NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT
BILTHOVEN, THE NETHERLANDS

Report no. 318902003 RESTRICTED PUBLICATION

Residual effects of prolonged heavy cannabis use

J.G.C. van Amsterdam, J.W. van der Laan, and J.L. Slangen

October 1996

This investigation has been performed at the request of the The Healthcare Inspectorate, within the framework of project 318902.

National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands
tel. +31-30-2749111, fax +31-30-2742971

MAILINGLIST

1-5 Hoofdinspecteur voor Farmacie en Medische Technologie, drs. P.H. Vree
6 Directeur-Generaal, dr. H.J. Schneider
7 Directeur Volksgezondheid RIVM., Dr. G. Elzinga
8 Directeur sector IV, Dr. Ir. G. de Mik.
9 Dr. A. Opperhuizen, hoofd Laboratorium voor Effecten Onderzoek
10 Drs. J.W. Dorpema, hoofd Laboratorium voor Geneesmiddelen en Medische Hulpmiddelen
11 Prof. dr. J.L. Slangen (extern)
12 Dr. J.G.C. van Amsterdam (RIVM-LEO)
13 Dr. J.W. van der Laan (RIVM-LGM)
14 Dr. H. van Loveren (RIVM-LPI)
15 Bureau BAIS
16-17 Bureau Rapportenregistratie
18 Bureau Voorlichting en Public Realtions
19-24 Reserve exemplaren

CONTENTS

SUMMARY IN DUTCH

Recente literatuur werd geraadpleegd om na te gaan of langdurig gebruik van grote hoeveelheden cannabis (dagelijks gebruik gedurende minimaal 6 maanden) leidt tot aanhoudende cognitieve effecten en effecten op het immuunsysteem. Het resultaat van deze studie is weergegeven in het huidige rapport.
Het vaststellen van achterblijvende (na stoppen van het gebruik) cognitieve effecten, die eventueel door langdurig en zwaar gebruik van cannabis worden bereikt is erg moeilijk door de vele storende factoren. In wat mindere mate geldt dit eveneens voor de immunologische effecten. Vele, zo niet alle studies over cognitief gedrag hebben te lijden van een te korte abstinentieperiode (<24 uur), het ontbreken van toezicht gedurende deze abstinentie en gebrekkige 'matching' van de controle-groepen. Voorts kunnen sommige effecten -indien zij onder gebruikers en niet-gebruikers worden aangetroffen- soms eerder worden toegeschreven aan residuen, die nog in het lichaam aanwezig zijn tijdens de test dan aan daadwerkelijke veranderingen in het centrale zenuwstelsel. Daarbij moet opgemerkt worden, dat actieve cannabinoïden opgeslagen kunnen zijn in vet-depôts, van waaruit zij vervolgens vrijgezet kunnen worden.
Resterende cognitieve effecten worden zelden na langdurig gebruik van grote doses cannabis waargenomen. Als zij al worden waargenomen zijn ze zeer mild van karakter, zeker in vergelijking met alcoholmisbruik. Er is wel gesuggereerd dat cannabis verscheidene psychopathologische syndromen zou induceren, maar een 'cannabis-psychose' is nooit gekarakteriseerd. Cannabis kan reeds bestaande mentale ziektebeelden negatief beïnvloeden en de schadelijke effecten van cannabis bij schizofrene patiënten worden onderkend. Anderen echter beweren dat schizofrene patiënten juist cannabis gebruiken om de storende symptomen van hun ziekte te onderdrukken.
Ten aanzien van de immuniteit worden tegengestelde resultaten gerapporteerd, hoewel algemeen wordt aangenomen, dat tetrahydrocannabinol (THC), de belangrijkste psychoactieve component van cannabis, immunosuppressieve effecten bezit. Men zou daarom een verhoogd risico voor en bevordering van de ontwikkeling van verschillende ziektes verwachten. Klinische resultaten geven echter aan dat de immunosuppressieve effecten van cannabis in het algemeen geen belangrijke weerslag hebben op de gezondheid van de gebruikers. Uitzonderingen zijn bepaalde vormen van maligniteit van het ademhalingstelsel (mondholte, tong en de pharynx), die relatief vaak bij jongeren voorkomen, hoofd- en nek-carcinoma en ontstekingen in het respiratoire gebied, die leiden tot CARA (vooral chronische bronchitis). De effecten zijn wat dat betreft redelijk groot, maar vergelijkbaar met het gebruik van tabak. Enerzijds is er een trend voor verhoogde gevoeligheid voor infecties waargenomen, hoewel anderzijds tekenen van hoge incidentie in de literatuur ontbreken. Een definitief oordeel kan hierover vooralsnog niet gegeven worden, omdat epidemiologische studies in de huidige literatuur ontbreken.
Conclusie: Literatuurgegevens ondersteunen niet de stelling, dat cannabis uitgesproken en langdurige neuropsychologische effecten (inclusief de pro-schizofrene effecten) induceert of dat cannabis in hevige mate de gezondheid aantast tengevolge van een verminderde immunologische afweer. Indien dergelijke effecten aanwezig zijn, zijn ze relatief klein, behalve op het respiratoire systeem.

TREFWOORDEN: cannabis, marijuana, tetrahydrocannabinol, cognitieve effecten, immuniteit

ABSTRACT

Recent scientific literature was consulted to find answers to two of the following questions:
1. does prolonged heavy cannabis use (daily use for at least 6 months) produce persistent cognitive effects, and
2. does prolonged heavy cannabis use affect the activity of the immune system.
The result of the survey is described in the present report.
Establishment of residual cognitive effects and to a lesser extent the establishment of residual immunological effects, putatively produced by prolonged heavy cannabis use, is difficult because of many confounding variables. Most if not all studies on cognitive effects suffer from the short abstinence period (< 24 hours), the lack of supervision during abstinence and the poor matching of control groups. Furthermore differences between chronic users and controls, when present, may be partly ascribed to drug residues still present in the body during testing rather than lasting alteration of the central nervous system. Note that active cannabinoids may be stored in fat-depots and subsequently be released from them.
Following prolonged heavy cannabis use residual cognitive effects are seldom observed and when noticed they are mild, at least in comparison with effects of alcohol abuse. Cannabis is suggested to induce several psycho pathological states but a 'cannabis psychosis' has not been characterised. Cannabis can exacerbate pre-existing mental disorders and the detrimental effects of cannabis in schizophrenics are well recognized. Others, however, argue that schizophrenics consume cannabis to relieve the symptoms of their illness.
Conflicting results of effects on immunity are reported though it is established that tetrahydrocannabinol (THC), the major psychoactive component of cannabis, retains immunosuppressive effects. One should therefore anticipate an increased risk for and promotion of the development of various diseases. Clinical results, however, show that the immunosuppressive effects of cannabis generally do not have a great impact on the health status of users. Exceptions are certain forms of respiratory tract malignancy (oral cavity, tongue and pharynx) relatively frequently observed in young individuals, head and neck carcinoma and respiratory inflammation leading to COPD (notably chronic bronchitis). Effects of cannabis are in this respect fairly large though still comparable with the effects of tobacco use. Trends of increased susceptibility to infections have indeed been reported but are not alarming considering the absence in literature of reports on high incidence of infections among cannabis users. Conclusive epidemiological data are however not available.
In conclusion, recent data in literature do not support the claim that chronic heavy cannabis use produces pronounced persistent neuropsychological effects (including pro-schizophrenic effects) or that health status of cannabis users is at risk due to impaired functioning of the immune sytem. If present the effects are small except for effects on respiratory tract.

INDEX WORDS: cannabis, marijuana, tetrahydrocannabinol, cognitive effects, immunity

1. AIM OF THE STUDY

The Healthcare Inspectorate (IGZ) has asked to evaluate long-term effects of chronic heavy cannabis use. From the first screening of literature based on the combination of the terms "chronic" and ["cannabis" or "marijuana"] effects on cognitive functioning and the immune system appeared to be most prominent.
Consequently, recent literature data were gathered to evaluate persistent effects of prolonged heavy cannabis use (daily use during more than 6 months) with emphasizes on cognitive functioning as measured by neuropsychological tests and the effects on the immune system.

2. ACCOUNTANCY

The question raised by Drs. Vree and Dr. Lousberg (IGZ) reads: Does chronic use of cannabis by youngsters lead to health complications or does it promote such complications? The research should be directed to immunological and neuropsychological effects. In addition, the effects of THC and cannabis as a whole should be differentiated and mainly recent literature should be consultated.

Methodological appraoch
References are by Medline literature searches and consultation of relevant serial works.
Used search startegy/profiles:

#1: "cannabis"/all subheadings or "marijuana"/all subheadings or "cannabinol"/all subheadings or "tetrahydrocannabinol"/all subheadings or "cannabinoids"/all subheadings

This gives in the most recent Medline database (1/96 to 6/96) 1207 hits. To limit this number of hits, #1 was combined with other entries:
#2 #1 and "TG=human"
#3 #1 and "Review"
#4 #1 and "Chronic"
#5 #1 and "Infection"

Other strategies were
#5 "substance-abuse-psychology"/all subheadings or "marijuana-abuse-psychology"/all subheadings or "marijuana-smoking-psychology"/all subheadings or "mental-retardation, -psychosocial"/all subheadings or psychophysiologic-disorders"/all subheadings
#6 #5 and #1

To specifically trace information published in other EEC-countries like France, Belgium, Germany, Suisse and Austria strategy #7 - #9 was applied:
#7 #1 and LA=FRENCH
#8 #1 and LA=GERMAN
#9 #1 and FRANCE

Depending on the data described in the obtained references additional searches in more ancient data bases (up to 1971) were performed. For information on specific items like 'flashback', 'cannabis psychosis' and 'schizophrenia' these entries were combined with #1.

Results
Data summarized from reports described international scientific journals are described in the present report. The chapters on neuropsychological and immunological effects were reviewed by and discussed with two senior experts (Prof. J.L. Slangen, emeritus professor of the University of Utrecht, and Dr. van Loveren, immunotoxicologist, respectively) and their comments incorporated in the final draft. The conclusion is led down in chapter 10 (Discussion and attempt at a synthesis).

3. INTRODUCTION

3.1 Definitions

The terms cannabis and marijuana are used without further differentiation. Hashish contains higher concentrations of THC. It is difficult to give a sound definition for prolonged heavy cannabis use. In the studies reviewed a large variety of heavy use is accepted. In general prolonged heavy cannabis use is defined as 'daily use during more than half a year'.
Cannabis contains some 62 cannabinoids and 364 other organic compounds. THC (Mol. weight of 314) is used as equivalent of the (-) isomer of delta-9-tetrahydrocannabinol, the main psychoactive principle of cannabis (Hawks, 1982), and 11-OH-THC, its principle metabolite.

Figure 1. Chemical structures of cannabinoids.

3.2 Modes of action

A receptor with a specific binding profile for cannabinoids has been reported and the first endogenous cannabinoid ligand described is anandamide, an arachidonyl-ethanolamide (Mechoulam et al. 1995; Devane et al. 1992; Devane, Axelrod, 1994). Using the radiolabeled ligand ^{3}H-CP-55940 it has been shown that binding to the cannabinoid receptor is saturable and has high affinity (Smith et al. 1994; Devane et al. 1988). Its stereoselectivity is extremely high (100-fold) (Mechoulam et al. 1991). Anadamide displaces this radiolabeled ligand with a K_d value of 100 nM and some of its synthetic analogs have an extremely high affinity with a K_d value of 40 pM (Mechoulam et al. 1991). Anadamide produces similar effects as THC (antinociception in the tail flick test, hypothermia, hypomotility and catalepsy in mice) though with a 1.3-18 times lesser potency (Smith et al. 1994). CP-55940-binding is distributed heterogeneously throughout the brain with the greatest abundance in basal ganglia, hippocampus and cerebellum (Herkenham et al. 1990; Bidaut Russell et al. 1990). The relative potencies of cannabinoids to inhibit CP-55940-binding were found to parallel their analgesic activity, as well as to regulate adenylate cyclase in-vitro (Devane et al. 1988). Compton et al. (Compton et al. 1993) demonstrated that the binding affinity of 60 cannabinoids (displacement of ^{3}H-CP-55940) were consistent with the pharmacological potencies in vivo (spontaneous motor activity, hypothermia, catalepsy and locomotor activity) in mice. Their findings suggest that a single receptor accounts for all of the behavioral and pharmacological effects. This was confirmed by the same group using synthetic anandamide analogs (Adams et al. 1995; Adams et al. 1995).
To date two cannabinoid receptor subtypes CB1 and CB2 have been identified which both retain affinity for CP-55940, anandamide and THC (Felder et al. 1995). CB1 is mainly expressed in the central nervous system and, to a lower extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus and tonsils (Gerard et al. 1991). In contrast, the CB2 gene, which is not expressed in the brain

(Munro et al. 1993), was particularly abundant in immune tissues, with an expression level 10-100-fold higher than that of CB1. Although CB2 mRNA was also detected in some other peripheral tissues, its level remained very low. In spleen and tonsils, the CB2 mRNA content was equivalent to that of CB1 mRNA in the central nervous system. Among the main human blood cell sub-populations, the distribution pattern of the CB2 mRNA displayed important variations. The rank order of CB2 mRNA levels in these cells was B-cells > natural killer cells >> monocytes > poly-morphonuclear neutrophil cells > T8 cells > T4 cells (Daaka et al. 1995; Galiegue et al. 1995).
The CB1 receptor transduces signals in response to CNS-active cannabinoids and is coupled to G_i-proteins which inhibit adenylyl cyclase activity. Therefore, cellular cAMP decreases upon CB1 receptor activation by THC. In contrast to its capacity to serve as an agonist for the CB1 receptor, tetrahydrocannabinol (THC; the centrally most active component of cannabis) was able to induce only a very slight inhibition of adenylyl cyclase at the CB2 receptor, including receptors in splenocytes. Moreover, THC even antagonizes the agonist induced inhibition of adenylyl cyclase mediated by CB2. Apparently, THC acts as a weak antagonist at the CB2 receptor (Bayewitch et al. 1996) though others report inhibition of forskolin-induced cAMP-synthesis via CB2-receptor activation (Slipetz et al. 1995). To date no clear quantatative structure activity relationsships (QSAR) studies with respect to CB2-receptor binding and functional immunological activity have been reported. The pharmacology of cannabinoid receptors is reviewed by Howlett (Howlett, 1995).
Other modes of action of THC include the modulation of arachidonic acid metabolism. THC induces a rise in PGE_2 and PGF_2 (Bhattacharya, 1986). Cyclooxygenase inhibitors like aspirin attenuate the antinociceptive, cataleptic and hypotensive effects of THC and some behavioral effects of THC in humans (Perez Reyes et al. 1991). Burstein et al. (Burstein et al. 1995; Burstein et al. 1994) found that cannabinoid-induced increase in eicosanoid production is due to a receptor mediated stimulation of arachidonic acid release. Finally it was suggested that THC interacts with cellular membranes thereby altering membrane fluidity and affecting selective permeability. It is remarkable that the IC_{50} values for inhibition of cAMP accumulation by cannabinoids were in the low nanomolar range (Felder et al. 1992) while the release of arachidonic acid and intracellular calcium required doses in the sub-millimolar range.

3.3 Fate in the organism

Residual effects are effects measured during drug abstinence. Due to the long residence time of active cannabinoids and their metabolites in the body, residual effects may erroneously be interpreted as a neurotoxic effect or consequence of chronic heavy cannabis use. It is therefore important to give some information on the presence asnd fate of THC in the organism. Furthermore it should be noted that THC is not the only pharmacologically active principle of cannabis. Cannabinol (CBN) and cannabidiol (CBD) retain their own specific pharmacological profile and may sometimes even block the depressant effect of THC (Krantz et al. 1971) or diminish the metabolism of THC (Jones, Pertwee, 1972) via inhibition of hepatic drug metabolism.

3.2.1 Absorption and accumulation

Cannabis cigarettes ordinarily contain 300-500 mg of solid material. Since cannabis has a relative THC content of 1%, there is 3-5 mg of THC in the cigarette. On average, 18% of the THC content (0.6-1 mg) of a cannabis cigarette is absorbed through the lungs of the smoker. The plasma level in man after inhaling 10 mg of THC is 20-70 ng/ml (Gallanter et al. 1972) and the minimal plasma level of THC associated with psychotropic effect is 25 ng/ml. Peak concentrations occur at 15 min after administration. The onset of drug effect following

smoking is almost immediate. Levels of cannabis in the blood generally do not exceed 0.5 µg/ml (500 ng/ml). Soon after the last 'puff' THC-plasma level rapidly decreases and one hour later as little as 5% of the original concentration attained remains in the blood. Differences in smoking technique can cause the relative amount absorbed to fluctuate between 2-50%.

Cannabis	THC	THC absorped by inhalation	plasma level
500 mg	5 mg	1 mg	2-7 ng/ml

Oral ingestion of THC produces a more variable plasma level of THC than does smoking and the amount of drug absorbed is about one-third of that which would be absorbed by smoking giving a bioavailability of oral THC of 4-12%. After oral consumption (e.g. space-cake) the onset of drug effect is within 30-120 minutes, maximal effects are obtained at 0.5-1 h after consumption and effects decrease after 6-8 hours. It should be noted that after oral use THC is less effective than an equivalent dose absorbed following smoking because the psycho-inactive THC-phenol is converted to the psycho-active THC-acid by pyrolysis.
The THC molecule is not ionized (contains no nitrogen atom or carboxylic acid residue, cf. Fig.1) and has a high lipophilicity. Therefore THC is tightly bound to plasma proteins like albumin. Only 3% is not bound and able to pass biological membranes and the blood brain barrier. The partition of cannabinoids in the cell membranes is promoted by its high lipid solubility and leads to an average tissue concentration of 2-5 µg/ml THC (Klein et al. 1987). An important part of the dose (incl. THC and other metabolites) accumulates in fat stores especially in chronic users. Both plasma bound and organ depots may then serve as a reservoir from which the free drug can be slowly released over long periods of time (Seth, Sinha, 1991; Johansson et al. 1988; Johansson et al. 1989). Consequently THC may persist at CNS receptor sites and plasma levels do not reflect the time course of CNS activity.

3.2.2 Elimination
The storage in and the release from fat stores and as well as the considerable redistribution of drug from the plasma compartment into tissues makes the elimination profile of THC fairly complicated. Indeed, THC shows multiple phases of elimination which may be responsible for the very large variation in plasma half-lives from 2 hours to several days (60 hr) reported (Johansson et al. 1988; Johansson et al. 1989; Seth, Sinha, 1991; Wall, Perez Reyes, 1981). Short half-lives are reported in older studies in which plasma levels were only measured up to 72 hours after administration because of poor analytical detection limits.
Elimination rate depends on the frequency of use; the elimination half-life has been estimated at 28 hours in experienced users and 56 hours in non-users (Seth, Sinha, 1991). Using the deuterium-labelled THC analogue [$^{2}H_{2}$]-delta^{9}-THC, which enables to measure very small amounts of THC, an elimination half-life of 4.1 days (98 hrs.) was determined in chronic users. Weeks or even months after cannabis abstinence metabolites may still be recovered from the urine of chronic users (Ellis, Jr. et al. 1985). Wall et al. (Wall, Perez Reyes, 1981) observed that 72 hr after administration of THC 50% of the dose was still in the tissues and body organs. No significant differences in elimination rates are observed between men and women (Wall, Perez Reyes, 1981).
Regardless of the route of administration (p.o., i.v. or inhalation) the greater part of THC-metabolites is found in faeces (35-65%). The cannabinoids enter the intestines via biliary secretion. Enterohepatic circulation of THC could contribute to the long half-life as well, but

probably only to a small degree. It has been suggested that 70% of the ingested THC is taken up by the tissues, while only 30% is metabolised and can be measured in urine.

4. ACUTE DESIRED AND ACUTE ADVERSE EFFECTS

Acute effects are defined as effects observed within 10-120 minutes after exposure to cannabis. Acute effects may still be present in chronic users during drug abstinence: they can last for up to 4-24 hours after having smoked a single cannabis cigarette (containing 20 mg of THC). Therefore, an overview is given now of acute effects observed in infrequent users following cannabis use.
It is difficult to disentangle desired effects of cannabis from adverse effects. Therefore desired and adverse effects are outlined within the same paragraph. Some subjects use cannabis to obtain hallucinations (desired effect) while others -often the more naive and infrequent users- experience anxious sensations (adverse effect).

4.1 Neuropsychological effects

A number of performances are reported to be affected (often in a dose dependent way) by acute cannabis use: car driving (leading to an increased risk of accidental injury (Taschner et al. 1994; Robbe, 1994; Gieringer, 1988) aeroplane-flying, rotary pursuit, reaction time, accuracy in divided attention tasks, estimation of elapsed time and distance, sustained attention and short-term memory. For reviews cf. Hollister (Hollister, 1988; Hollister, 1986).
Much more unpleasant for the individual are effects like anxiety, panic reactions, toxic delirium, paranoid state, dysphoria and manic state (Thomas, 1993; Smith, 1968). Individuals with a personal or family history of psychosis are in this respect especially susceptible (Ghodse, 1986; Andreasson et al. 1987).

4.2 Non-neuropsychological effects

Various non-neuropsychological acute effects are observed as well. Rather mild effects on body sway, hand tremor and reddening of the conjunctivae are seen. Tachycardia (dose-dependent) and orthostatic hypotension are other regular features of cannabis intoxication, but frequent users appear to develop tolerance rapidly. Still, premature arterial contractions, premature ventricular contractions, myocardial infarction, T-wave, S-T segment and P-wave changes and second-degree heart block have been observed in acute and chronic cannabis users (Akins, Awdeh, 1981; Jones et al. 1976). Finally it is in this respect interesting to note that propanolol reverses tachycardia, but not the subjective or behavioral effects, suggesting that multiple receptors are involved in the acute actions of cannabis.
If the mother smoked cannabis during pregnancy placenta abruption, premature labor, lower birth weight (Linn et al. 1983) and long-lasting developmental effects are observed more frequently (Zuckerman et al. 1989; Hatch, Bracken, 1986). Besides new-borns, adolescents and persons with pre-existing morbidity are at higher risk. Cannabis may exacerbate symptoms of cardiovascular- (Akins, Awdeh, 1981; Prakash et al. 1975) and respiratory disease (Tashkin, 1993). The possible association between cannabis use and schizophrenia (Andreasson et al. 1987; Thomas, 1993) is further outlined in paragraph 7. Finally, individuals who are or have been dependent upon alcohol or other drugs seem to be more vulnerable to the side-effects of cannabis.
Because the topic of this overview is the long-term effects of prolonged use of cannabis the acute desired effects and acute adverse effects are not further discussed here.

5. CHRONIC ADVERSE EFFECTS

Before the effects of chronic cannabis use on cognitive behaviour and immunity are summarized an overview is given of the main adverse effects observed after prolonged cannabis use. Further some introducing remarks on confounding factors and other methodological pitfalls encountered in the research of neuropsychological and immunological long-term effects of cannabis are made.

5.1 Main adverse effects in chronic users

The listing does not pretend to be complete. Examples of adverse effects are:

- reduced educational attainment in adolescents due to cognitive impairment (Kandel et al. 1986). The effect is not specific for cannabis as other drugs like alcohol induce a similar effect;
- development of a cannabis dependence syndrome, characterised by a loss of control over cannabis use;
- hormonal effects (modulation of levels of luteinizing hormone, follicle-stimulating hormone, testosterone and prolactin);
- subtle forms of cognitive impairment which persists while the user remains chronically intoxicated, and may not reverse after abstinence;
- exacerbation of psychotic symptoms in individuals with schizophrenia (Ghodse, 1986; Andreasson et al. 1987);
- respiratory diseases such as chronic bronchitis associated with smoking (Bloom et al. 1987; Tashkin, 1993);
- increased risk of cancer of the neck, oral cavity, pharynx, tongue and oesophagus (Taylor, 1988; Donald, 1986; Donald, 1991);
- leukemia (Zuckerman et al. 1989; Hatch, Bracken, 1986) and other birth defects in the offspring of woman using cannabis during pregnancy (Hingson et al. 1982; Linn et al. 1983).

5.2 Specific problems in the research of chronic adverse effects

Cognitive and neurotoxic effects

1. The term 'residual effects' is ambiguous. The term may refer to impairment induced by drug- or metabolite-residue's still present in the body after acute intoxication (cf. Fate in the organism, paragr. 3.2). The compound consumed or its metabolites are directly responsible for the measured effect. "Residual effects" may also refer to CNS damage that persists after the active compounds have been eliminated from the body (Pope, Jr., Yurgelun Todd, 1996). Indeed, heavy cannabis consumption (over 200 µg/kg, after smoking) can provoke effects (psychosis) lasting up to a week.
2. It is difficult to quantify the total amount of cannabis ingested by subjects as it largely depends on the smoking technique, quality of the cannabis (percentage of THC depends on the origin) and the elimination rate (depends on the experience of the user; cf. Fate in the organism, paragr. 3.3). This difficulty is minimized in laboratory studies in which a known amount of cannabis (of known quality) or THC is administered and tests are done at known time points after intake. One should, however, be aware that THC is not the only psychoactive principle in cannabis.

   It is not easy to assess long-term effects of months or years of daily cannabis use in laboratory studies. Therefore naturalistic studies are often performed. In such studies (comparing habitual heavy smokers with non-smokers) individuals can be evaluated which use the drug more heavy or over longer periods than could be ethically duplicated in the

laboratory. In such studies control of intake of cannabis and polydrugs use before testing and within the period of strict abstinence form additional problems.

3. Comparison of cannabis users with non users with respect to cognitive effects is influenced by many confounding variables (Block, Ghoneim, 1993). In particular:
   - premorbid difference in basal neuropsychological functioning (not related to cannabis);
   - premorbid psycho pathology;
   - certain aberrations/deviations in character ;
   - sex differences (heavy users of cannabis are rather male than female) ;
   - other: individual sensitivity, lifestyle, background, study habits, financial income, social status, IQ, education, etc. (e.g. (Konings et al. 1995).
4. Abrupt discontinuation of heavy cannabis use, as required in studiesof long-term effects, may precipitate a withdrawal syndrome characterized by insomnia, restlessness and irritability. Such a syndrome might well influence the study.
5. An important confounding factor is polydrug use because residual effects may not be solely due to the consumption of cannabis. Frequently studies reported in the international literature refer to subjects which use cannabis together with other drugs like alcohol, cocaine or XTC which have their own, sometimes pronounced, psychotropic effects. This is less relevant for Dutch studies because polydrug use is practiced relatively rare in the Netherlands: of the Dutch cannabis users (12-20 years) only 4.1% ever used heroin and 9.1% ever used cocaine (cited in (Ossebaard, 1996)). The self-reported lifetime prevalences in this group of drug users are 0.7% for heroin and 1.5% for cocaine (Kuipers et al. 1993).
6. Finally, long-term neuropsychological effects of cannabis (like 'cannabis psychosis') must be distinguished from actual psychiatric disorders.

Immunological effects

1. It is obvious that problems mentioned earlier for studies of cognitive effects are also relevant for the determination of long-term immunological effects (points 1, 2 and 5).
2. In addition to point 5: many cannabis users abuse concurrently drugs like cocaine, opiates or alcohol. Such drugs often may have opposing actions regarding the immune system. For instance alcohol (Madden et al. 1984) and cocaine (Donahoe et al. 1986) enhance the rate of rosette formation while opiates depress this T-cell parameter (McDonough et al. 1980; Donahoe et al. 1986).
3. In addition, many in-vitro studies have been performed in which cells are exposed to huge concentrations of THC. Concentrations of 10-100 µg/ml are no exception. Such concentrations are (patho)physiologically irrelevant considering an averaged plasma level of about 10-50 nanogram per ml reached after smoking 5-10 mg of THC which is approximately equivalent to one joint (Schwartzfarb et al. 1974; Gallanter et al. 1972).
4. It is not clear which of the 62 cannabinoids and 364 other organic compounds in cannabis is/are responsible for immunological effects. It must be admitted, however, that THC seems to be not only the most active psychoactive component but also retains the most pronounced immunosuppressive activity. It has been reported that psycho-activity is not related to immunosuppressive effects (Smith et al. 1978).
5. The choice of dose is very important as cannabinoids often show a biphasic or bell-shaped effect: low dose increased cAMP while high dose produced a decline in cAMP e.g. (Dolby, Kleinsmith, 1974).
6. The high lipophilicity of the cannabinoids makes it very difficult to perform in vitro testing and the solvent used (often DMSO) may induce its own effects.

6. ADVERSE EFFECTS OF CHRONIC CANNABIS USE: SELECTED ITEMS

6.1 Cognitive effects

Clinical impressions of many observers suggest that chronic cannabis use impairs cognitive function. Experimental studies of this issue have frequently been methodologically weak, ambiguous in outcome or both (Block, Ghoneim, 1993). Of about two dozen of studies conducted, a minority of studies has reported some cognitive impairments from chronic cannabis use while the majority has found that impairments were absent or negligible. The data from early studies are reviewed by Wert and Raulin (Wert, Raulin, 1986).

From a recent review of literature (Pope, Jr. et al. 1995) dealing with long-term neuropsychological effects, it was concluded that the data from literature support a 'drug residue' effect on attention, psychomotor tasks, and short term memory during the 12-24 hour period immediately after cannabis use. However, evidence is as yet insufficient to support or refute a more prolonged 'drug residue' effect.

Most studies which were reviewed by Pope and Wert and coworkers (Wert, Raulin, 1986; Pope, Jr. et al. 1995) suffer from the following methodological shortcoming: a crucial requirement for evaluating performance of chronic cannabis users is the inclusion of a group of non-using subjects who are matched on relevant demographic characteristics. Most importantly, some measure of intellectual functioning must be obtained before the onset of drug use. For a summary of confounding variables cf. paragraph 5.2, 'Specific problems in research of chronic effects'. It should be further noted that: (1) even in studies reporting some impairment, cumulatively, many more tests have been found unimpaired than impaired; (2) sometimes, specific tests showing impairment in one study have not shown impairments in others; (3) studies have varied widely in methodological soundness; (4) the limited education and frequent illiteracy of subjects in many studies from developing countries (Page et al. 1988) -and the special populations involved in some studies, i.e. prisoners (Soueif, 1975)- raise questions about generalizability of the results to typical, educated individuals in industrial societies and appropriateness of the standardized psychological tests used, many of which were developed for such individuals (Block, Ghoneim, 1993).

In the older studies reviewed by Wert and Raulin only one study by Culver et al. matched controls and users on pre drug, intellectual and personality dimensions (Culver, King, 1974). In that study no impairment in users was found. Poor supervision during abstinence is another major problem. It appears that in the many studies performed no or only little attention is paid as to whether users actually interrupted smoking cannabis: users are kindly requested not to smoke before testing or when arriving 'high' at the day of testing are requested to return for testing at a later time. Other studies simply fail to indicate the period of abstinence.

Varma et al. (Varma et al. 1988) were the first to rigorously supervise a group of heavy oral users in India (mean duration 6.7 years with average daily use of 150 mg THC) for a 12-h period by hospitalising them overnight to ensure abstinence before testing. Psychological tests measuring intelligence, memory and other cognitive functions were given to the 26 users and non users. In only three of the thirteen neuropsychological tests (pencil tapping, time estimation, and size estimation) users performed worse than non users showing at most a modest effect. Users did not differ in intelligence or memory tests. In addition, the users suffered disability in personal, social and vocational areas and indicated higher psychotism (introvert) and neuroticism scores.

Mendhiratta et al. (Mendhiratta et al. 1978) applied primarily tests of attention, concentration, and motor speed in their evaluation of 50 Indian cannabis users. Users performed worse than non-users on virtually all tests (7 out of 9) in the study. However, differences in either (acute)

drug presence or motivational state could have accounted for the observed effects. Only formal (not rigorous) supervision of 12 hours or more was employed, groups were not well matched and testing was not blind.
In a follow-up study in Costa Rica Page et al. (Page et al. 1988) compared 30 non-users with 27 users (9.6 joints per day for a mean of 17 years). In this study which was not supervised tests were performed 12-24 h after last use. In only 3 of the approximately 20 tests (Buschke's verbal selective reminding, underlining test, and continuous performance test) users were impaired in comparison with non-users. The results obtained in the three tests suggest that users show slower rates of information processing in self-paced mentioned activities for abstinence of cannabis use that require sustained attention in learning lists of unrelated words. On the other hand though, the results in the other 17 neuropsychological tests (on e.g. intelectual capacity, reaction time, psychomotor speed) argue against a residual effect (CNS alteration) of prolonged cannabis use. Certainly when one takes into account the massive cumulative exposure to cannabis (a mean of 30 years and 105000 joints per subject).

Only three studies with well-matched controls are available. Schwartz et al. compared a small sample of 10 cannabis-dependent users with 9 well-matched non-user controls in order to ascertain that the long-term effects of cannabis use (short-term auditory/verbal- and visual/spatial memory) are reversible and performance will increase upon cessation of cannabis use. However, after two days of abstinence the former cannabis users still performed significantly worse than the controls on the Benton visual retention test and the Wechsler memory scale prose passages. No differences were observed in five other neuropsychological tests (Buschke's test, digit span and coding, complex figure drawing, recalling paired words and short memory after distraction). After six weeks of supervised abstinence subjects in the cannabis using group showed some improvement on both tests though not at a statistically significant level (Schwartz et al. 1989). These results indicate a pair of long-term effects of chronic cannabis use. It should be noted that differences were observed in only 2 out of seven tests and that the small sample size renders the study vulnerable to the effects of one or two outliers in a given group.
In a nice study of Block et al. (Block, Ghoneim, 1993) the performance of 144 cannabis users and 72 non-users were compared following an unsupervised 24-h period of abstinence. The study also comprised intermediate users (5-6 joints per week during 5.8 years) and light users (1-4 joints per week during 5.5 years). Subjects were carefully matched on intellectual functioning before the onset of drug use on scores from tests (Iowa Tests of Basic Skills) performed during the fourth grade of grammar school (performed at age 9-10 years). Users were however more frequently male than controls (80% vs. 30%) and were likely to have abused other drugs. Present testing was performed on scholastic achievement (using the twelfth grade versions of the Iowa tests, normally performed at an age of 17-18 years), five neuropsychological tests including Buschke's selective reminding test and finally two psychomotor tests. Heavy cannabis use (>7 joints per week during 6.2 years) was associated with deficits in mathematical skills (quantitative thinking) and verbal expression (correctness and appropriateness of expression) and impairment in memory retrieval of high but not low imaginary words (Buschke's subtest). No effects were observed in other tests like text interpretation, picking closest synonym for a specified word, text learning, paired associate learning (associating pairs of words) and two psychomotor tests (critical flicker fusion and discriminat reaction time). Intermediate use (5-6 joints per week during 6 years) was associated with superior performance but intermediate and light users (1-4 joints per week) did not differ from non-users on any test. The deficits in quantitative thinking and verbal expression are not alarming as the effects are small and can be easily compensated. The authors

conclude that the linkage between heavy cannabis use and impairment was corrolational rather causal. Further the impairments observed may have been produced by confounding variables of other demographic characteristics which were not balanced like educational, socioeconomic and medical status. For example, heavy users may have attended school while under influence of cannabis' acute effects leading to an impaired level of achievement.
In a third very recent study Pope et al. (Pope, Jr., Yurgelun Todd, 1996) compared two samples of college undergraduates (aged 18-28 yrs, single blind): 65 heavy cannabis users, who had smoked a median of 29 days and at least 27 days in the past 30 days and who displayed cannabinoids in their urine, and 64 light users, who had smoked a median of 1 day and no more than 3 days in the last 30 days and who displayed no urinary cannabinoids. All subjects were abstinent before testing for a controlled minimum of 19 hours which is relatively short. Subjects received a battery of standard psychological tests to assess general intellectual functioning, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visospatial material. Heavy users displayed only a significant impairment as compared to light users on attentional/executive functions (perseveration on card sorting and reduced learning of word lists). These differences remained after controlling for potential confounding variables, such as estimated level of premorbid cognitive functioning, and use of alcohol and other substances in the two groups. In their conclusion the authors question whether the impairment is due to a residue of the drug in the brain, a withdrawal effect or a frank neurotoxic effect. It should be emphasized that the period of abstinence (19 hours) is relatively short considering the slow elimination rate. This makes an effect due to residual drug presence in the body likely. Anyway the cognitive impairments observed are not large relative to normal cognitive variability among individuals and finally, the cognitive effects associated with alcohol use are far more pronounced.
The results were commented in an editorial by Block (Block, 1996). Later, the study was criticised by Scheier and Botvin (Scheier, Botvin, 1996) who pointed at the poor matching of the two groups. Heavy cannabis users might have suffered from antecedent neuropsychological and behavioral deficits to a greater degree than occasional cannabis users and this was not accounted for in the study of Pope et al. On the other hand, Pope et al. controlled for verbal IQ and reported Scholastic Aptitude Test scores (school tests). These data and a number of psychological and behavioral measures did not suggest that premorbid differences could account for the observed residual effects. But that leaves the confounding of the psychosocial factors intact and the predicting power of the neuropsychological test is small and presumably not large enough to exclude the criticized confounding.
In a longitudinal study Scheier and Botvin (Scheier, Botvin, 1995) investigated the consequences of early adolescent drug use (cigarettes, alcohol, cannabis or polydrug use) on early-late adolescent cognitive efficacy by tracking a cohort of adolescents for 5 years. The findings show that early adolescent drug use had a small but significant negative long-term effect on later cognitive and affective self-management strategies.

In summary:
In all studies matching of users and non-users remains was only partly accomplished and the time between cannabis use and testing (duration of abstinence) was too short to assertain absence of active drug residues in the body. Based on the results of the three best studies performed (Schwartz et al, 1989; Pope et al, 1996; Block and Ghoneim, 1993) one must conclude that long-term cognitive effects are seldom observed and if present are mild in nature.

6.2 Event-related potentials

ERP- and EEG studies (cf. paragr. 6.3) are not generally accepted as a methodologically sound approach to assess changes/impairment of cognitive effects. The results should therefore be interpreted with caution.

Investigators in this field assign ERP (event related potential) components as markers of specific stages of information processing, reflecting the nature, timing, and duration of cognitive processes. The negative shift of the ERP wave form, which is referred to as processing negativity (PN), is thought to reflect the selection of relevant from irrelevant sources of information. Another component of interest is the P300, a large positive peak. The latency of this peak reflects the time taken to evaluate a stimulus while the amplitude is supposed to reflect the nature of this proces (Solowij et al. 1995).

A previous study (Solowij et al. 1991) comparing ERPs during a complex auditory selective attention test indicated that cannabis users showed larger processing negativity to an irrelevant source of information (inability to filter out relevant information) and reduced P300 amplitude (dysfunction in the allocation of attentional resources). In a later study (Solowij et al. 1995) the same technique was used to evaluate more specifically the effects of frequency and duration of cannabis use. Regular cannabis users (N=32; at least once a month for three years; mean frequency 12 days per month) were selected, had ceased cannabis use for at least six weeks, did not abuse alcohol and had no history of psychiatric or neurological illness and were compared with 16 control subjects. Cannabis users consumed more alcohol and had slightly less years of education. The authors conclude that the past duration of cannabis use continued to have an adverse effect upon electrophysiology (and therefore cognition) well after discontinuing use. The ability to focus attention and filter out irrelevant information was impaired progressively with the number of years of abuse but was unrelated with the frequency of use. The speed of information processing, measured by the latency of parietal P300, was delayed significantly with increasing frequency of use but was unaffected by duration of use. Partial recovery, however, may occur rapidly following cessation of cannabis use. In general, the relations between cannabis use and effects as shown in the paper of Solowij are extremely weak.

In a case study Solowij (Solowij et al. 1995) assessed cognitive behaviour of a 35 yr. old man who had used cannabis daily for 18 years, prior and several weeks post cessation. ERP measures showed no indication of improvement over 6 weeks of abstinence. In contrast when tested in the acutely intoxicated state prior to cessation of use, a dramatic normalisation of information processing in this individual was observed.

Patrick et al. (Patrick et al. 1995) studied ERPs in non-psychiatric patients who had used THC but abstained from THC for 24 hours prior to evoked potential testing and in nonusers (N=32 respectively 44). No differences were found between THC users (at least three years use but currently not abusing other drugs (tobacco and social alcohol excepted) and controls in performance on a cognitive task and no associated differences in ERP (P300 latency and amplitude) measures.

6.3 EEG-studies

A number of older studies (Rodin et al. 1970; Tassinari et al. 1996) secured clinical EEGs before and after acute THC exposure and reported a variety of transient minor EEG changes with no consistent effects being seen across studies (for review see Struve et al. (Struve et al. 1989)). From a nice double blind study (Fink et al. 1986; Fink et al. 1973) it became evident that inhaled THC (acute!) produced a dose-dependent transient increase in the relative alpha power and a decrease in beta.

Chronic THC exposure has been associated with decreased hippocampal neuronal and/or synaptic density in the rat (Scallet et al. 1987; Landfield et al. 1988) and electrical and anatomical changes in the septum of the rhesus monkey (Heath et al. 1980). From a review of neurological, psychological and neuropsychologicalreports until 1986 Wert and Raulin (Wert, Raulin, 1986) concluded that no persistent CNS sequelae have been demonstrated in humans.

A dose-dependent transient increase in the relative alpha power and a decrease in beta was also observed by Struve et al. (Struve et al. 1989) in ten heavy THC users (at least once a day for more than one year) and matched with ten non-users all selected from a pool of psychiatric inpatients. The quality of this study is rather poor because psychiatric diagnosis of THC users were primarily personality disorder or organic affective/delusional syndrome and none carried a diagnosis of schizophrenia or major affective disorder while the most frequent diagnosis in the patient non-user comparison group was schizoaffective psychosis, schizophrenia and nonpsychotic disorder. In addition, 70% of the THC-users were serious polydrug users. According to the authors the effects observed were not confounded by both group differences (diagnosis) and polydrug use because they are unrelated to alpha activity. The results show that in heavy users the largest increases are observed over bilateral frontal or frontal-central areas but the implications of the finding are for the authors not clear (Struve et al. 1989). In a subsequent study in which these results were confirmed it was shown that former long-term heavy THC-users who have abstained for at least 5 years from THC use do not show the topographic quantitative EEG features associated with chronic THC use. This suggests that the EEG changes following several years of daily THC use may be reversible with extended avoidance of cannabis (Winterer et al. 1994; Struve et al. 1994).
Finally, it is emphasized that the benefit of EEG-methodology in neurophysiological and psychiatric research (except for sleep research) was recently questioned because of its low specificity and high variability (Sweden, 1996). This is not surprising considering the range of EEG abnormalities in chronic THC users being 0-16.7% (across study weighted average of 9.7%) (Struve, Straumanis, 1990) which is very small compared with a weighted average of 17.8% EEG abnormalities which was calculated for 6752 normal adults from published normal control studies (Struve, 1984) (cited from (Struve et al. 1994)). The effect of THC on EEG must therefore be very high to give a decent signal to noise ratio.

6.4 Psychosis

An acute psychosis in clear consciousness may follow the use of large quantities of cannabis and a more persistent disturbance was brought about by one-time usage of cannabis in two cases (Gersten, 1980).
Psychosis as residual effect of cannabis use is recently reviewed by Thomas (Thomas, 1993). One group found a high prevalence of general psycho pathology amongst cannabis users, though non-using friends of the users showed equally high rates of mental disorder (Weller, Halikas, 1985; Halikas et al. 1972). There are only very few cases (three) showing persistent psychotic symptoms. For example one case (Keshaven, Lishman, 1986) reported in India refers to mental disturbances in a PhD student who had stopped smoking following heavy and regularly smoking ganja for about one year. The complaints lasted about six months. One year later features of depersonalisation and derealization and feelings of emotional dullness and apathy were still observed.
Smith used the term 'amotivational syndrome' to describe the loss of a desire to work or compete in regular users of cannabis. He illustrated the syndrome with two case reports. The 'syndrome' includes: diminished drive, decreased ambition, lessened motivation, dullness, apathy, shortened attention span, distraction, poor judgement, introversion, impaired

communication skills, decreased capacity to carry out complex plans and a progressive loss of insight. Tennant (Tennant, Jr., Groesbeck, 1972) reported 110 cases among 36000 American soldiers stationed in Germany who smoked large amounts of hashish (50-600 g monthly for 3-12 months) and showed changes in personality. In a follow-up study in nine of the subjects it appeared that after discontinuation of cannabis use, memory, alertness, concentration and calculating ability returned to normal within 2-4 weeks in most cases. The remainder showed persistent episodes of 'confusion', though these became less severe and less frequent over time. This was confirmed by others (Beaubrun, Knight, 1973). This syndrome is suggested to be caused by the slow release of active THC residues from fat cells (Ellis, Jr. et al. 1985; Johansson et al. 1988; Johansson et al. 1989).
Though laboratory studies have not produced any evidence for an amotivational syndrome it is still occasionally advocated (Wieviorka, 1995) though one admits that personality problems like depression may underly the syndrome (Musty, Kaback, 1995). Indeed, some studies indicate that consumption of cannabis initiates and sustains a depression (Tunving, 1985; Jones et al. 1976; Pillard, 1970).
The clinical picture of 'cannabis psychosis' is characterised as a mixture of affective and schizophrenia-like symptoms and can therefore not easily be distinguished from schizophrenia and it obscures the diagnosis of paranoid schizophrenia (Mathers, Ghodse, 1992; Imade, Ebie, 1991).
In conclusion: there is no experimental prove for a cannabis psychosis or a amotivational syndrome. Both may be the result of residual active THC components in the body or premorbid neuroaffective disorders in the user but they are not shown to be the result of chronic cannabis consumption.

6.5 Flashback

Relapse of symptoms experienced during intoxication without further exposure to a drug is termed 'flashback'. Indeed like after LSD-use, flashbacks may occur but are rare following cannabis use alone (Pillard, 1970; Tennant, Jr., Groesbeck, 1972; Keeler et al. 1968). Possibly they may be due to cannabinoids released from fat stores. As a rule a flashback may take place in cases where there is an intake of hallucinogenic drugs in the recent case history (Fischer, Taschner, 1991). Indeed, a few who have used both LSD and THC (on separate occasions) found that smoking cannabis triggers recurrences of the LSD experiences (Weil, 1970). A definite correlation between the amount of cannabis consumed and the occurrence of flashbacks does not exist (Fischer, Taschner, 1991). Some users find the recurring drug experience to be pleasant, but others regard flashbacks as threatening and disturbing.
Despite the very large number of users only very few reports on flashbacks have been described. Most of them are described in the older studies (from more than 25 years ago) suggesting that since then no alarming observations have been made.

6.6 Residual neurological items

Neurological complications such as dementia syndrome, impaired memory for recent events, hallucinosis, and delirium are relatively common in chronic cannabis users (Co et al. 1977; Campbell et al. 1971; Tunving, 1985; Stevens, Restak, 1976). Frank structural neurological damage (cerebral atrophy) from the chronic use of cannabis (3-11 years) was established in one study (Campbell et al. 1971) but others (Hannerz, Hindmarsh, 1983) could not confirm this in another group of heavy cannabis users (1 gram daily for ten years). It should be emphasized that these subjects also concurrently used ethanol, LSD and amphetamine which confounds the interpretation because alcohol is known to produce such damage (Hannerz, Hindmarsh, 1983).
The reports on neurological complications have been described in the more ancient literature

and few data were published since. In 1986 it was concluded from a large number of published reports that there is no evidence that cannabis produces gross structural cerebral damage and there is little evidence that it leads to impairment of neurological functions (Wert, Raulin, 1986).

6.7 Developmental effects

Cannabinoids do cross the human placental barrier and have been found in umbilical cord blood of newborns. Cannabinoids are also present in the milk of lactating mothers. Prenatal exposure to cannabinoids in both animals and humans have been shown to result in transitory behavioral delays followed by catch-up. Four years following prenatal cannabis exposure there were more behavioral problems and decreased performance on visual perceptual tasks, language comprehension, sustained attention and memory (Fried, 1995). It was estimated that the use of cannabis accounted for about 10% of the variance in the behavioral measures (Fried, 1995) which is not very impressive.

An assessment of sleep-EEG patterns found significant differences in the sleep cycling and motility of cannabis-exposed compared to non-exposed new-borns (Scher et al. 1988). These effects remained consistent over time and at 3 years of age disturbed sleep patterns were still significantly associated with prenatal cannabis exposure (Dahl et al. 1995).

Other studies (Ottawa Prenatal Prospective Study, OPPS) reported that at 48 months cannabis use was associated with lower scores in both verbal and memory domains (Fried, Watkinson, 1990). Later it was shown by the same group that 6-year old children showed impulsive and hyperactive behaviour (Fried et al. 1992). In follow-up OPPS-studies (O'Connell, Fried, 1991; Fried et al. 1992) referring to children of age 6-9 years effects were still noticeable though no longer statistically significant. On the other hand using a similar study design Streissguth (Streissguth et al. 1989) did not find any effect at the age of 48 months. In a longitudinal study Day et al. (Day et al. 1994) shows negative effects (short term memory, verbal reasoning) due to cannabis use during pregnancy (0.2-8.8 average daily joints during first and second trimester) at the age of three years.

One should bare in mind that the aforementioned studies suffer from many confounding variables: cannabis is often used by pregnant women in combination with alcohol and tobacco; assessing cognitive behaviour in young children is difficult and sociopsychological factors may be relatively important. Though the effects observed in the new-borns seem to be reversible the data indicate that pregnant women should be aware of harmful effects of cannabis and should therefore abstain from the consumption of cannabis (as well as from tobacco smoking and alcohol use).

7. RELATIONSHIP TO SCHIZOPHRENIA

In the U.S. cannabis use is high among psychotic/schizophrenic patients (35-65% versus 16% in normal population) (Soyka, 1994; Regier et al. 1988) maybe because cannabis relieves the patient from apathy, insomnia, depression, anxiety, low self-confidence and loss of creativity and initiative. Regarding the relation between schizophrenia and cannabis use the opinions of four different research groups are to be differentiated: use of cannabis leads to schizophrenia; the negative symptoms of schizophrenia lead to cannabis use; the course of schizophrenia is impaired by cannabis use; and finally: cannabis use is prevalent in youngsters with problems in lifestyle and social environment leading to inadequate coping and psycho pathology (Heller et al. 1992).

Tennant and Groesbeck noted an increase in the incidence of schizophrenia among U.S. army personnel in Europe from 1/1000 to 38/1000 and suggested that this was due to an increase in cannabis use. Evidence for an association between cannabis use and schizophrenia comes later from a prospective study by Andreasson (Andreasson et al. 1987) of 45570 Swedish conscripts screened for psychological disturbances at the age of 20 years when they were entering military service. Over a 15-year follow-up period, the relative risk of developing schizophrenia was 2.4 for cannabis users compared to non-users (at the time of conscription), and 6.0 for heavy users. This association persisted after allowance for other psychiatric illness, and for variations in social background. This study was rightly criticised by others (Johnson, 1990; Negrete, 1989; Johnson et al. 1988) on a number of points, notably that the schizophrenic breakdown may have been due to other drugs; there was no sequential relation or temporal link between cannabis use and admission for schizophrenia and schizophrenia may have been related to an underlying predisposing factor such as premorbid personality. Indeed, after analysing a smaller sample (8483 conscripts in Stockholm) the latter appeared indeed to be the case (Andreasson et al. 1989).

Some clinical studies have found that cannabis magnifies positive symptoms of schizophrenia in patients (established cases as classified in the ICD-9). Subjects (N=137) who were using cannabis during the 6-month observation period showed a significantly higher degree of delusional and hallucinatory activity than those who did not. Also they made a higher average number of visits to the hospital (Negrete et al. 1986). Though the groups were not well matched it is interesting to note that the active-users group presented the highest exhibition of delusional and hallucinatory activity compared to previous users (> 6 months) and non-users. Knudsen and Vilmar observed ten schizophrenic patients who had psychotic episodes following cannabis use despite verified adequate depot treatment with neuroleptics (Knudsen, Vilmar, 1984).

Data analysis of 62 schizophrenic patients (18-30 yrs. of which 39 were regular alcohol users) indicated the following factors influencing the course of the illness: continuing cannabis consumption; previous cannabis intake; non-compliance with treatment and stress (Martinez Arevalo et al. 1994). In a comment of Cohen it was stated that one must pay more attention to simultaneous alcohol consumption. At least one should exclude in the studies of cannabis the consumption of other drugs (Cohen, 1994).

Thus it is clear that cannabis use negatively affects the course of schizophrenia. One should, however, note that other socially accepted drugs like alcohol (Drake et al. 1989; Drake et al. 1990; Castaneda et al. 1996), coffee (Mikkelsen, 1978; De Freitas, Schwartz, 1979) and medical drug treatment also appear to enhance or magnify the symptoms of schizophrenia.

8. EPIDEMIOLOGY OF DRUG ABUSE RELATED DISEASES

8.1 Pulmonary effects

Heavy cigarette smoking and alcohol consumption are major independent etiologic factors of lung cancer (Spitz et al. 1988). Although cannabis has similar respiratory irritants found in tobacco smoke the carcinogenic factors are 50-70% greater in cannabis. Smoke of cannabis contains a number of irritants and carcinogens. It is therefore probable that habitual smoking of cannabis over years can produce clinically substantial lung damage and respiratory malignancy (Tashkin, 1993).

The insoluble particulate (tar) phase of the smoke from cannabis contains about 50% more of some carcinogenic aryl hydrocarbons including benzo[*a*]pyrene than the smoke from a comparable quantity of unfiltered Kentucky reference tobacco. Painting of smoke condense (tar) from cannabis cigarettes on the skin of mice led to the development of metaplastic and neoplastic lesions that correlate with carcinogenicity (Cottrell et al. 1973).

Inhalation or 'puff' volume is about 2/3 greater; the depth of smoke inhalation is about 40% greater and breath holding four times longer than those characteristic of tobacco. So the smoking of one cannabis cigarette (800-900 mg, 1-3% THC) led to the disposition in the lower respiratory tract of about a fourfold greater quantity of insoluble smoke particulates (tar) than did smoking of a filtered tobacco cigarette (Wu et al. 1988). In addition, cannabis cigarettes do not contain filters and generate twice as much tar per unit weight, assuming a similar smoking profile (Rickert et al. 1982). Finally, cannabis smoke condense induced a number of mutations in the Ames test which was comparable with tobacco (Wehner et al. 1980).

Extensive metaplastic and dysplastic changes (precursors of bronchial carcinoma) have been noted in bronchial epithelium of heavy habitual cannabis smokers (Gong, Jr. et al. 1987). Donald has suggested that cannabis use is causally related to increased incidence of head, neck and tongue carcinoma in young patients (Richter et al. 1995; Caplan, Brigham, 1990; Taylor, 1988; Donald, 1986; Donald, 1991) and the number of young patients with squamous cell carcinoma of the oral cavity, tongue and pharynx is rapidly increasing.

Clinical comparison studies by the group of Tashkin et al. of 144 heavy habitual smokers of cannabis only, 135 smokers of cannabis + tobacco, 70 smokers of tobacco only, and 97 control non-smokers revealed an association between heavy regular use of cannabis (3-4 joints per day for > 5 years) and symptoms of acute bronchitis (Tashkin et al. 1987). On the other hand while tobacco smoking is associated with abnormalities in small airways function and diffusing capacity, physiologic studies in heavy habitual cannabis smokers have not shown similar evidence of parenchymal lung destruction (Tashkin et al. 1987). Other symptoms observed in chronic cannabis users are dysplastic and inflammatory changes in tracheobronchial mucosa (Gong, Jr. et al. 1987), increased numbers of alveolar macrophages and neutrophils in BAL (Barbers et al. 1987) and impaired microbicidal activity of alveolar macrophages compared with tobacco smokers (Sherman et al. 1991; Sherman et al. 1991).

Taylor identified 10 patients (all younger than 40 years old) out of 887 patients of all ages in whom respiratory tract cancer had been developed. Only two of these ten patients had no history of cannabis use implicating cannabis as an important cause of respiratory tract cancer, especially in young persons. Cases on respiratory tract malignancy have been reported bu others (Ferguson et al. 1989; Almadori et al. 1990; Taylor, 1988; Donald, 1986; Donald, 1991).

Thus though acute THC induces bronchodilatation, chronic cannabis use is destructive to pulmonary tissue and function. Abnormalities in pulmonary function from chronic irritation can

occur, and chronic obstructive pulmonary disease (COPD) may result (Laviolette, Belanger, 1986; Jones et al. 1976)

8.2 Infections

Like other drugs of abuse (opiates, cocaine and alcohol) cannabis depresses the activity of the immune system which increases the risk for microbial infections (Specter, 1994). Clinically, one might thus assume that sustained impairment of immunity might lead to increased prevalence of infections. In 1894 the Hemp Drug Commission (Anonymous1894) reported that heavy users seemed to present a decreased resistance to the causes of dysentery. Diarrhoeic disorders were said to be unusually frequent among them.

Scholtens (Scholtens, 1905) reported in 1905 that cannabis users in Surinam were more susceptible to tuberculosis and gastro-enteritis while Abdulla (Abdulla, 1953) reported a higher susceptibility to schistosomiasis. Much later the association of cannabis use and increased incidence of infection was described in a case-report by Juel-Jensen in 1972 (Juel Jensen, 1972) who reported recurrent activation of genital herpes simplex lesions (HSV) infection in cannabis smoking subjects. Animal studies have confirmed that THC could increase the severity to HSV infection and is the result of depressed immune functions (Morahan et al. 1979; Cabral et al. 1986). It was demonstrated that timing of administration of THC was important. Disease was enhanced when THC was used shortly after infection or both shortly before and after exposure to the virus (Specter, 1994).

Guarisco (Guarisco et al. 1988) noticed isolated uvulitis secondary to cannabis. A variety of somatic disturbances has been reported in long-term users of THC; these include conjunctivitis, chronic bronchitis, hepatic enlargement, arthritis and gastro-enteritis.

A survey of literature however learns that only a limited number of case-reports on decreased immunological competence or impaired host-resistance in cannabis users are reported. In fact no strong effects have been reported sofar. Though there remains a need for epidemiological studies it should however be noted that such studies are difficult to perform because of the confounding variables mentioned before.

In conclusion: though there are some indications that cannabis -as expected from immunological studies- decreases the resistance towards infections by microorganisms, no strong increase in infections amoung heavy cannabis users have been reported. To further evalate in this respect the health effects of cannabis use epidemiological studies should be performed in the future.

8.3 Oral effects

Darling (Darling, Arendorf, 1993; Darling, Arendorf, 1992) reviewed the effects of cannabis use with regard to oral/dental effects. Cannabis associated oral effects are: xerostomia (with predisposition to caries and periodontitis), severe gingivitis, oral mucosal disease, poor dentition., and abnormal stress response upon administration of adrenaline-containing local anaesthetic.

8.4 Hormonal effects

The effect of chronic cannabis use was assessed regarding luteinizing hormone, follicle-stimulating hormone and prolactin levels in human males (Vescovi et al. 1992). Both basal and stimulated levels of LH were reduced in cannabis users, whereas the other hormones were not affected. In another study studying in addition testosterone and cortisol in both men and women no differences could however be observed (Block et al. 1991).

Cannabis (4-16 joints per week during 4 weeks) reduces sperm concentrations and induces oligospermia with Leydig and Sertoli cell dysfunction. In addition, cannabis attenuates luteinizing hormone in male and female (Mendelson et al. 1986; Vescovi et al. 1992). Kolodny (Kolodny et al. 1974) found subnormal plasma testosterone concentrations and oligospermia in young men ranging from 18-28 years, during chronic intensive cannabis smoking. Studies using less-long-term exposure to cannabis have not confirmed these findings (Hollister, 1986).

The effects of cannabis on the female reproductive system have not been widely studied, but the drug may lead to increases in anovulatory menstrual cycles (Hollister, 1986) abnormal menstruation, failure to ovulate, and possibly teratological abnormalities (Bloodworth, 1985; Kolodny et al. 1974). Impaired fertility may occur from decreased testosterone levels, reduced sperm counts, and abnormalities in structure and function in sperm in males (Smith et al. 1982; Cone et al. 1986).

9. IMMUNITY

9.1 Introduction

The immunological effects of cannabinoid are probably mediated by a specific receptor located on various cells of the immune system. Among the main human blood cell populations, the distribution pattern of the CB2 mRNA displayed important variations. The rank order of the distribution was B-cells>NK-cells>>monocytes> polymorphonuclear neutrophil cells>T8 cells>T4 cells. The same order was observed in comparable cell-lines (Galiegue et al. 1995). These results suggest that CB2 is closely related to functions of the immune system.

The presence of immunological abnormalities in cannabis users is still a matter of debate and conclusive evidence that THC adversely affects immune system in adults is lacking. Still there has been an observed trend toward immunosuppression by THC regarding a broad array of humoral and cell-mediated immune responses. Data from animal studies are controversial, as well. This is partly due to the reasons outlined in paragr. 5.2.
For instance, normal pokeweed mitogen- (White et al. 1975) and phytohaemagglutinin-induced lymphocyte proliferation (Rachelefsky et al. 1976; Lau et al. 1976; Kaklamani et al. 1978; White et al. 1975) and normal T- and B-lymphocyte populations (Rachelefsky et al. 1976) have been noted in cannabis abusers by some investigators while others noted decreased phytohaemagglutinin or concanavalin-A (Daul, Heath, 1975) -induced lymphocyte proliferation, an impaired mixed lymphocyte culture response (Nahas et al. 1974) and aberrant lymphocyte populations (Barbers et al. 1987).
Recent studies on the effects of THC on the cytokine network which is very important in resistance to viral infections and the protection to a large number of other diseases incl. cancer do not give a clear picture. The effects are complex and not yet well understood.

9.2 Animal studies (in-vitro exposure)

The T-cell dependent antibody response (sheep erythrocytes) in-vitro was inhibited by 5-10 µg/ml THC while at a 10-fold lower dose THC enhanced the antibody response. Murine spleen cells incubated with 5 µg/ml THC induced a firm suppression (50-80%) of IL-1, IL-2 and IFN release (Friedman et al. 1988). Decreased in-vivo responsiveness to mitogenic stimulation of T-lymphocytes has been reported in rodents (Levy, Heppner, 1981). NK-cell activity is dose-dependently decreased in vitro by 5 µg/ml THC or 11-OH-THC at 1-18 hr (Klein et al. 1987; Friedman et al. 1995).
THC exposure suppresses multiple immunological functions of macrophages. THC (1-5 µg/ml) inhibited mouse macrophage spreading (phagocytosis) and inhibited phagocytosis of yeast particles (Lopez-Cepero 1986), whereas others could not find such effects in vivo (Munson et al. 1976). IL-1 production by macrophages is rather enhanced than suppressed by exposure to 2-10 µg/ml THC (Zhu et al. 1994; Shivers et al. 1994).
THC inhibits nitric oxide (NO) production by mouse peritoneal macrophages activated by LPS and IFN. Inhibition was already noted at concentrations as low as 0.5 µg/ml and was maximal at 7 µg/ml. The effect seems to be partly induced at the level of cAMP and delta-8-THC was more active than (-) delta-9-THC and the 11-OH-THC. The endogenous ligand anandamide was hardly effective while the psycho-inactive (+) isomer of delta-9-THC was some 3-fold less inhibitory than the (-) isomer (Coffey et al. 1996). Others, however, showed that anandamide was well capable to inhibit macrophage-mediated killing of TNF-sensitive cells (Cabral et al. 1995).

9.3 Animal studies (in-vivo exposure)

Using a number of classical in-vitro tests like the number of haemolytic plaque-forming cells, hemagglutinin titers and splenic weight, it was shown that THC (10-25 mg/kg), but not other cannabinoids reduced humoral immunity (Levy, Heppner, 1981; Baczynsky, Zimmerman, 1983). Susceptibility to infection with herpes simplex virus was increased in mice and guinea-pigs treated with 4-100 mg THC/kg/day (Cabral et al. 1986). In mice treatment with high dose of THC (38-150 mg/kg) firmly decreased the lethal dose of micro-organisms (Morahan et al. 1979). In a mouse infection model THC enhanced mortality upon a second infection (challenge) while it did not affect the primary infection (Klein et al. 1995).

Th_1 cells are related to cellular immunity and Th_2 cells to humoral immunity (e.g. stimulation of IgG_1 antibody production). In a mouse infection model a shift from Th_1 to Th_2 cell activity appears to be induced by THC (4 mg/kg i.v.) (Friedman et al. 1995). Indeed it was shown that mice infected with Legionella pneumonia plus THC (5 mg/kg) induced enhanced production of IgG_1 antibodies in drug-treated mice (Newton et al. 1994).

Subchronic (but not acute) treatment of ratswith THC (3 mg/kg s.c., 25 days) decreased NK-cell activity and the effect was reversed by naloxone-treatment (Patel et al. 1985). NK-cell activity was strongly inhibited in mice treated with 50 mg THC per kg i.p. (Friedman et al. 1988).

Early studies revealed that alveolar macrophages of rats exposed to cannabis smoke had a decreased bactericidal activity (Huber et al. 1975) and superoxide anion release (Draht et al. 1979). More recent studies indicate that THC is able to block macrophage cytokine production, including TNF (Zheng, Specter, 1996; Zheng et al. 1992) and Il-1 (Watzl et al. 1991) though others reported the opposite (Klein et al. 1995; Friedman et al. 1995). In serum of mice treated with 8 mg/kg THC the acute phase cytokines TNF and IL-6 are increased 2-3 fold.

Zimmerman (Zimmerman et al. 1991) used two synthetic cannabinoids to investigate the stereospecificity of the immunological response. HU210 the (-) isomer was some 80 times more psychoactive than THC while HU-211 the (+) isomer was in this respect completely inactive. Considering the immunomodulatory effects it appears that the (-) isomer is more effective than the (+) isomer suggesting that both 'systems' are mediated by similar active sites (receptors) .

9.4 Human studies (in-vitro exposure)

Friedman et al. (Friedman et al. 1988) shows that THC and 11-OH THC at non toxic doses can depress in vitro the functional activity of T- and B-cells as well as macrophages (production and release of soluble mediators of immunity incl. interleukins and interferons). Nahas et al. observed a 50% decrease in phytohaemagglutinin-induced human T-cell proliferation in vitro by 80 µg/ml THC (Nahas et al. 1976) which is an extremely high concentration. Synthetic cannabinoids (CP55,940 and WIN55212-2) as well as THC caused a dose-dependent increase of B-cell proliferation and displayed EC_{50}-values at low nanomolar concentrations. This cannabinoid-induced enhancing activity was inhibited by pertussis toxin which suggested a G_i-protein coupled receptor process (Derocq et al. 1995). Il-2 induced thymidine and uridine uptake in humanPBL was dose-dependently suppressed by THC (1-10 µg/ml). NK-cell activity was only affected at the highest concentration but the activity of LAK cells (IL-2 activated NK-cels) was again dose-dependently inhibited by THC (Trisler, Specter, 1994).

The production of cAMP in PBMC is inhibited by THC via a G_i-coupled mechanism (Diaz et al. 1993). The IC_{50} values for inhibition of cAMP accumulation were in the low nanomolar range and the effect was stereoselective (Felder et al. 1992). THC (1-10 µg/ml) also increased

in vitro the release of 12-HETE a member of the lipoxygenase pathway of arachidonic acid metabolism, while prostaglandin's were not affected (Specter et al. 1995).
Only little data are available regarding the effect of THC on the activity of neutrophils. Djeu et al. (Djeu, 1992) recently reported that THC inhibited PMN anti-fungal activity with ED_{50}-value of 2 µg/ml. This effect is probably due to inhibition (30%) of the production of super oxide anion in PMN's by THC 2 µg/ml. Release of beta-glucuronidase and lysozyme was impaired as well, though to a lesser extent. CBD (cannabidiol) retains no psychoactivity but shows a greater suppressive effect on the secretion of cytokines from human PBMC than THC at concentrations of 1-5 µg/ml (Watzl et al. 1991).

9.5 Human studies (in-vivo exposure)
Lymphocytes exposed to mitogens show morphological changes and divide rapidly which results in increased thymidine incorporation. It appears that THC inhibits in vitro thymidine incorporation in T- and B-lymphocytes obtained from controls. In lymphocytes of cannabis users thymidine incorporation was reduced (Nahas et al. 1974).
Rosette formation is another commonly used measure of cell-mediated immunity. THC in vitro or smoking of cannabis both decrease rosette formation (Cushman, Khurana, 1976; Gupta et al. 1974) though one day later rosette formation was again normalised suggesting that the effect is reversible and that factors other than exposure to cannabis itself may be involved (Petersen et al. 1976).
Three studies reported immunoglobulin concentrations in cannabis smokers. Coggins et al. (Coggins et al. 1976) described a single measurement of total serum globulin concentrations in a group of 84 smokers (daily use for 10-28 years) and showed that they were significantly lower than in a group of 156 controls studied in parallel. As a whole, however, using many other physiological (body weight, systolic blood pressure abdominal scars), serological parameters (blood sugar, urea, bilirubin, prothrobin time, blood cells, alkaline phosphatase, blood sedimentation albumin) and ECG the users were found to have only minimal differences in their health status from nonusers. In the other study (Rachelefsky et al. 1976), IgG levels of cannabis smokers were reported to be normal when compared to age-matched controls (data obtained from literature) ten years before. In a third study Ig-levels were determined in a well controlled environment for eight weeks. Levels in sera of 15 chronic male cannabis users (3-5 joints per week, 5-16 years) and 19 matched controls were determined in three different periods. Subjects in both groups smoked tobacco. In the cannabis smokers IgG concentrations were consistently lower (987 vs. 1154) and IgD consistently higher (4.2 versus 2.4) than in the control group studied in parallel. These differences were however not accentuated by the use of cannabis during four weeks. Thus there was no observable 'drug-effect' (Nahas, Osserman, 1991).
The number of alveolar macrophages and neutrophils in the bronchoalveolar lavage are increased in cannabis and tobacco smokers to a similar degree (Barbers et al. 1987) and ultrastructural differences of alveolar macrophages was observed between cannabis smokers and non-smokers (Mann et al. 1971). The basic difference between tobacco and cannabis use is supported by studies showing that basal and stimulated O_2^- production were significantly increased in tobacco smokers as compared to non-smokers. In contrast basal O_2^- production was actually lower in subjects who smoked cannabis compared to control (Sherman et al. 1991; Sherman et al. 1991). Gil et al. (Gil et al. 1995) found increases in lung alveolar permeability in chronic tobacco smokers. Cannabis smokers (>20 joints/wk for over 20 yrs) showed a smaller and less consistent increase. Sherman (Sherman et al. 1991) found only a trend toward genetic damage of DNA in alveolar macrophages in habitual cannabis smokers.

In summary: the animal and human studies performed in-vitro and in-vivo indicate that THC suppresses immunity. The action is not specific as various immune function are affected. No clearcut image of the immunosuppressive effect of THC can therefore at present be given. More data are required on effects of low dose of THC and repeated administration in animal infection models. In addition, basal activity of immune cells (basal release of eicosanoids and cytokines) should be measured in chronic users and compared with well-matched controls (tobacco smokers and non-smokers) or alternatively in animal models. It would further be interesting to follow the course of immunosuppression during abstinence (several days to weeks).
It must be mentioned that THC may not represent the only immuno-active compound and experiments on the immunological effects of cannabis instead of THC deserve attention.
Finally, one should be aware of cumulative effects of the highly lipophilic THC-molecule. Only little is not known about the relation between the average plasma level of some nanograms per ml and the tissue concentration finally attained in the immunocompetent cell.

10. DISCUSSION AND ATTEMPT AT A SYNTHESIS

Establishment of cognitive defects putatively caused by prolonged heavy cannabis use is troublesome because of the many confounding variables that preclude a correct conclusion. It is often difficult to disentangle the effects of cannabis from those of other drugs as cannabis use is highly correlated with use of other illicit drugs, especially at an early age. In addition, cannabinoids show a very long half-life of many days which hinders the assessment of effects in chronic heavy cannabis users after cessation of drug use. Almost no study investigates the long-term effects after sufficient abstinence time. At the same time the cannabis user may feel distressed and not fully concentrated during the abstinence period in which cognitive behaviour is evaluated. Well matching of groups is very difficult. Considering the numerous variables (socioeconomic, psychosocial, intellectual, educational, gender, personallity profile, premorbid psychopathology, lifestyle, medical care, differences in literacy and vulnerability) this is difficult to do.
Deficits in cognitive behaviour may be related to antecedents, concomittants and consequences of (chronic) drug use. With the available neuropsychological tests (lacking high sensitivity and selectivity) it is difficult to identify the contribution of each of the three factors. Very few studies have succeeded in teasing apart a single factor. Moreover some find effects of cannabis use for instance in the Buschke test while others fail.
Above noted factors also refer to immunological studies. In addition many immunological effects observed in-vitro are questionable because the very high concentrations used are clinically not relevant.

In conclusion it is established that chronic heavy cannabis use does not lead to severe side-effects in the domain of cognitive behaviour. When present effects are mild and certainly not alarming. Psychosis, gross structural cerebral changes and flashbacks are seldom observed and may be ascribed to concurrent use of other drugs. There is little evidence that cannabis can actually induce a psychotic disorder in previously asymptomatic individuals. However, a substantial risk remains that cannabis exacerbates the course of a pre-existing DSM-IV Axis I disorder.
Cannabis use leads to a large variety of immunosuppressive effects and increased vulnerability to infectious disease has been reported. However, the number of reports in literature are limited and not alarming suggesting that the impact of immunosuppression with regard to infections is low. Epidemiological studies relating the cannabis consumption with incidence of infections are however still lacking. Like tobacco, cannabis smoking affects broncho-pulmonary homeostasis leading to pulmonary inflammation (COPD) and head and neck carcinoma. Effects of cannabis are in this respect more severe but still comparable with tobacco use.
This conclusion is not new as nearly hundred years ago the Indian Hemp Drug Commission (Anonymous1894) which heard 1193 witnesses and commissioned a few experimental studies both with human subjects and primates, concluded that use of cannabis does not lead to any persistent psychiatric disorder. Eventual negative effects have to be looked for rather in the user than in the drug. It was suggested that the moderate use of cannabis does not have 'injurious' effects on the mind. 'except in persons who are vulnerable'; that cannabis does cause 'lunacy' or 'insanity' when taken in excess, or when used by 'predisposed' subjects. The latter refers to the relation between cannabis use and schizophrenia which is supported by data in recent literature indicating that use of cannabis impairs the course of schizophrenia. Note that other socially accepted drugs like alcohol, coffee and medical drugs also appear to enhance or magnify the symptoms of schizophrenia.

11. SUGGESTIONS FOR FUTURE RESEARCH

Cannabis clearly retains immunosuppressive activity but the impact is less clear. From the survey in literature it appears that most studies have been performed with doses of THC which are clinically not relevant. Other studies were carried out using combinations of active compounds (cannabis). Data obtained in such a way are difficult to interprete.
As stated above, more data are required on effects of low dose of THC and repeated administration in animal infection models. In addition, basal activity of immune cells (basal release of eicosanoids and cytokines) should be measured in chronic users and compared with well-matched controls (tobacco smokers and non-smokers) or alternatively in animal models. It would further be interesting to follow the course of immunosuppression during abstinence (several days to weeks).
It must be mentioned that THC may not represent the only immuno-active compound and experiments on the immunological effects of cannabis instead of THC deserve attention. One should be aware of cumulative effects of the highly lipophilic THC-molecule. Only little is known about the relation between the average plasma level of some nanograms per ml and the tissue concentration finally attained in the immunocompetent cell.
Furthermore, it is advised to perform controlled studies in which individuals are treated with known quantities of specified cannabinoids (but not cannabis) or in-vitro using low dose of the active principle(s). Finally, epidemiological data should become available describing the relation between incidence of infections and the patterns of cannabis use in a well-controled setting (matching of groups).

12. REFERENCES

Anonymous1894. Report of the Indian Hemp Drug Commission, 1893-1894.

Abdulla A, 1953. *Cannabis indica* als Volksseuche in Agypten. Schweiz Med Wochenschr 83:541

Adams IB, Ryan W, Singer M, Razdan RK, Compton DR, Martin BR, 1995. Pharmacological and behavioral evaluation of alkylated anandamide analogs. Life Sci 56:2041-2048

Adams IB, Ryan W, Singer M, Thomas BF, Compton DR, Razdan RK, Martin BR, 1995. Evaluation of cannabinoid receptor binding and in vivo activities for anandamide analogs. J Pharmacol Exp Ther 273:1172-1181

Akins D, Awdeh MR, 1981. Marijuana and second-degree AV block. South Med J 74:371-373

Almadori G, Paludetti G, Cerullo M, Ottaviani F, D'Alatri L, 1990. Marijuana smoking as a possible cause of tongue carcinoma in young patients. J Laryngol Otol 104:896-899

Andreasson S, Allebeck P, Engstrom A, Rydberg U, 1987. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 2:1483-1486

Andreasson S, Allebeck P, Rydberg U, 1989. Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. Acta Psychiatr Scand 79:505-510

Baczynsky WO, Zimmerman AM, 1983. Effects of delta 9-tetrahydrocannabinol, cannabinol and cannabidiol on the immune system in mice. I. In vivo investigation of the primary and secondary immune response. Pharmacology 26:1-11

Barbers RG, Gong H, Jr., Tashkin DP, Oishi J, Wallace JM, 1987. Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. Am Rev Respir Dis 135:1271-1275

Bayewitch M, Rhee MH, Avidor Reiss T, Breuer A, Mechoulam R, Vogel Z, 1996. (-)-Delta9-tetrahydrocannabinol antagonizes the peripheral cannabinoid receptor-mediated inhibition of adenylyl cyclase. J Biol Chem 271:9902-9905

Beaubrun MH, Knight F, 1973. Psychiatric assessment of 30 chronic users of cannabis and 30 matched controls. Am J Psychiatry 130:309-311

Bhattacharya SK, 1986. delta-9-tetrahydrocannabinol (THC) increases brain prostaglandins in the rat. Psychopharmacology Berl 90:499-502

Bidaut Russell M, Devane WA, Howlett AC, 1990. Cannabinoid receptors and modulation of cyclic AMP accumulation in the rat brain. J Neurochem 55:21-26

Block RI, 1996. Does heavy marijuana use impair human cognition and brain function? [editorial; comment]. JAMA 275:560-561

Block RI, Farinpour R, Schlechte JA, 1991. Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. Drug Alcohol Depend 28:121-128

Block RI, Ghoneim MM, 1993. Effects of chronic marijuana use on human cognition. Psychopharmacology Berl 110:219-228

Bloodworth RC, 1985. Medical problems associated with marijuana abuse. Psychiatr Med 3:173-184

Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MD, 1987. Respiratory effects of non-tobacco cigarettes. Br Med J Clin Res Ed 295:1516-1518

Burstein S, Budrow J, Debatis M, Hunter SA, Subramanian A, 1994. Phospholipase participation in cannabinoid-induced release of free arachidonic acid. Biochem Pharmacol 48:1253-1264

Burstein SH, Young JK, Wright GE, 1995. Relationships between eicosanoids and cannabinoids. Are eicosanoids cannabimimetic agents? Biochem Pharmacol 50:1735-1742

Cabral GA, Mishkin EM, Marciano Cabral F, Coleman P, Harris L, Munson AE, 1986. Effect of delta 9-tetrahydrocannabinol on herpes simplex virus type 2 vaginal infection in the guinea pig. Proc Soc Exp Biol Med 182:181-186

Cabral GA, Toney DM, Fischer Stenger K, Harrison MP, Marciano Cabral F, 1995. Anandamide inhibits macrophage-mediated killing of tumor necrosis factor-sensitive cells. Life Sci 56:2065-2072

Campbell AM, Evans M, Thomson JL, Williams MJ, 1971. Cerebral atrophy in young cannabis smokers. Lancet 2:1219-1224

Caplan GA, Brigham BA, 1990. Marijuana smoking and carcinoma of the tongue. Is there an association? Cancer 66:1005-1006

Castaneda R, Sussman N, Westreich L, Levy R, O'Malley M, 1996. A review of the effects of moderate alcohol intake on the treatment of anxiety and mood disorders. J Clin Psychiatry 57:207-212

Co BT, Goodwin DW, Gado M, Mikhael M, Hill SY, 1977. Absence of cerebral atrophy in chronic cannabis users. Evaluation by computerized transaxial tomography. JAMA 237:1229-1230

Coffey RG, Yamamoto Y, Snella E, Pross S, 1996. Tetrahydrocannabinol inhibition of macrophage nitric oxide production. Biochem Pharmacol 52:743-751

Coggins WJ, Swenson EW, Dawson WW, Fernandez Salas A, Hernandez Bolanos J, Jiminez Antillon CF, Solano JR, Vinocour R, Faerron Valdez F, 1976. Health status of chronic heavy cannabis users. Ann N Y Acad Sci 282:148-161

Cohen SI, 1994. Cannabis consumption and schizophrenia [letter; comment]. Br J Psychiatry 165:410-411

Compton DR, Rice KC, de Costa BR, Razdan RK, Melvin LS, Johnson MR, Martin BR, 1993. Cannabinoid structure-activity relationships: correlation of receptor binding and in vivo activities. J Pharmacol Exp Ther 265:218-226

Cone EJ, Johnson RE, Moore JD, Roache JD, 1986. Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol Biochem Behav 24:1749-1754

Cottrell JC, Sohn SS, Vogel WH, 1973. Toxic effects of marihuana tar on mouse skin. Arch Environ Health 26:277-278

Culver CM, King FW, 1974. Neuropsychological assessment of undergraduate marihuana and LSD users. Arch Gen Psychiatry 31:707-711

Cushman P, Khurana R, 1976. Marijuana and T lymphocyte rosettes. Clin Pharmacol Ther 19:310-317

Daaka Y, Klein TW, Friedman H, 1995. Expression of cannabinoid receptor mRNA in murine and human leukocytes. Adv Exp Med Biol 373:91-96

Dahl RE, Scher MS, Williamson DE, Robles N, Day N, 1995. A longitudinal study of prenatal marijuana use. Effects on sleep and arousal at age 3 years. Arch Pediatr Adolesc Med 149:145-150

Darling MR, Arendorf TM, 1992. Review of the effects of cannabis smoking on oral health. Int Dent J 42:19-22

Darling MR, Arendorf TM, 1993. Effects of cannabis smoking on oral soft tissues. Community Dent Oral Epidemiol 21:78-81

Daul CB, Heath RG, 1975. The effect of chronic marihuana usage on the immunological status of rheusus monkeys. Life Sci 17:875-881

Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor P, Stoffer DS, Cornelius MD, Geva D, 1994. Effect of prenatal marujuana exposure on the cognitive development of offspring at age three. Neurotoxicol Teratol 16:169-175

De Freitas B, Schwartz G, 1979. Effects of caffeine in chronic psychiatric patients. Am J Psychiatry 136:1337-1338

Derocq JM, Segui M, Marchand J, Le Fur G, Casellas P, 1995. Cannabinoids enhance human B-cell growth at low nanomolar concentrations. FEBS Lett 369:177-182

Devane WA, Axelrod J, 1994. Enzymatic synthesis of anandamide, an endogenous ligand for the cannabinoid receptor, by brain membranes. Proc Natl Acad Sci U S A 91:6698-6701

Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC, 1988. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 34:605-613

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R, 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor [see comments]. Science 258:1946-1949

Diaz S, Specter S, Coffey RG, 1993. Suppression of lymphocyte adenosine 3':5'-cyclic monophosphate (cAMP) by delta-9-tetrahydrocannabinol. Int J Immunopharmacol 15:523-532

Djeu JY, 1992. Cytokines and anti-fungal immunity. Adv Exp Med Biol 319:217-223

Dolby TW, KLEINSMITH LJ, 1974. The effect of delta-9-THC on the in-vivo levels of cAMP in the mouse brain. Biochem Pharmacol 23:1817-1825

Donahoe RM, Nicholson JK, Madden JJ, Donahoe F, Shafer DA, Gordon D, Bokos P, Falek A, 1986. Coordinate and independent effects of heroin, cocaine, and alcohol abuse on T-cell E-rosette formation and antigenic marker expression. Clin Immunol Immunopathol 41:254-264

Donald PJ, 1986. Marijuana smoking--possible cause of head and neck carcinoma in young patients. Otolaryngol Head Neck Surg 94:517-521

Donald PJ, 1991. Advanced malignancy in the young marijuana smoker. Adv Exp Med Biol 288:33-46

Draht DB, Shorey JM, Price L, Huber GL, 1979. Metabolic and functional characteristics of alveolar macrophages recovered from rats exposed to marijuana. Infect Immun 25:268-272

Drake RE, Osher FC, Noordsy DL, Hurlbut SC, Teague GB, Beaudett MS, 1990. Diagnosis of alcohol use disorders in schizophrenia. Schizophr Bull 16:57-67

Drake RE, Osher FC, Wallach MA, 1989. Alcohol use and abuse in schizophrenia. A prospective community study. J Nerv Ment Dis 177:408-414

Ellis GM, Jr., Mann MA, Judson BA, Schramm NT, Tashchian A, 1985. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin Pharmacol Ther 38:572-578

Felder CC, Joyce KE, Briley EM, Mansouri J, Mackie K, Blond O, Lai Y, Ma AL, Mitchell RL, 1995. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol Pharmacol 48:443-450

Felder CC, Veluz JS, Williams HL, Briley EM, Matsuda LA, 1992. Cannabinoid agonists stimulate both receptor- and non-receptor mediated signal transduction pathways in cells transfected with an expressing cannabinoid receptor clones. Mol Pharmacol 42:838-845

Ferguson RP, Hasson J, Walker S, 1989. Metastatic lung cancer in a young marijuana smoker [letter]. JAMA 261:41-42

Fink M, Volavka J, Dornbush R, Crown P, 1973. Effects of cannabis on human EEG and heart rate--evidence of tolerance development on chronic use. pp. 703-4. In: Ban TA, et al , ed - Holland,

Fink M, Volavka J, Panayiotopoulos CP, Stefanis C, 1986. Quantitative EEG studies of marijuana, delta 9-tetrahydrocannabinol, and hashish in man. pp. 383-91. In: Braude MC, Szara S, ed

Fischer J, Taschner KL, 1991. [Flashback following use of cannabis--a review] Flashback nach Cannabiskonsum--eine Ubersicht. Fortschr Neurol Psychiatr 59:437-446

Fried PA, 1995. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings--it's easy to throw the baby out with the bath water. Life Sci 56:2159-2168

Fried PA, O'Connell CM, Watkinson B, 1992. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment [see comments]. J Dev Behav Pediatr 13:383-391

Fried PA, Watkinson B, 1990. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. J Dev Behav Pediatr 11:49-58

Fried PA, Watkinson B, Gray R, 1992. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. Neurotoxicol Teratol 14:299-311

Friedman H, Klein T, Specter S, Pross S, Newton C, Blanchard DK, Widen R, 1988. Drugs of abuse and virus susceptibility. Adv Biochem Psychopharmacol 44:125-137

Friedman H, Klein TW, Newton C, Daaka Y, 1995. Marijuana, receptors and immunomodulation. Adv Exp Med Biol 373:103-113

Galiegue S, Mary S, Marchand J, Dussossoy D, Carriere D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P, 1995. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem 232:54-61

Gallanter M, Wyatt RJ, Lemberger L, Weingartner H, Vaughan TB, Roth WT, 1972. Effects on humans of delta-9-tetrahydrocannabinol administered by smoking. Science 176:934

Gerard CM, Mollereau C, Vassart G, Parmentier M, 1991. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochem J 279:129-134

Gersten SP, 1980. Long-term adverse effects of brief marijuana usage. J Clin Psychiatry 41:60-61

Ghodse AH, 1986. Cannabis psychosis. Br J Addict 81:473-478

Gieringer DH, 1988. Marijuana, driving, and accident safety. J Psychoactive Drugs 20:93-101

Gil E, Chen B, Kleerup E, Webber M, Tashkin DP, 1995. Acute and chronic effects of marijuana smoking on pulmonary alveolar permeability. Life Sci 56:2193-2199

Gong H, Jr., Fligiel S, Tashkin DP, Barbers RG, 1987. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. Am Rev Respir Dis 136:142-149

Guarisco JL, Cheney ML, LeJeune FE, Jr., Reed HT, 1988. Isolated uvulitis secondary to marijuana use. Laryngoscope 98:1309-1312

Gupta S, Grieco MH, Cushman P, Jr. 1974. Impairment of rosette-forming T lymphocytes in chronic marihuana smokers. N Engl J Med 291:874-877

Halikas JA, Goodwin DW, Guze SB, 1972. Marihuana use and psychiatric illness. Arch Gen Psychiatry 27:162-165

Hannerz J, Hindmarsh T, 1983. Neurological and neuroradiological examination of chronic cannabis smokers. Ann Neurol 13:207-210

Hatch EE, Bracken MB, 1986. Effect of marijuana use in pregnancy on fetal growth. Am J Epidemiol 124:986-993

Hawks RL, 1982. The constituents of cannabis and the disposition and metabolism of cannabinoids. NIDA Res Monogr 42:125-137

Heath RG, Fitzjarrell AT, Fontana CJ, Garey RE, 1980. Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. Biol Psychiatry 15:657-690

Heller H, Dingemans P, Linszen D, 1992. Cannabis en schizophrenie. Tijdschrift Psychiatrie 34:699-708

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC, 1990. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 87:1932-1936

Hingson R, Alpert JJ, Day N, Dooling E, Kayne H, Morelock S, Oppenheimer E, Zuckerman B, 1982. Effects of maternal drinking and marijuana use on fetal growth and development. Pediatrics 70:539-546

Hollister LE, 1986. Health aspects of cannabis. Pharmacol Rev 38:1-20

Hollister LE, 1988. Cannabis--1988. Acta Psychiatr Scand Suppl 345:108-118

Howlett AC, 1995. Pharmacology of cannabinoid receptors. Annu Rev Pharmacol Toxicol 35:607-634

Huber GL, Simmons GA, McCarthy CR, 1975. Depressant effect of marijuana smoke on antibactericidal activity of pulmonary alveolar macrophages. Chest 68:769-773

Hunt CA, Jones RT, 1980. Tolerance and disposition of tetrahydrocannabinol in man. J Pharmacol Exp Ther 215:35-44

Imade AG, Ebie JC, 1991. A retrospective study of symptom patterns of cannabis-induced psychosis. Acta Psychiatr Scand 83:134-136

Johansson E, Agurell S, Hollister LE, Halldin MM, 1988. Prolonged apparent half-life of delta 1-tetrahydrocannabinol in plasma of chronic marijuana users. J Pharm Pharmacol 40:374-375

Johansson E, Halldin MM, Agurell S, Hollister LE, Gillespie HK, 1989. Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. Eur J Clin Pharmacol 37:273-277

Johnson BA, 1990. Psychopharmacological effects of cannabis. Br J Hosp Med 43:114-6,118-20,122

Johnson BA, Smith BL, Taylor P, 1988. Cannabis and schizophrenia [letter]. Lancet 1:592-593

Jones RT, Benowitz N, Bachman J, 1976. Clinical studies of cannabis tolerance and dependence. Ann N Y Acad Sci 282:221-239

Jones RT, Pertwee RG, 1972. A metabolic interaction in vivo between cannabidiol and delta-9-tetrahydrocannabinol. Br J Pharmacol 45:375-377

Juel Jensen BE, 1972. Cannabis and recurrent herpes simplex. Br Med J 4:296

Kaklamani E, Trichopoulos D, Koutselinis A, Drouga M, Karalis D, 1978. Hashish smoking and T-lymphocytes. Arch Toxicol 40:97-101

Kandel DB, Davies M, Karus D, Yamaguchi K, 1986. The consequences in young adulthood of adolescent drug involvement. An overview. Arch Gen Psychiatry 43:746-754

Keeler MH, Reifler CB, Liptzin MB, 1968. Spontaneous recurrence of marihuana effect. Am J Psychiatry 125:140-142

Keshaven MS, Lishman WA, 1986. Prolonged depersonalization following cannabis abuse [letter]. Br J Addict 81:140-142

Klein TW, Newton C, Friedman H, 1987. Inhibition of natural killer cell function by marijuana components. J Toxicol Environ Health 20:321-332

Klein TW, Newton C, Zhu W, Daaka Y, Friedman H, 1995. delta 9-Tetrahydrocannabinol, cytokines, and immunity to Legionella pneumophila. Proc Soc Exp Biol Med 209:205-212

Knudsen P, Vilmar T, 1984. Cannabis and neuroleptic agents in schizophrenia. Acta Psychiatr Scand 69:162-174

Kolodny RC, Masters WH, Kolodner RM, Toro G, 1974. Depression of plasma testosterone levels after chronic intensive marihuana use. N Engl J Med 290:872-874

Konings E, Dubois Arber F, Narring F, Michaud PA, 1995. Identifying adolescent drug users: results of a national survey on adolescent health in Switzerland. J Adolesc Health 16:240-247

Krantz JC, Berger HJ, Welch BL, 1971. Blockade of delta-9-THC depressant effect by cannabinol in mice. Am J Pharm 143:149-152

Kuipers SBM, Mensink C, de Zwart WM, 1993. National youth health care survey on smoking, drinking, drug use and gambling. (Abstract)

Landfield PW, Cadwallader LB, Vinsant S, 1988. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. Brain Res 443:47-62

Lau RJ, Tubergen DG, Barr M, Jr., Domino EF, Benowitz N, Jones RT, 1976. Phytohemagglutinin-induced lymphocyte transformation in humans receiving delta9-tetrahydrocannabinol. Science 192:805-807

Laviolette M, Belanger J, 1986. Role of prostaglandins in marihuana-induced bronchodilation. Respiration 49:10-15

Levy JA, Heppner GH, 1981. Alterations of immune reactivity by haloperidol and delta-9-tetrahydrocannabinol. J Immunopharmacol 3:93-109

Linn S, Schoenbaum SC, Monson RR, Rosner R, Stubblefield PC, Ryan KJ, 1983. The association of marijuana use with outcome of pregnancy. Am J Public Health 73:1161-1164

Madden JJ, Donahoe RM, Smith IE, Martinson DE, Moss Wells S, Klein L, Falek A, 1984. Increased rate of E-rosette formation by T lymphocytes of pregnant women who drink ethanol. Clin Immunol Immunopathol 33:67-79

Mann PEG, Cohen AB, Finley TN, Ladman AJ, 1971. Alveolar macrophages: structural and functional differences between nonsmokers and smokers of marijuana and tobacco. Lab Invest 25:111-120

Martinez Arevalo MJ, Calcedo Ordonez A, Varo Prieto JR, 1994. Cannabis consumption as a prognostic factor in schizophrenia [see comments]. Br J Psychiatry 164:679-681

Mathers DC, Ghodse AH, 1992. Cannabis and psychotic illness [see comments]. Br J Psychiatry 161:648-653

McDonough RJ, Madden JJ, Falek A, Shafer DA, Pline M, Gordon D, Bokos P, Kuehnle JC, Mendelson J, 1980. Alteration of T and null lymphocyte frequencies in the peripheral blood of human opiate addicts: in vivo evidence for opiate receptor sites on T lymphocytes. J Immunol 125:2539-2543

Mechoulam R, Ben Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR, et al, 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 50:83-90

Mechoulam R, Devane WA, Breuer A, Zahalka J, 1991. A random walk through a cannabis field. Pharmacol Biochem Behav 40:461-464

Mendelson JH, Mello NK, Ellingboe J, Skupny AS, Lex BW, Griffin M, 1986. Marihuana smoking suppresses luteinizing hormone in women. J Pharmacol Exp Ther 237:862-866

Mendhiratta SS, Wig NN, Varma VK, 1978. Some psychological correlates of long-term heavy cannabis users. Br J Psychiatry 132:482-486

Mikkelsen EJ, 1978. Caffeine and schizophrenia. J Clin Psychiatry 39:732-736

Morahan PS, Klykken PC, Smith SH, Harris LS, Munson AE, 1979. Effects of cannabinoids on host resistance to Listeria monocytogenes and herpes simplex virus. Infect Immun 23:670-674

Munro S, Thomas KL, Abu Shaar M, 1993. Molecular characterization of a peripheral receptor for cannabinoids [see comments]. Nature 365:61-65

Munson AE, Levy JA, Harris LS, Dewey WL, 1976. Effects of delta 9-tetrahydrocannabinol on the immune system. pp. 187-97. In: Braude MC, Szara S, ed

Musty RE, Kaback L, 1995. Relationships between motivation and depression in chronic marijuana users. Life Sci 56:2151-2158

Nahas GG, Desoize B, Armand JP, Hsu J, Morishima A, 1976. Natural cannabinoids: apparent depression of nucleic acids and protein synthesis in cultured human lymphocytes. pp. 177-86. In: Braude MC, Szara S, ed

Nahas GG, Osserman EF, 1991. Altered serum immunoglobulin concentration in chronic marijuana smokers. Adv Exp Med Biol 288:25-32

Nahas GG, Suciu Foca N, Armand JP, Morishima A, 1974. Inhibition of cellular mediated immunity in marihuana smokers. Science 183:419-420

Negrete JC, 1989. Cannabis and schizophrenia [editorial]. Br J Addict 84:349-351

Negrete JC, Knapp WP, Douglas DE, Smith WB, 1986. Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. Psychol Med 16:515-520

Newton CA, Klein TW, Friedman H, 1994. Secondary immunity to *Legionella pneumonia* and Th1 activity are suppressed by delta-9-tetrahydrocannabinol injection. Infect Immun 62:4015-4020

O'Connell CM, Fried PA, 1991. Prenatal exposure to cannabis: a preliminary report of postnatal consequences in school-age children. Neurotoxicol Teratol 13:631-639

Ossebaard HC, 1996. Netherlands' cannabis policy [letter]. Lancet 347:767-768

Page JB, Fletcher J, True WR, 1988. Psychosociocultural perspectives on chronic cannabis use: the Costa Rican follow-up. J Psychoactive Drugs 20:57-65

Patel V, Borysenko M, Kumar MS, Millard WJ, 1985. Effects of acute and subchronic delta 9-tetrahydrocannabinol administration on the plasma catecholamine, beta-endorphin, and corticosterone levels and splenic natural killer cell activity in rats. Proc Soc Exp Biol Med 180:400-404

Patrick G, Straumanis JJ, Struve FA, Nixon F, Fitz Gerald MJ, Manno JE, Soucair M, 1995. Auditory and visual P300 event related potentials are not altered in medically and psychiatrically normal chronic marihuana users. Life Sci 56:2135-2140

Perez Reyes M, Burstein SH, White WR, McDonald SA, Hicks RE, 1991. Antagonism of marihuana effects by indomethacin in humans. Life Sci 48:507-515

Petersen BH, Graham J, Lemberger L, 1976. Marihuana, tetrahydrocannabinol and T-cell function. Life Sci 19:395-400

Pillard RC, 1970. Marihuana. N Engl J Med 283:294-303

Pope HG, Jr., Gruber AJ, Yurgelun Todd D, 1995. The residual neuropsychological effects of cannabis: the current status of research. Drug Alcohol Depend 38:25-34

Pope HG, Jr., Yurgelun Todd D, 1996. The residual cognitive effects of heavy marijuana use in college students [see comments]. JAMA 275:521-527

Prakash R, Aronow WS, Warren M, Laverty W, Gottschalk LA, 1975. Effects of marihuana and placebo marihuana smoking on hemodynamics in coronary disease. Clin Pharmacol Ther 18:90-95

Rachelefsky GS, Opelz G, Mickey MR, Lessin P, Kiuchi M, Silverstein MJ, Stiehm ER, 1976. Intact humoral and cell-mediated immunity in chronic marijuana smoking. J Allergy Clin Immunol 58:483-490

Regier DA, Boyd JH, Burke JD, 1988. One month prevalence of mental disorders in the United States. Arch Gen Psychiatry 45:977-986

Richter B, Marangos N, Jeron A, Irscheid S, 1995. [3 different malignancies of the aerodigestive tract after chronic abuse of cannabis products] Dreiunterschiedliche Malignome des Aerodigestivtraktes nach chronischem Abusus von Cannabisproduken. HNO 43:728-731

Rickert WS, Robinson JC, Rogers B, 1982. A comparison of tar, carbon monoxide and pH levels in smoke from marihuana and tobacco cigarettes. Can J Public Health 73:386-391

Robbe HWJ, 1994. Cannabis and driving. Thesis Maastricht, The Netherlands

Rodin EA, Domino EF, Porzak JP, 1970. The marihuana-induced "social high". Neurological and electroencephalographic concomitants. JAMA 213:1300-1302

Scallet AC, Uemura E, Andrews A, Ali SF, McMillan DE, Paule MG, Brown RM, Slikker W, Jr. 1987. Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). Brain Res 436:193-198

Scheier LM, Botvin GJ, 1995. Effects of early adolescence drug use on cognitive efficacy in early-late adolescence: a developmental structure model. J subst abuse 7:379-404

Scheier LM, Botvin GJ, 1996. Cognitive effects of marijuana [letter]. JAMA 275:1547

Scher MS, Richardson GA, Coble PA, Day NL, Stoffer DS, 1988. The effects of prenatal alcohol and marijuana exposure: disturbances in neonatal sleep cycling and arousal. Pediatr Res 24:101-105

Scholtens J, 1905. Mededelingen over her gebruik van Ganja (*Cannabis indica*) in Suriname en over de krankzinnigheid, die er het gevolg van is (Cannabinismus). Psychiat Neurol Bladen Nederland 9:244

Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P, 1989. Short-term memory impairment in cannabis-dependent adolescents. Am J Dis Child 143:1214-1219

Schwartzfarb, Needle, Chavez-Chase, 1974. Effect of marihuana and THC on leukocyte migration. J Clin Pharmacol 14:35-41

Seth R, Sinha S, 1991. Chemistry and pharmacology of cannabis. Prog Drug Res 36:71-115

Sherman MP, Campbell LA, Gong H, Jr., Roth MD, Tashkin DP, 1991. Antimicrobial and respiratory burst characteristics of pulmonary alveolar macrophages recovered from smokers of marijuana alone, smokers of tobacco alone, smokers of marijuana and tobacco, and nonsmokers. Am Rev Respir Dis 144:1351-1356

Sherman MP, Roth MD, Gong H, Jr., Tashkin DP, 1991. Marijuana smoking, pulmonary function, and lung macrophage oxidant release. Pharmacol Biochem Behav 40:663-669

Shivers SC, Newton C, Friedman H, Klein TW, 1994. delta 9-Tetrahydrocannabinol (THC) modulates IL-1 bioactivity in human monocyte/macrophage cell lines. Life Sci 54:1281-1289

Slipetz DM, O'Neill GP, Favreau L, Dufresne C, Gallant M, Gareau Y, Guay D, Labelle M, Metters KM, 1995. Activation of the human peripheral cannabinoid receptor results in inhibition of adenylyl cyclase. Mol Pharmacol 48:352-361

Smith DE, 1968. Acute and chronic toxicity of marijuana. J Psychedelic Drugs 2:37-47

Smith DE, Moser C, Wesson DR, Apter M, Buxton ME, Davison JV, Orgel M, Buffum J, 1982. A clinical guide to the diagnosis and treatment of heroin-related sexual dysfunction. J Psychoactive Drugs 14:91-99

Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR, 1994. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. J Pharmacol Exp Ther 270:219-227

Smith SH, Harris LS, Uwaydah IM, Munson AE, 1978. Structure-activity relationships of natural and synthetic cannabinoids in suppression of humoral and cell-mediated immunity. J Pharmacol Exp Ther 207:165-170

Solowij N, Grenyer BF, Chesher G, Lewis J, 1995. Biopsychosocial changes associated with cessation of cannabis use: a single case study of acute and chronic cognitive effects, withdrawal and treatment. Life Sci 56:2127-2134

Solowij N, Michie PT, Fox AM, 1991. Effects of long-term cannabis use on selective attention: an event-related potential study. Pharmacol Biochem Behav 40:683-688

Solowij N, Michie PT, Fox AM, 1995. Differential impairments of selective attention due to frequency and duration of cannabis use. Biol Psychiatry 37:731-739

Soueif MI, 1975. Chronic cannabis users: Further analysis of objective test results. Bull Narc 27:1-26

Soyka M, 1994. [Addiction and schizophrenia. Nosological, clinical and therapeutic questions. 2. Substance dependence and schizophrenia] Sucht und Schizophrenie. Nosologische, klinische und therapeutische Fragestellungen. 2. Drogenabhangigkeit und Schizophrenie. Fortschr Neurol Psychiatr 62:186-196

Specter S, 1994. Drugs of abuse and infectious diseases. J Fla Med Assoc 81:485-487

Specter S, Diaz S, Liu C, 1995. Cannabinoid stimulation of arachidonate metabolism in human peripheral blood mononuclear leukocytes. Adv Exp Med Biol 373:97-101

Spitz MR, Fueger JJ, Goepfert H, Hong WK, Newell GR, 1988. Squamous cell carcinoma of the upper aerodigestive tract. A case comparison analysis. Cancer 61:203-208

Stevens H, Restak R, 1976. Neurological complications of drug abuse. Ann Clin Lab Sci 6:514-520

Streissguth AP, Bookstein FL, Sampson PD, Barr HM, 1989. Neurobehavioral effects of prenatal alcohol: Part III. PLS analyses of neuropsychologic tests. Neurotoxicol Teratol 11:493-507

Struve FA, Straumanis JJ, 1990. Electroencephalographic and evoked potential methods in human marihuana research: historical review and future trends. Drug Develop Res 20:369-388

Struve FA, Straumanis JJ, Patrick G, 1994. Persistent topographic quantitative EEG sequelae of chronic marihuana use: a replication study and initial discriminant function analysis. Clin Electroencephalogr 25:63-75

Struve FA, Straumanis JJ, Patrick G, Price L, 1989. Topographic mapping of quantitative EEG variables in chronic heavy marihuana users: empirical findings with psychiatric patients. Clin Electroencephalogr 20:6-23

Struve F, 1984. Clinical electroencephalography as an assessment method in psychiatric practice. In: Hall R, Beresford TP (eds.), Handbook of Psychiatric Diagnostic Procedures. N.Y. Spectrum, pp. 1-48

Sweden Bv, 1996. Does electrophysiological investigation in psychiatry still have future? Acta Neuropsychiatrica 8:43-44

Taschner KL, Stosberg K, Tossmann HP, Kleiner D, Wiesbeck G, 1994. [Sequelae of cannabis use--results of a survey of experts on traffic accidents and "echopsychoses" (flash-back)] Folgen des Cannabiskonsums--Ergebnisse einer Expertenbefragung zu Strassenverkehrsdelikten und "Echopsychosen" (Flash-Back). Versicherungsmedizin 46:11-13

Tashkin DP, 1993. Is frequent marijuana smoking harmful to health? [editorial; comment]. West J Med 158:635-637

Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, Spivey GH, Gong H, 1987. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis 135:209-216

Tassinari CA, Ambrosetto G, Peraita Adrados MR, Gastaut H, 1996. The neuropsychiatric syndrome of delta 9-tetrahydrocannabinol and cannabis intoxication in naive subjects: a clinical and polygraphic study during wakefulness and sleep. pp. 357-75. In: Braude MC, Szara S, ed

Taylor FM, 1988. Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population. South Med J 81:1213-1216

Tennant FS, Jr., Groesbeck CJ, 1972. Psychiatric effects of hashish. Arch Gen Psychiatry 27:133-136

Thomas H, 1993. Psychiatric symptoms in cannabis users [see comments]. Br J Psychiatry 163:141-149

Trisler K, Specter S, 1994. Delta-9-tetrahydrocannabinol treatment results in a suppression of interleukin-2-induced cellular activities in human and murine lymphocytes. Int J Immunopharmacol 16:593-603

Tunving K, 1985. Psychiatric effects of cannabis use. Acta Psychiatr Scand 72:209-217

Varma VK, Malhotra AK, Dang R, Das K, Nehra R, 1988. Cannabis and cognitive functions: a prospective study. Drug Alcohol Depend 21:147-152

Vescovi PP, Pedrazzoni M, Michelini M, Maninetti L, Bernardelli F, Passeri M, 1992. Chronic effects of marihuana smoking on luteinizing hormone, follicle-stimulating hormone and prolactin levels in human males. Drug Alcohol Depend 30:59-63

Wall ME, Perez Reyes M, 1981. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol 21:178S-189S

Watzl B, Scuderi P, Watson RR, 1991. Influence of marijuana components (THC and CBD) on human mononuclear cell cytokine secretion in vitro. Adv Exp Med Biol 288:63-70

Wehner FC, van Rensburg SJ, Thiel PG, 1980. Mutagenicity of marijuana and Transkei tobacco smoke condensates in the Salmonella/microsome assay. Mutat Res 77:135-142

Weil AT, 1970. Adverse reactions to marihuana. Classification and suggested treatment. N Engl J Med 282:997-1000

Weller RA, Halikas JA, 1985. Marijuana use and psychiatric illness: a follow-up study. Am J Psychiatry 142:848-850

Wert RC, Raulin ML, 1986. The chronic cerebral effects of cannabis use. II. Psychological findings and conclusions. Int J Addict 21:629-642

Wert RC, Raulin ML, 1986. The chronic cerebral effects of cannabis use. I. Methodological issues and neurological findings. Int J Addict 21:605-628

White SC, Brin SC, Janicki BW, 1975. Mitogen-induced blastogenic responses of lymphocytes from marihuana smokers. Science 188:71-72

Wieviorka S, 1995. [Medico-psychological aspects of cannabis consumption] Aspects medico-psychologiques de la consommation de cannabis. Rev Prat 45:1367-1370

Winterer G, Schmidt LG, Frick K, Ulrich G, 1994. ["Neuroadaptation" in long-term cannabis abuse. A clinical and electroencephalographic case study] "Neuroadaptation" bei langjahrigem Cannabiskonsum. Eine klinische und elektroenzephalographische Fallbeobachtung. Nervenarzt 65:635-637

Wu TC, Tashkin DP, Djahed B, Rose JE, 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 318:347-351

Yesavage JA, Leirer VO, Denary M, Hollister LE, 1985. Carry-over effect of marihuana intoxication on aircraft pilot performance: a preliminary report. Am J Psychiatry 142:1325-1329

Zheng ZM, Specter S, 1996. Delta-9-tetrahydrocannabinol suppresses tumor necrosis factor alpha maturation and secretion but not its transcription in mouse macrophages. Int J Immunopharmacol 18:53-68

Zheng ZM, Specter S, Friedman H, 1992. Inhibition by delta-9-tetrahydrocannabinol of tumor necrosis factor alpha production by mouse and human macrophages. Int J Immunopharmacol 14:1445-1452

Zhu W, Newton C, Daaka Y, Friedman H, Klein TW, 1994. delta 9-Tetrahydrocannabinol enhances the secretion of interleukin 1 from endotoxin-stimulated macrophages. J Pharmacol Exp Ther 270:1334-1339

Zimmerman AM, Titishov N, Mechoulam R, Zimmerman S, 1991. Effect of stereospecific cannabinoids on the immune system. Adv Exp Med Biol 288:71-80

Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson SM, Kayne H, Parker S, Vinci R, Aboagye K, Fried LE, et al, 1989. Effects of maternal marijuana and cocaine use on fetal growth [see comments]. N Engl J Med 320:762-768