A TOXICOLOGICAL SURVEY OF ACUTE PSYCHOSES IN CAPE COLOURED MALES WITH SPECIAL REFERENCE TO THE CANNABINOIDS.

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SUMMARY

Many South African psychiatrists, and particularly those working in psychiatric hospitals with Black and Coloured patients, have the firm clinical impression that in many of these patients acute psychotic illness is associated with the abuse of cannabis.

Most of the previous work in this field had been done by clinicians of Eastern countries where the use of cannabis has been endemic for thousands of years. However, those workers were handicapped because they lacked both the sophisticated techniques for standardized psychiatric evaluation and the availability of an assay to confirm cannabis use.

It was decided to investigate acute psychoses in Cape Coloured males admitted to Valkenberg Hospital with the following aims:

i. To identify a cohort of acutely psychotic patients who had recently been using cannabis and to compare them with a matched control group who were free of any drugs. The recently available EMIT^{R} immunochemical analytical technique was used for the detection of urinary cannabinoids. To exclude the contribution of other psychotropic agents to the aetiology of the psychoses, gas chromatography was performed to detect ethanol and thin-layer chromatography to screen for other psychotropic agents.

ii. To assess the comprehensive mental state of patients on admission and then again after a 7-10 day period the Present State Examination (PSE), a well validated and standardized diagnostic instrument, was used.

iii. To determine serum creatinine phosphokinase (CPK) and serum lactate dehydrogenase (LDH) levels (indicators of muscle damage) in view of the published reports of elevated levels in psychotic patients.

Patients were studied in three groups based on the urinary cannabinoid concentration on admission:

High cannabis group (n=20): these patients had initial levels greater than or equal to 60 µg Cross-Reacting Cannabinoids per gramme creatinine (µgCRC/g creatinine).

Low cannabis group (n=20): these patients had initial levels less than or equal to 59 µgCRC/g creatinine.

Psychotic control group (n=20): these were patients in whom urinary cannabinoids were absent on admission and who were matched as closely as possible with the high cannabis group with regard to clinical diagnosis, age, social class and number of previous admissions.

Our results showed that:

i. The only detectable toxins present were the cannabinoids which occurred in 60% of the randomly selected patients.

ii. The presence of urinary cannabinoids was an important factor in the nature and course of psychiatric illness. The psychosis described in this study was one in which a hypomanic component and a lack of the more typical schizophrenic symptoms were the outstanding features. Seven (35%) of the patients in the high cannabis group presented with a manic psychosis which was clinically indistinguishable from naturally occurring mania. Although the remainder of the patients in the high cannabis group were diagnosed on the PSE as paranoid schizophrenia, they differed from paranoid schizophrenic controls in having a

prominent affective colouring and lacking the typically schizophrenic features of auditory hallucinations, flattening of affect, and incoherence of speech.

The illness in the cannabis groups resolved rapidly (7–10 days) compared to the controls. Even when exactly matched with the control group for total amount of medication received, the cannabis groups still exhibited a more rapid remission rate, particularly with regard to the psychotic symptoms. In contrast, the symptomatology of the control group remained virtually unchanged after the 7–10 day period.

The CPK and LDH levels were significantly raised in the high cannabis group; this reflected the muscular overactivity which characterized the hypomanic behaviour in this group.

In essence, this study, preliminary as it was, succeeded in delineating a psychosis in which excessive quantities of cannabis appeared to play a major aetiological role. Suggestions for further research were discussed.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

1.1. INTRODUCTION

Names are legion for the plant material first classified in 1753 by Linnaeus as Cannabis sativa. Kif, ganga, hemp, boom, pot, weed, Mary Jane, grass, Durban Poison, and marijuana are only a few synonyms used for the herb most generally known in South Africa as 'dagga'. All of these terms have an ethnographic and geographic specificity and this study will use the term cannabis.

1.1.1. Geographic Migration of Cannabis

This herb originated south and east of the Caspian Sea in semi-desert regions and gradually it spread to the Himalayas and Central Asia. Six thousand years ago man used the plant for its fibre content rather than for its medicinal values. Schultes (1973) (quoted by du Toit, 1976) suggested that Neolithic man in China and China Turkestan used the plant for fibre. The earliest written record of this plant and its medicinal use was in a Chinese Pharmacopoeia of Emperor Shen Nuhng (2737 B.C.). Scythians cultivated the plant in the Volga regions some 3000 years ago (Schultes, 1973). At about the same time, the herb was used in Egypt and gradually it spread to Morocco and Spain in the 14th century (Rosenthal, 1971; as cited by du Toit, 1976). It was introduced to Chile by the Conquistadores for the production of fibre for cordage (du Toit, 1976). Part of the geographical spread of cannabis was due to its association with migrant Muslim communities; Arab traders were responsible for its spread down the east coast of Africa. In the southern part of Africa the herb was used in pre-Portuguese times - before A.D. 1500 (du Toit, 1976). It is thought that cannabis was introduced to modern European society by the return-

ing troops from Napoleon's Egyptian campaign in 1798 (Grinspoon, 1969; Mechoulam and Gaoni, 1967).

1.1.2. Use of Cannabis in Southern Africa

Cannabis was long used and accepted throughout sub-Saharan Africa by the Khoikhoi herders, San people and Bantu-speaking Nations by the time the Europeans settled at the Cape of Good Hope (du Toit, 1976). The first written record of the term 'dagga' in Southern Africa was by Jan van Riebeeck (the first Governor of the Dutch settlement at the Cape of Good Hope) in 1658. In his diary it is spelt as 'daccha'.

Early workers were confused by the various preparations (which may or may not have included cannabis) which were eaten or drunk, since Leonotus leonoris, in addition to Cannabis sativa, was also frequently smoked. References to 'Wild Hemp', 'Klip Dagga', and 'Red Dagga' do not always exclude cannabis, just as references to 'dagga' do not necessarily exclude Leonotus. The superficial similarity in appearance and apparent related effects of both plants led to this confusion (James, 1970; du Toit, 1976). Du Toit (1976) suggested that while many of the early writers used the term 'dagga', they might have been observing the use of Cannabis sativa along with other herbs and roots including Leonotus and Salsola.

Cannabis was used in African and Dutch folk medicine to treat snake bite, to facilitate child-birth, and as a remedy for malaria, black-water fever, blood poisoning, anthrax and dysentery. It was also used to treat asthma by all race groups (du Toit, 1976). Cannabis was described in the Extra Pharmacopoeia of the Pharmaceutical Society of

Great Britain, for the last time in 1967 as formerly being prescribed for "mania, and nervous disorders, as a cerebral sedative or narcotic, ... the relief of migraine and of headache due to hypertension" (Todd, 1967).

1.1.3. Smoking Paraphernalia

A variety of pipe forms and methods of smoking have been used: (du Toit, 1976).

i. Gourd Water Containers

A gourd was used to contain the water, and a hole was made in the neck over which the mouth of the smoker was placed. The pipe bowl was placed in another hole in the gourd (directly or attached by a connecting reed). The smoker inhaled through the aperture, thereby drawing the smoke through the water, thus cooling and condensing the smoke.

ii. Horn Water Containers

A hollow horn was used in place of a gourd. The horn was half-filled with water and the pipe stem entered at an angle; the smoke was inhaled through the open end of the horn. A short piece of the shin bone of a small animal was a more simple form of this type of pipe.

iii. Sandstone and Earthenware Water Containers

A hollow rectangular block or a simple hand-moulded container with two holes, one to hold the pipe bowl and the other for the insertion of a reed mouthpiece, was fashioned.

iv. Ground and Wet Sand Pipes

The pipe was made in the ground, either below the surface or built up on the ground surface. Campbell (1822) (quoted by du Toit, 1976) explained how the Batlapin (Botswana) "dug a hole in the ground the shape of a basin, in which they formed with their finger, a round passage, down one side, and up the other, in the shape of an inverted bow, this they arched over with clay, and filled their tobacco (or rather wild hemp) with a lighted cinder at one end, and putting their mouths close to the other they sucked out the smoke".

v. Modern Adaptations

Shaw (1938) quoted a case where a commercial brick had been hollowed out to form an earthenware container. A pickle jar and a coconut shell have also been used (Shaw, 1938). Two basic forms of smoking are used in modern urban conditions, a pipe with a clay bowl and a cigar form (du Toit, 1976). The pace of modern life and the fear of discovery have necessitated the dispensing with the paraphernalia of a leisurely smoke (du Toit, 1976). The tops of broken bottles (nekkies), cans, pumpkins and clay pots have all been used (Levin, 1974; du Toit, 1976). The home-rolled, crude cigarette (zol, skyf, reefer, joint) can be smoked on its own or through a reed or bamboo 'cigarette holder' (du Toit, 1976).

1.1.4. Early Scientific Research in Southern Africa

The earliest known treatise on cannabis in South Africa was read by Dr R.M. Armstrong, one-time district surgeon in Cradock, Cape Province, before the Chirurgical Society in Grahamstown, Cape Province on 31 July, 1855 (du Toit, 1976). Armstrong (quoted by du Toit, 1976) collected

samples of cannabis in the Cradock district, discussed the morphological features of the plant and questioned "... Hottentots and other Natives who were in the habit of using the dacca as to the effect it had on them ... the time of gathering the plant ... if they used both male and female plants". He found that "... there was a peculiar dullness about the eye, the conjunctiva was of a dirty yellow colour and the lassitude of the whole system was particularly observed in the muscles of the face ... when allowed to use their favourite herb (the dacca) that they changed their appearance altogether from being dull, stupid and morose they became lively, talkative and communicative ... that when they smoked the dacca, that it caused a pleasing excitement, and even in some instances an intoxicating effect". No discussion or other study followed Armstrong's account.

More than half a century passed before cannabis was given further detailed attention. C.J.G. Bourhill conducted the first full study of Cannabis sativa in southern Africa between 1908 - 1912, the results of which were submitted to the University of Edinburgh as a thesis for the degree of Doctor of Medicine in 1913 (du Toit, 1976). Bourhill observed 627 male inhabitants of the Pretoria Native Asylum and at a number of mining compounds. Part of Bourhill's thesis dealt with 'dagga insanity' and he claimed that 18% of all patients studied between 1908 - 1912 suffered from this malady. Quantitative material on physical criteria such as pulse, temperature and urine, general conclusions with respect to memory, hallucinations and illusions were presented (du Toit, 1976). The use of the label 'dagga insanity' by Bourhill is questionable since there was difficulty in the exclusion of alcohol as a factor and, according to Ames (1958), there was no good reason why many of the cases could not have been schizophrenics

who smoked cannabis since "his emphasis of auditory hallucinations is much more suggestive of schizophrenia than cannabis intoxication".

Nearly 25 years later as a result of a resolution passed at the Medical Congress held at Grahamstown in 1935, another serious investigation of 72 Black patients was undertaken by the medical staff of Pretoria Mental Asylum. Participation was voluntary. The patients were observed while smoking cannabis and the results recorded. These results are questionable as the authors themselves seem to be doubtful of the information gleaned and some of the effects observed may well have been due to the activation of the original psychosis.

1.1.5. Components of Cannabis

Cannabis is not a single uniform plant but is an 'unstable' species with hundreds of chemovariants arising due to inherent genetic plasticity, human manipulations, and environmental influences (Nahas, 1973). The latter, including climate, are not as important as hereditary factors in the determination of the cannabinoid content of the plant (Doornbos et al, 1971). Broadly speaking, two main plant-types occur: the fibre-type plant having a delta-9-tetrahydrocannabinol (Δ^9-THC) content of less than 0,2%; the drug-type plant having a Δ^9-THC content of 3,4 - 4,8% (Nahas, 1973).

At present it is estimated that there are 50 different compounds with potential pharmacological activity in cannabis (Hollister, 1974). These compounds are the cannabinoids, a term defined by Mechoulam and Gaoni (1967 a,b)"as the group of C21 compounds typical of and present in Cannabis Sativa, their carboxylic acids, analogs and transformation products". The cannabinoids are concentrated in the leaves and flower-

ing tops of the plant. It is the opinion of the scientific community that cannabis and its preparations can be evaluated on the Δ^9-THC content alone, since this is the recognised psychogenic compound (Mechoulam and Gaoni, 1965; Mechoulam and Gaoni, 1967(a); Isbell, 1967; Hollister et al, 1968).

1.1.6. Research on Cannabis in South Africa

It is estimated that in excess of 300 million people world-wide use this drug in one or more of its preparative forms. Internationally more than 7 000 scientific papers have been published on Cannabis sativa encompassing its vast chemistry, biochemistry and biosynthesis (Turner et al, 1980), and many more papers concern themselves with the sociological, psychological, pathological and psychiatric aspects of the drug's use and abuse. However, in view of the widespread use of cannabis in South Africa, relatively little has been published on this subject in this country (James, 1970; du Toit, 1976). In an early paper on the subject, Ames (1958) administered single doses of cannabis to human volunteers and noted the following features: thought disorder, delusions, temporal disorientation, disturbances of visual perceptions, visual psuedohallucinations, body image disturbances, depersonalization and euphoria. Logie, Morley and Bensusan (1972) surveyed the use of cannabis among university students in Johannesburg. Levin (1974) described psychiatric morbidity associated with cannabis use in South African national servicemen. A major comprehensive ethnographic study on cannabis use in Africa was done by du Toit (1976) and it is the definitive work on the subject.

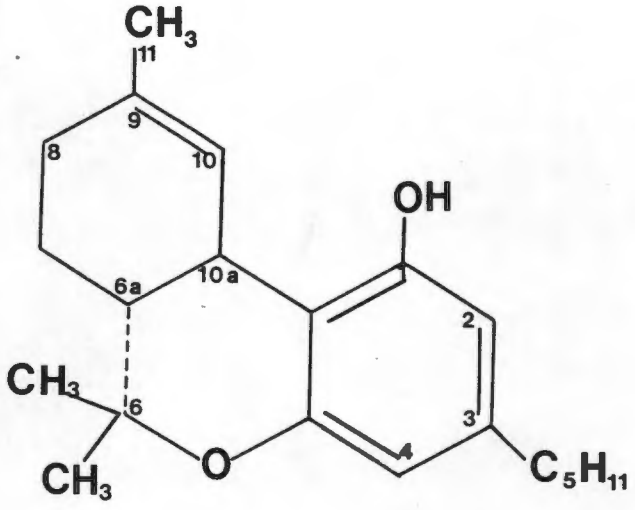
The reason for the dearth of published papers in South Africa could be that possession of cannabis carries a heavy punishment thereby making the task of obtaining spontaneous and reliable information extremely difficult. Unfortunately the feelings of Shapiro (1951) still apply 30 years later: "a careful study of the social effects and the psychological actions of dagga is long overdue".

1.2. NOMENCLATURE OF THE CANNABINOIDS

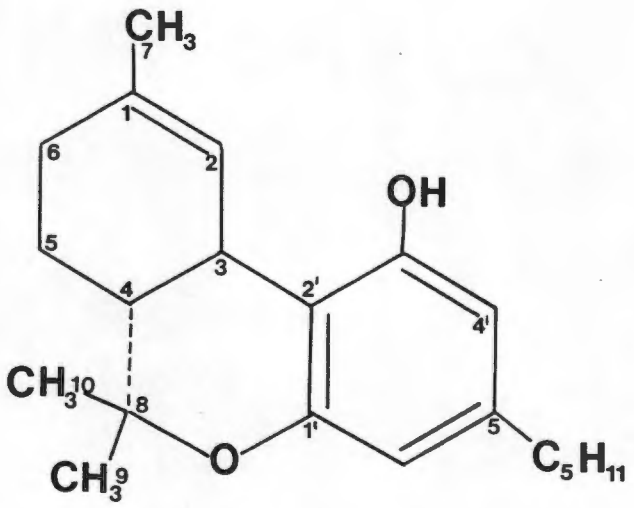
Currently two systems are used for the numbering of the cannabinoids. The one system uses the formal rules for the numbering of pyran-type compounds such as the cannabinoids. The disadvantages of this system are, that in passing from one compound to another in a series, a carbon atom frequently has its number changed and this system is not applicable to cannabinoids that are not pyrans. This system has been adopted by "Chemical Abstracts". The second numbering system, has a biogenetic basis where the cannabinoids are seen as substituted monoterpenoids. The advantages of this system are that in the majority of chemical transformations a carbon will usually retain its number, and all the cannabinoids, whether containing a pyran ring or not, can be numbered in this way. (See Figure 1.2.1)

1.3. STRUCTURE-ACTIVITY RELATIONSHIPS

The chemistry of the cannabinoids is complex and it has been estimated that at least 50 compounds have been isolated from various strains of Cannabis sativa which possess potential pharmacological activity. Structure-activity relationships have been extensively studied in animals, but the majority of findings remain to be validated in humans (Mechoulam and Edery, 1973).



Δ^9 - Tetrahydrocannabinol [Δ^9-THC]
Formal Numbering System



Δ^1 - Tetrahydrocannabinol [Δ^1-THC]
Monoterpenoid Numbering System

FIG. 1.2.1. Nomenclature of cannabinoids.

It was long suspected that Δ^9-THC was the major active component of cannabis (Adams, 1942; Leowe, 1946). Chemical studies over the last fifteen years have definitely established that the structure of Δ^9-THC is the laevo-isomer (Mechoulam and Gaoni, 1964; Mechoulam and Gaoni, 1965) and this is considered to be the principle psychoactive component of cannabis. Besides Δ^9-THC, the two most abundant cannabinoids in cannabis are cannabidiol (CBD) and cannabinol (CBN). According to Field and Arndt (1979) South African cannabis appears to rank among the more potent classes of Cannabis sativa in terms of the Δ^9-THC content, but the CBD content seems to be very low, even though the exact CBD content could not be accurately determined.

Mechoulam et al (1970) found that CBD, CBN, cannabichromene, cannabigerol, and cannabicyclol were inactive in monkeys and did not alter the response of these animals to concurrently given doses of Δ^9-THC. Hollister (1974) confirmed that both CBD and CBN lacked pharmacological activity in man. He compared the effects of Δ^9-THC and Δ^8-THC in man using oral doses and found that the spectrum of clinical effects was similar with both isomers, but Δ^8-THC was considered to be only 75% as potent as Δ^9-THC. The potency of the 11-hydroxy metabolites of Δ^9-THC and Δ^8-THC were also investigated using intravenous administration of these metabolites. Typical chemical effects were observed - pulse rate markedly increased, and reddened conjunctivae. It was concluded that the 11-hydroxy metabolites of Δ^9-THC and Δ^8-THC were approximately 20% more potent than their parent compounds and these metabolites had the same ratio of potency as the parent compounds i.e. 11-hydroxy-Δ^8-THC was 75% as potent as 11-hydroxy Δ^9-THC. On the other hand, Perez-Reyes (1972) found that Δ^9-THC and 11-hydroxy Δ^9-THC were equally potent and that the 11-hydroxy compound had a very rapid onset of action, a longer

duration of action and mimicked the action of Δ^9-THC.

8-α-Hydroxy-Δ^9-THC and 8-β-Hydroxy-Δ^9-THC have had very little pharmacological study in any animal species. Hollister (1974) found that placement of the hydroxyl group in the 8-position created an active metabolite, but one which was much less potent than when the hydroxyl group was in the 11-position. The 8-β-hydroxy metabolite of Δ^9-THC was judged to be $\frac{2}{3}$ as potent as the 8-α-hydroxy metabolite. Tetrahydrocannabivarin was found to be 25% as potent as Δ^9-THC.

Hollister maintains that the qualitative actions of THC will persist, though the potency may alter radically, so long as the fundamental structure of THC remains, irrespective of change of length of side chain, production of hydroxy metabolites at the 8- or 11-position and placement of double bonds.

Although the metabolism of Δ^9-THC produces a more potent 11-hydroxy metabolite, it is not settled whether the parent compound must be hydroxylated to this metabolite to possess its characteristic pharmacological activity or not. Present evidence favours Δ^9-THC as the active principle in mice and the 11-hydroxy-metabolite in man (King et al 1976).

The whole picture of structure-activity relationships remains incomplete and, to date, no compound has been found in cannabis which is qualitatively different from, or more active than, Δ^9-THC itself.

1.4. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION AND TOXICITY

The pharmacological activity of any drug is usually affected by the dose, the vehicle, and the route of administration. Cannabis is ingested in some countries but in Western cultures it is generally inhaled by smoking (Thomas and Chesher, 1973; King et al, 1976). Cannabis frequently contains Δ^9-tetrahydrocannabinolic acids, 6a,7,8,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-3-pentyl-6-H-benzo[c] chromene-2 carboxylic acid and 6a,7,8,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-3-pentyl-6-H-benzo[c]chromene-4-carboxylic acid, which readily decarboxylate to yield Δ^9-THC when exposed to light and/or on heating (Baker et al, 1981). This phenomenon contributes to the greater activity of cannabis products when they are smoked compared with ingestion (Mechoulam et al, 1970). However, Truitt (1971) and Jaffe (1980) estimated that no more than 50% of the Δ^9-THC content of a marijuana cigarette is usually absorbed after smoking with pyrolytic transformations and loss as side-stream accounting for the deficit of Δ^9-THC absorption (Thomas and Chesher, 1973; Ohlsson et al, 1980).

The physicochemical properties of the drug itself are also important: Δ^9-THC is highly lipophilic, having an octanol : water partition coefficient of 3 000 (Paton and Pertwee, 1971), which accounts for the rapid absorption, accumulation and persistence of the drug (Paton, 1975). Figure 1.4.1. illustrates the general physiological disposition of a drug (Adapted from Lemberger, 1976).

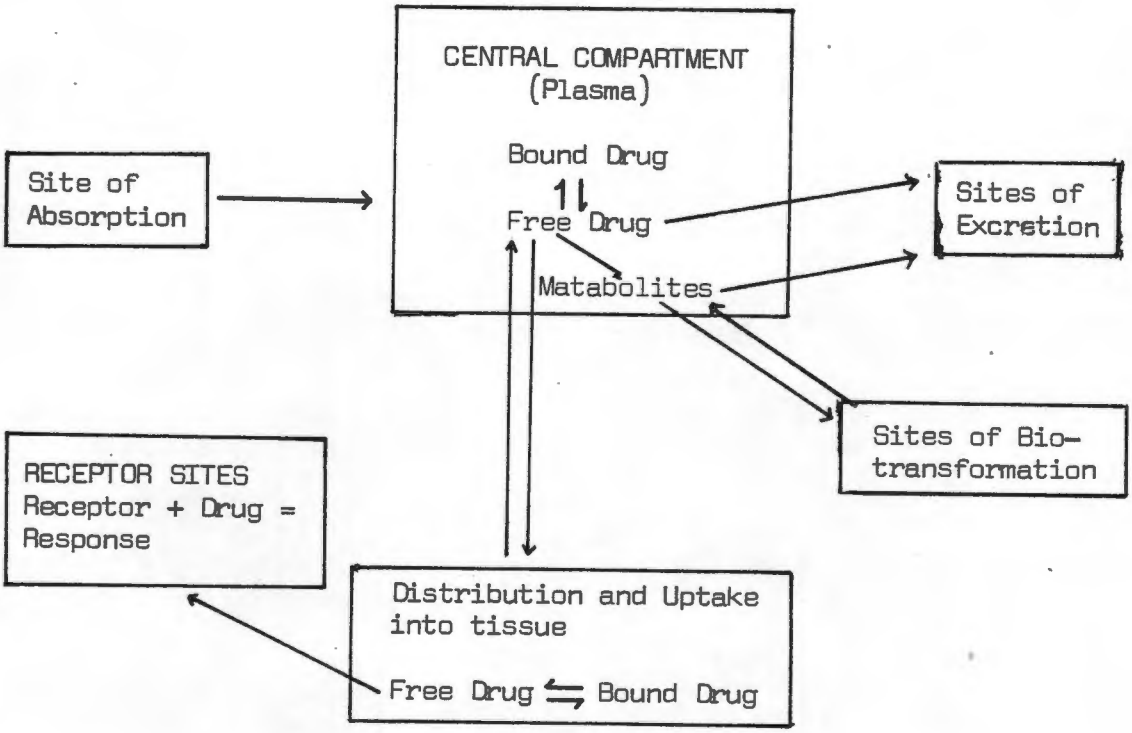


Figure 1.4.1 Schematic representation of the Physiological Disposition of Drugs

Therefore following intravenous administration, Δ^9-THC is rapidly taken up from the central compartment and redistributed to tissues where it is temporarily sequestrated, resulting in a rapid decline in the plasma levels of Δ^9-THC (Lemberger et al, 1973(b)). Lemberger (1973) and Ohlsson et al (1980) showed the plasma profiles of ^{14}C-Δ^9-THC after smoking and intravenous injection to be similar to each other, whereas plasma levels following oral ingestion were low and irregular.

The onset of effect of cannabis depends primarily on the route of administration: onset of effects were noticed within a few minutes of inhalation (Weil et al, 1968; Hollister, 1971; King et al, 1976; Jaffe, 1980) and within 30 to 60 minutes of ingestion (Thomas and Chesher, 1973; Jaffe, 1980). The rapid absorption of Δ^9-THC from

alveolar capillary surfaces following inhalation would account for the rapid onset of action; the delay in response to an ingested dose is explained by the slower absorption of the drug into the blood and tissue from the gastro-intestinal tract (Lamberger et al, 1972). It was noted that approximately three times as much cannabis was required orally to obtain the same pharmacological effects as that produced by inhalation (Claussen and Korte, 1976). Since it is rapidly absorbed, less Δ^9-THC or its active matabolite reached the brain when ingested than when smoked and the possible reasons for this are that Δ^9-THC might be converted to inactive compounds by gut flora, mucosal cells, and the liver (King et al, 1976).

Δ^9-THC is extensively bound to the lipoproteins of human plasma and further experiments suggest that albumin, α-lipoprotein and β-lipoprotein (to a minor degree) are involved in the protein binding of 11-hydroxy-Δ^9-THC (Whalqvist, 1970; Widmen et al, 1973). Acute animal experiments with injections of labelled drug have shown very high activity in the lung, liver, and kidney; moderate to high in the heart, salivary glands, gastric mucosa, bone marrow, Harderian cortex, spleen, placenta, adrenal cortex, follicular epithelium of the thyroid, pituitary, mammary gland, corpora lutea; low to moderate in the brain, epididymis, testes and foetus (Freudenthal et al, 1972; Kennedy and Waddel, 1972; Shannon and Fried, 1972; Ryrfeldtet al, 1973). Widman et al (1973) suggested that besides the lung, spleen and other fatty tissues, plasma proteins may also serve as a depot for Δ^9-THC and its hydroxylated metabolites. When allowance is made for the factor of blood flow, the distribution of the drug is generalised (Paton, 1975). Species variations make it difficult to extrapolate these results with any degree of confidence in man. There is no evidence of accumulation of Δ^9-THC or its metabolites in man (Hollister et al, 1972).

The presence of Δ^9-THC in the brain has generated considerable interest since this is the site of its most important pharmacological action. Δ^9-THC is metabolized chiefly in the liver (to a lesser degree in various other tissues) but not, however, in the brain (see below). Therefore 11-hydroxy-Δ^9-THC, the primary metabolite of Δ^9-THC, is formed outside the brain and transported there via the blood. Both Δ^9-THC and 11-hydroxy-Δ^9-THC rapidly penetrate the central nervous system as no effective blood-brain barrier exists. The reasons for the differences in brain penetration of Δ^9-THC and 11-hydroxy-Δ^9-THC are not known (Gill and Jones, 1972). Perez-Reyes et al (1976) found that 11-hydroxy-Δ^9-THC left the intravascular compartment of humans more rapidly than Δ^9-THC and penetrated the brain of mice four times faster. Ho et al (1970) showed that tissue concentrations in rat brains were constant over a period of 20 minutes to 8 hours following inhalation of tritiated-Δ^9-THC; a decline of less than 25% of the initial brain level was found seven days later. In mouse brain a ratio of 6:1 Δ^9-THC to 11-hydroxy-Δ^9-THC after intravenous dosing with Δ^9-THC was reported by Gill and Jones (1972) and a ratio nearer 2:1 by Christensen et al (1971) and Ryrfeldt et al (1973).

There are no data available regarding the presence of Δ^9-THC or any of its metabolites in the human brain; to extrapolate any data resulting from animal studies in this context is hazardous. Cannabinoid metabolism in man is complex and the marked species differences in metabolic patterns make the task of correlating <u>in vitro</u> and <u>in vivo</u> animal data with expectations in man even more difficult.

The liver is considered to be the main metabolic site for cannabinoids (Christensen et al, 1971; Caldwell and Sever, 1974; Wall, 1971; Wall, Brine and Perez-Reyes, 1976); other tissues such as the spleen, lung

and small intestine have been reported to be metabolically active (Widman et al, 1975; Paton, 1975; Greene and Saunders, 1972) and there is evidence that Δ^8- and Δ^9-THC may be partly metabolised at the site of its absorption (Lemberger et al, 1973). A microsomal drug-metabolising mixed-function oxygenase system involving cytochrome P450 is responsible for the matabolism of the cannabinoids to the hydroxylated metabolites. NADPH and molecular oxygen are required as cofactors in the pathway (Burstein and Kupfer, 1971).

Lemberger et al (1970) reported the presence of the 11-hydroxy metabolite in plasma as early as ten minutes after administration of Δ^9-THC but this rapid biotransformation does not lead to quick excretion (Caldwell and Sever, 1974). It was noted that chronic users of cannabis had a more rapid rate of metabolism than naïve subjects presumably because of enzyme induction by the cannabinoids (Lemberger et al, 1971 (a), (b)). Cannabidiol and cannabinol have a somewhat slower rate of metabolism (Hollister et al, 1972).

Drug metabolic processes, such as hydroxylation, almost invariably result in the metabolite being more polar, and hence more rapidly excreted, than the parent compound. This is typified by the primary transformation of Δ^9-THC, cannabidiol, and cannabinol into their 11-hydroxy derivatives (Agurell et al, 1976; Wall et al, 1972; Foltz et al, 1970; Burstein et al, 1970). Further hydroxylation to the 8,11-dihydroxy-Δ^9-THC and 8,11-dihydroxy-Δ^8-THC leads to reduced activity or inactivation (Wall, 1971).

Hydroxylation of the pentyl side chain at C'_1 and C'_2, further oxidation to acids, and conjugation, occur before elimination. The full pattern

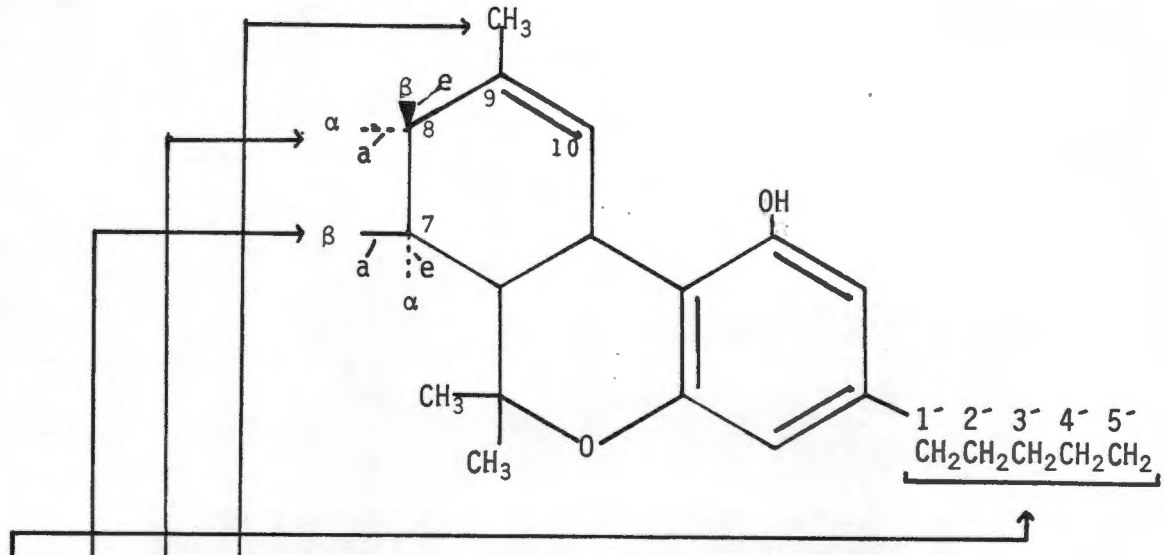
of conjugation is not yet clear (Burstein et al, 1972). However these compounds are highly polar and lack psychomimetic activity (Agurell et al, 1976). In man most of the urinary radioactivity is represented by the 11-carboxyl compound (Lemberger et al, 1973).

As has been shown, the metabolic profile of the cannabinoids is highly complex and can be represented as in Figure 1.4.2.

Studies on the excretion patterns of metabolites have relied mainly on the excretion of radioactivity from ^{14}C- and ^{3}H-labelled compounds. As may be expected of a lipophilic compound susceptible to metabolism, virtually no Δ^9-THC is excreted as such in the urine or the faeces (Lemberger et al, 1970; Hollister, 1974; Hollister et al, 1972; Caldwell and Sever, 1974; Lemberger, 1976), the major fraction of metabolites is excreted via the faeces (Agurell et al, 1969; Lemberger et al, 1974), with the majority of the urinary radioactivity represented by the 11-carboxyl compound (Lemberger et al, 1973). Excretion patterns of natural and synthetic cannabinoids other than Δ^9-THC are not known (King et al, 1976).

The elimination of Δ^9-THC in man is biphasic with an initial rapid disappearance from the plasma (in a few minutes), followed by a slow excretion over several days (Lemberger et al, 1971 (a); Hollister, 1971). Strong plasma lipoprotein binding (Wahlqvist et al 1970) and high affinity of Δ^9-THC for cellular components (Dingle et al, 1973) may account, in part, for the slow elimination.

The pharmacokinetics of ^{14}C-Δ^9-THC in man differ between regular users and naïve subjects. Major differences in the patterns of ex-



Hydroxylation at 11-position in vivo and in vitro or in combination with hydroxylation in other positions. Oxidation to a carboxyl compound frequently observed.

Hydroxylation at 8-position (only in the Δ^9-series) 8,11-dihydroxy metabolites frequently observed. 8α and 8β found only as minor metabolites.

Hydroxylation at 7-position (only in the Δ^8-series) 7,11-dihydroxy metabolites observed.

Dihydroxy metabolites 1',11; 2',11, etc. occasionally observed Hydroxylation at 1', 2', 3', 4'.

Figure 1.4.2. Hydroxylation sites of Cannabinoids observed in vivo and in vitro

a = axial; e = equatorial

(Adapted from Wall and Brine, 1976)

cretion radioactivity in the urine of chronic users of cannabis and naïve subjects were reported by Lemberger et al (1971 a,b). Although both groups of subjects excreted a given dose within the same time period, over a 7-day period the proportion of radioactivity excreted by the chronic group was larger than that of the naïve group. This evidence supported the claim that chronic users of cannabis had a more active metabolism than naïve subjects probably because of enzyme induction.

Lemberger et al (1971 a) reported the plasma half-life ($t_{\frac{1}{2}}$) of radioactivity in non-smokers of cannabis as double that of chronic smokers, with the values of $t_{\frac{1}{2}}$ = 56 hours for non-smokers and 27 hours for regular smokers. This discrepancy in the plasma half-lives was attributed to an increased rate of metabolism in chronic smokers rather than differences in tissue distribution (Lemberger et al, 1971 b). The $t_{\frac{1}{2}}$ in specific tissues such as brain is not known (Paton, 1973).

Cannabis is reported to be a safe drug (Leowe, 1946); animal experiments with various pure cannabinoid preparations support this claim. Thompson et al (1974) report an LD_{50} of oral Δ^9-THC one hundred times that of the intravenous route in Rhesus monkeys and Rosenkrantz, Fleischman and Grant (1981) report LD_{50} values for intravenous injection of cannabidiol and cannabichromene into Rhesus monkeys of 212mg/kg and 270mg/kg respectively at the 95% confidence level. However, acute toxicity does occur (Section 1.8.1.).

1.5. MECHANISM OF ACTION

The literature regarding the possible mechanism of action on the brain is controversial. To date, studies have concentrated on various animal species (Ho et al, 1976; Holtzman et al, 1969; Gallager et

al, 1972). Hollister (1974) found the clinical effects of Δ^9-THC in man were not primarily mediated through changes in the brain concentration of catecholamines. However, recent data are consistent with a picture of reduced sympathetic and enchanced parasympathetic activity (Benowitz and Jones, 1977). The work of Drew et al (1980) suggests that cannabis acts in the hippocampal region and produces behavioural changes similar to those resulting from lesions to that region. Effect on the concentration of any specific neurotransmitter has not been unequivocally demonstrated (Paton, 1975) and the mechanism of action in man remains obscure (Mechoulam and Corlini, 1978; Jaffe, 1980).

1.6. TOLERANCE AND DEPENDENCE

There is conflicting evidence in the literature with regard to the development of tolerance to, and dependence upon, cannabis. There is mounting evidence in favour of a development of tolerance and dependence. The mechanism of tolerance is complex and inadequately understood since there are a number of components of "tolerance" (see Figure 1.6.1., adapted from Thomas and Chesher, 1973).

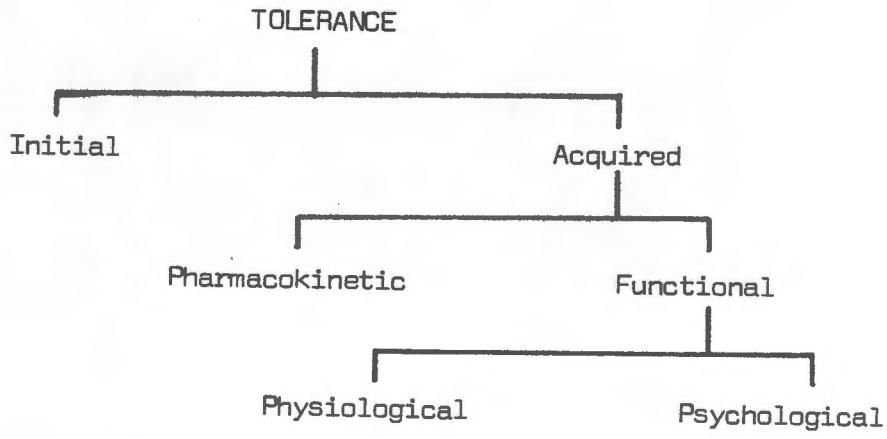


Figure 1.6.1. Components of Tolerance

Pharmacokinetic tolerance refers to alterations in absorption, distribution, metabolism, and excretion of a drug. Functional tolerance means that the target tissue becomes less sensitive to the same dose of the drug. Physiological tolerance implies that the target tissue undergoes changes to compensate for the drug. Psychological tolerance refers to the organism's ability to learn compensatory skills to offset the drug-effects on the target tissue. Tolerance to cannabis may be related to an adaption by the cells of the central nervous system (Lemberger and Rubin, 1978).

The development of tolerance to the different effects of the drug in animal species varies between species; daily administration of Δ^9-THC produces analgesia, hypothermia, and antithyroid effect in rats, ataxia and a general depression in dogs, and ptosis and docility in monkeys (Kaymakcalan and Deneau, 1972).

Cohen (1976) observed tolerance in relation to an increased heart rate, reduction of intraocular pressure and bronchial dilation. All these effects diminished significantly with continued use of the drug.

The issue of cannabis tolerance is further complicated by the development of "reverse tolerance", where an increased experience of the drug increases the sensitivity to its pharmacological effects. Weil et al (1968) showed that experienced habitual users required less cannabis than naïve subjects to produce the same effects. This phenomenon is in contrast to the usual tolerance where an increased experience of the drug leads to a decrease in sensitivity. Reverse tolerance is thought to be a consequence of enzyme induction leading to increased metabolism, in this case the increased rate of conversion of Δ^8- and

Δ^9-THC to their more potent 11-hydroxyl metabolites (see Section 1.4.) (Granville-Grossman, 1978; Lemberger and Rubin, 1978). Experienced users would have induced enzyme systems and would therefore need less drug to produce the desired effects as opposed to naïve subjects. Other suggestions for the development of reverse tolerance are that experienced users become adept in the techniques necessary to obtain the maximum absorption of the drug after its inhalation, and that they are more likely to perceive subtle drug-induced changes than naïve users (Hollister, 1971; Granville-Grossman, 1978; Lemberger and Rubin, 1978).

Jones et al (1976) reported that abrupt withdrawal of cannabis, following prolonged use of the drug, led to disturbances such as increased salivary flow, hand tremor, raised body temperature, hyperactivity, and raised intraocular pressure. Subjective complaints included impairment of appetite, loss of weight, sweating, chills, irritability, restlessness, sleep disturbances and occasional nausea and muscle spasms. These withdrawal symptoms essentially agreed with the earlier observations of Chopra and Jandu (1973). Bensusan (1971) reported intense abdominal cramps in young South African adults who were temporarily deprived of cannabis and he alleges that a definite withdrawal syndrome occurs following regular cannabis abuse. Chopra and Jandu (1976) and Bensusan (1971) emphasize that a large percentage of heavy cannabis users developed dependence on cannabis. However, based on studies in Western countries, Thomas and Chesher (1973) suggested that cannabis did not cause a true addiction but that a psychological dependence may develop in a very mild form. In contrast Granville-Grossman (1978) makes it clear that cannabis users take the drug for its pleasant effects; they show

neither drug-seeking behaviour nor craving for the drug on withdrawal and thus there is no psychological dependence.

1.7. PSYCHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF CANNABIS

Widespread use of cannabis in Western countries prompted a great deal of research into the psychological and physiological effects of cannabis use (Ames, 1958; Weil et al, 1968; Tart, 1970; Campbell et al, 1971; Negrete, 1973; Hollister, 1974; Tylden, 1974; Campbell, 1976; Chopra and Jandu, 1976; Cohen, 1976; Mellinger et al, 1976; Mendelson et al, 1978).

The effect of cannabis varies from individual to individual and there is considerable variation in the potency and effects of the drug. The expectations and personality of the user, dose of the drug, and the setting in which the drug experience takes place all have a strong influence on the subjective feelings and the objective signs observed following cannabis smoking (Negrete, 1973; Granville-Grossman, 1978). Effects due to cannabis are highly dose-dependent and at fairly high doses the agent has been thought to induce a psychotic illness presenting with hallucinations, delusional ideas, disorganised thought processes, depersonalization, alterations of time sense, and panic. This is dealt with in detail in Section 1.8.

1.7.1. Psychological Effects

Ames et al (1979) conducted an important study with baboons after administration of varying oral doses of cannabis. Neuropathological examination revealed no significant abnormalities. However, the animals showed behavioural changes (possibly indicative of cannabis encephalopathy). A striking feature was that all the animals became increasingly apathetic and none more aggressive; these changes were dose-related. Tart (1970), on the basis of his knowledge of the effects of cannabis, designed and distributed a questionnaire among college students (mainly Californians) with the instruction that it should be answered only by experienced users of cannabis. Experienced users were considered to be those individuals who had used the drug

on a minimum of twelve occasions. The questionnaire contained 206 items related to the alleged effects of the drug and 14 items not related to known effects. This was intended to test the truthfulness of the respondents The study provides a fairly comprehensive listing of the characteristic subjective effects of the drug which were defined as those rated by more than 50% of the respondents as "very often" or "usual". These are presented in a modified form (Table 1.7.1.1.) and include effects on the mood, memory, motor co-ordination, cognitive ability, sensorium, time sense and self perception.

The findings of Hollister (1971) concur with those of Tart (1970) in that pronounced euphoria, an altered time sense, sleepiness, difficulty in concentration and thinking and dream-like states were observed in subjects. It was also observed that vision was sharper (accompanied by distortions) and hearing was more discriminating. Jaffe (1980) reported enhanced visual imagery and a keener sense of hearing and Tylden (1974) alteration in mood and motivation in subjects, distortion of sight and sound, and euphoria. Both Hollister (1971) and Tylden (1974) described depersonalization as an effect of cannabis administration and prolonged depersonalization occurring months after cannabis use has been described by Szymenski (1981).

The effects of cannabis administration on various aspects of psychological performances were observed as early as the 1930's (Bromberg, 1934) and more systematic research has verified the earlier clinical descriptions. A wide range of impairment of intellectual performance has been found, including the following tasks: digit symbol substitution (Weil et al, 1968) choice reaction time (Clark and Nakashima, 1968), digits backwards and

Table 1.7.1.1. Characteristic Subjective Effects of Cannabis
(Adapted from Tart, 1970)

VISUAL EFFECTS
- Clarity of visual imagery
- Visual perceptions take on newer meanings

AUDITORY EFFECTS
- Quality of sound changes
- Notes of music are purer and more distinct

TACTILE EFFECTS
- Sense of touch is more sensual and exciting
- Touch sensations take on newer qualities

GUSTATORY EFFECTS
- Food is more enjoyable
- Newer qualities of taste sensations

OLFACTORY EFFECTS
- New qualities of smell sensations

SPACE-TIME PERCEPTION
- Changed experience of distance travelled
- Altered time sense

PERCEPTION OF BODY
- Greater awareness of individual body organs

PHYSICAL MOVEMENTS
- Enhanced feeling of relaxation
- Physical movements seem exceptionally well co-ordinated and smooth

INTERPERSONAL RELATIONS
- Enhanced awareness of others
- Less noisy and boisterous

SEXUAL EFFECTS
- Orgasm has new pleasurable qualities

THOUGHT PROCESSES
- Greater awareness of subtle humour
- Present time seems all important
- Difficulty in reading
- Greater acceptance of contradictions of views and ideas
- Short-term memory adversely affected

EMOTIONS
- More strongly felt
- Feel more child-like
- Euphoria is experienced

SELF CONTROL
- Greater acceptance of situations
- Can return to normal psychological state at will
- Difficulty in pursuing tasks

EFFECTS ON SLEEP
- Easier to go to sleep

forwards and serial subtractions (Melges et al, 1971; Manna et al, 1970). Other tasks such as concept formation (Klanoff et al, 1973) and reading comprehension (Clark et al, 1970) were also impaired.

Cannabis flashbacks - spontaneous recurrences of feelings and perceptions similar to those produced by the drug itself - have been reported. The occurrences may range from the vivid recreation of a drug-related experience to a mild evocation of a previous incident. The origin of such experiences is uncertain and those who have had them require little or no treatment (Stanton et al, 1976).

1.7.2. Effects of Cannabis in combination with Alcohol and other Drugs

Cannabis has been used in combination with alcohol and other drugs and the combined effects of these drugs have potentially important implications. The range of drug combinations is extremely wide but the commonest one is alcohol plus cannabis.

Animal studies of the behavioural effects of the alcohol-cannabis combination have generally found that the combined effect is greater than that of either when taken singly (Siemans et al, 1974; Pryor et al, 1977) the limited human research to date is generally consistent with the results of animal research. Experiments using alcohol levels within the range commonly found after social drinking showed that performance reductions from combined use with cannabis are greater than those from the use of either alone. Such decrements have been detected in reasoning, manual dexterity, and standing steadiness (Chesher et al, 1976; Chesher et al, 1977). Combined use increased reaction time and reduced cognitive performance and psychomotor

co-ordination more than either alone (Belgrave et al, 1979).

In a study of seven healthy male volunteers aged 20 - 29, Sulkovski and Vachon (1977) found that four of the seven developed intense nausea and vomiting after drinking a moderate amount of alcohol. All four men were markedly incapacitated during the height of the adverse effects, recovering in 3 - 4 hours. The fact that not all seven subjects tested were equally affected illustrates the large individual differences in responses. No adverse effects occurred when the experiment was repeated with half the initial dose.

Hemphill and Fisher (1980) found that of 604 White and Coloured male offenders in the Cape referred for inpatient psychiatric observation, 52% habitually indulged excessively in alcohol, drugs (mostly cannabis) or both. There was no evidence of a potentiating action between alcohol and cannabis towards violent behaviour. If anything, cannabis appeared to attenuate the action of alcohol and possibly to inhibit violent impulses in aggressive and psychopathic individuals.

Animal research has raised the question of a possible cross-tolerance between alcohol and cannabis (Siemans et al, 1979) but this has not yet been resolved in humans.

There have been few human studies of the interactive effects of cannabis with drugs other than alcohol. However, limited evidence suggest that such interactions may be significant. Benowitz and Jones (1977 (a)) showed that chronic cannabis use may affect the persistence of barbiturates in the body as well as their rate of absorption. The possibility that absorption, distribution and

metabolism of therapeutic drugs might be modified by concomitant cannabis use has been raised. Much work remains to be done in this area.

1.7.3. The Amotivational Syndrome

The term "amotivational syndrome" is used to describe the progressive changes in what are accepted as conventional levels of motivation (Thomas and Chesher, 1973). This syndrome was defined by the Canadian Commission of Inquiry on the Non-Medical Use of Hemp (quoted by Granville-Grossman, 1978) as "a set of symptoms including apathy, ineffectiveness and non-productiveness considered to reflect a deficit in general motivation ... resulting from the chronic use of certain drugs".

Thomas and Chesher (1973) in their review report that the syndrome manifests as a marked decline in personal hygiene, social interaction and sexual drive. In its extreme form the individual becomes very passive, his only interest being related to the acquisition and use of cannabis. There is also intellectual deterioration as manifested by shortened attention span, impaired ability to plan and organize normal activities of life, low frustration tolerance, and the use of magical or primitive modes of thought.

A study claiming to support the concept of an amotivational syndrome due to cannabis was that of Chopra and Jandu (1976) who observed 275 chronic users of cannabis in India. They noted that subjects were depressed, quiet, apathetic, and lacked interest in their surroundings, work and families. However, because the subjects were in poor physical health and malnourished, their apparent intellectual

deterioration could not be ascribed primarily to cannabis.

Mellinger et al (1976) studied 960 freshmen of the University of California at Berkeley over a $2\frac{1}{2}$ year period and noted that approximately 59% used cannabis. Of the cannabis users, 6% did not complete their courses of study compared to only 3% of the abstainers. On further analysis of the data, it emerged that failure to complete the course of study was dependent on social factors other than cannabis use. The concept of a cannabis-induced amotivational syndrome was thus considered to be invalid.

Campbell (1976), in a study of 1000 Canadian university students, reported that the higher the intake of cannabis the greater the tendency to poor examination scores although he recognized the contribution of socio-cultural factors.

Levin (1973) believes cannabis use to be implicated in a number of psychiatric conditions. Levin (1974) studied 444 white South African National Servicemen. A significant correlation between cannabis use and amotivation was found and cannabis use was therefore found to be a prominent factor in an amotivational syndrome.

Opinions therefore differ as to whether the relationship between chronic cannabis use and an amotivational syndrome is a casual or an associative one and more emphasis on social factors and psychological background is required when evaluating such a syndrome in Western countries. Much of the previous work relates to countries such as India and Jamaica where cannabis use is endemic (Thomas and Chesher, 1973; Thacore, 1973; Beaubrun and Knight, 1973; Knight, 1976).

1.7.4. Physiological Effects

Acute physiological effects of cannabis use has generated extensive investigation, particularly in the past 15 years (Weil et al, 1968; Cohen, 1976; Jaffe, 1980; Ohlsson et al, 1980).

The most consistently reported cardiovascular effects following cannabis use are a moderate increase in heart rate, an increase in systolic pressure, and a reddening of the conjunctivae (Weil et al, 1968; Jaffe, 1980; Ohlsson et al, 1980). The increase in heart rate is dose-dependent both in onset and duration of action and an increase of 20-50 beats per minute is not uncommon, tachycardias of 140 beats per minute having been reported (Jaffe, 1980).

Weil et al (1968) found no change in the respiratory rate in naïve users of cannabis but a significant increase in the respiratory rate of chronic users. This increase in respiratory rate was accompanied initially by a mild bronchial airways obstruction and later by dilation of the bronchi. The acute response to Δ^9-THC administration by oral, intravenous, or aerosol routes was relatively long-lasting with significant bronchodilation (Jaffe, 1980).

Cohen (1976), Crawford and Merrit (1979) and Merrit et al (1981) reported a lowering of intraocular pressure with no alteration of pupil size following the use of cannabis, which may therefore be useful in the treatment of glaucoma.

Blood sugar levels were not altered following the use of cannabis and therefore the hunger produced by the drug must be mediated by mechanisms other than those involving hypoglycaemia (Weil et al, 1968).

The possibility of damage to physical health by the long term use of cannabis has become a matter for serious concern and investigation in recent years but the findings to date tend to be equivocal.

Campbell et al (1971) did air encephalography on chronic users of cannabis who showed personality changes; they demonstrated a particular pattern of cerebral atrophy. Stefanis et al (1976) however, found no evidence of cerebral atrophy in 47 long-term cannabis users in Greece; and Co et al (1977), using computerized axial tomography, also failed to demonstrate cerebral atrophy among their chronic users of cannabis. DiBenedetto et al (1977) could not demonstrate deterioration of peripheral nerve function in heavy and casual users of cannabis.

Kolodney et al (1974) found depression of plasma testosterone levels in proportion to the degree of cannabis use. On withdrawal of the drug, or when cannabis use continued with the concomitant administration of human chorionic gonadotrophin, plasma testosterone levels were elevated above normal. Cohen (1976) showed that the smoking of cannabis caused a significant depression of plasma testosterone levels within 2 - 3 hours of administration, with chronic intoxication persistently associated with lowered plasma testosterone levels. However, Mendelson et al (1978) in a study of 24 males before, during and after a 21-day period of cannabis use, noted that plasma testosterone levels were unchanged and that chronic users had higher levels than casual users. The question of plasma testosterone elevation and depression in cannabis users thus remains unsettled.

Δ^9-THC has been investigated as an analgesic in humans. Noyes et al (1975) reported good analgesic activity in patients with chronic pain of metastatic carcinoma. Raft et al (1977) reported Δ^9-THC as a poor analgesic for surgical pain and pain induced by pressure and shock in experimental conditions. However cannabinoids are being investigated in the hope that one of them will prove to be an effective analgesic with a lower dependence liability than the narcotic analgesics in humans (Harris, 1979).

Sallan et al (1980) and The Lancet (Editorial, 1981) reported the use of Δ^9-THC as an antiemetic in patients receiving chemotherapy for cancer. However, there is some evidence to suggest that oral Δ^9-THC is not the ideal drug to prevent the emetic side-effects of cytotoxic chemotherapy (Colls, 1981). It has been claimed that cannabis has anti-convulsent and anti-pyretic actions and that it may be used in the treatment of wide-angle glaucoma (The Lancet, (Editorial), 1975; Pradhan, 1977; Newell et al, 1979) and cannabidiol has been used to treat epilepsy (Cunha et al, 1980).

Abel (1980) summarized the possible teratogenic effects of cannabis in various animal species and he concluded that the cannabinoids did not produce gross malformations except at relatively high doses. The oral route of administration produced the least and the intraperitoneal route the most teratogenic effects. Direct teratological potential of the cannabinoids remains equivocal. To date there is no available data on the possible teratogenic effects of cannabis in humans and further investigation is indicated.

1.8. CANNABIS PSYCHOSIS

Cannabis is usually smoked by subjects for its hedonistic qualities and the degree of intoxication achieved and the range of experiences is highly variable (see Section 1.8.). However, as varied as the pleasurable effects, so too are the adverse reactions, which are generally threatening and extremely unpleasant (Talbott and Teague, 1969). There is much controversy surrounding the cause and nature of these undesired psychological effects and Negrete (1973) has proposed a classification of possible psychological effects of cannabis. This scheme (modified slightly) is presented below and has been adopted as a working classification.

1.8.1. severe intoxication

1.8.2. pathological intoxication

1.8.3. acute cannabis psychosis

1.8.4. sub-acute and chronic cannabis psychosis

1.8.1. Severe Intoxication

The ratio of the lethal dose to the effective dose of cannabis is high. However, in larger than customary doses, or among those with a particular sensitivity to the drug, following administration of the drug, paranoid ideas may be expressed, dizziness, depression, fatigue and visual impairment may be experienced. Objective effects may include loss of control of behaviour, clouding of consciousness and disturbance of memory. Physical disturbances such as headaches, gastro-intestinal distress, soreness and dryness of the tongue, cough and a bad taste in the mouth may also be experienced.

On the administration of much larger amounts of cannabis, or with accidental overdosage, more serious disturbances are noted. Garret,

Braithwaite and Teale (1977) reported a case of a young man who was found collapsed and unresponsive; features of decorticate rigidity were noted with brisk deep reflexes and equivocal plantar responses. Twelve hours after hospitalization the patient began to improve and over the next two days he seemed to be hallucinating and his speech was incoherent. After 4 days he recovered completely. Analysis by radioimmunoassay of a sample of the patient's blood showed cannabinoid levels of 180µg/ℓ cannabinoids.

Intravenous administration of crude cannabis extracts resulting in an acute illness with multi-system involvement, including gastro-intestinal, cardiovascular, haematologic and pulmonary manifestations have been reported. All observed abnormalities reversed within a few days of onset with no significant sequelae (Hendersen et al, 1968; King and Cowen, 1969; Gary and Kelong, 1970; King and Petchet, 1970; Lundberg, Andersen and Prosnitz, 1971; Payne and Brand, 1975; Farber and Huertas, 1976; Vaziri et al, 1981).

1.8.2. Pathological Intoxication

Occasionally the common psychological experiences of the drug may be replaced by unpleasant feelings of anxiety, fear (especially of becoming insane) and a sense of helplessness. Occasionally acute depression, severe depersonalization and derealization are associated with these unpleasant feelings. The individual usually has a good recollection of the events and the symptoms experienced. Because of their benign course, the majority of these reactions subside spontaneously and are not brought to the medical practitioner's attention.

1.8.3. Acute Cannabis Psychosis

Reports of acute psychoses have appeared in the literature. These occurred among chronic users of cannabis (who had no previous history of psychiatric illness) usually after a period during which the drug was taken in larger than customary doses (Dhunjibhoy, 1930; Bromberg, 1934; Davison and Wilson, 1972; Thacore, 1973; Chopra and Smith, 1974; Thacore and Shukla, 1976; Talbott and Teague, 1969).

This category includes all those psychotic and hallucinatory experiences which follow a cannabis experience. This type of psychosis is less common in developed Western countries and this diagnostic category has evoked considerable scepticism and controversy. The clinical picture is pleomorphic but generally full recovery is the rule after a period of a few days to a few weeks.

Thacore (1973) noted the schizophrenia-like nature of the illness in four Indian cases where the prominent symptoms included paranoid ideation, anxiety, apprehension, suspiciousness, and auditory hallucinations: all these features cleared within a few days. There was no disturbance of memory, disorientation, nor clouding of consciousness. In a separate study Thacore and Shukla (1976) compared 25 consecutive cases of schizophrenia-like psychosis attributed to cannabis with 25 consecutive patients with paranoid schizophrenia. Those patients with cannabis psychosis differed from the cases of schizophrenia in terms of behavioural manifestations; they demonstrated bizarre and violent behaviour and possessed some insight into the nature of their illness. Patients with cannabis psychosis shared rapid ideation and flight of ideas, whereas the characteristic thought disorder was found mostly in schizophrenic patients.

Chopra and Smith (1974), in contrast to the case descriptions of Thacore (1973) Thacore & Shukla (1976) where there was no evidence of obvious organic mental disturbance, cited 200 cases of acute psychotic reactions among Indians with the following organic symptoms present: sudden onset of confusion, emotional lability, depersonalization, delusions, visual hallucinations, temporary amnesia, disorientation, and delirium. Recovery was extremely rapid in those patients without a previous history of psychiatric disturbance , but recovery of patients with a history of personality disturbance was less certain.

Talbott and Teague (1969) observed a clinical syndrome of acute psychosis associated with cannabis derivatives in 12 American soldiers in Vietnam. The syndrome was characterised by organic and paranoid features. These cases differed from those described by Thacore (1973), Thacore and Shukla (1976) and Chopra and Smith (1974) in that in all the American patients the symptoms resulted from a first exposure to the drug. Talbott and Teague (1969) were convinced that cannabis was directly and essentially involved in the development of the syndrome although they recognized that extraneous factors, such as environmental stress, might have affected the symptoms.

The case of a young white Englishman, reported by Davison and Wilson (1972), demonstrated that cannabis caused the patient's mental disturbance. The improvement in his condition was rapid in hospital but relapses occurred on a number of occasions during weekend leave and shortly after discharge. When the possibility of a drug-induced psychosis was realised and suggested to the patient, he admitted to cannabis smoking prior to the psychotic episodes.

"Ganja" psychosis, as described by Knight (1976), is included in this diagnostic category. The clinical features in Jamaican patients were a history of disturbed (aggressive) behaviour and schizophrenic-like features following several days of unaccustomed cannabis use - either in larger than usual amounts, or by persons who had not previously used the drug. Many of these patients were ultimately diagnosed as schizophrenic (Knight, 1976).

Bourhill (1912), quoted by du Toit (1980), found that 18% of all males admitted to the Pretoria Native Asylum suffered from "dagga insanity". Watt and Breyer-Brandwijk (1932) found that cannabis could precipitate an acute psychosis in their South African Blacks. Tocker (1966) described a psychosis similar to schizophrenia in South African Blacks who habitually used cannabis.

1.8.4. Sub-Acute and Chronic Cannabis Psychosis

The psychoses in this category are believed to be caused by heavy, chronic consumption of the drug, characterised by severe deterioration of the higher cognitive functions. Negrete (1973) cites the work done by Christozov (1965) on 140 cases in Morocco. Although patients manifested symptoms of schizophrenia, Christozov recommended that this diagnosis be discarded since patients showed complete recovery.

Spencer (1971) reported a number of cases of sub-acute schizophrenia-like psychoses in the Bahamas. The features of the illness included aggressive behaviour, gross psychomotor over activity, bizarre and grandiose delusions, passivity and amnesia for the onset of their illness. These lasted a few weeks only and they were apparently

precipitated by the excessive use of cannabis. However, this psychosis, which differed from classical schizophrenia and manic-depressive illness, was specifically related to the habitual use of cannabis by predisposed individuals.

Chronic schizophreniform psychosis in Jamaicans has been described by Knight (1976). Cannabis use was considered a contributory factor to the cause of the psychosis.

Kolansky and Moore (1971; 1972; 1975) reported a number of cases in the United States all of whom demonstrated symptoms which began while using cannabis - flattening of affect, impairment of memory, delusions, and depression. The severity of symptoms correlated with the frequency and duration of cannabis use. It was concluded that the drug was the cause of mental disturbances and that Δ^9-THC caused chemical damage to the cerebral cortical cells resulting in an encephalopathy. Kolansky and Moore (1975) considered the psychological symptoms to be representative of the cerebral atrophy as reported by Campbell et al (1971) (see Section 1.7.3.).

Treffert (1978) reported 4 cases of well-documented schizophrenia in which the use of cannabis allegedly induced an exacerbation of psychotic symptoms in patients whose psychoses were in partial or total remission prior to use. It was concluded that "while marijuana can perhaps be safely used by many persons, this is not so with the schizophrenic".

Most of the work derives from the East where cannabis has been used for centuries (Dhunjibhoy, 1930; Bromberg, 1934; Christozov, 1965;

Thacore, 1973; Chopra and Smith, 1974; Thacore and Shukla, 1976). The paucity of descriptions from Western countries might be ascribed to the mildness of local cannabis preparations and the relatively recent use of the drug (Milman, 1969; Persyko, 1970; Jaffe, 1980).

In summary, cannabis-induced psychosis is a highly controversial subject and its existence will continue to be debated upon for many years. Some argue that a valid clinical syndrome exists, having a central core and consistent signs and characteristics; others refute the existence of a cannabis-induced psychosis and maintain that affected individuals had a predisposition to psychosis which, on exposure to the drug, declared itself overtly. The present study has attempted to address itself to this problem.

CHAPTER TWO

2.1. PATIENT SELECTION

This study formed part of the Medical Research Council Clinical Psychiatry Research Unit's study entitled 'The Course and Progress of Serious Mental Illness'. Coloured male patients from certain magisterial districts of the Valkenberg Hospital catchment area of the Western Cape were selected (see Appendix). Patient selection was done independently of the investigator. It was made randomly and included every fourth patient from these specified areas admitted to the Coloured admission ward of Valkenberg Hospital. All selected patients were investigated with respect to urinary cannabinoids, toxicological screening, and ethanol determination; the PSE was also administered in each case on two occasions - on admission and seven days later.

Patients were studied in three groups of twenty each on the basis of the following criteria:

i. Those patients in whom urinary cannabinoid levels exceeded 60 micro grammes cross-reacting cannabinoids per gramme creatinine (µgCRC/g creatinine) on admission; this group was described as the 'high cannabis' group.

ii. Those patients in whom urinary cannabinoid levels were less than or equal to 59µgCRC/g creatinine on admission; this group was described as the 'low cannabis' group.

iii. Those patients in whom urinary cannabinoids were not detected on admission. This group served as the control group and were matched as closely as possible with the high cannabis group with reference to

clinical diagnosis on admission, race, sex, age, first or multiple admissions to Valkenberg Hospital, and social class (see Appendix); this group was described as the 'psychotic control' group.

2.2. PRESENT STATE EXAMINATION

In psychiatry, mental disorders are not dealt with as discrete clinical entities but rather as constellations of overlapping symptoms; this results in a blurring of diagnostic categories. Techniques for classifying abnormal mental states are many, the most familiar being a clinical diagnosis. Since laboratory tests are infrequently available for the confirmation of diagnosis, history taking and clinical observations are critical in this field.

The traditional medical approach to diagnosis may be too narrow for dealing with psychotic patients. Psychiatric and medical interviews share the same objective: they elicit information from a patient, lead to an accurate diagnosis and result in an effective treatment. They differ, however, in detail and emphasis. The techniques of questioning range from a non-directive (patient-orientated) interview to a directive (doctor-orientated) interview. In general a compromise between these extremes is used to satisfy the needs of both parties - the patient's need to communicate and the doctor's need to elicit information.

The advances in the pharmacological, biochemical, and genetic aspects of psychiatry emphasize the need for a more scientific approach to clinical analysis. The Present State Examination (PSE) was devised for this purpose.

The PSE is a guide to structuring a clinical interview to assess the 'present mental state' of adult patients. Wing and his colleagues (1967) developed the PSE as a research instrument to represent the current clinical practice and teaching. Although originally constructed in English, the PSE has been translated into other languages including Arabic (Okasha and Ashour, 1981), Afrikaans, and Xhosa (MRC Clinical Psychiatry Research Unit, 1981).

Studies on its reliability have been carried out and coefficients of variation in measuring psychotic symptomatology for various symptoms based on a single interview ranged from 0,62 to 0,97. The reliability between interviewer and observer ratings ranged from 0,58 to 0,96 (Wing et al, 1967; Kendell et al, 1968). The inter-observer reliability ratings of individual items have been extensively studied by the US-UK Diagnostic Project and the World Health Organization in various countries. High levels of reliability have been achieved even when there were marked transcultural differences (Wing et al, 1974).

The PSE is virtually a miniature textbook of 'functional' psychopathology and, together with the glossary of definitions of symptoms, can be used as a standardization of the diagnostic examination common to world psychiatry (Wing et al, 1974).

The interview is structured by following a question-schedule (see Appendix) to elicit information concerning 140 rateable items, most of which represent psychiatric symptoms defined in a glossary of definitions. Glossary definitions are given as clearly as possible so that ratings are comparable even when undertaken by psychiatrists

of different schools of thought; this makes reliability the outstanding feature of the PSE. The PSE ratings are made by a competent interviewer familiar with the glossary definitions and able to reach a good clinical judgement on the presence or absence of symptoms. Experience and training are therefore important (Wing and Sturt, 1978).

Based on the interview which covers symptoms experienced during the previous four weeks, and abnormalities of speech, behaviour and affect observed during the interview itself, the interviewer records his decision as to whether each symptom is absent or present and, if present, to a moderate or severe degree. A computer programme named CATEGO processes the data rated during the interview to give a standardized diagnostic grouping according to the International Classification of Diseases (1965 Revision). The majority of symptoms are grouped into 38 'syndromes' (such as 'auditory hallucinations' or 'situational anxiety') and a score can be derived for each syndrome, consisting of the summed ratings on the constituent items. The syndrome scores can themselves be summed to give a total PSE score. The syndromes can be summed into four subclasses: behaviour speech and other syndromes (BSO), delusional and hallucinatory syndromes (DAH), specific neurotic syndromes (SNR), and non-specific neurotic syndromes (NSN). (See Appendix)

As a reliable system of measurement and classification, the PSE allows comparison with diagnoses given by clinicians and the class allocation given by the CATEGO Programme. The scientific uses of the PSE are the description (in terms of symptoms, syndromes and classes) of psychopathological characteristics of groups of people at a specific point in time, the provision of an instrument capable of reliably providing scores representing various areas of psychopathology and valuable for

measuring change.

2.2.1. Method for Implementing PSE

Every patient admitted to the study was subjected to two PSE assessments. The initial PSE was administered as soon after admission as possible, and seven days were allowed to elapse before a second PSE was administered. The second PSE was to assess the change in symptomatology over that period. If in certain cases the seven-day period between PSEs could not be strictly adhered to owing to patient non-co-operation or other factors the time interval between PSE assessments was allowed to be extended to eight to ten days.

All interviews were performed by trained members of the MRC Clinical Psychiatry Research Unit; all completed PSE ratings were computerized by the Medical Research Council, Bellville.

2.3. URINARY CANNABINOID ASSAY

2.3.1. Introduction

Several qualitative tests have been available for the detection of cannabinoids but these methods could only detect cannabinoids in plant material and were too insensitive for use with biological fluids from man.

Major problems were associated with the development of detection methods for cannabinoids in biological fluids; tetrahydrocannabinol is highly lipophilic and therefore distribution from the central compartment is rapid; the oral effective dose in humans is 20-50 µg/kg body weight and the amount absorbed when smoked is 25-50 µg/kg

(Mechoulam and Gaoni, 1967 (b)) so that blood levels would be expected to be low; a major proportion of the metabolites is excreted in the faeces.

Several years ago Schneider et al (1973) described a homogenous immunoassay technique that utilized the observation that certain enzymes can be inhibited by antibodies directed against the haptens to which the enzymes were covalently bound. This technique, called Enzyme Multiplied Immunoassay Technique (EMIT^{R}) is used for the micro-analysis of specific compounds in biological fluids. 'Homogenous' enzyme immunoassay was so termed to distinguish this method from other immunochemical methods that are 'heterogenous', in which at some stage the antigen is physically separated from the antibody to which it is bound.

The principle of the EMIT^{R} assay:
A drug is labelled with an enzyme. When the enzyme-labelled drug becomes bound to an antibody against the drug, the activity of the enzyme is reduced. Free drug in a sample competes with the enzyme-labelled drug for the antibody, and thereby decreases the antibody-induced inactivation of the enzyme. Enzyme activity correlates with the concentration of the free drug in the sample and it is measured by an absorbance change resulting from the enzyme's catalytic action on a substrate (Rubenstein et al, 1972).

In the performance of an EMIT^{R} assay for urinary cannabinoids urine is mixed with a reagent containing a tetrahydrocannabinol derivative together with the coenzyme nicotinamide adenine dinucleotide (NAD) for the enzyme malate dehydrogenase. Binding occurs to any drug in the urine that is 'recognized' by the antibody. A drug labelled with the

enzyme malate dehydrogenase is then added. The labelled drug combines with any remaining unfilled antibody binding sites, and the enzyme activity is thereby proportionally reduced. The residual enzymatic activity is directly related to the concentration of the drug present in the urine. The active enzyme converts NAD to NADH, resulting in an absorbance change that is measured spectrophotometrically.

Using different enzymes this technique has been used clinically to assay various compounds: lysozyme from Micrococcus luteus in the determination of opiates (Schneider et al, 1973); glucose-6-phosphate dehydrogenase from Leuconostoc mesenteroides in the measurement of digoxin (Chang et al, 1975); pig heart mitochondrial malate dehydrogenase in the assays for morphine (Rowley et al, 1975), thyroxine (Ullman et al, 1975), and cannabinoids (Rowley et al, 1976). The latter enzyme, labelled with a derivative of Δ^9-THC, was used by Rodgers et al (1978) for the measurement of cannabinoid metabolites and Δ^9-THC in urine.

Rodgers et al (1978) used 11-nor-Δ^9-THC-9-carboxylic acid, a metabolite of Δ^9-THC, to calibrate the EMIT^R assay quoted in this study. It was shown that with 15µg 11-nor-Δ^9-THC-carboxylic acid per liter as the cut-off concentration, the assay could detect 25µg 11-nor-Δ^9-THC-9-carboxylic acid with greater than 95% confidence. The assay was found to be most sensitive to 11-nor-Δ^9-THC-9-carboxylic acid and to 11-hydroxy-Δ^9-THC, with the response to cannabinol and Δ^9-THC itself approximately 39% less.

The cross-reactivity of the assay to a number of other drugs, natural hormones and their metabolites was also examined and none of these

compounds was found to cross-react significantly, even when their concentration grossly exceeded that normally found in the urine. Pooled normal urine was supplemented with 15, 25, and 75 µg 11-norΔ^9-THC-9-carboxylic acid per liter to determine the precision of the cannabinoid enzyme immunoassay. Each portion was analyzed repetitively by a single operator. The results showed high precision at all three concentrations (Table 2.3.1.1.).

Table 2.3.1.1. Precision of replicate cannabinoid assays of pooled urine containing 11-nor-Δ^9-THC-9-carboxylic acid (From Rodgers et al, 1978). Due to the unavailability of 11-nor-Δ^9-THC-9-carboxylic acid the validation of Rodgers et al (1978) who used the identical materials and equipment is quoted.

Concentration (µg/ℓ)	15	25	75
Assayed Mean (µg/ℓ)	15,1	25,3	74,9
Replicate Assays	20	20	20
SD (µg/ℓ)	0,60	0,75	1,48
CV (%)	4,0	3,0	2,0

Very recent work by O'Connor and Rejent (1981) tested the validity of the EMIT^R system by comparing it with other established analytical methods including RIA and two different GC/MS procedures. They suggested that the EMIT^R assay may be superior to other techniques in sensitivity, ease, speed of performance, and capacity for multi-sampling handling. Peel and Perrigo (1981) found the method precise, useful, and applicable in the screening of blood samples for the presence of cannabinoids. It should be noted that the period of intoxication lasts for anything from one to four hours (Paton and Pertwee, 1973), while the peak cannabinoid concentration in human urine occurs between two to six hours and can remain high for longer than twenty four hours following exposure to the drug (Rodgers et al, 1978), the assay is thus limited in that it cannot measure the degree of intoxication but is useful as an

indicator of the recent use of cannabinoids. The advantages of the homogenous immunoassay for cannabinoids lie in the non-invasive collection of sample, only 50µℓ being required; the assay itself requires little sample manipulation or operator training, is relatively cheap (R4.50 per assay), and rapid (45 seconds). More important, this assay was the only practical choice for this study; patients may have been delayed entry into the hospital and further delayed before a sample could be taken and the chances of detecting any meaningful cannabinoid level in the blood at the time of admission were negligible.

2.3.2. Instruments and Operating Conditions

i. Spectrophotometer

A Stasar 111 spectrophotometer (Gilford Instrument Laboratories, Ohio, USA), equipped with a 3017T thermal control unit was used. The enzyme reaction was monitored by the change in absorbance at 340nm. The mode was set at concentration, the concentration calibrator was adjusted for an amplification factor of 2,667 amplification, the temperature was set at 30°C, sample volume at 0,5-0,7ml, vacuum at 200-250mmHg, and the slit at 0,8mm.

ii. Data Processor

A Syva CP-5000 EMIT^{R} Clinical Processor was used. The instrument interfaces with the spectrophotometer and was programmed to assign a sample number, provide a printed record of the initial absorbance of a sample, and print the change of absorbance as a function of time. The instrument controlled the timing of the assay and was set to provide a fifteen second delay for temperature equilibration after

the sample was aspirated into the flow cell, followed by two absorbance readings, thirty seconds apart.

iii. Pippeter-Diluter

A Syva Pippeter-Diluter (Model 1500) was used. The instrument was set to aspirate 50µℓ of sample and to deliver the sample plus 250µℓ of buffer solution.

iv. Miscellaneous Apparatus

Plastic containers were used to collect the urine samples and Vacutainer® glass tubes for the storage thereof. These containers are used routinely for the storage of drug-containing specimens. 2ml disposable conical beakers (Fisher Scientific Company, Pittsburgh, USA) were used in the assay.

2.3.3. Reagents

The EMIT®-d.a.u. Cannabinoid Urine Assay and the EMIT®-d.a.u. Cannabinoid Urine Calibrators were manufactured by Syva, Palo Alto, USA.

The EMIT®-d.a.u. Cannabinoid Urine Assay was supplied containing:

i. EMIT® Cannabinoid Antibody/Coenzyme Reagent A

ii. EMIT® Cannabinoid Reagent B

iii. EMIT® Cannabinoid Buffer Concentrate

i. EMIT® Cannabinoid Antibody/Coenzyme Reagent A

This was supplied as a lyophilized preparation in a rubber-stoppered clear glass vial. The reagent contained a standardized preparation of immunized sheep gamma-globulin, the coenzyme nicotinamide adenine

dinucleotide (NAD), stabilizers, and preservatives. The reagent also contained 0,15M glycine to buffer the reagent at pH 5,0.

ii. EMIT^{R} Cannabinoid Reagent B

Reagent B was supplied as a lyophilized preparation in a rubber-stoppered clear glass vial. The reagent contained an unspecified Δ^{9}-THC derivative chemically coupled with pig-heart mitochondrial malate dehydrogenase. The reagent also contained stabilizers, preservatives, and 0,01M Tris-HC1 to buffer the preparation at pH 7,4.

Reagent A and Reagent B were supplied to be used together; it was considered mandatory that the Reagent A and the Reagent B supplied in any one kit be used together.

iii. EMIT^{R} Cannabinoid Buffer Concentrate

The buffer concentrate was supplied as a clear liquid in a rubber-stoppered clear glass vial. The buffer concentrate contained malate as enzyme substrate.

The EMIT^{R}-d.a.u. Cannabinoid Calibrators were supplied in rubber-stoppered amber-coloured glass vials. Calibrators were supplied containing 0, 20, and 75µg/ml 11-nor-Δ^{9}-THC-9-carboxylic acid as lyophilized preparations.

2.3.4. Collection and Storage of Urine Samples

A single urine sample was collected from each patient within one hour (or as soon as possible) after admission to the hospital ward. Within twenty four hours of collection two 5ml aliquots were drawn from the

bulk specimen. One aliquot was retained for the cannabinoid assay. The second aliquot was sent to Conradie Hospital Regional Laboratory for urinary creatinine determinations; the cannabinoid assay is semi-quantitative and a urinary creatinine determination would allow an improved result to be reported.

The pH of each specimen was checked on collection of each sample using Merck® Universal Indicator strips.

Samples that could not be assayed immediately upon collection were stored in rubber-stoppered glass tubes at -20°C. The samples were allowed to stand at room temperature for at least two hours and the pH checked prior to the assay.

Subsequent samples were taken each morning between 7 a.m. and 8 a.m. from patients in whom cannabinoids were detected in the initial sample. This procedure was repeated until a negative assay result was obtained for two succesive days.

2.3.5. Preparation and Storage of Reagents

Reagent A was reconstituted by the addition of 8,0ml distilled water. Reagent B was reconstituted by the addition of 6,0ml distilled water. The reagents were allowed to equilibrate overnight at 2-8°C before use and thereafter they were stored at 2-8°C. The reconstituted reagents could be used for twelve weeks under normal conditions.

Each Cannabinoid Urine Calibrator was reconstituted by the addition of 3,0ml distilled water and allowed to equilibrate overnight at 2-8°C before use. The reconstituted calibrators could be used for at least fourteen days under normal conditions.

The Buffer Concentrate was diluted to 150ml with distilled water. The diluted buffer was stored at room temperature in a glass-stoppered opaque glass container and could be used for twelve weeks under normal conditions.

2.3.6. Assay Procedure

All samples and reagents were allowed to approach room temperature by standing at ambient temperature for at least one hour prior to use. All instruments were set and checked for the correct settings. The spectrophotometer was zeroed using distilled water. Sufficient disposable cups were set in the work rack. The assay was run as follows:

i. Using the Pippeter-Diluter, 50µℓ sample (or calibrator) was sampled and delivered with 250µℓ buffer into a 2ml disposable cup.

ii. Using the Pippeter-Diluter, 50µℓ Reagent A was sampled and delivered with 250µℓ buffer to the same cup.

iii. 30 seconds was allowed to elapse for Reagent A and sample (or calibrator) to equilibrate.

iv. The spectrophotometer flow cell was purged with water.

v. Using the Pippeter-Diluter. 50µℓ Reagent B was sampled and delivered with 250µℓ buffer to the same cup.

vi. The contents of the cup were aspirated into the spectrophotometer flow cell. The cup was discarded. The printer was automatically activated by the aspiration of the sample to time and record the change of absorbance.

vii. The above procedure was repeated with each sample.

Before any samples were assayed the calibrators were run in duplicate and a blank was run. The blank consisted of buffer solution. The first sample from each patient was assayed in duplicate but subsequent samples were assayed once only.

Table 2.3.6.1. Validation of EMIT® assay for the determination of cannabinoids in urine.

Concentration (ng/ml)	Number of samples	Mean ΔA^{+}	Standard Deviation	Coefficient of variation	Standard error of the mean
0	5	409,00	0,63	0,15	0,28
20	5	455,80	0,26	0,26	0,11
75	5	500,80	0,75	0,15	0,33

+After aspiration of the sample two readings are automatically made on each sample, the first at 15 seconds and the second at 45 seconds. The difference between the two readings (ΔA) is used to calculate results.

2.4. TOXICOLOGICAL SCREEN

2.4.1. Introduction

Chromatography is the separation of the components of a mixture by utilizing their different relative absorptions onto a stationary phase. Development (elution) of the mixture is carried out by passing a mobile phase over a stationary phase which may be a solid (or,

more rarely, a viscous liquid), and the mobile phase may be a gas (gas chromatography (GC)) or a liquid (high pressure liquid chromatography (HPLC)), or thin layer chromatography (TLC)).

The local practice to screen for unknown drugs is to extract plasma with isopropanol, salt out the water with ammonium sulphate to evaporate the extract. The latter is redissolved in methanol and is spotted near one corner of each of ten 5cm x 5cm fluorescent thin-layer plates for TLC. A fluorescent indicator is incorporated into the stationary phase to yield a light-green fluorescence when exited by UV light of wavelength 254nm. This facilitates the identification of some classes of chemicals (Johnson, 1968; van der Meer, 1976). It is virtually impossible to cause a separation of all the compounds that may be present using one mobile phase and a two-dimensional separation using two different solvent systems is considered more appropriate. The choice of solvent remains essentially a matter of trial and error (Snyder, 1975) and ideally one solvent should separate acidic drugs and the other solvent basic drugs (van der Meer, 1976). Therefore the plates are run first in one dimension to separate the acids, then the other at right angles with the basic eluent to separate the bases. Most of the endogenous, but extracted material remains at the origin and the fats and very non-polar drugs run to the opposite corner. The other drug-spots are distributed about the plate in a fairly predictable pattern, the position being determined by certain variables in the composition of the plate and by the balance of polarity and intrinsic acidity or basicity of the drug. A known reference compound is run in the margin of the plate as a check on the conditions of chromatography; paracetamol is usually used but, if a particular drug is suspected to be present, that will be used instead.

Once the chemicals have been separated on the plate a number of methods can be used to identify the compounds - for example UV spectrophotometry, mass spectrophotometry, HPLC, and GC, all of which require complex and expensive equipment. The most widely used technique for the visualization of compounds on chromatograms is the spraying of plates with specific reagents. Each reagent is designed to indicate the presence of certain reactive groups on the drug molecule (van der Meer, 1976). In theory one should be able to identify about 150 drugs simultaneously present on each plate but in practice the limit is a good deal lower, about 50. Tables displaying migratory distances and specific reactions of chemicals to specific colouring reagents have been drawn up and are used to identify the drugs present on TLC chromatograms.

2.4.2. Apparatus and Reagents

Centrifugation of samples was performed using a bench-top centrifuge (Roto-Uni 11, West Germany) with the speed set at 2500 min^{-1}. A Vortex mixer (Scientific Industries Inc. New York, USA) Model K-550-GE was used to mix various solutions.

Ammonium sulphate, isopropanol, and methanol were guaranteed Reagent Grade chemicals (Merck, Darmstadt, Germany). An 11ml glass-stoppered Quickfit test tube and a 25ml round-bottomed Quickfit flask were used for the extraction procedure. Disposable Pasteur pipettes were used to transfer solutions. A Büchi Rotovapor (W. Büchi, Flawl, Switzerland) was used to evaporate the serum extract to dryness.

Thin-layer chromatography was carried out on silica gel 60 F_{254} plates (Merck, Darmstadt, Germany). The plates were split into 5cm x

5cm squares and marked lightly in pencil with a 3cm x 3cm square ruled in the middle (Figure 2.4.2.1.)

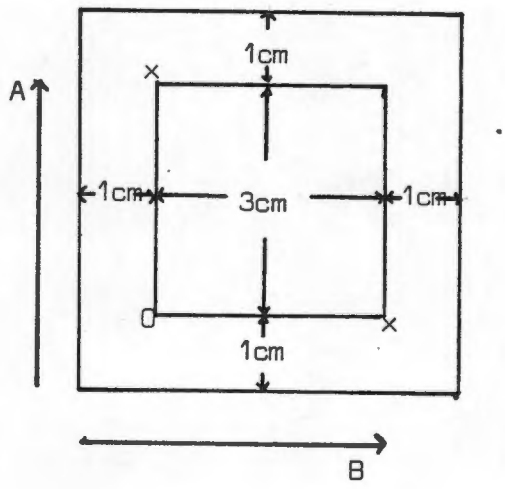


Figure 2.4.2.1. Demarcation of silica gel plates

A = direction and distance of elution with acid eluent

B = direction and distance of elution with alkaline eluent

O = origin

x = position of spotting of external reference standard

1µℓ micropipettes were used to spot the extract onto the plates. A UV lamp set at 254nm and 360nm was used to view the prepared plates.

2.4.3. Sample Collection and Extraction Procedure

A 10ml blood sample was drawn from each patient as soon as possible after admission to the hospital ward. The samples were stored at 2-8°C and then separated by centrifugation before analysis. 5ml serum and 4ml isopropanol were thoroughly mixed for two minutes, then 3g ammonium sulphate was added and dissolved as completely as possible using a

vortex mixer. The mixture was separated by centrifugation and the upper, isopropanol, layer was collected and evaporated under reduced pressure at 60°C. The residue was triturated with 200µℓ methanol and the resulting mixture was again separated by centrifugation. The clear supernatant was distributed evenly between the origins of the TLC plates by repeated application of 1µℓ aliquots, solvent being evaporated in a stream of hot air between applications.

All plates were eluted simultaneously. The elution was performed in two dimensions succesively, at right angles. The eluting solvent in the first dimension (acid elution) was 94% formaldehyde dimethyl acetal; in the second dimension (alkaline elution) the eluting solvent was ethyl acetate: methanol: concentrated aqueous ammonia:: 85:10:5 and was freshly prepared. An external reference standard of paracetamol was run in the margins of each plate.

The spots formed by drugs present were located, in the first instance, by the quenching of inherent fluorescence of the TLC plates at 254nm. In addition partial identification could be made by observing fluorescence when the plate was exited by light of wavelength 360nm. The apparent migration distances of the spots under acidic and under basic conditions were calculated relative to the paracetamol = 100 units.

The following visualizing reagents were then used: iodine, Dragendorff's, iodoplatinate, Marquis', Mandelin's, Forrest's, FPN, diphenylcarbazone, Trinder's, and mercurous nitrate. (See Appendix G for formulations). From all the data gained, the identification of any drug spots could be made.

2.5. ETHANOL DETERMINATION

2.5.1. Introduction

Gas Chromatography (GC) is limited to those substance or their derivatives which vaporize without decomposing. The most widely used detector in GC, responding with high sensitivity to all organic compounds, is the flame ionization detector which measures the ionization current generated when a compound emerges from the chromatographic column and burns in a hydrogen flame. The sensitivity of this detector enables 10^{-9} g of many components to be detected and does not respond to inorganic gases or water (Andrews, 1970).

GC allows the detection and identification of a variety of volatile substances, including the common alcohols. A suitable internal standard is selected whose elution properties resemble those of the substance to be determined and known concentration of the internal standard is added to the sample under investigation. The relative response of internal standard compared with that of the alcohol to be measured allows an accurate result to be established.

GC has become a widely accepted analytical technique for the detection and quantification of various alcohols in blood, tissue and plasma. The advantages of GC in this context are its capacity for measuring volatiles, its speed and the micro-volume sample required (Freudiger and Vignau, 1965; Mather and Assimosis, 1965; Davis, 1966; Andrews, 1970).

2.5.2. Instrumentation and Operating Conditions

A Gow-Mac Series 750 Gas Chromatograph, Model 69-752 (Gow-Mac Instrument Co. New Jersey, USA) fitted with a flame ionization detector was used for the detection of ethanol in plasma.

A 1,2 m, 2mm i.d. glass column packed with 0,2% Carbowax 1500 on Carbopack A 60/80 mesh was used under the following conditions: injection port temperature at 120°C, the detector at 140°C, and the column oven at 115°C. Nitrogen was used as the carrier gas with a flow rate of 20 ml/minute, hydrogen was set at a flow rate of 30 ml/minute and oxygen at 300 ml/minute.

A Hewlett Packard Automation System 3385A Integrator/recorder was used to record the chromatograms and retention times.

2.5.3. Reagent and Sample Preparation

i. Solvent test solution

1 ml each of methanol, ethanol, acetone, isopropanol, and n-propanol were mixed and diluted to 500 ml with distilled water to give final concentrations of 157 mg%, 157 mg%, 157 mg%, 156 mg%, 160 mg% respectively. All reagents were guaranteed Reagent Grade (Merck, Darmstadt, Germany).

ii. Internal Standard

1 ml isopropanol and 1 ml n-propanol were mixed and diluted to 1000 ml with distilled water to give concentrations of 78,1 mg% and 80,2 mg% respectively.

iii. Ethanol control solution

1 ml absolute ethanol was diluted to 500 ml with distilled water. The resulting solution had a concentration of 158 mg%.

iv. Standard ethanol solutions

2,0 ml absolute ethanol was diluted to 500 ml with distilled water. The resulting solution had an ethanol concentration of 316 mg%; this was labelled Solution A. Various subsidiary standards containing 158 mg%, 79 mg%, and 31,6 mg% were made by dilutions of Solution A.

200 µl of the standard solutions were mixed with 200 µl of internal standard solution and the tubes were sealed with Parafilm. Five aliquots of each standard solution were prepared.

From the blood sample drawn from each patient (See Section 2.2.3.) 200 µl serum was mixed with 200 internal standard in a tube and sealed with Parafilm.

2.5.4. Assay Procedure

i. 1 µl of the test solution was injected directly onto the column and the retention times (R_T) were recorded. The solvents elute in the following order: methanol, ethanol, acetone, isopropanol, n-propanol.

ii. The syringe was rinsed 20 times with distilled water.

iii. 1 µl of the prepared sample from each standard solution was injected directly on to the column and the R_T values were recorded.

The syringe was washed 20 times between each injection.

iv. The plasma samples were injected in the same way.

Following the determination of the standard solutions, 1 µl of the prepared sample from each patient was assayed in the same way.

The ratios of ethanol to isopropanol were calculated for standard and serum samples. The ratios for the standards were used to prepare a standard curve which, in turn, was used in the determination of ethanol concentrations in the plasma samples.

Table 2.5.4.1.

Ethanol Concentration of Standard Solutions (mg%)	Number of Samples	Mean Ethanol/ Isopropanol Ratio	Standard Deviation	Coefficient of Variation (%)	Observed Concentration
0	4	0,00	0,00	0,00	0,00
31,6	4	0,344	0,010	2,9	30,5
79	4	0,937	0,005	0,53	79,5
158	4	1,910	0,011	0,57	160
316	4	3,780	0,010	0,26	315

Table 2.5.4.1. Validation of ethanol determination by Gas Chromatography

Slope = 0,012
Y-intercept = 0,020
r = 0,9998

See Figure 2. .4.1. Calibration curve for the determination of ethanol in serum by gas chromatography. Co-ordinates plotted represent the means of the observed values.

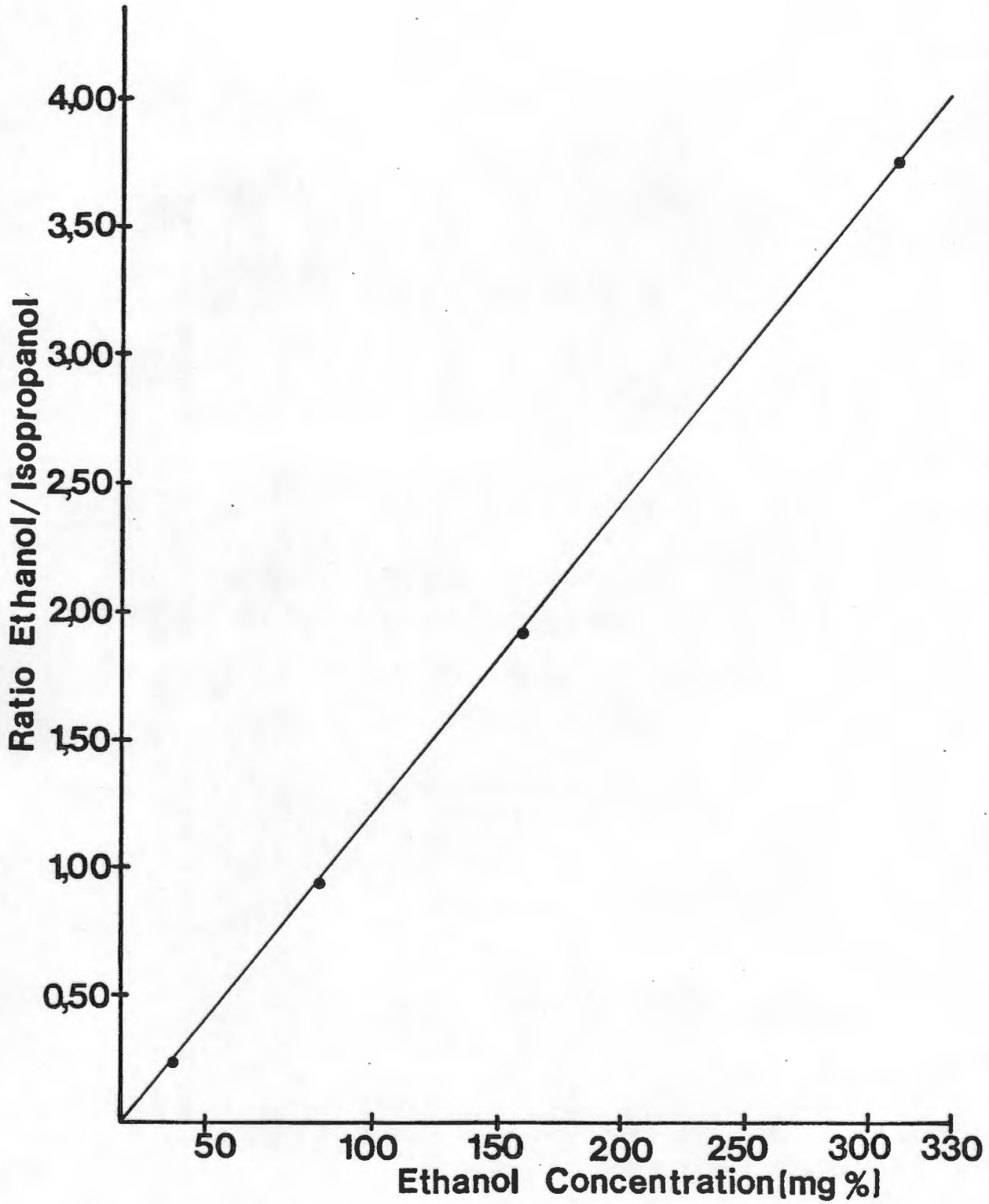
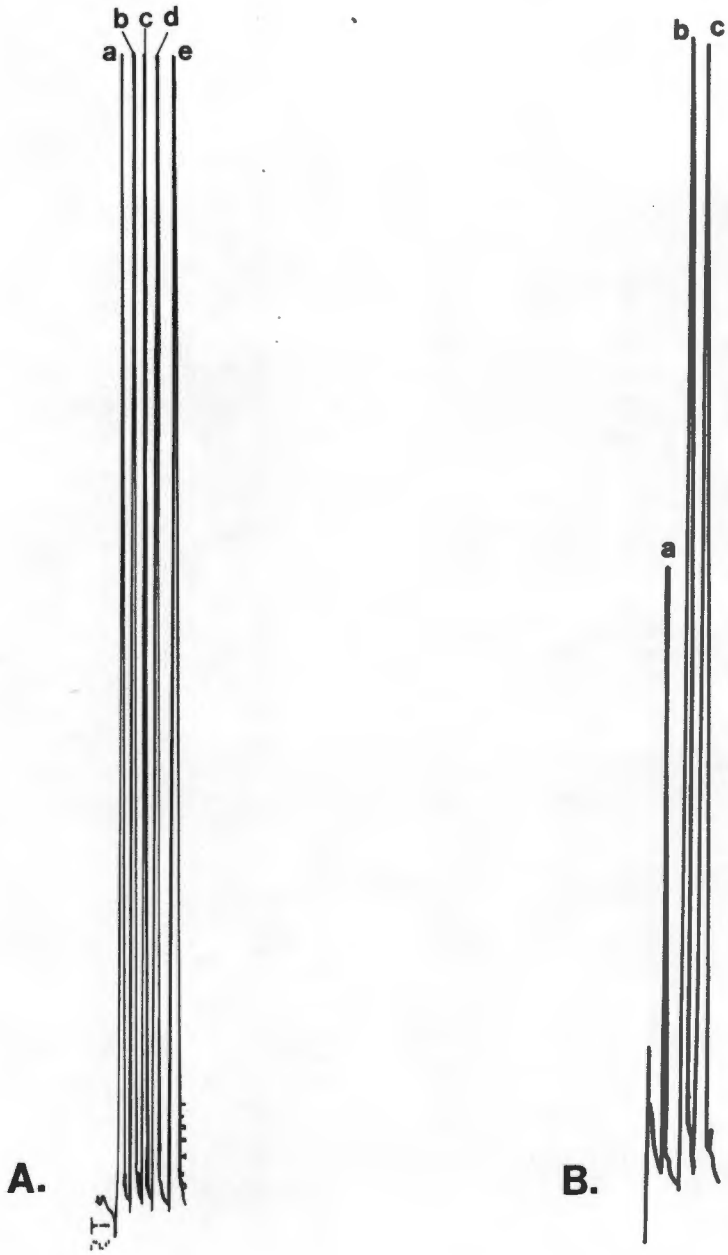


Fig. 2.5.4.1. Calibration curve for the determination of ethanol in serum by gas chromatography coordinates plotted represent the means of the observed values.



A. FIG. 2.5.4.2. Chromatogram of test solution.
a = methanol (157 mg %; R_T = 0,56)
b = ethanol (157 mg %; R_T = 0,87)
c = acetone (157 mg %; R_T = 1,19)
d = isopropanol (156 mg %; R_T = 1,49)
e = n-propanol (160 mg %; R_T = 1,96)

B. FIG 2.5.4.3. Chromatogram of a standard solution.
a = ethanol (31,6 mg %; R_T = 0,87)
b = isopropanol (78,1 mg %; R_T = 1,49)
c = n-propanol (80,2 mg %; R_T = 1,96)

2.6. SERUM CREATININE PHOSPHOKINASE (CPK) AND SERUM LACTATE DEHYDROGENASE (LDH) DETERMINATIONS

There are a number of publications which document the association between elevated serum CPK and acute psychosis (Meltzer, 1968, 1969, 1970, 1973a, 1973b; Meltzer et al, 1969, 1970, 1971; Taylor and Abichandani, 1980). Elevated serum CPK levels occurred in psychotic patients with a variety of psychiatric diagnoses; levels of 5 to 10 times normal values were noted, and on occasion 50 times the normal value (Meltzer, 1969). Despite the heterogeneity of psychotic diagnoses, Guterman (1973) and Gosling et al (1972) suggested that specific psychiatric disorders are more commonly represented. A significant correlation between elevated CPK levels and the "non-affective aspects of the psychosis" was found (Guterman, 1973), and Gosling et al (1972) reported that CPK elevation was more likely to be found in patients with mania and paranoid schizophrenia than in patients with depression and the nonparanoid schizophrenias. However, Meltzer (1973b) suggested that Gosling's data may be explained by a greater delay in the admission of depressed patients and non-paranoid schizophrenic patients to hospital; this would increase the chances of missing elevated serum CPK levels.

Farber and Huertas (1976) reported 2 patients with adverse effects following the intravenous injection of a cannabis preparation; serum CPK and serum LDH levels were elevated in both cases and remained so for six days following admission to hospital.

Therefore serum CPK and LDH determinations were done on the majority of patients admitted to the study; the assays were performed by the Conradie Hospital Regional Laboratory.

CHAPTER THREE

3.1. PHARMACOLOGICAL ASSAYS

3.1.1. Ethanol Determination

Analyses of samples from all patients were done. No ethanol was present in any patient.

3.1.2. Toxicological Screens

Toxicological screens were performed on all patients. No positive result was found in any patient.

3.1.3. Cannabinoid Determinations

Sixty percent of all the randomly selected patients screened had a positive result i.e. the urinary cannabinoid level was above 20ng/ml - the lower detection limit of the assay used. (See Table 3.1.1.).

Table 3.1.1. Initial urinary cannabinoid determinations of randomly selected patients who were positive for cannabinoids (n = 49)

Urinary cannabinoid concentration (ng/ml)[+]			
20–100[++]	101–200	201–500	> 500
23 (46,9%)	9 (18,4%)	10 (20,4%)	7 14,3%)

[+] The assay used was semi-quantitative (see Section 2.3.). For the purpose of further analysis these results were converted to µgCRC/g creatinine to quantify the results.

[++] 20ng/ml was the lower detection limit of the assay (see Section 2.3.).

This indicates that the only detectable toxins present in the patients on admission were the cannabinoids.

3.2. PATIENT SELECTION, CATEGO CLASSIFICATION OF PSEs, AND SYNDROME PROFILES

3.2.1. Patient Selection

All patients selected were Coloured males. There were twenty patients in each group - the high cannabis group, the low cannabis group, and the psychotic control group. (See Tables 3.2.1., 3.2.2., and 3.2.3.). However, in view of the small number of manic patients obtained in the psychotic control group, seven additional manic patients (with CATEGO classifications of Manic-Depressive psychosis, manic type) were accepted into the study.. These patients fulfilled all the criteria for selection (see Section 2.1.) except that they were assessed on the PSE only on admission. The seven patients together with three manic patients (CATEGO diagnosis) in the psychotic control group constituted the 'manic control' group. None of these patients had detectable urinary cannabinoids. (See Appendix I for case studies).

Age of patients

The ages of patients in the high cannabis group ranged from 17-52 years with a median age of 23 years, in the low cannabis group from 18-50 years with a median age of 28 years, and in the psychotic control group from 16-52 years with a median age of 25 years. There were no significant differences among the three groups with regard to age.

Urinary cannabinoid levels on admission

The urinary cannabinoid levels on admission ranged from 80-435 µgCRC/g

creatinine with a median level of 262 µgCRC/g creatinine (high cannabis group); low cannabis group from 4,9-56,5 µgCRC/g creatinine with a median level of 16 µgCRC/g creatinine.

Previous admissions

The number of patients in the high cannabis group, the low cannabis group, and the psychotic control groups who had one or more previous admissions to Valkenberg Hospital was 14, 12, and 16 respectively. Of these patients the median number of admissions was 1, 2, and 2 respectively. There were no significant differences among the three groups with respect to the number of admissions.

Social Class

Two patients in the high cannabis group and 2 in the psychotic control group were assigned a social class of II; the other patients in all three groups were assigned a social class of III.

Period between PSE assessments

The period between PSE assessments in all three groups ranged from 7-9 days with a median period of 7 days. The number of patients in each of the three groups with a 7-day period between PSEs was 14; the number of patients in the high cannabis group, the low cannabis group and the psychotic control group with an 8-day period between PSEs was 4, 4, and 5 respectively; and the number of patients in the same three groups with a 9-day period between PSEs was 2, 2, and 1 respectively. There were no significant differences among the three groups with respect to period between PSE assessments.

Table 3.2.1. High cannabis group

Initials	Age	Urinary cannabinoid level on admission (µgCRC/g creatinine)	Social Class	Previous Admissions	Provisional Clinical Diagnosis on Admission
CM	21	200,9	III	4	Paranoid schizophrenia
AA(1)	22	390,3	III	5	Hypomania
JS	19	211,8	III	0	Hypomania
FJ	22	250,1	II	1	Paranoid psychosis
GM	38	303	III	3	Hypomania
JvR	27	109	III	1	Paranoid schizophrenia
AS	24	101,7	III	1	Schizophreniform psychosis
JF	21	292	III	0	Schizophreniform psychosis
JG	26	103	III	0	Paranoid schizophrenia
RJ	30	80	III	2	Hypomania
FD	23	432,8	III	2	Paranoid schizophrenia
RS	18	289,5	II	0	Paranoid schizophrenia
WW	23	86,8	II	1	Paranoid psychosis
AP	18	106,4	III	1	Paranoid schizophrenia
JP	21	310	III	0	Schizophreniform psychosis
RM	33	273	III	1	Schizophreniform psychosis
AA(2)	26	103	III	9	Paranoid schizophrenia
MI	27	383,5	III	1	Paranoid psychosis
MJ	52	435	III	7	Paranoid schizophrenia
GD	17	412,5	III	0	Paranoid psychosis

(AA(1) and AA(2) refer to two different patients with the same initials).

Table 3.2.2. Low cannabis group

Initials	Age	Urinary cannabinoid level on admission (µgCRC/g creatinine)	Social Class	Previous Admissions	Provisional Clinical Diagnosis on Admission
DN	22	19,2	III	0	Social and behavioural problems
AS	34	57,3	III	8	Chronic schizophrenia
RM	30	10,1	III	1	Hypomania
GvW	26	24,9	III	4	Chronic schizophrenia
JvdL	36	20,1	III	0	Paranoid schizophrenia
AJ	30	6,7	III	5	Schizo-affective disorder
JM	19	4,9	III	0	Schizophreniform psychosis
LA	46	13,4	III	1	Paranoid schizophrenia
BW	24	10,5	III	0	Schizo-affective disorder
EM	50	13,5	III	2	Aggressive and anti-social behaviour
GD	18	7,6	III	0	Schizophreniform psychosis
SC	49	8,5	III	2	Hypomania
FJ	24	10,5	III	1	Paranoid schizophrenia
YD	24	21,1	III	0	Hypomania
EW	23	56,5	III	2	Paranoid psychosis
DM	23	26,2	III	0	Schizophreniform psychosis
AF	27	18,4	III	0	Schizophreniform psychosis
JLR	29	9,3	III	2	Hypomania
LK	37	29,8	III	1	Paranoid schizophrenia
DW	32	49,5	III	3	Hypomania

Table 3.2.3. Psychotic control group

Initials	Age	Urinary cannabinoid level on admission (µgCRC/g creatinine)	Social Class	Previous Admis-sions	Provisional clinical diagnosis on admission
KA	29	-	II	1	Paranoid schizophrenia
AE	26	-	III	6	Paranoid schizophrenia
SG	52	-	III	7	Paranoid schizophrenia
JV	16	-	III	0	Early schizophrenia
HM	27	-	III	1	Paranoid schizophrenia
MP	25	-	III	1	Paranoid schizophrenia
GT	18	-	III	3	Paranoid schizophrenia
LJ	20	-	III	1	Schizophreniform psycho-sis
GJ	20	-	III	0	Schizophreniform psychosis
DP	18	-	III	2	Paranoid schizophrenia
LA	23	-	III	2	Paranoid schizophrenia
RE	16	-	II	0	Schizophreniform psychosis
FA	25	-	III	2	Schizophreniform psychosis
AD(1)	30	-	III	3	Paranoid schizophrenia
CK	20	-	III	0	Hypomania
AD(2)	39	-	II	9	Hypomania
JK	30	-	III	5	Hypomania
JM	30	-	III	1	Paranoid schizophrenia
NF	23	-	III	1	Paranoid schizophrenia
DB	25	-	III	1	Paranoid schizophrenia

(AD(1) and AD(2) refer to two patients with the same initials).

Medication during the period between PSE assessments

All patients received neuroleptic medication during the period between PSEs (see Tables 3.2.4., 3.2.5., 3.2.6.). The total dose received by patients in the high cannabis group ranged from 7 - 207 units with a median of 34 units, in the low cannabis group from 6 - 214 units with a median of 42 units, and in the psychotic control group from 16 - 64 units with a median of 44 units (see Table 3.2.7. for equivalent doses of medication). The Kruskal-Wallis one-way analysis of variance by ranks was used to test for significant differences among the three groups with respect to the total amount of neuroleptic medication during the period between PSEs; there were no significant differences.

3.2.2. CATEGO Classification

The CATEGO classification of completed PSEs was made according to the International Classification of Diseases (1967 Edition) and is presented in Tables 3.2.8 , 3.2.9., and 3.2.10.

3.2.3. Syndrome Profiles

3.2.3.1. Syndrome profiles of PSE1

Syndrome profiles were drawn up for each of the three groups and are presented in Figure 3.2.1. and Tables 3.2.11., 3.2.12., and 3.2.13. for the high cannabis group, the low cannabis group and the psychotic control group respectively. (See Table 3.2.14. for the CATEGO syndrome abbreviations).

Table 3.2.4. Total medication received during the period between PSE1 and PSE 2 in the high cannabis group

	Medication (units/period between PSE1 and PSE2)+					
Patient	Flu-phenazine decanoate	Chlor-promazine HCl	Halo-peridol	Trifluoperazine dihydrochloride	Pimozide	Total
CM	8	6			28	42
AA(1)		6	35	28		69
JS			70	28		98
FJ	9	6		36		51
GM				28		28
JvR		6		28		34
AS	7		70			77
JF		24				24
JG		7		48		55
RJ		14	105	28		147
FD		6		28		34
RS		6		28		34
WW	7	14				21
AP	7			28		35
JP		7	200			207
RM	7			14		21
AA(2)	14	14				28
MI	7					7
MJ	9	18				27
GD	8	16				24

+Medication is reported as units, see Table 3.2.7. for equivalent doses

Table 3.2.5. Total medication received during the period between PSE1 and PSE2 in the low cannabis group

Patient	Medication (units/period between PSEs)+					
	Fluphenazine decanoate	Chlorpromazine H Cl	Haloperidol	Trifluoperazine dihydrochloride	Clothiapine	Total Daily Units
DN		6				6
AS	8	6		32		46
RM	7	6		42		55
GvW	16	6				22
JvdL		6				6
AJ	7		35			42
JM		27		18		45
LA		7		27		34
BW		6		42		48
EM		7			7	14
GD		6		14		20
SC		6	80			86
FJ	14			28		42
YD		14	200			214
EW	7	6		28		41
DM	7	7		28		42
AF	14			56		70
JLR		6	70			76
LK		14		28		42
DW	7			28		35

+Medication is reported as units, see Table 3.2.7. for equivalent doses

Table 3.2.6. Total medication received during the period between PSE1 and PSE2 in the psychotic control group

	Medication (units/period between PSE1 and PSE2)+				
Patient	Flu-phenazine decanoate	Chlor-promazine HCl	Halo-peridol	Trifluoperazine dihydrochloride	Total Daily Units
KA	14	28			42
AE	8	39			47
SG	7	13			20
JV		38			38
HM	7		35		42
MP	7	9			16
GT	18	9			27
LJ		26		32	58
GJ	14		35		49
DP	7	55			62
LA		27		21	48
RE		16		48	64
FA	14	27			41
AD(1)	8	22		16	46
CK		5	42		47
AD(2)			52		52
JK		42			42
JM		7		28	35
NF				28	28
DB	7	68			55

+Medication is reported as units, see Table 3.2.7. for equivalent doses

Table 3.2.7. Dose relationship among neuroleptics (adapted from Hollister, 1978).

1 unit ≡ 25mg Fluphenazine decanoate+ per month

≡ 100mg Chlorpromazine HCl

≡ 2mg Haloperidol

≡ 5mg Trifluoperazine dihydrochloride — per day

≡ 2mg Pimozide

≡ 40mg Clothiapine

+The calculation of daily dose of Fluphenazine decanoate was adapted from Hollister, 1978.

To identify any differentiating features of the psychoses on admission in the three groups, syndrome profiles of PSE1 for each group were compared; (see Figure 3.2.1.). The Chi-square test for independent samples was used to test for significant differences among the three groups and to test where the most significant differences lay; the significant differences are summarized in Table 3.2.15.. From these results it is clear that on admission the high cannabis group is characterized by a higher frequency of hypomania, agitation and disorientation. The psychotic control group is characterized by a higher occurrence of hysteria, auditory hallucinations, flattening, visual hallucinations, and incoherent speech. The low cannabis group has no characterizing features.

3.2.3.2. Comparison of syndrome profiles of PSE1 of patients in the high cannabis group and the psychotic control group with CATEGO classifications of Paranoid schizophrenia or Manic-Depressive psychosis, manic type

It is evident that in the CATEGO classification of the first PSE in the high cannabis group Paranoid Schozophrenia and Manic-Depressive

psychosis, manic type predominate (see Table 3.2.8.). Therefore it was decided to compare patients in the high cannabis group with a CATEGO classification of Paranoid schizophrenia with patients in the psychotic control group with the same diagnostic classification (see Figure 3.2.2. and Table 3.2.16.). Similarly patients in the high cannabis group with a CATEGO classification of Manic-Depressive psychosis, manic type were compared with patients in the manic control group. (See Figure 3.2.3. and Table 3.2.17.). The Chi-square test for independent samples was used to test for significant differences.

The results (Tables 3.2.16. and 3.2.17.) indicate that with respect to manic psychosis, the high cannabis group does not differ significantly in its profile from the endogenous psychosis. With the paranoid schizophrenics, on the other hand, there are significant differences between the two groups. The 'high cannabis' paranoid schizophrenics have a higher incidence of agitation and simple depression and a lower incidence of auditory hallucinations and hysteria than their 'psychotic control' counterparts.

3.2.3.3. Assessment of improvement in the symptomatology between PSE1 and PSE2

To assess the improvement in symptomatology over the period between PSE1 and PSE2 (7 - 9 days), the McNemar test for the significance of changes was used. Each patient was compared with himself and, in this context, improvement means total improvement i.e. where the patient scored on a particular syndrome on PSE1, this score achieved zero on the second PSE. The syndrome profiles of PSE1 and PSE2 of the high cannabis group, the low cannabis group, and the psychotic control group are presented in Figures 3.2.4., 3.2.5., and 3.2.6. respectively.

Table 3.2.8. CATEGO classification of PSE1 and PSE2 of the high cannabis group

Initials	Urinary cannabinoid level at the time of PSE1 (µgCRC/g creatinine)	PSE1 Score	CATEGO classification of PSE1	Urinary cannabinoid level at the time of PSE2 (µgCRC/g creatinine)	PSE2 Score	CATEGO classification of PSE2	Period between PSE1 and PSE2 (days)
CM	325,40	30	Paranoid schizophrenia	26,6	3	Insufficient symptoms present to allow classification	8
AA(1)	389,30	22	Manic-Depressive psychosis manic-type	116	10	Manic-Depressive psychosis manic type	7
JS	147,60	26	Manic-Depressive psychosis manic type	95,8	15	Manic-Depressive psychosis manic type	7
FJ	157,50	29	Manic-Depressive psychosis, circular type, currently depressed	0	5	Unspecified paranoid psychosis	9
GM	248,60	18	Manic-Depressive psychosis manic type	66,3	5	Insufficient symptoms present to allow classification	7
JvR	184	39	Paranoid schizophrenia	56	16	Paranoid schizophrenia	7
AS	101,70	23	Manic-Depressive psychosis manic type	0	7	Unspecified paranoid psychosis	7
JF	47,1	32	Catatonic schizophrenia	20,6	30	Manic-Depressive psychosis, manic type	8
JG	103	47	Paranoid schizophrenia	0	20	Paranoid schizophrenia	8

Table 3.2.8. (continued)

Initials	Urinary cannabinoid level at the time of PSE1 (µgCRC/g creatinine)	PSE1 Score	CATEGO classification of PSE1	Urinary cannabinoid level at the time of PSE2 (µgCRC/g creatinine)	PSE2 Score	CATEGO classification of PSE2	Period between PSE1 and PSE2 (days)
RJ	80	19	Manic-Depressive psychosis, manic type	150	7	Manic-Depressive psychosis, circular type currently depressed	7
FD	197	51	Paranoid schizophrenia	87,2	14	Unspecified paranoid psychosis	7
RS	176,80	73	Paranoid schizophrenia	53,2	14	Paranoid schizophrenia	7
WW	29,90	12	Manic-Depressive psychosis, manic type	0	2	Insufficient symptoms present to allow classification	7
AP	22,30	38	Paranoid schizophrenia	0	7	Unspecified paranoid psychosis	7
JP	63,40	52	Paranoid schizophrenia	19,7	3	Unspecified paranoid psychosis	7
RM	87,20	30	Catatonic schizophrenia	28,9	13	Unspecified paranoid psychosis	7
AA(2)	136	26	Paranoid schizophrenia	43,2	12	Manic-Depressive psychosis, manic type	7
MI	54,5	19	Unspecified paranoid psychosis	17,3	6	Unspecified paranoid psychosis	7
MJ	42,2	26	Paranoid schizophrenia	0	16	Paranoid schizophrenia	9
GD	113	84	Paranoid schizophrenia	0	26	Unspecified paranoid psychosis	8
mean (± SD)	135,32 (± 98)	33,33 (±19,9)		39,04 (± 44,21)	11,84 (±7,71)	median	7

Table 3.2.9. CATEGO classification of PSE1 and PSE2 of the low cannabis group

Initials	Urinary cannabinoid level at the time of PSE1 (µgCRC/g creatinine)	PSE1 Score	CATEGO classification of PSE1	Urinary cannabinoid level at the time of PSE2 (µgCRC/g creatinine)	PSE2 Score	CATEGO classification of PSE2	Period between PSE1 and PSE2 (days)
DN	19,2	22	Paranoid schizophrenia	10,6	6	Insufficient symptoms present to allow classification	7
AS	49,1	17	Unspecified paranoid psychosis	0	1	Insufficient symptoms present to allow classification	8
RM	10,1	24	Unspecified paranoid psychosis	0	10	Manic-Depressive psychosis, manic type	7
G/W	17	27	Manic-Depressive psychosis, manic type	0	16	Unspecified paranoid psychosis	8
JvdL	21,8	31	Unspecified paranoid psychosis	0	8	Insufficient symptoms present to allow classification	7
AJ	6,7	16	Unspecified paranoid psychosis	0	8	Manic-Depressive psychosis, manic type	7
JM	11,6	28	Paranoid schizophrenia	0	0	Insufficient symptoms present to allow classification	9
LA	13,4	29	Paranoid schizophrenia	0	13	Catatonic schizophrenia	9
BW	7,6	60	Paranoid schizophrenia	0	3	Insufficient symptoms present to allow classification	7
EM	12,1	31	Manic-Depressive psychosis, circular type, currently depressed	0	3	Insufficient symptoms present to allow classification	7

Table 3.2.9. (continued)

Initials	Urinary cannabinoid level at the time of PSE1 (µgCRC/g creatinine)	PSE1 score	CATEGO classification of PSE1	Urinary cannabinoid level at the time of PSE2 (µgCRC/g creatinine)	PSE2 score	CATEGO classification of PSE2	Period between PSE1 and PSE2 (days)
GD	7,6	42	Paranoid schizophrenia	0	28	Paranoid schizophrenia	7
SC	8,5	19	Manic-Depressive psychosis, manic type	0	15	Manic-Depressive psychosis, manic type	8
FJ	23,5	19	Paranoid schizophrenia	0	6	Paranoid schizophrenia	7
YD	21,1	9	Unspecified paranoid psychosis	0	1	Insufficient symptoms present to allow classification	8
EW	56,5	28	Paranoid schizophrenia	0	26	Paranoid schizophrenia	7
DM	16,2	13	Manic-Depressive psychosis, circular type, currently depressed	0	0	Insufficient symptoms present to allow classification	7
AF	35	40	Paranoid schizophrenia	0	30	Paranoid schizophrenia	7
JlR	3,2	5	Insufficient symptoms present to allow classification	0	8	Insufficient symptoms present to allow classification	7
LK	8,6	29	Paranoid schizophrenia	12,9	30	Paranoid schizophrenia	7
DW	19,2	31	Manic-Depressive psychosis, manic type	0	24	Manic-Depressive psychosis, manic type	7
Mean (±SD)	18,4 (±13,9)	26 (±12,3)		1,1 (±3,5)	10,3 (± 9,8)	Median	7

Table 3.2.10. CATEGO classification of PSE1 and PSE2 of the psychotic control group

Initials	Urinary cannabinoid level at the time of PSE1 (µgCRC/g creatinine)	PSE1 score	CATEGO classification of PSE1	Urinary cannabinoid level at the time of PSE2 (µgCRC/g creatinine)	PSE2 score	CATEGO classification of PSE2	Period between PSE1 and PSE2 (days)
KA	-	34	Paranoid schizophrenia	-	19	Manic-Depressive psychosis, circular-type, currently depressed	7
AE	-	16	Paranoid schizophrenia	-	16	Paranoid schizophrenia	8
SG	-	48	Paranoid schizophrenia	-	44	Paranoid schizophrenia	7
JV	-	21	Paranoid schizophrenia	-	15	Paranoid schizophrenia	8
HM	-	50	Paranoid schizophrenia	-	39	Paranoid schizophrenia	7
MP	-	24	Paranoid schizophrenia	-	22	Paranoid schizophrenia	7
GT	-	20	Paranoid schizophrenia	-	12	Paranoid schizophrenia	9
LJ	-	71	Paranoid schizophrenia	-	51	Paranoid schizophrenia	8
GJ	-	41	Paranoid schizophrenia	-	48	Paranoid schizophrenia	7
DP	-	53	Paranoid schizophrenia	-	41	Paranoid schizophrenia	7
LA	-	23	Paranoid schizophrenia	-	10	Paranoid schizophrenia	7
RE	-	48	Paranoid schisophrenia	-	24	Paranoid schizophrenia	8

Table 3.2.10. (continued)

Initials	Urinary cannabinoid level at the time of PSE1 (µgCRC/g creatinine)	PSE1 score	CATEGO classification of PSE1	Urinary cannabinoid level at the time of PSE2 (µgCRC/g creatinine)	PSE2 score	CATEGO classification of PSE2	Period between PSE1 and PSE2 (days)
FA	-	22	Unspecified paranoid psychosis	-	12	Manic-Depressive psychosis, manic type	7
AD(1)	-	22	Paranoid schizophrenia	-	21	Paranoid schizophrenia	8
CK	-	31	Manic-Depressive psychosis, manic type	-	27	Manic-Depressive psychosis, manic type	7
AD(2)	-	35	Manic-Depressive psychosis, manic type	-	28	Manic-Depressive psychosis, manic type	7
JK	-	29	Manic-Depressive psychosis, manic type	-	9	Manic-Depressive psychosis, manic type	7
JM	-	38	Paranoid schizophrenia	-	31	Paranoid schizophrenia	7
NF	-	6	Paranoid schizophrenia	-	2	Insufficient symptoms present to allow classification	7
DB	-	5	Paranoid schizophrenia	-	7	Paranoid schizophrenia	7
Mean (±SD)		21,26 (±18,29)			22,4 (±15,36)	Median	7

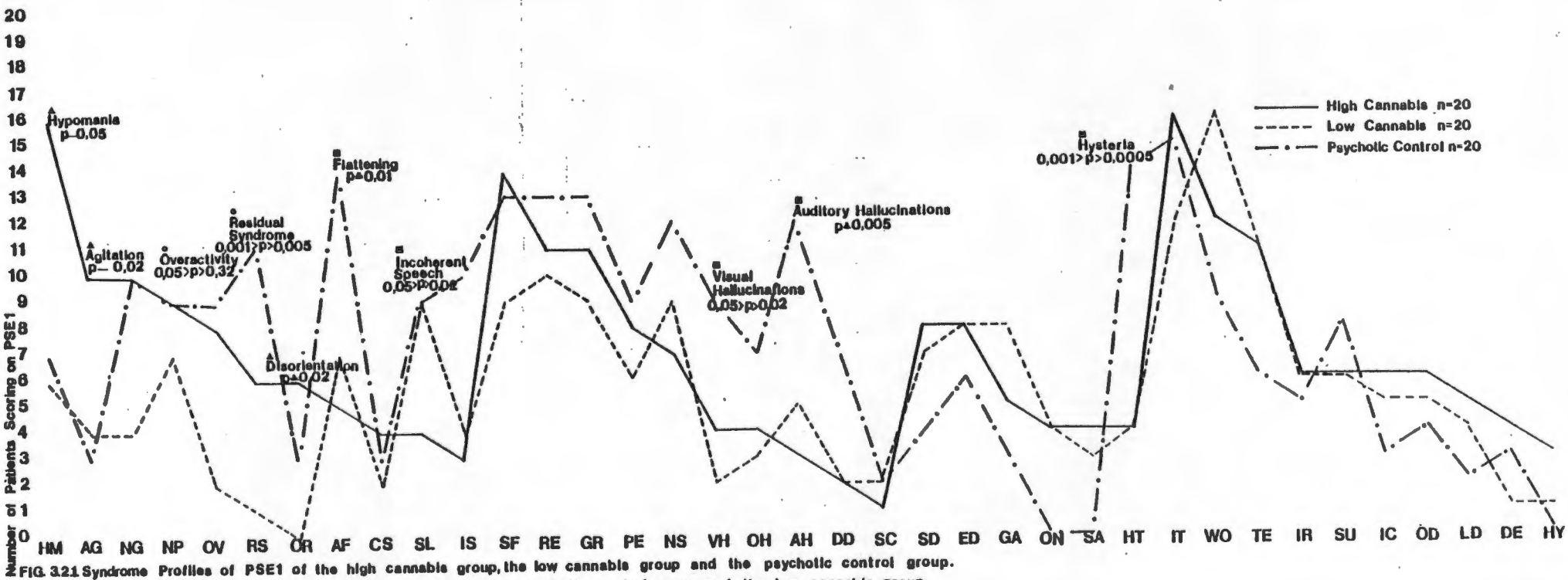


FIG. 3.21 Syndrome Profiles of PSE1 of the high cannabis group, the low cannabis group and the psychotic control group.

▲High cannabis group scores significantly more than the psychotic control group and the low cannabis group.

●High cannabis group, psychotic control group score significantly more than the low cannabis group.

■High cannabis group and the low cannabis group score significantly less than the psychotic control group.

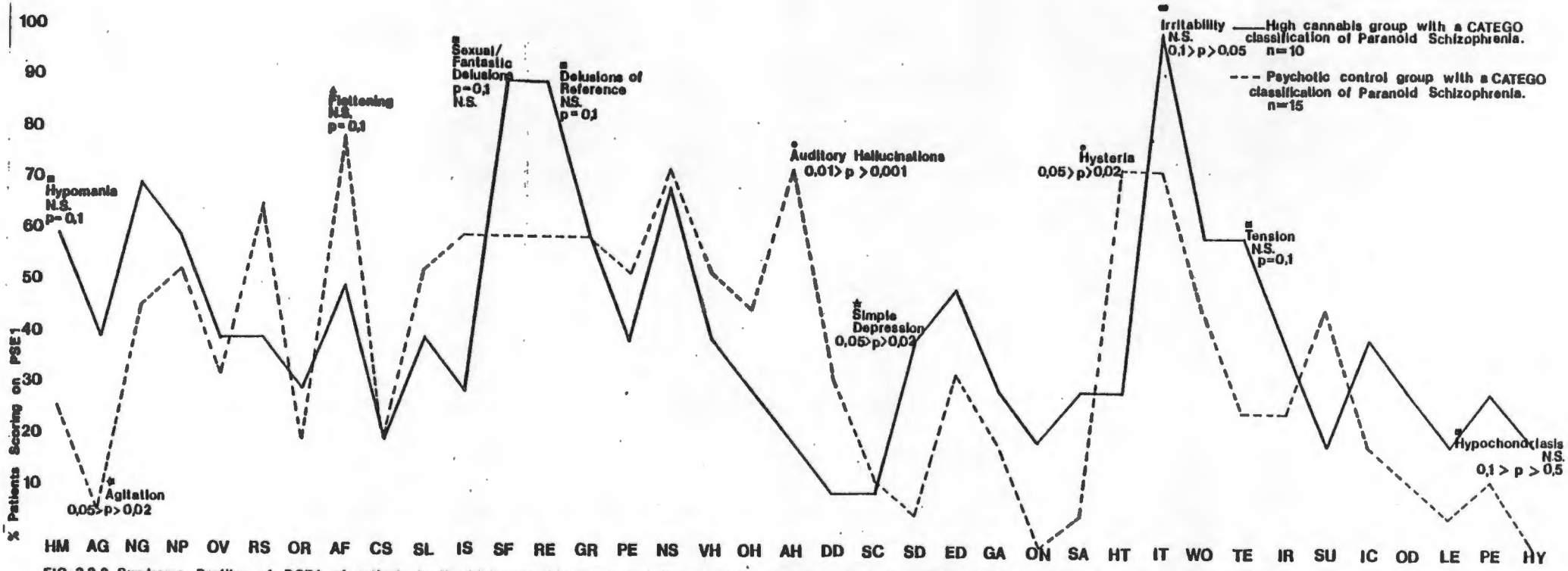


FIG. 3.2.2. Syndrome Profiles of PSE1 of patients in the high cannabis group and the psychotic control group with a CATEGO classification of Paranoid Schizophrenia.

- ★ The high cannabis paranoid schizophrenics score significantly more than the psychotic control paranoid schizophrenics.
- • The high cannabis paranoid schizophrenics score significantly less than the psychotic control paranoid schizophrenics.
- ■ A non-significant trend for the high cannabis paranoid schizophrenics to score more than the psychotic control paranoid schizophrenics.
- ▲ A non significant trend for the high cannabis paranoid schizophrenics to score less than the psychotic control paranoid schizophrenics.

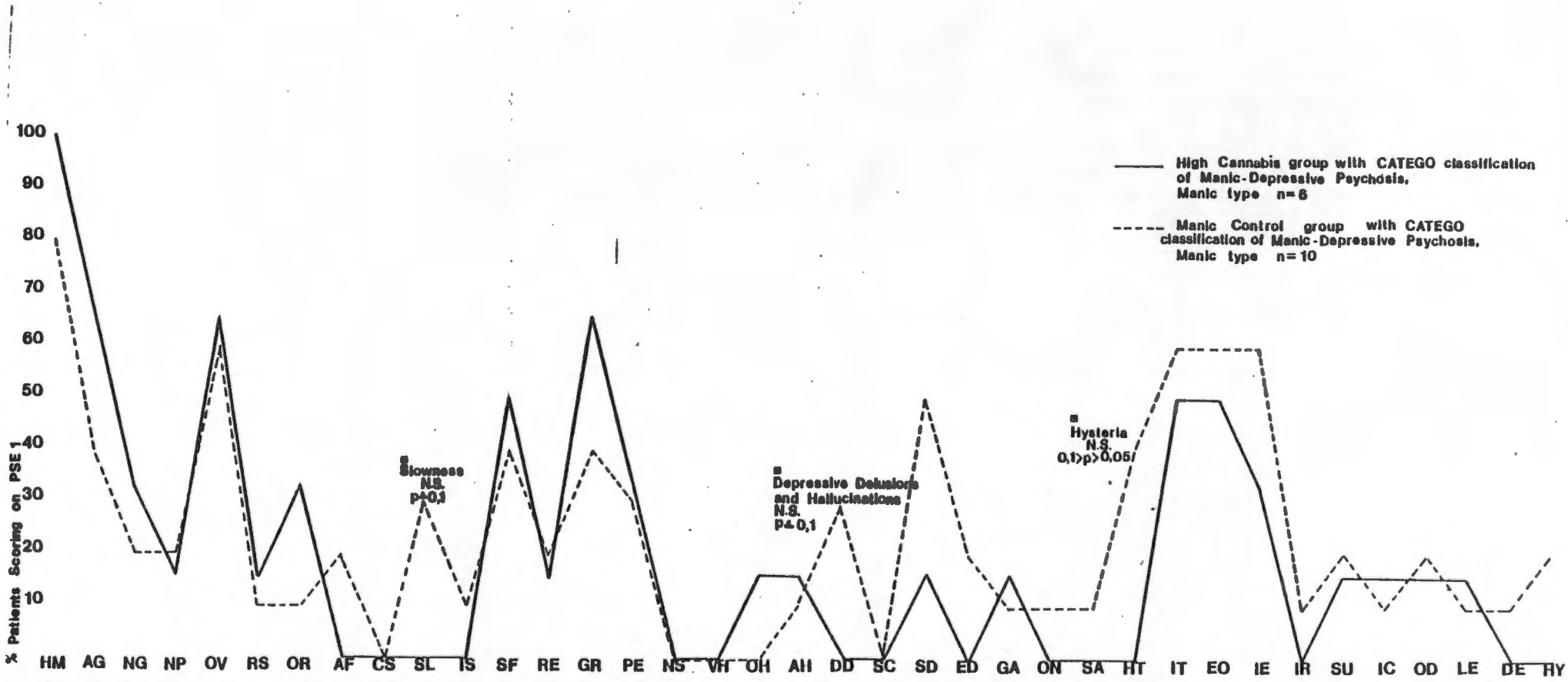


FIG 3.2.3. Syndrome Profile of PSE1 of Patients in the high cannabis group and the negative cannabis group with a CATEGO classification of Manic-Depressive Psychosis, Manic type.
a A non-significant trend for the high cannabis manics to score less than the negative cannabis manics.

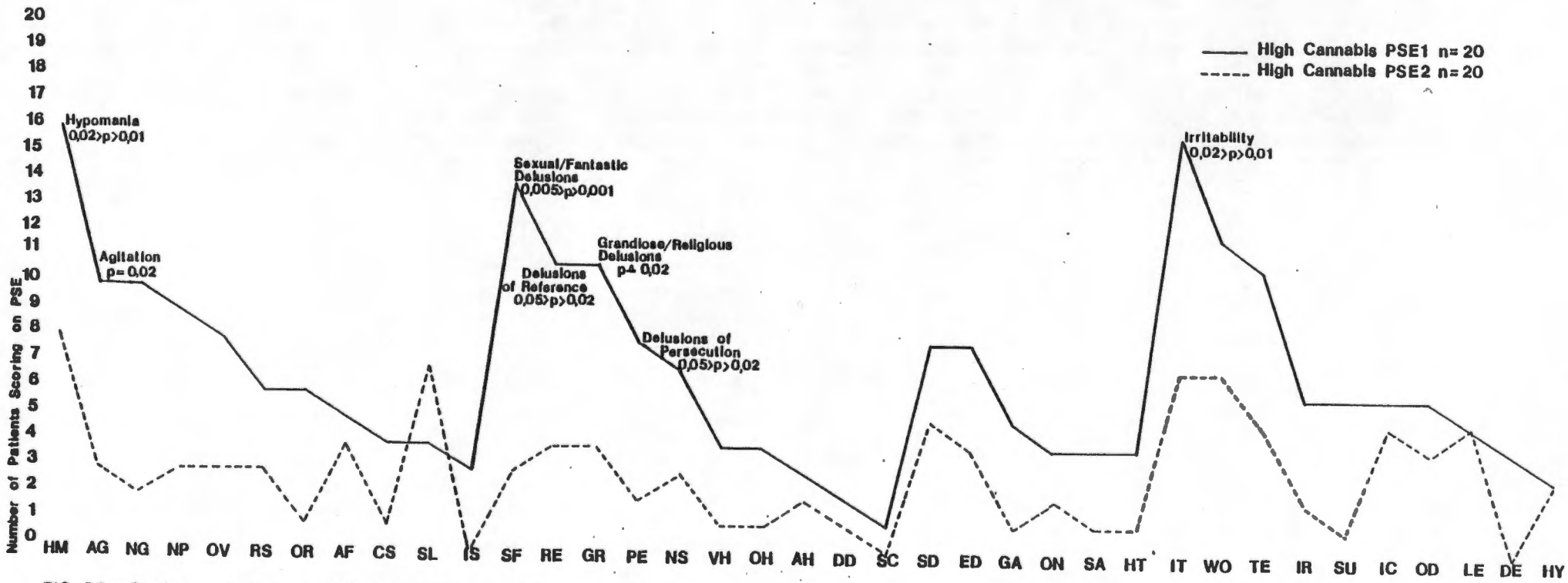


FIG 3.2.4. Syndrome Profiles of PSE1 and PSE2 in the high cannabis group.

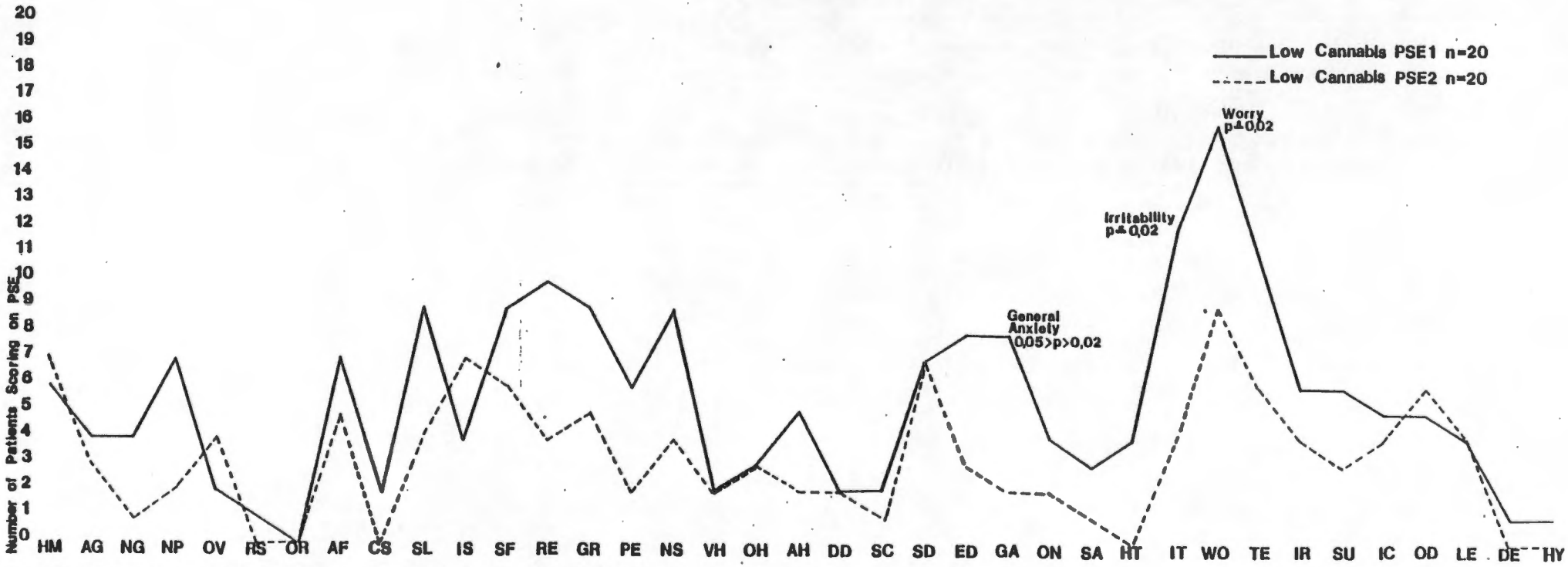


FIG 3.2.5. Syndrome Profiles of PSE1 and PSE2 in the low cannabis group.

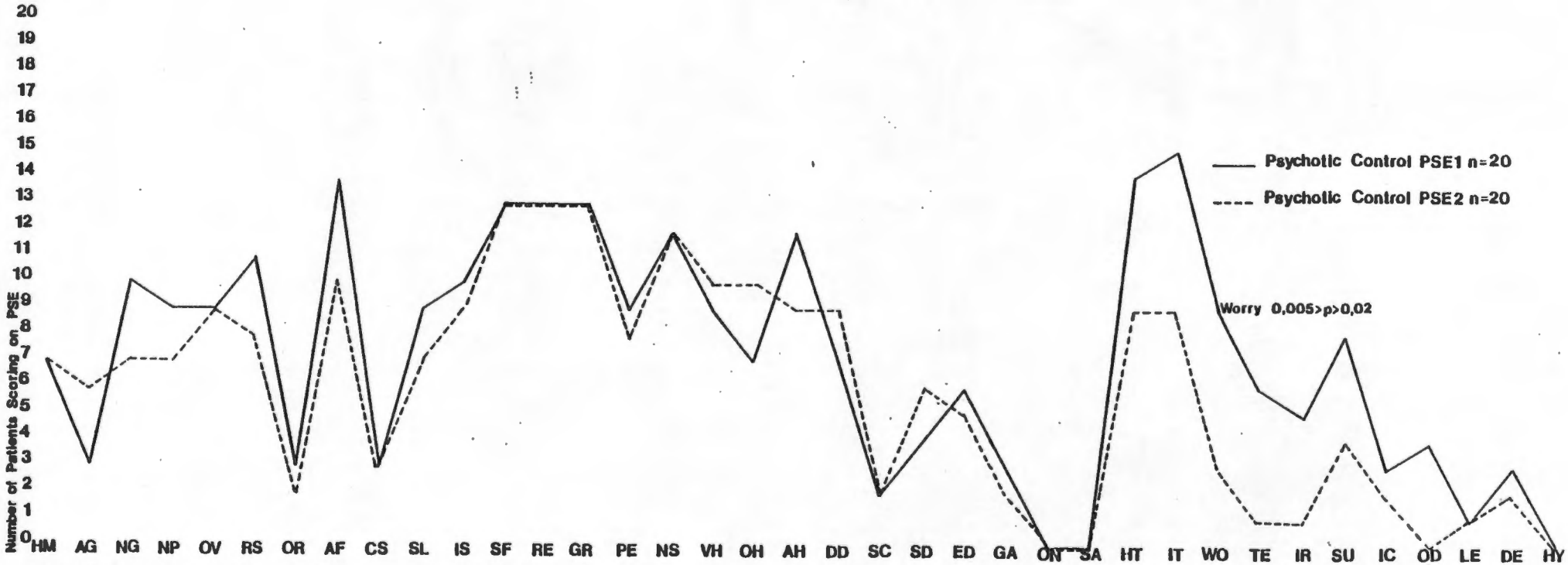


FIG. 3.2.6. Syndrome profiles of PSE1 and PSE2 in the psychotic control group.

Table 3.2.11. Features of the syndrome profiles of PSE1 in the high cannabis group

PSE Syndromes (numbers refer to number of patients scoring on a syndrome)

More than 10 patients scoring		6 - 10 patients scoring		5 or less patients scoring	
Hypomania	16	Agitation	10	Flattening	5
Sexual & fantastic delusions	14	Selfneglect	10	Slowness	4
Delusions of reference	11	Overactivity	8	Incoherent speech	3
Grandiose & religious delusions	11	Residual syndrome	8	Visual hallucinations	4
Irritability	16	Disorientation	6	Olfactory hallucinations	4
Worry	12	Non-specific psychosis	9	Auditory hallucinations	3
Tension	12	Delusions of persecution	8	Depressive delusions and hallucinations	2
		Nuclear syndrome	8	Sub-cultural delusions	1
		Simple depression	8	General anxiety	5
		Special features of depression	8	Obsessional neurosis	4
		Ideas of reference	6	Situational anxiety	4
		Social unease	6	Hysteria	4
		Loss of interest and concentration	6	Lack of energy	4
		Other symptoms of depression	6	Depersonalization	4
				Hypochondriasis	3
				Catatonic syndrome	4

Table 3.2.12. Features of the syndrome profiles of PSE1 in the low cannabis group.

PSE Syndromes

More than 10 patients scoring		6 - 10 patients scoring		5 or less patients scoring	
Irritability	12	Hypamania	6	Agitation	4
Worry	16	Non-specific psychosis	7	Self neglect	4
Tension	11	Flattening	7	Residual syndrome	1
		Slowness	9	Overactivity	1
		Sexual and fantastic delusions	9	Disorientation	0
		Delusions of reference	10	Incoherent speech	4
		Grandiose and religious delusions	6	Visual hallucinations	2
		Delusions of persecution	6	Olfactory hallucinations	3
		Nuclear syndrome	9	Auditory hallucinations	5
		Simple depression	7	Depressive delusions and hallucinations	2
		Special features of Depression	8	Sub-cultural delusions	2
		General anxiety	8	Obsessional neurosis	4
		Ideas of reference	6	Situational anxiety	3
		Social unease	6	Hysteria	4
				Loss of interest and concentration	5
				Other symptoms of depression	5
				Lack of energy	4
				Depersonalization	1
				Hypochondriasis	2
				Catatonic syndrome	2

Table 3.2.13. Features of the syndrome profiles of PSE1 in the psychotic control group

PSE Syndromes

More than 10 patients scoring		6 - 10 patients scoring		5 or less patients scoring	
Residual syndrome	11	Hypomania	7	Agitation	3
Flattening	14	Non-specific psychosis	9	Disorientation	3
Sexual and fantastic delusions	13	Overactivity	9	Sub-cultural delusions	3
Delusions of reference	13	Slowness	9	Simple depression	4
Grandiose and religious delusions	13	Self neglect	10	General anxiety	3
Nuclear syndrome	12	Incoherent speech	10	Obsessional neurosis	1
Auditory hallucinations	12	Delusions of persecution	9	Incoherent speech	3
Hysteria	14	Visual hallucinations	9	Lack of energy	1
Irritability	15	Olfactory hallucinations	7	Other symptoms of Depression	4
		Depressive delusions and hallucinations	7	Depersonalization	3
		Special features of Depression	6	Hypochondriasis	0
		Situational anxiety	10	Catatonic syndrome	3
		Worry	9	Ideas of reference	5
		Tension	8	Loss of interest and concentration	3
		Social unease	8		

Table 3.2.14. CATEGO syndrome abbreviations

HM	Hypomania
AG	Agitation
NG	Self neglect
NP	Non-specific psychosis
OV	Overactivity
RS	Residual Syndrome
OR+	Disorientation
AF	Flattening
CS	Catatonic syndrome
SL	Slowness
IS	Incoherent speech
SF	Sexual and fantastic delusions
RE	Delusions of reference
GR	Grandiose and religious delusions
PE	Delusions of persecution
NS	Nuclear syndrome
VH	Visual hallucinations
OH	Olfactory hallucinations
AH	Auditory hallucinations
DD	Depressive delusions and hallucinations
SC	Sub-cultural delusions of hallucinations
SD	Simple depression
ED	Special features of depression
GA	General anxiety
ON	Obsessional neurosis
SA	Situational anxiety
HT	Hysteria
IT	Irritability
WO	Worry

TE Tension

IR Ideas of reference

SU Social unease

IC Loss of interest and concentration

OD Other symptoms of depression

LE Lack of energy

DE Depersonalization

HY Hypochondriasis

+Organic impairment (OR) was not assessed on the PSE. However, it was felt that the orientation of a patient was an important factor of the psychosis. Therefore, by referral to the clinical notes some assessment of the orientation of the patient could be made; a patient was rated as '2' if he was totally disorientated, '1' if he was orientated for time or place only, and '0' if he was correctly orientated. The abbreviation 'OR' used by the PSE for organic impairment now represents disorientation. This score is not reflected in the total PSE scores.

Table 3.2.15. Significant differences in the PSE on admission between the high cannabis group, the low cannabis group, and the psychotic control group

<u>High cannabis group scores significantly more than the psychotic control group and the low cannabis group in:-</u>

Syndrome	No. of patients out of 20 scoring on syndrome			p value
	High	Low	Control	
Hypomania	16	6	7	0,05
Agitation	10	4	3	≤ 0,02
Disorientation	6	0	3	≤ 0,02

<u>High cannabis group and psychotic control group score significantly more than the low cannabis group in:-</u>

Residual syndrome	6	1	11	0,01>p>0,0005
Overactivity	8	2	9	0,05>p>0,02

<u>High cannabis group and low cannabis group score significantly less than the psychotic control group in:-</u>

Hysteria	4	4	14	0,001>p>0,0005
Auditory Hallucinations	3	5	12	≤ 0,005
Flattening	5	7	14	≤ 0,01
Visual Hallucinations	4	2	9	0,05>p>0,02
Incoherent speech	3	4	10	0,05>p>0,02

Table 3.2.16. Summary of significant differences and non-significant trends in PSE1 between the high cannabis patients and psychotic control patients with CATEGO classifications of paranoid schizophrenia

Syndrome	Number of patients scoring on syndrome		p value
	High cannabis n = 10	Psychotic control n = 15	
Agitation	4	1	0,05>p>0,02
Auditory Hallucinations	2	11	0,01>p>0,001
Simple Depression	4	1	0,05>p>0,02
Hysteria	3	11	0,05>p>0,02
Hypomania	6	4	0,1 (NS)
Flattening	5	12	0,1 (NS)
Sexual and Fantastic delusions	9	9	0,1 (NS)
Delusions of reference	9	9	0,1 (NS)
Irritability	10	11	0,1>p>0,05 (NS)
Tension	6	4	0,1 (NS)
Hypochondriasis	3	2	0,1>p>0,05 (NS)

Table 3.2.17. Non-significant trends in the high cannabis patients with CATEGO classifications of Manic-Depressive psychosis, manic type, and the manic control group (PSE1)

Syndrome	Number of patients scoring on syndrome		p value
	High cannabis n = 6	Manic control n = 10	
Slowness	0	3	0,1 (NS)
Depressive delusions and hallucinations	0	3	0,1 (NS)
Hysteria	0	4	0,1>p>0,05 (NS)

A summary of significant improvements are presented in Table 3.2.18.

The results in Table 3.2.18 indicate that the overall trend in the high cannabis group was one of marked improvement. Significant improvements were registered in the following syndromes - hypomania, agitation, sexual and fantastic delusions, delusions of reference, grandiose and religious delusions, delusions of persecution, and irritability.

The profiles of the low cannabis group and the psychotic control group indicate significant improvement only in some of the neurotic syndromes - general anxiety, worry, and irritability. It must be noted that the psychotic control group shared virtually no improvement in the psychotic symptomatology in the period between PSE1 and PSE2.

To assess any consistant improvement from PSE1 to PSE2 in the 4 sub-scores and the total scores in the three groups, the Wilcoxon matched-pairs, signed-ranks test (corrected for ties) was used. In this context improvement indicated that there was a decrease in score (eg. 3 → 2) and not necessarily a total improvement (eg. 2 → 0) as was the case with the McNemar test for the significance of changes. The results are summarized in Table 3.2.19.

Table 3.2.19. indicates that there was a significant improvement in all the sub-scores (BSO, DAH, SNR, and NSN) with the exception of (in the high cannabis group) the specific neurotic syndrome sub-scores. Although all three groups improved significantly on the total PSE score, it is clear from the median values that the high cannabis

group and the low cannabis group improve markedly whereas the psychotic control group improved only marginally.

All three groups were on neuroleptic medication throughout the period between PSE assessments. There were no significant differences in the total amount of medication among the groups. However, it was decided to select a sub-population from each group who were matched as closely as possible for total amount of medication received. The Wilcoxon matched-pairs signed-ranks test was used and the results are presented in Table 3.2.20.

Table 3.2.20. indicates that the high cannabis group improved in all four sub-scores, the low cannabis group and the psychotic control group improved in only some of the sub-scores. However, all three groups improved significantly on the overall PSE score, but the median values of the total scores in each group indicate that the high cannabis and low cannabis groups improved to a marked extent while the improvement in the psychotic control group was marginal. It must be remembered that the three groups here were matched as closely as possible for the total amount of medication during the period between PSEs. This close matching of the groups for medication did not in any way reduce the magnitude of the improvement.

3.3. PSE SYNDROMES CORRELATED WITH URINARY CANNABINOID CONCENTRATIONS

The Spearman rank correlation coefficient (corrected for ties) was used to correlate urinary cannabinoid concentrations at the time of the first PSE with the syndrome scores of PSE1. Those syndromes that had a significant correlation with urinary cannabinoid concentrations are presented in Table 3.3.1.

Table 3 2.18. Summary of significant improvements[+] in syndromes from PSE1 to PSE2 in the high cannabis group, the low cannabis group and the psychotic control group

Syndrome	Number of patients out of 20 scoring on syndrome								
	High Cannabis			Low Cannabis			Psychotic control		
	PSE1	PSE2	p value	PSE1	PSE2	p value	PSE1	PSE2	p value
Hypomania	16	8	0,02>p>0,01	6	7	NS	7	7	NS
Agitation	10	3	0,02	4	3	NS	4	6	NS
Sexual & Fantastic Delusions	14	3	0,005> p>0,001	9	6	NS	13	13	NS
Delusions of Reference	11	4	≤ 0,02	10	4	NS	13	13	NS
Grandiose & religious Delusions	11	4	≤ 0,02	9	5	NS	13	13	NS
Delusions of Persecution	8	2	0,05>p>0,02	7	1	NS	9	8	NS
General anxiety	5	1	NS	8	2	0,05>p>0,02	3	2	NS
Worry	12	7	NS	16	9	≤0,02	9	3	0,05>p>0,02
Irritability	16	7	0,02>p>0,01	12	4	≤0,02	15	9	NS

[+]Improvement means a total improvement i.e. scoring on a syndrome in PSE1 and not scoring on that syndrome in PSE2.

Table 3.2.19. Significant improvements in syndrome sub-scores from PSE1 to PSE2 in the high cannabis group, the low cannabis group and the psychotic control group

BEHAVIOUR, SPEECH AND OTHER SYNDROMES

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	8	2	$<0,01$
Low cannabis	6	2	$0,02<p<0,01$
Psychotic control	9,5	8	$0,02<p<0,01$

DELUSIONAL AND HALLUCINATORY SYNDROMES

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	10,5	4	$<0,01$
Low cannabis	10	1,5	$<0,01$
Psychotic control	14,5	12,5	$<0,01$

SPECIFIC NEUROTIC SYNDROME

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	2	2	NS
Low cannabis	3	0,5	$<0,01$
Psychotic control	2	1,5	$<0,01$

NON-SPECIFIC NEUROTIC SYNDROME

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	8,5	3	$<0,01$
Low cannabis	6,5	2,5	$0,02<p<0,01$
Psychotic control	5	3	$<0,01$

TOTAL PSE SCORE

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	30	12,5	$<0,01$
Low cannabis	27,5	9	$<0,01$
Psychotic control	30	23	$<0,01$

Table 3.2.20. Significant improvements in syndrome sub-scores from PSE1 to PSE2 in the high cannabis group (n=10), the low cannabis group (n=10), and the psychotic control group (n=10) matched for total neuroleptic medication received between PSE assessments

BEHAVIOUR, SPEECH AND OTHER SYNDROMES

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	8	2	<0,01
Low cannabis	6,5	2	NS
Psychotic control	8,5	6	NS

DELUSIONAL AND HALLUCINATORY SYNDROMES

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	10,5	4,5	<0,01
Low cannabis	15	3,5	<0,01
Psychotic control	14,5	12,5	0,05

SPECIFIC NEUROTIC SYNDROME

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	2	0	< 0,01
Low cannabis	4,5	1,5	0,02
Psychotic control	2,5	2,5	NS

NON-SPECIFIC NEUROTIC SYNDROME

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	7,5	2,5	<0,01
Low cannabis	6,5	5	NS
Psychotic control	6	3	0,02

TOTAL PSE SCORE

Group	Median value of PSE1	Median value of PSE2	p value
High cannabis	30	8,5	<0,01
Low cannabis	30	1,5	<0,01
Psychotic control	34,5	23	0,02

Table 3.3.1. Syndrome significantly correlated with urinary cannabinoid concentrations

Syndrome	rho	Correlation	p value
Hypomania	0,4894	positive	0,001
Overactivity	0,3176	positive	0,05
Disorientation	0,4430	positive	0,01>p>0,001

These results indicate that hypomania, overactivity, and disorientation were probably dose-related.

3.4. SERUM CREATININE PHOSPHOKINASE (CPK) AND SERUM LACTATE DEHYDROGENASE (LDH) DETERMINATIONS

The serum CPK and serum LDH determinations are presented in Tables 3.4.1., 3.4.2., and 3.4.3.

Twenty percent of patients in the high cannabis group, 50% in the low cannabis group and 35% in the psychotic control group had CPK levels within the normal range (0-130 IU/L). Eighty percent of patients in the high cannabis group, 50% in the low cannabis group and 65% in the psychotic control group had CPK levels above the upper limit of normal. A summary of CPK levels in the three groups is presented in Table 3.4.4.

Table 3.4.1. Serum CPK and serum LDH determinations in the high cannabis group (CPK n=15; LDH n=12)

Patient	CPK (IU/L)	LDH (IU/L)
CM	228	422
AA(1)	446	447
JS	4425	788
JvR	125	679
JF	99	732
FD	1077	469
RS	332	659
WW	1914	594
AP	174	876
JP	1622	738
RM	125	-
AA(2)	445	-
MI	111	890
MJ	155	-
GP	273	769
Median	273	706
Normal value	0-130 IU/L	0-375 IU/L

Table 3.4.2. Serum CPK and serum LDH determinations in the low cannabis group (CPK n=10; LDH n=9)

Patient	CPK (IU/L)	LDH (IU/L)
DN	160	858
JvdL	131	-
JM	125	237
LA	131	220
BW	111	140
YD	-	494
EW	958	-
DM	765	400
AF	81	460
JlR	2007	923
LK	-	738
DW	130	-
Median	131	460
Normal range	0-130 IU/L	0-375 IU/L

Table 3.4.3 Serum CPK and serum LDH determinations in the psychotic control group (CPK n=16; LDH n=13)

Patient	CPK (IU/L)	LDH (IU/L)
KA	105	593
AE	137	626
SG	192	237
HM	131	434
MP	81	237
GT	125	858
LJ	228	429
GJ	242	-
DP	534	2167
LA	290	137
RE	87	244
FA	155	-
AD(1)	273	62
CK	3100	3407
JK	806	1154
DB	125	-
Median	146	432
Normal range	0-130 IU/L	0-375 IU/L

Table 3.4.4. Summary of serum CPK levels in the high cannabis group, the low cannabis group, and the psychotic control group

Group	Range	Median CPK level (IU/L)	Number of samples
High cannabis	99–1914	273	15
Low cannabis	81–2007	131	10
Psychotic control	81–3100	146	17

Normal range: 0–130 IU/L

p value: 0,05

These results indicate that there was a significant difference among the three groups with respect to the serum CPK levels, with the high cannabis group having significantly more elevated levels than the low cannabis group and the psychotic control group. (Chi-square test used).

A correlation between serum CPK levels and the PSE score on over-activity on PSE1 was done using the Spearman rho correlation co-efficient. There was a significant correlation between overactivity and CPK levels ($p = 0,02$).

Serum LDH determinations

No patients in the high cannabis group, 11% of patients in the low cannabis group, and 35% in the psychotic control group had levels within the normal range (0–375 IU/L). All the patients in the high cannabis group, 89% of patients in the low cannabis group, and 65% of patients in the psychotic control group had LDH levels above the upper limit of normal. A summary of LDH levels is presented in Table 3.4.5.

Table 3.4.5. Summary of LDH determinations in the high cannabis group, the low cannabis group and the psychotic control group

Group	Range	Median LDH level (IU/L)	Number of samples
High cannabis	422-890	706	12
Low cannabis	140-923	460	9
Psychotic control	137-3407	432	14

Normal range: 0-375 IU/L
p value: 0,02

These results indicate that there was a significant difference among the three groups with respect to the serum LDH determinations; the high cannabis group had significantly more elevated levels than the low cannabis group and the psychotic control group.

There was no significant correlation between the PSE score on over-activity on PSE1 and the LDH levels.

3.5. ASSESSMENT OF URINARY CANNABINOID CONCENTRATIONS

3.5.1. Daily urinary cannabinoid determinations

Daily urinary cannabinoids were determined in patients in the high cannabis group and the low cannabis group until no cannabinoids were detected for two successive days (see Table 3.5.1. and 3.5.2.). Urinary cannabinoid results are reported as µgCRC/g creatinine to allow quantification (see Section 2.3.).

Tables 3.5.1. and 3.5.2. and Figures 3.5.1. and 3.5.2. indicate that the excretion of cannabinoids is not constant.

Table 3.5.1. Daily urinary cannabinoid concentrations in the high cannabis group

Daily urinary cannabinoid concentration (µg CRC/g creatinine)

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
CM	200,9	260,5	106,5	61	71	40,3	33	26	26,6	24	22	Neg	Neg												
AA[1]	290,3	470	457	375	389,3	130	147	73,6	98,8	56	42,1	116	86	72,6	48,9	81,5	80	76	69	65,4	42	36	35	Neg	Neg
JS	211,8	147,6	122	114,5	88,8	54,5	38,2	42,1	28,2	103	95,8	54	51	Neg	Neg										
FJ	250,1	148,7	127	86	71,5	45,9	65,4	87,1	72,1	65	60,1	37	22,3	Neg	Neg										
GM	303	248,6	188,7	66,3	86,1	80,3	72	50,2	35,9	Neg	Neg														
JvR	109	213,8	72,9	94,3	184	100,1	82,3	67,4	98	75,3	52,8	56	39,6	26,7	Neg	Neg									
AS	101,7	61	46,7	53,7	29,2	Neg	Neg																		
JF	292	72,9	62	225,9	86,9	64,5	60,5	61,1	57,3	Neg	Neg														
JG	103	47	21	Neg	Neg																				
RJ	80	128,6	94,7	82,9	133,7	94	86,4	62,4	150	25	Neg	Neg													
FD	432,8	187	28,4	87,4	46,9	197,2	75,6	53,1	57,8	69,7	32,3	43,2	87,2	61,7	25,5	43,2	25	Neg	Neg						
RS	289,5	300,1	176,8	85,6	42,6	64	56,7	53,9	39,2	53,2	Neg	Neg													
WW	86,8	93,7	92,3	53,5	32,5	31,4	28,3	26	25,7	Neg	Neg														
AP	106,4	81	57,4	50,5	35,7	22,3	25	26,3	48,3	56,4	45.3	27,3	Neg	Neg											
JP	310	87	75	82,4	63,4	57,5	45,7	34,5	29,9	30,8	51	19,7	27,6	Neg	Neg										
RM	273	309,4	164,2	87,2	57,6	42,6	49,4	38,7	31,1	26,7	28,8	Neg	Neg												
AA[2]	103	136	130	60,2	39	75,4	64,2	51,3	43,1	46,1	Neg	Neg													
MI	383,5	144,7	49,8	54,4	59,5	63,7	53	50,9	40,1	20,3	17,3	Neg	Neg												
MJ	435	161,1	44,4	42	30,4	34,7	42,7	32,8	23,3	Neg	Neg														
GD	412,5	311,9	152,9	113	64	103,5	46	32,4	42,2	Neg	Neg														

Table 3.5.2. Daily urinary cannabinoid concentrations in the low cannabis group.

	Daily urinary cannabinoid concentration (µgCRC/g creatinine)										
	1	2	3	4	5	6	7	8	9	10	11
Patient											
DN	19,2	12,4	10,0	19,4	14,5	11,5	10,6	Neg	Neg		
AS	57,3	44,3	48,5	24,7	26,3	20,1	49,1	Neg	Neg		
RM	10,1	10,4	Neg	Neg							
GvW	24,9	24,6	17,0	Neg	Neg						
JvdL	20,1	21,8	18,3	12,2	13,6	Neg	Neg				
AJ	6,7	4,5	Neg	Neg							
JM	4,9	6,4	11,6	Neg	Neg						
LA	13,4	9,7	Neg	Neg							
BW	10,5	8,0	7,6	Neg	Neg						
EM	13,5	13,3	38,0	12,1	Neg	Neg					
GD	7,6	7,8	Neg	Neg							
SC	8,5	9,5	Neg	Neg							
FJ	10,5	7,2	Neg	Neg							
YD	21,1	18,1	Neg	Neg							
EW	56,5	45,5	60,0	38,8	60,0	Neg	Neg				
DM	26,2	22,9	16,2	11,3	14,2	20,2	15,0	Neg	Neg		
AF	18,4	52,5	49,9	34,9	29,7	21,0	Neg	Neg			
JlR	9,3	8,4	6,1	Neg	Neg						
LK	29,8	24,7	8,6	6,8	7,9	7,3	Neg	Neg			
DW	49,5	37,4	21,0	Neg	Neg						

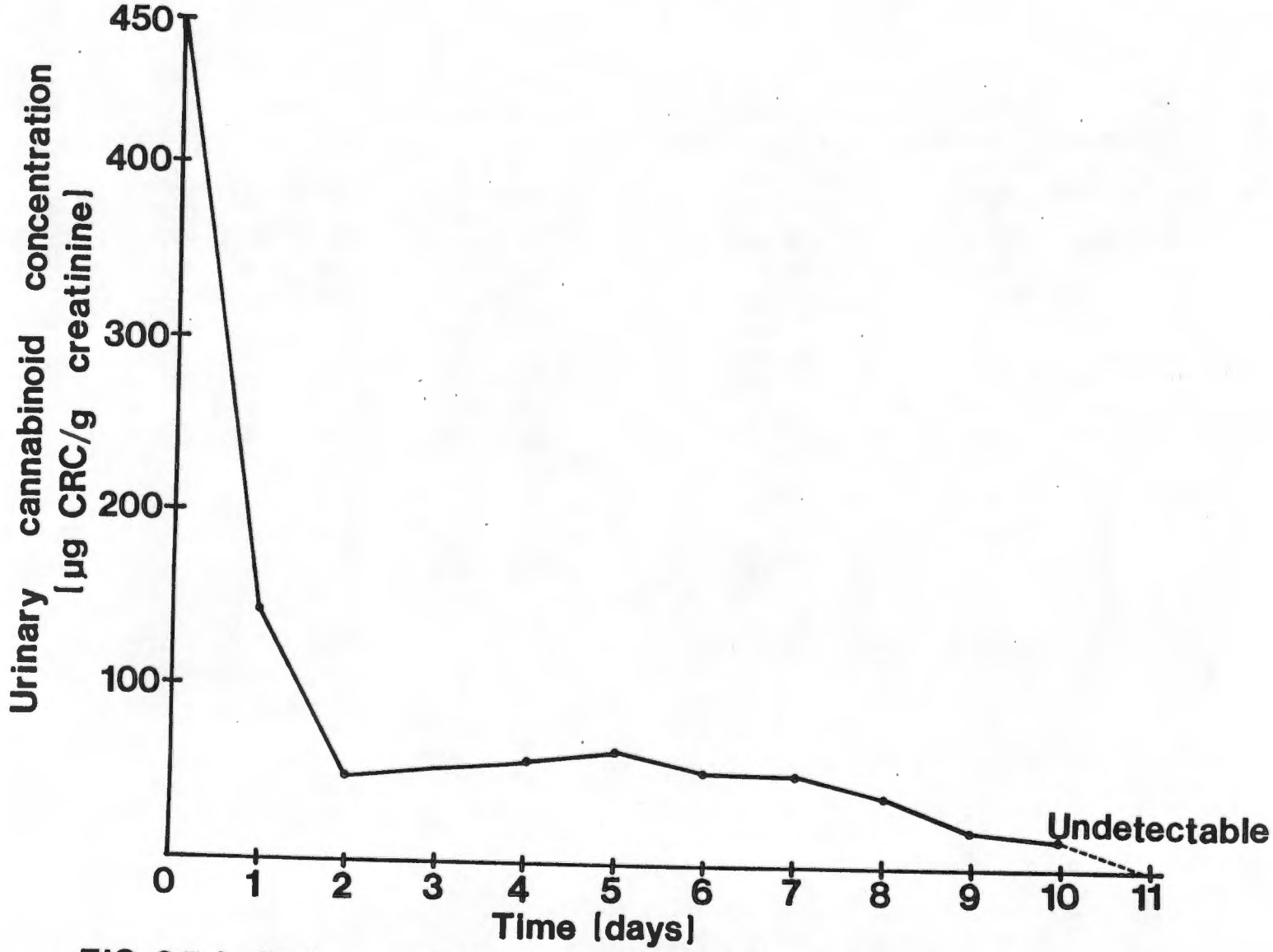


FIG. 3.5.1. Daily urinary cannabinoid concentration in a high cannabis patient (M I)

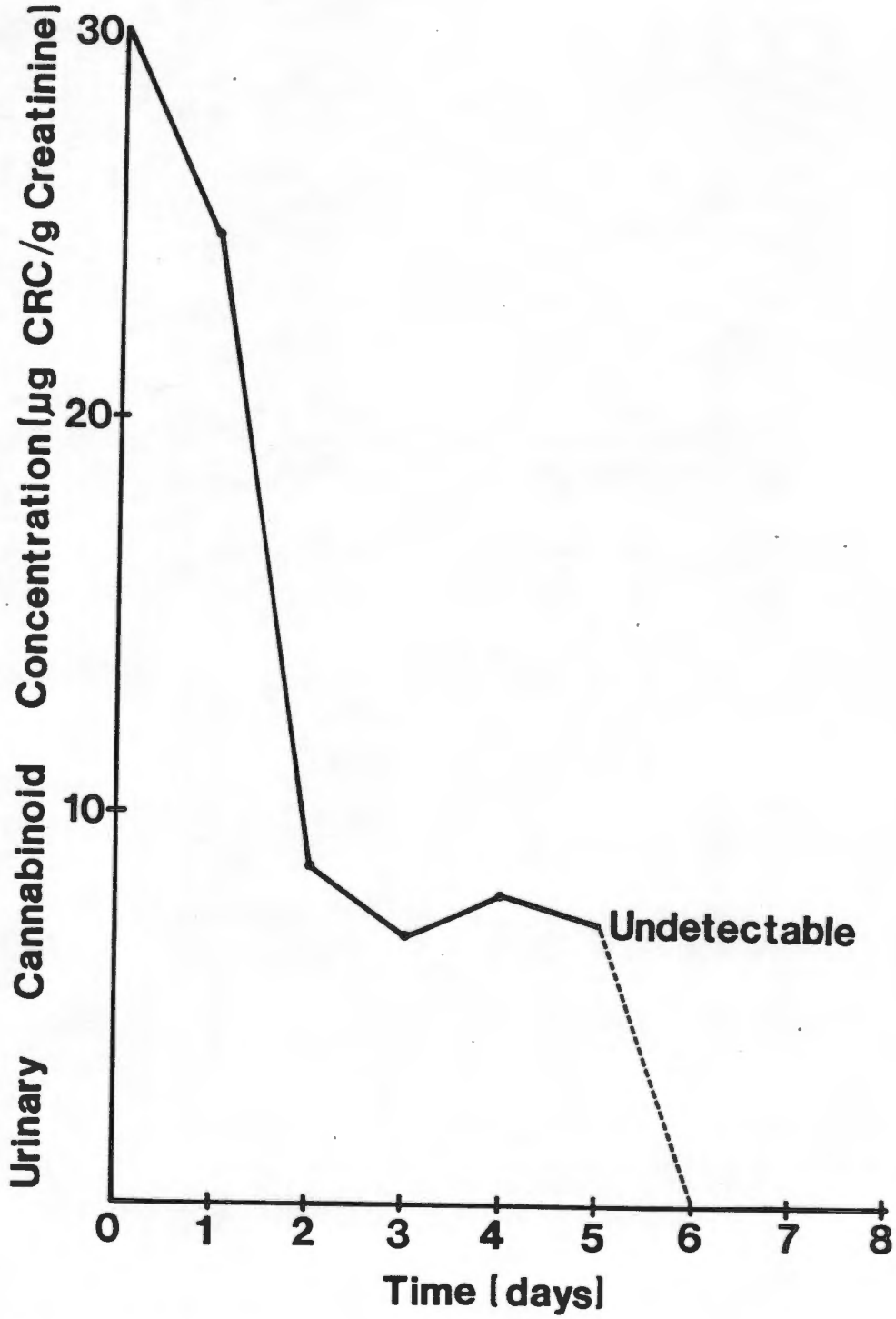


FIG. 3.5.2. Daily urinary cannabinoid concentration in a low cannabis patient (LK)

3.5.2. Time Period required for a patient to have undetectable urinary cannabinoids

A linear regression analysis of the initial urinary cannabinoid concentration versus days to level below detection was done on data obtained from the cannabis groups (see Table 3.5.3.). A slope of 0,0254 $\pm$ 0,0008*, a y-intercept of 4,11 $\pm$ 0,334* and r = 0,749 ($p<0,001$) were obtained. Inherent factors in the assay used i.e. a cut-off point of 20ng/mℓ taken as zero may account for the line not passing through the origin. However, the following equation may be useful to calculate the number of days a patient would require to be free of urinary cannabinoids if the initial concentration was known:

$$y = mx + c$$

where

y = number of days to undetectable levels
m = slope
x = initial concentration (µgCRC/g creatinine)
c = y-intercept

*Equations to calculate the slope $\pm$ confidence intervals and the y-intercept $\pm$ confidence intervals were from Scientific Tables, Documenta Geigy, seventh Edition 1970 p 174.

Table 3.5.3. Initial urinary cannabinoid concentrations of patients in the high cannabis group and the low cannabis group and the period required for levels to be undetectable

Patient	*	Time Period (Days)
CM	200,9	11
AA(1)	390,3	23
JS	211,8	13
FJ	250,1	14
GM	303	9
JvR	109	14
AS	101,7	5
JF	292	9
JG	103	3
RJ	80	10
FD	432,8	17
RS	289,5	10
WW	86,8	9
AP	106,4	12
JP	310	13
RM	273	11
AA	103	10
MI	383,5	11
MJ	435	9
GD	412,5	9

Patient	*	Time Period (Days)
DN	19,2	7
AS	57,3	7
RM	10,1	2
GvW	24,9	3
JvdL	20,1	6
AJ	6,7	2
JM	4,9	3
LA	13,4	2
BW	10,5	3
EM	13,5	4
GD	7,6	2
SC	8,5	2
FJ	10,5	2
YP	21,1	2
EW	56,5	5
DM	26,2	7
AF	18,4	6
JlR	9,3	3
LK	29,8	6
DW	49,5	3

*Initial urinary cannabinoid concentration (µgCRC/g creatinine)

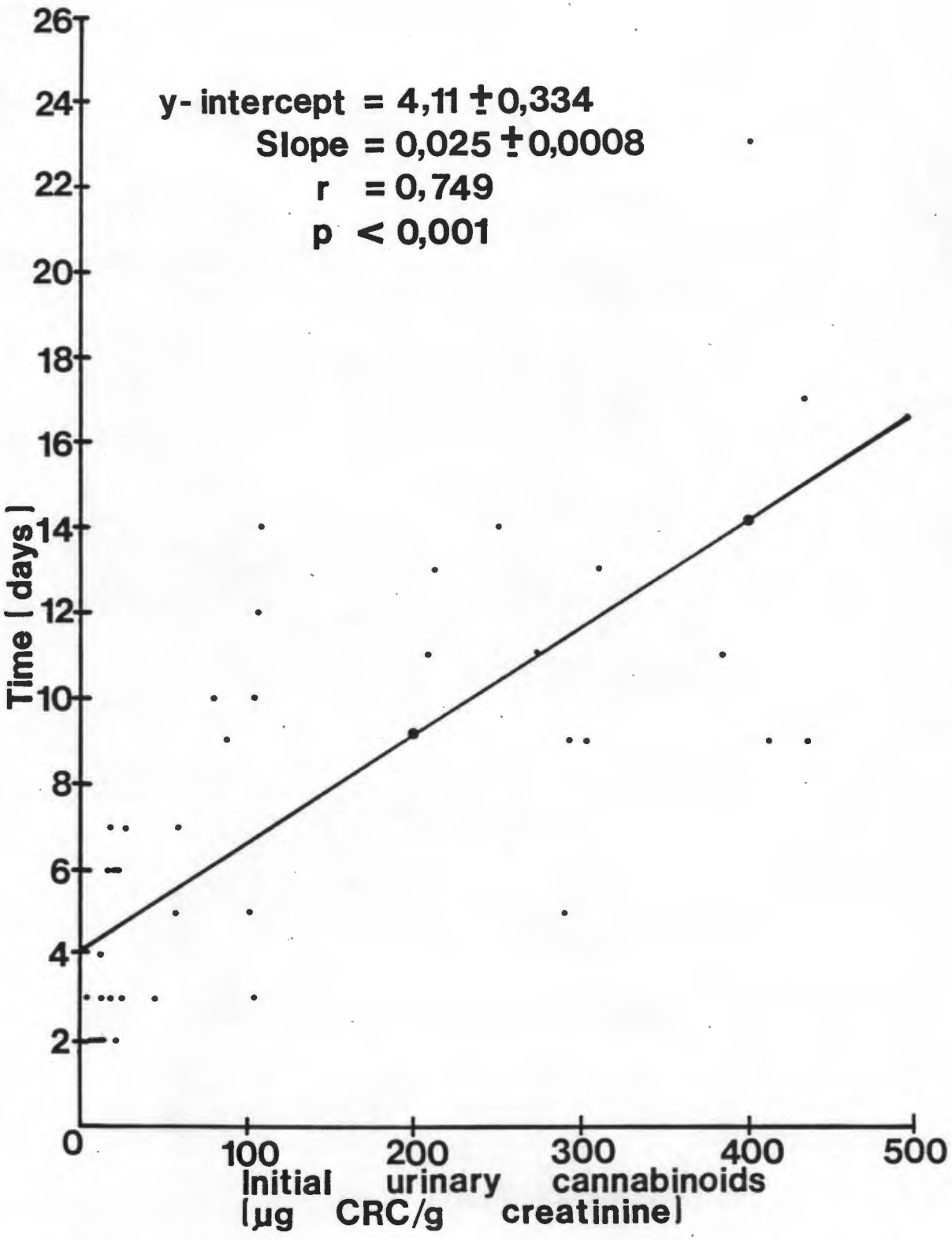


FIG.3.5.3. Linear regression analysis between the initial urinary cannabinoid concentration and the time required for a patient to be free of urinary cannabinoids.

3.6. SUMMARY OF RESULTS

I. The only detectable toxins were the cannabinoids. No patients showed evidence of ethanol or any other psychotropic agents.

II. There were no significant differences among the three groups with regard to age, social class and number of previous admissions.

III. There were no significant differences among the three groups with regard to neuroleptic medication received in the period between PSE assessments.

IV. The high cannabis group was characterized by a higher incidence of hypomania, agitation, and disorientation, the low cannabis group had no characterizing features, and the psychotic control group by a higher frequency of hysteria, auditory hallucinations, flattening, visual hallucinations, and incoherent speech.

V. With respect to manic psychosis, the high cannabis group did not differ significantly in its profile from that of the endogenous manic psychosis (manic control group). The paranoid schizoprenics in the high cannabis group had a higher incidence of agitation and simple depression and a lower incidence of auditory hallucinations and hysteria than the paranoid schizophrenics in the psychotic control group.

VI. The overall trend in the high cannabis group was one of marked improvement between PSE assessments with significant improvements in certain syndromes - hypomania, agitation, sexual and

fantastic delusions, grandiose and religious delusions, delusions of persecution, and irritability. The overall trend in the low cannabis group was one of improvement with significant improvements in some neurotic syndromes - general anxiety, worry, and irritability. The psychotic control group showed virtually no improvement in the psychotic syndromes and a significant improvement in only one neurotic syndrome - worry.

Although the three groups improved significantly on the total PSE score, the high cannabis group and the low cannabis group improved markedly whereas the psychotic control group improved only marginally.

Even when matched specifically for total neuroleptic medication received during the period between PSE assessments, the high cannabis group and the low cannabis group improved to a marked extent whereas the psychotic control group improved only marginally.

VII. Urinary cannabinoid concentrations correlated significantly with hypomania, overactivity and disorientation.

VIII. There were significant differences among the three groups with regard to CPK and LDH determinations; the high cannabis group had significantly more elevated levels than the low cannabis group and the psychotic control group. There was a significant correlation between overactivity and CPK levels.

IX. It was shown that where the initial urinary cannabinoid concentration is known it is possible to calculate the approximate time required for concentrations to become undetectable.

CHAPTER FOUR

Discussion

CHAPTER FOUR

Discussion

The group investigated was a recently hospitalized population who were admitted because of psychosis associated with behavioural disturbances. They therefore represent a select group and the discussion that follows does not pertain to cannabis abusers as a whole.

4.1. PRESENCE OF TOXINS

The only detectable toxins present on admission in the Coloured male patients studied were the cannabinoids. Sixty percent of the randomly selected patients were found to have these substances present; this is a large proportion and in comparison with a study in Jamaica, the value is almost double. Knight (1976) found 33% of the male admissions to a psychiatric hospital in Jamaica used cannabis. There are no figures available for other centres and it must be remembered that Knight's results were not confirmed by laboratory tests.

It is possible that the delay in patients reaching the hospital after the onset of psychosis may have reduced the levels of toxins to below the sensitivity of the assays employed. This is unlikely since psychotropic drugs generally have long half-lives, eg methaqualone has a half-life of 20–40 hours, and if the latter drug had been used, its presence would have been detectable up to about one week later.

The question of ethanol is more difficult. Its metabolism is fairly slow (100–110 mg/kg/hour) and follows zero order kinetics. Thus, if

the system were saturated, there would be an accumulation of ethanol. The assay used (GC) is highly sensitive (lowest level of sensitivity 10-20 μg/ml (Mather and Assimosis, 1965)) and accordingly if patients had been abusing ethanol heavily the latter would have been present at detectable concentrations up to 24 hours later, depending upon the dose and the individual clearance capacity. It seems therefore that the only exogenous factor substantially contributing to the psychoses was the cannabinoids.

No other study of cannabis-related psychiatric illnesses in the literature attempted to screen for the influence of other exogenous toxins. This constitutes an important omission and casts some doubt on the specificity of the findings of previous workers. Furthermore, no facilities were available for laboratory confirmation of cannabis abuse, so that workers were usually dependent on unreliable data such as the patient's own admission of cannabis use. In addition, when cannabis use is illegal or socially unacceptable many patients would have denied or minimized the taking of it.

In this study the EMIT^{R} method for the detection of urinary cannabinoids was a sensitive, reliable, and practical choice for qualitative identification and semi-quantitative estimation of major urinary cannabinoid metabolites. This method has become increasingly relied upon in situations of suspected drug abuse and its sensitivity, ease, speed of performance, and capacity for multisample handling may be considered to be superior to other techniques (RIA and GC/MS) (O'Conner and Rejent, 1981). Only recently has the EMIT^{R} method been successfully modified to detect cannabinoids in blood (Peel and Perrigo, 1981) but it is as yet unavailable commercially. Even so, blood levels

are less meaningful than urinary determinations since cannabinoids are rapidly sequestrated from the central compartment into the fatty tissues (volume of distribution 500ℓ).

4.2. AGE, PREVIOUS ADMISSIONS, AND SOCIAL CLASS OF THE CANNABIS GROUPS

The patients in the cannabis groups, with only minor exceptions, were generally young adults, i.e. less than 30 years old. This is comparable with patients in other studies (Spencer, 1971; Chopra and Smith, 1974; Thacore and Shukla, 1976) and indicates that it is a young population that is at risk.

Seventy percent of the high cannabis group and 60% of the low cannabis group had had one or more previous admissions to Valkenberg hospital prior to the current admission. In the high cannabis group, of the 6 patients (30%) who had had no previous admissions, only one patient was older than 21 years. It is possible that the youth of these patients contributed to the lack of previous psychiatric admissions. It would appear likely that the previous admissions were episodes of a cannabis-related illness.

All patients - except two in the high cannabis group who had a social class allocation of II - were allocated to social class III (see Appendix). Therefore it seems as if a socio-economically deprived population are more at risk. However, since this study was confined to hospitalized Coloured males, no comparison was made with other social classes or racial groups.

4.3. MEDICATION

Patients in all three groups received medication since it was deemed unethical to withhold this from these acutely ill patients. However, there were no significant differences among the three groups with regard to the amount of neuroleptic medication received during the inter-PSE period. (See Section 3.2.1.). (This is discussed in more detail in Section 4.5.).

Since the amount of neuroleptic medication received, as well as the age, social class, and number of admissions were comparable in all three groups, the presence or absence of the cannabinoids appeared to constitute the only differentiating factor in the three groups.

4.4. PRESENTATION OF PSYCHOSIS ON ADMISSION

The high cannabis group was distinguished from the other two groups by a higher incidence of hypomania, agitation, and disorientation (Figure 3.2.1.). The high incidence of hypomania and agitation confirms the reports in the literature by Spencer (1971), WHO (1971), Chopra and Smith (1974) and Thacore and Shukla (1976). Although only 30% of the high cannabis group was disorientated, this was significantly higher than the low cannabis group (0%) and the psychotic control group (15%). It must therefore be noted that the majority of the high cannabis group was correctly orientated and were thus not manifesting a classical toxic confusional state. The relatively low, but significant, incidence of some degree of disorientation in the high cannabis group is in agreement with the reports by WHO (1971), Tennant and Groesbeck (1972), and Chopra and Smith (1974). The low incidence of disorientation has a parallel with the description of

amphetamine psychosis (Connell, 1958). The latter is clinically indistinguishable from paranoid schizophrenia and the absence of disorientation is one of its outstanding features.

The psychotic control group was characterized by a higher frequency of hysteria, auditory and visual hallucinations, flattening of affect, and incoherent speech (Figure 3.2.1.). In contrast to the findings of WHO (1971), Thacore (1973), Chopra and Smith (1974), and Thacore and Shukla (1976) who showed that the predominant feature in their cases of cannabis-induced psychosis was auditory hallucinations, this study found a very low incidence of visual and auditory hallucinations in both the low and the high cannabis groups (the incidence of visual hallucinations in the high cannabis group, the low cannabis group and the psychotic control group was 20%, 10% and 45% respectively and the incidence of auditory hallucinations in the same three groups was 15%, 25% and 60% respectively. This is in agreement with Tennant and Groesbeck (1972) and Spencer (1971) who reported a very low incidence of auditory hallucinations.

It therefore appears that the psychosis in the high cannabis group presented with a strong hypomanic element and tended not to exhibit those features usually associated with a nuclear schizophrenic illness (affective flattening, auditory hallucinations, and incoherent speech).

The analyses of the syndrome profiles revealed no essential differences between the cannabis-related hypomanics and the control (endogenous) hypomanics (Figure 3.2.3.). However, although not significant, there was a distinct trend for the control manics to have more depressive symptoms (Table 3.2.17.).

A different picture emerged in the comparison of cannabis-related paranoid schizophrenics and control (endogenous) paranoid schizophrenics. (Figure 3.2.2.). The cannabis patients had a significantly higher incidence of agitation and simple depression and trends towards higher scores on hypomania and sexual and fantastic delusions, delusions of reference, irritability, tension and hypochondriasis. The high cannabis patients also had a significantly lower incidence of auditory hallucinations and hysteria and a non-significant trend towards less flattening of affect (Table 3.2.16.). It therefore seems that the high cannabis paranoid schozophrenics differed from their control counterparts in having a more affective (predominantly hypomanic) component and a lower incidence of those symptoms typical of a nuclear schizophrenic disorder.

These findings are in agreement with the work of Thacore and Shukla, (1976) who showed that their cannabis-related paranoid psychosis differed from patients with 'functional' paranoid schizophrenia in having a high degree of affective psychopathology. We found therefore that the psychoses in the high cannabis group were diagnosed either as hypomanic illness or a form of paranoid schizophrenia with a strong hypomanic colouring. Excessive cannabis administration in our patients was associated to a lesser or greater degree with hypomanic symptomatology. This manifested either as a pure hypomanic state or as a paranoid schizophrenic state with a marked affective component.

4.5. RATE OF IMPROVEMENT

It must be reiterated that there were no significant differences among the three groups with regard to the amount of neuroleptic

medication received during the period between PSE assessments. In this context improvement meant that in any particular patient there was a total resolution of a particular syndrome at the second PSE.

The overall trend in the high cannabis group in the inter-PSE period was one of marked improvement with significant differences in hypomania, agitation, sexual and fantastic delusions, grandiose and religious delusions, delusions of persecution (psychotic syndromes), and irritability (a neurotic syndrome). (Figure 3.2.4. and Table 3.2.18.). These rapidly resolving syndromes then belonged predominantly to the psychotic dimension. The low cannabis group showed overall improvement of syndromes with significant improvements in certain of the neurotic syndromes (general anxiety, worry, and irritability). In contrast, the psychotic control group showed virtually no change in the syndrome profile other than improvement in the neurotic syndrome of worry (see Figure 3.2.4., 3.2.5., and 3.2.6.).

The usual clinical impression is that it requires three weeks of neuroleptic therapy to control psychotic symptoms. This has been confirmed by Johnstone et al (1978) who studied forty five patients with acute schizophrenia. Their results are shown in Figure 4.1. and it is apparent that after one or two weeks of treatment with α-flupenthixol (a thioxanthene neuroleptic) there was no significant difference in symptomatology between placebo and active medication. Significant effects were only noted after three or four weeks of treatment.

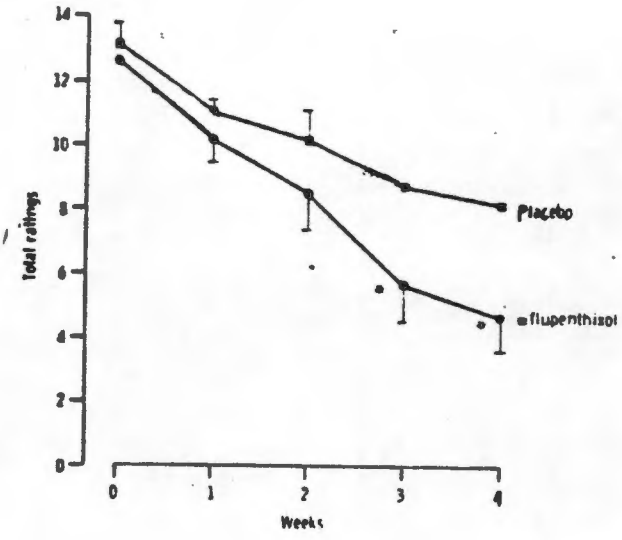


Figure 4.1. Improvement in total symptoms as a function of treatment with α-flupenthixol and placebo (from Johnstone et al, 1978)
*p <0,05 α-flupenthixol vs placebo

Johnstone et al (1978) also noted that schozophrenic patients with significant affective symptoms (schizo-affective sub-group) showed little drug effect when compared with the non-schizoaffective sub-group. This is pertinent as the majority of our patients in the high cannabis group had affective symptoms. Furthermore, improvements with regard to psychotic symptoms in the high cannabis, the low cannabis, and the psychotic control groups were as follows: 75%, 66%, and 15,8% respectively for the behaviour and speech syndromes and 62%, 85%, and 15,8% respectively for the delusional and hallucinatory syndromes. (Table 3.2.19.). This strengthens the argument that the rapid improvements were probably due to the progressive elimination of cannabinoids from the body with time. Ho et al (1970) reported that in mice 60% of an inhaled dose of cannabinoids reached the brain and less than a 25% decrease in brain concentrations occurred after

seven days. Studies of this kind have not been done in human subjects but in this study urinary cannabinoids were detected in some cases up to three weeks following admission to the hospital. The fact that patients had not recovered completely at the time of the second PSE may have been a reflection of residual brain cannabinoids.

In order to eliminate the influence of neuroleptic medication received during the period between PSE assessments, patients in the three groups were exactly matched for the total amount of medication received during that period and compared. These analyses confirmed that despite strict matching for medication our conclusions remained unchanged. The percentage improvement on the overall score in these cases was 71,6%, 95%, and 33,3% for the high cannabis group, the low cannabis group and the psychotic control group respectively. However, the improvements were specifically related to scores in the psychotic syndromes in which the psychotic control group remained basically unchanged (Table 3.2.20.). Since the presence of cannabinoids was the only distinguishing feature between the cannabis groups and the control group we hypothesize that this rapid and marked improvement in the cannabis groups is attributable to the progressively decreasing cannabinoid concentrations over the one week period.

4.6. THE LOW CANNABIS GROUP

The low cannabis group resembled the high cannabis group in terms of certain clinical symptoms i.e. the former had a lower incidence of hysteria, auditory and visual hallucinations, flattening of affect and incoherent speech compared to psychotic controls. On the other hand, it differed from the high cannabis group because, unlike the latter, there was no difference between the low cannabis and the

psychotic control groups in the incidence of hypomania and agitation (Figure 3.2.1. and Table 3.2.15.). The clinical course of the illness in the low cannabis group was very similar to that in the high cannabis group patients; there was a speedy resolution of the syndrome profiles after one week (see Figure 3.2.5. and Table 3.2.19.).

Several probabilities might explain these findings. Perhaps the most likely - in view of the marked short-term improvement compared with psychotic controls - is that these patients had much higher urinary cannabinoid concentrations at the onset of the illness and that owing to lengthy delays in admission to hospital, both the urinary cannabinoid levels and the intensity of psychotic symptomatology had diminished.

Another explanation is that as cannabis-induced psychosis may be dose-related, patients in the low cannabis group would have been more likely to show an attenuated form of this psychosis.

The third possibility is that the low cannabis group contained an admixture of cannabis precipitated psychoses as well as endogenous psychoses occurring irrespective of cannabis. Such a mixture would be expected to produce a clinical picture intermediate between the high cannabis patients and the psychotic control patients. If this were so, however, then the rate of improvement after one week should have been intermediate between the high cannabis group and the psychotic control group. This is not the case. Tables 3.2.19. and 3.2.20. clearly demonstrate, as mentioned above, that the low cannabis group improved markedly and possibly even at a greater rate than the high cannabis group.

Serum CPK and Serum LDH

The serum CPK and serum LDH levels were elevated in the three groups with the high cannabis group having significantly more elevated levels than the other two groups (Tables 3.4.1., 3.4.2., and 3.4.3.). These data are consistent with those of Meltzer (1968, 1969, 1970, 1973a, 1973b), Meltzer et al (1969, 1970, 1971) and Taylor and Abichandani (1981) who all reported elevated CPK levels in a heterogenous group of psychotic patients. More specifically, our results support those of Farber and Huertas (1976) who reported elevated CPK and LDH levels in two cases of acute cannabis intoxication, and the significantly elevated levels in our high cannabis group seem to confirm this.

Our results showed that there was a strong correlation between overactivity and CPK levels. As the predominant feature of the high cannabis group was a hypomanic colouring with concomitant overactivity and agitation, the elevated CPK levels would seem to reflect heightened muscular activity rather than the presence of the psychosis per se. The same explanation probably holds for the elevated LDH levels although the sample size was too small to obtain a significant correlation between this parameter and overactivity.

4.7. PREDICTION OF THE PERIOD REQUIRED FOR A PATIENT TO BE FREE OF DETECTABLE URINARY CANNABINOIDS

From the serial daily assessments of urinary cannabinoid concentrations it was possible to plot a linear regression for the relationship between time and initial urinary concentration (see Section 3.5.). Although approximate, this may have a place in the prediction of the time required for a patient to be free of detectable urinary cannabinoids where the initial level is known. For example, a patient with

an initial level of 400 µgCRC/g creatinine would require 14 days to be free of detectable urinary cannabinoids, and one with an initial level of 75 µgCRC/g creatinine would require 6 days.

4.8. CONCLUSIONS

The following are the main conclusions derived from our study.

I. Sixty percent of a random sample of Coloured males admitted to Valkenberg Hospital abuse cannabis.

II. The population at risk is young (median age 24) and most patients were in social class III.

III. The presence of urinary cannabinoids was an important factor in the nature and course of a psychotic illness.

IV. The high cannabis group exhibited certain syndromes which were of diagnostic importance - hypomania, overactivity, and some disorientation. This group were also markedly low on auditory hallucinations, flattening of affect, and incoherence of speech (these symptoms are more characteristic of a pure schizophrenic illness). It is relevant to note that in the majority of patients the illness occurred in a state of clear conciousness.

V. The manic psychosis in the high cannabis group was not significantly different in its profile from that of the functional psychosis. On the other hand the paranoid schizophrenics in the high cannabis group, when compared with control paranoid schizophrenics, showed a strong hypomanic element with a lower incidence of auditory hallucinations.

VI. The psychoses in the high cannabis group had an excellent prognosis: they were short-lived and resolved more rapidly and to a greater extent than those of the psychotic control group.

VII. High enzyme levels, especially CPK in the high cannabis group, were probably secondary to muscular overactivity and appear to confirm the strong hypomanic component of the psychosis.

Seven (35%) of the patients in the high cannabis group presented with a manic psychosis which was clinically indistinguishable from the naturally occurring mania except that the course of the illness was considerably shorter (7-10 days). The remainder of the patients were predominantly diagnosed by the PSE as paranoid schizophrenia. But on further analysis these patients differed from their matched controls in having a prominant affective colouring in addition to a lack of the typically schizophrenic features of auditory hallucinations, flattening of affect, and incoherence of speech. In fact, diagnosticians might be justified in regarding them as being more in the realm of schizo-affective psychosis than true schizophrenia. It is suggested that the psychosis delineated in this study would be best catogerized in the schedule suggested by Negrete (1973) as belonging to the classification 'Acute Cannabis Psychosis'. According to that scheme the most consistent feature of the latter diagnosis is a rapid remission rate.

4.9. CANNABIS: IS IT AN ETIOLOGICAL FACTOR?

The role that cannabis plays in the psychosis is debatable and it seems that there are three possibilities which will be considered in turn.

i. The presence of cannabis plays no role in the psychosis and is merely an incidental finding.

ii. Cannabis is a precipitant of a pre-existing and otherwise latent tendency to endogenous psychosis in certain individuals.

iii. Cannabis has a direct causative role in the psychosis.

The possibility that cannabis plays no role in the psychosis and is merely incidental to it is doubtful. Our data have unequivocally shown that the psychosis in the high cannabis group differs from the psychotic controls both in initial clinical presentation and subsequent course of illness. To some extent the same limitation holds true if cannabis acted as a precipitant of a pre-existing or latent psychosis. In this regard Treffert (1978) described four schizophrenic patients where cannabis use resulted in serious exacerbation of the illness. If cannabis merely acted as a precipitant then the resulting psychosis would conform in its clinical and prognostic aspects to the appropriate endogenous state. This has clearly not been demonstrated in the high cannabis group. The clinical characteristics of the low cannabis group however, were intermediate between the high cannabis and the psychotic control groups and it is probable that among these patients there were some where cannabis had exerted a trigger action.

The most acceptable explanation of our findings is that cannabis itself is causative of a psychosis; such an opinion has been held previously by several authors (Thacore, 1973; Chopra and Smith, 1976; Thacore and Shukla, 1976) all of whom are of Eastern cultures. However, these workers lacked the sophisticated techniques that were available to us in this study. Their classification of mental illness tended to be arbitrary and they lacked a standard diagnostic instrument. Even more serious was the unavailability of an appropriate pharmacological biochemical assay for cannabinoids. These methodological short-comings made their work unreliable and scientifically unacceptable. As far as the author is aware the present project has been the first of its kind in studying cannabis psychosis with scientifically acceptable diagnostic and analytical methods.

The psychosis described in our study was one in which a hypomanic colouring and a lack of the more typical schizophrenic features are outstanding features. The illness is short-lived and its course appears to be directly related quantitatively to the amounts of cannabis in the body tissues and, more specifically, in neural tissues.

The production of hypomania by high cannabis intake in our patients confirms the results of earlier volunteer studies. Ames (1958), Hollister (1971) and Tylden (1974) all noted that euphoria and excitability occurred after cannabis administration in an experimental setting (see Section 1.7.). These data again emphasize that cannabis has a direct causative link with the occurrence of hypomanic symptomatology.

It is interesting that Kotin, Post and Goodwin (1973) used Δ^9-THC to treat 8 hospitalized depressed patients; however the drug failed to produce significant euphoria or anti-depressant response during the period of administration. It is felt that the brief period of administration (seven days) and the low doses administered (0,3mg/Kg) may have been responsible for the lack of positive results.

The scepticism prevelant in Western cultures as to the existence of a valid clinical syndrome induced by cannabis seems to be based on a dearth of such psychotic cases in Western countries. Use of cannabis preparations in Eastern cultures has been endemic for centuries and it is used by all sectors of those societies (Thacore, Saxon, and Kumar, 1971, cited by Thacore, 1973). Despite prevalant cannabis use in the West it is possible that quantities taken by western users were far lower than in the East.

Carlini et al (1973) and Izquierdo et al (1973) showed that cannabidiol (CBD) (which has no hallucinogenic properties) was active in reducing or blocking convulsions produced in experimental animals. Other workers (Consroe and Walkin, 1977; Turkanis et al, cited by Mechoulam and Gaoni, 1978) confirmed these findings and showed that the effects of CBD were comparable with those of diphenylhydantoin and other drugs clinically effective in major seizures. A trial with human volunteers showed that CBD did not induce toxic effects and that CBD-treated patients showed significantly improved seizure control when compared to placebo-treated patients (Cunha et al, 1980).

The presence of cannabidiol in cannabis grown outside South Africa may have a protective action on individuals because of its anti-

convulsant properties. It is very important to emphasize that the cannabis grown in South Africa lacks cannabidiol (Field and Arndt, 1980). Teggin (1981) has speculated that this lack of cannabidiol (and therefore anti-convulsant activity) in the South African plant might render individuals more susceptible to a psychotic reaction. This possibility, combined with ready availability, cheapness and heavy usage, may be a factor in the high rate of cannabis-induced psychosis observed in South Africa. This area certainly warrants more specific investigation.

It must be borne in mind that the population studied was a select one in that it represented acutely psychotic patients admitted to a psychiatric hospital. From such a biased sample one cannot generalize to the population at large. No attempt was made in this study to investigate the urinary cannabinoid levels and psychiatric status in this community at large. Hence it is feasible that many individuals who habitually abuse cannabis might have had levels as high, or even higher, than our own sample without becoming disturbed and requiring hospitalization.

This study has shown the usefulness, simplicity, and relative inexpensiveness of the EMIT^{R} system for semi-quantitative assessments of urinary cannabinoids. It is recommended that in view of the importance of cannabis in the etiology of psychiatric illness, routine screening should be instituted of all psychiatric admissions. Such screening would aid in the evaluation, diagnosis and management of psychiatric patients and influence treatment and management and might have an important advantage in forensic psychiatry.

The fact that cannabis seems to be implicated in the production of hypomanic symptomatology is worthy of further research. Animal experiments directed at exploring the influence of neurotransmitters may help us to understand the biochemical mechanisms operative in hypomania.

In essence , the upshot of this preliminary study is that excessive quantities of cannabis play a major role in accounting for psychiatric morbidity among Cape Coloured male psychiatric patients in the Western Cape. This is a serious mental health problem and one that deserves to be investigated on many fronts. Such aspects as premorbid personality, socio-economic status, socio-cultural background, nutritional status, genetic predisposition, and local chemovariance in cannabis are some of the factors that conspire to produce the complex entity of cannabis-related psychosis that we have attempted to delineate.

APPENDIX

APPENDIX A

Magisterial Districts of Valkenberg Hospital catchment area from which patients were selected:

Bonnyvale

Bredasdorp

Caledon

Calitzdorp

Cape Town

George

Heidelberg

Hermanus

Joubertina

Knysna

Ladysmith

Mossel Bay

Oudtshoorn

Riversdal

Simonstown

Swellendam

Uniondale

Wynberg

APPENDIX B

Allocation of Social Class.

Pooled Family Income per Month	Levels of Education	Highest Occupation	Social Class
Greater than R 800-00	Higher than Std. 8	Professional	I
R 251-00 to R 800-00	Std. 4-7	Skilled labourer/ artisan Clerical/ Technical	II
R 0 - R 250-00	Up to Std. 3	Unskilled/ semi-skilled labourer	III

A patient was allocated a particular social class if he fulfilled two of the three criteria.

APPENDIX C FULL VERSION OF PRESENT STATE EXAMINATION

1. INTRODUCTION

The interviewer should introduce himself briefly, describe the purpose of the interview and explain about any recording equipment. The purpose of the introductory section is to obtain an overall picture of the symptomatology, in the subject's own words.

** To begin with, I should like to get an idea of the sort of problems that have been troubling you during the past month. What have been the main difficulties?

Record the main symptoms spontaneously mentioned.

Means of exploration, if subject gives inadequate information:

If subject's statement too brief	Can you tell me more about that?
If subject has no more to add	What else has been troubling you?
If statements are difficult to understand	Can you explain what you mean by ...?
If subject is vague	Could you give an example of ...?
If no other response forthcoming	Why did you come to the (hospital)?

RATE PATIENT'S ACCOUNT OF SYMPTOMS.

0 = Subject responds adequately
1 = Account somewhat inadequate but interview can proceed.
2 = Account seriously inadequate but interview proceeds in an attempt to rate some subjective responses, as well as behaviour, affect and speech.
3 = Impossible to continue with interview. Only behaviour, affect and speech section rated.

REASONS FOR INADEQUACY (TICK AS MANY AS APPROPRIATE).

Denial or guardedness	___	Inattention	___
Incoherence	___	Refusal	___
Irrelevance	___	Patient mute, stuporous,	___
Replies too brief	___	Other, specify	___
Poverty of content of speech	___		

IF (1) OR (2) CARRY ON WITH SECTION 2, UNLESS SUBJECT MENTIONS OR HINTS AT DELUSIONS OR HALLUCINATIONS→ SECTION 18.

Current treatment, if subject not seen in hospital or clinic
Rate the following if sufficient information has already emerged.
If not, use the suggested question:
May I ask if you are seeing any doctor for your nerves?
Or specify if psychosomatic complaints.

What kind of doctor is he?
Your own GP? A private doctor? Psychiatrist?

0 = No doctor
1 = GP
2 = Private doctor other than GP
3 = Psychiatrist
4 = Hospital out-patient (other than psychiatric)
5 = Other paramedical specialist, or osteopath
6 = Other specify

Are you attending for treatment any person who is not medically qualified, e.g. lay therapist, herbalist, acupuncturist, faith healer, Christian Science, church which forbids medical advice?

What were you complaining of at the time?

Specify type of treatment

Complaint

2. HEALTH, WORRYING, TENSION

** Is your physical health good?
(Does your body function normally?)

** Do you feel you are physically ill in any way?
(What is it that like? How serious is it?)

RATE SUBJECT'S OWN SUBJECTIVE EVALUATION OF PRESENT PHYSICAL HEALTH (irrespective of whether physical disease is present). ☐ (1)

0 = Feels physically very fit.
1 = Feels particular physical complaint but does not say positively feels fit.
2 = Feels unwell but not very seriously incapacitated.
3 = Feels seriously incapacitated by physical illness.

** What does your doctor say is wrong?
(Have you had a physical illness recently; colds, influenza, etc.?)

RATE PRESENCE OF PHYSICAL ILLNESS OR HANDICAP, taking results of recent investigations and physical state examinations into account. ☐ (2)

0 = No physical illness or handicap present.
1 = Mild but significant physical illness or handicap (e.g. influenza or limp).
2 = More serious physical illness or handicap present but not incapacitating or threatening to life (e.g. deafness or duodenal ulcer).
3 = Physical illness or handicap present which is incapacitating or threatening to life (e.g. blindness or carcinoma).

Specify illness, disabilities and duration:

RATE PSYCHOSOMATIC SYMPTOMS. ☐ (3)

Special projects only

** Have you worried a lot during the past month?
(What do you worry about?)
PROBE: (Money, housing, children, health, work, marriage, relatives, friends, neighbours, other).
(How much do you worry? Are you a worrier?)
If any indication of worry, use further probes:

** What is it like when you worry?
(What sort of state of mind do you of mind do you get into?)
(Do unpleasant thoughts constantly go round and round in your mind?)
(Can you stop them by turning your attention to something else?)

RATE WORRYING: A round of painful thought which cannot be be stopped and is out of proportion to the subject worried about. ☐ (4)

1 = Symptom definitely present during past month, but of moderate clinical intensity or intense less than 50% of the time.
2 = Symptom clinically intense more than 50% of the time.

** Have you had headaches, or other aches or pains, during the past month?
(What kind?)

RATE ONLY TENSION PAINS, e.g. 'band round head', 'pressure', 'tightness in scalp'. 'ache in back of neck', etc. not migraine.
1 = Symptom definitely present during past month, but of moderate clinical intensity, or intense less than 50% of the time. ☐ (5)
2 = Symptom clinically intense more than 50% of past month.

** Have you been getting exhausted and worn out during the day or evening, even when you haven't been working very hard?

RATE TIREDNESS OR EXHAUSTION: Do not include tiredness due to 'flu, etc. = 9.

1 = Only moderate form of symptom (tiredness) present; or

intense form (exhaustion) less than 50% of the time
2 = Intense form of symptom (exhaustion) present more than 50% of the past month. ☐ (6)

** Have you had difficulty in relaxing during the past month?
(Do your muscles feel tensed up?)
RATE MUSCULAR TENSION: Do not include a subjective feeling of nervous tension, which is rated later.
1 = Symptom definitely present during past month, but intensity, or intense less than 50% of the time.
2 = Symptom clinically intense more than 50% of past month. ☐ (7)

** Have you been so fidgety and restless that you couldn't sit still?

RATE RESTLESSNESS ☐ (8)

(Do you have to keep pacing up and down?)
1 = Only moderate form of symptom (fidgety restless) present; or intense form (pacing, can't sit down) less than 50% of the time.
2 = Intense form of symptom (pacing, etc.) present more than 50% of past month.

** Do you tend to worry over your physical health?

RATE HYPOCHONDRIASIS: Overconcern with possibility of death, disease or malfunction. Re-rate at end of interview if subject constantly reverts to hypochondriacal preoccupation.
Consider ratings of symptoms (1) and (3). ☐ (9)
1 = Symptom present during past month, but not (2).
2 = Subject constantly reverts to hypochondriacal preoccupations during interview.

** Do you often feel on edge or keyed up or mentally tense or strained?
(Do you generally suffer with your nerves?)
(Do you suffer from nervous exhaustion?)
RATE SUBJECTIVE FEELING OF 'NERVOUS TENSION':
There is no need for autonomic accompaniments for this symptom to be rated present.
1 = Symptom definitely present during past month, but of moderate intensity, or intense less than 50% of the time.
2 = Intense form of symptom present more than 50% of the past month. ☐ (10)

** Do you find that a lot of noise upsets you?
(Do noises sometimes seem to penetrate, or go through your head?)

RATE HYPERSENSITIVITY TO NOISE.
1 = Moderate degree during month.
2 = Severe degree during month. ☐

3. AUTONOMIC ANXIETY

In this section, rate only subjective anxiety with autonomic accompaniments, either free-floating or situational. Do not include worrying or nervous tension. Do not include anxiety due to, e.g. persecutory delusions, except in the special item (no. 13).

(CHECK LIST of autonomic accompaniments:

Blushing
Butterflies
Choking
Difficulty getting breath
Dizziness
Dry mouth
Giddiness
Palpitations
Sweating
Trembling)

** Have there been times lately when you have been very anxious or frightened?
(What was this like?)
(Did your heart beat fast?) Ask for other autonomic symptoms.
(How often in the past month?)

RATE FREE-FLOATING AUTONOMIC ANXIETY: Exclude if due to delusions. Exclude if purely situational. ☐ (11)
1 = Symptom definitely present, with autonomic accompaniment, during past month, but of moderate clinical intensity, or intense less than 50% of the time.
2 = Symptom clinically intense more than 50% of the time.

** Have you had the feeling that something terrible might happen?
(That some disaster might occur but you are not sure what? Like illness or death or ruination?)
(Have you been anxious about getting up in the morning because you are afraid to face the day?)
(What did it feel like?)

RATE ANXIOUS FOREBODING WITH AUTONOMIC ACCOMPANIMENTS ☐ (12)
1 = Symptom definitely present, with autonomic accompaniment, during past month, but of moderate clinical intensity, or intense less than 50% of the time.
2 = Symptom clincally intense more than 50% of the time.

RATE AUTONOMIC ANXIETY DUE TO DELUSIONS, etc. and if necessary defer to end of interview. ☐ (13)
0 = No anxiety due to delusions or hallucinations
1 = Subject complains of anxiety but no evidence of anxiety on examination.
2 = Clearly anxious or frightened because of delusions or hallucinations.

CUT OFF IF NO EVIDENCE OF ANXIETY OR IF ANXIETY DUE ONLY TO DELUSIONS → SECTION 4.

Have you had times when you felt shaky, or your heart pounded, or you felt sweaty, and you simply had to do something about it?
(What was it like?)
(What was happening at the time?)
(How often during the past month?)
RATE PANIC ATTACKS WITH AUTONOMIC SYMPTOMS: ☐ (14)
A panic attack is intolerable anxiety leading to some action to end it, e.g. leaving a bus, phoning husband at work, going to see a neighbour, etc.
1 = One to four panic attacks during the month.
2 = Panic attacks five times or more.

Do you tend to get anxious in certain situations, such as travelling, or being alone, or being in a lift or tube train?
(What situations? How often during the past month?)
(CHECK LIST: Can be presented on separate card and each item rated separately, if needed.
Crowds (shop, street, theatre, cinema, church).
Going out alone; being at home alone.
Enclosed spaces (hairdresser, phone booth, tunnel).
Open spaces, bridges.
Travelling (buses, cars, trains).
RATE SITUATIONAL AUTONOMIC ANXIETY. ☐ (15)
1 = Has not been in such situations during the past month but aware that anxiety would have been present if the situation had occurred.
2 = Situation has occurred during the past month and patient did feel anxious because of it.

What about meeting people, e.g. going into a crowded room making conversation?
(CHECK LIST: Present card if necessary:
Speaking to an audience.
Eating, drinking or writing in front of other people.
Parties)
RATE AUTONOMIC ANXIETY ON MEETING PEOPLE. ☐ (16)
1 = Has not been in such situations during the past month but aware that anxiety would have been present if the situation had occurred.
2 = Situation has occurred during the past month and patient did feel anxious because of it.

Do you have any special fears, like some people are scared of feathers or cats or spiders or birds?

(CHECK LIST: Present card if necessayr:
Heights, thunderstorms, darkness.
Animals or insects of any kind.
Dentists, injections, blood, injury.)

RATE ONLY SPECIFIC PHOBIAS, NOT GENERAL SITUATIONAL ANXIETY.

1 = Has not been in such situations during the past month but aware that anxiety would have been present if the situation had occurred.
2 = Situation has occurred during the past month and patient did feel anxious because of it.

☐ (17)

Do you avoid any of these situations (specify as appropriate) because you know you will get anxious?
(How much does it affect your life?)

RATE AVOIDANCE OF ANXIETY-PROVOKING SITUATIONS. ☐ (18)

1 = Subject tends to avoid such situations whenever possible.
2 = Marked generalisation of avoidance has occurred during past month, e.g. subject has not dared to leave the house or has gone out only if accompanied.

Describe anxiety symptoms and list phobias.

4. THINKING, CONCENTRATION, ETC.

** Can you think or is there any interference with your thoughts?

** Do your thoughts tend to be muddled or slow?
(Can you make up your mind about simple things quite easily?) (Make decisions about everyday matters?)

RATE SUBJECTIVELY INEFFICIENT THINKING (if due to intrusion of alien thoughts, rate 9). ☐ (19)

1 = Symptom definitely present during the past month, but of moderate clinical intensity, or intense less than 50% of the time.
2 = Symptom clinically intense more than 50% of the past month.

** What has your concentration been like recently?
(Can you read an article in the paper or watch a TV programme right through ?)
(Do your thoughts drift off so that you don't take things in?)

RATE POOR CONCENTRATION. ☐ (20)

1 = Only moderate form of symptom present during the past month (e.g. can read a short article, can concentrate if tries hard); or intense less than 50% of the time.
2 = Symptom clinically intense (cannot attempt to read or concentrate) more than 50% of the past month.

** Do you tend to brood on things?
(So much that you even neglect your work?)

RATE NEGLECT DUE TO BROODING. ☐ (21)

1 = Symptom has caused moderate impairment to work or social relationships.
2 = Marked impairment.

** What about your interests, have they changed at all?
(Have you lost interest in work, or hobbies, or recreations?)
(Have you let your appearance go?)

RATE LOSS OF INTEREST continuing during the past month.

1 = Symptom definitely present during the past month, but

of moderate clinical severity or severe loss less than 50% of the time. (22)

2 = Symptom clinically severe more than 50% of the past month.

** Have you become interested in new things at all?
IF EVIDENCE OF EXPANSIVE MOOD OR IDEAS → SECTION 9.
IF ODD IDEAS, EXPLORE FURTHER, PROCEED TO SECTION 15. IF APPROPRIATE.

** Have you suffered any lapses of memory recently? (PROBE ONLY)
IF EVIDENCE OF DISSOCIATION OR ORGANIC MEMORY LOSS → SECTION 16.

ANSWERS TO THESE QUESTIONS MAY SUGGEST THAT OTHER TYPES OF THOUGHT DISORDER ARE PRESENT, IF NOT, CUT OFF → SECTION 5.

IF ANY EVIDENCE OF THOUGHT DISORDER:

Are you in full control of your thoughts?
Can people read your mind?
Is anything like hypnotism or telepathy going on?

IF NECESSARY, PROCEED TO SECTION 13.

5. DEPRESSED MOOD

** Do you keep reasonably cheerful or have you been very dépressed or low spirited recently?
Have you cried at all?
(When did you last really enjoy doing anything?)

RATE DEPRESSED MOOD, N.B. When rating clinical severity of depression remember that deeply depressed people may not necessarily cry. See definition in glossary. (23)

1 = Only moderately depressed during past month, or deep depression for less than 50% of the time and tending to vary in intensity.

2 = Deeply depressed for more than 50% of the past month, and tending to be unvarying in intensity.

** How do you see the future?
(Has life seemed quite hopeless?)
(Can you see any future?)
(Have you given up or does there still seem some reason for trying?) Do you still think you might get better?

RATE HOPLESSNESS on subject's own view at present. (24)

1 = Hopelessness of moderate intensity but still has some degree of hope for the future (irrespective of time during month.)

2 = Intense form of symptom (patient has given up hope altogether).

USE JUDGEMENT ABOUT WORDING

** Have you felt that life wasn't worth living?
(Did you ever feel like ending it all?)
(What did you think you might do?)
(Did you actually try?)
(Did you ever think of ending your life?)

RATE SUICIDAL PLANS OR ACTS. ☐ (25)

1 = Deliberately considered suicide (not just a fleeting thought) but made no attempt.
2 = Suicidal attempt but subject's life never likely to be in serious danger except unintentionally.
3 = Suicidal attempt apparently designed to end in death (i.e. accidental discovery or inefficient means).

N.B. Examiner should judge clinically whether there was intent to end life or not. If in doubt, assume not.

IF EVIDENCE OF BOTH DEPRESSION AND ANXIETY RATE ANXIETY OR DEPRESSION PRIMARY.

If subject suffers from both anxiety and depression, and both have been rated as present, try to decide which is primary. (26)

0. Anxiety is primary. Depression appears to be entirely explicable in terms of the limitations placed on the subject by the symptoms of anxiety, e.g. being unable to leave the house, travel, meet people, etc., or being afraid of heart disease because of palpitations.
1. Anxiety and depression both present but seem independent of each other or it is not possible to decide whether one of them is primary.
2. Depression is primary. Anxiety is either a result of the depression (e.g. subject is frightened because of morbid or suicidal ideas) or it takes the form of fears of catastrophe, forebodings about illness or death, dread of having to face the day when first waking in the morning, preoccupation that something awful is going to happen. Panic attacks and situational anxiety, if present, are secondary to depression.

Is the depression worse at any particular time of day?
RATE MORNING DEPRESSION (particularly on waking)

0 = No depression.
1 = Not specially marked in mornings.
2 = Specially marked in mornings.

☐ (27)

6. SELF AND OTHERS

** Have you wanted to stay away from other people?
(Why?)
(Have ypu been suspicious of their intentions?
Of actual harm?)

RATE SOCIAL WITHDRAWAL ☐ (28)

1 = Only passive form of symptom, i.e. subject does not seek company but does not refuse it if offered; or, if active withdrawal, less than 50% of the month.
2 = Actively avoids company (refuses it if offered). Actively withdraws in this way for more than 50% of the month.

** What is your opinion of yourself compared to other people?
(Do you feel better, or not as good, or about the same as most?)
(Do you feel inferior or even worthless?)

RATE SELF-DEPRECIATION. ☐ (29)

1 = Some inferiority, not amounting to feeling of worthlessness. If subject considers self to be worthless, this intense form of the symptom is present less than 50% of the time.
2 = Subject considers self to be completely worthless. Symptom present more than 50% of the month.

** How confident do you feel in yourself:
(for example, in talking to others, or in managing your relations with other people?)

RATE LACK OF SELF-CONFIDENCE WITH OTHER PEOPLE. ☐ (30)
Consider only competence in social relationships, not competence at mechanical work, etc.

1 = Moderate lack of self-confidence, or intense lack less than 50% of the month.
2 = Intense lack of self-confidence more than 50% of the month.

** Are you self-conscious in public?
(Do you get the feeling that other people are taking notice of you in the street or a bus or a restaurant?)
(Do they ever seem to laugh at you or talk about you critically?)
(Do you consider people really are looking at you, or is it perhaps the way you feel about it?)

RATE SIMPLE IDEAS OF REFERENCE (NOT DELUSIONS). ☐ (31)

1= Marked self-consciousness only (irrespective of time during month).
2= Feels that people are criticising or laughing at self but can be reassured.

IF NO EVIDENCE OF GUILT, CUT OFF — SECTION 7
(IF EVIDENCE OF MISINTERPRETATIONS, DELUSIONS OF REFERENCE OR PERSECUTION — SECTION 15B, 15C).

IF EVIDENCE OF GUILT:

Do you have the feeling that you are being blamed for something, or even accused?
What about?

RATE GUILTY IDEAS OF REFERENCE. Do not include justifiable blame or accusation. Exclude delusions of guilt.

1= Subject feels blamed but not accused (irrespective of time during month).
2= Subject feels accused of some sin or misdemeanour. Not delusional. ☐ (32)

IF DELUSIONS OF REFERENCE MAY BE PRESENT → SECTION 15B.

Do you tend to blame yourself at all?
(If people are critical, do you think you deserve it?)

RATE PATHOLOGICAL GUILT ONLY. ☐ (33)

1= Subject feels over-guilty about some peccadillo (irrespective of time during month).
2= Subject feels to blame for everything that has gone wrong even when not his fault, but not delusional.

IF DELUSIONS OF GUILT MAY BE PRESENT → SECTION 15G.

Do you blame anyone else for your troubles?

IF DELUSIONS OF PERSECUTION → SECTION 15C.

7. APPETITE, SLEEP, RETARDATION, LIBIDO

** What has your appetite been like recently?
(Have you lost any weight during the past three months?)

RATE LOSS OF WEIGHT DUE TO POOR APPETITE.
Do not include changes due to physical illness. ☐ (34)

1= Less than 15 lbs (7 kg).
2= 7 kg (15 lbs) or more.

** Have you had any trouble getting off to sleep during the past month?
(How long do you lie awake?)
(What happens if you take sleeping tablets?)
(How often does it happen?)
☐ (35)

RATE DELAYED SLEEP.
1 = One hour or more delay (irrespective of sleeping tablets).
2 = Two hours or more delay (irrespective of sleeping tablets).
(In either case, ten or more nights during month.)

** Do you seem to be slowed down in your movements, or to have too little energy recently? How much has it affected you?
Do things seem to be moving too fast for you?)

RATE SUBJECTIVE ANERGIA AND RETARDATION. ☐ (36)

1 = Marked subjective listlessness and lack of energy.
2 = Marked retardation and underactivity (Irrespective of time during month).

IF NO APPETITE OR SLEEP DISTURBANCE, AND NO DEPRESSION, CUT OFF → SECTION 8.

IF SLEEP DISTURBANCE OR DEPRESSION:

Do you wake early in the morning?

RATE EARLY WAKING (one hour before usual). ☐ (37)

1 = One hour or more before ordinary time.
2 = Two hours or more before ordinary time.
(In either case, ten or more nights during month.)

Has there been any change in your interest in sex?

RATE LOSS OF LIBIDO WITHIN PRESENT EPISODE OF ILLNESS AND PERSISTING DURING PAST MONTH. ☐ (38)

1 = Marked loss of interest and performance.
2 = Almost total loss of libido.

Does the depression or tension get worse just before the start of the monthly period?

RATE PREMENSTRUAL EXACERBATION

☐ (39)

0 = No definite exacerbation.
1 = Marked exacerbation.

8. IRRITABILITY

** Have you been very much more irritable than usual recently?
(How do you show it?)
(Do you keep it to yourself, or shout, or even hit people?)

RATE IRRITABILITY.

1 = Keeps irritation to himself.
2 = Shows anger by shouting or quarrelling.
3 = Shows anger by hitting people, throwing or breaking things.

☐ (40)

9. EXPANSIVE MOOD AND IDEATION

** Have you sometimes felt particularly cheerful and on top of the world, without any reason?
(Too cheerful to be healthy?)
(How long does it last?)

RATE EXPANSIVE MOOD: not ordinary high spirits. ☐ (41)

1 = Moderately expansive mood (euphoria with marked element of inappropriateness or excitement, whether recognised by subject or not), present during past month, and persistent for hours at a time.* Do not include transient high spirits. Not necessarily described by subject.
2 = Intense form of symptom (elation or exaltation) definitely present during past month and persistent for hours at a time. Described by subject.

** Have you felt particularly full of energy lately, or full of exciting ideas?
(Do things seem to go too slowly for you?)
(Do you need less sleep than usual?)
(Do you find yourself extremely active but not getting tired?)
(Have you developed new interests recently?)

RATE SUBJECTIVE IDEOMOTOR PRESSURE. ☐ (42)

1 = Subjective equivalent of flight of ideas. Images and ideas flash through the mind, each suggesting others, at a faster rate than usual. State persists for hours at a time.* Definitely occurred during past month.
2 = As (1) but accompanied by very high energy output and activity which does not seem to make subject tired at the time. Definitely occurred during past month and persisted for hours at a time.*

IF NO EVIDENCE OF EXPANSIVE MOOD AND IDEATION, CUT OFF → SECTION 10.

IF EVIDENCE OF EXPANSIVE MOOD AND IDEATION:

Have you seemed super-efficient at work, or as though you had special powers or talents quite out of the ordinary?
Have you felt specially healthy?
Have you been buying any interesting things recently?

RATE GRANDIOSE IDEAS AND ACTIONS. ☐ (43)

1 = Subjective feeling of superb health, exceptionally high intelligence, extra-ordinary abilities, etc. Persistent for hours at a time.* Symptom occurred at some time during the month.
2 = Grandiose ideas have been translated into action during the month, e.g. overspending, gambling, etc., under the influence of grandiose ideas and expansive affect. Do not include compulsive gambling unless clearly of this type.

(→ GRANDIOSE DELUSIONS, SECTION 15D IF NECESSARY.)

* If symptom was more transient but very intense or frequently repeated, it may still be included.

10. OBSESSIONS

These symptoms are usually experienced as occurring against conscious resistance (see definition in glossary).

** Do you find that you have to keep on checking things that you know you have already done?
(Like gas taps, doors, switches, etc.)
(Do you have to touch or count things many times or repeat the same action over and over again?)
(What happens when you try to stop?)

RATE OBSESSIONAL CHECKING AND REPEATING. ☐ (44)

1 = Symptom of moderate intensity or, if severe, present less than 50% of the time.
2 = Symptom present in severe degree, more than 50% of the past month.

** Do you find it difficult to make decisions even about trivial things?
(Do you constantly have to question the meaning of the universe?)
(Do you get awful thoughts coming into your mind even when you try to keep them out?)
(What happens when you try to stop?)

RATE OBSESSIONAL CLEANLINESS AND SIMILAR RITUALS. ☐ (45)

1 = Symptom of moderate intensity or, if severe, present less time.
2 = Symptom present in severe degree, more than 50% of the past month.

** Do you find it difficult to make decisions even about trivial things?
(Do you constantly have to question the meaning of the universe?)
(Do you get awful thoughts coming into your mind even when you try to keep them out?)
(What happens when you try to stop?)

RATE OBSESSIONAL IDEAS AND RUMINATION. ☐ (46)

1 = Symptom of moderate intensity, or, if severe, present less than 50% of the time.
2 = Symptom present in severe degree, more than 50% of the past month.

11. DEREALISATION AND DEPERSONALISATION

** Have you had the feeling recently that things around you were unreal?
(As though everything was an imitation of reality, like a stage set, with people acting instead of being themselves?)
(What is it like? How do you explain it?)

RATE DEREALISATION. ☐ (47)

1 = Moderately intense form of symptom definitely occurred during the past month, and persisted for hours at a time. Things appear colourless and artificial, people appear lifeless and seem to act rather than being themselves.

2 = Intense form of symptom occurred during the past month and persisted for hours at a time, e.g. whole world appears like a gigantic stage set, with imitation instead of real objects and puppets instead of people. (If delusional, do not rate here but symptom 90.)

** Have you yourself felt unreal, that you were not a person, not in the living world?
(Or that you were outside yourself, looking at yourself from outside?)

(Or that you look unreal in the mirror?)
(Or that some part of your body did not belong to you?)
(How do you explain it?).

RATE DEPERSONALISATION ☐ (48)

1 = Moderately intense form of the symptom definitely occurred during the past month and persisted for hours at a time. Subject feels himself unreal, a sham, a shadow.

2 = Intense form of symptom definitely occurred during the past month and persisted for hours at a time. Subject feels he is dead, not a person, living in a parallel existence, a hollow shell, even that he does not exist. (If delusional, do not rate here but symptom 90.)

12. OTHER PERCEPTUAL DISORDERS (NOT HALLUCINATIONS)

** Do you ever get the feeling that something odd is going on which you can't explain?
(Or that familiar surroundings seem strange? How do you explain it?)

RATE DELUSIONAL MOOD: The subject feels that his familiar environment has changed in a way which puzzles him and which he may not be able to describe clearly. The feeling often accompanies delusion formation. ☐ (49)

1 = Symptom definitely present. No delusions have actually been formulated, though patient may feel that various delusional explanations are possible.
2 = Full delusional elaboration has occurred.

** Does your imagination sometimes play tricks on you?

** Is there anything unusual about the way things look or sound, or smell, or taste?
(Does your body function normally?)
(Is your own appearance normal?

CONTINUE BELOW CUT-OFF IF NECESSARY, EVEN IF (49) NOT PRESENT.

IF NO PERCEPTUAL ABNORMALITY → SYMPTOM 54.

IF THERE IS ANY HINT OF PERCEPTUAL ABNORMALITY, CONTINUE BYOND CUT-OFF POINT AND ALSO CONSIDER LATER SECTIONS. RATE ONLY BASIC EXPERIENCE, NOT DELUSIONAL ELABORATION.

In what way? Do sounds seem unnaturally clear or loud or things look vividly coloured or detailed? (How do you explain this?)

RATE HEIGHTENED PERCEPTION: e.g. subject intensely aware of cracks in a wall, details of a wallpaper pattern, colours in a picture. Sounds heard with exceptional clarity music appears particularly beautiful. ☐ (50)

1 = Subject unable to describe the symptom precisely, but examiner thinks it is likely to have been present at some time during the past month.
2 = Subject describes symptom. Definitely present at some time (even if only briefly) during the past month.

Do things seem dark or grey or colourless? (How do you explain it?)

RATE DULLED PERCEPTION: The reverse of symptom (50). Things look, sound and taste dull, flat colourless and uninteresting. ☐ (51)

1 = Subject unable to describe the symptom precisely, but examiner thinks it is likely to have been present at some time during the past month.
2 = Subject describes symptom. Definitely present at some time (even if only briefly) during the past month.

Does the appearance of things or people change in a puzzling way: e.g. distorted shapes or size or colour? (How do you explain it?)

RATE CHANGED PERCEPTION ☐ (52)

1 = Subject unable to describe the symptom precisely, but examiner thinks it is likely to have been present at some time during the past month.
2 = Subject describes symptom. Definitely present at some time (even if only briefly) during the past month.

Do you think your own appearance is normal? (Conviction that nose is too large, teeth misshapen, body crooked, etc. Ask questions here if convenient but rate symptom (89).)

Does your experience of time seem to have changed? (Does it go too fast or too slowly, or do you seem to live through experiences exactly as you have had them before?)

RATE CHANGED PERCEPTION OF TIME, INCLUDING DEJA VU ☐ (53)

1 = Subject unable to describe the symptom precisely, but examiner thinks it is likely to have been present at some time during the past month.
2 = Subject describes symptom. Definitely present at some time (even if only briefly) during the past month.

Do you feel you have lost your emotions in some way?
(that you are empty of all feeling, incapable of reacting emotionally?)
(Is this a definite change, or have you always been like that?)
(How do you explain it?) ☐ (54)

** RATE LOST EMOTIONS: Rate only subjective loss of affect i.e. subject can remember being able to react emotionally though this might have been months or even years ago.

1 = Symptom definitely present during the past month but less than 50% of the time.
2 = Symptom present more than 50% during the month.

13. THOUGHT READING, INSERTION, ECHO, BROADCAST

IF QUESTION HAS NOT BEEN COVERED IN SECTION 4 ASK:

** Can you think quite clearly or is there any interference with your thoughts?
(Are you in full control of your thoughts?)
(Can people read your mind?)
(Is anything like hypnotism or telepathy going on?)

IF NO EVIDENCE OF THOUGHT READING, etc., CUT OFF→ SECTION 14.

IF ANY EVIDENCE, ASK QUESTIONS BELOW:

(These symptoms are often recorded as false positives. The examiner must be satisfied that the subject is not simply assenting to a question he does not understand, but genuinely recognises the experience and can describe it so that the examiner recognises it). It is particularly important to know the relevant sections of the instruction Manual well before rating these symptoms.

Are thoughts put into your head which you know are not your own?
(How do do know they are not your own?)
(Where do they come from?) ☐ (55)

RATE THOUGHT INSERTION: Include only thoughts recognised as alien. Do not include delusional elaboration, only basic experience. (Exclude hallucinations.)

1 = Symptom described clearly, but subject thinks it may be due to 'own unconscious thoughts' etc., i.e. not certainly alien.
2 = Symptom described clearly and thoughts described as alien i.e. inserted into mind from elsewhere (even if subject does not know from where). Not hallucinations.

Do you ever seem to hear your own thoughts spoken alound in your head, so that someone standing near might be able to hear them?
(Are your thoughts broadcast, so that other people know what you are thinking?)
(How do you explain it?)

RATE THOUGHT BROADCAST. ☐ (56)

1 = Hears own thoughts 'spoken' aloud but not broadcast. Subject must really hear them aloud in his head. If in doubt rate (8) or (0).
2 = Thoughts transferred or broadcast so that others can share subject's thoughts even when they are not in the same room. (do not include 'thoughts being read' unless this is an explanation of thought broadcast. The subject must actually experience his thoughts being available to others.)

Do you ever seem to hear your own thoughts repeated or echoed?
(What is that like? How do you explain it?)
(Where does it come from?)

RATE THOUGHT ECHO OR COMMENTARY. ☐ (57)

1 = Thought echo, If any doubt, rate (8) or (0).
2 = Subject experiences alien thoughts related to his own thoughts, ie. association or comments on his own thoughts. Not hallucinations.

Do you ever experience your thoughts stopping quite unexpectedly so that there are none left in your mind, even when your thoughts were flowing freely before?)
(What is that like?)
(How often does it occur? What is it due to?)

Do your thoughts ever seem to be taken out of your head, as though some external person or force were removing them?
(Can you give an example?)
(How do you explain it?)

RATE THOUGHT BLOCK OR WITHDRAWAL ☐ (58)

1 = Thought block. Do not include if due to anxiety or lack of concentration; only if it occurs totally unexpectedly when thoughts are flowing freely. One single occasion is not sufficient for rating. Be very critical in rating this symptom.
2 = Delusional explanation that thoughts are withdrawn.

Can anyone read your thoughts?
(How do you know? How do you explain it?) ☐ (59)

RATE DELUSION OF THOUGHTS BEING READ: only if subject does not mean that people can infer his thoughts from his actions.
(Do not include subject reading thoughts of other people → 76)

1 = 'Partial' delusion. Subject entertains the possibility that thoughts might be read but is not certain about it. Exclude if subcultural explanation.
2 = Full delusion. Exclude if subcultural explanation. The term 'thought reading' is commonly used to mean the ability to tell what someone is thinking from the way they behave - this use should be excluded.

USE JUDGEMENT ABOUT WORDING.

** I should like to ask you a routine question which we ask of everybody. Do you ever seem to hear noises or voices when there is no one about, and nothing else to explain it? (Do you ever seem to hear your name being called?)

** Is that true of visions or other unusual experiences, which some people have?
(Touch , taste, smell, temperature, pain, etc.)

IF NO EVIDENCE FOR HALLUCINATION OF ANY SENSE, CUT OFF → SECTION 15.

IF EVIDENCE FOR NON-AUDITORY HALLUCINATIONS ONLY → SUBSECTIONS 14 B AND 14 C.

14A. AUDITORY HALLUCINATIONS

IF ANY EVIDENCE THAT AUDITORY HALLUCINATIONS MIGHT BE PRESENT:

Do your hear noises like tapping, or music? (What is it like?)
Does it sound like muttering or whispering?
Can you make out the words?

RATE NON-VERBAL AUDITORY HALLUCINATIONS. ☐ (60)

1 = Music, tapping, car engines, etc. Do not include tinnitus.
2 = Muttering, whispering but subject cannot make out any words at all.

What does the voice say?
(Write down examples of typical verbal hallucinations)
(If accusatory: Do you think that it is justified? Do you deserve it?)
Do you hear your name being called?

RATE VERBAL HALLUCINATIONS BASED ON DEPRESSION OR ELATION OR VOICE CALLING SUBJECT: ☐ (61)

Content is congruent with mood; e.g. 'He's dirty', in context of depression, or 'Go to Westminster', in elated subject who thinks he is Prime Minister. Include voice calling subject (e.g. calling name) or saying single words only. Be careful to distinguish from delusions of reference in which people whom the subject can see are thought to be talking about him.

RECORD EXAMPLES.

1 = Voice calling name, or single words only.
2 = Other verbal hallucinations; congruent with depressed mood.
3 = Other verbal hallucinations; congruent with elated mood.

Do you hear several voices talking about you?
Do they refer to you as 'he' (she)?
(What do they say?)
(Do they seem to comment on what you are thinking, or reading or doing?)

RATE VOICE(S) DISCUSSING SUBJECT IN THIRD PERSON OR COMMENTING ON THOUGHTS OR ACTIONS (NOT BASED ON DEPRESSION OR ELATION)

Do not include muttering or whispering if subject cannot make out words. Exclude 'dissociative' hallucinations (symptom 64). Do not include voice calling name or affectively based verbal hallucinations (symptom 61). There may be one voice commenting on subject's thoughts or actions, or several voices discussing the subject in the third person.

RECORD EXAMPLES. ☐(62)

1 = Hears a voice or voices commenting on thoughts or actions in third peron (e.g. 'Now he's going to go to bed 'or 'Why would he thing a thing like that?'). (2) not present.
2 = Hears voices talking about him/her in third person (e.g. 'I think he's a homosexual, don't you?' 'Yes he wears a pink pullover, that is a sign of it.') (1) may also be present.

Do they speak directly to you?
(Are they threatening or unpleasant?)
(Do they call you names?)
Do they give orders? (Do you obey?) ☐(63)

RATE VOICE(S) SPEAKING TO SUBJECT (NOT BASED ON DEPRESSION OR ELATION).

Include voice(s) speaking directly to subject, whether accusing threatening, giving orders or giving information. Exclude voice (s) calling name or based on depression or elation (symptom 61) or commmenting on subject's thoughts or actions (symptom 62) Exclude 'dissociative' hallucinations (symptom 63).

RECORD EXAMPLES.

1 = Pleasant, supportive or neutral voice(s) , not based on affect. No hostile voices.
2 = Hostile, threatening or accusing voice(s), thought to be undeserved and not based on affect.

N.B. If single isolated words, even with neutral affect, include under 61(1).

Can you carry on a two-way conversation with - ?
(You can reply, and then - replies to you, and you reply again just as in an ordinary conversation?)
(Do you see anything, or smell anything at the same time as you hear the voice?)
(Who is it you are talking to?)
(What is the explanation?)
(Do you know anyone else who has this kind of experience?)

RATE 'DISSOCIATIVE' HALLUCINATIONS (VERBAL AND/OR OTHER) ☐(64)

The subject can hold a two-way conversation with a presence (variously described as a person, ghost, spirit, god, etc. which may also be sensed in other ways, e.g. visually or by touch or smell. Often connected with people with whom the subject has had strong affective ties. Visual hallucinations can occur alone. There is usually a strong subcultural colouring, e.g. the subject belongs to a religious sect or to a subcultural group which sanctions hallucinatory experiences, or the subject has been under the influence of someone who is involved with such practices. Exclude hypnogogic hallucinations.

RECORD EXAMPLES.

1 = 'Dissociative' hallucinations present. Subject belongs to subcultural group or sect in which such experiences are sanctioned.
2 = 'Dissociative' hallucinations present. Subject does not belong to subcultural group as in (1). If not known, rate (1).

Are these voices in your mind or can you hear them through your ears?

Scoring: ☐ (65)

1 = Subject hears both pseudo-hallucinations (within mind) and true hallucinations (through ears).
2 = Subject hears pseudo-hallucinations only.
3 = Subject hears true hallucinations only.

How do you explain the voice?

RECORD EXPLANATION.

14B. VISUAL HALLUCINATIONS

IF QUESTION HAS NOT BEEN COVERED IN SECTION 12 OR 14A, ASK:

** Have you had visions, or seen things other people couldn't see?

IF NO EVIDENCE, HERE OR ELSEWHERE, FOR VISUAL HALLUCINATIONS CUT OFF — SECTION 15.

RATE VISUAL HALLUCINATION: In clear consiousness including pseudo-hallucinations. Exclude 'dissociative' visual hallucinations (symptom 64). ☐ (66)

1 = Formless visual hallucinations - flashes of light, shadows, etc.
2 = Formed visual hallucinations - people, objects like a 'fiery cross', faces, etc.

RATE DELIRIOUS VISUAL HALLUCINATIONS ☐ (67)

14C. OTHER HALLUCINATIONS

IF QUESTIONS HAVE NOT BEEN COVERED IN PREVIOUS SECTIONS:

** Is there anything unusual about the way things feel, or taste, or smell?

** Does your body function normally?

IF NO EVIDENCE FOR OTHER HALLUCINATIONS CUT OFF → SECTION 15A

IF ANY EVIDENCE FOR OTHER HALLUCINATIONS:

Do you sometimes notice strange smells that other people don't notice?
(What sort of thing?)
(How do you explain it?) ☐ (68)

RATE OLFACTORY HALLUCINATIONS: Exclude delusion that patient himself smells.

1 = Simple olfactory hallucination. Not delusionally elaborated. Subject smells oranges, death, a burnt smell, scent, etc., which other people cannot smell. Can offer no explanation.
2 = Delusional elaboration in addition, e.g. gas being put into room.

Do you seem to think that you yourself give off a smell which is noticed?
(What is the explanation?)

RATE DELUSION THAT SUBJECT SMELLS: Do not include simple preoccupation with body odour, e.g. in anxious subject who sweats a lot. ☐ (69)

1 = Subject irrationally thinks he gives off a smell but is not certain. Not sure that others have noticed it but thinks it possible.
2 = Subject sure that he gives off a smell and that others have noticed it and react accordingly.

Do you ever feel that someone is touching you, but when you look there is nobody there?
(Have you noticed that food or drink seems to have an unusual taste recently?)

RATE OTHER HALLUCINATIONS AND DELUSIONAL ELABORATION: Exclude hypochondriacal and nihilistic delusions rated in (90) and (91). ☐ (70)

1 = Sensation of touch, food tastes burnt, etc. but subject puzzled by the experience. No delusional elaboration.
2 = Delusional elaboration in additon, e.g. fantasy lover, food poisoned, etc.

Project No.

Subject No.

Card No.

15. DELUSIONS

Definition

Delusions may be of two kinds, primary and secondary. Both are rated together in the following symptoms except where specified. For example, primary delusions are specifically rated in symptom (82). They are defined here for convenience.

Primary delusions are based upon experiences in which a subject suddenly becomes convinced that a particular set of events has a special meaning (e.g. a subject undergoing a liver biopsy suddenly felt he had been chosen by God). The delusion cannot be explained and it is not shared by by other members of the subject's cultural social group.

Secondary delusions are delusional elaborations of primary delusions or other basic phenomena such as derealisation, perceptual distortions, hallucination, thought echo, mood changes, etc.

Above cut-off questions, likely to elicit delusions if present, are included in many of the preceding sections. There may also be evidence in the case-record or in the subject's spontaneous account.

IF NO EVIDENCE AT ALL THAT DELUSIONS ARE PRESENT, CUT OFF→ SECTION 16

RECORD IF ANY PSYCHOTIC PHENOMENA PRESENT, OTHER THAN DELUSIONS; USE JUDGEMENT AS TO WHETHER TO PROCEED BEYOND CUT-OFF.

IF ANY EVIDENCE FOR DELUSIONS, ASK ALL QUESTIONS NOT IN BRACKETS, AND ANY FURTHER QUESTION WHICH SEEM INDICATED.

RATING OF PARTIAL AND FULL DELUSIONS.

In general, all delusions are rated as follows:

1 = Partial delusions, which are expressed with doubt, or as possibilities which the subject entertains but is not certain about. This rating should not be used if it is clear that full delusions have been present during the month, or if the subject has acted as if fully deluded.
2 = Full delusions have been present at some time during the month. Fully convinced. No insight.

A useful question to elucidate the difference between partial and full delusions is as follows:

Even when you seem to be most convinced, do you really feel in the back of your mind that it might well not be true, that it might be imagination?

15A. DELUSIONS OF CONTROL

Definition

The subject's will is replaced by that of some external agency A simple statement that the radio is controlling the subject is not sufficient. (This statement, alone, should be rated 8.) The subject must describe a replacement of will by some other force.

Do not include feeling that life is planned and directed by fate, or that the future is present already in embryo, or that subject is not very stong-willed, or that voices give subject orders. Do not include simple identification with God or being under God's direction. Do not include subcultural or hysterical possession states or multiple peronality (→ 100).

Do you feel under the control of some force or power other than yourself?
(As though you were a robot or a zombie without a will of your own?)
(As though you were possessed by someone or something else?)
(What is that like?)
(Does this force make your movements for you without your willing it, or use your voice, or your handwriting? Does it replace your personality? What is the explanation?)

RATE DELUSIONS OF CONTROL. ☐ (71)

1 = Partial delusions
2 = Full delusions

15B. MISINTERPRETATIONS, MISIDENTIFICATION AND DELUSIONS OF REFERENCE.

Definition

Delusions of reference: Do not include simple self-consciousness of feeling that subject attracts comments, even if critical. These are rated under symptom 31.

There must be elaboration: e.g. someone crosses his knees in order to indicate that the subject is homosexual; or the whole neighbourhood is gossiping.

Delusional misinterpretations, etc. This is an extension of the delusion of reference, so that not only do people seem to refer to subject, but situations appear to be deliberately created to test him (exclude situations of medical treatment), or objects appear to have special meanings.

Do people seem to drop hints about you or say things with a double meaning, or do things in a special way so as to convey a meaning?
Does everyone seem to gossip about you?
(Do people follow you about or check up on you or record your movements?)
(How do they do it ? Why?)
(Are there people about who are not what they seem to be?)

RATE DELUSIONS OF REFERENCE. ☐ (72)

1 = Partial delusions
2 = Full delusions

Do things seems to be specially arranged?
(Is an experiment going on to test you out?
(Do you see any reference to yourself on TV or in the papers?
(Do you ever seem to see special meanings in advertisements, or shop windows, or in the way things are arranged?)
(How do you explain this?)

RATE DELUSIONAL MISINTERPRETATION AND MISIDENTIFICATION.

1 = Partial Delusions
2 = Full Delusions ☐ (73)

15C. DELUSIONS OF PERSECUTION

Is anyone deliberately tying to harm you, e.g. to poison you or kill you?
(How? Is there an organisation like the Mafia behind it?)
(Is there any other kind of persecution? How do you explain this?)

RATE DELUSIONS OF PERSECUTION ☐ (74)

1 = Partial delusions
2 = Full delusions

15D. EXPANSIVE DELUSIONS

Do you think that people are organising things specially to help you?

RATE DELUSIONS OF ASSISTANCE. ☐ (75)

1 = Partial delusions
2 = Full delusions

Is there anything special about you? Do you have special abilities or powers?
(Can you read people's thoughts?)
(Is there a special purpose or mission to your life?)
(Are you especially clever or inventive? How do you explain this?

RATE DELUSIONS OF GRANDIOSE ABILITIES ☐ (76)

1 = Partial delusions
2 = Full delusions

Can you do things other people can't do?

(Are you a very prominent person or related to someone prominent, like Royalty?)
(Are you very rich or famous?)
(How do you explain this?)

RATE DELUSIONS OF GRANDIOSE IDENTITY: (Exclude religious identification.

1 = Partial delusions
2 = Full delusions ☐ (77)

15E. DELUSIONS CONCERNING VARIOUS TYPES OF INFLUENCE AND PRIMARY DELUSIONS

Are you a very religious person?
(Specially close to Christ or God?)
(Can God communicate with you? How?)
(Are you yourself a saint?)
(How do you explain this?)

RATE RELIGIOUS DELUSIONS: Including delusional religious explanations of other experiences. Exclude intense religious belief or purely subcultural beliefs.

1 = Partial delusions
2 = Full delusions ☐ (78)

How do you explain the things that have been happening? (SPECIFY)
Is there anything like hyponotism, telepathy, or the occult going on?
What is the explanation?

INCLUDE DELUSIONAL EXPLANATIONS IN TERMS OF PARANORMAL PHENOMENA: e.g. hyponotism, telepathy, magic, witchcraft, etc. Exclude purely subcultural beliefs, → 83.

1 = Partial delusions
2 = Full delusions ☐ (79)

Is anything like electricity, or X-rays, or radio-waves affecting you?
(In what way? What is the explanation?)

INCLUDE DELUSIONAL EXPLANATIONS IN TERMS OF PHYSICAL FORCES e.g. radio, television, X-rays, electricity, transmitters, microphobes, machines of various kinds.

1 = Partial delusions
2 = Full delusions ☐ (80)

DELUSIONS OF ALIEN FORCES PENETRATING OR CONTROLLING MIND (OR BODY) ☐ (81)

Include any delusion, whether rated elsewhere or not, which involves an external force penetrating the subject's mind or body, e.g. rays turn liver to gold, alien thoughts pierce skull or are inserted into mind, hypnotism makes patient levitate, a spirit speaks with subject's voice, a radio transmitter has been implanted into brain and broadcasts thoughts or controls

actions, etc.

1 = Partial delusions
2 = Full delusions

Choose a likely delusion, and ask :

How did it come into your mind that this was the explanation? (Did it happen suddenly? How did it begin?)

RATE PRIMARY DELUSIONS : Based upon experiences in which subject suddenly becomes convinced that a particular set of events has a special meaning. (See definition on page 214.) Not based on mood or explanation of other abnormal experiences. (82)

1 = Partial delusions
2 = Full delusions

15F. OTHER DELUSIONS

(Examiner should question as appropriate.) (83)

RATE SUBCULTURALLY INFLUENCED DELUSIONS: Include only subjects who belong to small groups with definitely idiosyncratic beliefs; small sects, tribes, 'secret societies', etc.

0 = No significant subcultural influence. For example, an English subject believing he is influenced by TV would be rated (0) since, although the delusion depends on TV being available in England, it is not in any way specific to a small subcultural group.
1 = One or more of the 'delusions' rated earlier could easily be no more than a belief shared by other members of the subject's subcultural group, e.g. the Pentecostal church with the gift of tongues. Voodoo, witchcraft communicating with God, are other examples of beliefs which may be taken quite literally by groups of people who are not clinically deluded. Rate (1) if subject holds such beliefs without elaborating them further.
2 = As (1), but because of excitement, expansiveness, depression, confusion, intellectual retardation, etc., the subject holds the beliefs with exceptional fervour and conviction, or elaborates them further. Such a subject might well be regarded as abnormal by other members of his own sect or group.
3 = More specific delusional states, e.g. Koro, Witigo, etc.

(Do you have any reason to be jealous of anybody?)

MORBID JEALOUSY.

1 = Partial delusions
2 = Full delusions (84)

DELUSION OF PREGNANCY.
(Do you think a man can fall pregnant?)

1 = Partial delusions
2 = Full delusions (85)

SEXUAL DELUSIONS: Any delusion with sexual content, e.g. fantasy lover, sex changing, etc. Do not include an untrue claim that a subject is married or has children.

1 = Partial delusions
2 = Full delusions

☐ (86)

Have you had any unusual sexual experiences lately?
Do your sexual organs feel normal?
Have you had any unusual experience or adventures recently?

RATE FANTASTIC DELUSIONS, DELUSIONAL MEMORIES, DELUSIONAL CONFABULATIONS, FANTASTIC DELUSIONS:

Confabulation : Subject makes up delusions on the spot. Very rare. Delusional memories: Subject seems to be describing actual memories. Describes the same delusions time and again. Not confabulations. Rare, e.g. 'I came down to earth on a silver star.' Fantastic delusions: The commonest of the three e.g. England's coast melting.

1 = Partial delusions
2 = Full delusions

☐ (87)

15G. SIMPLE DELUSIONS BASED ON GUILT, DEPERSONALISATION, HYPOCHONDRIASIS, ETC.

Definition

These symptoms often appear to be based on a depressed mood and are relatively consistent and unelaborated. Do not include more bizarre elaborations of any of them, e.g. having a metal nose = possibly symptom 87, not 89. Having been turned into another specified person = possibly symptom 71, not 90. Liver turned to lead by X-rays = symptoms 80 and 81, not 91. England's coast melting = symptom 87, not 92.

Do you feel you have committed a crime, or sinned greatly, or deserve punishment?
(Have you felt that your presence might contaminate or ruin other people?)

RATE DELUSIONS OF GUILT ☐ (88)

1 = Subject has brought ruin to family by being in present condition, or thinks that symptoms are a punishment for not doing better, etc. Does not elaborate as in (2)
2 = Subjects says has sinned greatly or committed some terrible crime or brought ruin upon the world. May feel deserving of punishment, even of death or hell-fire, because of it.

(Do you think your appearance is normal?)
RATE SIMPLE DELUSIONS CONCERNING APPEARANCE: ☐ (89)

(Nose too large, teeth misshapen, body crooked, etc.)

1 = Strong feeling that there is something wrong with appearance; subject looks old or ugly or dead, skin cracked teeth misshapen, nose too large, body crooked, etc. Can be reassured temporarily. There may be only one limited preoccupation.
2 = Subject acts accordingly (plastic operations, etc.)

(Is anything the matter with your brain?)

RATE DELUSIONS OF DEPERSONALISATION: Subject has no head, does not exist, hollow instead of a brain, etc. ☐ (90)

1 = Unable to think, no thoughts in head, feels as though he has no brain or as though it does not function at all.
2 = Symptom more intense. Subject has no head, no brain, does not exist.

(Is anything the matter with your body?) ☐ (91)

RATE HYPOCHONDRIACAL DELUSIONS: Subject has incurable cancer, bowels are stopped up, insides are rotting, etc.

1 = Subject feels body is unhealthy, rotten, diseased, but without the force of (2)
2 = Subject has incurable cancer, bowels are stopped up or rotting away, etc.

(Do you have the feeling that something terrible is going to happen? What?)

RATE DELUSIONS OF CATASTROPHE: World is about to end, some catastrophe has happened or will occur, everything is evil and will be destroyed. ☐ (92)

1 = Subject feels sense of impending doom; something awful will happen. Non-specific but out of proportion to circumstances.
2 = Delusional conviction that world is about to end or some other enormous catastrophe is about to occur or has occurred. World is dirty, decayed, rotten: ie. further delusional elaboration of (1).

15H. GENERAL RATINGS OF DELUSIONS AND HALLUCINATIONS

(Include both partial and full delusions.)

CONSIDER BOTH DELUSIONS AND HALLUCINATIONS IN FOLLOWING RATINGS

RATE SYSTEMATISATION OF DELUSIONS

Scoring: ☐ (93)

0 = No delusions or hallucinations.
1 = Delusions and hallucinations not elaborated into a general system affecting much of the subject's experience. Include encapsulated delusions or isolated hallucinations.
2 = Some systematic elaboration, but substantial areas of the subject's experiences are not affected.
3 = Subject interprets practically all his experience in delusional terms.

RATE EVASIVENESS

Scoring: ☐ (94)

0 = No attempt at concealment suspected.
1 = Examiner suspects that there may be (either) delusions or hallucinations in the background, but the subject is not concealing much of the psychopathology.
2 = Examiner suspects that there is a considerable preoccupation with delusions (even a delusional system) or hallucinations, but the subject tries to conceal them.

3 = No concealment but other delusions or hallucinations probably present. Not elicited because of poor intelligence and education or incoherence or muteness, etc.

OVERALL RATING OF PREOCCUPATION WITH DELUSIONS AND HALLUCINATIONS

Scoring: ☐ (95)

0 = No delusions or hallucinations.
1 = No delusions or hallucinations definitely rated but examiner suspects that they may be present.
2 = Preoccupied with past delusions or hallucinations only. Not actively deluded or hallucinated at present.
3 = Delusions or hallucinations definitely present but subject is not preoccupied with them for much of the time. Can turn attention to other things without difficulty.
4 = Delusions or hallucinations present and take up most of the subject's attention. Preoccupied to the exclusion of many other matters.
5 = Patient can hardly discuss anything but delusions.

RATE ACTING OUT DELUSIONS

(Rate from case-record, etc.) ☐ (96)

Scoring:

0 = No delusions or hallucinations.
1 = Subject able to keep delusions or hallucinations to himself, or to confide them only to a few trusted people (sympathetic relatives, friends, doctors, etc.) He does not express them in public nor act upon them. Does not talk out loud to voices.
2 = Subject has acted upon delusions or hallucinations during past month, or expressed them in public (i.e. outside the small circle of people who would be expected to be sympathetic). This has not, however, resulted in severe social disturbance or a social crisis.
3 = As (2) but acting out, or public expression, has resulted in severe social disturbance or a social crisis.

16. SENSORIUM AND FACTORS AFFECTING

** Have you had any lapses of memory recently?
(Have there been any periods in which you completely forgot what happened?)
(What was it like?)
(How do you explain it?)

RATE FUGUES, BLACKOUTS, AMNESIA LASTING MORE THAN ONE HOUR: Irrespective of aetiology. ☐ (97)

1 = less than 12 hours.
2 = 12-24 hours.
3 = more than 24 hours.

** What medicines or drugs do you take?
(Do you take anything for your nerves or your mood?)
(Obtain list of drugs.)
(Who prescribes?)

RATE DRUG ABUSE DURING MONTH. One category only.

1 = Cannabis
2 = Amytal, etc.
3 = LSD, amphetamine, etc.
4 = Cocaine, heroin, etc. (98)

** May I ask about your drinking habits? How much do you usually drink each day?

(Is alcohol in any way a problem for you? In what way?)
(CHECK LIST: Present on card if needed. During the past month have you: had family problems because of drinking?
missed work because of drinking?
had morning shakes or other withdrawal symptoms?
had blackouts for several hours?
heard voices or seen visions?)

RATE ALCOHOL ABUSE DURING PAST MONTH (99)

1 = Agrees alcohol has been a problem but not 2.
2 = Any check-list item applies.

RATE DISSOCIATIVE STATES DURING PAST MONTH: (100)

'Narrowing of consciousness which serves an unconscious purpose and is commonly accompanied or followed by a selective amnesia'. e.g. trance, possession state, fugue, hypersomnia, stupor, etc.
Do not include if caused by drugs, alcohol, epilepsy, etc.

1 = Present during month, not at examination.
2 = Present at examination.

RATE CONVERSION SYMPTOMS, e.g. paralysis, anaesthesia, blindness, tremor, seizures, etc. if mentioned during interview.

1 = Present during month, not at examination. (101)
2 = Present at examination.

RATE CLOUDING OR STUPOR AT EXAMINATION (102)

1 = Clouding: Inadequate comprehension of external impressions, with perplexity, and impairment of attention and orientation.
2 = Stupor: Subject appears comatose but there is no clouding or impairment of consciousness.

IF ANY SUSPICION OF POOR MEMORY OR DISORIENTATION:

May I ask one or two standard question we ask of everybody?
How old are you?
Can you tell me the year and the month?
What is the name of the Prime Minister?

RATE ORGANIC IMPAIRMENT OF MEMORY. See glossary for definition.

1 = Mild
2 = Moderate
3 = Severe (103)

17. INSIGHT

** Do you think there is anything the matter with you?
(What do you think it is?)
(Could it be a nervous condition?)
(What do you think the cause is?)
(Why did you need to come to hospital?)
(Do you think (specify delusions or hallucinations) were part of a nervous condition?)

IF PSYCHOTIC SYMPTOMS (i.e. SYMPTOMS FROM SECTIONS 12 - 15):

0 = Full insight (in intelligent subject, able to appreciate the issues involved).
1 = As much insight into the nature of the condition as social background and intelligence allow.
2 = Agrees to a nervous condition but examiner feels that subject does not really accept the explanation in terms of a nervous illness (e.g. gives delusional explanation, the result of persecution, or rays, etc.).
3 = Denies nervous condition entirely.
9 = Psychotic illness not present.

☐ (104)

IF NEUROTIC SYMPTOMS (i.e. SYMPTOMS FROM SECTION 1 - 11 ONLY)

0 = Full insight (in intelligent subject, able to appreciate the issues involved).
1 = As much insight into the nature of the condition as social background and intelligence allow.
2 = Gives physical explanation for neurotic symptoms.
3 = Denies neurotic symptoms entirely.
9 = Neurotic illness not present.

☐ (105)

** Of all the problems you have told me about, which one affects you most?
How much does it interfere with your work or your relationships with other people?
(Have you actually been out of work, or been unable to do do some housework, or go shopping, travelling, etc. during the past month?)
(Have the symptoms impaired your efficiency in any other way?)

RATE SOCIAL IMPAIRMENT DUE TO NEUROTIC CONDITION ☐ (106)

0 = No neurotic or psychotic symptoms present.
1 = Neurotic symptoms present but little diminution of subject's efficiency or interference with everyday activities.
2 = Neurotic symptoms interfere with subject's efficiency to a moderate extent but are not incapacitating, e.g. subject neglects housework or can't enjoy leisure activities or social relationships, or finds work-efficiency reduced because of worry, tension, irritability, depression, anxiety, etc. Subject does not, however, stop work altogether or completetely neglect household.
3 = Subject severely incapacitated by neurotic symptoms: had to have at least a week off work during past month; was housebound for a week or more; was actively withdrawn from all social relationships, etc. The subject does not have to be totally incapacitated for the whole

month for this rating to be made, but impairment has to be very severe.

8 = Examiner unsure.

9 = Psychotic condition present.

(If both psychotic and neurotic condition, rate whichever shows more impairment.)

RATE SOCIAL IMPAIRMENT DUE TO PSYCHOTIC CONDITION ☐ (107)

0 = No neurotic or psychotic symptoms present.

1 = Psychotic symptoms present but little diminution of subject's efficiency or interference with everyday activities.

2 = Psychotic symptoms interfere with subject's efficiency to a moderate extent but are incapacitating, e.g. subject neglects housework or can't enjoy leisure activities or social relationships, or finds work-efficiency reduced. Subject does not, however, stop work altogether or completely neglect household.

3 = Subject severely incapacitated by psychotic symptoms: had to have at least a week off work during past month ; was housebound for a week or more; was actively withdrawn from all social relationships, etc. The subject does not have to be totally incapacitated for the whole month for this rating to be made, but impairment has to be very severe.

8 = Examiner unsure.

9 = Neurotic condition, and no psychotic condition, present.

FINAL QUESTION

** Have there been any other things lately that I haven't covered?

Specify;

Note here any points that seem to be important or unusual about the subject or the interview which are not covered in the schedule.

Reconsider schedule to make sure that all obligatory questions have been asked. Also consider whether behaviour, affect and speech rating can be made or whether further observation or examination is necessary. IF NOT, THIS IS THE END OF THE INTERVIEW.

18-20. BEHAVIOUR, AFFECT AND SPEECH

RATINGS

0 = Symptom absent
1 = Present in fairly severe degree, or very severe but intermittent during interview.
2 = Present in very severe degree and almost continuous during interview.
8 = Examiner not sure.
9 = Subject not examined, or examination not appropriate.

N.B. If in doubt, rate (0). A rating of (1) means there is no doubt about the symptom being present in fairly severe form.

Behaviour during interview ☐(108)

Self -neglect (cleanliness, shaven, make-up, state of hair and clothes).

Bizarre appearance (secret documents openly displayed, special clothes or ornaments with symbolic significance, etc. Do not include mannerism or posturing = symptom 116). ☐(109)

Slowness and underactivity (sits abnormally still, walks abnormally slowly, delay in performing movements). ☐(110)

Agitation (Fidgety, restlessness, pacing, frequent unnecessary movements). ☐(111)

Gross excitement and violence (throws things, runs or jumps about, waves arms wildly, shouts or screams). ☐(112)

Irreverent behaviour (sings, facetious, silly jokes, flippant remarks, unduly familiar). ☐(113)

Distractibility (stops talking or changes subject due to distraction by trivial noises or events outside the room or turns attention to furniture, etc.) ☐(114)

Embarrassing behaviour (making sexual suggestions or advances to interviewer; loss of social restraint - scratches genitals, passes loud flatus, etc.) ☐(115)

Mannerisms and posturing (odd, stylised movements or acts, usually idiosyncratic to the patient, often suggestive of special meaning or purpose: assuming and maintaining uncomfortable or inappropriate postures). ☐(116)

Stereotypies, etc. (constant repetition of movement or postures such as rocking, rubbing, grimacing: no special significance). ☐(117)

Behaves as if hallucinated (non-verbal: as though hears voices or visions: lips move soundlessly, looks round, giggles to self not just from embarrassment, shyness, etc.). ☐(118)

Catatonic movements
(Negativism: does the opposite of what is asked. ☐(119)
Ambitendence: begins to take proffered hand, then withdraws; etc.
Echopraxia: imitates examiner's movement.
Flexibilitas cerea: arm remains where it is put, for at least 15 seconds.

Mitgehen: excessive co-operation in passive movement.
Echolalia: imitates words and phrases with same intonation and inflection of voice.)

(These items can be separately rated in special projects.)

Affect during interview

Observed anxiety (tense worried look or posture, feaful apprehensive look, frightened tone of voice, tremor). ☐ (120)

Observed depression (sad, mournful look, tears, gloomy tone of voice, deep sighing, voice chokes on distressing topic). ☐ (121)

Histrionic (feeling expressed in exaggerated, dramatic, histrionic manner). ☐ (122)

Hypomanic affect (unduly cheerful, smiling, euphoric, elated). ☐ (123

Hostile irritability (unco-operative, irritable, angry, overtly hostile, discontented, haughty, antagonistic). ☐ (124)

Suspicion ☐ (125)

Perplexity (puzzlement) ☐ (126

Lability of mood (whether lability of one mood, or changing from one mood to another). ☐ (127)

Blunted affect (expressionless face and voice, uniform blunting whatever the topic of conversation, indifference to distressing topics, whether delusional or normal). ☐ (128)

1 = Blunting not uniform, e.g. at times responds affectively but at other times is markedly flat; or responds with some evidence of affect, but definitely less than expected.
2 = Severe and uniform blunting.

Incongruity of affect (emotion is shown, but not congruent with topic). ☐ (129)

Speech during interview

Slow speech (long pauses before answering, long pauses between words). ☐ (130)

Pressure of speech (more copious speech than normal, too rapid speech, very loud voice, too circumstantial speech). ☐ (131)

Non-social speech (talks, mutters, whispers, out loud, out of context of conversation with examiner). ☐ (132)

Muteness

1 = Almost mute, fewer than twenty words in all.
2 = Totally mute. ☐ (133)

Restricted quantity of speech (subject frequently fails to answer, questions have to be repeated, restricted to minimum necessary, no extra sentences, no additional comments). ☐ (134)

Neologisms and idiosyncratic use of words or phrases, e.g. 'One is called "Per-God" and the other is called "Per-the-Devil", ☐ (135)

' ... miracle-willed through God's "tarn-harn" ... ', 'Well, there is a frequenting of clairvoyance ...': 'Per-God', 'Per-the-Devil' and 'tarn-harn' are neologisms; 'frequenting clairvoyance' is an example of ordinary words used idiosyncratically. DO NOT RATE THIS SYMPTOM PRESENT UNLESS EXAMPLES ARE WRITTEN DOWN.

Disorder of content of speech

Three types of disordered content are specified: in each case, the effect is to make it very difficult to grasp what the subject means. However, the symptoms are defined in terms of specific components so that it should, in most cases, be possible to say that whether one, two, or all three symptoms are present. If in doubt, rate hierarchically, i.e. rate incoherence in preference to flight of ideas and flight of ideas in preference to poverty of speech.
If the patient does not talk enough to give a rateable sample of speech, rate all three symptoms Y.

Incoherence of speech. The subject's meaning is obscured by distorted grammar, lack of logical connection between one part of a sentence and another or between sentences, sudden irrelevances or 'Knight's move', grossly pedantic phrases, answering off the point, etc. For example: ☐ (136)

'We've seen the downfall of the radium crown by the Roman Catholics, whereas when you come to see the drinking side of the business, God saw that Noah, if he lost his reason, he got nobody there to look after them.

'I did suggest to you, that intrinsic or congenital sentiment of refinement of disposition would be so miracle-willed through God's "tarn-harn" as to assume quite the opposite.

'I believe we live in a world , in an age, where the elements are a force that elders of professionalism hope, not to conquer, but to control.

'What's your address?" 'It's supposed to be Salisbury near Birmingham.'
(Vorbeireden.)

DO NOT RATE THIS SYMPTOM PRESENT UNLESS EXAMPLES ARE WRITTEN DOWN.

A rating of 2 means that very little normal speech is present.
N.B. A free flow of delusions is not necessarily incoherent. A subject may talk about delusions quite coherently.

Flight of ideas. Words are associated together inappropriately by sound or rhyme (clang association). Altogether the original aim of the sentence may quickly be lost, a path can be traced through associations of the white-black-coffin or ring or ring-wrong variety, or through associations with distracting stimuli, e.g.

'How is your appetite ?' 'I feel as if I have lost my appetite. I have had an orange. A real juicy orange' (See patient walking past window.) 'She is going for E.C.T. Etcetera treatment or teddy bear's picnic. I call it.'

DO NOT RATE THIS SYMPTOM PRESENT UNLESS EXAMPLES ARE WRITTEN DOWN

A rating of 2 means that very little normal speech is present.

Poverty of content of speech. The subject talks freely but so vaguely that little information is given in spite of the number of words used: rambles on without coming to a point; may wander far from original theme. Exclude incoherence or flight of ideas. Rate only if severe and always give written example. ☐ (138)

Misleading answers. Subject's answers are misleading because answers 'yes or 'no' to everything, or frequent self-contradictions, or appears to be deliberately misleading. Do not include incoherence, flight of ideas or poverty of speech here. ☐ (139)

Re-rate adequacy of interview

0 = Ratings made adequately represent the symptoms present.
1 = Some problem but key symptoms have been rated.
2 = Serious question as to adequacy of interview for rating key symptoms (other than sections 18-20).
3 = Only sections 18-20 could be rated. ☐ (140)

Check that every box has an entry except those below ticked cut-off points.

Complete coding sheet if one is being used.

For glossary of definitions see Wing, Cooper and Sartorius, (1974).

APPENDIX D

CATEGO syndrome abbreviation and symptom composition

Abbreviation	Syndrome	Symptoms	
HM	Hypomania	41	Subjective euphoria
		42	Ideomotor pressure
		43	Grandiose ideas and actions
		123	Hypomanic affect
		137	Hypomanic content of speech
AG	Agitation	111	Agitation on examination
NG	Self-neglect	108	Self-neglect
NP	Non-specific psychosis	49	Unfamiliar and delusional mood
		50	Heightened perception
		53	Changed perception of time
		60	Hears music, tapping etc.
		61	Hears voices calling name
		66	Minor visual hallucinations
		70	Other minor hallucinations
		94	Evasiveness concerning delusions
		102	Clouding or stupor
		117	Stereotypes
		125	Suspicion
		126	Perplexity
		129	Incongrous affect
OV	Overactivity	112	Gross excitement

		113	Irreverent behaviour
		115	Embarrasing behaviour
RS	Residual Syndrome	60	Hears muttering, whispering
		118	Behaves as if hallucinated
		132	Non-social speech
OR	Organic impairment	67	Delirious visual hallucinations
		103	Organic impairment of memory
AF	Flattening	128	Blunt affect
CS	Catatonic syndrome	116	Mannerism and posturing
		119	Catatonic movements
SL	Slowness	110	Slowness and underactivity
		130	Slow speech
		133	Muteness
		134	Restriction of quantity of speech
IS	Incoherent Speech	135	Neologisms
		136	Incoherence of speech
SF	Sexual and Fantastic Delusions	59	Thoughts read
		70	Delusional elaboration of hallucinations
		75	Delusions of assistance
		79	Delusional explanation (hyponotism etc.)
		80	Delusional explanation (rays etc.)

		84	Morbid jealousy
		85	Delusions of pregnancy
		86	Sexual Delusions
		87	Fantastic Delusions
		89	Delusions concerning appearance
		90	Delusions concerning lack of organs
		82	Primary delusions
RE	Delusions of Reference	72	Delusions of reference
		73	Delusions of misinterpretation
GR	Grandiose and Religious Delusions	76	Delusions of grandiose ability
		77	Delusions of grandiose indentity
		78	Religious delusions
PE	Delusions of Persecution	74	Delusions of Persecution
NS	Nuclear Syndrome	55	Thought intrusion
		56	Thought broadcast
		57	Thought commentary
		58	Thought withdrawal
		62	Voices about patient
		71	Delusions of control
		81	Delusions of alien penetration
VH	Visual Hallucinations	66	Visual hallucinations

OH	Olfactory hallucinations	68	Olfactory hallucinations
		69	Delusion that patient smells
AH	Auditory hallucinations	63	Voices to patient (not depressive)
DD	Depressive Delusions and Hallucinations	61	Depressive hallucinations
		88	Delusions of guilt
		91	Hypochondrical delusions (bowels blocked up)
		92	Delusions of catastrophe
SC	Sub-cultural delusions of hallucinations	64	'Sub-cultural' hallucinations
		83	'Sub-cultural' delusions
SD	Simple Depression	19	Inefficient thinking
		23	Depressed mood
		24	Hopelessness
		25	Suicidal plans or acts
		121	Depression on examination
ED	Special features of depression	32	Guilty ideas of reference
		33	Guilt
		51	Dulled perception
		54	Lost affect
SA	General anxiety	11	Anxiety
		14	Panic attacks
		120	Anxiety on examination

ON	Obsessional Neurosis	44	Checking and reporting
		45	Cleanliness and rituals
		46	Obsessional ideas and rumination
SA	Situational anxiety	15	Situational anxiety
		17	Specific phobias
		18	Anxiety avoidance
HT	Hysteria	64	Dissociative hallucinations (not sub-cultural)
		100	Dissociative states
		101	Conversion symptoms
		122	Histrionic
IT	Irritability	40	Irritability
		124	Hostile irritability
WO	Worry	4	Worrying
		6	Tiredness
		10	Nervous tension
		21	Neglect through brooding
		35	Delayed sleep
TE	Tension	5	Tension pains
		7	Muscular tension
		8	Restlessness
IR	Ideas of reference	31	Ideas of reference

SU	Social unease	16	Anxiety on meeting people
		28	Social withdrawal
		30	Lack of self confidence
IC	Loss of interest and concentration	20	Poor concentration
		22	Loss of interest
OD	Somatic symptoms of Depression	27	Morning depression
		34	Loss of appetite
		37	Early waking
		38	Loss of libido
		39	Premenstrual exacerbation
LE	Lack of energy	36	Subjective anergia
DE	Depersonalization	47	Derealization
		48	Depersonalization
HY	Hypochondriasis	9	Hypochondriasis

APPENDIX E

Subscores derived from the PSE.

BEHAVIOUR, SPEECH AND OTHER SYNDROMES (BSO)

	Possible score
Hypomania	10
Agitation	2
Self neglect	2
Non-specific psychotic syndrome	26
Overactivity	6
Residual syndrome	6
Catatonic syndrome	4
Flattening	2
Slowness	8
Incoherence of speech	4
	70

DELUSIONAL AND HALLUCINATORY SYNDROMES (DAH)

	Possible score
Sexual and fantastic delusions	24
Delusions of reference	4
Grandiose and religious delusions	6
Delusions of persecution	2
Nuclear syndrome	14
Visual hallucinations	2
Olfactory hallucinations	4
Auditory hallucinations	2

Depressive delusions and hallucinations	8
Sub-cultural delusions and hallucinations	3
	69

SPECIFIC NEUROTIC SYNDROMES (SNR)

	Possible score
Simple depression	10
Special features of depression	10
General anxiety	6
Obsessional neurosis	6
Situational anxiety	6
Hysteria	8
	46

NON-SPECIFIC NEUROTIC SYNDROMES (NSN)

	Possible score
Irritability	4
Worry	10
Tension	6
Ideas of reference	2
Social unease	6
Loss of interest and concentration	4
Somatic symptoms of depression	9
Lack of energy	2
Depersonalization	4
Hypochondriasis	2
	49

TOTAL PSE SCORE (TOT) 234

APPENDIX F1. CATEGO SYNDROME SCORES OF PSE1 OF PATIENTS IN THE HIGH CANNABIS GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
CM	1	-	-	3	-	-	-	1	-	2	1	1	2	-	2	3	-	1	-	-	3	-	3	-	-	-	-	1	4	-	2	-	-	-	-	-	-	-	-	8	12	3	7	30
[1] AA	9	1	-	-	-	-	-	-	-	-	-	2	-	6	2	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12	10	0	0	22
JS	8	-	1	-	1	1	2	-	-	-	-	2	-	4	-	-	-	-	-	-	-	-	-	2	-	-	-	1	3	-	2	-	-	-	-	-	-	-	11	7	2	6	26
FJ	1	1	-	3	-	-	1	-	-	-	-	-	4	-	2	-	-	-	-	1	-	1	-	-	3	-	1	4	2	1	-	2	-	3	1	-	-	-	4	8	5	13	30
GM	7	-	-	-	1	-	-	-	-	-	-	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-	-	-	-	-	-	-	-	8	6	0	4	18
JvR	-	-	1	-	-	-	-	1	-	1	-	2	4	-	-	6	1	-	-	-	-	5	1	1	-	-	-	3	6	-	-	2	3	-	2	-	-	-	3	13	7	16	39
AS	4	2	-	2	3	-	1	-	-	-	-	-	4	6	2	-	-	-	2	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	12	14	0	2	28
JF	3	1	-	-	-	-	-	-	1	-	-	-	-	-	2	-	-	-	-	-	-	6	1	1	-	2	-	2	1	2	1	4	-	2	1	-	1	-	6	2	10	14	32
JG	-	-	-	6	-	-	-	1	-	-	1	6	4	5	2	8	-	-	-	-	-	-	1	-	3	2	-	3	2	1	2	-	-	-	-	-	-	-	8	25	6	8	47
RJ	2	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	1	4	2	-	-	1	4	1	-	-	-	4	0	2	13	19
FD	10	2	2	2	2	-	2	-	-	-	-	1	2	5	2	-	-	-	-	-	-	-	-	-	-	-	-	4	5	3	-	-	-	4	-	-	-	-	23	12	0	16	57
RS	1	-	1	3	-	-	-	-	-	-	-	4	4	-	-	7	-	2	-	-	-	7	4	2	2	6	-	2	9	4	2	5	2	4	2	-	-	-	5	17	21	30	74
WW	6	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	9	0	0	3	12
AP	-	1	2	2	2	1	-	1	-	-	-	8	4	4	-	6	1	-	-	-	-	-	-	-	-	-	-	1	3	-	-	-	-	-	-	2	-	-	8	23	2	5	38
JP	7	1	1	-	3	1	-	-	1	-	1	8	4	4	-	8	-	-	-	-	-	-	-	-	-	-	-	1	5	-	-	-	-	-	-	4	-	-	18	24	1	9	52
RM	4	-	1	-	-	1	-	-	1	-	-	6	-	4	-	-	-	-	-	-	-	-	-	2	-	-	-	-	4	1	-	-	-	-	-	4	-	-	9	10	2	9	30
[2] AA	3	1	1	5	1	1	2	-	1	2	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	3	-	4	-	-	1	-	-	-	1	-	15	1	1	9	26
MI	1	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	4	3	-	1	-	-	3	-	-	2	1	2	-	-	-	-	-	1	2	8	8	20
MJ	6	-	-	2	-	-	-	-	-	1	-	1	4	4	-	-	1	-	1	-	-	-	-	-	-	-	-	1	3	-	2	-	-	-	-	-	-	-	9	11	1	5	26
GD	-	-	1	-	-	1	2	1	-	-	-	10	2	4	2	12	1	2	-	2	-	7	6	5	-	3	-	3	6	2	2	-	4	3	-	2	2	-	4	35	21	24	84

APPENDIX F2. CATEGO SYNDROME SCORES OF PSE2 OF PATIENTS IN THE HIGH CANNABIS GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
CM	-	-	1	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	0	0	0	3
[1]AA	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	4	4	0	2	10
JS	5	-	-	-	1	-	-	-	-	-	-	-	4	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7	8	0	0	15
FJ	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	5	0	0	5
GM	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	0	0	0	5
JvR	-	-	-	-	-	-	-	-	1	-	-	2	-	-	-	3	-	-	1	-	-	-	2	-	-	-	-	2	-	-	-	1	-	-	1	-	-	-	2	6	4	4	16
AS	4	2	-	-	2	-	-	-	-	1	-	-	4	6	2	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	9	12	1	1	23
JF	4	2	-	2	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	2	3	4	-	-	-	1	-	-	1	-	9	4	16	11	30
JG	-	-	-	-	-	-	-	1	-	1	-	-	-	5	-	1	-	-	-	-	-	3	1	-	1	1	-	-	1	1	-	-	2	1	1	-	-	-	2	6	6	6	20
RJ	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	1	-	-	-	-	2	-	-	-	-	1	0	3	3	7
FD	-	-	-	-	-	-	-	1	-	2	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-	4	5	2	3	14
RS	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	5	-	-	-	-	-	-	-	-	1	-	-	3	-	-	-	1	-	1	-	-	-	-	1	7	1	5	14
WW	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	0	0	0	2
AP	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	1	3	0	3	7
JP	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	2	0	0	1	3
RM	-	-	-	-	-	-	-	-	-	-	-	4	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	2	-	-	-	-	2	-	-	-	-	0	7	2	4	13
[2]AA	1	1	1	3	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	8	0	1	3	12
MI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	0	1	3	2	6
MJ	3	-	-	-	-	-	-	-	-	1	-	-	2	4	-	-	-	-	1	-	-	-	-	-	-	-	1	3	-	-	-	-	-	-	-	-	-	-	5	7	1	3	16
GD	-	-	-	-	-	-	-	-	-	1	-	2	-	-	2	-	-	-	-	-	-	5	-	1	-	-	-	-	6	-	1	-	2	2	1	-	2	-	2	4	6	14	26

APPENDIX F3. CATEGO SYNDROME SCORES OF PSE1 OF PATIENTS IN THE LOW CANNABIS GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
DN	-	-	-	3	-	-	-	-	-	2	-	-	-	-	-	2	-	-	-	-	-	-	2	-	-	-	-	5	-	1	2	2	-	-	1	-	-	5	2	4	11	22
AS	-	-	-	6	-	-	-	1	-	-	1	6	4	5	2	8	-	-	-	-	-	-	1	-	3	2	-	3	2	1	2	-	-	-	-	-	-	-	8	25	6	8	47
RM	-	1	-	-	-	-	-	-	-	-	-	-	4	-	2	-	-	-	-	-	1	-	-	3	-	2	-	1	2	1	-	1	-	-	-	-	-	-	4	8	6	6	24
GvW	-	-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	6	-	1	-	-	-	2	3	2	-	-	-	-	1	-	1	-	6	6	7	14	27
JvdL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	1	1	-	-	-	3	5	2	2	2	3	2	1	-	-	-	1	2	8	20	31
AJ	-	-	-	6	-	-	-	2	-	-	3	-	4	4	2	-	-	-	-	-	-	-	-	-	-	-	-	1	1	3	-	-	-	-	-	-	-	-	11	10	0	5	26
JM	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	1	-	1	7	4	2	4	1	2	-	-	-	-	1	0	4	21	26
LA	-	-	-	-	-	-	-	2	1	2	-	-	4	2	2	5	-	-	2	-	-	-	-	-	-	-	-	1	2	-	1	-	1	-	-	-	-	-	-	7	17	1	4	29
BW	5	1	1	10	-	-	-	1	-	2	-	3	3	4	-	9	1	3	1	-	-	-	-	1	1	-	1	-	5	1	1	-	1	3	-	-	1	-	20	24	4	12	60
EM	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	1	-	5	1	1	1	-	-	3	6	-	2	4	-	3	1	-	-	-	1	3	8	19	31
GD	-	-	-	3	-	-	-	-	-	3	-	6	4	-	-	5	1	2	2	-	-	2	1	1	2	-	-	-	4	3	-	-	-	1	2	-	-	-	6	20	6	10	42
SC	5	-	-	-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	2	-	-	-	-	-	-	-	-	-	6	10	1	2	19
FJ	1	1	-	-	-	-	-	-	-	-	1	2	2	6	-	2	-	2	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	3	14	1	1	19
YD	-	-	1	-	-	-	-	-	-	4	-	-	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	0	0	3	9
EW	1	-	1	2	2	1	-	-	1	2	-	2	4	6	2	2	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	10	16	0	2	28
DM	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	4	2	-	-	-	-	2	-	-	-	4	0	1	8	13
AF	1	-	2	3	-	-	-	2	-	-	-	9	-	6	2	1	-	-	2	2	-	-	2	-	-	-	1	3	2	2	-	-	-	-	-	-	-	8	22	3	7	40
JLR	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	3	-	-	-	-	-	-	-	-	1	0	1	3	5
LK	-	-	-	-	-	-	-	1	-	-	3	6	-	3	-	5	-	-	2	-	-	-	-	-	-	-	-	-	6	-	-	-	-	-	-	-	-	5	18	0	6	29
DW	9	-	-	-	2	-	-	-	-	-	-	6	2	4	1	-	-	-	-	-	-	-	3	-	-	-	-	3	-	2	-	-	-	-	-	-	-	-	11	12	3	5	31

APPENDIX F4. CATEGO SYNDROME SCORES OF PSE2 OF PATIENTS IN THE LOW CANNABIS GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
DN	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	1	-	-	-	-	-	2	0	1	3	6
AS	-	-	-	-	-	-	-	1	-	1	-	-	-	5	-	1	-	-	-	-	-	3	1	-	1	1	-	-	1	1	-	-	2	1	1	-	-	-	2	6	6	6	20
RM	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	2	-	-	-	-	2	2	-	-	-	-	-	-	-	-	2	1	3	4	10
GvW	-	1	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	2	-	3	-	-	-	3	2	3	-	-	-	-	-	-	-	-	1	2	5	8	16
JvdL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	2	-	2	-	1	2	-	-	-	-	0	0	1	7	8
AJ	4	1	1	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	0	0	0	8
JM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0
LA	-	1	-	-	-	-	-	2	-	2	-	-	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	7	5	0	1	13
BW	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	0	1	0	2	3
EM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	0	0	1	2	3
GD	-	-	-	-	-	-	-	-	-	-	-	4	3	-	-	3	1	2	-	-	-	2	1	-	2	-	-	-	3	3	-	-	-	1	2	-	-	-	1	13	5	9	28
SC	5	-	-	-	-	-	-	-	-	-	-	4	-	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	10	0	0	15
FJ	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	2	0	1	6
YD	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	0	1
EW	1	-	-	-	1	-	-	-	-	-	1	2	4	6	2	4	1	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	7	1	5	14
DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0
AF	4	-	-	3	-	-	-	1	-	-	2	-	-	4	-	-	-	2	1	2	-	-	-	-	-	-	-	3	2	1	2	-	-	2	1	-	-	-	10	9	0	11	30
JLR	-	-	-	-	-	-	-	2	-	3	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	7	0	0	1	8
LK	1	-	-	-	1	-	-	-	-	-	1	2	4	-	-	4	-	-	-	-	-	2	1	-	-	-	-	2	7	-	2	1	1	-	1	-	-	-	3	10	3	14	30
DW	9	-	-	2	4	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	2	-	-	-	-	-	-	-	-	15	2	2	5	24

APPENDIX F5. CATEGO SYNDROME SCORES OF PSE1 OF PATIENTS IN THE PSYCHOTIC CONTROL GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
KA	-	-	-	3	-	2	-	1	-	3	1	4	-	6	-	-	-	1	1	2	3	-	-	-	-	-	1	1	1	2	-	-	-	-	-	-	-	-	11	18	1	4	34
AE	-	-	1	-	2	-	-	2	2	-	2	-	-	-	-	2	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	12	3	1	0	16
SG	-	-	1	-	1	1	2	1	-	-	1	6	4	4	2	8	1	2	2	2	-	-	2	-	-	-	2	2	2	-	-	2	-	-	-	-	-	-	5	31	6	6	48
JV	-	-	-	3	-	-	-	-	-	1	-	-	-	2	-	8	-	-	-	-	-	-	-	1	-	-	-	3	1	-	2	-	-	-	-	-	-	-	4	10	1	6	21
HM	-	-	1	5	1	2	-	1	-	1	1	4	4	4	2	8	1	-	1	-	-	1	-	-	-	-	1	2	4	-	2	1	-	2	-	-	-	-	13	24	2	11	50
MP	2	-	-	3	-	2	-	1	-	1	1	4	2	4	-	-	1	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	10	12	2	0	24
GT	-	-	-	-	-	-	-	2	-	3	-	-	-	-	-	-	-	-	2	-	-	-	1	-	-	-	-	-	1	1	-	2	2	-	-	-	-	-	8	3	3	6	20
LJ	-	-	1	5	-	1	-	2	4	4	-	5	4	-	-	10	-	4	1	1	-	7	4	-	-	-	-	3	-	-	2	4	2	1	2	4	-	-	17	25	11	18	71
GJ	2	-	1	-	3	1	-	-	-	-	-	12	4	3	2	6	1	-	-	-	-	-	-	-	-	-	2	3	-	-	-	-	-	-	-	-	-	8	28	2	3	41
DP	6	-	-	-	2	2	-	2	1	-	1	9	4	6	2	8	1	2	-	-	-	-	-	-	-	-	1	2	-	2	-	-	-	-	-	-	-	-	16	32	1	4	53
LA	-	-	-	2	-	1	2	1	-	-	-	-	-	-	-	7	1	1	2	-	-	-	1	-	-	-	1	2	1	-	1	1	-	-	-	-	-	-	4	11	3	5	23
RE	5	-	-	3	-	-	-	1	-	-	1	7	4	6	-	4	-	-	2	2	-	-	1	2	-	2	1	3	-	1	-	2	-	-	-	1	-	-	10	25	6	7	48
FA	-	-	-	3	-	-	-	2	-	1	3	2	4	2	2	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	9	10	0	3	22
[1]AD	-	1	1	-	-	-	2	1	-	3	2	-	4	-	-	6	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9	12	1	0	22
CK	6	-	1	-	1	-	-	-	-	-	-	2	2	4	2	-	-	-	1	2	-	-	-	-	-	-	3	-	-	2	-	-	-	-	-	4	-	-	9	13	3	6	31
[2]AD	8	1	-	-	2	-	-	-	-	-	-	4	2	6	2	-	-	-	-	2	-	1	-	-	1	-	-	4	2	-	-	-	-	-	-	-	-	-	11	16	2	6	35
JK	-	1	1	-	1	-	-	7	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	3	6	4	-	1	-	2	-	-	-	-	10	1	2	16	29
JM	-	-	2	2	-	1	-	2	-	2	1	3	4	4	2	-	1	2	2	2	2	-	-	-	-	-	1	3	-	-	-	-	1	1	-	-	-	-	10	22	1	5	28
NF	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	6	1	1	3	-	-	-	2	-	-	-	3	1	2	-	1	1	-	-	-	-	-	-	4	13	3	5	25
DB	3	-	1	-	3	2	-	-	-	-	-	11	5	3	1	5	2	-	-	-	-	-	-	-	-	-	3	3	-	-	-	-	-	-	-	-	-	8	30	2	3	43

APPENDIX F6. CATEGO SYNDROME SCORES OF PSE2 OF PATIENTS IN THE PSYCHOTIC CONTROL GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
KA	-	-	-	3	-	-	-	1	-	4	-	2	-	3	-	-	-	-	-	2	2	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	8	10	0	1	19
AE	-	-	1	-	3	-	-	-	2	-	2	-	-	-	-	2	-	-	1	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	11	3	1	1	16
SG	-	-	-	-	1	1	1	-	-	-	1	6	4	4	2	8	1	2	2	2	-	1	2	-	-	-	2	3	-	-	-	2	-	-	-	-	-	-	3	31	5	5	44
JV	-	-	-	3	-	-	-	-	-	-	-	2	-	2	-	5	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	3	9	0	3	15
HM	2	1	-	4	2	2	-	1	-	-	1	4	4	4	2	6	-	-	1	-	-	-	-	-	-	-	2	3	-	-	-	-	-	-	-	-	-	-	13	21	2	3	39
MP	-	1	1	-	-	1	-	1	-	-	1	6	2	4	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	8	13	1	0	22
GT	-	-	-	-	-	-	-	2	-	2	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	1	1	-	2	1	-	-	-	-	-	3	0	4	5	12
LJ	-	-	-	4	-	1	-	2	1	4	-	3	4	-	-	10	-	2	1	-	-	4	2	-	-	-	-	-	-	1	4	-	-	1	4	-	-	13	21	6	11	51
GJ	1	1	1	-	4	2	-	-	-	-	-	12	4	5	2	6	1	-	-	-	-	-	-	-	-	-	2	5	-	-	-	-	-	-	-	-	-	-	11	30	2	5	48
DP	4	-	-	-	1	2	-	2	1	-	1	5	4	6	2	4	1	2	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	13	24	1	3	41
LA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	1	2	2	-	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	7	3	0	10
RE	-	-	-	2	-	-	-	1	-	1	-	2	2	4	2	2	-	-	-	1	-	2	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	13	4	3	24
FA	-	-	-	3	-	-	-	2	-	-	3	-	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	4	0	0	12
AD	-	1	1	1	-	-	1	1	-	2	2	-	4	-	-	6	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	12	1	0	21
CK	6	-	1	-	1	-	-	-	-	-	-	2	2	4	2	-	-	-	1	2	-	-	-	-	-	-	3	-	-	-	-	-	-	-	2	-	-	9	13	3	2	27
2AD	8	-	1	-	2	-	-	-	-	1	1	4	2	4	-	-	-	-	-	2	-	-	-	-	-	-	-	1	2	-	-	-	-	-	-	-	-	-	13	12	0	3	28
JK	4	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	6	1	1	1	9
JM	-	-	2	-	-	1	-	1	-	2	1	2	4	3	2	-	1	2	2	1	3	-	-	-	-	-	-	2	-	-	-	-	1	-	-	-	-	-	8	20	0	3	31
NF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	2	3	-	1	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	9	3	0	12
DB	2	2	-	-	4	1	-	-	-	-	-	11	5	6	1	6	2	-	-	-	-	-	-	-	-	-	3	4	-	-	-	1	-	-	-	-	-	-	12	31	2	5	50

APPENDIX F7. CATEGO SYNDROME SCORES OF PSE1 OF PATIENTS IN THE MANIC CONTROL GROUP.

CATEGO SYNDROMES

PATIENTS	HM	AG	NG	NP	OV	RS	OR	AF	CS	SL	IS	SF	RE	GR	PE	NS	VH	OH	AH	DD	SC	SD	ED	GA	ON	SA	HT	IT	WO	TE	IR	SU	IC	OD	LE	DE	HY	DI	BSO	DAH	SNR	NSN	TOT
MS	4	-	-	-	-	1	-	-	-	1	-	-	-	-	2	-	-	-	-	-	-	1	2	-	-	-	-	3	1	-	-	-	-	-	-	-	-	-	5	0	1	4	10
BG	5	-	-	1	2	-	-	-	-	-	-	1	-	2	-	-	-	-	-	-	-	-	-	-	-	-	1	-	3	2	-	-	-	-	-	-	-	-	8	4	1	5	18
SJ	8	2	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11	0	0	0	11
HS	-	-	-	4	1	-	-	1	-	3	-	2	-	-	-	-	-	-	-	-	-	2	-	-	-	-	1	2	3	1	-	-	-	-	-	-	1	-	11	5	3	7	26
JP	5	-	-	-	-	-	1	-	-	-	-	-	-	4	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	5	0	1	11
PvZ	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	3	3	-	3	-	3	8	2	2	4	4	5	1	-	2	-	4	1	13	31	49
GJ	4	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	-	-	-	0	1	8	3	12

APPENDIX G

Formulation of Visualizing agents for toxicological screens.

i IODINE REAGENT

Dissolve 2,5g iodine in 250ml carbon tetrachloride

ii DRAGENDORFF'S REAGENT

Stock solution: Dissolve 5,2g bismuth carbonate and 15g sodium iodide in 50ml glacial acetic acid. Filter sodium acetate crystals after 12 hours through a scintered glass funnel. Dilute 60ml of the filtrate with 25ml glacial acetic acid. Store in a dark bottle.

Working solution: 10ml stock solution
60ml ethyl acetate
25ml glacial acetic acid

iii IODOPLATINATE REAGENT

Dissolve 1g of hexachloroplatanic acid and 20g potassium iodide in 400ml water. Dilute to 2L with 2N hydrochloric acid (400cHCL/2L).

iv MARQUIS REAGENT

Add 20ml formaldehyde solution to 200ml concentrate sulphuric acid After spraying, view under long UV. Heat at 100^{o}C for 5-10 minutes. Note colour change.

V MANDELIN'S REAGENT

Add 2,5g ammonium monovadonate to 250ml concentrate sulphuric acid and stir for 30 minutes. Allow the sediment to settle overnight. Fitler though a scintered glass funnels.

vi FORREST REAGENT

Dissolve 125mg potassium dichromate in about 150ml water. Add 20ml concentrate sulphuric acid, 12,5ml perchloric acid (60%) and 30ml nitric acid (65%). Dilute to 250ml with water.

vii FPN REAGENT

Dissolve 1,25g ferric nitrate $9H_2O$ in 50ml water. Add 15ml perchloric acid (60%) and 38ml nitric acid (65%). Dilute to 200ml with water.

viii DIPHENYL CARBAZONE REAGENT

Make up a 0,1% diphylcarbazone solution in ethanol.

ix TRINDER'S REAGENT

Dissolve 10g mercuric chloride and 15g ferric nitrate $9H_2O$ in 200ml water and 30ml Hydrochloric acid. Dilute to 250ml with water.

x MERCUROUS NITRATE REAGENT

Dissolve 1g mercurous nitrate in 100ml water.

APPENDIX H 1. CASE STUDIES - HIGH CANNABIS GROUP

Initials	Age	Number and Diagnosis of Previous Admissions	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication
CH	21	4-Paranoid Schizophrenia	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	45	Pimozide 8mg daily. Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 100mg if required.
AA(1)	22	5-Toxic Psychosis	Nil	Cannabis	Hypomania	Manic-Depressive psychosis, manic type	61	Trifluoperazine 10mg twice daily. Chlorpromazine HCL 100mg if needed. Haloperidol 10mg three times daily.
JS	19	Nil	Nil	Cannabis; occasional methaqualone	Hypomania	Manic-Depressive Psychosis is manic type	34	Haloperidol 15mg twice daily for 2 days, then 10mg twice daily. Orphenadrine HCL 50mg twice daily. Chlorpromazine HCL 100mg if required.
FJ	22	1-Toxic psychosis	Nil	Cannabis; occasional methaqualone	Paranoid psychosis	Manic-Depressive Psychosis circular type, currently depressed	18	Fluphenazine decanoate 25mg monthly. Trifluoperazine 10mg twice daily. Chlorpromazine HCL 100mg if required.
GH	38	3-Hypomania	Nil	Cannabis	Hypomania	Manic-Depressive Psychosis, manic type	19	Amitriptyline 100mg at night. Trifluoperazine 10mg twice daily.
JvR	27	1-Schizophrenia	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	40	Trifluoperazine 10mg twice daily. Chlorpromazine HCL 100mg if required.
AS	24	1-Bizarre and inappropriate behaviour	Nil	Cannabis	Schizophreniform Psychosis	Manic-Depressive Psychosis, manic type	15	Fluphenazine decanoate 25mg monthly. Orphenadrine HCL 100mg twice daily. Haloperidol 100mg twice daily.
JF	21	Nil	Nil	Cannabis; occasional ethanol	Schizophreniform psychosis	Catatonic schizophrenia	76	Chlorpromazine HCL 100mg twice daily and at night. Amitriptyline 75mg at night.
JG	26	Nil	Nil	Cannabis	Paranoid schizophrenia	Paranoid Schizophrenia	11	Trifluoperazine 15mg twice daily. Chlorpromazine HCL 100mg at night and 100mg if needed
RJ	30	2-Mixed affective psychosis	Nil	Cannabis	Hypomania	Manic-Depressive psychosis is manic type	61	Chlorpromazine HCL 200mg at night. Trifluoperazine 10mg twice daily. Haloperidol 10mg three times a day.

H 1. Continued

Initials	Age	Number and Diagnosis of Previous Admissions	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication
FD	23	2-Schizophreniform psychosis	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	26	Trifluoperazine 10mg twice daily. Chlorpromazine HCL 100mg if required. Orphenadrine HCL 50mg if needed.
RS	18	Nil	Nil	Cannabis; occasional methaqualone	Paranoid Schizophrenia	Paranoid Schizophrenia	10	Trifluoperazine 10mg twice daily. Chlorpromazine HCL 100mg if required. Orphenadrine HCL 50mg if required.
WW	23	1-Schizophrenia	Nil	Cannabis	Paranoid psychosis	Manic-Depressive psychosis, manic type	17	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 200mg at night. Orphenadrine HCL 50mg twice daily.
AP	18	1-Schizophreniform psychosis	Nil	Cannabis; occasional ethanol	Paranoid Schizophrenia	Paranoid Schizophrenia	10	Fluphenazine decanoate 25mg monthly. Trifluoperazine 10mg twice daily. Orphenadrine HCL 100mg twice daily.
JP	21	Nil	Nil	Cannabis	Schizophreniform psychosis	Paranoid Schizophrenia	21	Chlorpromazine HCL 10mg at night. Haloperidol 100mg at night. Orphenadrine HCL 50mg twice daily.
RM	33	1-Schizophrenia	Nil	Cannabis	Schizophreniform psychosis	Catatonic Schizophrenia	34	Fluphenazine decanoate 25mg monthly. Trifluoperazine 5mg twice daily. Benzhexol 5mg twice daily.
AA(2)	26	9-Drug induced psychosis	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	17	Fluphenazine decanoate 50mg monthly. Chlorpromazine HCL 200mg at night.
MI	27	1-Paranoid psychosis	Nil	Cannabis	Paranoid psychosis	Unspecified paranoid psychosis	13	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 50mg twice daily and 100mg at night. Orphenadrine HCL 50mg if required.
MJ	52	7-Schizophrenia, Schizo affective disorder, Hypomania	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	10	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 200mg at night and 100mg if required.
GD	17	Nil	Nil	Cannabis	Paranoid psychosis	Paranoid schizophrenia	30	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 50mg twice daily and 100mg at night. Orphenadrine HCL 50mg if required.

APPENDIX H 2. CASE STUDIES - LOW CANNABIS GROUP

Initials	Age	Number and Diagnosis of Previous Admissions	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication
DN	22	Nil	Nil	Cannabis; ethanol	Social and behavioural problems	Paranoid Schizophrenia	47	Chlorpromazine HCL 100mg if required. Pericyazine 10mg twice daily.
AS	34	8-Schizophrenia	Nil	Cannabis	Chronic Schizophrenia	Unspecified paranoid psychosis	22	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 10mg twice daily. Chlorpromazine HCL 100mg if required.
RM	30	1-treatment for drug abuse	Nil	Cannabis; ethanol	Hypomania	Unspecified paranoid psychosis	100	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 15mg twice daily. Chlorpromazine HCL 100mg if required.
GvW	26	4-Schizophrenia	Nil	Cannabis; occasional methaqualone	Chronic Schizophrenia	Manic-Depressive psychosis, manic-type	41	Fluphenazine decanoate 50mg monthly. Chlorpromazine HCL 100mg if required.
JvdL	36	Nil	Nil	Cannabis	Paranoid Schizophrenia	Unspecified paranoid psychosis	37	Chlorpromazine HCL 100mg if required. Amitriptyline 75mg at night.
AJ	30	5-Schizophrenia (2) -Affective disorder (3)	Nil	Cannabis	Schizo-affective disorder	Unspecified paranoid Psychosis	42	Fluphenazine decanoate 25mg monthly.. Haloperidol 5mg twice daily. Orphenadrine HCL 50mg twice daily.
JM	19	Nil	Nil	Cannabis	Schizophreniform psychosis	Paranoid Schizophrenia	34	Trifluoperazine dihydrochloride 5mg twice daily. Chlorpromazine HCL 100mg twice daily and at night.
LA	46	1-Schizophrenia	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	39	Trifluoperazine dihydrochloride 5mg in the morning and 10mg at night. Chlorpromazine HCL 100mg if required.
BW	24	Nil	Nil	Cannabis	Schizo-affective disorder	Paranoid Schizophrenia	9	Trifluoperazine dihydrochloride 15mg twice daily. Chlorpromazine HCL 100mg if required. Orphenadrine HCL 100mg twice daily.
EM	50	2-Aggressive and anti-social behaviour	Nil	Cannabis; ethanol	Aggressive, anti-social behaviour	Manic-Depressive psychosis circular type currently depressed.	8	Chlorpromazine HCL 50mg twice daily. Clothiapine 40mg if required.

H 2. Continued

Initials	Age	Number and Diagnosis of Previous Admissions	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication
GD	18	Nil	Nil	Cannabis	Schizophreniform psychosis	Paranoid Schizophrenia	40	Trifluoperazine dihydrochloride 5mg twice daily. Chlorpromazine HCL 100mg if required.
SC	49	2-Hypomania	Nil	Cannabis; occasional ethanol	Hypomania	Manic-Depressive psychosis, manic type	15	Chlorpromazine HCL 100mg if required. Haloperidol 10mg twice daily.
FJ	24	1-Schizophrenia	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	66	Fluphenazine decanoate 50mg monthly. Trifluoperazine dihydrochloride 10mg twice daily. Orphenadrine HCL 100mg twice daily.
YD	24	Nil	Nil	Cannabis	Hypomania	Unspecified paranoid psychosis	27	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 10mg twice daily. Orphenadrine HCL 100mg twice daily. Chlorpromazine HCL 100mg if required
EW	23	2-Schizophrenia	Nil	Cannabis	Paranoid psychosis	Paranoid Schizophrenia	27	Chlorpromazine HCL 200mg at night. Haloperidol 50mg twice daily.
DM	23	Nil	Nil	Cannabis	Schizophreniform psychosis	Manic-Depressive psychosis, circular type, currently depressed	9	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 10mg twice daily. Chlorpromazine HCL 100mg if required.
AF	27	Nil	Nil	Cannabis	Schizophreniform psychosis	Paranoid schizophrenia	69	Fluphenazine decanoate 50mg monthly. Trifluoperazine dihydrochloride 20mg twice daily.
JIR	29	2-Affective Psychosis	Nil	Cannabis; occasional ethanol	Hypomania	Insufficient symptoms to allow classification	11	Haloperidol 10mg twice daily. Chlorpromazine HCL 100mg if required Orphenadrine HCL 50mg twice daily.
LK	37	1-Schizophrenia	Nil	Cannabis	Paranoid Schizophrenia	Paranoid Schizophrenia	16	Trifluoperazine dihydrochloride 10mg twice daily. Chlorpromazine HCL 200mg at night.
CW	32	3-Schizophrenia	Nil	Cannabis	Hypomania	Manic-Depressive psychosis, manic type	27	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 10mg twice daily.

APPENDIX H 3. CASE STUDIES - PSYCHOTIC CONTROL GROUP

Initials	Age	Number and Diagnosis of Previous Admissions	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication
KA	29	1-Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	40	Fluphenazine decanoate 50mg monthly. Chlorpromazine HCL 100mg twice daily and 200mg at night.
AE	26	6- Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	60	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 200mg twice daily.
SG	52	7-Schizophrenia	Previous Myocardial Infarction; Hypertensive	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	43	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 100mg at night and when required.
JV	16	Nil	Nil	Nil	Early Schizophrenia	Paranoid Schizophrenia	14	Chlorpromazine HCL 50mg twice daily. Orphenadrine HCL 50mg twice daily.
HM	27	4-Paranoid Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	34	Fluphenazine decanoate 25mg monthly. Haloperidol 5mg twice daily. Lithium carbonate 500mg twice daily. Orphenadrine HCL 100mg twice daily.
MP	25	1-Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	14	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 50mg at night and 100mg if required. Orphenadrine HCL 100mg if required.
GT	18	3-Schizophrenia	Nil	NiL	Paranoid Schizophrenia type illness	Paranoid Schizophrenia	30	Fluphenazine decanoate 50mg monthly. Chlorpromazine HCL 100mg at night.
LJ	20	1-Schizophrenia	Nil	Nil	Schizophreniform Psychosis	Paranoid Schizophrenia	53	Trifluoperazine dihydrochloride 10mg twice daily. Benzhexol 2mg twice daily. Chlorpromazine HCL 100mg if required.
GJ	20	Nil	Nil	Nil	Schizophreniform Psychosis	Paranoid Schizophrenia	60	Fluphenazine decanoate 50mg monthly. Haloperidol 5mg twice daily. Benzhexol 5mg twice daily.
DP	18	2-Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	14	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 200mg twice daily, 300mg at night and 100mg if required. Orphenadrine HCL 100mg if required.

H 3. Continued

Initials	Age	Number and Diagnosis of Previous Admission	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication.
LA	23	Nil	Nil	Nil	Schizophreniform psychosis	Paranoid Schizophrenia	30	Trifluoperazine dihydrochloride 5mg twice daily. Chlorpromazine HCL 100mg at night.
RE	16	Nil	Nil	Nil	Schizophreniform psychosis	Paranoid Schizophrenia	9	Trifluoperazine dihydrochloride 15mg twice daily. Chlorpromazine HCL 200mg at night. Orphenadrine HCL 50 mg twice daily.
FA	25	2-Schizophrenia	Nil	Nil	Schizophreniform psychosis	Unspecified paranoid psychosis	14	Fluphenazine decanoate 50mg monthly. Chlopromazine HCL 25mg three times a day.
AD1	30	3-Paranoid Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	18	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 5mg twice daily. Chlorpromazine HCL 200mg at night and 100mg if required.
CK	20	Nil	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	30	Chlorpromazine HCL 25mg three times a day. Haloperidol 15mg twice daily. Orphenadrine HCL 100mg twice daily.
AD2	39	9-Manic-Depressive psychosis	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	22	Haloperidol 15mg twice daily and 5mg if required. Orphenadrine HCL 100mg twice daily.
JK	30	5-Unspecified psychosis	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	15	Chlorpromazine 200mg twice daily and 200mg at night.
JH	30	1-Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	15	Trifluoperazine dihydrochloride 10gm twice daily. Chlorpromazine HCL 100mg if required. Orphenadrine HCL 100mg if required.
NF	23	1-Schizophrenia	Nil	Nil	Paranoid Schizophrenia	Paranoid Schizophrenia	15	Trifluoperazine dihydrochloride 10mg twice daily. Orphenadrine HCL 100mg twice daily.
DB	25	1-Schizophreniform psychosis	Nil	Nil	Schizophreniform psychosis	Paranoid Schizophrenia	58	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 100mg twice daily, 200mg at night and 100mg if required.

APPENDIX H 4. CASE STUDIES - MANIC CONTROL GROUP

Initials	Age	Number and Diagnosis of Previous Admissions	Medical History	Substance Abuse	Clinical Diagnosis on Admission	PSE1 CATEGO Classification	Length of Hospitalization (days)	Medication
MS	25	2-Hypomania	Nil	Nil	Schizophreniform psychosis	Manic-Depressive psychosis, manic type	61	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 10mg twice daily. Chlorpromazine HCL 100mg if required. Orphenadrine HCL 50mg if required.
BG	22	7-Hypomania	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	20	Trifluoperazine dihydrochloride 100mg twice daily. Chlorpromazine HCL 100mg at night.
SJ	16	Nil	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	13	Fluphenazine decanoate 25mg monthly. Trifluoperazine dihydrochloride 10mg twice daily.
HS	16	Nil	Nil	Nil	Schizophreniform psychosis	Manic-Depressive psychosis, manic type	31	Chlorpromazine HCL 25mg if required. Haloperidol 15mg twice daily.
JP	23	1-Mixed affective disorder	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	53	Haloperidol 15mg twice daily. Orphenadrine HCL 50mg twice daily. Chlorpromazine HCL 100mg if required. Lithium carbonate 400mg in the morning, 800mg at night.
PvZ	20	Nil	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	35	Chlorpromazine HCL 100mg if required. Haloperidol 50mg twice daily. Orphenadrine HCL 50mg twice daily.
GJ	21	5-Mixed affective disorder	Nil	Nil	Hypomania	Manic-Depressive psychosis, manic type	150	Fluphenazine decanoate 25mg monthly. Chlorpromazine HCL 25mg if required. Orphenadrine HCL 100mg if required.

APPENDIX I

Statistical Tests used

The following tests were used as applicable in this study.

1. Chi squared test (Siegel, 1956 Table C).
2. McNemar test for the significance of changes (Siegel, 1956 Table C).
3. Wilcoxon matched-pairs signed-ranks test (Siegel, 1956 Table G).
4. Spearman rank correlation coefficient (Siegel, 1956 Table B).
5. Kruskal-Wallis one-way analysis of variance (Siegel, 1956 Table C).

All p values quoted were for 2 tailed tests and a p value of less than or equal to 0,05 was regarded as statistically significant.

APPENDIX J

Suppliers of materials and equipment

Stasar III Spectrophotometer (Gilford Instrument Laboratories Ohio, U.S.A)	American Hospital Supply Co. (Pty) Ltd. P.O.Box 816 Cape Town 8000
Syva CP 5000 EMIT^{R} Clinical Processor (Oxbridge Incorporated California , U.S.A.)	
Syva Pipetter-Diluter Model 1500 (CAVRO Scientific Instruments California, U.S.A.)	
EMIT^{R} - d.a.u. Cannabinoid Assays EMIT^{R} - d.a.u. Cannabinoid Calibrators (Syva, California, U.S.A.)	
Silica gel 60F $_{254}$ plates ammonium sulphate Isopropanol, methanol (Merck, Darmstadt, Germany)	T & C Scientific Supplies (Pty) Ltd., P.O.Box 2953 Cape Town 8000
Gow.Mac Series 750 Gas Chromatograph (Model 69-752) (Gow-Mac Instruments, New Jersey, U.S.A.)	Packard Instruments (Pty) Ltd., P.O.Box 401 Bellville 7530
Hewlett Packard Automation System 3385A Integrator Recorder (Hewlett Packard, U.S.A.)	

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