting (48 hours) psychotic episodes after smoking marijuana may be exhibiting early signs of schizophrenia”. In a previous study, Arendt found that nearly half the people who had an episode of cannabis-induced psychosis went on to develop schizophrenia within the next 6 years. In this study they looked at the genetic roots of both conditions by comparing the family histories of 609 treated for cannabis induced psychosis and 6476 treated for schizophrenia or a related psychiatric condition. Those treated for cannabis-induced psychosis were found to have the same likelihood of having a ‘first degree’ relative with schizophrenia as did those treated for schizophrenia. This suggested to the researchers that the 2 conditions are the same. Other researchers have shown that pot-smoking roughly doubles the risk of schizophrenia but it happens sooner if they use cannabis. It looks like it is a gradual process but people should not use cannabis if they want to avoid an increased risk of schizophrenia. Anyone with prolonged period of psychosis after marijuana should seek help early. The sooner it is diagnosed and treated, the better the prognosis. (Based on a nationwide survey of all individuals born in Denmark between Jan 1st 1995 and July 1st 1990 – 2,276,309 people).

2009 Gutierrez et al. 91 in-patients and 192 healthy controls were studied. Results as follows:

In relation to the increased risk of schizophrenia which the interaction between cannabis consumption and *COMT* gene variability might confer, in our study we only found evidence that could support this interaction in the female group and not in the male group. These tendencies did not reach statistical significance, possibly due to a lack of sampling capacity. However, they point in the same direction as the findings of Caspi et al and should be explored in greater depth in a larger sample. New studies along these lines should be developed, ideally in the context of longitudinal designs, in order to clarify, on the one hand, the modulatory role of the *COMT* gene on the risk cannabis poses in the development of schizophrenia and, on the other, on the magnitude of this effect.

2009 Henquet et al studied 31 patients with a psychotic disorder and 25 healthy controls. They found that carriers of the *COMT* Met/Val allele, but not the Met/Met genotype showed an increase in hallucinations after cannabis exposure. The findings confirm that in people with psychometric evidence of liability, *COMT* Val/Met genotype moderates the association between cannabis and psychotic phenomena in the flow of daily life.

2009 Aldandashi and Blackman looked at 12 to 17 year olds of both sexes presenting with either mood disorder or psychosis. They found that substance misuse is more likely to cause psychosis than mood disorder and cannabis (42.85%) use more likely than amphetamine (28.57%) or cocaine (14.28%). Alcohol is more likely to produce mood disorders than cannabis.

2009 Morrison and Murray published the results of their experiments carried out at London’s Institute of Psychiatry and mentioned previously in this report. 21 healthy male participants (21 to 50) were recruited from staff and students from King’s College, London. They had all previously taken cannabis on at least one occasion. They concluded that: ‘THC can induce a transient acute psychotic reaction in psychiatrically well individuals. The extent of the psychotic reaction was not related to the degree of anxiety or cognitive impairment’.

2009 Rubino et al looked at early-onset cannabis use and cognitive deficits.

2009 Hickman asked how many cannabis users may need to be prevented in order to prevent one case of schizophrenia (England and Wales). The figures he came up with were very large BUT he used data from 1997-1999 – before the huge increase in THC and skunk. So they are not really relevant now. In men 20-24 heavy users it ranged from 2800 to 4700 for 35-39 years old. In women, 20-24, 5470 (25-29) to 10,870 in 35-39s. For heavy use and psychosis men 20-24 1360, to 2480 in women of 16-19. around 2.2 million are thought to use cannabis regularly. If 200,000 men of 20-24 were heavy users it would mean around 70 cases. Schizophrenia is a chronic very serious condition and expensive to treat. Psychosis would occur in 147 of them! This is no light matter!

2009 Frisher et al found that the incidence of schizophrenia or psychosis in the general population between 1996 and 2005 had shown no increase. The data was collected from 183 GP practices in England, Wales, Scotland and N Ireland. Almost 600,000 patients each year were investigated, roughly 2.3% of the UK Population aged between 16 and 44. However Professor Robin Murray (Institute of Psychiatry, London, an expert in schizophrenia) criticized the experiment. He said,

“I have known about this study since its inception and advised the authors that they were unlikely to be able to come up with meaningful results. Firstly, a major problem concerns the diagnoses. In my experience GP diagnoses of psychiatric disorders are not very accurate. Secondly, we do not know how many cases of psychosis are dealt with exclusively by psychiatrists and GPs don't know.

The only place with good data on schizophrenia over the years is Camberwell. The incidence has doubled since 1964. Migration accounts for some of that but it has gone up even in the white population. (Boydell et al 2003)

Perhaps more importantly from a theoretical point of view, we estimated that cannabis might account for 10% of all cases of schizophrenia. We do not know what has been happening to the other 90% caused for other reasons.

So I don't think this study tells us much”.

The leading researcher Dr Martin Frischer said, “We concentrated on looking into the incidence of schizophrenia during those years and not specifically at cannabis use. “It was relatively low-key research so I don't believe it will re-ignite the debate on whether the drug should be legalised.” The research was partly commissioned by the ACMD of which Prof Llana Crome is a member.

Degenhardt et al in 2009 said that “Pot is a risk for psychosis”. They conducted a review of the evidence for the relationship. One study found an interaction between marijuana use and a polymorphism of the gene that codes for dopamine. About 25% of the cohort who were homozygous for the polymorphism were nearly 11 times more likely to have developed a schizophreniform disorder than those with the same polymorphism who did not use cannabis. Another study estimated that eliminating all marijuana use would reduce the incidence in the UK by about 8%, “assuming the relationship was causal”.

2009 Di Forte et al looked at 280 first-episode psychosis patients who had used cannabis and 174 controls, screened for previous psychotic illness. and recruited in the local PCT area. There was no difference in the cases or controls in terms of cannabis use. However the cases were around 6 times more likely to use daily and nearly 7 times more likely to use sinsemilla or skunk.

2010 A paper from Ontario by Joyce et al on anxiety and mood disorders (AMD) looking at 14,531 adults from 2001 to 2006 provided epidemiological evidence that both light and heavy cannabis use is linked with AMD.

2010 Malone and others looked at adolescent cannabis use and psychosis in a review. They concluded: ‘Epidemiological evidence suggests that cannabis use is a risk factor for schizophrenia, while cannabis use in individuals with a predisposition for schizophrenia results in an exacerbation of symptoms and worsening of the schizophrenic prognosis. The neuro-developmental characteristic of adolescence probably creates a more vulnerable circumstance for cannabis to produce psychotic-like symptoms and possibly cause schizophrenia.

2010 March 26th Michael Compton MD, MPH wrote a paper, ‘Evidence Accumulates for Links Between Marijuana and Psychosis’ for Medscape Psychiatry and Mental Health.

He summarized 2 avenues of research: 1) 'associations between cannabis use and clinical manifestations of psychosis' and 2) 'the biologic plausibility of the observed links'.

- 1) First: Cannabis is the most frequently abused illegal drug among people suffering from schizophrenia. And in those with psychotic disorders, the initiation of cannabis often precedes onset by several years.

Secondly: Adolescent cannabis use is more and more being recognized as an independent risk factor for both psychosis and schizophrenia.

Third: Genetic factors like variants of the COMT gene (normal form met/met) may predispose adolescent users to an increased risk of psychotic disorders. A val/met form of the gene increases the risk in adolescents about fivefold while the val/val increases it around tenfold. The release of dopamine is substantially increased.

Fourth: Cannabis use before the appearance of psychiatric symptoms may be associated with an earlier age of onset of psychotic and perhaps prodromal symptoms.

Fifth: A potential association in the general population between cannabis use and schizotypal symptoms or proneness to psychosis is emerging in research studies.

- 2) First The endogenous cannabinoid (neurotransmitter anandamide) and so the exogenous cannabinoid THC modulate the release of neurotransmitters including dopamine and glutamate by interacting with the CB1 cannabinoid receptor in regions implicated in schizophrenia.

Secondly: There is an increased CB1 receptor density in brain regions associated with schizophrenia.

Third: Patients with schizophrenia have raised levels of endogenous cannabinoids in the blood and cerebrospinal fluid.

Fourth: Administration of THC to patients cause both patients and controls to experience transient cognitive impairments and schizophrenia-like symptoms, both positive and negative.

To sum up, it has been suggested that "the endocannabinoid system is altered in schizophrenia and that dysregulation of the system, perhaps induced by exogenous cannabis, can interact with neurotransmitter systems in a way so that a 'cannabis hypothesis' can be integrated with other neurobiologic hypotheses (e.g. those involving dopamine and glutamate)".

He concluded that, "A growing body of clinical and epidemiological research suggests significant but complex links between cannabis use and psychosis. Concurrently, ongoing neurobiologic research is revealing findings in the endocannabinoid system that appear to support the biologic possibility of such links".

2010 May, Foti et al examined the relationship between cannabis use and the course of illness in schizophrenia over 10 years of follow-up after first psychiatric hospitalization. 229 patients were assessed 5 times, at first admission, after 6 months, 2, 4 and 10 years. They conclude: 'Cannabis use is associated with an adverse course of psychotic symptoms in schizophrenia, and vice versa, even after taking into account other clinical, substance use, and demographic variables'.

June 2010 Henquet and others discovered that pot smoking can worsen schizophrenia. Marijuana gives people with schizophrenia a quick rush but worsens their psychotic symptoms within a few hours. 47 healthy people and 48 psychiatric patients were recruited in Holland, they were all regular cannabis users the results showed that the schizophrenics were more sensitive than the healthy individuals to both the positive and negative effects of the drug. These findings help to explain previous findings that show that schizophrenics who smoke marijuana require more hospitalization, respond less well to medication and have more trouble with memory tests. Henquet says it's likely that marijuana triggers schizophrenic symptoms in people who have genetic mutations that sensitize them to the drug's psychotic effects.

2010 Henquet and others investigated the effects of cannabis on psychotic symptoms and mood in patients with psychosis (n=42) and healthy controls (n=38). Conclusions: 'Patients with psychosis are more sensitive to both the psychosis-inducing and mood-enhancing effects of cannabis. The temporal dissociation between acute rewarding effects and sub-acute toxic influences may be instrumental in explaining the vicious circle of deleterious use in these patients'.

2010 Dekker et al concluded that 'The findings indicate that patients suffering from schizophrenia have associations towards cannabis similar to controls, but they have stronger negative explicit cannabis associations. The strong negative explicit associations towards cannabis could imply that users of cannabis engage in a behaviour they do not implicitly like. Explicit relaxing expectancies of cannabis might be an important mediator in the continuation of cannabis use in patients and controls'.

2010 Marise Machielsen and others concluded there was a specific association between cannabis use and psychotic symptomatology.

2010 August, De Haan, a psychiatrist from Amsterdam Medical Centre found 60% of youngsters who have a psychosis are smoking marijuana. The risks have increased over the years because the joints are stronger. He says the cases confirm the link that has been established by science.

2010 September Morgan et al investigating the role of cannabidiol found that people who smoke potent strains of cannabis (e.g. Skunk) low in cannabidiol (CBD) are at far greater risk of acute memory loss than people who smoke other types of the drug e.g. hash. 134 users between 16 and 23 were tested for memory. The researchers found that people smoking cannabis with a low percentage of CBD performed much worse on the memory tests when intoxicated than when they were sober. In contrast those smoking cannabis high in CBD performed just as well on the tests when they were intoxicated as when sober. The amount of THC was identical.

Unbelievably the authors issued some HR advice! 'On the back of this study we believe users should be made aware of the risk of memory impairment from smoking low-dose CBD strains. They should be encouraged to use strains containing higher levels of cannabidiol instead'.

2010 October 8th CBS in the Netherlands (Centraal Bureau voor de Statistiek, Gov institution gathering statistical info about the Netherlands) reported that cannabis use increases the risk for mental health issues. 18,500 people were studied. 4% of 15 to 65 year olds had smoked cannabis in the previous month (more than a quarter reported smoking on a daily or near daily basis). The study found that nearly 20% of male cannabis users had psychological problems compared with nearly 10% of non-users. More than 28% of females had psychological problems versus more than 14% of non-users.

2010 November Staci Ann Gruber, speaking at Neuroscience 2010, the annual meeting of The Society of Neuroscience reported that people who start using marijuana at a young age have greater cognitive shortfalls. Researchers also found that the more marijuana a person used corresponded to greater difficulties in focus and attention. (Teen's brains are only about 80% developed and are not completed till the 20s or 30s).

2010 McGrath and others, using sibling pairs among over 3800 young adults, concluded that 'Early cannabis use is associated with psychosis-related outcomes in young adults. The use of sibling pairs reduces the likelihood that unmeasured confounding explains these findings. This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults'.

2010 Stilo and Murray in a review on schizophrenia research said, 'Acute ingestion of cannabis or its active ingredient THC was found to precipitate acute psychotic episodes in experimental studies, and continuing use of cannabis is known to exacerbate existing psychotic illnesses'.

2010 Skinner et al found among university students in Ireland (Galway) that cannabis use increases the risk of developing psychiatric symptoms, worsened by earlier and heavier use.

2010 Jouanjus et al looked at cannabis-related hospitalizations among 200 patients admitted to the public hospitals of the Toulouse area of France between Jan 2004 and Dec 2007. They found that one of the adverse events (AE) was lethal. Psychiatric disorders occurred in 57.7%, leading to 18.2% of

AEs, central and peripheral nervous system disorders, 15.8%, acute intoxication 12.1%, respiratory system disorders 11.1%, and cardiovascular disorders 9.5%.

2011 January. Estrada G and others found more confirmation for the COMT polymorphism interaction with cannabis use. 157 young psychiatric patients, mean age 17.01 years, were examined to find out if, a) age at first cannabis use and age at emergence of psychiatric disorders are related and b) such a relationship is modulated by the Val158Met genotype. It was found that those who started using cannabis earlier had an earlier age onset of psychiatric disorders, the distribution of the Val158Met was not different either between diagnosis groups or between cannabis and non-cannabis users. An interaction between Val158Met genotypes and cannabis use was observed specifically on age at emergence of psychiatric disorders with Val/Val genotype carriers showing an earlier age at onset than Met carriers. They concluded that The COMT Val158Met genotype seems to modulate the association between cannabis and age at onset of psychiatric disorders. These results are consistent with previous studies.

2011 Jan Lagerberg et al looked at the onset of bipolar disorder. They looked at 151 patients in treatment with a special focus on excessive alcohol and cannabis use. Patients with excessive alcohol use had a significantly later onset compared with patients with excessive cannabis use, whether it preceded or followed bipolar disorder onset. Lifetime use of cannabis predicted an earlier onset independent of the sequence of onsets. This indicates that an early onset may increase the risk of cannabis use and cannabis use may trigger bipolar disorder in vulnerable individuals.

2011 June. Large et al. published a very important meta-analysis on psychosis and age of onset. They identified 83 studies involving 8167 participants who used cannabis or other substances and 14,352 who did not. Individuals who used cannabis developed psychosis about 2.7 years younger than those who did not. Those who used any type of substance developed it 2 years younger while in those using alcohol there was no correlation. These findings support the view that cannabis use precipitates schizophrenia and other psychotic disorders perhaps through an interaction between genetic and environmental disorders by disrupting brain development.

“The results of this study provide strong evidence that reducing cannabis use could delay or even prevent some cases of psychosis. Reducing the use of cannabis could be one of the few ways of altering the outcome of the illness because earlier onset of schizophrenia is associated with a worse prognosis and because other factors associated with age at onset, such as family history and sex cannot be changed. “ The results of this study confirm the need for a renewed public health warning about the potential for cannabis use to bring on psychotic illness”.

2011 Feb Ashtari et al investigated adolescent brain development particularly on the hippocampus. They looked at 14 (18-20) ‘treatment seeking’ adolescents with heavy prior cannabis use (5.8 joints/day) after an abstinence of 6.7 months and 14 normal controls. The users showed significantly smaller volumes of the right and left hippocampus compared to controls. So heavy cannabis use after an average 6.7 months abstinence lend support to the theory that cannabis users may impart long-term structural and functional damage. Or the volumetric abnormalities may present a risk factor for cannabis dependence. These data have potential significance for understanding the observed relationship between early cannabis exposure at adolescence and subsequent development of adult psychopathology reported in the literature for schizophrenia and related psychotic disorders.

2011 Feb 23rd Morrison investigated whether cannabis (synthetic THC) elicits schizophrenia – like negative symptoms distinct from sedation. 22 healthy subjects attended 2 sessions in which either THC or placebo was given., random order and double blind conditions. They concluded that ‘At plasma concentrations resembling recreational use, THC elicited schizophrenia-like negative symptoms that were not merely attributable to sedation. In the community, negative effects may be an adverse effect of cannabis use’.

2011 Lebel found that in the development of the white matter in the brain, structural changes are still ongoing into young adulthood. 103 healthy people between 5 and 32 were scanned at least twice using MRI. Young adult brains were continuing to develop wiring to the frontal lobe., tracts responsible for complex cognitive tasks such as inhibition, high-level functioning and attention. An important observation was that in some people several tracts showed reductions in white matter integrity over time, which is associated with brain degeneration. Further research is needed to determine whether

different clinical disorders like psychiatric disease and neurological disease may be linked to brain structure as the brain ages.

2011 Demirakca et al found that a lower volume in the right hippocampus in chronic cannabis users was corroborated. Higher THC and lower CBD was associated with this volume reduction indicating neurotoxic effects of THC and neuroprotective effects of CBD. This confirms existing pre-clinical and clinical results. As a possible mechanism the influence of cannabinoids on hippocampal neurogenesis is suggested.

2011 March Compton et al looked at pre-illness cannabis use and the onset of psychosis. 109 first-episode hospitalised patients were studied. 42% of those who had used cannabis daily had an acute mode of onset of psychosis, only 20% of those without prior daily cannabis use had an acute onset.

2011 April, Solowij and others concluded that 'Long-term cannabis use in healthy individuals is associated with smaller cerebellar white-matter volume similar to that observed in schizophrenia. Reduced volumes were even more pronounced in patients with schizophrenia who use cannabis. Cannabis use may alter the course of brain maturational processes associated with schizophrenia'.

2011 April Kuepper et al conducted a study into whether an urban environment plays a role in moderating the effects of adolescent cannabis use on psychosis risk. Nearly 2000, 14 to 24 year olds, living in Munich or the rural surrounding were investigated. Cannabis and psychotic symptoms were assessed over a 10 year period. They concluded that exposure to environmental influences associated with urban upbringing may increase vulnerability to the psychotomimetic effects of cannabis use later in life.

2011 Dr Jussi Hirvonen and others in a presentation at the annual meeting of the Society of Nuclear Medicine in San Antonio Texas on 6th June said that imaging scans show that chronic daily use of marijuana can have a detrimental effect on the brain. They found a decrease in the number of receptors involved in a variety of important mental and bodily functions, including pleasure, pain tolerance, movement coordination, memory, appetite and concentration. The brains of 30 chronic daily marijuana smokers were studied over roughly 4 weeks. The CB1 receptors had decreased by around 20% compared to those of the healthy controls who had limited lifetime exposure to cannabis. After a month of abstinence, 14 were re-scanned and the number of receptors were found to have notably increased, suggesting the effects may be reversible. This research has not yet appeared in a peer-reviewed journal. The study was a collaboration between The US National Institute of Mental Health and the US National Institute on Drug Abuse (NIDA).

2011 Kuepper R et al concluded that, 'Cannabis use (in adolescence) is a risk factor for the development of incident psychotic symptoms. Continued cannabis use might increase the risk for psychotic disorder by impacting on the persistence of symptoms'. 1923 individuals (German), age 14 to 24 at baseline were studied and assessed 3 times for cannabis use and psychotic symptoms, baseline, 3.5 years (T2) and 8.4 years (T3). The incidence rate of psychotic symptoms over the time, baseline to T2 was 31% in exposed individuals, 20% in non-exposed. From T2 to T3 these rates were 14% and 8% respectively.

2011 October 25th Jones et al found that 'cannabis can cause chaos in the brain'. The nerve activity becomes unco-ordinated and inaccurate. Rats were given a drug mimicking the psychoactive ingredient in cannabis. Co-ordinated brainwaves across the hippocampus (memory) and prefrontal cortex (planning, decision making, social behaviour) were completely disrupted. The scientists believe the results may help explain the links between cannabis and schizophrenia. Jones said, ' Marijuana use is common among schizophrenia sufferers and recent studies have shown that the psychoactive ingredient of marijuana can induce some symptoms of schizophrenia in healthy volunteers'.

2011 Van Winkel et al looked at the AKT1 gene. In Holland and Belgium, 740 non-affected siblings of people with schizophrenia and similar conditions, and 419 controls with no first-degree relatives suffering from such disorders, were studied. Already known was that a gene associated with schizophrenia is AKT1, that cannabis has been associated with these disorders and that siblings of those with psychotic disorders were more likely to develop a psychotic disorder than the rest of the population. They found that the non-psychotic siblings of people with schizophrenia or similar disorders, were twice as likely to be diagnosed with psychotic illness after cannabis use than the general population. The AKT1 gene variation appears to be implicated.

2011 Zammit concluded that 'Cannabis increases risk of psychosis irrespective of underlying COMT genotypes. These findings argue against the widely held belief that the risk of developing psychosis following use of cannabis is dependent on variation within COMT.

2011 September Welch and others found that cannabis use impacts on brain thalamic volumes in people at familial risk of schizophrenia. In the Edinburgh High Risk Study (EHRS), MRI scans were obtained at point of entry to the study and approximately 2 years later. 66 individuals were involved in the study, substance use data were available for 57 of them of whom 25 consumed cannabis between the two assessments. They concluded that there was a significant volume loss bilaterally in the thalamus, more highly significant on the right. These losses remained significant when individuals using other drugs were removed from the analysis.

2011 December Cheetham discovered that cannabis users are born with smaller front part of brain. The orbitofrontal cortex controlling memory, reward and decision-making is 6% smaller in children who go on to smoke cannabis compared with those who don't. This could make them more likely to experiment with cannabis as they may be more impulsive and less capable of calculated decision making. This could act as an early warning system! Scans of 121 12 year olds were taken before they started to experiment, then questioned at 16. 28 admitted smoking pot, 23% less than 10 times. Co-founding factors eliminated, the group had the smaller brains. Other studies on long term users found that the drug seems to affect the size of other areas of the brain. These are normal in children who had smoked the drug so it seems to be regular heavy smoking that is causing the damage.

2012 Bhattacharyya examined the effects of THC and CBD on regional brain functioning during salience processing. 15 healthy men, occasional cannabis users were given THC, CBD or a placebo on 3 occasions. The aberrant processing of salience is thought to be a fundamental factor underlying psychosis. 'THC and CBD differentially modulate prefrontal, striatal and hippocampal function during attentional salience processing. These effects may contribute to the effects of cannabis on psychotic symptoms and on the risk of psychotic disorders'. There was no significant difference between the cannabidiol and placebo conditions.

2012 April 29th (Italy – 3rd Biennial Schizophrenia International Research Conference in Florence) O'Donoghue found that obstetric complications had the strongest significant influence on age of onset of psychosis, followed by cannabis use. A total of 608 patients with first episode psychosis were studied. Five factors were considered – Sex, social class of origin, family history of psychosis, cannabis use and obstetric complications. 19% of patients had a family history of psychosis, 44% had had an obstetric complication. Only 3 of the 5 factors were associated with an earlier onset of psychosis – Being male, a history of cannabis use and obstetric complications. Patients with a history of cannabis use had a median age of onset of 22.8 years, obstetric complications was 24.6 years and being male, 26 years.

Dr Mary Cannon, Dublin, said 'Without these risk factors your age of onset is about 30, but if you have 2 of them, this drops to about 20. That amounts to 10 years of very significant life...'

2012 Jan 12th Lynch et al looked at 'The Cannabis-Psychosis Link'. Several findings are interesting:

1. More than 16m Americans regularly use cannabis, typically beginning in adolescence. In the USA, 4% of cannabis users have a diagnosis of either cannabis abuse or dependence, but in schizophrenics the proportion of people with a co-morbid cannabis use disorder is 25%. Cannabis use disorders are especially common in younger and 1st episode patient samples and in samples of high proportions of males.
2. THC interacts with the dopamine (pleasure neurotransmitter) system. Dopamine, which provides a pivotal role in mediating the reinforcing effects of most drugs of abuse, is increased. This increased dopaminergic drive could underlie the abusive property of the drug and increase the positive psychotic symptoms induced by THC. (Murray and many others believe that the increase in dopamine is likely to be the cause of the psychosis, those with schizophrenia and psychosis have an excess of dopamine in the brain)
3. Moore et al in The Lancet 2007 in a systematic review surveyed the literature on this topic. The 'psychosis' outcomes required a diagnosis of a primary psychotic disorder or affective psychosis, or the occurrence of delusions, hallucinations or thought disorder during the study period. Results from 7 cohort studies showed a 40% increased risk of psychosis in cannabis users compared with non-users. The data also revealed a dose-response effect – the risk of psychotic symptoms was increased approximately 50% to 200% in those who used cannabis frequently compared with non-users.

4 Age at onset of psychosis and cannabis use: The Dunedin Multidisciplinary Health and Development Study conducted a prospective longitudinal study of adolescent cannabis use, taking into account psychotic symptoms that occurred before cannabis use. The data were compiled from a birth cohort that consisted of 1037 individuals born in Dunedin, New Zealand. Information about psychotic symptoms was obtained at age 11, and drug use was assessed by self-reports at ages 15 and 18 and by a standardized interview schedule at age 26. Two psychosis-related outcomes were measured—the presence of symptoms of schizophrenia and the diagnosis of schizophreniform disorder.

The results showed that those who had used cannabis by ages 15 and 18 had more schizophrenia symptoms than controls, a finding that remained significant after controlling for the presence of psychotic symptoms at age 11. However, the increased likelihood of schizophreniform disorder at age 26 was no longer significant after controlling for psychotic symptoms at age 11. Taken together, this suggests that early cannabis use confers higher risk of psychosis.

2012 April Whelan et al found in brain scans almost 2000 14 year olds, that some nerve networks don't work so well in some teenagers, making them more impulsive. These were in the orbitofrontal cortex, which is involved in decision-making and linked with experimentation with alcohol, cigarettes and illegal drugs in early adolescence, and offer poor inhibitory control. Another separate neural network which is involved with the symptoms of ADHD was NOT connected with this decision-making area. The researchers were able to 'fish out' 7 networks involved where impulses were successfully inhibited, but another 6 when inhibition failed. A genetic variation in a norepinephrine transporter gene was also involved.

2012 Feb Ersche et al looked at the brain 'wiring' of 50 biological siblings, one addicted to cocaine or amphetamines, the other with no history of drug abuse. A child of drug-addicted parents is 8 times more likely to become an addict than one in a drug-free home. Self-control was tested. People with poor self-control, including most drug addicts, find it difficult to exercise this. All of the sibling pairs did worse than the 50 unrelated healthy volunteer controls. Brain scans showed that each of the sibling pairs had abnormal interconnections between parts of the brain that exercise control and those involved with drive and reward. Also some individual brain structures were larger – the putamen, responsible for habit-forming, and the medial temporal lobe – learning and memory. The interesting thing is that although the sibling brains were similarly wired (wrongly) one of the pair had not used drugs. So there may be a way of helping vulnerable youngsters.

2012 Feb Anglin et al used prospective data from 804 participants was used to determine associations between early cannabis use and later schizotypal symptoms, accounting for important potential confounds (e.g., adolescent schizotypal symptoms). They found that Cannabis use with onset prior to age 14 strongly predicted SPD symptoms in adulthood, independent of early adolescent SPD symptoms, major depression, anxiety disorder, other drug use, and cigarette use. There was no interaction effect of early cannabis use and early adolescent SPD symptoms on SPD symptoms into adulthood.

2012 May Manrique-Garcia and others found that cannabis-related psychosis may not increase the risk for schizophrenia. They looked again at the 50,000 individuals, military conscripts in Sweden, who had reported their cannabis use since adolescence and over a 35 year period.

'The study revealed that the individuals who used cannabis regularly were almost four times more likely to develop schizophrenia than those who never used cannabis and more than twice as likely to experience a brief psychosis episode. The results also showed that the risk for future psychosis and schizophrenia weakened over the long-term. Manrique-Garcia said, "Of the cases related to cannabis use, 60% occurred during the first decade compared with 45% among non-users of cannabis." However, the findings also demonstrated a clear relationship between dose and risk. In particular, those who used the highest amounts of cannabis for the longest periods of time had the highest risk of schizophrenia. This risk was increased by early episodes of psychosis, regardless of whether they were cannabis induced or not. The individuals who experienced episodes of cannabis-induced psychosis and those who had non-cannabis-related psychotic episodes were equally at risk for [schizophrenia](#). But Manrique-Garcia points out that the individuals with cannabis-related psychosis may not have experienced any psychotic episodes if they had not used cannabis. Further research is needed to determine if this would ultimately decrease their risk for the later development of schizophrenia'.

2012 May. Behan et al looked at adolescent cannabis use and its effects on the COMT gene, first written about in 2005 (Caspi). They used mice whose COMT gene had been 'knocked out'.

Behan said, "This is the first study to show that the combined effects of the COMT gene with adolescent cannabis use cause physical changes in the brain regions associated with schizophrenia. It demonstrates how genetic, developmental, and environmental factors interact to modulate brain function in schizophrenia and supports previous behavioural research which has shown the COMT gene to influence the effects of adolescent cannabis use on schizophrenia-related

behaviours' The 3 areas of the brain assessed in this study were found to show changes in cell size, density and protein levels.

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One cannot vote for a medicine

Scientific approval basis is essential

(Distributed to all MPs Feb. 2000.)

E.U. Rules¹ set out various criteria for the acceptance of a drug for medical use, these include:

1. *All active ingredients have to be identified and their chemistry determined. They have to be tested for purity with limits set for all impurities including pesticides, microbes & fungi and their products. These tests have to be validated and reproduced if necessary in an official laboratory.*

The cannabis plant contains some 400 chemicals, a multiplicity of ingredients that vary with habitat – impossible to standardise and often contaminated with microbes, fungi or pesticides.²

2. *Animal testing will include information on fertility, embryo toxicity, immuno-toxicity, mutagenic and carcinogenic potential. Risks to humans, especially pregnant women and lactating mothers, will be evaluated.*

Cannabis has been shown to reduce sperm production.³ Babies born to cannabis-using mothers are smaller, have learning and behavioural problems and are 10 times more likely to develop one form of leukaemia.⁴ The immune system is impaired.⁵ Smoking herbal cannabis results in the inhalation of three times as much tar as from a tobacco cigarette.⁶

3. *Adequate safety and efficacy trials must be carried out. They must state the method of administration and report on the results from different groups, i.e. healthy volunteers, patients, special groups of the elderly, people with liver and kidney problems and pregnant women. Adverse drug reactions (ADR) have to be stated and include any effects on driving or operating machinery.*

Presumably it is envisaged that cannabis would be smoked. No medicine prescribed today is smoked. Concentration, motor-co-ordination and memory are all badly affected.⁷ Changes in the brain have been observed⁸ and U.S.A. clinics are now coping with more cases of psychosis caused by cannabis than by any other drug. It is essential to note that the content of THC (Tetrahydrocannabinol – the psychoactive ingredient in cannabis) is on average ten times higher than it was in the 1960s.⁹ The fat-soluble THC lingers in the body for weeks¹⁰ and the ability to drive safely is impaired for at least 24 hours after smoking cannabis.¹¹ Although ten times as many people use alcohol, cannabis is implicated in a similar number of road accidents.¹²

4. *The drug must be accepted by qualified experts. Their detailed reports need to take account of all the relevant scientific literature and the potential of the drug to cause dependence.*

There are numerous accounts of both psychological and physical dependencies in cannabis use.¹³ Some 77,000 people are admitted annually to hospitals in U.S.A for cannabis dependence, 8,000 of them as emergencies.¹⁴ To date there are over 12,000 scientific publications relating to cannabis.¹⁵

THC has already undergone all the medical tests. It is available on prescription in tablet form for the relief of nausea from chemotherapy and appetite stimulation in AIDS patients. However marinol (USA) and nabilone (UK), synthetic forms of THC and identical in action to it, are not the first drugs of choice among oncologists in Washington D.C. ranking only 9th in the treatment of mild nausea and 6th for more severe nausea.¹⁶ The warning on nabilone reads,

‘THC encourages both physical and psychological dependence and is highly abusable. It causes mood changes, loss of memory, psychoses, impairment of co-ordination and perception, and complicates pregnancy’.

Other Cannabinoids: Cannabis contains around 60 cannabinoids that are unique to the plant. Some of these could be similarly extracted, purified and tested for safety and efficacy. In the report “Therapeutic Uses Of Cannabis” (BMA, 1997) the British Medical Association said,

“It is considered here that cannabis is unsuitable for medical use. Such use should be confined to known dosages of pure or synthetic cannabinoids given singly or sometimes in combination”.

WHAT THE EXPERTS HAVE SAID

Dr Eric Voth MD, FACP (Chairman of the International Drug Strategy Institute) said in a letter to the editor of the New England Journal of Medicine (Jan 1997), “**Long term effects aside, contaminants, purity, standardisation of dose etc are all reasons to not use an impure herb as a medicine. Whether terminal or not, should we support smoking Foxglove plant to obtain Digoxin for heart failure, or Yew tree bark to obtain Taxol for breast cancer? If so, then supporters of smoked marijuana better be ready to support smoking tobacco for weight control and anxiety. We must have compassion for the sick and suffering and we must offer them reliable and quality medicine, not crude substances that threaten their well being**”.

Glaucoma: The pressure in the eye caused by this condition can be reduced by smoking cannabis but Professor Keith Green, Director of Ophthalmic Research at the Medical College of Georgia said some 6 ‘joints’ a day would be required, rendering the patient effectively ‘stoned’ and incapable of useful activities.

Multiple Sclerosis: Dr Donald Silberg, Chief of Neurology, Pennsylvania school of Medicine said, “I have not found any legitimate or scientific works which show that marijuana is medically effective in treating Multiple Sclerosis or spasticity. The use of marijuana especially for long-term treatment would be worse than the illness itself”.

DOES THE PUBLIC REALLY WANT THIS?

Nov 1996: Proposition 200 permitted physicians in Arizona to prescribe pure marijuana with no limitation on the age of the patient or disorder involved.

Jan 1997: A public opinion poll revealed that 85% of registered voters believed that proposition 200 should be changed and 60% wanted it repealed, 70% said it gave children the impression that drugs are OK for recreational use.¹⁷

HOW DID THE CAMPAIGN GET STARTED?

In 1979: Keith Stroup, an American pot-using lawyer, and the then head of NORML (National Organisation for Reform of Marijuana Laws) said, “We will use the medical marijuana argument as a red herring to give pot a good name.”¹⁸

Early 1990s Richie Cowan, Stroup’s successor at NORML, echoed him when he said, “Medical marijuana is our strongest suit. It is our point of leverage which will move us toward the legalisation of marijuana for personal use.”¹⁹

A Last Word From Dr Eric Voth

“We cannot by-pass the usual safety and efficacy process of the FDA (Food and Drugs Administration) because of the hue and cry of a self-preserving drug culture which seeks to add medicinal applications of marijuana, mixed messages of legalisation of illegal drugs, harm reduction and tolerance of drug use.”²⁰

Update April 2008. A paper by H Kalant was entitled “Smoked Marijuana as Medicine: Not Much Future”. It concluded, “The lack of convincing evidence thus far makes it unlikely that future studies will demonstrate any significant advantage of smoked marijuana over oral or parenteral use of pure cannabinoids. Therefore, no persuasive reason is evident for running the added risks associated with smoking. (21)

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Drug Education in UK Schools (2006)

Common sense surely dictates that drug education in schools should be based on prevention, that teachers will be doing everything they can to try to stop children from ever starting to use drugs. And in the government documents, Tackling Drugs Together and its various updates, prevention is indeed the stated aim. Sadly there is a great lack of common sense today.

For the past 15 years or so, the philosophy behind drug education has been one of harm reduction: - "Children will use drugs anyway, we must tell them how to do it safely and give them *informed choices*". Harm reduction has its legitimate place when dealing with a drug user on a one to one basis to lessen the risks, e.g. inhaling the fumes from heated heroin instead of injecting, with a view to getting him or her to stop. It has *no* place in the classroom.

If we analyse the statement we can begin to understand why drug use has risen and is still rising. "Children will use drugs anyway" is simply not true. Drug use is *not* the norm. 30 or 40% may *try* them, but how many try cigarettes, 95%? Regular drug taking in Britain today is around 10%. "We must tell them how to do it safely". There is no guaranteed safe way to take any drug, legal or illegal, and the phrase "informed choices" is indefensible. Currently they are not being properly informed, harm reduction literature *always* plays down the risks of cannabis. Nor should there be a choice, drug taking is illegal. Do we let them choose to spray graffiti or pilfer from shops, other illegal activities? Children are not miniature adults. Their brains will not be fully developed till they are in their twenties. They are incapable of making critical life decisions. QCA and DfES guidelines on drug education both advocate choice at key stage 2, 7 to 11 year olds! In the entire QCA document I failed to find the word prevention. The harm reduction approach does not *tackle* drugs it *accommodates* or even *condones* them.

On the government's drug information website FRANK the warnings of the dangers of drugs especially cannabis are woefully inadequate and sometimes inaccurate. "There is minimal risk of physical dependence, and there should be no problem stopping (unless you get addicted to the tobacco)". Some users have written of the almost impossible task of stopping and the dreadful withdrawal symptoms they have experienced. Lots of very dubious risk reduction tips are given, "Give one drug plenty of time to kick in or wear off before taking another" is just one of their "gems" of advice. One of my sixth formers who phoned FRANK pretending to be a pot user, was told that mixing alcohol and cannabis would simply exaggerate the effects, in fact it could be fatal, they are both depressants. Stronger varieties, he was told, would make everything crisper and brighter and he would feel more relaxed. In reality he could suffer an acute psychotic episode. Drugscope, the charity advising the government, does not want people with small amounts of any drugs in their possession to be arrested. The organisation "Connexions" sent out a leaflet on cannabis to schools. It mimicked a "Rizla" packet, said virtually nothing about the dangers but had masses of advice on risk reduction. My sixth form thought it positively encouraged drug use. I succeeded in getting it banned.

Talking to a roomful of parents whose children were all psychotic or schizophrenic because of cannabis was one of the most harrowing evenings I have spent. Shattered families, wasted talent.

Our children are being betrayed. As adults we have a duty to protect our vulnerable offspring. We don't let them eat poisonous berries, or cross main roads till they are old enough, why do we abandon them to drugs?

Clearly something has to be done.

The whole thrust of drug education must move from harm reduction to prevention. Prevention has always been better than cure and always will be. To quote from Dr Patrick Dixon's book, "The Truth about Drugs" 1998, "The majority of teenagers do not use any illegal drugs and never have – the biggest weapon we have in prevention is normalisation, helping those under pressure to see the truth, which is that abstention from illegal drugs and tobacco is the norm at any age of childhood, adolescence or adulthood".

Prevention worked in the USA. The idea that drug taking was not the norm was hammered home. This was the much ridiculed "Just say no" campaign. Between 1979 and 1991, the number of drug users fell from 23 to 14 million. Cannabis and cocaine use halved. It's working now. Under the new drug tsar, John Walters, they have seen an 11% decline in drug use over 2 years, the target was 10%. Surveys show that about 70%

of youngsters are deterred by concern over physical and psychological damage, 60% by parental disapproval, around half are afraid of becoming addicted or losing self control, and 40% by the law.

Prevention is not only “Just say no” and never has been. Everyone in America co-operated, teachers, police, parents, social and youth workers, customs officers, the children themselves. The message went out loud and clear that drug taking was not normal, not acceptable and most definitely harmful.

I have found that, if I explain to pupils, simply and scientifically, using diagrams of cells, how mind-altering drugs affect the brain and body, relate these to the adverse health, psychological and social consequences, lost educational opportunities and employment prospects, they begin to realise just how futile that lifestyle would be. I know, they tell me. The controversies around drugs are also aired, the medical arguments and “gateway” theory in the case of cannabis, the views of libertarians and legalisers, effects on family and friends, why the law is in place and the effects of its relaxation. A surprising number of children wanted “shock horror stories” when asked what would put them off drugs but by far the largest request was for facts about their health, put over in a non-patronising way. A multi-faceted approach will hopefully deter most children. I am not a fan of drug education games. “Pretend you’re a drug dealer” to my mind sends a very questionable message, and playing around with syringes, foil, matches, cigarette papers and drink bottles as suggested in QCA guidelines fills me with horror.

More difficult to change is the culture of acceptance of drugs now widespread in our society. Years of campaigning against tobacco has eventually seen smoking as a minority and largely socially unacceptable habit. But everyone must pull together. Attitudes to drugs vary widely, there is a lot of hypocrisy and double-standards. Kate Moss at first was condemned for her cocaine use then suddenly most of her lucrative contracts were restored. T-shirts, bags and jackets promote cannabis. Pop songs glamorise drugs and charities like Release and Transform actively lobby for legalisation.

The Swedes have the right idea. *All* drugs are treated alike. There are no Classes, drug use is very low. The question of re-classifying cannabis would never have arisen. Admissions of cannabis users to hospitals in the UK for mental illnesses have risen by 40% since it was suggested.

Children *need* and *want* rules and regulations. The only way they feel safe and secure is when they have boundaries to kick against. Teachers who fail to control classes gain no respect. I often hear children use their parents as an excuse when they don’t want to do something. A few years ago I listened to a young girl in The House of Lords where I was taking part in a conference on cannabis, she said, “...you adults have to say that you care, that you feel strongly about what we do – don’t leave it as a choice. If you don’t want us to do drugs then say so – and why. You don’t ask us to choose whether to steal, or attack people, so why leave us to choose about drugs?”

It was like a breath of fresh air.