DRUGS, PERSONALITY, SLEEP AND PERFORMANCE

by

DAVID IAIN CARRUTHERS-JONES, B.Sc. (Psychol. London)

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Summary

An attempt has been made to study some of the disruptive effects of a variety of established and new drugs on people, during both chronic administration and withdrawal. A number of measures have been used including performance tests, sleep EEG, self-rating mood scales and two personality scales, but relatively less emphasis has been placed on the sleep EEG measures.

Chapter 1 discusses the background to research in this area and outlines some of the problems involved in the prescription of drugs. Appreciation of the hazards of over generous prescribing, in terms of both the psychological welfare of the patient and disruptive side-effects, is increasing and official bodies have been established to assess the full range of drugs' effects in relation to their suitability for marketing.

Following reviews of earlier research on performance, sleep and subjective feeling states (Chapter 2) and the methodology (Chapter 3), an experiment is described in which the effects of three hypnotics were compared in young adults (Chapter 4). Two newer drugs, mesoridazine and Perlapine, were compared with sodium amylobarbitone and placebo. Thanks to the inclusion of the placebo group it was clear that performance tended to improve, on most tests, with repeated testing, and that while administration of a

drug may not cause a large decrement in performance a transformation of the drug groups' data, to allow for the placebo group changes, may help to quantify more realistically the drugs' effects.

The value of this study in relation to real-life is discussed in Chapter 5. Such relevance is important in experimental studies of this type and possible methods of improvement are suggested, including the modification of existing tests, the introduction of new ones and the use of subjects in an age group similar to that for which the drug is most likely to be prescribed. From a review of the literature, it was apparent that there may be quite different response patterns in different age groups on a variety of tests and, therefore, the most appropriate modification was considered to be the use of subjects in an older age group.

The first study using older subjects is described in Chapter 6. Assessment of the effects of mesoridazine on seven subjects indicated little disruption of either performance or sleep parameters during both administration and withdrawal. However, examination of the raw performance data suggested inter-individual differences in response to the administration of the drug.

Chapter 7 reviews research into inter-individual differences in performance patterns. In Chapter 8 retrospective analysis of part of the data from the studies described in Chapters 4 and 6 is carried out: results indicated that there might be differences between extraverts and introverts, as assessed by the E.P.I., in response to mesoridazine and that this effect might be consistent across age groups.

The criterion for selection as a subject in the study, described in Chapter 9, was an E-scale score of at least one and a half standard deviations above or below the mean on Form A of the Eysenck Personality Inventory. The aim was to attempt to replicate, using a larger sample, the findings described in Chapter 8. Although some differences were found between the groups, notably on subjective sleep quality and morning vitality, these were not as clear as expected on the performance measures and were against the prediction on the subjective measures.

The effects of two preparations considered to promote sleep, nitrazepam and Horlicks, were compared in Chapter 10. Both improved sleep, objectively and subjectively, and had little effect on performance, even with continued administration.

Chapter 11 describes a pilot study of the effect of a new hypnotic, temazepam, on the sleep of three

older subjects. Temazepam increased sleep duration, reduced sleep onset latency and had little effect on the overall proportion of stages REM and NREM 3 + 4. Subjective sleep quality and mood were initially improved. Withdrawal produced a subjective deterioration of feeling on all four scales. It reduced total sleep time and increased sleep onset latency.

The results of the studies, and their implications, are discussed in Chapter 12. The suitability and sensitivity of some of the tests employed are evaluated in relation to the findings of others and possible modifications are outlined.

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Co-operative Studies

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(a) A study of the effects of mesoridazine on sleep and performance.

(b) A study of the effects of nitrazepam and Horlicks.

The following studies were carried out jointly with Dr S. Lewis:-

(a) An experimental comparison of the effects of three hypnotics.

(b) A study of the effects of temazepam on sleep in older subjects.

CONTENTS

CHAPTER 1

INTRODUCTION

Introduction

Life is a constant interaction between organism and environment. Change and stress may be transitory, as in a disagreement with a friend or colleague, or there may be difficulty in getting off to sleep, or stress may be major as in the death of a close relative. Any stress carries an emotional price-tag: recurring stresses may be more than we can cope with.

Leslie Weatherhead, in his book, "Psychology in the Service of the Soul", published in 1929, felt that stress could be coped with by "having a cold bath .... substituting the undesired or stressful mental picture by a religious one .... and having a prayer".

Although possibly valid then and still for some nowadays, this type of response to stress has become less common and many people, especially in Western society, try to cope with the variety of stresses, described by Alvin Toffler in his book, "Future Shock", by taking drugs. The drugs may be available generally, such as alcohol and nicotine, or on prescription from a doctor.

The consumption of drugs meant to calm the nerves and improve mood and sleep quality has risen astronomically in recent years. In 1969 doctors in Britain wrote over 13 million prescriptions for barbiturates, 6 million for non-barbiturate hypnotics, 5 million for chlordiazepoxide, 5 million for anti-depressants, and a further 5 million for amphetamines.

We are all aware of the beneficial therapeutic effects that these drugs may have, but their side-effects have been less well publicised and appreciated, even within medical circles. It is important to ensure, however, that a patient, while under treatment, is not adversely affected or at risk in his daily life. If he is affected, or at risk, then one problem is merely being replaced by another, which may be more dangerous in that its existence may not be fully recognised by doctor or patient. In the late 1960's a small but growing number of doctors began to appreciate the dangers of the barbiturates and started a voluntary prescribing ban. Yet still over one-half of all sleeping pills prescribed are barbiturates. Prescribing of barbiturates fell from 17.2 million prescriptions in 1965 to 13.1 million in 1970. Non-barbiturate prescriptions rose, during the same period, from 2.9 to 7.1 million. Ironically, the main increase involved a new drug called Mandrax which, it was gradually realised, was just as dangerous as the barbiturates. The drug is particularly open to overdose and abuse and there have been over 8,000 cases a year of Mandrax and barbiturate poisoning. Prescription rates of Mandrax are now reduced in favour of a new money-spinner, Mogadon, yet there is evidence that, while Mogadon is not toxic (General Practitioners' Research Group Rep. 79, 1965; Smith, 1966) or as abused as

Mandrax, it can still cause a decrement in intellectual and psychomotor performance for up to 24 hours after a single dose is taken (Malpas, Rowan, Joyce and Scott, 1970).

Pressures of work and advertising make it difficult for the doctor to consider the merits and demerits of drugs and the welfare of his patients as carefully as he would like. In 1973 drug companies spent more money in Britain on advertising than on research and the result is that doctors, deluged with promotional material, too often prescribe blindly in a jungle of competing products. In its 1966 annual report the Committee on Safety of Drugs stated that it was not concerned with efficacy of drugs except where safety was involved. After admitting that it had granted product licences to a number of "relatively worthless" drugs, it went on to say that: "There are some who believe that it is impossible to make this artificial distinction between the efficacy of a drug and its safety; others consider that responsibility regarding efficacy must be left to the prescribing doctor and that there is a limit to the extent to which the public should be protected from spending their money on medicines as long as they are not actually harmful".

This complacent attitude is now beginning to disappear and the 1973 Annual Report of the Committee

on Safety of Medicines, set up by the Medicines Commission indicated that official attitudes are hardening. But there is still a long way to go as more than two-thirds of the drugs rated by the now defunct Standing Joint Committee on the Classification of Drugs as unacceptable on either grounds of safety or efficacy are still being prescribed in Britain.

Reasons for this situation are not difficult to find. Drugs continue to be promoted by brand name and it is very difficult for doctors to obtain comprehensive, independent and comparative information about drugs' effectiveness. It has been a hallowed tradition in medicine that any doctor must be permitted to prescribe what he thinks best for his patient. This liberality is admirable but it presupposes that the doctor in the years since his graduation has remained informed, educated and critical of each and every medical preparation the industry has promoted; this promotion being executed with ever-increasing pressure and skill.

Doctors, it may be argued, are not susceptible, as are other mortals, to the wiles of the clever advertiser but history suggests that clinical experience is not always a reliable guide to efficacy. It took, for example, hundreds of years to counteract the clinical impression that bleedings, sweatings, vomitings and purgings were beneficial and gold is still used by

reputable medical scientists in the treatment of rheumatoid arthritis. The modern drug jungle is probably no less haphazard judging by the survey commissioned by the Sainsbury Committee into doctors' prescribing habits. Asked what they would give for five common illnesses, a group of 463 practitioners prescribed 30 different drugs for osteoarthritis, 35 for childhood eczema, 35 for acute adult diarrhoea, 40 for an acute attack of bronchitis, and more than 40 for a peptic ulcer. Several of the drugs have since been rated by both British and American classification bodies as either ineffective or potentially toxic.

Unfortunately two of the major recommendations of the Sainsbury Committee have been ignored. The first was that all drugs should be marked with their therapeutic grading and that a comprehensive guide for doctors of approved drugs should be published. The second was that the Medicines Commission should be responsible for this rating of drugs according to effectiveness.

In the United States a tougher attitude has been taken to claims for drugs. In 1966 the Food and Drugs Administration launched an evaluation study of more than 4,000 drugs which had been marketed before efficacy requirements had been introduced. For each of their drugs, the companies were instructed to submit evidence of effectiveness including the relevant references.

This would allow judgement of whether the claims made could be substantiated. The panels placed drugs in one of four categories. The top rating "effective" was given where there was substantial evidence of efficacy based on well-controlled trials. The next rating was "probably effective". This was given to those claims which were supported by research to some extent, but on which additional evidence was required. The third rating "possibly effective" where little efficacy was evident though the panel thought there was a possibility that such evidence could be developed. The fourth rating "ineffective" was given to those drugs for which there was no acceptable evidence of efficacy. Seven per cent of the F.D.A. reviewed drugs received this last rating, a ruling that enforced the removal of the preparations from the market. Of the 4,369 drugs reviewed, 41 per cent were rated as effective for one or more condition but there was indisputable evidence for only 19 per cent of the claims made.

Nowadays, the F.D.A. require evidence that a new preparation has produced favourable results and no unfavourable and dangerous indications in at least four species, before that product can be marketed in the United States. This has led to an increase in the amount of research required and concurrently an increase in interest in research into the effects of drugs on

people's daily lives. The effects of drugs on sleep patterns have been extensively researched in recent years, as have the effects on performance in a variety of tasks considered to employ some of the skills that people use in their everyday life.

CHAPTER 2

REVIEW OF MEASURES OF PERFORMANCE

An enormous variety of performance tasks have been used by experimenters in their attempts to differentiate between different categories of people and different types of drugs. McNair (1973) in a review of studies concerning the behavioural effects of chlordiazepoxide, diazepam and meprobamate, and rating the sensitivity of various measures, listed 43 different performance measures. McNair found that only 10 measures showed significant results in at least 50 per cent of the studies reviewed per measure. He did not go far enough, however, and neither examined the methodology of any of the studies nor weighted for the number of studies referring to each test. Had he done so, doubts about even some of the supposedly more sensitive measures might have been aroused for, first, some of the methodologies are not clear and the analyses are simplistic, and second, his rating is given in some instances on the basis of reviewing only one or two studies per measure, for example, in the cases of the highly rated continuous performance and visual threshold tasks.

Although there are so many different tasks, they tend to fall into broad categories in attempting to measure some particular component of the battery of human skills. Thus some tasks, although different in detail as a result of the experimenters' theories,

preferences and idiosyncrasies, will attempt to measure dexterity, while others are used to measure memory, decision-making, persistence, or vigilance.

Interest and research into the nature of vigilance started long before its application in psychopharmacology until by now there is an extensive literature including many books (Buckner and McGrath, 1963; Sanders, 1967; Davies and Tune, 1970; Mackworth, 1969, 1970; Stroh, 1971; Kornblum, 1973). Mackworth (1950), in his classic monograph, which reported the first comprehensive experimental studies of vigilance performance, traced the historical antecedents of the subject to Wundt, Helmholtz and James, but the term "vigilance" appears to have been first used in a technical sense by the British neurologist, Henry Head in 1923 and the first field investigations focussing on the effects of fatigue, boredom and monotony were carried out by Wyatt and his colleagues (Wyatt and Fraser, 1929; Wyatt and Langdon, 1932).

The development of radar in both Britain and the United States, in the 1930's and 1940's, necessitated a considerable amount of research into the human factors involved in the detection of information presented on radar displays. Ditchburn (1943) was one of the first investigators of the psychological aspects of the lookout's job. He was interested in rates of

performance deterioration and concluded that a lookout's vigilance began to deteriorate almost as soon as he began the task and reached a minimum quickly. This conclusion was supported by other researchers using simulated radar and sonar tasks (Lindsley, 1944; Solandt and Partridge, 1946). However, it was Mackworth (1950), following an ingenious series of experiments, who pointed out the theoretical as well as practical implications of watchkeeping behaviour.

Mackworth examined the characteristics of the conditions under which watchkeeping vigils were conducted and noted that not only did the subjects find the vigils prolonged, boring and inactive, but they also found that signals, when they occurred, were small, brief and difficult to discriminate. With these factors in mind, Mackworth devised the Clock Test which simulated the essentials of the radar operator's task while allowing, at the same time, strict experimental controls over the test situation.

Mackworth supplemented his Clock Test experiments with two other studies, one concerned with a radar display and the other with an auditory vigilance task. Performance and decrement in these two tasks were essentially similar to results in the Clock Test. As a result of this extensive series of experiments, Mackworth concluded that the decrement function was

independent of modality and that central rather than peripheral factors mediated performance.

Since 1950, a good deal of vigilance research has been rationalised on the grounds that it is an area which is directly relevant to radar-scanning, various military observation tasks, the safe operation of vehicles and many industrial situations. Whether or not there are strict military or industrial applications vigilance research continues to receive a considerable amount of attention both from research theorists and from workers interested in the effects of drugs.

Although a wide variety of techniques have been employed in the study of vigilance performance most researchers agree that the term 'vigilance tasks' refers to a group of task situations having certain features in common. Essentially a subject is required to respond over relatively long periods of time to the occurrence of infrequent stimulus changes. In the meantime there is a stream of stimuli which have to be neglected while the subject maintains "a state of readiness to detect and respond to certain specified small changes" (Mackworth, 1957). As J.F. Mackworth (1969) has pointed out, this definition contains an ambiguity, since a subject who is more 'ready' to detect a signal may also be more 'ready' to think he has detected one when in fact no signal occurred. A change in readiness

may imply either a change in criterion or a change in sensitivity or both. Both changes may in fact occur in a vigilance task.

Correct detections is the response measure most frequently used in vigilance tests. When vigilance is low, detections are few, while when vigilance is high, most of the signals will be detected. The type of stimulus used as a signal can take virtually any form. Generally the stimuli comprise one of two types. In the first, stimuli are presented continuously or intermittently. The target is the stimulus which is slightly different from the majority. In the second type the signal may consist of a discrete stimulus which has been either added to or subtracted from the environment. In this latter situation, changes in efficiency with time on task do not seem to occur (Martz and Harris, 1961), but in a situation where target signals have to be discriminated from non-target signals decrements do occur with time (Mackworth, 1950).

Vigilance tasks can be divided into sensory and cognitive types on the basis of the stimulus characteristics of the task, but whichever type is used the nature of the signal is specified for the observer before the task begins and a practice session is usually given. Signals, which are usually brief and near the observer's threshold, occur at irregular intervals although, in

order to examine changes in performance over time, the task is generally divided into sub-periods of equal length with the same number of signals occurring in each but at different intervals. Some vigilance tasks lasting as little as 5 minutes have been used (Thompson, Opton and Cohen, 1963) but tasks tend to be prolonged and sometimes extend over several hours (Webb and Wherry 1960). An attempt is made to emphasise the boring and monotonous nature of the task and as little extra-task stimulation as possible is provided.

Factors influencing vigilance performance fall into three broad categories; task, response and responder factors. The first two categories will be discussed briefly while some of the relevant responder factors will be discussed here and others will be discussed at appropriate points in later chapters. There are several task factors involved in the study of vigilance but some of the more important ones include:-

Signal Magnitude. The longer a signal lasts, and the higher its energy level, the greater is the likelihood of it being detected and consequently the performance decrement with time on task will be less (Adams, 1956). Mackworth and Taylor, 1963, found that signal duration did influence the initial level of detection but not the decrement, while Davenport (1968), studying the effects of signal duration and signal intensity simultaneously

within a factorial design concluded that performance improved with increases in both duration and intensity.

Signal Distribution. Until 1960, almost all of the research done supported the hypothesis that increasing the number of signals improved detection performance (Jenkins, 1953; Kappauf and Powe, 1959). A lot of more recent research has also supported this position, (Loeb and Binford, 1968; Broadbent and Gregory, 1965; Martz, 1966), although some workers have reported the opposite effect (Baker et al, 1962) and several studies have detected no significant effect (Wilkinson, 1964; Stern, 1966; Stroh, 1969).

Stimulus Frequency. This area has not received as much attention as signal frequency. Generally, it has been reported that vigilance performance improves as the number of non-signal stimuli decreases (Jerison, 1965; Taub and Osborne, 1968) although Budin (1966) reported no significant effects and Stroh (1969) reported a decrease in vigilance performance with decreased stimulus frequency.

Signal-to-stimulus ratio. Several studies have indicated that the ratio of target signals to non-target stimuli is of great importance in vigilance performance (Colquhoun, 1962; Jerison, 1966; Johnston et al, 1966), although opposition has come from Jerison (1965), Taub and Osborne (1968) and

Stroh (1969). Colquhoun (1962) has suggested that signal probability, rather than the total number of either signals or stimuli, is the important determiner and this may in part explain the differences between his studies and others. Colquhoun employed a small number of non-signal stimuli so that the signal probability was 0.5 whereas the highest signal probability employed by Jerison (1961) was 0.04, and by Taub and Osborne (1968) was 0.06. Stroh (1969) employed signal probabilities varying between 0.0017 and 0.17.

Task Duration. The major portion of any decrement in performance takes place in the first hour of work (Mackworth, 1950) but the degree of decrement is related to several factors, including expected length of time on task (Jerison, 1958) and anticipation of the end of the task. Davis (1948) in a study of pilot error noted that in the last few minutes of a long and complex task performance deteriorated markedly, possibly because the subject's attention was pre-empted by factors other than the task. Most vigilance studies, however, report the opposite result (Alluisi and Hall, 1963; Bergum and Lehr, 1965; Catalano, 1973).

Noise/irrelevant auditory stimulation. All reviewers of the effects of noise on efficiency have noted that noise may either improve, impair or have no effect on

performance (Davies, 1968). It generally appears, however, that difficult tasks involving noise of higher pitch and intensity show greater decrement (Broadbent, 1951, 1954, 1957).

Response Factors

Correct detections and ommission errors. Detection rate has always been the most important measure used in studies of vigilance performance. The score is usually either plotted against time or expressed as a raw total score, sometimes in the form of a percentage and sometimes as the probability of the signal being detected. Omission errors represent the number of signals the observer failed to detect. In most vigilance tasks the detection rate declines with time on task with the largest decline occurring in the first half-hour. There is evidence, however, that decline begins from the very first signal and that the length of delay from the start of the task to the first signal can be important.

Commission errors. A commission error is made when a signal is reported when none in fact was presented. In early studies false positive identifications were ignored since few occurred. Alternatively omission and commission errors were summed to form a composite error score. Traditionally, commission errors have been attributed to a "reprehensible tendency to guess" and

changes in false positive rate were considered not to be related to correct detections (Broadbent and Gregory, 1963b). Other researchers have found positive correlations between the two measures (Colquhoun, 1961). Finally, it has been noted that within any experiment the majority of commission errors are made by a minority of the subjects and this has led to the emphasis of individual differences in the generation of commission errors (Wiener, 1963), possibly based on different perceptions of the demand characteristics of the task (Orne, 1962).

Decision criteria. Since the early 1960's changes in approach to the analysis of vigilance performance have occurred. It was realised that false alarms are not unimportant but that they are related to correct detection and that correct detection and false positive detection rates vary depending on changes in the subjects' discrimination and criterion.

Signal detection theory is based on the assumption that there is no finite threshold for detection of signals. It suggests that there is an overlap between the distributions of noise alone and noise plus signal and that any particular observation might have come from either distribution. The decision as to whether the observer will accept an event as a signal is based on the probability that the event is a signal and the values

attached by the observer to the decisions that are possible. An observer may be cautious and reserve detection only for events he is certain about or he may be lax and detect all the events he suspects are signals as well as the ones he is sure about. With this strategy he is more likely to obtain more correct detections but he is almost certain to make more commission errors as well. d' is the measure of the subject's discrimination process, while beta is a measure of the decision process. These measures are derived from psychophysical data (Green and Swets, 1966) and are used in an attempt to specify whether changes both in the number of correct detections and the number of false positives reflect a change in the sensitivity of the sensory system or a change in the observer's criterion value.

Loeb and Binford (1964) examined changes in an auditory vigilance task. Half second pulses were separated by two second intervals. The signal was a slightly louder pulse, which occurred 40 times in 80 minutes. The main change was an increasing strictness of criterion (beta) but with little change in d'. A later study, however, found a marked increase in d' on an auditory task, suggesting some learning, which improved sensitivity, between the first and ninth sessions, as they also replicated the 'beta' increase found in the earlier study (Binford and Loeb, 1966).

Responder Factors

Responder factors are the patterns of response obtained from subjects which are not the result of manipulation of the task factors and experimenter-imposed response requirements but of such things as time of day, frequency of testing and age and individual differences.

Time of day

Performance at the same task does not remain uniform throughout the 24 hour period. Diurnal variations in performance appear to be associated with the diurnal body temperature rhythm (Kleitman, 1933; Colquhoun, 1971b). A simplistic representation is the two-state hypothesis. The 24 hour cycle is divided into two phases, the sleep phase and the active phase. During the former phase body temperature, blood pressure, respiration rate and urinary excretion are at low levels while during the latter phase the levels are higher. It is only the peak and the trough of the rhythms that coincide with the phases, however, and oscillations continue throughout the 24 hours. Generally, performance levels are higher during the day but again there are oscillations with some researchers finding performance peaking around midday (Kleitman and Doctorsky, 1933) while others have found a "post-lunch dip" which does not

seem to be related to whether or not the subjects have had lunch (Colquhoun 1971b). Recent work has related differences in pattern of performance through the day to personality factors and this will be discussed at a later point.

Frequency of resting

The pattern of responding in terms of both correct detections and commission errors changes with repeated testing. The importance of pre-task training has been highlighted by the work of Colquhoun and Baddeley (1967) and Floyd, Griggs and Baker (1961). Improvement is particularly indicated by a decreasing number of commission errors which will be high initially but will decline rapidly with practice (Bakan, 1955; Gettys, 1964; Buckner, Harabedian and McGrath, 1960, 1965). Alluisi and Hall (1963), on the other hand, found an improvement between the first and second session but a decline in the fourth session, when performance was the same as in the first session.

Mackworth (1950) found that the initial level of detection in the three tasks that he studied was lower in the second session while Buckner, Harabedian and McGrath (1960, 1965) using an auditory vigilance task found that there was a decrease in performance from day to day. Binford and Loeb (1966) found a considerable improvement in detections from session

to session with false alarms high initially but rapidly decreasing. Binford and Loeb suggested that several changes take place in a vigilance task with repeated testing. Changes in criterion occur mainly in early sessions, while subjects are adjusting their criterion to suit the signal probability that they find. Once learning has reached a maximum, a decrement in detections will still occur and the extent of this will be influenced by a variety of factors, including drugs, noise, fatigue and distraction.

THE EFFECTS OF DRUGS ON MEASURES OF PERFORMANCE

The effects of drugs on measures of performance

Early research into, and theories of, drug action in performance tended to differentiate only between stimulants and depressants. It was assumed that the extent and type of effect of different drugs in the same category would be similar. Thus in vigilance performance the normal pattern is one of decreasing detections and commission errors. Stimulants were considered to maintain detection rate while not affecting the false positive detection pattern. Depressants, on the other hand, were considered to reduce detections and increase or stabilise false positive detections, thus indicating a reduction in sensitivity (d') through the session.

Steinberg (1954) suggested that central depressant drugs may act selectively to impair newly acquired rather than well-established behaviour, and will show a greater effect on performance with greater complexity of task. While leading in the right direction the diversity of drugs and their pharmaco-kinetic effects had still not been recognised. Thus diversity goes beyond not only differentiation into stimulants and depressants but also beyond divisions of tranquillizing agents and hypnotics and indeed drugs prescribed for similar symptoms may have quite different actions. Linnoila and Mattila (1973a) point out such differences between diazepam and chlordiazepoxide.

Barbiturates

Von Felsinger, Lasagna and Beecher (1953) found impaired performance on a battery of psychological tests including tasks of visual perception, attention and computation between 5½ and 7½ hours after a small dose of pentobarbitone sodium (100 mg.). Support for these results came from a study which showed that pentobarbitone significantly reduced a mean detection rate compared to a control group (Talland and Quarton, 1966). Kornetsky, Vates and Kessler (1959) compared the effects of another barbiturate, quinalbarbitone (100 mg. and 200 mg.), with chlorpromazine (100 mg. and 200 mg.). Examination of the hypnotic and residual effects on performance showed that 15 hours post-medication there was significant impairment on a digit symbol substitution task, symbol copying and tapping speed for both doses of chlorpromazine and the higher dose of quinalbarbitone.

In later studies, involving one of the above authors, quinalbarbitone was found to have caused a greater performance deficit on an unpaced digit symbol substitution task than did chlorpromazine, with the opposite being true on a paced version of the DSST and the continuous performance task (Kornetsky and Orzack, 1964; Mirsky and Kornetsky, 1964).

Talland and Quarton (1965) found small but reliable barbiturate effects with both simple and choice visual reaction time tests. These results were supported by Frankenhaeuser and Post (1966).

Low doses of barbiturates, i.e. less than 100 mg. have generally been considered to have little deleterious effect on psychological tests. However, it has been shown that amylobarbitone (60 mg.) can depress critical flicker frequency (Turner, 1965) and that amylobarbitone (50 mg.) can have an adverse effect on performance in a one-hour vigilance task in which the subjects were required to distinguish two different tones (Bye et al, 1974). A 100 mg. dose also caused a lengthening of simple auditory reaction time.

Barbiturates tend to potentiate the effects of alcohol. A study of performance on a typing task found that phenobarbitone (150 mg.) slowed performance and reduced errors and that alcohol speeded performance and increased errors, while the two together speeded typing still further and further increased errors (Joyce et al, 1959).

Miller (1962) studied the effects of phenobarbitone (30 mg.) three times daily for 6 days. Under simulated driving conditions subjects were required to brake on the appearance of a red light. The barbiturate caused slower reaction times.

Tranquillizers and hypnotics

In recent years there have been an increasing number of drugs of this type, which have been gradually gaining ground in competition with the barbiturates, both for the relief of anxiety and, at higher dose levels, the induction of sleep. They have been generally considered to be safer than barbiturates and theoretically the administration of such a drug should enhance driving and other skilled performance in hyper-anxious patients. On the other hand, reduced anxiety with drug-taking may reduce aggression thresholds and uncontrolled behaviour may occur where it did not before (Lynch et al, 1975; Ashworth, 1975).

Malpas et al (1970) compared the effects of single doses of nitrazepam (5 or 10 mg.), amylo-barbitone (100 or 200 mg.) or placebo in normal healthy subjects who took the treatment before going to bed in their own homes and attended the laboratory for testing next day. Assessment was by sleep questionnaire, subjective mood scale, card-sorting and EEG. Subjects did not report morning hangover effects after any treatment and rated themselves having had a better night's sleep after the high doses of both drugs than after placebo. No subjective feelings of drowsiness were reported after any drug treatment but decision time in the card-sorting task was significantly slowed after both drugs in the larger doses, and after the

lower dose of amylobarbitone in the complex part of the task for up to 17 hours after treatment. Malpas et al concluded that the effects of nitrazepam are at least as prolonged as those of amylobarbitone and pointed out that certain kinds of performance may be significantly slowed the next day even though the subjects may be unaware of this.

Malpas (1972) examined the time course of the sedative effects of nitrazepam (5 or 10 mg.) and amylobarbitone (100 or 200 mg.) with particular regard to the times of onset of drug effect and the times of maximal effect. Card-dealing and digit symbol substitution tasks and subjective ratings were used in assessment. Results on the objective tests showed a marked dose-related effect on both drugs with nitrazepam having effects more marked than those of amylobarbitone. The two drugs were subjectively rated as similar at the high doses with clear dose-related differences for amylobarbitone. However, subjects seemed unable to differentiate between the two doses of nitrazepam and it was suggested that a subject's willingness or ability to judge his state accurately may be more impaired by nitrazepam than by amylobarbitone.

Malpas and Joyce (1969) examined the effects of nitrazepam (5 or 10 mg.) and amylobarbitone (100 or 200 mg.) on card-dealing, card-sorting and digit symbol substitution (DSST) when the subjects had had a light

meal before attending the laboratory. The slowing effects of the larger dose of amylobarbitone were not apparent until 90 minutes after administration, whereas the effects of nitrazepam were clear at 30 minutes. This is in contrast to a later study where the effects of amylobarbitone appeared after 30 minutes and those of nitrazepam after 30 minutes (Malpas, 1972).

Bond and Lader (1972) tested normal subjects on a battery of physiological and psychological tests twelve hours after a hyponotic dose of butobarbitone sodium (100 and 200 mg.) or nitrazepam (5 or 10 mg.) and compared with a placebo. The tests used included self-ratings, the Gibson spiral maze, cancellation, arithmetic, tachistoscopic number recognition, reaction time, tapping, card-sorting, the digit symbol substitution test and several electrophysiological measures. There were clear differences between the drugs and placebo in several tests. At the lower dose levels nitrazepam caused more impairment than butobarbitone but at the higher doses, where effects were marked, there was little difference between the drugs. It seemed that the impairment was greater in the motor aspects of performance. Tapping rate and the motor aspect of the card-sorting task was severely impaired, while reaction time was prolonged. However, while digit symbol substitution decision-time, card-sorting and arithmetic were affected

the decrement was smaller. Self-rated quality and onset of sleep were affected by both doses of both drugs. Both doses of nitrazepam and the higher dose of butobarbitone induced significantly greater feelings of sleepiness on wakening but only the effect of the latter lasted until the testing session.

Bond and Lader (1973) examined performance on a battery of tests 12, 15, and 18 hours after a hypnotic dose of butobarbitone (150 mg.), flurazepam (15 or 30 mg.) or a placebo. The measures included subjective self-ratings of sleep quality and onset, and feeling on wakening, and tests of auditory reaction time, complex visual reaction time, tapping, cancellation, card-sorting, symbol copying and DSST. DSST was most affected and was significantly impaired by both drugs at the first testing. The symbol copying task was affected for a longer period but only by flurazepam. It was suggested that flurazepam exerts a motor impairment while butobarbitone affects the cognitive element of the DSST. The conclusion about the effect of butobarbitone appeared to conflict with results in an earlier study where greater emphasis was placed on the detrimental effect that the barbiturate had on the motor aspects of performance (Bond and Lader, 1972).

Both flurazepam and butobarbitone exerted an adequate hypnotic effect but caused sleepiness on

wakening. Subjects rated themselves as having felt more alert after taking placebo, more discontented after butobarbitone, and more relaxed and calm after flurazepam. It was concluded that flurazepam had effects similar to nitrazepam in that the subjective effects were less unpleasant than the barbiturate, but the disruptive effects lasted longer.

Adams (1974), using the same drugs and dose levels as Bond and Lader (1972), assessed performance the following day on a variety of tasks including short-term memory, proof reading, concept identification, visual search and lines classification. A significant drug effect was found only on the memory task and then only with the higher dose levels of the drugs. Despite the fact that no subjective or EEG evaluations were made it was suggested that the results indicated that the effect of the drugs on performance resulted from a deterioration in quality of the induced sleep. Bond and Lader (1972), using psychomotor, subjective and EEG assessment, in the examination of such a hypothesis, found no relationship between sleep quality and subsequent performance.

Jaatala et al (1971) examined the effects of another benzodiazepine, diazepam, on subjective and objective measures. Subjective effects of the drug were marked with an increase in "euphoria" in men and

in "depressivity" and "withdrawing" in women. Diazepam impaired performance on a DSST and also affected the ability to repeat numbers series in both sexes.

Chlordiazepoxide, in single doses of less than 40 mg., in several studies, has shown little effect on psychomotor performance or driving skills (Idestrom and Cadenius, 1963; Kielholz et al, 1967, 1969; Austen et al, 1971). Higher doses have caused reversible eye muscle imbalance and impaired perception (Murray, 1961).

Diazepam (Valium 2.5 mg. and 5 mg.) has been shown adversely to affect vigilance (Bye et al, 1974) and to increase the adverse effects of alcohol (Myrsten et al, 1967).

The study of the effects of tranquillizers and hypnotics on performance patterns is only beginning and while the effects of these drugs in interaction with alcohol has been even more limited, the practical importance is evident. Linnoila and his colleagues in Helsinki have taken a lead in undertaking large-scale studies into the effects of a variety of drugs, alone and in combination with alcohol, on performance tasks and simulated driving skills. The performance tasks included tests of choice reaction, co-ordination and divided attention.

Linnoila and Mattila (1973a) found that diazepam alone shortened reaction time and reduced the number of mistakes on a choice reaction test. When it was given in combination with alcohol, however, all parameters measured were markedly impaired without similar loss in subjective capacity of performance. In the simulated driving test diazepam increased collision frequency and neglect of the rules, coupled with serious steering errors, and a reduction in tachycardia induced by an emergency situation (Linnoila and Mattila, 1973b).

Chlordiazepoxide (10 mg. and 25 mg.) caused dose-related reductions in reaction time and had little effect on co-ordination (Linnoila and Mattila, 1973a). In combination with alcohol there was little enhancement of the alcohol-induced impairment of attention, reaction time, reaction errors and co-ordination performance. The differences between the effects of diazepam and chlordiazepoxide were suggested to be related to the pharmacokinetics of the two drugs since the former is more rapidly absorbed. The lack of potentiation of alcohol is in support of other reports (Frankenhaeuser et al, 1965; Dundee, 1969).

Nitrazepam (10 mg.) did not modify skills significantly when used as a hypnotic with testing 10

hours after administration. When tested in combination with alcohol, subjects were still unaffected but attention was impaired after 30, 90 and 150 minutes (Linnoila and Mattila, 1973a).

Tricyclic antidepressants

Antidepressants have been found to be a potential danger to drivers, since patients taking tricyclic antidepressants have commonly found small doses of alcohol have caused very strong effects (Ashworth, 1975). Amitrityline (8 mg./kg.) has potentiated the adverse effects of alcohol on normal subjects, while the drug alone produced a decrement on the pursuit rotor task (Landauer et al, 1969; Milner and Landauer, 1971).

Phenothiazines

Most research falling into this category has used chlorpromazine (CPz). The limited amount of research there has been has underlined the paradoxical situation of testing drugs in normal subjects when the drugs are intended for abnormal populations. In all the studies examining the effects of CPz on schizophrenics, performance improved when the drug was administered, while when CPz was administered to animals and normal humans a performance decrement occurred.

Gilgash (1961) showed improvement in intellectual functioning with CPz administration in catatonic schizophrenics, and Daston (1959) found an improvement in Wechsler Memory Scale subtests with chronic schizophrenics. Similarly, prochlorperazine has been found to improve performance on the Wechsler Digit Symbol and Digit Span subtests (Lehmann, 1959).

In animal research, Wilson (1965) found that CPz reduced detections by monkeys to a very low level, and Kornetsky and Bain (1965) found that CPz reduced the responding rate of rats in a kind of vigilance task.

Brimer, Schnieden and Simon (1964) examined the effects of CPz (50 mg.) and chlordiazepoxide (10 mg.) on tests of judgement of conceptual relationships. They found greater decremental effects with CPz than with chlordiazepoxide.

Kornetsky and Orzack (1964) and Mirsky and Kornetsky (1964) found that although a group given chlorpromazine performed better than a group given quinalbarbitone on an unpaced version of the DSST, the chlorpromazine group performed at a poorer level on a paced DSST task on a CPT.

Loeb et al (1965) found significant decreases in sensitivity during an auditory vigilance task with a group of subjects given chlorpromazine.

Milner and Landauer (1971) studied the effects of chlorpromazine and alcohol on pursuit rotor and choice reaction performance. Chlorpromazine (1 mg./kg.) caused deterioration in performance levels next morning and potentiated the deleterious effects of alcohol on the pursuit rotor.

Amphetamine and other stimulants

Amphetamines generally improve vigilance performance. Loeb et al (1965) found that although there was no difference in the initial level of detection, the usual decrement with time on task did not occur. Mackworth, J.F. (1965), using only a visual vigilance task and interpreting the data using signal detection theory, also found the initial level unchanged and the progressive decrement reduced after amphetamine.

Talland and Quarton (1966) showed an absolute improvement in performance on a visual vigilance task in a group given methamphetamine (15 mg. per 150 lb. body weight). Other researchers using a smaller dose (5 mg.) found little effect (Neal and Pearson, 1966).

Even though amphetamine has the effect, at least at higher dose levels, of inhibiting the appearance of a performance decrement it appears to have little effect on commission errors (Hearst and Whalen, 1963; Mackworth, 1965; Loeb et al, 1965; Neal and Pearson, 1966).

Talland and Quarton (1965) failed to find an amphetamine effect with either a simple or choice visual reaction time task. Frankenhaeuser and Post (1966), on the other hand, found a clear effect on simple visual reaction time.

Trumbo and Gaillard (1975) compared the effects of an amphetamine, phentermine (20 mg.) and a barbiturate, hexobarbital (600 mg.), on visual and auditory serial reaction time and found that the amphetamine effect was specific to visual RT and occurred only when time uncertainty was maximal. The barbiturate effect was specific to auditory RT, and was independent of the amount of time uncertainty involved. These differences were explained by the hypothesis that the barbiturate may have reduced the immediate arousal properties of the auditory signals whereas the amphetamine facilitated performance by enhancing the subjects' ability to maintain recepter orientation, attention to the task and motor preparation.

Brown et al (1974) examined the effects of amphetamine (10 mg.) and fenfluramine (30 mg.) on tapping, reaction time, digit symbol, card-sorting and cross-out tests. It was hypothesised that amphetamine would increase speed and decrease accuracy, that fenfluramine would decrease scores, and that a combination of the two would produce performance patterns lying between the two extremes. Subjects performed before drug administration and at 45, 90, 150 and 210 minutes after ingestion. Findings revealed significant differences between

amphetamine and fenfluramine but no consistent differences between fenfluramine and placebo. Performance in the combination condition was similar to that under amphetamine alone.

Amphetamine, in a single therapeutic dose, temporarily increases alertness but large doses may produce irritability and inability to concentrate. Residual effects include tiredness and depression. These effects have implications for driving and other skilled performance requirements. Preliminary results of work at the Road Research Laboratory suggest that consumption of amphetamines may cause greater disruption than alcohol (Ashworth 1975) and a Canadian study found that people taking amphetamine either alone or in combination with other drugs had higher than average accident rates for their age, sex and driving experience while those dependent on barbiturates or tranquillizers had lower than expected rates (Smart et al, 1969). It has been suggested that the latter finding is due to a disinclination to drive after taking the drug (Ashworth, 1975).

Alcohol

The effects of alcohol, although dependent on age, personality and setting, are secondary to central nervous system depression. This characteristically includes dose-related increasing impairment of thought processes and decreased mechanical efficiency. Evans et al, (1974) used a series of doses of alcohol calculated to produce a blood alcohol concentration of 0, 25, 50, 75 and 100 mg.% and evaluated psychomotor impairment and subjective impression. Performance on all measures, including pursuit meter, wobble board, delayed auditory feedback and a modified Cornell Medical Index, showed a linear dose-related deterioration.

Lewis (1973) administered two different dose levels of alcohol and assessed performance on card-sorting, hand-eye co-ordination and problem solving of differing degrees of complexity. On the easy tasks there were no significant differences between the drug and control groups but on the more difficult tasks a dose-related decrement was found.

Moskowitz and DePry (1968) examined the effect of alcohol on auditory detection under conditions of concentrated and divided attention. The two tasks were presented binaurally, one required the detection of a tone and the other required the recall of six

digits. The concentrated attention condition involved the performance of one of the tasks while the other was ignored: the divided attention task involved performance of both tasks simultaneously. An alcohol treatment of 0.52 gms. alcohol/kg. bodyweight did not impair performance of either task under the concentrated attention condition but division of attention severely impaired accuracy.

A more recent study has examined the effect of alcohol on division of attention in the visual modality (Moskowitz and Sharma, 1974). Subjects were required to fixate on a central light while attempting to detect signals in their peripheral field of vision. The central light, under the three different information load conditions, either remained constant or blinked at one of two different speeds with the subjects being required to report the number of blinks that had occurred in a twenty-second trial. The peripheral lights were presented at any one of thirty-two different positions at angles ranging from 12 to 102 degrees. Results were similar to those in the previously reported study since the simplest test condition showed no alcohol-induced impairment of detection. Furthermore, inaccuracy increased as a function of increasing information processing demands, with the deficit being unevenly

distributed between the tasks and the greater impairment being in peripheral detection. Hockey (1970) demonstrated that the deficit is not intrinsically in peripheral detection but is related to attentional priorities established by training or by the conditions of the experiment.

These data suggest that performance of practical tasks requiring the co-ordination of information from a diversity of sources will be deleteriously affected if a subject has received alcohol. The effect of alcohol on driving skills has been studied by several researchers and it has been mainly conducted using simulators. The assessment of impairment in real-life driving situations has been rare (LeDain et al, 1972; Klonoff, 1974).

Generally, in assessment on a simulator, performance has been affected in a manner similar to that found on the tests already mentioned. Drew, Colquhoun and Long (1958), testing the effects of small amounts of alcohol found "impairment followed absorption of alcohol into the blood stream such that the larger the blood alcohol level, the larger the effect". There was no sign of a threshold level which had to be exceeded before impairment was manifested.

Moskowitz (1971) described two experiments examining alcohol-induced impairment in simulator performance. In the first, most of the information came from a film projection on a screen, while in the second a subsidiary task was added. Although in both studies the average peak blood alcohol level was 0.085% there was no alcohol effect in the first study; in the second, however, there was a marked and significant impairment on many of the performance assessment measures and an increase in within-subject variability.

The studies of Linnoila and his colleagues in Helsinki, into the effects of alcohol on a variety of skills including choice reaction, co-ordination and divided attention as well as driving skills, have already been mentioned. Simply, a decrement on the tests was found when alcohol alone was administered and this interacted with some of the other drugs tested to increase impairment and errors even further (Linnoila and Mattila, 1973a,b).

From an early date attempts have been made to assess the effect of alcohol in driving skills. Epidemiological studies have compared the accident rates of drivers taking alcohol with those of non-drugged drivers. Borkenstein (1963) conducted a survey of over 10,000 subjects and calculated that a driver with 60 mg./100 ml. blood alcohol

concentration was twice as likely to have an accident as a sober driver. Goldberg and Havard (1968) have suggested that the probability is six times greater at 100 mg./100 ml. and twenty-five times higher at 150 mg./100 ml.

Marihuana

A number of studies have reported the effects of marihuana on vision. Significant decrements have been demonstrated on autokinesis (Sharma and Moskowitz, 1972), central vision signal detection (LeDain, Campbell, Lehmann, Stein and Bertrand, 1972), and peripheral signal detection (Moskowitz, Sharma and McGlothlin, 1972).

Caldwell, Myers, Domino and Mirriam (1969) found no effect on auditory absolute, differential frequency and amplitude thresholds under conditions where subjects controlled the levels of marihuana consumed.

Moskowitz and McGlothlin (1974) controlled the amount received and subjects received 0, 50, 100 and 200 µg Δ^9-THC per kg. bodyweight. There were two conditions of signal detection. In the concentrated attention condition subjects were required to detect the presence or absence of a tone in a three-second burst of white noise. In the divided attention condition subjects had to repeat a series of 6 digits presented simultaneously with the noise burst. Significant dose-dependent decrements were obtained under both experimental conditions. Signal detection theory analysis indicated a dose dependent reduction in sensitivity (d'), independent of change in the subjects detection criterion (B), with a tendency to an increase in false positive identifications.

Evans et al (1973) examined the effects of different dose levels (0, 3, 6, 9 μg per kg. of Δ^9-THC) on performance and found a linear decrement in stance stability but no dose-related impairment of mental performance, as evaluated by delayed auditory feedback, or hand-eye co-ordination, although in the latter task there was an impairment when comparing placebo against drug.

Kiplinger et al (1971), on the other hand, demonstrated a dose-related linear decrement in both psychomotor and mental performance. They used higher concentrations (0, 6.25, 12.5, 25 and 50 μg per kg. THC). Other studies by the same group of researchers support these results (Manno, Kiplinger, Scholz and Forney, 1971).

Casswell and Marks (1973) studied the effects of marihuana on a divided attention task and on driving in a simulator in both naive and experienced smokers. A decrement was found in both groups on the attention task while no decrement was found in the simulator.

Other studies on the drug's effects on driving skills have shown clear detrimental effects. Rafaelson et al (1973) studied the effects of both cannabis and alcohol and found that both drugs increased the time required to brake and start,

while alcohol increased and cannabis decreased the number of gear changes.

Klonoff (1974) examined the effects of marihuana in low and high doses (cigarettes contained either 4.90 mg. Δ^9-THC or 8.40 mg. Δ^9-THC) on driving performance in both a restricted traffic free area and during peak traffic flow hours in a city centre. Klonoff concluded that marihuana does have a detrimental effect on driving skills, especially under normal city street driving conditions and at night.

A REVIEW OF MEASURES OF SLEEP

With the developing use of the electro-encephalogram sleep research was able to move away from reliance on motility and estimates of sleep latency, quality and duration. At first, stages of sleep were based on the presence or absence of alpha rhythm and the amount of high voltage slow wave activity. However, the major discovery resulting from the use of all-night EEG was that sleep is not a unitary state but comprises two separate types. This realisation arose from the pioneering work of Aserinsky, Dement and Kleitman (Aserinsky and Kleitman, 1953, 1955; Dement and Kleitman, 1957). There are available several reviews of the physiology and psychology of the two types of sleep (Oswald, 1962; Jouvet, 1965; Koella, 1967; Freemon, 1972).

The two sleep states can be differentiated by the EEG, but usually two other polygraphic variables are used as well. These measure changes in chin muscle tension and eye movements. The two sleep states are commonly known as REM (rapid eye movement) and NREM (non-rapid eye movement). The former type is characterised by low voltage EEG with rapid, jerky movements of the eyes occurring in intermittent bursts and commonly preceded by a second or two of 2-3 c/sec "saw-tooth" waves. Chin EMG is almost absent, respiration is variable and shallow, heart rate is

rapid and blood pressure is variable. If subjects are wakened from REM sleep they generally describe their immediately preceding mental life as dream-like and vivid.

NREM sleep contains EEG slow waves, spindles and K-complexes. There is slow, regular respiration and heart rate. Blood pressure is irregular and the chin EMG decreases from wakefulness. Eye movements are either non-existent or slow and rolling. Mental life has been described as thought-like and repetitive. This state is customarily divided into stages 1, 2, 3 and 4 (Rechtschaffen and Kales, 1968).

Discussion about the need for and the value of sleep, has taken place since the time of Hippocrates, and continues today. Some consider sleep to be vestigial in humans and produce as evidence, people who seem normal yet need little sleep but generally sleep is considered to be necessary since it occupies such a large proportion of our existence and since it is generated by active brain stem mechanisms (Jouvet, 1972). It seems that rather than being a passive state due to the loss of waking stimuli, it exerts a major role in central nervous systems functioning, and REM sleep is additionally intriguing since firstly, the neural activity of the brain is at levels equal to that of aroused waking (Hobson and McCarley,

1971) and secondly it shows a unique ontogenetic pattern of greatest occurrence in infancy and least occurrence in old age (Roffwarg, Muzio and Dement, 1966).

Sleep may be considered to be homeostatically regulated since deprivation leads to compensation. Total sleep deprivation leads to an excess of REM sleep on recovery nights. However, this is not usually manifested until the second recovery night, while the first night of undisturbed sleep shows an excess of stage 4 (Berger and Oswald, 1962). This is suggestive of restorative priority.

Selective deprivation of stage 4 sleep leads to excess on subsequent recovery nights (Agnew et al, 1964). Restriction of sleep to 5 hours nightly for several nights led to an absolute increase in the duration of stage 4 in preference to compensation of stages 1, 2 and 3 which are more common in the later part of the night's sleep (Dement and Greenberg, 1966). This led to the suggestion that stage 4 is "worth more" than stage 2. REM sleep deprivation leads to a compensatory rebound, as well (Moruzzi, 1969). Dement (1960) woke subjects every time a REM period started and kept them awake for 2 minutes before allowing them to go back to sleep. Since NREM sleep normally precedes REM sleep, REM deprivation

occurred. When normal sleep was allowed on subsequent nights a REM rebound occurred with a gradual return to baseline levels after several nights.

In the cat, normal REM time is about 15% of total recording time but REM rebounds as high as 40% have been reported following deprivation (Jouvet, Vimont and Delorme, 1965). The amount of REM rebound has been found to be directly proportional to the amount of REM sleep lost during the deprivation period (Jouvet et al, 1964). Also, during deprivation the number of attempts to enter REM sleep increases dramatically after only a few hours (Stern and Morgane, 1974) and the intensity of REM sleep, as measured by eye movement density and muscular twitches, also increases (Dement, 1967).

There is, therefore, evidence that both kinds of sleep are necessary. Disruption of the normal patterns could be considered to be undesirable since it immediately leads to attempts to compensate for the losses whether they be general or specific. Initially the rebound is large but with time it reduces until the normal pattern has been regained.

Given acceptance of this point of view, it is not unreasonable to suggest that if a drug were to distort the normal proportions of the two kinds of

sleep the effect could properly be regarded as an adverse or undesirable one. There has been, therefore, an increase in the amount of research into the effects of drugs on sleep patterns. There has been interest especially in the drugs which help people to sleep or, in smaller doses, to reduce anxiety. The mushrooming of this area of research has been called an "ever increasing 'hypnoplethora' (Koella, 1967).

There are several problems endemic in sleep research. The expense and laboriousness of all-night polygraphy limits the number of subjects and the number of nights monitored in any single study. The diversity of results from different laboratories even when using the same drug could be attributed to a variety of causes including different dose levels, insufficient numbers of subjects, insufficient acclimatization to the laboratory, designs testing the effects of different drugs on consecutive nights and the taking of unmonitored naps or surreptitious drugs.

The effects of different dose levels of chlorpromazine on sleep are varied. Low doses increase REM, high doses depress REM, and intermediate doses show no change in sleep stage percentages (Lewis and Evans, 1969). The construction of that

traditional pharmacological tool, the dose-response curve would be appropriate but using human subjects would involve an enormous amount of recording.

It is difficult also to get the right sort of subjects and persuade them to abstain from alcohol or other social drugs for any length of time (Mellinger et al, 1971).

The 'non-independence of successive nights' effect was first described in addicts (Oswald and Thacore, 1963) and confirmed experimentally by Rechtschaffen and Maron (1964) and Oswald and Priest (1965). Brannen and Jewett (1969) administered two phenothiazines on successive nights alternately. They concluded that promethazine had little effect while trifluoperazine increased REM. The validity of this conclusion is doubtful since it was impossible to differentiate between one of the drugs' pharmacological action and the amount of compensation occurring as a result of the action of the drug taken the previous night.

Only a small number of research workers have studied the effect on sleep of both repeated administration and withdrawal of a drug. Generally, any initial disruption reduces with time and sleep patterns return towards normal but the degree of disruption and the speed of return to normal differ

with different drugs. These factors and the effects of withdrawal are important points to consider in relation to the therapeutic use of the drug.

A further problem is that most studies use healthy normal volunteers. It is probable, however, that effects such as anxiety or depression will interact with a drug to modify the drug's effect on sleep (Akindele et al, 1970). Akindele (1969) noted that in normal subjects phenelzine increased stage 2 sleep, while in a depressed patient the amount of stage 2 was initially depressed but later recovered to above pre-drug levels with an eventual return to normal. In another experiment using phenelzine, two normal volunteers showed a fall in percentage REM sleep with a marked withdrawal rebound. Three depressed women subjects, however, showed total REM abolition (coupled with greatly improved mood) after a week on the drug (Akindele, Evans and Oswald, 1970). In this study there was prolonged inhibition of REM sleep, a function generally thought to be essential. The smallness of the REM rebound on withdrawal urges reconsideration of the hypothesis that the REM type of sleep is a time of special importance for cerebral protein synthesis (Oswald, 1969). It may be that there can be occasional dissociation of sleep-type - specific manifestations.

SLEEP AND DRUG EFFECTS:

A REVIEW

Barbiturates

Oswald et al (1963) were the first to study the effects of barbiturates on sleep in depressed patients. REM percentage was found to fall from 20.6% on placebo nights to 14.8% on nights when heptabarbitone (400 mg) was given. Age matched control subjects showed a drop from 23.3% to 11.8% and in both groups there was a drop in the number of eye movements per unit time. The increase in NREM sleep was distributed over all four stages. Baekeland (1967) using pentabarbitone confirmed the depression of REM but pointed out that the periodicity in the cyclic alternation of the two kinds of sleep appeared to be unaffected so that REM appeared when expected but was of shortened duration. Again the NREM increase was distributed across the four stages.

Other studies with barbiturates have shown the NREM increase going to only one stage. Lester and Guerrero-Figueroa (1966) studied both phenobarbitone and thiopentone and found that both drugs increased the percentage of stage 4 sleep. Williams and Agnew (1969), however, found decreased REM and increased stage 2 with pentobarbitone. This result was supported by a study using amylobarbitone (Haider, 1969).

Longitudinal studies on the effects of drugs are costly and time-consuming. Consequently the use of only a few subjects is common. Oswald and Priest (1965)

recorded the sleep of two men for a number of consecutive nights. Five baseline nights were followed by nine nights when 400 mg amylobarbitone were taken nightly. REM percentage dropped for the first few nights and then returned towards normal. The dose was increased to 600 mg nightly for the next nine nights. A REM decrease again occurred with a similar return toward normal. Abrupt withdrawal produced abnormally short REM onset latencies coupled with a marked increase in REM percentage especially in the early part of the night. This pattern of disruption, although gradually decreasing, did not return to normal for five weeks. Evans and Lewis (1968) replicated this study and found that chlorpromazine blocked the REM rebound.

The withdrawal of barbiturates leads not only to an increase in the amount of REM sleep in the form of a rebound but it also leads to an increase in the number of eye movements per unit time (Kales, 1969; Oswald, 1969b). There is, therefore, a physiological increase in REM intensity. Furthermore, there is an increase in the amount and vividness of dreaming with nightmares frequently described (Kales and Jacobson, 1967; Oswald and Priest, 1965).

Non-barbiturate tranquillizers and hypnotics

Oswald and Priest (1965) found that administration of nitrazepam reduced REM sleep and on withdrawal increased REM sleep and reduced REM onset latency for up to 4 weeks. These results were supported in another study with the additional finding that the drug delayed the appearance of the first REM period of the night (Loeb et al, 1966). Nitrazepam has also been shown to reduce sleep onset latency, shifts to and time spent in NREM stage 1 and increase total time spent in stage 2 sleep (Haider and Oswald, 1971).

Nitrazepam also has effects on REM intensity with a reduction in the frequency of rapid eye movements per unit time during REM sleep, and a rebound increase to above normal on withdrawal (Lewis, 1968), and on REM activity in relation to occurrence of nightmares (Oswald, 1965) and bizarre dream content (Oswald et al, 1973).

Hartmann (1967) found chlordiazapoxide increased REM onset latency and decreased whole night REM percentage. A later study found REM not greatly affected for the first few days but decreasing for the remainder of the four weeks on medication with a concomitant decrease in stages 3 and 4 and an increase in stage 2 (Hartmann and Cravens, 1973a). Sleep stage percentages returned to normal in the second week of withdrawal with no rebound phenomena noted.

Kales et al (1970a) reported that 30 mg flurazepam had little effect on REM sleep but significantly reduced stage 3 and 4, and that 60 mg reduced whole night REM percentage and increased REM onset latency. A long-term study in insomniac patients indicated that 30 mg of flurazepam greatly reduced sleep latency, slightly increased sleep time and decreased stage 4 (Kales et al, 1970b).

Hartmann (1967) found that flurazepam (30 mg) increased REM onset latency and reduced whole night REM percentage. A more recent study using a lower dose level (15 mg) found no inhibition of either REM or stage 4 sleep (Johns and Masterton 1974).

Perlapine is chemically unrelated to other hypnotics, but it has been claimed to be comparable in efficiency to nitrazepam, (Ando et al, 1970). Allen and Oswald (1973) found in a pilot study that 10 mg decreased intra-sleep restlessness and REM duration but did not alter stages 3 and 4 sleep. A further study confirmed these results and noted the occurrence of a shortlasting rebound.

Tricyclic anti-depressants

Imipramine has been shown to decrease REM sleep and enhance EEG sleep spindles in NREM sleep (Toyoda, 1964). Increased REM onset latency and total sleep time and decreased REM percentage has been demonstrated in cats (Hishikawa et al, 1965). Although imipramine does not appear to show dose effects, desmythyl-imipramine does in cats (Hishikawa et al, 1965) and in humans (Zung, 1969).

Oswald and his colleagues have studied the effects of several tricyclic anti-depressants on REM sleep and intra-sleep restlessness (Dunleavy et al, 1972; Brezinova et al, 1973). REM duration was reduced by imipramine, desipramine, chlorimipramine and doxepin but not by trimipramine or iprindole. The effect lessened during a month of administration with a withdrawal rebound lasting about a month. Intra-sleep restlessness was increased by imipramine, desipramine and chlorimipramine but with no rebound, while doxepin reduced intra-sleep restlessness.

Phenothiazines

Chlorpromazine and thioridazine have been used extensively as tranquillizers in geriatric and psychiatric practice. Patient complaints of sleepiness are not uncommon and it appears that the effects on sleep, especially in the case of chlorpromazine, are dose-related (Lewis and Evans, 1969). Low doses of chlorpromazine increased REM percentage, high doses depressed REM and intermediate doses did not change sleep stage percentages.

Evidence from animal studies have shown that chlorpromazine can shorten REM onset latency (Hishikawa et al, 1965) and in large doses can reduce REM sleep time over the whole night (Hishikawa et al, 1965; Jouvet, 1967).

Hartmann and Cravens (1973b) found significantly increased total sleep time and decreased wakening in normal young males, especially in the first few days, but found no difference in REM and NREM sleep stage distribution despite considerable effects on home sleep and mood variables.

Amphetamine and other stimulants

Rechtschaffen and Maron (1964) demonstrated that amphetamine can increase REM onset latency and the number of body movements and decrease the proportion of REM sleep and total sleep time. Increased wakefulness and general disturbance complicated the results. To overcome this, subjects were given pentobarbitone during the control period and then amphetamine was introduced as well. With the barbiturate percentage REM sleep was reduced and when amphetamine was introduced the amount of REM sleep halved. The decrease in REM could not, therefore, be accounted for in terms of increased sleep disturbance. This conclusion was confirmed by Baekeland (1967).

Withdrawal increases total sleep time and REM percentage and decreases REM onset latency (Oswald and Thacore, 1963). These disturbances may persist for up to two months.

Several amphetamine derivatives have been studied by Oswald and his colleagues (Oswald, 1970). Tranylcypromine was found markedly to reduce REM in an addict but with a rebound increase of up to 75% on withdrawal (Le Gassicke et al, 1965).

Lewis (1969b) compared several amphetamine derivatives and found that all except one affected REM sleep. The exception, fenfluramine, while still

disturbing sleep, did not alter REM in either amount or distribution. These findings were supported by Firth et al (1970). Another study from the same laboratory, however, found dose-related reductions of REM sleep, increases in intra-sleep restlessness and changes in slow-wave sleep (Lewis et al, 1971).

Subjective reports of sleep and mood after caffeine have revealed inter and intra-individual variability of reaction (Goldstein, Kaiser and Whitby, 1969). EEG sleep studies have either failed to show any effects of caffeine (Hartmann, 1965b) or showed disturbance only in the first 3 hours after caffeine (Muller-Limmroth, 1972) or have shown the whole night to be affected (Brezinova, 1974). In the last study sleep time in older subjects was decreased on average by two hours and sleep onset latency increased to over 60 minutes after a dose of caffeine (300 mg).

Alcohol

Gresham et al (1963) found that ethyl alcohol in substantial doses (1 mg/kg) reduced REM sleep in man. Yules et al (1966) using the same dose level found a decrease on the first night and a rise on subsequent nights. On stopping alcohol REM percentages remained above baseline on the first post-alcohol night. In a later paper the REM sleep decrease was reported to be compensated for in total sleep time by increases in NREM stage 4 (Yules et al, 1967). REM onset latency was not affected by either administration or withdrawal of alcohol.

Knowles et al (1968) studied the effects of two different dose levels (3.5 oz or 6.0 oz) in one subject. In the lower dose overall night REM percentage was not affected but when divided into halves it was seen that REM percentage in the first half was reduced and there was a concomitant increase in the second half of the night. On the larger dose there was a significant reduction in REM percentage. A rebound was reported on withdrawal with an increase particularly in the first part of the night.

A study of patients during withdrawal, including 5 subjects with delirium tremens, found that when they slept they had a high REM percentage: one patient had 300 minutes of REM sleep, one of the highest amounts

recorded (Yules et al, 1966). Another study of four alcoholic patients in withdrawal, found that although two had no sleep at all, the two that slept showed a high REM percentage and in one case there was 91 minutes of REM out of 91 minutes of sleep (Gross et al, 1966). The phenomenon of sleep onset REM has also been reported by Othmer et al (1970).

SELF RATED FEELING STATES:

A REVIEW

Subjective assessment of behaviour

"Subjective evaluation is important, if for no other reason than that the clinical use of tranquillizing and hypnotic agents is most frequently concerned with alleviation of patients' complaints" (Lasagna, 1954). Such evaluation can be made from two points of view. First, observer rating has been used mainly for clinical assessment. Exton-Smith, Hodkinson and Cromie (1963) described a study in which nursing staff were asked to make an assessment of the effect of a drug on a group of patients, both during sleep and on wakening. Using a four-point rating scale, observer-rating and self-rating assessments of the effects of four hypnotics were made. Comparison showed a high correspondence between the ratings of the observer and the observed but this was possibly due to there being only four categories.

Haider (1968) described a study in which the effects of two hypnotics were compared using both observer-rating and self-rating techniques. Nitrazepam (10 mg) and amylobarbitone (200 mg) were reported to be equally efficient in inducing and maintaining sleep and the subjects indicated little difference between the drugs in terms of side-effects. Clinical observation by staff, however, favoured nitrazepam since it was considered to induce more

relaxed sleep, less hangover and no confusion in a group of 102 geriatric patients.

Hamilton has developed the rating scale technique for the clinical assessment of behaviour (1960, 1967). Hamilton attempted to identify components of illness syndromes by factor analysis of clinical ratings and described 17 such components, rated on either 3- or 5-point scales, to be rated by two experienced observers working independently at the same interview.

A second approach, used both experimentally and clinically, is to get the subject or patient to rate how he feels by filling in comparison or analogue scales or adjective check lists. The self-rating technique was first described by Hayes and Patterson (1921). There are several advantages in the use of the analogue scale since it is simple and the rater may understand and complete the requirements quickly. It avoids professional preconception and prejudice and does not require verbal sophistication and prolonged co-operation and concentration.

Parsons (1963) used a paired comparisons scale with six successive paired comparisons and found little difference between three different barbiturates in terms of sleep quality and likelihood of morning hangover.

Some problems arise from scales of this sort, however, since what is good for one person may be only

average for another, and although sleep may have been considered good after a drug in that it increased sleep time, reduced restlessness and had no obvious effect on wakening, if a person or patient is impaired during the rest of the day in some way, then there has to be careful interpretation of what a score means (Kornetsky et al, 1959). Smith and Beecher (1960) pointed out the complexity of the problem in a study in which they measured subjective and objective disruption of performance in college athletes. The subjects had high levels of "well-being" and assessed their performance as being unusually good after 100 mg of secobarbitone. Objectively measured their performance was markedly impaired. Similarly, drugs may impair performance when subjective changes have not been reported (Munro-Faure et al, 1971).

In an attempt to remove the restrictions implicit in labels the advantages of the visual analogue scale have been reiterated in recent years (Gedye et al, 1961; Aitken, 1969), and they have been compared favourably with other scales in the assessment of mood changes induced by sedatives and minor tranquillizers in normal subjects (Kellner, 1972).

The most commonly used form of the visual analogue scale is the 10 cm line on which the subject is

required to place a mark in relation to how he feels. Repeated use allows fine discriminations to be made and response-set and positive negative skewing can, therefore, be reduced. The scales have been used in the study of the effects of analgesics in the treatment of rheumatoid arthritis (Joyce, 1968), and the comparative effectiveness of different drugs in the alleviation of depression (Zealley and Aitken, 1969), but they have been used most frequently in the study of drug effects, in both the short and the long term, in normal subjects (Akindele et al, 1970; Malpas, 1972; Bond and Lader, 1972, 1973; Oswald et al, 1971). Some studies have used only the self-rating mood scale (Zealley and Aitken, 1969; Dunleavy and Oswald, 1973), while others have used as many as 16 scales (Norris, 1971; Bond and Lader, 1974).

The ungraded 10 cm line scale has been used in two ways. In the first the word 'normal' was placed at one end of the line and the abnormal adjective was placed at the other end. This method was used in two studies described by Zealley and Aitken (1969). In both studies the 'normal-extreme depression' dimension was used to study the effect of different treatments on depressed patients and imipramine was shown to have a faster speed of action in the alleviation of depression than protriptyline.

The 10 cm line scale has been used more frequently, however, with opposing adjectives at each end of the line. Aitken (1969) described a study in which 90 fighter pilots were asked to indicate how apprehensive they might feel in 10 defined situations. The extremes of the scale were marked "maximal relaxation - maximal panic". In order that the data might approximate the normal distribution an arcsin transformation was used.

In most studies using analogue scales with opposing adjectives at each end the subjects are told that although there are no gradations on the 10 cm line the midpoint approximates normal and they are to place a mark on the line to indicate how they feel in relation to how they normally feel. This approach was used in a study described by Zealley and Aitken (1969). Using the 'happy - depressed' dimension they plotted mood swings in manic-depressive patients at intervals of twelve hours. These swings were rated by nursing staff and by the patients themselves and Zealley and Aitken reported that the patients were better guides to their affective state than were the nurses.

Malpas (1972) used a 16-item rating battery to estimate subjective feelings at intervals after taking

different drugs, including nitrazepam (5 mg and 10 mg), amylobarbitone (100 mg and 200 mg) and placebo. The sixteen dimensions were those grouped by Norris under the categories of mental sedation, physical sedation, calming effects and attitudes (Norris, 1971). The most noticeable effects were that the subjects felt both mentally and physically sedated with both doses of nitrazepam and with the higher dose of amylobarbitone. These differed significantly from placebo after forty minutes. Subjectively the higher doses had the same effect, with a dose-related effect evident for amylobarbitone but not for nitrazepam. Montagu (1971), using the same rating scales, and comparing quinalbarbitone (50 mg and 100 mg) with nitrazepam (3.75 mg and 7.5 mg) found essentially similar results.

Other experiments have been concerned with measuring effects over longer periods of time. Usually subjects sleep between being given the drug and carrying out the tests. In 1951, Goodnow et al investigated the effects of pentobarbitone and found that there was a deterioration in performance in comparison with placebo four hours after the drug was first taken and that this decrement diminished through the day. The subjects thought that the lassitude they felt had not impaired their performance.

In another study subjects were tested on a battery of measures twelve hours after a hypnotic dose of butobarbitone sodium (100 or 200 mg) or nitrazepam (5 or 10 mg) (Bond and Lader, 1972). Four visual analogue scales were used to assess sleep quality and onset, and feeling on wakening and at testing. Both doses of the barbiturate and the higher dose of nitrazepam improved sleep quality and only the lower dose of butobarbitone failed to reduce sleep onset latency. At the time of testing the higher dose of butobarbitone still induced feelings of sleepiness but the effects of nitrazepam had disappeared. A later study used three scales measuring sleep quality and onset and feeling on wakening, and a series of 16 scales to assess mood at the time of testing (Bond and Lader, 1973, 1974). Principal components analysis extracted three major factors from the series of scales, including alertness, contentedness and calmness. Testing was carried out 12, 15 and 18 hours after a hypnotic dose of either butobarbitone (150 mg), flurazepam (15 or 30 mg) or a placebo. Both drugs improved sleep quality, reduced sleep onset latency and increased sleepiness on wakening but statistical significance was not reached on the sleep onset measure after either drug: neither did subjects feel significantly more sleepy on wakening

after having received butobarbitone. The mood rating scales showed that the subjects, having taken the drugs, felt less alert, less contented, especially after the barbiturate, and calmer, especially after flurazepam.

Oswald and his colleagues have used visual analogue rating scales extensively in the assessment of the effects of a large variety of drugs, including amylobarbitone (Lewis, 1969), caffeine (Brezinova, 1974), chlorpromazine (Lewis, 1969a), fenfluramine (Oswald et al, 1971), imipramine (Oswald et al, 1972), nialamide (Akindele et al, 1970), perlapine (Allen and Oswald, 1973), phenelzine (Akindele et al, 1970), and quinalbarbitone (Lewis, 169a) and have found it a useful tool in association with EEG techniques.

CHAPTER 3

METHODOLOGY

The Experimental Design

There are two general models of research procedure - the extensive and the intensive. The former is based on the variation between subjects, with average and percentages relating to the group. The latter method uses fewer subjects and is based on changes in the subject on various occasions and under different conditions.

When examining the effects of repeated drug administration, theoretical and practical implications favour the intensive approach, despite possible objections. Poulton and Freeman (1966) have suggested that the first trial in a series in some way sets a "standard level" of performance for the subject, who then tends to repeat this level on subsequent trials. This may give misleading results in that if one fails to get significant effects from the independent variable one cannot be sure whether there is genuinely no difference between experimental treatments, or whether a real difference has been masked by a carry-over effect from the first trial. In answer to this it can only be said that if the effect of the administration of a drug is masked by such a "carry-over" effect from the first trial then the effect of the drug, in this instance, is slight.

Another possible objection is that when only small numbers of subjects are used it is not realistic to extrapolate these results to the population in general. While this criticism is accepted it must be pointed out that objections about group size can be raised anyway, whether the design be extensive or intensive, since whether one is better entitled to discuss the population at large on the basis of results from forty rather than twenty subjects is arguable.

When the effects on behaviour of a single dose of a drug are compared with behaviour under placebo conditions the merits and demerits of the two approaches may be finely balanced. It has to be suggested, however, that the underlying theoretical basis of the argument is insecure since whichever method or design is employed, the applicability of the single dose experiment to a general population who almost never take single doses of drugs is limited. Invariably, therapeutic drugs are taken several times; at least once a day and usually for at least a week. If one is interested in the long-term effects of a drug during both administration and withdrawal, then the only approach possible, both theoretically and practically, is the intensive one where intra-subject changes over time is the important

factor. Inevitably there will be inter-subject differences and although these are not unimportant a greater emphasis should be placed on whether a drug generally affects subjects' behaviour and whether subjects are more affected at some times than at others. This knowledge can only be achieved by a repeated measures approach.

Subjects

A variety of subjects was used in the studies to be described. Only the characteristics and procedure common to all will be described here, while details relevant only to a particular study will be described in the appropriate section.

All subjects were in good physical and mental health. All were obtained through personal contact; none were recruited through advertising since it has been reported that subjects obtained in this way may not be a representative sample of the general population (Rosenthal, 1965). Rosenthal and Rosnow (1969) reported that volunteers tend to come from higher educational and occupational levels, have a higher need for approval, higher intelligence and lower authoritarianism than non-volunteers. It was also suggested that sociability, arousal seeking, conventionality, birth order and age might be important factors. McLaughlin and Harrison (1973) studied personality differences in volunteering for experiments of four types: general, boring, social or shock. They reported that subjects who volunteered for the general and social experiments were significantly more extraverted, as assessed by use of the Eysenck Personality Inventory, while significantly more high neuroticism-extraverts volunteered for the shock experiment.

It was pointed out to the subjects that, first, all the drugs had been in clinical use; second, throughout the period of the study subjects would have to refrain from taking any drugs, including alcohol, other than the experimental one, and third they would have to maintain reasonably regular bedtimes. Since the studies lasted at least two weeks, subjects were paid for their co-operation according to the length of the study. Before a subject was finally included in a study, he was formally interviewed by Dr I. Oswald in order to assess physical and psychological suitability.

Individuals taking any other drugs, or who had any medical condition which might be adversely affected by the drug, or which might impair the absorption, metabolism or excretion of the drug, were automatically excluded.

Drugs Administration

For the whole of each of the experiments, subjects took a capsule about half an hour before retiring to bed. All studies were divided into three sections. In the first part of the study matched placebo pills were taken in order to allow pill-taking orientation and stabilization and the recording of baseline measures. In the second part of the experiment the pills contained a drug, and in the third part the pills again contained an inert mixture in order to assess both the objective and subjective effects of withdrawal without the subject being aware of this from the appearance of the pills.

Performance Laboratory Procedure

Subjects reported to the laboratory at 0820 hours. Each testing session lasted approximately two hours and was started at 0830, 1230 and 1630 hours. The subjects, therefore, worked a "two hours on - two hours off" schedule between the hours of 0830 and 1830 hours.

The first attendance at the laboratory was devoted to orientation and task practice. No record of progress was kept or used in the analysis of the studies reported here. Emphasis was placed primarily on the subjects understanding of, and familiarization with, the various tasks.

Tasks

Auditory Vigilance: A test of the subjects' ability to remain attentive to monotonous stimuli and to notice and report the infrequent occurrence of a different stimulus. Subjects listened for one hour to a series of 500 m. sec. "bleeps" embedded in 85db white noise. The "bleeps" occurred regularly at 2 second intervals. The subjects' task was to identify and respond to the forty "bleeps" lasting 400 m. sec., which were randomly distributed among the 1760 longer "bleeps", by pressing a button. The subjects' ability to be accurate was assessed in terms of correct identification of target stimuli and in the rate of false

positive identifications. In some of the studies signal detection theory was employed to assess any changes in the detectability of the stimulus (d') and in the subjects' criterion for identification (beta).

Manual dexterity. This is a test of hand-eye co-ordination and fine finger movement. It consists of the subject putting an oblong pellet down a tube using the preferred hand. The pellet fitted the tube only in one orientation. Six one-minute trials were administered at each testing session. The mean score was assessed from the number of pellets inserted on trials 2 - 5 inclusive. Trial 1 was omitted since it was considered a "warm-up" and trial 6 was omitted to counter the "end-spurt" effect (Catalano, 1973).

Digit Symbol Substitution. The subject translated numerals into corresponding symbols. This was an adaptation of the coding sub-test of the Wechsler Adult Intelligence Scale and was considered a high concentration memory task. Two forms were used in the studies reported here. The first lasted ten minutes and used seven symbols. Four sheets, each containing 200 digits, were presented with the code and the subjects were instructed to work as steadily and accurately as possible. Mean score of correct substitutions was the criterion.

The second form, used in the studies in which the first form was not used, lasted five minutes and employed a key comprising 8 symbols. Fifteen equivalent versions were again used in order that carry-over from session to session and possibly week to week should be prevented.

Card-sorting. Packs of 32 cards were sorted onto a perspex board (30 x 22½ cm) which was divided into 8 one cm deep compartments (11 x 7 cm). The cards were shuffled before each trial and the subject lifted the cards singly from the table, turned the card face upwards and sorted according to the trial criterion, using only the preferred hand.

Cards were sorted into 2, 4 or 8 categories on the basis of either compartment position or card detail. The former procedure allowed assessment of motor speed since the subject simply placed the card in one of 2, 4 or 8 categories serially. The latter procedure yielded a sorting time comprising both a motor and a decision component since the subject had not only to move the card but also decide the appropriate category for the card on the basis of the number of dots on the upturned card.

Subjects performed each task twice in a counter-balanced order. Decision or information-processing time was calculated, by category, as the mean sorting

time minus the mean movement time. This task permitted assessment and comparison of a drug's effect on increasingly complex tasks.

Sleep Laboratory Procedure

Subjects reported to the laboratory in the late evening. After having prepared for bed, subjects had silver disc electrodes attached to the frontal bosses and outer canthi for eye movement monitoring. Electrodes in the midline, F_z - C_z - P_z distribution of the international 10/20 system of electrode placement gave an EEG record, while electrodes over the sub-mental muscles were used to record muscle tone.

The subjects retired to a dark, quiet, air-conditioned room and data collection was continuous from approximately 2230 hours to 0730 hours.

Prior to any experimental manipulation, baseline records were obtained. The first two records for every subject were discarded in view of the 'first night effect' (Agnew et al, 1966), which reduces percentage REM sleep and stage 3 - 4 sleep and increased stages 1 - 2 and shifts to stage 1 or wakefulness.

Self-rating Procedure

Subjects were asked to complete visual analogue rating scales on a variety of parameters daily for the duration of each study. Five scales were used in all, but each study included a maximum of four. All studies yielded measures of sleep quality and anxiety while some also included mood and concentration and others morning vitality and concentration but not mood.

Scales were of the 10 cm type. Subjects were told that the midline, which was not marked, approximated their usual feeling on this dimension and that they were to place a mark on the line to indicate how they felt in relation to how they usually felt. The raw score was the distance from the left hand end of the line to the mark in millimetres.

In each study each subject's baseline scores were averaged and each post-baseline score was calculated in terms of its deviation from the baseline mean. The mean of the subjects' baseline means was then calculated and the group mean deviation from the group baseline mean for each day of the study was plotted.

CHAPTER 4

AN EXPERIMENTAL COMPARISON OF THE EFFECTS OF THREE HYPNOTICS

Introduction

The study involved the comparison of the immediate and prolonged effects of two dose levels of mesoridazine (5 mg and 10 mg), two dose levels of Perlapine (5 mg and 10 mg), amylobarbitone (200 mg) and placebo. Withdrawal effects were also studied.

The phenothiazines have been reported as effective tranquillizing and hypnotic agents in both children and adults (Eveloff, 1966). Chlorpromazine and thioridazine seem to have been the two most frequently examined drugs in the phenothiazine family.

Mesoridazine is a sulfoxy side chain derivative of thioridazine which has been reported to be three times as potent (Mena et al, 1966; Prusmack et al, 1966). Clinical trials showed significant improvement in groups of children with behaviour problems (Baldwin et al, 1967) and a study comparing mesoridazine, chlorpromazine and placebo in pre-adolescent children with very severe behaviour problems emphasised the effectiveness of mesoridazine (Kenny et al, 1968).

Mesoridazine has been recommended for use in the active phase of alcohol withdrawal (Conn, 1972), but has been compared unfavourably in this context with haloperidol and hydroxyzine hydrochloride (Palestine,

1973). No assessment has been made, however, of the effects of mesoridazine, at a hypnotic dose level, on performance and sleep in a controlled laboratory setting.

Perlapine (6-(4-Methyl-1-piperazinyl)-morphanthridine) is a dibenzoheteroepine derivative which is structurally related to clozapine (Stille et al, 1973). Stille et al considered the drug's sedative and hypnotic effects to result from a strong inhibitory action on the reticular formation: others have reported the hypnotic effect to be comparable in efficiency to nitrazepam (Ando et al, 1970). Recently reported research on the effects of perlapine on the metabolism of the biogenic amines in the brain of the rat has indicated increased turnover of dopamine in the striatum, noradrenaline in the brain stem, and 5-HT in the brain (Burki et al, 1975). In people, perlapine has been shown to reduce sleep onset latency, decrease intra-sleep restlessness, have little suppressive effect on stages 3 - 4 NREM sleep and cause only slight depression of REM sleep with limited rebound effects on withdrawal (Allen and Oswald, 1973).

Allen (1972) studied the effects of perlapine on the performance of five adults on a battery of tasks soon after waking. Neither a 10 mg nor a 20 mg dose impaired continuous arithmetic, digit symbol

substitution, manual dexterity or card-sorting. On the contrary, some improvement over pre-drug baselines was reported, particularly when the drug was withdrawn. These changes did not, however, reach statistical significance.

Perlapine was included in this study to ascertain whether these results were replicable and whether practice or drug effects were instrumental in the improvement in performance, however slight. This would be determined by comparison with the group which received placebo throughout the study.

A placebo control group was included to ascertain the effects of practice on performance over time. If no control group is included it is difficult to determine whether changes in performance patterns are the result of increasing familiarity with the task or of the different treatment conditions under which the subject performed the task. It may be that performance on a particular task shows improvement over several weeks. Thus improvement may occur markedly under placebo conditions but may also occur to a lesser extent despite the disrupting effect of a drug. If no placebo comparison is available a spurious conclusion of a drug-induced performance potentiation may occur when in fact a comparison of drug and placebo patterns would have underlined a relative decremental effect masked by the practice improvement.

A barbiturate group was included since the prescription of barbiturates as hypnotics has been widely reported and criticised (Dunlop, 1970). Comparison of the effects of barbiturates and non-barbiturate hypnotics has been infrequent and almost all have been single dose studies (Kornetsky et al, 1959; Malpas et al, 1969; Bond and Lader, 1972, 1973; Adams, 1974). Disruptive objective and subjective effects have been reported from both categories of drugs, with the barbiturates tending to have greater disruptive subjective effects (Haider, 1968) and the benzodiazepines, notably nitrazepam, showing clear residual effects on performance (Bond and Lader, 1972).

The effects of a barbiturate, mesoridazine and perlapine on performance have not previously been compared using either a single dose or chronic dose procedure.

Subjects

Subjects for this study were young male volunteers obtained through personal contact. The age range was 20-29 years.

The 36 subjects were divided into six equal groups. Each subject attended the laboratory at

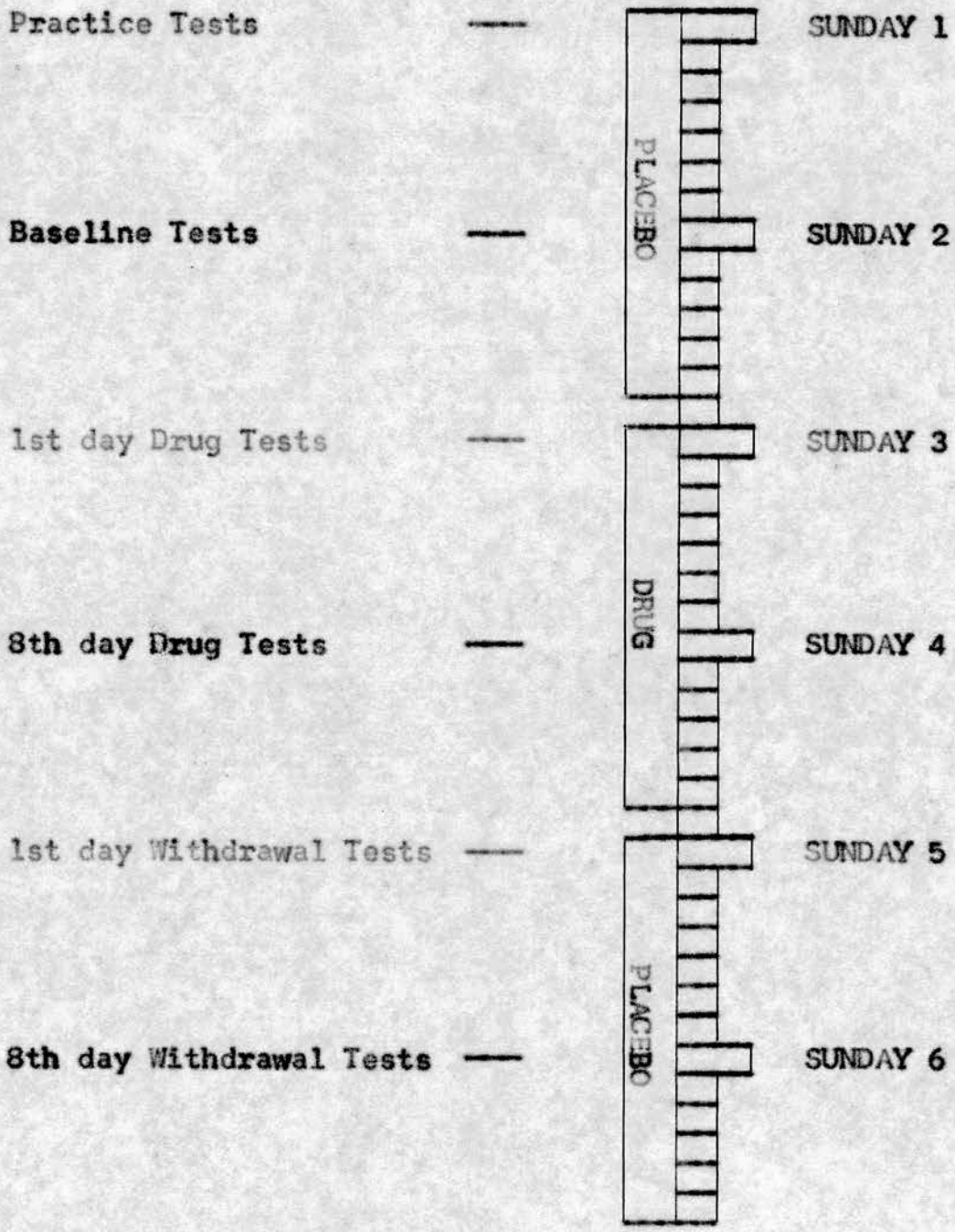
weekly intervals for six weeks. Placebo control capsules were administered for the first, second, fifth and sixth weeks and active drugs' capsules for the third and fourth weeks. The placebo group received placebo capsules for the whole six week period. Capsules were taken on each evening of the study period about 30 minutes before retiring to bed.

Procedure

The regime for each group was as follows:-

Week	1	2	3	4	5	6
Group						
1	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
2	"	"	Mesoridazine	MES (5 mg)	"	"
3	"	"	MES (10 mg)	MES (10 mg)	"	"
4	"	"	Perlapine	PLP (5 mg)	"	"
5	"	"	PLP (10 mg)	PLP (10 mg)	"	"
6	"	"	Amylobarbitone (200mg)	Amylobarbitone (200mg)	"	"

The testing regime for all groups was as follows:-


Practice Tests
Baseline Tests
1st day Drug Tests
8th day Drug Tests
1st day Withdrawal Tests
8th day Withdrawal Tests
PLACEBO
DRUG
PLACEBO
SUNDAY 1
SUNDAY 2
SUNDAY 3
SUNDAY 4
SUNDAY 5
SUNDAY 6

As the experiment spanned nine months, it was considered important to control for any possible seasonal variations in performance. Consequently each set of six subjects attending the laboratory contained one subject from each group.

There were three two-hour testing sessions in each test day. These sessions started at 1030, 1430 and 1830 hours.

Tests

1. Performance Tests
   - 1.1 Auditory vigilance
   - 1.2 Manual dexterity
   - 1.3 Digit-symbol substitution
   - 1.4 Card-sorting.
2. Self-rated assessments

The following parameters were self-rated by the subjects using 10 cm line scales:

- 2.1 Sleep quality
- 2.2 Mood
- 2.3 Anxiety
- 2.4 Concentration.

Results

The methods of analysis employed were:-

(a) Analysis of variance on the raw data.

(b) A transformation of the raw data was calculated in an attempt to allow for the

practice effects evidenced by the placebo group (Table 1) and to show more clearly any drug effects. Hence if a drug had little effect the transformed values of the group would approximate to zero.

For each group the week to week differences were calculated by subtraction from the group's own baseline score. Then a measure of the drug's effect was calculated by subtracting the corresponding placebo group week transformed score from the drug group score. Thus if the placebo group change was -0.5 and the drug group change was -0.75 then the transformed performance decrement effect of the drug is -0.25. Equally if the placebo group change is +2.5 and the drug group change is -2.5 then the decrement in the drug group is -5.0.

(c) For the self-rated assessment scores, the first of which was completed on rising and the others on retiring, the group mean score while on baseline placebo was calculated and equalised to the scale mid-point. The group mean score was then plotted for each subsequent day of drug administration and withdrawal.

TABLE 1

PLACEBO GROUP PERFORMANCE SCORES

Weeks	1 Mean	1 SD	2 Mean	2 SD	3 Mean	3 SD	4 Mean	4 SD	5 Mean	5 SD
Task										
1. Vigilance										
Correct Detection	22.7	± 4.9	21.7	± 2.8	19.4	± 5.2	19.2	± 7.2	20.2	± 7.5
Commission Errors	5.67	± 4.75	3.39	± 3.44	3.17	± 3.32	1.94	± 2.41	0.89	± 0.62
d'	3.128	± 0.426	3.267	± 0.353	3.108	± 0.46	3.145	± 0.475	3.712	± 1.037
(log beta)	4.30	± 1.01	5.04	± 1.04	4.96	± 0.91	5.29	± 0.84	5.81	± 0.49
2. Manual Dexterity	37.79	± 1.66	38.57	± 2.46	40.31	± 1.56	40.96	± 1.96	43.13	± 3.04
3. Digit Symbol Substitution	204.22	± 26.3	206.5	± 18.7	218.8	± 19.8	218.8	± 24.7	229.1	± 24.4
4. Card-sorting										
Decision Level of Complexity 1	12.26		13.45		13.85		13.25		13.19	
2	18.01		18.51		18.67		18.33		18.05	
3	19.35		20.45		20.04		19.03		19.04	
Movement 1	25.66		24.40		22.80		22.78		21.78	
2	21.63		20.68		19.74		19.38		18.73	
3	24.59		22.84		21.97		21.66		20.89	

1. Auditory Vigilance

1.1 Correct detections (Figure 1 Table 2)

Analysis of variance showed significant differences between the groups' overall detection scores ($p < 0.001$) but there was no groups x weeks interaction and so statistical comparison of administration and withdrawal effects was not possible.

Examination of Figure 1, however, indicates a tendency to decreasing detections through the period of the experiment. Transformation of the data in terms of group mean score deviation from placebo group score clarifies the effects of the drugs (Figure 1). Mesoridizine, at both dose levels, appeared to decrease detection on administration although this effect had disappeared by the second drug week. Withdrawal was associated with reduced detections and the decrement, although not large, lasted for at least a week.

The effects of Perlapine were paradoxical. The higher dose showed no initial effect but a delayed beneficial effect on detections with a slight decremental effect on withdrawal. The lower dose level, however, caused a large disruption of detection which had not disappeared by the second withdrawal week.

TABLE 2

VIGILANCE

Correct Detections

Source of Variation	DF	SS	MS	VR
Groups	5	1878.66	375.73	8.436***
Weeks	4	1720.90	430.22	9.659***
Sessions	2	1085.09	542.55	12.181***
Groups Weeks	20	411.77	20.59	0.462
Groups Sessions	10	404.02	40.4	0.907
Weeks Sessions	8	754.67	94.33	2.118*
Groups Weeks Sessions	40	754.00	18.85	0.423
Residual	450	20042.98	44.54	
TOTAL	539	27052.07	50.19	

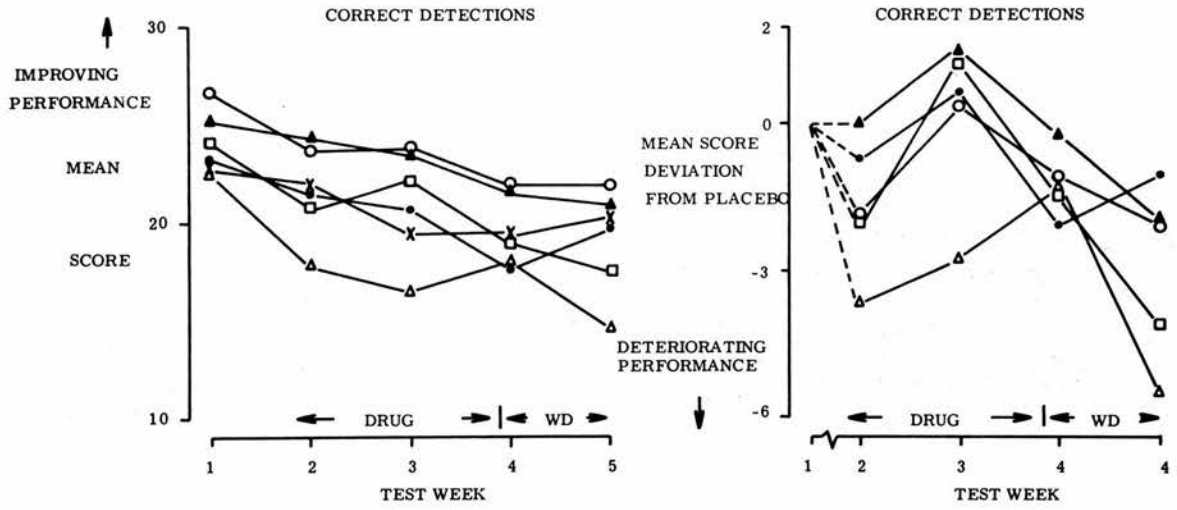
Commission Errors

Groups	5	302.96	60.59	1.736
Weeks	4	1252.39	313.10	8.972***
Sessions	2	71.67	35.84	1.027
Groups Weeks	20	420.47	21.02	0.602
Groups Sessions	10	139.75	13.98	0.400
Weeks Sessions	8	352.57	44.07	1.263
Groups Weeks Sessions	40	512.23	12.81	0.367
Residual	450	15704.47	34.90	
TOTAL	539	18756.52	34.80	

*** $p < 0.001$

** $p < 0.01$

* $p < 0.05$



KEY

X Placebo

O Mesoridazine (5 mg)

● " (10 mg)

△ Perlapine (5 mg)

▲ " (10 mg)

□ Amylobarbitone (200 mg)

FIGURE 1 Vigilance Performance in Young Adults

Initial administration of amylobarbitone suggested a deleterious effect on detection but the largest disruption appeared in the withdrawal period.

1.2 Commission errors (Figure 2 Table 2)

There were no statistically significant differences either between the groups or in the Group x weeks interaction.

At both dose levels mesoridazine had little effect on commission error rate but withdrawal was associated with an increase, especially at the lower drug level.

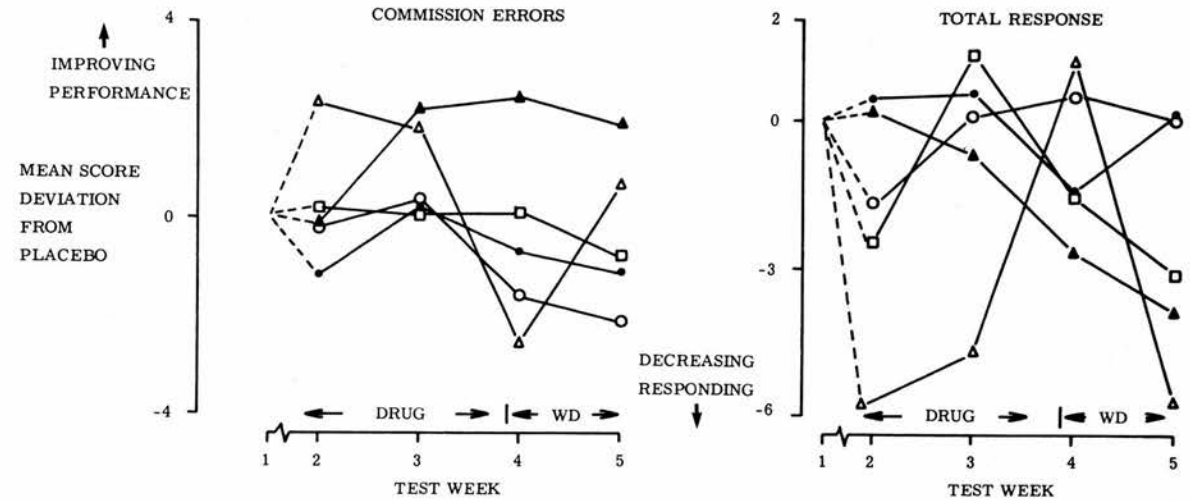
Perlapine again appeared to have paradoxical effects. At the lower dose (5 mg) there was a marked and immediate reduction in false positive detections with a sharp increase immediately upon withdrawal. The larger dose level, on the other hand, showed little effect until the second drug week when there was a reduction in commission error rate which continued through withdrawal.

Amylobarbitone had little effect in administration or withdrawal.

1.3 Response rate (Figure 2)

This measure is obtained by summing correct detection and commission error rate. It gives

FIGURE 2



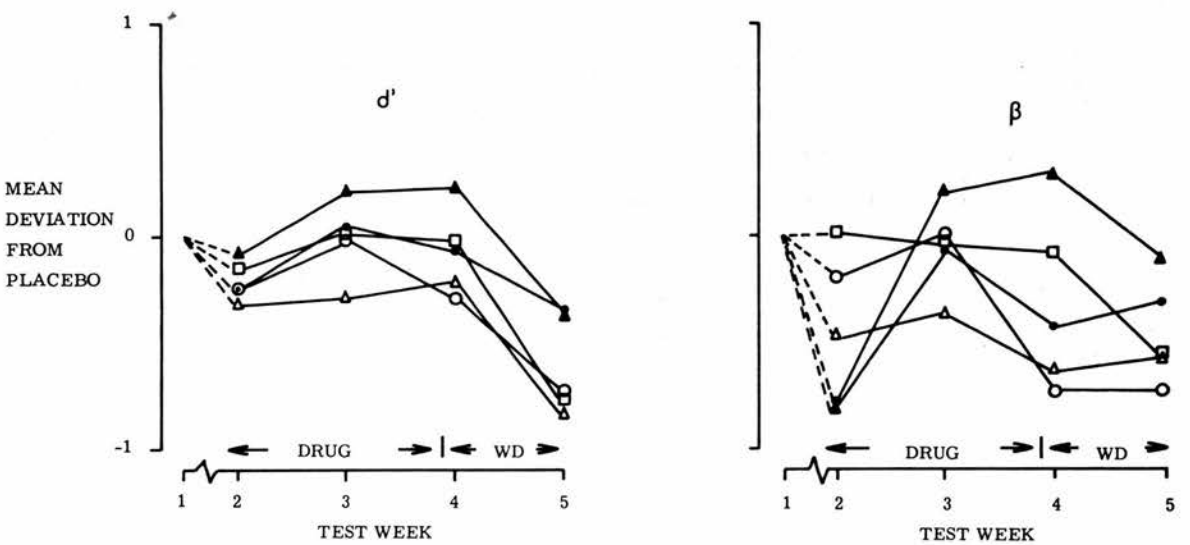


FIGURE 3

an indication of whether a drug had an effect on response rate as a whole rather than on one of the components alone.

There was a statistically significant difference between overall group response rates ($p < 0.001$) but there was not a significant Group x weeks interaction.

Mesoridazine had little effect on overall responding at either dose level. The lower dose level caused a slight initial reduction in responding but this had disappeared by the second drug week. The larger dose level affected response rate only on withdrawal.

Perlapine (10 mg) appeared to have a delayed decremental effect which continued into withdrawal. Perlapine (5 mg), however, caused an immediate and significant decrease in responding which initially disappeared on withdrawal, as a result of the large increase in commission errors.

Amylobarbitone caused a reduction in response rate both on initial administration and on withdrawal.

1.4 d' (Figure 3 Table 3)

d' is a measure of sensitivity derived from the proportion of correct detections to

TABLE 3

VIGILANCE

d'

Source of Variation	DF	SS	MS	VR
Groups	5	10.2282	2.0456	4.585***
Weeks	4	1.2525	0.3131	0.702
Sessions	2	5.9016	2.9508	6.614**
Groups Weeks	20	8.1718	0.4086	0.916
Groups Sessions	10	4.2443	0.4244	0.951
Weeks Sessions	8	6.2953	0.7869	1.764
Groups Weeks Sessions	40	9.5395	0.2385	0.535
Residual	450	200.7565	0.4461	
TOTAL	539	246.3896	0.4571	

(Beta)

Groups	5	20.656	4.131	2.013
Weeks	4	75.966	18.991	9.254***
Sessions	2	1.059	0.530	0.258
Groups Weeks	20	26.112	1.306	0.636
Groups Sessions	10	11.029	1.103	0.537
Weeks Sessions	8	10.184	1.273	0.620
Groups Weeks Sessions	40	24.987	0.625	0.304
Residual	450	923.545	2.052	
TOTAL	539	1093.539	2.029	

commission errors. Statistical analysis showed significant differences between the overall group ($p < 0.001$) but there was no significant interaction effect.

The slight initial drop in d' in both mesoridazine groups reappeared on withdrawal. This was a result of the gradual decline in correct detection with a concomitant rise in commission errors.

The lower dose level of Perlapine reduced d' and this reduction was sustained into withdrawal. The larger dose in contrast increased d' in relation to placebo, while amylobarbitone showed little effect.

1.5 β (beta) (Figure 3 Table 3)

Beta is a measure of change in criterion used by the subject to identify target stimuli.

There were no statistically significant differences between the groups. Initial drug administration reduced beta in all non-barbiturate groups but this had disappeared by the second drug test day in all except the Perlapine low dose group. Beta was again reduced on withdrawal.

Amylobarbitone had little effect on beta.

2. Manual dexterity (Figure 4 Table 4)

Analysis of variance showed significant differences between the groups on overall mean total scores ($p < 0.001$), as well as an improvement in overall week scores and through the day. There was no significant groups x weeks interaction.

Mesoridazine had little effect on the performance of this task except on withdrawal of the lower dose. Perlapine (5 mg) affected dexterity only on withdrawal while the higher dose level improved performances.

Amylobarbitone was associated with greatest disruption in late withdrawal.

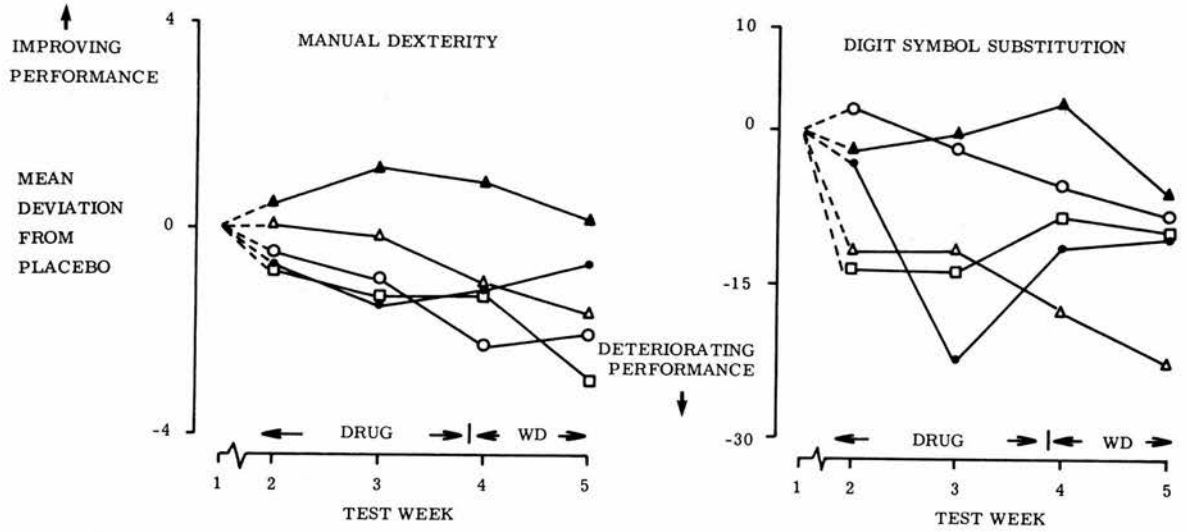
3. Digit Symbol Substitution (Figure 4 Table 4)

There were significant differences between group mean scores ($p < 0.001$) and between week mean scores ($p < 0.001$) but there was not a groups x weeks interaction.

Mesoridazine (5 mg) caused a deterioration of digit symbol substitution only on withdrawal while mesoridazine (10 mg) caused a cumulative deterioration which declined on withdrawal.

Perlapine (5 mg) had an immediate deleterious effect which increased on withdrawal while the higher dose had little effect. Amylobarbitone caused the largest onto-drug disruption. Withdrawal reduced this effect but performance was still poor in comparison with placebo in the second withdrawal week.

FIGURE 4



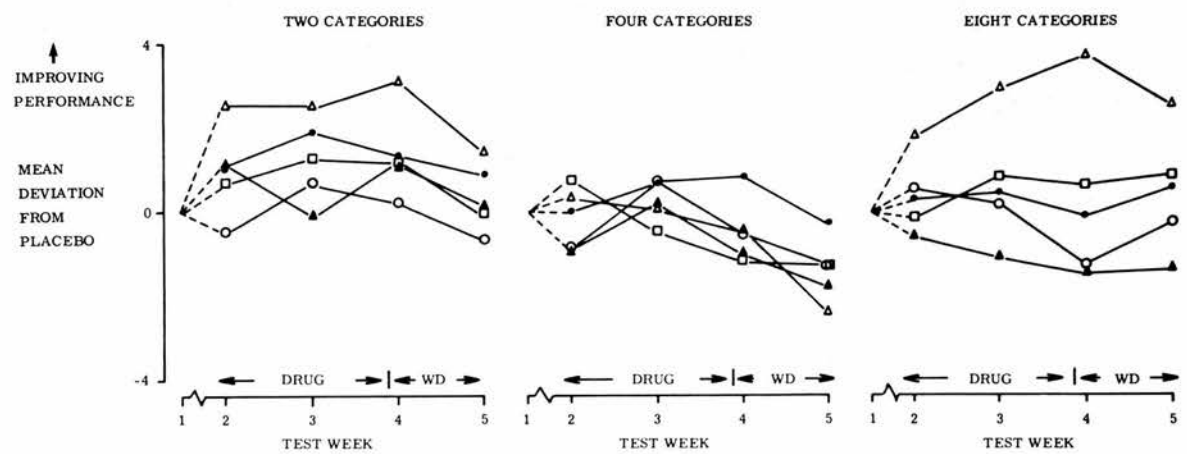


FIGURE 5

TABLE 4

Manual Dexterity

Source of Variation	DF	SS	MS	VR
Groups	5	731.67	146.33	10.016***
Weeks	4	1158.44	289.61	19.823***
Sessions	2	655.71	327.85	22.441***
Groups Weeks	20	148.25	7.41	0.507
Groups Sessions	10	39.05	3.91	0.267
Weeks Sessions	8	21.22	2.65	0.182
Groups Weeks Sessions	40	88.71	2.22	0.152
Residual	450	6574.37	14.61	
TOTAL	539	9417.37		

Digit Symbol Substitution

Groups	5	30026.4	6005.3	9.207***
Weeks	4	20865.1	5216.3	7.997***
Sessions	2	2420.2	1210.1	1.855
Groups Weeks	20	10531.7	526.6	0.807
Groups Sessions	10	4299.3	429.9	0.659
Weeks Sessions	8	3310.5	413.8	0.634
Groups Weeks Sessions	40	4740.7	118.5	0.182
Residual	450	293524.8	652.3	
TOTAL	539	369718.5		

TABLE 5

CARD-SORTING: DECISION TIME

Source of Variation	DF	SS	MS	VR
Groups	5	853.31	170.66	14.968***
Weeks	4	89.60	22.40	1.965
Sessions	2	30.68	15.34	1.345
Category	2	14515.68	7257.84	636.549***
Groups Weeks	20	187.11	9.36	0.821
Groups Sessions	10	23.62	2.36	0.207
Weeks Sessions	8	29.17	3.65	0.320
Groups Category	10	129.35	12.94	1.134
Weeks Category	8	162.19	20.27	1.778
Sessions Category	4	114.37	28.59	2.508*
Groups Weeks Sessions	40	282.26	7.06	0.619
Groups Weeks Category	40	234.98	5.87	0.515
Groups Sessions Category	20	49.49	2.47	0.217
Weeks Sessions Category	16	159.68	9.98	0.875
Groups Weeks Sessions Category	80	393.25	4.92	0.431
Residual	1350	15392.50	11.40	
TOTAL	1619	32647.21		

4. Card-sorting (Figure 5 Table 5)

There were significant inter-group overall mean differences ($p < 0.001$). Mesoridazine and amylobarbitone had little effect on card-sorting, even at the eight category level.

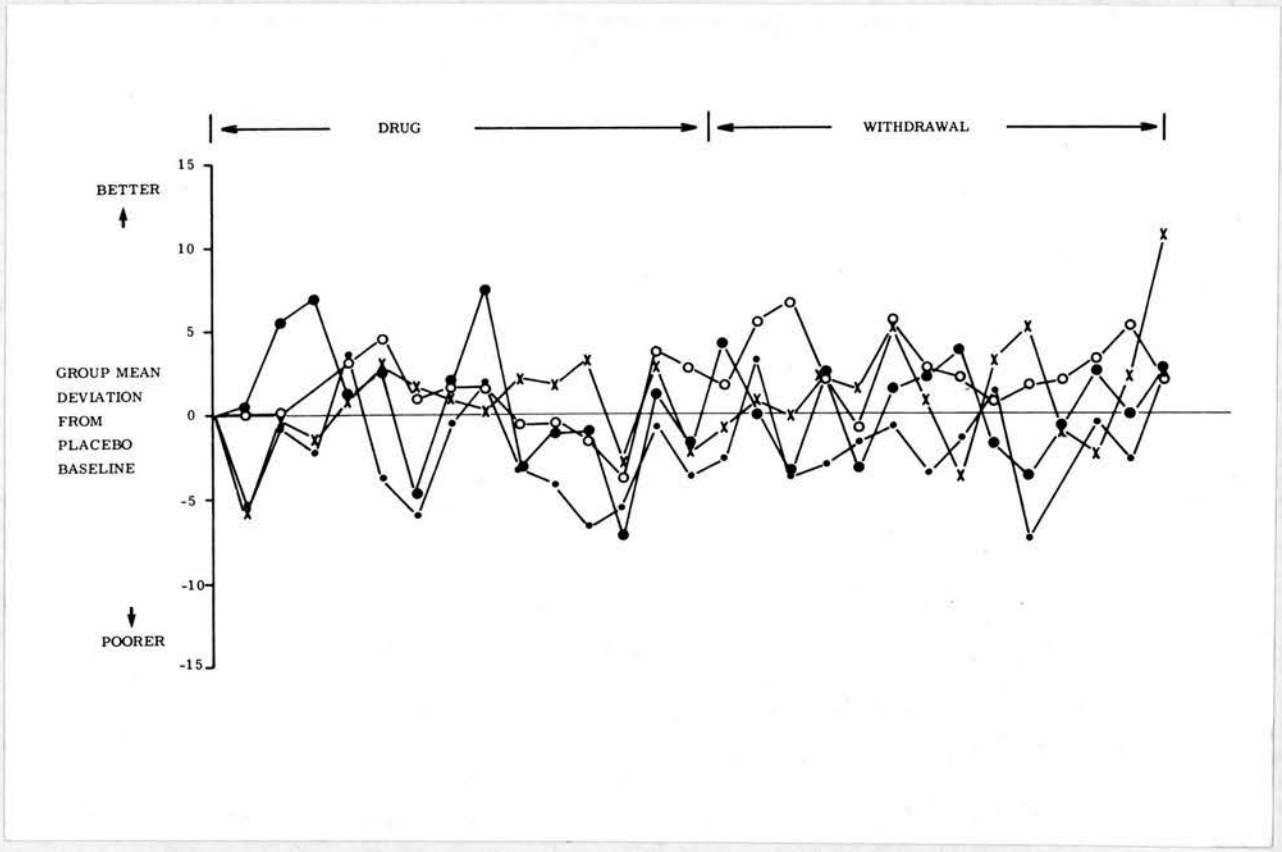
The lower dose of Perlapine enhanced sorting speed at the simple and complex levels but not at the intermediate level, while the higher dose level caused relatively greater decrement with increasing task complexity.

5. Self-rated feeling states (Figures 6-11)

Subjective feeling scales were completed daily by all subjects.

Mesoridazine did not appear to affect subjective feelings to any great extent. At the lower dose level there was an initial beneficial effect on sleep quality and an impairment in concentration on withdrawal. At the higher dose there was an increase in anxiety which lasted until withdrawal.

Perlapine, on the other hand, produced marked initial deleterious effects on all four measures with a subsequent improvement in sleep quality at the 5 mg level. The other three measures at the lower dose level and all measures at the 10 mg level continued to show marked fluctuations which only diminished on withdrawal.



KEY

X Quality of sleep

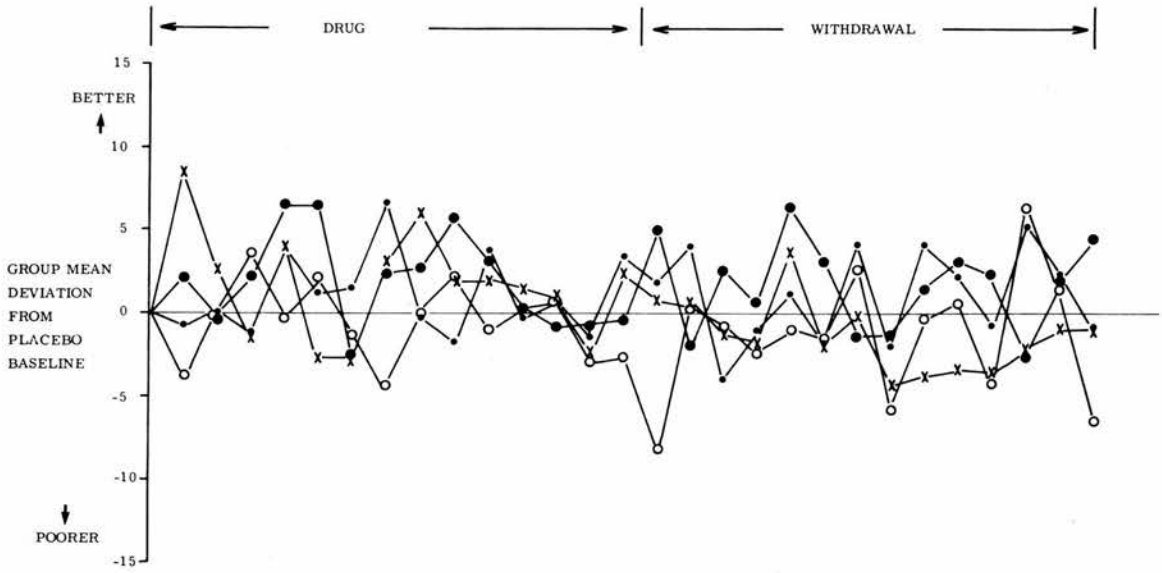
● Anxiety

0 Concentration

• Mood

FIGURE 6 Self-rated feeling states: placebo group

FIGURE 7 Self-rated feeling states: mesoridazine (5 mg)



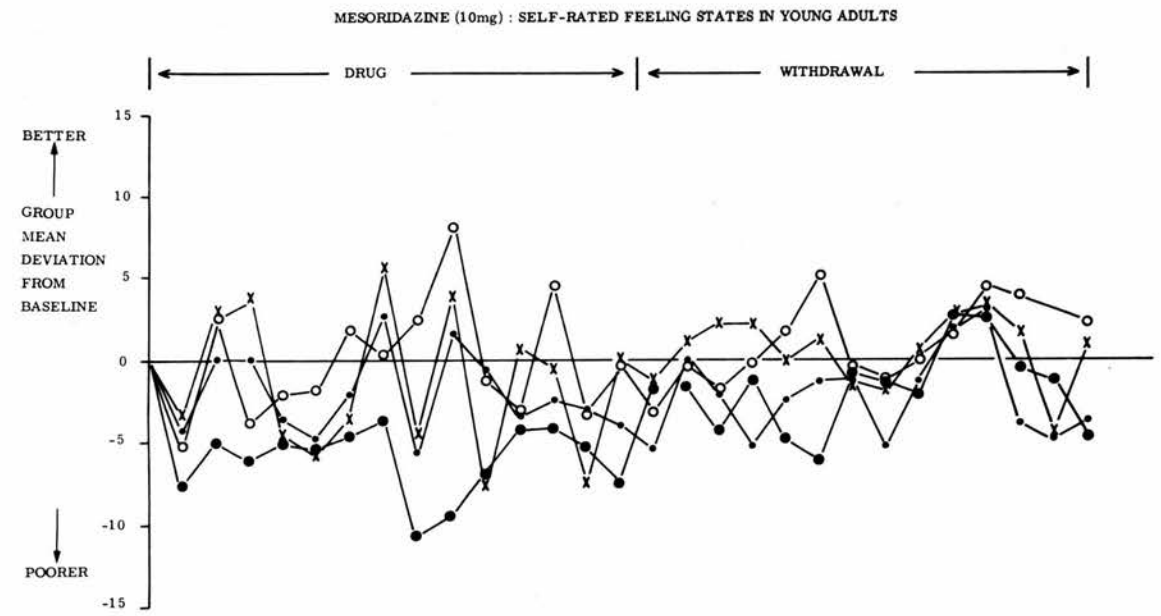
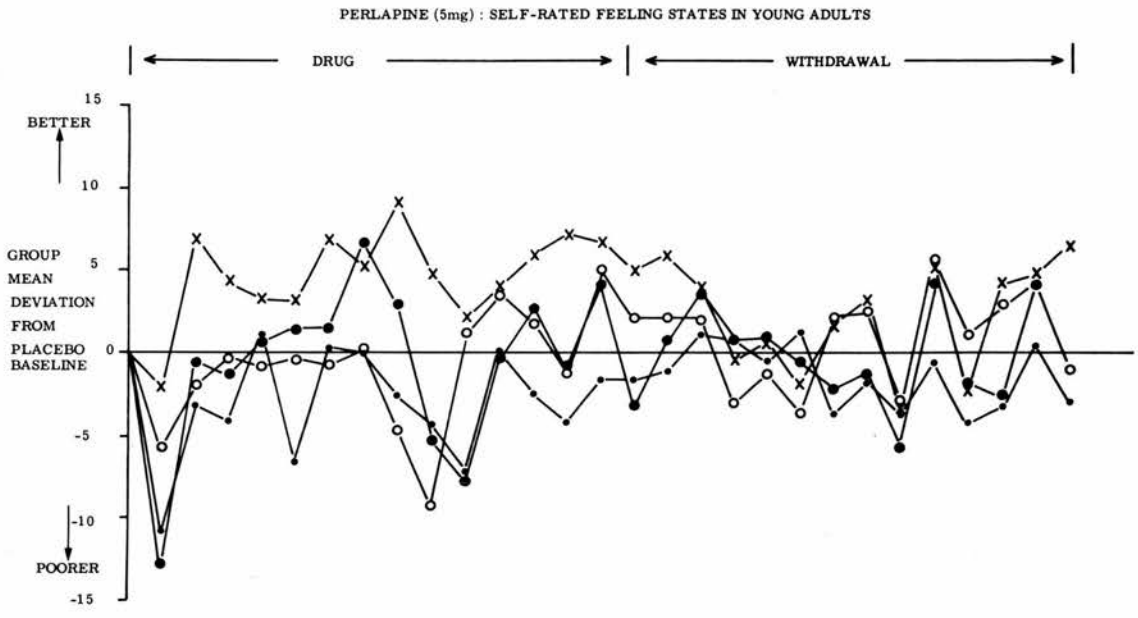


FIGURE 8

FIGURE 9



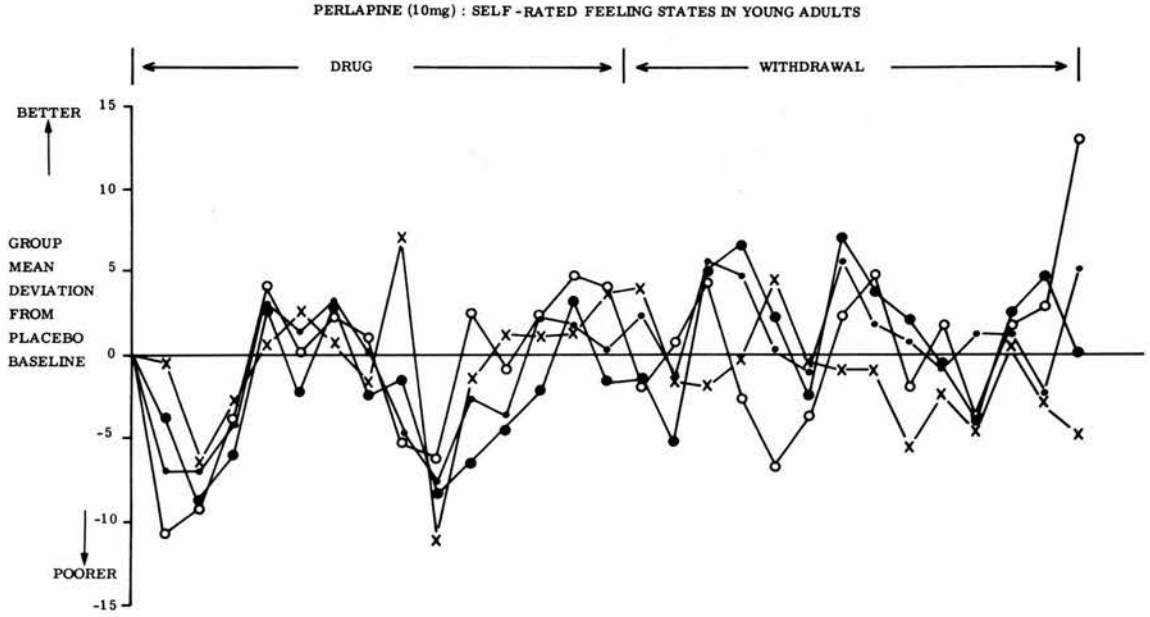


FIGURE 10

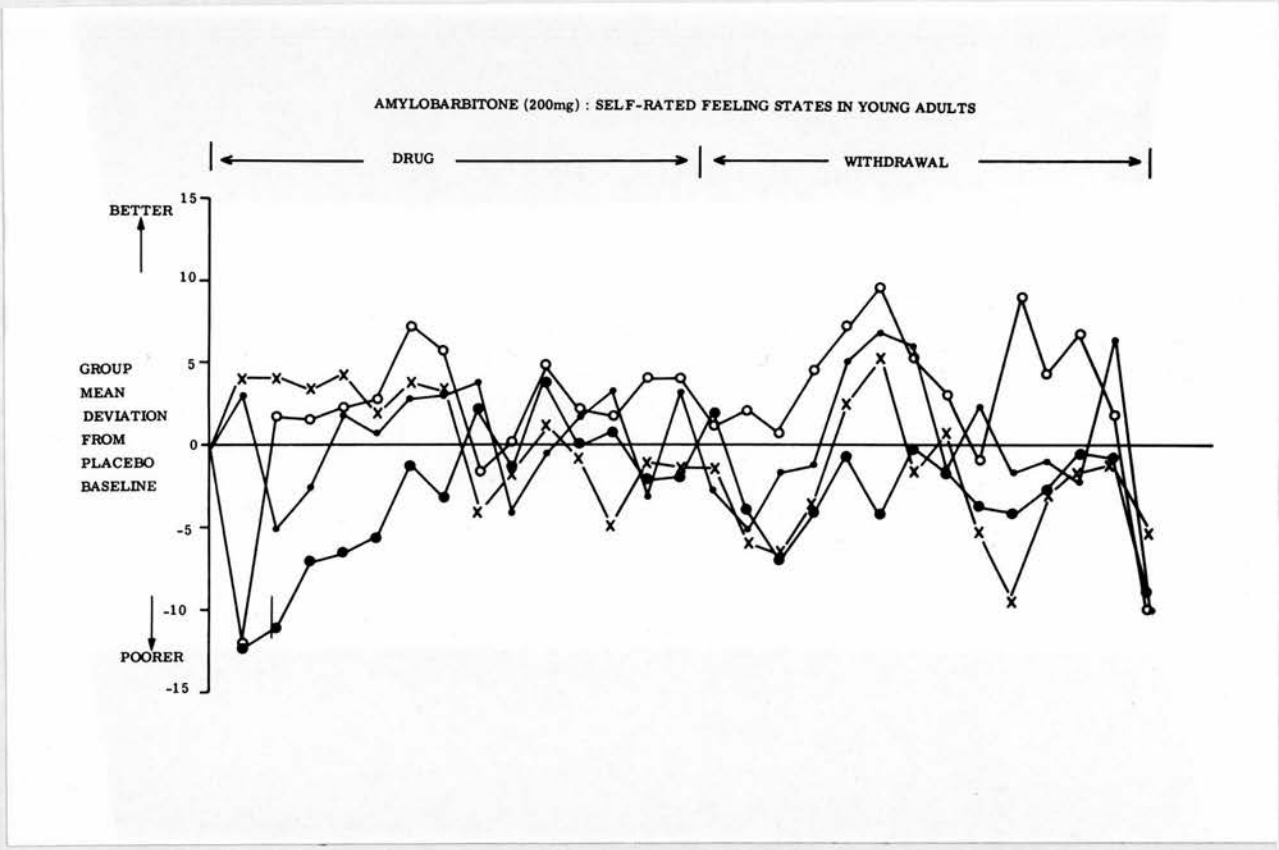

AMYLOBARBITONE (200mg) : SELF-RATED FEELING STATES IN YOUNG ADULTS
DRUG
WITHDRAWAL
BETTER
POORER
GROUP MEAN DEVIATION FROM PLACEBO BASELINE
15
10
5
0
-5
-10
-15

FIGURE 11

Amylobarbitone produced the greatest initial subjective disruption but this had disappeared by the second drug week and although there was a slight depression on some of the measures on withdrawal, this was not marked. There was, however, an increase in day to day variability.

Discussion

There were no significant groups x weeks interactions in the analysis of variance but there were significant group overall mean differences on almost all the measures. Although this does not allow comparisons following either the Tukey or the Scheffe procedure, it was clear that all the drugs to a greater or lesser extent altered performance on one aspect or another of the test battery.

Generally Perlapine appeared to affect performance and self-rated feelings more than either mesoridazine or amylobarbitone and the effects of Perlapine were not clearly related to dose level. Certainly in several of the tests the lower dose appeared to cause greater disruption both on administration and withdrawal, but this differentiation was not so noticeable in the self-rated feeling data.

Allen (1972) compared Perlapine (10 mg and 200 mg) with flunidazepam (2 mg and 4 mg) on a variety of tests and concluded that Perlapine had no deleterious effects

on performance and indeed showed some improvement over pre-drug baselines during both administration and withdrawal. Since comparison of results is restricted to the 10mg level of Perlapine the conclusion drawn in this study with regard to the administration period is similar. At this dose level the drug appeared to have no significant detrimental effect on performance, and indeed on manual dexterity and vigilance. Perlapine (10 mg) appeared slightly to enhance performance although this effect tended to disappear on withdrawal. Unfortunately, Allen (1972) and Allen and Oswald (1973) did not assess the effects of Perlapine on self-rated feelings and it is not possible to compare the degree of subjective effects experienced by the subjects. The comparison would have been useful in relation to both the marked subjective disruption noticed in the 10 mg Perlapine group in this study despite the lack of effect on objective tests, and also to attempts to interpret the apparently paradoxical dose level effects of this drug.

Perlapine (5 mg) appeared to have some effect on performance. Vigilance was affected with a reduction in responding with the administration of the drug and an increase, especially of false positive identifications, on its withdrawal. Card-sorting, on the other hand, was beneficially affected, especially at the simple and complex levels.

The sustained deleterious effect of Perlapine (5 mg) on digit symbol substitution and the slight effects on both manual dexterity and card-sorting do little to clarify the question of whether the effect of Perlapine is principally on the cognitive or motor aspect of performance. It was clear, however, that there was disruption of subjective feeling at the lower dose level as well as at the 10 mg level (Figure 9). Although sleep quality was generally improved until the drug was withdrawn, there were disruptions of mood, anxiety and concentration which continued into the second drug week. These disruptions were not as considerable as those induced by the larger dose, however, and it may have been that the effects at the lower dose level were not substantial or disorienting enough for the subjects to be aware of them. If this were so, then the disruption of performance might be indicative of the drug's true effect while the subjects given Perlapine (10 mg) were sufficiently disrupted to be aware of their impairment and consequently the performance tests measured this attempt to overcome deleterious effects of the drug by way of extra compensatory effort.

In contrast to the effects of both doses of Perlapine, mesoridazine had little effect on objective

performance. Any slight initial effects were not sustained except at the higher dose level in the digit symbol substitution task. At the lower dose level subjective effects were negligible while at the higher dose level there was a transitory initial effect on three parameters and a continued effect only on anxiety.

Amylobarbitone did not have noticeably disruptive effects on performance. Bond and Lader (1972) noted that a barbiturate (butobarbitone 100 mg) caused less disruption of performance than did nitrazepam (5 mg and 10 mg), but pointed out that butobarbitone (200 mg) also caused disruption. In this study, amylobarbitone caused less disruption than did Perlapine, especially in comparison with the lower dose level. However, there was little difference between the effects of mesoridazine, at either dose level, and amylobarbitone, especially when withdrawn.

There were notable differences between the effects of mesoridazine and amylobarbitone on subjective feelings. Amylobarbitone caused marked initial disruption, which in the case of anxiety levels was sustained, and there was also an effect on withdrawal. Haider (1968) also reported a greater disruption with a barbiturate (amylobarbitone 200 mg) than with a non-barbiturate (nitrazepam 10 mg).

The degree of disruption induced by amylobarbitone was similar to that caused by the higher dose of Perlapine and greater than that caused by the lower dose of Perlapine and both doses of mesoridazine. A possible explanation for the paradoxical results of the two dose levels of Perlapine has been outlined and it may be that a similar situation occurred with the amylobarbitone group. Such an explanation could not be acceptable without a replication study and the use of tests which do not allow the true effects of a drug to be hidden by compensatory effort.

This study underlines the complexity of possible drug effects. Thus the higher dose of mesoridazine had an initially deleterious effect on vigilance, manual dexterity and digit symbol substitution but did not affect card-sorting. Continued administration was associated with an improvement in vigilance and card-sorting which might have indicated tolerance if these were the only tests used, but both manual dexterity and digit symbol substitution showed progressive performance deterioration which was reduced with withdrawal. On the card-sorting task, however, withdrawal was associated with progressive deterioration on the simple and intermediate but not the complex levels, and in the vigilance correct detections and commission errors both increased.

The difficulty of interpretation of such a complexity of results is obvious. It does reinforce, however, the importance of the use of a battery of tests sampling different skills in our behavioural repertoire when assessing a drug's effects and it also challenges the validity of single dose studies assessing effects for only 24 hours after a drug's administration.

Single dose studies have yielded a lot of information about the initial effects of drugs and the residual effects as the drugs are excreted from the body. Several researchers have shown that hypnotic drugs in single doses may affect behavioural performance and physiological function for up to 18 hours (Kornetsky et al, 1959; Malpas et al, 1970). Pharmacokinetic studies have shown that even after the effects on performance tests have disappeared the drug is still active and the rate of disappearance is slow. Balasubramaniam et al, (1970) showed that for amylobarbitone the decay of serum concentration lasted over 48 hours and appeared as a double exponential function with the first component having a half-life of 0.6 hours and the second a mean half-life of 21 hours.

Other single dose studies have compared different drugs under similar conditions and have examined both physiological and psychological functions (Bond and

Lader, 1972, 1973; Malpas et al, 1970) and in at least one instance biochemical function as well (Bond and Lader, 1972).

Several studies have examined the relationship between prognosis and plasma levels in patients and underlined the importance of the rate of absorption and excretion of a drug and its metabolites for symptom control and improvement (Klein et al, 1974; Koch and Rohling, 1974; Mackay and Healey, 1974). The use of such a detailed approach can do much to clarify the real effects of a drug and to separate out the effects of artefacts in a way not possible with examination solely of psychological function.

It is regrettable that such a multifunction examination has not been possible in these studies. The use of a chronic administration design is much more relevant to the practical therapeutic drug-taking procedure and the use of EEG and bioassay techniques might have clarified several results which can only be described as paradoxical and explained tentatively when only the psychological function data is available.

It was stated in the introduction that a placebo group was included in this study in order to assess the effects of practice on the tests employed. On several of the tests such effects

were apparent and in these cases improvement occurred on each of the five test weeks (Table 1). Both manual dexterity and digit symbol substitution showed clear practice improvement despite the devotion of one whole day to orientation at the beginning of the study. There was an improvement in vigilance performance as measured by d', and commission errors but there was a reduction in correct detections as well. Practice appeared to have little effect on card-sorting in either its motor or cognitive component.

Examination of the self-rated feeling state data of the placebo group is also instructive. The spontaneous fluctuations that occur over a long period of time are clear. These fluctuations occur naturally, and not in response to a drug, as a result of day-to-day occurrences during work and social life and could be considered as "noise". As such it is important for comparison with groups receiving drugs since deflections, for better or worse, might be interpreted as drug effects when in fact the deviation does not exceed the normal.

The value of the inclusion of the placebo group is clear. Were it not for the inclusion of the placebo group conclusions about the lack of effect or even slightly potentiating effects of some of the drugs might have been drawn. Awareness of the effect of

practice on several of these tasks allows for transformation of the raw data to a form in which it is clear that there are effects both initially and on withdrawal and to the formulation of the conclusion that although in some instances a drug may have little effect on psychomotor performance there are occasions when an expected improvement may be inhibited until tolerance develops or even until the drug has been withdrawn.

CHAPTER 5

DISCUSSION OF TASK AND SUBJECT PARAMETERS IN RELATION TO THE CLINICAL USE OF DRUGS

There are drawbacks in the type of subjects that have generally been used in experimental studies. For practical reasons mainly men are used, the vast majority of whom are young. When we look, however, at the potential market for the drugs' therapeutic use we find that the largest proportion are middle-aged, or older, and female. Ideally then, we would use such people and patients suffering from neurotic or psychiatric illness in our studies, but in the former it is difficult to get a sufficient number to participate, and in the latter to withdraw patients' medications and substitute a drug of unproven beneficial value is unethical, as well as unpractical.

At a theoretical level, also, our choice of subjects is unsatisfactory. The inverted U theory suggests that anxiety or arousal enhances performance up to an unspecifiable optimal point beyond which performance is hindered. If our anxious subject is beyond the optimal point then the administration of an anxiolytic might improve performance, where the same dose of anxiolytic in a subject whose anxiety level is not beyond the optimal point will result in a performance decrement. It is difficult, therefore, to extrapolate from data from normals to people with neurotic problems.

Given that we are attempting to study how well a drug enables a subject to cope with stress, without deleterious side effects, we are faced with several ways in which we can modify our approach to mimic the clinical situation more closely.

First, we can retain the tasks and the young male subjects but vary the amount of stress under which our subjects work. Second, we can again use the same subjects but change the tasks we require them to perform, and third, we can use the same or new tasks but with a more appropriate type of subject.

In the first category, there are a wide variety of ways in which stress can be varied.

Noise has been widely used as a distractor and stressor. Broadbent in his book 'Decision and Stress' (1971) writes extensively on its advantages and failings. In general 95db appears to be the critical level above which subjects find it difficult to cope. The major problem is habituation but if noise and quiet are alternated then habituation is largely prevented. The degree of difference between the noise level and the quiet appears to be critical.

Such a method could be additionally refined by building in a system of incentives to improved performance by setting targets at, or slightly better than, the subjects' ability, with or without reduction

of the noise level as a reward.

An incentive system without the use of noise could be based on financial reward or penalty. The problem with incentive systems and noise stressing, however, is that each subject has to have a tailor-made schedule because while performance patterns between subjects may be similar and intra-subject variance very small, actual levels of performance and sensitivity may vary greatly. It would be virtually impossible to determine and maintain such systems while testing several subjects simultaneously, and moreover, it would be difficult to recreate exactly similar levels of stress on each of the several times the subject attends the laboratory.

Another way of studying stress may be in terms of experimenter and interaction effects. Several researchers have looked at the effects of friendly or serious experimenters on subjects. The problems of assessing and controlling conditions are many and interpretation of results can be difficult. For example Starkweather (1959) looked at the effect of giving different combinations of drugs to people working in pairs on a trail-marking task. He suggested that a subject given a depressant would be slower than a subject given a stimulant, and that a pair given depressants would be slower than pairs in which one subject was given a stimulant and one a

depressant, or in which both were given a stimulant. His results showed paradoxically that the pairs receiving depressants performed significantly better than the pairs receiving stimulants.

A second way of modifying our experimental approach is to introduce tasks which in themselves have a stressful or distracting component. There are a variety of tasks which come into this category.

The choice reaction-time test can be used either as an experimenter-paced or subject-paced task with a variable amount of monitoring and response-requirement complexity. The divided attention task is a variation on the same theme. Moskowitz and DePry (1968) used such a task in studies on the effect of alcohol, testing the hypothesis that performance decrement would be greater in the drug condition in the divided attention task than it would in a vigilance task. Their results supported the hypothesis.

The advantage of using a divided attention task is that it may closely resemble the conditions that people have to face every day. A special type of divided attention task is the driving simulator. Most research has studied the effects of alcohol but other drugs have also been tested (Drew, Colquhoun and Long, 1958; Rafaelsen et al, 1973).

Another divided attention task has been developed by Alluisi (1972) in an attempt to study a more realistic work situation. He has used a Multiple Task Test Performance Battery which includes three watchkeeping and three active tasks. The three watchkeeping tasks have to be continuously monitored while one of the active tasks is performed. Alluisi has been specifically interested in endurance limits and the effects of illness and has not considered drug effects in any consistent way.

In the critical tracking task the subject attempts to track accurately a moving target. The complexity of the tracking pattern and the difficulty of control of the subjects' styles can be varied during the testing session without the subject being fully aware of this. The criteria are how many errors the subject makes and for how long he persists at the task.

So far I have considered only modifications of the experimental procedure but a major contribution in the attempt to obtain a realistic idea of a drug's side-effects must include the use of appropriate subjects. A review of the psychopharmacological literature will show that whatever drug has been tested the subjects almost invariably comprise healthy young male university students or naval ratings.

McNair (1973) reports 95% of subjects came into this category. These types of subjects are easy to obtain since some undergraduates have to provide a number of hours as a subject as part of their course requirements, and others are placed in a situation where it is difficult to contract-out.

It is suggested that it is more relevant to use subjects who are similar in age and type to those people who are likely to be the drug's potential or actual therapeutic market. In the case of sleeping pills and anxiolytics, this market is largely middle-aged and female. Even when such a subject sample is used it can still only be suggested that the results obtained may be typical of the population at large. A more positive statement is not possible since even in an older age group the peculiarities of the volunteers may preclude generalization to the population as a whole (McLauchlin and Noble, 1973).

There is ample evidence from a variety of researchers that the performance patterns of young people can be quite different from those of older people. Examples are given below.

It is generally agreed that decreasing speed in responding to stimuli is a normal part of ageing. There are, however, substantial individual variations (Maddox and Douglass, 1974), and some older people are

capable of responding even faster than some younger people. At Duke University, Botwinick, with various collaborators, has been studying reaction time in older people both longitudinally and in comparison with younger people. Botwinick and Thompson (1966) analysed reaction time into two components, pre-motor time and motor time and found that the elderly were slower in both parts. Other researchers have found longer latencies only in motor-time (Waugh, Fozard, Talland and Erwin, 1973). A second study by Botwinick showed that the elderly improved their reaction time with practice under certain conditions, while younger subjects did not (Botwinick and Thompson, 1967). Two further studies showed that there are greater individual differences along the elderly and that some of the slower reactions may be related to lack of exercise (Botwinick and Thompson, 1968a, 1968b). A later study indicated also that the intensity of the stimulus and the preparatory interval can be important (Botwinick and Storandt, 1973).

In the processing of non-verbal stimuli older women exhibit a marked lack of proficiency (Elias and Kinsbourne, 1974) while both sexes may show a reduced efficiency of reasoning performance and memory compared with younger subjects (Brinley, Jovick and McLaughlin, 1974). Rimoldi and Vander Woude (1969) have published

data indicating first an increment and later a decrement in problem-solving ability with increasing age while Schaie and Labouvie (1974) have, on the other hand, challenged the assumption of generalised cognitive deficit in the elderly.

Davies and Griew (1965) reviewing the literature on age differences in vigilance performance concluded that age was not a significant factor.

Davies and Tune (1969) suggested that no difference in either detection or commission errors' rate between younger and older adults was found by York (1962), Griew and Davies (1962) and Davies and Griew (1963). In the latter two papers it had been hypothesised that if a difference in performance existed then it was in the reception and organization of the incoming sensory data that the effects would be most likely to be apparent. In their first experiment Griew and Davies required subjects to listen to digits for 40 minutes. Three consecutive odd digits were the target. Older subjects detected significantly fewer signals than did younger subjects while there was no difference between commission error rates. This difference was attributed to short term memory effects and not to vigilance decrement. In the second experiment a written list was checked against a spoken list. No significant age differences occurred. The task variables were again radically changed, but still no consistent age differences were found.

Despite these results there has been evidence over the last ten years that age differences in vigilance do exist. Surwillo and Quilter (1964), using the Mackworth Clock Test, found that an older group of subjects detected an average 64.4% of signals compared with 72.0% by a younger group. The performance pattern was similar until the last quarter when the younger subjects improved while the older subjects continued to deteriorate.

Harkins et al (1974) found that young subjects made fewer omission and commission errors and Tune (1966a,b), requiring subjects to listen to digits presented at the rate of one per second, found that whereas younger and older subjects made approximately the same number of correct detections, the older subjects made many more errors of commission. The argument advanced to account for this finding was that older people were insuring themselves against failure to detect wanted events by reporting many events as wanted, even though they were not. In terms of signal detection-theory analysis the results demonstrated a reduction in detection efficiency with age because the older subjects adopted a less cautious criterion. These results have also been interpreted as showing that older subjects may be underaroused and, therefore, make more responses in order to keep up arousal in a monotonous situation.

Supportive data for under-arousal being a causal factor has been produced by other researchers (Sanford and Maule, 1971; Neal and Pearson, 1966). In the latter study, using a similar auditory vigilance task, they found that giving subjects a depressant drug, and thus presumably lowering their arousal level, resulted in a significantly higher proportion of false positive responses. Furthermore, Davies and Krkovic (1965) showed a decrease in EEG alpha activity in a 90-minute task concomitant with a decrease in vigilance efficiency.

There is ample evidence that older people show less confidence and greater caution (Botwinick, 1966), especially in novel situations (Craik, 1969). Wallach and Kogan (1961) found that aspects of decision-making changed with age in the direction of reduced confidence in judgements and in greater "deterrence of failure". A study by Botwinick, Brinley and Robbin (1958) showed that older subjects generally preferred to gather more information from a display before committing themselves to a response, and Welford (1961) showed that older people require relatively more data for confidence than for accuracy.

Initially the diversity of findings is hard to reconcile but it appears that in tasks where decisions are experimenter-paced, older subjects seem to perform

similarly to younger subjects in correct detection but make many more false-positive detections. This may be related to arousal levels or simply to the "deterrence of failure" strategy, i.e. increases in response rate raise the probability of correct detections as well as increasing false alarms. Support for the deterrence strategy comes from subject-paced studies where older subjects generally gather more information than they need before committing themselves to a decision.

It would appear then that there are differences in response patterns and levels between subjects of different ages. The extent of these differences would seem to indicate that the most suitable method of assessment of the effects of drugs which are most likely to be prescribed to an older age group is not to make the testing procedure more complicated but to use subjects of that age group. Although it is more difficult to obtain such volunteers, the greater extrapolative validity may well justify the endeavour.

CHAPTER 6

A STUDY OF THE EFFECTS OF MESORIDAZINE ON SLEEP AND PERFORMANCE

Introduction

Mesoridazine, a derivative of thioridazine, has been suggested to be useful, in comparison with chlorpromazine, in the control of severe behaviour problems in pre-adolescent children (Baldwin et al, 1967; Kenny et al, 1968) and to be less successful than haloperidol in the control of problems occurring in the acute phase of alcohol withdrawal (Palestine, 1973). A study reported earlier, comparing the effects on performance and feeling states of mesoridazine (5 mg and 10 mg), Perlapine (5 mg and 10 mg) and amylobarbitone (200 mg), found that mesoridazine had an effect on performance not statistically different from placebo. Neither was there disruption of self-rated subjective feeling state.

A pilot study of the effects of a hypnotic dose of mesoridazine on all-night EEG and other electrophysiological features in two middle-aged women found that there was a reduction in intra-sleep restlessness and no effect on either REM or NREM stages 3 - 4 (Oswald and Lewis, unpublished). The lack of sleep disruption in subjects considered to be representative of the group for whom hypnotics are most frequently prescribed, coupled with apparently limited disruption of daytime performance, indicated that mesoridazine might be a hypnotic of potentially wide therapeutic use.

Thus a larger study was planned using more subjects and studying both sleep EEG and daytime performance in an older age group.

Subjects

Seven subjects were used: 4 women of ages 48, 55, 56 and 62, and three men aged 52, 59 and 60. None had taken CNS drugs in the previous year. They took no alcohol throughout the period of the study and followed a regular way of life. They were chosen to represent, by age and sex distribution, the typical population of hypnotic users. They were in satisfactory physical health, but had a high incidence of personal problems, e.g. one had become widowed in the preceding year, another had been divorced, and another had had a major change of life circumstances.

Procedure

The present author was not principally involved in the sleep study but, since the sleep and performance studies were planned to run together and employed the same subjects, the results of both will be reported, with relatively less emphasis placed on the former. The aim is solely to maintain continuity and completeness.

The testing and recording regime for the study was as follows:-

Weeks	Drug	Sleep	Performance
		Laboratory nights	
Orientation 1	Placebo	0	Orientation
" 2	"	0	"
Testing 1	"	2 - 3	Baseline
" 2	Drug	3	Drug (D_1)
" 3	"	0	D_8
" 4	"	1 - 3	D_{15}
" 5	Placebo	3	Withdrawal (W_1)
" 6	"	0	W_8
" 7	"	1 - 3	W_{15}

In the sleep part of the study each subject attended the sleep laboratory on a total of nineteen nights, spread over seven weeks. The intervals between nights were the same for all subjects. Where 2 - 3 and 1 - 3 is shown above this means that there were one or two adaptation nights under full laboratory conditions preceding actual recording nights. Mesoridazine (10 mg) or matching placebo capsules were taken prior to retiring to bed throughout the whole period of the study, including the orientation weeks.

The subjects came to the sleep laboratory and were prepared for the night's recording in a way similar to that described earlier. Recording started at approximately 2230 hours and continued until 0715

hours, so giving a period of 8.5-9 hours for recording.

At the end of the study all records were coded and scored blind in random order in terms of the conventional sleep stages defined by Rechtschaffen and Kales (1968). The raw scores were processed to give data concerning the amount of sleep, sleep onset latency (first NREM stage two), the latency to REM sleep onset, the amount of each stage of sleep, the amount and distribution of periods of wakefulness during the night, the distribution of transitions between stages of sleep during the night, and percentages.

In the performance part of the study all seven subjects reported to the psychopharmacology laboratory at 0815 hours on nine consecutive Sundays, the first two of these being allocated to laboratory orientation and task practice. On each of the nine days, there were three sessions starting at 0830, 1230 and 1630 hours following the "two hours on - two hours off" schedule.

The first two attendance days were for orientation only and performance scores on these days were not included in the analysis. The seven days of analysed testing included the 16th placebo (pre-drug) day, the day after the first drug night (D_1), the day after the eighth drug night (D_8), the day after the 15th drug

night (D_{15}), the day after the first night of withdrawal placebo (W_1), the eighth withdrawal placebo day (W_8), and the 15th withdrawal placebo day (W_{15}).

The tasks included:

Performance

(1) Auditory vigilance

(2) Manual dexterity

(3) Digit symbol substitution

(4) Card-sorting

Subjective Feeling State

(1) Sleep quality

(2) Morning vitality

(3) Anxiety

(4) Concentration.

Results

In general, mesoridazine did not greatly affect the normal pattern of sleep. There were large inter-individual differences in sleep onset latency and sleep duration. Mesoridazine had little effect on the former but mean total sleep time was greatest on the first drug night and least on the first withdrawal night. Intra-sleep restlessness and time spent in stage 1 (drowsiness) declined during drug administration and showed a rebound on withdrawal.

Sustained administration did not suppress NREM sleep stages 3 - 4. As is common in this age group,

two subjects had very little stage 3 - 4 sleep, but in their cases as well there was no indication of any change induced during drug administration.

The clearest effect of the drug was on REM sleep duration, which was increased, with a negative rebound most marked on the second withdrawal night. The six drug nights contained a higher percentage of REM sleep than eight out of nine of the non-drug nights. Increased REM sleep percentage was accompanied by reduced REM onset latencies while taking the drug and this effect disappeared on withdrawal.

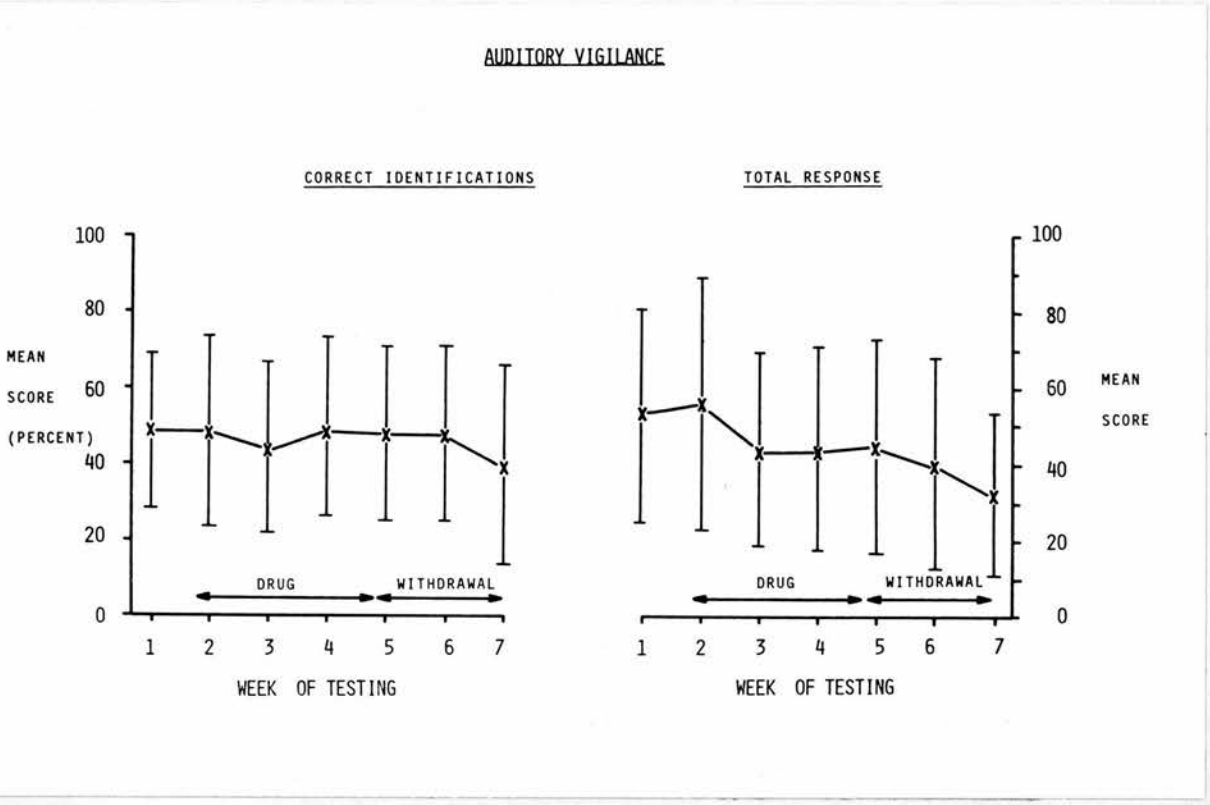
Performance

All data were analysed using analysis of variance (Winer, 1962).

1. Auditory Vigilance.

(1) Correct identifications. There was a slight deterioration in accuracy from the beginning to the end of the testing period. This change was not statistically significant and there was no overall day mean onto-drug decrement (Figure 12 Table 6). Neither was there a withdrawal effect. Examination of morning session accuracy scores indicates that there was no obvious onto- or off-drug hangover effect which might have been hidden by averaging over the three sessions in the day (Table 6) and there was no weeks sessions interaction.

FIGURE 12



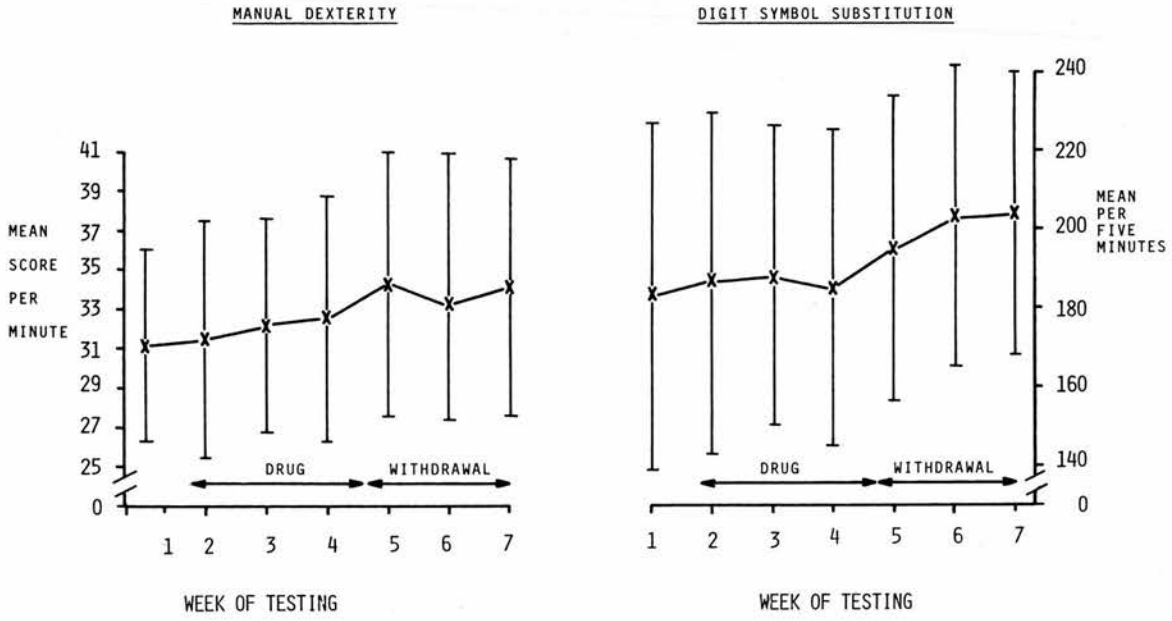


FIGURE 13

TABLE 6

VIGILANCE: CORRECT DETECTIONS

SESSION	1	2	3	
WEEK				MEAN
1	21.86 ± 9.118	18.00 ± 9.678	18.71 ± 7.297	19.52
2	21.43 ± 10.96	20.29 ± 11.368	16.43 ± 8.121	19.38
3	18.00 ± 10.015	20.00 ± 8.963	15.00 ± 7.483	17.67
4	18.00 ± 10.52	20.29 ± 7.89	20.86 ± 9.805	19.71
5	19.71 ± 8.915	16.57 ± 9.378	21.29 ± 9.638	19.19
6	15.96 ± 9.173	20.57 ± 9.467	21.14 ± 9.72	19.19
7	14.43 ± 11.19	15.57 ± 9.744	17.43 ± 10.85	15.81

TABLE 7

VIGILANCE: FALSE POSITIVE DETECTIONS

SESSION	1	2	3	
WEEK				MEAN
1	41.14 ± 35.611	29.86 ± 26.041	31.71 ± 36.62	34.2
2	35.29 ± 37.02	40.86 ± 49.68	34.43 ± 34.29	36.9
3	28.57 ± 33.331	23.43 ± 21.44	28.00 ± 33.011	26.7
4	18.00 ± 17.72	25.29 ± 32.09	31.14 ± 45.447	24.8
5	33.14 ± 37.548	19.43 ± 22.97	25.57 ± 31.8	26.0
6	18.57 ± 25.8	26.29 ± 40.54	20.00 ± 29.705	21.6
7	22.86 ± 34.705	10.86 ± 10.46	16.43 ± 26.895	16.7

(2) False positive identifications. There was a steady, but non-significant, decline over the seven week period. This pattern is not different from the one expected during repeated testing. Examination of the morning session data indicates that there was an increase in false positive identifications on the morning following mesoridazine withdrawal (W_1), but there was also an increase in inter-subject variability (Table 7).

(3) Total responsivity. This measure has been considered by some to be more indicative of change than either errors of omission or commission alone. Apart from a slight increase on first administration there was a decline in responsivity through the study (Figure 12). There were no statistically significant changes, either through the weeks or sessions, and possible effects, e.g. week 2 session 2, and week 6 session 2 (Table 8), were confounded by inter-subject variability.

(4) d'. This transformation, based on signal detection theory, showed a gradual, non-significant, rise in sensitivity through the study (Table 9). In neither day nor morning session scores was there any indication of an onto- or off-drug effect.

TABLE 8

VIGILANCE: TOTAL RESPONSE

SESSION	1	2	3	
WEEK				MEAN
1	63.00 ± 32.161	47.86 ± 20.481	50.43 ± 33.11	53.8
2	56.71 ± 29.199	61.14 ± 41.719	50.86 ± 28.5	56.2
3	46.57 ± 29.24	43.43 ± 16.94	43.00 ± 30.392	44.3
4	36.00 ± 15.055	45.57 ± 26.153	52.00 ± 38.492	44.5
5	52.86 ± 34.624	36.00 ± 20.866	46.86 ± 28.656	45.2
6	34.43 ± 22.187	46.86 ± 35.32	41.14 ± 24.086	40.8
7	37.29 ± 32.366	26.43 ± 8.482	33.86 ± 23.583	32.5

TABLE 9

VIGILANCE: d'

SESSION	1	2	3	
WEEK				MEAN
1	2.207 ± 0.662	2.141 ± 0.987	2.244 ± 0.672	2.197
2	2.347 ± 0.996	2.530 ± 0.867	2.204 ± 0.836	2.360
3	2.395 ± 0.485	2.414 ± 0.822	2.263 ± 0.800	2.357
4	2.237 ± 0.968	2.280 ± 0.843	2.425 ± 1.001	2.295
5	2.401 ± 0.836	2.397 ± 0.966	2.403 ± 1.044	2.400
6	2.604 ± 1.065	2.473 ± 0.948	2.869 ± 1.258	2.649
7	2.484 ± 1.246	2.379 ± 1.043	2.765 ± 1.053	2.545

TABLE 10

VIGILANCE: BETA (LOG)

SESSION	1	2	3	
WEEK				MEAN
1	2.37 ± 0.56	2.44 ± 0.48	2.61 ± 0.42	2.47
2	2.29 ± 0.49	2.36 ± 0.61	2.46 ± 0.54	2.37
3	2.50 ± 0.73	2.65 ± 0.45	3.03 ± 0.76	2.72
4	2.89 ± 0.66	2.86 ± 0.56	2.71 ± 0.57	2.82
5	2.57 ± 0.53	3.33 ± 0.78	2.84 ± 0.63	2.91
6	3.67 ± 0.82	3.23 ± 0.61	3.88 ± 0.85	3.59
7	3.20 ± 0.86	3.18 ± 0.64	3.65 ± 0.73	3.34

(5) β (beta). A change in beta is suggested to be a change in the criterion employed by a subject in his decision of whether a signal is a target signal or not. The upward trend through the study described an increase in caution as the study progressed (Table 10). There was a slight reduction in caution, in comparison with baseline, which persisted through the day, on first taking the drug, but this did not persist and no withdrawal effect was evident.

2. Manual dexterity.

The general pattern through the study was of improvement. Neither administration nor withdrawal appeared to inhibit improvement, certainly in the later sessions of the day (Figure 13, Table 11) and there was not a significant weeks or weeks X sessions effect. However, it should be pointed out that out of twenty-one mean observations in this task the poorest was on the morning after the drug was first administered.

3. Digit symbol substitution (Figure 13)

Mesoridazine appeared to have little effect on the pattern of improvement expected in this task with repeated testing. Performance was poorer in the third drug week (D_{15}) and this was the result of a depression solely in the morning session score. Although this decrement was contributed to by six out of the seven

TABLE 11

MANUAL DEXTERITY

SESSION	1	2	3	
WEEK				MEAN
1	30.25 ± 5.02	31.75 ± 5.31	31.64 ± 4.23	31.21
2	30.11 ± 6.89	32.11 ± 6.46	32.21 ± 4.87	31.48
3	31.46 ± 5.47	31.96 ± 5.87	33.32 ± 5.25	32.25
4	31.64 ± 6.50	32.75 ± 6.15	33.07 ± 6.10	32.49
5	31.46 ± 4.64	33.04 ± 9.37	38.40 ± 6.01	32.73
6	31.89 ± 5.80	33.71 ± 6.26	34.11 ± 5.85	33.24
7	32.93 ± 5.75	34.11 ± 7.02	35.32 ± 6.76	34.12

TABLE 12

DIGIT SYMBOL SUBSTITUTION

SESSION	1	2	3	
WEEK				MEAN
1	176.29 ± 45.61	185.00 ± 44.16	189.29 ± 42.19	183.5
2	179.71 ± 46.48	187.14 ± 47.01	194.29 ± 35.92	187.0
3	190.71 ± 41.95	184.71 ± 37.01	190.00 ± 34.35	188.5
4	177.14 ± 44.38	191.71 ± 41.23	188.57 ± 35.07	185.8
5	197.71 ± 38.99	197.29 ± 40.00	192.29 ± 37.42	195.8
6	204.86 ± 38.08	208.57 ± 36.61	196.86 ± 38.08	203.4
7	206.57 ± 31.00	212.43 ± 42.43	195.14 ± 34.06	205.0

subjects it was not of sufficient magnitude to achieve statistical significance (Table 12).

4. Card-sorting: Decision time.

Analysis of variance revealed no significant changes in performance on this task at any level of complexity during either administration or withdrawal of mesoridazine. Examination of the mean overall day data (Tables 13 and 14) indicates a progressive impairment at the simple and complex levels which disappeared on withdrawal. The decrement appeared to occur, however, in the lunch-time and afternoon sessions and an improvement occurred, at all levels of complexity, in the morning session with continued administration. This paradoxical effect disappeared on withdrawal and, at the more complex levels of card-sorting, the first withdrawal day morning session scores were the slowest sorting scores of the whole study (Tables 13 and 14). This possible withdrawal effect was not significant statistically, however, and it had disappeared by the lunch-time testing session.

Self-rated Subjective Feeling States

There was a clear indication that sleep was rated as improved overall during the period of drug administration and apart from a brief deterioration on the first morning after a blank pill had again been given, the improvement continued into withdrawal.

TABLE 13

CARD-SORTING: DECISION TIME

Two Categories

SESSION	1	2	3	
WEEK				MEAN
1	12.71	13.10	13.49	13.10
2	14.59	13.19	12.53	13.43
3	13.46	13.40	14.11	13.66
4	13.71	14.54	14.39	14.21
5	13.90	14.53	13.39	13.94
6	14.61	14.60	13.37	14.16
7	14.40	11.49	12.63	12.84

Four Categories

1	19.56	17.90	17.81	18.43
2	18.04	17.31	19.97	18.44
3	18.36	19.03	17.79	18.36
4	16.83	16.79	19.64	17.75
5	20.21	19.77	18.33	19.44
6	19.96	18.41	16.69	18.35
7	17.50	18.76	18.07	18.11

TABLE 14

CARD-SORTING: DECISION TIME

Eight Categories

SESSION	1	2	3	
WEEK				MEAN
1	23.71	24.06	21.13	22.97
2	22.13	20.87	20.03	21.01
3	22.99	21.37	21.54	21.97
4	20.99	23.16	22.59	22.24
5	24.27	20.34	20.74	21.79
6	23.04	20.40	20.84	21.43
7	22.20	19.39	20.86	20.81

There was a fairly clear indication of a hang-over effect on morning vitality twenty minutes after rising for the period of drug administration. Withdrawal brought some initial improvement.

There was some reduction in anxiety with drug administration, especially initially, but this was not noticeably below the mean. It is interesting to note that there was no acute anxiety rebound on withdrawal.

Immediately following the first night of administration of the active drug, there was an obvious subjective impairment of self-rated concentration. Following this, there was a continued depression of ability to concentrate but this was only slightly below the mean.

Discussion

In the dose used, and in middle-aged volunteers, mesoridazine appeared to have little effect on either sleep, psychomotor performance or self-rated feeling states. Some previous evidence had suggested that a phenothiazine, in a small clinical dose, could increase REM sleep duration slightly (Lewis and Evans, 1969), but there had been no previous report of a hypnotic drug increasing REM duration over a prolonged period and causing a negative rebound on withdrawal.

Mesoridazine is also notable for its lack of suppression of NREM sleep stages 3 - 4. If certain

sleep stages are related to particular restorative processes, and there is evidence supporting both REM sleep (Oswald, 1969a) and NREM sleep stages 3 - 4 (Honda et al, 1969; Sassin et al, 1969) in such roles, then a lack of disruption similar to that occurring during mesoridazine administration might be of relevance and importance during long-term hypnotic administration.

In comparison with temazepam, reported in another section not to have disruptive effects on overall sleep parameters, mesoridazine caused less change in hour by hour distribution of REM sleep and caused less disruption of subjective feeling states both on administration and withdrawal.

The subjective ratings suggest an improvement in sleep quality and a slight reduction in anxiety and morning vitality. The onto-drug impairment of concentration had disappeared by the second drug day and there was a withdrawal effect only on sleep quality on the first night of withdrawal. This is in contrast to what has been reported, using these techniques, for nitrazepam (Oswald et al, unpublished), temazepam, perlapine and sodium amylobarbitone as reported in other sections, and for sodium amylobarbitone and benzoctamine (Ogunremi et al, 1973).

The lack of disruption of psychomotor performance both when mesoridazine was first given and when it was abruptly withdrawn, was remarkable. No measure showed a reliable and statistically significant drug-associated change through the period of the study. Performance on certain tasks tends to improve with repeated testing. Manual dexterity and digit symbol substitution are examples of this type. On the former task the lowest mean session score was on the morning after the drug was first administered, but the difference between this score and the mean baseline morning session score was less than 1%, while the standard deviation of each was at least 20%, and the mean midday session score was over 1% better than the corresponding mean baseline session score. In view of the inter-subject variability it would be unreasonable to ascribe to the drug an effect other than a possible inhibition of performance improvement. Similarly with digit symbol substitution, although there was a deterioration of performance on the morning session of the third drug test day this possible effect had disappeared by the midday session and no extrapolative importance can be attached to it. Withdrawal had no effect on the performance of these two tasks, even on the morning after the drug was first replaced by a placebo.

The drug appeared possibly to have some slight effect on performance of the other two tasks at this point, however, for there was an increase in false positive detections in the vigilance task and an increase in decision sorting time, which increased with increasing task complexity. These effects had disappeared by midday.

The overall effect of mesoridazine on performance was, at the most, slight and transitory and no consistent effect was noticed, even on initial administration and withdrawal. Whether the lack of effect resulted from limited drug impairment or from insufficient test sensitivity will be discussed in a later section. The lack of effect, however, is in contrast to the effects of other hypnotics on performance. In a study reported earlier, perlapine was shown to be associated with impairment of performance and disruption of self-rated subjective feelings in young adults. A similar pattern of disruption was noted, in the same study, in a group receiving amylobarbitone. Even in subjects given only a single dose of a hypnotic significant disruption of performance has been shown. For example, several barbiturates have been shown to cause decrements on a variety of psychological tests, including pentobarbitone (Von Felsinger et al, 1953), quinalbarbitone (Kornetsky

et al, 1959), amylobarbitone (Malpas et al, 1970; Malpas, 1972), and butobarbitone (Bond and Lader, 1972, 1973), as have several non-barbiturate hypnotics, including flurazepam (Bond and Lader, 1973), nitrazepam (Bond and Lader, 1972; Malpas et al, 1970) and diazepam (Bye et al, 1974).

The only scores in this study which are comparable with those in the studies mentioned above are on the morning after first administration since the "residual" effects referred to in some of the studies cannot be compared to the possible effects of abrupt withdrawal after continued administration. The acute effects of mesoridazine on performance would appear to be less disruptive than the acute effects of other hypnotics. Little is known about the effects of these other hypnotics on performance with continued administration and it may be that disruption diminishes. Sleep studies have reported, however, that while tolerance usually develops and sleep stage patterns return towards normal this process may take several weeks and there may be disruption on withdrawal as well.

The lack of disruption of psychomotor performance coupled with the limited effects on subjective feeling states and slow wave sleep, and the potentiation of REM sleep, would indicate that mesoridazine is a hypnotic suitable for wide clinical application yet

there were large inter-individual differences in response pattern. Some subjects appeared to show rapid changes, while others appeared to be affected more gradually through the period of taking the drug and for longer through the day.

It was considered that such differences might be related to personality factors and a "post-hoc" analysis was undertaken in an attempt to discover a possible relationship. The results of this analysis will be discussed in Chapter 8.

CHAPTER 7

REVIEW AND DISCUSSION OF INDIVIDUAL DIFFERENCES IN PERFORMANCE

The use of normal subjects without resort to attempts at differentiation employing one or other personality typology presupposes either a homogeneity of response pattern among subjects or that any differences will balance out. These attitudes may be satisfactory for some research areas but it is reasonable to assume that if there are different types of personality and that these different kinds of people have different response patterns in performance tasks and on other parameters then the pattern of response to drugs will also be different.

Implicitly there are difficulties in comparing personality types. Individual 'atypicality' of response to drugs may be almost as common as typicality. Von Felsinger et al (1955, 1956) found approximately 50% of subjects on such drugs as morphine, amphetamine and phenobarbitone produced atypical responses. The reason for this may lie in the variety of other factors involved in personality but not used as criteria in a particular study. Subjects may have one personality factor in common, but may differ in others and a particular response pattern is likely to result from the interaction of several different factors. A personality type implies a pattern of characteristics but the more precise one becomes, the more difficult it is to find subjects who match all the criteria. The holistic approach is often forced to settle for less precision than it would

like and this unfortunately may make it difficult to test adequately the predictive hypothesis. The more general traits, such as introversion-extraversion and neuroticism, seem to represent a compromise here.

Eysenck (1957) has developed a theory postulating two fundamental dimensions of personality: extraversion and neuroticism. Eysenck has inferred that underlying these behaviourally measured dimensions there are physiological substrata. The level of neuroticism is considered to be related to the strength of autonomic nervous system activation in the presence of anxiety-provoking stimuli. Extraversion is considered to be related to the level of cortical arousal and is a function of the rate of build-up and dissipation of inhibition. Extraverts are supposed to have a slow build-up and rapid dissipation of inhibition while the excitatory processes in introverts are supposed to be rapid and the inhibitory processes weak and slow. Eysenck (1967) has suggested that differences are a function of the level of activity in the ascending reticular-activating system.

In terms of this theory, introverts are expected to perform better in vigilance tasks than are extraverts since the persistently heightened arousal level of introverts facilitates vigilant attention and prevents

performance decrements which result from inhibition increments and consequent lowered arousal.

Most researchers have used the extraversion-introversion dimension when trying to relate personality traits to performance, but others have used less well-known criteria and this sometimes makes inter-study comparison difficult.

Halcomb and Kirk (1965) used the California Psychological Inventory and the Wonderlic Personnel Test and found that while subjects scoring low on "flexibility" had higher reaction times and subjects high on "self-control" had a slower vigilance decline, subjects who had both "high achievement via independence" and intelligence scores displayed no significant performance decrement with time.

Halmiova (1965) has studied vigilance performance in relation to a "psychobiographical" dimension, "strength of the nervous system". Eysenck (1967) suggested that a weak nervous system corresponds to introversion. Halmiova found that strong nervous system subjects made fewer omission and commission errors and showed a decrease in reaction time with time on task. These results are a contradiction of what others have found.

Klapper and McCollach (1972) studied the effects of two stimulant drugs (caffeine, 500 mg;

methylphenidate, 20 mg) and two depressant drugs (secobarbitone, 200 mg; amylobarbitone, 250 mg) on 31 non-patient volunteers divided into groups of normals, neurotic triad, high Ma and Pd, or psychotic tetrad patterns on the basis of their MMPI profiles. One motor (pegboard) and two cognitive tasks (addition, DSST) were used and results showed that the neurotic triad group were affected by the stimulants but not by the depressants, the Ma and Pd group responded to both drug types, while the psychotic tetrad group was sensitive to depressants and not to stimulants.

Patkai has carried out a series of studies on habitual "morning" and "evening" workers, comparing day-time variations in performance and catecholamine excretion (Patkai, 1970; 1971a, b; Patkai et al, 1967). Adrenaline excretion was highest in morning workers in the morning while evening workers showed constant excretion values. Morning workers performance, on the other hand, showed little variation while evening workers showed a gradual improvement through the day. Patkai (1971a) related "morning" and "evening" types to extraversion-introversion, as measured by Cattell's 16PF inventory, and found a significant correlation between introversion and morning workers, and between extraversion and evening workers.

Jung (1923) has pointed out that for the extravert "interest and attention follow objective happenings, and, primarily, those of the immediate environment". It follows that the extravert is more sensitive to novelty and that repetitive stimuli will rapidly lose their stimulating effect. The introvert, on the other hand, 'interposes a subjective view between the perception of the object and his own action'. Thus the introvert will be more affected by his motivation and desire to do the task well, than by the habituating effects of the stimulus.

Broadbent (1958) reported several experiments in which extraverts, diagnosed in a variety of ways, were shown to perform poorly in comparison with introverts in prolonged tasks. Broadbent also found that introverts showed a greater tendency to continue with prolonged training, even though there were no differences in intelligence.

McGrath and his colleagues have studied individual differences in performance. Using a battery of seventeen tests yielding thirty different scores, low correlations were obtained between the various vigilance scores and the psychological test measures (McGrath et al, 1960). Further experiments led to the conclusion that none of the original significant correlations appeared in the cross-validation studies and none of

the new tests yielded significant correlations with any of the vigilance performance scores (McGrath, 1963a, 1963b; Buckner and McGrath, 1963b).

Bakan (1959), assessing personality with the use of the sociability scale of the Heron Inventory (Heron, 1956), studied the interaction between temperament and time on task. The primary task comprised listening, for 80 minutes, to digits presented at the rate of one per second; response was required to the occurrence of three successive and different odd digits which were presented at a rate of 10 per 16 minutes. Introverts performed better than extraverts at this task. When a secondary task was introduced, however, this difference disappeared. Bakan interpreted the results in relation to reinforcement theory and suggested that there was a greater extinguishing of responses in the extravert group. Others have suggested that an arousal theory interpretation would be more appropriate since in a vigilance situation extraverts may need more stimulation to maintain a level of arousal adequate for accurate vigilance (Stroh, 1971). A later study assessed performance on a similar vigilance task by groups of extraverts, introverts and 'normals' (Bakan, Belton and Toth, 1963). The performance of normals and extraverts, in terms of errors of omission, deteriorated

with time on task but introverts improved from the first to the second period and deteriorated only in the last period. It would appear then that differences might be considered in terms of the superior performance of introverts rather than the inferior performance of extraverts.

Tune (1966b) used a modification of Bakan's task and found no difference between introverts and extraverts in terms of errors of omission. However, introverts were reported to make fewer errors of commission as a result of greater caution. Other studies have reported that extraverts made significantly fewer errors of commission (Davies and Hockey, 1966; Davies et al, 1969). It might be possible to explain these results in terms of both reinforcement and arousal theory, but Davies and his colleagues have favoured the latter.

Davies and Hockey (1966) reported an experiment in which the interaction of signal frequency, noise level and temperament were studied in a visual checking task. Extraverts, selected by use of the MPI, showed a deterioration in correct detection with time on task at both signal frequency levels in quiet conditions whereas introverts did not. Neither group showed deterioration under noise conditions (95dB). Extraverts made fewer commission errors in quiet than

in noise: the reverse was true in the introvert group. Interpretation of these results was made in terms of arousal theory and it was suggested that noise raised the arousal level of the extravert group to that of the introvert group in quiet conditions. It was suggested that noise may encourage extraverts to adopt a more risky decision criterion than normal, while making introverts more cautious. Davies and Tune (1970) pointed out that in this study the calculated values were based on group means rather than on individual scores and it may be that the meaningfulness of some of the results is doubtful, particularly in view of the objections to the applicability of signal detection theory to vigilance data of this sort put forward by Jerison (1967a) and others.

Jerison (1967) has argued that the application of the signal detection model is inappropriate since values of beta computed from vigilance data are not measures of caution, but are artefacts due to the pooling of observations made under different conditions of attentiveness during the vigil. This point of view will be discussed in more detail in Chapter 12.

Davies et al (1969) reported three studies which, by again indicating that introverts and extraverts prefer different levels of stimulation for accurate performance, give support to the arousal theory point

of view. Subjects were required, in the first study, to detect the occurrence of three successive and different odd digits under two noise conditions. The control condition was silence (50dB); the experimental condition comprised continuous varied auditory stimulation (VAS) i.e. alternating music and speech, at a level of 80dB. While the performance of introverts was similar under both conditions, extraverts improved with VAS, with the reduction in commission errors being statistically significant. In the second study the same task was performed under silent conditions but there was the opportunity to select periods of VAS as frequently as the subjects wished. Extraverts requested VAS significantly more often than did introverts. In the third study the task was performed under VAS conditions and extraverts were found to request periods of silence on significantly fewer occasions than introverts. It would appear from these results that extraverts felt that VAS enabled them to perform the vigilance task more effectively, while introverts felt that silence was preferable. Thus while the introverts performed adequately under control conditions, extraverts appeared to need extra stimulation to maintain their effort. An explanation in terms of an arousal hypothesis would seem appropriate, but further

experimentation, using a variety of intensity levels and tasks, would have helped to clarify the degree of variety required for the facilitation of performance without consequent disruption.

Colquhoun (1960) tested subjects at three different times of day (1000, 1230 and 1500 hours) and found that introverts, as assessed by the sociability scale of the Heron Inventory (1956), had a high detection rate in the morning while in the afternoon a high detection rate was associated with extraversion. A later study confirmed these results and also showed that afternoon performance was better than morning performance (Colquhoun 1962a). In a further study a significant positive correlation was found between introversion, assessed by the Heron Scale and speed of work in a cancellation task when subjects were tested in isolation at 0830 hours (Colquhoun and Corcoran, 1964). Zero correlations were found with testing at 1330 hours, and also at 0830 hours when subjects were tested in a group. If these results are interpreted in terms of an arousal hypothesis then it may be suggested that the presence of others is sufficiently arousing for the performance of extraverts to be affected.

Kleitman (1933) related diurnal variations in performance and body temperature and identified 'morning'

and 'evening' types. Blake (1965, 1967) attempted to clarify this relationship in terms of differences between extraverts and introverts in performance and body temperature variation. Blake (1965) showed that cancellation performance varied with body temperature at five different times of day with a positive correlation across subjects between performance and body temperature at each time of day. In a later paper it was shown that the correlation between introversion and oral temperature gradually changed from being significantly positive to being significantly negative through the day (Blake, 1967). This result was replicated in another study using a letter cancellation task; as was the finding of a clear positive correlation between temperature and output at all five testing times (Blake, 1971). Further studies, reported in the same paper and using a variety of tasks, including vigilance, calculations, serial reaction, card-sorting and reaction time, produced essentially similar results.

The presence of wide individual differences in the generation of commission errors has frequently been noted (Bakan, 1955; Wiener, 1963), but their investigation as the main dependent variable was first undertaken by Krupski et al (1971). It was hypothesised that the kind of person who makes commission errors was likely to be impulsive and at a chronically low level of

physiological arousal. Since impulsivity is one of the components of extraversion (Eysenck and Eysenck, 1963) extraversion was suggested to be positively correlated with commission errors. Results showed that commission errors were related to vigilance decrement and low electrodermal arousal. The correlation between extraversion and commission errors, although not significant, suggested there may be a relationship, especially with the impulsivity component.

Further evidence in support of a relationship between the impulsivity component, rather than the sociability component of extraversion, and performance pattern has been provided by Thackray and his colleagues (Thackray et al, 1973, 1974). In the earlier experiment, individuals who had rated themselves as highly distractable in their daily lives were found to be unable to sustain attention during a monotonous task, while self-rated low distractability subjects sustained attention with no decrement. In the latter experiment extraverted subjects showed increasing lapses of attention while introverts did not and impulsivity was the component responsible for the decrement. It must be pointed out that in neither of these studies was shown any relationship between commission errors and any of the personality variables.

The two dimensions of E and N have been discussed and used extensively as a research tool. More recently it has been suggested that there exists a "set of correlated behaviour variables indicative of predisposition to psychotic breakdown, demonstrable as a continuous variable in the normal population and independent of E and N" (Eysenck and Eysenck, 1968b).

Eysenck and Eysenck (1968c) suggested that "P (Psychoticism) might be a personality variable of interest in connection with many experimental investigations: that it may determine differential performance either alone, or in conjunction with E and/or N; and the experimental study of P might throw much needed light on the nature and meaning of psychoticism as a personality variable".

The value of the PEN Inventory has been investigated both as a clinical and as a research tool.

McPherson et al (1974) found that P scale scores did not discriminate between 77 psychotics, 32 neutorics and 112 normals. However, within the psychotic group those patients who had delusions of 'disintegration' thought disorder and affective flattening had significantly higher scores than those psychotics who did not.

Davis (1974), having used the PEN Inventory with over 100 patients, suggested that P is not orthogonal

to E and N, that only 5 items meet the Eysenck and Eysenck (1968a) criteria for use as a scale and that the P scale is simply a broader measure of emotionality than N.

Claridge and Birchall (1973) and Claridge and Chappa (1973) examined the P scale in relation to the two-flash threshold and electrodermal activity and concluded that there is a distinctive and unstable kind of central nervous system organisation underlying "psychoticism" which at the lower end of the continuum falls within normal personality dimensions but which at the upper end can be seen in the psychotic disorders.

Stroh (1970) has used the PEN Inventory in the study of the performance of a large number of subjects on a visual vigilance task. Correlational analysis revealed no significant relationship between vigilance performance and either E or N, but there was a significant inverse relationship between P and d'.

That it is oversimplifying to generalise about the effect of stimulant or depressant drugs on people as a whole, or on different groups, is evident, in view of the multiplicity and variety of effects which a single drug may have. Koestler reported different effects obtained using LSD and mescaline in groups of subjects from the West Coast and the East

Coast of America (Koestler, 1961). The former group experienced a great variety of subjective effects while the latter group reported few. Such differences emphasise the importance of personality and environment on the effects of a drug.

A complicating factor is that drugs considered to have a certain type of action do not always have it so predictably. For example, barbiturates generally depress activity yet under some circumstances doses which normally depress activity may stimulate it (Hill et al, 1957) and in very small doses the effects may be predominantly stimulant (Read et al, 1960). When drug combinations are used, a technique which has been employed in psychiatry, it has been found that amphetamines can counteract the deleterious effects of cyclobarbitone and that a mixture can produce effects which could not be obtained by either drug separately (Steinberg, 1961, 1964; Steinberg and Rushton, 1963).

Paradoxical effects have been noted in clinical situations as well, and recently there has been discussion in the British Medical Journal on the effects on patients of benzodiazepines prescribed for anxiety and depression resulting from situations of interpersonal tension. There have been several reported instances of aggression with a very young child or marital partner usually being the catalyst (Lynch et al, 1975).

As none of the above reports studied groups selected for differences such as personality type, the need for caution in the construction of hypotheses and the interpretation of results is evident (Trouton and Eysenck, 1960).

A theory postulating a greater amount of cortical control for introverts and a greater susceptibility to depressant drugs of extraverts due to the reduction of cortical control was first suggested by McDougall (1929).

Eysenck (1960) extended McDougall's suggestion when he stated "depressant drugs increase cortical inhibition, decrease cortical excitation and thereby produce extraverted behaviour patterns. Stimulant drugs decrease cortical inhibition, increase cortical excitation and thereby produce introverted behaviour patterns".

Studies in which the differential effects of alcohol on performance has been examined have shown greater effects in extraverts. Drew, Colquhoun and Long (1958) found that in "a skill resembling driving" extraverts did not change either control movements or speed very much, that they were less consistent in control movements and that they showed large increases in error when under the influence of alcohol. Introverts, on the other hand, changed speed considerably, increased control movements and made significantly fewer errors.

Jones (1974) tested extraverts and introverts on Sets I and II of Raven's Progressive Matrices. On Set I no significant differences were found between the groups. At this stage both groups were on the ascending limb of the blood alcohol curve. On Set II, however, introverts scored better than extraverts while on the descending limb of the blood alcohol curve under placebo conditions extraverts performed better than introverts.

Dinard and Defayolle (1972) studied the differences in performance patterns between extraverts and introverts, as defined by Eysenck, on nocturnal vigilance tasks. Although very small groups were used the introverts performed significantly better than extraverts and maintained their detection levels through the night. However, in a variety of other tasks extraverts performed better, making fewer errors and faster reactions. Librium appeared to have a stimulant action on the vigilance of stable introverts and neurotic extraverts shortening reaction time and reducing the number of omission errors. The reverse pattern occurred in stable extraverts and neurotic introverts. Librium appeared to make overall performance patterns more homogeneous by attenuating the inter-individual differences established in the absence of treatment.

The effects of a stimulant, caffeine, on vigilance performance in extraverts and introverts have been studied (Keister and McLauchlin, 1972). It was hypothesised that the stimulant would "decrease cortical inhibition, increase cortical excitation and thereby produce introverted behaviour patterns". The effect of the caffeine would be to maintain the continued efficiency characteristic of the introvert thereby inhibiting the performance decrement usually expected under placebo conditions in the extravert. The task was similar to that used by Bakan (1959). As hypothesised under the no-drug condition, the extraverts showed a decrement from the first to the last third of the task, while the introverts did not, and under the effects of caffeine both extraverts and introverts showed no decrement between the first and last third of the task.

Generally it seems then that extraverts make more errors of omission and show a greater decrement with time on task than do introverts. It may be, however, that consideration should be given to the 'abnormal' response pattern of introverts since in not showing a decrement with time on task they appeared in one study to perform differently from normals (Bakan et al, 1963). Intervening factors may affect this simple differentiation. Noise (Davies and Hockey, 1966;

Davies et al, 1969) a secondary task (Bakan, 1959), caffeine (Keister and McLaughlin, 1972) and chlordiazepoxide (Dinard and Defayolle, 1972) have abolished differences in response pattern and it has been suggested that these factors have served to raise the arousal of extraverts to a level similar to that of introverts under the monotonous conditions of the basic vigilance task.

The relationship between errors of commission and temperament is less clear. Hypotheses derived from Eysenck's theory have suggested that there should be a positive correlation between commission errors and extraversion. While there has been some support for this suggestion (Tune, 1966b) results which have indicated the opposite (Davies and Hockey, 1966; Davies et al, 1969) or which have been inconclusive (Krupski et al, 1971; Thackray et al, 1973, 1974) have also been reported.

CHAPTER 8

A RETROSPECTIVE ANALYSIS OF PERFORMANCE IN TWO AGE GROUPS

Since the Eysenck Personality Inventory, Form A, had been administered routinely to all subjects participating in experiments in the psychopharmacology laboratory, a "post-hoc" analysis of part of the data from two experiments described earlier was undertaken. It is recognised that great caution must be taken in extrapolation from such analyses, especially where only small numbers of subjects are used, and the aim was solely to obtain illumination on some of the factors possibly involved in relation to heterogeneous responsivity.

The data to be re-analysed was generated by the two groups which had received the 10 mg dose of mesoridazine. The first group, comprising male young adults, received mesoridazine nightly for two weeks and were also studied over a two week withdrawal period. The second group, comprising male and female middle-aged subjects, received the drug for three weeks and were studied over three weeks of withdrawal. The two groups are not strictly comparable, therefore, and neither was this the intention. However, if a dissimilarity of response pattern between personality type was indicated and if this difference was consistent across age groups then if such an effect was replicable, the finding would be of relevance in the clinical application of the drug.

Procedure

There were six subjects in the young adults' group. The three with the highest extraversion scale scores were deemed extraverts and the other three subjects were called introverts. In the older group, which contained seven subjects, the three highest E scale scorers were allocated to the extraversion group and the lowest three to the introvert group. The scores of the fourth highest E scale scorer were not included. The comparison is therefore between higher and lower scorers on the E scale rather than 'extraverts' and 'introverts'. E scale scores were 22, 22 and 16 for the high extraversion group and 9, 12 and 14 for the lower extraversion group of young adults, and 16, 17 and 18 for the higher and 8. 10 and 11 for the lower extraversion groups of older subjects.

Results

The extraverts tended to be less affected by the drug than the introverts who, in both age groups, showed at least an initial deterioration in performance on several of the tests when first administered the drug.

In the vigilance task, correct detections by the extraverts of both age groups increased on receiving the drug, while in both groups of introverts

the detection rate fell. In the older age group this difference reached statistical significance ($p < 0.002$) (Table 16). Similarly, in both age groups, false positive detections showed an onto-drug decline in extraverts and a rise in introverts. Consequently the signal detection theory transformations d' and beta showed differences between the personality types across the age groups with onto-drug increases in both d' and beta for both groups of extraverts and corresponding decreases for the introverts with the exception of d' in the older age group (Tables 15-17).

A similar pattern of onto-drug improvement in extraverts and deterioration in introverts was evident on the manual dexterity task. In both age groups overall performance was significantly better in the former (Tables 18 and 19).

While the performance level of the introvert groups was higher overall on the digit symbol substitution task the degree of disruption that occurred when mesoridazine was administered was relatively greater (Figures 14,15). These differences reached statistical significance only in the older age group (Tables 20 and 21).

In the card-sorting decision time task both groups of extraverts showed an improvement while on

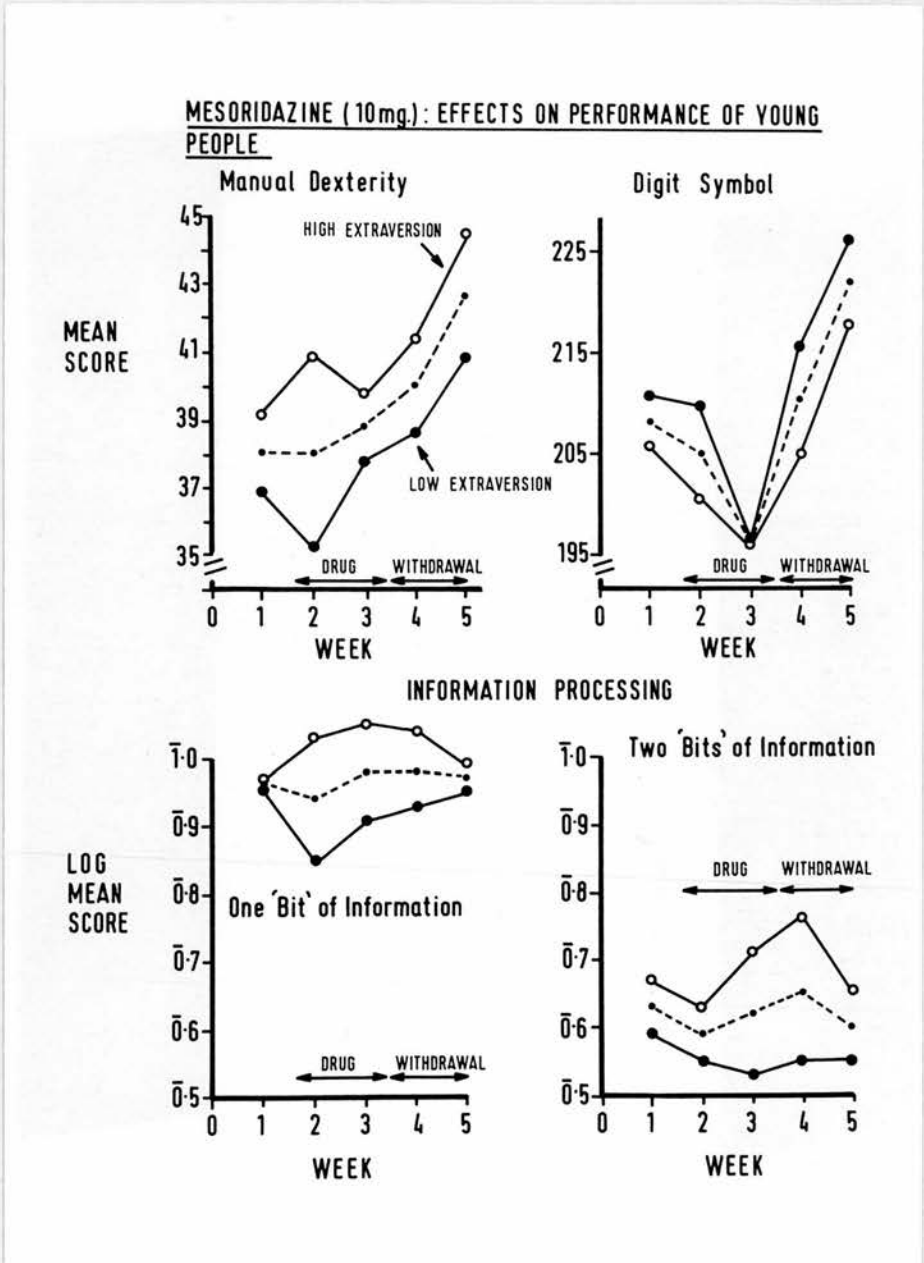

MESORIDAZINE (10mg.): EFFECTS ON PERFORMANCE OF YOUNG PEOPLE
Manual Dexterity
Digit Symbol
MEAN SCORE
HIGH EXTRAVERSION
LOW EXTRAVERSION
DRUG
WITHDRAWAL
WEEK
INFORMATION PROCESSING
LOG MEAN SCORE
One 'Bit' of Information
Two 'Bits' of Information

FIGURE 14

TABLE 15

VIGILANCE IN YOUNGER SUBJECTS

Correct Detections

Weeks	1 (Baseline)	2 (D_1)	3 (D_8)	4 (W_1)	5 (W_8)
Groups					
High E	21.22	22.44	20.78	17.56	19.89
Low E	25.22	20.44	20.44	17.56	19.33

False Positive Detections

Groups					
High E	7.89	4.22	2.44	2.00	1.22
Low E	2.00	3.56	2.00	1.78	1.33

d'

Groups					
High E	2.792	3.140	3.244	3.130	3.540
Low E	3.693	3.144	3.357	3.120	3.374

(beta) (Log transformation)

Groups					
High E	3.88	4.38	5.14	5.25	5.75
Low E	5.49	4.91	5.39	5.22	6.01

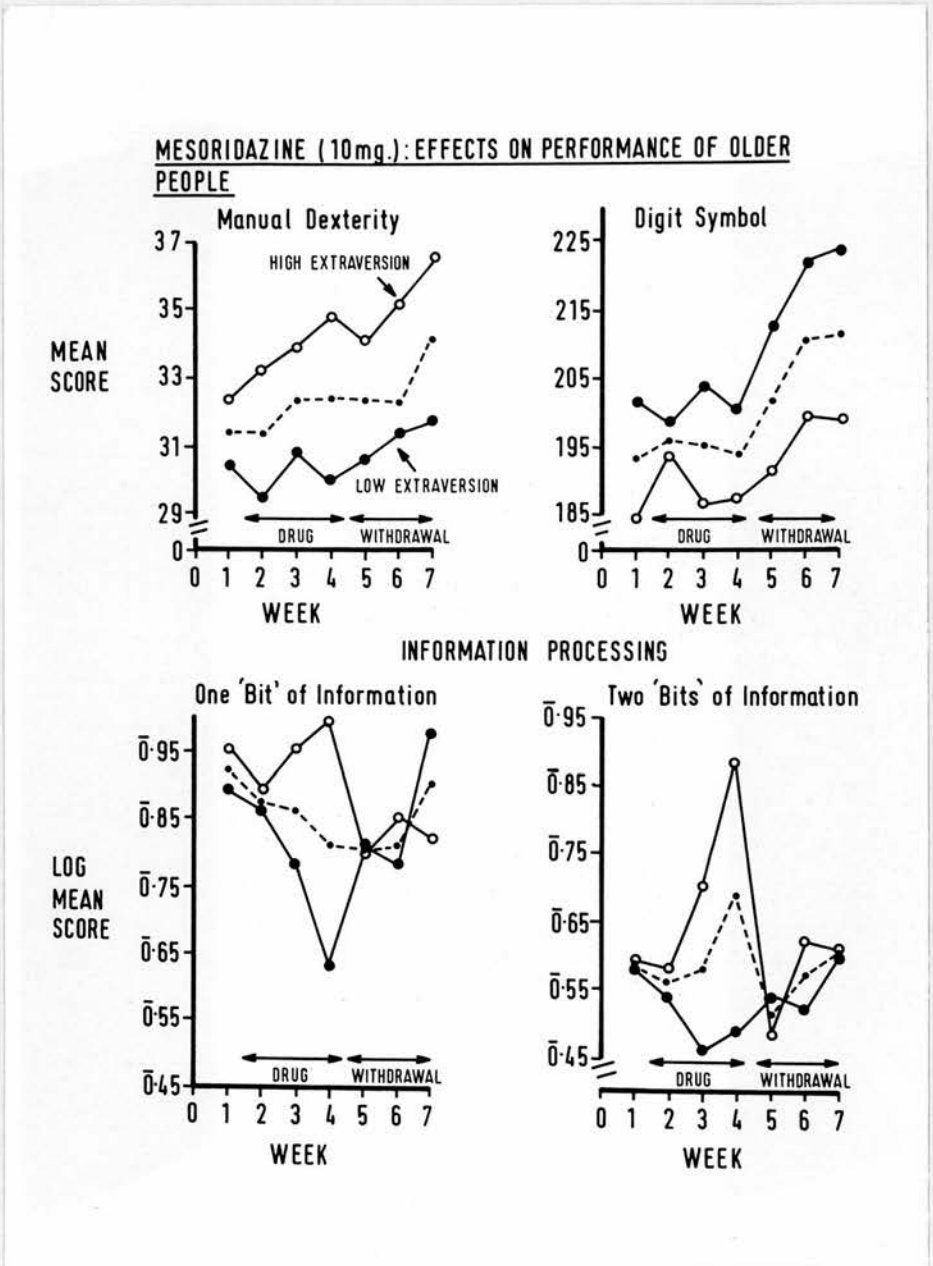

MESORIDAZINE (10mg.): EFFECTS ON PERFORMANCE OF OLDER PEOPLE
Manual Dexterity
Digit Symbol
MEAN SCORE
HIGH EXTRAVERSION
LOW EXTRAVERSION
DRUG
WITHDRAWAL
WEEK
INFORMATION PROCESSING
One 'Bit' of Information
Two 'Bits' of Information
LOG MEAN SCORE

FIGURE 15

TABLE 16

VIGILANCE IN OLDER SUBJECTS

Correct Detections

Weeks	1 (Placebo)	2 (D_1)	3 (D_8)	4 (D_{15})	5 (W_1)	6 (W_8)	7 (W_{15})
Groups							
High E	24.67	27.56	24.00	26.22	26.67	26.56	24.56
Low E	18.33	15.67	15.56	19.00	17.11	16.33	11.44

Source of Variation	DF	SS	MS	VR
Groups	1	2876.22	2876.22	75.833***
Weeks	6	263.65	43.94	1.159
Sessions	2	1.73	0.87	0.023
Groups Weeks	6	160.89	26.81	0.707
Groups Sessions	2	46.03	23.01	0.607
Weeks Sessions	12	564.83	47.07	1.241
Groups Weeks Sessions	12	238.54	19.88	0.524
Residual	84	3186.00	37.93	
TOTAL	125	7337.86		

Levels of Significance:

*** $p < 0.001$

** $p < 0.01$

* $p < 0.05$

TABLE 17

VIGILANCE IN OLDER SUBJECTS

False Positive Detections

Weeks	1	2	3	4	5	6	7
Groups							
High E	32.1	22.0	19.6	17.7	26.1	18.8	11.4
Low E	18.2	28.7	14.6	10.0	10.4	4.8	5.6

d'

Weeks	1	2	3	4	5	6	7
Groups							
High E	2.315	2.653	2.673	2.748	2.688	2.917	3.030
Low E	2.567	2.702	2.656	2.599	2.817	3.048	2.840

(beta) (Log transformation)

Weeks	1	2	3	4	5	6	7
Groups							
High E	2.65	2.75	3.03	3.06	3.00	3.74	3.59
Low E	2.82	2.60	3.08	3.51	3.64	4.34	4.12

TABLE 18

MANUAL DEXTERITY IN YOUNGER SUBJECTS

Weeks	1	2	3	4	5
Groups					
High E	39.17	40.89	39.83	41.36	44.56
Low E	36.93	35.25	37.78	38.67	40.89

Source of Variation	DF	SS	MS	VR
Groups	1	239.28	239.28	10.103**
Weeks	4	275.36	68.84	2.907*
Sessions	2	160.04	80.03	3.379*
Groups Weeks	4	38.77	9.69	0.409
Groups Sessions	2	19.07	9.54	0.403
Weeks Sessions	8	9.80	1.23	0.053
Groups Weeks Sessions	8	35.24	4.41	0.186
Residual	60	1421.04	23.68	
TOTAL	89	2198.60		

TABLE 19

MANUAL DEXTERITY IN OLDER SUBJECTS

Weeks	1	2	3	4	5	6	7
Groups							
High E	32.36	33.17	33.86	34.81	34.08	35.19	36.63
Low E	30.44	29.47	30.83	30.03	30.61	31.43	31.71

Source of Variation	DF	SS	MS	VR
Groups	1	420.75	420.75	9.264**
Weeks	6	110.16	18.36	0.404
Sessions	2	85.22	42.61	0.938
Groups Weeks	6	28.43	4.74	0.104
Groups Sessions	2	0.11	0.06	0.001
Weeks Sessions	12	11.08	0.93	0.020
Groups Weeks Sessions	12	12.11	1.01	0.022
Residual	84	3815.11	45.43	
TOTAL	125	4482.97		

TABLE 20

DIGIT SYMBOL SUBSTITUTION IN YOUNGER SUBJECTS

Weeks	1	2	3	4	5
Groups					
High E	205.7	200.6	196.0	205.1	218.1
Low E	210.9	209.8	196.2	215.9	226.4

TABLE 21

DIGIT SYMBOL SUBSTITUTION IN OLDER SUBJECTS

Weeks	1	2	3	4	5	6	7
Groups							
High E	184.7	193.6	186.4	187.4	191.6	199.7	199.1
Low E	201.8	198.3	204.0	200.1	212.8	222.2	224.0

Source of Variation	DF	SS	MS	VR
Groups	1	9378	9378	5.917*
Weeks	6	6854	1142	0.721
Sessions	2	921	460	0.290
Groups Weeks	6	1255	209	0.133
Groups Sessions	2	468	234	0.148
Weeks Sessions	12	2837	236	0.149
Groups Weeks Sessions	12	963	80	0.051
Residual	84	133126	1585	
TOTAL	125	155800		

TABLE 22

CARD SORTING: DECISION TIME IN YOUNGER SUBJECTS

Two Categories					
Weeks	1	2	3	4	5
Groups					
High E	12.78	11.76	11.40	11.74	12.74
Low E	12.44	13.81	13.19	12.93	12.41
Four Categories					
Groups					
High E	16.97	17.36	15.77	15.06	16.91
Low E	17.88	18.63	19.11	18.90	18.49
Eight Categories					
Groups					
High E	19.53	18.46	18.01	19.07	18.09
Low E	18.58	21.51	20.43	18.84	18.43

TABLE 23

Source of Variation	DF	SS	MS	VR
Groups	1	120.801	120.801	12.087***
Weeks	4	21.614	5.403	0.541
Sessions	2	6.425	3.212	0.321
Category	2	2114.436	1057.218	105.786***
Groups Weeks	4	66.551	16.638	1.665
Groups Sessions	2	2.899	1.449	0.145
Weeks Sessions	8	48.678	6.085	0.609
Groups Category	2	25.643	12.831	1.283
Weeks Category	8	18.089	2.261	0.226
Sessions Category	4	15.565	3.891	0.389
Groups Weeks Sessions	8	34.449	4.311	0.431
Groups Weeks Category	8	41.009	5.126	0.513
Groups Sessions Category	4	25.439	6.360	0.636
Weeks Sessions Category	16	155.837	9.739	0.975
Groups Weeks Sessions Category	16	118.505	7.407	0.741
Residual	180	1798.899	9.994	
TOTAL	269	4614.875		

TABLE 24

CARD SORTING: DECISION TIME IN OLDER SUBJECTS

Two Categories

Weeks	1	2	3	4	5	6	7
Groups							
High E	13.09	13.77	13.40	12.67	14.78	14.37	14.33
Low E	13.33	13.94	14.87	17.39	14.50	15.38	12.54

Four Categories

Groups							
High E	18.06	18.04	16.73	15.57	19.59	17.40	17.51
Low E	18.03	18.64	20.21	19.91	18.79	19.06	17.71

Eight Categories

Groups							
High E	23.17	23.04	21.90	22.39	22.69	22.58	21.79
Low E	23.34	20.11	22.89	23.47	20.99	21.28	19.73

the drug, in comparison with baseline, and both groups of introverts showed a decline at all three different levels of complexity, although these differences were significant statistically only in the younger age group (Figures 14,15 Tables 22,24).

The effect of the drug on subjective feeling states appeared to be greater on introverts as well. Figure 16 shows that in the older age group, while there was little initial difference in the effect of mesoridazine on self-rated subjective concentration, the introverts continued to be affected throughout the drug period, in terms of frequency of fluctuations greater than two standard deviations from the mean, and that this effect continued into withdrawal.

Discussion

This 'post-hoc' analysis of data gathered in earlier experiments yielded information of interest on several grounds. First, the consistent difference of response patterns between extraverts and 'introverts', across age groups, with the administration of mesoridazine occurred on almost all the parameters. Despite the small numbers involved statistically, significant differences were obtained on several of the comparisons, and notably on the manual dexterity and vigilance tasks.

It had been concluded, especially in the study of the effects of mesoridazine on subjects in the older age

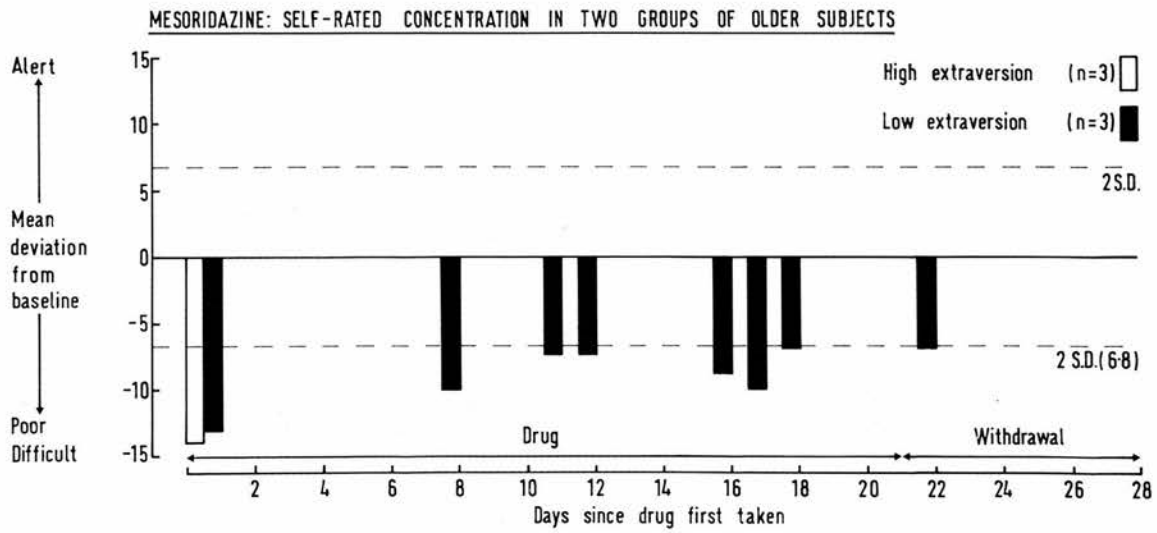

MESORIDAZINE: SELF-RATED CONCENTRATION IN TWO GROUPS OF OLDER SUBJECTS
Alert
Mean deviation from baseline
Poor Difficult
15
10
5
0
-5
-10
-15
High extraversion (n=3)
Low extraversion (n=3)
2S.D.
2 S.D.(6·8)
Drug
Withdrawal
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Days since drug first taken

FIGURE 16

group, that the drug had little disruptive effect on performance, even with continued administration and abrupt withdrawal. More detailed examination of the data has suggested, however, when the subjects are divided into groups on the basis of an extensively documented typology, that not only may the drug have an initially deleterious effect on performance but that disruption may in some cases increase with continued administration. It is possible, also, that abrupt withdrawal might, in some instances, cause a deterioration where no decrement had occurred on initial administration.

Averaging of subjects' performance scores is intended to give a general picture of the general trend of change with repeated testing under different conditions. These data are sometimes adequate but when the effects of a drug are being assessed, greater caution is needed since, while the majority may not be affected, there may be some who are affected to the extent of being at risk in some situations, e.g. driving. This 'post-hoc' analysis suggested that some people may be affected more than others, both objectively and subjectively, and that the extent of the effects may be related to personality type. However, retrospective analysis of data from such small groups is of little value unless the results can be replicated using larger

groups of subjects. Consequently a larger study was planned and this is described in chapter 9.

CHAPTER 9

A COMPARISON OF THE EFFECTS OF MESORIDAZINE ON TWO GROUPS OF OLDER SUBJECTS

Introduction

A further study was designed as a result of the possibility that mesoridazine has differential effects on different personality types. It was predicted that if there were differences between groups examined on a 'post-hoc' basis, and that if these differences were consistent across subjects of different ages, then the differences should be greater in subjects selected for their polarised scores on the same parameter. The hypotheses were put forward that introverts would be affected to a greater extent than would extraverts of the same age group on both a battery of psychomotor performance tests and self-rated feeling states, and both initially and with continued administration.

Subjects

A large number of individuals, all over the age of fifty and known to be willing to be subjects in studies in either the sleep or performance laboratory, were sent a study description. If willing to volunteer for this study, they were asked to complete the Eysenck Personality Inventory, Form A. All subjects chosen had scored at least one and a half standard deviations above or below the mean. The extravert group had a mean age of 56 years and a mean E scale score of 16.75 (S.D. =2.71; range = 14-21)

and the introvert group had a mean age of 58 years and a mean E scale score of 6.75 (S.D. = 2.12; range = 4-9). The N and L scale scores for the two groups were not significantly different. The extravert group had a mean N scale score of 8.5 (S.D. = 4.63) and an L scale mean of 2.63 (S.D. = 1.41); the N scale mean for the introvert group was 7.5 (S.D. = 4.84) and the L scale mean score was 3.13 (S.D. = 1.96). There were eight subjects in each group. The extravert group contained five women and three men; the introvert group contained three women and five men. None had taken CNS drugs in the preceding months and all agreed to refrain from taking alcohol for the period of the study.

Procedure

Subjects attended the laboratory weekly over a period of six weeks. The first attendance was for orientation and practice and scores were not included in the analysis. Testing weeks 1 and 2 provided placebo baseline scores. The active drug was administered for the first time the night before test day 3 and by test day 4 the subjects had had eight nights of mesoridazine (10 mg). The subjects continued to receive the drug capsules for another six nights before they were substituted by matched placebo controls.

Thus on test day 5 the subjects had received placebo again for the first time the night before testing, and a measure of any early withdrawal effects would be obtained.

Subjects reported to the laboratory at 0915 hours on each test day and the three testing sessions, following the "two hours on - two hours off" schedule, started at 0930, 1330 and 1730 hours.

The test measures included:

Performance tasks

(1) Auditory vigilance

(2) Manual dexterity

(3) Digit symbol substitution (DSST)

(4) Card-sorting

(5) Logical reasoning.

Self-rating scales

(1) Quality of sleep

(2) Morning vitality

(3) Anxiety

(4) Concentration.

In the auditory vigilance task subjects were instructed to respond more fully than was required in the other studies. The task was the same as described in the methodology (Chapter 3) i.e. signals occurred every two seconds and lasted 500 msec, while target signals occurred infrequently and lasted 400 msec.

Detection of a target signal was recorded, first, by pressing an identifier button and, second, by pressing one of the three confidence buttons, which corresponded to the opinions - 'very sure', 'reasonably sure' and 'not at all sure'. Binford and Loeb (1966) studied response patterns during a vigilance task in a group which simply reported whether or not they thought a signal had occurred and in a group allowed three categories of response confidence. They reported that correct detections improved only slightly over 9 sessions while commission errors decreased, with the multiple criterion group making consistently fewer errors. Using signal detection theory analysis, they concluded that there was a gradual decrease in the discriminability of the stimulus and an increase in the level of caution employed by the subjects, thus indicating a reduction in confusion about the characteristics of the signal with repeated testing.

A confidence level rating method has been used in both auditory and visual vigilance tasks in the detection of a target signal (Broadbent and Gregory, 1963a). It was concluded that the ratio of detections to false positive detections became less as responses of lower confidence levels were included, and that there was little change in d' during the session, while increased with the most cautious criterion but not with the riskiest criterion.

The Logical Reasoning task was included, for the first time, since it was felt that none of the other tasks in the battery adequately measured intellectual agility. The DSST task measures concentration and memory, while the card-sorting task measures information processing, at varying levels of complexity, but is straightforward and subject-paced. It was considered that an experimenter-paced test of correct and incorrect syllogism recognition might detect any drug-induced impairment of intellectual function. Forty slides of simple logical propositions were projected onto a large screen so that the words were clearly legible to all subjects. The 40 slides were projected onto the screen for 5 seconds each by an automatic projector, which had been cued to pause for five seconds after the twentieth slide. The first twenty slides contained statements including the word 'follows', e.g.

A follows B BA

A follows B AB

B is followed by A BA

B is followed by A AB

The subject's task was to decide whether the statements were logically consistent. The second block of twenty slides followed a similar pattern but the word 'follow' was substituted by 'precede'.

This form of reasoning task was used in preference to others since any impairment of this faculty is more likely to be detected in an experimenter-paced task. Furthermore, the task requirements are fairly simple and a long-term practice effect is unlikely to occur, while the rearrangement after each session of the presentation order within each twenty slide block precludes the possibility of a high number of correct responses as a result of a response set rather than examination of and response to each slide individually.

A second placebo baseline test day was included in this design to establish whether repeated testing under placebo conditions resulted in an improvement in performance in a way similar to that reported in Chapter 4 in young adults. With only one baseline record a lack of change from baseline could be interpreted as either a lack of drug effect or as an inhibition of improvement. With two baseline records, however, it might be possible to draw conclusions about a drug's effects on the basis of the degree of difference between the two baselines. Thus an improvement in performance from the first to the second baseline followed by a continued improvement with the introduction of the drug might indicate that the drug does not have a noticeably deleterious effect while a

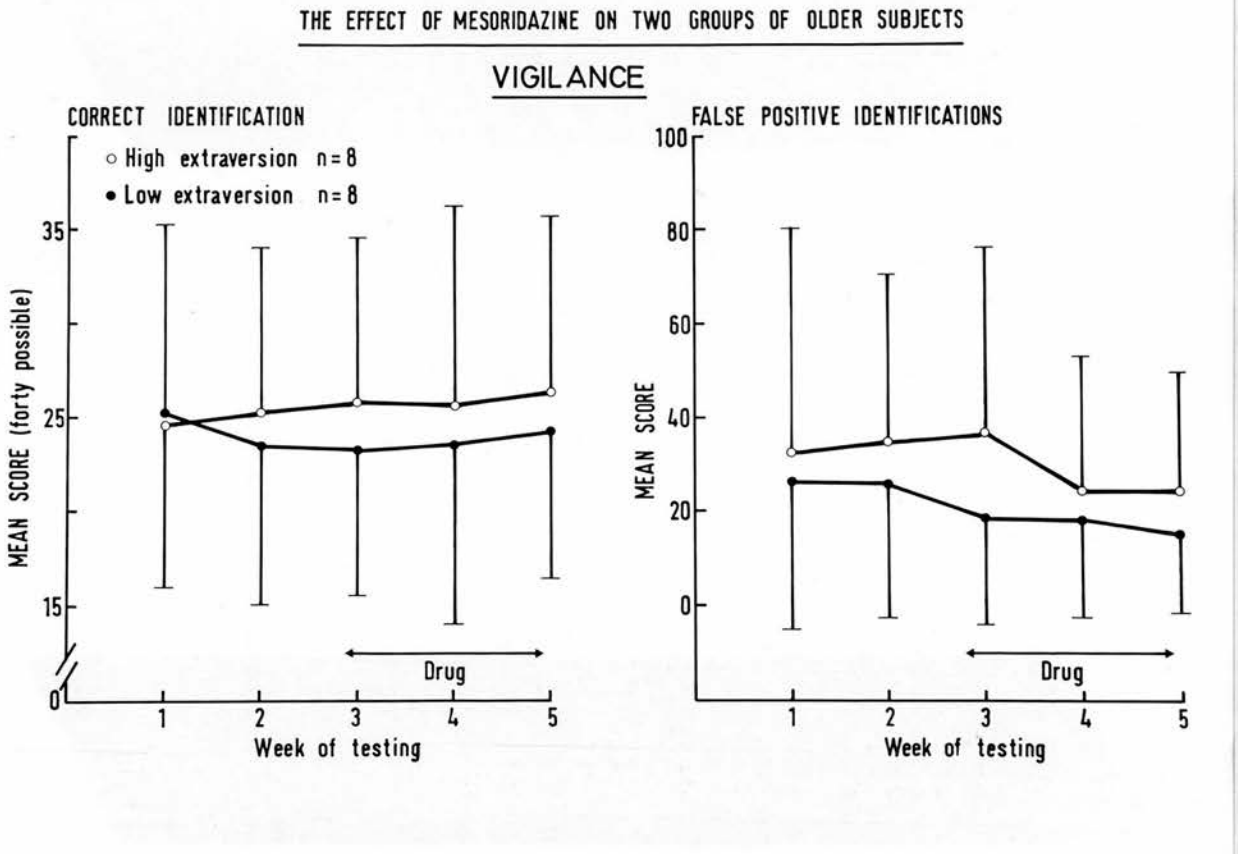
pattern of either no change or decrement might indicate that the drug has either an inhibitory or more deleterious effect.

During the second placebo test day, subjects completed two further personality inventories. The Eysenck Personality Inventory, Form B, and the PQ inventory were administered in order to assess test-retest reliability in the two groups and to examine the assertion that the 'Psychoticism' scale is of experimental value (Eysenck and Eysenck, 1968c; Claridge and Birchall, 1973; Claridge and Chappa, 1973; Stroh, 1970). The PQ Inventory, a development of the PEN Inventory, has several different forms and an example of the version used is enclosed in Appendix 1.

Results

Analysis of variance revealed no statistically significant differences between the correct detection rates of the two groups. Examination of the overall mean scores by week revealed that the extravert group detected more signals after the first week, with a slight improvement on taking the drug and also on its withdrawal, while the introvert group showed an onto-drug decrement which disappeared on withdrawal (Table 25Figure 17). Examination of the morning session data showed a decrement, with the introduction

FIGURE 17



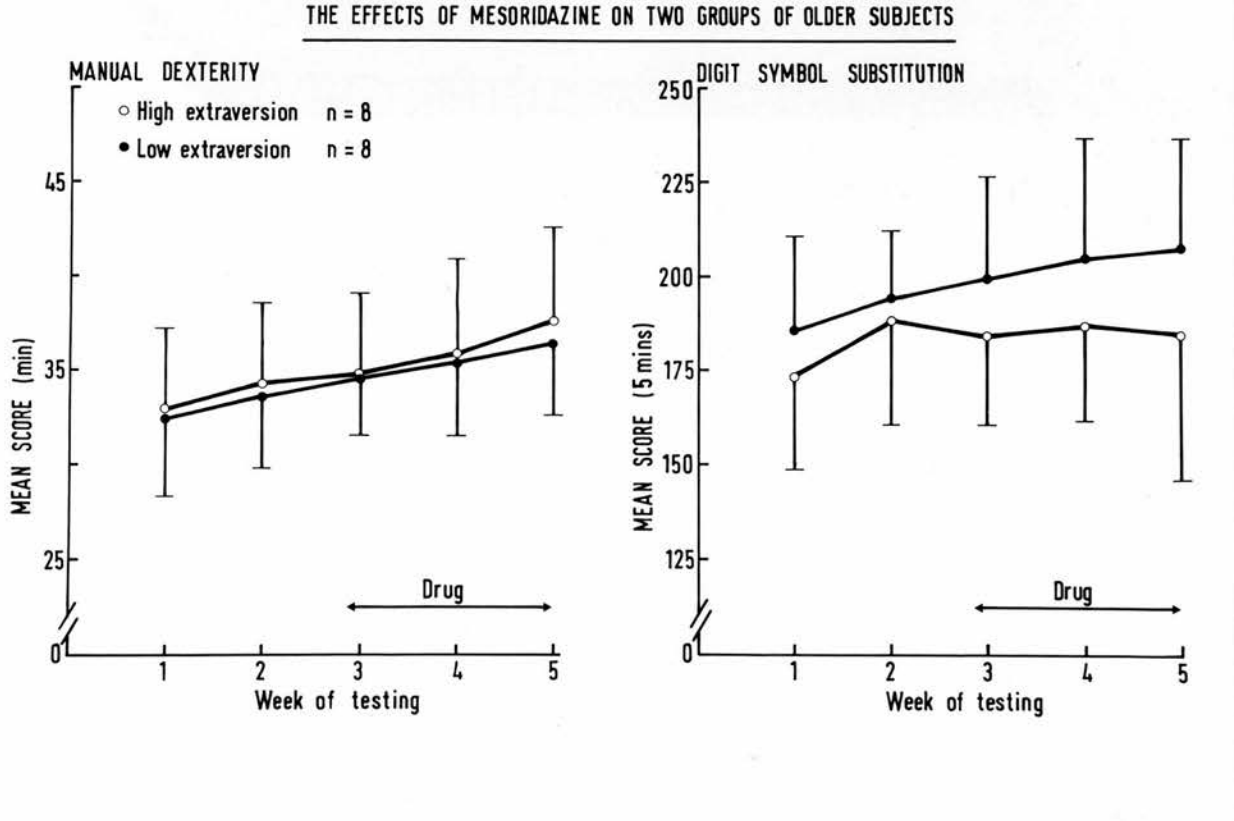


FIGURE 18

TABLE 25

VIGILANCE: CORRECT DETECTIONS

SESSIONS		1	2	3	Mean	S.D.
Groups	Weeks					
High E	1	26.87	23.75	23.50	24.71	8.7
	2	27.11	24.00	24.75	25.29	8.7
	3	26.25	24.63	26.63	25.83	8.7
	4	26.50	24.25	26.11	25.63	10.7
	5	26.00	28.37	24.37	26.25	9.4
Low E	1	25.25	25.11	25.11	25.17	10.1
	2	25.87	22.62	21.87	23.46	8.4
	3	22.50	24.87	22.62	23.33	7.8
	4	21.75	22.75	26.00	23.50	9.5
	5	25.00	24.37	23.11	24.17	7.7

of the drug, in both groups but the impairment was relatively larger and increased in the introvert group, disappearing only on withdrawal.

More detailed examination of the correct detection vigilance data, by dividing the one hour task into 15 minute sections and scoring the mean correct detections in each section in order to assess any change in response pattern through the session, indicated that the performance of both groups deteriorated with time on task under baseline conditions (Table 26). On the first baseline test day the overall mean score of the introvert group was slightly better but this pattern was reversed on the second baseline test day. Examination of these data by session revealed no significant pattern of difference. Drug administration appeared to have little effect on overall mean detection scores in either group, with the introvert group continuing to show more deleterioration through the sessions. Withdrawal produced an improvement in detection rates in both groups (Table 26). Examination of the morning session data revealed that the extravert group was less affected by the introduction of the drug. Withdrawal showed an improvement in detections, especially in the earlier part of the session, but a decrement did occur in the last quarter where improvement had been the pattern in previous weeks. The

introvert group showed an onto-drug decline in detection in the morning session, especially in the first part of the session (Table 28). This decrement had disappeared by midday. A similar, but less marked, decrement was evident after eight days on the drug, but this was abolished with withdrawal. In the last quarter of the withdrawal test day morning session the introvert group also showed a progressive decline in detections through the session where the previous pattern was one of late improvement. It may be, therefore, that withdrawal of the drug improves alertness but impairs the ability to sustain attention and improve performance in anticipation of the end of the task.

The correct detection confidence level chosen by subjects in both groups tended to increase with repeated testing. In both groups, on both baseline days, there was a percentage increase in high confidence detections through the day, with subjects being relatively more confident in their detections in the later sessions of the second baseline test day (Table 29). Introduction of the drug did not impair the percentage of high confidence detections in either group, indeed there was an increase, notably in the morning session in both groups. The pattern of increasing confidence in detection continued on the second drug test day and

TABLE 26

VIGILANCE: CORRECT DETECTIONS

Mean score by quarter hour

Weeks		1	2	3	4	5
		Mean SD	Mean SD	Mean SD	Mean SD	Mean SD
Groups						
High E	1	6.9±2.5	7.4±3.1	7.0±319	7.1±4.5	7.7±4.4
	2	5.3±2.2	6.6±4.3	6.3±3.9	6.8±4.6	6.8±4.3
	3	5.8±2.9	6.1±3.3	6.3±3.7	6.0±4.8	6.4±4.3
	4	5.9±2.6	5.8±3.8	6.1±3.9	5.8±4.4	5.4±4.7
Low E	1	7.3±4.3	7.2±4.3	6.9±4.2	7.2±4.1	7.3±4.0
	2	6.4±3.8	6.5±4.1	6.5±4.0	6.0±3.9	6.1±4.0
	3	6.2±3.5	5.0±4.1	4.7±3.7	4.6±5.1	5.6±4.0
	4	5.7±4.0	4.9±4.0	4.9±4.0	5.6±4.6	5.4±3.5

TABLE 27

Source of variation	DF	SS	MS	VR
Groups	1	40.017	40.017	5.173*
Weeks	4	8.090	2.022	0.261
Sessions	2	8.033	4.017	0.519
Division	3	432.554	144.185	18.640***
Groups Weeks	4	23.598	5.899	0.763
Groups Sessions	2	3.958	1.979	0.256
Weeks Sessions	8	34.843	4.355	0.563
Groups Division	3	26.675	8.892	1.149
Weeks Division	12	26.685	2.224	0.287
Sessions Division	6	41.608	6.935	0.896
Groups Weeks Sessions	8	22.833	2.854	0.369
Groups Weeks Division	12	40.210	3.351	0.433
Groups Sessions Division	6	21.450	3.575	0.463
Weeks Sessions Division	24	90.183	3.758	0.486
Groups Weeks Sessions Division	24	53.008	2.209	0.286
Residual	840	6497.723	7.735	
TOTAL	959	7371.465		

TABLE 28

VIGILANCE: CORRECT DETECTIONS

Morning Session Scores by Quarter-hour

Weeks		1	2	3	4	5
Groups						
High E	1	7.250	7.250	7.000	6.750	8.500
	2	6.750	7.375	5.875	6.750	6.375
	3	6.250	5.875	6.375	6.125	6.250
	4	6.625	6.500	6.500	6.875	4.875
Low E	1	7.375	7.375	5.875	6.500	8.000
	2	6.125	6.000	6.500	6.250	6.250
	3	6.750	5.500	4.375	4.250	5.875
	4	5.250	6.000	5.750	5.750	4.875

TABLE 29

VIGILANCE: CORRECT DETECTIONS

Detections at the highest confidence level as a percentage of total detections

Weeks	1	2	3	4	5
Groups					
Morning Session					
High E	48	47	59	74	48
Low E	48	49	56	66	64
Midday Session					
High E	49	63	63	70	76
Low E	53	53	61	67	67
Afternoon Session					
High E	53	61	75	76	73
Low E	56	60	65	59	64

remained most noticeable in the morning session. The general pattern of increasing confidence in the correctness of correct detections was disrupted by the withdrawal of mesoridazine. In the midday and afternoon sessions there was little difference from confidence levels while on the drug and in the morning session there was a decrease in percentage high confidence detections, especially in the extravert group which showed a decline from 74% to 48%.

False positive detections declined with repeated testing in introverts. There was a slight onto-drug increase in commission errors in the extravert group but this was not statistically significant and the pattern of responding was essentially similar in the two groups, although the level was significantly higher in the extravert group (Table 30 Figure 17). However, on the morning after first taking the drug the extravert group made more commission errors than at any other time in the study, while the introvert group showed a decline, which persisted through the day.

Examination of the false positive detection data by quarter-hour showed that there was little decline in detection levels with time on task in either group under placebo conditions (Tables 31,32). The extravert group responded at a higher rate on both baseline days and this pattern was not affected by mesoridazine or its

TABLE 30

VIGILANCE: FALSE POSITIVE DETECTIONS

SESSION					
Weeks		1	2	3	Mean
Groups					
High E	1	42.9	27.5	26.7	32.4
	2	40.4	28.7	33.6	34.1
	3	44.9	29.6	33.5	36.0
	4	24.2	22.1	26.5	24.3
	5	21.1	25.9	23.6	23.5
Low E	1	30.6	23.5	24.0	26.0
	2	29.0	26.5	22.1	25.9
	3	24.2	17.2	13.9	18.5
	4	20.9	17.5	16.7	18.4
	5	13.1	14.7	17.4	15.1

Source of Variation	DF	SS	MS	VR
Groups	1	5217	5217	5.036*
Weeks	4	4473	1118	1.079
Sessions	2	1659	830	0.801
Groups Weeks	4	1077	269	0.260
Groups Sessions	2	193	97	0.093
Weeks Sessions	8	1689	211	0.204
Groups Weeks Sessions	8	547	68	0.066
Residual	210	217553	1036	
TOTAL	239	232408		

TABLE 31

VIGILANCE: FALSE POSITIVE DETECTIONS

Mean score by quarter-hour

Weeks		1	2	3	4	5
Groups						
High E	1	8.75	9.43	9.33	6.96	7.69
	2	7.67	8.17	8.58	5.29	6.00
	3	7.30	7.50	9.00	4.71	5.00
	4	8.67	9.17	9.19	6.67	4.75
Low E	1	5.96	5.93	5.79	4.50	4.67
	2	5.33	6.17	5.71	5.19	3.11
	3	5.08	5.71	5.11	4.46	3.04
	4	5.54	6.37	5.54	5.96	4.30

TABLE 32

Source of Variation	DF	SS	MS	VR
Groups	1	1292.70	1292.70	17.439***
Weeks	4	969.55	242.39	3.270**
Sessions	2	369.00	184.50	2.489*
Division	3	207.85	69.30	0.935
Groups Weeks	4	174.19	43.56	0.588
Groups Sessions	2	46.19	23.11	0.313
Weeks Sessions	8	453.66	56.71	0.765
Groups Division	3	47.15	15.73	0.212
Weeks Division	12	93.98	7.75	0.105
Sessions Division	6	166.55	27.76	0.374
Groups Weeks Sessions	8	166.19	20.78	0.280
Groups Weeks Division	12	83.05	6.93	0.093
Groups Sessions Division	6	64.08	10.68	0.144
Weeks Sessions Division	24	309.66	12.00	0.174
Groups Weeks Session Division	24	324.11	13.51	0.183
Residual	840	62266.69	74.13	
TOTAL	959	67033.63		

withdrawal. The difference in response level between the groups was statistically significant ($p < 0.001$). Administration of the drug was associated with an increase in responses in the extravert group and a concomitant decline in the introvert group. There was a reduction in commission errors by both of the groups in the second drug week, this was substantial in the former group, while scores increased in the extravert group and decreased in the introvert group on the withdrawal test day.

There were no differences between the two groups on the manual dexterity task, even on the morning after first administration and after withdrawal (Table 33 Figure 18). Throughout, the extravert group were slightly quicker, but there was greater inter-subject variability; both groups improved through the day and from week to week, but these changes were not statistically significant.

The extravert group was significantly slower on the DSST ($p < 0.001$) (Table 34 Figure 18). There was a non-significant overall mean onto-drug decline in performance in this group and a similar occurrence on withdrawal. Examination of the data by sessions indicated that the onto-drug decrement occurred in the midday and afternoon sessions and that in the morning session there was a slight improvement over both baseline morning session scores. Withdrawal of mesoridazine did not appear to

TABLE 33

MANUAL DEXTERITY

SESSIONS		1	2	3	Mean S.D.
Groups					
High E	1	31.71	32.97	33.22	32.64 ± 4.56
	2	33.31	34.28	35.16	34.5 ± 4.25
	3	34.01	34.91	35.41	34.78 ± 4.19
	4	34.81	36.25	36.31	35.79 ± 5.00
	5	36.44	37.94	38.06	37.48 ± 5.22
Low E	1	31.59	32.78	32.81	32.40 ± 4.15
	2	32.37	34.00	34.66	33.68 ± 3.91
	3	33.47	35.53	34.87	34.63 ± 3.05
	4	34.16	35.84	36.13	35.37 ± 3.96
	5	36.73	35.19	37.22	36.37 ± 3.79

TABLE 34

DIGIT SYMBOL SUBSTITUTION

SESSIONS					
Groups					
High E	1	170.63	177.87	169.63	172.71 ± 24.5
	2	181.00	191.75	191.11	187.97 ± 28.2
	3	183.37	185.00	184.75	184.04 ± 24.4
	4	185.00	188.75	186.87	186.87 ± 23.6
	5	191.50	187.63	173.75	183.96 ± 38.9
Low E	1	181.50	186.75	192.25	186.83 ± 24.2
	2	188.13	189.35	205.87	194.43 ± 28.9
	3	201.75	199.02	198.75	199.83 ± 28.8
	4	209.50	208.87	196.11	204.83 ± 31.1
	5	211.37	199.75	209.00	206.71 ± 31.1

Source of Variation				
Groups	1	14260.4	14260.4	16.343***
Weeks	4	8120.7	2030.2	2.326
Sessions	2	57.7	28.9	0.033
Groups Weeks	4	1707.6	426.9	0.489
Groups Sessions	2	809.4	404.7	0.464
Weeks Sessions	8	3285.8	410.7	0.471
Groups Weeks Sessions	8	2013.9	251.7	0.288
Residual	210	183256.0	872.6	
TOTAL	239	213511.4		

affect performance in the morning session either but performance was relatively poorer on both of the later sessions. The introvert group also showed a pattern of slight onto-drug morning session improvement and afternoon session decrement but in this instance the effect persisted into the second drug week. Withdrawal had little effect.

The extravert group made significantly more errors in the logical reasoning task ($p < 0.05$) (Table 35). The general pattern, in both groups, showed a decline in errors with repeated testing, but there was a slight and non-significant increase in errors on the morning after first taking the drug. This effect did not persist until the midday session. Withdrawal had little effect on extraverts and did not inhibit the gradual, but non-significant, decrease in errors by the introvert group.

There were no statistically significant differences between the groups on the card-sorting task. Overall mean scores were higher after the extraverts went onto the drug, at all levels of complexity. The same was true for the introverts at the two simpler levels (Figure 19, Tables 36, 37). Withdrawal of the drug was associated with a slight improvement in the performance of the extraverts and a slight deterioration in the performance of the introverts.

THE EFFECTS OF MESORIDAZINE ON TWO GROUPS OF OLDER SUBJECTS

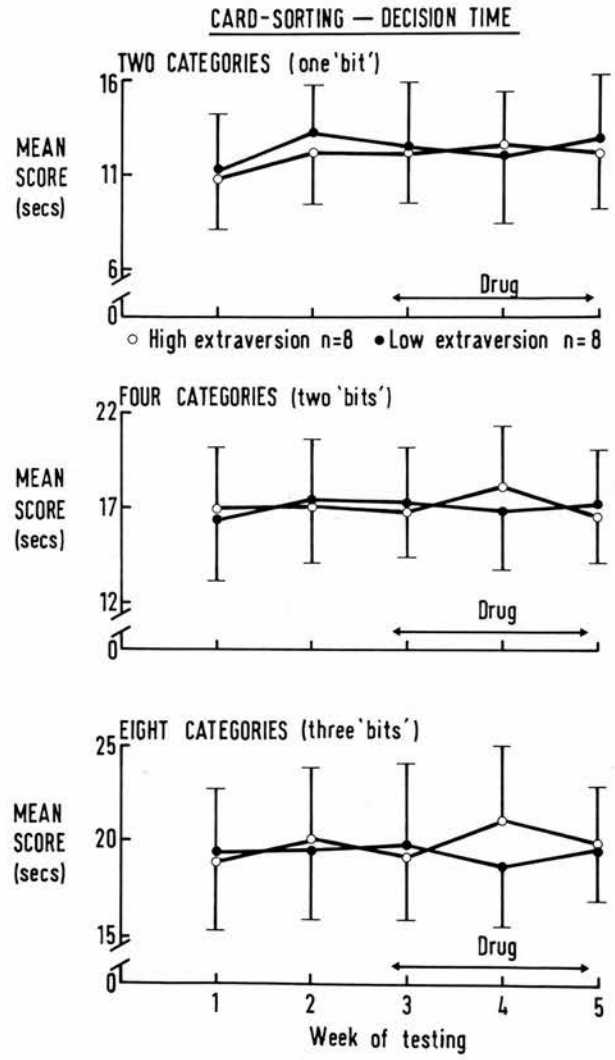


FIGURE 19

TABLE 35

LOGICAL REASONING

SESSIONS		1	2	3	Mean
Groups					
High E	1	4.75	6.00	3.13	4.63
	2	2.75	2.87	2.75	2.79
	3	3.00	2.12	2.12	2.43
	4	2.12	1.00	1.25	1.46
	5	1.87	2.25	1.37	1.83
Low E	1	2.25	1.62	1.50	1.79
	2	0.75	3.75	0.50	1.67
	3	1.50	2.00	1.00	1.50
	4	0.87	0.87	2.50	1.42
	5	0.50	0.50	0.50	0.50

Source of Variation	DF	SS	MS	VR
Groups	1	93.75	93.75	5.679*
Weeks	4	121.21	30.30	1.836
Sessions	2	16.43	8.22	0.497
Groups Weeks	4	49.21	12.30	0.745
Groups Sessions	2	7.07	3.54	0.214
Weeks Sessions	8	44.63	5.58	0.338
Groups Weeks Sessions	8	50.97	6.37	0.386
Residual	210	3466.74	16.51	
TOTAL	239	3849.99		

TABLE 36

CARD-SORTING: DECISION TIME

Morning Session

Category		1	2	3
Groups	Weeks			
High E	1	9.55	16.10	18.45
	2	12.06	16.41	21.44
	3	10.89	17.84	20.49
	4	11.44	17.41	21.06
	5	12.74	17.22	20.32
Low E	1	10.85	16.45	21.26
	2	13.35	18.37	21.25
	3	12.45	17.55	20.54
	4	12.94	17.22	18.03
	5	13.91	17.06	20.64

Midday Session

High E	1	10.83	17.56	18.71
	2	13.71	18.54	19.51
	3	13.17	16.19	19.07
	4	13.69	18.30	21.11
	5	11.82	16.66	19.19
Low E	1	11.81	17.00	19.31
	2	13.36	16.61	18.65
	3	11.73	17.00	18.85
	4	11.77	16.76	19.51
	5	12.54	17.86	18.22

TABLE 37

CARD-SORTING: DECISION TIME

Afternoon Session

Category		1	2	3
Groups	Weeks			
High E	1	12.56	17.22	19.36
	2	11.30	16.40	19.42
	3	12.67	16.39	18.11
	4	12.54	18.60	21.09
	5	11.93	15.94	20.09
Low E	1	11.22	15.76	17.36
	2	12.97	16.96	18.86
	3	12.76	16.57	20.44
	4	11.30	16.55	18.69
	5	12.12	16.19	20.37

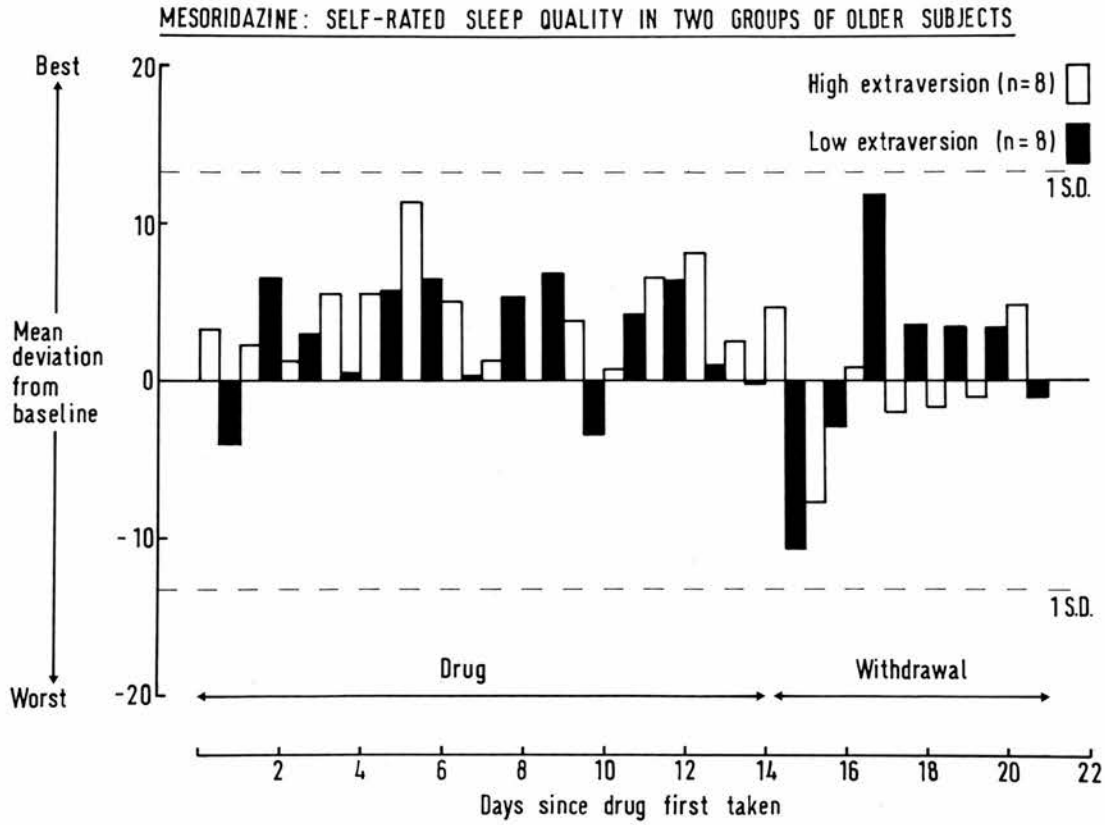
Week Mean Score

High E	1	10.98	16.96	18.84
	2	12.36	17.13	20.11
	3	12.25	16.80	19.23
	4	12.55	18.10	21.90
	5	12.16	16.61	19.87
Low E	1	11.30	16.40	19.31
	2	13.23	17.32	19.59
	3	12.31	17.04	19.94
	4	12.00	16.85	18.74
	5	12.86	17.04	19.74

The presentation of the self-rated feeling state data takes two forms. In the first, the data were calculated by taking the mean of each subject's drug and withdrawal day deviations from his baseline mean, as described in the methodology. Using this approach, sleep quality was rated as better than under placebo conditions by both groups (Figure 20). Withdrawal had a deleterious effect initially, especially for the introvert group, but this effect quickly disappeared. Morning vitality was reported by both groups to be impaired during the administration of the drug, especially in the second week, but this disruption disappeared on withdrawal (Figure 21). Mesoridazine had little effect on self-rated anxiety and concentration in either group for the period of the study (Figures 22, 23).

Examination of the raw data, however, led to the conclusion that there was wide inter-subject variability, under placebo baseline conditions, in the estimation of self-rated feelings both from day-to-day and from week-to-week. Some reported little fluctuation while others reported good sleep one night and very poor sleep the following night. Calculation of post baseline fluctuations based solely on baseline means tends to give disproportionate emphasis to the reports of the latter type of subject, with the paradoxical possibility

FIGURE 20



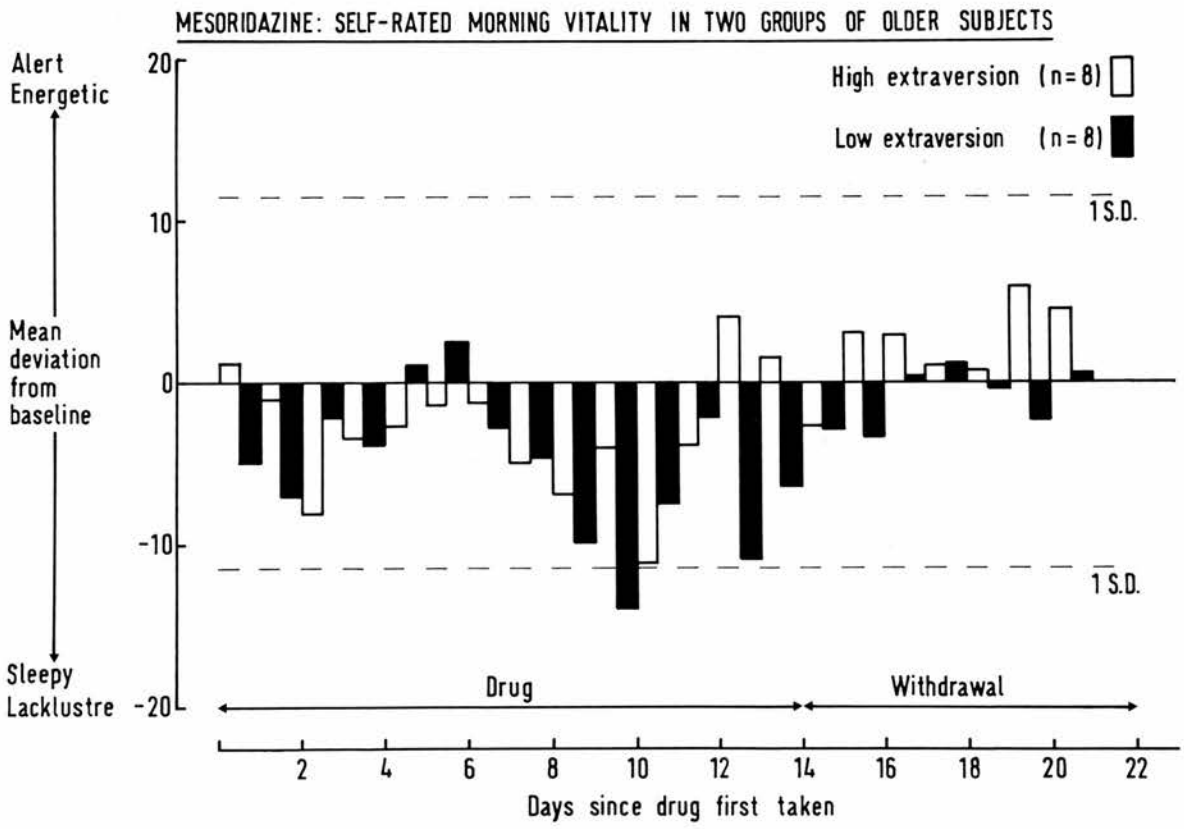
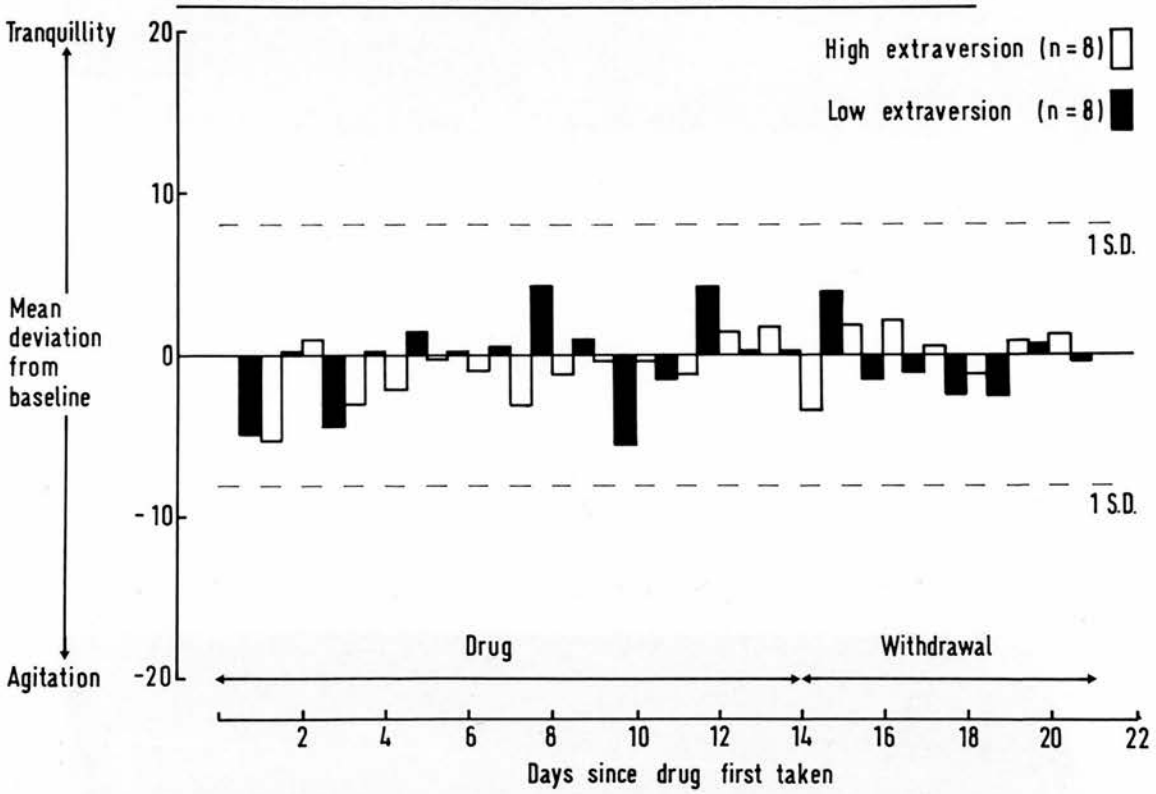


FIGURE 21

FIGURE 22



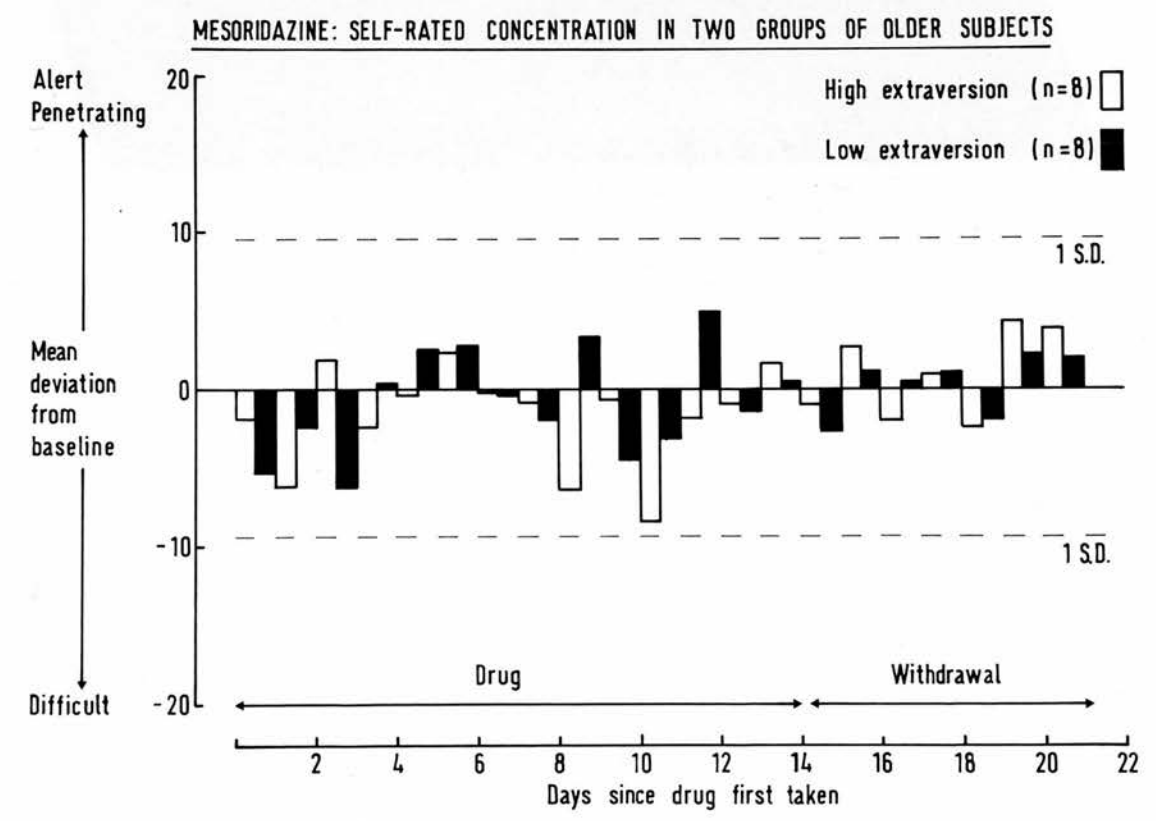


FIGURE 23

TABLE 38

SELF RATED SLEEP QUALITY

Week by week comparison

Source of Variation	DF	SS	MS	VR
Groups	1	115749	115749	3.505
Weeks	5	716496	143299	4.339***
Days	6	179471	29912	0.906
Groups Weeks	5	368451	73690	2.231*
Groups Days	6	203579	33930	1.027
Weeks Days	30	467616	15587	0.473
Groups Weeks Days	30	547765	18259	0.553
Residual	588	19420016	33027	
TOTAL	671	22019136		

Placebo weeks two and three compared with drug weeks

Source of Variation	DF	SS	MS	VR
Groups	1	312909	312909	7.970***
Condition	1	480973	480973	12.251***
Days	13	241336	18564	0.473
Groups Condition	1	102284	102284	2.605
Groups Days	13	281351	21642	0.551
Condition Days	13	275095	21162	0.539
Groups Condition Days	13	141674	10898	0.278
Residual	392	15390374	39261	
TOTAL	447	17225984		

TABLE 39

SELF RATED MORNING VITALITY

Second and third placebo weeks compared with drug weeks

Source of Variation	DF	SS	MS	VR
Groups	1	49335	49335	1.520
Condition	1	785197	785197	24.191***
Days	13	426565	32813	1.011
Groups Condition	1	125427	125427	3.864*
Groups Days	13	164881	12683	0.391
Condition Days	13	380069	29236	0.901
Groups Condition Days	13	220059	16928	0.522
Residual	392	12723850	32459	
TOTAL	447	14875379		

that such a report might not be any larger than occurred under baseline conditions and even then might obliterate a relatively large fluctuation reported by the former type of subject.

In order to assess a more equitable distribution of reported disruption, the same self-rated feeling data are presented in another form. A second transformation of the data was carried out. The baseline mean and standard deviation were calculated for each subject and the post-baseline fluctuations were calculated as percentages of the baseline standard deviation. Thus a subject who reported little fluctuation during baseline would have a small standard deviation and post-baseline changes, which might be small in relation to the reports of others but which were large in comparison with baseline fluctuations, would be given the relative emphasis they warranted. The swamping effect of the reports of subjects with large fluctuations, on the other hand, would be diminished since post-baseline fluctuations would be reduced when calculated as a percentage of their large baseline standard deviations.

Examination of self-rated sleep quality in this way showed that while the introvert group reported little change with the introduction of the drug, they did experience a slightly deleterious effect on initial withdrawal (Figure $_{25}$). The extravert group, on the

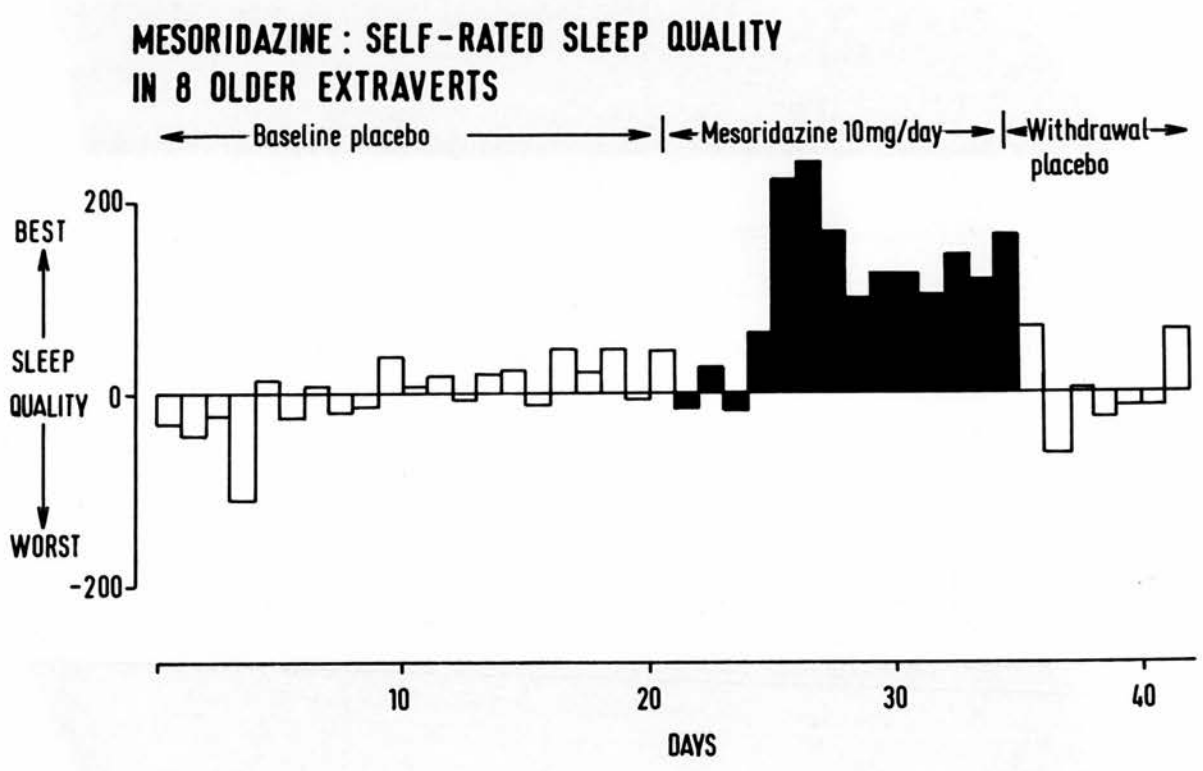
other hand, reported an improvement in sleep quality, especially initially, which disappeared on withdrawal without noticeable disruption (Figure 24). Statistical comparison over the whole study revealed a Groups X Weeks interaction ($p < 0.05$) and comparison of the second and third placebo weeks with the two drug weeks confirmed the difference in reported sleep quality between the two groups while receiving the drug (Table 38).

Morning vitality was reported to be reduced on receiving the drug by both groups. This effect was greater in the second drug week and the effect was overall greater in the extravert group (Figures 26, 27). There was a significant Groups X Conditions interaction ($p < 0.05$) (Table 39). Withdrawal caused little disruption in either group but there was a tendency for the extraverts to rate their vitality positively and for the introverts to rate negatively.

Mesoridazine and its withdrawal had little effect on self-rated anxiety in either group (Figures 28, 29). Indeed three of the four highest mean ratings of anxiety for both groups in the whole experiment occurred at the start of the study and are probably associated with attendance at the laboratory for the first time.

Mesoridazine and its withdrawal had no observable effect on concentration in the introvert group (Figure 31).

FIGURE 24 Feeling state rated as a percentage of baseline standard deviation.



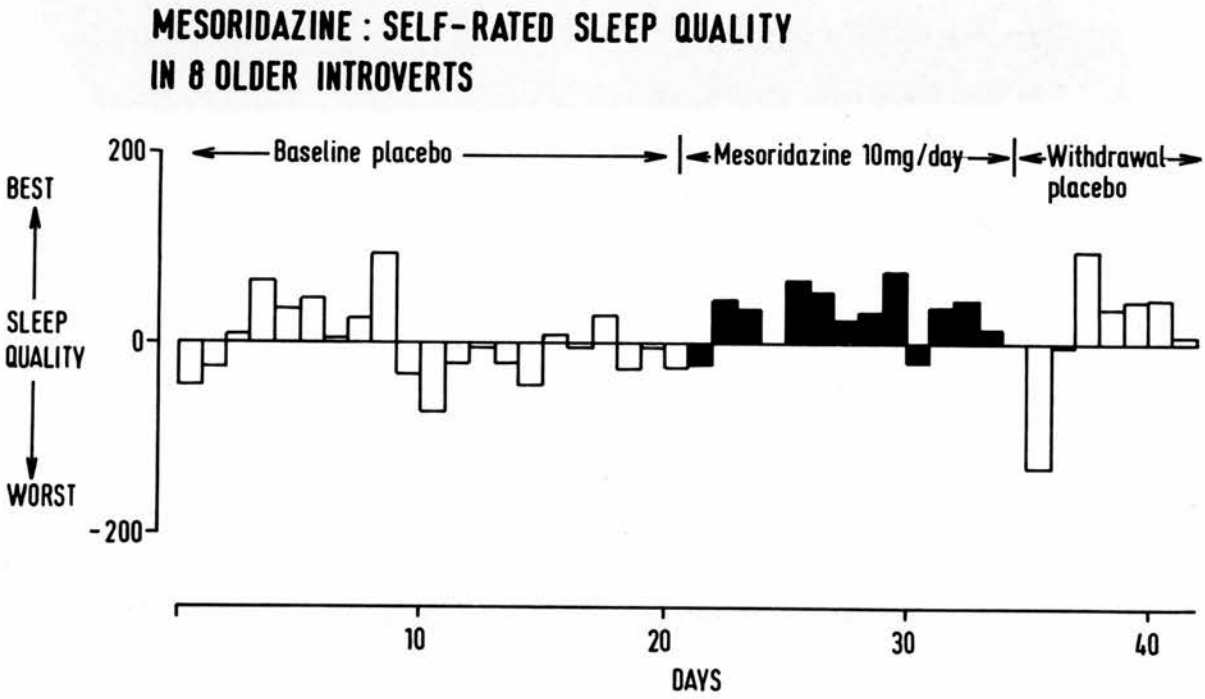
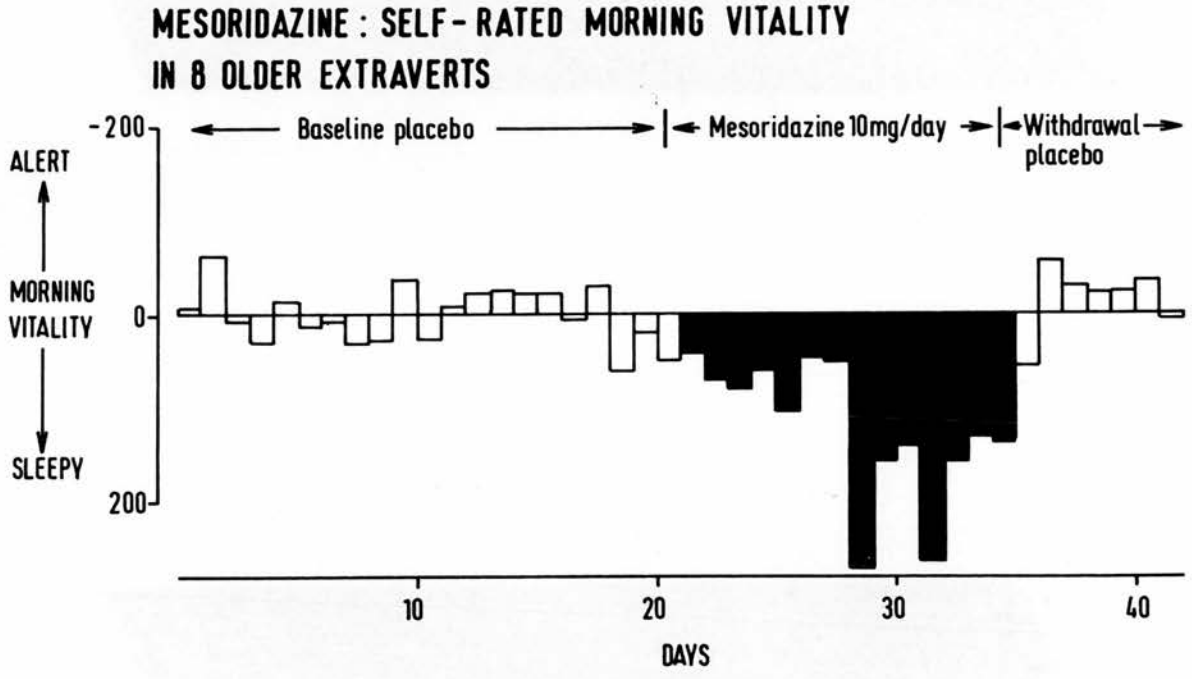


FIGURE 25

FIGURE 26



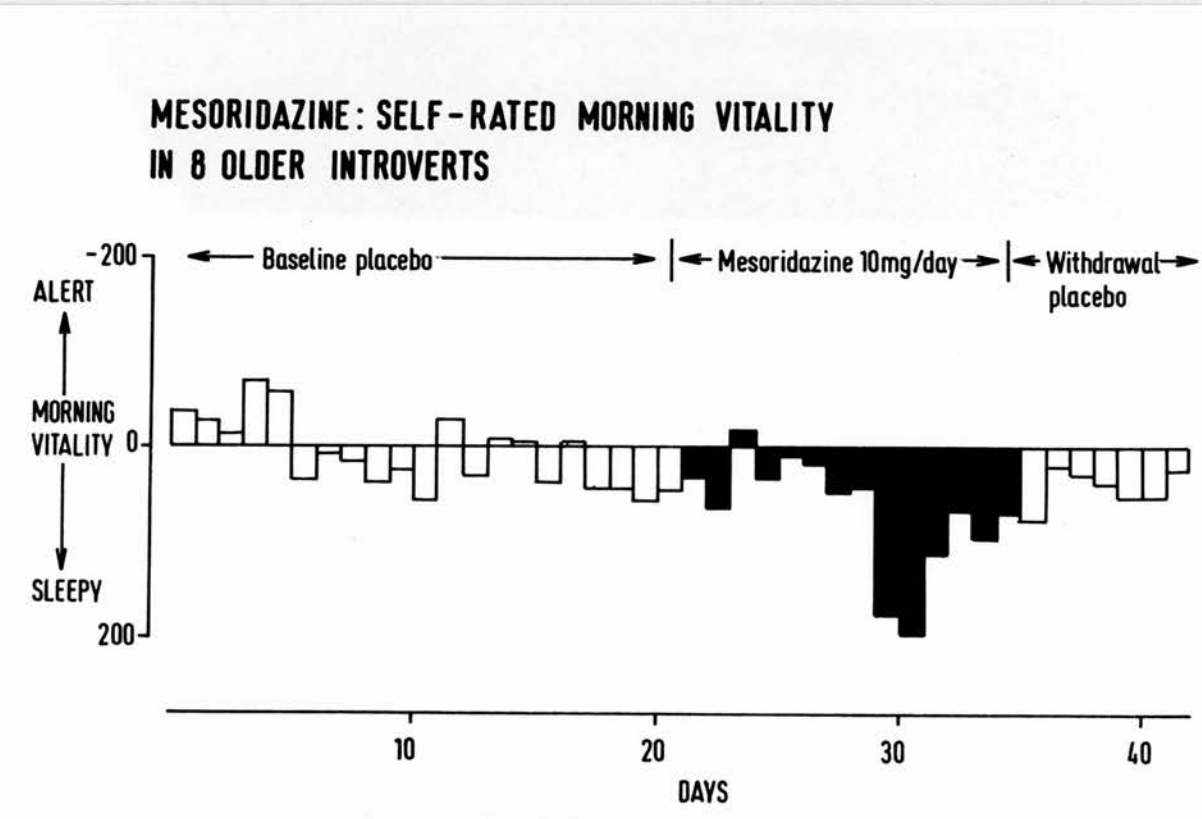
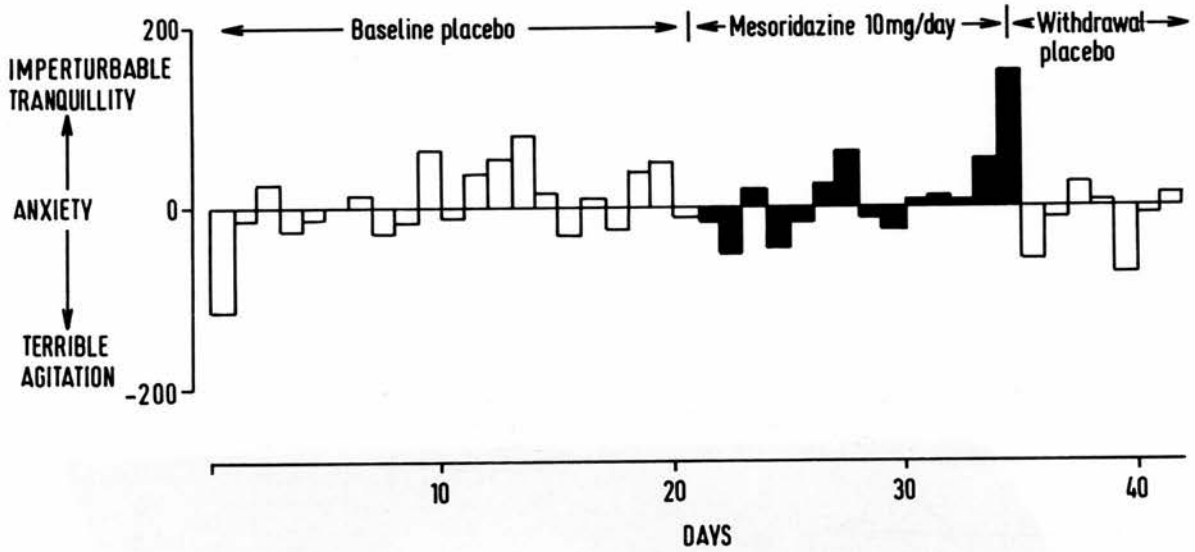


FIGURE 27

FIGURE 28



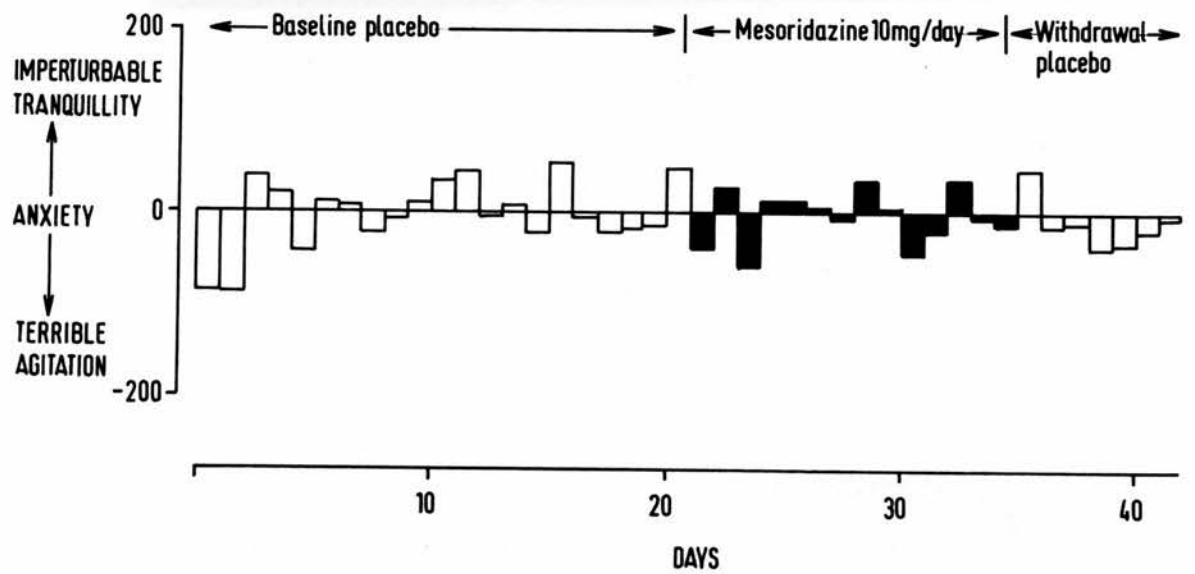


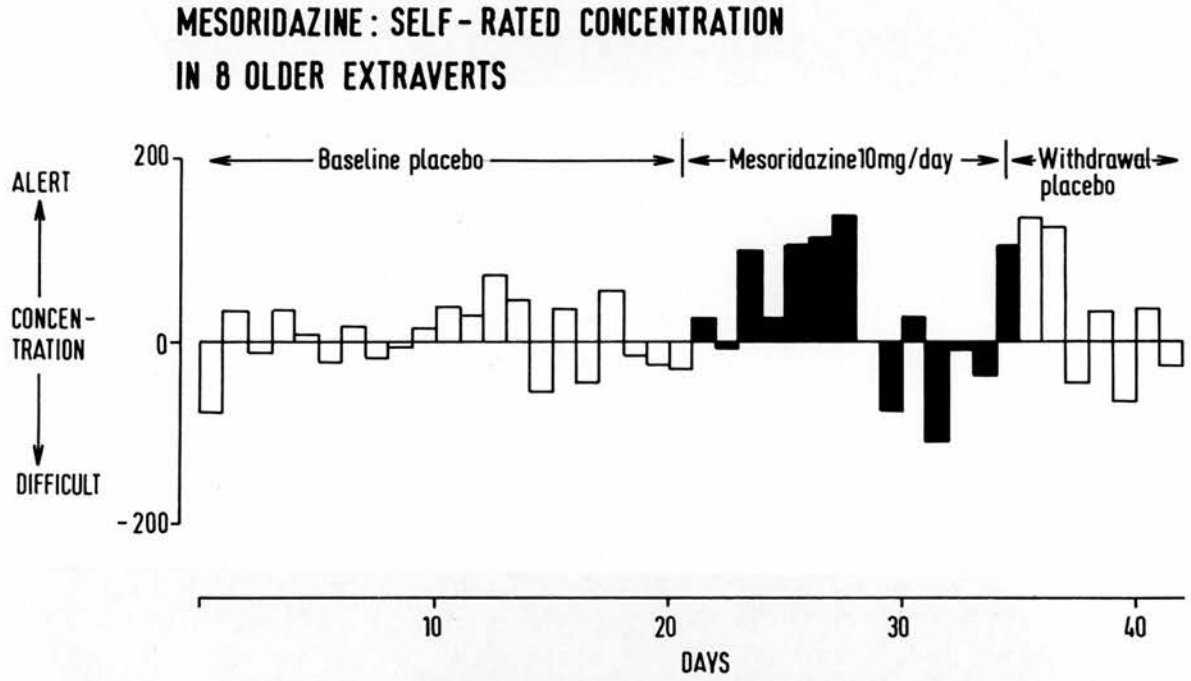
FIGURE 29

In the extravert group, however, there was an initial, but non-significant facilitatory effect, which disappeared in the second drug week (Figure 30).

Discussion

There were significant differences between the extraverts and introverts on several of the measures used. Only on the manual dexterity and card-sorting tasks were no differences found and examination of the data revealed similarities between response patterns in this study and the 'post-hoc' analysis reported earlier. In both studies extraverts showed a slight onto-drug improvement in vigilance correct detections, while introverts' accuracy slightly declined. The deterioration in the introvert group continued into the second drug test day and declined only on withdrawal. Overall accuracy was greater in the extravert group, a pattern also found in the previous study, and this was seen to result from the decline in the number of detections with time on task in the introvert group since the detection rates in the early part of the sessions did not differ. This finding is in contradiction to the reports of others. Generally, decrements with time on task have been found in extravert groups. However, in this study, on both baseline days, a greater first to last quarter decline occurred in the introvert group in every session.

FIGURE 30



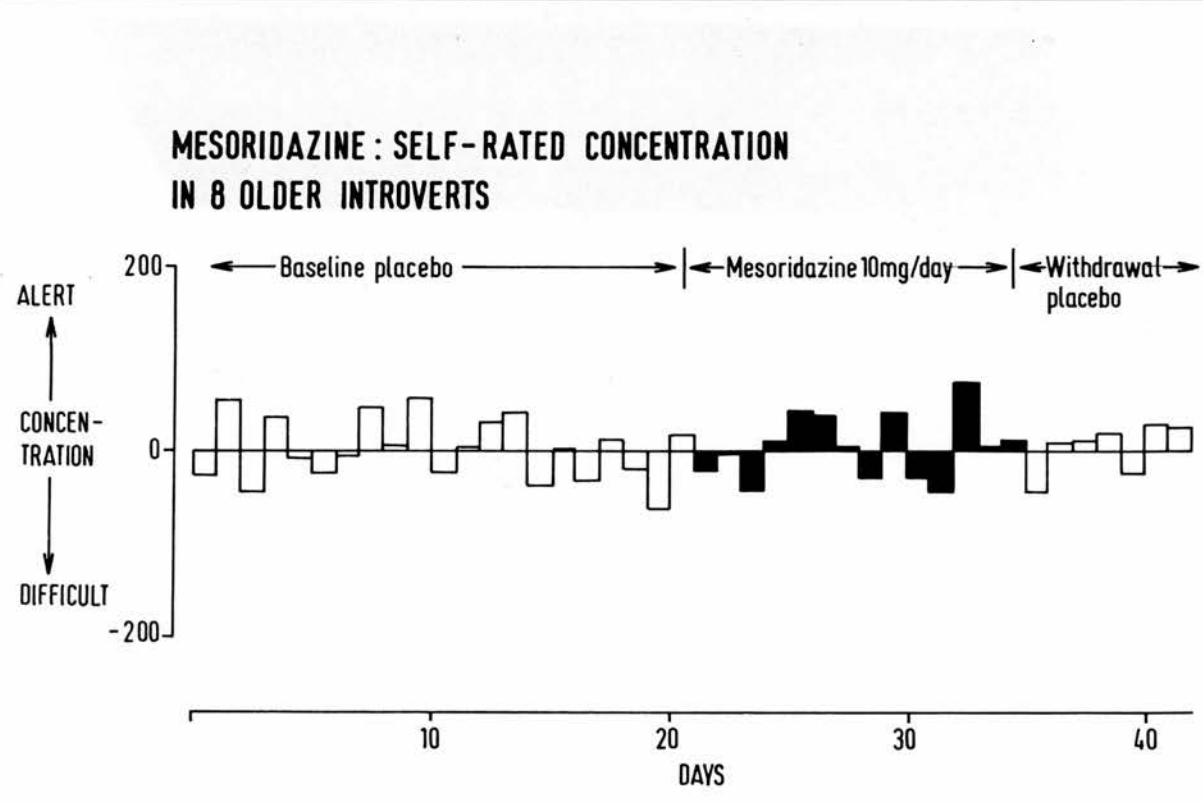


FIGURE 31

During baseline and drug administration, morning session accuracy of detection decreased through the first three quarters of the task and increased again in the last quarter in both groups. This 'end-spurt' phenomenon, which has also been reported by others, occurred even though the subjects were deprived of their watches. On the test day following withdrawal, however, this pattern did not occur. Both groups showed a progressive decline from first to last quarter, with higher than usual initial detections. It may be, therefore, that the withdrawal of mesoridazine improved alertness but inhibited the ability to maintain attention over a sustained period of time.

The possibility that detection may have been disrupted on the morning after a placebo first replaced the active drug is supported, in the extravert group at least, by the evidence that the confidence the subjects placed in their detection accuracy was diminished.

False positive detections again showed a decline with repeated testing and were at a higher level in the extravert group. Introduction of the drug increased errors by the extravert group, especially in the morning session, while errors by the introvert group declined. Thus mesoridazine increased response rate in the former group and decreased it in the latter.

In the retrospective analysis described in Chapter 8, both groups were reported to improve on the manual dexterity task with repeated testing; the extravert group being quicker throughout and showing an onto-drug improvement, while the introvert group showed a concomitant decrement. In this study, both groups again showed progressive improvement, and the extraverts were again quicker, but introduction of the drug had no effect on either group, even in the morning session.

The extravert group were again slower on the digit symbol substitution task. Both groups showed an onto-drug morning session improvement in performance which disappeared later in the day. The introvert group showed a similar deterioration through the day when tested after having received the drug for eight days.

While the introduction of mesoridazine did result in a reduction in the correct detection rate in the introvert group the general onto-drug deterioration which was reported in the 'post-hoc' analysis was not evident in this study. The pattern of response was often similar in the two groups and the significant differences in the statistical analyses refer more to the differences in level of response between the two groups. The extravert group had more correct and false positive detections in the vigilance task and

were quicker in the manual dexterity task but the lack of significant statistical interactions implies that the introduction and withdrawal of the drug had little disruptive effect.

It was evident, however, that the drug was not without effect because both groups of subjects rated their feelings while taking the drug as significantly different from their feelings under placebo baseline conditions. It was suggested, in the introduction, that the introvert group would report greater subjective disruption while taking the drug than would the extravert group. The reverse was true. The introvert group did report disruption of morning vitality and a transient withdrawal effect on sleep quality, but clearly the greater disruption occurred in the extravert group. Although sleep quality was improved, morning vitality was also clearly affected and this disruption disappeared only on withdrawal of mesoridazine.

In the conclusion of Chapter 8 it was suggested that the exercise of caution in the interpretation of the extent of a drug's effect is essential. The possibility of the need for such caution had been suggested by the retrospective analysis of part of the data from the studies described in Chapters 4 and 6. Thus, while the results of the main studies had indicated that the introduction of mesoridazine had

little effect on performance, the division of the subjects into groups on the basis of personality type had suggested differential response patterns. Consequently, it was predicted that the performance of individuals having low scores on the E scale of the Eysenck Personality Inventory would be more affected by the introduction of mesoridazine than would the performance of individuals with high E scale scores. This study not only failed to support that hypothesis but, in some instances, implied the opposite. In the extravert group the disruption of morning vitality, especially with continued administration of mesoridazine, coupled with the positive assessment of sleep quality, indicated a possible hazard since although the subject had had subjectively better sleep, he was also less alert. The lack of a drug-induced effect on performance on the battery of tests does not preclude the possibility of a deleterious effect on skilled performance since in a performance laboratory a subject may be able to compensate for a drug's effects by increasing effort when this would not be possible in a 'real-life' situation. This problem will be discussed in Chapter 12.

Eysenck Personality Scale Test-retest Scores

As described earlier, subjects for this study were selected on the criterion that their scores were, at least, one and a half standard deviations above or below the mean of the total group tested, on Form A of the E.P.I. The mean E scale score of the extravert group was 16.75 (standard deviation 2.71) and of the introvert group 6.75 (S.D. 2.12). On the third attendance at the performance laboratory, which was the second placebo baseline test day, all the subjects were asked to complete Form B of the E.P.I. and the PQ Inventory. On this occasion the E scale scores were only slightly different from before for the extravert group (16.75 mean, 2.55 S.D.) but were increased for the introvert group (mean 12.25, S.D. 2.55). The E scale scores for the extraverts and introverts on the PQ Inventory were 14.38 (S.D. 6.00) and 9.25 (S.D. 4.60) respectively. Thus while there was similarity between the E scale scores in the extravert group ($r = .71$) there was an increase from test to retest in the introvert group which was contributed to by every subject in the group. There was no accompanying change in either the N scale or L scale scores. On the former there was a slight increase from 7.50 (S.D. 4.84) to 9.88 (S.D. 3.09) and on the latter a decrease from 3.13 (S.D. 1.96) to 0.88 (S.D. 0.99).

It has been suggested that extraversion is a highly desirable social trait (Gorman, 1968). If such a socially conditioned need for approval does exist then it may be supposed that it will be more in evidence in social situations. Thus a subject is more likely to adopt a strategy emphasising his social desirability when completing an inventory in an environment in which there are other people, including the person whom the subject assumes will be assessing his answers, than when he is alone in his own home.

An explanation of the introvert to ambivert change in the introvert group in terms of such a hypothesis can only be tentative since such a change was not predicted or expected and no scale or inventory designed to specifically assess social desirability was included. Furthermore, the hazards of 'post-hoc' extrapolation are well appreciated.

However, a correlation between introversion and social desirability scale scores has been reported (Farley, 1966; Gorman, 1968) and it has been suggested that socio-cultural differences are of importance (Stanley, 1973).

The PQ Inventory

It has been suggested that 'psychoticism', as measured by the P scale of the PEN Inventory, is a parameter of experimental value (Eysenck and Eysenck,

1968c). This assertion has been examined and its value both supported (Claridge and Chappa, 1973; Claridge and Birchall, 1973; Stroh, 1970) and questioned (McPherson et al, 1974; Davis, 1974).

Although it has always been an implicit assumption in Eysenck's theory that psychoticism forms a dimension of personality additional to extraversion and neuroticism (Eysenck, 1952) the P scale of the PEN inventory represents the first attempt to measure this dimension and there have been several versions of the inventory. The version employed in this study was current in March 1974 and normative data for subjects over the age of 50 years was limited (S.B.G. Eysenck, personal communication).

The mean P scale score for men aged 50-70 years was 2.56 (S.D. 2.49) and for women in the same age range was 2.45 (S.D. 2.45). This difference was not statistically significant. The P scale score range in this study was 0 to 24 and the 16 subjects were divided into high and low P scorers. The high P group had a mean higher than the normative data mean (mean = 7.25, S.D. 6.82; range 4 to 24) and the low P group had a mean lower than the norm (mean = 0.88, S.D. 0.64; range 0 to 2). There was no statistical difference between the E, N and L scale scores of the two groups. The high P scale score group comprised six women and

two men; the low P group contained two women and six men.

Results

Analysis of variance revealed no significant differences between the two groups' correct detection rates in the vigilance task. Examination of the data indicated that there was an onto-drug decrement in the low P group, especially in the morning session and with increasing time on task. This effect had disappeared by the afternoon session.

There was a significantly higher false positive detection rate in the high P group ($p < 0.002$). There was an onto-drug increase in commission errors in the high P group and a concomitant decrease in the low P group, which was especially clear in the morning session. There was no evidence, however, that either continued administration or withdrawal of mesoridazine had any effect on the expected decline of commission errors with repeated testing.

Performance on the manual dexterity task was not significantly affected by the drug. There was an onto-drug deterioration in the high P group but there was little inhibition of the pattern of improvement expected with repeated testing.

The high P group were significantly slower overall on the digit symbol substitution task ($p < 0.002$).

Throughout the study they showed little improvement in performance level. The low P group, on the other hand, improved through the study, noticeably in the morning sessions, but there was a suggestion of deterioration in the afternoon sessions of the second drug and withdrawal test days.

In the card-sorting task the low P group had significantly shorter decision times than did the high P group ($p < 0.002$). There was no interaction at any level of complexity, however, but there was an indication of an onto-drug morning session decrement in the high P group and improvement in the low P group.

The clearest indication of any difference in reaction to the introduction and withdrawal of the drug appeared in the self-rating data. In the first week of taking the drug both groups reported an improvement in sleep quality. This effect disappeared for the high P group with continued administration, and withdrawal had no noticeable effect. For the low P group, however, continued administration brought a continued improvement in sleep quality, which quickly disappeared on withdrawal of the drug.

The drug had little initial effect on morning vitality and although the high P group reported feeling less alert than the low P group, the effect did not become noticeable until the second week of

administration. The former group reported feeling more impaired during the second drug week than they did in the first week of the drug, but their reports did not exceed one standard deviation of the baseline mean. In the latter group, however, the deterioration of morning vitality in the second drug week was reported to be more than twice the baseline standard deviation and this difference was statistically significant ($p < 0.02$).

Discussion

There were differences in the level of performance of subjects divided into two groups on the basis of scores either above or below the mean normative P scale score, as assessed on the PQ inventory. The introduction of mesoridazine did not have a significant effect on performance patterns and neither did its withdrawal. The drug, however, did improve sleep quality and impair morning vitality in both groups. In the high P group the benefits were in the first week of taking the drug since sleep quality improved while alertness was only slightly affected. The sleep quality of the low P group improved with continued administration but waking drowsiness increased as well and although the subjects managed to overcome their substantial feelings of reduced alertness in the performance laboratory, their ability to cope in 'real-life' might not be so effective.

Although the use of the P scale has differentiated between subjects on both subjective and objective parameters, and could possibly be described as of experimental value on this basis, much more extensive assessment in both normal and abnormal subject groups is needed before doubts about its usefulness will be dispelled. In its present form, the PQ inventory is open to criticism on several issues, including the validity of its construction according to the criteria laid down by the inventory's creators (Davis, 1974) and the scale's ability to differentiate between normal and psychotic groups (McPherson et al, 1974).

In the EPI and the PQ inventories the means for the E and N scales are approximately the median of the range and the population is roughly equally distributed on either side. On the P scale, however, the mean is very heavily skewed towards the lower end of the range and is increasingly skewed with increasing age, especially in men. This would be acceptable if it could be shown that there was a correlation between increasing P and increasing psychoticism but this has not been done (McPherson et al, 1974) and several subjects in this study had P scores well in excess of the mean yet none manifested any symptoms of psychiatric illness when interviewed by a consultant psychiatrist.

It is known that if a test is developed in a particular environment its usefulness and validity in another environment may be limited. Thus the EPI was constructed in Britain and its validity in Iran may not be clear unless a specially constructed Persian version is employed (Hosseini et al, 1973). Little consideration has been given, however, to intra-cultural differences. It is intuitively clear that even within Britain there will be inter-personal differences in response to questionnaires which will result not so much from personality differences as from differences in early training and in present environment. In a loosely constructed questionnaire excessive rigidity in scoring paradoxical, but perfectly honest, responses may lead to a miscategorization of the subject. Thus in the PQ inventory there are several questions, especially in the P and L scales, which might reasonably be answered in different ways. Middle-aged subjects from a Scottish Presbyterian home are very likely to respond differently from a young adult with a poor home background and to indicate that they do not have bad habits, were never cheeky to their parents, would not dodge paying taxes and would always wash before a meal (see Appendix 1; questions 21, 57, 76 and 61 respectively). Similarly, several items on the P scale might be answered 'wrongly' and it is less likely

that an affirmative answer will be obtained to the question 'Do you lock up your house carefully at night?' in a rural area than in London. In these circumstances the relevance of this question and others, including the usefulness of insurance schemes and marriage and whether one arrives early or on time for appointments and trains (questions 19, 47, 63 and 81) is dubious.

CHAPTER 10

EXPERIMENTAL COMPARISON OF NITRAZEPAM AND HORLICKS

A Comparison of the Effects of Nitrazepam and Horlicks on Older Subjects

Introduction

The characteristics of sleep change with age (Williams et al, 1974), and the most obvious effect is increasingly broken sleep with increasing age (Feinberg, 1968). It is a popular belief, however, that we all need 7 or 8 hours sleep a night and that if we do not achieve this then medical help is needed. Consequently there have been several reports of increasing consumption of sleeping pills concomitant with increasing complaints of insomnia in older people (Weiss et al, 1962; Johns et al, 1971).

There have been reports, as well, of the disruptive effects of hypnotic drugs on sleep patterns during both administration and withdrawal (Oswald et al, 1973) and on objectively and subjectively assessed psychological function (Malpas et al, 1970; Bond and Lader, 1972, 1973). Oswald et al (1973) described the effect of nitrazepam as diminishing restlessness, but also reducing REM sleep and stages 3-4 NREM with continued administration. If the function of sleep is to be considered important in relation to synthetic processes for both growth and renewal (Oswald, 1969a, 1970b) then disruption of the normal stage distribution may be detrimental. Furthermore, studies comparing

different hypnotics have concluded that some drugs cause more disruption in waking behaviour than others, but almost all have shown some disruption of one facet or another. Thus, Haider (1968) described greater subjective disruption with amylobarbitone (200 mg) than with nitrazepam (10 mg), but the reverse effect occurred on objective performance when butobarbitone (100 mg) and nitrazepam (5 mg) were compared (Bond and Lader, 1972). Such "behavioural toxicity" is as important to evaluate as physiological toxicity since poor reaction and judgement can be as dangerous as renal damage. Miller (1962) was one of the first to appreciate this problem and test subjects, given a variety of chronically administered drugs including meprobamate and chlordiazepoxide, on a battery of tests of skills required in normal daily life.

Since many hypnotics disrupt both the normal distribution of sleep stages through the night and daytime skills, research continues to attempt to isolate preparations that can improve sleep quality without distorting the other facets of our life. While no drug can do this, some products, including Horlicks, have been credited this power for several generations.

Laird and Drexel (1934) reported that after a meal of cornflakes and milk, young adults' nocturnal sleep was less restless than after a heavy meal, and

Southwell et al (1972) have reported that sleep after Horlicks was less disturbed at the end of night for young adults. These studies measured only body movement frequency and discrimination between movements during sleep and during episodes of wakefulness was not possible. An added disadvantage was their use of only young adults whose sleep often leaves little scope for improvement.

Brezinova and Oswald (1972) hypothesised that sleep after Horlicks would be of greater duration and less broken, especially in older subjects. Using electroencephalography, they found that in a group of ten young adults restlessness towards the end of the night was diminished after Horlicks. In eight middle-aged subjects, Horlicks reduced the number of periods of wakefulness especially in the later part of the night and also prolonged sleep duration. Repeated administration increased these effects and this result is in contrast to the effects of hypnotic drugs which generally became less effective with serial administration.

The present study was designed to compare effects of prolonged administration of nitrazepam and Horlicks in a group of middle-aged men and women, with the hypothesis that both sleep and performance would be less disrupted by Horlicks.

Subjects and procedure

Subjects for this study were middle-aged volunteers recruited through personal contact. The minimum age limit was 45 years. Preference was given to subjects who were in good physical health and who considered themselves poor sleepers but who had not used either sleeping or nerve pills in the previous months.

Selection of subjects had to be effected carefully since the study spanned nine months for each volunteer. During this period, except for six weeks in the middle, the subjects were required to abstain from alcohol and maintain regular hours.

Subjects were invited to participate in two concurrent studies. One involved sleeping in the laboratory at intervals over the nine months' period for electroencephalographic recording, and the other involved attending the performance laboratory on 10 occasions. Ten subjects participated in the sleep study while 8 agreed to participate in the performance study as well. There was an even sex split.

Attendance at the sleep laboratory was required on sixty nights as described below:-

Weeks 1 and 2	a total of 8 nights
" 3 " 4	free
" 5 " 6	a total of 7 nights
" 7, 8, 9 and 10	free
" 11 and 12	a total of 8 nights
" 13 " 14	free
" 15 " 16	a total of 7 nights
" 17 to 22	interval for holidays
" 23 and 24	a total of 8 nights
" 25 " 26	free
" 27 " 28	a total of 7 nights
" 29 to 32	free
" 33 and 34	a total of 8 nights
" 35 " 36	free
" 37 " 38	a total of 7 nights

At bedtime during weeks 5-14 and 27-36 volunteers took either nitrazepam (Mogadon) or Horlicks food drink. Those who took nitrazepam in weeks 5 to 14 were given the drink in weeks 27 to 36 and vice versa. The pill or the drink were taken at home as well as in the laboratory and subjects were instructed to take the preparations half an hour before retiring to bed and to make up the drink with half a pint of hot milk.

Volunteers for the performance study were asked to attend the laboratory on 10 occasions by day between 0815 and 1830 hours. The days fell once in each of:-

Week 1	Practice and orientation
" 2	Placebo baseline performance
" 5	Early drug performance
" 9/10	Re-orientation and practice
" 11/12	Late drug performance
" 23	Practice and re-orientation
" 24	Baseline performance
" 27	Early drug performance
" 31/32	Practice
" 33/34	Late drug performance

In the course of each test day, the subjects had three testing sessions starting at 0830, 1230 and 1630 hours therefore working the "two hours on, two hours off" schedule.

Performance tests included:-

1. Auditory vigilance
2. Manual dexterity
3. Digit symbol substitution (10 minute version)
4. Card-sorting.

The present author was not principally involved in the sleep study but since the sleep and performance studies were planned to run together and employ the

same subjects the results of both will be reported, but only briefly in the case of the former and only for the sake of continuity and completeness.

Results

The methods of analysis employed were:-

(a) Analysis of variance on the raw data.

(b) A transformation of the data by which drugs' scores were calculated by subtraction from the relevant baseline scores. Thus when the subjects were soon to receive Horlicks the baseline whole day mean correct vigilance detection score was 17 detections. Having received Horlicks for the first time the previous night, the mean detection score fell to 14.5. This has been plotted on Figure as a mean deviation from placebo of -2.5. After consumption of Horlicks daily for six weeks, mean vigilance performance score for the whole day was 18.83 detections. This has been represented on Figure 32 as an improvement of +1.83 over baseline. This technique, similar to that used in the previous study, allowed comparison of the relative effects of nitrazepam and Horlicks when baseline performance scores differed.

(c) The technique used for analysis of the self-rated feeling data was similar to that described in the methodology.

1. Auditory vigilance

Analysis of variance revealed no significant differences between the effects of nitrazepam and Horlicks on vigilance in the group of eight older adults. Both preparations were associated with some depression of accuracy of detection on the day following the first administration but this effect, if real, had disappeared after six weeks taking nitrazepam and an improvement over baseline occurred with Horlicks (Figure 32). Examination of the morning session scores indicated a slight impairment after first taking Horlicks and nitrazepam, but after six weeks this had disappeared.

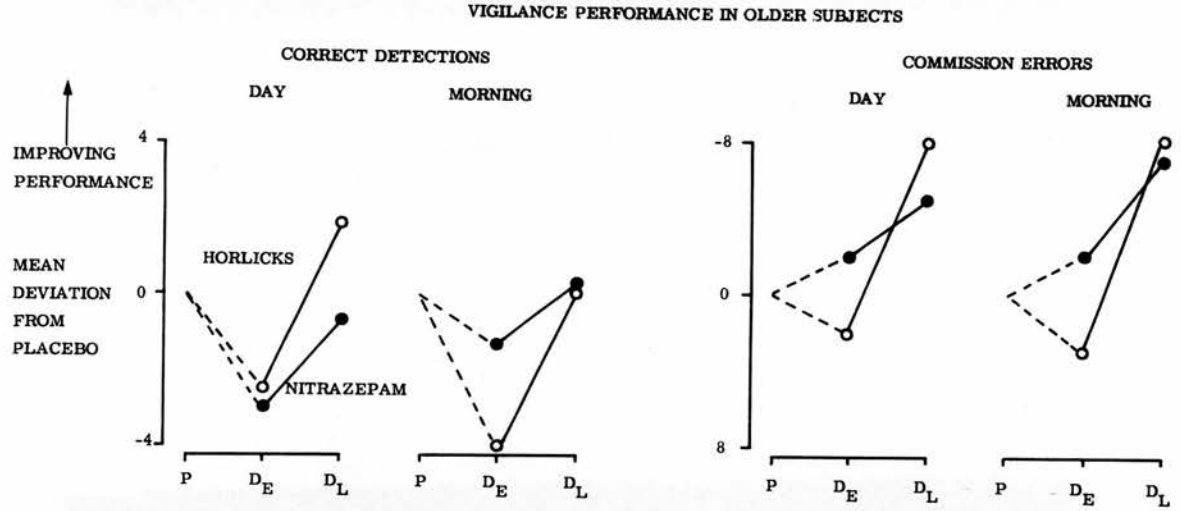
Commission errors were slightly increased but not significantly so, after taking Horlicks while continued Horlicks and the taking of nitrazepam did little to affect the pattern of responding expected as a result of repeated testing (Figure 32).

2. Manual dexterity

Analysis of variance revealed significant differences, on the manual dexterity task, between scores after Horlicks and after nitrazepam ($p < 0.05$). The interaction was not significant (Table 40).

Examination of the transformed data (Figure 33) showed that nitrazepam initially hindered performance and that this effect, in comparison with baseline, disappeared with continuous administration.

FIGURE 32



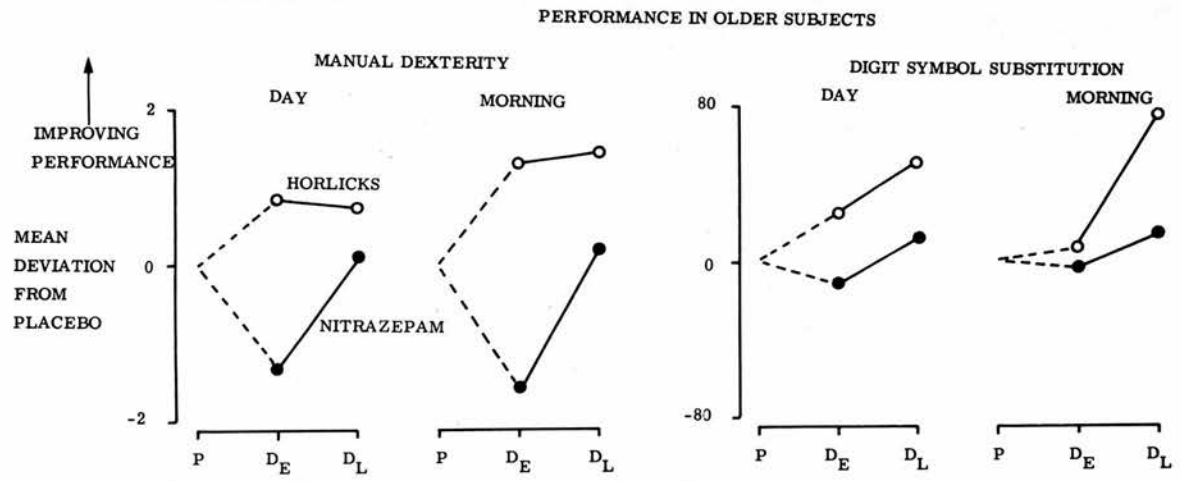


FIGURE 33

3. Digit symbol substitution

Statistically there was no difference between the effects of nitrazepam and Horlicks on this task but Figure 33 indicates that performance was rather poorer after nitrazepam than after Horlicks, both initially and after prolonged administration; there was no decrement, however, in comparison with baseline.

4. Card-sorting: decision-time

Yet again there were no significant differences between the effects of the two preparations. Whole day mean scores for the three levels of complexity differed only slightly from baseline (Figure 34). Mean morning session scores followed the same trends but the inter-preparation differences were more pronounced, with Horlicks having a deleterious effect at each level of complexity initially in comparison both with baseline and with nitrazepam. This decrement did not disappear at the intermediate level with continued administration.

5. Sleep EEG

Both preparations reduced intervening wakefulness over the first seven hours of sleep. Nitrazepam had a greater effect than Horlicks on this parameter but it also reduced REM sleep in the first 3 hours of sleep and caused a large increase in intervening wakefulness on withdrawal.

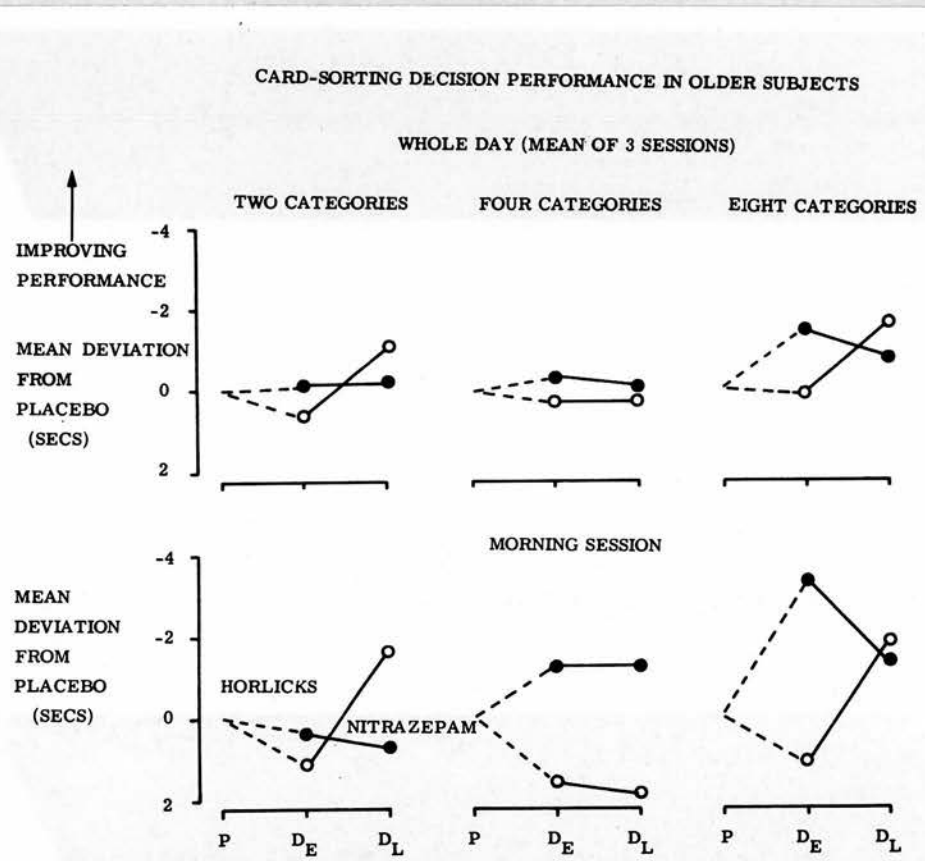

CARD-SORTING DECISION PERFORMANCE IN OLDER SUBJECTS
WHOLE DAY (MEAN OF 3 SESSIONS)
TWO CATEGORIES
FOUR CATEGORIES
EIGHT CATEGORIES
IMPROVING PERFORMANCE
MEAN DEVIATION FROM PLACEBO (SECS)
-4
-2
0
2
MORNING SESSION
HORLICKS
NITRAZEPAM
P
D_E
D_L

FIGURE 34

TABLE 40

Manual Dexterity

Source of Variation	DF	SS	MS	VR
Blocks	1	194.25	194.25	4.485*
Conditions	2	10.90	5.45	0.126
Sessions	2	89.47	44.73	1.033
Blocks Conditions	2	28.85	14.43	0.333
Blocks Sessions	2	1.93	0.96	0.022
Conditions Sessions	4	2.18	0.55	0.013
Blocks Conditions Sessions	4	3.66	0.92	0.021
Residual	126	5457.10	43.31	
TOTAL	143	5788.35		

It was predicted, from an earlier study, that Horlicks would have a greater effect on intervening wakefulness in the second part of the night with continued administration than would nitrazepam. The prediction was supported and indeed it was the lowest mean level of intervening wakefulness of the whole study. Thus while it appeared that nitrazepam was relatively short acting, in that its principal effect on wakefulness is in the first part of the night and there is also an immediately disruptive effect on wakefulness and sleep quality on its withdrawal, the effects of Horlicks took longer to appear and disappear.

Discussion

There was a significant difference between the effects of nitrazepam and Horlicks on only one of the seven measures of the test battery. This one - manual dexterity - only just reached significance, but the difference was in the predicted direction. The other measure which showed results in the predicted direction was digit symbol substitution. The other five measures, in the vigilance and card-sorting tasks, all suggested, although the differences were not significant, that Horlicks had a greater deleterious effect on performance with initial administration than did nitrazepam. This effect was accentuated in the

morning session. With continued administration this effect disappeared and performance, with the exception of intermediate-complexity card-sorting, appeared to be better, although not significantly so, than on either baseline or nitrazepam.

Nothing was previously known about the possible effects of Horlicks on performance measures and the hypothesis was derived from two different types of source. The first was the beneficial effects that Horlicks appeared to have on sleep, without any concomitant disruption of the sleep stages' distribution (Brezinova and Oswald, 1972), and with the reduction in the number of body movements (Southwell et al, 1972). The second type of source has regard to the disruptive effects that nitrazepam has been reported to have on sleep stages, at least initially (Lehmann and Ban, 1968; Lob et al, 1968; Haider and Oswald, 1971). This disruption may take up to a month to return towards normal sleep, especially after a drug overdose (Haider and Oswald, 1970, 1971). Such evidence has support in performance studies. Several researchers have reported disruption on a wide variety of tests, even after the administration of a single dose (Bond and Lader, 1972; Haider, 1968; Malpas et al 1970).

On all measures, except complex card-sorting, performance did not deteriorate with continued administration of nitrazepam. Indeed, in comparison with baseline any decrement had disappeared and performance was at least marginally improved on all measures except mean vigilance correct detections.

Although the effect was not statistically significant, Horlicks caused greater disruption on five of the seven measures, especially in the morning session. The extent of the disruption may be underestimated since other researchers and the previous study have shown that repeated testing produces improvement in performance in most tests. This improvement may not be detectable unless a group receiving only placebo is included, since this is the only way that the progress of drug receiving groups can be monitored for the existence of a drug induced inhibition of improvement. Should older subjects improve with practice in the way that young adults do anything less than an improvement over baseline must be considered a decrement with additional negative weighting given to performance levels poorer than baseline.

In the light of such admittedly theoretical weighting it might be suggested that the initially disruptive effects of Horlicks disappear with

prolonged administration while even after six weeks nitrazepam may have a deleterious effect since on several measures performance was little better than baseline.

CHAPTER 11

A STUDY OF THE EFFECTS OF TEMAZEPAM ON SLEEP

A study of the effects of Temazepam on the sleep of older subjects

The benzodiazepine group of drugs have found extensive use in clinical practice in the treatment of insomnia. Not only have they been found to be effective therapeutically, they have the added merit of being particularly safe in overdose (Oswald et al, 1973).

In a sleep study of the new benzodiazepine, temazepam, Maggini et al (1969) found that, in a patient population the drug had little effect on sleep. Other benzodiazepines, however, have been found to disrupt sleep patterns. Oswald and Priest (1965) found that nitrazepam reduced REM sleep in normal volunteers, with withdrawal causing REM rebound and reduced REM onset latency. Other studies have supported these findings (Lehmann and Ban, 1968; Haider and Oswald, 1971) and it has also been shown that nitrazepam, in common with some barbiturates, reduces the frequency of rapid eye movements per unit time during REM sleep, with a rebound increase above normal after withdrawal (Lewis, 1968).

The effects of chlordiazepoxide on sleep have been investigated at different dose levels. Hartmann (1967) using 100 mg chlordiazepoxide found increased REM onset latency and decreased REM percentage over

the night. A later study using a lower dose (50 mg) administered daily for one month found no initial effect but a decrease in both REM and NREM stages 3 and 4 appeared after a few days and remained until withdrawal (Hartmann and Cravens, 1973).

Kales, Kales, Scharf and Tan (1970) have reported that another benzodiazepine hypnotic, flurazepam, had little effect on REM sleep but significantly reduced NREM stage 4 with a 30 mg dose, while 60 mg caused a significant reduction in REM duration and an onset delay. However, a single smaller dose (15 mg) has been reported to have only the beneficial effects of reducing sleep onset latency and wakefulness and increasing sleep duration (Johns and Masterton, 1974).

A new benzodiazepine, flunidazepam, has been shown to reduce REM percentage when first administered (Oswald et al, 1973). After three weeks' administration, REM sleep in the second 3 hours of the night showed an excess over baseline, while the initial decrease of NREM stages 3 and 4 continued until withdrawal.

Maggini et al (1969) reported that changes in REM and NREM stages 3 and 4 did not appear to occur with temazepam. The main effects appeared to be an increase in sleep duration and a decrease in sleep

onset latency. The purpose of this study was to examine whether or not sleep disruption resulted from chronic administration.

Subjects

Three volunteer male subjects in the age range 50-60 years were used. Their general health was assessed by a physician. Two had had depressive illness in the recent past. One of the two was subsequently discovered to have late onset epilepsy of vascular origin for which he was taking an anti-convulsant drug, but no medication was being taken by either of the other volunteers. All agreed to refrain from alcohol throughout the study.

Procedure

Temazepam (20 mg nocte) was administered in the form of Scherer capsules for ten consecutive nights. The capsules were taken approximately 15 minutes before retiring to bed.

There was a 14 day placebo capsule baseline period before the drug period, and a similar period of placebo administration after the withdrawal of the drug.

The subjects reported to the laboratory at 2130 hours and were in bed with the lights out, by 2230 hours. They were instructed to be in bed on non-laboratory nights by 2300 hours, at the latest. As all three subjects were in full employment, they were

not able to sleep to spontaneous awakening; they had to be wakened in the morning in time to have breakfast and arrive at work in time, but they did not rise any earlier than they would normally have done.

Sleep recording

The method of recording sleep was similar to that described by Haider and Oswald (1971). The analysis of the records was according to international criteria (Rechtschaffen and Kales, 1968).

There were two adaptation nights, three non-consecutive placebo baseline nights, three recordings during the drug period (nights 1, 2 and 9) and three during withdrawal (nights 2, 3 and 12).

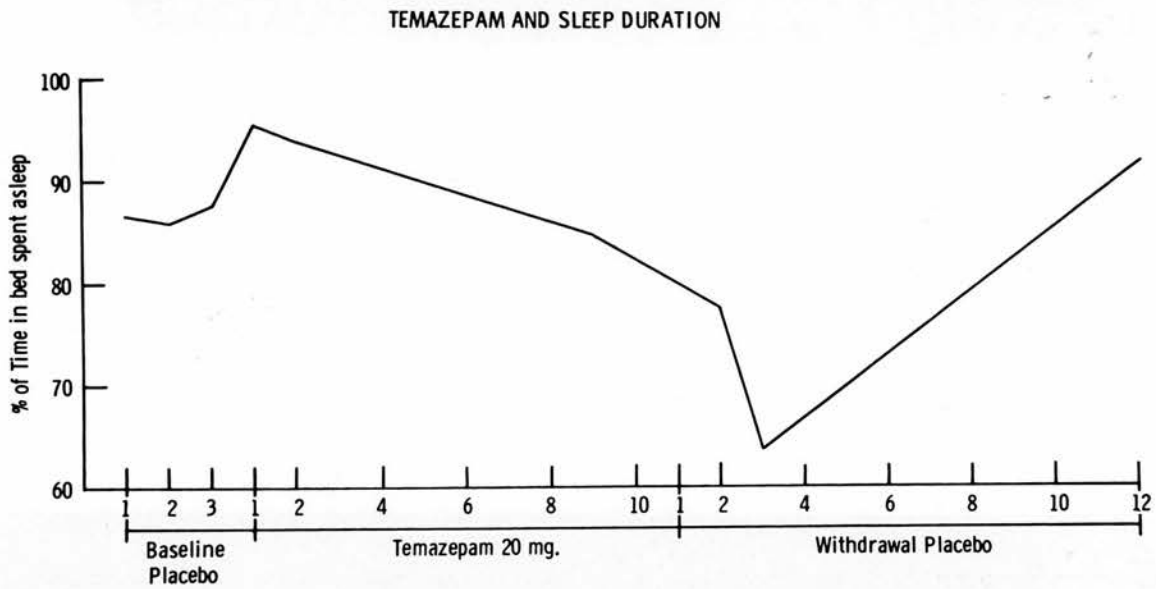
Subjective feeling states

Every morning on rising the subjects completed visual analogue scales to indicate how they felt they had slept and how wide awake they felt. In the evening, before retiring, they assessed, in a similar manner, their mood and anxiety level during the day. All four scales were completed on each of the 38 days of the study.

Results

1. Total sleep time (Figure 35). During the baseline period about 85% of the time in bed was spent asleep. On administration of temazepam, the proportion of time spent asleep rose to 95% but after nine days on the drug

FIGURE 35



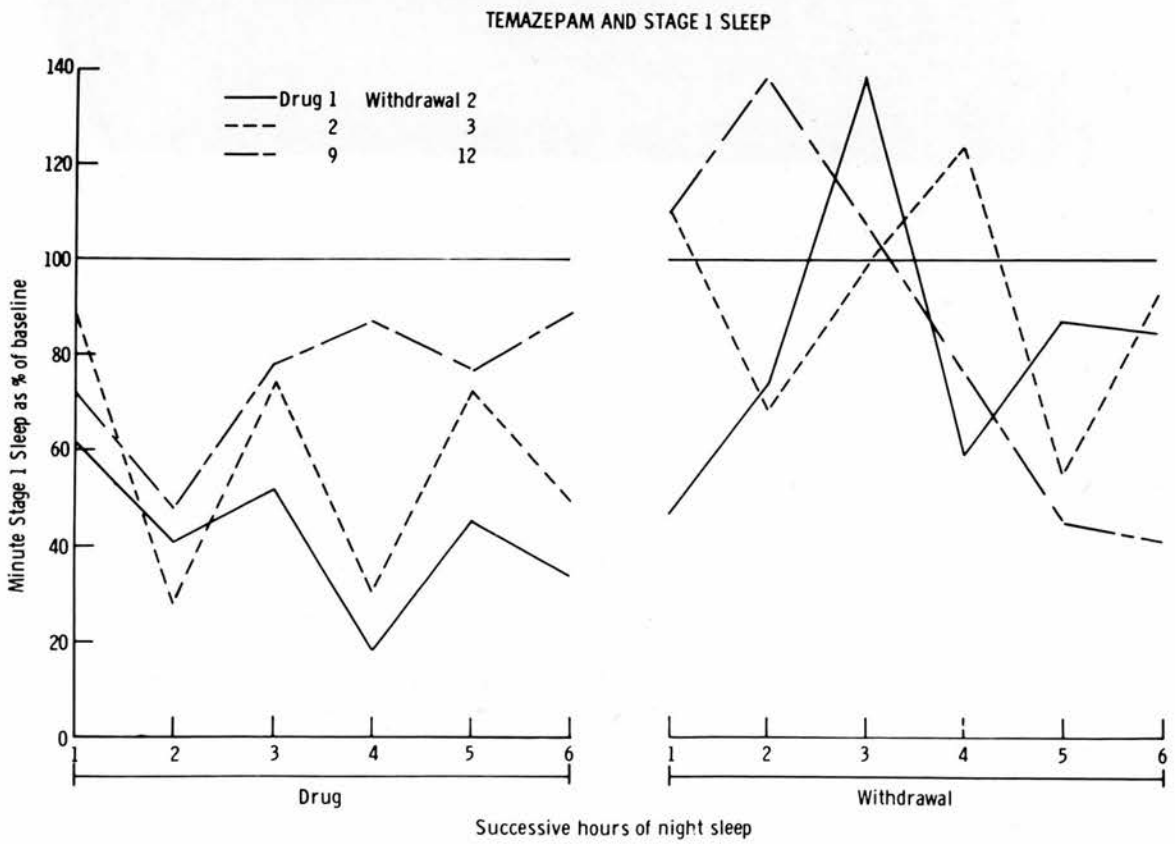


FIGURE 36

the total sleep time had returned to pre-drug values. Drug withdrawal resulted in an immediate decrease in total sleep time. On withdrawal night 3 the proportion of time in bed spent asleep was only 63%. This mean figure was skewed since one subject slept for only 219 minutes out of an available 510 minutes but the other two subjects had shortened sleep durations as well. By the 12th withdrawal night all three subjects had returned to baseline sleep duration levels.

2. Delay to sleep onset. The sleep onset latency reflected very much the changes noted in total sleep time. The subjects went to sleep more quickly when on the drug. Though there was a withdrawal effect which had disappeared by the 12th withdrawal day, this had to be seen in the light of one subject on withdrawal night 3 taking 193 minutes to go to sleep.

3. Sleep disturbance. This was assessed by noting the number of shifts from any stage of sleep to stage 1 (drowsiness) or stage 0 (awake). Since there were variations in total sleep time, the parameter was measured over the first six hours of sleep. There was no notable change except for a slight decrease in sleep disturbance towards the end of the first drug night. Withdrawal of temazepam increased sleep disturbance, especially on night 12. However, this

could have been due to the subjects not having been in the laboratory for several nights previously.

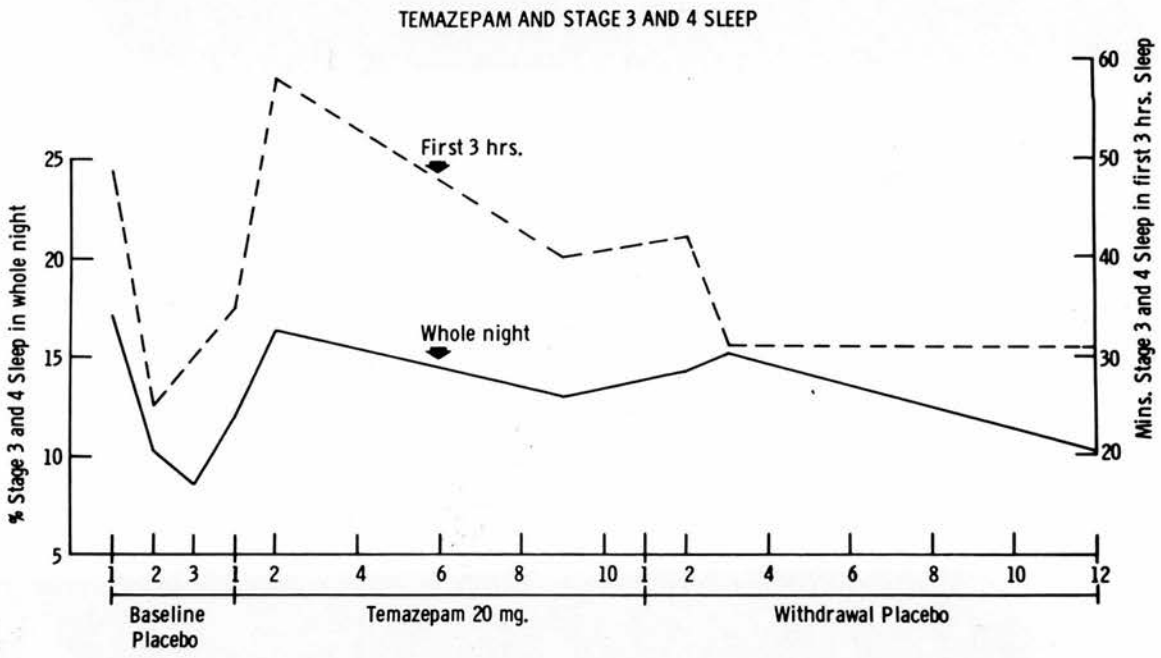
4. Stage 1 sleep (Figure 36). Temazepam reduced the amount of stage 1 sleep over the whole night for the whole of the drug period. Withdrawal did not produce a marked rebound, although there was a tendency for there to be more stage 1 in the early part than in the late part of the night.

5. Stage 2 sleep. This sleep stage was unaltered by either administration or withdrawal of temazepam.

6. Slow wave sleep (stages 3 and 4). Temazepam caused little change in the percentage of stages 3 and 4 in the night, even in withdrawal. However, on the first night of drug administration there did appear to be a slight increase in the amount of slow wave sleep in the first 3 hours of sleep (Figure 37).

7. REM sleep. The overall proportion of REM sleep in the night remained similar to baseline levels both on administration and withdrawal. Consideration of the distribution of REM sleep over the first six hours of sleep reveals an internal compensation while taking temazepam. Thus, on the first night of drug ingestion there was a very small percentage of REM sleep in the first hour in relation to the amount of REM sleep occurring in the first hour on the baseline nights. Later on in the night, however, the percentage of REM

FIGURE 37



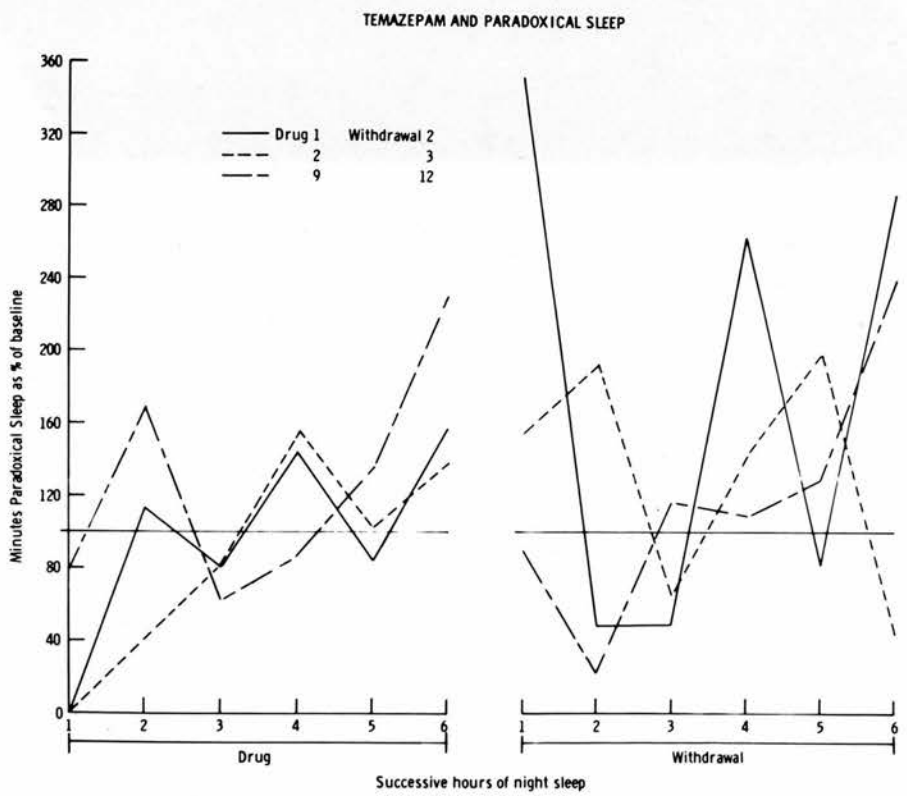


FIGURE 38

sleep rose to a level higher than that which occurred at the equivalent time on the baseline nights (Figure 38). In the sixth hour of sleep the REM sleep percentage was 160% of baseline levels. On the second and ninth drug nights there was a similar pattern of lower than baseline REM percentage in the first hour of sleep and higher than baseline percentage in the sixth hour of sleep. Indeed on the ninth drug night the REM percentage in the sixth hour of sleep was 240% higher than baseline.

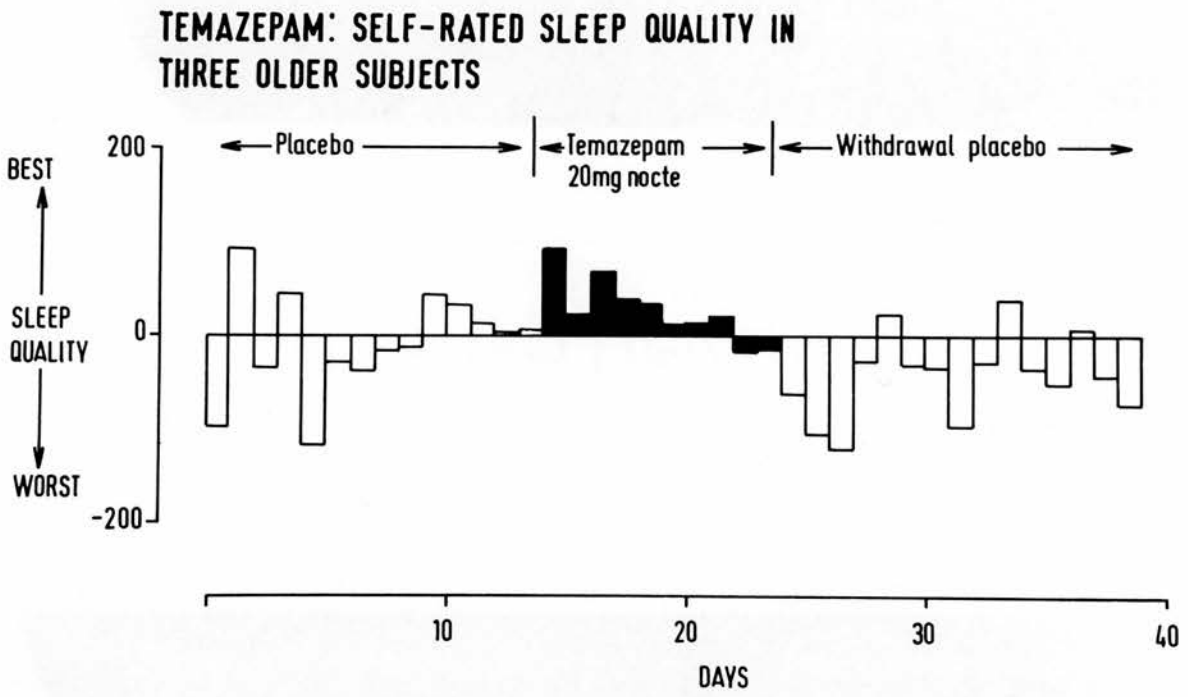
Withdrawal of temazepam had no clear effect on REM sleep. On the three recorded withdrawal nights there were alternating periods of increase and decrease, in relation to baseline. On the second withdrawal night, overall night mean REM percentage was over 180% higher than under baseline conditions, but the hour by hour REM percentage ranged from 360% of baseline in the second and third hours of sleep. Similarly, on the third withdrawal night, hour by hour REM percentage ranged from 190% of baseline in the second and fifth hours of sleep to 40% of baseline in the sixth hour, and on the twelfth withdrawal night the percentage ranged from 20% in the second hour to 240% in the sixth hour. On the two last-mentioned nights, however, the overall night mean REM percentages were only 120% of baseline overall night mean REM percentage.

8. Subjective feeling states. These data were analysed by calculating the baseline mean and standard deviation for each subject and then plotting post-baseline fluctuations from the baseline mean as percentages of the baseline standard deviation. Thus a subject who reported little fluctuation during baseline would have a small standard deviation and post-baseline changes, which might be small in relation to the reports of others but which were large in relation to baseline fluctuations, would be given the relative weighting they warranted. The swamping effect of the reports of subjects with large fluctuations, on the other hand, would be diminished since post-baseline fluctuations would be reduced when calculated as a percentage of their large baseline standard deviations.

(1) Sleep quality (Figure 39). Temazepam initially improved sleep quality but this effect disappeared quickly. Withdrawal, on the other hand, brought about marked feelings of worsened sleep. These feelings were most evident in the first three days but continued until the end of the study.

(2) Morning vitality (Figure 40). At no point did the subjects report feeling more lively in the morning after temazepam than they

FIGURE 39



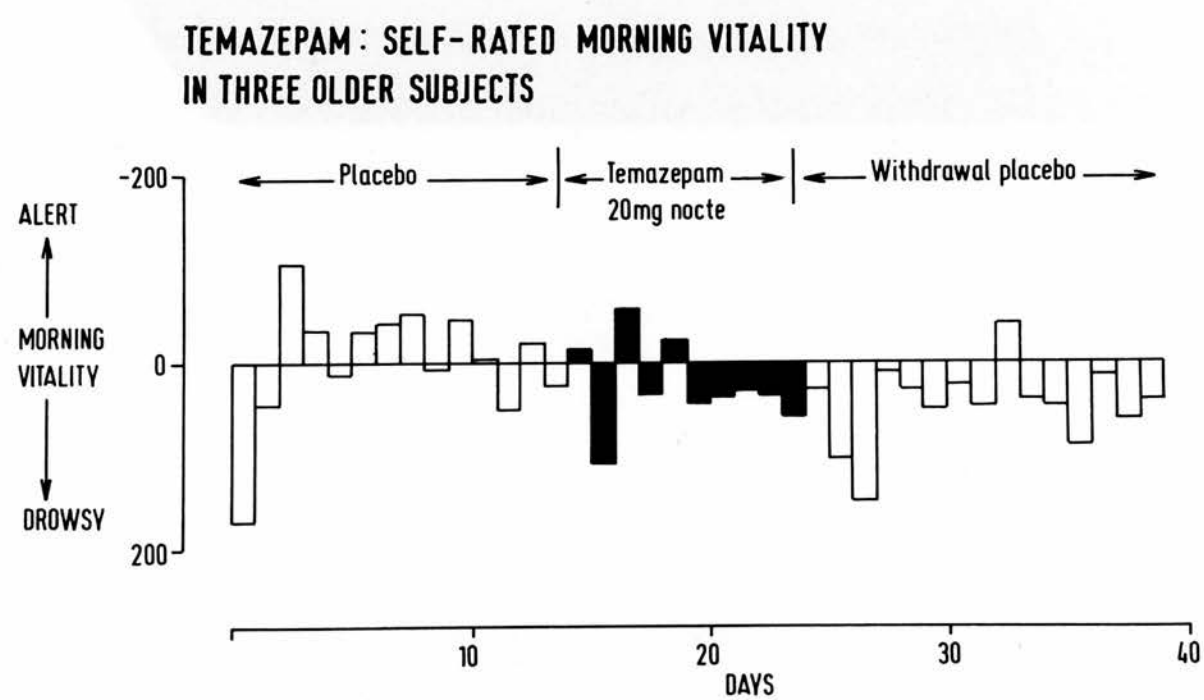


FIGURE 40

did during the placebo baseline period. Indeed both starting and stopping the drug induced noticeable feelings of increased drowsiness, particularly on the second day of administration and the second and third days of withdrawal.

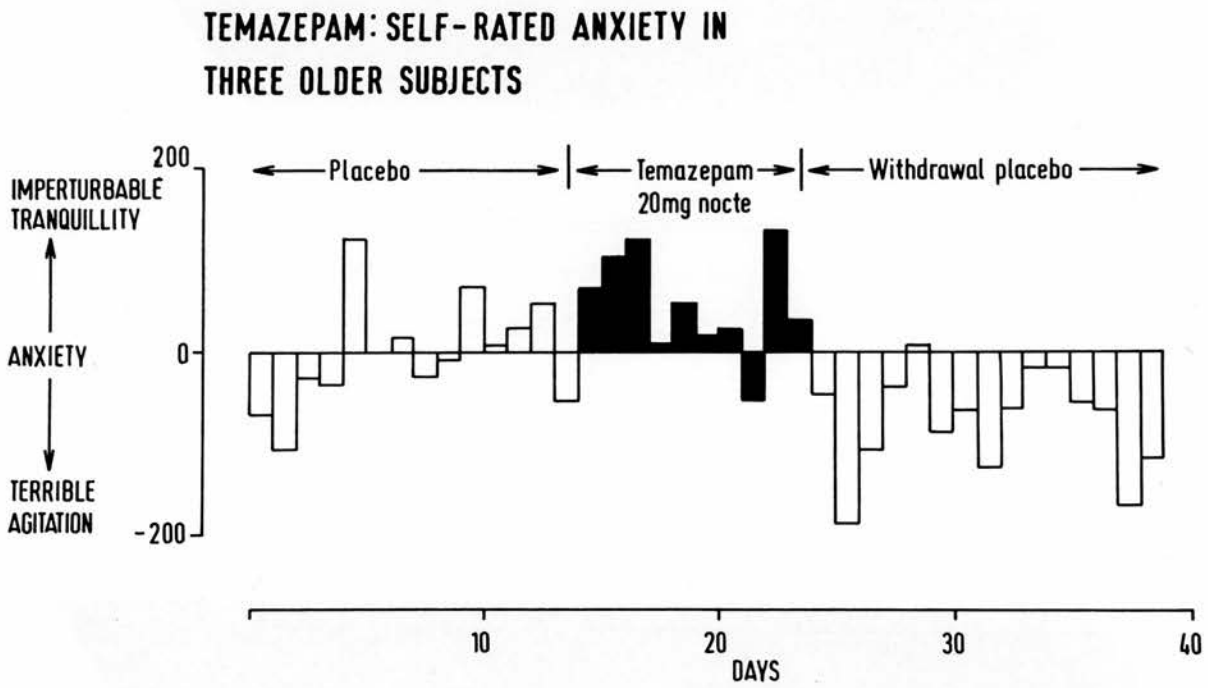
(3) Anxiety (Figure 41). Temazepam reduced feelings of anxiety, especially initially. The most marked effects appeared with the withdrawal of the drug. Agitation increased noticeably by the second day and remained evident for the remainder of the study.

(4) Mood (Figure 42). Initial drug-induced elevation of mood quickly disappeared and withdrawal of temazepam led to reports of depression, which reached a peak on the third withdrawal day. Despite a subsequent reduction in the degree of depression an effect persisted for at least 14 days.

Discussion

At a dose of 20 mg temazepam initially increased sleep duration and decreased sleep onset latency. Apart from a reduction of stage 1 sleep, which persisted for the whole of the drug period, sleep stages, in terms of overall night mean percentages, were not greatly altered. However, there were changes in the distribution

FIGURE 41



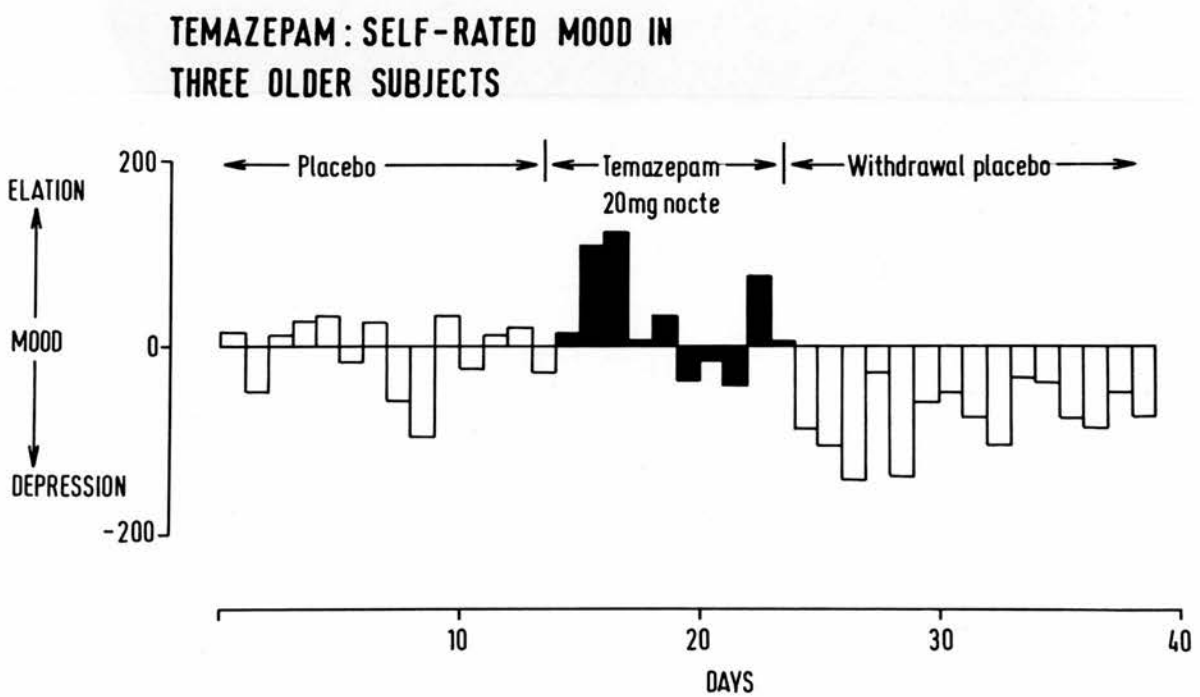


FIGURE 42

of some of the stages in the night. On the first two drug nights, for example, there was a lower than baseline percentage of REM sleep in the early part of the night and a higher than baseline amount in the later part of the night. Flunidazepam has been reported to have a similar effect (Oswald et al, 1973). Similarly on the second drug night there was a higher than baseline amount of stages 3 - 4 sleep in the first three hours of sleep and a lower than baseline amount in the second three hours of sleep.

Although temazepam initially improved sleep, in terms of increased duration, and reduced restlessness, this advantage had disappeared by the ninth drug night. Withdrawal caused some disruption initially, especially of sleep duration, but generally, there is accord, in terms of overall night sleep stage percentages, between these results and those of Maggini et al (1969).

From the subjects' point of view, the benefits of temazepam were at best short-lived, while withdrawal brought about unpleasant feelings. For the first three days of taking the drug, the subjects reported improved sleep, reduced anxiety and elevated mood, but these effects quickly diminished, while morning vitality was reduced for most of the drug period. The major disruptive effects, however, appeared on withdrawal and rose to a peak on the third day. Although

subsequently not so marked, self-rated feelings were rated above the mean on only five occasions out of a possible 48 over the four rating scales.

It must be pointed out, however, that only three subjects were studied and while every attempt was made to control conditions as carefully as possible, there was considerable inter-subject variability in the degree of variation from baseline values during drug administration and withdrawal. The problem of extrapolation might possibly have been made more difficult by the fact that one of the subjects, undetected until the end of the study, was taking another drug as well. Consequently the usefulness of statistical techniques was considered limited and no analysis was carried out beyond the averaging of the objective measures and the transformation of the subjective data as described earlier.

However, the possibility that a similar pattern of response to the administration and withdrawal of the drug, i.e. initial improvement of sleep on taking the drug, and some disruption on withdrawal, should not be disregarded since, as was mentioned earlier, two of the three subjects had not long previously been receiving out-patient treatment for depression. Furthermore, inter-subject variability is not unusual and the trend of response is as important to consider as the degree.

It is interesting to note that one, little-used, criterion of hypnotic property (Isaacs, 1967) was spontaneously reported by one of the subjects. This subject (J.S.) awoke on all five pre-drug nights in the laboratory to urinate, a practice which also occurred at home. On taking the drug, this habit ceased, only to reappear during the withdrawal period.

The occurrence of the most apparent effects in the few days after starting and stopping the drug is a pattern not unlike that found in studies of other drugs (Lewis et al, 1970; Lewis and Oswald, 1969; Lewis et al, 1971; Oswald et al, 1971). Fuccella et al (1972), from a study of healthy volunteers, suggested that the drug was almost totally cleared from plasma in about twenty-four hours. However, the total amount of the metabolites recovered was just over two-thirds of the dose administered. The excretion of the remaining third would probably extend over several days and might possibly be related to the changes in the subjects' feeling states.

CHAPTER 12

CONCLUDING DISCUSSION

It is difficult to relate some of the results from studies reported in the preceding chapters to the work of others. The principal reason for this problem arises from the lack of significant drug effects, but also from the fact that few others have tested most of the drugs used here, e.g. Perlapine, mesoridazine and temazepam, and few have assessed behaviour, especially performance, following chronic drug administration and withdrawal. Necessarily then the studies reported here have often to be related to studies which are not strictly comparable, either in relation to drugs used or design employed. For example, Bond and Lader (1972, 1973) tested drugs considered to have the same type of effect to those studied here and assessed the drugs' effects using tests quite similar to those employed here, but their results are comparable to those reported here to only a limited extent since the single test time in the first study and the three test times in the second study were all within eighteen hours of taking the first and only dose of the drug.

Similarly, Bixler, Scharf and Kales (1972) described a study examining the effects of three drugs, secobarbitone (100 mg), glutethimide (500 mg) and flurazepam (30 mg), on performance of a selection of tests including the Wilkinson continuous addition

test, the Moskowitz divided attention and vigilance test, a DSS task and a pursuit rotor, with repeated administration for three days. Results indicated that the effect of the barbiturate was strongest on the first day of administration, while the effects of the other two drugs were delayed and variable. It is difficult to draw clear conclusions about the effects of drugs from studies such as this, in comparison with the studies reported here, since although the tests may have been sensitive and have covered a span of skills, only a small number of subjects were used (n = 3), the drugs were given for only three days, no consideration was taken of possible withdrawal effects and no record was made of subjective feeling states.

Accepting the limited nature of possible comparison however, several problems remain since there are conflicting reports of many drugs' effects. For example, Bond and Lader (1972) reported that butobarbitone had little effect on performance of a DSST since the drug's effect was mainly to impair simple motor performance, yet an earlier paper reported that barbiturates had a significant effect on DSST performance while not affecting scores on a continuous performance task requiring frequent motor responses (Mirsky and Kornetsky, 1964).

Generally, however, drugs have been reported to disrupt performance, but only for a limited length of time, e.g. twelve hours (Bond and Lader, 1973), although disruption may be measurable on the EEG for longer, and often only on some of the tests used. For example, Adams (1974), examining the effects of nitrazepam (5 and 10 mg) and butobarbitone (100 and 200 mg), on performance of five tests, reported that only on an experimenter-paced short-term memory task was there any decrement and then only at the higher dose level. In the study assessing the effects of nitrazepam reported here, no significant drug effect was found (Chapter 10) but no memory task was used and the subjects were from a different age group. Similarly, the only study assessing the effects of a barbiturate reported here found no significant drug effect on any of the tasks whereas others have reported significant effects using similar tests and similar dose levels (Bond and Lader, 1972, 1973). Some disruption of performance was evident following amylobarbitone, however, and even though the effect was not significant, subjects appeared to be more disrupted than those receiving placebo (Chapter 4).

The effects of the other drugs investigated here have not been previously examined on a performance test battery; the only information available derived

from biochemical and sleep studies. The latter type of study had indicated that the drugs were not associated with excessive disruption of sleep stage distribution. Consequently it might be conjectured that if the drugs cause little disruption of sleep it is possible that there might be little disruption of performance either. The results in several of the studies supported the suggestion that introduction of the drugs caused no significant change in behaviour (Chapters 4, 6, 10 and 11), but it may have been, in some instances, not that there was no effect but that the methods of assessment employed were not sensitive enough to detect the changes. This possibility will be discussed later.

When results are not clear-cut, it is even less easy to attempt to fit them into some form of theoretical framework than it is to relate to others' results. Several theories have been suggested to account for performance patterns and especially vigilance phenomena. One of the earliest attempts suggested that the vigilance decrement was caused by the onset of an inhibitory state similar to that found in classical conditioning (Mackworth, 1950). This point of view was adopted following Mackworth's finding that the introduction of a novel stimulus during a task returned performance to its initial

level. This point of view might explain not only the gradual decline of detection with time on task, but also the decline with repeated testing. Generally, however, this theory has not gained acceptance and more recent work has proposed an inhibition-arousal type of theory suggesting that an increase in inhibition leads to a reduction in arousal which results in a vigilance decrement (J.F. Mackworth, 1968).

A second conditioning theory was developed by Holland (1958). The detection of a signal was assumed to be a rewarding experience which acted as reinforcement towards continued performance. Although there has been little experimental work related to this paradigm, it has achieved some support (Jerison and Pickett, 1964; Stroh, 1971).

Another approach has attempted to interpret vigilance in terms of the data-processing characteristics of the perceptual system (Broadbent, 1953, 1958). Filter theory assumes that the perceptual system cannot cope with all incoming information and that, therefore, some form of selectivity is required. A selective filter differentiates between important and less important stimuli according to variable criteria. It has been suggested that during the performance of a task these

criteria change as task stimuli lose their novelty and consequently filter deviations result in a decline in vigilance accuracy. Although the results reported here do not disagree with this theory, it is difficult to assert that they support it since, if it is assumed that novelty deteriorates with continued presentation of the stimulus to be detected, the simplest method of testing the theory is to vary the rate of presentation of the target stimulus. Only one target stimulus presentation rate was employed in this series of studies.

It has been suggested that the presentation of stimuli serves two functions, one of which is to enable the making of decisions about the presence or absence of signals; the other is to maintain a general state of alertness (Hebb, 1955). Monotonous conditions were considered to lead to a reduced level of alertness, and consequently poorer performance, whereas variety and change inhibited decrement. These suggestions were founded on the results of the investigation of various physiological indices of arousal, which were initiated by the work of Moruzzi and Magoun (1949). The long series of studies that followed demonstrated a relationship between cortical arousal and the reticular formation, although more recent research has indicated the importance of the

limbic system and the existence of two arousal systems, rather than one (Green and Arduini, 1954), between which there is 'a dynamic balance' (Routtenberg, 1968). Eysenck has suggested that the two arousal systems are related to the two personality dimensions, extraversion and neuroticism. Thus, according to Eysenck, introverts have higher reticular formation induced cortical arousal (Eysenck, 1967). Under normal conditions, Eysenck's theory would predict that introverts would perform better on a vigilance task since extraverts, already at a lower level of arousal, would decline still further and would consequently show a greater decrement with time on task. Under quiet conditions (70dB) this pattern has been reported to occur but the level of background noise is evidently of importance since under noisy conditions (95dB) neither introverts nor extraverts showed a decrement of correct detection (Davies and Hockey, 1966). Similarly, Davies et al (1969) reported that extraverts performed better when background noise level was 80dB than when it was 50dB, while introverts performed equally well under both conditions but preferred the quieter condition if given the choice. In the studies reported in the earlier chapters the background noise level was 85dB and it was not variable. It would seem that noise of this intensity could, in comparison with the

studies mentioned above, be classified as 'noisy'. Extrapolation from the studies by Davies and his colleagues would, therefore, lead to the hypothesis that there would be no difference in correct detection between the introverts and extraverts under placebo conditions. A statistically significant difference in correct detection between introverts and extraverts was reported in Chapter 9 only when performance was assessed in relation to time on task. While extraverts detected slightly fewer signals than introverts on the first test day, the reverse was true on the second test day. On both placebo test days the correct detection performance of both groups deteriorated both through the day and with time on task; the first quarter to last quarter decrement was consistently greater in the introvert group. Thus there is only tentative agreement with the results reported by Davies.

Tune (1966b) reported that introverts made fewer errors of commission than extraverts. A similar result was found in the study reported earlier. False positive detections were consistently more frequent in the extravert group, although neither group showed a decline in commission errors with time on task. Other researchers, however, have found that introverts made significantly more commission

errors than did extraverts (Davies and Hockey, 1966; Davies et al, 1969).

A general finding in the studies reported earlier relates to response patterns in the vigilance task. A decrement in detection rate was evident, in both younger and older subjects, both with time on task and with repeated testing. There was also a gradual reduction in commission errors with repeated testing. Others have reported similar patterns (Davies and Tune, 1970, p 211) and the progressive decline has been related to a decline in the level of arousal (Davies and Krkovic, 1965). Bakan (1957) described the behaviour of subjects in the monotonous vigilance situation as being initially attentive, and this phase would be longer if reinforcement was given, but with attention being gradually reduced with the monotony until a state of drowsiness or sleep exists. Subjects often try to combat this and employ a variety of strategies, including singing, whistling, day-dreaming and moving about. All of these approaches have been noted in the studies reported here and some others have been detected as well, including drawing, talking, muttering and reading. Subjects, when asked about this have replied that it was done to keep themselves awake since they would have felt guilty should they have fallen asleep.

Signal detection theory has been applied to vigilance performance in order to understand the way in which decisions are made about the presence or absence of a signal on the basis of sensory information which has already been processed. Most studies using this approach have reported that a decline in the detection rate is associated with a displacement of beta in the direction of increased caution. Others, however, have reported that changes in d' were associated with a detection decrement but that interpretation of beta was not valid since "it seemed more sensitive to the inevitable violation of detection theory assumptions" (Mackworth and Taylor, 1963). This is one of several difficulties in relation to the applicability of signal detection theory to vigilance situations.

Signal detection theory was originally derived from psychophysical data and deals with the situation where an observer is instructed to detect the presence of faint signals and decide whether "some sensory event was caused by a signal or by some random process, such as background noise" (Green and Swets, 1966, p 30). The theory has been applied to three main categories of psychophysical situation. In the first the observer is presented on each trial with a single stimulus which may be either noise alone or signal

plus noise, and is required to indicate his decision. In the second situation the observer can indicate his level of confidence about each trial's decision while in the third situation the signal may be presented in one of two or more intervals and the observer is required to select the interval he considers to have contained the signal.

Signal detection theorists have assumed, in analysing results from such experimental procedures, that in the absence of a signal there is a randomly varying constantly maintained neural discharge occurring in some part of the nervous system, and that the size of this varies about a mean such that it follows a normal distribution, and shows an increase only when a signal is presented.

Already then there are fundamental differences between the vigilance situation and the classical psychophysical situation to which signal detection theory was originally applied. In the vigilance situation the length of an observation period, in the psychophysical sense, is unspecified. Secondly, the observer in a vigilance task, is not required to make a response after each observation period. Furthermore, the length of the testing session is usually not long in psychophysical studies, while in vigilance experiments the session is inevitably prolonged.

Thus, the level of neural activation will be different after observation periods in which a response was made and after periods when no response was made, regardless of the correctness of the decision, and these levels will change with time on task. Thus the rationale for the vigilance task, i.e. to study the changes in alertness in terms of correct and incorrect detection rates over time, are in fundamental contradiction with the basic assumption of signal detection theory, that the observer's attention to the display is unchanging.

Jerison and his colleagues have distinguished three ways in which a subject may observe a display during a long vigil (Jerison, Pickett and Stenson, 1965). Alert observing was defined as the "optimum observing of the psychophysical experiment", blurred observing as the "process that increases the variance in both the N and the S-N distributions relative to that of alert observing" and distraction was described as including "the daydreaming or autistic behaviour that often occurs in prolonged vigils" (Jerison, Pickett and Stenson, 1965, p 120). The high levels of beta which would result from the latter two categories would inevitably skew results and render as psychologically meaningless the values of this decision process in signal detection theory terms. Jerison has suggested

that a response criterion of 1.0 indicates that an observer "accepts an even money bet on his sensory information that a particular stimulus which he reports as a signal is, in fact, a signal" (Jerison, 1967a, p 286). Psychophysical experiments have indicated that a beta value of 1.0 is common and a value in excess of 4.0 is unusual yet at the end of a vigil values of 250.0 (Loeb and Binford, 1964) and 500.0 (Jerison, Pickett and Stenson, 1965) have been reported.

So far discussion of the applicability of signal detection theory to the vigilance task situation has focussed mainly on beta. However, the usefulness of d' has also been questioned. Mackworth and Taylor (1963) reported changes in d' to be associated with vigilance decrement but Green and Swets (1966) in their discussion of this experiment concluded that the vigilance decrement could largely be accounted for by changes in beta rather than changes in d'. The changes in d', on the other hand, were more likely to be related to fatigue, which has been shown to have affected performance in several studies (Berger and Mahneke, 1954; Mackworth, 1964; Welford, 1968).

Thus while beta has been shown to be of doubtful extrapolative validity in the vigilance situation, its usefulness has been indicated by the originators of signal detection theory to be greater than that of d'

in detecting vigilance decrements. Interpretive problems are further compounded if unequal variances occur since the table values for d' and beta, which are used by most researchers, assume a Gaussian distribution (Freeman, 1973), even though the possibility of such a distribution occurring is unlikely (Taylor, 1967; Mackworth, 1970).

A further problem arises from the different methods used to obtain the calculated values. Some researchers obtain d' and beta by first calculating the group mean correct and false positive detections' scores and transforming the mean into SDT values (Davies and Hockey, 1966) while others calculate the SDT value for each score for each subject and subsequently average the SDT scores. The latter approach was used in the studies reported earlier but even so, examination of the raw transformed scores led to the conclusion that extrapolation in terms of the signal detection theory parameters of detectability and caution were meaningless and shed no light on the effects of the drugs and of repeated testing that could not be gleaned from a simpler examination of the correct and false positive detection rates and their respective standard deviations. Indeed, the range of both inter- and intra-subject scores was prodigious, especially with

regard to beta. In the study comparing the effects of three hypnotics in young adults, beta scores ranged, over the whole study, from 2.071 to 1007.817, and in the examination of the effects of mesoridazine on a group of older subjects on one day one subject had a beta score of 22.491 at lunchtime and a score of 935.710 four hours later. In the light of these results and the preceding discussion, the value of the interpretation of the vigilance data in signal detection theory terms was considered to be limited and d' and beta were not calculated in Chapters 9 and 10.

When results are inconclusive where others have found clear-cut differences between groups and drug-induced changes in performance as well, it might be reasonable to conclude that the methods of assessment used in the study have not been sensitive enough. When other data regarding a drug's effect is sparse or contradictory, however, it is not so easy to determine whether the lack of significance results from the drug's lack of effect or from insufficient test sensitivity.

In the studies reported here it may be that both of these possibilities occurred. Confidence about the non-effect of the drugs could be increased if the results were replicated. In the case of mesoridazine this occurred. The drug was tested in three studies;

in none of them were markedly deleterious effects on performance found. In one of the studies EEG sleep data confirmed that disruption was not extensive and the only evidence of a significant drug effect appeared in the self-rating feeling state data in the study of the effects of the drug in different personality types. Despite this agreement across three studies, however, the drug's lack of disruptive effect cannot be assumed, since the same tests were used in all the studies. The study of the drug at several dose levels would have given a clearer indication of whether, and at what dose in relation to its clinical usage, disruptive effects occur.

The lack of significant impairment in the group which received amylobarbitone (200 mg) in the study comparing the effects of the three hypnotics gives little help in the assessment of the sensitivity of the performance tests used since other research workers have reported that the disruptive effects of barbiturates, in comparison with the benzodiazepines, tend to be more subjective (Haider, 1968) than objective (Bond and Lader, 1972). Similar results occurred in the study reported here. While the performance of the group did not differ significantly from the other groups, their subjective response to the drug, especially initially, was clearly greater than all the other groups excepting the perlapine (5 mg) group.

McNair (1973) analysed and reviewed research studies examining the effects of chlordiazepoxide, diazepam and meprobamate. The drug sensitivity of 43 performance measures was evaluated and ranked in terms of the percentage of studies using that test which had reported significant results. Thus four studies reported the use of the Continuous Performance task: two reported that the drug facilitated performance, one reported a decrement and one reported non-significant drug placebo differences. The 75% significant results' rating that McNair gave this test the second highest ranked 'high sensitivity' measure. Although there are several drawbacks implicit in this review, including the pooling of facilitatory and deleterious results, the lack of consideration of the number of studies which have used a particular test and the consideration of only three drugs, it does indicate the possibility that the tests used in the studies reported in previous chapters are, apart from the digit symbol substitution task, of low sensitivity in determining the existence of drug effects. For example, four studies assessing the effects of these drugs in comparison with others on auditory vigilance reported no statistically significant effects (Bakan, 1961; Holmberg and William-Olsen, 1963; Idestrom and Cadenius, 1963; Pearson and Neal, 1970).

A variety of measures were used in the studies reported here, each intended to assess a different facet of skilled behaviour, since it was appreciated that drugs may affect only particular skills. Some drugs have been reported by other researchers to affect only motor performance. Thus, Bond and Lader (1972), studying the effects of butobarbitone and nitrazepam, reported that simple, repetitive, motor tasks, such as tapping and the motor part of card-sorting, were severely impaired while cognitive measures, such as DSST and arithmetic, were unaffected. Kornetsky and Orzack (1964), on the other hand, reported cognitive impairment following barbiturate administration. In the light of conflicting reports, such as these, the usefulness of a battery of test measures is evident.

Some, however, have used as few as two tests and yet have still consistently produced results of practical value and importance. Moskowitz and his colleagues at the Institute of Transportation and Traffic Engineering in Los Angeles have examined, in both visual and auditory modalities, the effects of alcohol and marihuana on concentrated and divided attention and reported that, while concentrated attention may not be impaired by either drug, the ability to assimilate and respond to information from

several sources simultaneously, as in a driving situation, is severely, but differentially, affected by both drugs (Moskowitz, 1973).

It may be then that the tasks employed in the studies reported here have not been sufficiently difficult for the subjects. If this has been the case then subjects who have felt affected by the drugs have been able to compensate for their impairment by making an extra effort. The need then would be to employ tasks which do not allow such compensation by making, under baseline conditions, demands which require the subject to be performing near to the limit of his capabilities. At the same time, however, the task must not be sufficiently interesting to increase the subject's motivation. Tasks similar to those used by Moskowitz seem suitable since the demand made on the subject can be varied so that the degree of complexity with which the subject can cope before deterioration may be assessed. Furthermore, the cause of the deterioration can be isolated since both the cognitive and the motor aspects of the tasks can be evaluated independently.

Subjects' performance may have been affected by the laboratory environment. In several of the studies subjects attended the laboratory in groups of six. Although subjects could not see each other during the

testing sessions, because each sat in a screened booth, it was extremely difficult to limit social interaction both during and between sessions. An attempt was made to do so, especially during test sessions, but the degree of success was limited by several factors, including the need to maintain goodwill and motivation to continue participation over at least six weeks and sometimes several months. The age of many of the subjects was another complicating factor. In four of the studies, subjects were middle-aged and experimentally naive. Some found it difficult to accept instructions from someone considerably younger than themselves and to appreciate that conversations should terminate when testing sessions started. Others clearly found the presence of subjects of the opposite sex distracting and occasionally instances of interpersonal tension occurred. It may be that such factors as these interfered with performance: it is difficult to quantify such social effects but their potential disruptiveness is undeniable and they were possibly relevant in the introversion to extraversion swing of E scale scores by one of the groups in the study examining the effects of individual differences in drug response (Chapter 9). The differential effects of social factors on different personality types has

certainly been noted by others (Colquhoun and Corcoran, 1964).

The possibility of disruption of performance by pharmacological agents other than the experimental drug is of importance as well. Several researchers have made attempts to control for this by instructing subjects not to take alcohol on the evening before or during the test day (Bond and Lader, 1972, 1973) and others have forbidden the use of tea, coffee and cigarettes as well (Adams, 1974). In the studies reported here, subjects were requested to abstain from alcohol for the period of the experiment; this in some cases was for nine months. It was not considered practical, however, to request subjects to give up cigarettes as well, but an attempt was made to control smoking on the experimental days. Cigarettes were not 'confiscated' from subjects before experimental sessions since it was considered a possibility that subjects would merely compensate for their deprivation by smoking more before and between the experimental sessions. Such behaviour is difficult to control, especially with older subjects.

It is undeniable, however, that cigarette smoking may influence behaviour at all levels. While there are wide inter-individual differences in consumption, and therefore the probability of consequent disruption, it has been suggested that anyone smoking more than

10 cigarettes a day is maintained at a fairly permanent and definite drug level (Tong et al, 1974). Tong et al suggested that in all instances a stimulant dose is taken but others have suggested that the situation is more complicated than this and that smokers may alter their nicotine intake depending on the perceived significance of the task (Ashton and Watson, 1970; Watson, 1975). Furthermore, there is evidence suggesting that men may smoke more in low arousal situations, whereas women may smoke more in high arousal situations (Frith, 1971).

There is experimental evidence that nicotine may affect performance in different ways. Frankenhaeuser et al (1970, 1971) have reported that while intake of nicotine led to reduced scores in a choice reaction test, it also led to the maintenance of a higher level of efficiency in the reaction time portion of a vigilance task. Tarriere, Hartemann and Niarfeix (1966) found that when subjects who were smokers were allowed to smoke during a 150-minute visual vigilance task, their performance was significantly better than when they were not allowed to smoke. In the latter condition their performance was poorer than the performance of non-smokers. Similarly, nicotine has been reported to influence heart rate (Elliot and Thysell, 1968), performance on tapping and pursuit

rotor learning tasks (Frith, 1967, 1968) and driving skills (Heimstra et al, 1967).

Awareness of the effects of nicotine on performance tasks, both alone and in interaction with the experimental drug, does not simplify the dilemma facing an experimenter interested in the chronic effects of drugs since although two approaches are possible, both have their disadvantages. The first alternative involves the exclusion of smokers from the experimental sample. Allowing for social, cultural, occupational and age factors, this might involve the exclusion of subjects who are representative of a large percentage of the population. For example, figures published by Todd (1972) indicated that, if subjects were drawn from the Registrar-General's Social Class 1, exclusion of smokers would make the experimental sample representative of 47% of the population whereas if subjects were drawn from Social Class 5, the sample would represent only 27% of the population. Thus exclusion of smokers would inevitably mean that the sample would be unrepresentative of the general population.

There has been research into why people smoke and some of the results have implications for pathology. Seltzer (1967), in a review of the literature, reported that smokers tended to be more extraverted, had more

neurotic traits and displayed more signs of psychological tension. Consequently, it may be that such individuals are more frequently prescribed drugs and, therefore, may be precisely the sort of person who should be used as a subject in the sort of studies described here. The second alternative, of including smokers and accepting the possibility of synergistic or antagonistic interaction with the experimental drug, would seem, therefore, despite its drawbacks, to be the more suitable approach.

It was suggested in Chapter 5 that performance patterns are different in different age groups and that if a drug is to be prescribed principally for an older age group then logically the drug must be tested in that age group. Consequently, a comparison was made (Chapter 8) of both placebo baseline and drug performance scores by young adults and by older adults in the studies described in Chapters 4 and 6. It was suggested that age-group differences could be demonstrated not only in response pattern but also in response level under placebo conditions and that the introduction of mesoridazine, while not causing significantly different objective effects, may cause disruption of subjective feeling states and that this effect may be greater in an older group, especially initially.

It can be suggested, as a principle, therefore, that when a drug is to be tested in humans, in order to establish whether the extent of its side-effects might interfere with the patient's behaviour, it should be tested in the age group which is likely to contain most patients receiving the preparation. Only by testing a drug in a group as similar as possible to the majority of proposed recipients will any idea of the possible effects be obtained.

The inter-group differences described in Chapter 9 were not as clear as those suggested in Chapter 8. There were differences, however, and inter-individual differences in response to drugs should be examined further in order to isolate the factors of greatest importance in relation to degree and pattern of response. At the present time and state of knowledge the area is only of theoretical interest but if one or more reliable dimensions of responsivity were to be isolated then there would be important clinical implications.

The existence of differences in inter-individual response patterns is evident and there have been many attempts to elucidate the important variables. Several personality scales have been used to do this, and the Eysenck scales have been used more extensively than others, but, as has been mentioned (Chapter 9),

severe doubts about the various scales have been raised and few would unequivocably accept their validity and usefulness. If one or more important variables could be identified and be shown to be reliable indicators of differential response to drugs in different types of people, then this would be of importance in the prescription of drugs and the selection of dose levels.

Straightforward experimental procedures have often been used to answer a number of the questions about drugs' effects. For example, questions have been asked about movement speed, as assessed by tapping a Morse key, about movement accuracy and about reaction speed as well as memory and speed of addition. In some cases tasks have been more complex but almost always the approach has been academic and the suggestion made that these tasks represent an attempt to assess the effects of drugs on laboratory analogues of skills required in everyday life. While it may be true that some of the tasks require the use of such skills the usefulness of this approach, beyond academic interest, is open to discussion. Thus Miller (1962) has suggested that even when a drug effect is evident on the performance of a task there exists a problem of how much deterioration is 'permissible' before it constitutes a hazard. The answer necessarily depends on the nature of the hazard since it may be that in some

situations there is a margin for error, while in other situations the margin may be so slim that even fully conscious alertness may not be adequate, e.g. driving.

It is, perhaps, natural to try to be as 'academic' or 'scientific' as possible but as long as conclusions can only be drawn in 'real-life' terms of 'possible' or 'likely' disruption it may be more relevant to assess drug effects in relation to the real situations of driving (Klonoff, 1974), flying (O'Conner, 1972) and work (Alluisi, 1972), rather than simplified laboratory analogues.

Work behaviour is characterised by sustained performance, for long periods of time, of tasks which are typically complex and multi-dimensional. Generally, attention is divided and the individual has to monitor several sources simultaneously while assessing the probability of response requirement and compensating for distraction. In comparison, laboratory assessment usually depends on single channel input and output assessed in terms of speed and accuracy. The simple-mindedness of the laboratory approach has been criticised and some attempts have been made to achieve realism by the use of work-situation simulation. For example, Alluisi (1972) described a multiple-task performance battery which required monitoring of,

and response to, six tasks. The tasks included three watch-keeping tasks which the subject monitored for the whole of the test period, and three active tasks measuring computation, target identification and code solving. The use, in this way, of tasks similar to those encountered in a work situation, and the testing of subjects over periods of several hours and for several days a week, is more likely to achieve a situation, in terms of both performance pattern and attitude, from which meaningful conclusions can be drawn. Although Alluisi and his colleagues have been interested principally in assessing the efficiency of different work-sleep cycles the possible usefulness of this approach in the assessment of drug effects is clear.

The usefulness of the study of the effects of repeated administration of drugs is evident. The argument has already been put that the amount of extrapolation possible from single dose studies is limited since almost all drugs administered for therapeutic purposes are taken chronically. No light is shed on whether a drug having an initially disruptive effect continues to have such an effect or whether there is a disruptive effect on withdrawal, if only a single dose is used. However, a drug which is a promising new effective therapeutic agent is more likely to be marketed if the side effects

during continued administration are slight or transitory than if the effects continue to be disruptive and also affect parameters such as sleep quality, vitality and anxiety, and a preparation already on the market should be more likely, all things being equal, to be prescribed if its effects are known to be less disruptive than those of another equally suitable drug.

Ideally the effects of drugs over the whole day should be studied. Only by twenty-four hour assessment would it be possible to detect not just the gross effects on sleep stages and sleep duration and on performance levels and once-a-day self-rated feelings, but also possible daytime compensation for night-time sleep disruption, the relationship between a particular sleep stage and lower alertness, and whether poor performance is related to the effects of the drug itself or the sleep disruption it causes.

The effects of drugs are seen not only at the psychological and psychophysiological levels but at the biochemical level as well and any study claiming to examine the effects of drugs with thoroughness should include this facet. Bond and Lader (1972) used spectrofluorimetry to measure plasma nitrazepam levels as one of a large variety of measures in an attempt at blanket coverage and demonstrated that there is a relationship between the proportion of EEG

fast wave activity (13.5 to 26.0 Hz) and the dose level of nitrazepam. Only one blood sample was taken from each subject, however, and the amount of information that could be drawn was limited. The study would have yielded much more useful information had it involved repeated drug administration and repeated blood sampling in order to assess changing blood concentration levels and their relationship with changes in performance.

Cox, Simpson and Rothschild (1973) demonstrated the usefulness of repeated sampling of blood when the effects of a drug on performance under different conditions are being assessed. Testing performance on a stellate pursuit rotor they found little difference in performance between a group which received glucose and noise stress, a group which received glucose but no noise stress and a group receiving neither; a group receiving noise stress but no glucose performed at an inferior level. On the basis of these results the inference might be drawn that noise stress (80dBA) impaired performance and glucose may inhibit the occurrence of a decrement. The complementary blood glucose data not only supported the inference but clarified the picture considerably, since while blood glucose level fell for all groups, the fall was greater in the two groups receiving noise stress,

whose levels fell to below baseline, and greatest in the group which had the extra glucose reserve. It was clear that the extra glucose enabled the subjects to overcome the effect of the noise, and maintain their performance level but in doing this glucose reserves were markedly depleted. Thus by the use of several lines of approach a more complete picture can be constructed and interpretation can become more reliable.

In conclusion, perhaps it may be said that large-scale general theories similar to those outlined earlier, may be of less use in the attempt to understand some of the problems, factors and mechanisms involved in this field of research than the more empirical approach involved in the use of limited theories. The diversity of action and discipline effect of drugs which have similar therapeutic effects has been shown by a number of research workers using a large selection of measures. It is suggested that a more harmonious and realistic approach should be taken to assess the effects of drugs. Thus certain basic principles would be followed. First, tests would be used which have been shown to be sensitive to drug effects and which realistically measure skills employed in either everyday or working life, e.g. driving, flying, etc. In this way the extent of disruption can

be assessed practically and the effects of new drugs can be assessed in comparison with established ones. Second, design of experiments would take notice of, and attempt to elucidate the effects of factors such as individual differences and drugs which are commonly taken, e.g. nicotine and alcohol. Third, drugs would be assessed using subjects in the age group for which the drug is, or will be, principally prescribed. Fourth, the effects of drugs would be assessed according to the way they are prescribed. Thus evaluation of hypnotics should allow for periods of continued administration with assessment at intervals until several weeks after the drug has been withdrawn.

APPENDIX

PERSONALITY QUESTIONNAIRE

OCCUPATION_____ AGE_____ SEX_____

INSTRUCTIONS

Please answer each question by putting a circle around the "YES" or the "NO" following the question. There are no right or wrong answers, and no trick questions. Work quickly and do not think too long about the exact meaning of the question.

PLEASE REMEMBER TO ANSWER EACH QUESTION

1. Do you have many different hobbies? YES NO
2. Do you stop to think things over before doing anything? YES NO
3. Does your mood often go up and down? YES NO
4. Have you ever taken the praise for something you knew someone else had really done? YES NO
5. Are you a talkative person? YES NO
6. Would being in debt worry you? YES NO
7. Do you ever feel "just miserable" for no reason? YES NO
8. Were you ever greedy by helping yourself to more than your share of anything? YES NO
9. Do you lock up your house carefully at night? YES NO
10. Are you rather lively? YES NO
11. Would it upset you a lot to see a child or an animal suffer? YES NO

12. Do you often worry about things you should not have done or said? YES NO

13. If you say you will do something, do you always keep your promise no matter how inconvenient it might be? YES NO

14. Would you enjoy parachute jumping? YES NO

15. Can you usually let yourself go and enjoy yourself at a lively party? YES NO

16. Are you an irritable person? YES NO

17. Have you ever blamed someone for doing something you knew was really your fault? YES NO

18. Do you enjoy meeting new people? YES NO

19. Do you believe insurance schemes are a good idea? YES NO

20. Are your feelings easily hurt? YES NO

21. Are <u>all</u> your habits good and desirable ones? YES NO

22. Do you tend to keep in the background on social occasions? YES NO

23. Would you take drugs which may have strange or dangerous effects? YES NO

24. Do you often feel "fed-up"? YES NO

25. Have you ever taken anything (even a pin or button) that belonged to someone else? YES NO

26. Do you like going out a lot? YES NO

27. Do you enjoy hurting people you love? YES NO

(Please turn over)

28. Are you often troubled about feelings of guilt? YES NO
29. Do you sometimes talk about things you know nothing about? YES NO
30. Do you prefer reading to meeting people? YES NO
31. Do you have enemies who want to harm you? YES NO
32. Would you call yourself a nervous person? YES NO
33. Do you always say you are sorry when you have been rude? YES NO
34. Do you have many friends? YES NO
35. Do you enjoy practical jokes that can sometimes really hurt people? YES NO
36. Are you a worrier? YES NO
37. As a child did you do as you were told immediately and without grumbling? YES NO
38. Would you call yourself happy-go-lucky? YES NO
39. Do good manners and cleanliness matter much to you? YES NO
40. Do you worry about awful things that might happen? YES NO
41. Have you ever broken or lost something belonging to someone else? YES NO
42. Do you usually take the initiative in making new friends? YES NO
43. Can you easily understand the way people feel when they tell you their troubles? YES NO
44. Would you call yourself tense or "highly-strung"? YES NO
45. Do you throw waste paper on the floor when there is no waste paper basket handy? YES NO
46. Are you mostly quiet when you are with other people? YES NO
47. Do you think marriage is old-fashioned and should be done away with? YES NO

48. Do you feel self pity now and again? YES NO
49. Do you sometimes boast a little? YES NO
50. Can you easily get some life into a rather dull party? YES NO
51. Do people who drive carefully annoy you? YES NO
52. Do you worry about your health? YES NO
53. Have you ever said anything bad or nasty about anyone? YES NO
54. Do you like telling jokes and funny stories to your friends? YES NO
55. Do most things taste the same to you? YES NO
56. Do you sometimes sulk? YES NO
57. As a child were you ever cheeky to your parents? YES NO
58. Do you like mixing with people? YES NO
59. Does it worry you if you know there are mistakes in your work? YES NO
60. Do you suffer from sleeplessness? YES NO
61. Do you always wash before a meal? YES NO
62. Do you nearly always have a "ready answer" when people talk to you? YES NO
63. Do you like to arrive at appointments in plenty of time? YES NO
64. Have you often felt listless and tired for no reason? YES NO
65. Have you ever cheated at a game? YES NO

66. Do you like doing things in which you have to act quickly?_____YES NO

67. Is (or was) your mother a good woman?_____YES NO

68. Do you often feel life is very dull?_____YES NO

69. Have you ever taken advantage of someone?_____YES NO

70. Do you often take on more activities than you have time for?_____YES NO

71. Are there several people who keep trying to avoid you?_____YES NO

72. Do you worry a lot about your looks?_____YES NO

73. Are you always polite even to unpleasant people?_____YES NO

74. Do you think people spend too much time safeguarding their future with savings and insurances?_____YES NO

75. Have you ever wished that you were dead?_____YES NO

76. Would you dodge paying taxes if you were sure you could never be found out?_____YES NO

77. Can you get a party going?_____YES NO

78. Do you try not to be rude to people?_____YES NO

79. Do you worry too long after an embarrassing experience?_____YES NO

80. Have you ever insisted on having your own way?_____YES NO

81. When you catch a train do you often arrive at the last minute?_____YES NO

82. Do you suffer from "nerves"?_____YES NO

83. Have you ever deliberately said something to hurt someone's feelings?_____YES NO

84. Do you hate being with a crowd who play harmless jokes on one another? YES NO

85. Do your friendships break up easily without it being your fault? YES NO

86. Do you often feel lonely? YES NO

87. Do you always practice what you preach? YES NO

88. Do you sometimes like teasing animals? YES NO

89. Are you easily hurt when people find fault with you or the work you do? YES NO

90. Would life with no danger in it be too dull for you? YES NO

91. Have you ever been late for an appointment or work? YES NO

92. Do you like plenty of bustle and excitement around you? YES NO

93. Would you like other people to be afraid of you? YES NO

94. Are you sometimes bubbling over with energy and sometimes very sluggish? YES NO

95. Do you sometimes put off until tomorrow what you ought to do today? YES NO

96. Do other people think of you as being very lively? YES NO

97. Do people tell you a lot of lies? YES NO

98. Are you touchy about some things? YES NO

99. Are you always willing to admit it when you have made a mistake? YES NO

100. Would you feel very sorry for an animal caught in a trap? YES NO

101. Did you mind filling in this form? YES NO

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL THE QUESTIONS

Form 6

P.Q. SCORING KEY

	25 Items	21 Items	23 Items	21 Items
	P	E	N	L
1	-2	1	3	-4
2	-6	5	7	-8
3	-9	10	12	13
4	-11	15	16	-17
5	-19	18	20	21
6	23	-22	24	-25
7	27	26	28	-29
8	31	-30	32	37
9	35	34	36	-41
10	-39	38	40	-49
11	47	42	44	-53
12	51	-46	52	-57
13	55	50	60	61
14	-59	54	64	-65
15	-63	58	68	-69
16	-67	62	72	-76
17	71	66	75	-80
18	74	70	79	87
19	-78	77	82	-91
20	81	92	86	-95
21	85	96	89	99
22	88		94	
23	93		98	
24	97			
25	-100			

P.Q. AGE NORMS

AGES	P		E		N		L		
MALES	n	M	S.D.	M	S.D.	M	S.D.	M	S.D.	n
16-19	540	4.63	3.27	14.46	4.27	10.69	5.08	6.05	3.80	563
20-29	768	4.19	3.26	13.72	4.79	9.81	5.09	6.50	3.88	649
30-39	404	3.27	2.75	12.85	4.73	9.33	5.18	7.53	4.51	181
40-49	327	3.09	2.59	12.38	5.14	9.17	5.06	8.07	4.08	126
50-59	208	2.57	2.51	10.76	5.29	10.12	5.40	9.10	4.06	73
60-69	65	2.56	2.47	10.44	4.97	8.51	5.60	11.58	5.15	32
	2,312	3.78	3.09	13.19	4.91	9.83	5.18	6.80	4.14	1,624

FEMALES										
16-19	590	2.99	2.56	13.31	4.61	13.28	5.22	6.78	3.92	680
20-29	1,366	2.79	2.41	12.89	4.70	12.87	4.99	7.17	3.85	1,098
30-39	544	2.28	2.20	11.97	4.95	12.57	5.28	8.84	4.05	285
40-49	416	2.35	2.11	12.24	4.92	12.63	5.38	8.86	3.87	203
50-59	273	2.21	1.96	11.61	4.98	12.11	5.36	11.09	4.75	140
60-69	73	2.69	2.94	12.07	5.40	10.19	5.55	12.06	4.89	56
	3,262	2.63	2.36	12.60	4.83	12.74	5.20	7.73	4.18	2,462

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